COURT FILE NO: C70528

COURT OF APPEAL FOR ONTARIO
(Appeal in an application)

B E T W E E N :

THE ATTORNEY GENERAL OF ONTARIO

Applicant (Respondent in appeal)

-and-

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHUURMAN, DEAN WANDERS, RANDY FREY, HARVEY FREY, and DANIEL GORDON

Respondents (Appellants)

A N D B E T W E E N:

HER MAJESTY THE QUEEN IN ONTARIO

Applicant (Respondent in appeal)

-and-

THE CHURCH OF GOD (RESTORATION) AYLMER, HENRY HILDEBRANDT, ABRAM BERGEN, JACOB HIEBERT, PETER HILDEBRANDT, SUSAN MUTCH, ELVIRA TOVSTIGA, and TRUDY WIEBE

Respondent (Appellants)

APPLICATION UNDER the *Reopening Ontario (A Flexible Response to COVID-19) Act*, S.O. 2020, c. 17, s. 9

EXHIBIT BOOK

May 11, 2022

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COURT FILE NO: CV-21-95-0000

ONTARIO SUPERIOR COURT OF JUSTICE

BETWEEN

THE ATTORNEY GENERAL OF ONTARIO

Applicant (Responding Party)

-and-

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHUURMAN, DEAN WANDERS, RANDY FREY, HARVEY FREY, AND DANIEL GORDON

Respondents (Moving Parties)

AFFIDAVIT OF REV. JACOB REAUME
(Constitutional Challenge)
(Sworn June 4, 2021)

I, JACOB REAUME, of the [redacted] in the Province of Ontario, MAKE OATH AND SAY:

1. I am one of the Respondents (Moving Parties) herein, and as such have personal knowledge of the matters hereinafter deposed to, except where they are based on information and belief, in which case I verily believe them to be true.

2. I am the senior pastor of the Respondent, Trinity Bible Chapel ("**TBC**") and have been pastoring there since 2009. I achieved a baccalaureate degree in Religious Education in 2003 and have a Master of Divinity from the Southern Baptist Theological Seminary in Louisville, Kentucky. I was ordained as a Minister on November 20, 2005, and served in churches across Ontario and the United States before becoming a lead Pastor at TBC. In 2020, I helped found and became Chancellor of King Alfred Academy, a private Christian school which operates out of the TBC campus. I was

born and raised in Guelph, have been happily married for 20 years, and I have 5 children with another on the way.

3. The other personal Respondents are elders and associate pastors of TBC and form the leadership team of the church.

4. Trinity Bible Chapel has been in existence for 20 years. Prior to the first lockdown in March of 2020, we often had between 600-700 people in attendance for services each week, usually including between 100-150 university students. Our facility can safely house over 900 people based on fire code regulations, including the sanctuary and a large gymnasium.

Initial Response to Covid-19 and Government Restrictions

5. In the early months of the first lockdown, commencing in March 2020, the TBC facility was shut down for in-person services, provided online productions, and our staff members called each regularly attending household to provide pastoral guidance. At that time, we were banned from any gathering of more than five people and drive-in services were not permitted. In the very earliest stages of the declared public health emergency, we did not know what we were dealing with and were prepared to give the government the benefit of the doubt for a short period of time.

6. On April 23, 2020, we submitted an open letter to governing officials requesting that they work with us to reopen. In it we included our proposed course of action to mitigate the spread of Covid-19. We received no substantive reply. Attached hereto and marked as **Exhibit "A"** to this my Affidavit is a copy of the said letter and risk management addendum.

7. After the first lockdown had continued for some weeks, we became involved with a group of pastors who started a website called Reopen Ontario Churches. The group wrote a letter to our authorities in May of 2020, providing recommendations and seeking a safe re-opening of our churches. Our pleas and lobbying were ignored. Attached hereto and marked as **Exhibit "B"** to this my Affidavit is a copy of the letter.

8. We, and other church leaders in our group, expressed eagerness to get back to public gatherings in some capacity, as we were by that point several months into the first lockdown and were growing increasingly concerned about the well-being of our parishioners and the broader community.

9. After drive-in services were permitted, our church conducted one service in this fashion on June 7, 2020. However, drive-in services are a poor substitute for in-person gatherings, as people are not able to partake of the Lord's Supper or participate in other important practices and ceremonies, such as baptism, and cannot meaningfully interact with one another.

10. On June 2, 2020, while severe gathering restrictions were still in effect, including the prohibition on groups of more than five (5) congregating outdoors, the Waterloo Chief of Police, Bryan Larkin, issued a news release concerning planned Black Lives Matter protests in the region. Attached hereto and marked as **Exhibit "C"** to this my Affidavit is a true copy of the press release, downloaded from the Waterloo Regional Police Service website. The police chief expressed full support for the protest and advised that its officers would be in attendance to provide protection and to stand in solidarity with those in attendance. Local media reported that the crowd "may have been between 12,000 and 20,000 strong". Attached hereto and marked as **Exhibit "D"** to this my Affidavit is a copy of a CTV Kitchener article covering the event.

11. In the News Release, Chief Larkin wrote, "We realize that this event is being held during a health crisis. But, we also realize that you are hurting. You are grieving. And you are justifiably angry. We realize that this is a time for us all to come together in an attempt to heal, to show support, and to pave the way for a better future for all."

12. To the best of my knowledge and information, no charges were laid despite the fact thousands of people breached the gatherings restrictions in force at that time. My perspective on the arbitrariness of the gathering restrictions, and the hypocrisy of their selective enforcement, was impacted by these actions.

13. Shortly thereafter, the Ontario Government announced that houses of worship would be permitted to open to 30% capacity, effective June 12, 2020.

14. Following that announcement, our church switched back to in-person services, which was a great and profound relief. We initially maintained 30% building capacity limits, set up a massive overflow section in our gymnasium to space people out further, provided access to hand sanitizers and face masks, and developed a comprehensive policy to mitigate the spread of COVID-19. For example, when serving the Lord's Supper all elders wore masks. We implemented public health protocols, in accordance with the document dated June 25, 2020, attached hereto as **Exhibit "E"** to this Affidavit.

15. It was a wonderful blessing to our community to meet in person over the summer months. However, as the fall approached the Government began making public comments about potential further restrictions. In early autumn, we wrote a letter to our local MPP asking for churches to remain open and continue to operate safely. Attached hereto and marked as **Exhibit "F"** to this my Affidavit is a true copy of the said letter, dated September 18, 2020, to which we did not receive a response.

16. On or about November 3, 2020, the Ontario Government abandoned its Stage 1, 2 and 3 approach, and introduced a colour-coded system and some apparently objective benchmarks for imposing further restrictions. For each of the stages, including "red", houses of worship were to remain at 30% capacity.

17. It was not long before the Government changed gears again, and introduced a more restrictive "grey zone", modelled on the earlier Stage 1 restrictions. Toronto and Peel were the first areas to go back into the grey zone, which permitted houses of worship to only have ten (10) persons in attendance, regardless of building capacity.

Church Response to Threats of Second Lockdown

18. On December 3, 2020, fearing that the restrictions would spread to other parts of the province, I wrote an open letter advising that TBC would practice peaceful civil disobedience in the event of a second lockdown. At that time, Waterloo Region was

still open at 30% capacity for churches. Attached hereto and marked as **Exhibit "G"** to this my Affidavit is a true copy of this letter. I posted it publicly on our website and forwarded it to multiple provincial and federal representatives, as well as the mayor and other officials at the Region of Waterloo, who provided no substantive replies.

19. Indeed, the Premier announced on December 21, 2020, that the entire province, regardless of case counts or the presence or absence of any crisis regionally, would begin a four-week lockdown on Boxing Day. Attached hereto and marked as **Exhibit "H"** to this my Affidavit is a copy of the province's news release.

20. The effect of these restrictions was a gross and substantial interference in the practice of our faith, individually and collectively.

21. We made the decision as a leadership team to continue to exercise our fundamental freedoms guaranteed under the *Charter of Rights and Freedoms* and to assemble in person for worship services with the risk mitigation protocols in place. We continued to make online services available for those who chose, for health or other reasons, not to attend in person. At that point, nine months into Covid-19, the lockdown harms I was observing and counselling my parishioners about were mounting. I wanted to provide hope and comfort to our congregation and our community through the continuation of our religious practices in association with other members of our faith community.

22. On December 23 I sent a letter to the Chief of Police and copied the mayor of Woolwich Township, inviting him to support our constitutional rights, just as he had supported the Black Lives Matter marches in June, which were also held during gathering restrictions. Attached hereto and marked as **Exhibit "I"** to this my Affidavit is a true copy of the letter. The Mayor replied with a brief email saying they would like compliance and that the police would be in touch with me.

23. On December 24, I received a visit from two police officers at the church. They advised that a second lockdown would be going into effect on December 26 across the entire province. I informed the officers that I could not, in keeping with my conscience and religious convictions, agree to a further shutdown of our church and that, while I had

not had occasion to bury anyone dying of Covid-19, our church community was impacted by other lockdown harms which I believe were imposing far more damage to the vast majority of the population than Covid-19, including suicides.

24. On or about December 26, 2020, Ontario placed the entire province under a "shutdown", which severely restricted many of the activities of Ontarians, including their attendance at places of worship which were limited to a hard cap of 10 persons indoors, regardless of capacity.

25. On December 27, 2020, and January 3, 2021, our church opened at approximately 30% capacity, as usual, and we were blessed to be in fellowship with one another and participate in corporate worship and prayer.

26. Although we initially adhered quite closely to public health protocols, as the Region of Waterloo's treatment of our church became more punitive, their approach had the opposite effect. In accordance with provincial and local public health guidance, we do not enquire into the reasons for an attendee's decision not to wear a mask. We assume that they, as adults, are capable of making their own health decisions. We did ask that anyone who is feeling unwell stay away from in-person services.

27. I believe that Trinity Bible Chapel is being observed very closely, however public health has never contacted us about an outbreak. In fact, in response to a Freedom of Information request to the Regional Municipality of Waterloo for any references in their documents to "Jacob Reaume", "Randy Frey", "Trinity Bible Chapel", or "King Alfred Academy", we received a letter indicating that they had approximately 6000 emails and 144 documents on file for the period between March 1, 2020, and January 14, 2021. Attached hereto and marked as **Exhibit "J"** to this affidavit is a true copy of the letter from the Regional Municipality of Waterloo, dated February 16, 2021.

28. Furthermore, the government's own published data shows that places of worship in general are not responsible for community spread of Covid-19, even though many have been open during the reporting period to at least some degree (30%, more or less). Attached hereto and marked as **Exhibit "K"** to this affidavit is a copy of a document

published by Public Health Ontario, entitled "*COVID-19 Outbreaks and Cases in Ontario, by Setting: February 16, 2020 to December 26, 2020*." The government has had this information since at least January 11, 2021, according to the report date.

29. The document includes various tables, which note the following data for the entire Province of Ontario:

> Table 1: Fewer than 1% (0.55%) of all outbreaks (23 / 4151) are due to places of worship.
>
> Table 2: Fewer than 1% (0.56%) of all outbreak cases (221 / 39774) are due to places of worship.
>
> Table 3: Places of worship account for 0.1% (5 / 3460) of all outbreak associated hospitalizations.
>
> Table 3: Places of worship account for 0% (0 / 3681) of all outbreaks associated deaths.

30. My observation and belief is that these times of isolation, due to the government's restrictive actions, have harmed people and society by perpetuating loneliness, hopelessness, fear, poverty, division, anger, the deterioration of relationships, and a plethora of other evils which will become more evident with time. These observations do not surprise me because the restrictive actions of the government have wrongfully reduced human beings to biological units with little purpose to existence other than to avoid contracting and spreading a virus.

31. Scripture teaches us that people are much more than biological units. We are created in the image of God with dignity and worth to live free, love one another, worship together, grow families, eat with each other, laugh and cry together, embrace one another, exchange goods and services, and build things. Central to the Christian life is the ministry of the church, and TBC asserts that the church must remain open.

The Government's Response – Charges and Contempt

32. On December 30, 2020, I, along with five other church leaders, Will Schuurman, Dean Wanders, Randy Frey, Harvey Frey and Daniel Gordon, were issued summonses to attend court on the charge of "being an owner/occupier of the said premises did host

or organize at prescribed premises being a place of worship and the number of people in attendance exceeded the number permitted contrary to s. 10.1 of the *Reopening Ontario Act* Ontario Regulation 82/20 Schedule 4 s. 1(d)" ("the *Act*").

33. On January 6, 2021, Pastor Will Schuurman and I were issued two summonses each for a service held on January 3, 2021, on charges of "attended gathering of more than 10 people for the purposes of a religious service, rite or ceremony contrary to the *Act*," and "host a gathering at a prescribed premises where the number of people in attendance exceeded the number permitted under a continued s. 7.0.2. contrary to the *Act*, section 10.1(1)."

34. Four other church elders, Dean Wanders, Randy Frey, Harvey Frey and Daniel Gordon, as well as Trinity Bible Chapel, also received summonses to attend court on the charge of "Host a gathering at a prescribed premises where the number of people in attendance exceeded the number permitted under a continued s. 7.0.2. contrary to the *Act*, section 10.1(1)." These charges also related to the service on January 3, 2021.

35. On January 7, 2021, we received a letter from counsel to the Attorney General of Ontario (the "**AG**"), threatening to bring a Section 9 Application under the *Act* to restrain TBC and anyone acting on its behalf from contravening Regulation 82/20 unless we provided an undertaking that there would be no further gatherings in excess of ten people at TBC.

36. Despite serious reservations and acting against our consciences, we undertook not to have any further gatherings at TBC in excess of ten people until January 23, 2021, which was the end of the scheduled second lockdown date. We abided by that undertaking.

37. Unfortunately, the goalposts moved again. On January 14, 2021, Premier Doug Ford issued a "stay-at-home order", following a declaration of a "state of emergency", extending the second lockdown to at least February 11, 2021.

38. On January 15, 2021, we received a second letter from the AG, once again threatening to bring enforcement proceedings unless we provided a second undertaking that there

would be no further gathering in excess of ten people at TBC until at least February 11, 2021.

39. After much deliberation among our church elders, we decided that we were no longer able to provide undertakings not to have in-person services because to do so deeply violates our sincerely held Christian beliefs and would sear our consciences. Furthermore, as indicated above, the gross interference with our essential communal religious practices was harmful to our parishioners on many levels. On January 21, 2021, we informed counsel to the AG through our lawyer that we would not be signing any further undertakings.

40. A motion was brought by the AG with a return date of the following day, January 22, 2021, at which time the Order of the Honourable Mr. Justice P.R. Sweeny was made, restraining TBC and those associated with it from violating Ontario Reg. 82/20 by holding gatherings of more than 10 persons in conjunction with the operations of the church.

41. We subsequently held two in-person services on January 24, 2021. Although some in the media have been critical of our decision, I have received many dozens of heart-felt emails and letters from people who either attended, or wished they could have attended, or who aren't even Christian but expressed a renewed bond with the church. We did what we set out to do – we shared hope and love with an oppressed and psychologically-ravaged community.

42. Following those services, Pastor Schuurman and I each received two more summonses to court, and the other elders and TBC each received one.

43. The AG brought an immediate motion for contempt, which was heard on January 27, 2021. We were found in contempt by Justice Sweeny of his order. Pending sentencing, scheduled for February 11, and feeling pressured by the weight of the state against us, we expressed a willingness through our lawyer to refrain from opening our facility for in-person services temporarily, and did in fact hold drive-in services only on January 31 and February 7, 2021.

44. On February 11 we attended a sentencing hearing via Zoom on the contempt matter, and later learned when we received the court's endorsement that we were to be fined $83,000, inclusive of costs. This has now been paid.

45. Immediately thereafter, the province returned to the colour-coded framework, and Waterloo Region was placed into the "Red Zone", which meant religious gatherings were limited to 30% of room capacity. Attached hereto and marked as **Exhibit "L"** is a copy of Ontario's news release to this effect, dated February 12, 2021.

46. While the Waterloo Region was in the Red Zone, we continued to hold services and enjoyed a brief reprieve from heavy-handed enforcement to conduct our religious worship in relative peace. We did not turn anyone away who wished to worship with us.

47. Effective on or about March 15, 2021, Ontario amended Regulation 89/20 to remove the 10-person cap and replace it with a 15% capacity limit for regions in the "Grey Zone" or "Shutdown Zone". Attached hereto and marked as **Exhibit "M"** is a copy of Ontario's news release, dated March 12, 2021.

48. On or about April 3, 2021, Waterloo Region was moved into the "Grey Zone" and church services were then required to be limited to 15% of building capacity. On or about April 7, 2021, Ontario declared a third state of emergency across the entire province.

49. On Thursday, April 8, one of Waterloo Region's by-law officers visited our church to hand deliver two new summonses to appear in court. One summons was for Trinity Bible Chapel, and the other summons was for me. This pertained to the offence of worshipping the risen Christ together on Resurrection Sunday (Easter), on April 4.

50. On April 11, 2021, we noticed Region of Waterloo by-law officers observing our parishioners through binoculars from across the street. We felt uncomfortable and violated by this invasion of our privacy and by our women and children being peered at by officers as we gathered for worship.

51. On April 14, 2021, we were served through our lawyer with a second Motion for Contempt by the AG, for the services held on April 4 and 11.

52. On April 15, 2021, Waterloo Region by-law officers visited our church to hand deliver two new summonses to appear in court. One summons was for Trinity Bible Chapel, and the other summons was for me. This was the church's fourth summons. Each summons to the church carries a maximum penalty of $10 million. This was my seventh summons. Each summons to me carries a maximum penalty of $100,000 and one year in jail.

53. On April 15 and 16, 2021, our staff packed up our church offices because we faced a hearing on April 16 to have us locked out of our facility. The anticipation and the result of this action created stress to our staff and hindered our ability to provide pastoral care to our congregation.

54. The AG's motion was set for April 16, 2021, at which time the contempt hearing was adjourned and the AG's interim injunction request to lock the doors was denied, since there was a lack of clarity over whether the original order (limiting us to 10 persons) was still in effect.

55. After Justice P.R. Sweeny's oral ruling on April 16, while we were still in Zoom court, the AG brought a motion without notice for a new enforcement order. Justice Sweeny made a further Order pursuant to s. 9 of the *ROA*, mandating, in essence, that TBC and those connected with the church be restrained from contravening the maximum size of gathering as permitted from time to time under various regulations for the purpose of a religious service, rite or ceremony.

56. Subsequently, the entire province was placed again under a "shutdown" order, and as of April 19, 2021, and continuing to date, places of worship are again restricted to a maximum of ten persons inside the building, regardless of capacity limits.

57. Our congregation continued meeting but were impeded by the presence of police and/or by-law enforcers near our property. On April 25, several members of our congregation were charged for attending church. We have been under constant threat

of more summonses, more fines for contempt, potential jail time, and being locked out of our church indefinitely. The stress on our leaders, parishioners and volunteers, as law-abiding citizens, cannot be overstated.

58. On April 30, 2021, a new contempt motion was brought to court, based on the order of April 16. An interim injunction was granted to lock the church doors, even though we did not have an opportunity to file responding materials or cross-examine the AG's witnesses.

59. The following day, on May 1, the church doors were locked by the Sheriff. I went to the parking lot that afternoon, with a small informal group of people (about 30), and we prayed and sang outdoors. I received two new charges for organizing and hosting an illegal gathering. A number of our parishioners were also charged. There were so many cruisers and unmarked vehicles observing I could not easily count them all.

60. On May 6, 2021, that injunction was continued by Justice Krawchenko, pending a return to at least 30% capacity for religious gatherings. Further sentencing for contempt has been scheduled for July, 2021.

61. We now have more than 30 charges before the courts, and we are facing maximum penalties of over $40 million with jail time, plus a further contempt penalty. We were continually monitored by bylaw officials and/or police, who attended many Sundays and parked near our church to count heads and intimidate worshipers. Police have driven by my home (at the end of a dead-end street), which is something I have not previously observed. I believe that this is to intimidate my family and me.

62. To say that our Charter-guaranteed freedoms to worship, assemble, associate, and express ourselves have been infringed is an understatement.

63. Additionally, we have been targeted relentlessly in the media, faced threats from members of the public, and even our lender has frozen our line of credit and has reminded us that they can call our loan anytime. When we took out our loan, we agreed to abide by the law of the land as part of our lending agreement. We are a church, and

we are a church in what claims to be a free country. We did not foresee the day when the consequences of inviting the community to church in Canada would be illegal.

64. The inconsistencies and hypocrisy of our leaders and health officials over the last months only reinforced our perspective. While the church could not meet, leaders such as Finance Minister Rod Phillips and Health Table advisor and hospital executive, Dr. Tom Stewart, to name just two, travelled to sunnier climates by air for vacation time. Attached hereto and marked as **Exhibits "N"** and **"O"** are two news articles containing those stories.

65. While the church could not meet, big-box stores like the Walmart located within 2.3 km of our church, have remained open throughout, with hundreds of people able to congregate there. LCBO stores, and others the government has deemed "essential" remain open.

66. While the church could not meet, a movie was filmed in Kitchener. Attached hereto and marked as **Exhibit "P"** to this Affidavit is a CTV article detailing this story.

67. While we were being charged for meeting with 30 people outdoors in our parking lot and praying, only a week later on May 8, the nearby Farmer's Market parking lot was packed. Attached hereto and marked as **Exhibit "Q"** to this Affidavit is a photograph taken by Al Vandergaag, one of TBC's members, and emailed to me.

68. Also on May 8, a nearby rally against "White Lives Matter" attracted 50 people. No charges were reportedly laid. Attached hereto and marked as **Exhibit "R"** to this Affidavit is a copy of the CTV news article detailing that event.

69. On May 9, I spoke at a rally organized by MPP Randy Hillier in Waterloo. A bylaw officer attended at my home to deliver a summons, charging me for that attendance. Police accompanied the officer. My wife was home and answered the door. She advises me, and I verily believe, that she asked the officer why police were accompanying bylaw, and the officer replied, "You might have a handgun."

70. On May 15, 2021, while the church was not permitted to gather outdoors in numbers greater than 10, the nearby Farmer's Market (1.2 km away) was again packed. Attached hereto and marked as **Exhibit "S"** to this Affidavit is a series of 6 photographs taken that day by a member of TBC's congregation and emailed to me.

71. On May 24, 2021, while the church was not permitted to gather outdoors, many people enjoyed nearby Shade's Mills Conservation Authority. Attached hereto and marked as **Exhibit "T"** to this Affidavit is a photo of the park that day, sent to me by an attendee of my congregation.

72. On June 3, 2021, a vigil was scheduled for Waterloo Park to commemorate the lives of children lost to the Residential School in Kelowna BC. According to the article in Kitchener Today, attached hereto and marked as **Exhibit "U"**, police advised that they would not be monitoring the event.

Offering Hope to the Community

73. We (being myself and the leadership at TBC) believe that a person's overall well-being must take into account much more than merely their physical health. Mental and spiritual health are critical as well. The seemingly endless lockdowns and stay-at-home orders, never before imposed on the entire population, are exclusively concerned with a single virus. This seems outrageous and unjustifiable to us.

74. People in Trinity Bible Chapel's congregation make their own informed decisions where they are comfortable going, whether it be the grocery store or to worship services. These are personal choices that TBC leaves to each individual's consideration and conscience.

75. Online video productions cannot replace the peaceful assembly and association of our members. For a week or two during a crisis it might be reasonable, but for a protracted period of time it is untenable. Church is not a show or spectacle on our screens – it is a participatory experience. It involves communal prayer, song, and fundamental rituals such as communion and baptism. Physical gathering is essential to us, to our well-being, to our faith, and to civil society.

76. In my open letter to the community, dated January 22, 2021, attached hereto and marked as **Exhibit "V"**, I noted: "People are lonely, afraid, despairing of life itself, and facing financial ruin, among many other deprivations and tribulations. This is all during the darkest and coldest season of the year. If ever our fellow Ontarians needed hope, it is now. Out of neighbourly love, I am personally openly inviting anyone and everyone to experience the hope of the Gospel and the warmth of Christian worship at Trinity Bible Chapel this Sunday during our two Lord's Day services at 9:00 AM and 11:15 AM."

77. I noted that this was done in love for God and neighbour and stated: "Risking reputation and financial viability to offer eternal hope and warm Christian fellowship to a world in despair is an act of love that I am certain Jesus smiles on."

78. Therefore, up until May 1 and the locks being put on our church, we continued to open our doors to members of the public and regular congregants at TBC, allowing them to attend or not at their own discretion. Many returned to gather and worship. We have observed these past many months that those attending TBC were healthy people and were very happy when they attended.

79. Personally, I have never experienced a more palpable manifest presence of God's Holy Spirit during public worship than I did on that Sunday, January 24 (for which we were first found in contempt). On Sunday, February 21, we baptized 13 individuals, some of whom traced their conversion to those weeks in January, especially January 24.

Freedom of Religion, Conscience and Expression, and the Scriptural Foundation

80. We are bound by our faith to gather for corporate worship, and to engage in communal prayer, preaching, singing, and partaking of the Lord's Supper and other important rites. The government's restrictions have prohibited, limited, and punished us for worshiping as our faith and consciences require.

81. Since its creation, TBC has served our Lord and community by preaching the Good News of the Gospel of Jesus Christ. We do this primarily through our in-person worship

services. In addition to those services, we provide many other supports and services to the benefit of not only our congregation, but the community as a whole. These include, but are not limited to sponsoring foreign missionaries, contributing to local pregnancy centres through, for example, baby bottle drives (fundraising for struggling new mothers), assisting those in need, offering hope to those in despair, comforting the bereaved, providing pastoral care for families and singles, counselling broken marriages toward restoration, visiting the sick and lonely, sponsoring refugees and helping immigrants integrate into our community. In other words, we have been doing some of what the church does best and what the community needs most.

82. When we opened TBC, we chose the word “chapel” to identify with the Dissenting churches of seventeenth century England. During that century, the state church required all congregations to conform to a set form of liturgy and teaching. Bound by conscience as conscience was bound by Scripture, thousands dissented from that imposition. They were Dissenters or Nonconformists. Being forced to separate from the state church many were jailed and persecuted. Their spiritual descendants were economically disadvantaged for generations. Being excluded from the official state church, they formed chapels.

83. In our day, we desire to uphold their convictional example. We ourselves being bound by conscience as conscience is bound by Scripture dissent from the popular non-Scriptural beliefs of our own day. By God’s grace, we will not conform to any standard that opposes Scripture, whether that standard comes from government, another religious body, or a combination of both. In that respect, we are Nonconformists. We are Dissenters. To communicate that commitment, we have chosen to call ourselves a “chapel.”

84. I sincerely believe that Scripture commands us to meet for worship in person, that the definition of “church” requires us to gather in person, and that the Law of God demands we gather at least weekly. This has been articulated in our church doctrinal statement and each of our members has taken a solemn oath and covenant before God to meet regularly for worship, prayer, and to partake together of the Lord’s Supper. This is

found at page 6 of TBC's Constitution, which is attached hereto and marked as **Exhibit "W"** to this my affidavit:

> We will not forsake the assembling of ourselves together, nor neglect to pray for ourselves and others. We will regularly participate together in the ordinance of the Lord's Supper.

85. Being bound by Scripture to be with each other, members of Trinity Bible Chapel therefore have solemnly covenanted before God to worship together and be with each other regularly. To not be together is to violate God's commands and our own solemn oath and covenant. Scripture, which is God's Word to us, commands Christians to gather in person for church (Hebrews 10:24-25). Regularly meeting in person was the pattern established by Christ's apostles: "And they devoted themselves to the apostles' teaching and the fellowship, to the breaking of bread and the prayers" (Acts 2:42).

86. According to our doctrinal statement, located on page 3 of our Constitution, "The Scriptures command believers to gather locally in order to devote themselves to worship, prayer, teaching of the Word, fellowship, the ordinances of baptism and communion, service to the local body through the development and use of talents and spiritual gifts, and outreach to the world to make disciples. Wherever God's people meet regularly in obedience to this command, there is the local expression of the Church under the watchful care of a plurality of elders."

87. Christian meetings include fellowship, which entails togetherness, sharing of goods and food, showing hospitality and presence of person, much like a family unit (Acts 4:32-37). The New Testament upholds the church as a spiritual family, so much that the bonds within the church are stronger than blood relations (Matthew 10:37;13:53-58; Luke 14:26). For this reason, Christians often refer to each other as "brother" and "sister." To operate as a church, Christians are expected to experience fellowship regularly with one another like a family that lives under the same roof.

88. Embedded in the definition of church is gathering together. The New Testament word for church is the Greek word, *ekklesia*. Etymologically, *ekklesia* is the combination of two words that together mean "called out," as in a group of people called out to gather.

The definition of the word demands that a church not be reduced to less than a physical, in-person gathering of people. The lexical range of *ekklesia* includes "assembly," "gathering," "a specific Christian group assembly, gathering ordinarily involving worship and discussion of matters of concern to the community," and "the totality of Christians living and meeting in a particular locality." Where there is no physical gathering, there is no church. For the church to exist, it must gather.

89. The pattern since God created the world has been for those who believe in Him to meet officially for worship at least once weekly. The Ten Commandments were written in stone by the finger of God, thus signifying the abiding authority of God's Law. The fourth commandment reads, "Remember the Sabbath day, to keep it holy. Six days you shall labor, and do all your work, but the seventh day is a Sabbath to the LORD your God" (Exodus 20:8-11). The Old Testament Israelite community set aside the seventh day for rest and public congregational worship: to do otherwise was a transgression of the Law. Christ was raised from the dead on the first day of the week, and since then Christian churches have regularly met on the first day, Sunday, for worship, prayer, preaching, and the ordinances (Acts 20:7; 1 Corinthians 16:1-2).

90. To cease meeting together for worship at least weekly is to be a disobedient Christian. Scripture describes the church as a body with many parts. As a human body cannot exist without all its parts fastened together so the church cannot exist without all its people together. Saint Paul wrote, "Now you are the body of Christ and individually members of it" (1 Corinthians 12:27). Each individual is a valuable part of the church, and the church as a whole needs each individual. A church that does not gather is like a body with its parts scattered across a city. A body exists as parts together, and the church exists as Christians together.

91. The church must be together to fulfill its mission because its mission depends on in-person togetherness and physical presence. The Scriptures command the church to partake of the Lord's Supper together (1 Corinthians 11:17-34), to baptize new converts (Matthew 28:19), to anoint the sick with oil (James 5:14), and to ordain elders and pastors with the laying on of hands (1 Timothy 5:22). None of these actions are

possible while separate or isolated. Each must be done in person because the New Testament presupposes that the church will be together.

92. Jesus epitomized Christian togetherness by incarnating as a man in the flesh. “And the Word became flesh and dwelt among us” (John 1:14). Some have expected church services to be held online, but that betrays the Scriptural notion of an unmediated ministry. Had God conceived of something other than the normalcy of an in-person ministry, he might have sent a picture or a hologram or a pixelated representation of Himself on a computer screen. Instead, God incarnated in the person of Christ by being born of a virgin, living and eating among men, performing miracles, being crucified, and rising bodily from the dead. Christians still wait expectantly for the bodily return of Jesus Christ to earth. Because of Christ’s example to us, I believe that we must be physically present with each other.

Extent of Christian Obedience to Governing Authorities

93. While obedience to Federal, Provincial, and Municipal regulations is typically easily given, such as is the case with fire safety codes, municipal drainage requirements, and following federal, provincial and municipal law to the letter, a lockdown order to cease meeting as a church body for fellowship and worship contradicts the commandments of God, and in such a case we are compelled to listen to God instead of the government. We serve our Lord and God above all others. Further, while I respect the power and scope of various legislative and executive bodies in Canada to regulate public matters, the matters of a church are to be governed by the elders of a church (Acts 20:28; 1 Timothy 5:17; Titus 1:7).

94. Scripture commands Christians to be subject to governing authorities. “Let every person be subject to the governing authorities. For there is no authority except from God, and those that exist have been instituted by God” (Romans 13:1). The command, however, is not ultimate. In such cases when government edicts contradict God’s commands, Christians must obey God over government.

95. Confronted with governing authorities that required them to disobey God, Saint Peter and the other apostles once said, “We must obey God rather than men” (Acts 5:29). Faced with a temporary, 30-day prohibition on praying to anyone except the King, Daniel continued to pray to his God (Daniel chapter 6). Charged by Pharaoh with killing the newborn Hebrew boys, the Hebrew midwives “feared God, and did not do as the king of Egypt had commanded them” (Exodus 1: 15-17). Commanded by the king of Babylon to bow to a golden statue, three Jewish men refused, because of their belief in and devotion to God, even though the king threatened them with death (Daniel chapter 3).

96. To be absolutely clear, the Bible teaches us to honour all those in authority, and we do. But we believe that the state’s authority comes from above. “Let every person be subject to the governing authorities. For there is no authority except from God, and those that exist have been instituted by God” (Romans 13:1). God has designed all authorities, courts included, as delegated powers. He has given them power, and that power must be held in high regard by all men.

97. As noted in my blog post, dated February 25, 2021, attached hereto and marked as **Exhibit “X”**, Christians throughout history have often found themselves conflicted when earthly rulers order them to do what God forbids or forbids them from doing what God commands. In such instances, we must obey God over government. We believe that the church must meet. We further believe that Christ, not the government, has crown rights over the church and His worship.

98. The laws prohibiting us from worshiping together violate our consciences because our consciences are held captive by Jesus. We acted on our consciences and held an $83,000 act of worship, with potentially many more thousands or millions to be paid for other such acts of worship.

99. I and the church have received hundreds of messages of support from not only those who attended our services, but from across the province and beyond. Many share their personal struggles through these lockdowns, and express gratitude that our stand has provided them hope and encouragement in their faith.

100. I swear this affidavit *bona fide*, in support of our motion, and for no other or improper purpose.

SWORN REMOTELY by videoconference by Jacob Reaume at the [redacted], before me at the City of London, in the County of Middlesex, this 4th day of June, 2021 in accordance with O.Reg. 431/20 Administering Oath or Declaration Remotely

A Commissioner, etc.

LISA D.S. BILDY
BARRISTER & SOLICITOR

REV. JACOB REAUME

EXHIBIT A

This is Exhibit "A" referred to
in the Affidavit of
Jacob Reaume
Sworn before me this 4th day
of June A.D., 2021
A Commissioner for Oaths in and for Ontario

LISA D.S. BILDY
BARRISTER & SOLICITOR

TRINITY BIBLE CHAPEL

April 23, 2020

RE: Worship Services and COVID-19

Attention:

Prime Minister of Canada - Hon. Justin Trudeau and local MPs
Premier of Ontario - Hon. Doug Ford and local MPPs
Chief Public Health Officer of Canada - Dr. Theresa Tam
Chief Medical Health Officer of Ontario - Dr. David Williams
Local Mayors of Waterloo, Kitchener, Cambridge, Guelph & Woolwich
Region of Waterloo Public Medical Health Officer Dr. Hsiu-Li Wang
Region of Waterloo Health Managers

Dear Governing Authorities:

Please be assured that you have our sincere thanks, support and prayers during this unprecedented time of isolation due to COVID-19. You are indeed well aware of the huge social and financial implications that this crisis has on Canadian individuals and institutions.

As countries around the world are gradually lifting some of the more restrictive measures that have been put in place, we want to express to you how eager we are to work with you so that we, too, can gather in face to face worship services.

Experts agree, a quarantine can help to keep people from getting the virus. It can, however, also be detrimental to a person's physical and mental health. Cabin fever and depression can become the unintended consequences of isolation. Solitary confinement, for example, is now deemed cruel and unusual by the federal government and medical professionals. We desperately need the company of others to sustain our well-being.

We concur with scientists who warn of a potential "echo-pandemic." Social ills could be rising soon, such as: substance abuse, domestic violence, suicide and general despair.

We do not need to belabour these points. You are also keenly aware, that matters of personal faith are cherished and shared in community. Online communication helps but it is not a satisfactory substitute. This past Easter season was particularly difficult, as you can imagine. Furthermore, we have not been able to practice ordinances like baptism and partake in the Lord's Supper/Communion.

Today, all informed people agree with our Lord's words when He quoted a passage (Deuteronomy 8:3) which was about 1,500 years before He lived on earth: "Man shall not live by bread alone …" (Matthew 4:4).

We have observed how other essential services, such as grocery stores, have been operating during this time. They practice social-distancing, which we can also practice, and much more. We have a team of enthusiastic volunteers motivated by a high calling to serve and protect our congregation. Please see the attached addendum that outlines potential COVID-19 protocols for a worship service. We will gladly receive further guidelines and instructions from our local health authorities.

If grocery stores can remain open with certain protocols, worship services can do the same.

We continue to respect your important leadership role. Our operations remain compliant with your instructions, keeping ourselves, fellow citizens and neighbours safe. It is our desire that you can similarly respect our roles as leaders within our faith community, trusting us to practice physical distancing when being together for a worship service.

Please let us know at your earliest convenience if the measures in the addendum are sufficient to conduct our next worship service.

We continue to pray to the Creator, our Heavenly Father, being thankful for your commitment to protect us all and that He will give you wisdom and protect you in the days ahead.

Yours sincerely,

TRINITY BIBLE CHAPEL

Jacob Reaume
Senior Pastor

Will Schuurman
Associate Pastor

Randy Frey
Pastor of Christian Education

Chris Cattle
Elder Chair

Siva Gnanunanthan
Elder Secretary

Jeff Bauman
Elder

cc.
Members of Parliament:
Bardish Chagger, Waterloo
Tim Louis, Kitchener-Conestoga
Raj Saini, Kitchener Centre
Marwan Tabbara, Kitchener South-Hespeler

Bryan May, Cambridge
Lloyd Longfield, Guelph
Dave Mackenzie, Oxford
John Nater, Perth-Wellington
Michael Chong, Wellington-Halton Hills

Members of Provincial Parliament:
Catherine Fife, Waterloo
Mike Harris, Kitchener-Conestoga
Amy Fee, Kitchener South-Hespeler
Belinda Karahalios, Cambridge
Mike Schreiner, Guelph
Ernie Hardeman, Oxford
Randy Pettapiece, Perth-Wellington
Ted Arnott, Wellington-Halton Hills

Mayors:
Dave Jaworsky, Waterloo
Berry Vrbanovic, Kitchener
Cam Guthrie, Guelph
Kathryn McGarry, Cambridge
Sandy Shantz, Woolwich Township

Julie Kalbfleisch, Manager, Information & Communications, Region of Waterloo Public Health
Akio Franco, Manager, Health Protection & Investigation, Region of Waterloo Public Health

ADDENDUM

Potential Safety Protocol during COVID-19 outbreak

When gatherings are limited to 5 persons

Attendance at Sunday church worship is cancelled – all communication is conducted online. There will be no smaller mid-week meetings until further notice.

When gatherings are limited to 15 persons

Worship services will continue online.

Attendance at mid-week Home Church (Small Groups) can begin with the following stipulations:

No refreshments are served, physical contact is to be avoided (no hugs or handshakes) and hand sanitizer is applied upon entering the home. Each person shall cover their nose and mouth with a scarf, handkerchief or mask. People from different households shall try to sit separately, as much as possible.

The following people will not attend a Home Meeting:

- Anyone who has travelled outside of Canada within 14 days
- Anyone who has a compromised pre-existing health condition
- Anyone who is not feeling completely healthy
- Anyone who has had contact with an unhealthy person within 14 days
- Anyone who does not have a free conscience to attend
- All those 70 years old and above

When gatherings are limited to 250 people

Mid-week Small Group meeting will continue with the same protocols as before.

Attendance at the Sunday worship service can begin with the following stipulations:

Parking lot attendants are to direct a two-metre social-distance line-up as people enter the building.

Upon entering the building each person shall apply hand sanitizer that will be made available.

Each person shall have their nose and mouth covered with a scarf, handkerchief or mask, except those on the main stage when speaking or singing.

All doors to enter and inside the building are to remain open, reducing the touching of surfaces.

There will be no drinks made or brought into the building.

Each washroom will be assigned a person who will wipe with sanitizer anything that is touched by hands three times every 15 minutes before the worship service and three times every 15 minutes after the worship service.

There will be no separate gatherings for children, they will remain under the supervision of their parents.

Ushers will escort all people to their seats – ensuring households will sit together and there will be a separation of at least two seats between each household.

There will be no collection-plate or bag passed through the aisle, rather a box for donations will be placed near the sound-technician's desk.

The total attendance will not exceed 60% of the building's seating capacity.

The following people will not attend the worship service:

- Anyone who has travelled outside of Canada within 14 days
- Anyone who has a compromised pre-existing health condition
- Anyone who is not feeling completely healthy
- Anyone who has had contact with an unhealthy person within 14 days
- Anyone who does not have a free conscience to attend
- All those 70 years old and above

After the service, people will remain seated waiting to be escorted by the ushers in single-file to their vehicles, again maintaining two metre social-distancing.

There is to be no loitering or socializing in the parking lot.

If there is another service scheduled within three hours, the ushers will swipe and sanitize the arm-rest of each seat.

When gatherings are unlimited

Our worship service will be conducted as we have done previously – still being mindful to practice good hygiene.

EXHIBIT B

This is Exhibit "B" referred to
in the Affidavit of
Jacob Reaume

Sworn before me this 4th day
of June A.D., 2021

A Commissioner for Oaths in and for Ontario

LISA D.S. BILDY
BARRISTER & SOLICITOR

May 11, 2020

Rev. Dr. Aaron Rock
Rev. Dr. Joe Boot
[redacted]

Hon. Premier Doug Ford
Premier of Ontario
Legislative Building
Queen's Park
Toronto, ON M7A 1A1

RE: REOPENING ONTARIO CHURCHES

Dear Premier Ford:

Thank you for your continued service to our communities and province and for the tireless effort you have made on all our behalf during the COVID-19 related crisis. We recognize that your role is not easy, and we commend you for your diligent work. We have prayed for you and are grateful for the news that COVID-19 related deaths remain well below what was feared and that the curve has been flattened in many of our communities.

As you may be aware, the Bible and centuries of tradition oblige Christians to gather weekly for worship and witness around the Word of God and sacraments – we need one another to flourish in our service to Christ (Ex. 20:9-11; 1 Cor. 16:1-2; Heb. 10:24-25; Acts 2:42, 20:7). Neither confessional Christian faith nor the Church institute can faithfully exist without a Lord's Day gathering. This divine obligation and hard-won historic freedom is so important for Christians, that it supersedes all human legislation and regulation. The church is not comparable to a sports or dance club and cannot be dismissed as non-essential by an expert in any field. We would respectfully remind the civil government that the church does not exist by permission of the state, for its establishment and rule is found in Jesus Christ himself. Please remember, the existence and freedom of the church institute long predates the founding of the Christian Dominion of Canada (our Coat of Arms citing Psalm 72:8), so we cannot stress enough how troubling and perplexing these times have been for us. Nonetheless, we are thankful to live in a nation shaped by and indebted to the Christian faith, constitutionally recognizing the supremacy of God in our Charter, and we are grateful for a government that affirms religious freedom. Thank you for continuing to champion religious liberty in Ontario.

Over the past two months, church government has cooperated with civil government by suspending our worship services and mercy ministries, leaving us with the following dilemma: (1) to love our neighbour, as Jesus taught us, by suspending our services to potentially help slow the spread of the virus, or (2) to obey the Word of God which obliges us to meet for worship, sacraments and spiritual ministry to both the healthy and the sick. In weighing this dilemma, whilst seeking to respect civil authority in light of God's ultimate authority, we rightly chose to voluntarily and temporarily cease meeting. We did so to demonstrate love to our fellow citizens during a time of great uncertainty as well as difficulty for civil authorities working with limited information. As Christians, we do not fear death because of the resurrection hope that is ours through Christ, but we deeply desire to show love to all people.

That said, never in 1500 years of Western history has the Church of Jesus Christ not met for Easter or missed months of worship and ministry – even in times of war or plague far more devastating than COVID-19. Never before has the church been denied the opportunity to be with the sick in the hour of their death. Never before has the church ceased to celebrate the sacraments, pray together, offer counsel to the afflicted, visit the prisoner, officiate weddings and funerals, or fellowship together. The inhumanity of abandoning people in their deepest hour of grief or need is gut-wrenching for followers of Christ.

The consequences of the lockdown on people's lives are far-reaching. We know as pastors that addictions are resurfacing and that isolation, unemployment and economic ruin are taking their toll on family relationships and physical and mental health. Our service to the poor and disadvantaged in the community has been curbed, with serious implications for the most vulnerable. To save lives are we actually sacrificing lives? In short, we implore you that we must start meeting very soon because of our obligations to God and because our people need us. We cannot delay.

We are committed, faithful and reasonable citizens and desire to be collaborative rather than be perceived as unreasonable people. Many of our members hold prominent positions in society in law, medicine, politics, education and business. As churches, we have researched, read, listened to and discussed all the relevant issues. As such, we would like the provincial government to support the reopening of churches and ministries by early June, pending any unforeseen circumstances. Given the access people have to other services like grocery stores and the recent announcement to open access to retail stores in malls, to garden centres and to other areas of public gathering, this seems like more than a reasonable course of action.

Here is our reasonable plan:

1. To communicate and enforce health protocols in our churches based on the provincial government guidelines.

2. To initially limit access to our services and ministries to approximately 40% of our building capacities to permit physical distancing, expanding that number as circumstances permit. This will allow for plenty of room between persons well beyond two metres in most facilities and acknowledges that not all church facilities have equal capacity.

3. To provide a clean facility including hand sanitizers and wiping down of common surfaces between services.

4. To continue offering online messages as we are able, so that those who are not comfortable or cannot meet in person due to age or health challenges can at least watch from home.

5. To require attendees to explicitly affirm that they have no symptoms, have not travelled out of the country within the last fourteen days and have not been in contact with anyone with the virus in order to attend.

We would humbly request a response from you by May 29th and are very willing to meet with you or consider any further advice you have to offer us. We would also request that the Premier appoint an additional person to the Ontario Jobs and Recovery Committee who can be an ongoing voice for faith groups. We are anticipating a positive response and continued good relationship with civil authorities as we seek to honour our Creator and Saviour in the nation.

You are greatly appreciated and honoured amongst us.

Pro Rege,

Please note this letter has been cc'd and emailed to:
Premier of Ontario
Deputy Premier of Ontario

Ministry of the Attorney General
Ontario Ministry of Health

Church Signatories at time of publication:

- Harvest Bible Church (Windsor)
- Westminster Chapel (Toronto)
- Trinity Bible Chapel (Waterloo)
- Calvary Baptist Church (Windsor)
- Life-Giver Church (Windsor)
- Grace Ministries (Windsor)
- New Beginnings Community Church Windsor (Tecumseh)
- Rawdon Street Baptist Church (Brantford)
- West London Alliance Church (London)
- Harvest Bible Chapel Niagara (St. Catharines)
- Maple City Baptist Church (Chatham)
- New Song Church (Windsor)
- Bluewater Baptist Church (Sarnia)
- Redemption Bible Chapel (St. Thomas)
- Windsor Christian Fellowship (Windsor)
- ARPA Canada (Ottawa)
- Sarnia Gospel Hall (Sarnia)
- Beth Tikvah Synagogue (Toronto)
- Dorchester Christian Family Centre (Dorchester)
- New Living Church (North York)
- Lighthouse Bible Church (Toronto)
- New Horizon United Reformed Church (Scarborough)
- New Horizons Baptist Church (London)
- Olivet Baptist Church (Toronto)
- Jubilee Canadian Reformed Church (Ottawa)
- Bethel Canadian Reformed Church (Richmond Hill)
- Mountain View Christian Church (Hamilton)
- Hope Centre - Congregation (Brampton)
- Guelph Christian Life Church (Guelph)
- Truth Community Church (Thamesford)
- Kingsway Christian Church (Toronto)
- Burgessville Heritage Reformed Church (Burgessville)
- Churchill Baptist Church (Caledon)
- The Church of God of Aylmer (Aylmer)
- First Baptist Church Welland (Welland)
- Crossroads Alliance Church (Ingersoll)
- Rosedale Baptist Church (Welland)
- Grace U B Church (Sherkston)
- International Gospel Centre (Kitchener)
- Ancaster Canadian Reformed Church (Ancaster)
- Heritage Reformed Church of Bradford (Aurora)
- West Toronto Baptist Church (Toronto)
- Grace Baptist Church (Alliston)
- Church in Strathroy (Strathroy)
- Islington Baptist Church (Etobicoke)

- Canadian Reformed Church Fergus North (Fergus)
- Hope Reformed Church (Brampton)
- Park Lawn Baptist Church (Etobicoke)
- Zion United Reformed Church (Sheffield)
- Ajax Alliance Church (Ajax)
- Trinity Baptist Church (Burlington)
- Grimsby Bible Church (St. Catharines)
- Fellowship Canadian Reformed Church (Burlington)
- Living Hope Free Reformed Church (Chatham)
- Ebenezer Free Reformed Church (Dundas)
- Grace Canadian Reformed Church (Brampton)
- New Life Pentecostal Church (North York)
- Emmaus Church (Burlington)
- Trinity Associate Reformed Presbyterian (Chatham)
- Lighthouse Church (Amherstburg)
- Covenant Orthodox Presbyterian Church (Komoka)
- Emmanuel Orthodox Presbyterian Church (Meaford)
- Lanark Baptist Church (Lanark)
- Lighthouse Gospel Church (Port Burwell)
- Hillside Reformed Presbyterian (Almonte)
- Kitchener-Waterloo Christian Fellowship (Kitchener)
- Leamington Gospel Hall (Leamington)
- Grace Free Reformed Church (Brantford)
- Tilbury Regular Baptist (Tilbury)
- Grace Canadian Reformed Church Of Kerwood (Kerwood)
- Lighthouse Gospel Church (Mornington)
- Bath Road Baptist Church (Kingston)
- Walsh Baptist Church (Norfolk County)
- Jerseyville Baptist Church (Jerseyville)
- Fellowship Baptist Church (Parry Sound)
- Central United Church (Unionville)
- Marantha Free Reformed Church (Hamilton)
- Living Water Reformed Church (Brantford)
- Covenant Christian Church - URCNA (Wyoming)
- Cornerstone United Reformed Church (London)
- Canadian Reformed Church of Smithville (Smithville)
- Wilmar Heights Baptist Church (Scarborough)
- Living Hope Fellowship (Warford)
- Streetlight Christian Church (Hamilton)
- Near North Baptist Church (North Bay)
- Faith Worship Centre (North York)
- RCCG Faith Chapel (Orleans)
- Spring Creek Canadian Reformed Church (Tintern)
- Hope Presbyterian Church (Kingston)
- RCCG City of David (Kanata)
- Maple Avenue Baptist Church (Georgetown)
- Kingdom Worship Centre (Hamilton)

- Trumpet Of Truth Christian Ministries (Woodstock)
- Northgate Ministries (Perth)
- Salem United Reformed Church (Bowmanville)
- Faith ARP (Tillsonburg)
- Aylmer EMMC Church (Aylmer)
- Good News Assembly of God (Mississauga)
- The Redeemed Christian Church of God Overcomers Chapel (Ottawa)
- The Revival Centre (Hamilton)
- Guthrie Presbyterian, St. Andrew's (Alvinston)
- Su Presencia Church (Kitchener)
- Lighthouse Church (Oshawa)
- Pinewoods Chapel (Angus)
- Church180 (Ajax)
- Calvary Baptist Church (Ottawa)
- Sovereign Grace Family Church (Belleville)
- Hill City Baptist Church (Peterborough)
- Potters Clay Ministries (Hamilton)
- Attercliffe Canadian Reformed Church (Attercliffe)
- Grand Bend Church of God (Grand Bend)
- Signs, Wonders and Miracles Ministries (Toronto)
- St. Clair Evangelical Missionary Church (Toronto)
- Bethel United Reformed Church (Woodstock)
- Pinery Baptist Church (Thedford)
- Braidwood Bible Chapel (Peterborough)
- Free Reformed Church (Bornholm)
- Spiritual Hospital (Toronto)
- Providence Baptist Church (Kitchener)
- Hope Reformed Church (Powassan)
- Trinity Canadian Reformed Church (Glanbrook)

- River Jordan Ministries (Ottawa)
- Free Reformed Church Oxford County (Norwich)
- Sovereign Grace Baptist Church (London)
- West Toronto Victory Church (Mississauga)
- 3rd Heaven Ministries (Milton)
- Faith Chapel North Bay (North Bay)
- The Potter's House (Scarborough)
- Living Hope Alliance Church (Georgetown)
- Lakeside Church (Haliburton)
- True Vine Ministries (Brampton)
- Breakthrough Life Church (Brampton)
- Redemption Canadian Reformed Church (Flamborough)
- M and M Ministries (Guelph)
- Chiefswood Christian Fellowship (Oshweken)
- Willowdale Baptist Church (North York)
- First Baptist Church Owen Sound (Owen Sound)
- Faith Church (Willowdale)

- Chapel Place Presbyterian Church (Markham)
- Inspire Church (Toronto)
- Bramalea Baptist Church (Brampton)
- Wings of Fire Ministries (Hamilton)
- Westmount Bible Chapel (Peterborough)
- Beacon Bible Chapel (Tillsonburg)
- Gentle Shepard Community (Flesherton)
- Freedom Center (Oakville)
- Peoples Church of Sarnia-Lambton (Wyoming)
- Church 180 (Mississauga)
- Faith Baptist Church (Oakville)
- Open Bible Baptist Church (Ayr)
- Iglesia Cristiana Alianza (Etobicoke)
- New Creation Reformed Presbyterian Church (Kitchener)
- Victory Chapel Ottawa (Ottawa)
- Tabernacle of the Congregation (Simcoe)
- Wyoming Christian Reformed Church (Wyoming)
- Move Church (Franktown)
- Gilmour Memorial Baptist Church (Selwyn)
- St. Thomas Free Reformed Church (St. Thomas)
- Providence Community Church (St. Catharines)
- The Dwelling Place (Hagersville)
- Milverton Christian Fellowship (Milverton)
- United Reformed Church of Thunder Bay (Thunder Bay)
- Elliott Heights Baptist Church (Hamilton)
- First Baptist Church (Perth)
- Immanuel Reformed Church (Nobleton)
- Queensway Baptist Church (Toronto)
- Bethel Free Reformed Church (Mitchell)
- Bethel United Reformed Church of Aylmer (Aylmer)
- Catch The Fire (Brampton)
- Wellspring Community Church (Welland)
- First Filipino Baptist Church (Toronto)
- The Christian Centre (St. Catharines)
- Netherlands Reformed Congregation (Norwich)
- Aylmer Full Gospel Church Inc. (Aylmer)
- Catch The Fire (Newmarket)
- Covenant Canadian Reformed Church (Grassie)
- St. Paul Coptic Orthodox Church (London)
- Lighthouse Ministries (London)
- Tabernacle of Prayer (Ottawa)
- Milton Bible Church (Milton)
- Catch the Fire (Barrie)
- Promise Worship Centre International (Kitchener)
- Catch The Fire (Stratford)
- Norwich Baptist Church (Norwich)
- Immanuel United Reformed Church (Listowel)
- Dresden Christian Reformed Church (Dresden)
- Coptic Orthodox Diocese of Ottawa, Montreal & Eastern Canada (Ottawa)
- Hespeler Baptist Church (Cambridge)

- Providence United Reformed Church (Strathroy)
- Redeeming Grace Reformed Church (Brantford)
- Southdale Bible Chapel (London)
- Every Nation Church Mississauga (Mississauga)
- Church Planting Ministries Inc (Mississauga)
- The Evangelical Presbyterian RPCNA (Toronto)
- Jesus New Covenant International Ministries (Markham)
- Forward Baptist Church (Toronto)
- Greenwood Baptist Church (North Bay)
- Grace Baptist (Sunderland)
- Heritage Reformed Church (Jordan Station)
- Kingsway Church (Balmoral)
- Center Community Church (Lindsay)
- Providence Free Reformed Church (St. George)
- The Bridge - The IEMELIF Church of Canada (Mississauga)
- Springford Reformed Church (Springford)
- Rehoboth United Reformed Church (Hamilton)
- Grace Covenant Church (Sheffield)
- Emmanuel Baptist Church (Exeter)
- Old Reformed Congregation (Salford)
- Word of Life Community (Leamington)
- Springfield Baptist Church (Springfield)
- Russell Reformed Presbyterian Church (Russell)
- Hallelujah Fellowship Baptist Church (Toronto)
- Hope Bible Church (Oakville)
- Stoney Creek Church of Christ (Hamilton)
- Grace Church Newmarket (Newmarket)
- Adoration URC (Vineland)
- Bradford Community Church (Bradford)
- Truth Tabernacle (Markham)
- Aldergrove Gospel Chapel (Aldergrove)
- First Baptist Church (Goderich)
- Mission City Bible Church (Brantford)
- St. Katharines Greek Orthodox Church (St. Catharines)
- River of Life (Midland)
- Eagles Nest Fellowship (Ancaster)
- Destiny Christian Center (Sault Ste. Marie)
- The Ministry Company (London)
- Power of the Cross Church (Toronto)
- Calvary Baptist Church (Espanola)
- Grace Family Church (Sudbury)
- Bergthaler Mennonite Church (Leamington)
- Wheatley Baptist Church (Wheatley)
- Dawn Valley Bible Methodist Church (Tupperville)
- Banwell Community Church (Tecumseh)
- Centralia Faith Tabernacle (Centralia)
- The ARK New Beginnings Assembly (Ingersoll)
- Neustadt Baptist Church (Neustadt)

- St. Philopateer & St. Demiana Coptic Church (Newmarket)
- West Ottawa Community Church (Ottawa)
- Grace Baptist Church (Essex)
- Graceway Baptist Church (Milton)

EXHIBIT C

This is Exhibit "C" referred to
in the Affidavit of
Jacob Beaune
Sworn before me this 4th day
of June A.D., 2021

A Commissioner for Oaths in and for Ontario

WRPS Supports Solidarity March for Black Lives Matter - "We Stand United With You."

Show More

Posted on June 02, 2020

On June 3, 2020, our community will come together to walk through downtown Kitchener as part of a peaceful Solidarity March for Black Lives Matter.

If you are taking part, please know that you have the full support of your Police Service.

As your Chief of Police, I want you to know that our members will be there to not only ensure your safety and the safety of the public, but to show that we stand united with you.

They will ensure you have the support needed to practice your democratic right and have your voice heard.

Because that voice is needed.

The fight against racism isn't just an American issue. It isn't just a Canadian issue. It's an issue throughout the entire world, including right here in Waterloo Region.

As your Chief of Police, I can assure you that the members of the Waterloo Regional Police Service stand together with you in your anger over the events that have unfolded recently. We are appalled, disheartened, and deeply saddened. Many of our members are grieving alongside the rest of the world and are questioning the actions of the officers in Minneapolis. They are frustrated that their hard work to build bridges and trust within the community has been set back by actions that simply can't be understood nor accepted.

As police officers, we have an obligation to preserve life, to keep people safe, and to keep our community safe. Every day our members do this job and do it very well. But, we are not perfect. We know there is work to do and we are committed to working with you and our community partners to ensure everyone feels safe and included. Our Equity, Inclusion, and Diversity Unit is committed to ensuring all tools, training, and education is provided to our members to ensure we continue to build and maintain your trust.

It's my promise to you, on behalf of our Service, that we will do whatever it takes to be better.

We realize this event is being held during a health crisis. But, we also realize that you are hurting. You are grieving. And you are justifiably angry. We realize that this is a time for us all to come together in an attempt to heal, to show support, and to pave the way for a better future for all.

We want to thank the organizers of this event for taking health precautions, including mandatory face coverings, available hand sanitizer, and requests for physical distancing. The event is also being shared virtually on Facebook as an option for those who do not wish to jeopardize their health or the health of others.

We encourage you all to practice the proper health precautions and to make this peaceful march one that sends a message to our entire community – that we all have a role to play in confronting and ending systemic racism.

On behalf of the Waterloo Regional Police Service, thank you for sharing your voice and for demanding change that will make our community, our country, and our world a stronger, safer and more inclusive place to live.

Contact Us

Waterloo Regional Police Service
P.O. Box 3070, 200 Maple Grove Road, Cambridge, ON N3H 5M1
T: (519) 570-9777 (WRPS), F: (519) 650-1793, For emergencies, please dial: 9-1-1,

The TTY (TDD) number for the Deaf to contact is 1-888-420-1777

EXHIBIT D

This is Exhibit "D" referred to
in the Affidavit of
Jacob Reaume
Sworn before me this 4th day
of June A.D., 2021

A Commissioner for Oaths in and for Ontario

KITCHENER | News

As it happened: Thousands of people gather for peaceful Black Lives Matter march in Kitchener

Chase Banger and Nicole Lampa

Nicole Lampa
CTV News Kitchener Videographer
@NicoleLampa | Contact

Chase Banger
CTVNewsKitchener.ca Digital Content Producer
Contact

Published Wednesday, June 3, 2020 7:13AM EDT
Last Updated Thursday, June 4, 2020 10:12AM EDT

SHARE:

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KITCHENER -- Thousands turned out for a peaceful solidarity march in downtown Kitchener on Wednesday evening to protest anti-Black racism and police brutality.

The KW Solidarity March for Black Lives Matter was organized following a number of recent high-profile, police-involved deaths of black people in both Canada and the United States.

The event began around 5 p.m., but hundreds of people had arrived more than an hour before.

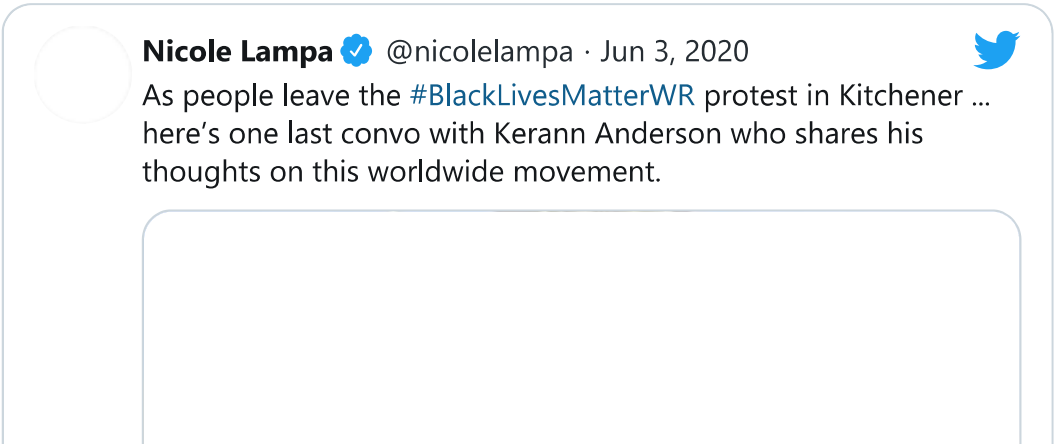
Several Black and Indigenous speakers addressed the crowd before the march set out from Gaukel and Joseph Streets, including MPP Laura Mae Lindo, who was wearing a mask and sunglasses.

"Behind the shades are tears, because I am looking down this street and I know that there is hope for my five-year-old son," she told the crowd, holding back tears.

Fellow protester Kerann Hutchinson echoed the sentiment, saying he was taking the risk during the pandemic so his kids can have a better life.

"It means a lot to me but it means more for my kids. I'm here mainly, I don't want my kids to grow up in the same environment, in the same fear that we have to grow up in," he said.

"I hope that people take the message and make a change. Make a change for all of us."



Lindo acknowledged the danger of thousands of people turning out during the pandemic, saying she felt that she didn't have a choice.

"I need you to recognize that anti-Black racism is a public health crisis," she told the crowd.

She also criticized Premier Doug Ford for suggesting that Canada did not have the same "systemic, deep roots" of racism as the U.S. Less than 24 hours later, he backpedaled those comments.

"Of course there's systemic racism in Ontario, there's systemic racism across the country," Ford said during a sitting at Queen's Park on Wednesday.

His answer came after he was asked by Opposition Leader Andrea Horwath about her call for the immediate collection of race-based data as it relates to COVID-19.

The speakers were joined by thousands of people in the march, which travelled down Charles Street to Frances Street before turning right down King and eventually looping back around to the terminal.

Organizers told CTV before the march began that they had received online threats, but by the end of the scheduled event at 7 p.m., the demonstration had remained peaceful.

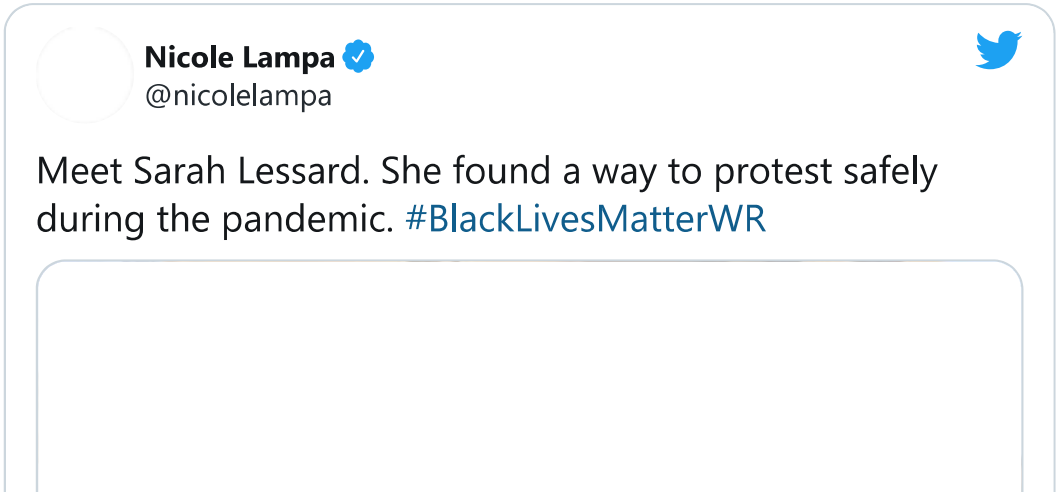
Police were on hand to help the flow of traffic and to keep people safe, but organizers stress that they were not there to walk with them.

"We asked police not, explicitly not to march with us, but let them know that this is an issue that could endanger other people," one organizer told CTV.

Most people who participated were wearing masks and other personal protective equipment, but with such a large crowd, six feet of space for physical distancing was hard to find.

Some people parked their cars along the march route, holding signs out their windows and honking.

"I just knew I had to be here and support in some way, but I wanted to be as safe as possible so I thought, 'get in there and figure it out,'" said Sarah Lessard.



6:36 PM · Jun 3, 2020

8 See the latest COVID-19 information on Twitter

Despite the crowd, as Regional Chair Karen Redman suggested on Tuesday, police officers were there to offer support, not issue tickets.

On Thursday morning, police confirmed that the protest was a peaceful one and that no charges were laid. They said they were not able to offer a crowd estimate, but others suggested that the crowd may have been between 12,000 and 20,000 strong.

The march ended with all attendees sitting on Charles Street next to the former bus terminal with fists raised. Shortly after, the crowd began dispersing.

Nicole Lampa
@nicolelampa

7:04 PM · Jun 3, 2020

23 6 Copy link to Tweet

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Thousands of people gathered in downtown Kitchener in support of the Black Lives Matter solidarity march (Provided)

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EXHIBIT E

This is Exhibit "E" referred to
in the Affidavit of
Jacob Reaume
Sworn before me this 4th day
of June, A.D., 2021
A Commissioner for Oaths in and for Ontario

Trinity Bible Chapel
Risk Mitigation Strategy for Sunday Services

1. Sign-ups will be needed for people to indicate which of the two services they would like to attend: 8:30am or 10:30am. If those services go over 160 people, then we will add a third service. Part of the Sign-up process will be to answer questions on a waiver. The waiver questions will be answered with yes or no to the following:
    a. I confirm that I will not attend the service if I have a fever of over 38C
    b. I confirm that I will not attend the service if I have a new cough or a worsening chronic cough.
    c. I confirm that I will not attend the service if I have a sore throat.
    d. I confirm that I will not attend the service if I have new or worsening shortness of breath.
    e. I confirm that I will not attend the service if I have any flu like symptoms including a runny nose.
    f. I confirm that I will not attend the service if I have nausea or vomiting.
    g. I confirm that I will not attend the service if I have recently tested positive for the novel coronavirus.
    h. I confirm that I will not attend the service if I am currently waiting for the results from a laboratory novel coronavirus test.
    i. I confirm that I will not attend the service if I have travelled outside of Canada in the last 14 days by car, air, train or bus.
    j. I confirm that I will not attend the service if I have been in contact with anyone who has tested positive for the novel coronavirus in the last 14 days.
    k. For those who are over the age of 65: I confirm that I understand that if I am over the age of 65 years old and have heart disease, lung disease, kidney disease or an auto-immune disease, I am at higher risk in contracting the virus if I choose to attend the service.
2. Two parking lot attendants will be present, one at each entrance to the parking lot to direct people to park in the back of the building and inform everyone that they must only enter the building through the back doors.
3. One greeter and two staff members will be stationed at the back doors to greet people. They will have a checklist of those that signed up. Anyone who didn't sign up will be directed to enjoy the service using the FM transmitter in parking lot. The greeter will open the door for people arriving. The inside sets of doors will be propped open, this provides for contactless entry to the building for those attending. The greeter will be instructed to NOT initiate physical contact with anyone arriving at the doors. The greeter (as well as a staff member) will also have a people counter clicker to use to track how many people are in the building as will the staff person at the door to double check numbers.
4. A hand sanitizing station will be present right inside the doors at the back of the building. Hand sanitizer will be recommended to all those who enter. There will also be a hand sanitizing station at the front doors used as the exit.
5. Two ushers will be present at the double set of wood doors into the worship center and they will be propped open. The usher will direct people to find a seat in any row that is not blocked off (every other row of seats will be blocked off which is 5' apart). The ushers will also assist people in spacing themselves out well from other families.
6. An offering box will be available on a table at the back of the auditorium for receiving cheques only from those that wish to give that way. But in announcements it will be encouraged to still continue giving online.
7. The connect folder will remain online and people will be directed to that in the announcements in the service.
8. The coffee bar will be closed and behind curtains so that no drinks or beverages are being offered.

9. In the washrooms, the doors into the washrooms will all be propped open (including the women's as there is no traffic going past that washroom at this time), there will be two containers of wipes in each washroom to allow people the option of wiping down surfaces before they touch them. Hand sanitizer will be available in the washrooms as well. We will have one container of wipes in the wheelchair washroom as well. The washrooms will be cleaned and sanitized between services.
10. There will be no children's ministry. And the doors to the construction area will be locked and signs posted that there is no access.
11. In order to move people out of the worship center, people are dismissed by the usher row by row, similar to at a funeral. And they are directed to head straight outside the building. Two staff members will be in the lobby to direct them to front doors. Have both sets of doors open. Exit only out the front doors (except those with physical limitations whose car might be in the back parking lot).
12. After the service, we have a team of volunteers wipe down the common touch areas in the worship center, all the chair arms at the ends of the open rows and the washrooms.
13. An attendee who becomes ill during the service is required to go home.

The legislation pertaining to numbers 14-17 is unclear. We are seeking legal counsel. For this Sunday we are being cautious by posting 14-17 within our risk mitigation strategy.

14. The Province of Ontario requires us to abide by the Waterloo Region's recommendation that staff and volunteers should use a mask/face covering at all times while providing services. This includes greeters, ushers, and pastors administering baptisms.
15. The Province of Ontario requires us to abide by the Waterloo Region's recommendation that we encourage all attendees to bring their own non-medical masks/face coverings.
16. The Province of Ontario requires us to abide by the Waterloo Region's recommendation that we avoid physical contact and greet each other with a smile, wave or bow.
17. The Province of Ontario requires us to abide by the Waterloo Region's recommendation that there is no congregational singing, chanting, or choirs.

Suggested Signage:

1. No Entry signs posted on the metal screen at end of office hallway, on the construction door by the washrooms, and attached to the drapes hanging in front of the coffee bar area.
2. A Covid warning sign on the back doors (a copy of the one that is already there) warning people to not enter the building if they have any symptoms of coronavirus or been in contact with anyone who has or tested positive or been outside of Canada in the last 14 days.

EXHIBIT F

This is Exhibit "F" referred to
in the Affidavit of
Jacob Reaume

Sworn before me this 4th day
of June A.D., 20 21

A Commissioner for Oaths in and for Ontario

TRINITY
BIBLE CHAPEL

Mr. Mike Harris
MPP for Kitchener-Conestoga
[redacted]

September 19, 2020

Dear Mr. Harris,

We offer you warm greetings and assure you that our church continues to pray for governing officials on a regular basis. We hold you in high honour because Scripture teaches us that you, a governing official, are appointed by God as His servant to punish evil and reward good (Romans 13:1-6). We send this letter with grave concerns over the looming threat of another government lockdown this fall.

As elders of a fairly large church within your riding, we believe that flattening the curve and keeping our population healthy are good objectives and our church has taken measures to assist in reducing the contraction and transmission of COVID-19. However, the actions and mandates by the government have produced deleterious effects on the population worse than the avoidance of sickness. The loneliness of isolation, the psychological trauma, the postponing of medical treatments, the hindrance to the education of children, the closure of business, the deterioration of relationships within families, and the unprecedented increase of Ontario's debt are but a few of the effects we note. Our understanding is that since July 17 in our region, only one person has died of COVID-19 and not a single person is presently hospitalized with the virus. By way of comparison, as of today COVID-19 has killed 0.019% of Ontario's population while 0.11% of Ontarians die from tobacco related deaths each year. With countless businesses and families destroyed by the emergency orders, the sale of tobacco has continued throughout. This is not to protest the sale of tobacco but rather to point out a glaring

inconsistency in policy: The fearmongering and devastation associated with the COVID-19 lockdown are radically disproportionate to the actual risk when we consider the metrics. Jesus called this "straining a gnat while swallowing a camel." It is a fixation on the smaller things to the detriment of the greater things.

As Canadians, we are heirs of ancient liberties that have existed since time immemorial, and these liberties, as our Charter indicates, are rooted in the supremacy of God and the rule of law. Some of our ancestors came to Canada seeking freedom, and some also fought in wars against external threats to our freedom. With heartfelt sorrow we believe that our own government has now become a threat to our freedom by enforcing arbitrary laws without scientific or ethical substantiation to fight a virus that presents a fraction of a fractional risk to us. As Christians our primary allegiance is to God because He purchased us by the blood of His Son, and God commands us to gather on the Lord's Day for worship. We, with the data we have presently, cannot support any future lockdowns that interfere with Christian worship or the spiritual education of children.

The members of our congregation are among your most peaceful and productive constituents. Furthermore, we are reasonable and intelligent people who are willing to be influenced by objective data. But our patience has waned with the inordinate and oppressive policy founded on sensationalized reporting. Please do not attempt another lockdown, and please support an immediate end to these emergency measures.

Sincerely,

Harvey Frey,
Elder Chairman

Randy Frey,
Pastor/Elder

Jacob Reaume,
Sr. Pastor/Elder

Will Schuurman,
Elder Chairman

Dean Wanders,
Elder

EXHIBIT G

This is Exhibit "G" referred to
in the Affidavit of
Jacob Reaume
Sworn before me this 4th day
of June, A.D., 2021

A Commissioner for Oaths in and for Ontario

You're invited to our drive-in service this Sunday with live outdoor preaching! MORE INFORMATION

TRINITY BIBLE CHAPEL

JESUS ABOUT CONNECT MINISTRIES SERMONS BLOGS GIVE

THE PASTOR'S BLOG

BY JACOB REAUME

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January 8, 2021

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January 22, 2021

PRESS RELEASE – ALL ELDERS OF TRINITY BIBLE CHAPEL CHARGED
December 31, 2020

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HERE WE STAND: THE CHURCH MUST MEET

By Jacob Reaume | December 3, 2020 | Tagged: *church, covid-19, government*

This document has the full support of all pastors and elders of Trinity Bible Chapel.

To all who witness.

An open letter to the executive branches of Ontario and Canada, Municipal Regulatory Authorities, Judges, and all those who may be blessed by our commitment to obedience to our Lord and Saviour Jesus Christ who purchased us by His very own blood.

RE: Trinity Bible Chapel's position founded on the Word of God to remain open and meeting under Threat of Lockdown

This letter is intended to give notice and reasoning as to why Trinity Bible Chapel ("TBC"), located in Waterloo Region, Ontario will remain open in the event of a lockdown or similar order issued by the Province or Municipal government (a "lockdown").[1] TBC asserts that its religious belief, which freedom is protected under section 2(a) and 2(c) of the Constitution Act, 1982 (the "Charter"), requires it to meet regularly in person. Further TBC asserts that the Province has not demonstrated that the restrictions currently put in place with respect to COVID-19 or a lockdown would be effective, nor would they be considered the "least restrictive means" or a "minimal impairment", an essential branch of the seminal Oakes test, the proportionality test required to be satisfied whenever the Provincial/Federal government violates a person's (including a corporation's) constitutional rights.

In addition to the violation of religious freedom and a point that we wish not to belabour, a lockdown would represent an offence under section 176 of the Canada Criminal Code, obstructing or violence to or arrest of an officiating clergyman, since such a lockdown order would be an unconstitutional and unlawful restriction of religious freedom. An offence under section 176(1) of the Canada Criminal Code is an indictable offence carrying serious consequences. Despite the historic independence the church has enjoyed from the Federal and Provincial government, seen both in legal precedent and codified in the Canadian Constitution (British North America Act, 1867), Charter and the Canada Criminal Code, along with other

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December 31, 2020

ABOUT THE AUTHOR

JACOB REAUME

Born and raised in Guelph, Jacob holds a Master of Divinity from The Southern Baptist Theological Seminary in Louisville, Kentucky. He became pastor of Trinity Bible Chapel in August, 2009. Jacob is married to his high school sweetheart, Joanna, and together they have five children.

ABOUT THE CHURCH

major acts of legislation (e.g. Income Tax Act, Corporations Act, Land Transfer Act, etc.), this independence has been seemingly abandoned by the rules set by the Province.

Biblical Requirement to Meet Regularly as a Church

TBC has, since its beginning, served our Lord and community by preaching the Gospel of Jesus Christ, sponsoring foreign missionaries, contributing to local pregnancy crisis centers, assisting those in need, offering hope to those in despair, comforting the bereaved, providing pastoral care for families and singles, counseling broken marriages towards restoration, visiting the sick and lonely, sponsoring refugees, helping immigrants integrate into our community, educating children, officiating at weddings and funerals, and performing a plethora of other good deeds which have positively contributed to the welfare of thousands of individuals. Our observation is that these times of isolation, due to the government's restrictive actions, have harmed people and society by perpetuating loneliness, hopelessness, fear, poverty, division, anger, the deterioration of relationships, and a plethora of other evils which will become more evident with time. These observations do not surprise us because the restrictive actions of the government have wrongfully reduced human beings to biological units with little purpose to existence other than to avoid contracting and spreading a virus.[2] Scripture teaches us that people are much more than biological units. We are created in the image of God with dignity and worth to live free, love one another, worship together, grow families, eat with each other, laugh and cry together, embrace one another, exchange goods and services, and build things. Central to the Christian life is the ministry of the church, and TBC asserts that the church must remain open.

TBC believes that Scripture commands us to meet for worship in person, that the definition of "church" requires us to gather in person, and that the Law of God demands we gather at least weekly. This has been articulated in our church doctrinal statement, and each of our members has taken a solemn oath and covenant before God to meet regularly for worship, prayer, and the Lord's Supper.

Scripture, which is God's Word to us, commands Christians to gather in person for church (Hebrews 10:24-25). Regularly meeting in person was the pattern established by Christ's apostles: "And they devoted themselves to the apostles' teaching and the fellowship, to the breaking of bread and the prayers" (Acts 2:42). Christian meetings include fellowship, which entails togetherness, sharing of goods and food, showing hospitality, and presence of person, much like a family unit (Acts 4:32-37). The New Testament upholds the church as a spiritual family, so much that the bonds within the church are stronger than blood relations (Matthew 10:37; 13:53-58; Luke 14:26). For this reason, Christians often refer to each other as "brother" and "sister." To operate as a church, Christians are expected to experience fellowship regularly with one another like a family that lives under the same roof.

Embedded in the definition of church is gathering together. The New Testament word for church is the Greek word, *ekklesia*. Etymologically, *ekklesia* is the combination of two words that together mean "called out," as in a group of people called out to gather. The definition of the word demands that a church not be reduced to less than a gathering of people. The lexical range of *ekklesia* includes "assembly," "gathering," "a specific Christian group assembly, gathering ordinarily involving worship and discussion of matters of concern to the community," and "the totality of Christians living and meeting in a particular locality."[3] Where there is no physical gathering there is no church. For the church to exist it must gather.

The pattern since creation has been for believers to meet officially for worship at least once weekly. The Ten Commandments were written in stone by the finger of God, thus signifying the abiding authority of God's Law. The fourth commandment reads, "Remember the Sabbath day, to keep it holy. Six days you shall labor, and do all your work, but the seventh day is a Sabbath to the LORD your God" (Exodus 20:8-11). The Old Testament community set aside the seventh day for rest and public congregational worship: to do otherwise was a transgression of the Law. Christ was raised from the dead on the first day of the week, and since then churches have regularly met on the first day, Sunday, for worship, prayer, preaching, and the ordinances (Acts 20:7; 1 Corinthians 16:1-2). To cease meeting together for worship at least weekly is to be a disobedient Christian.

THE FIRST EIGHT YEARS: A CELEBRATION OF ANSWERED PRAYER

Scripture describes the church as a body with many parts. As a human body cannot exist without all its parts fastened together so the church cannot exist without all its people together. Saint Paul presses this analogy,

> For the body does not consist of one member but of many. If the foot should say, "Because I am not a hand, I do not belong to the body," that would not make it any less a part of the body. And if the ear should say, "Because I am not an eye, I do not belong to the body," that would not make it any less a part of the body. If the whole body were an eye, where would be the sense of hearing? If the whole body were an ear, where would be the sense of smell? But as it is, God arranged the members of the body, each one of them, as he chose. If all were a single member, where would the body be? As it is, there are many parts, yet one body (1 Corinthians 12:14-20).

In essence, the church is a composition of members that function in harmony. It is a body, and as a body all the parts must be together. Saint Paul continues, "Now you are the body of Christ and individually members of it" (1 Corinthians 12:27). Each individual is a valuable part of the church, and the church as a whole needs each individual. A church that does not gather is like a body with its parts scattered across a city. A body exists as parts together, and the church exists as Christians together.

The church must be together to fulfill its mission because its mission depends on togetherness and physical presence. The Scriptures command the church to partake of the Lord's Supper together (1 Corinthians 11:17-34), to baptize new converts (Matthew 28:19), to anoint the sick with oil (James 5:14), to ordain elders and pastors with the laying on of hands (1 Timothy 5:22), and to greet each other with a holy kiss (1 Corinthians 16:20). None of these actions are possible while separate or isolated. Each must be done in person because the New Testament presupposes that the church will be together.

Jesus epitomized Christian togetherness by incarnating as a man in the flesh. "And the Word became flesh and dwelt among us" (John 1:14). Some have expected church services to be held online, but that betrays the Scriptural notion of an unmediated ministry. Had God conceived of something other than the normalcy of an in-person ministry, he might have sent a picture or a hologram or a pixelated representation of Himself on a computer screen. Instead, God incarnated in the person of Christ by being born of a virgin, living and eating among men, performing miracles, being crucified, and rising bodily from the dead. Christians still wait expectantly for the bodily return of Jesus Christ to earth. Because of Christ's example to us, TBC believes that we must be physically present with each other.

Ironically, politicians and medical bureaucrats are calling for people to self-isolate this Christmastime out of what they consider "love for neighbour" to "reduce the spread." Yet, Christmas is the season that celebrates God's act of love when He became a man and dwelt among men. The concept of healthy people self-isolating to love their neighbours is not only completely foreign to Scripture but is also condemned as foolish and selfish by Scripture: "Whoever isolates himself seeks his own desire; he breaks out against all sound judgment" (Proverbs 18:1). It is noteworthy that the indoor gathering of three wise men with Mary, Joseph, and Jesus would be an illegal gathering in a lockdown, as would Christ's miraculous feeding of the five thousand and His Last Supper with His twelve disciples. The call to isolate is a call that is contrary to Christ's example at Christmas when He became a man, and it is furthermore a contravention of God's demands on His people.

In accordance with the practice of the ancient church, TBC has taught since its inception that the church must meet. So fundamental to our existence is our gathering together that it is captured in TBC's doctrinal statement, a foundational document to the church, which all members agree to uphold:

> The Scriptures command believers to gather locally in order to devote themselves to worship, prayer, teaching of the Word, fellowship, the ordinances of baptism and communion, service to the local body through the development and use of talents and spiritual gifts, and outreach to the world to make disciples. Wherever God's people meet regularly in obedience to this command, there is the local expression of the Church under the watchful care of a plurality of elders.

Another foundational document to TBC is the church covenant. In accordance with that covenant, all members of TBC have taken a solemn oath and covenant to meet together for worship, prayer, and to partake together of the Lord's Supper:

> We will not forsake the assembling of ourselves together, nor neglect to pray for ourselves and others. We will regularly participate together in the ordinance of the Lord's Supper.

Being bound by Scripture to be with each other, members of TBC therefore have solemnly covenanted before God to worship together and be with each other regularly. To not be together is to violate God's commands and our own solemn oath and covenant.

Extent of Christian Obedience to Governing Authorities

Scripture also commands Christians to be subject to governing authorities. "Let every person be subject to the governing authorities. For there is no authority except from God, and those that exist have been instituted by God" (Romans 13:1). The command, however, is not ultimate. In such cases when government edicts contradict God's commands, Christians must obey God over government. Confronted with governing authorities that required them to disobey God, Saint Peter and the other apostles once said, "We must obey God rather than men" (Acts 5:29). The Lord Jesus predicted that governments would oppose His Law to the point of punishing His people through court systems (Matthew 10:16-25). Tradition and history recount that all of Christ's apostles, except one, were martyred for their obedience to God instead of man. History indicates that the one apostle who did die of natural causes, Saint John, was once imprisoned on the Isle of Patmos and also boiled in oil for his obedience to God instead of man. The apostles, along with the Lord Jesus and the earlier prophets, exhibited Christian faithfulness under the threat of government penalty. They "suffered mocking and flogging and even chains and imprisonment. They were stoned, they were sawn in two, they were killed with the sword" (Hebrews 11:36-37). When the government commands what God forbids or forbids what God commands, Christians must obey God over the government.

Typically obedience to Federal, Provincial, and Municipal regulations is easily given, such as is the case with fire safety codes, municipal drainage requirements, and other building codes. But a lockdown order to cease meeting as a church body for fellowship and worship would contradict the commandments of God, and in such a case TBC is compelled to listen to God instead of the government. Further, while TBC respects the power and scope of various legislative and executive bodies in Canada to regulate public matters, the matters of a church are to be governed by the elders of a church (Acts 20:28; 1 Timothy 5:17; Titus 1:7).

The Scriptures command the church to meet. The church must meet to be a church. God's Law teaches us to meet no less than once weekly. This is written in our church doctrinal statement, and every member of our church has taken a solemn oath and covenant before God to meet. Under threat of prosecution and public shaming, TBC will, with God's help, obey God over government.

Conclusion

While our desire is to work with the Province to care for the health of our community, TBC respectfully advises that it must practice civil disobedience in the event of a government lockdown. By God's grace, Canada was founded on Christian principles, as enumerated in the preamble of the Charter, namely the supremacy of God and the rule of law. While it is still our hope and prayer that another lockdown does not occur in our region, TBC will, with God's help and by His grace, continue to meet if any lockdown or similar order by the Province or Municipal government does occur and firmly states that the sincere belief and religious practice of regular Sunday meetings fall under the fundamental freedoms of religion and peaceful assembly found in sections 2(a) and 2(c) of the Charter.

To all those who read, we encourage you to prayerfully consider the biblical requirement of Christians to physically gather as a body and the blessing provided by this gift of fellowship.

SUPPLEMENTAL MATERIALS

Pastor Jacob Reaume and Trinity Bible Chapel hosted a webinar with constitutional litigator James Kitchen and Pastor Aaron Rock called "Conflicting Duties: Christian Worship and the Magistrate's Quarantine" on May 14, 2020. It can be accessed here.

Pastor Will Schuurman wrote several blogs on the Trinity Bible Chapel website in late May on related topics including "COVID-19 and Romans 13" on May 23, 2020 and "On Gathering, Assembly Bans, and Romans 13" on May 26, 2020. You can access them here and here.

Pastor Jacob Reaume and Trinity Bible Chapel were involved with the Reopen Ontario Churches Campaign in late May and early June, 2020. Several hundred churches petitioned the government to open the church, and the petition can be accessed here.

Pastor John Macarthur and Grace Community Church of Sun Valley, California wrote a blog called "Christ, not Caesar, Is Head of the Church" on July 24, 2020, in which they declared that their church will not abide by California lockdown orders. It can be accessed here.

Pastor Jacob Reaume and Trinity Bible Chapel were involved with and among the first signatories of the Niagara Declaration, drafted in September, 2020 in which many Canadian churches and politicians asserted the divine, historic, and legal independence of the church from the state. It can be accessed here.

Pastor Aaron Rock, senior pastor of Harvest Bible Church in Windsor, Ontario, authored a blog exhorting churches to obey God over the state, under threat of lockdown, called, "A Call to Divine Obedience, over Civil Obedience." It can be accessed here.

Pastor Jacob Reaume, senior pastor of Trinity Bible Chapel, was asked to pray at a worship protest, held November 29, 2020, at Queen's Park. The full video of the protest can be accessed here.

The Ezra Institute for Contemporary Christianity in Grimsby, Ontario, with Rev. Dr. Joe Boot, recently produced a series of podcasts responding to the threat of a second lockdown on the church. You can access them here, here, and here.

The Justice Centre for Constitutional Freedoms, on December 3, 2020 released a report that government data demonstrates that the lockdown is more deadly than COVID-19. The news release, which links to the report, is available here.

FOOTNOTES

1 The intent of this letter is to declare why TBC will remain open and ask its members and community to attend worship services. In declaring that, we are also declaring that under most circumstances Christians must be in church. Notwithstanding that declaration, we continue to teach that there are extenuating circumstances in which absence from church attendance is excusable and permitted. Thus, we will continue to offer a livestream option for those that would like to view our worship services from a distance. ↵

2 At the time of writing this, nine months into the pandemic, more than 99.967% of Canadians have not died from COVID-19. ↵

3 Walter Bauer, *A Greek-English Lexicon of the New Testament and Other Early Christian Literature*, ed. Frederick W. Danker, 3rd ed. (Chicago: University of Chicago Press, 2000), p. 303-304. ↵

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RELATED POSTS

EXHIBIT H

This is Exhibit "H" referred to
in the Affidavit of
Jacob Reaume

Sworn before me this 4th day
of June A.D., 20 21

A Commissioner for Oaths in and for Ontario

NEWS RELEASE

Ontario Announces Provincewide Shutdown to Stop Spread of COVID-19 and Save Lives

Government Providing Grants of up to $20,000 to Small Businesses Impacted by New Public Health Measures

December 21, 2020
Office of the Premier

TORONTO — As COVID-19 cases continue to rise at an alarming rate, the Ontario government, in consultation with the Chief Medical Officer of Health and other health experts, is imposing a Provincewide Shutdown. Additional restrictions will be put into place and reinforce that Ontarians should stay at home as much as possible to minimize transmission of the virus and prevent hospitals from becoming overwhelmed. The Provincewide Shutdown will go into effect as of Saturday, December 26, 2020, at 12:01 a.m.

Details were provided today by Premier Doug Ford, Christine Elliott, Deputy Premier and Minister of Health, Stephen Lecce, Minister of Education, Dr. David Williams, Chief Medical Officer of Health, and Dr. Naveed Mohammad, President and CEO, William Osler Health System.

"The number of daily cases continue to rise putting our hospitals and long-term care homes at risk," said Premier Ford. "We need to stop the spread of this deadly virus. That's why, on the advice of Dr. Williams and other health experts, we are taking the difficult but necessary decision to shutdown the province and ask people to stay home. Nothing is more important right now than the health and safety of all Ontarians."

In response to these exceptional circumstances, the Provincewide Shutdown would put in place time-limited public health and workplace safety measures similar to those in other jurisdictions. It would help stop the trend of high COVID-19 transmission in communities, preserve health system capacity, safeguard vulnerable populations and those who care for them, and save lives. Measures include, but are not limited to:

- Restricting indoor organized public events and social gatherings, except with members of the same household (the people you live with). Individuals who live alone may consider having exclusive close contact with one other household.
- Prohibiting in-person shopping in most retail settings - curbside pickup and delivery can continue. Discount and big box retailers selling groceries will be limited to 25 per cent capacity for in-store shopping. Supermarkets, grocery stores and similar stores that primarily sell food, as well as pharmacies, will continue to operate at 50 per cent capacity for in-store shopping.
- Restricting indoor access to shopping malls - patrons may only go to a designated indoor pickup area (by appointment only), essential retail stores that are permitted to be open (e.g. pharmacy, grocery store), or, subject to physical distancing and face covering requirements, to the food court for takeout purchases. Shopping malls may also establish outdoor designated pickup areas.
- Prohibiting indoor and outdoor dining. Restaurants, bars and other food or drink establishments will be permitted to operate by take out, drive-through, and delivery only.

On the advice of the Chief Medical Officer of Health, all Ontarians are advised to stay home as much as possible with trips outside the home limited to necessities such as food, medication, medical appointments, or supporting vulnerable community members. Employers in all industries should make every effort to allow employees to work from home.

The current COVID-19 Response Framework will be paused when the Provincewide Shutdown comes into effect. The impacts of these time-limited measures will be evaluated throughout the 14 days in Northern Ontario and 28 days in Southern Ontario to determine if it is safe to lift any restrictions or if they need to be extended.The Chief Medical Officer of Health will assess and apply lessons learned thus far to the COVID-19 Response Framework to ensure appropriate and effective measures are in place to protect the health of Ontarians and enable economic recovery after the Provincewide Shutdown ends. This will include an assessment of how a revised approach for the safe reopening of retail may be operationalized, according to the latest available evidence.

"This was not an easy decision before the holidays, but we have reached a tipping point," said Minister Elliott. "We continue to see sharp increases in hospitalizations and occupancy in intensive care units is reaching concerning levels. Urgent action must be taken to prevent our health care system from becoming overwhelmed. By implementing a Provincewide Shutdown, we can work to stop the virus in its tracks, safeguard hospital capacity, and save lives."

The government is also providing $12.5 million to implement a High Priority Communities Strategy to contain the virus in high-risk communities. The strategy will take a tailored, community-based approach to fund community agencies in 15 priority communities in the York, Peel, Durham, Ottawa, and Toronto regions. The funding will also allow for the hiring of community ambassadors to make people aware of available services and assistance, for coordination of increased testing opportunities and for the arrangement of wraparound supports for those who are COVID-positive. Additional funding of $42 million will also be available to establish isolation centres.

The province will work with our local municipal partners to establish new isolation centres to help those who may need to isolate following testing.

"We continue to see the number of cases in the province grow and the trends in public health indicators worsen. Additional measures are needed provincewide in order to interrupt this concerning growth," said Dr. Williams. "We must work together to enable everyone to follow these new and time-limited restrictions and protect our health system and our communities."

The government is working to limit the transmission of COVID-19 in workplaces by supporting essential businesses in doing whatever is necessary to keep workers safe. The Ministry of Labour, Training and Skills Development is leading a multi-ministry COVID-19 Safety Team. The team will partner with local authorities to carry out additional enforcement blitzes in sectors where they are needed most.

New School Protocols

While transmission in schools remains low, all publicly funded and private elementary and secondary schools are to move to teacher-led remote learning when students return from the winter break on January 4, 2021. This action is being taken in support of the Government's broader efforts to limit the spread of COVID-19.

Schools located in the following Public Health Unit regions can resume in-person instruction on January 11, 2021 for both elementary and secondary students:

- The District of Algoma Health Unit
- North Bay Parry Sound District Health Unit
- Northwestern Health Unit
- Porcupine Health Unit
- Sudbury and District Health Unit
- Thunder Bay District Health Unit
- Timiskaming Health Unit

For schools in all other Public Health Unit regions, elementary school students are planned to be able to return to in-person learning on January 11, 2021, and secondary school students will continue learning remotely until January 25, 2021, at which point they may resume in-person learning. During this period, child care centres, authorized recreational and skill building programs and home-based child care services will remain open. From January 4-8, 2021, when elementary students move to remote learning, before and after school programs will be closed and emergency child care for health care and frontline workers will be provided. As part of the government's efforts to protect the most vulnerable, boards will be required to make provisions for continued in-person support for students with special education needs who cannot be accommodated through remote learning for whom remote learning is challenging.

"While our schools are not a source of rising community transmission, we can play an important part of the solution to save lives from COVID-19," said Minister Lecce. "During this period, students will pivot to teacher-led online learning, with child care provided for our frontline workers. We are taking proactive and preventative action to protect schools following the holiday break to ensure kids can continue in-class learning — something we believe is so important — for the remainder of the year."

The New Ontario Small Business Support Grant

The government recognizes that small businesses impacted by these necessary public health measures will require additional support so they can continue serving their communities and employing people in Ontario once the COVID-19 pandemic is over. That is why the government is announcing the new *Ontario Small Business Support Grant*, which will provide a minimum of $10,000 and up to $20,000 to eligible small business owners to help navigate this challenging period.

"Ontario's business owners have shown remarkable resolve and ingenuity throughout the pandemic. They know better than anyone what they need to come through this very difficult time, so they can continue to serve and employ people in their communities," said Rod Phillips, Minister of Finance. "The new *Ontario Small Business Support Grant* will provide significant financial support to eligible small business owners in addition to the other supports made available to our small business community."

Small businesses required to close or restrict services under the Provincewide Shutdown will be able to apply for this one-time grant. Each small business will be able to use the support in whatever way makes the most sense for their individual business. For example, some businesses will need support paying employee wages or rent, while others will need support maintaining their inventory.

Eligible small businesses include those that:

- Are required to close or significantly restrict services subject to the Provincewide Shutdown effective 12:01 a.m. on December 26, 2020;
- Have less than 100 employees at the enterprise level; and
- Have experienced a minimum of 20 per cent revenue decline in April 2020 compared to April 2019.

Starting at $10,000 for all eligible businesses, the grant will provide businesses with dollar for dollar funding to a maximum of $20,000 to help cover decreased revenue expected as a result of the Provincewide Shutdown. The business must demonstrate they experienced a revenue decline of at least 20 per cent when comparing monthly revenue in April 2019 and April 2020. This time period was selected because it reflects the impact of the public health measures in spring 2020, and as such provides a representation of the possible impact of these latest measures on small businesses.

Essential businesses that are allowed to remain open will not be eligible for this grant. More information about the *Ontario Small Business Support Grant* is available here. Further details, including how to apply, will be announced in January 2021.

Businesses that are impacted by the Provincewide Shutdown will also be eligible for the property tax and energy cost rebates. In November, the government launched a program to provide rebates to offset fixed costs such as property tax and energy bills for businesses that are required to shut down or significantly restrict services due to provincial public health measures. These rebates will continue to be available for businesses impacted by the Provincewide Shutdown and earlier restrictions. Business can apply for the rebates here.

Quick Facts

- Currently, hospitalizations for COVID-19 have increased by 74 per cent over the last four weeks and are more than 15 times higher than they were at the beginning of September. Intensive care unit (ICU) occupancy for COVID-19 has more than doubled over the last four weeks and is 20 times higher than at the beginning of September.
- Ontario currently has 915 COVID-19 patients requiring acute care, 265 patients in ICU, with 152 on a ventilator.
- Based on the latest modelling data, cases across the province are continuing to grow and the number of people requiring an intensive care bed is projected to rise well above 300 people within the next 10 days.
- Some jurisdictions around the world, including those in Canada have implemented similar time-limited measures to respond to a dramatic resurgence in cases. Based on their experiences, measures of four to six weeks are expected to interrupt transmission of COVID-19 in Ontario.
- Municipalities and local medical officers of health may have additional restrictions or targeted requirements in their region.
- Get tested if you have symptoms compatible with COVID-19, or if you have been advised of exposure by your local public health unit or through the COVID Alert App. Visit Ontario.ca/covidtest to find the nearest testing location.
- The Ontario Small Business Support Grant is part of the Province's more than $13.5 billion in support for people and jobs outlined in the 2020 Budget, Ontario's Action Plan: Protect, Support, Recover. It is also in addition to $4.8 billion to address critical areas to support a strong long-term recovery that helps workers, employers and communities get back on their feet, while building the foundation for recovery and growth.
- To find the right supports, visit COVID-19: Support for People, which has information about the many available and free mental health services and supports.
- To stay safe you can download the COVID Alert App free from the Apple and Google Play app stores.
- To date, as part of the province's COVID-19 immunization program, over 3,000 frontline health care workers have been vaccinated.
- Schools continue to be safe, and according to data reported by school boards, as of Friday, December 18: approximately 99.64 per cent of students in Ontario have not reported a case of COVID-19; approximately 92 per cent of schools across

the province have had either no cases or one case reported within the last 14 days; and approximately 80 per cent of schools do not have an case of COVID-19.

Additional Resources

- Ontario Supporting High Priority Communities
- Ontario Building On Supports for Employers During COVID-19
- The Digital Main Street program helps main street businesses build their online presence and reach more customers.
- Property Tax and Energy Cost Rebates
- Visit Ontario's website to learn more about how the province continues to protect the people of Ontario from COVID-19.
- COVID-19: provincewide shutdown
- **If you have questions about what will be open or impacts to your business or employment, call the Stop the Spread Business Information Line at 1-888-444-3659.**

Related Topics

Government

Learn about the government services available to you and how government works. Learn more

Health and Wellness

Get help navigating Ontario's health care system and connecting with the programs or services you're looking for. Learn more

Media Contacts

Ivana Yelich
Premier's Office
Ivana.Yelich@ontario.ca

Alexandra Hilkene
Minister Elliott's Office
Alexandra.Hilkene@ontario.ca

EXHIBIT I

This is Exhibit "I" referred to
in the Affidavit of
Jacob Reaume

Sworn before me this 4th day
of June A.D., 2021

A Commissioner for Oaths in and for Ontario

TRINITY
BIBLE CHAPEL

Mr. Bryan M. Larkin
Chief of Police
Waterloo Regional Police Service
[redacted]

cc:
Her Worship Sandy Shantz
Mayor of Woolwich Township
[redacted]

December 23, 2020

Dear Mr. Chief Larkin,

On December 18, 2020, a Christian pastor in India's Jarkhand State was shot in the head. On December 10, 2020, extremists in Alexandria, Egypt attacked three Christian men, leaving one dead and two injured with their private property destroyed. On November 17, 2020, three Christians were hacked to death, one burned to death, and four properties destroyed in Sulawesi, Indonesia. On October 29, 2020, three Christians were stabbed to death in Nice, France while worshipping at a church. Globally, one Christian is martyred every two hours simply because he obeys Jesus Christ by faith.[1]

The Regional Municipality of Waterloo, effective December 26, 2020 with the rest of Ontario, will be under lockdown, thus restricting churches to 10 person gatherings. Our church has had protocols to mitigate the spread of COVID-19 since the spring. Thanks be to God, not one outbreak has been traced back to our congregation of over 600 people.

After a tragic killing in the United States, a large demonstration and mass gathering took place in Kitchener on June 3, 2020. You offered the "full support" of the police, and, to those who gathered, you said, "I want you to know that our members will be there to not only ensure your safeby and the safety of the public, but to show that we stand united with you."[3] Occurring while Ontarians were restricted to outdoor gatherings of 5 or less persons, the "crowd may have been between 12,000 and 20,000 strong."[4] You explained to participants, even as they contravened lockdown orders, that police "will ensure you have the support needed to practice your democratic right and have your voice heard."[5]

We affirm that the constitutional rights of Canadians and matters of justice must be prioritized. As part of our regular public gathered worship of Jesus Christ we plan to meet at church in solidarity with our persecuted Christian brothers and sisters across the globe every Sunday, perhaps with mid-week services, for the duration of the lockdown. We hereby invite you to join us for these gatherings. As already indicated in a letter to our governing officials,[5] Trinity Bible Chapel holds the sincere religious belief that we must continue to regularly gather for worship. We intend to do so in accordance with our ancient freedoms protected under section 2(a) and 2(c) of the Constitution Act, 1982. We are heartened to know that each of your members has taken an oath to uphold the Constitution of Canada, each is accountable to the Office of the Independent Police Review Director, and each stands as our equal under the law. Therefore, we would be honoured to have your "support" as "needed to practice our democratic right and have our voice heard" at our church services.

Note that we will have a policy in place to mitigate the spread of COVID-19. We have offered to work with local health and government authorities on several occasions to prevent another lockdown of our church, and sadly we feel marginalized by the silence they have offered us.

Please support us in sending a message to all Canadians that our constitution must be upheld, that persecuted Christians deserve a voice, and that King Jesus must be honoured above all earthly governments.

We conclude by assuring you that as Christians we believe that law enforcement has been instituted by God to punish evil and protect the good.[6] We are peaceful and productive citizens who hold you in high honour, and as such we believe in a fully funded police force.

Sincerely in King Jesus,

Jacob Reaume,
Sr. Pastor
Trinity Bible Chapel

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[1] From https://htp.org/, accessed December 23, 2020.
[2] From https://www.wrps.on.ca/en/news/wrps-supports-solidarity-march-for-black-lives-matter-we-stand-united-with-you.aspx, accessed December 23, 2020.
[3] From https://kitchener.ctvnews.ca/as-it-happened-thousands-of-people-gather-for-peaceful-black-lives-matter-march-in-kitchener-1.4966927, accessed December 23, 2020.
[4] From https://www.wrps.on.ca/en/news/wrps-supports-solidarity-march-for-black-lives-matter-we-stand-united-with-you.aspx, accessed December 23, 2020.
[5] See https://trinitybiblechapel.ca/here-we-stand-the-church-must-meet/, accessed December 23, 2020.
[6] See Romans 13:1-7.

EXHIBIT J

This is Exhibit "J" referred to
in the Affidavit of
Jacob Reaume
Sworn before me this 4th day
of June A.D., 20 21

A Commissioner for Oaths in and for Ontario

REGIONAL MUNICIPALITY OF WATERLOO

OFFICE OF THE REGIONAL CLERK

[redacted]

February 16, 2021
File: A17-30/2021005

By Email: [redacted]

Dear Mr. Reaume:

Subject: Freedom of Information Request Fee Estimate and Extension

This letter is in response to your freedom of information request for - All emails and/or memos and/or documents containing mention of "Jacob Reaume", and/or "Randy Frey", and/or "Trinity Bible Chapel", and or "King Alfred Academy" from 2020/03/01 to 2021/01/14.

Through searches by our Information and Technology Services program using the search terms you have provided they have found approximately 6,000 emails and 144 documents.

Section 45 of the Municipal Freedom of Information and Protection of Privacy Act (MFIPPA) allows the Region to charge fees for access requests. Regulation 823 under MFIPPA sets the searching fee at $30.00 per hour of search time and processing of the records (redacting out information), and also allows the Region to request a 50% down payment where the fee estimate is $100.00 or more, before taking any further steps to process the request. An initial assessment of searching (fee waived) and processing for the records indicates that it will take an estimated 150 hours for redacting the information.

150 hours processing time @ $30 per hour		$4,500
	TOTAL	**$4,500**

You are asked to pay a 50% **($2,250.00)** down payment in order to proceed with this request.

Alternatively, if you would like to receive an index of the records and select the information you are interested in we can reduce this cost.

Please forward the deposit amount by cheque, payable to the Region of Waterloo, attention to: **Oriana Sharp, 150 Frederick Street, 2nd Floor, Kitchener, Ontario, N2G 4J3.** A sample report and report with attachments can be provided upon request to help you make your decision.

[redacted]

Due to the large volume of records that have to be reviewed for this request and limited staff time due to redeployment for COVID-19 response, a time extension of 90 days after the down payment is received. This time extension is being claimed according to section 20 of MFIPPA.

If you would like to appeal this fee estimate or have a review of the time extension, please contact the Information and Privacy Commissioner of Ontario at 2 Bloor Street East, Suite 1400, Toronto ON M4W 1A8 (Telephone: 1-800-387-0073; Website: www.ipc.on.ca). You must commence an appeal within 30 days, and submit a $25 appeal fee to the Commissioner. If you have any questions about this letter or MFIPPA, please contact me at 519-575-4006 or at osharp@regionofwaterloo.ca.

Yours sincerely,

Oriana Sharp
Manager, Information Management & Archives

EXHIBIT K

This is Exhibit "K" referred to
in the Affidavit of
Jacob Beaune

Sworn before me this 4th day
of June A.D., 2021

A Commissioner for Oaths in and for Ontario

Enhanced Epidemiologic Summary

COVID-19 Outbreaks and Cases in Ontario, by Setting: February 16, 2020 to December 26, 2020

This report includes the most current information available from the Ontario Ministry of Health (MOH) Case and Contact Management Solution (CCM) and other case management systems (CCM plus) as of **January 11, 2021.**

Please visit the interactive Ontario COVID-19 Data Tool to explore recent COVID-19 data by public health unit, age group, sex, and trends over time.[1] A Daily Epidemiological Summary, a Weekly Epidemiological Summary, as well as additional Enhanced Epidemiological Reports are available on the Public Health Ontario website.[2,3]

Purpose

This report provides an epidemiologic summary of cumulative confirmed COVID-19 outbreaks and outbreak-associated cases in Ontario by setting, with a focus on outbreaks and cases reported from other settings (i.e., outbreaks and associated cases outside of congregate care, congregate living and education settings). This report includes all COVID-19 cases linked to an outbreak.

Highlights

- In Ontario, from February 16, 2020 to December 26, 2020, there were 39,774 confirmed COVID-19 cases associated with 4,151 outbreaks reported across all settings. In comparison, there were 136,496 non-outbreak associated cases of COVID-19 reported in Ontario during the same period.
- Of the 4,151 outbreaks, 38.8% were in congregate care settings, 11.3% in congregate living settings, 17.7% in education settings, and 32.2% in other settings (Table 1).
    - Overall, long-term care homes (within congregate care settings) accounted for the largest proportion of all outbreaks (905/4,151, 21.8%).
    - Within other settings, workplaces accounted for the majority of outbreaks (872/1,335, 65.3%).
- Of the 39,774 outbreak-associated cases, 63.2% were in congregate care settings, 7.1% in congregate living settings, 6.2% in education settings, and 23.5% in other settings (Table 2).
    - Overall, long-term care homes accounted for the largest proportion of all reported outbreak-associated cases (18,475/39,774, 46.4%).

    - Within other settings, workplaces accounted for the majority of outbreak-associated cases (6,991/9,344, 74.8%).

    - Overall, across all setting types, a median of 2 cases (interquartile range [IQR]: 1-6) per outbreak was reported, with the highest median associated with farm workplace outbreaks (median of 14 cases per outbreak, maximum of 240 cases).

- Deaths were reported in 9.3% of all outbreak associated cases (Table 3).

    - Overall, long-term care homes accounted for the largest proportion of all outbreak-associated deaths (2,911/3,681, 79.1%).

- Compared to non-outbreak cases, a higher proportion of females and individuals 80 years and older were associated with outbreaks (Table 4).

- During the first wave of the pandemic, outbreaks were most commonly reported in congregate care settings. While fewer total outbreaks were reported during the first wave, these outbreaks were generally associated with more cases, peaking at 2,929 cases during week 16 (April 12, 2020 to April 18, 2020).

- In wave two, from August 30, 2020 (week 36) onward, the total number of outbreaks reported weekly increased. The number of outbreaks in congregate care continued to be significant, and outbreaks reported within congregate living, education, and other settings increased. Outbreak-associated cases have been steadily rising from week 36 onward.

Limitations

- The findings presented in this report include all cases and settings where local public health units declared an outbreak in a given setting. The outbreaks included in this report do not present the complete picture of settings where COVID-19 is being transmitted in Ontario, and may under-represent outbreaks in settings where contact tracing is more difficult.

- Outbreak-associated cases in this report do not include secondary cases acquired from outbreak-associated cases. As such, this report likely under-represents the true magnitude of cases impacted by a COVID-19 outbreak.

- Outbreak-associated cases in this report include all cases directly linked to an outbreak as determined by the local public health unit, but may not reflect where the case acquired the infection. Cases could represent employees, residents or members of the public.

- Definitions of outbreaks, including the number of cases, vary across settings. In addition, due to variations in data entry processes across public health units, some outbreaks included in this report may not have met the criteria included in an outbreak definition (i.e. size or duration of outbreak). Further there is no provincial outbreak definition for several setting types classified within the other settings category; as such, there may be variation in declaring outbreaks by public health unit.

- Trends in outbreaks reported across settings and within settings over time should be interpreted with caution, as provincial restrictions resulted in closures of several settings (e.g., school settings were subject to closure during wave one, and were permitted to open approximately

around week 36). The results in this report therefore do not represent a comprehensive assessment of risk in different settings.

Outbreak Characteristics

Table 1. Cumulative summary of confirmed COVID-19 outbreaks reported between February 16, 2020 and December 26, 2020, by setting type: Ontario

Setting Type	Number of outbreaks	Median number of cases per outbreak (IQR)	Maximum number of cases per outbreak	Median duration of closed outbreaks in days [1] (IQR)
Congregate care	**1,612**	**2 (1 - 9)**	**316**	**9 (0 - 21)**
Long-term care homes	905	2 (1 - 8)	316	9 (0 - 22)
Retirement homes	475	2 (1 - 7)	128	6 (0 - 18)
Hospitals	232	6 (3 - 12)	103	13 (6 - 21)
Congregate living	**470**	**2 (1 - 6)**	**215**	**6 (0 - 13)**
Correctional facility	16	2 (1 - 18)	114	3 (0 - 20)
Shelter	86	2 (1 - 5)	215	3 (0 - 13)
Group home/supportive housing	309	2 (1 - 6)	84	6 (0 - 13)
Short-term accommodations	7	1 (1 - 3)	5	4 (2 - 4)
Congregate other	52	4 (1 - 8)	75	7 (1 - 14)
Education	**734**	**2 (1 - 4)**	**50**	**6 (2 - 11)**
Child care	238	1 (1 - 2)	28	3 (0 - 9)
School – Elementary[2]	348	3 (2 - 4)	50	7 (4 - 12)
School – Elementary/secondary[2]	24	4 (2 - 6)	46	6 (2 - 14)
School – Secondary[2]	111	2 (2 - 5)	40	9 (5 - 16)
School – Post-secondary[2]	13	2 (2 - 3)	9	5 (5 - 6)

Setting Type	Number of outbreaks	Median number of cases per outbreak (IQR)	Maximum number of cases per outbreak	Median duration of closed outbreaks in days [1] (IQR)
Other settings[3]	**1,335**	**3 (1 - 6)**	**240**	**9 (5 - 16)**
Bar/restaurant/nightclub	122	3 (2 - 5)	40	7 (4 - 11)
Medical/health services	59	3 (1 - 5)	17	7 (4 - 13)
Medical/dental clinics	26	3 (1 - 4)	14	5 (4 - 10)
Other[4]	33	2 (1 - 5)	17	8 (5 - 18)
Personal service settings	11	2 (1 - 4)	16	15 (6 - 22)
Recreational fitness	49	5 (2 - 10)	54	5 (1 - 9)
Gym/fitness studios	14	2 (1 - 7)	54	5 (4 - 10)
Sporting teams/leagues	14	7 (3 - 9)	44	1 (0 - 7)
Other[5]	21	5 (2 - 10)	48	7 (2 - 13)
Retail	141	2 (1 - 4)	47	8 (4 - 12)
Grocery stores/pharmacies	34	2 (1 - 4)	36	12 (9 - 20)
Other[6]	107	2 (1 - 4)	47	6 (4 - 12)
Culture and other recreation	71	5 (2 - 12)	60	8 (4 - 13)
Places of worship	23	6 (3 - 15)	30	9 (7 - 12)
Private events	18	8 (2 - 15)	36	7 (5 - 13)
Other[7]	30	3 (1 - 6)	60	7 (4 - 14)
Workplace	872	3 (1 - 7)	240	11 (6 - 19)
Construction	83	2 (1 - 3)	8	8 (3 - 13)
Logistics	95	3 (1 - 10)	202	15 (8 - 23)
Farm	53	14 (4 - 42)	240	23 (14 - 45)
Food processing	115	5 (2 - 11)	168	17 (8 - 25)

Setting Type	Number of outbreaks	Median number of cases per outbreak (IQR)	Maximum number of cases per outbreak	Median duration of closed outbreaks in days [1] (IQR)
Manufacturing	298	3 (1 - 7)	57	12 (7 - 19)
Other[8]	228	3 (1 - 5)	56	7 (4 - 11)
Unknown	10	2 (0 - 15)	42	3 (0 - 22)
Total	**4,151**	**2 (1 - 6)**	**316**	**8 (2 - 16)**

Notes: Due to reporting delays and potential variations in data entry processes across public health units, there may be additional COVID-19 cases that have not yet been entered in CCM plus, or have not been entered as linked to an outbreak. As such, some outbreaks may have zero linked cases. This includes 121 outbreaks in congregate care, 46 outbreaks in congregate living, 61 outbreaks in education, and 204 outbreaks in other settings. Ongoing re-classification of settings for reported outbreaks can result in outbreak counts that may differ from counts previously reported in other reports. See Appendix A for full descriptions of outbreak categories.

[1]The median duration of outbreaks was only measured for outbreaks with a "Closed" Outbreak Classification status. Outbreak length was calculated using the 'Outbreak Date' as the start date and the 'Outbreak Date End' as the end date. The "Outbreak Date" is a calculated field used to determine the outbreak declared date using the following hierarchy of date fields (Onset date of the first case > Reported Date > Created Date). The "Outbreak Date End" is a calculated field used to determine the end date of the outbreak using the following hierarchy of date fields (Onset date of the last case > Date the outbreak was declared over). Due to variations in data entry practices and variability in case definitions, this can result in outbreaks having a duration length of 0 days (i.e. if only a single case is linked to an outbreak, the symptom onset date for the first and last case will be the same).

[2]Cumulative counts include COVID-19 school outbreaks reported starting week 36 (August 30 to September 5, 2020).

[3]Not all settings were open during the reporting period due to provincial public health measures.

[4]Captures outbreaks classified as having taken place in other medical/health-service related settings, including community health centres, home care services and wellness clinics.

[5]Captures outbreaks classified as having taken place in recreational settings including athletic facilities, recreational/community centres, golf courses, tennis courts and indoor playgrounds.

[6]Captures outbreaks classified as having taken place in auto dealerships and standalone retailers, as well as big box stores, among other retail settings.

[7]Captures outbreaks classified as having taken place in theatres, banquet halls (not including weddings), private transportation, private residences, and other community settings.

[8]Captures outbreaks classified as having taken place in locations such as: offices, banks, municipal services (e.g., fire station, police station), and veterinary clinics.

Data Source: CCM plus

Characteristics of outbreak-associated Cases

Table 2. Cumulative summary of confirmed COVID-19 cases associated with outbreaks reported between February 16, 2020 and December 26, 2020, by setting type: Ontario

Setting Type	Number of cases	Proportion male[1] (%)	Median age[2] (IQR)
Congregate care	**25,150**	**27.4**	**73 (49 - 87)**
Long-term care homes	18,475	26.7	74 (50 - 87)
Retirement homes	4,098	25.1	80 (49 - 89)
Hospitals	2,577	37.0	55 (36 - 78)
Congregate living	2,809	**54.3**	**41 (29 - 54)**
Correctional facility	286	89.5	35 (27 - 45)
Shelter	685	57.4	40 (31 - 52)
Group home/supportive housing	1,431	45.5	44 (30 - 56)
Short-term accommodations	14	50.0	40 (24 - 48)
Congregate other	393	55.2	38 (28 - 55)
Education	**2,471**	**46.4**	**13 (8 - 29)**
Child care	471	29.3	23 (3 - 41)
School – Elementary[3]	1,338	48.8	11 (8 - 13)
School – Elementary/secondary[3]	173	65.3	17 (13 - 36)
School – Secondary[3]	450	50.2	16 (14 - 19)
School – Post-secondary[3]	39	41.0	19 (17 - 27)
Other settings[4]	**9,344**	**67.3**	**38 (27 - 51)**
Bar/restaurant/nightclub	471	46.3	28 (23 - 43)
Medical/health services	221	28.1	42 (29 - 53)
Medical/dental clinics	95	26.3	39 (27 - 48)

Setting Type	Number of cases	Proportion male[1] (%)	Median age[2] (IQR)
Other[5]	126	29.4	46 (31 - 57)
Personal service settings	36	11.1	35 (25 - 42)
Recreational fitness	411	60.8	32 (21 - 54)
Gym/fitness studios	109	33.0	30 (27 - 37)
Sporting teams/leagues	127	84.3	40 (15 - 52)
Other[6]	175	61.1	40 (21 - 62)
Retail	508	60.0	35 (24 - 51)
Grocery stores/pharmacies	131	55.7	36 (23 - 53)
Other[7]	377	61.5	35 (24 - 51)
Culture and other recreation	620	51.8	33 (21 - 53)
Places of worship	221	52.9	40 (27 - 57)
Private events	193	54.9	30 (23 - 49)
Other[8]	206	47.6	28 (18 - 48)
Workplace	6,991	72.6	39 (29 - 51)
Construction	202	90.1	40 (28 - 51)
Logistics	1,211	58.8	36 (26 - 49)
Farm	1,779	86.6	35 (28 - 43)
Food processing	1,253	66.4	41 (30 - 52)
Manufacturing	1,681	75.1	47 (34 - 56)
Other[9]	865	63.1	41 (29 - 54)
Unknown	86	58.1	30 (21 - 47)
Total	**39,774**	**39.8**	**54 (34 - 81)**

Notes: See Appendix A for full descriptions of outbreak categories.

[1]Not all cases have a gender reported. The denominator for calculating male case percentages includes all cases.

[2]Includes all cases linked to an outbreak regardless of attendance/residence within the outbreak setting. Therefore, the range of ages of cases associated with an outbreak may not align with expected ages within that setting.
[3]Cumulative counts include COVID-19 school outbreaks reported starting week 36 (August 30 to September 5, 2020).
[4]Not all settings were open during the reporting period due to provincial public health measures.
[5]Captures outbreaks classified as having taken place in other medical/health-service related settings, including community health centres, home care services and wellness clinics.
[6]Captures outbreaks classified as having taken place in recreational settings including athletic facilities, recreational/community centres, golf courses, tennis courts and indoor playgrounds.
[7]Captures outbreaks classified as having taken place in auto dealerships and standalone retailers, including big box stores, among other retail settings.
[8]Captures outbreaks classified as having taken place in theatres, banquet halls (not including weddings), public and private transportation, private residences and other community settings.
[9]Captures outbreaks classified as having taken place in offices, banks, municipal services (e.g. fire station, police station), and veterinary clinics, among others.
Data Source: CCM plus

Severity

Table 3. Cumulative summary of hospitalizations and deaths among confirmed COVID-19 cases associated with outbreaks reported between February 16, 2020 and December 26, 2020, by setting type: Ontario

Setting Type	Number of hospitalized cases (% of outbreak-associated cases)	Number of deaths (% of outbreak-associated cases)	% of all outbreak-associated hospitalizations	% of all outbreak-associated deaths
Congregate care	**3,070 (12.2%)**	**3,626 (14.4%)**	**88.7%**	**98.5%**
Long-term care homes	1,517 (8.2%)	2,911 (15.8%)	43.8%	79.1%
Retirement homes	672 (16.4%)	418 (10.2%)	19.4%	11.4%
Hospitals	881 (34.2%)[1]	297 (11.5%)	25.5%	8.1%
Congregate living	**233 (8.3%)**	**33 (1.2%)**	**6.7%**	**0.9%**
Correctional facility	4 (1.4%)	0 (0.0%)	0.1%	0.0%
Shelter	94 (13.7%)	3 (0.4%)	2.7%	0.1%
Group home/supportive housing	110 (7.7%)	20 (1.4%)	3.2%	0.5%
Short-term accommodations	0 (0.0%)	0 (0.0%)	0.0%	0.0%
Congregate other	25 (6.4%)	10 (2.5%)	0.7%	0.3%
Education	**6 (0.2%)**	**0 (0.0%)**	**0.2%**	**0.0%**
Child care	1 (0.2%)	0 (0.0%)	<0.1%	0.0%
School – Elementary[2]	4 (0.3%)	0 (0.0%)	0.1%	0.0%
School – Elementary/secondary[2]	0 (0.0%)	0 (0.0%)	0.0%	0.0%
School – Secondary[2]	1 (0.2%)	0 (0.0%)	<0.1%	0.0%
School – Post-secondary[2]	0 (0.0%)	0 (0.0%)	0.0%	0.0%
Other settings[3]	**151 (1.6%)**	**22 (0.2%)**	**4.4%**	**0.6%**
Bar/restaurant/nightclub	6 (1.3%)	0 (0.0%)	0.2%	0%

Setting Type	Number of hospitalized cases (% of outbreak-associated cases)	Number of deaths (% of outbreak-associated cases)	% of all outbreak-associated hospitalizations	% of all outbreak-associated deaths
Medical/health services	15 (6.8%)	5 (2.3%)	0.4%	0.1%
Medical/dental clinics	0 (0.0%)	0 (0.0%)	0.0%	0.0%
Other[4]	15 (11.9%)	5 (4.0%)	0.4%	0.1%
Personal service settings	0 (0.0%)	0 (0.0%)	0.0%	0.0%
Recreational fitness	2 (0.5%)	0 (0.0%)	0.1%	0.0%
Gym/fitness studios	0 (0.0%)	0 (0.0%)	0.0%	0.0%
Sporting teams/leagues	1 (0.8%)	0 (0.0%)	<0.1%	0.0%
Other[5]	1 (0.6%)	0 (0.0%)	<0.1%	0.0%
Retail	8 (1.6%)	1 (0.2%)	0.2%	<0.1%
Grocery stores/pharmacies	2 (1.5%)	0 (0.0%)	0.1%	0.0%
Other[6]	6 (1.6%)	1 (0.3%)	0.2%	<0.1%
Culture and other recreation	20 (3.2%)	4 (0.6%)	0.6%	0.1%
Places of worship	5 (2.3%)	0 (0.0%)	0.1%	0.0%
Private events	4 (2.1%)	2 (1.0%)	0.1%	0.1%
Other[7]	11 (5.3%)	2 (1.0%)	0.3%	0.1%
Workplace	93 (1.3%)	12 (0.2%)	2.7%	0.3%
Construction	3 (1.5%)	1 (0.5%)	0.1%	<0.1%
Logistics	15 (1.2%)	0 (0.0%)	0.4%	0.0%
Farm	22 (1.2%)	3 (0.2%)	0.6%	0.1%
Food processing	24 (1.9%)	4 (0.3%)	0.7%	0.1%
Manufacturing	16 (1.0%)	2 (0.1%)	0.5%	0.1%

Setting Type	Number of hospitalized cases (% of outbreak-associated cases)	Number of deaths (% of outbreak-associated cases)	% of all outbreak-associated hospitalizations	% of all outbreak-associated deaths
Other[8]	13 (1.5%)	2 (0.2%)	0.4%	0.1%
Unknown	7 (8.1%)	0 (0.0%)	0.2%	0.0%
Total	**3,460 (8.7%)**	**3,681 (9.3%)**	100.0%	100.0%

Notes: See Appendix A for full descriptions of outbreak categories.
[1]Hospitalized cases associated with outbreaks classified within a hospital can include patients, staff or other hospital visitors. The number of hospitalized cases in hospital outbreak settings is lower than the total number of cases reported in hospital outbreak settings (Table 2), as the total number of cases includes healthcare workers in the facility who may not have been hospitalized.
[2]Includes COVID-19 school outbreaks reported starting week 36 (August 30 to September 5, 2020).
[3]Not all settings were opened during the reporting period due to provincial public health measures.
[4]Captures outbreaks classified as having taken place in other medical/health-service related settings, including community health centres, home care services and wellness clinics.
[5]Captures outbreaks classified as having taken place in recreational settings including athletic facilities, recreational/community centres, golf courses, tennis courts and indoor playgrounds.
[6]Captures outbreaks classified as having taken place in auto dealerships and standalone retailers, including big box stores, among other retail settings.
[7]Captures outbreaks classified as having taken place in theatres, banquet halls (not including weddings), public and private transportation, private residences and other community settings.
[8]Captures outbreaks classified as having taken place in offices, banks, municipal services (e.g. fire station, police station), and veterinary clinics, among others.
Data Source: CCM plus

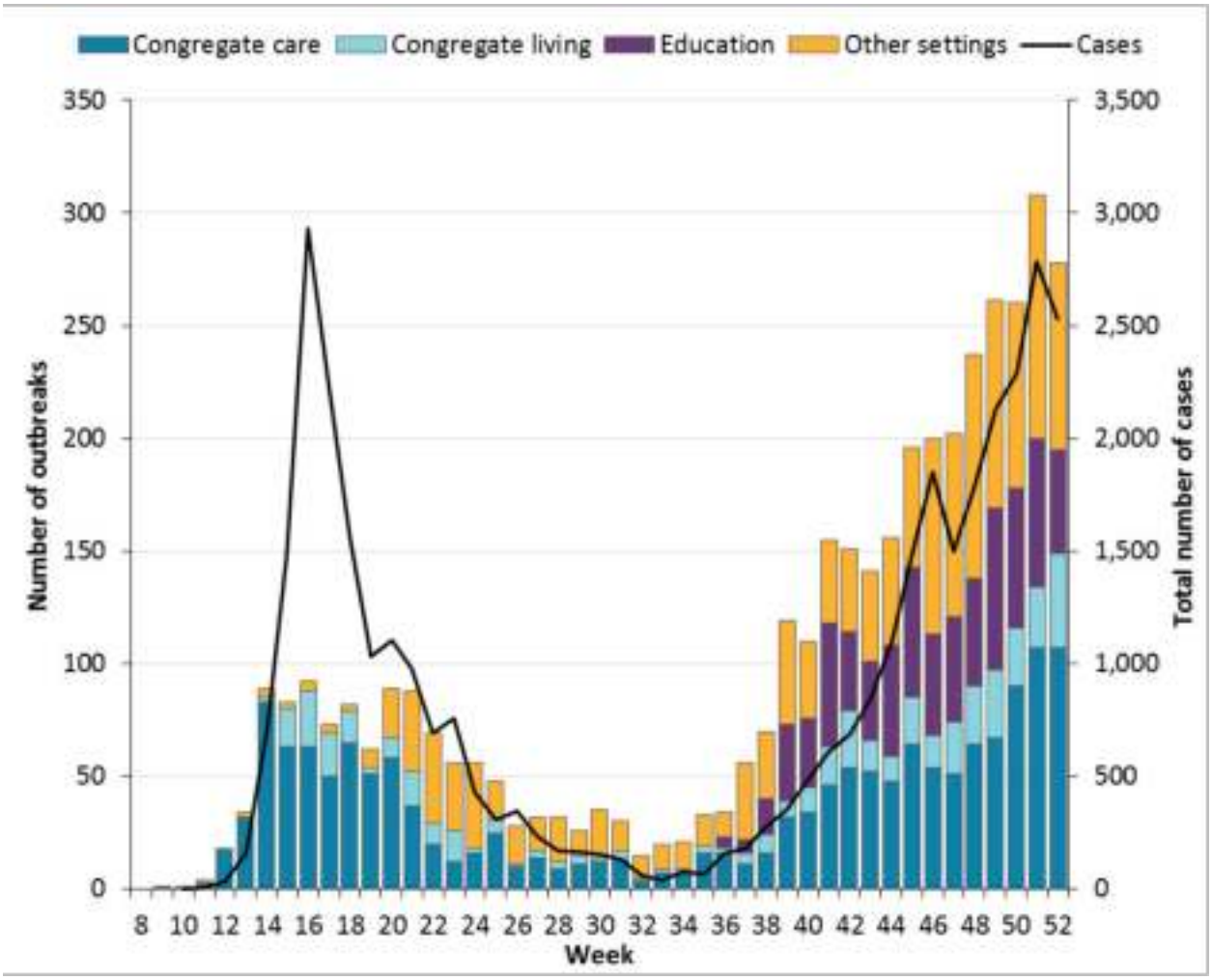
Table 4. Demographic characteristics of non-outbreak and outbreak-associated cases reported between February 16, 2020 and December 26, 2020

	Non-outbreak cases	Outbreak cases
Total number of cases	**136,496**	**39,774**
Gender: Female	65,801 (48.2%)	23,567 (59.3%)
Gender: Male	70,030 (51.3%)	15,840 (39.8%)
Age: 19 and under	19,856 (14.5%)	2,512 (6.3%)
Age: 20-39	54,023 (39.6%)	9,796 (24.6%)
Age: 40-59	40,039 (29.3%)	10,425 (26.2%)
Age: 60-79	19,086 (14.0%)	6,466 (16.3%)
Age: 80 and over	3,473 (2.5%)	10,565 (26.6%)

Note: Not all cases have an age or gender reported. The denominator for calculating percentages includes all cases.
Data Source: CCM plus

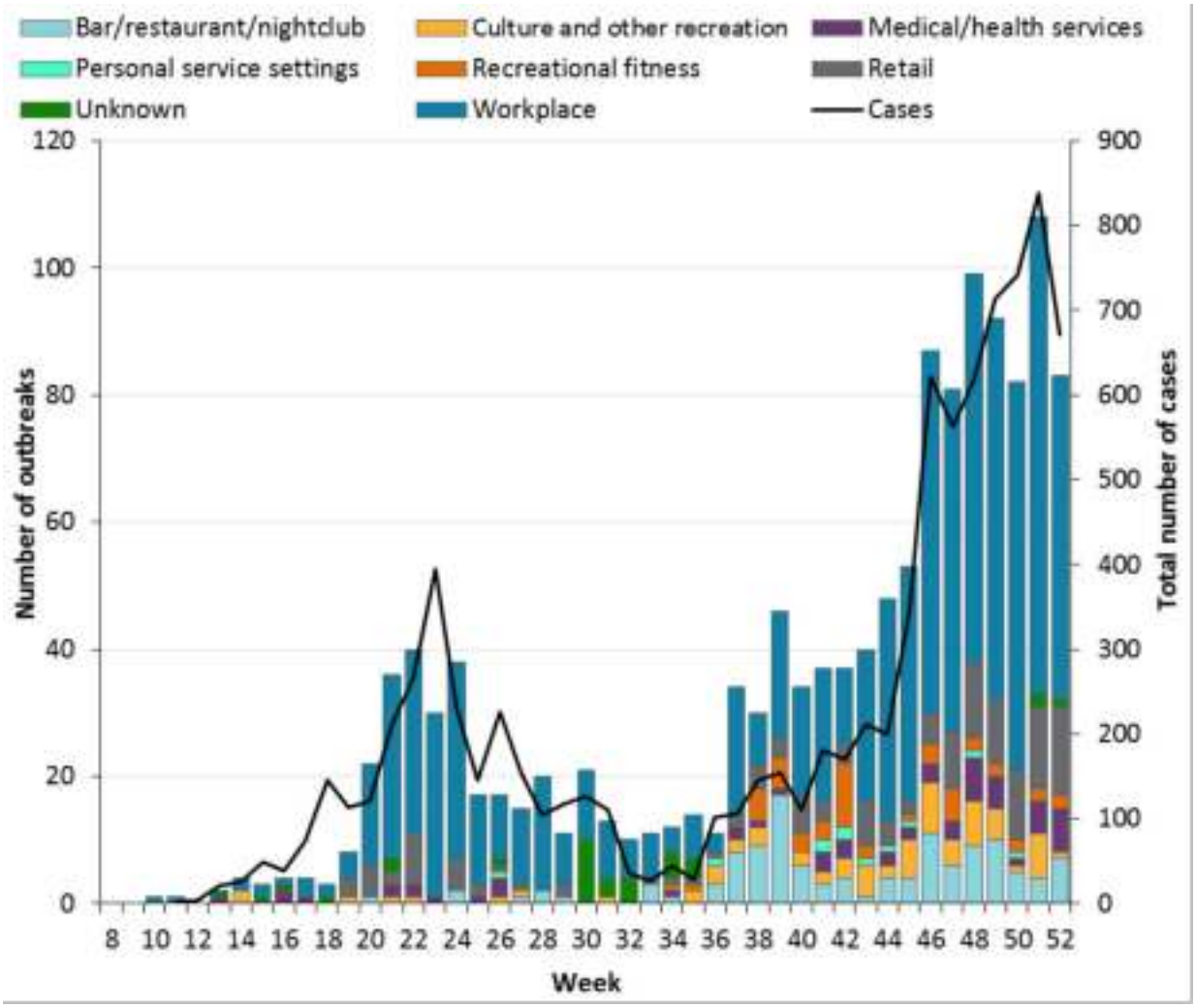
Time Trends

Figure 1a. Total number of public health unit declared COVID-19 outbreaks, and number of confirmed outbreak-associated cases, by setting type and week, reported between week 8 (February 16, 2020) and week 52 (December 26, 2020): Ontario



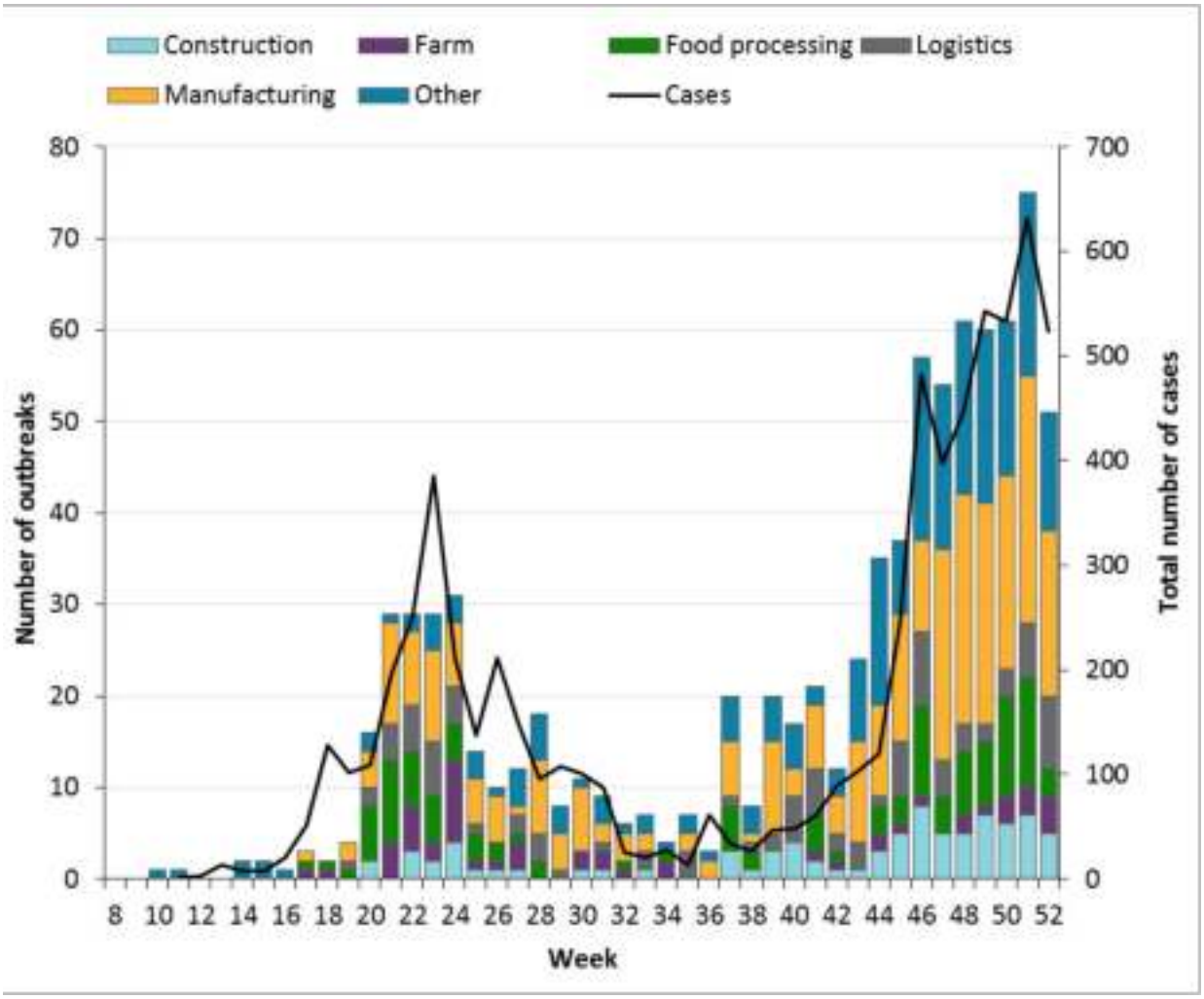
Notes: Number of outbreaks is based on week the outbreak was declared, while total number of cases is based on case reported week. Since many outbreaks are still ongoing, there were 3,261 cases with case reported dates that occurred outside of the week ranges of focus and were therefore not included in the figure. Includes outbreaks that are ongoing and outbreaks that are no longer active. Not all settings were open during the reporting period due to provincial public health measures. See Appendix A for full descriptions of outbreak categories.
Data Source: CCM plus

Figure 1b. Number of public health unit declared COVID-19 outbreaks in other settings, and number of confirmed other setting outbreak-associated cases, by setting type and week, reported between week 8 (February 16, 2020) and week 52 (December 26, 2020): Ontario



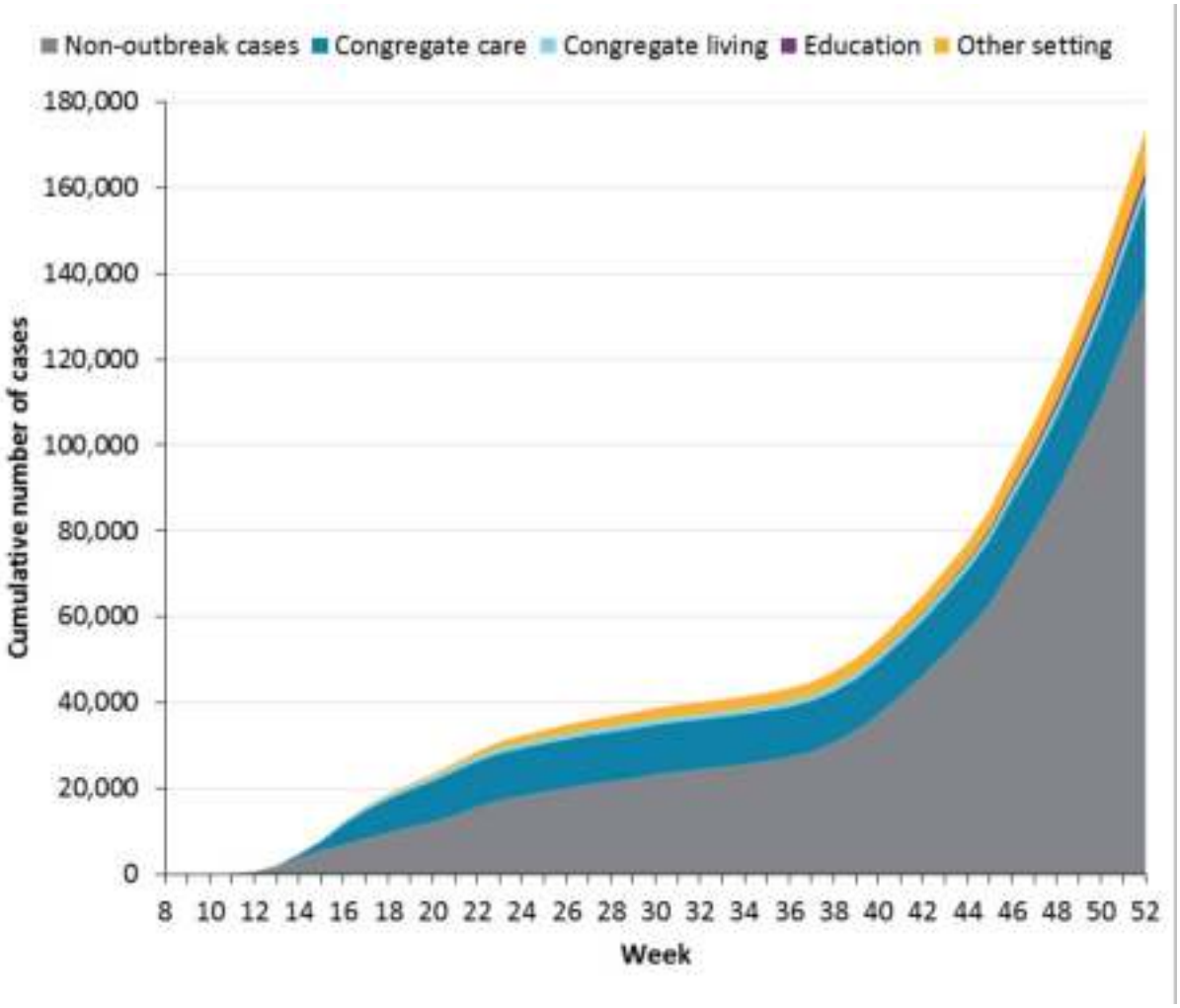
Notes: Number of outbreaks is based on week the outbreak was declared, while total number of cases is based on case reported week. Since many outbreaks are still ongoing, there were 399 cases with case reported dates that occurred outside of the week ranges of focus and were therefore not included in the figure. Includes outbreaks that are ongoing and outbreaks that are no longer active. Not all settings were open during the reporting period due to provincial public health measures. See Appendix A for full descriptions of outbreak categories.
Data Source: CCM plus

Figure 1c. Number of confirmed public health unit declared COVID-19 workplace[1] outbreaks, and number of confirmed workplace outbreak-associated cases, by setting type and week, reported between week 8 (February 16, 2020) and week 52 (December 26, 2020): Ontario



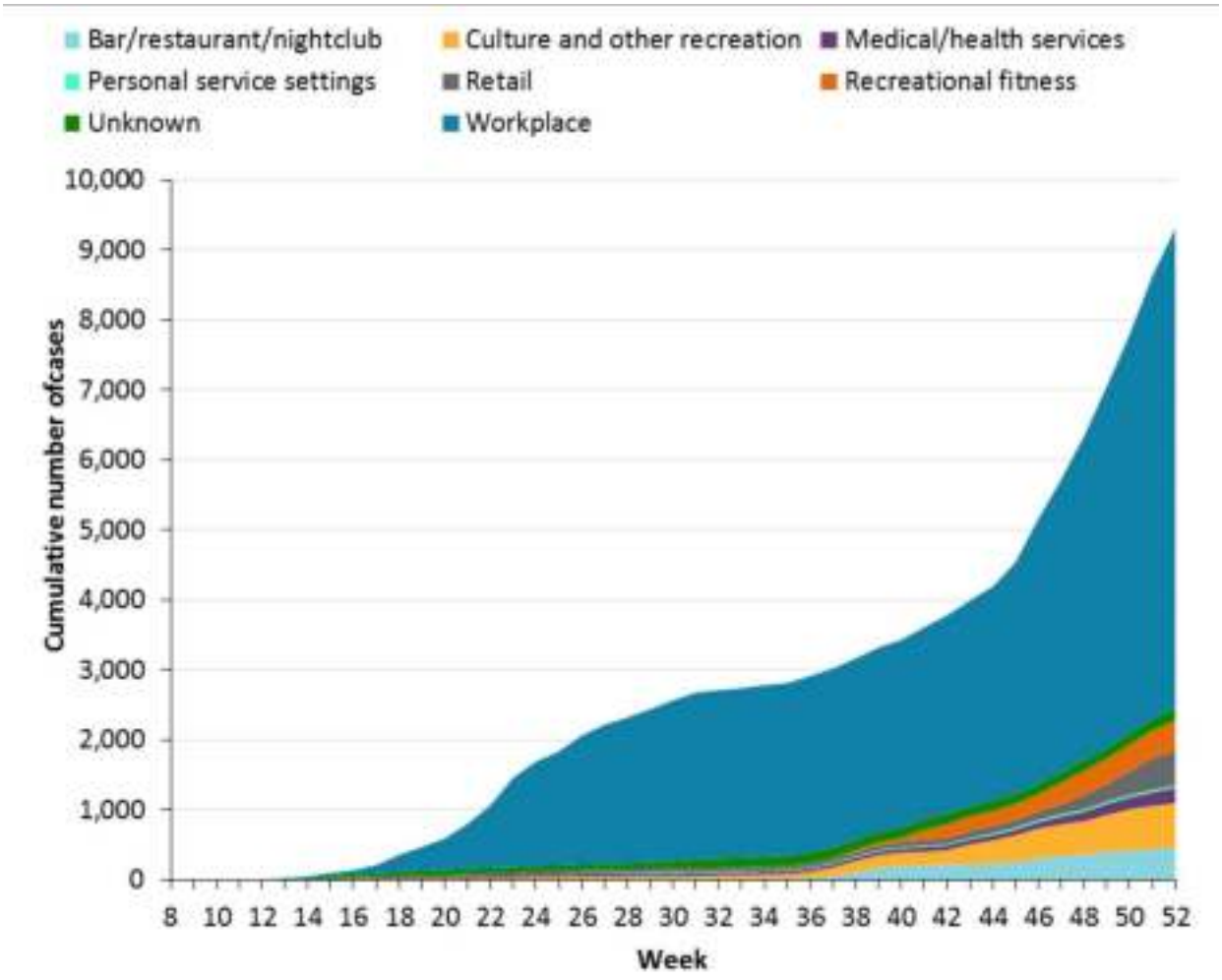
Notes: Number of outbreaks is based on week the outbreak was declared, while total number of cases is based on case reported week. Since many outbreaks are still ongoing, there were 347 cases with case reported dates that occurred outside of the week ranges of focus and were therefore not included in the figure. Includes outbreaks that are ongoing and outbreaks that are no longer active. Not all settings were open during the reporting period due to provincial public health measures. See Appendix A for full descriptions of outbreak categories.
[1]Workplaces do not include publically-accessible settings where people may also work (i.e., restaurants, gyms).
Data Source: CCM plus

Figure 2a. Cumulative number of outbreak and non-outbreak cases, by setting type and week, reported between week 8 (February 16, 2020) and week 52 (December 26, 2020): Ontario



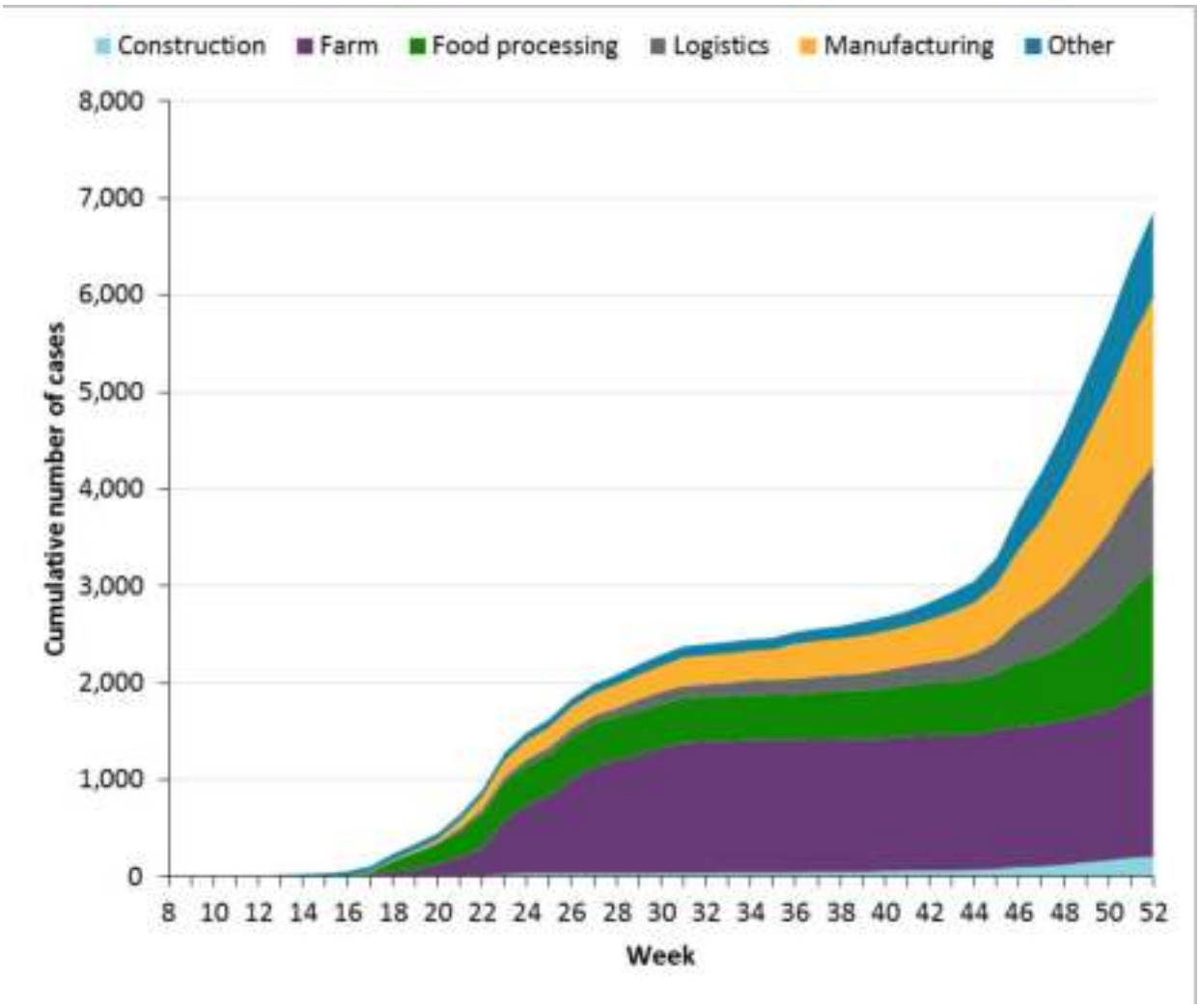
Notes: Based on case reported week. Non-outbreak cases refers to all COVID-19 cases not linked to a declared outbreak reported between weeks 8 and 52. Since many outbreaks are still ongoing, there were 3,267 outbreak-linked cases with case reported dates that occurred outside of the week ranges of focus and were therefore not included in the figure. Includes outbreaks that are ongoing and outbreaks that are no longer active. Not all settings were open during the reporting period due to provincial public health measures. See Appendix A for full descriptions of outbreak categories.
Data Source: CCM plus

Figure 2b. Cumulative number of confirmed cases from other setting outbreaks, by setting type and week, reported between week 8 (February 16, 2020) and week 52 (December 26, 2020): Ontario



Notes: Based on case reported week. Since many outbreaks are still ongoing, there were 399 cases with case reported dates that occurred outside of the week ranges of focus and were therefore not included in the figure. Includes outbreaks that are ongoing and outbreaks that are no longer active. Not all settings were open during the reporting period due to provincial public health measures. See Appendix A for full descriptions of outbreak categories.
Data Source: CCM plus

Figure 2c. Cumulative number of confirmed cases from workplace[1] outbreaks, by setting type and week, reported between week 8 (February 16, 2020) and week 52 (December 26, 2020): Ontario



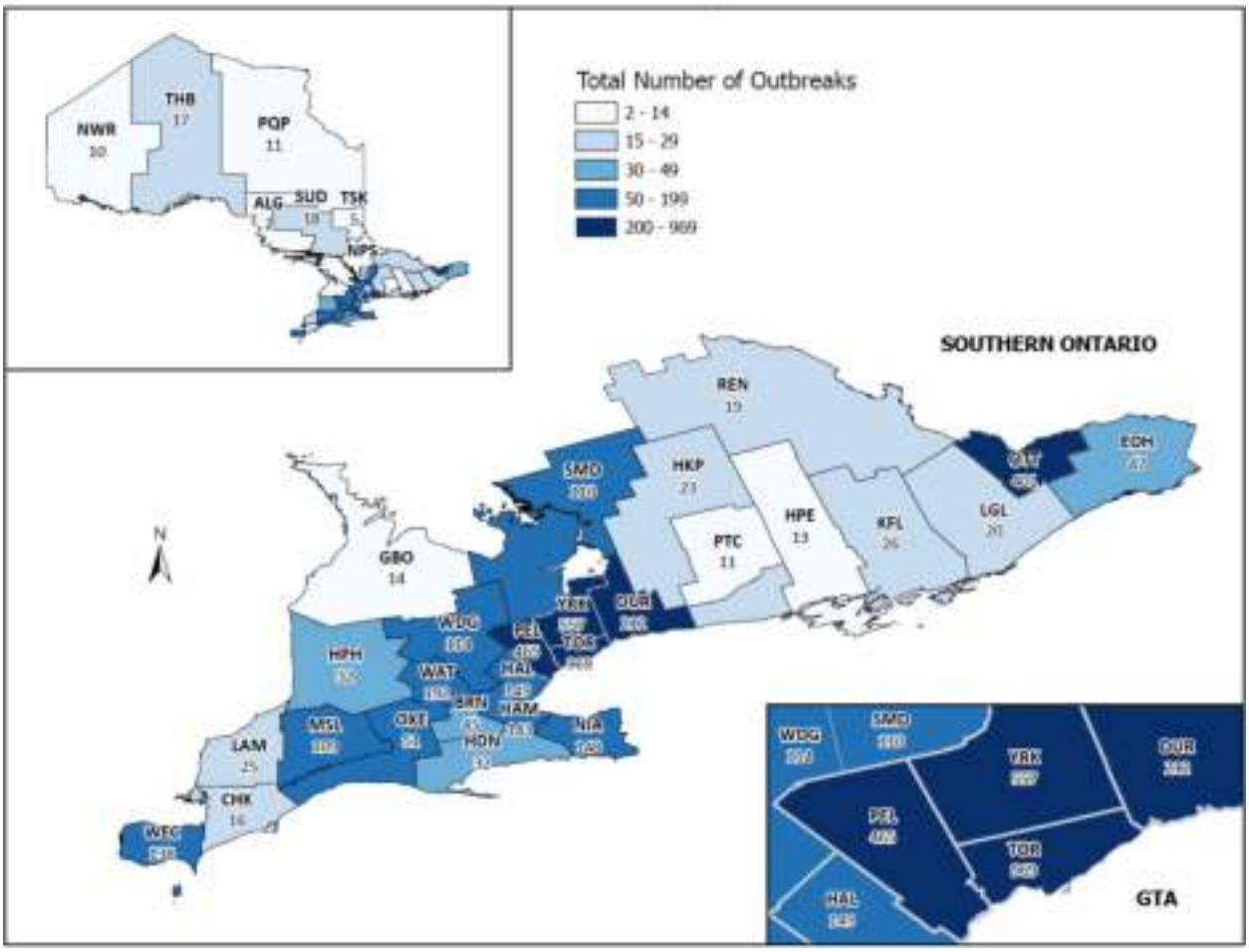
Notes: Based on case reported week. Since many outbreaks are still ongoing, there were 347 cases with case reported dates that occurred outside of the week ranges of focus and were therefore not included in the figure. Includes outbreaks that are ongoing and outbreaks that are no longer active. Not all settings were open during the reporting period due to provincial public health measures. See Appendix A for full descriptions of outbreak categories.

[1]Workplaces do not include publically-accessible settings where people may also work (i.e., restaurants, gyms).

Data Source: CCM plus

Geography

Figure 3. Number of confirmed COVID-19 outbreaks reported between February 16, 2020 and December 26, 2020 by public health unit: Ontario



Note: Includes outbreaks that are ongoing and outbreaks that are no longer active. Cut-offs for map categories were determined by natural breaks and adjusted for round numbers. Geography is based on public health unit where the outbreak was declared. Not all settings were open during the reporting period due to provincial public health measures. There was one outbreak that involved cases from Ontario and outside of Ontario and was not assigned to a public health unit. The data in this map are also available in Appendix B.
Data Source: CCM plus

Technical Notes

Data Sources

- The data for this report were based on:
    - Information extracted from the Ontario Ministry of Health (Ministry) integrated Public Health Information System (iPHIS) database for Toronto Public Health as of **January 11, 2021 at 1 p.m.**
    - Information successfully uploaded to the Ministry from Local Systems: Toronto Public Health (Coronavirus Rapid Entry System) CORES as of **January 11, 2021 at 2 p.m.**
    - Information successfully extracted from the Public Health Case and Contact Management Solution (CCM) for all other PHUs by PHO as of **January 11, 2021 at 1 p.m.**
- CCM and CCM plus (which includes CCM, iPHIS and CORES) are dynamic disease reporting systems, which allow ongoing updates to data previously entered. As a result, data extracted from CCM and the Local Systems represent a snapshot at the time of extraction and may differ from previous or subsequent reports. This applies to both case and outbreak data.

Data Caveats:

- The data included are for outbreaks reported in Ontario from February 16, 2020 to December 26, 2020 and cases linked to those outbreaks up until January 11th, 2021.
- Only confirmed outbreaks are included in this report.
- The outbreak data for these settings are restricted to those in which an outbreak was declared by the public health unit. The data also do not include cases linked to these settings as an exposure. Outbreaks are declared by the local medical officer of health or their designate in accordance to the Health Protection and Promotion Act and criteria outlined in Ministry guidance documents.[4]
- For outbreaks declared in certain settings such as long-term care, hospitals, educational settings, and workplaces, there are provincial outbreak definitions.[5-7] These definitions may have single case thresholds, and may also include changes in the case thresholds for declaring an outbreak over time (i.e.,., the threshold for declaring an outbreak in a child care setting increased from one to two cases as of November 9, 2020).[8] However, there is no provincial case definition for several other setting types reported as other settings. As such, a standard approach to declaring an outbreak across these settings may differ by public health unit.
    - All other setting outbreaks were manually classified based on the name, address, and additional relevant information available in CCM for the outbreak, as entered by the PHU. other setting outbreaks consisted of outbreaks outside of congregate care settings (i.e., hospitals, long-term care, retirement home), congregate living settings (i.e., correctional facilities, shelters, group homes, other congregate), and education settings (i.e., childcare settings and schools). All outbreak classifications are mutually exclusive. However, an outbreak declared in a restaurant may have been a workplace outbreak if cases were

identified among staff only. For the purposes of this report, a setting-based hierarchy was used.

    - Outbreaks reported in the workplace – arm category may include cases related to shared living amongst farm staff. As such, some of these outbreaks may be more similar to outbreaks in congregate living settings.

- For additional information regarding outbreak setting type classification definitions, please refer to Table 1 in the Appendix. Some outbreaks may be misclassified due to lack of information to assist with the manual classification process.

- All outbreaks reported as confirmed in CCM plus were included in these analyses regardless of whether the case data in CCM plus supported the outbreaks' classification.

- Due to reporting delays and potential variations in data entry processes across public health units, there may be additional COVID-19 cases that have not yet been entered in CCM plus, or have not been entered as linked to an outbreak. As such, some outbreaks may have zero linked cases as of the data extraction date. Results should be interpreted with caution due to potential under-detection of outbreak associated cases.

- The data only represent cases reported to public health units and recorded in CCM plus. As a result, all counts will be subject to varying degrees of underreporting due to a variety of factors, such as disease awareness and medical care seeking behaviours, which may depend on severity of illness, clinical practice, changes in laboratory testing, and reporting behaviours.

- Lags in CCM plus data entry due to weekend staffing may result in lower case counts than would otherwise be recorded.

- Outbreak-associated cases do not include secondary cases acquired from outbreak-associated cases.

- The data for these settings are restricted to those in which an outbreak was declared by the public health unit. They do not include cases linked to these settings as an exposure.

- Cases with unknown or missing ages were excluded from age-specific analyses.

- Only cases meeting the confirmed case classification as listed in the MOH COVID-19 case definition are included in the report counts from CCM plus.[4] This includes persons with a positive detection of serum/plasma immunoglobulin G (IgG) antibodies to SARS-CoV-2, which was added to the confirmed case definition on August 6, 2020.

- Cases of confirmed reinfection, i.e., where genome sequencing indicates the two episodes are caused by different viral lineages, added to the confirmed case definition on November 20, 2020, are counted as unique investigations.

- Case reported week uses the date the case was reported to the public health unit.

    - Outbreak reported week uses the date the public health unit reported the outbreak. If this date is unavailable, the date the public health unit created the outbreak is used.

    - Reported weeks were created to align with the Public Health Agency of Canada (PHAC) influenza surveillance weeks.

- ‘Cases associated with school outbreaks’ include cases that are linked to an outbreak, by school classification type (Elementary, Elementary/Secondary, Secondary, Post-Secondary), that met the definition of a school outbreak.

- School classification types are defined by the Ministry of Education. Some schools classified as secondary may also have an intermediate school in the same location that start in Grade 7.

    - Elementary/Secondary schools include public or private schools educating children in a combination of elementary and secondary grades (e.g., Kindergarten to Grade 8, Grades 9 to 12, and Kindergarten to Grade 12).

- School outbreaks include outbreaks declared on or after week 36 (August 30 to September 5, 2020).

- Hospitalization includes all cases for which a hospital admission date was reported at the time of data extraction. It includes cases that have been discharged from hospital as well as cases that are currently hospitalized. Emergency room visits are not included in the number of reported hospitalizations.

- Deaths are determined by using the outcome field in CCM. Any case marked ‘Fatal’ is included in the deaths data. The CCM field Type of Death is not used to further categorize the data.

- Ongoing outbreaks are those that are reported in CCM plus as ‘Open’ and without a ‘Declared Over Date’ recorded. Closed outbreaks are ‘Closed’ or have a ‘Declared Over Date’ recorded in CCM plus or where the outbreak start date (determined by the onset date of first case, or if missing the reported date, or if missing the created date) is more than 5 months from the current date, even for outbreaks where the outbreak status value selected in CCM/iPHIS is 'OPEN'.

- Orientation of case counts by geography is based on the diagnosing health unit (DHU). DHU refers to the case's public health unit of residence at the time of illness onset and not necessarily the location of exposure. Cases for which the DHU was reported as MOH (to signify a case that is not a resident of Ontario) have been excluded from the analyses.

- COVID-19 cases from CCM plus for which the Classification and/or Disposition was reported as ENTERED IN ERROR, DOES NOT MEET DEFINITION, IGNORE, DUPLICATE, or any variation on these values have been excluded. The provincial case count for COVID-19 includes cases that are counted once across all systems from which the case data are obtained. Duplicate records may exist if these records were not identified and resolved prior to data upload to the Ministry.

Appendix A: Definitions of outbreak settings

Table A1. Definitions for various setting types including congregate care, congregate living, education, and other settings.

Setting type	Definitions
Congregate care	
Long-term care homes	A facility that provides care and services for people who no longer are able to live independently or who require onsite nursing care, 24-hour supervision or personal support. LTC Homes are governed under the Long Term Care Homes Act (LTCHA) and Ontario Regulation 79/10.
Retirement homes	A residential complex or the part of a residential complex, that is occupied primarily by persons who are 65 years of age or older, that is occupied or intended to be occupied by at least the prescribed number of persons who are not related to the operator of the home, and where the operator of the home makes at least two care services available, directly or indirectly, to the residents. Retirement homes are governed under the Retirement Homes Act, 2010, S.O. 2010, c. 11.
Hospitals	Any institution, building or other premises or place that is established for the purposes of the treatment of patients and that is approved under the Public Hospitals Act, R.S.O. 1990, c. P.40.
Congregate living	
Correctional facility	An institution established or continued under section 14, whether it is operated or maintained by the Ministry or by a contractor, but does not include a place of open custody, a place of secure custody, a place of temporary detention or a lock-up established under section 16.1 of the *Police Services Act*; ("établissement correctional"). Ministry of Correctional Services Act, R.S.O. 1990, c. M.22.
Shelter	A facility set up to provide for the needs of homeless people; often including temporary residence, food, sanitation and other forms of support.
Group Home/Supportive Housing	A home providing staff-supported residential accommodation in a group setting for special populations that need a supervised living environment. Common examples include children and youth in care, individuals with developmental or physical disabilities, individuals recovering from substance abuse, teenaged mothers, or victims of domestic violence.

Setting type	Definitions
Short-term accommodations	A short-term rental is all or part of a dwelling unit that is offered for accommodations for less than 28 consecutive days with or without payment. This includes but is not limited to bed and breakfasts (B&Bs), hotels and motels.
Congregate other	Other setting in which persons live in a group setting with shared amenities.
Education	
Child care	Facility that provides temporary care for or supervision of children and is operated under the Child Care and Early Years Act, 2014, S.O. 2014, c. 11.
School – Elementary	Elementary schools include a public or private school educating children in elementary (Kindergarten to Grade 8) grades
School - Elementary/Secondary	Elementary/ Secondary schools include a public or private school educating children in a combination of elementary (Kindergarten to Grade 8) and secondary (Grade 9 to 12) grades (e.g., K-12 combined).
School – Secondary	Secondary schools include a public or private school educating children in secondary (Grade 9 to 12) grades
School - Post-secondary	Educational facility offering the highest level of educational attainment including apprenticeships or trades certificate or diploma; general or vocational college, or other non-university certificate or diploma; university certificate or diploma below bachelor level; or a university degree.
Other settings	
Bar/restaurant/nightclub	A facility for socialization/entertainment where food and/or drinks may be served.

Setting type	Definitions
Medical/Health Service	A facility or business that provides health or medical services in a community or non-institutional setting. This includes but is not limited to doctors offices or clinics, wellness clinics, dental offices, and at home care.
Personal service settings	A facility that provides personal services including invasive services that is operated under the O. Reg. 136/18. (e.g. tattoo parlours, hair salons, tanning studios).
Recreational fitness	A facility that provides activities where the primary purpose of the activity is participation, with the related goals of improved physical fitness, fun, and social involvement.
Retail	A setting in which goods and/or services are sold to individual consumers for their personal use. This includes but is not limited to grocery stores, pharmacies, and shopping malls.
Culture and other recreation	A setting in which social gatherings take place, including places of worship, indoor and outdoor private events (including weddings and funerals), and other community gathering spaces.
Workplace – Construction	A workplace comprised of employees working on developing, maintaining or repairing residential and non-residential buildings, or parts within. Outbreaks and cases captured in this setting include outbreaks associated with construction worksites and may include offices related to the construction industry.
Workplace – Logistics	A workplace comprised of employees working in warehouses, transportation, shipping or postal services.
Workplace – Farm	A workplace comprised of an area of land and its buildings used for growing crops and/or rearing animals, including greenhouses.
Workplace - Food Processing	A food service establishment that is a commercial operation that processes food for human consumption, and provides processed food for sale and distribution to other business entities such as restaurants and grocery stores.
Workplace – Manufacturing	A workplace comprised of employees working at a production line, where labour and machinery are used to produce goods from raw materials and smaller components.

Setting type	Definitions
Workplace – other	Other places of employment including offices, banks, municipal services (e.g. fire station), and veterinary clinics, among others.
Unknown	Setting that cannot be classified due to missing or inadequate data.

Appendix B: Outbreaks across public health units

Table A2. Number of confirmed COVID-19 outbreaks reported between February 16, 2020 and December 26, 2020 by public health unit: Ontario

Public Health Unit Name	Abbreviation	Number of outbreaks
Algoma Public Health	ALG	2
Brant County Health Unit	BRN	45
Chatham-Kent Public Health Services	CHK	16
City of Hamilton Public Health Services	HAM	143
Durham Region Health Department	DUR	212
Eastern Ontario Health Unit	EOH	47
Grey Bruce Health Unit	GBO	14
Haldimand-Norfolk Health Unit	HDN	32
Haliburton, Kawartha, Pine Ridge District Health Unit	HKP	23
Halton Region Public Health	HAL	149
Hastings & Prince Edward Public Health	HPE	13
Huron Perth Public Health	HPH	32
Kingston, Frontenac, Lennox & Addington Public Health	KPL	26
Lambton County Public Health	LAM	25
Leeds, Grenville and Lanark District Health Unit	LGL	20
Middlesex-London Health Unit	MSL	109
Niagara Region Public Health	NIA	148
North Bay Parry Sound District Health Unit	MPS	6
Northwestern Health Unit	NWR	10
Ottawa Public Health	OTT	401

Public Health Unit Name	Abbreviation	Number of outbreaks
Peel Public Health	PEL	465
Peterborough Public Health	PTC	11
Porcupine Health Unit	PQP	11
Public Health Sudbury & District	SUD	18
Region of Waterloo Public Health and Emergency Services	WAT	192
Renfrew County and District Health Unit	REN	19
Simcoe Muskoka District Health Unit	SMD	110
Southwestern Public Health	OXE	51
Thunder Bay District Health Unit	THB	17
Timiskaming Health Unit	TSK	5
Toronto Public Health	TOR	969
Wellington-Dufferin-Guelph Public Health	WDG	114
Windsor-Essex County Health Unit	WEC	138
York Region Public Health	YRK	557

Note: Includes outbreaks that are ongoing and outbreaks that are no longer active. Geography is based on public health unit where the outbreak was declared. Not all settings were open during the reporting period due to provincial public health measures. There was one outbreak that involved cases from Ontario and outside of Ontario and was not assigned to a public health unit.
Data Source: CCM plus

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For Further Information

For more information, email cd@oahpp.ca.

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Ontario

EXHIBIT L

This is Exhibit "L" referred to
in the Affidavit of
Jacob Reaume
Sworn before me this 4th day
of July A.D., 2021
A Commissioner for Oaths in and for Ontario

NEWS RELEASE

Ontario Returning 27 Public Health Regions to Strengthened COVID-19 Response Framework

Province Extending Shutdown and Stay-at-Home Order in Regions at Highest Risk

February 12, 2021
Health

TORONTO — In consultation with the Chief Medical Officer of Health, the Ontario government is transitioning twenty-seven public health regions out of the shutdown and into a revised and strengthened *COVID-19 Response Framework: Keeping Ontario Safe and Open* (the "Framework"). The four remaining public health regions, Toronto Public Health, Peel Public Health, York Region Public Health and North Bay Parry Sound District, will remain in the shutdown, and the Stay-at-Home order and all existing public health and workplace safety measures will continue to apply to these four public health regions.

"The health and safety of Ontarians remains our number one priority. While we are cautiously and gradually transitioning some regions out of shutdown, with the risk of new variants this is not a reopening or a return to normal," said Christine Elliott, Deputy Premier and Minister of Health. "Until vaccines are widely available, It remains critical that all individuals and families continue to adhere to public health measures and stay home as much as possible to protect themselves, their loved ones and their communities."

Based on a general improvement in trends of key indicators, including lower transmission of COVID-19, improving hospital capacity, and available public health capacity to conduct rapid case and contact management, the following public health regions will be moving back to the Framework on Tuesday, February 16, 2021 at 12:01 a.m. and will no longer be subject to the Stay-at-Home order:

Grey-Lockdown:

- Niagara Region Public Health

Red-Control:

- Chatham-Kent Public Health;
- City of Hamilton Public Health Services;
- Durham Region Health Department;
- Halton Region Public Health;
- Middlesex-London Health Unit;
- Region of Waterloo Public Health and Emergency Services;
- Simcoe-Muskoka District Health Unit;
- Southwestern Public Health;
- Thunder Bay District Health Unit;
- Wellington-Dufferin Guelph Public Health; and
- Windsor-Essex County Health Unit.

Orange-Restrict:

- Brant County Health Unit;

- Eastern Ontario Health Unit;
- Haldimand-Norfolk Health Unit;
- Haliburton, Kawartha, Pine Ridge District Health Unit;
- Huron Perth Public Health;
- Lambton Public Health;
- Ottawa Public Health;
- Porcupine Health Unit; and
- Public Health Sudbury and Districts.

Yellow-Protect:

- Algoma Public Health;
- Grey Bruce Health Unit;
- Northwestern Health Unit; and
- Peterborough Public Health.

Green-Prevent:

- Leeds, Grenville and Lanark District Health Unit; and
- Timiskaming Health Unit.

For North Bay Parry Sound District, Peel Public Health, Toronto Public Health and York Region Public Health, it is proposed that the shutdown measures and the Stay-at-Home order will continue to apply until at least Monday, February 22, 2021. Please visit Ontario.ca/covidresponse for the full list of public health region classifications.

After returning to the Framework, public health regions will stay in their level for at least two weeks at which time, the government will assess the impact of public health and workplace safety measures to determine if the region should stay where they are or be moved to a different level. Public health regions will move up through the levels, if necessary, based on the set indicators and thresholds outlined in the Framework.

Visitor restrictions for long-term care homes will once again apply to those homes in the public health regions that are in the Orange-Restrict level or higher. In addition, long-term care homes must implement enhanced testing requirements.

Recognizing the risk posed by new variants to the province's pandemic response, Ontario is introducing an "emergency brake" to allow the Chief Medical Officer of Health, in consultation with the local medical officer of health, to immediately advise moving a region into Grey-Lockdown to interrupt transmission. Local medical officers of health also have the ability to issue Section 22 orders under the *Health Protection and Promotion Act*, to target specific transmission risks in the community.

"While the trends in public health indicators are heading in the right direction, we still have work to do," said Dr. David Williams, Chief Medical Officer of Health. "Everyone is strongly advised to continue staying at home, avoid social gatherings, only travel between regions for essential purposes, and limit close contacts to your household or those you live with."

The Chief Medical Officer of Health will continue to consult with public health and other experts, review data, and provide advice to the government on the appropriate and effective measures that are needed to protect the health of Ontarians.

Quick Facts

- Find out what level and which regional public measures are in place for your area.
- On February 10, 2021, Hastings Prince Edward Public Health, Kingston, Frontenac and Lennox & Addington Public Health, and Renfrew County and District Health Unit moved to the Framework at the Green-Prevent level.

- To help stop the spread of COVID-19 and safeguard health system capacity, Ontarians are strongly urged to continue staying at home and limit trips outside their household and between other regions for essential reasons only, not to gather with individuals outside of their household, and to wear a face covering when within two metres distance of another individual who is not part of their household (both indoor and outdoor) or when required, with limited exceptions.
- Ontario has implemented a six-point plan to deal with the new variants of concern which includes mandatory on-arrival testing of international travelers, enhanced screening and sequencing, maintaining public health measures to keep people safe, strengthening case and contact management to track the spread of new cases, enhanced protections for vulnerable populations, and leveraging the latest data to inform public health decisions.
- To support the province's economic recovery, the government has updated the Framework to allow for a safer approach to retail. Limited in-person shopping in Grey-Lockdown zones will be permitted with public health and safety measures, such as limiting capacity to 25 per cent in most retail settings.
- Digital tools have been an important part of the provincial response to COVID-19. To date, almost 6 million self-assessments have been completed using Ontario's health screening tool to help Ontarians navigate their symptoms and decide on next steps. Now, revised and updated screening tools for workers/employees and customer/visitors will help keep Ontarians safe and healthy by pre-screening for symptoms before leaving for work or to visit a business as the province re-opens. The tools help workplaces and businesses meet screening requirements.
- To support the safe return of in-person learning, Ontario has introduced new measures to continue to protect students and staff against COVID-19 in the classroom.

Additional Resources

- Ontario Extending Stay-at-Home Order across Most of the Province to Save Lives.
- Find out about the latest public health measures, advice and restrictions.
- To find the right supports, visit COVID-19: Support for People, which has information about the many available and free mental health services and supports.
- Get tested if you have COVID-19 symptoms, or if you have been advised of exposure by your local public health unit or through the COVID Alert App. Visit Ontario.ca/covidtest to find the nearest testing location.
- Visit Ontario's COVID-19 vaccine web page to view the latest provincial data and information on COVID-19 vaccines.
- Visit Ontario's COVID-19 information website to learn more about how the province continues to protect the people of Ontario from the virus.

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A Commissioner for Oaths in and for Ontario

NEWS RELEASE

Ontario Moving Three Regions to New Levels in the COVID-19 Response Framework

Province also adjusting capacity limits for some events in Grey-Lockdown

March 12, 2021
Health

TORONTO — On the advice of the Chief Medical Officer of Health, the Ontario government is moving three public health regions to new levels in the revised and strengthened *Keeping Ontario Safe and Open Framework*, including moving Lambton Public Health into Grey-Lockdown. Decisions were made in consultation with the local medical officers of health and are based on the trends in public health indicators and local context and conditions.

"The latest modelling suggests we are at a critical stage in our fight against this devastating virus, and that the actions we take now will help ensure people stay safe," said Christine Elliott, Deputy Premier and Minister of Health. "As we near completion of Phase One and prepare to rollout Phase Two of our vaccine distribution plan next month, we urge everyone to continue following all public health measures and advice to help prevent further transmission and protect our health system capacity."

Based on the latest data, the following three public health regions will be moving from their current level in the Framework to the following levels effective Monday, March 15, 2021 at 12:01 a.m.:

Grey-Lockdown

- Lambton Public Health

Red-Control

- Northwestern Health Unit

Yellow-Protect

- Leeds, Grenville and Lanark District Health Unit.

In addition, effective today at 12:01 a.m., the government, on the advice of the Chief Medical Officer of Health, activated an "emergency brake" in the Public Health Sudbury and Districts region, moving it to the Grey-Lockdown level. The decision was made due to the concerning trends in public health indicators and in consultation with the local medical officer of health.

Please visit Ontario.ca/covidresponse for the full list of public health region classifications.

On the advice of the Chief Medical Officer of Health, the province is also adjusting capacity limits for weddings, funerals, and religious services, rites or ceremonies held in regions currently in the Grey-Lockdown level of the Framework. Effective Monday, March 15, 2021 at 12:01 a.m., weddings, funerals, and religious services, rites or ceremonies will be permitted to allow for up to 15 per cent total occupancy indoors, or up to 50 people outdoors.

"While the data shows that Ontario's vaccine rollout is helping to save lives, the next few months are critical" said Dr. David Williams, Chief Medical Officer of Health. "We all must remain vigilant and continue following public health advice and measures to prevent transmission, as variants of concern are continuing to become more prevalent throughout the province and threaten to undue all of the positive gains we have all worked so hard to achieve."

The Chief Medical Officer of Health will continue to consult with public health and other experts, review data, and provide advice to the government on the appropriate and effective measures that are needed to protect the health of Ontarians.

Quick Facts

- Find out what level and which public health and workplace safety measures are in place for your area.
- From March 3 to 9, 2021, Lambton Public Health's case rate increased by 30.9 per cent, to 110.0 cases per 100,000 people, well above the provincial average. During the same period of time, the number of COVID-19 hospitalizations in the region have increased by 33.3 per cent.
- Based on the latest modelling data, Ontario's vaccine rollout is making a positive difference and helping to save the lives of some of our most vulnerable, however, the rate of decline in the number of new cases and positivity rates are showing signs of slowing down. As variants of concern continue to spread throughout the province, the number of patients requiring hospitalization and intensive care will likely rise once again if public health measures are not followed by all Ontarians.
- To help stop the spread of COVID-19 and safeguard health system capacity, everyone is strongly urged to continue staying at home and limit trips outside their household and to other regions for essential purposes only, and not to gather with individuals outside of their household. In addition, people are required to wear a face covering when within two metres distance of another individual who is not part of their household (both indoor and outdoor), with limited exceptions.
- Local medical officers of health continue to have the ability to issue Section 22 orders under the Health Protection and Promotion Act, and municipalities may enact by-laws, to target specific transmission risks in the community.
- Healthy people are essential for a healthy economy. On March 24, 2021, the government will release the 2021 Ontario Budget. It will focus on protecting people's health, with a plan to defeat COVID-19, and provide support for people and jobs.

Additional Resources

- Toronto, Peel and North Bay-Parry Sound Public Health Regions Returning to Strengthened COVID-19 Response Framework
- Refer to the Ministry of Health's COVID-19 Advice: Religious Services, Rites or Ceremonies for advice on the delivery or provision of a religious service, rite or ceremony.
- To find the right supports, visit COVID-19: Support for People, which has information about the many available and free mental health services and supports.
- Get tested if you have COVID-19 symptoms, or if you have been advised of exposure by your local public health unit or through the COVID Alert App. Visit Ontario.ca/covidtest to find the nearest testing location.
- Visit Ontario's COVID-19 vaccine web page to view the latest provincial data and information on COVID-19 vaccines.
- Visit Ontario's COVID-19 information website to learn more about how the province continues to protect the people of Ontario from the virus.

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BREAKING

Ontario's COVID-19 positivity rate drops as province records more than 1,500 cases, 58 deaths

TORONTO | NEWS

Rod Phillips resigns as Ontario finance minister following secret pandemic getaway

Chris Herhalt
Web Content Writer, CP24
@_Herhalt | Contact

Published Thursday, December 31, 2020 8:25AM EST
Last Updated Thursday, December 31, 2020 7:00PM EST

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TORONTO -- Ontario Finance Minister Rod Phillips has resigned from his key role in cabinet over his secret vacation to a luxurious Caribbean island as the COVID-19 pandemic ran rampant in the province.

"Today, following my conversation with Rod Phillips, I have accepted his resignation as Ontario's Minister of Finance," Ontario Premier Doug Ford said in a statement.

"At a time when the people of Ontario have sacrificed so much, today's resignation is a demonstration that our government takes seriously our obligation to hold ourselves to a higher standard," he said.

Related Stories

- **Ford admits he knew of Ontario finance minister's vacation two weeks ago, regrets not asking him to return**
- **Ontario's finance minister apologizes after leaving country for personal trip earlier this month**

The Ajax MPP left for St. Barts, a tiny, 10,000-inhabitant island known as a hideaway for yachts and boutique luxury hotels, on Dec. 13, calling the decision a "dumb, dumb mistake."

"It was a significant error in judgment – a dumb, dumb mistake, I apologize for it, I regret it," he told CP24's Steve Ryan at Pearson International Airport upon his return on Thursday morning.

He said that he could not really explain why he went ahead with the trip at the time that he did.

“I have been asking myself that same thing over the last number of days,” he said

With his departure, Treasury Board President Peter Bethlenfalvy has been tapped to assume the role of minister of finance in addition to his existing duties.

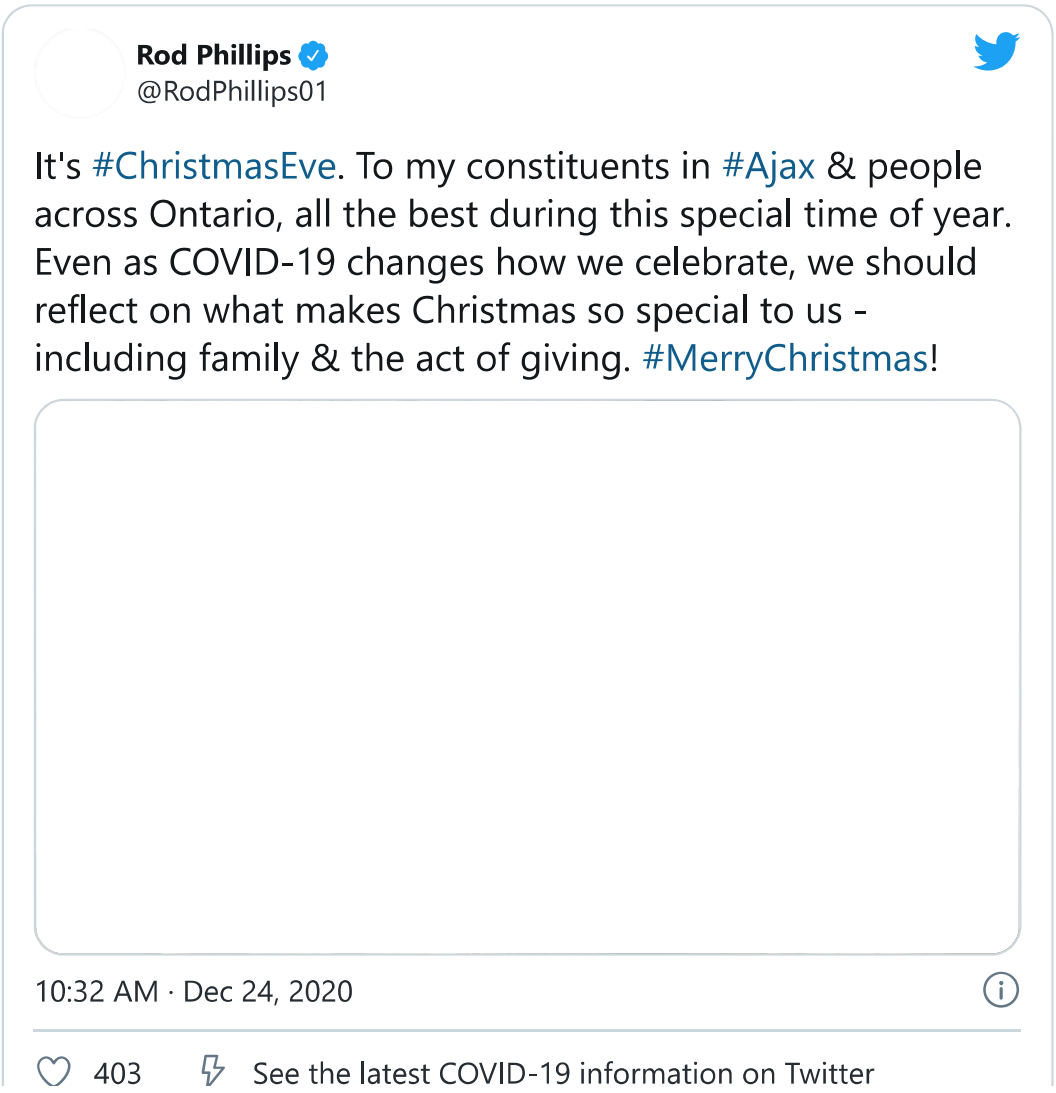
He will be the Ford government's third finance minister in as many years.

"I know that important work will continue and I wish Minister Bethlenfalvy all the best as he takes on this additional responsibility," Phillips said in a statement released after his resignation was made public.

"I would like to thank my family, political staff and the officials at the Ministry of Finance."

His office released a plethora of tweets and Instagram posts during the time he was away, including one where he sat next to a gingerbread house and a glass of eggnog and thanked healthcare workers dealing with packed hospitals, as “we all make sacrifices this Christmas.”

Many of the posts made it appear as if he was in his riding when he was not.



Phillips said it was not his intention to deceive anyone about the trip when he sent the videos, tweets and Instagram posts.

"I understand why some people believe that is the case but it is not – many politicians, in fact most politicians pre-plan and pre-load messages on social media," he said.

But he said the messages may have made it look that way given where he was and he knows the public is upset.

"I do understand that I have angered many people – I have to work to regain their confidence."

In a Zoom call Phillips participated in while he was away, first pointed out by the Ontario Liberal Party, the sound of the ocean tide crashing into the beach can be heard when he unmuted himself to speak.

Ontario Liberal Party | Parti Libéral de l'Ontario
@OntLiberal

.@RodPhillips01 are those waves we hear behind your Queen's Park Zoom background? This is disgraceful, and Ford knew about it for two weeks.
#onpoli

Date: Dec. 16, 2020

Ontario's two top public health officials both expressed concerns about foreign travel at the time he departed for the vacation.

The federal government has also been warning Canadians not to embark on non-essential travel since early November.

Ford said Wednesday he wasn't told about the trip ahead of time, but did learn about it shortly after it began, and should have demanded Phillips return immediately.

Phillips said that he didn't tell Ford about the trip because the Premier has better things to do.

"Premier Ford has far more important things to do than worry about the travel of his ministers," he said.

Ford has said it's "unacceptable" for any public official to ignore the province's COVID-19 guidelines, which urge residents to avoid non-essential travel.

Phillips said earlier this week he chose to go ahead with the trip not knowing the province would be placed under lockdown on Boxing Day.

In an interview with CP24 on Thursday afternoon, Liberal Leader Steven Del Duca said that the incident is yet another example of the Ford government failing to "lead by example."

"He clearly undermined the confidence that the people of Ontario had in him but there is a much bigger question for me and I think for everyone living in this province and that is the fact that Doug Ford has not held himself and his members of caucus and cabinet to the same level of accountability, not just in this case but all the way through this pandemic," he said.

"From Doug Ford going up to his cottage when he told the people of Ontario not to, him celebrating Mother's Day with his family when he told the rest of us not to, his MPP Sam Oosterhoff from Niagara gathering without proper physical distancing and boasting about it on social media and now Rod Phillips."

Ontario NDP leader Andrea Horwath also released a statement on Thursday in which she pointed out that Ford "knew about Rod Phillips' trip to St. Barts two weeks ago."

She said than rather than asking for Phillips resignation then, Ford "helped him keep the trip a secret."

"Phillips' resignation from cabinet today is not because of Phillips' vacation, it's because they got caught," she said.

Phillips will remain in the Progressive Conservative caucus as the MPP for Ajax.

His salary will decline from $165,450 to $116,500.

He will now self-isolate until Jan. 13.

RELATED IMAGES

Ontario Finance Minister Rod Phillips looks on as he delivers baked goods and coffee to frontline health wor at Humber River Hospital ahead of the Ontario budget during the COVID-19 pandemic in Toronto on Thursc November 5, 2020. THE CANADIAN PRESS/Nathan Denette

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NEWS INSIDERS

Hospital CEO resigns from Ontario COVID-19 advisory table after holiday trip to Dominican Republic

BY NEWS STAFF

Posted Jan 5, 2021 10:01 pm EST Last Updated Jan 6, 2021 at 5:54 am EST

CEO of St. Joseph's Health System Dr. Tom Stewart. Photo credit: https://sjhs.ca/

The CEO of St. Joseph's Health System and Niagara Health, Dr. Tom Stewart, has resigned from Ontario's COVID-19 advisory board after travelling to the Dominican Republic over the holidays.

A statement from the Senior Vice President of St. Joseph's Brian Guest said Stewart had been approved for vacation from Dec. 18 and Jan. 5 and during that time, he travelled to the Dominican Republic.

Stewart said he "regret[s]" this non-essential travel and apologized. "I recognize everyone should be avoiding non-essential travel now, including me."

> "As a health system leader, my actions in no way reflect the tireless dedication and commitment of the staff at St. Joseph's Health System, who continue to live the legacy of our organization every day," said Stewart in the statement.

He is currently self-isolating at home for two weeks.

St. Joseph's Health System is made up of several different health sites in Niagara, Hamilton, Brantford, Kitchener & Guelph.

RELATED: Here's a list of politicians who travelled abroad despite pandemic era advice to stay home (https://www.680news.com/2021/01/03/heres-a-list-of-politicians-who-travelled-abroad-despite-pandemic-era-advice-to-stay-home/)

Deputy Minister of Health Helen Angus release a statement late Tuesday night saying she had accepted his resignation from the Ontario COVID-19 Science Advisory Table, the LTC Incident Management System Table and the Health Coordination Table,.

> "The people of Ontario have made countless sacrifices during the pandemic and it remains critically important that everyone continues to follow public health advice," read the statement.

In March, the Ministry of Health welcomed Stewart to the government's Command Table that was set up to provide strategic direction to the province about the novel coronavirus outbreak.

A number of politicians have recently admitted to leaving the country over the December holiday period, even as their constituents adhered to public health guidance meant to curb the spread of COVID-19, including Ontario Finance Minister Rod Phillips who has since resigned from his role.

The federal and provincial government have both repeatedly asked Canadians not to travel abroad during the pandemic and urged citizens to avoid gathering with family outside their household over the holidays.

Earlier Tuesday, Prime Minister Justin Trudeau expressed disappointment in federal and provincial politicians who have travelled abroad, despite months of recommendations against non-essential travel.

With files from The Canadian Press

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KITCHENER | News

Crew set to film Christmas movie in downtown Kitchener this week

CTVNewsKitchener.ca
Staff
@CTVKitchener | Contact

Published Monday, January 18, 2021 9:37AM EST

Christmas decorations adorn a tree in Ottawa in a Dec.14, 2014 file photo. (Adrian Wyld/THE CANADIAN PRESS)

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KITCHENER -- Downtown Kitchener is getting a temporary festive makeover as a Canadian film crew arrives to shoot a movie.

Crews will start shooting "Loving Christmas" on Monday at the corner of King and Queen streets. The shoot is expected to continue through Friday.

The city said that it expects minimal disruption for residents and businesses in the area. On Monday, for example, the sidewalk closest to Queen Street will be closed.

Related Stories

- **Tom Cruise rants at 'Mission: Impossible' crew in London over COVID-19 safety**
- **'Best wishes, warmest regards': Ont. motel featured in 'Schitt's Creek' up for sale**
- **Late night hosts return to filming their shows remotely due to surging COVID-19 cases**

Under its stay-at-home order, the provincial government allows film and television production to go ahead, the city said in a news release.

Crew members must follow certain COVID-19 safety guidelines, which the city said were developed by the Ontario Ministry of Health and the film industry.

Some of these measures include having an on-site COVID-19 officer, daily testing, enhanced cleaning, the use of masks and physical distancing on sets and medical-grade air purification systems when working indoors.

The province stopped both film and television production in Ontario for several months last year as it worked to get the first wave of the pandemic under control.

The Ontario government allowed those activities to restart on June 12.

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KITCHENER | News

Wilmot Township anti-racism rally in response to 'White Lives Matter' march sees no opposition

Heather Senoran
CTV News Kitchener Videographer
@HeatherSenoran | Contact

Published Saturday, May 8, 2021 7:16PM EDT

02:11 / 02:11

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BADEN -- Despite being organized in response to an anticipated "White Lives Matter" march, an anti-racism rally in Wilmot Township saw no opposition on Saturday.

Roughly 50 people could be seen at Castle Kilbride around noon with signs that displayed inclusive and anti-racism messages.

Aashay Dalvi, an organizer the rally, was met with a different message at the very same location a year ago.

Related Stories

- **Anti-racism rally planned in Wilmot Township amid posters promoting 'White Lives Matter' parade**

"They told me I need to go back to my country," said Dalvi. "Told me I look like a monkey."

Dalvi and others planned the rally after a poster circulated in Wilmot Township promoting a "White Lives Matter" march scheduled for May 8.

"Oppression continues to exist," said Dalvi. "The posters are evident of that."

Karen Redman, the chair of the Region of Waterloo, says the timing for any kind of in-person gathering isn't right.

"This is during a stay-at-home order," she said. "We still see a lot of COVID-19 being spread in the community, so that's a huge concern."

Organizers of the rally say there were volunteers going around to make sure everyone was properly spaced. There was also a PPE table out for anyone who needed it.

"White supremacy is a public health crisis," said Dalvi. "It is time we recognized it as it is."

Some at the rally say it was worth it to show up despite the current COVID-19 restrictions.

"As white people we need to recognize that and stop it out," one protester tells CTV News.

Redman acknowledges that racism exists in the region, and pointed to the anti-racism advisory committee meant to combat systemic racism.

"It has been community led and continues to inform both policies and practices within the region," she said.

Waterloo regional police were on site of the rally to monitor and ensure public safety and say that they will work with bylaw on potential charges under the reopening Ontario act.

Police add that the hate crime team is still working to find the people behind the posters.

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Vigil held to honour 215 Indigenous children found at former residential school

a[illegible]ut 14 hours ago By: Aastha Shetty

1 / 3 The sound of drumming filled Victoria Park on Thursday evening during the vigil for the 215 children whose remains were recovered in a mass grave site at Kamloops Residential School. | Aastha Shetty / Kitchener Today

A deep rumble from the drum circle vibrated through Victoria Park Thursday, as people hummed and chanted in memory of the 215 Indigenous children whose remains were recovered at Kamloops Residential School.

Those children -- lost for years, were finally found last month, buried in a mass grave at the residential school.

The pain of the tragedy continues to ripple through the local Indigenous community, who placed pairs of shoes around the clock tower to help people visualize the severity of the finding. Attendees also placed toys and candles.

"We need people to know the magnitude of the situation," said organizer of the vigil, Jack Skye Forler.

"We are still facing ignorance, we are still facing discrimination, our communities are still being marginalized and this is the time everyone is starting to listen," they said. "We just need people to listen."

Forler said allies can help by lowering their flags, amplifying Indigenous voices and calling on the government to thoroughly search every residential property for mass grave sites.

"There are so many countless children who have perished in these schools and nobody knows where they are. Families were never notified. They never came home. It's completely obvious to us that there are these mass grave sites scattered across Turtle Island. So it's important to us that we bring these children home."

With deep emotion in their voice, Forler added they are speaking out for children who can't anymore -- and they want to tell all the children who have not been found yet that they are loved.

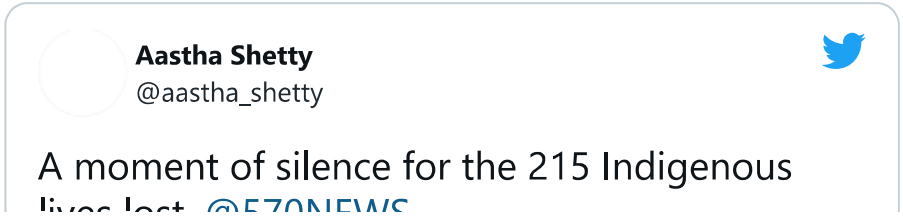
"It's emotional because I am sitting here and I am allowed to embrace my culture and I am allowed to grow my hair and I am allowed to be alive. But those children did not have the same fate as I did," they said.

"It's important that we get the message out and that people understand where we are coming from and understand the magnitude of the situation."

They noted Kitchener bylaw had contacted organizers in advance to inform them that bylaw officers will not be attending the event.

"As far as I am aware, we will not be worrying about tickets, but I do have a GoFundMe set in place if tickets do become a problem."

More than a hundred people were seen attending the vigil on Thursday.



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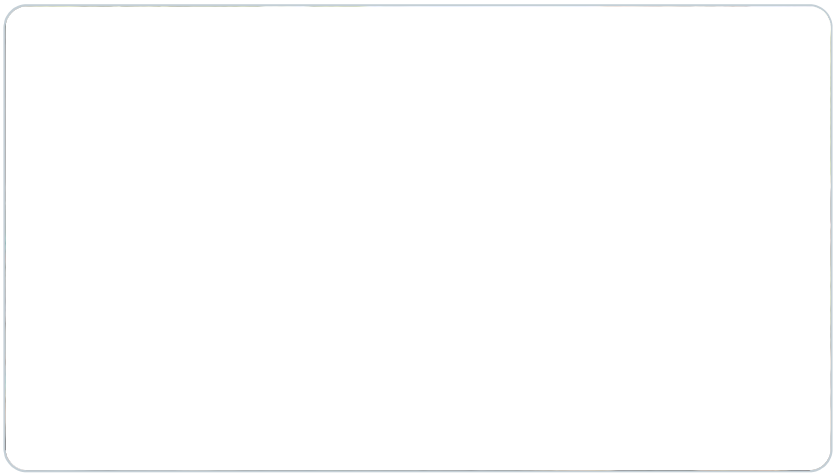

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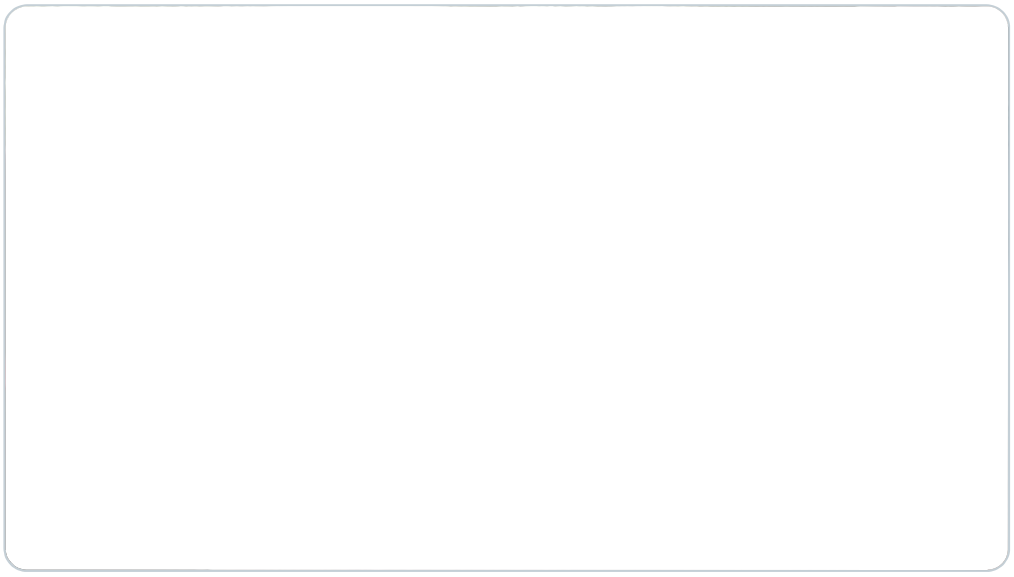
@aastha_shetty

Drummers tighten their circle for a softer chant. Many, many people listen. Some can't help swaying to the beat. @570NEWS



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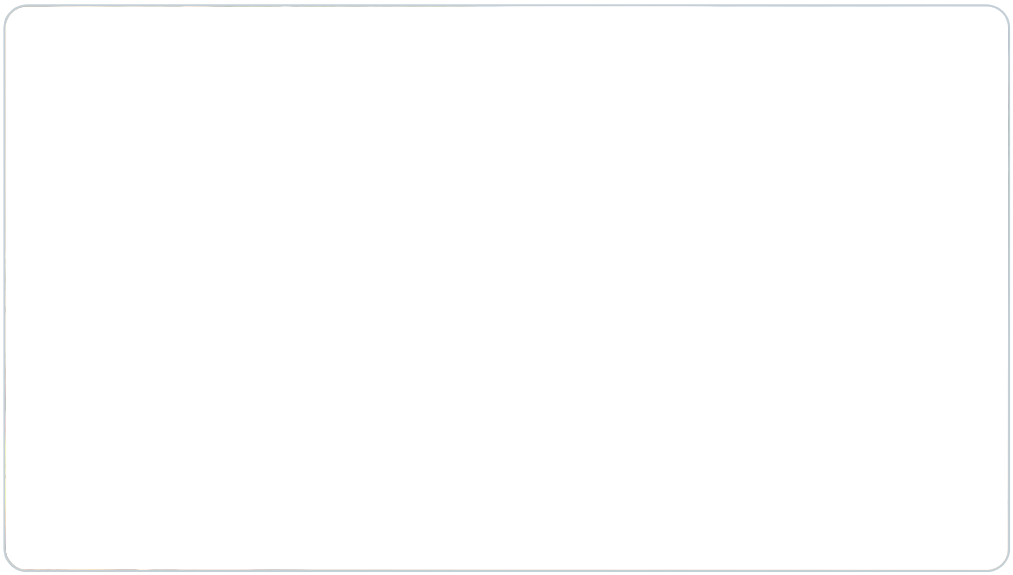
Jack says the Indigenous community wants the Canadian government to search every single residential school on Turtle Island for lost children. The crowd cheers.@570NEWS



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Comments (3)

We welcome your feedback and encourage you to share your thoughts. We ask that you be respectful of others and their points of view, refrain from personal attacks and stay on topic. To learn about our commenting policies and how we moderate, please read our Community Guidelines.

AM alex moi about 7 hours ago

censorship on a full swing? no more freedom of speech?

JH jojo hansen about 6 hours ago

you read this article.. and that was your takeaway.. ok alex.

GH Greasy Hair about 5 hours ago

The Pope needs to say a few things...

JM Jebby Mongo about 5 hours ago

Great coverage, such a sad story. Thank you Aastha Shetty.

About the Author: Aastha Shetty

Read more

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EXHIBIT V

This is Exhibit "V" referred to
in the Affidavit of
Jacob Beaune
Sworn before me this 4th day
of June A.D., 2021
A Commissioner for Oaths in and for Ontario

TRINITY BIBLE CHAPEL IS OPEN SUNDAY (DV): YOU'RE INVITED!

By Jacob Reaume | January 22, 2021 | Tagged: *covid-19*

Dear Neighbours and fellow Ontarians:

I hereby cordially invite you to learn of the good news of Jesus Christ and experience the joy of Christian worship. We are opening the doors of Trinity Bible Chapel this Sunday when we will hold in-person Lord's Day services at both 9:00 AM and 11:15 AM.

Ten months have passed since our provincial government called us to shutdown our regular lives for fourteen days to flatten the curve. Since that time, officials and media have provided regular updates on case and death counts. As of today, 98.03% of Canadians have not tested positive for COVID-19 and more than 99.9499% of Canadians have not died of COVID-19.

While I see every death as tragic, I believe that life is much greater than avoiding a virus. We will never get this time back, and we are not guaranteed tomorrow. The focus on mitigating the risk of spreading this contagion has now superseded nearly every aspect of our lives. Commerce has slowed almost to a halt. Childhood education has been compromised. Families are forbidden from visiting each other. Weddings and funerals are impeded. Most importantly, as I pointed out in an earlier blog, the Christian Church is forbidden to exist in its most basic essence which is as a gathering.

People are lonely, afraid, despairing of life itself, and facing financial ruin, among many other deprivations and tribulations. This is all during the darkest and coldest season of the year. If ever our fellow Ontarians needed hope, it is now. Out of neighbourly love, I am personally openly inviting anyone and everyone to experience the hope of the Gospel and the warmth of Christian worship at Trinity Bible Chapel this Sunday during our two Lord's Day services at 9:00 AM and 11:15 AM.

I understand that some will libel me as selfish and unneighbourly for making this offer. Please note that as a disciple of Jesus Christ I am fully committed to both the Golden Rule and Christ's second greatest commandment: "So whatever you wish that others would do to you, do also to them, for this is the Law and the Prophets" (Matthew 7:12) and "You shall love your neighbour as yourself" (Matthew 22:39). Even as I am committed to obeying those commandments in faith, I am also committed to applying them in a way consistent with the teachings of Jesus.

Jesus visited the sick and lonely because He loves them. Jesus asks us to welcome the destitute because He is full of mercy. Jesus taught us to show hospitality to our neighbours because people need our presence. Jesus desires for us to gather together for worship because the church is a gathering. Jesus commands us to be together because He became a man to be with us. Not once did Jesus ever tell us to love our neighbours with saying, "Stay home. Stay safe." In fact, He completed His earthly ministry by commissioning His disciples to go into all the nations to teach people His way of mercy and love (Matthew 28:18-20). He did this amidst the scorn of effete and sanctimonious Pharisees who libeled Him and demanded His crucifixion in part for spending time with unclean sinners. Jesus commanded us to love our neighbours, and Jesus has sufficiently taught us how to love our neighbours by His Word and example.

Risking reputation and financial viability to offer eternal hope and warm Christian fellowship to a world in despair is an act of love that I am certain Jesus smiles on.

Some have suggested that the church is not being specifically targeted by our government, and therefore we must set aside Christ's command to meet for the sake of obeying the government's command not to meet. Do people not gather at *Walmart*, at *Costco*, on movie sets, and at the *Beer Store*? Is the mission of the church not more important than a bottle of whiskey at the *LCBO* or a bag of *Cheetos* at the *Dollar Store*, both entities being deemed "essential" while the church is deemed "unessential"? How can one say the church is not targeted when these establishments are full of people? In Daniel's time, King Darius decreed to "establish an ordinance and enforce an injunction" (Daniel 6:7) to cease public worship, irrespective of creed. Daniel openly and publicly resisted Darius under threat of being fed to lions (Daniel 6:10). In the end God vindicated Daniel (Daniel 6:25-28). Persecution by the state is generally not specifically targeted on Christians, but rather it targets those who dissent from state dogma. Christians have often found themselves under the ire of overreaching states, not because they are singled out, but rather because their allegiance to God transcends state doctrine. Nowhere does Scripture actually say Christians should only resist the state's imposition upon the church if the state is specifically targeting them. Rather, we have historically resisted when the state forbids what God commands or commands what God forbids. In this case, the state has forbidden the church from existing because the church is not less than a gathering. Obedience to God over the state is necessary.

Some are very much in line with that thinking, but they wonder when such resistance is necessary. Should it not only occur after a specific timeframe? We have now been under some type of government restrictions for ten months. Christ's public earthly ministry lasted roughly three years. We have been impeded by our government from fully discharging our duties for ten months now, almost one third of the time Christ spent publicly ministering to the crowds and to His disciples. I contend that that is far too long. I further contend that our government's timeline and our government's objectives in this effort can no longer be trusted. They regularly change deadlines of lockdowns ending even as they regularly change goals. "Hope deferred makes the heart sick, but a

desire fulfilled is a tree of life" (Proverbs 12:12). How many deadlines have they now missed since this all began? Eventually one needs to ask whether he can be considered reasonable and wise to continue believing their promises. The acceptable timeframe for compliance has come and gone.

Trinity Bible Chapel exists to glorify God by fulfilling the great commission in the spirit of the great commandment. The great commission to go into the whole world with His Gospel is in full effect and has not been put on hiatus by this lockdown. The great commandment to love our neighbours must be upheld. I am choosing to love our neighbours and fellow Ontarians by inviting whoever reads this to church Sunday. To the lonely, to the downcast, to the impoverished, to the hopeless, to the downtrodden. To the Christians wanting to worship. To the curious who wonder what the big deal is. To the skeptic who would like to see a smile. Do you need to be around people? Do you need to have your spirits lifted? Do you need help? Do you need hope? Do you need encouragement? Would you like some light in the darkness? We as a church are eager to serve you.

We have, since our founding, provided an essential service to our members and to our community. We intend to continue to proclaim in word and deed the mercy of our Saviour, the forgiveness of sins by the cross, and the hope of eternal life in Christ to a broken world. Please come. Please be welcomed. Please have hope. Please know that you are loved.

Sincerely,

Pastor Jacob B. Reaume

Sr. Pastor of Trinity Bible Chapel

P.S. Our Risk Mitigation Strategy to help prevent the spread of contagion will be in effect.

EXHIBIT W

This is Exhibit "W" referred to
in the Affidavit of
Jacob Reaume

Sworn before me this 4th day
of June A.D., 2021

A Commissioner for Oaths in and for Ontario

THE CONSTITUTION OF TRINITY BIBLE CHAPEL

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ARTICLE I: PURPOSE

The object of Trinity Bible Chapel ("TBC"), as set out in its Letters Patent, is to advance and teach the religious tenets, doctrines, observances and culture associated with the Christian faith. Specifically, the purpose and mission of TBC is to glorify God through the fulfillment of the Great Commission in the spirit of the Great Commandment (Matthew 28:19-20; Matthew 22:37-39).

ARTICLE II: PILLARS

At the outset of Trinity Bible Chapel, four pillars were established as the biblical priorities for this ministry.

1. Proclaiming the authority of God's Word without apology (Hebrews 4:12; 2 Timothy 4:1-5).
2. Lifting high the name of Jesus Christ in worship (John 12:32; 4:23, 24).
3. Believing firmly in the power of prayer (Ephesians 6:18; James 5:16; Jeremiah 33:3).

4. Sharing the good news of Jesus Christ with boldness (Ephesians 6:19-20; Romans 1:16; Matthew 9:36-38).

ARTICLE III: DOCTRINAL STATEMENT

THE SCRIPTURES

We believe the sixty-six books of the Old and New Testaments to be the full record of God's self-disclosure to mankind. Different men, while writing according to their own styles and personalities, were supernaturally moved along by the Holy Spirit to record God's very words, inerrant in the original writings. Therefore, those applying themselves to study its literal, historical-grammatical context can accurately understand God's Word. Scripture is fully trustworthy as our final and sufficient authority for all of life (2 Timothy 3:16-17; 2 Peter 1:20-21).

THE TRIUNE GOD

We believe in the one living and true God, eternally existing in perfect unity as three equally and fully divine Persons: the Father, the Son, and the Holy Spirit. Each member of the Godhead, while executing distinct but complementary roles in redemptive history, has precisely the same nature, attributes, and being, and is equally worthy of the same glory and honor and obedience (John 17:3; Matthew 28:19-20; John 1:1-4; Acts 5:3-4).

GOD THE FATHER

We believe God the Father created all things in six literal days for His glory according to His own will, through His Son, Jesus Christ. He upholds all things by the Word of His power and grace, exercising sovereign headship over all creation, providence, and redemption (Revelation 4:11; Colossians 1:17, Hebrews 1:1-3).

GOD THE SON

We believe that Jesus Christ, the eternal Son of God, moved by love in accordance with the will of the Father, took on human flesh. Conceived through the miraculous work of the Holy Spirit, He was born of the virgin Mary. He, being fully God and fully man, lived a sinless life and sacrificially shed His blood and died on the cross in our place accomplishing redemption for all who place their faith in Him. He arose visibly and bodily from the dead three days later and ascended into heaven, where, at the Father's right hand, He is now Head of His Body the Church, the only Savior and Mediator between God and man, and will return to earth in power and glory to consummate His redemptive mission (John 1:1, 14, 18; John 14:8-9; 1 Timothy 3:16; Acts 1:3, 9; Hebrews 7:25-26; 1 John 2:1).

GOD THE HOLY SPIRIT

We believe that the Holy Spirit, in all that He does, glorifies the Lord Jesus Christ during this age. He convicts the world of sin, righteousness, and judgment. He draws the unredeemed to repentance and faith, and at salvation imparts new spiritual life to the believer, bringing that person into union

with Christ and the Body of Christ. The Holy Spirit sanctifies, seals, fills, guides, instructs, comforts, equips, empowers, permanently indwells at salvation, and bestows spiritual gifts to the believer for Christ-like living and service (John 16:8; 13:15; Titus 3:5; Ephesians 1:22; 4:11-12; Romans 8:9-17; 12:4-8; 1 Corinthians 3:16; 12:4-5, 11-13, 19; Galatians 5:25; Hebrews 2:1-4; 2 Corinthians 12:12).

MANKIND

We believe that God created mankind—male and female—in His own image and likeness, free of sin, to glorify Himself and enjoy His fellowship. Tempted by Satan but in the sovereign plan of God, man freely chose to disobey God, bringing sin, death and condemnation to all mankind. All human beings therefore, are totally depraved sinners by nature and by choice. Alienated from God without defense or excuse and subject to God's righteous wrath, all of mankind is in desperate need of the Savior (Genesis 3:1-6; Romans 3:10-19; Romans 1:18, 32).

SALVATION

We believe that the Lord Jesus Christ died for our sins according to the Scriptures, as the substitutionary atonement in our place, and that salvation is found in none other than Jesus Christ. Before Creation, God chose those who would be saved and granted this unearned grace solely based on His sovereign good pleasure. Jesus Christ's death on the cross was the sole and complete payment for sins, fully satisfying God's righteous wrath, for each person that turns from sin in repentance and places his or her faith in Christ alone by grace alone. At salvation each person is made a new creation by the Holy Spirit, declared righteous before God, and secured as an adopted child of God forever. Genuine faith continues in obedience and love for Jesus Christ with a life eager to glorify God and persevere to the end (Romans 8:37-39; 2 Corinthians 5:17, 21; 1 John 2:4-6; Philippians 1:6; 1 Thessalonians 5:23-24).

THE CHURCH

We believe that upon placing one's faith in the Lord Jesus Christ as Savior, the believer is made part of the Body of Christ, the one universal Church, of which Jesus Christ is the Head. The Scriptures command believers to gather locally in order to devote themselves to worship, prayer, teaching of the Word, fellowship, the ordinances of baptism and communion, service to the local body through the development and use of talents and spiritual gifts, and outreach to the world to make disciples. Wherever God's people meet regularly in obedience to this command, there is the local expression of the Church under the watchful care of a plurality of elders. A church's members are to work together in love and unity, intent on the ultimate purpose of glorifying Christ (Ephesians 1:22-23; Acts 2:42-46; 1 Corinthians 14:26; Matthew 28:18-20; Ephesians 4:16).

BAPTISM AND COMMUNION

We believe Christian baptism is the immersion of a believer in water in the name of the Father, the Son and the Holy Spirit. It is an act of obedience and symbolizes the believer's faith in the crucified, buried and risen Saviour, the believer's death to sin, burial of the old life, and resurrection to walk in newness of life in Christ Jesus. It is a public testimony to the believer's faith in the final resurrection of the dead.

The Lord's Supper is the united commemoration, by believers, of Christ's death until He comes and should be preceded by a careful self-examination (Acts 2:41; Romans 6:3-6; 1 Corinthians 11:20-29).

MISSIONS

We believe it is the aim, duty, and privilege of every believer and local church fellowship to glorify God by responding as active participants in the Great Commission call of Jesus Christ to go and make disciples of all nations. We believe the primary focus and priority of this call is centered on efforts that establish, strengthen, and reproduce biblically-based churches, which will then plant churches that plant churches for future generations and God's glory (Matthew 28: 18-20).

THE INTERMEDIATE STATE

At death the soul separates from the body. Believers' souls pass into the conscious blissful presence of God until the resurrection when they will be reunited with their bodies to inherit their eternal reward. Unbelievers' souls pass into a state of conscious punishment until they are reunited with their bodies to face the final judgment (2 Corinthians 5:6-8; Philippians 1:23; 1 Thessalonians 4:13-18; Luke 23:43; Luke 16:24-26).

THINGS TO COME

We believe in and expectantly await the glorious, visible and personal return of the Lord Jesus Christ. The blessed hope of His return has vital bearing on the personal life, service, and mission of the believer. We believe in the bodily resurrection of both the saved and the lost. The lost will be raised to judgment and consciously experience eternal wrath in the lake of fire. The saved will be raised to eternal joy in the new heaven and new earth in the manifested presence of God (1 Thessalonians 4:13-18; Acts 1:3, 9; Hebrews 7:25-26; Revelation 20:11-15; Revelation 21).

ARTICLE IV: CHRISTIAN LIVING

SECTION 1 – CONCERNING CONDUCT

The Bible teaches that all believers are saints, set apart unto God and are thus called to live godly, obedient lives honoring Christ in all they do. As well they are responsible to live in such a manner as not to bring reproach upon their Saviour and Lord (Romans 12:1-2; 1 Peter 1:14-19; 2 Timothy 2:19; Titus 2) lest the Word of God be blasphemed (1 Timothy 6:1; Titus 2:5). As Christians we should obey the Word of our Lord, seek the things which are above, walk as He walked, and accept as our responsibility the duty and privilege of bearing the Gospel to a lost world (1 John 2:3; Colossians 3:1; Matthew 28:19-20).

A victorious and fruitful Christian life is possible only for those who have presented themselves wholly to Christ and walk by the power of the Holy Spirit, which all believers are called to do (Romans 12:1-2; Galatians 5:16; Ephesians 5:18; Romans 6-7).

SECTION 2 – STATEMENT ON MARRIAGE, GENDER AND SEXUALITY

We believe that God wonderfully and immutably creates each person as male or female. These two distinct complementary genders together reflect the image and nature of God (Genesis 1:26-27). Rejection of one's biological sex is a rejection of the image of God within that person.

We believe that the term "marriage" has only one meaning: the uniting of one man and one woman in a single, exclusive and lifelong union, as delineated in Scripture. We believe that God intends sexual intimacy to occur only between a man and a woman who are married to each other. We believe that God has commanded that no intimate sexual activity be engaged in outside of a marriage between a man and a woman (Genesis 2:18-25; 1 Corinthians 6:18; 7:2-5; Hebrews 13:4). Further, we reject the notion that two people of the same gender can marry each other; this is unnatural and evil before the Lord.

We believe that any form of sexual immorality (including but not limited to adultery, fornication, homosexual behavior, bisexual conduct, bestiality and use of pornography) is sinful and offensive to God (Matthew 15:18-20; 1 Corinthians 6:9-10; Ephesians 5:3).

We believe that in order to preserve the function and integrity of TBC as the local Body of Christ and to provide a biblical role model to the TBC members and the community, it is imperative that all persons employed by TBC in any capacity, or who serve as volunteers, agree to and abide by this Statement on Marriage, Gender and Sexuality (Matthew 5:16; Philippians 2:14-16; 1 Thessalonians 5:22).

We believe that God offers redemption and restoration to all who confess and forsake their sin, seeking His mercy and forgiveness through Jesus Christ (Acts 3:19-21; Romans 10:9-10; 1 Corinthians 6:9-11).

We believe that every person must be afforded compassion, love, kindness, respect and dignity (Mark 12:28-31; Luke 6:31). Hateful and harassing behavior or attitudes directed toward any individual are to be repudiated and are not in accord with Scripture nor the doctrines of TBC.

SECTION 3 – STATEMENT ON THE SANCTITY OF HUMAN LIFE

We believe that all human life is sacred and created by God in His image. Human life is of inestimable worth in all its dimensions, including pre-born babies, the aged, the physically or mentally challenged, and every other stage or condition from conception through natural death. We are therefore called to defend, protect and value all human life (Psalm 139.)

SECTION 4 – CONCERNING RELIGIOUS SEPARATION

Because of God's holy nature and the believers' high calling, Scripture teaches and commands personal and ecclesiastical separation from religious apostasy (2 John 7-11; Romans 16:17; Titus 3:10), from all worldly and sinful pleasures, practices, and associations (1 John 2:15-17; James 4:4; 2 Timothy 3:1-5), and from professing believers living in willful and unrepentant disobedience to the Word of God (2 Thessalonians 3:6, 14-15).

This does not include separation from unbelievers who need the Word of God and the Gospel of Jesus Christ (1 Corinthians 5: 9-13).

SECTION 5 – CONCERNING CHURCH MEMBERSHIP

The New Testament clearly indicates that groups of people who were followers of the Lord Jesus Christ identified themselves with and committed themselves to a particular local church body.

Therefore, in order to implement the principles of accountability and commitment to the local body of Christ, as defined in the New Testament and practiced in the early churches, TBC recognizes the need for a formal membership covenant. Membership at TBC is for all who are believers in the Lord Jesus Christ, have publicly been recognized as a believer through baptism by immersion in water, and are willing to submit to the authority of the local church (Matthew 16:19).

The New Testament expects believers to belong to a local church. Membership in a local church is good and proper in that it is the expression of fellowship, accountability and identification with a group of believers in the furtherance of the Gospel (Acts 2:42-46; Hebrews 10:25; 1 John 2:9-11; Ephesians 4:1-4).

Each member of TBC is required to sign and adhere to the following Membership Covenant:

> Having been brought by divine grace to repentance and genuine faith in the Lord Jesus Christ and to give ourselves completely to Him for the furtherance of His kingdom, and having been baptized by immersion upon our profession of faith in the name of the Father and of the Son and the Holy Spirit, we do now, relying on His gracious aid, solemnly and joyfully renew our covenant with each other.
>
> We will work and pray for the unity of the Spirit in the bond of peace.
>
> We will walk together in brotherly love, as becomes the members of a Christian church, exercise affectionate care and watchfulness over each other and faithfully admonish and entreat one another as occasion may require.
>
> We will not forsake the assembling of ourselves together, nor neglect to pray for ourselves and others. We will regularly participate together in the ordinance of the Lord's Supper.
>
> We will endeavour to seek the salvation of our family and friends.
>
> We will rejoice at each other's joy, and with tenderness, sacrificial love and sympathy bear one another's burdens and sorrows.
>
> We will seek to restore anyone who is caught in any transgression, while watching ourselves lest we too be tempted. We will seek the purity of the church by supporting restorative church discipline as it is taught in Scripture.
>
> We will seek, with God's help, to live carefully in the world, denying ungodliness and worldly lusts, and remembering that we have been buried by baptism and raised again from the symbolic grave, and so there is on us a special obligation now to lead a new and holy life.
>
> We will work together for the continuance of a faithful evangelical ministry in the church, as we sustain its worship, ordinances, discipline and doctrines.
>
> We will financially contribute regularly, cheerfully, willingly, and sacrificially to support the expenses and ministries of TBC, the relief of the poor, and the spread of the Gospel through all nations.
>
> We consent to and give TBC permission to take, keep and use photo or video images of us for the purposes of TBC, including promoting the church.

We will, under the Lordship of Christ, submit to and follow the elders as they care for our souls as men who will give an account.

If we leave TBC, we commit that as soon as possible, we will seek to unite with another Bible-believing church, where we can faithfully carry out the spirit of this covenant and the principles of God's Word.

We agree to live under and abide by the Constitution and By-Laws of Trinity Bible Chapel and the Elder-led governance structure they reflect.

May the grace of the Lord Jesus Christ, and the love of God, and the fellowship of the Holy Spirit be with us all. Amen.

We believe that every Christian should give of their means as God enables, as a positive command of Scripture and as an act of worship. Members of TBC should financially support the church regularly, sacrificially, willingly and gladly as God directs. The offering of one's resources to God through the local church is the normal and expected behavior of every Christian. Old Testament tithing is not required in the New Testament church but we believe that the giving of the first fruits of God's provision modeled in the Old Testament is a worthy pattern to be followed (Exodus 23:19; Deuteronomy 26:1-11; Proverbs 3:9; 1 Corinthians 16:2; 2 Corinthians 9:5-15; Matthew 6:19-21; Luke 12:34).

All members are required to regularly participate in services of the Church including Sunday worship service, prayer meetings and member meetings. Members are strongly encouraged to participate regularly in the small group ministry. Members who give reasons for absences to the satisfaction of the Elders shall remain members in good standing. Such reasons may include illness, military service, missionary work or schooling.

Members should financially support the Church regularly, sacrificially, willingly and gladly as God directs.

All members are expected to follow the commands and principles which are clearly taught in the Word of God and to demonstrate this daily in every area of their lives. Examples of disobedience to these commands and principles include illegal use of drugs, use of pornography, substance abuse, sexual immorality, homosexual activities, adultery, divorce, abortion and abuse of others.

SECTION 6 – GENDER ROLES

We believe that both Adam and Eve were created in God's image, equal before God as persons and distinct in their manhood and womanhood (Genesis 1:26-27, 2:18). Distinctions in masculine and feminine roles are ordained by God as part of the created order, and should find an echo in every human heart (Genesis 2:18, 21-24; 1 Corinthians 11:7-9; 1 Timothy 2:12-14). Adam's headship in marriage was established by God before the Fall, and was not a result of sin (Genesis 2:16-18, 21-24, 3:1-13; 1 Corinthians 11:7-9).

The Fall introduced distortions into the relationships between men and women (Genesis 3:1-7, 12, 16). In the home, the husband's loving, humble headship tends to be replaced by domination or passivity; the wife's intelligent, willing submission tends to be replaced by usurpation or servility. In the church, sin inclines men toward a worldly love of power or an abdication of spiritual

responsibility, and inclines women to resist limitations on their roles or to neglect the use of their gifts in appropriate ministries.

The Old and New Testaments emphasize the equally high value and dignity which God attached to the roles of both men and women (Genesis 1:26-27, 2:18; Galatians 3:28), and affirm the principle of male headship in the family and in the covenant community, the church (Genesis 2:18; Ephesians 5:21-33; Colossians 3:18-19; 1 Timothy 2:11-15).

Redemption in Christ aims at removing the distortions introduced by the curse. In the family, husbands should forsake harsh or selfish leadership and grow in love and care for their wives; wives should forsake resistance to their husbands' authority and grow in willing, joyful submission to their husbands' leadership (Ephesians 5:21-33; Colossians 3:18-19; Titus 2:3-5; 1 Peter 3:1-7). In the church, redemption in Christ gives men and women an equal share in the blessings of salvation; nevertheless, some governing and teaching roles within the church are restricted to men (Galatians 3:28; 1 Corinthians 11:2-16; 1 Timothy 2:11-15). In all of life Christ is the supreme authority and guide for men and women, so that no earthly submission-domestic, religious, or civil-ever implies a mandate to follow a human authority into sin (Daniel 3:10-18; Acts 4:19-20, 5:27-29; 1 Peter 3:1-2).

In both men and women a heartfelt sense of call to ministry should never be used to set aside biblical criteria for particular ministries (1 Timothy 2:11-15, 3:1-13; Titus 1:5-9). Rather, biblical teaching should remain the authority for testing our subjective discernment of God's will. The office of elder/pastor/bishop/overseer is scripturally reserved only for qualified men, not women. Within the church, women are not to serve in positions in which they exercise authority over men or in which they teach doctrine to men (1 Timothy 2:12). We desire to see qualified women serving in all positions within the church, except those which are specifically forbidden by Scripture.

ARTICLES III (Doctrinal Statement) and IV (Christian Living) do not exhaust the extent of our beliefs. The Bible itself, as the inspired and infallible Word of God that speaks with final authority concerning truth, morality, and the proper conduct of mankind, is the sole and final source of all that we believe. For purposes of TBC's faith, doctrine, practice, policy, and discipline, the elders are TBC's final interpretive authority on the Bible's meaning.

ARTICLE V: AMENDMENTS

On the rare occasion that amendments to this Constitution are needed, such amendments must be unanimously agreed upon by all the elders.

EXHIBIT X

This is Exhibit "X" referred to
in the Affidavit of
Jacob Reaume

Sworn before me this 4th day
of June A.D., 2021

A Commissioner for Oaths in and for Ontario

OUR $83,000 ACT OF WORSHIP

By Jacob Reaume | February 25, 2021 | Tagged: *covid-19*

On January 22, 2021, the Ontario Superior Court of Justice ordered that Trinity Bible Chapel and her elders not hold gatherings of more than 10 persons. Upon receiving the order, I invited the community to church on January 24:

> People are lonely, afraid, despairing of life itself, and facing financial ruin, among many other deprivations and tribulations. This is all during the darkest and coldest season of the year. If ever our fellow Ontarians needed hope, it is now. Out of neighbourly love, I am personally openly inviting anyone and everyone to experience the hope of the Gospel and the warmth of Christian worship at Trinity Bible Chapel this Sunday during our two Lord's Day services at 9:00 AM and 11:15 AM.

I noted, this was done in love for God and neighbour:

> Risking reputation and financial viability to offer eternal hope and warm Christian fellowship to a world in despair is an act of love that I am certain Jesus smiles on.

That's precisely what we did. Personally, I have never experienced a more palpable manifest presence of God's Holy Spirit during public worship than I did on that Sunday. Many others – I have lost track of how many – shared similar experiences. Pastor Will Schuurman recounted his experience of that Lord's Day on Twitter:

Pastor Will later posted this:

On Sunday, February 21, we baptized 13 individuals, some of whom traced their conversion to those weeks in January, especially January 24.

This week the Ontario Superior Court of Justice handed down our sentence for having church on January 24. The service cost us $83,000. That is our fine, and here is how it breaks down. Pastor Will and I each owe $5,000. Pastor Randy owes $4,000. Each of the other elders owe $3,000. The church itself owes $15,000. And we have been ordered to pay $45,000 to cover the legal fees of the Ministry of the Attorney General. The Ministry of the Attorney General claims their lawyers spent 104 hours to prosecute us for holding services on January 24 – charges for which we pled guilty. Evidently, the MAG was very motivated, and the prosecutors

worked tirelessly against our church. So that is a grand total of $83,000. These fines will not and cannot be appealed. They are final.

If you would like to help cover the costs please visit the Go Fund Me page that a member of our church setup (click here), but please note you will not receive a receipt for the Go Fund Me contributions. Money donated to the Go Fund Me can be used to cover all and any of these fines.

If you would like to make a larger contribution to our legal fund, you can donate to the church (click here and select legal fund), but please note that, while the church will provide a tax receipt, money donated to the church cannot be used to cover the fines of the individual elders or pastors. It can be used to cover church fines.

We remain grateful to the legal team at the Justice Centre for Constitutional Freedoms. They have been representing us *pro bono* throughout this ordeal. We ask that you please consider donating to them to support their ongoing advocacy for liberty (click here and select the "defending religious freedom" campaign).

We will pay $83,000 for having church on January 24. I could say it was the most extravagantly priced service I've ever held, but that would not be factual. Every service I've held has cost Christ His very own blood, which is worth infinitely more than any dollar amount.

I was heartened by something Pastor Steve Richardson recently pointed out. In reference to Matthew 26:6-13, he explained the anointing of Christ by Mary with the alabaster jar. The alabaster jar of ointment would have been worth the equivalent of a retirement savings. It was expensive, and that dear woman paid a lot of money for one quick act of worship. She thought Christ was worth it. The disciples, however, were "indignant, saying, 'Why this waste? For this could have been sold for a large sum and given to the poor?" Jesus defended her saying, "She has done a beautiful thing for me." Chief among the woman's accusers was Judas (John 12:4-5). The woman thought Christ was worth the money, but Judas thought He wasn't. She went down in history for doing good, but Judas was a traitor who would have been better off not being born.

On January 24, we worshipped Christ extravagantly at the price of $83,000. He is worth that and so much more. Our fine is nothing near what Mary spent on Jesus for her one quick extravagant act of worship. And we cannot compare it to the price of blood He paid so that we would worship Him. As we've sung many times:

> Were the whole realm of nature mine,
>
> That were a present far too small;
>
> Love so amazing, so divine,

> Demands my soul, my life, my all.

The most difficult thing to us is not the dollar value. Rather, we are troubled by how the court has perceived our actions as disrespectful. In his citation, the Honourable Justice noted the following:

> "The position of the Contemnors appears to be as follows: we will abide as long as this does not go on too long, and if it does, we may not comply."
>
> "There is no apology or demonstration of remorse for the conduct of the case. The Contemnors assert that they are conflicted. However, they do not apologize for their breach of this Order."
>
> "There was no sincere apology, and as I have noted, there was no apology at all."
>
> "The Contemnors reject the authority of the court by their actions."

To be absolutely clear, we respect the court and its authority. The Bible teaches us to honour all those in authority, and we do. But like all authority, the authority of our courts is derived. The court's authority comes from above. "Let every person be subject to the governing authorities. For there is no authority *except from God*, and those that exist have been *instituted by God*" (Romans 13:1). God has designed all authorities, courts included, as delegated powers. He has given them power, and that power must be held in high regard by all men.

Our offence is that we believe that God is our Supreme Authority, above and beyond all parliaments and courts. We agree with the preamble to the Canadian Charter of Rights and Freedoms, which reads, "Whereas Canada is founded upon principles that recognize the supremacy of God and the rule of law." God is supreme. Jesus Christ is the King of kings and Lord of lords, and, I add, He is the Judge of judges. His Law is the rule of all law.

Christians, throughout history, have often found themselves conflicted when earthly rulers order them to do what God forbids or forbids them from doing what God commands. In such instances, we must obey God over government. We believe that the church must meet. We further believe that Christ, not the government, has crown rights over the church and His worship.

The enemies of Christ prosecuted him before a court on the charge that Christ claimed supremacy over Caesar (John 19:12). In essence, they claimed He held Caesar's laws in contempt. The prosecutors won, and Christ was sentenced to crucifixion.

Early Christians suffered similar allegations. The message they preached was called "gospel" which means "good news." Their proclamation was contemptuous to Caesar. "Good news" or "gospel" was how the Empire announced the birth or ascension of an emperor. By calling the message of Christ "gospel" Christ's early disciples proclaimed that Christ is something better than Caesar.

Christ is the Emperor of emperors, and the gospel proclaims that He is supreme over all kings and lords. Furthermore, the early Church articulated the simple doctrinal statement that "Jesus is Lord" (1 Corinthians 12:3; Romans 10:9; Philippians 2:11). By saying that they were saying that Caesar is not lord. Saying "Jesus is Lord" and acting on it was considered treasonous. The Roman Empire was totalitarian, and it did not offer Christians the opportunity to conscientiously dissent from Caesar's claim as supreme lawgiver. For claiming that Jesus is Lord and with their proclamation of "gospel," the early Christians were tried in courts. The courts found them guilty so they paid.

If Caesar had left them alone to self-govern, he would have found them to be his best citizens. After all, the New Testament admonishes us to "Honour the emperor" (1 Peter 2:17). But Caesar demanded more than honour. He wanted first place in their lives, and that was something they could not give him. First place is reserved for Christ. Christ has purchased us by His blood, and therefore Christ, not Caesar, owns us.

On a smaller scale, we at Trinity Bible Chapel find ourselves in a similar place. Proclaiming the "good news" of stopping the spread of a virus, our lawmakers have made laws that forbid what God commands and command what God forbids. The Ontario Superior Court of Justice ordered us to comply with those laws. We didn't. Those laws violate our consciences because our consciences are held captive by Jesus. He is Lord, and He has the best good news. We acted on our consciences.

In our $83,000 act of worship, may King Jesus receive His crown rights and may He find a reward for His suffering.

If you would like to help cover the costs please visit the Go Fund Me page that a member of our church setup (click here), but please note you will not receive a receipt for the Go Fund Me contributions. Money donated to the Go Fund Me can be used to cover all and any of these fines.

If you would like to make a larger contribution to our legal fund, you can donate to the church (click here and select legal fund), but please note that, while the church will provide a tax receipt, money donated to the church cannot be used to cover the fines of the individual elders or pastors. It can be used to cover church fines.

We remain grateful to the legal team at the Justice Centre for Constitutional Freedoms. They have been representing us *pro bono* throughout this ordeal. We ask that you please consider donating to them to support their ongoing advocacy for liberty (click here and select the "defending religious freedom" campaign).

ATTORNEY GENERAL OF ONTARIO

APPLICANT

and

TRINITY BIBLE CHAPEL et al.

RESPONDENTS

COURT File No. CV-21-00000095-0000

ONTARIO
SUPERIOR COURT OF JUSTICE

Proceeding commenced at Kitchener

AFFIDAVIT OF JACOB REAUME
(Sworn June 4, 2021)

Justice Centre for Constitutional Freedoms
[redacted]

Lisa Bildy
[redacted]

COURT FILE NO: CV-21-95-0000

ONTARIO SUPERIOR COURT OF JUSTICE

BETWEEN

THE ATTORNEY GENERAL OF ONTARIO

Applicant (Responding Party)

-and-

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHUURMAN, DEAN WANDERS, RANDY FREY, HARVEY FREY, AND DANIEL GORDON

Respondents (Moving Parties)

AFFIDAVIT OF CRAIG WILLIAMS
(Sworn June 4, 2021)

I, M. CRAIG WILLIAMS, of the [redacted] in the Province of Ontario, MAKE OATH AND SAY:

1. I attend church services at Trinity Bible Chapel, and as such have personal knowledge of the matters hereinafter deposed to, except where they are based on information and belief, in which case I verily believe them to be true.

2. I am 54 years of age and the married father of one teenage son, currently in grade 12. I reside in Cambridge, Ontario, and am presently on long-term disability, although I used to be an insurance salesman.

3. I have been a churchgoer for my entire adult life, and even attended Bible College, although I would not have considered myself “saved”. I think I was going through the motions and trying to come to terms with whether God could even love

someone like me (I grew up in an abusive home, and that has had long-term impacts).

4. Over the years, I have struggled with my mental health (one of the reasons for being on disability) and developed personally destructive behaviours, such as drinking, showing anger, watching pornography, and gluttony.

5. For the first nine months of the lockdown, I participated in online services with my regular church. The church did open within the capacity restrictions when that was permitted; however, they also enforced social distancing and masking, even during singing. My faith was weak already, and this didn't help.

6. In about late November, I saw a YouTube video with Pastor Jacob Reaume speaking at a rally. I was moved by his words. He preached "God first" and that really came through him and resonated with me in a way that is difficult to describe. My wife and I decided to start attending his church, even though it was a bit of a drive from our home.

7. The improvement in my life since attending Trinity Bible Chapel has been dramatic. I have lost 30 pounds, and have stopped drinking and using pornography. My wife and I are in a very good place in our marriage. I've started writing again (I was a published author a decade ago) and feel renewed purpose in my life.

8. I am in the process of becoming a member at Trinity Bible Chapel, and hopefully will have completed the necessary steps by September. On February 21, 2021, I was baptized at TBC with great joy and celebration. I am finally saved.

9. Attending church in person has been so important for me personally, psychologically and spiritually, and for my marriage too. But for my teenage son, I believe that attending Trinity Bible Chapel in person has saved his life.

10. My son has been struggling with the lockdowns, the loss of his social connections, and worries about his future as a current grade 12 student. He advises me, and I verily believe, that even when attending school, the rules and restrictions have

been unnatural and unbearable. Most days, he could barely pull himself out of bed. As a parent, I wanted to be able to provide him with encouragement and hope, and I have tried to do that, but there seems to be no end in sight to these restrictions, even with the promise of vaccines. Hope was in short supply.

11. Last November or so, when my son was participating in an online youth group meeting with our former church, he apparently drew a picture of himself with a gun to his head. The youth pastor contacted the police, who arrived at our home. Our son was not deemed to be imminently at risk of suicide, so he remained in our home and we tried to work through his fears and hopelessness with him.

12. Then, in December, we all started going to Trinity Bible Chapel. We heard a genuine love for Jesus and his people in Pastor Jacob's message, and felt a deep connection to those around us in the service. When we go to church, we see people's faces, hug one another, sing praise to God. Fear and terror dissipate, and we are human again.

13. My son's mental state had improved immensely, thanks to being able to attend church and youth Bible studies in person. He had hope again.

14. When the court locked the church's doors on May 1, 2021, I attended the informal gathering in the church parking lot that day to sing and pray before the locks were changed. The police turned up and noted who was in attendance.

15. The following Monday evening, the police came to my home around 9 p.m. to hand deliver a ticket. Although the conversation was cordial, my son was badly shaken by it. He was unable to sleep, despite reassurance from his mother and me. It took a visit from Pastor Reaume to calm our autistic son down and help get him back to a semblance of normal.

16. We have been immensely grateful to Pastor Reaume and the Trinity Bible Chapel leadership. They have saved us in more ways than one.

17. To me, and to my family, it is utterly essential to our lives—physically, mentally, spiritually, and emotionally—to be able to assemble together for worship with other Christians and to practice our faith fully as God commands.

18. I swear this affidavit *bona fide*, in support of the motion, and for no other or improper purpose.

SWORN REMOTELY by videoconference by Craig Williams at the [redacted] before me at the City of London, in the County of Middlesex, this 4th day of June, 2021 in accordance with O.Reg. 431/20 Administering Oath or Declaration Remotely

A Commissioner, etc.

LISA D.S. BILDY
BARRISTER & SOLICITOR

M. CRAIG WILLIAMS

ATTORNEY GENERAL OF ONTARIO

APPLICANT

and

TRINITY BIBLE CHAPEL et al.

RESPONDENTS

COURT File No. CV-21-00000095-0000

ONTARIO
SUPERIOR COURT OF JUSTICE

Proceeding commenced at Kitchener

AFFIDAVIT OF CRAIG WILLIAMS
(Sworn June 4, 2021)

Justice Centre for Constitutional Freedoms
[redacted]

Lisa Bildy
[redacted]

Court File No. CV-21-08

ONTARIO

SUPERIOR COURT OF JUSTICE

B E T W E E N:

HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO

Applicant

- and -

THE CHURCH OF GOD (RESTORATION) AYLMER, HENRY HILDEBRANDT, ABRAM BERGEN, JACOB HIEBERT, PETER HILDEBRANDT, SUSAN MUTCH, ELVIRA TOVSTIGA and TRUDY WIEBE

Respondents

AFFIDAVIT OF HEINRICH HILDEBRANDT
(Sworn June 4, 2021)

I, HEINRICH (HENRY) HILDEBRANDT, of the [redacted] in the Province of Ontario, MAKE OATH AND SAY:

1. I am one of the Respondents herein, and as such have personal knowledge of the matters hereinafter deposed to, except where they are based on information and belief, in which case I verily believe them to be true.

2. I am the pastor at The Church of God ("**the Church**"), located in Aylmer, Ontario, and have held that position since April of 1993. The Church is a not-for-profit non-denominational religious organization, incorporated in 1992. I was born in Mexico and immigrated to Canada in 1985, becoming a Canadian citizen in 1989. I have been married since 1982 and have two adult sons.

3. The other personal Respondents are elders or former elders of the Church.

4. Since its inception, the Church has been the spiritual home for a congregation comprised mainly of small-town and rural parishioners, many of whom come from a Mennonite background and speak Low German. The congregation currently numbers approximately 260 people. Our facility can safely house over 400 people.

5. Church is not merely a Sunday morning event for our congregation. It is a way of life for us, as a traditional community. We would normally hold full services at least three times per week (Sunday mornings and evenings, and Wednesday evenings) as well as prayer services on Saturdays. We operate a school in our building and our parishioners have always used it as a sort of community centre. It was the home base for social events, support groups, BBQs and soccer nights. Our church members dress in distinctive plain and modest clothing, which is also a reflection of how central to our way of life the Church is.

6. Given the demographics of my parishioners, and the fundamental importance to my congregation of communal worship, it has been of utmost importance to me as their pastor to at least bring them together for one worship service per week throughout the lockdown, and I tried to do so creatively while honouring the government's restrictions from the outset.

Initial Response to Covid-19 and Government Restrictions

7. On or about March 17, 2020, the Ford government declared a state of emergency due to the outbreak of Covid-19 and began issuing unprecedented lockdown orders.

8. On March 24, 2020, we learned through an Order in Council that church was not essential, as the cabinet ordered the closing of "non-essential" businesses and institutions, including churches and other faith settings. The Church initially abided by these restrictions.

9. On Sunday, April 12, 2020, which was the Christian holy celebration of Easter, and by then nearly a month into the lockdown, we held a small "drive-in" sunrise service at the

Church. We followed the guidance from Saskatchewan, which had just permitted drive-in services as along as certain rules were followed.

10. We had prepared official signage instructing congregants to remain in their vehicles with the windows rolled up, and not to leave their cars or enter the church building for any reason. The signs were placed along the driveway into the church, and in prominent locations around the parking lot. A platform was built overlooking the parking lot, with markings to show where up to five different members of the worship team would stand – each 2 meters apart. We purchased and set up an FM low-frequency broadcast system to deliver our own service to the car radios of each attendee. We did not collect offerings, nor did we encourage or require anyone to roll down their windows. To our knowledge, none did, nor did they exit their vehicles.

11. While we were in the parking lot, two Aylmer Police constables came by to speak with us in a very friendly manner. Constable Nelson DaCosta said that this seemed to be an innovative way to do church. He and Constable Jordan Babb advised that it was not necessary to space out the vehicles, and that we could use the entire parking lot. Constable DaCosta asked us to let him know if we were planning to do this again.

12. With the blessing of police, the encouragement of my congregation, and having conducted a successful and safe service, I decided to continue with the drive-in services. Unfortunately, someone in the community took a photo of the vehicles in the parking lot and made a post on Facebook about it, leading to complaints to police.

13. Rather than assure those who complained that the Church and I were not breaking any laws and were not in fact “gathering” as prohibited under the order, since congregants never left their personal vehicles, the Police chose to crack down. I am advised by my son, Herbert Hildebrandt, and verily believe that Inspector Nick Novacich called him on April 22, 2020 to advise that we were not to proceed with a further service, or that I and my parishioners would face tickets of $750 or other penalties of up to $100,000 and a year in jail.

14. In a statement released publicly on April 24, 2020, Aylmer Police Chief Zvonko Horvat advised that, after consultation with county prosecutors, “it has been determined that this gathering is in violation of the EMCPA and that those attending could be subject to facing charges for failing to comply with an order during a declared emergency.” The Chief went on to state, “We would like to assure our residents that this is an active investigation and we will be monitoring all faith based groups in our community to ensure that these Emergency Orders are being followed. Those who do not adhere to these orders will result in the Aylmer Police taking enforcement action.” Attached hereto and marked as **Exhibit “A”** to this affidavit is a copy of the Chief’s statement, as posted on Facebook on April 24, 2020.

15. This was the genesis of a toxic relationship in the Town of Aylmer, between our Church, which was trying to meet the needs of our congregation in a completely safe manner, the police chief, who chose a heavy-handed approach to dealing with churchgoers, and some townspeople, who behaved like Stasi informants as they regularly harassed our Church and monitored us every Sunday, looking for any transgression and calling in complaints to the police.

16. All of this forced my congregants and the Church leadership into a difficult bind – we were made to choose between our peaceful Christian deference to authorities, and the exercise of our fundamental freedoms of peaceful assembly and religion, since it is our sincerely held religious belief that we are called to regular communal worship.

17. Efforts to resolve the matter of drive-in services through discussion with the Police Chief and our local Member of Provincial Parliament, as well as a legal demand letter, proved unsuccessful. In a statement I posted to the Church website, I noted, “Liquor stores are considered essential and their parking lots are not under any scrutiny. Liquor is essential, but God is not? Drive-thru establishments are under no threat of closure and their parking lots are regularly filled with customers looking to have a chat with their friends. We are not asking for special treatment or privileges, equality would be satisfactory.” Attached hereto and marked as **Exhibit “B”** to this affidavit is a printout of my statements and press releases on the Church of God of Aylmer website.

18. On April 25, 2020, I announced on our church website and social media that we would proceed to hold a third service on April 26, under threat of penalty. I condemned any show of force or resistance to police, stating “Christians are peaceful people and have always sought the opportunity for peaceful assembly, as guaranteed in the *Canadian Charter of Rights and Freedoms*.” The service proceeded without incident on April 26, and all congregants remained in their vehicles, with windows rolled up. Police attended on the property without a warrant and videotaped all of the parishioners and their vehicles during the Sunday service. The Police had advised by a public statement in advance that no tickets would be issued at the service, but the results of their investigation would be presented to a Crown Attorney to determine whether charges would be laid.

19. On April 30, 2020, I issued a press release on behalf of the Church, media interest having grown significantly in light of the public dispute. In it, I expressed gratitude to the police for their forbearance, and noted that this provided the Premier and his cabinet the opportunity to clarify their guidance surrounding drive-in services, as many other jurisdictions across Canada and the United States were then doing; however, the government failed to do so at that time.

20. In May of 2020, we commenced a constitutional challenge against the Aylmer Police and the Ontario government over the harassing and threatening behaviour concerning drive-in services. Shortly after the application was filed, Ontario amended the regulations to permit drive-in services. Attached hereto and marked as **Exhibit “C”** to this my Affidavit, is a copy of a news release from our lawyers, the Justice Centre for Constitutional Freedoms, detailing that information.

21. We did continue to meet with drive-in services until the Ontario Government announced that houses of worship would be permitted to open to 30% capacity, effective June 12, 2020. This was also the result of lobbying efforts by a coalition of faith leaders in which our lawyer, my son Herbert and the Church were involved.

22. Although we did make do with drive-in services, they are a poor substitute for in-person gatherings, as people are not able to partake of the Lord’s Supper or participate in

other important practices and ceremonies such as baptism, and cannot meaningfully interact with one another. Following the announcement that churches were able to open, we immediately switched back to in-person services, which was a great joy and relief to us.

23. At that time, we implemented public health protocols such as posting signs and making masks and sanitizer available. In conversation with the police, we established the appropriate capacity of the building and adhered to that limit. If people wanted extra space for physically distanced seating, that was made available in the overflow room. We also accommodated drive-in services for those who weren't yet ready to come in the building. And, as we had always done even before Covid, we reminded people to stay away if they or a family member were feeling unwell.

24. It was a wonderful blessing to our community to meet in person over the summer months. However, as the fall approached the government began making public comments about potential further restrictions. On September 28, 2020, our lawyer sent a letter to the Premier reminding him of our *Charter*-guaranteed right to freedom of peaceful assembly and worship, and the essential nature of corporate or communal worship for people of faith. Our lawyer asked that, at a minimum, places of worship remain open at 30% capacity. Attached hereto and marked as **Exhibit "D"** to this my Affidavit is a true copy of the letter.

25. On or about November 3, 2020, the Ontario Government abandoned its three-stage regime, and introduced a colour-coded system and some apparently objective benchmarks for imposing further restrictions on a regional basis. For each of the colours, including "red", houses of worship were to remain at 30% capacity.

26. It was not long before the Government changed gears again, and introduced a more restrictive "grey zone", modelled on the earlier Stage 1 restrictions. Toronto and Peel were the first areas to go back into the grey zone, which permitted houses of worship to only have ten (10) persons in attendance, regardless of building capacity, however that did not apply to us.

The Second Lockdown – Community and Police Hostility Grows

27. On December 21, 2020, the Premier announced that the entire province, regardless of case counts or the presence or absence of any crisis regionally, would begin a four-week lockdown on Boxing Day. Attached hereto and marked as **Exhibit "E"** to this my Affidavit is a copy of the province's news release.

28. On or about December 26, 2020, Ontario placed the entire province under a "shutdown", which severely restricted many of the activities of Ontarians, including their attendance at places of worship which were limited to a hard cap of 10 persons indoors, regardless of capacity. However, numerous businesses were granted exemptions, including but not limited to "big box" or discount retailers and liquor stores, provided they limited the number of persons inside to 25% of their building capacity; warehouses and distribution centres that support online retail (such as Amazon); various manufacturing facilities; construction activities; and fitness centres catering to "elite" athletes.

29. As a result of my early dispute with the police, which the media reported on widely, I become somewhat well known as a spokesperson for the importance of our *Charter* freedoms, and gave various speeches in person and online. In November, I was invited by a local couple to speak at a rally in Aylmer. This rally apparently angered many in the community, some of whom held a counter protest. Organized opposition and hostility toward me, my family and our Church began to pick up steam.

30. On December 27, we held a drive-in service in accordance with the law. Unfortunately, during the service some people had stepped out of their cars and the police, who were monitoring, charged my son Herbert with organizing a gathering over 10 people. The police called him over in the middle of the service. That was the first charge in relation to a service that anyone in our church had faced. We had worked very hard to try to comply over the preceding nine months, despite the hardships this entailed for our community.

31. On that Sunday, local community members held a full demonstration against us, which they called “Plague Rat Tour”. This “tour” started at the church, where at least 15 or more vehicles lined up along both sides of the highway in front of our church. Throughout our drive-in service, they honked their horns and blasted through a megaphone, trying to disrupt the service as much as possible. Although the police were in attendance, as they almost always were for our services, they left these protestors alone. Part way through the service, the protestors left and did a drive-by of the homes of our parishioners that they knew of, and others who were part of the “movement”, including the local couple who invited me to join their protest in November. Security camera footage, as well as advice from members of my congregation who had stayed home from church that day, informed me of this and I verily believe it to be true.

32. This community group, calling itself “Canadians Against Freedom Rallies and Misinformation”, has continued to harass me, my family and our Church. Posters with my face or my son’s have been plastered around the town, saying “Lock Him Up!” Attached hereto and marked as **Exhibit “F”** to this Affidavit are true photos of one depicting Herbert, and another poster affixed to a post with our church shown in the background. Both of these photos were taken by Herbert, and he advises and I believe them to be accurate depictions.

33. We continued with permissible drive-in services until January 24. At the conclusion of the service, we allowed people into the building for a “tour” and received charges for that.

34. The following week, on January 31, we joined other Ontario congregations in holding our service inside the Church as an act of civil disobedience. This resulted in the Attorney General obtaining an interim order on February 5, followed by a final order on February 12, enforcing compliance with the regulations. We reverted back to drive-in services for Sunday February 7 and 14.

35. From about February 16 until just before Easter Sunday, capacity for religious services in our region was at 30%. There were no charges laid for our indoor services during that period.

36. The Ford government reduced capacity again to 15%, just in time for Easter Sunday, the holiest day in the Christian calendar. This remained in effect until April 19, at which time (and continuing presently) the limit for religious services was further reduced to 10 people, indoors or out.

37. Ultimately, we as a church decided that we could no longer refrain from in-person services. We held a service on Easter Sunday, as well as the following Sunday.

38. On April 14, 2021, we were served through our lawyer with a Motion for Contempt by the Attorney General's office for the services held on April 4 and 11.

39. On April 18, we had police surveilling our property from the woods behind the building.

40. On April 20, I am aware that there was a gathering of fewer than ten people in a choir practice at the Church, while a business meeting occurred in another wing of the building, also with fewer than ten people. Our members were in compliance with the regulations, as far as I understood. The business meeting involved two police officers, who went outside when the Aylmer Police turned up. According to the CBC, police were tipped off by a complaint, which is typical. A heated exchanged occurred between the officers, and the off-duty police (from a different force) were charged. Attached hereto and marked as **Exhibit "G"** is a CBC article dated April 23, 2021.

41. After a brief adjournment, we were in court for the contempt proceedings on April 30, 2021, at which time Justice B.G. Thomas found church elder Peter Wall, the Church, and me guilty of contempt of his order of February 12, 2021.

42. On May 14, 2021, we returned for the sanctions hearing and were ordered to pay a total of $117,000 in fines and costs, payable within 90 days. The Sheriff was also ordered to lock our church doors.

43. Later that day, while we were in the Church holding a service, the Sheriff, a locksmith and numerous police officers arrived and entered the building. All parishioners were asked to leave, and did so in an orderly fashion. A video recording of the event was

taken by my son, Herbert, and posted to YouTube at this link: https://www.youtube.com/watch?v=WJbEl8XWak4

44. On May 16, we held an outdoor service on the lawn of the church, which attracted approximately 300 people. There was a police drone circling over the church. This was a greater number than usual.

45. We were then served on May 21 with a second Notice of Motion for a finding of contempt, with a hearing before Justice Thomas scheduled later that same day. A brief adjournment was granted to May 31.

46. We held outdoor services on May 23 and May 30, before returning to court on May 31, 2021. The services grew in size each week, as punitive measures by the government increased. During the service on May 30, I asked if anyone felt ready to commit themselves to Christ, and at least a dozen people, not normally part of our church, came forward. There was much tearful rejoicing as these individuals felt the power of God working in their lives and committed themselves to Christ. To me, this made every penny of every fine worthwhile.

47. On May 31, 2021, Justice Thomas again found the Church, church elder Peter Wall, and me in contempt of the court order of February 12, 2021. We were ordered to pay a total of $66,000 in fines and costs, forthwith.

48. The Church has now received about six charges, each with a maximum penalty of $10 million. I have personally received twelve charges, each carrying a maximum penalty of $100,000 and one year in jail.

49. Many of our members have been charged too. After one service, the police made late evening visits to their homes while it was dark outside to give them tickets.

50. We are under constant threat of more summonses, potential jail time, and are now locked out of our church building. The stress on our leaders and parishioners, as normally law-abiding citizens, cannot be overstated; although our commitment to following God's Word and our resolve to accept any punishment, including

imprisonment, fortifies us. To say that our *Charter*-guaranteed freedoms to worship, assemble, associate, and express ourselves have been infringed is an understatement.

51. While we met outdoors for peaceful religious services on May 16, many other gatherings likewise took place outdoors that weekend, including pro-Palestinian demonstrations. I am not aware of charges being laid. Indeed, the Prime Minister tweeted on May 16, 2021, that "Everyone has the right to peacefully assemble and express themselves freely in Canada…." Attached hereto and marked as **Exhibit "H"** to this Affidavit is a screenshot of the tweet.

52. To the best of my knowledge, information and belief, there have been no Covid outbreaks associated with the Church, despite our meetings and the very close observation of our church by local public health officials, police and the broader community. I have not buried a single person who has died from Covid.

53. Meanwhile, the nearby Police College has had at least three outbreaks, yet has argued that it should be permitted to continue with in-person learning. Attached hereto and marked as **Exhibit "I"** to this Affidavit is a copy of a newspaper article, dated March 15, 2021, containing this information which I believe to be true.

54. While the church could not legally meet, LCBO stores, marijuana dispensaries and many other businesses the government has deemed "essential" remain open.

Why We Continue to Meet

55. To our parishioners, church is indeed an essential service, and we believe it is not for the government to decide what is essential to us.

56. Although the Church of God is non-denominational, most of our congregants come from a Mennonite tradition, which has a long history of state persecution, societal disdain for its pacifism and way of life, and movement of its people from country to country in order to be able to worship in peace without unreasonable state interference.

57. Those of us now living in Canada place great trust in the *Charter of Rights and Freedoms* to protect our right to worship, assemble, associate and express ourselves freely, and have marched in many rallies over the last year to remind Canadians to treasure our inheritance of a free society.

58. As a pastor, ministering to my church and the broader community that has reached out to me over the last year, I verily believe that the government's unprecedented actions have harmed people and society by perpetuating loneliness, hopelessness, fear, poverty, division, anger, the deterioration of relationships.

59. The effect of these restrictions was a gross and substantial interference in the practice of our faith, individually and collectively. Our faith is fundamental to our lives. It is not a "non-essential" service – it goes to the core of who we are as Christians.

60. We, being myself and the Church's membership and leaders, are bound by our faith to gather for corporate worship, and to engage in communal prayer, preaching, singing, and partaking of the Lord's Supper and other important rites. The government's restrictions have prohibited, limited, and punished us for worshiping as our faith and consciences require.

61. We sincerely believe that Scripture commands us to meet for worship in person, that the definition of "church" requires us to gather in person, and that the Law of God demands we gather at least weekly.

62. We are peaceful people. We do not desire conflict with government. In fact, we seek to avoid it and to live at peace with all people (Rom 12:18; 1 Tim 2:1; Heb 12:14). However, when the church is forced by the state to be closed (ten people permitted is essentially a closure) or drastically limited in attendance for such a protracted period with no clear end in sight, I believe the cost is simply too great to my parishioners, to my conscience and to the principles of a free society on which this country was founded.

63. I swear this affidavit *bona fide*, in response to these proceedings, and for no other or improper purpose.

SWORN REMOTELY by videoconference by Henry Hildebrandt at the [redacted] in [redacted] before me at the City of London, in the County of Middlesex, this 4th day of June, 2021 in accordance with O.Reg. 431/20 Administering Oath or Declaration Remotely

A Commissioner, etc.

LISA D.S. BILDY
BARRISTER & SOLICITOR

REV. HENRY HILDEBRANDT

EXHIBIT A

This is Exhibit "A" referred to
in the Affidavit of
Henry Hildebrandt
Sworn before me this 4th day
of June A.D., 2021

A Commissioner for Oaths in and for Ontario

LISA D.S. BILDY
BARRISTER & SOLICITOR

The Aylmer Police Service respects everyone's rights to peaceful assembly for freedom of expression, and religion. Our role throughout this CoVID-19 response is to maintain the health and safety of all the residents of Aylmer by ensuring that the Emergency Management Civil and Protection Act, O.Reg 52/20 is adhered to.

The *Emergency Management and Civil Protection Act* (EMCPA), was enacted by our Provincial Government on March 17th, 2020 and several emergency orders have been made under the Act to contain the spread of COVID-19 and to ensure that essential services continue to be provided and Ontarians are supported.

One of these orders that have been made under Ontario Regulation 52/20 states the following:

> SCHEDULE 1
> ORGANIZED PUBLIC EVENTS, CERTAIN GATHERINGS
> Prohibition
> **1.** (1) Subject to subsection (3), no person shall attend,
> (a) an organized public event of more than five people, including a parade;
> (b) a social gathering of more than five people; or
> (c) a gathering of more than five people for the purposes of conducting religious services, rites or ceremonies.
> (2) For greater certainty, subsection (1) applies to an event or gathering even if it is held at a private dwelling.
> (3) Subsection (1) does not apply to the following:
> 1. A gathering of members of a single household.
> 2. A gathering for the purposes of a funeral service that is attended by not more than 10 persons. O. Reg. 99/20, s. 3.

Last Sunday, April 19th, 2020 our communications centre received over (15) calls of reports that a certain Faith based group had gathered in a parking lot in their vehicles to listen to a service being delivered outside by their Pastor.

After consultation with our Elgin County Prosecutor(s), it has been determined that this gathering is in violation of the EMCPA and that those attending could be subject to facing charges for failing to comply with an order during a declared emergency.

We would like to assure our residents that this is an active investigation and we will be monitoring all faith based groups in our community to ensure that these Emergency Orders are being followed. Those who do not adhere to these orders will result in the Aylmer Police taking enforcement action.

EXHIBIT B

This is Exhibit "B" referred to
in the Affidavit of
Henry Hildebrandt
Sworn before me this 4th day
of June A.D., 2021

A Commissioner for Oaths in and for Ontario

LISA D.S. BILDY
BARRISTER & SOLICITOR

Join us Sunday for a livestreamed service at 10:30 AM Eastern. An hour prior to the service, app.gospeltrumpet.com will go live with all the relevant links for audio and video feeds.

For those of you that would like to listen live in our parking lot, please review the instructions in the graphic below. These guidelines are not suggestions and we will strictly enforce them. You must be in a vehicle and remain in your vehicle at all times with your windows rolled up to park in the parking lot at any time. This includes all members of the congregation, visitors, and media.

Tune in to 87.9 FM to listen live to the broadcast within a 750 meter radius of our meetinghouse.

Alberta, Saskatchewan, Manitoba, and New Brunswick have all endorsed outdoor, drive-in services as allowable under their Emergency Acts, as well as California, Mississippi, Kentucky, Tennessee, Ohio, Kansas, Florida, and many other countries across the globe.

Ontario, now it's your turn. Cars in a parking lot are not gathering, they are parking. Gatherings are defined by physical presence without barriers.

ALBERTA: https://www.discoverairdrie.com/local/church-at-the-drive-in-for-easter

SASKATCHEWAN: https://www.lifesitenews.com/news/govt-authorities-reverse-ban-on-drive-in-religious-services-after-legal-challenge

MANITOBA: https://www.chvnradio.com/news/what-does-the-non-critical-business-closures-mean-for-churches

NEW BRUNSWICK: https://atlantic.ctvnews.ca/n-b-churches-transition-to-drive-in-services-as-province-eases-covid-19-restrictions-1.4913183

CALIFORNIA: https://www.theblaze.com/news/california-now-will-allow-drive-in-church-services-amid-coronavirus-shelter-in-place-order-reversing-course-after-lawsuit

https://www.theatlantic.com/photo/2020/04/photos-easter-services-distanced-world/609898/

PRESS RELEASES

RE: FREEDOM OF RELIGIOUS ASSEMBLY

April 30, 2020 – 14:00

We extend our gratitude to Canadians across the country that have prayed, called, emailed, commented, and messaged us this past week. The support and passion for freedom in this country has been overwhelming. God is sovereign and His Word will prevail. This nation was founded on the principles of religious freedom and peaceful assembly and we pray that we will enjoy these privileges for many years to come.

This afternoon, we received notice that the Aylmer Police Service will not proceed with charges for those that parked in our parking lot and tuned into the service that was broadcast last Sunday morning, as well as the persons that

conducted the service from our outdoor platform. We are grateful for that and believe it is the right decision. This allows the Premier and his cabinet the opportunity to swiftly provide clear enforcement directives pertaining to the Emergency Act that uphold public safety while respecting the right of people to express their faith in a safe manner. We continue to hope for a political resolution to this situation that does not put our local police in an unenviable position, and we thank the Aylmer Police for their continued service and protection to our community.

Provinces across Canada and countries around the globe are endorsing drive-in services as a temporary measure as it allows for an expression of community without violating public health objectives.

Pastor Henry Hildebrandt

RE: FREEDOM OF RELIGIOUS ASSEMBLY

April 25, 2020 – 17:00

This past week has been defined by an unexpected amount of upheaval for our faith community. As a matter of fact, it has been a moment of truth for Christians across Ontario and the country.

Last Sunday morning we held our second drive-in service in as many weeks, with the full approval, permission, and encouragement of the Aylmer Police Service. A follow-up call from a constable on Sunday afternoon confirmed no violations were observed by the officers present and that we were cleared continue to worship in this manner until this crisis abates.

Tomorrow morning, at 10:30, the Lord willing, we will hold our third drive-in service under the threat of hefty fines, disruption, and physical roadblocks by order of the Aylmer Chief of Police. We have attempted, unsuccessfully, to reach an acceptable compromise with him these past 6 days. Regrettably, he has allowed his judgement to be clouded by one inaccurate post on Facebook that generated hundreds of comments and 15 complaint calls to the police service (this post has since been deleted). Our offer to hire off-duty officers from the Aylmer force, to ensure compliance with the law, was unceremoniously dismissed. Unfortunately, the Chief has also decreed that his officers must enforce the law as he interprets it, recklessly abandoning the discretion and interpretation used successfully in the past weeks, both here in Aylmer and across the country and the continent. One thing is clear to us at

this moment, he finds himself on the wrong side of history and we extend our gratitude and pray for blessings and wisdom on the officers of the Aylmer Police Service as they are thrust into this unenviable position.

Our local MPP, Minister Jeff Yurek, has been a tremendous help for us during this crisis. We are grateful to him and his constituency office for their advocacy on our behalf. Their communication has been consistent and responsive, but we are still awaiting further guidance from the Attorney General. The Justice Centre for Constitutional Freedoms deserves special mention for their assistance. They have worked overtime to find a solution and clarify any legal questions we had. Several prominent London law firms have reached out to us and provided invaluable, precise legal advice and we expect to hear more from them in the coming days.

Drive-in services at a place of worship are not illegal and there is absolutely no legal foundation for such a claim. Parades are specifically forbidden under the Ontario EMCPA and yet no fines are levied for such daily displays across Ontario, and, I might add, rightfully so. In fact, police officers are actively participating in such parades, with impunity. Liquor stores are considered essential and their parking lots are not under any scrutiny. Liquor is essential, but God is not? Drive-thru establishments are under no threat of closure and their parking lots are regularly filled with customers looking to have a chat with their friends. We are not asking for special treatment or privileges, equality would be satisfactory.

We have considered returning to our livestream broadcasts alone and complying with an interpretation of the Emergency Act that is an abrogation of the rights of all Canadians of faith. However, we cannot do so in good conscience. We have arrived at a point where we must draw a line in the sand and stand up for all who value justice and reject unreasonable, unjustifiable curbs of our freedoms.

Everyone is welcome to join us tomorrow in a livestream broadcast of our service that will be posted on our website at www.churchofgod.com. We will not be gathering for a service as defined by the Act, but our parking lot will be open to anyone that wishes to park there, stay in their vehicle at all times with their windows rolled up, and tuned in to the station that will be posted on the signage onsite.

We will not condone any show of force or resistance to the police. In fact, we strongly condemn it. Christians are peaceful people and have always sought the opportunity for peaceful assembly, as guaranteed in the Canadian Charter of Rights and Freedoms.

"And the LORD, He it is that doth go before thee; He will be with thee, He will not fail thee, neither forsake thee: fear not, neither be dismayed." Deuteronomy 31:8

Pastor Henry Hildebrandt

April 22, 2020 – 14:00

We are grateful to our federal, provincial, and municipal government leaders for their commitment to public service during this time of crisis and appreciate their responsibility for the wellbeing of the people they serve.

The COVID-19 crisis has rapidly changed a lot of what our society considers normal and essential in a few short weeks. Faith communities have not been unaffected, in fact they have been singled out in many cases across the world and especially in Canada and certain states, south of the border. The Bible teaches Christians to be good citizens and obey the reasonable demands of our government. It does not, however, teach blind obedience to the authorities when onerous restrictions are placed on our freedoms. In fact, we are guaranteed the right to religious freedom and peaceful assembly in the Canadian Constitution, subject only to such reasonable limits prescribed by law as can be demonstrably justified in a free and democratic society. We now find ourselves debating what constitutes a justifiable, reasonable limit.

This past Sunday, April 19, 2020, we conducted a drive-in service at our meetinghouse parking lot in Aylmer, Ontario. Contrary to widely shared social media posts, attendees listened in to the service via low-power FM transmission while remaining in their vehicles, with their windows rolled up to ensure physical distancing requirements were adhered to. Strict guidelines were prescribed prior to the service and compliance was strictly enforced by our team. The service itself was conducted by 5 persons from an open-air platform that was visible to those in the parking lot. The meetinghouse itself was closed to the use of anyone, including bathroom facilities. There was no physical gathering at this location that contravened the Emergency Act, at any time.

Prior to this, our congregation continued to meet in accordance with previous guidelines of 50 or fewer persons in our building and on Easter Sunday there was a smaller drive-in service where those that participated in their vehicles livestreamed a service from another congregation, but, again, with no physical

livestreamed a service from another congregation, but, again, with no physical interaction. The Aylmer Police attended each one of these services and found no one in violation of the current Emergency Act. We have actively reached out to them and informed them of our intentions prior to the April 19th service.

We were informed Monday, April 20th, by the Aylmer Police that they had sought the opinion of the Crown Attorney's Office and that they were of the opinion that we were, in fact, in violation of the Emergency Act and that they would be taking active enforcement action if any further drive-in services were held in the future.

Now, we find ourselves confronted with a much greater dilemma than just deciding on what we do next Sunday. The question is, what is essential? If faith and the communal expression of faith is not essential, then is this an attack on faith (for we strictly followed all physical contact guidelines)? We are not asking for special treatment, just equal treatment. Christians have always believed that their faith and the reasonable expression of that faith is essential to their general well-being, as well as their mental and spiritual health. We believe that being arbitrarily separated from each other is detrimental to our community.

Just 300 meters south of us, during our service, hundreds of people interacted in a local grocery store and its parking lot. The same thing happened at the local Beer Store, LCBO, Tim Horton's parking lot, Dollarama, and the list goes on. Our drive-in service did not endanger the public, in fact we took far more stringent measures than any major retailer has done during this entire crisis. Yet, it is our faith community that is singled out for public criticism, false accusations, and a directive to cease any active operations, whether they follow the guidelines provided by the government or not.

It is imperative that we find a resolution to this as quickly as possible. There must be an allowable expression of faith that is deemed essential while we are allowing the interaction of customers at establishments that exist solely for the sale of alcohol, coffee, donuts, and fast food.

Pastor Henry Hildebrandt

EXHIBIT C

This is Exhibit "C" referred to
in the Affidavit of
Henry Hildebrandt
Sworn before me this 4th day
of June A.D., 20 21

A Commissioner for Oaths in and for Ontario

LISA D.S. BILDY
BARRISTER & SOLICITOR

Ford government amends prohibition on gatherings to permit drive-in religious services

May 19th, 2020

AYLMER, ONTARIO: The Justice Centre is pleased to report that the Ford government in Ontario has amended its order prohibiting gatherings to now expressly allow for drive-in religious services.

The amendment, posted on May 16, 2020 to the government's website, follows the filing of a Charter challenge by the Justice Centre against the Aylmer Police Service and the Ontario government last week. This court action challenged the government's infringement of a church's freedom of peaceful

assembly, and asked the court for clarification as to what is permitted under emergency legislation. The Aylmer Police had repeatedly threatened to fine the Church of God of Aylmer, despite the church using strict "social distancing" measures to comply with the law while hosting drive-in-only church services. Police attended the drive-in services in a show of force, and filmed both church representatives and parishioners in their cars during the worship service. The police were fully aware that worshipers were not leaving their parked cars, and that they were not interacting with each other in person.

The province's order under the *Emergency Management and Civil Protection Act* previously prohibited gatherings of more than five people, including for the purposes of conducting religious services, rites or ceremonies. Despite the fact that many stores and businesses remained open, with varying degrees of success in limiting physical contact between customers, churches and other religious centres had been singled out and effectively closed.

Like all laws in this country, the *Emergency Management and Civil Protection Act* is subject to the *Canadian Charter of Rights and Freedoms*, which guarantees citizens that the government will not infringe their freedoms of peaceful assembly and religion, among other fundamental freedoms, unless the restriction on freedom is demonstrably justified. Where there is a pressing and substantial concern, such as a declared public health emergency, the government may impose reasonable and narrow restrictions on *Charter* freedoms, but the government must violate those freedoms as little as possible, only to the extent necessary to achieve an important goal.

"We are pleased that the Ford government has finally clarified the order, and is now permitting this congregation and others to worship in peace" said Justice Centre staff lawyer Lisa Bildy. "However, this could have been done six weeks ago without putting congregants in the uncomfortable position of exercising their freedoms, even in a manner which posed no public health risks, under constant threat of punishment."

"As the province continues to reopen, I am hopeful that faith groups will not be an afterthought again, but will be permitted to broaden their ability to come together for worship in lockstep with the reopening of other businesses and institutions. Other provinces are already allowing outdoor services, and even indoor ones with reduced numbers and appropriate spacing. Ontario is quite a bit behind on this."

EXHIBIT D

This is Exhibit "D" referred to
in the Affidavit of
Henry Hildebrandt
Sworn before me this 4th day
of June A.D., 2021

A Commissioner for Oaths in and for Ontario

LISA D.S. BILDY
BARRISTER & SOLICITOR

Justice Centre
for Constitutional Freedoms

September 28, 2020

The Honourable Doug Ford
Premier of Ontario
[redacted]

Dear Premier Ford,

Re: Restrictions on Religious Freedoms and Further Lockdowns

I write on behalf of a coalition of faith leaders in Ontario, who are concerned about ongoing and potentially increasing restrictions on religious gatherings heading into the fall season.

Currently, places of worship are limited to 30% capacity. With attendance ramping up following the summer vacation period, this sometimes means turning parishioners away or coordinating multiple services which do not permit the faith community to meet as one body.

Faith groups have gone above and beyond to comply with restrictions and intrusive public health requirements over the past challenging six months, but have typically been an afterthought for your government. As you know, it took legal action or the threat thereof to legalize drive-in services and to get the doors open even to 30%, even though other groups, including non-essential businesses, were operating. Our clients would like to be able to conduct their worship services as they deem appropriate for the general wellbeing of their parishioners, including increasing access to their facilities – but at a minimum, they are asking that you not impose any further limitations or restrictions.

As faith leaders, our clients see the damage first-hand that these measures have on people, as their physical, mental, spiritual and emotional well-being is jeopardized. And citizens' freedoms to assemble and associate with one another, whether for religious reasons or otherwise, are so vital to the human condition and to Canada's liberal democratic order, that they are described as "fundamental freedoms" and are enshrined in our constitution. Attempts to restrict them must be subject to the most exacting scrutiny.

We understand that you are facing enormous political pressure from some quarters to "do something" about the increasing numbers of positive test results, including further lockdowns (although the overwhelming majority of these "cases" will never amount to

illness, let alone death, and may even reflect significant "false positives"[1]). However, there are also burgeoning numbers of citizens who believe that restrictions on their ability to worship, assemble and associate are unconstitutional and unjustified, and widespread protests can be expected to continue and grow.

Indeed, the Justice Centre has been reminding federal and provincial governments, through published reports and litigation, that infringements on the *Charter* rights and freedoms of Canadians are unconstitutional unless they can be demonstrably justified in a free and democratic society. In June, we published a paper on the Ontario lockdown measures entitled "*Unprecedented and Unjustified: A Charter Analysis of Ontario's Response to Covid-19*"[2]. That which was already evident in June is even more obvious in September – widespread lockdowns of healthy individuals are not minimally impairing, proportional or rational.

There is also no compelling evidence that lockdowns work, particularly when one considers the experiences of various countries around the world such as Peru (which locked down heavily and still suffered large losses) and Sweden (which did not lock down but appears to be avoiding the recent significant uptick in positive tests seen in other European countries).[3]

With recent news that your government is being lobbied by various doctors to impose another lockdown[4], we are concerned that insufficient consideration is being given to opposing views. We hope that your Command Table is avoiding groupthink, and an undue and unrelenting deference to the "precautionary principle", by hearing from doctors and experts who do not agree with the assessment contained in the news article cited in this paragraph. Should that not be the case, we would be pleased to connect you with such experts by arranging a meeting with members of your health team and cabinet.

Our clients and a growing number of Ontarians are troubled by the shifting goals of restrictive measures: from initially protecting the health care system, to what appears to be the unattainable objective of eradicating or supressing this virus at any cost. Increasing case tallies are seldom placed in the proper context, by explaining that the number of individuals being tested has risen vastly since we saw similar case numbers in the spring (naturally exposing a greater number of "cases", particularly asymptomatic ones); and, that there has been a dramatic decline in the numbers of hospitalizations and deaths since the spring. This perpetuates fear in those citizens who do not appreciate that context; while at the same time, engenders distrust of government and experts in those who do – a situation that is extremely detrimental to our civic health.

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[1] https://www.nytimes.com/2020/08/29/health/coronavirus-testing.html

[2] https://www.jccf.ca/published_reports/unprecedented-and-unjustified-ontario-lockdown/

[3] https://www.msn.com/en-us/news/world/sweden-shows-lockdowns-were-unnecessary-no-wonder-public-health-officials-hate-it/ar-BB1904YN

[4] https://www.newswire.ca/news-releases/tighter-restrictions-needed-now-to-halt-spread-of-covid-19-in-ontario-856947463.html

We wish to remind you that, while you may be hearing some clamoring to close things down again, your government has an obligation to uphold the *Charter* rights of citizens even in difficult times and even in the face of public pressure, and must take back control of the province from public health officials who do not consider and are not equipped to consider the broader social and economic impacts of their policies.

While our clients are quite prepared to continue incorporating reasonable, science-based recommendations to help protect the health of their parishioners, they will not tolerate further restrictions on their freedom of religion, and are prepared to take legal action immediately should that happen.

We trust that will be unnecessary.

Yours very truly,

Lisa D.S. Bildy, JD, BA
Staff Lawyer, Justice Centre for Constitutional Freedoms

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cc. MPP Monte McNaughton via email: monte.mcnaughtonco@pc.ola.org
cc. MPP Belinda Karahalios via email: belinda@ola.org
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cc. MPP William Bouma via email: will.bouma@pc.ola.org
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EXHIBIT E

This is Exhibit "E" referred to
in the Affidavit of
Henry Hildebrandt
Sworn before me this 4th day
of June A.D., 20 01

A Commissioner for Oaths in and for Ontario

LISA D.S. BILDY
BARRISTER & SOLICITOR

NEWS RELEASE

Ontario Announces Provincewide Shutdown to Stop Spread of COVID-19 and Save Lives

Government Providing Grants of up to $20,000 to Small Businesses Impacted by New Public Health Measures

December 21, 2020
Office of the Premier

TORONTO — As COVID-19 cases continue to rise at an alarming rate, the Ontario government, in consultation with the Chief Medical Officer of Health and other health experts, is imposing a Provincewide Shutdown. Additional restrictions will be put into place and reinforce that Ontarians should stay at home as much as possible to minimize transmission of the virus and prevent hospitals from becoming overwhelmed. The Provincewide Shutdown will go into effect as of Saturday, December 26, 2020, at 12:01 a.m.

Details were provided today by Premier Doug Ford, Christine Elliott, Deputy Premier and Minister of Health, Stephen Lecce, Minister of Education, Dr. David Williams, Chief Medical Officer of Health, and Dr. Naveed Mohammad, President and CEO, William Osler Health System.

"The number of daily cases continue to rise putting our hospitals and long-term care homes at risk," said Premier Ford. "We need to stop the spread of this deadly virus. That's why, on the advice of Dr. Williams and other health experts, we are taking the difficult but necessary decision to shutdown the province and ask people to stay home. Nothing is more important right now than the health and safety of all Ontarians."

In response to these exceptional circumstances, the Provincewide Shutdown would put in place time-limited public health and workplace safety measures similar to those in other jurisdictions. It would help stop the trend of high COVID-19 transmission in communities, preserve health system capacity, safeguard vulnerable populations and those who care for them, and save lives. Measures include, but are not limited to:

- Restricting indoor organized public events and social gatherings, except with members of the same household (the people you live with). Individuals who live alone may consider having exclusive close contact with one other household.
- Prohibiting in-person shopping in most retail settings - curbside pickup and delivery can continue. Discount and big box retailers selling groceries will be limited to 25 per cent capacity for in-store shopping. Supermarkets, grocery stores and similar stores that primarily sell food, as well as pharmacies, will continue to operate at 50 per cent capacity for in-store shopping.
- Restricting indoor access to shopping malls - patrons may only go to a designated indoor pickup area (by appointment only), essential retail stores that are permitted to be open (e.g. pharmacy, grocery store), or, subject to physical distancing and face covering requirements, to the food court for takeout purchases. Shopping malls may also establish outdoor designated pickup areas.
- Prohibiting indoor and outdoor dining. Restaurants, bars and other food or drink establishments will be permitted to operate by take out, drive-through, and delivery only.

On the advice of the Chief Medical Officer of Health, all Ontarians are advised to stay home as much as possible with trips outside the home limited to necessities such as food, medication, medical appointments, or supporting vulnerable community members. Employers in all industries should make every effort to allow employees to work from home.

The current COVID-19 Response Framework will be paused when the Provincewide Shutdown comes into effect. The impacts of these time-limited measures will be evaluated throughout the 14 days in Northern Ontario and 28 days in Southern Ontario to determine if it is safe to lift any restrictions or if they need to be extended.The Chief Medical Officer of Health will assess and apply lessons learned thus far to the COVID-19 Response Framework to ensure appropriate and effective measures are in place to protect the health of Ontarians and enable economic recovery after the Provincewide Shutdown ends. This will include an assessment of how a revised approach for the safe reopening of retail may be operationalized, according to the latest available evidence.

"This was not an easy decision before the holidays, but we have reached a tipping point," said Minister Elliott. "We continue to see sharp increases in hospitalizations and occupancy in intensive care units is reaching concerning levels. Urgent action must be taken to prevent our health care system from becoming overwhelmed. By implementing a Provincewide Shutdown, we can work to stop the virus in its tracks, safeguard hospital capacity, and save lives."

The government is also providing $12.5 million to implement a High Priority Communities Strategy to contain the virus in high-risk communities. The strategy will take a tailored, community-based approach to fund community agencies in 15 priority communities in the York, Peel, Durham, Ottawa, and Toronto regions. The funding will also allow for the hiring of community ambassadors to make people aware of available services and assistance, for coordination of increased testing opportunities and for the arrangement of wraparound supports for those who are COVID-positive. Additional funding of $42 million will also be available to establish isolation centres.

The province will work with our local municipal partners to establish new isolation centres to help those who may need to isolate following testing.

"We continue to see the number of cases in the province grow and the trends in public health indicators worsen. Additional measures are needed provincewide in order to interrupt this concerning growth," said Dr. Williams. "We must work together to enable everyone to follow these new and time-limited restrictions and protect our health system and our communities."

The government is working to limit the transmission of COVID-19 in workplaces by supporting essential businesses in doing whatever is necessary to keep workers safe. The Ministry of Labour, Training and Skills Development is leading a multi-ministry COVID-19 Safety Team. The team will partner with local authorities to carry out additional enforcement blitzes in sectors where they are needed most.

New School Protocols

While transmission in schools remains low, all publicly funded and private elementary and secondary schools are to move to teacher-led remote learning when students return from the winter break on January 4, 2021. This action is being taken in support of the Government's broader efforts to limit the spread of COVID-19.

Schools located in the following Public Health Unit regions can resume in-person instruction on January 11, 2021 for both elementary and secondary students:

- The District of Algoma Health Unit
- North Bay Parry Sound District Health Unit
- Northwestern Health Unit
- Porcupine Health Unit
- Sudbury and District Health Unit
- Thunder Bay District Health Unit
- Timiskaming Health Unit

For schools in all other Public Health Unit regions, elementary school students are planned to be able to return to in-person learning on January 11, 2021, and secondary school students will continue learning remotely until January 25, 2021, at which point they may resume in-person learning. During this period, child care centres, authorized recreational and skill building programs and home-based child care services will remain open. From January 4-8, 2021, when elementary students move to remote learning, before and after school programs will be closed and emergency child care for health care and frontline workers will be provided. As part of the government's efforts to protect the most vulnerable, boards will be required to make provisions for continued in-person support for students with special education needs who cannot be accommodated through remote learning for whom remote learning is challenging.

"While our schools are not a source of rising community transmission, we can play an important part of the solution to save lives from COVID-19," said Minister Lecce. "During this period, students will pivot to teacher-led online learning, with child care provided for our frontline workers. We are taking proactive and preventative action to protect schools following the holiday break to ensure kids can continue in-class learning — something we believe is so important — for the remainder of the year."

The New Ontario Small Business Support Grant

The government recognizes that small businesses impacted by these necessary public health measures will require additional support so they can continue serving their communities and employing people in Ontario once the COVID-19 pandemic is over. That is why the government is announcing the new *Ontario Small Business Support Grant*, which will provide a minimum of $10,000 and up to $20,000 to eligible small business owners to help navigate this challenging period.

"Ontario's business owners have shown remarkable resolve and ingenuity throughout the pandemic. They know better than anyone what they need to come through this very difficult time, so they can continue to serve and employ people in their communities," said Rod Phillips, Minister of Finance. "The new *Ontario Small Business Support Grant* will provide significant financial support to eligible small business owners in addition to the other supports made available to our small business community."

Small businesses required to close or restrict services under the Provincewide Shutdown will be able to apply for this one-time grant. Each small business will be able to use the support in whatever way makes the most sense for their individual business. For example, some businesses will need support paying employee wages or rent, while others will need support maintaining their inventory.

Eligible small businesses include those that:

- Are required to close or significantly restrict services subject to the Provincewide Shutdown effective 12:01 a.m. on December 26, 2020;
- Have less than 100 employees at the enterprise level; and
- Have experienced a minimum of 20 per cent revenue decline in April 2020 compared to April 2019.

Starting at $10,000 for all eligible businesses, the grant will provide businesses with dollar for dollar funding to a maximum of $20,000 to help cover decreased revenue expected as a result of the Provincewide Shutdown. The business must demonstrate they experienced a revenue decline of at least 20 per cent when comparing monthly revenue in April 2019 and April 2020. This time period was selected because it reflects the impact of the public health measures in spring 2020, and as such provides a representation of the possible impact of these latest measures on small businesses.

Essential businesses that are allowed to remain open will not be eligible for this grant. More information about the *Ontario Small Business Support Grant* is available here. Further details, including how to apply, will be announced in January 2021.

Businesses that are impacted by the Provincewide Shutdown will also be eligible for the property tax and energy cost rebates. In November, the government launched a program to provide rebates to offset fixed costs such as property tax and energy bills for businesses that are required to shut down or significantly restrict services due to provincial public health measures. These rebates will continue to be available for businesses impacted by the Provincewide Shutdown and earlier restrictions. Business can apply for the rebates here.

Quick Facts

- Currently, hospitalizations for COVID-19 have increased by 74 per cent over the last four weeks and are more than 15 times higher than they were at the beginning of September. Intensive care unit (ICU) occupancy for COVID-19 has more than doubled over the last four weeks and is 20 times higher than at the beginning of September.
- Ontario currently has 915 COVID-19 patients requiring acute care, 265 patients in ICU, with 152 on a ventilator.
- Based on the latest modelling data, cases across the province are continuing to grow and the number of people requiring an intensive care bed is projected to rise well above 300 people within the next 10 days.
- Some jurisdictions around the world, including those in Canada have implemented similar time-limited measures to respond to a dramatic resurgence in cases. Based on their experiences, measures of four to six weeks are expected to interrupt transmission of COVID-19 in Ontario.
- Municipalities and local medical officers of health may have additional restrictions or targeted requirements in their region.
- Get tested if you have symptoms compatible with COVID-19, or if you have been advised of exposure by your local public health unit or through the COVID Alert App. Visit Ontario.ca/covidtest to find the nearest testing location.
- The Ontario Small Business Support Grant is part of the Province's more than $13.5 billion in support for people and jobs outlined in the 2020 Budget, Ontario's Action Plan: Protect, Support, Recover. It is also in addition to $4.8 billion to address critical areas to support a strong long-term recovery that helps workers, employers and communities get back on their feet, while building the foundation for recovery and growth.
- To find the right supports, visit COVID-19: Support for People, which has information about the many available and free mental health services and supports.
- To stay safe you can download the COVID Alert App free from the Apple and Google Play app stores.
- To date, as part of the province's COVID-19 immunization program, over 3,000 frontline health care workers have been vaccinated.
- Schools continue to be safe, and according to data reported by school boards, as of Friday, December 18: approximately 99.64 per cent of students in Ontario have not reported a case of COVID-19; approximately 92 per cent of schools across

the province have had either no cases or one case reported within the last 14 days; and approximately 80 per cent of schools do not have an case of COVID-19.

Additional Resources

- Ontario Supporting High Priority Communities
- Ontario Building On Supports for Employers During COVID-19
- The Digital Main Street program helps main street businesses build their online presence and reach more customers.
- Property Tax and Energy Cost Rebates
- Visit Ontario's website to learn more about how the province continues to protect the people of Ontario from COVID-19.
- COVID-19: provincewide shutdown
- **If you have questions about what will be open or impacts to your business or employment, call the Stop the Spread Business Information Line at 1-888-444-3659.**

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EXHIBIT F

This is Exhibit "F" referred to
in the Affidavit of
Henry Hildebrandt
Sworn before me this 4th day
of June A.D., 20__

A Commissioner for Oaths in and for Ontario

LISA D.S. BILDY
BARRISTER & SOLICITOR

Put This Menace

Behind Bars

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GOD'S NOT GIVING US THE PROBLEMS RIGHT NOW...
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EXHIBIT G

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London · Video

Toronto police investigate reports 2 officers charged at Aylmer church for allegedly defying COVID-19 rules

Man, 42, and woman, 41, from suburban Toronto among 4 who received $880 tickets from Aylmer police

Colin Butler · CBC News · Posted: Apr 23, 2021 12:53 PM ET | Last Updated: April 23

Toronto police are investigating this social media video

18 days ago | 3:48

Investigators are looking over this video circulating on social media to see if two Toronto Police officers were among the four people charged for allegedly violating pandemic health restrictions at an Aylmer, Ont., church. 3:48

The Toronto Police Service is investigating reports two of its off-duty officers were among people charged at a gathering at an Aylmer, Ont., church known for its rebellious stance against Ontario's pandemic health rules.

Connie Osborne, a spokesperson for Toronto police, said in an email Friday to CBC News that TPS is aware of a social media video that's been circulating and the information has been passed on to the law enforcement agency's Professional Standards Investigation Unit.

The video was published Thursday on social media channels belonging to Independent MPP Randy Hillier, who has taken defiant stances on the government's public health measures.

"Watch this video of Police Officers being charged for exercising their Charter rights," says Hillier. "You won't hear this in the news, but two officers attending a meeting in the Aylmer Church of God and practicing their right to assembly have been charged under the Reopening Ontario Act," he said on Facebook.

Complaints focused on large gathering

The two off-duty officers were reportedly among four people charged by the Aylmer Police Service on Tuesday night at the Church of God in connection with complaints about a large gathering at the house of worship.

Each of the following individuals was given an $880 ticket under the provincial act:

- A man, 42, from the Toronto suburb of North York.
- A woman, 41, from the Toronto suburb of Scarborough.
- Two men, 34 and 20, from Aylmer.

CBC News has tried to confirm the identities of the two individuals from the Greater Toronto Area, but the Aylmer and Toronto police services, and Ontario's Ministry of the Attorney General were unable to verify the information.

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EXHIBIT H

This is Exhibit "H" referred to
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A Commissioner for Oaths in and for Ontario

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er.com/JustinTrudeau/status/1394099973709565954

EXHIBIT I

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Local News

Ontario defends recruit influx before latest police college COVID outbreak

The province is defending its decision to resume in-person training at the Ontario Police College, saying a shortage of new police officers would have put communities at risk.

Dale Carruthers
Mar 15, 2021 • March 15, 2021 • 2 minute read • 6 Comments

The Ontario Police College north of Aylmer. (Mike Hensen/The London Free Press)

The province is defending its decision to resume in-person training in January at the Ontario Police College despite its latest COVID-19 outbreak, saying a shortage of new police officers would have put communities at risk.

All in-person classes have been suspended at the Aylmer-area campus since last month after a COVID-19 outbreak led to 112 infections — 104 of them resolved — since Feb. 22, the Solicitor General's Ministry said.

The college's latest outbreak — the third since it reopened in June — comes after the school resumed in-person classes in January, taking in 438 recruits from police forces across Ontario, even as the province's elementary and secondary schools were closed amid a stay-at-home order.

The government has been in close consultation with health officials and various ministries to develop safety measures to deliver the basic constable training program, the ministry's Brent Ross said.

STORY CONTINUES BELOW

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“The ministry also engaged police services and policing organizations across the province,” Ross said by email.

“Our policing partners made it clear that the safety of their communities relied on new police officers being trained for duty on a regular basis and a shortage of officers would place their communities at risk.”

Solicitor General Sylvia Jones wasn’t available for an interview, Ross said.

Classes at the college initially were suspended for 14 days Feb. 25, but that suspension has been extended indefinitely.

“The college is working with local public health to determine when it is safe to return to the in-person format, as well as any additional protocols necessary to ensure the continued health and safety of all,” Ross said.

A Southwestern Public Health spokesperson said the college must remain closed until at least March 24. No timeline for reopening was offered.

MPP Jeff Yurek (PC-Elgin–Middlesex–London), whose riding takes in the college, said he’s heard some concern from constituents about possible spread of the virus in the community.

Following the most recent outbreak, all of the roughly 700 recruits, instructors and staff were tested — some high-risk individuals were tested twice — and those who tested positive are isolating at the college or at home.

The school also strengthened safety measures, including screening staff and students for COVID

symptoms, adding isolation rooms, wearing personal protective equipment when social distancing isn't possible, and increasing cleaning.

"All the necessary cautions were put in place," Yurek said of the steps taken to reopen the school. "There was a definite need for police officers' training to be completed due to retirements and such going on throughout the province."

dcarruthers@postmedia.com

All our coronavirus-related news can be found at lfpress.com/tag/coronavirus.

Sign up for our weekday email newsletter at noonnewsroundup.lfpress.com/p/1.

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Court File No: CV-21-08

HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO	***and***	**CHURCH OF GOD (RESTORATION) AYLMER et al.**
Applicant		*Respondents*

ONTARIO
SUPERIOR COURT OF JUSTICE

Proceeding commenced at St. Thomas

AFFIDAVIT OF HENRY HILDEBRANDT

JUSTICE CENTRE FOR CONSTITUTIONAL FREEDOMS

#253-7620 Elbow Drive SW
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Lawyer for the Respondents

Court File No. CV-21-08

ONTARIO

SUPERIOR COURT OF JUSTICE

B E T W E E N:

HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO

Applicant

- and -

THE CHURCH OF GOD (RESTORATION) AYLMER, HENRY HILDEBRANDT, ABRAM BERGEN, JACOB HIEBERT, PETER HILDEBRANDT, SUSAN MUTCH, ELVIRA TOVSTIGA and TRUDY WIEBE

Respondents

AFFIDAVIT OF KAREN BERGEN
(Sworn June 4, 2021)

I, KAREN BERGEN, of the [redacted] in the Province of Ontario, MAKE OATH AND SAY:

1. I am a member of the Church of God (Restoration) Aylmer ("**the Church**"), and as such have personal knowledge of the matters hereinafter deposed to, except where they are based on information and belief, in which case I verily believe them to be true.

2. I have been attending the Church for twenty-seven years. That is as long as I have been alive because my mother started attending the church before I was born. She was one of the original members in the Aylmer area. In fact, Pastor Hildebrandt, along with his family, came to visit my parents and me in the hospital when I was born.

3. The Church has been my life ever since, from my earliest memories of Sunday school and grade school, school-end celebrations and potlucks, down to my baptism, graduation, wedding, and now more than ever, my life as a wife and mother.

4. I am a stay-at-home mother, and my husband works in the trades currently. I met my husband when we went to school at the Church together. Since graduating, I have taught at the school (mainly science, math and history), and my eldest daughter will attend there in the fall. I also sing in the choir, and sometimes teach adult Bible study.

5. The people with whom we have attended for all these years are so much more than Sunday associates—they are family. We are a community. Our lives are so interwoven and connected that is impossible to separate them. We rejoice together at the births of our babies, celebrate together at our weddings, and grieve together at the passing of friends. We work together to educate our children and improve the lives of others.

6. To deny us our right to physically gather is to attempt to destroy the very backbone of our culture and way of life. It is not just the four walls of our building that we want, though they do hold sentimental value. It is the relationship with our people that we must have. There is no way that closeness can be replaced by watching an image on a screen.

7. Drive-in services cannot replace this connection either. Yes, it is nice to see your brother's vehicle and know he is there—about as nice as it would be to have him come and see you in prison where you can wave at him through the bars. Forget about any one-on-one conversations.

8. The feeling of loneliness and isolation that comes after a few weeks of these virtual methods is simply devastating to us, and to our children especially, who cannot develop good social skills when they have no one they are allowed to be social with.

9. Our lives cannot exist isolated and separated. Although other people may find the idea foreign these days, this desire to be connected to each other in a tight community drives us to meet and be reassured by each others' presence, regardless of the consequences.

10. And there have been consequences. When our church became targeted, there was a noticeable shift in the behavior of our previously friendly townspeople. The first change was in the police officers. Up to this point we had enjoyed a good standing relationship with the majority of the officers. Some years back, Pastor Henry mentioned, and I verily believe, that he had been complimented by one of the officers on the good behavior of our people, specifically the teenagers. But now, that relationship has regressed to pure, unabashed animosity in the case of some, though definitely not all, of our local officers.

11. The attitude of many, though again, definitely not all, of the store owners in town has become so hostile that I would sometimes rather do my shopping fifteen to thirty minutes out of town to avoid the unpleasant local experience. I try to spare my daughters from this by not bringing them with me on local shopping trips.

12. With the attention that our congregation has received, and the influx of people wanting to show solidarity with us or join us for worship, it has been quite a change for us. We have gone from knowing everyone personally, where they live and what they do for a living, to being surrounded by many new faces. It has, however, opened my eyes to how many people hunger for this same sense of community, as they join us to share our vision and burden.

13. I swear this affidavit *bona fide*, and for no other or improper purpose.

SWORN REMOTELY by videoconference)
by Karen Bergen at the [redacted])
[redacted], before me at the City of)
London, in the County of Middlesex, this 4th)
day of June, 2021 in accordance with O.Reg.)
431/20 Administering Oath or Declaration)
Remotely)
)

Karen Bergen
KAREN BERGEN

A Commissioner, etc.

LISA D.S. BILDY
BARRISTER & SOLICITOR

HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO	and	**CHURCH OF GOD (RESTORATION) AYLMER ET AL.**	CV-21-08
Applicant		Respondents	

ONTARIO
SUPERIOR COURT OF JUSTICE
Proceedings commenced at
St. Thomas

Affidavit Karen Bergen

JUSTICE CENTRE FOR CONSTITUTIONAL FREEDOMS

[redacted]

Lisa D. S. Bildy, [redacted]

Counsel for the Respondents The Church of God (Restoration) Aylmer, Henry Hildebrandt, Abram Bergen, Jacob Hiebert, Peter Hildebrandt, Susan Mutch, Elvira Tovstiga and Trudy Wiebe

Kitchener Court File No.: CV-21-00000095-0000
St. Thomas Court File No.: CV-21-08

ONTARIO
SUPERIOR COURT OF JUSTICE

B E T W E E N:

THE ATTORNEY GENERAL OF ONTARIO

Applicant (Responding Party)

-and-

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHUURMAN, DEAN WANDERS, RANDY FREY, HARVEY FREY and DANIEL GORDON

Respondents (Moving Parties)

A N D B E T W E E N:

HER MAJESTY THE QUEEN IN ONTARIO

Applicant (Responding Party)

-and-

THE CHURCH OF GOD (RESTORATION) AYLMER, HENRY HILDEBRANDT, ABRAM BERGEN, JACOB HIEBERT, PETER HILDEBRANDT, SUSAN MUTCH, ELVIRA TOVSTIGA, and TRUDY WIEBE

Respondents (Moving Parties)

AFFIDAVIT OF DR. THOMAS WARREN
(Sworn May 25, 2021)

I, **THOMAS WARREN**, of the [redacted] in the Province of, Ontario MAKE OATH AND SAY:

1. I am an Infectious Diseases consultant and Medical Microbiologist currently practicing in Oakville, Milton and Georgetown, Ontario, and as such have knowledge of the matters hereinafter deposed to.

2. I have been a member of the College of Physicians and Surgeons of Ontario since 2009. My curriculum vitae is attached hereto and marked as **Exhibit "A".**

3. I obtained my Doctor of Medicine (MD) from the University of Western Ontario in 2005, after which I completed a three-year residency in Internal Medicine through the University of Ottawa. Following my Internal Medicine residency, I completed a Fellowship in Infectious Diseases and a second residency in Medical Microbiology, both at the University of Toronto. During my residencies and fellowship, I regularly taught medical students and junior residents.

4. I have practiced in these specialty areas for ten (10) years. As part of my clinical practice, I teach through my appointment as an Assistant Clinical Professor (Adjunct) at McMaster University in Hamilton, ON. This includes supervising Infectious Diseases Clinical Rotations for physician assistant students, medical students, and Infectious Diseases fellows.

5. I am currently enrolled in a Master of Science (Epidemiology) at the London School of Hygiene and Tropical Medicine, University of London, with an expected completion date of 2022. Areas of study include the framework for understanding the epidemiology of infectious diseases and the mathematical theory underlying epidemiological studies.

6. In my medical microbiology residency, I was trained to develop, use and interpret reverse transcription polymerase chain reaction (RT-PCR) testing. I have practiced as a microbiologist for ten years in a microbiology laboratory that uses a variety of PCR tests. As an infectious diseases consultant, I interpret PCR test results in the context of clinical care.

7. The Moving Parties' counsel contacted me about providing expert testimony in support of their motion to set aside the enforcement order against them. I have

been asked to address issues surrounding the virus SARS-CoV-2 and Covid-19 disease, specifically: their description, PCR testing, asymptomatic transmission, and the utility of masks.

8. I acknowledge that in preparing this report and providing expert evidence, the Moving Parties' counsel explained that my role is to assist the court to determine the matters in issue. I further acknowledge that it is my duty to provide evidence that is fair, objective and non-partisan and to opine only on matters that are within my area of expertise. This duty prevails over any obligation that I may owe to any party on whose behalf I am engaged.

SARS-CoV-2 and COVID-19

9. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus. There are six other coronaviruses that are known to infect humans. Four coronaviruses, HCoV-NL63, HCoV-HKU1, HCoV-229E, and HCoV-OC43 circulate worldwide and together are the second most common cause of the common cold[1, 2]. Severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) infected 8096 people in 2003 resulting in 774 deaths[3]. After 2003 there has not been any further human to human transmission. Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in humans in 2012[4]. MERS-CoV continues to cause sporadic infection and outbreaks in the Arabian peninsula, as well as occasional other cases and outbreaks in other parts of the world linked to travelers to the Arabian peninsula[5].

10. Bats were the source of SARS-CoV-1[6] and are known to be a natural reservoir for related coronaviruses[7,8]. SARS-CoV-2 was likely circulating in bats for decades[9]. In late 2019, SARS-CoV-2 was first detected in humans and is established as the cause of the disease now designated coronavirus disease 2019 (COVID-19). Approximately 10-20% of persons with SARS-CoV-2 infection are asymptomatic[10,11]. In those who are symptomatic, there is a wide range of illness from those with mild symptoms such as runny nose to those with severe disease affecting particularly the respiratory tract with high mortality[12]. Most people with

SARS-CoV-2 infection are asymptomatic or have mild-moderate symptoms not requiring hospitalization. In one study of a relatively healthy population, those with COVID-19 requiring hospital care was < 2%, and the mortality rate was < 0.1%[11].

SARS-CoV-2 transmission and mortality

11. The timing of peak SARS-CoV-2 transmission is primarily affected by seasonal patterns (i). The scale of SARS-CoV-2 transmission in a susceptible population is primarily determined by population density (ii). The mortality of COVID-19 is primarily determined by the age structure of the population (iii). Each of these important factors for SARS-CoV-2 transmission and mortality is non-modifiable.

(i) The timing of peak SARS-CoV-2 transmission is primarily affected by seasonal patterns

12. The four human coronaviruses (OC43, 229E, NL63, HKU1) are known to have a seasonal pattern of increased transmission[1]. The peak of the transmission wave in the United States is in the coldest months of the year, usually January. SARS-CoV-2 transmission appears to have a similar seasonal pattern of transmission to the other seasonal human coronaviruses[13]. There are numerous studies that show climate (season) is one of the most important factors for SARS-CoV-2 transmission[14-26]. In general, colder temperatures are associated with increased SARS-CoV-2 transmission.

(ii) The scale of SARS-CoV-2 transmission is primarily determined by population density.

13. The transmission of SARS-CoV-2 is strongly associated with population density, particularly population-weighted density[15-18, 24, 27-31]. In the United States, incidence and mortality are ten times higher in the most densely populated areas compared to the least densely populated areas [32,33]. The association between population density and SARS-CoV-2 transmission has been identified in Europe[34], Italy[35], India[36,37], Argentina[38], Turkey[39], Algeria[40], Brazil[22], Japan[25], and China[41].

14. This is also evident in Canada. Provinces with the highest population density (e.g. Ontario) have the highest number of cases. Within provinces (e.g. Ontario), regions with the highest population density have the highest number of cases (e.g. Toronto).

(iii) The mortality of COVID-19 is primarily determined by the age structure of the population.

15. Age is the most important risk factor for COVID-19 mortality. Compared to persons under age 40, persons over the age of 80 have a greater than 300 times chance of dying from COVID-19[42]. The infection fatality ratio (IFR) in persons over 80 is approximately 1000 times the IFR in those under 20[43]. In Canada, 68% of deaths are in persons over 80, 87.5% of deaths are in persons over 70, and > 95% of deaths are in persons over 60[13].

16. The risk of death due to COVID-19 in persons under 60 is very small[44]. In Canada, there have been 1,010 COVID-19 deaths in persons < 60 years old as of April 16, 2021[13]. In Canada in 2018 there were 1,191 motor vehicle fatalities in persons under 55[45]. So, the risk of death due to COVID-19 in persons < 60 is less than the risk of death due to a motor vehicle fatality.

Asymptomatic transmission

17. A *British Medical Journal* editorial concisely summarizes the risk of asymptomatic transmission: "The transmission rates to contacts within a specific group (secondary attack rate) may be 3-25 times lower for people who are asymptomatic than for those with symptoms."[46] This is consistent with the conclusions from several peer-reviewed systematic reviews and meta-analyses[47-50].

18. To further exemplify the risk of asymptomatic transmission, it is useful to look specifically at a few large or comprehensive studies. A very large study in Wuhan China of 9,899,828 city residents found 300 asymptomatic cases but there were

no positive tests amongst 1,174 close contacts of asymptomatic cases[51]. Similarly, a very thorough study of 100 cases from Taiwan, found that "none of the 9 asymptomatic case patients transmitted a secondary case."[52]

19. Household transmission is one of the most important modes of transmission. In a meta-analysis of household transmission, which included 54 studies and 77 758 participants[53], transmission from asymptomatic cases was 0.7% compared to 18% transmission from symptomatic cases. In other words, symptomatic transmission was roughly 25 times higher than asymptomatic transmission.

20. Asymptomatic transmission does occur but the rates of transmission from asymptomatic persons is substantially less than from symptomatic persons and does not warrant being considered a significant contributor to the overall transmission burden.

Evidence for lockdown measures, including closing churches, to control SARS-CoV-2 transmission

21. Almost all of the research done prior to 2020 examining the effectiveness of interventions such as avoiding crowding (which would include church closure) to control respiratory tract infections was done with influenza. Prior to 2020, social distancing was a term that included quarantine, school closures, work closures as well as avoiding crowding.[54]

22. As noted in a recent systemic review, "clear biological and epidemiologic rationale supports the potential effectiveness of social distancing measures"[55] in the control of viral respiratory tract infections; however, the actual evidence for avoiding crowding by the general public for the control of viral respiratory tract infections is negligible.

23. A 2019 WHO review[54] of non-pharmaceutical public health measures for mitigating the risk and impact of epidemic and pandemic influenza found only three studies[56-

[58] relevant to "avoiding crowding". In all three studies the quality of evidence was rated as very low. Two of those studies were retrospective analysis of the 1918 pandemic,[56-57] both published in 2007. The limitations of studies done almost a century after an event should be self-evident, and hence the quality of that evidence is rated as very low. Importantly, in reference to "avoiding crowding" (which would include church closure) the WHO document notes[54]:

> Ethical considerations
>
> In urban locations it can be difficult to avoid crowding without considerable social costs.
>
> Modification, postponement or cancellation of mass gatherings may have cultural or religious considerations, in addition to public health aspects.
>
> Knowledge gaps
>
> There are still major gaps in our understanding of person-to-person transmission dynamics. Reducing mass gatherings is likely to reduce transmission in the community, but the potential effects are difficult to predict with accuracy. Large-scale RCTs [randomized controlled trials] are unlikely to be feasible.

24. A 2020 Cochrane systematic review[59] "found only one RCT [randomized controlled trial] of quarantine, and no trials of screening at entry ports or physical distancing [emphasis added]." Since there is a complete absence of high-quality evidence regarding physical distancing, the authors state: "Physical distancing represents another major research gap which needs to be addressed expediently, especially within the context of the COVID-19 pandemic setting as well as in future epidemic settings."[59]

25. In summary, while there is clear biological and epidemiological rationale for avoiding crowding, there is an absence of high-quality evidence, such as randomized-controlled trials, that prove the effectiveness of lockdown measures to avoid crowding in particular groups or contexts, including churches.

COVID-19 cases and deaths related to church outbreaks in the Canadian epidemiological context

26. The majority of deaths related to COVID-19 in Canada are related to outbreaks. As of April 3, 2021 there were 23,050 COVID-19 deaths in Canada, and 13,634 (59.1%) of those deaths were related to outbreaks[60]. Outbreaks are known to be important in the transmission of SARS-CoV-2, with perhaps 80% of all transmissions related to approximately 20% of infections, so-called superspreader events[61]. In Canada, 99.8% (13,600/13,634) of outbreak-related deaths are in settings that might be considered non-modifiable - long term care (12,473 deaths), healthcare (812 deaths), corrections/shelters (226 deaths), communities such as Indigenous communities (89 deaths)[60]. It is hard to imagine closing long term care homes, hospitals, corrections facilities and Indigenous communities - yet outbreaks in those settings account for 99.8% of outbreak-related COVID-19 deaths in Canada.

27. Religious gatherings appear to be grouped in the "Other" category which includes "social gatherings, office workplaces, recreational facilities, etc." in the Canadian epidemiologic summary[60]. The number of cases related to outbreaks in the "Other" category is 5,331. That is less than 1% (5,331/1,001,658) of all cases. Presumably, cases related to religious gatherings outbreaks make up only a fraction of cases in the "Other" category, with cases related to other social events more common, so the number of cases related to religious gatherings outbreaks is actually only a fraction of <1%.

28. Outbreak data from Ontario[62] show that less than 1% of all outbreaks (23/4151) are due to places of worship. Less than 1% of all outbreak cases (221/39774) are due to outbreaks at places of worship. Places of worship account for only 0.1% (5/3460) of all outbreak associated hospitalizations, and places of worship account for 0% (0/3681) of all outbreak associated deaths.

Evidence for masks in churches to prevent the spread of SARS-CoV-2

29. In short, and as stated by the World Health Organization (WHO), "there is only limited and inconsistent scientific evidence to support the effectiveness of masking of healthy people in the community to prevent infection with respiratory viruses, including SARS-CoV-2"[63].

30. The best evidence for any medical intervention comes from large randomized controlled trials or meta-analysis of randomized trials. There are no randomized controlled trials or meta-analysis of randomized controlled trials that support the effectiveness of masking of healthy people in the community to prevent infection with respiratory viruses, including SARS-CoV-2.

31. There is only one published randomized controlled trial on the effectiveness of masking of healthy people in the community to prevent infection with SARS-CoV-2. That study found there was no significant difference in SARS-CoV-2 infection rates between those who wore masks and those who did not wear masks[64].

32. Three recent meta-analyses show no benefit of masking healthy people in the community to prevent infection with respiratory viruses. Cochrane systematic reviews are widely recognized in the medical community as authoritative. A 2020 Cochrane meta-analysis of masks versus no masks in preventing viral respiratory illness found no difference in preventing influenza-like illness or laboratory confirmed illness[65]. Similarly, another meta-analysis published in 2020 showed that masks make no difference in preventing pandemic influenza in nonhealthcare settings[66]. Another meta-analysis by the WHO in 2019 also failed to show a substantial protective effect of face masks[67].

33. When the analysis is limited to the strongest types of evidence (randomized trials and meta-analyses of randomized trials), there is no evidence that healthy persons wearing masks in non-healthcare settings prevents the spread of SARS-CoV-2.

34. In the absence of evidence from randomized controlled trials and meta-analyses, the WHO's report on masking from December 1, 2020[63] references a number of other types of studies that purport to show that healthy persons wearing masks in non-healthcare settings prevents the spread of SARS-CoV-2; however, these studies have significant limitations that need to be considered.

35. The majority of the studies referenced by the WHO are ecological studies,[68-89] also called correlational studies. The ecological studies referenced by WHO compare mask use and COVID-19 rates between geographic region, such as country, state or city. The descriptive analysis of these rates does not provide an evidentiary base for concluding causation. Ecological studies have "many methodologic problems that severely limit causal inference, including ecologic and cross-level bias, problems of confounder control, within-group misclassification, lack of adequate data, temporal ambiguity, collinearity, and migration across groups."[90] The WHO report also acknowledges those studies have "have important limitations to consider"[63,91-93].

36. Cohort studies[94], case control[95-97] and case series[98-100] are all referenced in the WHO document, but these study types are considered much weaker than randomized controlled trials or meta-analysis. Due to the limitation of the study designs, particularly bias and confounding, the true effect of masking is uncertain. Many of these studies also have limited generalizability. For example, a study looking at secondary transmission of SARS-CoV-2 in households[94] has limited generalizability to universal masking in the wider general public. The findings from case series of persons who traveled on the same flight[98,99] cannot be generalized to universal masking.

37. Finally, a comment should be made on the study[101] by Chu et al. as that study is referenced by the WHO and has been widely cited in the media. As noted in the 2020 Cochrane review referenced above, the Chu et al. study "has been criticised for several reasons: use of an outdated 'Risk of bias' tool; inaccuracy of distance

measures; and not adequately addressing multiple sources of bias, including recall and classification bias and in particular confounding. Confounding is very likely, as preventive behaviours such as mask use, social distancing, and hand hygiene are correlated behaviours, and hence any effect estimates are likely to be overly optimistic."[65]

38. In summary, there is "inconsistent scientific evidence to support the effectiveness of masking of healthy people in the community to prevent infection with respiratory viruses, including SARS-CoV-2"[63]. Studies that support the effectiveness of masking are of poorer methodological quality and hence provide weaker evidence. Randomized controlled trial and meta-analysis, which provide stronger scientific evidence, do not support the effectiveness of masking of healthy people in the community to prevent infection with respiratory viruses, including SARS-CoV-2.

Polymerase chain reaction (PCR) for diagnosis of SARS-CoV-2 infection

39. Polymerase chain reaction (PCR) is a technology to amplify DNA fragments[102,103]. It is widely used in molecular biology, biotechnology, and medicine. Real time reverse transcription-polymerase chain reaction (real time RT-PCR) is a modification of PCR with an additional step of reverse transcription (RT) of RNA to DNA to enable amplification of an RNA target rather than a DNA target.

40. PCR is a relatively quick and inexpensive process that is highly sensitive. The process detects genetic material (DNA or RNA), even in minute quantities, and then copies it in a series of steps (cycles) that is usually done by a machine in a fully automated process. Each cycle doubles the amount of target DNA, and the newly created DNA is labeled with a fluorescent dye for detection. If a certain level of fluorescence is surpassed and detected by the machine, the test is considered positive. The cycle of the test that passes this threshold is called the cycle threshold (Ct).

41. PCR is commonly used in microbiology laboratories for the diagnosis of infectious diseases. While PCR can be the best diagnostic tool to diagnose many infections, it does have important limitations that also need to be considered.

Limitations of PCR

42. The World Health Organization (WHO) recognizes the limitations of PCR and advises that "health care providers must consider any result in combination with timing of sampling, specimen type, assay specifics, clinical observations, patient history, confirmed status of any contacts, and epidemiological information"[104]. The WHO guidance goes on to say that "disease prevalence alters the predictive value of test results; as disease prevalence decreases, the risk of false positive increases. This means that the probability that a person who has a positive result (SARS-CoV-2 detected) is truly infected with SARS-CoV-2 decreases as prevalence decreases, irrespective of the claimed specificity."

43. A positive RT-PCR result represents the identification of SARS-CoV-2 virus fragments, but a positive RT-PCR result does not necessarily indicate the entire virus is present, replication competent virus is present, or the patient has COVID-19. If the entire virus is not present in the person, or the virus is not replication competent, then the person is not infectious.

44. A study from Singapore[105] showed that the higher the Ct value, the larger degree of viral fragmentation and the less likely that an entire viral genome is actually present. In other words, the higher the Ct, the more likely it is that only bits of virus are being detected, and less likely that entire virus is present in the patient. Only complete virus particles can be replication competent and therefore infectious and transmissible.

45. Many studies have convincingly shown that the higher the Ct, the less likely replication-competent virus (infectious virus) can be detected through cell culture[106-113]. An editorial in *Clinical Infectious Diseases* concluded "that PCR

positivity is likely not a reliable surrogate marker for determining the infectious status of COVID-19 patients"[114]. A systematic review on the topic concluded that test results "with high cycle threshold are unlikely to have infectious potential."[115]

46. That a positive test does not necessarily indicate infectiousness is indicated by recommendations for stopping isolation in persons previously positive for SARS-CoV-2. The WHO[116-117], CDC[118], and Canadian jurisdictions[119] recommend discontinuing isolation of persons with COVID-19 ten days after symptom onset, and in persons who have tested positive for SARS-CoV-2 without symptoms ten days after their first positive RT-PCR result, even though it is well established that many persons in these groups will continue to have positive RT-PCR results after those time frames. Those guidelines recommend against RT-PCR testing in these groups because it is known that positive tests in these groups does not indicate infectiousness. This is a concrete application of the evidence that late in the course of SARS-CoV-2 infection, which corresponds to increasing Ct, there is no risk of transmission. In another example, Ontario uses point-of-care tests, that are less sensitive than RT-PCR, to rule out SARS-CoV-2 infection[120] in persons who are symptomatic without known contact with a positive case. In this case, even though a more sensitive test such as RT-PCR might detect more positives, a less sensitive test[121] is sufficient to rule out significant infection.

47. Evidence shows that the higher the Ct value, the more likely it is that a person is in the later stages of the infection, and therefore less infectious. The nearer the Ct value approaches 40, the closer the likelihood that the patient is infectious approaches zero. A report from the Emerging Sciences Group of the Public Health Agency of Canada[122] concludes that in symptomatic persons there is "a peak in viral load ranging from just before to during the first week after onset of illness" and in asymptomatic persons "viable virus and viral RNA was highest during the first week of infection and declined in subsequent weeks." In persons that are asymptomatic or mildly symptomatic, late in the course of illness the Ct value is

higher[110] and viable virus cannot be detected though cell culture. The likelihood of a positive cell culture correlates with disease severity[123], and therefore risk of infectiousness correlates with disease severity.

48. The Ct value early in the course of illness is significantly lower than the Ct value late in the course of illness[124]. The Ct value of pre-symptomatic persons has been shown to be low, and not be significantly different from symptomatic persons; in one study, the Ct value was 23.1 for pre-symptomatic persons compared to 24.8 in persons with typical symptoms[10]. There is a clear association between Ct value and stage of infection; the higher the cycle threshold[123], the more likely the patient is in the later stages of the infection, and the less likely the patient is infectious or at risk of transmitting the virus to another person.

SARS-CoV-2 infection versus COVID-19 disease

49. It is important to recognize the difference between SARS-CoV-2 infection and COVID-19 disease. This is an important distinction that is made with many other infections. As noted in a *British Medical Journal* editorial: "Unusually in disease management, a positive test result is the sole criterion for a Covid-19 case. Normally, a test is a support for clinical diagnosis, not a substitute."[125] In other words, for COVID-19, a positive test is sufficient to make the diagnosis, which is not done in other infections that are similarly mild and short-lived.

50. A positive SARS-CoV-2 PCR test means that a person has or recently had SARS-CoV-2 (virus) in their body; however, it does not mean that the person is infectious or that they have COVID-19 disease (i.e. symptoms). If we wanted to define specificity as diagnosing infectiousness or disease (i.e. symptoms or pathology), then the specificity of RT-PCR would be dramatically lower. This distinction can be better understood if we look at how PCR is used in other infections.

51. To cite just a few examples, positive PCR tests for Group A Streptococcus, Salmonella, E. coli O157, Campylobacter, C. difficile, Epstein-Barr Virus (EBV),

Cytomegalovirus (CMV) do not necessarily indicate disease. In the absence of symptoms or other tests indicating pathological effects, persons with positive PCR tests for those infections are not considered to have disease and they are usually not treated. The distinction between infection and disease is important. Over 50% of adult Canadians will be infected with EBV or CMV for most of their life; once acquired, those infections persist lifelong and PCR tests can detect those viruses, to varying degrees, throughout their lifetime. It would be inaccurate to say that over 50% of Canadians have disease associated with those viruses even though they can be detected by PCR.

52. A positive PCR result also does not necessarily indicate infectiousness. At any time, about 10% of school-aged children will have throat swabs positive for Group A Streptococcus (GAS)[126,127]. GAS can cause pharyngitis (strep throat), scarlet fever, rheumatic fever, and necrotizing fasciitis (flesh eating disease), but a positive test in an asymptomatic person is not considered significant in most cases.

53. Even a positive RT-PCR result in a person living with HIV does not necessarily mean that the person is considered infectious. According to Canadian law[128], "the combined effect of condom use and low viral load precludes a realistic possibility of transmission of HIV". Similarly, the Ontario Court of Appeal stated that "viral loads below a defined level, standing on their own, are sufficient to negate the realistic possibility of HIV transmission"[129].

54. The presence of SARS-CoV-2 virus as detected by PCR is necessary but not sufficient to indicate either infectiousness or COVID-19 *disease* properly defined. If a true positive is defined as the presence of complete virus, or replication competent virus (i.e. infectious virus) then the specificity of PCR is much lower and the number of false positives associated with PCR would be considered much higher.

Outdoor transmission of SARS-CoV-2

55. The risk of outdoor transmission of SARS-CoV-2 at outdoor religious services is negligible when physical distancing is maintained. The evidence for this assertion can be examined in two domains: First, by examining the evidence for outdoor transmission of other important respiratory tract infections such as tuberculosis (TB) and influenza; second, by examining the evidence for transmission of SARS-CoV-2 itself.

56. Since we only have just over one year of experience with SARS-CoV-2, it is helpful to look at the risk of outdoor transmission of two other very important respiratory tract infections, TB and influenza. TB is a respiratory tract infection that is transmitted through airborne particles. The *Canadian Tuberculosis Standards* published by the Public Health Agency of Canada state that TB "transmission is rarely thought to occur outdoors"[130] and the "risk of [outdoor] transmission is negligible provided they are not in very close contact with susceptible individuals for prolonged periods of time"[131]. The result is that "outdoor exposures are not investigated during a contact tracing exercise"[132].

57. Influenza is another important respiratory tract infection. In a systematic review of outdoor mass gatherings and respiratory disease (mostly influenza) performed by the United States Centers for Disease Control and Prevention, "no single-day mass gathering-related outbreaks were identified in our review"[133]. Similarly, a global review of outbreaks (including influenza outbreaks) at outdoor large gatherings from 1980 to July 2012 did not identify any outbreaks associated with single day gatherings[134]. These studies and others were included in a systematic review of outdoor transmission of SARS-CoV-2 and other respiratory viruses; influenza outbreaks only occurred in the context of multiday outdoor events or communal housing[135].

58. The primary mode of SARS-CoV-2 transmission is known to occur indoors. Household transmission (indoors) accounted for 78%-85% of all SARS-CoV-2 transmission in China in one report from the World Health Organization[136]. Household contacts and travel together were the most important sources of SARS-CoV-2 transmission in another study[137]. Outbreaks in indoor contexts such as long-term care facilities, hospitals and shelters have been established as an important source of indoor transmission in the Canadian context[138].

59. The evidence for outdoor SARS-CoV-2 transmission, when present, is negligible. In one comprehensive study from China[139], only one outdoor outbreak involving two cases occurred out of 7324 identified cases. The reason for negligible outdoor transmission is that airflow outdoors rapidly dilutes any SARS-CoV-2 virus present to negligible amounts not considered to be infectious[140].

60. As shown above, outdoor religious gatherings of short duration (less than 24 hours; no overnight component) should be considered safe based on the evidence. The risk of outdoor transmission of SARS-CoV-2 is negligible, similar to other important respiratory infections such as TB and influenza. As long as physical distancing can be maintained, outdoor religious gatherings should be considered safe.

61. I make this affidavit *bona fide*.

SWORN REMOTELY by videoconference by Dr. Thomas Warren at [redacted] before me at the City of London, in the County of Middlesex, this 25th day of May, 2021 in accordance with O.Reg. 431/20 Administering Oath or Declaration Remotely

A Commissioner, etc.

LISA D.S. BILDY
BARRISTER & SOLICITOR

DR. THOMAS WARREN

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This is Exhibit "A" referred to
in the Affidavit of
Dr. Thomas Warren

Sworn before me this 25th day
of May A.D., 20 21

A Commissioner for Oaths in and for Ontario

LISA D.S. BILDY
BARRISTER & SOLICITOR

Thomas A. Warren, MD

[redacted]

Employment

2011 -	**Infectious Diseases consultant & Medical Microbiologist** Halton Healthcare, Oakville ON
2010-2011	**Internal Medicine specialist – locum coverage** St. Michael's Hospital, Toronto ON Hamilton Health Sciences, Hamilton ON Lakeridge Health, Oshawa ON
2010-2011	**University of Toronto** Department of Laboratory Medicine & Pathobiology, Toronto ON *Resident, Medical Microbiology*
2008-2010	**University of Toronto** Department of Medicine, Division of Infectious Diseases, Toronto ON *Fellow, Infectious Diseases*
2005-2008	**University of Ottawa** Department of Medicine, Ottawa ON *Resident, Internal Medicine*
1997-2003	**University of Western Ontario** Department of Medicine, London ON *Computer Programmer & Web Developer*

Education

2018 -	**London School of Hygiene and Tropical Medicine, University of London** *Master's of Science (Epidemiology)* Expected Completion 2022
2010-2011	**Royal College of Physicians & Surgeons of Canada** *Residency in Medical Microbiology*

2008-2010	**Royal College of Physicians & Surgeons of Canada** *Fellowship in Infectious Diseases*
2005-2008	**Royal College of Physicians & Surgeons of Canada** *Residency in Internal Medicine*
2001-2005	**University of Western Ontario** Schulich School of Medicine & Dentistry *Doctor of Medicine*
1997-2001	**University of Western Ontario** *Bachelor of Science - Honors Microbiology & Immunology* *(Scholar's Electives Program)* Graduated With Distinction

Continuing Medical Education

2018	**IDEAS Foundations of Quality Improvement Program** May 30 McMaster University Hamilton, ON
2018	**Clinical Teaching Fundamentals** January - March McMaster University Hamilton, ON

Peer-Reviewed Publications

2015	**Warren T**, Lau R, Ralevski F, Rau N, Boggild AK. Fever in a visitor to Canada: a case of mistaken identity. *J Clin Microbiol.* 53:1783-1785.
2012	**Warren TA**, Yau Y, Ratjen F, Tullis E, Waters V. Serum galactomannan in cystic fibrosis patients colonized with *Aspergillus* species. *Medical Mycology.* 2012; 50: 858-860.
2010	**Warren TA**, McTaggart L, Richardson SE, Zhang SX. Candida bracarensis Bloodstream Infection in an Immunocompromised Patient. *Journal of Clinical Microbiology.* 2010; 48: 4677–4679.

Abstracts & Conference Presentations

2011 **Warren TA**, Yau Y, Waters V.
Serum galactomannan in cystic fibrosis patients colonized with Aspergillus species.
Poster session presented at: Association of Medical Microbiology and Infectious Disease (AMMI) Canada 2011 Annual Conference
2011 April 7-9; Montreal, QC.

2010 **Warren TA**, Yau Y, Waters V.
Serum galactomannan in cystic fibrosis patients colonized with Aspergillus species.
Poster session presented at: North American Cystic Fibrosis Conference
2010 October 21-23; Baltimore, MD.

2010 **Warren TA**, Govindapillai S, Tullis E, Devlin HR, Ferris W, Matukas LM.
Evaluation of Etest Combination Testing of Antibiotics Against Isolates from Patients with Cystic Fibrosis.
Poster session presented at: 50th Interscience Conference on Antimicrobial Agents and Chemotherapy
2010 September 12-15; Boston, MA.

2010 **Warren TA**, Rotstein C, Cole EH, Singer LG, Keshavjee SH, Husain S.
Posaconazole therapy in solid organ transplant recipients refractory to or intolerant of standard therapy.
Poster session presented at: Canadian Society for Transplantation Annual Conference
2010 August 12-15; Vancouver, BC.

2010 **Warren TA**, McTaggart L, Zhang S. Candida bracarensis
Blood Stream Infection in an Immunocompromised Patient: Case Report.
Poster session presented at: Focus on Fungal Infections
2010 March 3-5; New Orleans, LA.

2007 **Warren TA**, McCarthy AE.
A Ten-Year Retrospective Study of Vaccination Rates, Prophylactic Antibiotic Use, Serious Infection and Overwhelming Postsplenectomy Sepsis Rates in Splenectomized Patients.
Poster session presented at: Annual Meeting of the Infectious Diseases Society of America
2007 October 4-7; San Diego, CA.

Awards

2011 **Best Student Poster Award – 2011 Annual Conference**
Association of Medical Microbiology and Infectious Disease (AMMI) Canada
Montreal, QC

2010 **ASM ICAAC Infectious Diseases Fellows Grant**
2010 Interscience Conference on Antimicrobial Agents and Chemotherapy
Boston, MA

2008 **Internal Medicine CanMeds Award for Communication**
University of Ottawa, Department of Medicine
Ottawa, ON

2006 **Resident Research Day Award of Excellence – PGY1**
University of Ottawa, Department of Medicine
Ottawa, ON

2001 Laurene Paterson scholarship
University of Western Ontario
London, ON

1997-2001 **Dean's Honor List**
University of Western Ontario, Faculty of Science
London, ON

1997 **Western Scholarship of Excellence**
University of Western Ontario
London, ON

Appointments

2013 - **McMaster University**
Assistant Clinical Professor (Adjunct)
Department of Medicine, Faculty of Health Sciences
Hamilton, ON

Teaching

2012-2021 **Infectious Diseases** – Clinical Rotations
Supervised physician assistant students, medical students, residents and infectious diseases fellows from the University of Toronto and McMaster University
Oakville, ON

2009	**Pathobiology of Disease** *Taught microbiology to second year medical students* University of Toronto Toronto, ON
2008	**Pathobiology of Disease** *Taught microbiology to second year medical students* University of Toronto Toronto, ON
2008	**Physical Skills Development Course** *Taught physical exam skills to first year medical students* University of Ottawa Ottawa, ON

Memberships

Association of Medical Microbiology and Infectious Diseases Canada

Canadian Medical Association

Canadian Medical Protective Association

College of Physicians and Surgeons of Ontario

Ontario Medical Association

Royal College of Physicians and Surgeons of Canada

FORM 53

Kitchener Court File No.: CV-21-00000095-0000
St. Thomas Court File No.: CV-21-08

ONTARIO
SUPERIOR COURT OF JUSTICE

B E T W E E N:

THE ATTORNEY GENERAL OF ONTARIO

Applicant (Responding Party)

-and-

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHUURMAN, DEAN WANDERS, RANDY FREY, HARVEY FREY and DANIEL GORDON

Respondents (Moving Parties)

A N D B E T W E E N:

HER MAJESTY THE QUEEN IN ONTARIO

Applicant (Responding Party)

-and-

THE CHURCH OF GOD (RESTORATION) AYLMER, HENRY HILDEBRANDT, ABRAM BERGEN, JACOB HIEBERT, PETER HILDEBRANDT, SUSAN MUTCH, ELVIRA TOVSTIGA, and TRUDY WIEBE

Respondents (Moving Parties)

ACKNOWLEDGMENT OF EXPERT'S DUTY

---

1. My name is Dr. Thomas Warren. [redacted], Ontario.

2. I have been engaged on behalf of the Moving Parties, Trinity Bible Chapel et al. and The Church of God, et al., to provide evidence in relation to the above-noted court proceeding.

3. I acknowledge that it is my duty to provide evidence in relation to this proceeding as follows:

   (a) to provide opinion evidence that is fair, objective and non-partisan;

   (b) to provide opinion evidence that is related only to matters that are within my area of expertise; and

(c) to provide such additional assistance as the court may reasonably require, to determine a matter in issue.

4. I acknowledge that the duty referred to above prevails over any obligation which I may owe to any party by whom or on whose behalf I am engaged.

Date: May 25, 2021

Signature

NOTE: This form must be attached to any expert report under subrules 53.03(1) or (2) and any opinion evidence provided by an expert witness on a motion or application.

Kitchener Court File No.: CV-21-00000095-0000
St. Thomas Court File No.: CV-21-08

HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO	***and***	**CHURCH OF GOD (RESTORATION) AYLMER et al.**
THE ATTORNEY GENERAL OF ONTARIO	***and***	**TRINITY BIBLE CHAPEL et al.**
Applicants		*Respondents*

ONTARIO
SUPERIOR COURT OF JUSTICE

Proceeding commenced at St. Thomas

AFFIDAVIT OF DR. THOMAS WARREN

JUSTICE CENTRE FOR CONSTITUTIONAL FREEDOMS

[redacted]

Lisa D.S. Bildy [redacted]

[redacted]

Lawyer for the Respondents

Kitchener Court File No.: CV-21-00000095-0000
St. Thomas Court File No.: CV-21-08

ONTARIO
SUPERIOR COURT OF JUSTICE

B E T W E E N:

THE ATTORNEY GENERAL OF ONTARIO

Applicant (Responding Party)

– and –

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHUURMAN, DEAN WANDERS, RANDY FREY, HARVEY FREY and DANIEL GORDON

Respondents (Moving Parties)

A N D B E T W E E N:

HER MAJESTY THE QUEEN IN ONTARIO

Applicant (Responding Party)

-and-

THE CHURCH OF GOD (RESTORATION) AYLMER, HENRY HILDEBRANDT, ABRAM BERGEN, JACOB HIEBERT, PIETER HILDEBRANDT, SUSAN MUTCH, ELVIRA TOCSTIGA, and TRUDY WIEBE

Respondents (Moving Parties)

BOOK OF SOURCES FOR THE EXPERT REPORT OF DR. THOMAS WARREN

JUSTICE CENTRE FOR CONSTITUTIONAL FREEDOMS
[redacted]

Allison Pejovic
[redacted]

Lisa D. S. Bildy, [redacted]

Jorge Pineda
[redacted]

Counsel for the Respondents

INDEX

TAB*	SOURCE	BATES NUMBERING INDEX
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4.	Dawson P, Malik MR, Parvez F, Morse SS. What Have We Learned About Middle East Respiratory Syndrome Coronavirus Emergence in Humans? A Systematic Literature Review. Vector Borne Zoonotic Dis. 2019 Mar;19(3):174-192.	0023
5.	https://www.who.int/health-topics/middle-east-respiratory-syndrome-coronavirus- mers#tab=tab_1	0043
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Human coronavirus circulation in the United States 2014–2017☆

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ABSTRACT

Background: Human coronaviruses (HCoVs) -OC43, -229E, -NL63 and -HKU1 cause upper and lower respiratory tract infections. HCoVs are globally distributed and the predominant species may vary by region or year. Prior studies have shown seasonal patterns of HCoV species and annual variation in species prevalence but national circulation patterns in the US have not yet been described.
Objectives: To describe circulation patterns of HCoVs -OC43, -229E, -NL63 and -HKU1 in the US.
Study design: We reviewed real-time reverse transcription polymerase chain reaction (rRT-PCR) test results for HCoV-OC43, -229E, -NL63 and -HKU1 reported to The National Respiratory and Enteric Virus Surveillance System (NREVSS) by U.S. laboratories from July 2014–June 2017. We calculated the total number of tests and percent positive by week. For a subset of HCoV positive submissions with age and sex of the patient available, we tested for differences in age and sex across the four HCoV species using Chi Square and Kruskal Wallace tests.
Results: 117 laboratories reported 854,575 HCoV tests; 2.2% were positive for HCoV-OC43, 1.0% for HCoV-NL63, 0.8% for HCoV-229E, and 0.6% for HCoV-HKU1. The percentage of positive tests peaked during December – March each year. No significant differences in sex were seen across species, although a significant difference in age distribution was noted.
Conclusions: Common HCoVs may have annual peaks of circulation in winter months in the US, and individual HCoVs may show variable circulation from year to year. Different HCoV species may be detected more frequently in different age groups. Further years of data are needed to better understand patterns of activity for HCoVs.

1. Background

Human coronaviruses (HCoVs) HCoV-NL63, HCoV-HKU1, HCoV-229E, and HCoV-OC43 circulate worldwide and cause a range of respiratory symptoms [1]. Infections are often asymptomatic or associated with mild to moderate upper respiratory tract illness in immunocompetent children and adults; HCoVs are considered the second most common cause of the common cold [2]. Infections can also result in lower respiratory tract illness including bronchiolitis and pneumonia, especially in immunocompromised individuals, infants, and older adults [1]. Increased availability of molecular test methods and more frequent testing for multiple respiratory pathogens have allowed for opportunities to characterize circulation patterns of individual HCoVs.

Although HCoVs are globally distributed, the predominant species may vary by region or year [3–5]. Previous studies have shown seasonal patterns of HCoV species and annual variation in species prevalence [3,4,6]. However, national circulation patterns across the United States have not been described and few studies have described circulation of all four HCoVs across multiple years [6].

2. Objectives

Our objective was to describe laboratory detections of HCoVs

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-NL63, -HKU1, -229E, and -OC43 in the United States during 2014–2017, using data collected by The National Respiratory and Enteric Virus Surveillance System (NREVSS) [7].

3. Study design

NREVSS is a passive surveillance network established by the U.S. Centers for Disease Control and Prevention (CDC) in the 1980s that collects specimen test results for several respiratory and enteric viruses from multiple laboratories across the United States [7]. NREVSS currently collects data from three different sources: directly from clinical, state, and local laboratories; indirectly from state or local partners on behalf of laboratories within their jurisdictions; and indirectly through the Public Health Laboratory Interoperability Project (PHLIP).

PHLIP is a collaborative partnership between CDC, state and local public health labs (PHLs), and the Association of Public Health Laboratories (APHL) to strengthen the submission of automated specimen-level surveillance laboratory test results directly to CDC [8]. Laboratories submitting to NREVSS via PHLIP submit specimen level results for respiratory virus tests along with patient demographics, such as sex and age. The remaining majority of NREVSS participants (i.e. non-PHLIP submitters) submit weekly aggregates of positive detections for the four HCoV species by RT-PCR along with the aggregate number of RT-PCR HCoV tests performed.

To better understand HCoV circulation in the US, we assessed reports of specimens tested for HCoVs, and submitted to NREVSS during July 1, 2014–June 30, 2017. Reporting laboratories were excluded if they did not report HCoV results at the species level. We summarized the total number of HCoV tests submitted during the study period and calculated the overall percent positive for each HCoV species by week. Test numbers and positive HCoV results were also summarized separately for individual US census regions.

To understand demographics of patients with HCoV detections we further analyzed the subset of NREVSS data reported through PHLIP. We selected reports of specimens tested for all four HCoV species and calculated the percent positive for each HCoV species. We used all PHLIP reports with a single positive HCoV detection to test differences in age distribution among the four HCoV species using the Kruskal Wallis Test. Differences in sex distribution among the four HCoV species were tested using the Chi Square Test. We then summarized viral co-detections for each HCoV species using reports of specimens tested for all four HCoVs and which were also tested for the following viruses: parainfluenza viruses 1–4, respiratory syncytial virus (RSV), human metapneumovirus, human adenovirus, rhinovirus/enterovirus, influenza A and influenza B. Analysis was performed using R version 3.3.1.

4. Results

During July 1, 2014–June 30, 2017, 854,575 HCoV tests were reported by 117 laboratories in 42 states submitting to NREVSS. Overall, 18,804 (2.2%) were positive for HCoV-OC43, 8558 (1.0%) for HCoV-NL63, 7001 (0.8%) for HCoV-229E and 5225 (0.6%) for HCoV-HKU1. The number of HCoV tests submitted to NREVSS per week varied seasonally, with the testing peak occurring each year in winter, generally between December and March (Fig. 1A). Overall HCoV testing increased during the three years (Fig. 1A). The percent of HCoV positive tests varied throughout each year, and also peaked each year between December and March. The percent positive varied annually by HCoV species (Fig. 1B). HCoV-OC43 demonstrated a distinct peak each of the three years, with a less pronounced peak in 2016. HCoV-NL63 and HCoV-HKU1 demonstrated similar patterns to one another; both had a small peak in 2015 and larger peaks in 2016, although only HCoV-NL63 had a small peak in 2017. HCoV-229E showed a slight peak in 2015, no peak in 2016 and a relatively large peak in 2017 (Fig. 1B). The highest percent positive for any single species was 7.6% of tests positive for HCoV-OC43 in the week beginning December 31, 2016. Across each census region, minimal differences in seasonal and annual patterns of percentage of tests positive for each HCoV species were seen compared to national data (Fig. 2). The most notable difference was in the percentage of positive HCoV-OC43 tests during the 2016–2017 season, with the West region showing a peak percent positive of 5.0% and the Midwest region showing a peak percent positive of 12.4%.

Data reported to NREVSS through PHLIP was further analyzed to understand sex and age characteristics. During the study period, 20,806 specimens tested for all four HCoVs were submitted via PHLIP from six laboratories. Overall 1569 tests (7.5%) were positive for any HCoV; 852 (4.1%) were positive for HCoV-OC43, 255 (1.2%) for HCoV-NL63, 335 (1.6%) for HCoV-229E and 154 (0.7%) for HCoV-HKU1. The majority of specimens with a single HCoV detection (92.2% of 1543 specimens) included the sex of the patient, and approximately half (50.6%) of all these HCoV detections were reported as male. No significant difference was seen in the sex distribution between the four HCoVs ($p = 0.19$). Age was available for 1016 (67%) of specimens with a single HCoV detection and the median patient age of these specimens was 23 years (range 0–96 years). The patient age distribution of specimens with a single HCoV detection was significantly different between species

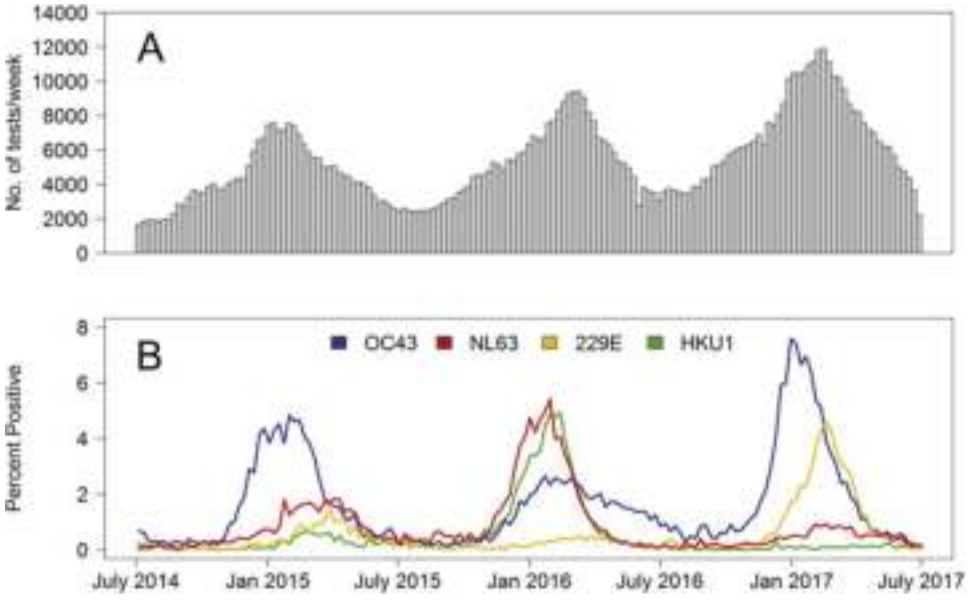

Fig. 1. A) The number of tests performed to detect any of the four human coronaviruses (HCoVs) -OC43, -NL63, -229E, and -HKU1 reported to the National Respiratory and Enteric Viruses Surveillance System (NREVSS) by week, July 2014–June 2017, B) The percentage of tests positive for HCoVs -OC43, -NL63, -229E, and -HKU1 reported to NREVSS by week, July 2014–June 2017.

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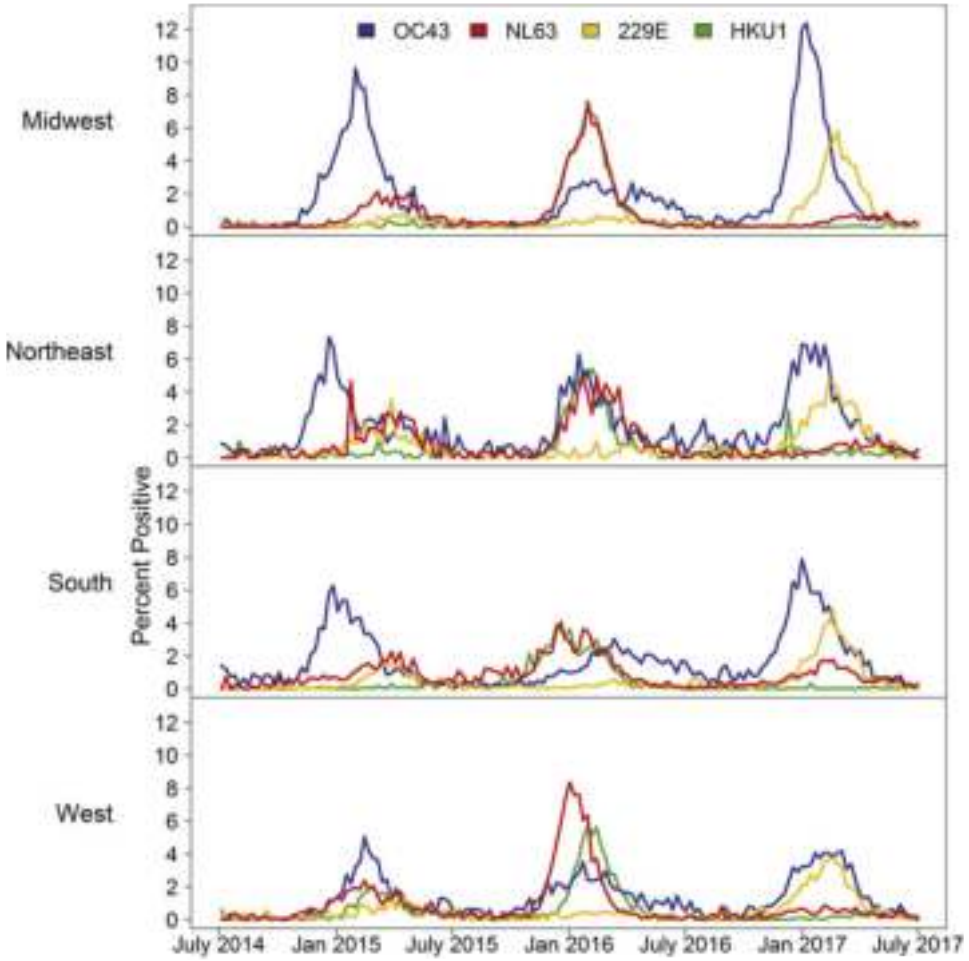

Fig. 2. The percentage of tests positive for human coronaviruses (HCoVs) -OC43, -NL63, -229E, and -HKU1 reported to the National Respiratory and Enteric Viruses Surveillance System (NREVSS) by week, stratified by US Census Region, July 2014–June 2017.

($p < 0.01$) (Fig. 3). The median ages of patients with specimens testing positive for a single HCoV species were as follows: HCoV-OC43, 24 years; HCoV-NL63, 11 years; HCoV-229E, 30 years; and HCoV-HKU1, 19 years. For HCoV-OC43, HCoV-NL63, and HCoV-HKU1 > 45% of detections were in children < 18 years old (Fig. 3). By contrast, 31% of HCoV-229E detections were in children < 18 years old (Fig. 3).

Among the 1569 HCoV positive detections reported via PHLIP, 1538 (98%) were also tested for parainfluenza viruses 1–4, respiratory syncytial virus (RSV), human metapneumovirus, human adenovirus, rhinovirus/enterovirus, influenza A and influenza B. Among these, 68.6% reported a single HCoV species detection only, 1.7% reported two or more HCoV species, and 30.2% detected another respiratory virus. The most common HCoV co-detections were HCoV-OC43 with HCoV-NL63 (8 specimens, 0.5%), and HCoV-OC43 with HCoV-229E (8 specimens, 0.5%). The most common co-detected non-HCoV viruses were RSV (11% of HCoV positive specimens), rhinovirus/enterovirus (6.6%), and influenza A (5.7%); 51 (3.3%) specimens had ≥2 viral species detected in addition to HCoV. Co-detection patterns were broadly similar among the four HCoVs (Table 1).

5. Discussion

This report is the first to describe the national patterns of circulation of the four common HCoV species in the United States during a multi-year period. During the study period, HCoVs showed a peak prevalence during December– March each year, which coincides with the winter respiratory virus season [7,9]. HCoV-OC43 was the most commonly detected HCoV with 2.2% of all tests positive. Different HCoV species predominated in different years; HCoV-OC43 appeared to peak annually, while HCoV-NL63, HCoV-HKU1, and HCoV-229E showed more variability, with distinct peaks in one or two of the three years studied. This is consistent with previously published site-specific data indicating that individual species may only demonstrate peak activity every 2–3 years [10,11].

Factors associated with annual differences in activity for HCoV species are currently unknown. Individual HCoV species activity could fluctuate independently, or cross-immunity within or between *Alphacoronavirinae* (HCoV-229E and HCoV-NL63) and *Betacoronavirinae* (HCoV-HKU1 and HCoV-OC43) might affect annual activity of the four HCoVs [4,12]. During the study period, HCoV-229E and HCoV-NL63 did not show large contemporaneous peaks of activity, although both showed smaller peaks of activity in 2014–2015. When data was visualized by census region, annual and seasonal patterns were similar to those seen nationally (Fig. 2).

The age distribution of patients with reported HCoV infections differed between HCoV species (Fig. 3). HCoV-229E detections were more common in adults > 18 years old compared to HCoV-HKU1, -NL63, and -OC43. HCoV-229E has previously been reported as disproportionately affecting immunocompromised individuals relative to the other HCoV species [4], possibly affecting the median reported age at infection. HCoV-NL63 showed the lowest median age of infection, and has been shown to be associated with croup in young children [13], which may lower the average age of infection. Non-HCoV viral co-detections were seen in 30% of specimens positive for HCoV, and 3.3% of specimens had two or more co-detected viral species. The clinical impact of coronaviruses in co-detections is not fully understood, with prior studies

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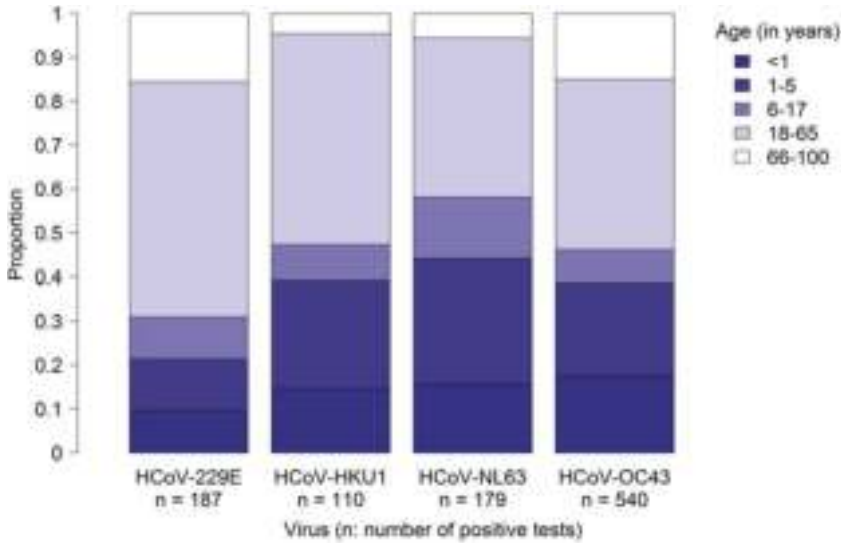

Fig. 3. Age distribution of human coronaviruses (HCoVs) -229E, -HKU1, -NL63 and -OC43 positive tests with age available reported to NREVSS via the Public Health Laboratory Interoperability Project (PHLIP), from July 2014–June 2017. Note, specimens with more than one coronavirus detected were excluded (n = 18).

Table 1
Frequency and percentage (in parentheses) of viral co-detections for by individual human coronavirus (HCoV) detection and all HCoV detections, reported to NREVSS via PHLIP from July 2014–June 2017.

	HCoV-OC43	HCoV-NL63	HCoV-229E	HCoV-HKU1	PIV	RSV	HMPV	HAdV	RV/EV	Flu A	Flu B	Any non-HCoV co-detection
HCoV-OC43 n = 836	836 (100)	8 (1.0)	8 (1.0)	4 (0.5)	28 (3.3)	100 (12.0)	23 (2.8)	54 (6.5)	59 (7.1)	44 (5.3)	10 (1.2)	259 (31.0)
HCoV-NL63 n = 253	8 (3.2)	253 (100)	3 (1.2)	5 (2.0)	5 (2.0)	26 (10.3)	10 (4.0)	13 (5.1)	19 (7.5)	11 (4.3)	0 (0.0)	74 (29.2)
HCoV-229E n = 325	8 (2.5)	3 (0.9)	325 (100)	0 (0.0)	16 (4.9)	21 (6.5)	9 (2.8)	11 (3.4)	11 (3.4)	27 (8.3)	5 (1.5)	89 (27.4)
HCoV-HKU1 n = 151	4 (2.6)	5 (3.3)	0 (0.0)	151 (100)	5 (3.3)	21 (13.9)	5 (3.3)	10 (6.6)	13 (8.6)	8 (5.3)	2 (1.3)	53 (35.1)
All HCoVs	836 (54.4)	253 (16.4)	325 (21.1)	151 (9.8)	54 (3.5)	164 (10.7)	47 (3.1)	86 (5.6)	101 (6.6)	87 (5.7)	17 (1.1)	465 (30.2)

PIV = parainfluenza virus, RSV = respiratory syncytial virus, HMPV = human metapneumovirus, HAdV = human adenovirus, RV/EV = rhinovirus/enterovirus, Flu A = influenza A, Flu B = influenza B

reporting both increased and unchanged morbidity and mortality with respiratory viral co-detections [14]. Single infections with HCoVs have been associated with morbidity due to lower and upper respiratory tract infections [4], however Prill et al demonstrated that HCoVs were not found more frequently in children hospitalized for acute respiratory illness and/or fever than asymptomatic controls [15].

There were limitations to this report. NREVSS is a passive, voluntary surveillance system, collecting results from specimens submitted to U.S. laboratories. Many HCoV infections are subclinical or mild, and do not require clinical care; therefore these infections are unlikely to require laboratory testing and would not be captured by NREVSS. The relative proportions of HCoV species reported here may not be representative of all HCoV infections. Within NREVSS all reporters of HCoV surveillance data at the species level were included, including those inconsistently reporting over time. This may result in certain laboratories or regions being overrepresented at certain times e.g. during winter, when the majority of respiratory virus tests are conducted.

Data reported to NREVSS through PHLIP represent a smaller subset of six laboratories that also report additional data including sex and age; data reported through PHLIP may not be representative of the entire NREVSS population. The overall percent of HCoV positive tests varied between PHLIP and NREVSS; the percent of HCoV positive tests submitted to NREVSS via PHLIP was 7.5%, vs 4.6% for NREVSS as a whole. This may result from differences in reporting laboratories; reporting through PHLIP is limited to military, state and public health laboratories, whereas data submitted directly to NREVSS through non-PHLIP sources primarily includes clinical laboratories. State and local public health laboratories test for a variety of reasons including surveillance and public health response to outbreaks and clusters of cases, whereas clinical laboratories often test in the course of managing individual cases.

Within the peak in detections noted during December-March, we were not able to define precise seasonal onset and offset periods for any individual HCoV species. Additionally, we assessed HCoV percent positivity over time based on the date of submission of a report to NREVSS rather than the date of specimen collection, and we anticipate that our findings may reflect this slight delay. Finally, aggregate data reported to NREVSS via PHLIP might include multiple specimens from the same patient, potentially impacting the demographic characteristics of reported cases.

Surveillance of HCoVs is important to determine seasonality and annual circulation patterns. Continued use of respiratory virus multiplex assay panels could facilitate further definition of HCoV circulation through public health surveillance in the future. Further years of data are needed to better understand patterns of activity for HCoVs, and studies with additional epidemiologic data will be useful to better characterize HCoV burden and spectrum of illness.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention.

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Ethical approval

Collection of data for the National Respiratory and Enteric Virus Surveillance System has been approved by Centers for Disease Control and Prevention as routine public health surveillance.

Competing interests

None declared.

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Review

Epidemiology, Genetic Recombination, and Pathogenesis of Coronaviruses

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Human coronaviruses (HCoVs) were first described in the 1960s for patients with the common cold. Since then, more HCoVs have been discovered, including those that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), two pathogens that, upon infection, can cause fatal respiratory disease in humans. It was recently discovered that dromedary camels in Saudi Arabia harbor three different HCoV species, including a dominant MERS HCoV lineage that was responsible for the outbreaks in the Middle East and South Korea during 2015. In this review we aim to compare and contrast the different HCoVs with regard to epidemiology and pathogenesis, in addition to the virus evolution and recombination events which have, on occasion, resulted in outbreaks amongst humans.

Trends

Six coronaviruses (CoVs) are known to infect humans: 229E, OC43, SARS-CoV, NL63, HKU1, and MERS-CoV.

Many CoVs are simultaneously maintained in nature, allowing for genetic recombination, resulting in novel viruses.

Recombination of CoV in camels has resulted in a dominant MERS lineage that caused human outbreaks in 2015.

A Brief Introduction to Human and Animal Coronaviruses

Coronaviruses (CoVs), of the family Coronaviridae, are enveloped viruses with a single-strand, positive-sense RNA genome approximately 26–32 kilobases in size, which is the largest known genome for an RNA virus [1]. The term 'coronavirus' refers to the appearance of CoV virions when observed under electron microscopy, in which spike projections from the virus membrane give the semblance of a crown, or *corona* in Latin [2,3]. All coronaviruses share similarities in the organization and expression of their genome, in which 16 nonstructural proteins (nsp1 through nsp16), encoded by open reading frame (ORF) 1a/b at the 5′ end, are followed by the structural proteins spike (S), envelope (E), membrane (M), and nucleocapsid (N), which are encoded by other ORFs at the 3′ end. CoVs are separated into four genera based on phylogeny: alpha-CoV (group 1), beta-CoV (group 2), gamma-CoV (group 3) and delta-CoV (group 4) (http://ictvonline.org/proposals/2008.085-122 V.v4.Coronaviridae.pdf). Within the beta-CoV genus, four lineages (A, B, C, and D) are recognized. Distinct from other beta-CoV lineages, lineage A viruses also encode a smaller protein called hemagglutinin esterase (HE), which is functionally similar to the S protein [4].

Since the early 1970s, a variety of pathological conditions in domestic animals have been attributed to CoV infections [5]. With the exception of infectious bronchitis virus (IBV), which causes avian infectious bronchitis in chickens [6], canine respiratory coronavirus (CRCoV), which causes respiratory disease in dogs [7], and mouse hepatitis virus (MHV), which can cause a progressive demyelinating encephalitis in mice [3,8], other CoV infections typically result in

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gastrointestinal symptoms. For instance, transmissible gastroenteritis coronavirus (TGEV) [9,10], bovine coronavirus (BCV) [11], feline coronavirus (FCoV) [12], canine coronavirus (CCoV) [13], and turkey coronavirus (TCV) [14] are known to cause enteritis in their respective hosts [1].

In humans, CoV infections primarily involve the upper respiratory tract and the gastrointestinal tract, and vary from mild, self-limiting disease, such as the common cold, to more severe manifestations, such as bronchitis and pneumonia with renal involvement [15]. The first human coronavirus (HCoV) was isolated during 1965 from the nasal discharge of patients with the common cold and termed B814 [16]. Currently, six different CoV strains are known to infect humans. These include: HCoV-229E (229E), HCoV-OC43 (OC43), severe acute respiratory syndrome coronavirus (SARS-CoV), HCoV-NL63 (NL63), HCoV-HKU1 (HKU1), and Middle East respiratory syndrome coronavirus (MERS-CoV) [17]. 229E and OC43 are the prototype viruses from the two main HCoV lineages (Alpha and Beta, respectively) that cause 15–29% of all common colds, and are the best characterized [18]. SARS-CoV is the aetiological agent that was behind an outbreak of severe respiratory disease through China during 2002–2003 [19], and MERS-CoV is the pathogen responsible for an ongoing outbreak of severe respiratory disease centered in the Middle East since 2012 [20]. In this review, we first compare and contrast the epidemiology and pathogenesis of the known CoVs infecting humans, in which CoVs that cause mild to severe disease in humans are newly emerged from a zoonotic source. Second, we describe the ecology of CoVs, and highlight evidence for viral recombination between the different CoVs within animal populations, which may result in the generation of novel CoVs that are transmissible and lethal to humans. Finally, we summarize the phylogeny, evolution, and genetic recombination of CoVs in detail.

Epidemiology and Pathogenesis of HCoV

The epidemiology and pathogenesis of each HCoV are discussed within the following sections and summarized in Table 1 and Figure 1, respectively. In general, 229E, OC43, and NL63 are distributed globally (Figure 1A) and tend to be transmitted predominantly during the winter season in temperate-climate countries [21], while NL63 showed a spring–summer peak of activity from a study in Hong Kong [22].

Human Coronavirus 229E (alphacoronavirus)

Strain 229E was discovered during 1966, when researchers were characterizing five novel agents that were isolated from the respiratory tract of humans who had contracted the common cold [23]. 229E was adapted to grow in WI-38 lung fibroblast cell lines, and was later shown to be morphologically identical to IBV and MHV [24]. Symptoms of 229E infection include general malaise, headache, nasal discharge, sneezing, and a sore throat [25]. A small portion of patients (10–20%) will also exhibit fever and cough. The incubation time is approximately 2–5 days, followed by illness lasting between 2 and 18 days, and clinically indistinguishable from respiratory tract infections caused by other pathogens, such as rhinovirus and influenza A [18]. 229E is distributed globally (Figure 1A).

Human Coronavirus OC43 (betacoronavirus, lineage A)

Strain OC43 was discovered, during 1967, in the nasopharyngeal wash of a patient with the common cold, and is adapted to grow in organ cultures containing suckling mouse brains. Similar to 229E, OC43 is morphologically indistinguishable from IBV and MHV [24], and patients infected with OC43 present the same clinical symptoms as that of 229E [24]. However, there is no serological cross-reactivity between 229E and OC43 [24]. OC43 is also distributed globally (Figure 1A).

SARS-CoV (betacoronavirus, lineage B)

Patients infected with SARS-CoV initially present with fever, myalgia, headache, malaise, and chills, followed by a nonproductive cough, dyspnea, and respiratory distress generally

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Table 1. Comparison of Clinical Symptoms, Incubation Time, Median Time to Death, and Case Fatality Rates of Human Coronaviruses

HCoV	Clinical Symptoms	Case Fatality Rate	Incubation Period	Median Time to Death	Refs
229E	General malaise Headache Nasal discharge Sneezing Sore throat Fever and cough (10–20% of patients)	N/A[a]	2–5 days	—	[18,81,82]
OC43	General malaise Headache Nasal discharge Sneezing Sore throat Fever and cough (10–20% of patients)	N/A	2–5 days	—	[18,82–84]
SARS-CoV	Fever Myalgia Headache Malaise Chills Nonproductive cough Dyspnea Respiratory distress Diarrhea (30–40% of patients)	9%	2–11 days	23 days	[19,42,85–88]
NL63	Cough, Rhinorrhea Tachypnea Fever Hypoxia Obstructive laryngitis (croup)	N/A	2–4 days	—	[89–92]
HKU1	Fever Running nose Cough Dyspnea	N/A	2–4 days	—	[2,32–34,93,94]
MERS-CoV	Fever Cough Chills Sore throat Myalgia Arthralgia Dyspnea Pneumonia Diarrhea and vomiting (one-third of patients) Acute renal impairment	36%	2–13 days	14 days	[41–43,95,96]

[a]N/A, not applicable.

5 to 7 days later, which may result in death (http://www.who.int/csr/sars/en/WHOconsensus.pdf?ua=1). Other notable features in some cases include infection of the gastrointestinal tract, liver, kidney, and brain. Diffuse alveolar damage, epithelial cell proliferation, and an increase in macrophages is seen in SARS-CoV infection of the lung. Lymphopenia, hemophagocytosis in the lung, in addition to white-pulp atrophy of the spleen observed in SARS patients, are similar to fatal H5N1 influenza virus infections [1]. Diarrhea is observed in approximately 30–40% of SARS infections (http://www.cdc.gov/sars/about/faq.html).

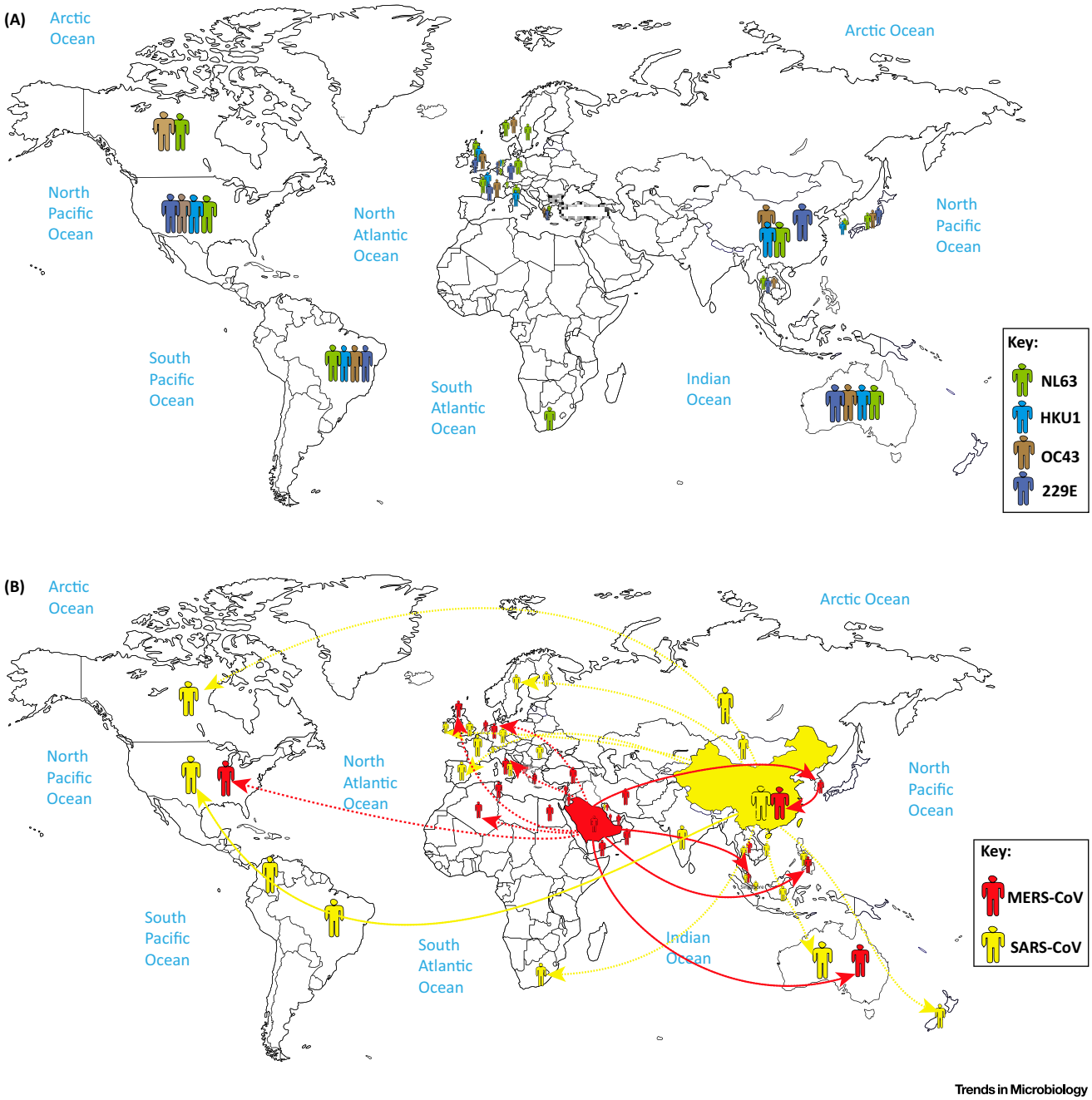

Figure 1. Global Distribution of Human Coronaviruses. (A) Green, blue, brown, and purple represent the global distribution of the NL63, HKU1, OC43, and 229E human coronaviruses, respectively. (B) Red and yellow represent the global distribution of MERS-CoV and SARS-CoV, respectively.

An outbreak of disease caused by SARS-CoV, originating from Guangdong Province in southern China during November 2002, eventually spread to other countries in Asia, in addition to North America and Europe (37 countries/regions in total) over 9 months (http://www.who.int/ith/diseases/sars/en/) (Figure 1B). An eventual 8273 cases were reported, with 775 deaths for a case fatality rate (CFR) of 9%, and the majority of cases and deaths occurred in mainland China and in Hong Kong [19]. The elderly were more susceptible to SARS disease, with a mortality rate of over 50% (http://www.cdc.gov/sars/surveillance/absence.html).

Human Coronavirus NL63 (alphacoronavirus)

NL63 is primarily associated with young children, the elderly, and immunocompromised patients with respiratory illnesses [26]. NL63 was a novel HCoV isolated from a 7-month-old child with coryza, conjunctivitis, fever, and bronchiolitis in the Netherlands during late 2004 [26], and an independent investigation described the isolation of virtually the same virus from a nasal sample collected from an 8-month-old boy suffering from pneumonia in the Netherlands [27]. NL63 was also detected in New Haven, USA, during 2005 amongst 79 of 895 children, and was initially called HCoV-NH (NH), but genetic and phylogenetic analyses showed that NH and HKU1 likely are the same species [26,28]. Infections with NL63 typically result in mild respiratory disease similar to the common cold, characterized by cough, rhinorrhea, tachypnea, fever, and hypoxia, and resolve on their own [29]. Obstructive laryngitis, also known as croup, is frequently observed with NL63 infections. A study estimated that NL63 accounts for an estimated 4.7% of common respiratory diseases [26]. NL63 is distributed globally (Figure 1A).

Human Coronavirus HKU1 (betacoronavirus, lineage A)

HKU1 was first discovered during January 2005 in a 71-year-old patient from Hong Kong who had been hospitalized with pneumonia and bronchiolitis [30]. The symptoms of HKU1 respiratory tract infections are not able to be separated from those caused by other respiratory viruses. Most patients present with fever, running nose, and cough for infections in the upper respiratory tract, whereas a fever, productive cough, and dyspnea are the common symptoms presenting for infections in the lower respiratory tract [31]. Most HKU1 infections are self-limiting, with only two deaths reported in patients with pneumonia due to HKU1 [32]. Although HKU1 is clinically relatively mild in children, HKU1 infection is associated with a high incidence of seizures, and was found in a patient with meningitis [33,34]. HKU1 cases outside Asia were detected in New Haven, USA, in 2 out of 851 children [35], and also in Australia [36], France [37], and Brazil [38], indicating a global distribution for the virus (Figure 1A).

MERS-CoV (betacoronavirus, lineage C)

MERS-CoV was first isolated from the lungs of a 60-year-old patient who had died from a severe respiratory illness in Jeddah, Saudi Arabia, 2012 [39]. Clinical manifestations of MERS-CoV infection range from asymptomatic to severe pneumonia with acute respiratory distress, septic shock, and renal failure resulting in death [40]. A typical disease course begins with fever, cough, chills, sore throat, myalgia, and arthralgia, followed by dyspnea and rapid progression to pneumonia [40–43]. Approximately one-third of patients present with gastrointestinal symptoms, such as diarrhea and vomiting. Acute renal impairment was the most striking feature of disease caused by MERS-CoV, which is thus far unique for human CoV infections [40,44]. Seventy-five percent of patients with MERS disease also had at least one other comorbidity, and patients who died were more likely to have a pre-existing/underlying condition [40]. Countries around the Arabian Peninsula are known to be endemic for MERS-CoV, and Saudi Arabia has reported the most cases, but since its discovery in 2012, cases have been occasionally exported to other countries through travel, sometimes causing clusters of secondary outbreaks (Figure 1B) [45]. As of December 31, 2015, a total of 1621 laboratory-confirmed infections have been reported, with 584 deaths (CFR = 36.0%) over 26 countries (http://www.who.int/csr/disease/coronavirus_infections/en), making MERS-CoV one of the most dangerous viruses known to humans.

Ecology of Human Coronaviruses

Based on currently available evidence, 229E, OC43, NL63, and HKU1 are well adapted to humans, and the viruses widely circulate in the human population (Figure 2), with most cases causing mild disease in immunocompetent adults, and none of these viruses have been found to be maintained within an animal reservoir. However, in the case of SARS-CoV and MERS-CoV, the viruses are not as well adapted to being maintained in humans, and thus are likely spread

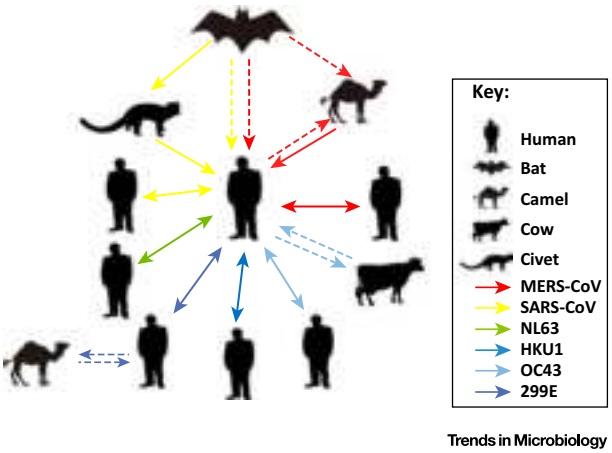

Figure 2. Intra- and Inter-Species Transmission of Human Coronaviruses. Red, yellow, green, blue, brown, and purple arrows represent transmission of MERS-CoV, SARS-CoV, NL63, HKU1, OC43, and 229E, respectively, between bats, camels, cows, humans, and masked palm civets (shown in a legend on the side of the figure). Unbroken arrows represent confirmed transmission between the two species in question, and broken arrows represent suspected transmission.

mainly in zoonotic reservoir(s), with occasional spillover into the susceptible human population, possibly via an intermediate host species.

Regarding SARS-CoV, epidemiology data implicated masked palm civets (*Paguma larvata*) from live animal markets (LAM) in Guangdong Province, China, as a route of exposure to SARS-CoV [46]. However, masked palm civets from the wild or from farms without LAM exposure were largely negative for SARS-CoV [47]. This suggests that palm civets were an intermediate host, but not a reservoir for SARS-CoV [48]. Subsequent studies have shown that wild horseshoe bats (Rhinolophidae family), which can also be found in LAM in China and served in some Chinese restaurants in Guangdong, China, have detectable levels of antibodies against SARS-CoV and a SARS-CoV-like virus (SARSr-Rh-Bat CoV) [49,50], suggesting a bat origin for SARS-CoV. An evolutionary relationship between coronaviruses and bats was proposed, in which the ancestor for SARS-CoV first spread to bats of the Hipposideridae family, then Rhinolophidae, then masked palm civets and eventually humans [51]. Recently, two new SARS-like CoVs were isolated in horseshoe bats, and these viruses showed the highest relationship to SARS-CoV from all known bat coronaviruses [52]. ORF8 analysis of the SARS-like CoVs in bats suggests that Chinese horseshoe bats are the natural reservoirs of SARS-CoV [52,53], and that intermediate hosts might not be needed for direct human infection, particularly for some bat SARS-CoV-like viruses [52].

In the case of MERS-CoV, studies in Oman, Saudi Arabia, Qatar, United Arab Emirates, and Jordan have shown that dromedary camels are seropositive for neutralizing antibodies against MERS-CoV [54], as well as camels of Middle East origin in Africa, including Egypt, Kenya, Nigeria, Ethiopia, Tunisia, Somalia, and Sudan [55]. Subsequent studies on dromedary camels in Saudi Arabia [56], Qatar [57], and Egypt [58] show that live MERS-CoV can be isolated primarily from the nasal swabs of camels, showing that camels are potential source of MERS-CoV infection. However, many confirmed cases lack contact history with camels [59], suggesting direct human-to-human transmission, or through contact with a yet-to-be-identified animal species that is maintaining MERS-CoV. Studies on HKU4, a coronavirus of bat origin and the most phylogenically closely related to MERS-CoV, had shown that HKU4 is able to utilize the CD26 receptor for virus entry [60]. As CD26 is a known receptor for MERS-CoV [61], the similarity in receptor specificity of these two CoVs supports the hypothesis that MERS-CoVs is also a bat-originated CoV. However, live MERS-CoV has not been isolated from wild bats, nor have viral sequences been detected.

A recent investigation discovered that multiple HCoV species, including MERS-CoV, beta-CoV group A, and a 229E-like virus, circulate amongst dromedary camels in Saudi Arabia [62]. Furthermore, multiple lineages of circulating MERS-CoV in these camels had resulted in a dominant,

recombinant MERS-CoV strain that was responsible for the MERS-CoV outbreaks during 2015 [62]. These results show that various CoVs of human and animal origin are currently circulating in the wild, providing ample opportunity for CoVs to undergo evolution and genetic recombination, thereby resulting in recombinant CoVs that may potentially be more deadly to humans. In the following sections, we summarize the evolution and genetic recombination of the current HCoVs.

Phylogeny, Evolution and Genetic Recombination in Human Coronaviruses

Phylogenetic Analysis

The phylogenetic tree for the CoVs of zoonotic and human origin was constructed based on the full genome. It can be observed that 229E and NL63 belong to the alpha-CoV genus and are

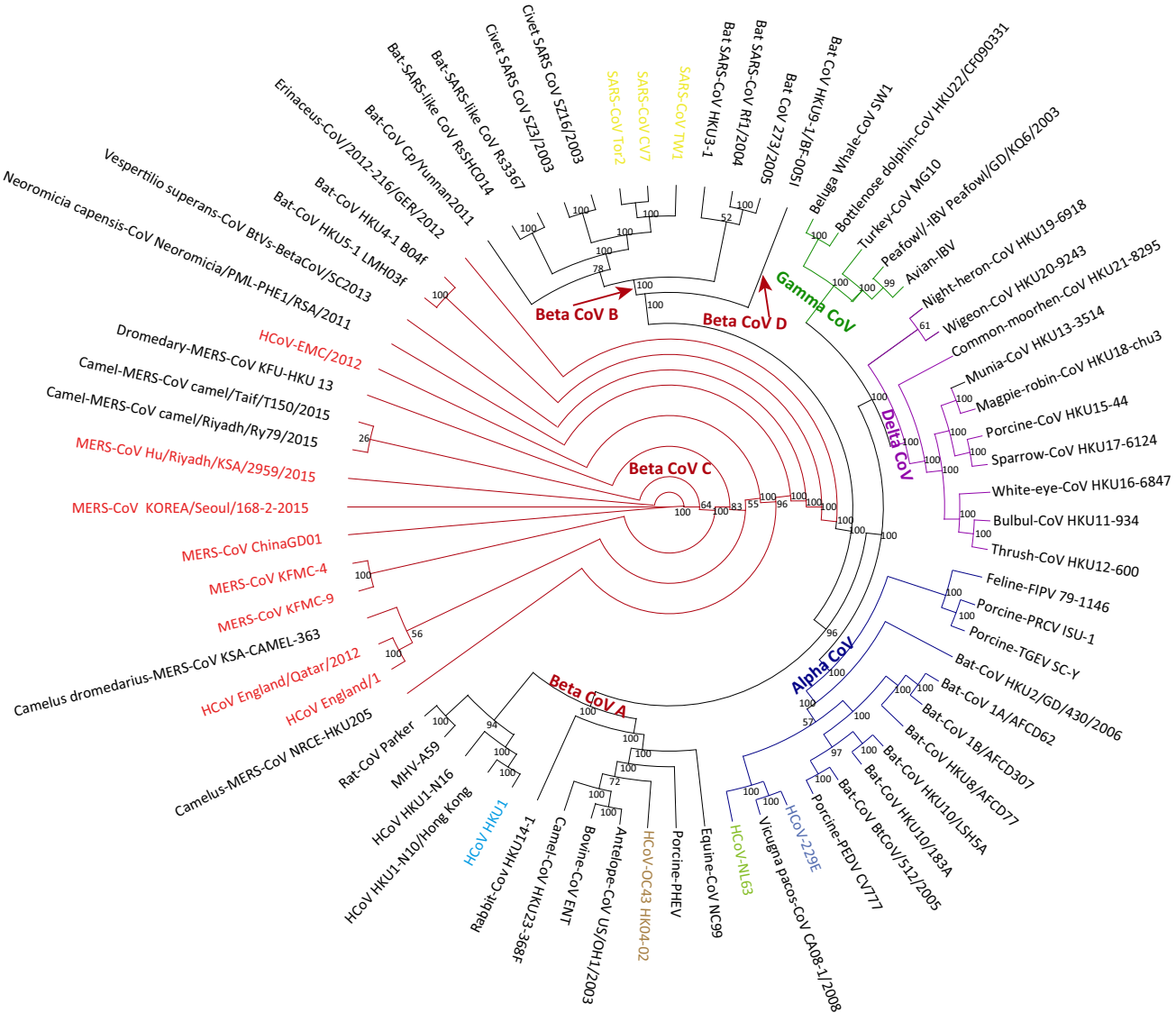

Figure 3. Phylogenetic Tree of Known Animal and Human Coronaviruses. Phylogenetic analysis of the full-length genome sequences of coronaviruses publicly available in GenBank was performed using RAxML, with 1000 bootstrap replicates. Lines with different colors represent different coronavirus species, Alpha-coronaviruses (blue lines), Beta-coronaviruses (red lines for Beta-coronavirus C, and black lines for Beta-coronavirus A, B, and D), Gamma-coronaviruses (green lines), and Delta-coronaviruses (purple lines). Human isolates are highlighted with different colors, whereas strains from other hosts are shown in black. Numbers at the branches represent bootstrap values obtained in the phylogenetic analysis.

grouped together with porcine epidemic diarrhea virus (PEDV), TGEV, porcine respiratory coronavirus (PRCV), feline infectious peritonitis virus (FIPV), and some bat-derived coronaviruses (Figure 3). The topology of the phylogeny is similar to the tree constructed based on the RNA-dependent RNA polymerase gene [55].

OC43, HKU1, SARS-CoV, and MERS-CoV belong to the beta-CoV genus. Lineage A includes OC43 and HKU1, MHV, porcine hemagglutinating encephalomyelitis virus (PHEV), in addition to equine, rabbit, camel, bovine, antelope-derived animal coronaviruses. Lineage B includes SARS-CoV, SARS-like viruses of bat and palm civet origin, and some bat-derived CoVs. Lineage C includes MERS-CoV and some bat-derived viruses. Lineage D contains only bat-derived coronavirus (Figure 3). In contrast to alpha- and beta-CoVs, gamma-CoVs consist mainly of avian coronaviruses (such as IBV), as well as CoVs isolated from aquatic animals, whales, and dolphins. CoVs of wild-bird origin are clustered into the delta-CoV, which also contains some swine-derived CoVs (Figure 3).

In general, alpha- and beta-CoVs primarily include CoVs from mammals, whereas gamma- and delta-CoVs mostly include CoVs of avian origin. Notably, all currently known HCoVs belong to either the alpha- or betacoronavirus genera, which also contain CoVs of mainly bat origin.

Mutation and Genetic Recombination in Coronaviruses

The estimated mutation rates in CoV are moderate to high compared to other single-stranded RNA (ssRNA) viruses, and the average substitution rate for CoVs was $\sim 10^{-4}$ substitutions per year per site [63]. The nucleotide mutation rate of IBV for the hypervariable region in the S gene was estimated to be $0.3–0.6 \times 10^{-2}$ per site per year [64]. The S gene of OC43 possessed an average rate of $6.410.58 \times 10^{-4}$ substitution rates per site per year [65]. Additionally, the S gene of 229E possessed a rate of $\sim 3 \times 10^{-4}$ substitutions per site per year [63]. For SARS-CoV, the mutation rate in the whole genome was estimated to be $0.80–2.38 \times 1^{-3}$ nucleotide substitutions per site per year, and the nonsynonymous and synonymous substitution rates were estimated to be $1.16–3.30 \times 10^{-3}$ and $1.67–4.67 \times 10^{-3}$ per site per year, respectively, which is similar to other RNA viruses [66]. The evolutionary rate for MERS-CoV genomes was estimated as 1.12×10^{-3} substitutions per site per year (95% credible interval [95% CI], 8.76×10^{-4}; 1.37×10^{-3}) [67]. Furthermore, the large RNA genome in CoV allows for extra plasticity in genome modification by mutations and recombinations, thereby increasing the probability for intraspecies variability, interspecies 'host jump', and novel CoVs to emerge under the right conditions [68–70].

The major reason for recombination may be at the replication step in the virus life cycle. During replication, a set of subgenomic RNAs is generated, increasing the homologous recombination rate among closely related genes from different lineages of CoVs or other viruses by template switching [33]. Concurrently, circulating CoVs in multiple host species likely contribute to increases in the rate of recombination events. However, the exact mechanism of genetic recombination in CoVs remains unclear: recombination site 'breakpoints' in the viral genome – the crossing point of the recombinant genes between two distinct viral strains or genotypes – appear to be random, as different recombinant strains have different breakpoints.

Genetic recombination has been previously documented for animal CoVs, for instance: MHV [71], TGEV [72], as well as feline and canine coronaviruses [73,74]. Genetic recombination for other HCoVs including OC43, NL63, HKU1, SARS-CoV [51], and MERS-CoV have also been documented and are discussed in detail below.

OC43 has diverged into five distinct genotypes (A to E). Genotype A is typified by the prototype VR759 strain that was isolated in 1967 [75]. Genotypes B and C are two naturally circulating viruses. Genotype D emerged via recombination between genotypes B and C viruses at the

Key Figure

Genetic Recombination in Human Coronaviruses

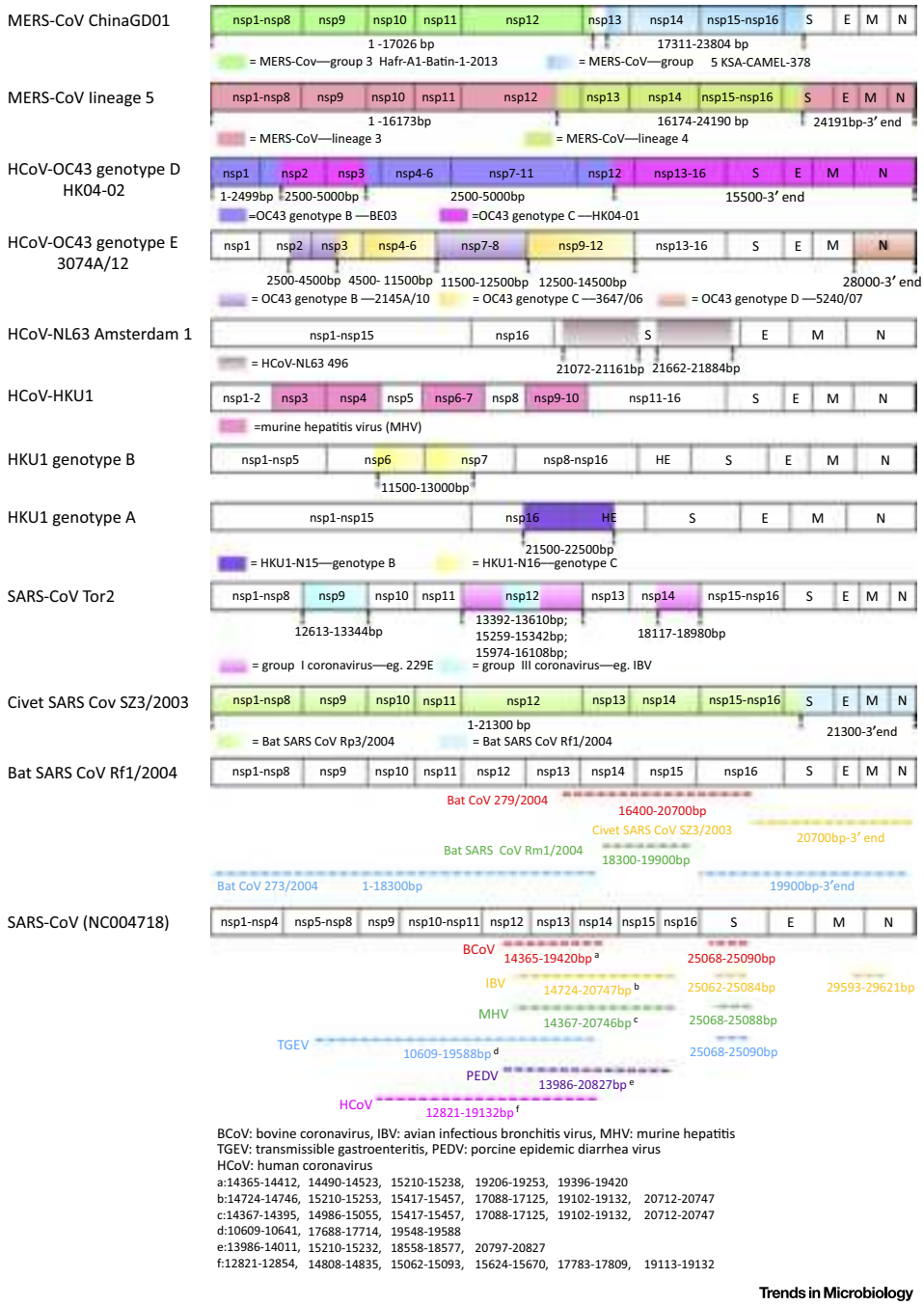

Figure 4. The colored regions of each human coronavirus indicate genetic recombination at the genomic sites with coronaviruses of zoonotic origin. Specific nucleotide locations where recombination occurred are also shown in broken lines.

breakpoint of 2500–5000 bp in the NSP2–NSP3 gene and 15500 bp-3′end in NSP12-N genes [75] (Figure 4, Key Figure). Genotype E, identified in 2014, emerged by recombination amongst the genotype B, C, and D viruses with different breakpoints in the genes compared to the generation of genotype D [76] (Figure 4). A study in France, between 2001 and 2013, demonstrated that OC43 strains have more recombination patterns in Lower Normandy, and circulating OC43 viruses have a high genetic diversity [17].

NL63 also has the potential for genetic recombination, and one such example is between the Amsterdam 1 and 496 strains. Recombination site breakpoints were identified in two parts of the S gene [63] (Figure 4).

Recombination events have been observed for different genotypes of HKU1, in which recombination breakpoints were found on genotypes B and C in the nsp6-nsp7 and nsp16-HE genes, respectively [70] (Figure 4). HKU1 was also shown to be able to recombine with other animal beta-CoVs, such as MHV, at the nsp3, nsp4, nsp6, nsp7, nps9, and nsp10 genes [77] (Figure 4).

SARS-CoV has a possible recombinant history with lineages of alpha- and gamma-CoV [78]. Many specific breakpoints and a large number of smaller recombinant regions had been identified in the RNA-dependent RNA polymerase (RDRP, nsp12 gene) at the following locations: nucleotides 13 392–13 610, 15 259–15 342, and 15 974–16 108 based on the sequence of the SARS-CoV TOR2 strain [78]. Recombination locations were also identified in the nsp9 and most of nsp10 gene located at 12 613–13 344, and parts of nsp14 (18 117–18 980) [78]. Another study analyzing the genome of the SARS-CoV CV7 strain had shown that seven putative recombination locations were found between SARS-CoV and six other coronaviruses: PEDV, TGEV, BCV, 229E, MHV, and IBV (Figure 4). This further suggests that SARS-CoV emerged via serial horizontal transmission and by genetic recombination, enhancing the adaptation process to its new host [79].

Recombination was also detected between the SARS-related bat-associated CoV (SARSr-Bat CoVs), in which recombination between the Rp3 strain from Guangxi Province and Rf1 strain from Hubei Province, China, generated a new strain (SARSr-Civet CoV SZ3) in civets, with a breakpoint at the nsp16/spike and S2 region [51] (Figure 4). Furthermore, the SARS-CoV Rf1/2004 strain is itself a recombinant from the bat CoV 279/2004, bat CoV Rm1/2004 and civet CoV SZ3/2003 [51] (Figure 4).

A recent study showed that the epidemic MERS-CoV experienced recombination events between the different lineages, which occurred in dromedary camels in Saudi Arabia [62]. Lineages 3 and 5 viruses were predominant during July and December 2014; however, lineage 5 became dominant within the camel population by 2015. Lineage 5, which is closely associated with the MERS-CoV causing the outbreak in South Korea in 2015, as well as recent human infections in Riyadh, Saudi Arabia, is a recombinant virus between lineages 3 and 4, or groups 3 and 5 of clade B (Figure 4) [62,80].

Concluding Remarks

The result from a high frequency of recombination events in CoVs is the generation of novel viruses with a high genetic diversity, with unpredictable changes in virulence during human infections. With multiple species of CoVs circulating in the wild amongst different animal species that may constantly interact with one another, it is likely not a matter of if, but when, the next recombinant CoV will emerge and cause another outbreak in the human population. As such, some crucial future areas of investigation include: (i) the prevalence of HCoVs already circulating within the animal population, (ii) the commonality of coronavirus recombination in animals, (iii) animals which may potentially serve as mixing vessels for the generation of novel recombinant

Outstanding Questions

How common is coronavirus recombination in animals?

Can coronavirus undergo recombination in animal hosts other than camels?

Is there a way to predict the potential emergence of a novel recombinant coronavirus in the human population?

CoVs, and (iv) a surveillance network to monitor and predict the potential emergence of a highly virulent, recombinant CoV from animals (see Outstanding Questions). Furthermore, lessons from the SARS-CoV and MERS-CoV outbreaks must be urgently learned in advance to effectively prepare for the next CoV outbreak.

Author Contributions

Shuo Su and Gary Wong contributed equally to this manuscript.

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World Health Organization

Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003

(Based on data as of the 31 December 2003.)

24 July 2015 | Meeting report

Overview

	Cumulative number of cases									
Areas	Female	Male	Total	Median age (range)	Number of deaths^a	Case fatality ratio (%)	Number of imported cases (%)	Number of HCW affected (%)	Date onset first probable case	Date onset last probable case
Australia	4	2	6	15 (1-45)	0	0	6 (100)	0 (0)	26-Feb-03	1-Apr-03
Canada	151	100	251	49 (1-98)	43	17	5 (2)	109 (43)	23-Feb-03	12-Jun-03

	Cumulative number of cases								
China	2674	2607	5327^b	Not available	349	7	Not Applicable	1002 (19)	16-Nov-02	3-Jun-03
China, Hong Kong Special Administrative Region	977	778	1755	40 (0-100)	299	17	Not Applicable	386 (22)	15-Feb-03	31-May-03
China, Macao Special Administrative Region	0	1	1	28	0	0	1 (100)	0 (0)	5-May-03	5-May-03
China, Taiwan	218	128	346^c	42 (0-93)	37	11	21 (6)	68 (20)	25-Feb-03	15-Jun-03
France	1	6	7	49 (26 - 61)	1	14	7 (100)	2 (29)^d	21-Mar-03	3-May-03
Germany	4	5	9	44 (4-73)	0	0	9 (100)	1 (11)	9-Mar-03	6-May-03
India	0	3	3	25 (25-30)	0	0	3 (100)	0 (0)	25-Apr-03	6-May-03
Indonesia	0	2	2	56 (47-65)	0	0	2 (100)	0 (0)	6-Apr-03	17-Apr-03
Italy	1	3	4	30.5 (25-54)	0	0	4 (100)	0 (0)	12-Mar-03	20-Apr-03
Kuwait	1	0	1	50	0	0	1 (100)	0 (0)	9-Apr-03	9-Apr-03
Malaysia	1	4	5	30 (26-84)	2	40	5 (100)	0 (0)	14-Mar-03	22-Apr-03
Mongolia	8	1	9	32 (17-63)	0	0	8 (89)	0 (0)	31-Mar-03	6-May-03

	Cumulative number of cases								
New Zealand	1	0	1	67	0	0	1 (100)	0 (0)	20-Apr-03	20-Apr-03
Philippines	8	6	14	41 (29-73)	2	14	7 (50)	4 (29)	25-Feb-03	5-May-03
Republic of Ireland	0	1	1	56	0	0	1 (100)	0 (0)	27-Feb-03	27-Feb-03
Republic of Korea	0	3	3	40 (20-80)	0	0	3 (100)	0 (0)	25-Apr-03	10-May-03
Romania	0	1	1	52	0	0	1 (100)	0 (0)	19-Mar-03	19-Mar-03
Russian Federation	0	1	1	25	0	0	Not Available	0 (0)	5-May-03	5-May-03
Singapore	161	77	238	35 (1-90)	33	14	8 (3)	97 (41)	25-Feb-03	5-May-03
South Africa	0	1	1	62	1	100	1 (100)	0 (0)	3-Apr-03	3-Apr-03
Spain	0	1	1	33	0	0	1 (100)	0 (0)	26-Mar-03	26-Mar-03
Sweden	3	2	5	43 (33-55)	0	0	5 (100)	0 (0)	28-Mar-03	23-Apr-03
Switzerland	0	1	1	35	0	0	1 (100)	0 (0)	9-Mar-03	9-Mar-03
Thailand	5	4	9	42 (2-79)	2	22	9 (100)	1 (11)^d	11-Mar-03	27-May-03
United Kingdom	2	2	4	59 (28-74)	0	0	4 (100)	0 (0)	1-Mar-03	1-Apr-03
United States	13	14	27	36 (0-83)	0	0	27 (100)	0 (0)	24-Feb-03	13-Jul-03^e

	Cumulative number of cases									
Viet Nam	39	24	63	43 (20-76)	5	8	1 (2)	36 (57)	23-Feb-03	14-Apr-03
Total			8096		774	9.6	142	1706		

a. Includes only cases whose death is attributed to SARS.
b. Case classification by sex is unknown for 46 cases.
c. Since 11 July 2003, 325 cases have been discarded in Taiwan, China. Laboratory information was insufficient or incomplete for 135 discarded cases, of which 101 died.
d. Includes HCWs who acquired illness in other areas.
e. Due to differences in case definitions, the United States has reported probable cases of SARS with onsets of illness after 5 July 2003.

WHO TEAM

Emergency Response

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REVIEW

What Have We Learned About Middle East Respiratory Syndrome Coronavirus Emergence in Humans? A Systematic Literature Review

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Abstract

Background: Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in humans in 2012. A systematic literature review was conducted to synthesize current knowledge and identify critical knowledge gaps.
Materials and Methods: We conducted a systematic review on MERS-CoV using PRISMA guidelines. We identified 407 relevant, peer-reviewed publications and selected 208 of these based on their contributions to four key areas: virology; clinical characteristics, outcomes, therapeutic and preventive options; epidemiology and transmission; and animal interface and the search for natural hosts of MERS-CoV.
Results: Dipeptidyl peptidase 4 (DPP4/CD26) was identified as the human receptor for MERS-CoV, and a variety of molecular and serological assays developed. Dromedary camels remain the only documented zoonotic source of human infection, but MERS-like CoVs have been detected in bat species globally, as well as in dromedary camels throughout the Middle East and Africa. However, despite evidence of camel-to-human MERS-CoV transmission and cases apparently related to camel contact, the source of many primary cases remains unknown. There have been sustained health care-associated human outbreaks in Saudi Arabia and South Korea, the latter originating from one traveler returning from the Middle East. Transmission mechanisms are poorly understood; for health care, this may include environmental contamination. Various potential therapeutics have been identified, but not yet evaluated in human clinical trials. At least one candidate vaccine has progressed to Phase I trials.
Conclusions: There has been substantial MERS-CoV research since 2012, but significant knowledge gaps persist, especially in epidemiology and natural history of the infection. There have been few rigorous studies of baseline prevalence, transmission, and spectrum of disease. Terms such as ''camel exposure'' and the epidemiological relationships of cases should be clearly defined and standardized. We strongly recommend a shared and accessible registry or database. Coronaviruses will likely continue to emerge, arguing for a unified ''One Health'' approach.

Keywords: MERS, MERS-CoV, coronaviruses, zoonotic disease, severe acute respiratory infection (SARI), MERS epidemiology

Introduction

SEPTEMBER 2012 SAW THE identification of a novel human coronavirus, now known as Middle East respiratory syndrome coronavirus (MERS-CoV) (ProMED-mail 2012, Zaki et al. 2012). MERS-CoV is a beta-coronavirus distinct from but genetically related to the SARS (severe acute respiratory syndrome) coronavirus (Hilgenfeld and Peiris 2013, de Wit et al. 2016).

As MERS was identified a few years after the 2003 SARS outbreak, which spread across continents and raised pandemic concerns, there has been continuing concern about the

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pandemic potential of MERS-CoV (Hilgenfeld and Peiris 2013, de Wit et al. 2016). To assess and anticipate potential epidemic spread of MERS-CoV, it is essential to better understand the virology; human clinical characteristics, possible therapeutic and preventive options; epidemiology and transmission; and animal interfaces and possible origins and natural hosts.

MERS was first identified in a patient with lower respiratory disease by a physician in Saudi Arabia, and subsequently, the virus was identified and characterized from this patient's sputum sample by researchers in Saudi Arabia and at Erasmus Medical Center in the Netherlands. Since then (to December 2018), 2266 laboratory-confirmed MERS-CoV cases and 804 deaths across 27 countries (35.5% crude case

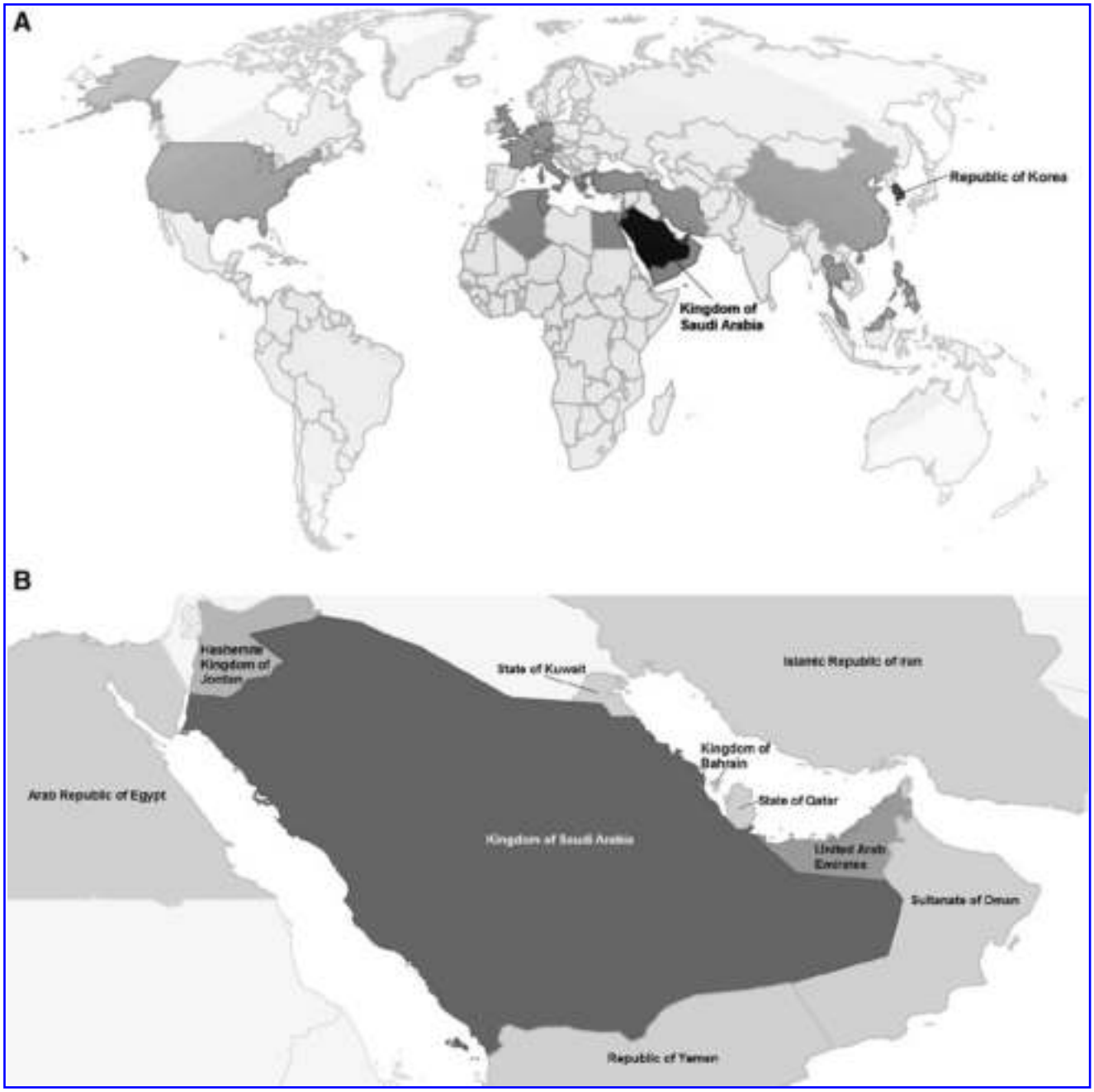

FIG. 1. **(A)** Map of countries having at least one laboratory-confirmed human MERS-CoV case, 2012–2016. *Darker shades* indicate greater numbers of laboratory-confirmed cases. **(B)** *Inset* of Fig. 1A showing Gulf countries having at least one laboratory-confirmed human MERS-CoV case. *Darker shades* indicate greater numbers of laboratory-confirmed cases. Data Source: World Health Organization (www.who.int/emergencies/mers-cov/en *and* www.who.int/emergencies/mers-cov/risk-assessment-july-2017.pdf). This map was generated using R software (*R Foundation* for Statistical Computing, Vienna, Austria) and the ''googleVis'' package (Gesmann et al. 2017). MERS-CoV, Middle East respiratory syndrome coronavirus.

fatality rate [CFR]) have been reported to the WHO (Fig. 1), with the majority of cases (1888) and deaths (730) reported from Saudi Arabia (World Health Organization 2018a, World Health Organization/EMRO 2018). Cases continue to occur (World Health Organization/EMRO 2018).

Although the first known MERS-CoV cases were from Jordan (confirmed retrospectively, and the source is still unknown) (Hijawi et al. 2013), about 80% of MERS-CoV cases originate from or passed through Saudi Arabia. The infection is likely zoonotic; although origins and transmission are poorly understood, the dromedary camel is the one documented source of human zoonotic infection (Memish et al. 2014e).

A systematic review of MERS-CoV research was conducted to survey our current understanding of MERS-CoV and to identify research gaps in four major areas: (1) virology; (2) clinical characteristics, outcomes, and therapeutic and preventive options; (3) epidemiology and transmission; and (4) animal interface and the search for natural hosts of MERS-CoV.

Materials and Methods

We conducted a systematic literature review, using Embase, Google Scholar, MEDLINE/PubMed, supplemented by Thomson-Reuters ''Web of Science''™ (all databases), to identify peer-reviewed published articles on MERS-CoV available by July 14, 2017. All searches were for articles published from 2012 onward, since MERS was first identified in 2012. The following search terms were used in all the databases for matches in title only (Google Scholar), title or abstract (Embase and MEDLINE/PubMed), or topic (''Web of Science''): ''novel coronavirus,'' ''novel coronavirus EMC,'' ''novel coronavirus Erasmus,'' ''hCoV-EMC,'' ''MERS-CoV'' (a PubMed ''MeSH'' term), ''MERS coronavirus,'' ''Middle East Respiratory Syndrome,'' and ''Middle East Respiratory Syndrome Coronavirus'' (a PubMed MeSH term).

We reviewed the titles and abstracts of all resulting citations to identify relevant articles for this systematic review, following PRISMA guidelines (Fig. 2) (Moher et al. 2009). For all nonduplicate articles, excluding opinion and editorial pieces, on MERS-CoV or a related topic, we retrieved the full-text version and indexed the citation. Inclusion criteria were peer-reviewed primary research articles about MERS-CoV published between 2012 and mid-July 2017 (inclusive, with periodic updates to 2018) and adding unique information about MERS-CoV to the knowledge base within at least one of the four key themes: (1) virology; (2) clinical characteristics, outcomes, and therapeutic and preventive options; (3) epidemiology and transmission; and (4) animal interface and search for natural hosts of MERS-CoV.

Only English language publications (or with an English-language abstract available) were included. Of the 3364 titles retrieved, 407 were unique (nonduplicate), scientific research works relevant to MERS-CoV, and of these, 208 were originally included in the review based on the inclusion criteria (some interim updates have been made during article preparation).

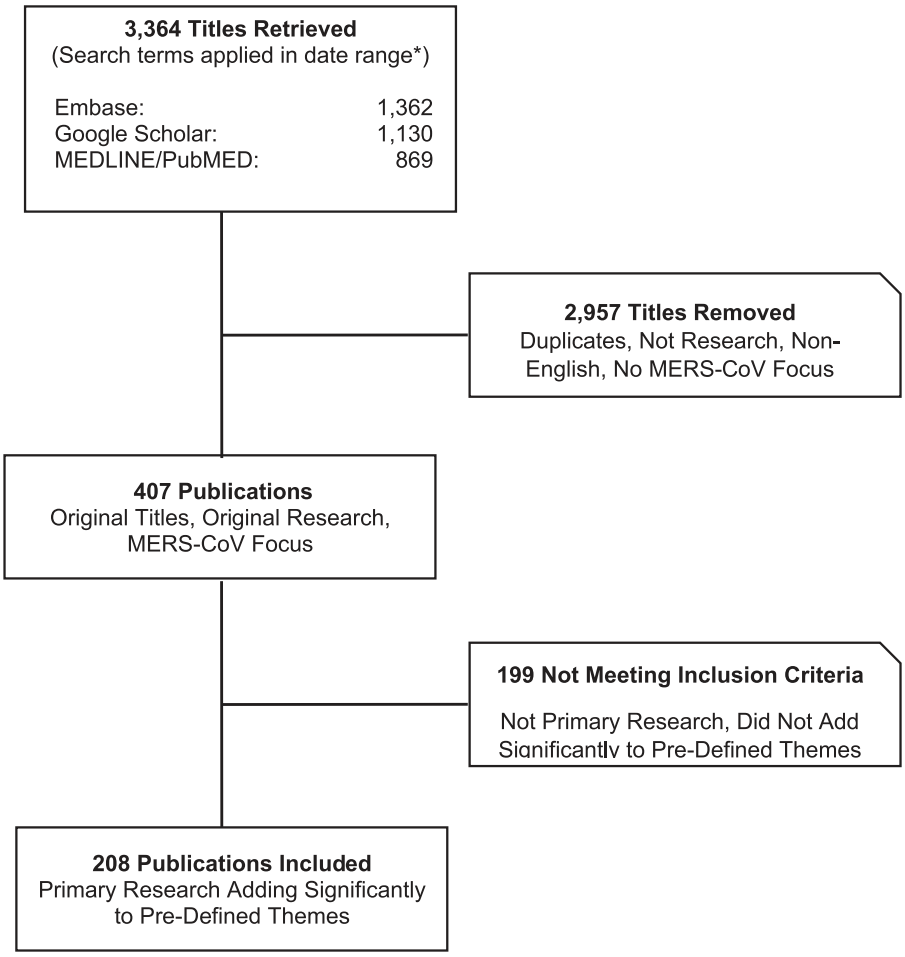

FIG. 2. Study selection diagram for systematic literature review on MERS-CoV (*For complete search terms and applicable date ranges, see the Materials and Methods section.).

Results

Virology

The pathogen causing MERS has been identified as a coronavirus, now named MERS-CoV, classified in the family *Coronaviridae* (subfamily *Coronavirinae*) (ICTV 2016). Coronaviruses are a family of enveloped, approximately spherical, positive-sense, single-stranded RNA viruses with genome length 26–32 kilobases (kb). Of the four described coronavirus genera, alpha- and beta-coronaviruses are believed to originate from bat species, whereas gamma- and delta-coronaviruses are believed to be of avian origin (Woo et al. 2012).

Within the beta-coronavirus genus, four lineages have been described: A, B (which includes SARS-CoV), C, and D. MERS-CoV is a beta-coronavirus of lineage C (Cotten et al. 2013), the first of this lineage known to infect humans. There are two main recognized clades (genetic sublineages) of MERS-CoV, clade A, which includes the earliest known MERS-CoV strains (EMC/2012 and Jordan-N3/2012), and clade B, which includes newer cases (Cotten et al. 2013), although additional genotypes are revealed by genomic sequencing (Chu et al. 2015), suggesting the existence of additional clades.

The genome of MERS-CoV is ~30 kb and encodes 10 proteins: 2 replicase polyproteins (ORFs 1a and 1b), including the RNA-dependent RNA polymerase (RdRp); 4 structural proteins: envelope (E), M (membrane), N (nucleocapsid), and S (surface spike glycoprotein), and 4 nonstructural proteins (ORFs 3, 4a, 4b, and 5) (Kim et al. 2015; review: de Wit et al. 2016).

Particular attention has understandably focused on the S (spike) surface protein, which confers receptor specificity (Qian et al. 2013) and is considered the major determinant of coronavirus host range (Graham and Baric 2010, Hulswit et al. 2016). The main route of entry for MERS-CoV is dipeptidyl peptidase 4 (DPP4, also known as CD26) on the host cell surface (Raj et al. 2013), which is utilized by the receptor-binding domain of the MERS-CoV spike protein (Chen et al. 2013, Raj et al. 2013, 2014).

The virus readily replicates in A549 (human lung), Huh-7 (human liver), and the widely used Vero E6 (African green monkey kidney) cell lines (Raj et al. 2013, Eckerle et al. 2014), among others. Culture, *in vitro* and *ex vivo*, has also been used to help determine cell tropism and identify potential natural hosts of the virus. MERS-CoV can infect a variety of human cell types and tissues in culture, including macrophages, fibroblasts, and endothelial cells (Scobey et al. 2013, Tao et al. 2013, Hin et al. 2016). In an *ex vivo* study using human lung explants, MERS-CoV infected both alveolar epithelial cells and macrophages (Type II pneumocytes), with resulting alveolar damage (Hocke et al. 2013).

Interestingly, although kidney failure is frequently described in fatal cases and the virus grows well in a number of kidney and liver cell lines, in the one autopsy report that has been published, viral antigen was detected by immunohistochemical staining only in pneumocytes and lung interstitial epithelial cells, and not in the kidney or other extrapulmonary sites (Ng et al. 2016).

Replication was demonstrated in goat, camel (Eckerle et al. 2014), and equid origin cell lines (Meyer et al. 2015), but was not detected in cattle, sheep, or rodent cell lines tested (Eckerle et al. 2014).

Given the interest in bats as a natural host for many coronaviruses, especially since SARS, and the currently unknown origin of MERS-CoV, several bat cell lines have been tested to determine if they could support MERS-CoV replication (Müller et al. 2012, Cai et al. 2014, Eckerle et al. 2014).

As a broad generalization, the virus was reported to replicate well (roughly comparable with growth in Vero E6 cells) in kidney and lung cells from *Rousettus aegyptiacus* and other Old World pteropid (fruit) bats (Müller et al. 2012, Cai et al. 2014), to a lesser degree in cell lines from Old World insectivorous bats (Müller et al. 2012, Eckerle et al. 2014), and very little, if at all, in lung cells from several New World bats (Müller et al. 2012, Cai et al. 2014). However, as a caveat, no replication was found in the *Rousettus aegyptiacus* embryo cell lines tested (Cai et al. 2014).

Adaptation to cells from other bat species that are normally refractory to infection because of having a somewhat different DPP4 protein was recently demonstrated *in vitro* (Letko et al. 2018), resulting from selection of spike protein mutations that permitted binding to the new DPP4. A similar change, from bat to human-type receptor, was observed with SARS in 2003 (Letko et al. 2018).

Animal models for MERS-CoV include transgenic mice expressing human DPP4 (Cockrell et al. 2014, Zhao et al. 2014, Agrawal et al. 2015), which develop respiratory disease and are the most widely used model; marmosets (Falzarano et al. 2014); rhesus macaques (de Wit et al. 2013, Munster et al. 2013, Yao et al. 2014); camels (Barlan et al. 2014); horses (Barlan et al. 2014), and alpacas (Adney et al. 2016). However, there is no animal model that clearly mimics human clinical MERS (review: Baseler et al. 2016).

Diagnostic assays. The main laboratory assays for MERS-CoV are molecular tests to detect viral RNA, and serology (for prior infection) (CDC 2014, World Health Organization 2018b).

Reverse transcription PCR either real time or conventional, is now standard. For diagnostic screening, PCR primer sets to regions upstream of the E gene (''up-E'') are most frequently used, with ORF1a or ORF1b for confirmation (Corman et al. 2012a, 2012b). Sensitivity was reported as ~3.4 viral gene copies/25 μL reaction for up-E and ~64 copies for ORF1b, with specificity approaching 100% using a test panel of other known coronaviruses and clinical respiratory samples (Corman et al. 2012a). ORF1a PCR was reported to have comparable sensitivity and specificity to up-E (Corman et al. 2012b). Commercial kits are available, with comparable results reported (Corman et al. 2014c, Seong et al. 2016, Mohamed et al. 2017).

For sequencing, tests have been developed that may be better suited for strain differentiation, targeting regions of the RdRp (RNA polymerase) or N (nucleocapsid) genes (Corman et al. 2012b); there are a number of publications reporting on their use (Corman et al. 2012b; CDC 2014, Lu et al. 2014).

Another PCR test, targeting the S (spike) region, was developed to monitor circulation of MERS-CoV variants (Abd et al. 2013, Smits et al. 2015). Other types of nucleic acid tests have also been used (Shirato et al. 2014), as has immunohistochemistry (Ng et al. 2016).

Serologic samples are usually screened using enzyme-linked immunosorbent assay (ELISA) (Reusken et al. 2013a). If the sample is ELISA positive, CDC and other agencies formerly recommended confirmatory testing, first

by immunofluorescence assay (IFA) and then by the gold standard plaque-reduction neutralization test or microneutralization (CDC 2014), but now recommend going directly to microneutralization assay (CDC 2014, revised). Other serological tests such as pseudoparticle neutralization (Perera et al. 2013) and array-based serology (Reusken et al. 2013a) have also been developed.

Unfortunately, there are pitfalls in serology, including cross-reactivity and false negatives. In 2014, CDC preliminarily reported a MERS-CoV case with a positive ELISA and IFA, but later retracted the case report due to a negative microneutralization result (Breakwell et al. 2015). Consequently, CDC no longer recommends IFA but instead now recommends using two different ELISA tests, with microneutralization for confirmation (CDC 2014, revised). Conversely, low or waning antibody response after infection, which would yield false negatives, has also been reported (Alshukairi et al. 2016, Choe et al. 2017). False negatives are further discussed below in the section on Host Response.

Clinical characteristics and outcomes

Clinical findings have been described and reviewed in detail (Assiri et al. 2013a, Saad et al. 2014, Rasmussen et al. 2015, World Health Organization 2015). The incubation period is ~5–7 days (in some cases up to 12 days) (Assiri et al. 2013a, 2013b). Fever, cough, shortness of breath, and pneumonia (with abnormal chest radiography) are the most frequently noted signs; myalgia, diarrhea, vomiting, abdominal pain, chills or rigors, or malaise are also seen (Assiri et al. 2013a, Drosten et al. 2013, Eckerle et al. 2013, Guery et al. 2013, Ajlan et al. 2014, Arabi et al. 2014, Faure et al. 2014, Kapoor et al. 2014, Scheuplein et al. 2015, Hunter et al. 2016). Renal failure or pulmonary failure and shock were commonly described in severe and fatal cases. Overall CFR is ~35.5% (World Health Organization 2018a).

Viral excretion from the respiratory tract has been documented through the first month of illness (Memish et al. 2014d, Poissy et al. 2014, Spanakis et al. 2014), with greater viral loads detected in lower respiratory tract specimens compared with upper respiratory tract (Drosten et al. 2013, Guery et al. 2013, Kapoor et al. 2014). Viral excretion for short periods was reported in urine and stool, although viral loads were low (Drosten et al. 2013). There was at least one report that MERS-CoV secondary cases (individuals infected by a primary case) clear infection earlier than primary cases (Memish et al. 2014d).

Disease outcomes differed by age and comorbidities (Assiri et al. 2013a, 2013b, Khalid et al. 2014, Saad et al. 2014, Alsahafi and Cheng 2016). Most cases in Saudi Arabia have occurred among men, ages 45 or older, and those living in areas of lower relative humidity and high temperature (Alghamdi et al. 2014). A review of 939 cases in Saudi Arabia found that CFR increases with age, from 12.5% among those 19 years or younger to 86.2% among those 80 years or older (Alsahafi and Cheng 2016). Mortality was more frequent and rapid in individuals with comorbidities such as diabetes, chronic renal disease, and, in one study, higher body mass index (Assiri et al. 2013a, 2013b, Al-Tawfiq et al. 2014, Khalid et al. 2014, Saad et al. 2014, Alsahafi and Cheng 2016). More severe disease has been associated with higher viral load (Feikin et al. 2015).

There are a handful of case reports on MERS outcomes in other vulnerable populations, including three cases in pregnant women and one in an HIV-positive individual.

In the three documented cases of pregnant women with MERS-CoV infection, one woman in her second trimester of pregnancy (~5 months) experienced a stillbirth; the mother survived (Payne et al. 2014). The two other women were reported to be in their third trimester (32 weeks) when they presented with MERS. A healthy infant was delivered in each of these cases, although one mother died despite interferon (IFN) treatment (Malik et al. 2016), and one recovered despite the severity of her symptoms (Alserehi et al. 2016). Both were apparently healthy before infection and in their 30s. It is therefore possible that infection during the third trimester may be associated with better fetal outcomes, while other factors may be more critical for maternal outcome, but the numbers are too small to generalize.

There has been at least one published case of an individual with HIV/AIDS acquiring MERS-CoV (Shalhoub et al. 2015). This patient was probably infected with MERS-CoV during a hospital stay and subsequently shed virus for 38 days. The patient recovered after treatment (Shalhoub et al. 2015).

Host response

There have been a number of studies on immune function (Corman et al. 2016, Zhao et al. 2017). Neutralizing antibodies were detected in many patients, but several studies suggested that neutralizing antibodies induced during infection did not appear to be protective (Corman et al. 2016, Zhao et al. 2017), and it has been suggested that higher antibody titers may be more closely correlated with greater viral load and consequently worse prognosis (Zhao et al. 2017).

Kinetics of response may also be important. An antibody kinetics study with 17 patients in South Korea (from the same research group that later reported waning antibody titers in patients over a 1-year follow-up) found that most patients produced a robust neutralizing IgG antibody response beginning at about 2 weeks and peaking by about 3 weeks; delayed response was generally correlated with a less favorable prognosis (Park et al. 2015).

Persistence of antibody generally seems to follow a similar pattern. Detectable neutralizing antibody titers (≥20) have been reported in some patients up to 34 months (Payne et al. 2016). However, results varied considerably even within this group, and most reports indicate that duration of antibody response, as well as its magnitude, seemed most closely correlated with disease severity and that antibodies could be low or even absent in mild or asymptomatic infection (Alshukairi et al. 2016, Choe et al. 2017). These reports of low or waning antibody titers, especially in asymptomatic or mildly symptomatic individuals, may make serology problematic as a marker of population prevalence.

There is evidence that innate immunity, including IFNs and cytokines, and cellular immunity by $CD8^+$ (presumably ''killer'') T cells may play important roles in host defense and recovery (Faure et al. 2014, Zhao et al. 2017). Zhao et al. (2017) compared the role of antibodies and T cells in human MERS cases, and found that survivors mounted a vigorous $CD8^+$ T cell response even in the absence of a detectable antibody response.

Macrophages also appear to play an important role, but there are limited and somewhat ambiguous data from the mouse model (Coleman et al. 2017), human cells (Zhou et al. 2014), and patients (Faure et al. 2014). With a number of viruses, it is not unusual for resting macrophages to be permissive for replication but for macrophages to show antiviral activity after activation (such as by IFN-γ) (Morse and Morahan 1981). Dendritic cells have been reported to produce IFN in response to infection (Scheuplein et al. 2015).

One challenge to overcome is the effect of the virus on host defenses. A caveat is that much of this research (although not all) has been done *in vitro* and may not necessarily be comparable with the immunological results described above in patients. MERS-CoV has been reported to inhibit host innate immunity (Lau et al. 2013). Impaired IFN and cytokine responses may mediate some of these effects, based on assays on cells from MERS patients (Faure et al. 2014, Scheuplein et al. 2015), although the numbers of patients were small. *In vitro* studies have shown that MERS-CoV could downregulate expression of IFN-stimulated gene subsets (Yang et al. 2013), chemokines (Mielech et al. 2014), and IFN-β. Another study found that MERS-CoV may cause delayed induction of proinflammatory cytokines together with suppression of the host's innate antiviral response (Lau et al. 2013).

Virus replication in human monocyte-derived macrophages has been described, with increased expression of tumor necrosis factor α (up to a 3-fold increase over normal levels), interleukin 6 (up to almost a 6-fold increase), interleukin 12, IFN-γ, and chemokines (some at a 10-fold or more increase and even more prominently than with SARS-CoV) being reported (Zhou et al. 2014).

Therapeutic and preventive options

Currently, the main treatment strategy is symptomatic supportive care; mechanical ventilation and ICU admission are usually required for severe cases.

Published data on applied therapeutic regimens for MERS-CoV patients are scarce, but there have been efforts to develop interventions.

Two case reports have documented the use of a combination of ribavirin and IFN α2b as a therapy for MERS-CoV patients, with divergent results. In one report, this therapy was given to five patients but all five died. However, all five patients had comorbidities and were diagnosed late in the course of their illness, suggesting the therapy may have been delivered too late to prove effective (Al-Tawfiq et al. 2014). In another report, this therapy was given to one patient who eventually recovered (Khalid et al. 2015).

In a retrospective cohort study of 44 patients with severe MERS (requiring ventilatory support), treatment with ribavirin and pegylated IFN α2a (note, not 2b) appeared to increase short-term survival (14 days), although by 28 days only 10 of the patients were still living (6/20 survivors in treated group compared with 4/24 surviving in the comparison group) (Omrani et al. 2014).

Among promising studies evaluating therapies in animal models, one *in vivo* study found that the combination of ribavirin and IFN α2b therapy significantly improved outcomes among MERS-CoV-infected rhesus monkeys (Falzarano et al. 2013). In another study, using the common marmoset model, lopinavir/ritonavir and IFN α1b (separately and in combination) also proved promising (Chan et al. 2015).

Although neutralizing antibodies induced during infection did not appear to be protective during natural infection (Corman et al. 2016, Zhao et al. 2017), human convalescent sera containing neutralizing antibodies conferred dose-dependent protection in a mouse model (Zhao et al. 2017). The readily available sera from MERS-immune camels apparently were also an effective treatment for MERS-infected mice and reduced the severity of pathological changes in murine lung tissue (Zhao et al. 2015). Several monoclonal antibodies (mAbs) (Mou et al. 2013, Ohnuma et al. 2013, Du et al. 2014, Jiang et al. 2014, Tang et al. 2014, Ying et al. 2014, Houser et al. 2016) and conventional antibodies (Zhao et al. 2013) have demonstrated effective neutralization of MERS-CoV, and could serve as potential therapeutic agents, at least in the interim.

High-throughput screening and other methods have identified additional promising compounds in several classes (Chan et al. 2013, de Wilde et al. 2013, 2014, Gao et al. 2013, Shirato et al. 2013, Adedeji et al. 2014, Dyall et al. 2014, Hart et al. 2014, Lu et al. 2014, Lundin et al. 2014, Tao et al. 2014, Wrensch et al. 2014, Corti et al. 2015, Liu et al. 2015). These include inhibitors against both viral (Kilianski et al. 2013, Lei et al. 2014, Kumar et al. 2017) and host (Gierer et al. 2015) proteases needed to process the virus. However, it was reported that inhibiting proprotein convertases inhibits host cell processing of the spike protein but did not affect viral infectivity or cell-to-cell spread (Gierer et al. 2015).

Other targets studied have included viral entry inhibitors (Zhao et al. 2013, Du et al. 2015) and protein 4a, which the researchers found suppressed innate antiviral response (Siu et al. 2014).

Vaccine development. Development of a human (and possibly camel) vaccine for MERS-CoV should be a key priority, given concerns about its spread and pandemic potential, but vaccine development can be a long process that is often driven by economics (Modjarrad 2016).

Much of the focus thus far has centered on the identification of the residues within the receptor-binding domain of the spike protein, conferring the best chance of protection (Du et al. 2013a, 2013b, Lan et al. 2014, Ma et al. 2014a, 2014b). A number of other antigens, some in viral vectors, have been tested in the laboratory (Song et al. 2013, Kim et al. 2014).

A replication defective full-length cDNA clone of the MERS-CoV genome has been developed for identifying future vaccine candidates (Almazán et al. 2013). Vaccine candidates for dromedary camels have also been investigated, and have been reported to elicit protective responses (using the MERS-CoV spike protein in a poxvirus vector) (Haagmans et al. 2016).

There are special challenges to developing a MERS vaccine. The sporadic nature of human MERS-CoV infection and the difficulty of identifying suitable animal models for challenge studies make controlled trials difficult. Disease in camels usually appears mild (Adney et al. 2014), reducing the economic incentive for immunization. A camel vaccine could also be given in combination with a required vaccine, e.g., rabies, as suggested by Wirblich et al. (2017), or camelpox, as suggested by Haagmans et al. (2016).

Correlates of protection and duration of immunity are also uncertain. There are reports of strong antibody responses (Haagmans et al. 2016), but it has been suggested that the presence of neutralizing antibodies may not be protective in camels (Hemida et al. 2014) or humans (Corman et al. 2016, Zhao et al. 2017), and waning antibody titers have been reported in humans who have recovered from MERS-CoV infection (Choe et al. 2017). On the contrary, the reports of protection of mice by passive transfer of neutralizing antibodies suggest that this might be overcome by optimizing timing and dose (Zhao et al. 2017).

Research on MERS-CoV vaccine candidates is ongoing, and at least one candidate vaccine has now progressed to a Phase I human clinical trial (Modjarrad 2016, CEPI 2017). In a promising development, the recently launched Coalition for Epidemic Preparedness Innovations (CEPI) has listed MERS vaccine as one of its initial targets.

Epidemiology and transmission

The source of infection for most primary cases (the first known human case in a potential or putative chain of transmission) remains unknown. Baseline incidence and prevalence are unknown as only clinical cases or those found through contact tracing are generally identified. The few population-based studies that have been done appear to show low prevalence in the general population. A serological study of 10,009 individuals in Saudi Arabia found 15 seropositive for MERS-CoV, 7 of whom were occupationally camel-exposed (shepherds and slaughterhouse workers) (Müller et al. 2015), although the occupational samples were collected for a separate study and therefore may not be representative. In another study of 57,363 persons with suspected MERS-CoV infection tested by Saudi Arabia from April 2015 to February 2016, only 384 (0.7%) tested positive (Bin Saeed et al. 2017).

Most work has been done on symptomatic MERS patients because they are most likely to be detected and identified. Even so, one analysis suggested that at least 62% of even symptomatic cases were undetected (Cauchemez et al. 2014), and a study using data from travelers suggested that there may have been as many as 3250 severe cases from September 2012 to January 2016, about 2.3 times the number of cases confirmed (O'Hagan et al. 2016).

Determination of primary versus secondary cases is also challenging. One estimate is that 61% of MERS-CoV are primary cases, who tend to be mostly middle-aged males, compared with secondary cases who tend to be younger and distributed more evenly by sex (Gossner et al. 2016). The official overall CFR stands at ~35.5% (World Health Organization 2018a). However, it has been suggested that the CFR among primary cases, estimated to be 74%, is likely inflated due to detection bias; CFR among secondary cases is estimated to be 20% (Cauchemez et al. 2014).

The main known exposures are health care-associated infections and contact with camels. Aside from the health care setting, the mechanisms for the introduction of the virus into human populations are poorly understood. Occupational exposure risks are also poorly characterized, both in health care and for those who work with camels.

As with SARS, many cases have been health care facility-associated (Drosten et al. 2015), but the mechanism of infection is unclear for many individuals (Fanoy et al. 2014). Active case finding, typically among perceived risk groups or those hospitalized with pneumonia, has been used with varying success to identify cases (Gierer et al. 2013, Aburizaiza et al. 2014, Memish et al. 2014a).

Nosocomial transmission due to inadequate infection control is well established as a significant driver of MERS-CoV infections in humans (Al-Abdallat et al. 2014, Maltezou and Tsiodras 2014, Oboho et al. 2015, Alraddadi et al. 2016, Assiri et al. 2016, Hastings et al. 2016), notably during the spring 2014 outbreak in Saudi Arabia and the late spring 2015 outbreak in South Korea. A review (Maltezou and Tsiodras 2014) of 536 known MERS-CoV cases at the time of the review using publicly available data found 11 possible or confirmed health care-associated transmission events leading to substantial morbidity and mortality, often involving patients having comorbidities.

Infection control lapses were apparently responsible for virtually all reported health care transmission events, highlighting the need for strengthened infection control capacity worldwide. However, specific breaches in infection control were usually not identified and probably varied (Maltezou and Tsiodras 2014). Some high-risk procedures were identified, usually aerosol generating procedures, including hemodialysis and respiratory intensive care (Assiri et al. 2013b).

Secondarily infected health care workers tended to have milder symptoms and better prognoses. In the 2014 outbreak in Saudi Arabia, one study analyzed 191 symptomatic cases of MERS-CoV and found that 20.9% were health care workers (additional infected health care workers were asymptomatic, so that 30.6% of the 255 total cases analyzed were health care workers), and most patients had contact with a health care facility (Oboho et al. 2015). In a cluster of 9 MERS-CoV cases in Jordan, 6 were health care workers at the outbreak hospital, and no MERS-CoV transmission was detected at 2 transfer hospitals with adequate infection control (Al-Abdallat et al. 2014).

A health care-associated outbreak occurred in South Korea in the late spring of 2015 through July 2015, arising from one infected individual returning from the Gulf states (Cowling et al. 2015, Hui et al. 2015, Park et al. 2015). An analysis of 185 South Korean MERS-CoV cases using publicly available data delineated three generations of secondary infections (more than half of the cases were from the second generation) (Lee and Wong 2015). Overall, 154 cases were hospital-associated (Lee and Wong 2015), primarily affecting non-health care workers, spread by conditions such as close contact with the patients in crowded hospital or emergency rooms (Lee 2015b) and patients switching facilities (Lee 2015a, 2015b).

Direct contact could be inferred in only about 10% of the cases, and some authors suggested that fomite transmission could be important (Lee and Wong 2015, Seo et al. 2016, also reviewed in Otter et al. 2016). Earlier reports demonstrated that MERS-CoV is relatively stable in the environment, reported recoverable on surfaces after 48 h at 20°C and 48% relative humidity and for at least 12 h at 30°C with 30% humidity (van Doremalen et al. 2013), or in liquid at 25°C after 2 h (Leclercq et al. 2014). In a study of four laboratory-confirmed MERS-CoV patient rooms in two South Korean hospitals, MERS-CoV viral RNA was found on environmental

surfaces, including bedsheets and medical equipment, up to 5 days after a patient's last PCR-positive respiratory specimen; viable virus was also detected (Seo et al. 2016).

However, there were apparently few reports of infections in hospital laundry or maintenance workers, contrary to what would be expected for environmental transmission. It is possible that they were not identified or reported. We could find only two publications specifically mentioning infection in hospital cleaners (Hastings et al. 2016, Liu et al. 2016). Hastings et al. (2016) investigated a 2014 outbreak in King Fahd General Hospital and reported 1 MERS-CoV case among 1295 maintenance or housekeeping personnel. However, it appears that only symptomatic cases were tested, and specific details on this case were not provided.

Many reports from contact tracing identified family members, friends, coworkers, and other persons who had close contact with the patient. These include reports from Saudi Arabia (Memish et al. 2013b, Omrani et al. 2013, Drosten et al. 2014), as well as the United Kingdom (Pebody et al. 2012, Health Protection Agency (HPA) UK Novel Coronavirus Investigation Team 2013, Thomas et al. 2014), Iran (Yavarian et al. 2015), Tunisia (Abroug et al. 2014), China (Wu et al. 2015), Greece (Tsiodras et al. 2014), Germany (Buchholz et al. 2013, Reuss et al. 2014), Malaysia (Premila Devi et al. 2014), France (Mailles et al. 2013), and Italy (Puzelli et al. 2013).

Family clusters were identified in a number of these reports, but at most only a small percentage of contacts became cases, suggesting that close contact is not as important a risk factor as health care-associated transmission, and direct human-to-human transmission appears limited. Although the outbreak in South Korea also involved close contact among family members and other patients in hospital rooms, this may be more appropriately categorized as health care-associated transmission (Kang et al. 2017).

However, there is relatively little information on asymptomatic individuals, most of whom are detected by contact tracing. In one study, an asymptomatic health care worker excreted MERS-CoV for over 5 weeks (Al-Gethamy et al. 2015). In the spring 2014 outbreak in Saudi Arabia, an estimated 25.1% of laboratory-confirmed MERS-CoV was asymptomatic (Oboho et al. 2015). An analysis of 65 MERS-CoV patients in United Arab Emirates found that 35% were asymptomatic, and 1 individual yielded positive lower respiratory tract specimens for more than 2 weeks (Hosani et al. 2016). Al Hammadi et al. reported two asymptomatic men who had contact with infected camels; infection was confirmed by PCR in both men, and in all eight camels in the group (Al Hammadi et al. 2015). However, the actual frequency of asymptomatic individuals compared with symptomatic individuals is largely unknown.

Parameters for transmission dynamics are important for mathematical modeling of spread. Due to the heterogeneity in transmission, an important characteristic of infection dynamics, R_0 (the basic reproductive rate in a susceptible population), has been difficult to pinpoint. Estimates have ranged from 0.50 to 0.69 (Breban et al. 2013, Poletto et al. 2014) to between 0.8 and 1.3 (Cauchemez et al. 2014). $R_0 > 1$ is required for an outbreak to be self-sustaining (Anderson and May 1991). For specific locations, one model suggested an R_0 of 3.5–6.7 in Jeddah and 2.0–2.8 in Riyadh (Majumder et al. 2014), but these likely did not correct for effect of superspreading in health care settings (Kucharski and Althaus 2015). One mathematical model suggested the risk of secondary transmission following an imported MERS-CoV case is 22.7% (95% CI: 19.2–25.1%), with the risks of generations 2, 3, and 4 estimated to be 10.5%, 6.1%, and 3.9%, respectively (Nishiura et al. 2015).

Travel-related cases. Despite the mass gathering of individuals at the annual Hajj pilgrimage (Khan et al. 2013), to date it has not resulted in any known MERS-CoV transmission events (Barasheed et al. 2014, Benkouiten et al. 2014, Gautret et al. 2014, Memish et al. 2014b, 2014c, Aberle et al. 2015, Annan et al. 2015), confirming modeling estimates for the 2014 Hajj (Lessler et al. 2014). Two travelers returning to the Netherlands from a separate pilgrimage (Umrah) in May 2014 were found to have MERS-CoV (Kraaij-Dirkzwager et al. 2014). Many of the travel-related cases have been tabulated (Pavli et al. 2014, Sridhar et al. 2015, Carias et al. 2016). In all these cases, casual transmission (outside of family and health care settings) has not been observed.

The animal interface and search for natural and reservoir hosts of MERS-CoV

Dromedary camels are the only documented zoonotic source of human infection, and there is considerable circumstantial evidence supporting camel-to-human transmission, including evidence of camels and humans becoming infected with an identical MERS-CoV (Azhar et al. 2014, Ferguson and Kerkhove 2014, Memish et al. 2014e). Identical genomic sequences of MERS-CoV were isolated from a camel owner who died from MERS-CoV and his camel who had rhinorrhea at that time; identical MERS-CoV RNA fragments were later detected in the air at the camel barn (Azhar et al. 2014). Serology suggested that the camel was infected before the owner (Azhar et al. 2014). Critics have suggested that the identical sequences may be due to cross-contamination (Drosten et al. 2014), but the authors maintain that the isolates were collected on different days and processed in different facilities. Other epidemiologic investigations have found similar evidence, but directionality was not implied (Ferguson and Kerkhove 2014, Memish et al. 2014e).

In outbreak sites, viral genomic sequences from camels have matched those published for humans, and one analysis of MERS-CoV among camels showed that many of the camel viruses can be classified into clades that correlate with human outbreaks (Alagaili et al. 2014). Interestingly, three dromedary camel strains of MERS-CoV had similar viral replication competence to human strains in Vero-E6 cells and human respiratory tract explants (Chan et al. 2014).

This evidence suggests that camels would appear involved in cross-species transmission of MERS-CoV, although the precise mechanism and frequency remain uncertain.

Occupational exposure to camels would seem a particularly strong risk factor for infection, but its relative importance and relative risk of different exposures are not well documented (Hemida et al. 2015). As camels are widely used in the region for a variety of purposes, many people have contact with camels, and exposure is often invoked in non-occupational primary cases. Assessment of camel exposure is further complicated by the varying and sometimes vague

Table 1. Location, Methods, and Results of Recent Middle East Respiratory Syndrome Coronavirus Camel Seroprevalence Studies

Countries (reference)	*Year(s)*	*Test(s) used*[a]	*No. of samples*	*No. of positives (%)*
Egypt (Perera et al. 2013)	2013	ppNT	110	108 (98.2)
Egypt, Somalia, Sudan (Müller et al. 2014)	1983–1997	rELISA	189	159 (84.1)
		MNT		153 (81.0)
Egypt, Sudan, others (Ali et al. 2017a)	2015–2016	MNT	1031	871 (84.5)[b]
Ethiopia (Reusken et al. 2014b)	2010–2011	S1 microarray	188	181 (96.3)[c]
Jordan (Reusken et al. 2013b)	2013	Nt	11	11 (100.0)
Kenya (Corman et al. 2014b)	1992–2013	rELISA	774	228 (29.5)
		IFA		213 (27.5)
		MNT		133 (17.2)
Nigeria (Reusken et al. 2014b)	2010–2011	S1 microarray	358	337 (94.1)[c]
Oman (Reusken et al. 2013c)	2013	PRNT	50	50 (100.0)
Saudi Arabia (Alagaili et al. 2014)	1992–2010	ELISA	264	230 (87.1)
	2013	ELISA	203	150 (73.9)
Saudi Arabia (Hemida et al. 2014)	1993	ppNT	131	118 (90.1)
Saudi Arabia (Hemida et al. 2013)	2012–2013	ppNT	310	280 (90.3)
Tunisia (Reusken et al. 2014b)	2009	S1 microarray	204	99 (48.5)[c]
United Arab Emirates (Meyer et al. 2014)	2003, 2013	rIFA	651	632 (97.1)
		Nt		509 (80.5)
United Arab Emirates (Alexandersen et al. 2014)	2005	Nt	11	9 (81.8)

[a]ppNT, pseudoparticle neutralization; rELISA, recombinant enzyme-linked immunosorbent assay; MNT, microneutralization; PRNT, plaque reduction neutralization test; rIFA, recombinant immunofluorescence assay; Nt, serum neutralization.
[b]Seroprevalence reported higher in camels imported from Sudan (543/594; 88.7%) and East Africa (71/98; 72.4%) than resident (257/339; 5.8%); total 41/1078 nasal swabs reported PCR positive, 35/41 from Sudan.
[c]The exact number was not reported, and has been imputed from the reported percentages.

definitions used to classify camel exposure, and the multiple types of possible exposures. Even so, it has been hypothesized that camel exposure is commonly underreported (Gossner et al. 2016). There is a critical need for clearer definitions and measurements of ''camel exposure,'' and to standardize methodology.

Evidence to date indicates that MERS-like coronaviruses have been circulating in camels since at least the 1980s, before the first detection of MERS-CoV in humans (Müller et al. 2014). Seropositivity has been found consistently in African and Middle Eastern camels since 1983 (Table 1). There is virologic evidence of MERS-CoV infection in camels in Qatar (Ferguson and Kerkhove 2014, Haagmans et al. 2014, Raj et al. 2014), Egypt (Chu et al. 2014, Ali et al. 2017a, 2017b), Oman (Nowotny and Kolodziejek 2014), Saudi Arabia (Hemida et al. 2014), Sudan, and elsewhere (Chu et al. 2015, Ali et al. 2017a).

Increasing genomic evidence suggests a diversity of coronaviruses in camels throughout the Middle East and Africa, including in major source countries for camel imports to the Middle East, cross-neutralizing with MERS-CoV but having divergent sequences and probably not human pathogens (Chu et al. 2015, 2018). This may explain the high apparent seropositivity in camels in Africa in the absence of known human cases of MERS.

Maintenance of the virus in the camel population remains an open question. Symptomatic MERS-CoV infection has been documented in both calves and adult camels (Adney et al. 2014), and viral shedding was detected in nasal secretions up to 7 days postinoculation with MERS-CoV (Adney et al. 2014), as well as in milk and possibly feces (Hemida et al. 2014, Reusken et al. 2014a). Camel milk has been suggested as a possible source of infection for both humans and camel foals (Hemida et al. 2014, Reusken et al. 2014a, van Doremalen et al. 2014). One study demonstrated that added MERS-CoV can survive in milk for at least 48 h at both 4°C and 22°C, although not detected after pasteurization (van Doremalen et al. 2014).

Other possible livestock hosts for MERS-CoV have been investigated, and have generally been negative (Hemida et al. 2013, Perera et al. 2013, Reusken et al. 2013b, 2013c, Alagaili et al. 2014, Alexandersen et al. 2014, van Doremalen et al. 2014, Meyer et al. 2015). One study found 15 seropositive alpacas, which are members of the camelid family, in Qatar (Reusken et al. 2016). Experimentally infected alpacas in one study demonstrated upper respiratory tract infection, viral shedding, and transmission to other alpacas (Adney et al. 2016).

The search for the origins and natural hosts of MERS-CoV continues. Bat species across the world are known to host a wide variety of coronaviruses, including beta-coronaviruses (the genus to which MERS-CoV belongs) (Anthony et al. 2013, Corman et al. 2013, Lelli et al. 2013, Memish et al. 2013a), and bats tend to show greater coronavirus diversity than other mammals (Drexler et al. 2014, Anthony et al. 2017). Consequently, much research has focused on the possible origin of MERS-CoV in bats. Possibly further supporting this hypothesis, in bat cell lines MERS-CoV has been reported to replicate only in those cell lines that express DPP4, the functional human receptor for the virus, and not in bat cell lines lacking DPP4 expression (Raj et al. 2013, Cai et al. 2014).

It is possible that MERS-CoV itself may be a relatively new introduction in humans. A phylogenetic analysis utilizing 65 complete or partially complete MERS-CoV genomic sequences (32 from Saudi Arabian cases in 2013) estimated that the most recent common ancestor was in March 2012 (95% CI: December 2011–June 2012) (Cotten et al. 2014).

One study, from analysis of an S1 subunit in its spike gene, suggested that MERS-CoV may have arisen from intraspike

recombination between two ancestral coronaviruses (Corman et al. 2014).

The virus has not been isolated from a bat, although a portion of MERS-CoV RNA sequence apparently was identified in a bat (the insectivorous bat *Taphozous perforatus*, the Egyptian tomb bat) in Saudi Arabia in the same site as an early human case (100% nucleotide match, although this was only ~180 nucleotides in the relatively well-conserved RdRp region) (Memish et al. 2013a). MERS-like coronaviruses, including the closely related HKU4, which also uses a DPP4 receptor, and HKU5, first identified by Woo et al. in 2006 (Woo et al. 2006, Lau et al. 2013, Matthews et al. 2014, Wang et al. 2014), and others have been identified in bat species in China (Matthews et al. 2014, Yang et al. 2014), Mexico (Anthony et al. 2013), South Africa (Ithete et al. 2013, Corman et al. 2014a), and Uganda (Anthony et al. 2017).

Discussion and Conclusions

Since the detection of MERS-CoV in 2012, a large body of research has been amassed, as evidenced by the hundreds of unique results from our database searches. The virus has rapidly been characterized, and its functional human receptor swiftly identified. Species and cellular tropism studies have complemented clinical investigations, and laboratory work has provided further insights on MERS-CoV pathogenesis.

Observational research from outbreaks in the Middle East and South Korea has generated a growing repository of clinical data, basic epidemiology, and genome sequences. Other studies have evaluated the roles of human/animal interfaces, health care settings, family clusters, and travel in MERS-CoV transmission. Furthermore, bats have been implicated as the possible origin of MERS-CoV, while dromedary camels have been shown to be likely sources of many human infections. There has been progress in developing therapeutics and vaccines. Although these have not yet progressed to full clinical trials, they could in the foreseeable future.

A major reason we undertook this review was to determine what gaps still exist. Of the publications we originally identified, the largest category (80 publications) was in laboratory or basic science studies, followed by surveillance (59), animal interfaces (55), clinical aspects and health care (50), therapeutics and vaccines (42), while human transmission and epidemiology was one of the sparsest (35, including investigations of hospital outbreaks and travel-related cases), noting that these categories are not necessarily exclusive and there is overlap.

In general, continued surveillance for MERS-CoV in affected countries should continue, prioritizing surveillance in humans, camels, and bats, given their apparent importance. As serology may not be reliable, due to cross-reactions and possibly waning antibodies, virologic surveillance and sequencing should also be attempted on selected specimens whenever feasible.

Although the role of bats is yet to be fully elucidated, and evidence is lacking that bats are a source of human infection, the diversity of coronaviruses, including MERS-like coronaviruses, in bat species across the globe indicates that continued research and ongoing surveillance of coronaviruses in bats are justified (Lau et al. 2013, Lelli et al. 2013, Yang et al. 2014).

A number of key gaps remain in epidemiology, including transmission, population-based incidence or prevalence rates, and geographic and demographic distributions of infections. Based on the limited human seroprevalence data so far, it seems likely that population prevalence is low, but the baseline should be established. It is also not clear whether seropositivity is a reliable indicator of prior infection. The finding of variable low antibody titers at 1 year postinfection (Choe et al. 2017) indicates that methods other than traditional serosurveys may be required (Reusken et al. 2013a, Malik et al. 2016). If serology is not reliable, this raises the question of how to screen populations. There are methods that are both more sensitive and more specific for antibody detection (Mishra et al. 2018), as well as assays of cellular immunity (Zhao et al. 2017), but are costlier and more difficult for population screening.

Contact tracing has identified asymptomatic infections, but studies of their frequency and transmissibility have been limited. Many of those infected are health care workers in whom these questions could be systematically studied. Relatively little is known about the natural history of human asymptomatic infections. Further studies of virus shedding, seroconversion, and transmission in asymptomatic infections are needed. Some evidence suggests that secondary cases have lower average CFRs and that subsequent links in the chain of MERS-CoV infection may decrease in severity.

Exposure in most primary cases is still largely inferential at best. While camels are apparently often the likely source, the definitions of camel exposure are varied, preventing clear epidemiological inferences. Definitions of the exposures and the methodology and metrics for determining exposure should be clarified and standardized. Even if camels are a principal source of human infections, this would still not explain a substantial portion of primary human cases that did not have apparent camel exposure before infection. This raises questions about how and where these other primary cases acquired MERS-CoV infection, whether through other animal species, unidentified zoonotic exposure, unrecognized infectious persons (such as asymptomatic infectious individuals), or environmental contamination.

Consequently, clarifying the routes of transmission remains crucial and should receive emphasis. To date, there is no compelling evidence of direct human-to-human transmission, such as through droplets, but secondary infection has been reported. It is often unclear how health care workers become infected. There is possible evidence of environmental contamination (fomites) in health care settings (nosocomial transmission) and close contact with an active MERS-CoV case.

Various infection control lapses have been documented, but rarely a specific event or route (Ben Embarek and Van Kerkhove 2015, Alraddadi et al. 2016, Van Kerkhove et al. 2016). Rigorous infection control therefore remains essential and could prevent many secondary cases. In the interim, better documentation or identification of the specific lapses that led to infection would be of great value in understanding mechanisms of transmission and is one of the greatest knowledge gaps. Much of the evidence for fomite transmission, for example, remains anecdotal (Van Kerkhove et al. 2016).

The mechanisms supporting chains of human MERS-CoV transmission need to be more fully evaluated. These gaps indicate a need for additional research, and also for consistent

terminology and clear definitions. Although the epidemiological literature on MERS-CoV is large, much of it is fragmented and inconsistently reported. It is often difficult to deduce the sequence of infections, relationships between cases, or specific exposures. A comprehensive and consistent database or registry should be a priority.

Genome sequencing has proved useful in several respects. Genome sequencing was used to help determine viral circulation and ancestry (Cotten et al. 2014), and to differentiate apparently similar and serologically cross-reacting coronaviruses in camels, addressing the (still unresolved) question of why MERS seems regionally limited, while many camels are imported from other places (Chu et al. 2015, 2018). It has also been used to reconstruct the transmission events and help to establish chains of infection (Assiri et al. 2013b, Cotten et al. 2013), but it must be noted that there is a pressing need for more rigorous conventional epidemiology as well to validate the methodologies. These approaches might well serve a complementary function in advancing our understanding.

There remains a need for effective therapeutics and vaccines. Treatment remains symptomatic, with insufficient clinical data on other therapeutic options. These options will always be limited in number, but their development should be approached more systematically with shared protocols and critical comparison of results. As a number of drug and vaccine candidates have been identified, there may be more options available for future clinical trials. There appear to be efforts underway to develop some clinical trials based on standardized protocols. This is needed, despite the challenges presented by the sporadic nature of the cases, and the relative rarity of clinical MERS.

There were several limitations in this systematic review of MERS-CoV. Only publications in English or with English language abstracts were eligible for inclusion, although most of the cases have been in Arabic-speaking areas and Korea. However, hundreds of English language reports were available from countries around the world, including the Middle East and South Korea, minimizing this concern. Second, this review contains publications indexed by these databases by July 2017, so it is possible that some publications, especially recently published articles or manuscripts still in production, were unintentionally excluded from the review. We updated our literature review periodically during the preparation of this article to minimize the number of missed publications. Third, ''gray literature'' was not included, such as government reports and technical documents, and most meeting abstracts, although it is likely that important findings would have been submitted for journal publication.

As an emerging infection of zoonotic origin (Morse 1995), a unified One Health approach that engages the human health, livestock and companion animal, wildlife, and environment sectors will be crucial in dealing with MERS (Morse 2012, Morse et al. 2012). It could serve as an excellent case study for epidemiology and response to a new zoonotic, or emerging, infection.

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Middle East respiratory syndrome coronavirus (MERS-CoV)

Overview | Symptoms | Treatment

Middle East respiratory syndrome coronavirus (MERS-CoV) is a virus transferred to humans from infected dromedary camels. It is a zoonotic virus, meaning it is transmitted between animals and people, and it is contractable through direct or indirect contact with infected animals. MERS-CoV has been identified in dromedaries in several countries in the Middle East, Africa and South Asia. In total, 27 countries have reported cases since 2012, leading to 858 known deaths due to the infection and related complications.

The origins of the virus are not fully understood but according to the analysis of different virus genomes it is believed that it may have originated in bats and later transmitted to camels at some point in the distant past.

Human-to-human transmission is possible, but only a few such transmissions have been found among family members living in the same household. In health care settings, however, human-to-human transmission appears to be more frequent.

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35% of patients with
MERS-CoV have died

May be an overestimate as mild cases may be missed by existing surveillance systems

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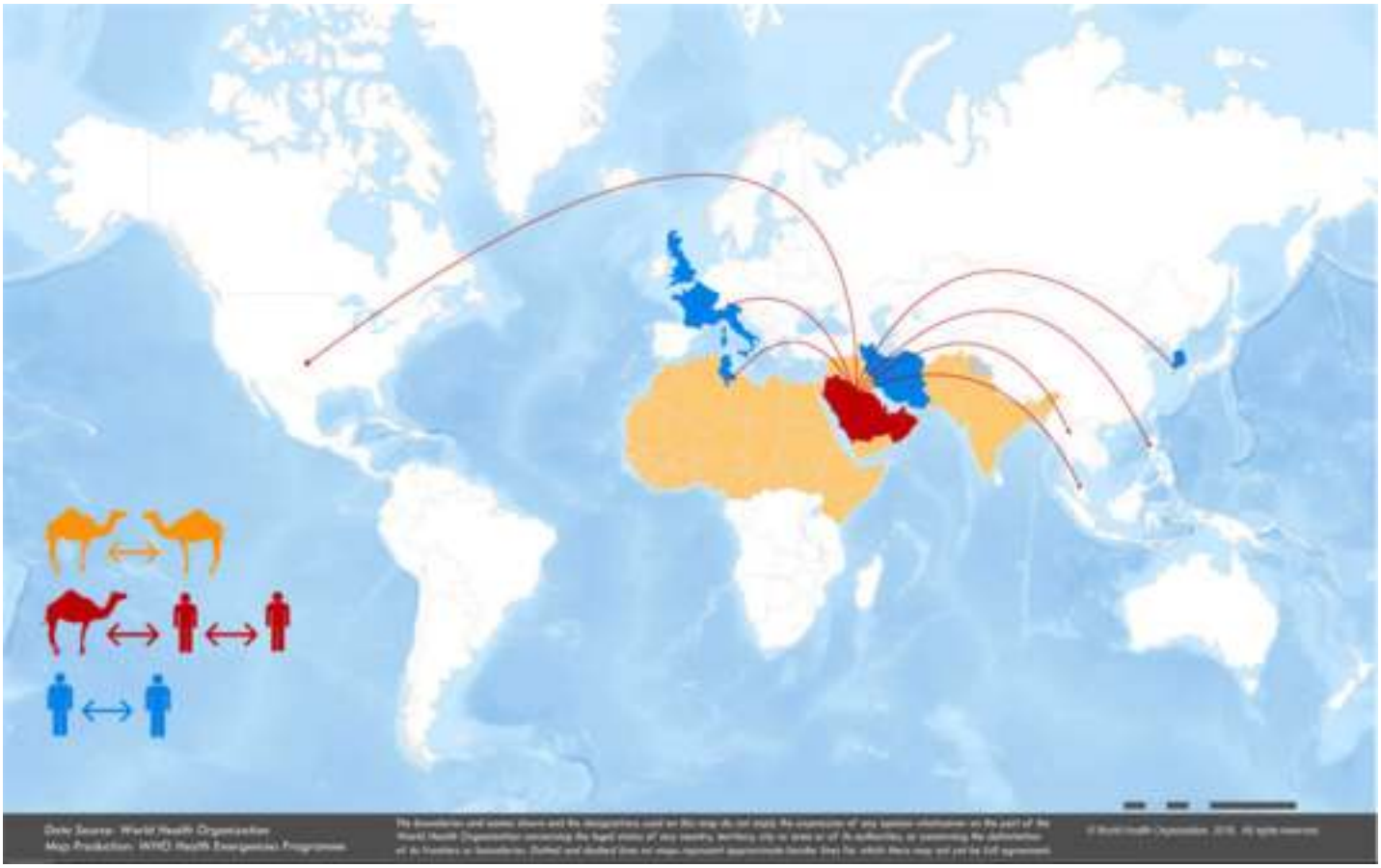

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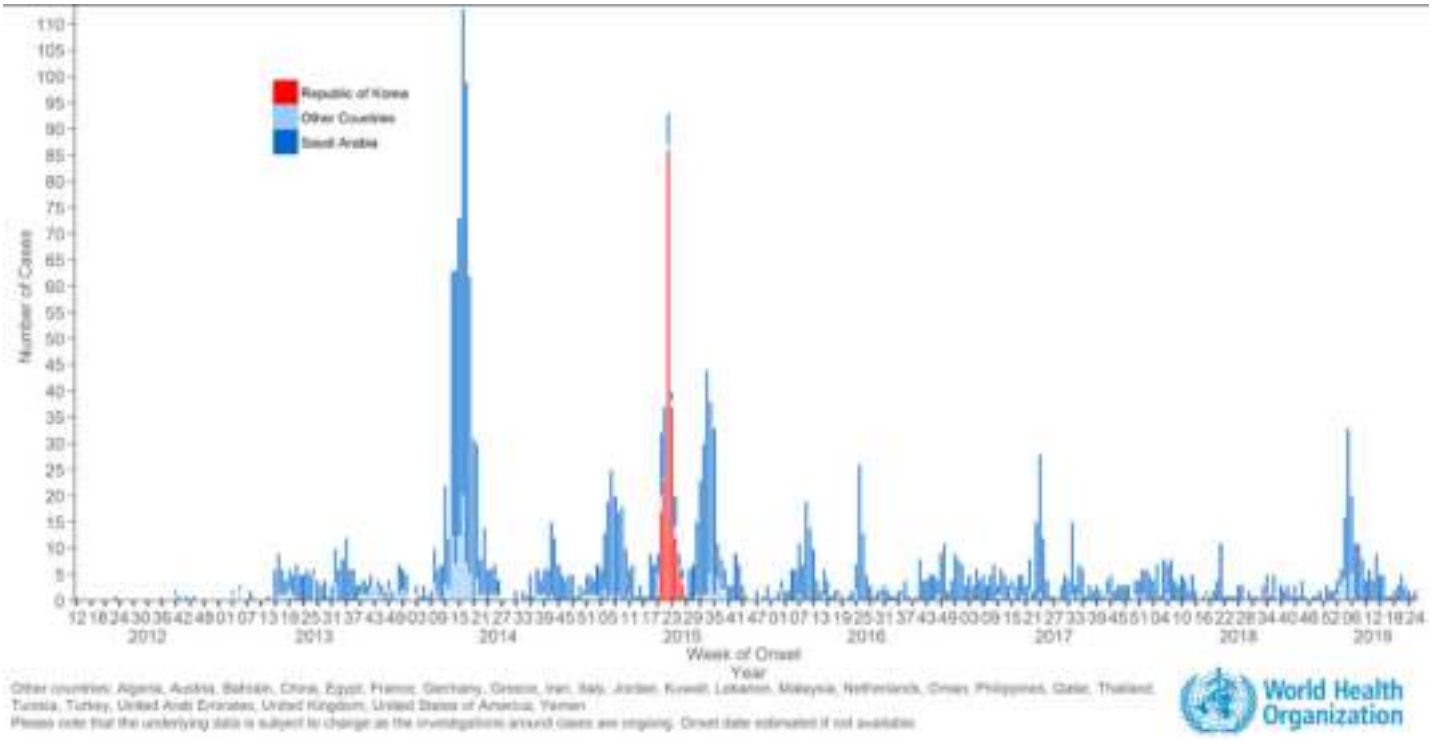

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SARS and MERS: recent insights into emerging coronaviruses

Emmie de Wit[1], Neeltje van Doremalen[1], Darryl Falzarano[2] and Vincent J. Munster[1]

Abstract | The emergence of Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 marked the second introduction of a highly pathogenic coronavirus into the human population in the twenty-first century. The continuing introductions of MERS-CoV from dromedary camels, the subsequent travel-related viral spread, the unprecedented nosocomial outbreaks and the high case-fatality rates highlight the need for prophylactic and therapeutic measures. Scientific advancements since the 2002–2003 severe acute respiratory syndrome coronavirus (SARS-CoV) pandemic allowed for rapid progress in our understanding of the epidemiology and pathogenesis of MERS-CoV and the development of therapeutics. In this Review, we detail our present understanding of the transmission and pathogenesis of SARS-CoV and MERS-CoV, and discuss the current state of development of measures to combat emerging coronaviruses.

Nosocomial transmission
Transmission of an infectious agent by staff, equipment or the environment in a health care setting.

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This century has seen the global spread of two previously unknown coronaviruses. In November 2002, the first known case of severe acute respiratory syndrome (SARS) occurred in Foshan, China[1]. New cases emerged in mainland China, and by February 2003, more than 300 cases had been reported, around one-third of which were in health care workers[1]. Individuals who were infected and subsequently travelled spread the outbreak to Hong Kong[2] and from there to Vietnam, Canada and several other countries[3]. In March 2003, the WHO established a network of laboratories to determine the causative agent of SARS. A remarkable global effort led to the identification of SARS coronavirus (SARS-CoV) in early April of that year[4–6]. By July 2003 and after a total of 8,096 reported cases, including 774 deaths in 27 countries[7], no more infections were detected, and the SARS pandemic was declared to be over. Five additional SARS cases, resulting from zoonotic transmission, occurred in December 2003–January 2004 (REF. 8), but no human SARS cases have been detected since. Measures of infection control, rather than medical interventions, ended the SARS pandemic. However, certain SARS-CoV-like viruses found in bats have recently been shown to be able to infect human cells without prior adaptation[9,10], which indicates that SARS could re-emerge.

In June 2012, 10 years after the first emergence of SARS-CoV, a man in Saudi Arabia died of acute pneumonia and renal failure. A novel coronavirus, Middle East respiratory syndrome coronavirus (MERS-CoV), was isolated from his sputum[11]. A cluster of cases of severe respiratory disease had occurred in April 2012 in a hospital in Jordan and was retrospectively diagnosed as MERS[12], and a cluster of three cases of MERS in the UK was identified in September 2012 (REF. 13). MERS-CoV continued to emerge and spread to countries outside of the Arabian Peninsula as a result of travel of infected persons; often, these imported MERS cases resulted in nosocomial transmission. In May 2015, a single person returning from the Middle East started a nosocomial outbreak of MERS in South Korea that involved 16 hospitals and 186 patients[14]. As of 26 April 2016, there have been 1,728 confirmed cases of MERS, including 624 deaths in 27 countries[15].

This Review highlights the pandemic and epidemic potential of emerging coronaviruses and discusses our current knowledge of the biology of SARS-CoV and MERS-CoV, including their transmission, their pathogenesis and the development of medical countermeasures. Key features of these viruses are the dominance of nosocomial transmission, and pathogenesis that is driven by a combination of viral replication in the lower respiratory tract and an aberrant host immune response. Several potential treatments for SARS and MERS have been identified in animal and *in vitro* models, including small-molecule protease inhibitors, neutralizing antibodies and inhibitors of the host immune response. However, efficacy data from human clinical trials are lacking but are needed to move these potential countermeasures forward.

Replication of SARS-CoV and MERS-CoV

SARS-CoV and MERS-CoV belong to the Coronavirus genus in the *Coronaviridae* family and have large, positive-sense RNA genomes of 27.9 kb and 30.1 kb,

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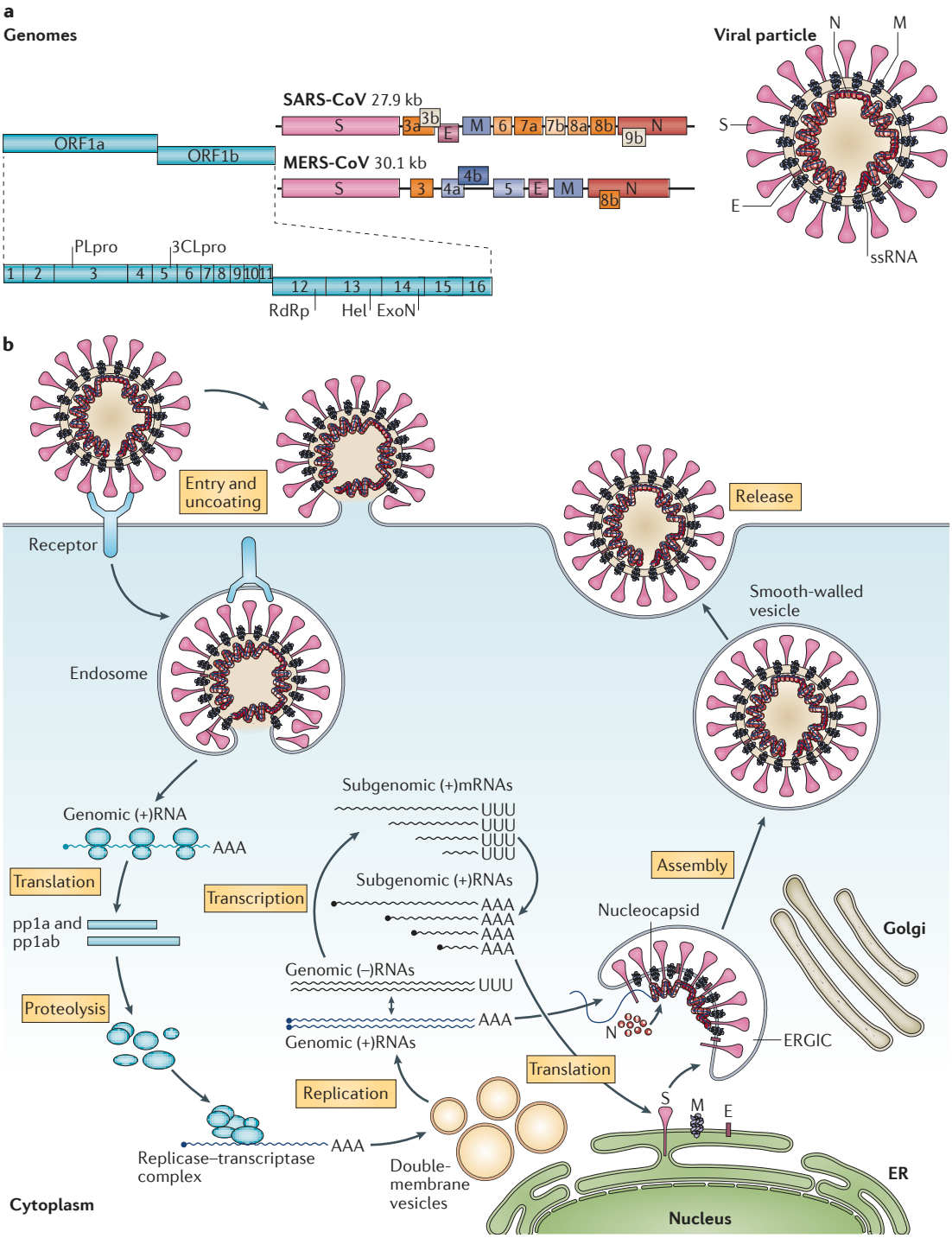
Proofreading
The correction of errors that are acquired during the replication of DNA or RNA.

respectively (FIG. 1a). Similarly to all viruses in the order *Nidovirales*, SARS-CoV and MERS-CoV have a unique coding strategy: two-thirds of the viral RNA is translated into two large polyproteins, and the remainder of the viral genome is transcribed into a nested set of subgenomic mRNAs[16,17] (FIG. 1b). The two polyproteins, pp1a and pp1ab, encode 16 non-structural proteins (nsp1–nsp16)[18] that make up the viral replicase–transcriptase complex. The polyproteins are cleaved by two proteases, papain-like protease (PLpro; corresponding to nsp3) and a main protease, 3C-like protease (3CLpro; corresponding to nsp5). The nsps rearrange membranes that are derived from the rough endoplasmic reticulum (RER) into double-membrane vesicles, in which viral replication and transcription occur[19]. One unique feature of coronaviruses is the exoribonuclease (ExoN) function of nsp14 (REF. 20), which provides the proofreading capability required to maintain a large RNA genome without the accumulation of detrimental mutations[21,22]. SARS-CoV and MERS-CoV transcribe 12 and 9 subgenomic RNAs,



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ER–Golgi intermediate compartment
(ERGIC). A cellular compartment that facilitates transport between the endoplasmic reticulum (ER) and the Golgi complex.

Super spreaders
Infected individuals who each infect a disproportionately large number of secondary cases.

respectively, and these encode the four structural proteins spike (S), envelope (E), membrane (M) and nucleocapsid (N), as well as several accessory proteins that are not involved in viral replication but interfere with the host innate immune response or are of unknown or poorly understood function.

The envelope spike glycoprotein binds to its cellular receptor, angiotensin-converting enzyme 2 (ACE2) for SARS-CoV and dipeptidyl peptidase 4 (DPP4) for MERS-CoV[23]. After membrane fusion, either directly with the host cell membrane or with the endosome membrane, the viral RNA genome is released into the cytoplasm, and the RNA is uncoated to allow translation of the two polyproteins, transcription of the subgenomic RNAs and replication of the viral genome (FIG. 1b). Newly formed envelope glycoproteins are inserted in the RER or Golgi membranes; genomic RNA and nucleocapsid proteins combine to form nucleocapsids, and the viral particles bud into the ER–Golgi intermediate compartment (ERGIC). Virion-containing vesicles subsequently fuse with the plasma membrane to release the virus[24].

Reservoirs and transmission

The first indication of the source of SARS-CoV was the detection of the virus in masked palm civets and a raccoon dog and the detection of antibodies against the virus in Chinese ferret badgers in a live-animal market in Shenzhen, China[25]. However, these animals were only incidental hosts, as there was no evidence for the circulation of SARS-CoV-like viruses in palm civets in the wild or in breeding facilities[26]. Rather, bats are the reservoir of a wide variety of coronaviruses, including SARS-CoV-like and MERS-CoV-like viruses[27] (FIG. 2).

Figure 1 | **SARS-CoV and MERS-CoV structure and replication. a** | The single-stranded RNA (ssRNA) genomes of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) encode two large polyproteins, pp1a and pp1ab, which are proteolytically cleaved into 16 non-structural proteins (nsps), including papain-like protease (PLpro), 3C-like protease (3CLpro), RNA-dependent RNA polymerase (RdRp), helicase (Hel) and exonuclease (ExoN). An additional 9–12 ORFs are encoded through the transcription of a nested set of subgenomic RNAs. SARS-CoV and MERS-CoV form spherical particles that consist of four structural proteins. The envelope glycoprotein spike (S) forms a layer of glycoproteins that protrude from the envelope. Two additional transmembrane glycoproteins are incorporated in the virion: envelope (E) and membrane (M). Inside the viral envelope resides the helical nucleocapsid, which consists of the viral positive-sense RNA ((+)RNA) genome encapsidated by protein nucleocapsid (N). **b** | Following entry of the virus into the host cell, the viral RNA is uncoated in the cytoplasm. ORF1a and ORF1ab are translated to produce pp1a and pp1ab, which are cleaved by the proteases that are encoded by ORF1a to yield 16 nsps that form the RNA replicase–transcriptase complex. This complex localizes to modified intracellular membranes that are derived from the rough endoplasmic reticulum (ER) in the perinuclear region, and it drives the production of negative-sense RNAs ((–)RNAs) through both replication and transcription. During replication, full-length (–)RNA copies of the genome are produced and used as templates for full-length (+)RNA genomes. During transcription, a subset of 7–9 subgenomic RNAs, including those encoding all structural proteins, is produced through discontinuous transcription. In this process, subgenomic (–)RNAs are synthesized by combining varying lengths of the 3′end of the genome with the 5′ leader sequence necessary for translation. These subgenomic (–)RNAs are then transcribed into subgenomic (+)mRNAs. Although the different subgenomic mRNAs may contain several ORFs, only the first ORF (that closest to the 5′end) is translated. The resulting structural proteins are assembled into the nucleocapsid and viral envelope at the ER–Golgi intermediate compartment (ERGIC), followed by release of the nascent virion from the infected cell.

Thus, the search for the reservoir of MERS-CoV initially focused on bats, but a serological survey in dromedary camels from Oman and the Canary Islands showed a high prevalence of MERS-CoV-neutralizing antibodies in these animals[28]. In addition, MERS-CoV RNA was detected in swabs that were collected from dromedary camels at a farm in Qatar that was linked to two human cases of MERS, and infectious virus was isolated from dromedary camels in Saudi Arabia and Qatar[29–32]. Serological evidence for the circulation of a MERS-CoV-like virus in dromedary camels has been obtained in the Middle East, Eastern Africa and Northern Africa, dating back as far as 1983 (REF. 33). Dromedary camels in Saudi Arabia harbour several viral genetic lineages[34], including those that have caused human outbreaks. Taken together, these data strongly point to the role of dromedary camels as a reservoir for MERS-CoV. The ubiquity of infected dromedary camels close to humans and the resulting continuing zoonotic transmission may explain why MERS-CoV continues to cause infections in humans, whereas SARS-CoV, without the continuing presence of an infected intermediate host and with relatively infrequent human–bat interactions, has caused no more infections in humans.

Human-to-human transmission of SARS-CoV and MERS-CoV occurs mainly through nosocomial transmission; 43.5–100% of MERS cases in individual outbreaks were linked to hospitals, and very similar observations were made for some of the SARS clusters[35,36]. Transmission between family members occurred in only 13–21% of MERS cases and 22–39% of SARS cases. Transmission of MERS-CoV between patients was the most common route of infection (62–79% of cases), whereas for SARS-CoV, infection of health care workers by infected patients was very frequent (33–42%)[35]. The predominance of nosocomial transmission is probably due to the fact that substantial virus shedding occurs only after the onset of symptoms[37,38], when most patients are already seeking medical care[39]. An analysis of hospital surfaces after the treatment of patients with MERS showed the ubiquitous presence of viral RNA in the environment for several days after patients no longer tested positive[40]. Moreover, many patients with SARS or MERS were infected through super spreaders[14,35,37,41–43].

The pathogenesis of SARS-CoV and MERS-CoV

The clinical courses of SARS and MERS are remarkably similar, although there are subtle differences (BOX 1). Owing to the current sparsity of data on human MERS-CoV infections[44], the pathogenesis of this virus is poorly understood; however, similar mechanisms may underlie the pathogenesis of both MERS and SARS.

The binding of spike protein to ACE2 and the subsequent downregulation of this receptor contribute to lung injury during SARS[45]. Although it seems counter-intuitive that receptor downregulation would increase pathology, it has been shown that ACE2 can protect against acute lung injury. The downregulation of ACE2 results in the excessive production of angiotensin II by the related enzyme ACE, and it has been suggested that the stimulation of type 1a angiotensin II receptor

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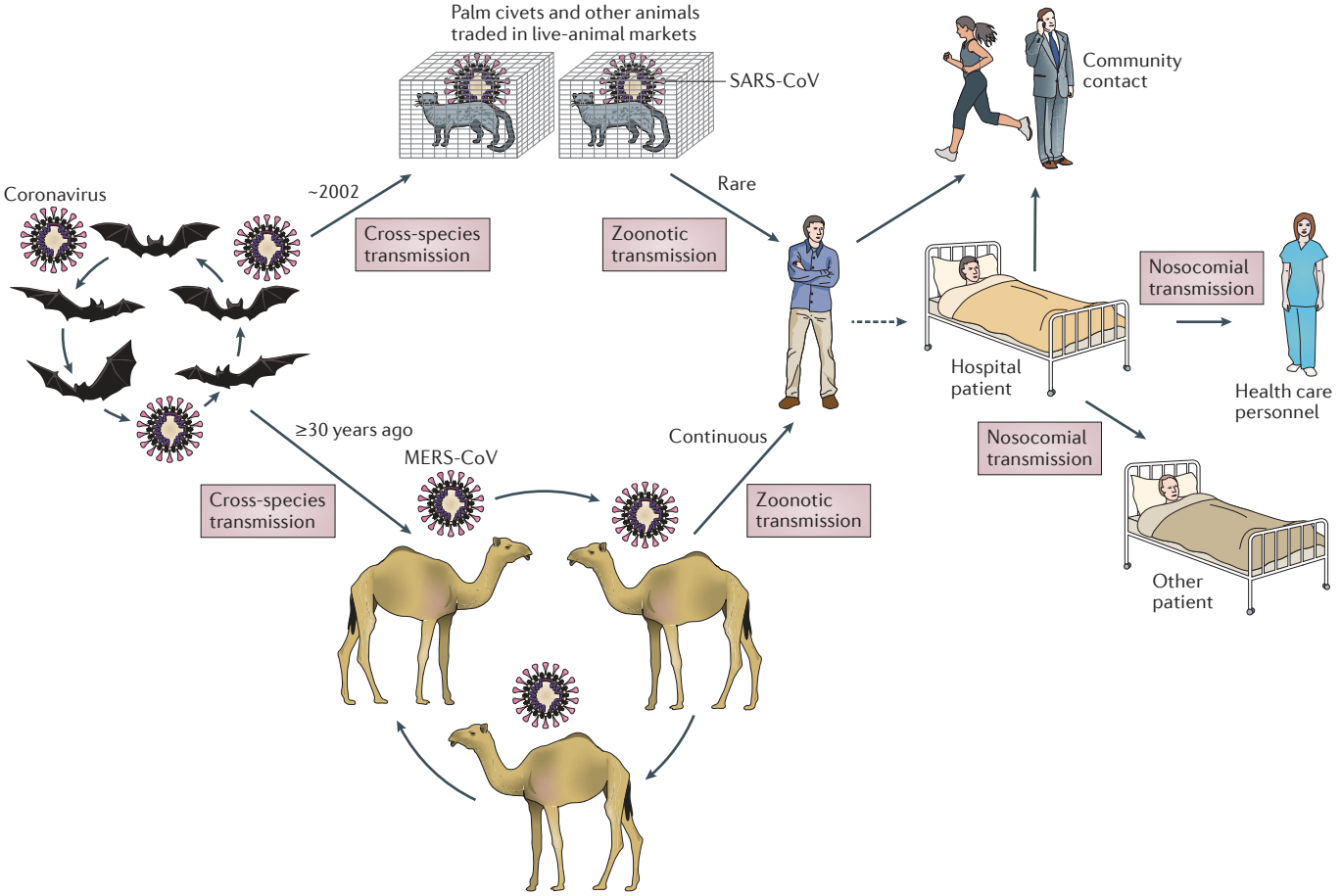

Figure 2 | **The emergence of SARS-CoV and MERS-CoV.** Bats harbour a wide range of coronaviruses, including severe acute respiratory syndrome coronavirus (SARS-CoV)-like and Middle East respiratory syndrome coronavirus (MERS-CoV)-like viruses. SARS-CoV crossed the species barrier into masked palm civets and other animals in live-animal markets in China; genetic analysis suggests that this occurred in late 2002. Several people in close proximity to palm civets became infected with SARS-CoV. A MERS-CoV ancestral virus crossed the species barrier into dromedary camels; serological evidence suggests that this happened more than 30 years ago. Abundant circulation of MERS-CoV in dromedary camels results in frequent zoonotic transmission of this virus. SARS-CoV and MERS-CoV spread between humans mainly through nosocomial transmission, which results in the infection of health care workers and patients at a higher frequency than infection of their relatives.

(AGTR1A) increases pulmonary vascular permeability, thus potentially explaining the increased lung pathology when the expression of ACE2 is decreased[46].

Immunopathology. The immune response is essential for the resolution of an infection, but it can also result in immunopathogenesis. One indication that immunopathogenesis may contribute to SARS was the observation that viral loads were found to be decreasing while disease severity increased[39,47]. It is unclear whether a similar trend applies to MERS[48,49]. Moreover, progression to acute respiratory distress syndrome (ARDS) is associated with the upregulation of pro-inflammatory cytokines and chemokines, particularly interleukin-1β (IL-1β), IL-8, IL-6, CXC-chemokine ligand 10 (CXCL10) and CC-chemokine ligand 2 (CCL2)[50,51]; increased plasma levels of these molecules have been detected in patients with SARS[52–55]. Retrospective longitudinal studies in patients who recovered from SARS versus those who succumbed to the disease have shown an early expression of interferon-α (IFNα), IFNγ, CXCL10, CCL2 and proteins that are encoded by IFN-stimulated genes (ISGs) in all patients, but only patients who survived then had gene expression profiles that are indicative of the development of an adaptive immune response. By contrast, patients who succumbed maintained high levels of CXCL10, CCL2 and ISG-encoded proteins, whereas spike-specific antibodies were present at low levels or were absent[56], which suggests that severe disease is related to the lack of a switch from an innate immune response to an adaptive immune response.

Experiments using Collaborative Cross mouse lines and mouse-adapted SARS-CoV identified one host gene, *Trim55*, as important for SARS pathogenesis. Although there was no difference in clinical signs or viral replication in *Trim55*$^{-/-}$ mice compared with wild-type mice, perivascular cuffing and the number of inflammatory cells in the lungs were reduced in the *Trim55*$^{-/-}$ mice[57].

Acute respiratory distress syndrome
(ARDS). A life-threatening condition in which the accumulation of fluid and inflammatory cells in the lungs decreases the exchange of oxygen and carbon dioxide to dangerously low levels.

Collaborative Cross mouse
One of a panel of recombinant inbred mouse strains derived from a genetically diverse set of founder strains and designed for the analysis of complex traits.

Perivascular cuffing
The aggregation of leukocytes around blood vessels.

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Box 1 | **Clinical features of SARS and MERS**

Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) have an incubation period of ~5 days, and 95% of patients develop disease within 13 days of exposure[14,38,144–146]. Common early symptoms are fever, chills, coughing, malaise, myalgia and headache, and less common symptoms include diarrhoea, vomiting and nausea[2,6,39,89,90,92,95,144,146–148]. Upper respiratory tract symptoms and viral shedding are rare, which explains difficulties in obtaining a laboratory diagnosis from nasal or nasopharyngeal swabs[149]. Abnormal chest X-rays are more common in patients with MERS (90–100%)[144,148] than in those with SARS (60–100%)[39,89]. Accordingly, only 20–30% of patients with SARS require intensive care and subsequent mechanical ventilation, whereas 50–89% of patients with MERS require intensive care[2,39,89,90,95,144,147,148]. The higher incidence of acute respiratory distress syndrome (ARDS) in individuals with MERS is reflected in the case fatality rate: this is ~36% for MERS compared with ~10% for SARS[15,145].

Comorbidities have an important role in both SARS and MERS. Several risk factors are associated with poor disease outcome, especially advanced age and male sex[2,14,39,144,146,148,150,151]. For MERS, additional risk factors for a poor outcome include diabetes mellitus, hypertension, cancer, renal and lung disease, and co-infections[14,144,146,148,150,151].

Health care settings seem to increase the risk of viral transmission owing to aerosol-generating procedures such as intubation and bronchoscopy. Appropriate hospital hygiene practices and awareness are crucial to limit future nosocomial outbreaks.

The involvement of the host immune response in the pathogenesis of SARS, and most likely also that of MERS, suggests that drugs which inhibit viral replication will need to be combined with treatments that control detrimental immune responses.

Immune evasion. SARS-CoV and MERS-CoV use several strategies to avoid the innate immune response. Viral pathogen-associated molecular patterns (PAMPs), such as double-stranded RNA (dsRNA) or uncapped mRNA, are detected by pattern recognition receptors (PRRs), such as retinoic acid-inducible gene I protein (RIG-I; also known as DDX58) or melanoma differentiation-associated protein 5 (MDA5; also known as IFIH1)[58]. This triggers complex signalling cascades involving MYD88 that lead to the production of type I IFNs and the activation of the transcription factor nuclear factor-κB (NF-κB). In turn, active NF-κB induces the transcription of pro-inflammatory cytokines (FIG. 3a). Type I IFNs signal through IFNα/β receptor (IFNAR) and downstream molecules such as signal transducer and activator of transcription (STAT) proteins to stimulate the production of antiviral proteins that are encoded by ISGs, such as IFN-induced protein with tetratricopeptide repeats 1 (IFIT1; FIG. 3b). Collectively, this establishes an antiviral immune response that limits viral replication in infected and in neighbouring cells (FIG. 3).

Infection of knockout mice revealed the importance of innate immunity. Infection of *Myd88*$^{-/-}$ and *Stat1*$^{-/-}$ mice, but not mice that were deficient in IFN receptors, with a mouse-adapted strain of SARS-CoV resulted in more severe disease than infection with a non-adapted SARS-CoV strain[59,60]. Moreover, MERS-CoV infection of wild-type mice that were transduced with human DPP4 caused mild disease, but symptoms were more severe in *Myd88*$^{-/-}$ mice and *Ifnar1*$^{-/-}$ mice[61].

SARS-CoV and MERS-CoV avoid host detection of their dsRNA by replicating in virus-induced double-membrane vesicles that lack PRRs[19,62,63]. Moreover, the recognition of SARS-CoV mRNAs, for example, by MDA5 and IFIT1 is prevented by capping of the viral mRNAs by nsp14 and the nsp10–nsp16 complex[64]. Recombinant SARS-CoV that lacks the methylation activity of nsp16 is attenuated and exhibits increased sensitivity to type I IFNs. This effect is dependent on IFIT1 or MDA5, as the same virus is not attenuated in mice that are deficient in either molecule[65]. Although mRNA capping has not yet been shown for MERS-CoV, structural similarity between the MERS-CoV nsp10–nsp16 complex and the SARS-CoV nsp10–nsp16 complex suggests that a similar mechanism exists to avoid host recognition of MERS-CoV mRNAs by cytosolic PRRs[66].

SARS-CoV encodes at least eight proteins that interact with the signalling cascades downstream of PRRs; in MERS-CoV, several proteins have been identified with similar functions (FIG. 3). The nucleocapsid protein of SARS-CoV has been associated with the suppression of RNAi in mammalian cells[67]. Furthermore, this protein antagonizes IFN induction, probably early in the signalling cascade, as downstream signalling molecules relieve the inhibition[68]. MERS-CoV ORF4a has a similar IFN-antagonistic function, involving the binding of dsRNA and subsequent inhibition of MDA5 activation[69], potentially through interaction with IFN-inducible dsRNA-dependent protein kinase activator A (PRKRA; also known as PACT), which interacts with MDA5 and RIG-I[70]. Moreover, MERS-CoV ORF4a, ORF4b, ORF5 and membrane protein inhibit the nuclear trafficking of IFN-regulatory factor 3 (IRF3) and activation of the *IFNB* promoter[71]. These viral proteins, except for ORF5, also inhibit the expression of genes that are under the control of an IFN-stimulated response element (ISRE), and ORF4a reduces the expression of genes that are stimulated by NF-κB[71]. Finally, MERS-CoV ORF4b interacts with TBK1 and inhibitor of NF-κB kinase-ε (IKKε), thereby suppressing the interaction between IKKε and mitochondrial antiviral-signalling protein (MAVS) and inhibiting the phosphorylation of IRF3 (REF. 72).

The membrane protein of SARS-CoV inhibits the formation of a signalling complex that contains IKKε, thus repressing the activation of IRF3 and IRF7 and their induction of type I IFN expression. The membrane protein of MERS-CoV inhibits IRF3 function and the expression of genes that are regulated by an ISRE, including IFNβ[71], but whether this occurs through a mechanism similar to that of SARS-CoV is unclear.

SARS-CoV PLpro disrupts NF-κB signalling[73] and blocks the phosphorylation of IRF3 indirectly[73,74]. Furthermore, SARS-CoV PLpro inhibits the induction of type I IFNs, potentially through the deubiquitylation of phosphorylated IRF3 (REFS 73,75). Similar functions have been described for MERS-CoV PLpro[76].

Experiments involving recombinantly expressed proteins, *in vitro* translation, protein overexpression and minireplicon systems have shown that nsp1 of SARS-CoV blocks the IFN response through the inhibition of

Type I IFNs
(Type I interferons). A group of IFNs, including IFNα and IFNβ, with immune-modulating and antiviral functions.

RNAi
A biological process in which small RNA molecules induce the degradation of specific mRNA molecules, thereby inhibiting gene expression.

Minireplicon systems
Systems in which a DNA molecule is produced that contains the viral leader and trailer sequences, with an assayable reporter replacing the viral ORFs. When combined with the expression of viral proteins in *trans*, this system can be used to model the viral life cycle without the necessity of using infectious virus.

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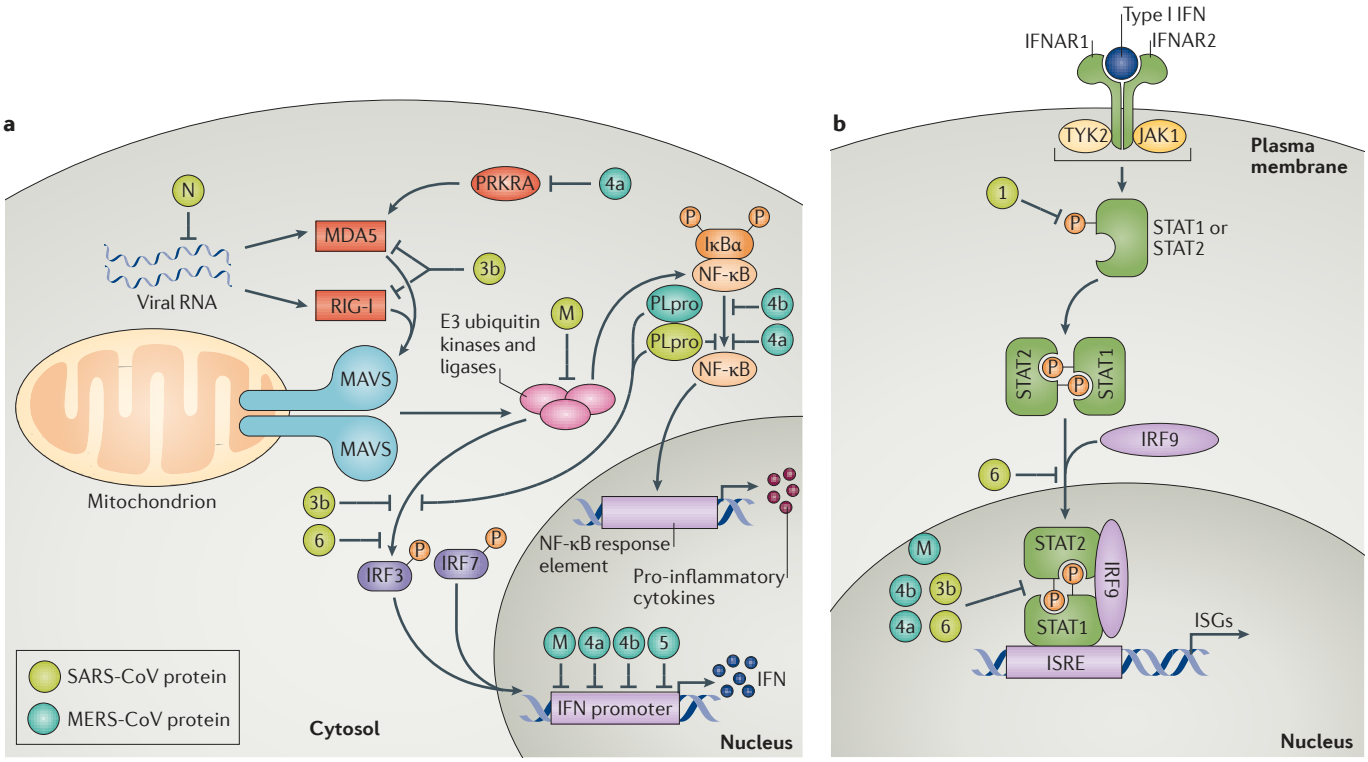

Figure 3 | **Evasion of the innate immune response by SARS-CoV and MERS-CoV. a** | The innate immune response is activated by the detection of viral pathogen-associated molecular patterns (PAMPs), such as double-stranded RNA (dsRNA) or uncapped mRNA. This occurs via host pattern recognition receptors (PRRs), such as retinoic acid-inducible gene I protein (RIG-I) and melanoma differentiation-associated protein 5 (MDA5), potentially via dsRNA-binding partners such as IFN-inducible dsRNA-dependent protein kinase activator A (PRKRA). Following PRR-mediated detection of a PAMP, the resulting interaction of PRRs with mitochondrial antiviral-signalling protein (MAVS) activates nuclear factor-κB (NF-κB) through a signalling cascade involving several kinases. Activated NF-κB translocates to the nucleus, where it induces the transcription of pro-inflammatory cytokines. The kinases also phosphorylate (P) IFN-regulatory factor 3 (IRF3) and IRF7, which form homodimers and heterodimers and enter the nucleus to initiate the transcription of type I interferons (type I IFNs). Both severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) have developed mechanisms to interfere with these signalling pathways, as shown; these subversion strategies involve both structural proteins (membrane (M) and nucleocapsid (N)) and non-structural proteins (nsp1, nsp3b, nsp4a, nsp4b, nsp5, nsp6 and papain-like protease (PLpro); indicated in the figure by just their nsp numbers and letters). **b** | Binding of type I IFNs to their dimeric receptor, IFNα/β receptor (IFNAR), activates the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signalling pathway, in which JAK1 and TYK2 kinases phosphorylate STAT1 and STAT2, which form complexes with IRF9. These complexes move into the nucleus to initiate the transcription of IFN-stimulated genes (ISGs) under the control of promoters that contain an IFN-stimulated response element (ISRE). Collectively, the expression of cytokines, IFNs and ISGs establishes an antiviral innate immune response that limits viral replication in infected and in neighbouring cells. Again, viral proteins have been shown to inhibit these host signalling pathways to evade this immune response. IκBα, NF-κB inhibitor-α.

STAT1, degradation of host mRNAs and inactivation of the host translational machinery through a tight association with the 40S ribosomal subunit[77–80]. Nsp1 of MERS-CoV also inhibits the translation of mRNAs and induces mRNA degradation, although the translational inhibition is achieved through a different mechanism than ribosome binding, which selectively targets the translation of nuclear mRNAs and thereby spares cytoplasmic viral mRNAs[81].

SARS-CoV ORF3b inhibits the production of type I IFN, the phosphorylation of IRF3 and gene expression from an ISRE promoter[82,83]. SARS-CoV ORF6 also blocks the nuclear translocation of STAT1 (REF. 83).

Both nsp7 and nsp15 from SARS-CoV were also suggested to be IFN antagonists, but the underlying mechanism is unknown[73]. nsp15 is an inhibitor of MAVS-induced apoptosis; however, this occurs through an IFN-independent mechanism[84]. Finally, transcriptomic and proteomic analysis of human airway cell cultures showed that MERS-CoV but not SARS-CoV induces repressive histone modifications that downregulate the expression of certain ISGs[85].

It should be noted that most of the interactions of SARS-CoV and MERS-CoV proteins with innate immune pathways were established in *in vitro* systems, which rely on the overexpression of viral and,

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Table 1 | **Potential therapeutics for MERS**

Treatment	Stage of development	References
Host protease inhibitors	*In vitro* inhibition	132
Viral protease inhibitors	*In vitro* inhibition	97,99,112–114
Repurposed FDA-approved drugs	*In vitro* inhibition	62,99,113,115
Monoclonal and polyclonal antibodies	Effective in mouse, rabbit and non-human primate models	118–121, 123–128
Convalescent plasma	Effective in a mouse model; clinical trial approved	122
Interferons	Effective in non-human primate models; off-label use in patients	87,97–99, 101–105,108–111
Ribavirin	Effective in a non-human primate model; off-label use in patients	87,88,101,102, 108–111
Mycophenolic acid	Failed to protect in a non-human primate model	97,99,105,113
Lopinavir and ritonavir	Effective in a non-human primate model; off-label use in patients	105,109–111

MERS, Middle East respiratory syndrome.

sometimes, cellular proteins, and these interactions have rarely been confirmed in the context of viral replication *in vitro* or *in vivo*.

Treatment of severe coronavirus infections

Several strategies are being considered to treat infections with MERS-CoV (TABLE 1) and SARS-CoV, including the use of antibodies, IFNs, inhibitors of viral and host proteases, and host-directed therapies.

Current therapies. In the absence of a clinically proven effective antiviral therapy against SARS-CoV and MERS-CoV, patients mainly receive supportive care, which is often supplemented by different combinations of drugs. Ribavirin[86] and various types of IFN have been given to patients with MERS in Saudi Arabia[87] and China[88], typically in combination with a broad-spectrum antibiotic and oxygen. The efficacy of treatments for SARS-CoV and MERS-CoV infection currently remains unclear. In addition, treatment for MERS is typically started only in a late disease stage, when immunopathology predominates and antiviral drugs are likely to provide little benefit.

Ribavirin was used most frequently during the SARS outbreak, often in combination with corticosteroids, which have an anti-inflammatory effect[2,89–92]. IFNα was also given, usually in combination with immunoglobulins or thymosins, which stimulate the development of T cells, and in a small number of cases in combination with ribavirin[93,94]. None of these treatments was tested in a clinical trial, which makes it difficult to assess their efficacy. In fact, retrospective analysis did not yield a treatment combination that was clearly effective. Moreover, the data from patients are contradictory about whether ribavirin, when used alone, provided a benefit or was possibly even detrimental[89,90,92,95]. *In vitro* coronaviruses have a lower sensitivity to ribavirin than other viruses. Deletion of the nsp14-encoding sequence increases the sensitivity of coronaviruses to ribavirin; however, the underlying mechanism is unclear and is not related to the proofreading function of nsp14 (REF. 96). Therefore, ribavirin should be considered only in combination with other antiviral treatments.

Although IFNs are effective against MERS-CoV *in vitro*[97–99], their effect in humans has yet to be proved. The effectiveness of IFN is increased *in vitro* if ribavirin is added[98,100], and a combined use of the two drugs reduces disease severity in a rhesus macaque model of MERS[101]. The potential side effects of these treatments, such as fatigue, depression and anaemia, have inhibited their use as a first-line treatment for MERS, and they are generally administered only after a patient's condition starts to deteriorate. For example, one study of five patients who were infected with MERS-CoV indicated no survival following ribavirin and IFNα2b therapy; however, therapy was not started until 10 days after admission[87]. A separate study found an improvement in survival 14 days after MERS diagnosis and the start of treatment, but not 28 days after[102]. In a third study, a combination of IFNα2a and ribavirin or IFNβ1a and ribavirin did not improve survival; however, some of the patients were more than 50 years old and had pre-existing renal failure[103]. In a single case in which ribavirin and IFNα2b were started shortly after admission to hospital, the patient started to improve on day 6 after admission and made a complete recovery[104].

IFNβ1b is a more potent inhibitor of MERS-CoV replication *in vitro* than other types of IFN[97,99], and an improved outcome of disease was observed in common marmosets after challenge with MERS-CoV[105]. Thus, the type of IFN that is used for treatment in humans should be reconsidered (usually, IFNα is used). Furthermore, ribavirin and/or IFNs should be tested in clinical trials to determine their efficacy in MERS treatment and to establish treatment protocols.

Additional antiviral treatments. The protease inhibitors lopinavir and ritonavir, which are used in combination to treat infection with HIV, improved the outcome of patients with SARS when combined with ribavirin, compared with patients who were treated with ribavirin alone[106,107]. Lopinavir showed no clear antiviral activity against MERS-CoV *in vitro*[97], and it is thus rarely used in patients with MERS. However, lopinavir and ritonavir improve the outcome in common marmosets when treatment is initiated 6 hours after infection with MERS-CoV[105]. Thus, the testing of lopinavir and ritonavir in clinical trials in patients with MERS should be reconsidered. One patient who received pegylated IFNα, ribavirin, lopinavir and ritonavir in combination had undetectable levels of MERS-CoV in the blood 2 days after the initiation of therapy; however, this patient did not survive[108]. The combination of IFNα, ribavirin, lopinavir and ritonavir was also used for MERS treatment in South Korea, but efficacy data are not yet available. However, three case reports indicate recovery in five out of seven patients who were treated with this combination[109–111].

As 3CLpro and PLpro are essential for cleavage of the viral polyproteins and are distinct from cellular proteases, they are ideal drug targets, in particular PLpro,

Ribavirin
A broadly active antiviral nucleoside analogue with several direct and indirect mechanisms of action; mainly used for the treatment of hepatitis C, in combination with interferon.

Pegylated
Having polyethylene glycol (PEG) attached, to a drug for example; this moiety improves the solubility, decreases the immunogenicity and increases the stability, of the drug of interest, thereby allowing a reduced dosing frequency to be used.

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which is involved in both viral replication and IFN antagonism. Indeed, most antiviral drug-like molecules have been developed against 3CLpro and PLpro, which was aided by the rapid report of crystal structures of these proteases[112].

PLpro was initially identified as a drugable target for SARS-CoV; recently, it has been noted that some of the compounds that target PLpro from SARS-CoV are also active against PLpro from MERS-CoV. For example, both 6-mercaptopurine and 6-thioguanine inhibit MERS-CoV and SARS-CoV *in vitro*[113]; however, the efficacy of these molecules has not yet been tested *in vivo*. Mycophenolic acid also inhibits the replication of MERS-CoV *in vitro*[97,99] through the inhibition of PLpro[113], but it had no effect in marmosets[105].

As new coronaviruses are likely to emerge from bats, protease inhibitors were designed against bat coronaviruses with the goal of developing a universal antiviral compound against emerging zoonotic coronaviruses. This approach yielded an inhibitor of Tylonycteris bat coronavirus HKU4 (HKU4-CoV), which is closely related to MERS-CoV[11]. This inhibitor, named SG85, indeed inhibits MERS-CoV replication *in vitro*[112]. Similarly, peptidomimetics that target and inhibit 3CLpro of MERS-CoV, HKU4-CoV and Pipistrellus bat coronavirus HKU5 (HKU5-CoV) have also been identified, but have not yet progressed beyond the *in vitro* stage[114].

Several other drugs that were approved for use in humans were shown to inhibit the replication of MERS-CoV *in vitro*, notably chloroquine, chlorpromazine, loperamide and cyclosporine A[62,99,113,115], although their mechanisms of action are unknown, and the benefit of cyclosporine A in patients is debatable owing to the immunosuppressive effect of the drug. Although cyclophilin inhibitors that do not result in immunosuppression are available, their activity against MERS-CoV has not yet been tested.

Antibody and plasma therapy. Plasma from convalescent patients and/or antibody therapies have been the leading proposed treatment for MERS so far[116]. There are several potential advantages to this approach. For example, as case numbers increase, the pool of survivors becomes larger; provided these individuals have sufficiently high antibody titres and are willing and able to donate plasma, this is a low-tech, reasonably safe treatment option. Furthermore, generation of monoclonal antibodies for use in humans is well established, with a fairly straightforward path to safety and efficacy testing. However, to date, there are very few reports on the use of convalescent plasma and none on the use of monoclonal antibodies as treatments for acute, severe respiratory disease in humans. A post hoc meta-analysis of 32 studies of either SARS or severe influenza found a significant reduction in the pooled odds of mortality when convalescent plasma was used[117]. However, study design was rated as low or very low quality, as there were generally a lack of control groups and a moderate-to-high risk of bias, which suggests that a properly designed clinical trial of convalescent plasma use in severe respiratory infections is needed[117]. Potent monoclonal antibodies that neutralize the MERS-COV spike protein *in vitro* have been developed[118–121]. However, with a few exceptions, *in vivo* data relating to the use of convalescent plasma or monoclonal antibodies in the treatment of MERS are currently lacking. Serum from high-titre dromedary camels decreased MERS-CoV loads in the lungs of mice that had been transduced with human DPP4 (REF. 122). Human polyclonal antibodies against the spike protein were generated by vaccinating transchromosomic bovines, and treatment with these antibodies reduced viral titres in the lungs of DPP4-transduced mice when treatment was administered 24 or 48 hours after challenge with MERS-CoV[123]. DPP4-transduced mice were also treated with humanized neutralizing monoclonal antibody 4C2h, which is directed against the receptor-binding domain of the MERS-CoV spike protein, 1 day after MERS-CoV challenge, and this treatment also decreased viral titres in the lungs[124], as did the neutralizing antibody LCA60, which was obtained from a convalescent patient and produced recombinantly[125]. Human neutralizing monoclonal antibodies REGN3048 and REGN3051 also provided a benefit in mice that expressed human DPP4 and were challenged with MERS-CoV[126]. The human neutralizing monoclonal antibody m332 reduced MERS-CoV replication in the lungs of rabbits following prophylactic, but not therapeutic, treatment[127]. Treatment of rhesus macaques with the human monoclonal antibody 311B-N1 day after challenge resulted in reduced lung pathology[128]. In all of these studies, viral replication was not completely inhibited, and there were some pathological alterations to the lungs, despite the therapy. Furthermore, none of the studies addressed the potential emergence of escape mutants *in vivo*.

Alternatively, antibodies that target the region of DPP4 that binds to the spike protein could be used to prevent entry of MERS-CoV; this approach was successful *in vitro*[129]. However, whether such a treatment would be feasible and would not have substantial adverse effects in humans remains to be determined.

Host-directed therapies. Host-directed strategies can also limit viral replication. For example, the spike protein of SARS-CoV is cleaved by cathepsin B and cathepsin L, transmembrane protease serine 2 (TMPRSS2) and possibly other host proteases[130,131]. Inhibition of host serine proteases by camostat reduced the entry of SARS-CoV and increased survival in a mouse model[132]. However, the targeting of host proteases is more likely to result in undesirable side effects than the targeting of viral proteases.

Another underappreciated strategy is attenuation of detrimental host responses. The development of such treatments would require a thorough understanding of the host responses that are involved in acute lung injury and ARDS, processes that are unfortunately poorly understood at the moment. Nonetheless, *in vitro* studies and limited studies in animal models with other respiratory viruses have shown that anaphylatoxin C5a is important for the development of acute lung injury, and blocking anaphylatoxin C5a can reduce lung pathology[133].

Peptidomimetics
Compounds that mimic biologically active peptides or proteins.

Anaphylatoxin C5a
A complement-activated molecule that is important for the recruitment to and activation of inflammatory cells in the lungs.

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Subunit vaccines
Vaccines that contain immunogenic parts of a pathogen rather than the entire pathogen.

DNA vaccines
Vaccines based on the direct introduction of a plasmid encoding an antigen; following *in situ* production of this antigen, an immune response is mounted against it.

Changes in gene expression during *in vitro* MERS-CoV infection were used to predict potential effective drugs. One of the drugs with predicted efficacy, the kinase inhibitor SB203580, modestly inhibited SARS-CoV and MERS-CoV replication following the treatment of cells prior to infection, but treatment after infection inhibited replication of only SARS-CoV and not MERS-CoV[134].

Vaccines. Vaccination could be used to prevent infection or to reduce disease severity, viral shedding and thereby transmission, thus helping to control MERS outbreaks. Several vaccination strategies were developed against SARS-CoV and tested in animals, such as an inactivated virus, a live-attenuated virus, viral vectors, subunit vaccines, recombinant proteins and DNA vaccines[135,136]. Similar approaches have been used for the development of experimental MERS-CoV vaccines[137]. To date, three MERS-CoV vaccines have been evaluated in non-human primates. In one study, rhesus macaques were primed with DNA encoding the spike protein, followed by boosts with spike DNA and with recombinant protein consisting of the spike subunit containing the receptor-binding domain, or primed and boosted once with the subunit protein. Both approaches reduced pathological changes in lung function in animals that were infected with MERS-CoV 19 weeks after the last vaccination[138]. Moreover, three vaccinations with a recombinantly expressed protein that contains the receptor-binding domain of the spike protein reduced viral loads and lung pathology in rhesus macaques that were infected 2 weeks after the last vaccination[139]. Three DNA vaccinations with a construct encoding the full-length spike sequence reduced viral loads and pathology in the lungs after challenge with MERS-CoV 5 weeks after the last vaccination[140].

One concern of vaccination in humans is vaccine-mediated enhancement of disease, a process in which the disease following infection is more severe in vaccinated individuals than in unvaccinated individuals. Although this was observed in only a small subset of vaccine studies that were carried out for SARS-CoV[136] and has not yet been observed in any of the published MERS-CoV vaccine studies, it is an important concern. Moreover, it is unclear who to vaccinate against MERS-CoV, as healthy individuals seem to be at little risk of severe disease. Older patients or patients with underlying disease, who have the highest risk of severe MERS, would be important target populations. However, vaccination in such patients can be problematic owing to their poor immune responses, as has been established for influenza virus[141]. In addition, vaccination of people with a high risk of exposure to MERS-CoV, such as health care workers, slaughterhouse workers and camel herders, is advisable[142].

Outlook

As our understanding of the pathogenesis of emerging coronaviruses increases, so will the opportunities for the rational design of therapeutics that target viral replication or immunopathology. The rational design of new drugs and the repurposing of existing compounds have already resulted in the development of PLpro inhibitors and the identification of kinase inhibitors that inhibit the replication of SARS-CoV and MERS-CoV *in vitro*. However, only a few potential treatments have progressed past the identification of an effect *in vitro*, and *in vivo* studies to select the most promising treatment options are required. The development of several mouse models of MERS is thus an important step forward (BOX 2). Owing to the acute nature of MERS and the important role of immunopathology, combination therapies aimed at simultaneously inhibiting viral replication, limiting viral dissemination and dampening the host response are likely to yield the best results. Furthermore, treatment should be started as early as possible, rather than waiting until the patient has already developed extensive lung damage.

The development of therapies against SARS and MERS needs to focus on testing in humans, in properly controlled clinical trials. The current non-standardized, uncontrolled approach to treatment is not informative and may not be beneficial to the patient. The recent Ebola outbreak has demonstrated that rapid clinical trial design and approval are possible and that exceptional situations call for deviations from normal procedures (BOX 3).

While treatments are being developed and evaluated, the prevention of viral transmission is key to reducing the burden of MERS. The large proportion of nosocomial MERS-CoV infections indicates that preventive measures in hospitals are currently either not fully implemented or insufficient. Prevention of zoonotic transmission from dromedary camels is another possibility to decrease the number of MERS cases. The

Box 2 | **Animal models**

Most of our understanding of the pathogenesis of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) comes from animal studies. Ideally, these models recapitulate all or specific aspects of human disease. Several mouse models have been established, for example by using mouse-adapted SARS coronavirus (SARS-CoV) or expressing human receptors in mice[152]. Although it has been recognized that mice might poorly mimic specific human responses to infection, the availability of knockout and transgenic mice enables the targeted study of virus–host interactions. Several non-human primate models have been developed for SARS-CoV and MERS coronavirus (MERS-CoV)[152]. The close relationship of non-human primates to humans often allows faithful recapitulation of a disease and the host response. However, these benefits are countered by the need for specialized husbandry, the sometimes limited availability of the animals and reagents, and high costs.

The pathogenesis of SARS-CoV and MERS-CoV in their respective reservoir hosts is not nearly as well studied as that in humans. Currently, only one experimental-infection study has been carried out in bats with MERS-CoV[153], and none has been carried out for other coronaviruses. Thus, data are mostly limited to the detection of coronaviruses in naturally infected bats. The detection of coronaviruses mainly in faecal samples from bats and not in oral swabs suggests that replication in bats occurs predominantly in the gastrointestinal tract[9,154,155]. By contrast, a combination of intratracheal and intranasal inoculation of masked palm civets with SARS-CoV resulted in interstitial pneumonia, with oral and rectal viral shedding[156].

The pathogenesis of MERS-CoV in dromedary camels has been studied experimentally in a limited number of animals. These animals developed transient mild disease; however, large quantities of MERS-CoV were shed from the upper respiratory tract, in line with the predominant replication of MERS-CoV in the nasal turbinates and larynx in these animals, which explains the frequent zoonotic transmission[157].

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Box 3 | **Preparing for emerging viruses: lessons from SARS-CoV, MERS-CoV and Ebola virus**

When the severe acute respiratory syndrome (SARS) outbreak developed into the first pandemic of the twenty-first century, it became clear that the medical and scientific communities were not adequately prepared for the emergence of highly pathogenic viruses. Whereas several months elapsed and several thousand cases of SARS were observed before the causative agent was identified as SARS coronavirus (SARS-CoV)[4–6], subsequent advances in molecular diagnostic tools, such as next generation sequencing, meant that Middle East respiratory syndrome coronavirus (MERS-CoV) was identified before it caused a large outbreak of MERS[11]. The availability of the full-length genome of MERS-CoV enabled the rapid development and distribution of diagnostic assays. The first animal models of disease, several treatment efficacy studies and the identification of the reservoir followed soon after. Unfortunately, the SARS pandemic did not yield solid clinical data on the efficacy of treatment regimens. These data are urgently needed for the treatment of MERS, as well as to prepare for novel coronaviruses that may emerge. Several studies have used synthetic biology to study the zoonotic transmission potential of SARS-CoV-like viruses from bats[9,10,158,159].

The Ebola virus outbreak in West Africa has highlighted the need for fast-tracking of potential treatments, as several clinical trials were started only towards the end of the outbreak. The combined experiences of the outbreaks of SARS, MERS and Ebola provide a blueprint for the response to emerging pathogens: after the identification of the causative agent, diagnostic assays need to be developed and distributed rapidly, and simultaneously, awareness of the new syndrome and reporting of (suspected) cases must be increased. In addition, infection control measures in health care facilities are essential. Research needs to focus on understanding the epidemiology, including pathogen transmission and identification of the reservoir and/or intermediate hosts. Animal models need to be developed, as well as therapeutic and prophylactic measures. Finally, promising treatments need to be fast-tracked into clinical trials.

first vaccines against MERS-CoV have been tested in dromedary camels[140,143]; indeed, when camels were vaccinated with a modified vaccinia virus that expresses the MERS-CoV spike protein, subsequent challenge of these animals with MERS-CoV resulted in less viral shedding than in unvaccinated animals[143], thereby potentially limiting the transmission to naive animals or to humans. Certainly, there has been progress in the development of vaccines and therapies against emerging coronaviruses, but more research and rigorous testing is required if we are to successfully combat these novel pathogens.

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Review of Bats and SARS

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Bats have been identified as a natural reservoir for an increasing number of emerging zoonotic viruses, including henipaviruses and variants of rabies viruses. Recently, we and another group independently identified several horseshoe bat species (genus *Rhinolophus*) as the reservoir host for a large number of viruses that have a close genetic relationship with the coronavirus associated with severe acute respiratory syndrome (SARS). Our current research focused on the identification of the reservoir species for the progenitor virus of the SARS coronaviruses responsible for outbreaks during 2002–2003 and 2003–2004. In addition to SARS-like coronaviruses, many other novel bat coronaviruses, which belong to groups 1 and 2 of the 3 existing coronavirus groups, have been detected by PCR. The discovery of bat SARS-like coronaviruses and the great genetic diversity of coronaviruses in bats have shed new light on the origin and transmission of SARS coronaviruses.

Severe acute respiratory syndrome (SARS) represents the 21st century's first pandemic of a transmissible disease with a previously unknown cause. The pandemic started in November 2002 and was brought under control in July 2003, after it had spread to 33 countries on 5 continents, resulting in >8,000 infections and >700 deaths (*1*). The outbreaks were caused by a newly emerged coronavirus, now known as the SARS coronavirus (SARS-CoV).

In late 2003 and early 2004, sporadic outbreaks were reported in the region of the People's Republic of China where the 2002–2003 outbreaks originated (*2*). However, molecular epidemiologic studies showed that the viruses responsible for the 2003–2004 outbreaks were not the same as those isolated during the 2002–2003 outbreaks (*3*). These findings indicate independent species-crossing events. They also indicate that a SARS epidemic may recur in the future and that SARS-like coronaviruses (SARS-like–CoVs) that originate from different reservoir host populations may lead to epidemics at different times or in different regions, depending on the distribution of the reservoirs and transmitting hosts. The recent discovery of a group of diverse SARS-like–CoVs in bats supports the possibility of these events and further highlights the need to understand reservoir distribution and transmission to prevent future outbreaks.

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Animal Origin of SARS Coronaviruses

Because of the sudden and unpredictable nature of the SARS outbreaks that started in November 2002 in southern People's Republic of China, structured and reliable epidemiologic studies to conclusively trace the origin of SARS-CoV were not conducted. However, accumulated studies from different groups, which used a variety of approaches, indicated an animal origin on the basis of the following findings. 1) Genome sequencing indicated that SARS-CoV is a new virus with no genetic relatedness to any known human coronaviruses (*4*,*5*). 2) Retrospective serologic studies found no evidence of seroprevalence to SARS-CoV or related viruses in the human population (*6*). 3) Serologic surveys among market traders during the 2002–2003 outbreaks showed that antibodies against SARS-CoV or related viruses were present at a higher ratio in animal traders than control populations (*7*–*9*). 4) Epidemiologic studies indicated that early case-patients were more likely than later case-patients to report living near a produce market but not near a farm, and almost half of them were food handlers with probable animal contact (*7*). 5) SARS-CoVs isolated from animals in markets were almost identical to human isolates (*9*). 6) Molecular epidemiologic analyses indicated that human SARS-CoV isolates could be divided into 3 groups from the early, middle, and late phases of the outbreaks and that early-phase isolates were more closely related to the animal isolates (*10*). 7) Human SARS-CoVs isolates from the 2003–2004 outbreaks had higher sequence identity to animal isolates of the same period than to human isolates from the 2002–2003 outbreaks (*3*).

Susceptible Animals in Markets and Laboratories

The first evidence of SARS-CoV infection in animals came from a study conducted in a live animal market in early 2003 (*9*). From the 25 animals sampled, viruses closely related to SARS-CoV were detected in 3 masked palm civets (*Paguma larvata*) and 1 raccoon dog (*Nyctereutes procyonoides*). In addition, neutralizing antibodies against SARS-CoV were detected in 2 Chinese ferret badgers (*Melogale moschata*). This initial study indicated that at least 3 different animal species in the Shenzhen market were infected by coronaviruses that are closely related to SARS-CoV.

Given the vast number of live animals being traded in animal markets in southern People's Republic of China, knowing which other animals are also susceptible to these viruses is crucial. Unfortunately, for a variety of reasons no systematic studies were conducted on traded animals during the outbreak period. Experimental infection of different animals therefore became a component of the SARS-CoV investigation.

Currently, >10 mammalian species have been proven to be susceptible to infection by SARS-CoV or related viruses (Table 1). Rats were also implicated as potentially susceptible animals that may have played a role in the transmission and spread of SARS-CoV in the well-publicized SARS outbreaks in the Amoy Gardens apartment block in Hong Kong Special Administrative Region, People's Republic of China (*23*). In Guangdong in 2004, the first human with a confirmed case of SARS was reported to have had no contact with any animals except rats (*2*). Experimentally, we have obtained serologic evidence that SARS-CoV replicates asymptomatically in rats (B.T. Eaton et al., unpub. data). Further studies are needed to clarify the potential role of rats in the transmission of SARS-CoV. Studies by 2 independent groups suggested that avian species were not susceptible to SARS-CoV infection and that, hence, domestic poultry were unlikely to be the reservoir or associated with the dissemination of SARS-CoV in the animal markets of southern People's Republic of China (*22,24*).

Role of Masked Palm Civets

Although in 1 live animal market, 3 species were found to be infected by viruses related to SARS-CoV (*9*), all subsequent studies have focused mainly on palm civets, possibly because the rate of detection was higher in civets or because the number of civets traded in southern People's Republic of China exceeds that of other wildlife groups.

The isolation of closely related SARS-CoV in civets during the 2002–2003 and 2003–2004 outbreaks and the close match of virus sequences between the human and civet isolates from each outbreak (*3*,*9*,*25*) strongly suggest that civets are a direct source of human infection. However, these studies did not clarify whether animals other than civets were involved in transmission of SARS-CoV to humans or whether civets were an intermediate host or the natural reservoir host of SARS-CoVs.

During the 2002–2003 outbreaks, none of the animal traders surveyed in the markets, who supposedly had very close contact with live civets, displayed SARS symptoms

Table 1. Animal species susceptible to infection by SARS coronavirus*

Animal				
Common name	Taxonomic name	Mode of infection	Clinical signs	References
Masked palm civet	*Paguma larvata*	Natural	None observed	(9)
		Experimental	Fever, lethargy, reduced appetite	(11)
Raccoon dog	*Nyctereutes procyonoides*	Natural	None observed	(9)
Chinese ferret badger	*Melogale moschata*	Natural	None observed	(9)
Cynamolgus macaque	*Macaca fascicularis*	Experimental	Lethargy, skin rash, respiratory distress	(12)
Rhesus macaque	*Macaca mulatta*	Experimental	Fever, low appetite	(13,14)
African green monkey	*Cercopithecus aethiops*	Experimental	None observed	(15)
Ferret	*Mustela furo*	Experimental	Lethargy, mild pulmonary lesions	(16)
Golden hamster	*Mesocricetus auratus*	Experimental	None observed	(17)
Guinea pig	*Cavia porcellus*	Experimental	None observed	(18)
Mouse	*Mus musculus*	Experimental	Aged animal (12–17 mo), weight loss, ruffled pelt, ruffled fur, slight dehydration	(19)
			Young animal (4–5 weeks), none observed	(20)
Rat	*Rattus norvegicus*	Experimental	None observed	B. T. Eaton et al., unpub. data
Domestic cat	*Felis domesticus*	Natural	Not reported	(18)
		Experimental	None observed	(18)
Pig	*Sus scrofa*	Natural	Not reported	(21)
		Experimental	None observed	(22)

*SARS, severe acute respiratory syndrome.

(*7*–*9*). During the 2003–2004 outbreaks, at least 1 human SARS patient had had no contact with civets (*2*). These observations seem to indicate that ≥1 other animal species may play a role in transmission of SARS-CoV to humans.

Most, if not all, civets traded in the markets are not truly wildlife animals; rather, they are farmed animals. Civet farming is relatively new in People's Republic of China and has rapidly expanded during the past 15 years or so. Tu et al. conducted the first comparative study of market and farmed civets (*26*). Serologic testing was performed on 103 serum samples taken from civets in an animal market in Guangdong and several civet farms in different regions of People's Republic of China in June 2003 and January 2004. No significant level of SARS-CoV antibody was detected in any of the 75 samples taken from 6 farms in 3 provinces. In contrast, of the 18 samples taken from an animal market in Guangdong Province in January 2004, 14 (79%) had neutralizing antibodies to SARS-CoV.

In a parallel study conducted between January and September 2004 (*27*), molecular analysis was used to investigate the distribution of SARS-CoV in palm civets in markets and on farms. PCR analysis of samples from 91 palm civets and 15 raccoon dogs in 1 animal market and 1,107 civets from 25 farms in 12 provinces showed positive results for all animals from the market and negative results for all animals from the farms. Similar results were obtained in wild-trapped civets in Hong Kong; none of the 21 wild civets sampled had positive antibody or PCR results for SARS-CoV (*28*).

Although not universally true, natural reservoir hosts tend to have coevolved with their viruses and usually do not display clinical signs of infection (*29*). However, when palm civets were experimentally infected with 2 strains of human SARS-CoV, all developed clinical signs of fever, lethargy, and loss of aggressiveness (*11*).

Civits' high susceptibility to SARS-CoV infection and wide presence in markets and restaurants strongly indicates an important role for civets in the 2002–2003 and 2003–2004 SARS outbreaks. However, the lack of widespread infection in wild or farmed palm civets makes them unlikely to have been the natural reservoir host.

SARS-like Coronaviruses in Bats

The presence of SARS-like–CoVs in different species of horseshoe bats in the genus *Rhinolophus* has recently been reported. We found, in a study of horseshoe bat species in different regions of mainland People's Republic of China in 2004 (*30*), that each of the 4 species surveyed had evidence of infection by a SARS-like–CoV: 2 species (*R. pearsoni* and *R. macrotis*) had positive results by both serologic and PCR tests, and 2 (*R. pussilus* and *R. ferrumequinum)* had positive results by either serologic or PCR tests, respectively. Bats with positive results were detected in the provinces of Hubei and Guangxi, which are >1,000 km apart. A group in Hong Kong (*31*) found that, when analyzed by PCR, 23 (39%) of 59 anal swabs of wild Chinese horseshoe bats (*R. sinicus*) contained genetic material closely related to SARS-CoV. They also found that as many as 84% of the horseshoe bats examined contained antibodies to a recombinant N protein of SARS-CoV. A previous study indicated a certain level of antigenic cross-reactivity between SARS-CoV and some group 1 coronaviruses (*6*) and that several group 1 coronaviruses had recently been found in bats. Therefore, the actual seropositive proportion of *R. sinicus* might be <84%. Nevertheless, the relatively high seroprevalence and wide distribution of seropositive bats is consistent with the serologic pattern expected from a pathogen's natural reservoir host (*29*).

Genome sequencing showed that the genome organization of all bat SARS-like–CoVs is almost identical to that of the SARS-CoVs isolated from humans or civets. They shared an overall sequence identity of 88% to 92%. The most variable regions were located in the 5′ end of the S gene, which codes for the S1 domain responsible for receptor binding, and in open reading frame 10 (ORF10 or ORF8, depending on the nomenclature used) region immediately upstream from the N gene (Figure, panel A, region b), which is known to be also prone to deletions of various sizes (*3*,*9*). Most human SARS-CoVs isolated during the late phase of the 2002–2003 outbreaks have a 29-nt deletion in this region; this deletion is absent in the civet isolates or human isolates from the early phase of the outbreaks (*3*,*9*). The bat viruses also lack the 29-nt deletion, indicating that SARS-CoVs and SARS-like–CoVs share a common ancestor.

Furthermore, sequence analyses indicated the existence of a much greater genetic diversity of SARS-like–CoVs in bats than of SARS-CoVs in civets or humans, which supports the notion that SARS-CoV is a member of this novel coronavirus group and that bats are a natural reservoir for it. The overall genome sequence identities between the human/civit SARS-CoVs and the bat viruses Rp3 (isolated from *R. pearsoni*) and HKU3–1 (isolated from *R. sinicus*) were 92% and 88%, respectively. The sequence identity between the bat isolates Rp3 and HKU3–1 is 89%, which indicates that the genetic divergence among the bat isolates is as great as the divergence between each of the bat viruses and the human/civet isolates. In addition, phylogenetic trees based on different protein sequences display different tree topologies, as shown in the Figure (panel B), which indicates the existence of multiple evolutionary pathways for different regions of the genome.

Diversity of Coronaviruses in Bats

The discovery of SARS-CoV has boosted the search for novel coronaviruses of human and animal origin. Bats

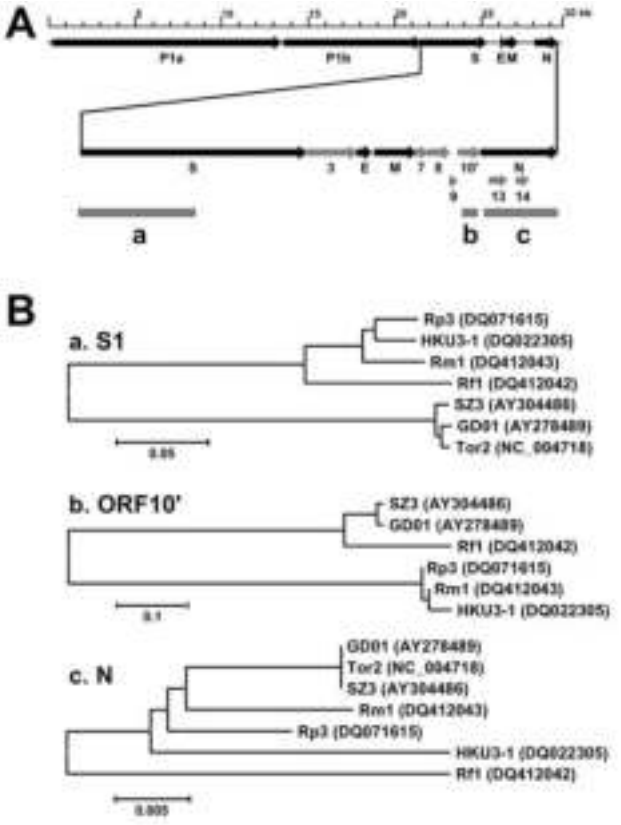

Figure. A) Genome diagram indicating the location of structural (dark arrow) and nonstructural (shaded arrow) genes and the different regions (shaded boxes) used for phylogeny analysis. B) Phylogenetic trees based on deduced amino acid sequences of the spike protein S1 domain (a), the open reading frame (ORF)10' (b), and the N protein (c). Because of lack of the ORF10' coding region in Tor2, Tor2 could not be included for the tree in (b). GD01, human isolate from early phase of the outbreak in 2003; Tor2, human isolate from late phase of the outbreak in 2003; SZ3, civet isolate from March 2003; Rp3, bat isolate from *Rhinolophus pearsoni*, December 2004; Rf1, bat isolate from *R. ferrumequinum*, November 2004; Rm1, bat isolate from *R. macrotis*, November 2004; and HKU3-1, bat isolate from *R. sinicus*, February 2005. GenBank accession nos. appear next to isolate names.

have been chosen as the main target because of their species diversity, large population size, broad geographic distribution, ability for long-distance migration, and habit of roosting in large groups. In addition to the SARS-like–CoVs described above, many other coronaviruses have been detected by PCR among diverse bat populations in Hong Kong (Table 2).

Poon et al. (*28*) conducted a surveillance study in Hong Kong during the summers of 2003 and 2004. From 162 swab samples collected from 12 bat species, they detected a novel group 1 coronavirus by sequencing of PCR products from the RNA-dependent RNA polymerase (RdRp) gene. The same virus or viruses of the same genetic lineage were found in 3 *Miniopterus* species (*M. pusillus, M. magnater,* and *M. schreibersii*). However, attempts to isolate virus by using 3 different cell lines (MDCK, FRhK4, and VeroE6) were unsuccessful.

In another study in Hong Kong during April 2004–July 2005, Woo et al. (*32*) sampled 309 individual bats representing 13 species from 20 different locations in rural Hong Kong. They detected coronavirus-related viral genomic RNA in 37 bats, representing a prevalence of 12%. Partial sequencing of *RdRp* and helicase genes identified 8 coronavirus genome types, 2 of which were the same as those reported previously (*28,30,31*). The other 6 novel types of coronaviruses were obtained from 6 different bat species and phylogenetically positioned in 2 of the existing 3 coronavirus groups. Four were in group 1, derived from bat species *M. magnater, M. pusillus, Myotis ricketti,* and *R. sinicus;* the other 2 were in group 2, from bat species *Pipistrellus abramus* and *Tylonycteris pachypus.* To accommodate the newly discovered genetic diversity of group 2 coronaviruses, the authors proposed the following subdivisions: group 2a (coronaviruses existing before the discovery of SARS-CoV), group 2b (SARS-CoV and SARS-like–CoVs), and group 2c (novel bat coronaviruses discovered in this study). Attempts to isolate virus in VeroE6, MRC-5, LLC-Mk2, FRhK-4, Huh-7.5, and HRT-18 were unsuccessful.

In another extensive study conducted in mainland People's Republic of China during November 2004–March 2006, Tang et al. (*33*) collected samples from 985 bats: 35 species in 14 genera and 3 families at 82 different sites in 15 provinces. A total of 64 (6.5%) bats had positive results from a PCR directed to a highly conserved 440-bp RdRp region. Among the 64 PCR-positive products sequenced, only 3 (all from the genus *Rhinolophus*) were clustered with known bat SARS-like–CoVs (or group 2b), 40 belonged to group 1, and the remaining 22 formed a separate cluster in group 2, most likely clustering with the group 2c viruses reported by Woo et al. (*32*). Attempts to isolate virus in VeroE6, FRHK4, and CV1 were unsuccessful.

In addition to the diversity of coronaviruses in bats, 3 more observations can be drawn from these studies. First, none of the bat coronaviruses discovered so far belonged to group 3. Second, with very few exceptions, most bat coronaviruses seem to be species-specific; i.e., different bat species from a similar location harbor different coronaviruses, whereas the same bat species from different geographic locations carry coronaviruses of the same genetic lineage (*32*,*33*). Third, among the 5 published studies involving bat coronaviruses (*28*,*30*–*33*), no researchers were able to isolate live virus from any of the swab samples collected despite the use of many different cell lines

Table 2. Coronaviruses detected in different species of bats

Group*	Viruses Name/strain	Bat species	Location of detection (People's Republic of China)	Reference
G1	Bat-CoV HKU.5	*Rhinolophus sinicus*	Hong Kong	(32)
	Bat-CoV HKU.6	*Myotis ricketti*	Hong Kong	(32)
	Bat-CoV HKU.7	*Miniopterus magnater*	Hong Kong	(32)
	Bat-CoV HKU.8	*Miniopterus pusillus* *M. magnater* *Miniopterus schreibersii*	Hong Kong	(28,32)
	BtCoV/701/05	*Myotis ricketti*	Anhui, Yunnan, Guangdong	(33)
	BtCoV/821/05	*Myotis ricketti*	Jiangxi, Guangxi	(33)
	BtCoV/512/05	*Scotophilus kuhlii*	Taiwan	(33)
	BtCoV/279/05	*Rhinolophus pearsoni* *Rhinolophus ferrumequinum*	Shandong	(33)
	BtCoV/A273/05	*M. schreibersii*	Fujian	(32)
	BtCoV/A811/05	*M. schreibersii*	Anhui, Fujian, Guangxi	(32)
G2b	Rp3	*R. pearsoni*	Guangxi	(30)
	Rm1 (BtCoV/273/04)	*Rhinolophus macrotis*	Hubei	(30)
	Rf1 (BtCoV/273/04)	*R. ferrumequinum*	Hubei	(30)
	Bat-SARS-CoV HKU3	*R. sinicus*	Hong Kong	(31,32)
	BtCoV/A1018/05	*R. sinicus*	Shandong	(33)
	BtCoV/273/04	*R. macrotis*	Hubei	(33)
	BtCoV/273/04	*R. ferrumequinum*	Hubei	(33)
G2c	Bat-CoV HKU4	*Tylonycteris pachypus*	Hong Kong	(32)
	Bat-CoV HKU5	*Pipistrellus abramus*	Hong Kong	(32)
	BtCoV/133/05	*T. pachypus*	Guangdong	(33)
	BtCoV/434/05	*Pipistrellus pipistrellus*	Taiwan	(33)
	BtCoV/365/05	*P. abramus* *R. ferrumequinum*	Anhui, Henan, Sichuan	(33)

*Group 2 was subdivided as in (32). A different classification was used in (33), in which G2b and G2c were designated G4 and G5, respectively.

and the presence of high levels of viral genetic materials shown by quantitative PCR.

Cross-species Transmission

Emergence of zoonotic viruses from a wildlife reservoir requires 4 events: 1) interspecies contact, 2) cross-species virus transmission (i.e., spillover), 3) sustained transmission, and 4) virus adaptation within the spillover species (*34*). These 4 transition events occurred during the SARS outbreaks and contributed to the rapid spread of the disease around the world.

The role of civets in directly transmitting SARS-CoV to humans has been well established. The most convincing case was the infection of a waitress and a customer in a restaurant where SARS-CoV–positive civets were housed in cages (*25*). Two key questions remain: What is the natural reservoir host for the outbreak SARS-CoV strains, and how were the viruses transmitted to civets or other intermediate hosts? Although not conclusive, the data obtained so far strongly suggest that bats (horseshoe bats in particular) are most likely the reservoir host of SARS-CoV. As indicated above, bat coronaviruses seem to be species-specific and SARS-like–CoVs discovered so far are exclusively associated with horseshoe bats. We hope that continued field study will eventually identify the direct progenitor of SARS-CoV among the 69 different known horseshoe species. The facts that the cross-species transmission of SARS-CoV seems to be a relatively rare event and that legal and illegal trading of wildlife animals between People's Republic of China and other countries occurs raise the possibility that the natural reservoir species may not be native to People's Republic of China. Thus, we should expand our search into regions other than Hong Kong and mainland People's Republic of China. Another approach to search for the natural reservoir of SARS-CoV is to conduct infection experiments in different bat species. If we assume that the progenitor viruses come from bats, chances are high that the human/civet SARS-CoVs are still capable of infecting the original reservoir species.

Without knowing the natural reservoir of SARS-CoV, predicting the exact mechanism of transmission from reservoir host to intermediate host is difficult. However, the fecal-oral route represents the main mode of transmission among animals. Although mixing of live reservoir hosts (e.g., bats) and intermediate hosts (e.g., civets) would be an efficient means of transmission, the main source of cross-species transmission in the animal trading chain (including warehouses, transportation vehicles, markets) may come from contaminated feces, urine, blood, or aerosols. This may also be true for civet-to-human transmission. As shown in the case of the infected restaurant

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customer in 2004, the customer had no direct contact with civets and was sitting at a table ≈5 m from the civet cages (*25*).

Although at this stage we cannot rule out the possibility of direct transmission from the natural reservoir host to humans, molecular epidemiologic studies (*2*,*10*) and studies of the receptor-S protein interaction (*35*) indicate that the progenitor viruses are unlikely to be able to infect humans and that a rapid viral evolution in an intermediate host (such as civets) seems to be necessary to adapt the virus for human infection. Ability to efficiently use the receptor molecules (ACE2 for human and civet) seems to be a major limiting factor for animal-to-human and human-to-human transmission (*35*). This also explains why the SARS-CoV was able to cause the human pandemic but the closely related bat SARS-like–CoVs were not. For the SARS-like–CoVs to infect humans, substantial genetic changes in the S1 receptor-binding domain will be necessary. These changes may be achieved in 1 of 2 possible ways. They could be achieved by genetic recombination, as coronaviruses are known to be able to recombine. For example, bat SARS-like–CoVs and another yet unknown coronavirus could coinfect an intermediate host, and the bat viruses would gain the ACE2 binding site in the S1 domain by recombination. The alternative is continuous evolution independent of recombination. Coronaviruses in bats could have a spectrum sufficiently diverse to encompass the progenitor virus for SARS-CoVs. The progenitor virus's ability to bind human ACE2 may be acquired or improved by adaptation (i.e., point mutations) in ≥1 intermediate host before it could efficiently infect humans. The existence of at least 3 discontinuous highly variable genomic regions between SARS-CoV and SARS-like–CoV indicates that the second mechanism is more likely.

In conclusion, the discovery of bat SARS-like–CoVs and the great genetic diversity of coronaviruses in bats have shed new light on the origin and transmission of SARS-CoV. Although the exact natural reservoir host for the progenitor virus of SARS-CoV is still unknown, we believe that a continued search in different bat populations in People's Republic of China and neighboring countries, combined with experimental infection of different bat species with SARS-CoV, will eventually identify the native reservoir species. A positive outcome of these investigations will greatly enhance our understanding of spillover mechanisms, which will in turn facilitate development and implementation of effective prevention strategies. The discovery of SARS-like–CoVs in bats highlights the increasingly recognized importance of bats as reservoirs of emerging viruses (*36*). Moreover, the recent emergence of SARS-CoVs and other bat-associated viruses such as henipaviruses (*37*,*38*), Menangle, and Tioman viruses (*36*), and variants of rabies viruses and bat lyssaviruses (*38*,*39*) also supports the contention that viruses, especially RNA viruses, possess more risk than other pathogens for disease emergence in human and domestic mammals because of their higher mutation rates (*40*).

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Bats Are Natural Reservoirs of SARS-Like Coronaviruses

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Severe acute respiratory syndrome (SARS) emerged in 2002 to 2003 in southern China. The origin of its etiological agent, the SARS coronavirus (SARS-CoV), remains elusive. Here we report that species of bats are a natural host of coronaviruses closely related to those responsible for the SARS outbreak. These viruses, termed SARS-like coronaviruses (SL-CoVs), display greater genetic variation than SARS-CoV isolated from humans or from civets. The human and civet isolates of SARS-CoV nestle phylogenetically within the spectrum of SL-CoVs, indicating that the virus responsible for the SARS outbreak was a member of this coronavirus group.

Severe acute respiratory syndrome (SARS) was caused by a newly emerged coronavirus, now known as SARS coronavirus (SARS-CoV) (*1*, *2*). In spite of the early success of etiological studies and molecular characterization of this virus (*3*, *4*), efforts to identify the origin of SARS-CoV have been less successful. Without knowledge of the reservoir host distribution and transmission routes of SARS-CoV, it will be difficult to prevent and control future outbreaks of SARS.

Studies conducted previously on animals sampled from live animal markets in Guangdong, China, indicated that masked palm civets (*Paguma larvata*) and two other species had been infected by SARS-CoV (*5*). This led to a large-scale culling of civets to prevent further SARS outbreaks. However, subsequent studies have revealed no widespread infection in wild or farmed civets (*6*, *7*). Experimental infection of civets with two different human isolates of SARS-CoV resulted in overt clinical symptoms, rendering them unlikely to be the natural reservoir hosts (*8*). These data suggest that although *P. larvata* may have been the source of the human infection that precipitated the SARS outbreak, infection in this and other common species in animal markets was more likely a reflection of an "artificial" market cycle in naïve species than an indication of the natural reservoir of the virus.

Bats are reservoir hosts of several zoonotic viruses, including the Hendra and Nipah viruses, which have recently emerged in Australia and East Asia, respectively (*9*–*11*). Bats may be persistently infected with many viruses but rarely display clinical symptoms (*12*). These characteristics and the increasing presence of bats and bat products in food and traditional medicine markets in southern China and elsewhere in Asia (*13*) led us to survey bats in the search for the natural reservoir of SARS-CoV.

In this study, conducted from March to December of 2004, we sampled 408 bats representing nine species, six genera, and three families from four locations in China (Guangdong, Guangxi, Hubei, and Tianjin) after trapping them in their native habitat (Table 1). Blood, fecal, and throat swabs were collected; serum samples and cDNA from fecal or throat samples were independently analyzed, double-blind, with different methods in our laboratories in Wuhan and Geelong (*14*).

Among six genera of bat species surveyed (*Rousettus*, *Cynopterus*, *Myotis*, *Rhinolophus*, *Nyctalus*, and *Miniopterus*), three communal, cave-dwelling species from the genus *Rhinolophus* (horseshoe bats) in the family *Rhinolophidae* demonstrated a high SARS-CoV antibody prevalence: 13 out of 46 bats (28%) in *R. pearsoni* from Guangxi, 2 out of 6 bats (33%) in *R. pussilus* from Guangxi, and 5 out of 7 bats (71%) in *R. macrotis* from Hubei. The high seroprevalence and wide distribution of seropositive bats is expected for a wildlife reservoir host for a pathogen (*15*).

The serological findings were corroborated by poylmerase chain reaction (PCR) analyses with primer pairs derived from the nucleocapsid (N) and polymerase (P) genes (table S1). Five fecal samples tested positive, all of them from the genus *Rhinolophus*: three in *R. pearsoni* from Guangxi and one each in *R. macrotis* and *R. ferrumequinum*, respectively, from Hubei. No virus was isolated from an inoculation of Vero E6 cells with fecal swabs of PCR-positive samples.

A complete genome sequence was determined directly from PCR products from one of the fecal samples (sample Rp3) that contained relatively high levels of genetic material. The genome organization of this virus (Fig. 1), tentatively named SARS-like coronavirus isolate Rp3 (SL-CoV Rp3), was essentially identical to that of SARS-CoV, with the exception of three regions (Fig. 1, shaded boxes). The overall nucleotide sequence identity between SL-CoV Rp3 and SARS-CoV Tor2 was 92% and increased to ~94% when the three variable regions were excluded. The variable regions are located at the 5′ end of the S gene (equivalent to the S1 coding region of coronavirus S protein) and the region immediately upstream of the N gene. These regions have been identified as "high mutation" regions among different SARS-CoVs (*5*, *16*, *17*). The region upstream of the N gene is known to be prone to deletions of various sizes (*5*, *16*, *18*).

Predicted protein products from each gene or putative open reading frame (ORF) of SL-CoV Rp3 and SARS-CoV Tor2 were com-

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Table 1. Detection of antibodies to SARS-CoV and PCR amplification of N and P gene fragments with SARS-CoV–specific primers. ND, not determined because of poor sample quality or unavailability of specimens from individual animals.

Sampling		Bat species	Antibody test: positive/total (%)	PCR analysis: positive/total (%)	
Time	Location			Fecal swabs	Respiratory swabs
Mar 04	Nanning, Guangxi	*Rousettus leschenaulti*	1/84 (1.2%)	0/110	ND
	Maoming, Guangdong	*Rousettus leschenaulti*	0/42	0/45	ND
		Cynopterus sphinx	0/17	0/27	ND
July 04	Nanning, Guangxi	*Rousettus leschenaulti*	ND	0/55	0/55
	Tianjin	*Myotis ricketti*	ND	0/21	0/21
Nov 04	Yichang, Hubei	*Rhinolophus pusillus*	ND	0/15	ND
		Rhinolophus ferrumequinum	0/4	1/8 (12.5%)*	ND
		Rhinolophus macrotis	5/7 (71%)	1/8 (12.5%)†	0/3
		Nyctalus plancyi	0/1	0/1	ND
		Miniopterus schreibersi	0/1	0/1	ND
		Myotis altarium	0/1	0/1	ND
Dec 04	Nanning, Guangxi	*Rousettus leschenaulti*	1/58 (1.8)	ND	ND
		Rhinolophus pearsoni	13/46 (28.3%)	3/30 (10%)‡	0/11
		Rhinolophus pussilus	2/6 (33.3%)	0/6	0/2

*Positive fecal sample designated Rf1 †Positive fecal sample designated Rm1 ‡Positive fecal samples designated Rp1, Rp2, and Rp3, respectively.

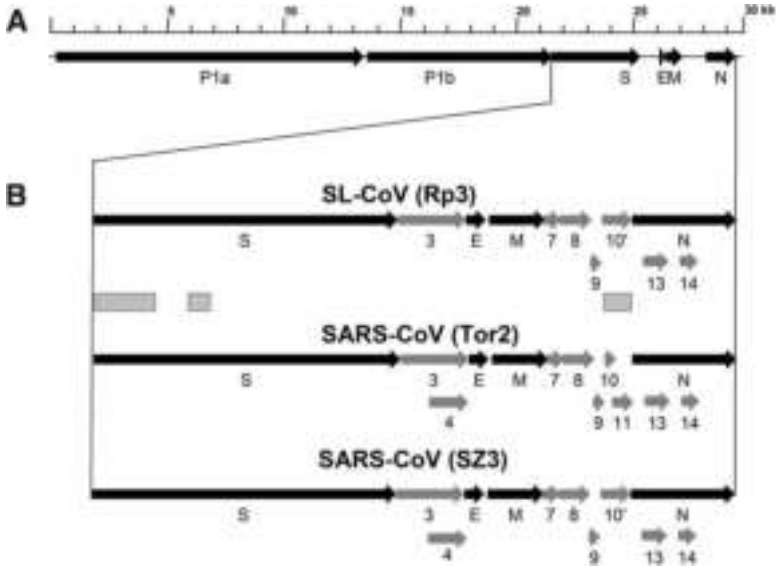

Fig. 1. Genome organization of, and comparison between, SL-CoV and SARS-CoV. (**A**) Overall genome organization of SL-CoV Rp3. (**B**) Expanded diagram of the 3′ region of the genome in comparison with SARS-CoV strains Tor2 and SZ3, following the same nomenclature used by Marra *et al*. (*4*). The genes (named by letters P, S, E, M, and N) present in all coronaviruses are shown in dark-colored arrows, whereas the SARS-CoV–specific ORFs are numbered and illustrated in light-colored arrows. ORF10′ follows the nomenclature by Guan *et al*. (*5*) to indicate that the single ORF present between ORF9 and N in SL-CoV is equivalent to the fusion of ORF10 and ORF11 in the same region in SARS-CoV Tor2. The shaded boxes mark the only three regions displaying significant sequence difference between the two viruses (table S2).

pared (table S2). The P, S, E, M, and N proteins, which are present in all coronaviruses, were similarly sized in the two viruses, with sequence identities ranging from 96% to 100%. The only exception was the S1 domain of the S protein, where sequence identity fell to 64%. The S1 domain is involved in receptor binding, whereas the S2 domain is responsible for the fusion of virus and host cell membranes (*19*). The sequence divergence in the S1 domain corroborated our serum neutralization studies, which indicated that although bat sera have a high level of cross-reactive antibodies (with enzyme-linked immunosorbent assay titers ranging from 1:100 to 1:6400), they failed to neutralize SARS-CoV when tested on Vero E6 cells. This finding suggests that S1 is the main target for antibody-mediated neutralization of this group of viruses, which is consistent with previous reports indicating that major SARS-CoV neutralization epitopes are located in the S1 region (*20*, *21*).

In addition to the five genes present in all coronavirus genomes, coronaviruses also have several ORFs between the P gene and the 3′ end of the genome that code for nonstructural proteins. The function of these nonstructural proteins is largely unknown. The location and sequence of ORFs are group- or virus-specific and hence can serve as important molecular markers for studying virus evolution and classification (*19*, *22*). SARS-CoV has a unique set of ORFs not shared by any of the known coronaviruses (*3*, *4*). Most of these ORFs were also present in SL-CoV, confirming the extremely close genetic relationship between SARS-CoV and SL-CoV (Fig. 1 and table S2).

Coronaviruses produce subgenomic mRNAs through a discontinuous transcription process not fully characterized (*19*). Conserved nucleotide sequences functioning as transcription regulatory sequences (TRSs) are required for the production of the subgenomic mRNAs. In SARS-CoV, such TRSs were identified at each of the predicted gene start sites (*3*, *4*). All of these TRSs were absolutely conserved between SARS-CoV Tor2 and SL-CoV Rp3 (table S3), further demonstrating that these two viruses are very closely related.

SL-CoV is completely different from a bat coronavirus (bat-CoV) recently identified by Poon *et al*. (*7*) from species of bats in the genus *Miniopterus* during a wildlife surveillance study in Hong Kong (Fig. 2). Because the complete genome sequence was not available for bat-CoV, only the trees covering the common sequences (i.e., parts of the P1b and S2 proteins) are shown. The phylogenetic analysis demonstrated that SL-CoV Rp3 and SARS-CoVs are clustered together but that bat-CoV is placed among the relatively distant group 1 viruses. Hereafter, SARS-CoVs and SL-CoVs will be collectively called the SARS cluster of coronaviruses.

In addition to the complete genome sequence of SL-CoV Rp3, partial genome sequences for the other four PCR-positive bat samples were also determined. Phylogenetic analysis based on the N protein sequences (Fig. 3A) revealed that the genetic variation among the SL-CoV sequences was much greater than that exhibited by SARS-CoVs (for simplicity, only three human and civet SARS-CoV isolates were used; the remainder are almost identical to those shown). This was especially obvious when SL-CoVs isolated from different bat species were compared. Moreover, the results suggested that SARS-CoVs nestle phylogenetically within the spectrum of SL-CoVs.

We also compared the "high mutation" regions in samples Rf1, Rm1, and Rp3. For the region upstream of the N gene, SL-CoVs from all three bat species contained a single ORF (ORF10′), similar to that found in SARS-CoV isolates from civets (*5*) and patients in the early phase of the outbreaks (*16*, *18*) but different from that in most human isolates, which

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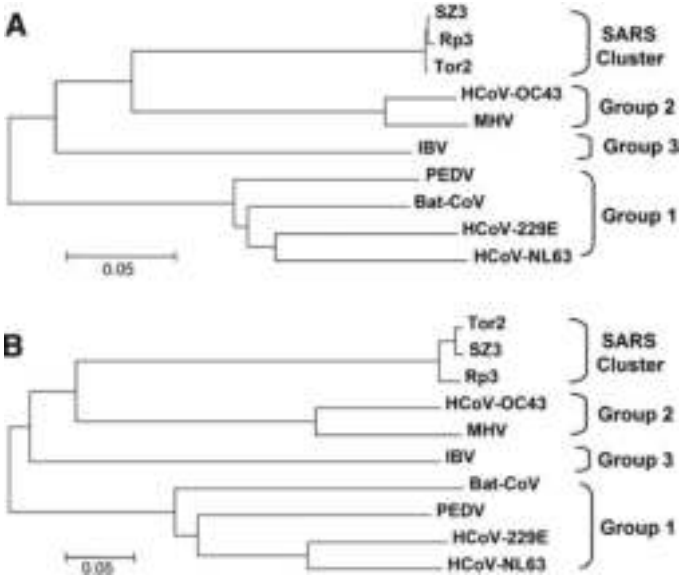

Fig. 2. Phylogenetic trees. (**A**) and (**B**) are trees based on deduced amino acid sequences of the same regions in P1b and S, respectively, as used by Poon *et al.* (*7*) for bat-CoV. Tor2 and SZ3, SARS-CoV strains Tor2 and SZ3; Rp3, SL-CoV Rp3; HCoV, human coronavirus; MHV, mouse hepatitis virus; PEDV, porcine epidemic diarrhea virus; IBV, avian infectious bronchitis virus.

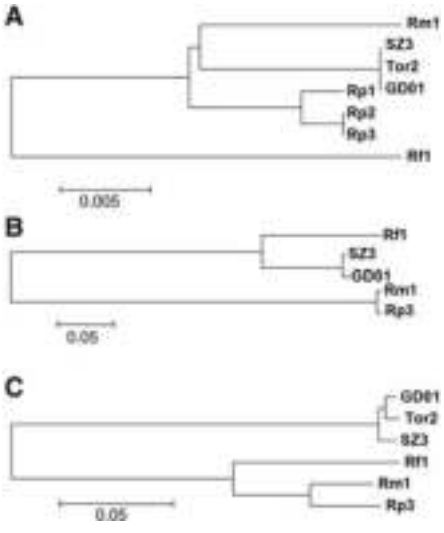

Fig. 3. Phylogenetic trees based on deduced amino acid sequences of (**A**) N, (**B**) ORF10′, and (**C**) S1 proteins. Tor2, SZ3, and GD01, different SARS-CoV strains; Rf1, Rm1, and Rp1-3, different SL-CoV sequences. The genetic distance scale shown for (A) is different from those for (B) and (C).

have a 29-nucleotide deletion in this region (*3*, *4*, *16*). ORF10′ in Rf1 codes for a protein having the same size (122 amino acids) as and more than 80% sequence identity to ORF10′ proteins of SARS-CoVs, but those in Rm1 and Rp3 code for a 121–amino acid protein with only 35% sequence identity (Fig. 3B and fig. S2). By contrast, analysis of the S1 protein regions (Fig. 3C and fig. S3) indicated that Rf1 was more closely related to SL-CoVs from two other bat species than to SARS-CoVs, suggesting that the SARS cluster of coronaviruses could recombine to increase genetic diversity and fitness, as is well documented for other coronaviruses (*19*). We were unable to sequence these regions for Rp1 or Rp2, owing to the poor quality of the fecal materials from these two animals. The limited amount of cDNA available was used up for N gene analysis and in initial sequencing trials with SARS-CoV–derived primers, which were largely unsuccessful. Judging from the close relationship of the N genes between Rp1, Rp2, and Rp3 (fig. S1), it is unlikely that Rp1 or Rp2 will have major sequence differences from Rp3 in the S1 or ORF10′ regions. This is not unexpected, considering that these three positive samples were obtained from the same bat species in the same location.

The genetic diversity of bat-derived sequences supports the notion that bats are a natural reservoir host of the SARS cluster of coronaviruses. A similar observation has been made for henipaviruses, another important group of emerging zoonotic viruses of bat origin, which show greater genetic diversity in bats than was observed among viruses isolated during the initial Nipah outbreaks in Malaysia (*23*–*26*). The overall nucleotide sequence identity of 92% between SL-CoVs and SARS-CoVs is very similar to that observed between Nipah viruses isolated from Malaysia and Bangladesh in 1999 and 2004, respectively (*25*) (fig. S4). SL-CoVs present a new challenge to the diagnosis and treatment of future disease outbreaks. The current tests and therapeutic strategies may not work effectively against all viruses in this group, owing to their great genetic variability in the S1 domain region of the S gene.

The genus *Rhinolophus* contains 69 species and has a wide distribution from Australia to Europe (*27*). They roost primarily in caves and feed mainly on moths and beetles. However, notwithstanding the predominant *Rhinolophus* findings in this study, it is highly likely that there are more SARS-related coronaviruses to be discovered in bats. Indeed, our positive serological findings in the cave-dwelling fruit bat *Rousettus leschenaulti* indicate that infection by a related virus could occur in fruit bats as well, albeit at a much lower frequency. A plausible mechanism for emergence from a natural bat reservoir can be readily envisaged. Fruit bats including *R. leschenaulti*, and less frequently insectivorous bats, are found in markets in southern China. An infectious consignment of bats serendipitously juxtaposed with a susceptible amplifying species, such as *P. larvata*, at some point in the wildlife supply chain could result in spillover and establishment of a market cycle while susceptible animals are available to maintain infection. Further studies in field epidemiology, laboratory infection, and receptor distribution and usage are being conducted to assess potential roles played by different bat species in SARS emergence.

These findings on coronaviruses, together with data on henipaviruses (*23*–*25*, *28*), suggest that genetic diversity exists among zoonotic viruses in bats, increasing the possibility of variants crossing the species barrier and causing outbreaks of disease in human populations. It is therefore essential that we enhance our knowledge and understanding of reservoir host distribution, animal-animal and human-animal interaction (particularly within the wet-market system), and the genetic diversity of bat-borne viruses to prevent future outbreaks.

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29. This work was jointly funded by a special grant for "Animal Reservoir of SARS-CoV," State Key Program for Basic Research Grant 2005CB523004, and State High Technology Development Program grant no.

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2005AA219070 from the Ministry of Science and Technology, People's Republic of China; the Sixth Framework Program "EPISARS" from the European Commission (no. 51163); the Australian Biosecurity Cooperative Research Centre for Emerging Infectious Disease (Project 1.007R); and an NIH/NSF "Ecology of Infectious Diseases" award (no. R01-TW05869) from the John E. Fogarty International Center and the V. Kann Rasmussen Foundation. For the full-length genome sequence of SL-CoV Rp3, see GenBank accession no. DQ71615. Additional GenBank accession numbers are given in the supporting material.

Supporting Online Material
www.sciencemag.org/cgi/content/full/1118391/DC1
Materials and Methods
Figs. S1 to S4
Tables S1 to S3
References and Notes

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Neurogenesis in the Hypothalamus of Adult Mice: Potential Role in Energy Balance

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Ciliary neurotrophic factor (CNTF) induces weight loss in obese rodents and humans, and for reasons that are not understood, its effects persist after the cessation of treatment. Here we demonstrate that centrally administered CNTF induces cell proliferation in feeding centers of the murine hypothalamus. Many of the newborn cells express neuronal markers and show functional phenotypes relevant for energy-balance control, including a capacity for leptin-induced phosphorylation of signal transducer and activator of transcription 3 (STAT3). Co-administration of the mitotic blocker cytosine-β-D-arabinofuranoside (Ara-C) eliminates the proliferation of neural cells and abrogates the long-term, but not the short-term, effect of CNTF on body weight. These findings link the sustained effect of CNTF on energy balance to hypothalamic neurogenesis and suggest that regulated hypothalamic neurogenesis in adult mice may play a previously unappreciated role in physiology and disease.

The obesity epidemic has prompted major efforts to develop safe and effective therapies (*1*, *2*). However, approved drugs for obesity have limited efficacy and act only acutely, with patients rapidly regaining weight after terminating treatment (*3*). Only the neurocytokine ciliary neurotrophic factor (CNTF) and Axokine, an analog of CNTF developed as a drug candidate for the treatment of obesity, appear to deviate from this paradigm. Rodents and patients treated with Axokine were reported to maintain lowered body weights weeks to months after the cessation of treatment (*4*, *5*). This feature of Axokine/CNTF action is unexplained and suggests that CNTF induces long-lasting changes in one or more elements of the energy-balance circuitry.

In rodents, CNTF is most potent when administered directly into the cerebrospinal fluid (*6*) and activates signaling cascades in hypothalamic nuclei involved in feeding control (*5*, *7*, *8*). For instance, CNTF activates phosphorylation of signal transducer and activator of transcription 3 (STAT3) in a population of hypothalamic neurons that substantially overlaps with those activated by leptin (*5*). However, in contrast to CNTF, leptin-treated animals do not maintain their lowered body weight after the cessation of treatment. We thus sought a CNTF-specific mechanism to explain this long-term effect.

CNTF supports the survival of neurons in vitro and in vivo (*9*) and has also been implicated in the maintenance of adult neural stem cells (*10*). Furthermore, other trophic factors, such as epidermal growth factor and fibroblast growth factor 2, are known to act as mitogens on adult neuronal progenitors (*11*, *12*), and they promote the functional regeneration of hippocampal pyramidal neurons (*13*). Neurogenesis in the adult brain is most clearly defined in the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampal formation (*14*). However, recent reports indicate that the neuroproliferative potency in the adult extends to other brain structures, including the hypothalamus (*15*–*17*). On the basis of these findings, we hypothesized that the long-term effect of CNTF on body-weight regulation might involve neurogenesis in the hypothalamus, which is the brain region most relevant for energy-balance regulation.

To assess the mitogenic potency of CNTF in the adult nervous system in vivo, we delivered the cell-proliferation marker bromodeoxyuridine (BrdU) alone (vehicle treatment) or together with CNTF directly into the cerebrospinal fluid of mouse brains (*18*). CNTF and BrdU were continuously infused for 7 days into the right lateral ventricle using osmotic minipumps. Mice were switched to a high-fat diet two months before surgery and were kept on this diet throughout the experiments. In accordance with previous results (*5*), CNTF-treated mice showed a marked reduction in body weights (Fig. 1A), which persisted after termination of CNTF delivery. Mice were killed 22 days after surgery, and brain sections were immunostained with an antibody against BrdU. Because BrdU incorporates into DNA of dividing cells, BrdU-positive ($BrdU^+$) cells are thought to represent newborn cells. Figure 1B shows coronal sections of vehicle- and CNTF-infused animals at the level of the arcuate, ventromedial, and dorsomedial nuclei, well-known hypothalamic centers for energy-balance regulation (*19*). In vehicle-infused animals, few $BrdU^+$ cells were detected in the parenchyma surrounding the third ventricle (Fig. 1B, left). Administration with CNTF led to a dramatic increase of BrdU+ cells (Fig. 1B, right). Note the higher density of $BrdU^+$ cells at the base of the third ventricle, which is part of the arcuate nucleus/median eminence.

The pattern of CNTF receptor (CNTFR) mRNA expression is consistent with this observation. In situ hybridization using a riboprobe against CNTFR mRNA revealed strong staining in the walls of the basal third ventricle and surrounding arcuate nucleus parenchyma (Fig. 1C). Because this section originated from an animal treated with both CNTF and BrdU, we colabeled with antibodies to BrdU. Many $BrdU^+$ cells were positive for CNTFR expression, indicating that CNTF, at least in part, directly promotes cell division by binding to CNTFR on putative neural progenitor cells (Fig. 1D, inset). By counting all newly generated cells in the caudal hypothalamus, CNTF treatment led to a marked increase of $BrdU^+$ cells over vehicle-infused animals (Fig. 1E). The total number of $BrdU^+$ cells in CNTF-treated animals remained constant for at least 2 weeks after the infusion period. Subsequently, the numbers decreased but plateaued at a high level. Vehicle-infused animals showed a similar fractional decrease over time. Thus it appears that the majority of hypothalamic $BrdU^+$ cells do not die or migrate to distant areas as reported for newborn neurons of the SVZ, which follow the rostral migratory stream toward the olfactory bulb (*20*).

To investigate the origin of adult-born cells in the hypothalamus, we examined CNTF and vehicle-infused brains every 12 hours starting 48 hours after surgery, a time when the infused CNTF/BrdU should just reach the ventricular system (*18*). Hypothalamic BrdU incorporation was first detected 60 to 72 hours

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Bats Are Natural Reservoirs of SARS-Like Coronaviruses

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Evolutionary origins of the SARS-CoV-2 sarbecovirus lineage responsible for the COVID-19 pandemic

Maciej F. Boni[1,8]✉, Philippe Lemey[2,8]✉, Xiaowei Jiang[3], Tommy Tsan-Yuk Lam[4], Blair W. Perry[5], Todd A. Castoe[5], Andrew Rambaut[6]✉ and David L. Robertson[7]✉

There are outstanding evolutionary questions on the recent emergence of human coronavirus SARS-CoV-2 including the role of reservoir species, the role of recombination and its time of divergence from animal viruses. We find that the sarbecoviruses—the viral subgenus containing SARS-CoV and SARS-CoV-2—undergo frequent recombination and exhibit spatially structured genetic diversity on a regional scale in China. SARS-CoV-2 itself is not a recombinant of any sarbecoviruses detected to date, and its receptor-binding motif, important for specificity to human ACE2 receptors, appears to be an ancestral trait shared with bat viruses and not one acquired recently via recombination. To employ phylogenetic dating methods, recombinant regions of a 68-genome sarbecovirus alignment were removed with three independent methods. Bayesian evolutionary rate and divergence date estimates were shown to be consistent for these three approaches and for two different prior specifications of evolutionary rates based on HCoV-OC43 and MERS-CoV. Divergence dates between SARS-CoV-2 and the bat sarbecovirus reservoir were estimated as 1948 (95% highest posterior density (HPD): 1879–1999), 1969 (95% HPD: 1930–2000) and 1982 (95% HPD: 1948–2009), indicating that the lineage giving rise to SARS-CoV-2 has been circulating unnoticed in bats for decades.

In December 2019, a cluster of pneumonia cases epidemiologically linked to an open-air live animal market in the city of Wuhan (Hubei Province), China[1,2] led local health officials to issue an epidemiological alert to the Chinese Center for Disease Control and Prevention and the World Health Organization's (WHO) China Country Office. In early January, the aetiological agent of the pneumonia cases was found to be a coronavirus[3], subsequently named SARS-CoV-2 by an International Committee on Taxonomy of Viruses (ICTV) Study Group[4] and also named hCoV-19 by Wu et al.[5]. The first available sequence data[6] placed this novel human pathogen in the *Sarbecovirus* subgenus of *Coronaviridae*[7], the same subgenus as the SARS virus that caused a global outbreak of >8,000 cases in 2002–2003. By mid-January 2020, the virus was spreading widely within Hubei province and by early March SARS-CoV-2 was declared a pandemic[8].

In outbreaks of zoonotic pathogens, identification of the infection source is crucial because this may allow health authorities to separate human populations from the wildlife or domestic animal reservoirs posing the zoonotic risk[9,10]. If stopping an outbreak in its early stages is not possible—as was the case for the COVID-19 epidemic in Hubei—identification of origins and point sources is nevertheless important for containment purposes in other provinces and prevention of future outbreaks. When the first genome sequence of SARS-CoV-2, Wuhan-Hu-1, was released on 10 January 2020 (GMT) on Virological.org by a consortium led by Zhang[6], it enabled immediate analyses of its ancestry. Across a large region of the virus genome, corresponding approximately to ORF1b, it did not cluster with any of the known bat coronaviruses indicating that recombination probably played a role in the evolutionary history of these viruses[5,7]. Subsequently a bat sarbecovirus—RaTG13, sampled from a *Rhinolophus affinis* horseshoe bat in 2013 in Yunnan Province—was reported that clusters with SARS-CoV-2 in almost all genomic regions with approximately 96% genome sequence identity[2]. Zhou et al.[2] concluded from the genetic proximity of SARS-CoV-2 to RaTG13 that a bat origin for the current COVID-19 outbreak is probable. Concurrent evidence also proposed pangolins as a potential intermediate species for SARS-CoV-2 emergence and suggested them as a potential reservoir species[11–13].

Unlike other viruses that have emerged in the past two decades, coronaviruses are highly recombinogenic[14–16]. Influenza viruses reassort[17] but they do not undergo homologous recombination within RNA segments[18,19], meaning that origins questions for influenza outbreaks can always be reduced to origins questions for each of influenza's eight RNA segments. For coronaviruses, however, recombination means that small genomic subregions can have independent origins, identifiable if sufficient sampling has been done in the animal reservoirs that support the endemic circulation, co-infection and recombination that appear to be common. Here, we analyse the evolutionary history of SARS-CoV-2 using available genomic data on sarbecoviruses. We demonstrate that the sarbecoviruses circulating in horseshoe bats have complex recombination histories as reported by others[15,20–26]. Despite the SARS-CoV-2 lineage's acquisition of residues in its Spike (S) protein's receptor-binding domain (RBD) permitting the use of human

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ACE2 (ref. [27]) receptors and its RBD being genetically closer to a pangolin virus than to RaTG13 (refs. [11–13,22,28])—a signal that suggests recombination—the divergence patterns in the S protein do not show evidence of recombination between the lineage leading to SARS-CoV-2 and known sarbecoviruses. Our results indicate the presence of a single lineage circulating in bats with properties that allowed it to infect human cells, as previously described for bat sarbecoviruses related to the first SARS-CoV lineage[29–31].

To gauge the length of time this lineage has circulated in bats, we estimate the time to the most recent common ancestor (TMRCA) of SARS-CoV-2 and RaTG13. We use three bioinformatic approaches to remove the effects of recombination, and we combine these approaches to identify putative non-recombinant regions that can be used for reliable phylogenetic reconstruction and dating. Collectively our analyses point to bats being the primary reservoir for the SARS-CoV-2 lineage. While it is possible that pangolins, or another hitherto undiscovered species, may have acted as an intermediate host facilitating transmission to humans, current evidence is consistent with the virus having evolved in bats resulting in bat sarbecoviruses that can replicate in the upper respiratory tract of both humans and pangolins[25,32].

Results

Recombination analysis and identification of breakpoint-free genome regions. Among the 68 sequences in the aligned sarbecovirus sequence set, 67 show evidence of mosaicism (all Dunn–Sidak-corrected $P < 4 \times 10^{-4}$ and 3SEQ[14]), indicating involvement in homologous recombination either directly with identifiable parentals or in their deeper shared evolutionary history—that is, due to shared ancestral recombination events. This is evidence for numerous recombination events occurring in the evolutionary history of the sarbecoviruses[22,33]; specifying all past events in their correct temporal order[34] is challenging and not shown here. Figure 1 (top) shows the distribution of all identified breakpoints (using 3SEQ's exhaustive triplet search) by the number of candidate recombinant sequences supporting them. The histogram allows for the identification of non-recombining regions (NRRs) by revealing regions with no breakpoints. Sorting these breakpoint-free regions (BFRs) by length results in two segments >5 kb: an ORF1a subregion spanning nucleotides (nt) 3,625–9,150 and the first half of ORF1b spanning nt 13,291–19,628 (sequence numbering given in Source Data, https://github.com/plemey/SARSCoV2origins). Eight other BFRs <500 nt were identified, and the regions were named BFR A–J in order of length. Of the nine breakpoints defining these ten BFRs, four showed phylogenetic incongruence (PI) signals with bootstrap support >80%, adopting previously published criteria on using a combination of mosaic and PI signals to show evidence of past recombination events[19]. All four of these breakpoints were also identified with the tree-based recombination detection method GARD[35].

The extent of sarbecovirus recombination history can be illustrated by five phylogenetic trees inferred from BFRs or concatenated adjacent BFRs (Fig. 1c). BFRs were concatenated if no phylogenetic incongruence signal could be identified between them. When viewing the last 7 kb of the genome, a clade of viruses from northern China appears to cluster with sequences from southern Chinese provinces but, when inspecting trees from different parts of ORF1ab, the N. China clade is phylogenetically separated from the S. China clade. Individual sequences such as RpShaanxi2011, Guangxi GX2013 and two sequences from Zhejiang Province (CoVZXC21/CoVZC45), as previously shown[22,25], have strong phylogenetic recombination signals because they fall on different evolutionary lineages (with bootstrap support >80%) depending on what region of the genome is being examined.

Despite the high frequency of recombination among bat viruses, the block-like nature of the recombination patterns across the genome permits retrieval of a clean subalignment for phylogenetic analysis. Conservatively, we combined the three BFRs >2 kb identified above into non-recombining region 1 (NRR1). Removal of five sequences that appear to be recombinants and two small subregions of BFR A was necessary to ensure that there were no phylogenetic incongruence signals among or within the three BFRs. Alternatively, combining 3SEQ-inferred breakpoints, GARD-inferred breakpoints and the necessity of PI signals for inferring recombination, we can use the 9.9-kb region spanning nucleotides 11,885–21,753 (NRR2) as a putative non-recombining region; this approach is breakpoint-conservative because it is conservative in identifying breakpoints but not conservative in identifying non-recombining regions. Using a third consensus-based approach for identifying recombinant regions in individual sequences—with six different recombination detection methods in RDP5 (ref. [36])—gives a putative recombination-free alignment that we call non-recombinant alignment 3 (NRA3) (see Methods).

All three approaches to removal of recombinant genomic segments point to a single ancestral lineage for SARS-CoV-2 and RaTG13. Two other bat viruses (CoVZXC21 and CoVZC45) from Zhejiang Province fall on this lineage as recombinants of the RaTG13/SARS-CoV-2 lineage and the clade of Hong Kong bat viruses sampled between 2005 and 2007 (Fig. 1c). Specifically, progenitors of the RaTG13/SARS-CoV-2 lineage appear to have recombined with the Hong Kong clade (with inferred breakpoints at 11.9 and 20.8 kb) to form the CoVZXC21/CoVZC45-lineage. Sibling lineages to RaTG13/SARS-CoV-2 include a pangolin sequence sampled in Guangdong Province in March 2019 and a clade of pangolin sequences from Guangxi Province sampled in 2017.

Because the SARS-CoV-2 S protein has been implicated in past recombination events or possibly convergent evolution[12], we specifically investigated several subregions of the S protein—the N-terminal domain of S1, the C-terminal domain of S1, the variable-loop region of the C-terminal domain, and S2. The variable-loop region in SARS-CoV-2 shows closer identity to the 2019 pangolin coronavirus sequence than to the RaTG13 bat virus, supported by phylogenetic inference (Fig. 2). On first examination this would suggest that that SARS-CoV-2 is a recombinant of an ancestor of Pangolin-2019 and RaTG13, as proposed by others[11,22]. However, on closer inspection, the relative divergences in the phylogenetic tree (Fig. 2, bottom) show that SARS-CoV-2 is unlikely to have acquired the variable loop from an ancestor of Pangolin-2019 because these two sequences are approximately 10–15% divergent throughout the entire S protein (excluding the N-terminal domain). It is RaTG13 that is more divergent in the variable-loop region (Extended Data Fig. 1) and thus likely to be the product of recombination, acquiring a divergent variable loop from a hitherto unsampled bat sarbecovirus[28]. This is notable because the variable-loop region contains the six key contact residues in the RBD that give SARS-CoV-2 its ACE2-binding specificity[27,37]. These residues are also in the Pangolin Guangdong 2019 sequence. The most parsimonious explanation for these shared ACE2-specific residues is that they were present in the common ancestors of SARS-CoV-2, RaTG13 and Pangolin Guangdong 2019, and were lost through recombination in the lineage leading to RaTG13. This provides compelling support for the SARS-CoV-2 lineage being the consequence of a direct or nearly-direct zoonotic jump from bats, because the key ACE2-binding residues were present in viruses circulating in bats.

Ancestry in non-recombinant regions. Using the most conservative approach to identification of a non-recombinant genomic region (NRR1), SARS-CoV-2 forms a sister lineage with RaTG13, with genetically related cousin lineages of coronavirus sampled in pangolins in Guangdong and Guangxi provinces (Fig. 3). Given that these pangolin viruses are ancestral to the progenitor of the

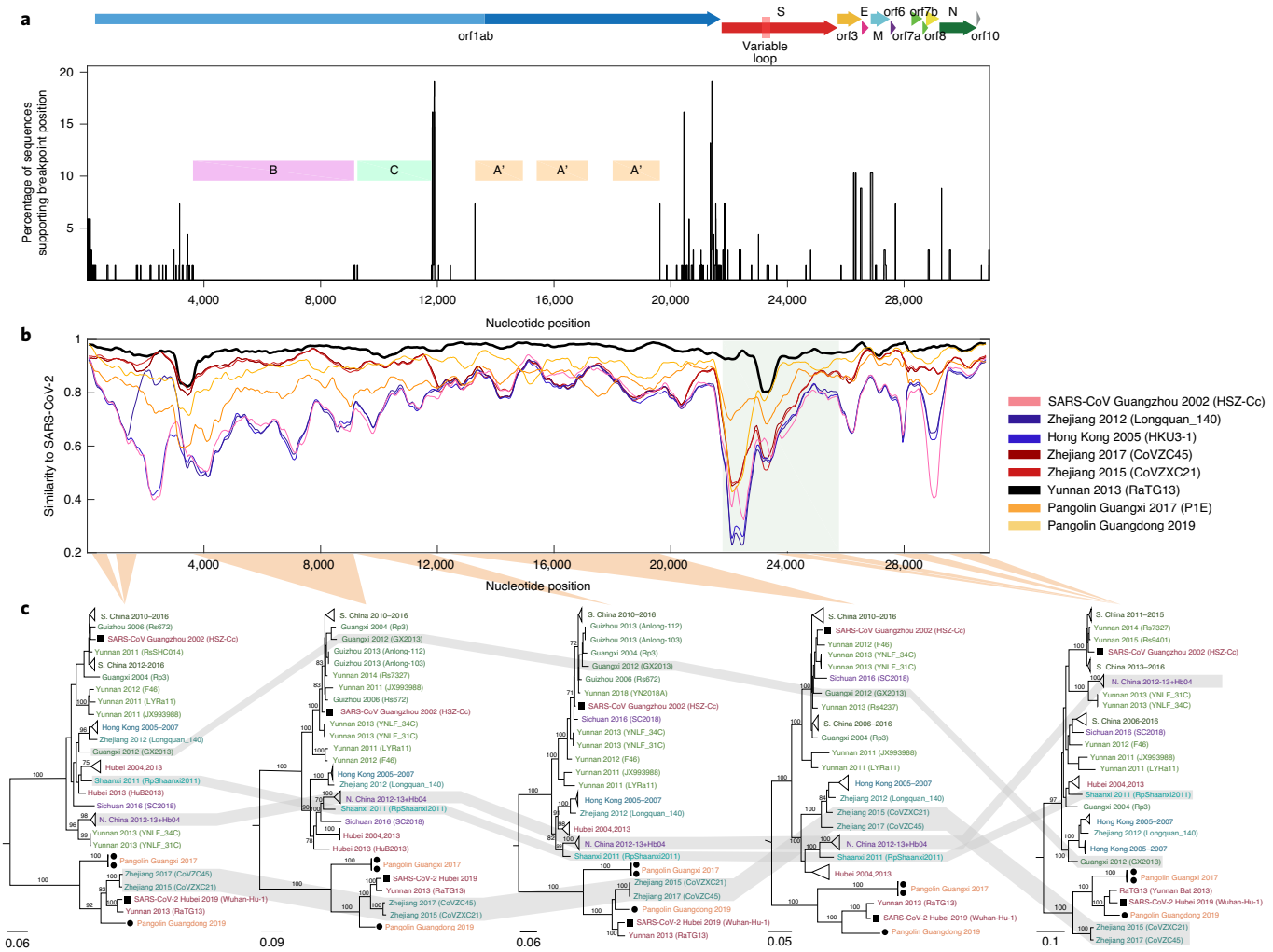

Fig. 1 | Breakpoints identified by 3SEQ. a, Breakpoints identified by 3SEQ illustrated by percentage of sequences (out of 68) that support a particular breakpoint position. Note that breakpoints can be shared between sequences if they are descendants of the same recombination events. Pink, green and orange bars show BFRs, with region A (nt 13,291–19,628) showing two trimmed segments yielding region A′ (nt 13,291–14,932, 15,405–17,162, 18,009–19,628). Regions B and C span nt 3,625–9,150 and 9,261–11,795, respectively. Concatenated region A′BC is NRR1. Open reading frames are shown above the breakpoint plot, with the variable-loop region indicated in the S protein. **b**, Similarity plot between SARS-CoV-2 and several selected sequences including RaTG13 (black), SARS-CoV (pink) and two pangolin sequences (orange). The shaded region corresponds to the S protein. **c**, Maximum likelihood phylogenetic trees rooted on a 2007 virus sampled in Kenya (BtKy72; root truncated from images), shown for five BFRs of the sarbecovirus alignment. Nucleotide positions for phylogenetic inference are 147–695, 962–1,686 (first tree), 3,625–9,150 (second tree, also BFR B), 9,261–11,795 (third tree, also BFR C), 12,443–19,638 (fourth tree) and 23,631–24,633, 24,795–25,847, 27,702–28,843 and 29,574–30,650 (fifth tree). Relevant bootstrap values are shown on branches, and grey-shaded regions show sequences exhibiting phylogenetic incongruence along the genome. S. China corresponds to Guangxi, Yunnan, Guizhou and Guangdong provinces. N. China corresponds to Jilin, Shanxi, Hebei and Henan provinces, and the N. China clade also includes one sequence sampled in Hubei Province in 2004.

RaTG13/SARS-CoV-2 lineage, it is more likely that they are also acquiring viruses from bats. While pangolins could be acting as intermediate hosts for bat viruses to get into humans—they develop severe respiratory disease[38] and commonly come into contact with people through trafficking—there is no evidence that pangolin infection is a requirement for bat viruses to cross into humans.

Phylogenies of subregions of NRR1 depict an appreciable degree of spatial structuring of the bat sarbecovirus population across different regions (Fig. 3). One geographic clade includes viruses from provinces in southern China (Guangxi, Yunnan, Guizhou and Guangdong), with its major sister clade consisting of viruses from provinces in northern China (Shanxi, Henan, Hebei and Jilin) as well as Hubei Province in central China and Shaanxi Province in northwestern China. Several of the recombinant sequences in these trees show that recombination events do occur across geographically divergent clades. The Sichuan (SC2018) virus appears to be a recombinant of northern/central and southern viruses, while the two Zhejiang viruses (CoVZXC21 and CoVZC45) appear to carry a recombinant region from southern or central China.

TMRCA for NRRs of SARS-CoV-2 lineage. To avoid artefacts due to recombination, we focused on NRR1 and NRR2 and the recombination-masked alignment NRA3 to infer time-measured evolutionary histories. Visual exploration using TempEst[39] indicates that there is no evidence for temporal signal in these datasets (Extended Data Fig. 2). This is not surprising for diverse viral populations with relatively deep evolutionary histories. In such cases, even moderate rate variation among long, deep phylogenetic branches will substantially impact expected root-to-tip divergences over a sampling time range that represents only a small fraction of

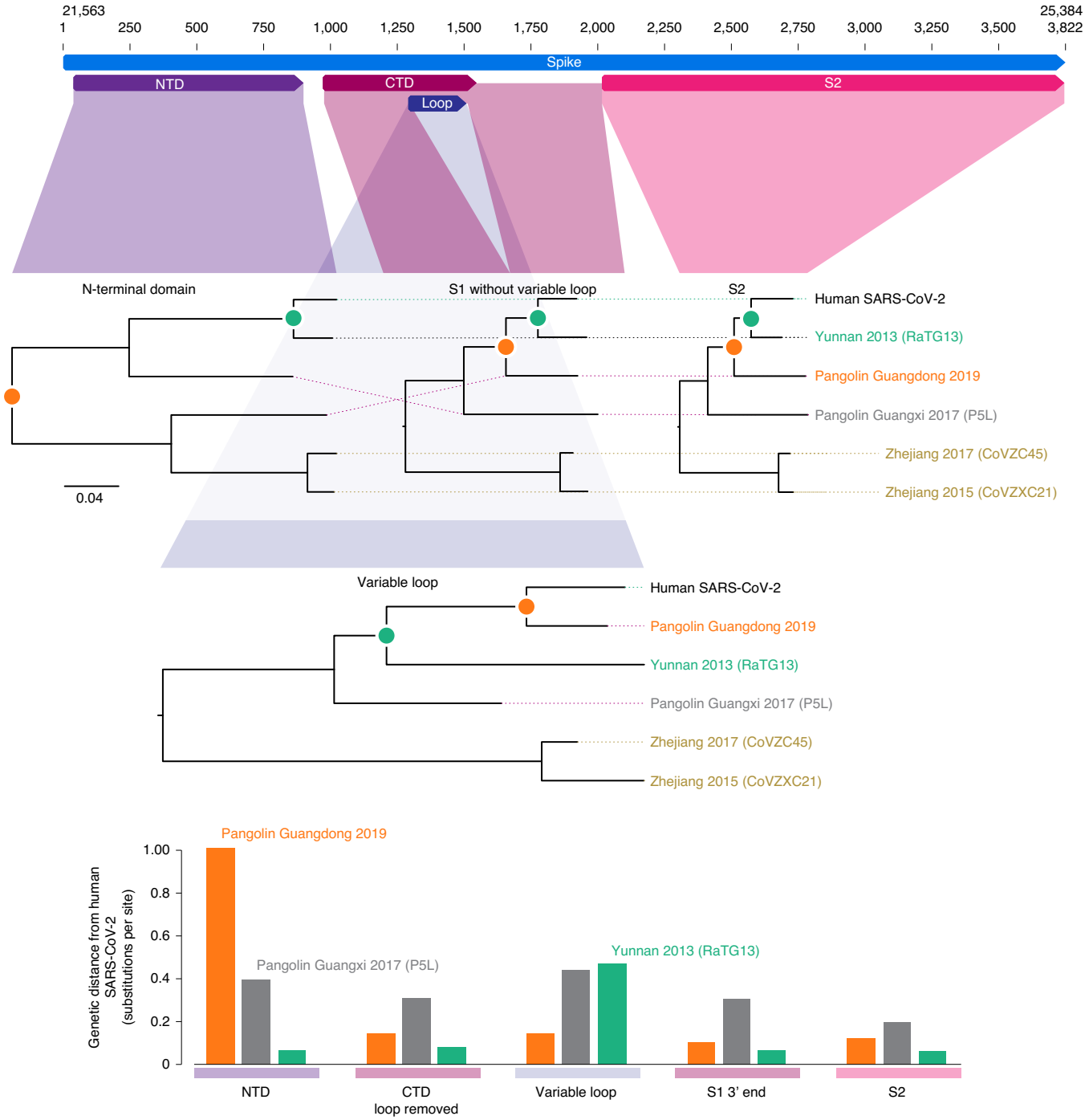

Fig. 2 | Phylogenetic relationships among SARS-CoV-2 and closely related sequences for subregions of the S protein. SARS-CoV-2 and RaTG13 are the most closely related (their most recent common ancestor nodes denoted by green circles), except in the 222-nt variable-loop region of the C-terminal domain (bar graphs at bottom). In the variable-loop region, RaTG13 diverges considerably with the TMRCA, now outside that of SARS-CoV-2 and the Pangolin Guangdong 2019 ancestor, suggesting that RaTG13 has acquired this region from a more divergent and undetected bat lineage. The genetic distances between SARS-CoV-2 and RaTG13 (bottom) demonstrate that their relationship is consistent across all regions except for the variable loop. The genetic distances between SARS-CoV-2 and Pangolin Guangdong 2019 are consistent across all regions except the N-terminal domain, implying that a recombination event between these two sequences in this region is unlikely. Uncertainty measures are shown in Extended Data Fig. 1. NTD, N-terminal domain; CTD, C-terminal domain.

the evolutionary history[40]. However, formal testing using marginal likelihood estimation[41] does provide some evidence of a temporal signal, albeit with limited log Bayes factor support of 3 (NRR1), 10 (NRR2) and 3 (NRA3); see Supplementary Table 1.

In the absence of a strong temporal signal, we sought to identify a suitable prior rate distribution to calibrate the time-measured trees by examining several coronaviruses sampled over time, including HCoV-OC43, MERS-CoV, and SARS-CoV virus genomes. These datasets were subjected to the same recombination masking approach as NRA3 and were characterized by a strong temporal signal (Fig. 4), but also by markedly different evolutionary rates. Specifically, using a formal Bayesian approach[42] (see Methods), we

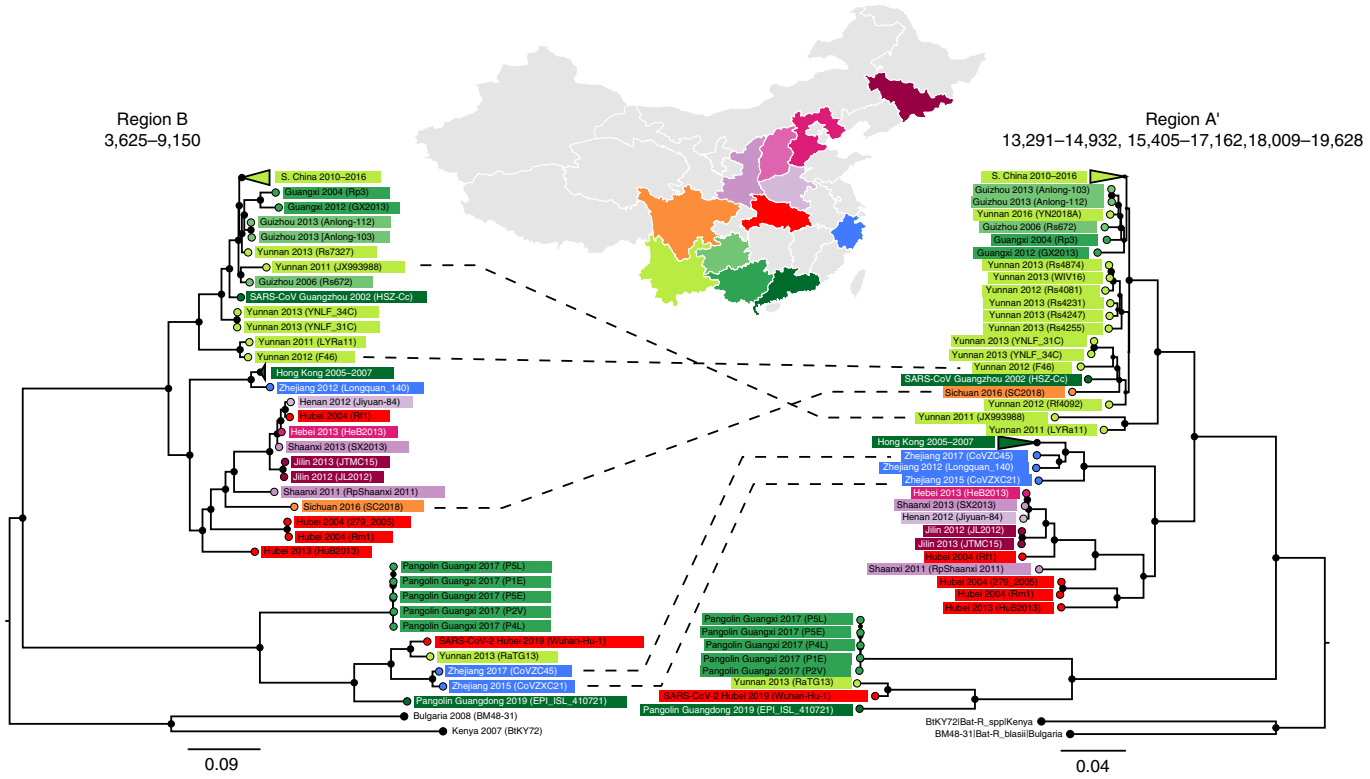

Fig. 3 | Maximum likelihood trees of the sarbecoviruses using the two longest BFRs, rooted on the Kenya/Bulgaria lineage. Region A has been shortened to A′ (5,017 nt) based on potential recombination signals within the region. Region B is 5,525 nt long. Sequences are colour-coded by province according to the map. Five example sequences with incongruent phylogenetic positions in the two trees are indicated by dashed lines.

estimate a fast evolutionary rate (0.00169 substitutions per site yr^{-1}, 95% highest posterior density (HPD) interval (0.00131,0.00205)) for SARS viruses sampled over a limited timescale (1 year), a slower rate (0.00078 (0.00063,0.00092) substitutions per site yr^{-1}) for MERS-CoV on a timescale of about 4 years and the slowest rate (0.00024 (0.00019,0.00029) substitutions per site yr^{-1}) for HCoV-OC43 over almost five decades. These differences reflect the fact that rate estimates can vary considerably with the timescale of measurement, a frequently observed phenomenon in viruses known as time-dependent evolutionary rates[41,43,44]. Over relatively shallow timescales, such differences can primarily be explained by varying selective pressure, with mildly deleterious variants being eliminated more strongly by purifying selection over longer timescales[44–46]. Consistent with this, we estimate a concomitantly decreasing non-synonymous-to-synonymous substitution rate ratio over longer evolutionary timescales: 1.41 (1.20,1.68), 0.35 (0.30,0.41) and 0.133 (0.129,0.136) for SARS, MERS-CoV and HCoV-OC43, respectively. In light of these time-dependent evolutionary rate dynamics, a slower rate is appropriate for calibration of the sarbecovirus evolutionary history. We compare both MERS-CoV- and HCoV-OC43-centred prior distributions (Extended Data Fig. 3) to examine the sensitivity of date estimates to this prior specification.

We infer time-measured evolutionary histories using a Bayesian phylogenetic approach while incorporating rate priors based on mean MERS-CoV and HCoV-OC43 rates and with standard deviations that allow for more uncertainty than the empirical estimates for both viruses (see Methods). Using both prior distributions, this results in six highly similar posterior rate estimates for NRR1, NRR2 and NRA3, centred around 0.00055 substitutions per site yr^{-1}. The fact that these estimates lie between the rates for MERS-CoV and HCoV-OC43 is consistent with the intermediate sampling time range of about 18 years (Fig. 5). The consistency of the posterior rates for the different prior means also implies that the data do contribute to the evolutionary rate estimate, despite the fact that a temporal signal was visually not apparent (Extended Data Fig. 2). Below, we report divergence time estimates based on the HCoV-OC43-centred rate prior for NRR1, NRR2 and NRA3 and summarize corresponding estimates for the MERS-CoV-centred rate priors in Extended Data Fig. 4. Divergence time estimates based on the HCoV-OC43-centred rate prior for the separate BFRs (Supplementary Table 3) show consistency in TMRCA estimates across the genome.

The divergence time estimates for SARS-CoV-2 and SARS-CoV from their respective most closely related bat lineages are reasonably consistent among the three approaches we use to eliminate the effects of recombination in the alignment. Using the most conservative approach (NRR1), the divergence time estimate for SARS-CoV-2 and RaTG13 is 1969 (95% HPD: 1930–2000), while that between SARS-CoV and its most closely related bat sequence is 1962 (95% HPD: 1932–1988); see Fig. 5. These are in general agreement with estimates using NRR2 and NRA3, which result in divergence times of 1982 (1948–2009) and 1948 (1879–1999), respectively, for SARS-CoV-2, and estimates of 1952 (1906–1989) and 1970 (1932–1996), respectively, for the divergence time of SARS-CoV from its closest known bat relative. The SARS-CoV divergence times are somewhat earlier than dates previously estimated[15] because previous estimates were obtained using a collection of SARS-CoV genomes from human and civet hosts (as well as a few closely related bat genomes), which implies that evolutionary rates were predominantly informed by the short-term SARS outbreak scale and probably biased upwards. Indeed, the rates reported by these studies are in line with the short-term SARS rates that we estimate (Fig. 4). The estimated divergence times for the pangolin virus most closely related to the SARS-CoV-2/RaTG13 lineage

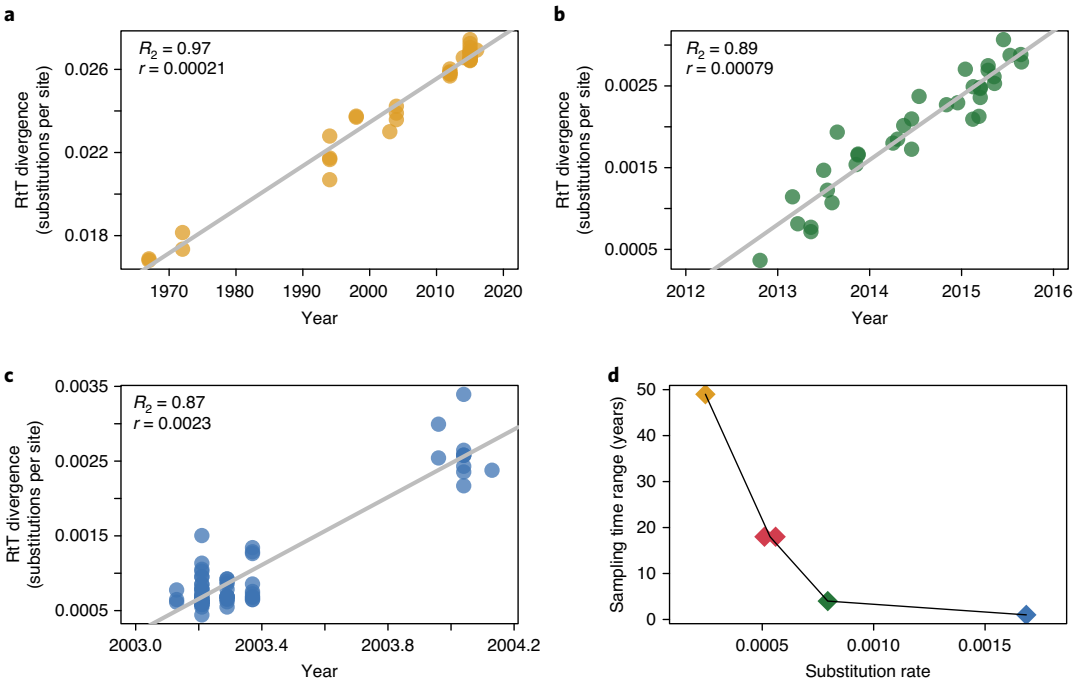

Fig. 4 | Temporal signal and mean evolutionary rate estimates for coronaviruses HCoV-OC43, MERS and SARS. a–c, Root-to-tip (RtT) divergence as a function of sampling time for the three coronavirus evolutionary histories unfolding over different timescales (HCoV-OC43 (n = 37; **a**) MERS (n = 35; **b**) and SARS (n = 69; **c**)). Decimal years are shown on the x axis for the 1.2 years of SARS sampling in **c**. **d**, Mean evolutionary rate estimates plotted against sampling time range for the same three datasets (represented by the same colour as the data points in their respective RtT divergence plots), as well as for the comparable NRA3 using the two different priors for the rate in the Bayesian inference (red points).

range from 1851 (1730–1958) to 1877 (1746–1986), indicating that these pangolin lineages were acquired from bat viruses divergent to those that gave rise to SARS-CoV-2. Current sampling of pangolins does not implicate them as an intermediate host.

Discussion

Identifying the origins of an emerging pathogen can be critical during the early stages of an outbreak, because it may allow for containment measures to be precisely targeted at a stage when the number of daily new infections is still low. Early detection via genomics was not possible during Southeast Asia's initial outbreaks of avian influenza H5N1 (1997 and 2003–2004) or the first SARS outbreak (2002–2003). By 2009, however, rapid genomic analysis had become a routine component of outbreak response. The 2009 influenza pandemic and subsequent outbreaks of MERS-CoV (2012), H7N9 avian influenza (2013), Ebola virus (2014) and Zika virus (2015) were met with rapid sequencing and genomic characterization. For the current pandemic, the 'novel pathogen identification' component of outbreak response delivered on its promise, with viral identification and rapid genomic analysis providing a genome sequence and confirmation, within weeks, that the December 2019 outbreak first detected in Wuhan, China was caused by a coronavirus[3]. Unfortunately, a response that would achieve containment was not possible. Given what was known about the origins of SARS, as well as identification of SARS-like viruses circulating in bats that had binding sites adapted to human receptors[29–31], appropriate measures should have been in place for immediate control of outbreaks of novel coronaviruses. The key to successful surveillance is knowing which viruses to look for and prioritizing those that can readily infect humans[47].

The difficulty in inferring reliable evolutionary histories for coronaviruses is that their high recombination rate[48,49] violates the assumption of standard phylogenetic approaches because different parts of the genome have different histories. To begin characterizing any ancestral relationships for SARS-CoV-2, NRRs of the genome must be identified so that reliable phylogenetic reconstruction and dating can be performed. Evolutionary rate estimation can be profoundly affected by the presence of recombination[50]. Because there is no single accepted method of inferring breakpoints and identifying clean subregions with high certainty, we implemented several approaches to identifying three classic statistical signals of recombination: mosaicism, phylogenetic incongruence and excessive homoplasy[51]. Our most conservative approach attempted to ensure that putative NRRs had no mosaic or phylogenetic incongruence signals. A second breakpoint-conservative approach was conservative with respect to breakpoint identification, but this means that it is accepting of false-negative outcomes in breakpoint inference, resulting in less certainty that a putative NRR truly contains no breakpoints. A third approach attempted to minimize the number of regions removed while also minimizing signals of mosaicism and homoplasy. The origins we present in Fig. 5 (NRR1) are conservative in the sense that NRR1 is more likely to be non-recombinant than NRR2 or NRA3. Because the estimated rates and divergence dates were highly similar in the three datasets analysed, we conclude that our estimates are robust to the method of identifying a genome's NRRs.

Due to the absence of temporal signal in the sarbecovirus datasets, we used informative prior distributions on the evolutionary rate to estimate divergence dates. Calibration of priors can be performed using other coronaviruses (SARS-CoV, MERS-CoV and HCoV-OC43), but estimated rates vary with the timescale of sample collection. In the presence of time-dependent rate variation, a widely observed phenomenon for viruses[43,44,52], slower prior rates appear more appropriate for sarbecoviruses that currently encompass a sampling time range of about 18 years. Our approach resulted in similar posterior rates using two different prior means, implying

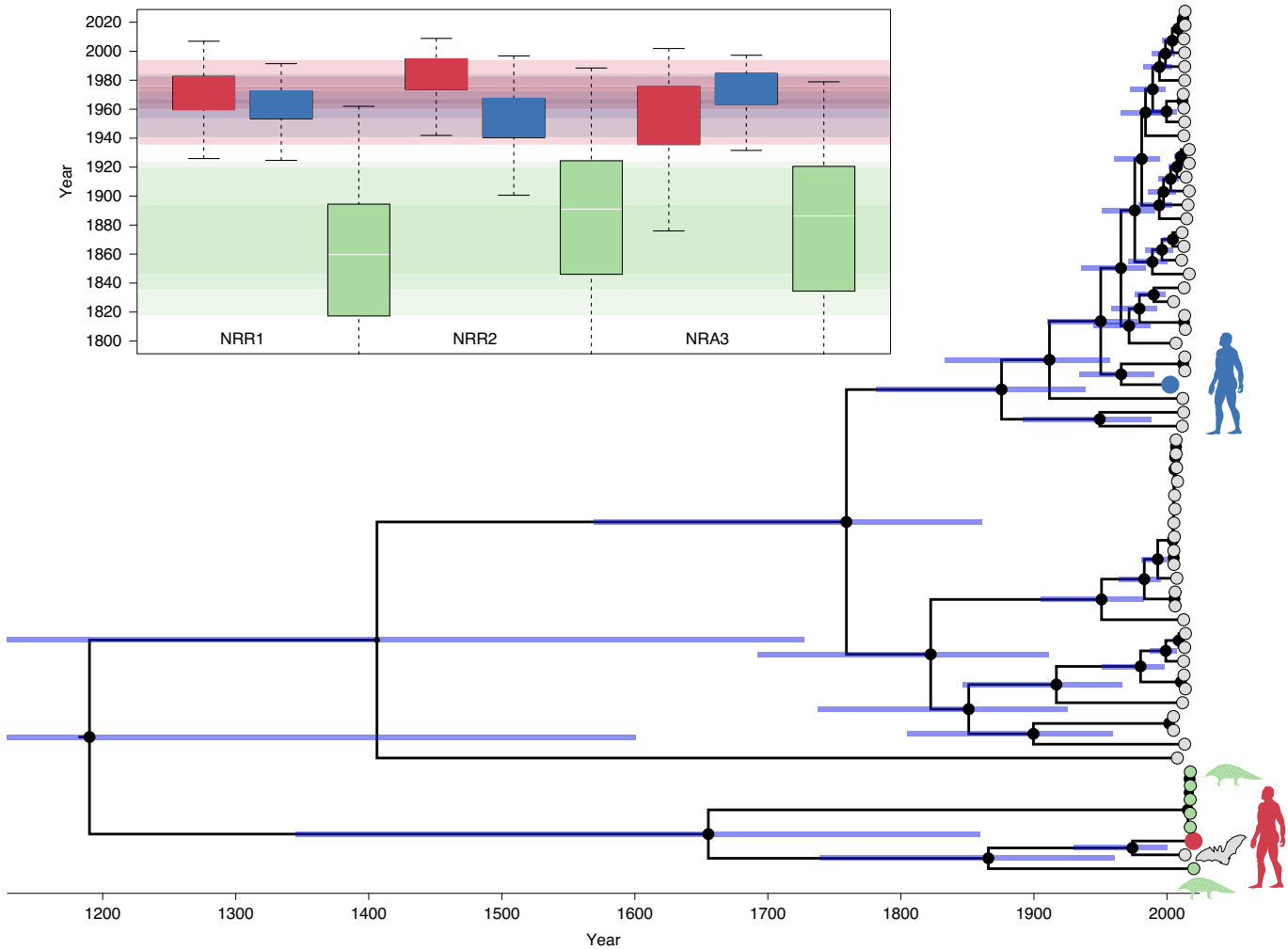

Fig. 5 | Time-measured phylogenetic estimates and divergence times for sarbecovirus lineages using an HCoV-OC43-centred rate prior. The time-calibrated phylogeny represents a maximum clade credibility tree inferred for NRR1. Grey tips correspond to bat viruses, green to pangolin, blue to SARS-CoV and red to SARS-CoV-2. The sizes of the black internal node circles are proportional to the posterior node support. 95% credible interval bars are shown for all internal node ages. The inset represents divergence time estimates based on NRR1, NRR2 and NRA3. The boxplots show divergence time estimates (posterior medians) for SARS-CoV-2 (red) and the 2002–2003 SARS-CoV virus (blue) from their most closely related bat virus. Green boxplots show the TMRCA estimate for the RaTG13/SARS-CoV-2 lineage and its most closely related pangolin lineage (Guangdong 2019). Boxplots show interquartile ranges, white lines are medians and box whiskers show the full range of posterior distribution. Transparent bands of interquartile range width and with the same colours are superimposed to highlight the overlap between estimates. In Extended Data Fig. 4 we compare these divergence time estimates to those obtained using the MERS-CoV-centred rate priors for NRR1, NRR2 and NRA3.

that the sarbecovirus data do inform the rate estimate even though a root-to-tip temporal signal was not apparent.

The relatively fast evolutionary rate means that it is most appropriate to estimate shallow nodes in the sarbecovirus evolutionary history. Accurate estimation of ages for deeper nodes would require adequate accommodation of time-dependent rate variation. While such models have recently been made available, we lack the information to calibrate the rate decline over time (for example, through internal node calibrations[44]). As a proxy, it would be possible to model the long-term purifying selection dynamics as a major source of time-dependent rates[43,44,52], but this is beyond the scope of the current study. The assumption of long-term purifying selection would imply that coronaviruses are in endemic equilibrium with their natural host species, horseshoe bats, to which they are presumably well adapted. While there is evidence of positive selection in the sarbecovirus lineage leading to RaTG13/SARS-CoV-2 (ref. [53]), this is inferred to have occurred before the divergence of RaTG13 and SARS-CoV-2 and thus should not influence our inferences.

Of importance for future spillover events is the appreciation that SARS-CoV-2 has emerged from the same horseshoe bat subgenus that harbours SARS-like coronaviruses. Another similarity between SARS-CoV and SARS-CoV-2 is their divergence time (40–70 years ago) from currently known extant bat virus lineages (Fig. 5). This long divergence period suggests there are unsampled virus lineages circulating in horseshoe bats that have zoonotic potential due to the ancestral position of the human-adapted contact residues in the SARS-CoV-2 RBD. Without better sampling, however, it is impossible to estimate whether or how many of these additional lineages exist. While there is involvement of other mammalian species—specifically pangolins for SARS-CoV-2—as a plausible conduit for transmission to humans, there is no evidence that pangolins are facilitating adaptation to humans. A hypothesis of snakes as intermediate hosts of SARS-CoV-2 was posited during the early epidemic phase[54], but we found no evidence of this[55,56]; see Extended Data Fig. 5.

With horseshoe bats currently the most plausible origin of SARS-CoV-2, it is important to consider that sarbecoviruses cir-

culate in a variety of horseshoe bat species with widely overlapping species ranges[57]. Nevertheless, the viral population is largely spatially structured according to provinces in the south and southeast on one lineage, and provinces in the centre, east and northeast on another (Fig. 3). This boundary appears to be rarely crossed. Two exceptions can be seen in the relatively close relationship of Hong Kong viruses to those from Zhejiang Province (with two of the latter, CoVZC45 and CoVZXC21, identified as recombinants) and a recombinant virus from Sichuan for which part of the genome (region B of SC2018 in Fig. 3) clusters with viruses from provinces in the centre, east and northeast of China. SARS-CoV-2 and RaTG13 are also exceptions because they were sampled from Hubei and Yunnan, respectively. The fact that they are geographically relatively distant is in agreement with their somewhat distant TMRCA, because the spatial structure suggests that migration between their locations may be uncommon. From this perspective, it may be useful to perform surveillance for more closely related viruses to SARS-CoV-2 along the gradient from Yunnan to Hubei.

It is clear from our analysis that viruses closely related to SARS-CoV-2 have been circulating in horseshoe bats for many decades. The unsampled diversity descended from the SARS-CoV-2/RaTG13 common ancestor forms a clade of bat sarbecoviruses with generalist properties—with respect to their ability to infect a range of mammalian cells—that facilitated its jump to humans and may do so again. Although the human ACE2-compatible RBD was very likely to have been present in a bat sarbecovirus lineage that ultimately led to SARS-CoV-2, this RBD sequence has hitherto been found in only a few pangolin viruses. Furthermore, the other key feature thought to be instrumental in the ability of SARS-CoV-2 to infect humans—a polybasic cleavage site insertion in the S protein—has not yet been seen in another close bat relative of the SARS-CoV-2 virus.

The existing diversity and dynamic process of recombination amongst lineages in the bat reservoir demonstrate how difficult it will be to identify viruses with potential to cause major human outbreaks before they emerge. This underscores the need for a global network of real-time human disease surveillance systems, such as that which identified the unusual cluster of pneumonia in Wuhan in December 2019, with the capacity to rapidly deploy genomic tools and functional studies for pathogen identification and characterization.

Methods

Dataset compilation. *Sarbecovirus data.* Complete genome sequence data were downloaded from GenBank and ViPR; accession numbers of all 68 sequences are available in Supplementary Table 4. Sequences were aligned by MAFFT[58] v.7.310, with a final alignment length of 30,927, and used in the analyses below.

HCoV-OC43. We compiled a dataset including 27 human coronavirus OC43 virus genomes and ten related animal virus genomes (six bovine, three white-tailed deer and one canine virus). The canine viral genome was excluded from the Bayesian phylogenetic analyses because temporal signal analyses (see below) indicated that it was an outlier.

MERS-CoV. We extracted a similar number ($n = 35$) of genomes from a MERS-CoV dataset analysed by Dudas et al.[59] using the phylogenetic diversity analyser tool[60] (v.0.5).

SARS-CoV. We compiled a set of 69 SARS-CoV genomes including 58 sampled from humans and 11 sampled from civets and raccoon dogs. This dataset comprises an updated version of that used in Hon et al.[15] and includes a cluster of genomes sampled in late 2003 and early 2004, but the evolutionary rate estimate without this cluster (0.00175 substitutions per site yr^{-1} (0.00117,0.00229)) is consistent with the complete dataset (0.00169 substitutions per site yr^{-1}, (0.00131,0.00205)).

Sarbecovirus, HCoV-OC43 and SARS-CoV data were assembled from GenBank to be as complete as possible, with sampling year as an inclusion criterion. MERS-CoV data were subsampled to match sample sizes with SARS-CoV and HCoV-OC43.

Recombination analysis. Because coronaviruses are known to be highly recombinant, we used three different approaches to identify non-recombinant regions for use in our Bayesian time-calibrated phylogenetic inference.

First, we took an approach that relies on identification of mosaic regions (via 3SEQ[14] v.1.7) that are also supported by PI signals[19]. Because 3SEQ is the most statistically powerful of the mosaic methods[61], we used it to identify the best-supported breakpoint history for each potential child (recombinant) sequence in the dataset. A single 3SEQ run on the genome alignment resulted in 67 out of 68 sequences supporting some recombination in the past, with multiple candidate breakpoint ranges listed for each putative recombinant. Next, we (1) collected all breakpoints into a single set, (2) complemented this set to generate a set of non-breakpoints, (3) grouped non-breakpoints into contiguous BFRs and (4) sorted these regions by length. A phylogenetic tree—using RAxML v8.2.8 (ref. [62,63]), the GTR + Γ model and 100 bootstrap replicates—was inferred for each BFR >500 nt.

We considered (1) the possibility that BFRs could be combined into larger non-recombinant regions and (2) the possibility of further recombination within each BFR.

We named the length-sorted BFRs as: BFR A (nt positions 13,291–19,628, length = 6,338 nt), BFR B (nt positions 3,625–9,150, length = 5,526 nt), BFR C (nt positions 9,261–11,795, length = 2,535 nt), BFR D (nt positions 27,702–28,843, length = 1,142 nt) and six further regions (E–J). Phylogenetic trees and exact breakpoints for all ten BFRs are shown in Supplementary Figs. 1–10. Regions A–C had similar phylogenetic relationships among the southern China bat viruses (Yunnan, Guangxi and Guizhou provinces), the Hong Kong viruses, northern Chinese viruses (Jilin, Shanxi, Hebei and Henan provinces, including Shaanxi), pangolin viruses and the SARS-CoV-2 lineage. Because these subclades had different phylogenetic relationships in region D (Supplementary Fig. 4), that region and shorter BFRs were not included in combined putative non-recombinant regions.

Regions A–C were further examined for mosaic signals by 3SEQ, and all showed signs of mosaicism. In region A, we removed subregion A1 (nt positions 3,872–4,716 within region A) and subregion A4 (nt 1,642–2,113) because both showed PI signals with other subregions of region A. After removal of A1 and A4, we named the new region A′. In addition, sequences NC_014470 (Bulgaria 2008), CoVZXC21, CoVZC45 and DQ412042 (Hubei-Yichang) needed to be removed to maintain a clean non-recombinant signal in A′. Region B showed no PI signals within the region, except one including sequence SC2018 (Sichuan), and thus this sequence was also removed from the set. Region C showed no PI signals within it. Combining regions A′, B and C and removing the five named sequences gives us putative NRR1, as an alignment of 63 sequences. We say that this approach is conservative because sequences and subregions generating recombination signals have been removed, and BFRs were concatenated only when no PI signals could be detected between them. The construction of NRR1 is the most conservative as it is least likely to contain any remaining recombination signals.

In our second stage, we wanted to construct non-recombinant regions where our approach to breakpoint identification was as conservative as possible. We call this approach breakpoint-conservative, but note that this has the opposite effect to the construction of NRR1 in that this approach is the most likely to allow breakpoints to remain inside putative non-recombining regions. In other words, a true breakpoint is less likely to be called as such (this is breakpoint-conservative), and thus the construction of a non-recombining region may contain true recombination breakpoints (with insufficient evidence to call them as such). In this approach, we considered a breakpoint as supported only if it had three types of statistical support: from (1) mosaic signals identified by 3SEQ, (2) PI signals identified by building trees around 3SEQ's breakpoints and (3) the GARD algorithm[35], which identifies breakpoints by identifying PI signals across proposed breakpoints. Because 3SEQ identified ten BFRs >500 nt, we used GARD's (v.2.5.0) inference on 10, 11 and 12 breakpoints. A reduced sequence set of 25 sequences chosen to capture the breadth of diversity in the sarbecoviruses (obvious recombinants not involving the SARS-CoV-2 lineage were also excluded) was used because GARD is computationally intensive. GARD identified eight breakpoints that were also within 50 nt of those identified by 3SEQ. PI signals were identified (with bootstrap support >80%) for seven of these eight breakpoints: positions 1,684, 3,046, 9,237, 11,885, 21,753, 22,773 and 24,628. Using these breakpoints, the longest putative non-recombining segment (nt 1,885–21,753) is 9.9 kb long, and we call this region NRR2.

Our third approach involved identifying breakpoints and masking minor recombinant regions (with gaps, which are treated as unobserved characters in probabilistic phylogenetic approaches). Specifically, we used a combination of six methods implemented in v.5.5 of RDP5 (ref. [36]) (RDP, GENECONV, MaxChi, Bootscan, SisScan and 3SEQ) and considered recombination signals detected by more than two methods for breakpoint identification. Except for specifying that sequences are linear, all settings were kept to their defaults. Based on the identified breakpoints in each genome, only the major non-recombinant region is kept in each genome while other regions are masked. To evaluate the performance procedure, we confirmed that the recombination masking resulted in (1) a markedly different outcome of the PHI test[64], (2) removal of well-supported (bootstrap value >95%) incompatible splits in Neighbor-Net[65] and (3) a

near-complete reduction of mosaic signal as identified by 3SEQ. If the latter still identified non-negligible recombination signal, we removed additional genomes that were identified as major contributors to the remaining signal. This produced non-recombining alignment NRA3, which included 63 of the 68 genomes.

Bayesian divergence time estimation. We focused on these three non-recombining regions/alignments for divergence time estimation; this avoids inappropriate modelling of evolutionary processes with recombination on strictly bifurcating trees, which can result in different artefacts such as homoplasies that inflate branch lengths and lead to apparently longer evolutionary divergence times. To examine temporal signal in the sequenced data, we plotted root-to-tip divergence against sampling time using TempEst[39] v.1.5.3 based on a maximum likelihood tree. The latter was reconstructed using IQTREE[66] v.2.0 under a general time-reversible (GTR) model with a discrete gamma distribution to model inter-site rate variation.

Time-measured phylogenetic reconstruction was performed using a Bayesian approach implemented in BEAST[42] v.1.10.4. When the genomic data included both coding and non-coding regions we used a single GTR + Γ substitution model; for concatenated coding genes we partitioned the alignment by codon position and specified an independent GTR + Γ model for each partition with a separate gamma model to accommodate inter-site rate variation. We used an uncorrelated relaxed clock model with log-normal distribution for all datasets, except for the low-diversity SARS data for which we specified a strict molecular clock model. For the HCoV-OC43, MERS-CoV and SARS datasets we specified flexible skygrid coalescent tree priors. In the absence of any reasonable prior knowledge on the TMRCA of the sarbecovirus datasets (which is required for grid specification in a skygrid model), we specified a simpler constant size population prior. As informative rate priors for the analysis of the sarbecovirus datasets, we used two different normal prior distributions: one with a mean of 0.00078 and s.d. = 0.00075 and one with a mean of 0.00024 and s.d. = 0.00025. These means are based on the mean rates estimated for MERS-CoV and HCoV-OC43, respectively, while the standard deviations are set ten times higher than empirical values to allow greater prior uncertainty and avoid strong bias (Extended Data Fig. 3). In our analyses of the sarbecovirus datasets, we incorporated the uncertainty of the sampling dates when exact dates were not available. To estimate non-synonymous over synonymous rate ratios for the concatenated coding genes, we used the empirical Bayes Renaissance counting'procedure[67]. Temporal signal was tested using a recently developed marginal likelihood estimation procedure[41] (Supplementary Table 1).

Posterior distributions were approximated through Markov chain Monte Carlo sampling, which were run sufficiently long to ensure effective sampling sizes >100. BEAST inferences made use of the BEAGLE v.3 library[68] for efficient likelihood computations. We used TreeAnnotator to summarize posterior tree distributions and annotated the estimated values to a maximum clade credibility tree, which was visualized using FigTree.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

All sequence data analysed in this manuscript are available at https://github.com/plemey/SARSCoV2origins. Note that six of these sequences fall under the terms of use of the GISAID platform.

Code availability

All custom code used in the manuscript is available at https://github.com/plemey/SARSCoV2origins.

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Author contributions

All authors contributed to analyses and interpretations. D.L.R. and X.J. performed recombination and phylogenetic analysis and annotated virus names with geographical and sampling dates. A.R. performed S recombination analysis. B.W.P. and T.A.C. performed codon usage analysis. M.F.B. performed recombination analysis for non-recombining regions 1 and 2, breakpoint analysis and phylogenetic inference on recombinant segments. P.L. performed recombination analysis for non-recombining alignment 3, calibration of rate of evolution and phylogenetic reconstruction and dating. T.T.-Y.L. collected SARS-CoV data and assisted in analyses of SARS-CoV and SARS-CoV-2 data. M.F.B., P.L. and D.L.R. wrote the first draft of the manuscript, and all authors contributed to manuscript editing.

Competing interests

The authors declare no competing interests.

Additional information

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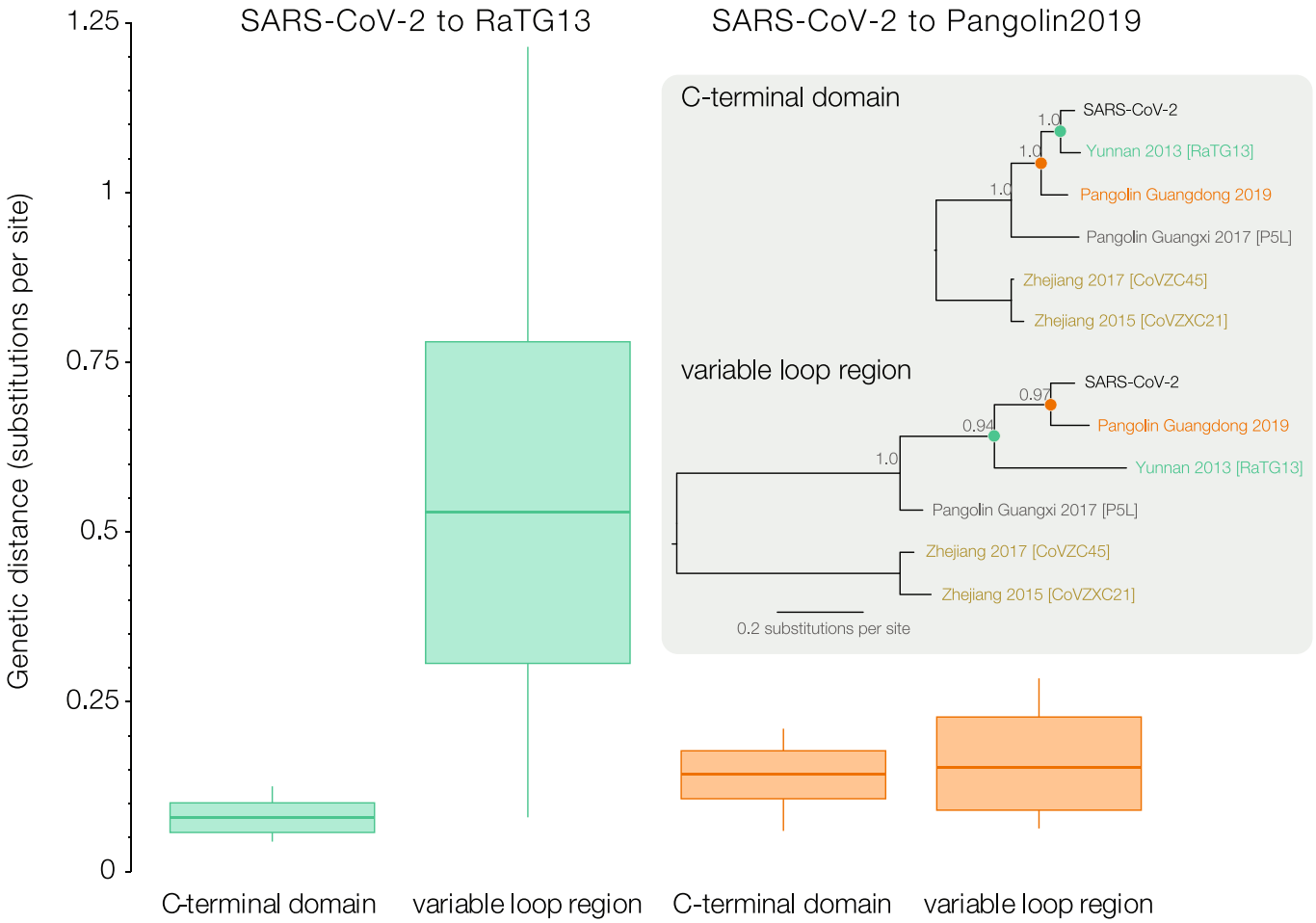
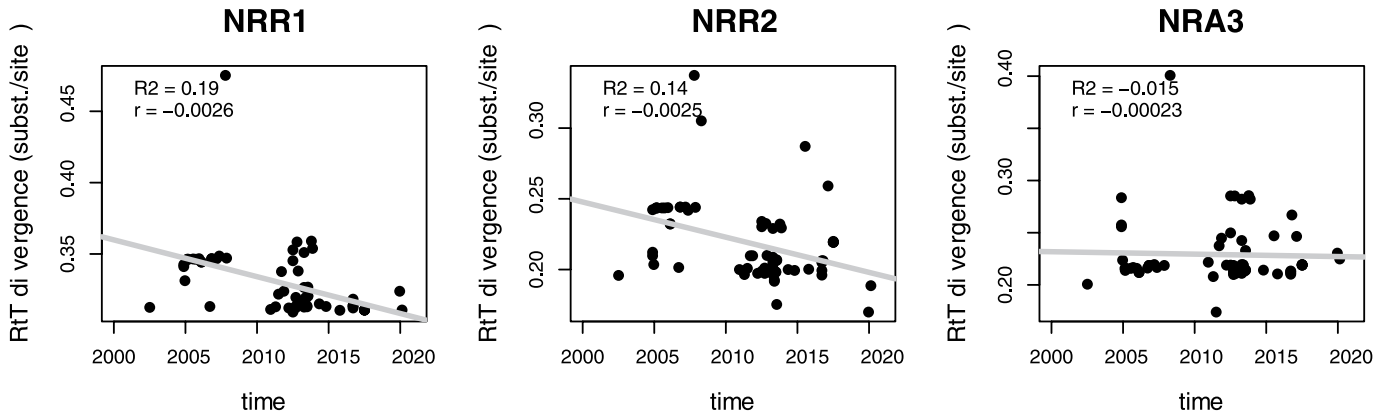
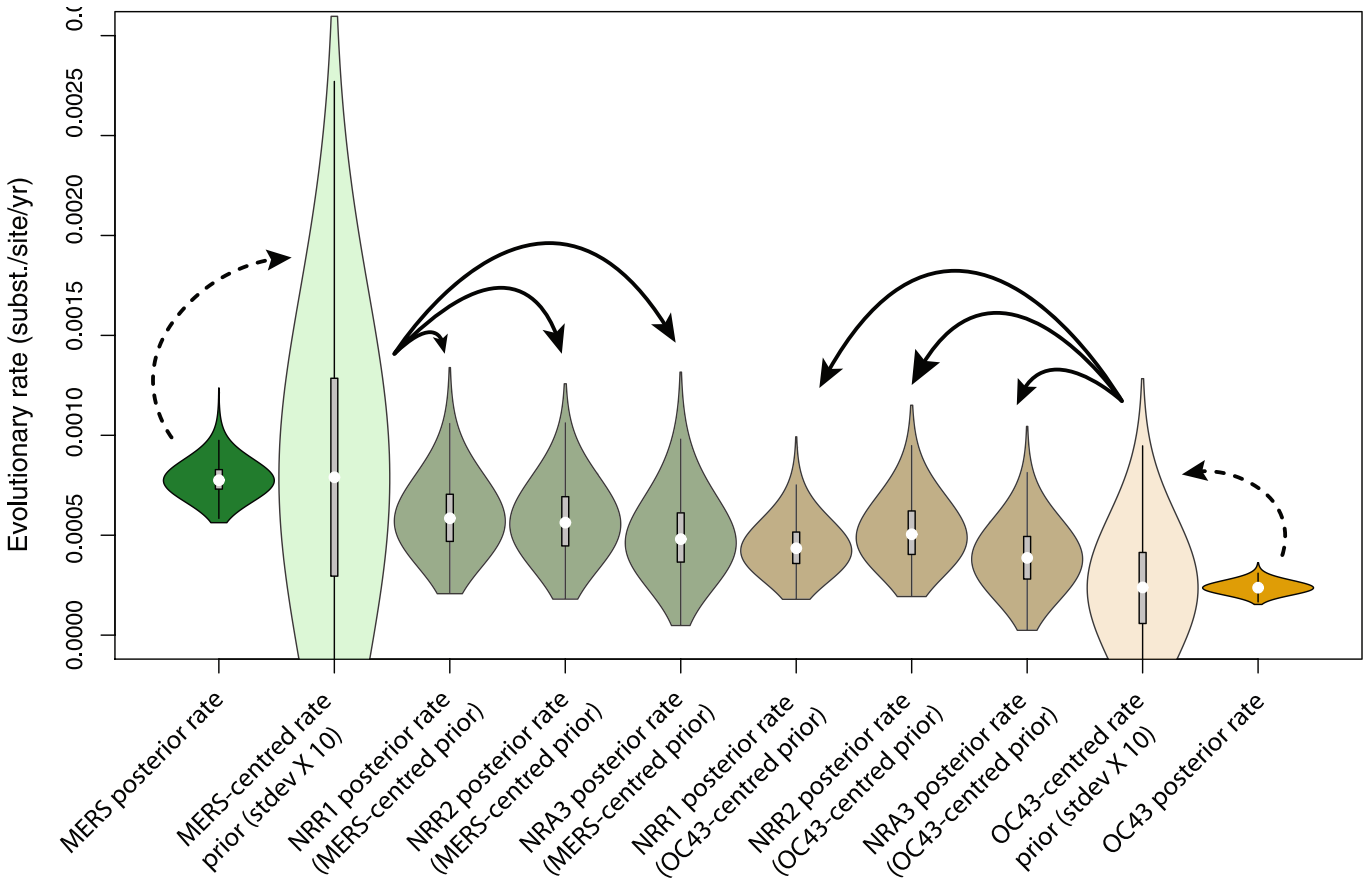


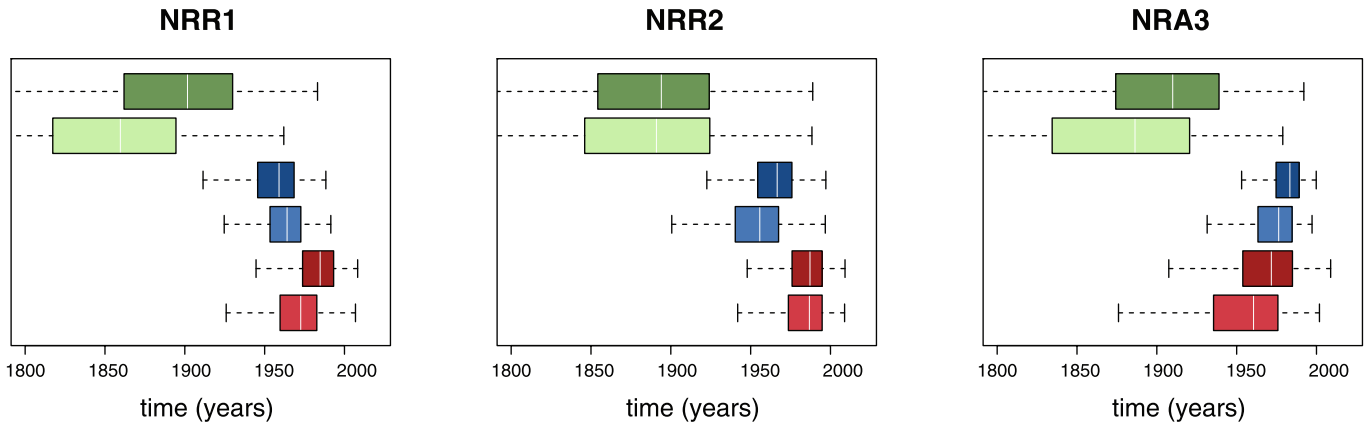
Extended Data Fig. 1 | Phylogenetic relationships in the C-terminal domain (CTD). Posterior means (horizontal bars) of patristic distances between SARS-CoV-2 and its closest bat and pangolin sequences, for the spike protein's variable loop region and CTD region excluding the variable loop. Boxes show 95% HPD credible intervals. Means and 95% HPD intervals are 0.080 [0.058–0.101] and 0.530 [0.304–0.780] for the patristic distances between SARS-CoV-2 and RaTG13 (green) and 0.143 [0.109–0.180] and 0.154 [0.093–0.231] for the patristic distances between SARS-CoV-2 and Pangolin 2019 (orange). Gray inset shows majority rule consensus trees with mean posterior branch lengths for the two regions, with posterior probabilities on the key nodes showing the relationships among SARS-CoV-2, RaTG13, and Pangolin 2019.



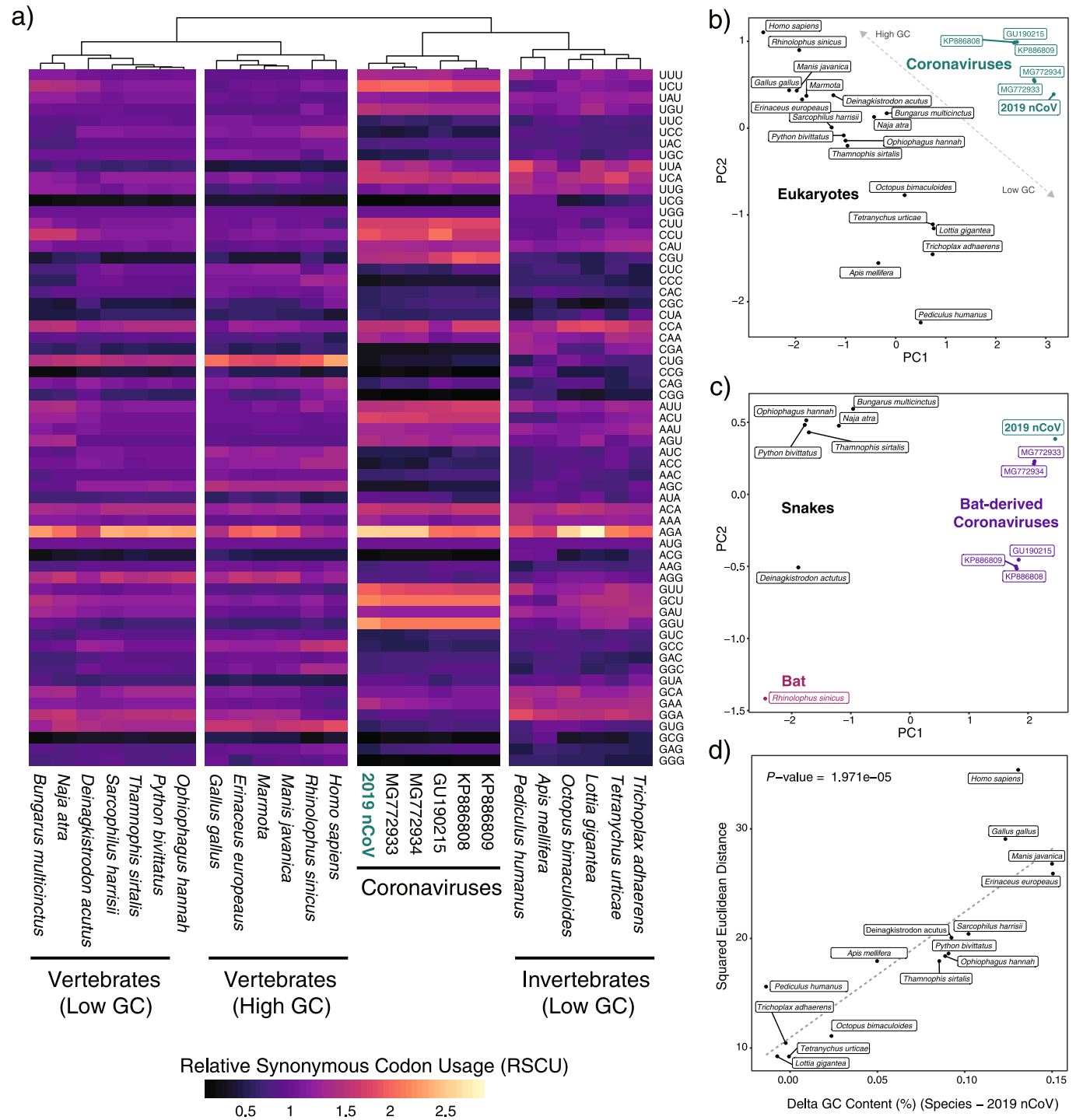
Extended Data Fig. 2 | Lack of root-to-tip temporal signal in SARS-CoV-2. Root-to-tip divergence as a function of sampling time for non-recombinant regions **NRR1** and **NRR2** and recombination-masked alignment set **NRA3**. The plots are based on maximum likelihood tree reconstructions with a root position that maximises the residual mean squared for the regression of root-to-tip divergence and sampling time.



Extended Data Fig. 3 | Priors and posteriors for evolutionary rate of SARS-CoV-2. Posterior rate distributions for MERS-CoV (far left) and HCoV-OC43 (far right) using BEAST on $n = 27$ sequences spread over 4 years (MERS-CoV) and $n = 27$ sequences spread over 49 years (HCoV-OC43). As illustrated by the dashed arrows, these two posteriors motivate our specification of prior distributions with standard deviations inflated 10-fold (light color). These rate priors are subsequently used in the Bayesian inference of posterior rates for **NRR1, NRR2**, and **NRA3** as indicated by the solid arrows.



Extended Data Fig. 4 | TMRCAs for SARS-CoV and SARS-CoV-2. Divergence time estimates based on the three regions/alignments where the effects of recombination have been removed. The red and blue boxplots represent the divergence time estimates for SARS-CoV-2 (red) and the 2002-2003 SARS-CoV (blue) from their most closely related bat virus, with the light- and dark-colored versions based on the HCoV-OC43 and MERS-CoV centered priors, respectively. Green boxplots show the TMRCA estimate for the RaTG13/SARS-CoV-2 lineage and its most closely related pangolin lineage (Guangdong 2019), with the light and dark coloured version based on the HCoV-OC43 and MERS-CoV centred priors, respectively. TMRCA estimates for SARS-CoV-2 and SARS-CoV from their respective most closely related bat lineages are reasonably consistent for the different data sets and different rate priors in our analyses. Posterior means with 95% HPDs are shown in Supplementary Information Table 2.



Extended Data Fig. 5 | Comparisons of GC content across taxa. Conducting analogous analyses of codon usage bias as Ji et al. (2020) with additional (and higher quality) snake coding sequence data and several miscellaneous eukaryotes with low genomic GC content failed to find any meaningful clustering of the SARS-CoV-2 with snake genomes (**a**). Instead, similarity in codon usage metrics between the SARS-CoV-2 and eukaryotes analyzed was correlated with coding sequence GC content of the eukaryote, with more similar codon usage being identified in eukaryotes with low GC content similar to that of the coronavirus (**b**).

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☒	☐ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☒	☐ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☐	☒ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	All in Methods section of paper.
Data analysis	Software used: RAxML (v8.2.8), 3SEQ (v1.7), RDP5 (v5), GARD (v2.5.0), BEAST (v1.10.4), BEAGLE (v3), MAFFT (v7.310), Neighbor-Nets (SplitsTree v4.15.1), PHI-Test (SplitsTree v4.15.1), IQTREE (v2.0), TempEst (v1.5.3), Tree Annotator (v1.10.4), FigTree(v1.4.2), Phylogenetic Diversity Analyzer Tool (v0.5), BBMap (v38.75), pheatmap (v1.0.12). All custom code available at https://github.com/plemey/SARSCoV2origins

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- All sequence data are available in GenBank and GISAID, with accession numbers listed in Supplementary Table S4.

All sequence data analyzed in this manuscript are available at https://github.com/plemey/SARSCoV2origins. Note that one of the sequences requires GISAID permissions from original authors, but will be made available either individually or publicly depending on original depositor's request.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☐ Life sciences ☐ Behavioural & social sciences ☒ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Ecological, evolutionary & environmental sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	Sarbecovirus genomes were downloaded from publicly available sources. Non-recombinant regions were identified. Evolutionary rate calibration for coronaviruses was performed using publicly available data sets for SARS, MERS, and OC43. An evolutionary rate was inferred for three putative non-recombinant regions of the sarbecoviruses. Time to the most common ancestor between SARS-CoV-2 and its closest bat-virus relative were computed.
Research sample	All available genomes (n=68) for sarbecoviruses -- including the SARS-CoV-2 genome; 27 genomes of human coronavirus OC43; 35 genomes of MERC-CoV; 69 genomes of SARS-CoV.
Sampling strategy	No sample size calculation was done as it was possible to use all samples (all available sequences) in the analysis.
Data collection	Publicly available sequence data were downloaded from GenBank and GISAID.
Timing and spatial scale	Sarbecovirus genomes were collected over an 18-year period (2002-2020), OC43 sequences from 1968 to 2016, MERS sequences from 2012 to 2015, and SARS-CoV sequences from 2002-2004.
Data exclusions	Sequences without 'sampling year' were excluded. This exclusion criterion was not formally pre-established, but this exclusion is both common and necessary when estimating evolutionary rates from sequence data. It goes without saying that sequences without dates must be excluded.
Reproducibility	N/A;
Randomization	N/A
Blinding	N/A

Did the study involve field work? ☐ Yes ☒ No

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

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Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility

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ABSTRACT

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can spread rapidly within skilled nursing facilities. After identification of a case of Covid-19 in a skilled nursing facility, we assessed transmission and evaluated the adequacy of symptom-based screening to identify infections in residents.

METHODS

We conducted two serial point-prevalence surveys, 1 week apart, in which assenting residents of the facility underwent nasopharyngeal and oropharyngeal testing for SARS-CoV-2, including real-time reverse-transcriptase polymerase chain reaction (rRT-PCR), viral culture, and sequencing. Symptoms that had been present during the preceding 14 days were recorded. Asymptomatic residents who tested positive were reassessed 7 days later. Residents with SARS-CoV-2 infection were categorized as symptomatic with typical symptoms (fever, cough, or shortness of breath), symptomatic with only atypical symptoms, presymptomatic, or asymptomatic.

RESULTS

Twenty-three days after the first positive test result in a resident at this skilled nursing facility, 57 of 89 residents (64%) tested positive for SARS-CoV-2. Among 76 residents who participated in point-prevalence surveys, 48 (63%) tested positive. Of these 48 residents, 27 (56%) were asymptomatic at the time of testing; 24 subsequently developed symptoms (median time to onset, 4 days). Samples from these 24 presymptomatic residents had a median rRT-PCR cycle threshold value of 23.1, and viable virus was recovered from 17 residents. As of April 3, of the 57 residents with SARS-CoV-2 infection, 11 had been hospitalized (3 in the intensive care unit) and 15 had died (mortality, 26%). Of the 34 residents whose specimens were sequenced, 27 (79%) had sequences that fit into two clusters with a difference of one nucleotide.

CONCLUSIONS

Rapid and widespread transmission of SARS-CoV-2 was demonstrated in this skilled nursing facility. More than half of residents with positive test results were asymptomatic at the time of testing and most likely contributed to transmission. Infection-control strategies focused solely on symptomatic residents were not sufficient to prevent transmission after SARS-CoV-2 introduction into this facility.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Jernigan at the Centers for Disease Control and Prevention, 1600 Clifton Rd., Mailstop A-31, Atlanta, GA 30333, or at jqj9@cdc.gov.

*A complete list of the investigators is included in the Supplementary Appendix, available at NEJM.org.

Ms. Arons and Ms. Hatfield contributed equally to this article.

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The first reported case of coronavirus disease 2019 (Covid-19) in the United States was diagnosed in a resident of Snohomish County, Washington, on January 20, 2020.[1] In late February, an outbreak was identified in a skilled nursing facility in neighboring King County; morbidity and mortality among residents were high, straining the regional health care system.[2,3]

We report another outbreak of Covid-19 in a separate skilled nursing facility in the same county. In the course of this outbreak investigation, Public Health–Seattle and King County (PHSKC) and the Centers for Disease Control and Prevention (CDC) identified residents with asymptomatic SARS-CoV-2 infection, which prompted further investigation. We performed serial point-prevalence surveys to assess the extent of transmission and to evaluate the adequacy of symptom-based screening of residents to identify infections. Initial findings of this investigation were previously reported.[4]

Description of the Outbreak

On February 29, 2020, in response to increased local awareness of Covid-19 in King County, Washington, administrative leadership at Facility A instituted enhanced infection-control measures. Nursing staff assessed residents twice daily for possible signs and symptoms of Covid-19, including fever (oral or temporal temperature measurement), cough, shortness of breath, and other symptoms. Health care personnel were assessed at the start of each shift with oral temperature measurement and screening for symptoms, including cough, shortness of breath, sore throat, or any other respiratory symptoms.

On March 1, one member of the health care staff tested positive for SARS-CoV-2 after having worked in a single unit (Unit 1) while symptomatic on February 26, the first day of symptoms, and on February 28. On March 5, the facility was informed that a hospitalized resident of Unit 1 (in whom symptoms had developed on March 2 and testing was done on March 3) had been diagnosed with Covid-19. Subsequently, all visitors were restricted and communal activities were canceled. PHSKC and the CDC initiated an outbreak investigation, and on March 6, provided on-site infection prevention and control recommendations, including the recommendation that all health care staff entering symptomatic residents' rooms wear eye protection, a gown, gloves, and a face mask (N95 respirators were not routinely available).[5] On March 8, the CDC and PHSKC offered testing to all residents in Unit 1; 13 of 15 residents present were tested for SARS-CoV-2 (2 residents declined). A total of 6 residents tested positive; of these, 4 had symptoms (e.g., fever, cough, shortness of breath, or sore throat) and 2 had been asymptomatic during the preceding 14 days. On March 9, the facility implemented Covid-19 transmission-based precautions for all residents of Unit 1, regardless of symptoms or infection status.

Methods

Study Population

Facility A is a 116-bed skilled nursing facility divided into four separate units with an equal mix of short- and long-term residents in each unit. There were 89 residents present at Facility A on March 3, the date of the first positive test in a resident. Facility A provided a list of full-time health care personnel by occupation. Results of positive SARS-CoV-2 tests obtained during postmortem examination or by outside health care providers during clinical evaluation of symptomatic residents and staff were provided to the CDC and PHSKC through March 26. All symptomatic health care personnel were advised to be tested by their health care provider; asymptomatic staff members were not tested as part of this investigation.

Point-Prevalence Surveys

On two occasions, residents in the facility were offered SARS-CoV-2 testing as part of a facility-wide point-prevalence survey. The first survey was performed for all assenting residents, including those who had previously tested positive, on March 13 (10 days after the first resident had tested positive for SARS-CoV-2). Nasopharyngeal and oropharyngeal swabs were collected in accordance with CDC guidelines.[6] A second survey was conducted 7 days later (March 19–20) for residents who had had either a negative test result or a positive result with atypical or no symptoms reported in the first survey.

Symptom Assessment

On the day of point-prevalence surveys, a standardized symptom-assessment form was completed by nurses for each resident tested. Symptoms present during the preceding 14 days were recorded on

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the basis of interview and review of medical records. Asymptomatic residents with a positive test result were reassessed for symptoms 7 days later. For additional details on symptom assessment, see the Supplementary Appendix, available with the full text of this article at NEJM.org.

Residents were classified as symptomatic if they had had at least one new or worsened typical or atypical symptom of Covid-19 in the preceding 14 days. Residents with subjective fever or temperature greater than 100.0°F (37.8°C), cough, or shortness of breath were classified as symptomatic with typical symptoms.[7] Residents were classified as symptomatic with atypical symptoms if their symptoms included only chills, malaise, increased confusion, rhinorrhea, nasal congestion, sore throat, myalgia, dizziness, headache, nausea, or diarrhea.

Asymptomatic residents were those who had no symptoms or only stable chronic symptoms (e.g., chronic cough without worsening). Presymptomatic residents were those who were asymptomatic at the time of testing but developed symptoms within 7 days after testing. Residents who did not develop symptoms in the 7 days after testing remained classified as asymptomatic.

LABORATORY TESTING

The Washington State Public Health Laboratory performed one-step real-time reverse transcriptase–polymerase chain reaction (rRT-PCR) on all samples, using the SARS-CoV-2 CDC assay protocol; cycle threshold (Ct) values were reported for two genetic markers: the N1 and N2 viral nucleocapsid protein gene regions.[8,9] Values below 40 cycles indicate a positive result for SARS-CoV-2.

All rRT-PCR–positive specimens from point-prevalence surveys were shipped to the CDC for viral culture using Vero-CCL-81 cells. Cells showing cytopathic effect were used for SARS-CoV-2 rRT-PCR to confirm isolation and viral growth in culture. Nucleic acid was extracted from rRT-PCR–positive specimens and amplified for subsequent sequencing (Oxford Nanopore MinION), with phylogenetic trees inferred with the neighbor-joining method.[10] Additional details on culture and sequencing methods are provided in the Supplementary Appendix.

ANALYSES

The daily proportions of residents with any known positive test for SARS-CoV-2 (including those tested as part of clinical management) were described according to their unit in the facility. The daily growth rate for the facility was estimated through regression analysis, using the log-transformed daily cumulative counts of all residents who were positive for SARS-CoV-2 from March 3 through March 20; doubling time was estimated by dividing the natural logarithm of 2 by the growth rate. Similarly, doubling time was estimated for all residents of King County, using case count data reported through the PHSKC Covid-19 data dashboard.[11]

All analyses were completed with SAS software, version 9.4 (SAS Institute). Data were collected as part of public health response and were deemed non–human subjects research by the CDC.

RESULTS

RESIDENTS

Of the 89 residents who lived in Facility A when the first resident with confirmed Covid-19 was tested, 57 (64%) had tested positive for SARS-CoV-2 either during the point-prevalence surveys, clinical evaluation, or postmortem examination as of March 26. Seventy-six residents participated in the first point-prevalence survey on March 13 (Fig. 1). Of these 76 residents, 48 (63%) tested positive in either the initial or subsequent point-prevalence surveys. Demographic characteristics, coexisting conditions, and symptoms of surveyed residents were similar, regardless of test result (Table 1).

Of the 48 residents who tested positive from the surveys, 17 (35%) reported typical symptoms, 4 (8%) reported only atypical symptoms, and 27 (56%) reported no new symptoms or changes in chronic symptoms at the time of testing (Table 1 and Table S1). Among the 27 residents classified as asymptomatic, 15 reported no symptoms and 12 reported only stable chronic symptoms. Fifteen (56%) residents who were asymptomatic at the time of testing had documented cognitive impairment; similar proportions were reported in symptomatic residents (Table S2).

In the 7 days after their positive test, 24 of the 27 asymptomatic residents (89%) had onset of symptoms and were recategorized as presymptomatic. The median time to symptom onset was 4 days (interquartile range, 3 to 5). The most common new symptoms were fever (71%), cough (54%), and malaise (42%) (Table S3).

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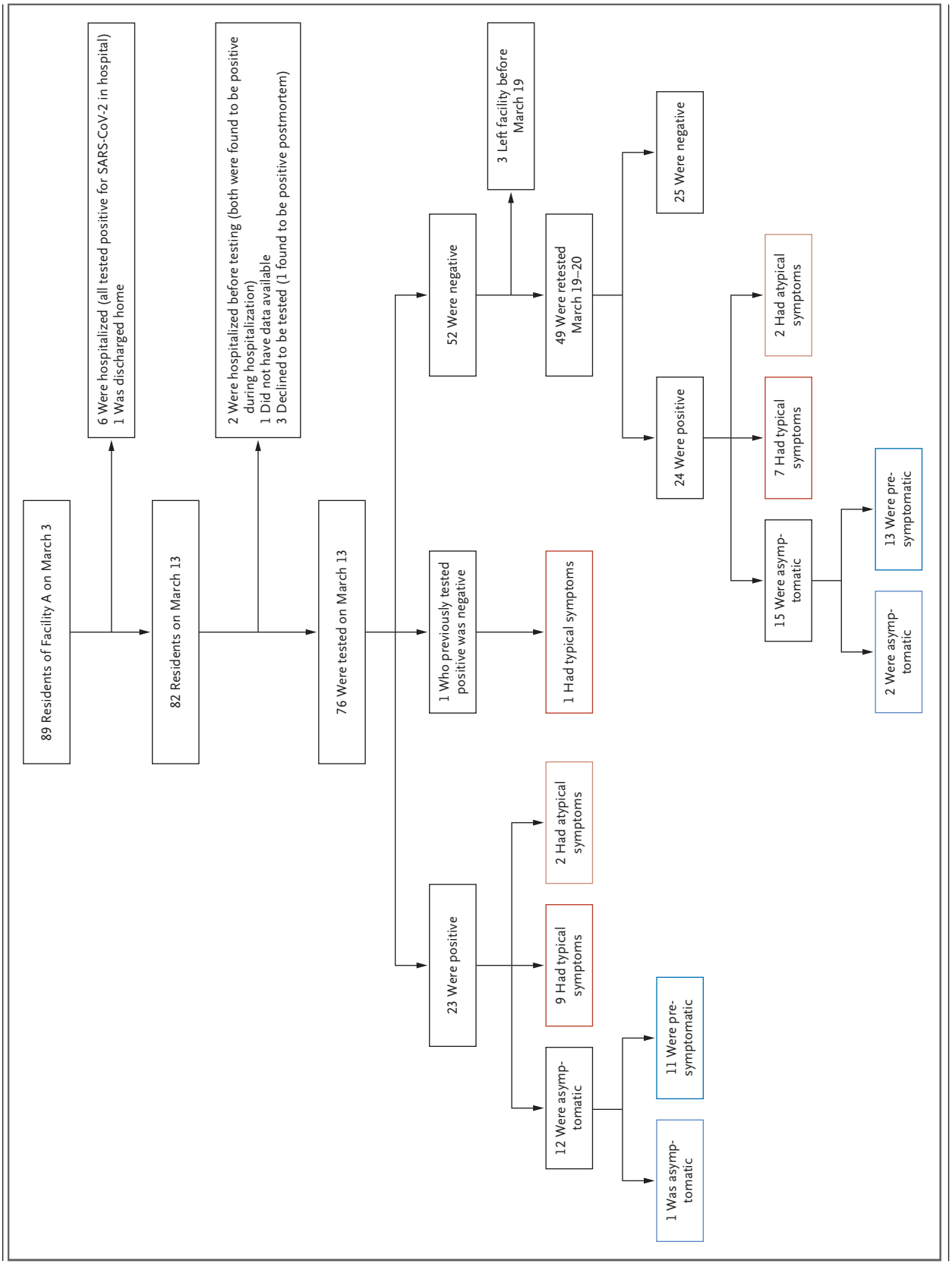

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Figure 1 (facing page). Residents in Facility A on March 3 through Two Point-Prevalence Surveys.

Shown are all 89 residents who lived in skilled nursing facility A from March 3, when the first resident tested positive for SARS-CoV-2. By March 13, the date of the first point-prevalence survey, 82 residents remained in the facility, and 76 were tested. By the second point-prevalence survey, 48 of the 76 residents tested in the point-prevalence surveys had been identified as positive. Overall, 57 residents were positive as of March 26. Cycle threshold values were available for 47 residents who tested positive in the point-prevalence surveys on March 13 and March 19–20.

CYCLE THRESHOLD AND VIRAL CULTURE

rRT-PCR Ct values for the N1 genetic markers for 47 residents ranged from 13.7 to 37.9; median Ct values for the four symptom status groups were similar (asymptomatic residents, 25.5; presymptomatic residents, 23.1; residents with atypical symptoms, 24.2; and residents with typical symptoms, 24.8) (Fig. 2). SARS-CoV-2 growth was identified from 31 of 46 rRT-PCR–positive specimens (Fig. 2). Viral growth was observed for specimens obtained from 10 of 16 residents with typical symptoms, 3 of 4 with atypical symptoms, 17 of

Table 1. Demographic Characteristics and Reported Symptoms in Residents of Facility A at the Time of Testing.*

Characteristics	SARS-CoV-2 Test Results	
	Positive† (N=48)	Negative‡ (N=28)
Overall		
Positive result during initial facility-wide cohort testing — no. (%)	23 (48)	—
Mean age (±SD) — yr	78.6±9.5	73.8±11.5
Length of stay at Facility A <90 days before testing — no. (%)	23 (48)	14 (50)
Coexisting conditions — no. (%)		
Any coexisting condition	47 (98)	28 (100)
Chronic lung disease	18 (38)	8 (29)
Diabetes	18 (38)	11 (39)
Cardiovascular disease	39 (81)	17 (61)
Cerebrovascular accident	19 (40)	8 (29)
Renal disease	18 (38)	9 (32)
Received hemodialysis	3 (6)	1 (4)
Cognitive impairment	28 (58)	13 (46)
Obesity	11 (23)	6 (21)
Symptoms during the past 14 days — no. (%)		
In symptomatic residents§	21 (44)	11 (39)
At least one typical Covid-19 symptom	17 (35)	8 (29)
Only atypical Covid-19 symptoms	4 (8)	3 (11)
In asymptomatic residents	27 (56)	18 (64)
No symptoms	15 (31)	14 (50)
Only stable, chronic symptoms	12 (25)	3 (11)

* Results include all residents who were present in the facility on March 13 and assented to screening. Facility-wide cohort symptom screens and point-prevalence surveys were performed on March 13 and March 19–20, 2020.

† Residents categorized as positive include those with at least one positive test from facility-wide point-prevalence surveys on March 13 or March 19–20 and one resident who tested negative on March 13 but tested positive before March 13.

‡ Residents categorized as negative include 3 residents who had only one negative swab on March 13 and were not retested.

§ Typical symptoms include fever, cough, and shortness of breath. Atypical symptoms include chills, malaise, sore throat, increased confusion, rhinorrhea or nasal congestion, myalgia, dizziness, headache, nausea, and diarrhea.

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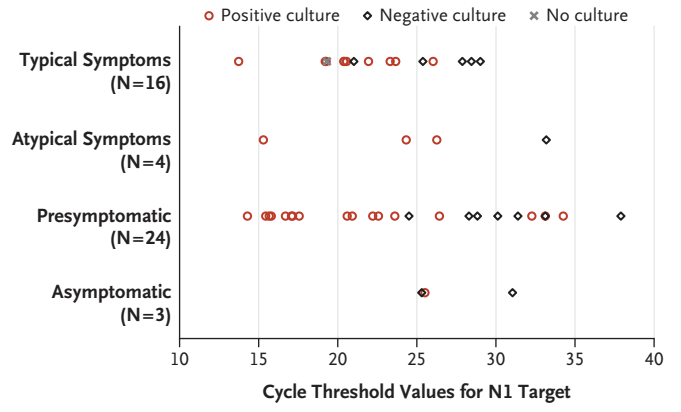

Figure 2. Cycle Threshold Values and Results of Viral Culture for Residents with Positive SARS-CoV-2 Tests According to Their Symptom Status.

Shown are N1 target cycle threshold values and viral culture results for 47 residents' first positive test for SARS-CoV-2 stratified by the resident's symptom status at the time of the test. One positive test was not assessed for culture growth. Typical symptoms include fever, cough, and shortness of breath; atypical symptoms include chills, malaise, increased confusion, rhinorrhea or nasal congestion, myalgia, dizziness, headache, nausea, and diarrhea.

24 who were presymptomatic, and 1 of 3 who remained asymptomatic.

We observed no correlation between Ct values and the number of days from the first evidence of typical symptoms. Ct values consistent with a high viral load were identified among residents who tested positive before typical symptom onset (median Ct value among 26 observations, 24.0; interquartile range, 20.4 to 28.5) and those who tested positive 7 or more days after typical symptom onset (median Ct value among 8 observations, 25.0; interquartile range, 21.3 to 28.2) (Fig. 3, and Fig. S1). Viable virus was isolated from specimens collected 6 days before to 9 days after the first evidence of typical symptoms.

PREVALENCE AND TRANSMISSION IN THE FACILITY

We estimated the doubling time among residents to be 3.4 days (95% confidence interval [CI], 2.5 to 5.3) (Table S4). The doubling time for the surrounding King County was 5.5 days (95% CI, 4.8 to 6.7). As of April 3, a total of 11 of the 57 residents with SARS-CoV-2 infection identified by March 26 had been admitted to the hospital (including 3 in intensive care) and 15 had died (mortality, 26%). The unit where presumed introduction of infection took place and where the first resident with SARS-CoV-2 infection lived (Unit 1) had the highest prevalence in the facility at the end of the first point-prevalence survey. Although other units identified SARS-CoV-2 infection in residents later, their prevalence also continued to increase (Fig. 4, and Fig. S4).

By the time of the first point-prevalence survey, 11 of 138 full-time staff members (8%) had had a positive test for SARS-CoV-2. By March 26,

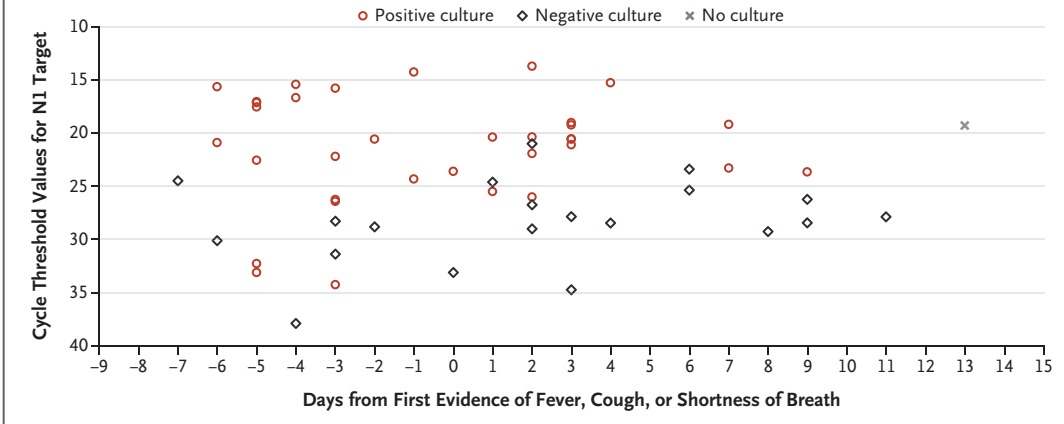

Figure 3. Cycle Threshold Values Relative to First Evidence of Fever, Cough, or Shortness of Breath.

Shown are N1 target cycle threshold values and viral culture results for each resident's positive tests for SARS-CoV-2 shown by day since the first evidence of fever, cough, or shortness of breath (N=55). Dates of onset of typical symptoms were known for 43 residents; 12 residents with two specimens that were positive for SARS-CoV-2 are also included. One positive test was not assessed for culture growth. The relationship between the first test and the second test for residents who had two positive tests is shown in Figure S2.

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a total of 55 of the 138 (40%) had reported symptoms, 51 (37%) had been tested, and 26 (19%) had received a positive test result. Of the 26 staff members with positive tests, 17 were nursing staff and 9 had occupations that provided services across multiple units during their shift (therapists, environmental services, dietary services). No staff members with Covid-19 were hospitalized.

Thirty-nine specimens from 34 residents were sequenced. All sequences were identical or highly similar to sequences reported in previous analyses of Covid-19 cases in Washington (Fig. S3). Of the 34 residents whose specimens were sequenced, 27 (79%) had sequences that fit into two clusters with one nucleotide difference (Fig. S4 and Table S5).

DISCUSSION

Twenty-three days after identifying the first resident with SARS-CoV-2 infection, Facility A had a 64% prevalence of Covid-19 among residents, with a case fatality rate of 26% despite early adoption of infection-control measures. In addition, Covid-19 was diagnosed in 26 members of the staff (19%). These findings are strikingly similar to descriptions of the first Covid-19 outbreak in a U.S. skilled nursing facility, which occurred in the same county at nearly the same time.[2] In the investigation reported here, more than half of the residents with positive tests were asymptomatic at the time of testing. Transmission from asymptomatic residents infected with SARS-CoV-2 most likely contributed to the rapid and extensive spread of infection to other residents and staff. Symptom-based infection-control strategies were not sufficient to prevent transmission after the introduction of SARS-CoV-2 into this skilled nursing facility.

Although we are unable to quantify the contributions of asymptomatic and presymptomatic residents to transmission of SARS-CoV-2 in this facility, evidence suggests that these residents had the potential for substantial viral shedding.

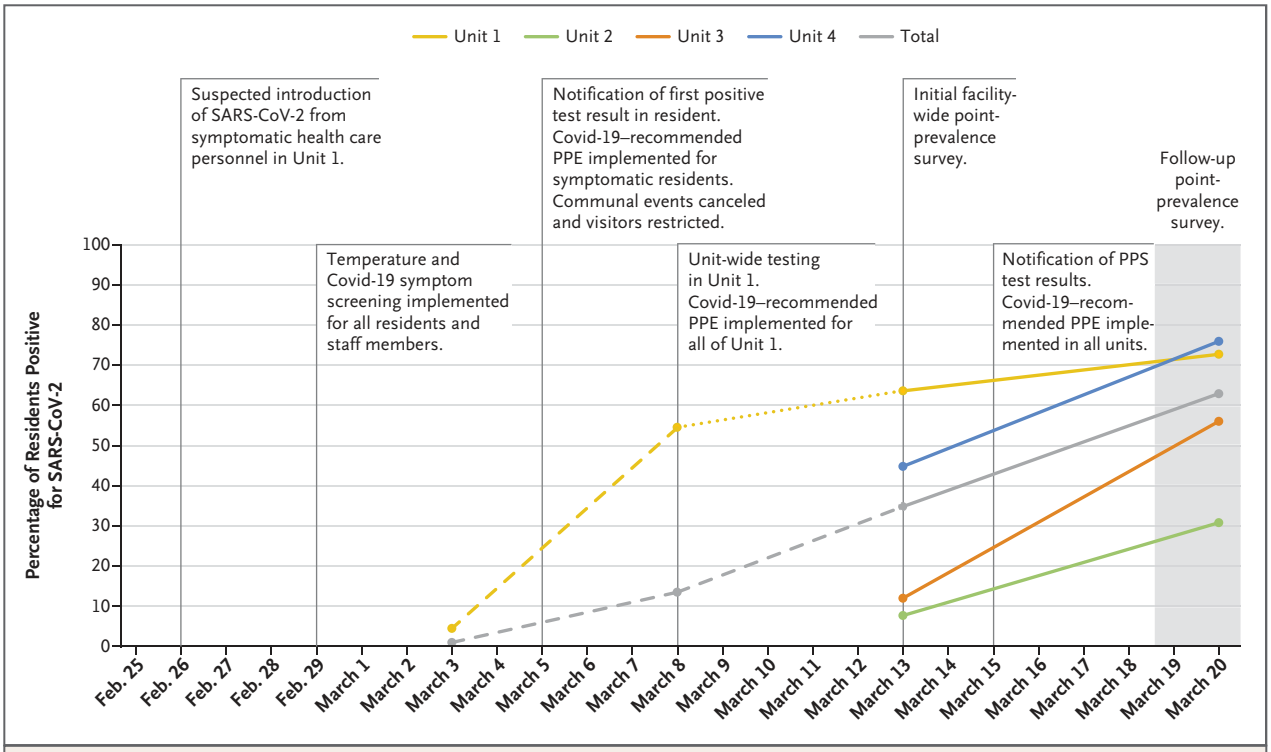

Figure 4. Timeline Showing Prevalence, Notable Events, and Implementation of Infection Prevention and Control Measures at Facility A.
Dashed lines indicate the prevalence of Covid-19 based on test results obtained during clinical evaluation of symptomatic residents before a unit-wide or facility-wide point-prevalence survey (PPS); the dotted line indicates the prevalence based on results from a unit-specific point-prevalence survey; and solid lines indicate the prevalence based on results from clinical evaluation and a facility-wide point-prevalence survey. PPE denotes personal protective equipment.

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Ct values indicating large quantities of viral RNA were identified, and viable SARS-CoV-2 was isolated from specimens of asymptomatic and presymptomatic residents. Evidence of transmission from presymptomatic persons has been shown in epidemiologic investigations of SARS-CoV-2.[12-14]

We estimated that the doubling time in this facility was 3.4 days, which is faster than that of the surrounding community, 5.5 days. The accelerated doubling time was likely to have been due to inadequately controlled intrafacility transmission, which sequencing and spatiotemporal data suggest was the primary driver of new infections. Shedding of high viral titers from the respiratory tract, including shedding before the onset of symptoms, might have led to droplet and possibly aerosol transmission. Residents and staff members with undetected SARS-CoV-2 infection are likely to have contributed to transmission through interactions between and among residents and staff. The contribution of indirect contact transmission in this outbreak is not known. However, contaminated environmental surfaces and shared medical devices could also have played a role. Most of the early transmission appeared to have occurred in Unit 1, where the initial introduction of SARS-CoV-2 took place, several days before other units were involved. Early recognition of initial SARS-CoV-2 introduction combined with early interventions in all units might prevent spread within a facility.

The CDC and PHSKC confirmed Covid-19 infection in 26 symptomatic staff members associated with this skilled nursing facility as of March 26; these staff members most likely contributed to intrafacility transmission. A concurrent study of King County health care personnel with Covid-19 showed that 65% worked while symptomatic and that 17% of symptomatic health care personnel initially had mild, nonspecific symptoms and no fever, cough, shortness of breath, or sore throat.[15] The potential for viral shedding from staff members with SARS-CoV-2 infection during either the presymptomatic or the mildly symptomatic phase of the illness reinforces current recommendations for expanded symptom screening for health care personnel and universal use of face masks for all health care staff in long-term care facilities.[5]

Current interventions for preventing SARS-CoV-2 transmission in health care settings rely primarily on the presence of signs and symptoms to identify and isolate residents and staff who might have Covid-19. The data presented here suggest that sole reliance on symptom-based strategies may not be effective to prevent introduction of SARS-CoV-2 and further transmission in skilled nursing facilities. Impaired immune responses associated with aging and the high prevalence of underlying conditions, such as cognitive impairment and chronic cough, make it difficult to recognize early signs and symptoms of respiratory viral infections in this population.[16] Studies have shown that in the elderly, including those living in skilled nursing facilities, influenza often manifests with few or atypical symptoms, delaying diagnosis and contributing to transmission.[17,18] Furthermore, symptom-based cohorting strategies could inadvertently increase the risk of SARS-CoV-2 exposure for uninfected residents, given that typical symptoms were common in those who tested negative.

Our investigation demonstrated a poor correlation between symptom onset and viral shedding that was potentially due to the difficulty of ascertaining precise dates of symptom onset or to differences in viral shedding in this population. Studies in other populations show that SARS-CoV-2 shedding is highest early in the illness.[19,20] Our investigation shows that some facility residents shed virus for more than 7 days after symptom onset, a finding seen in some other populations.[21] These data support current recommendations preferring a test-based strategy to discontinue transmission-based precautions for residents of skilled nursing facilities.[22] If a non–test-based strategy is used, these data support extending the duration of transmission-based precautions.[22]

Because asymptomatic or presymptomatic residents might play an important role in transmission in this high-risk population, additional prevention measures merit consideration, including using testing to guide the use of transmission-based precautions, isolation, and cohorting strategies. The ability to test large numbers of residents and staff with rapid turn-around times may expedite cohorting of residents and staff in locations designated for the care of those with SARS-CoV-2 infection either in different locations within individual facilities or in separate facilities.

This investigation has several limitations. First, challenges in symptom ascertainment may

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have resulted in misclassification of symptom grouping for some residents. However, multiple sources of symptom data were used to minimize such misclassification. The accuracy of symptom ascertainment for this investigation is likely to be equivalent to, if not exceed, symptom screening in most skilled nursing facilities, and thus, these findings should be generalizable to this setting. Second, because this analysis was conducted among residents of a skilled nursing facility, it is not known whether the findings apply to the general population, including younger persons, those without underlying medical conditions, or similarly aged populations in the general community or in other long-term care settings. Third, asymptomatic staff members were not tested; therefore, we are unable to document their role in transmission in this facility.

SARS-CoV-2 can spread rapidly after introduction into skilled nursing facilities, resulting in substantial morbidity and mortality and increasing the burden on regional health care systems. Unrecognized asymptomatic and presymptomatic infections most likely contribute to transmission in these settings. During the current Covid-19 pandemic, skilled nursing facilities and all long-term care facilities should take proactive steps to prevent introduction of SARS-CoV-2. These steps include restricting visitors and nonessential personnel from entering the building, requiring universal use of face masks by all staff for source control while in the facility, and implementing strict screening of staff. Our data suggest that symptom-based strategies for identifying residents with SARS-CoV-2 are insufficient for preventing transmission in skilled nursing facilities. Once SARS-CoV-2 has been introduced, additional strategies should be implemented to prevent further transmission, including use of recommended personal protective equipment, when available, during all resident care activities regardless of symptoms.[5] Consideration should be given to test-based strategies for identifying residents and staff with SARS-CoV-2 infection for the purpose of excluding infected staff and cohorting residents, either in designated units within a facility or in a separate facility designated for residents with Covid-19.

The findings and conclusion in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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ORIGINAL ARTICLE

An Outbreak of Covid-19 on an Aircraft Carrier

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ABSTRACT

BACKGROUND

An outbreak of coronavirus disease 2019 (Covid-19) occurred on the U.S.S. *Theodore Roosevelt*, a nuclear-powered aircraft carrier with a crew of 4779 personnel.

METHODS

We obtained clinical and demographic data for all crew members, including results of testing by real-time reverse-transcriptase polymerase chain reaction (rRT-PCR). All crew members were followed up for a minimum of 10 weeks, regardless of test results or the absence of symptoms.

RESULTS

The crew was predominantly young (mean age, 27 years) and was in general good health, meeting U.S. Navy standards for sea duty. Over the course of the outbreak, 1271 crew members (26.6% of the crew) tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection by rRT-PCR testing, and more than 1000 infections were identified within 5 weeks after the first laboratory-confirmed infection. An additional 60 crew members had suspected Covid-19 (i.e., illness that met Council of State and Territorial Epidemiologists clinical criteria for Covid-19 without a positive test result). Among the crew members with laboratory-confirmed infection, 76.9% (978 of 1271) had no symptoms at the time that they tested positive and 55.0% had symptoms develop at any time during the clinical course. Among the 1331 crew members with suspected or confirmed Covid-19, 23 (1.7%) were hospitalized, 4 (0.3%) received intensive care, and 1 died. Crew members who worked in confined spaces appeared more likely to become infected.

CONCLUSIONS

SARS-CoV-2 spread quickly among the crew of the U.S.S. *Theodore Roosevelt*. Transmission was facilitated by close-quarters conditions and by asymptomatic and presymptomatic infected crew members. Nearly half of those who tested positive for the virus never had symptoms.

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The U.S.S. *THEODORE ROOSEVELT* was conducting operations in the western Pacific Ocean when an outbreak of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred on board. On identification of the outbreak, the ship was diverted to U.S. Naval Base Guam. The base hospital, a 42-bed inpatient facility, provides medical care for U.S. military beneficiaries and others in the region. Although the initial response was handled by the medical staffs of the ship and Naval Hospital Guam, it was quickly augmented by a joint medical task force.

This report provides key findings from the U.S. Navy response and epidemiologic investigation of the outbreak. Over the course of the response, every member of the crew of the U.S.S. *Theodore Roosevelt* was evaluated, tested, placed in isolation or quarantine, and monitored on a daily basis to ensure their well-being. Our findings offer insights into the epidemiology and outcomes of SARS-CoV-2 infection in healthy, fit, military-aged adults who are housed in close quarters.

METHODS

INITIAL RESPONSE TO THE OUTBREAK AND FOLLOW-UP

The ship had been at sea for 13 days when three crew members presented to the medical department with symptoms suggestive of coronavirus disease 2019 (Covid-19). All three underwent testing by real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) and were found to be positive for SARS-CoV-2. Over the next 24 hours, additional symptomatic crew members and approximately 400 close contacts were identified by contact tracing. Four days after the first positive test result was reported, the ship reached Naval Base Guam. Crew members with confirmed cases of Covid-19 were placed in isolation on Naval Base Guam or in the base hospital. Persons with one or more negative Covid-19 tests and no symptoms were quarantined in hotels off base or on Naval Base Guam. In addition, essential personnel who were uninfected stayed aboard the ship in port.

All members of the crew underwent screening for signs and symptoms of Covid-19 and testing by rRT-PCR. Those who tested positive for SARS-CoV-2 were placed in isolation and received twice-daily symptom, temperature, and pulse oximetry checks. Those who tested negative were placed in quarantine. Ultimately, 4079 SARS-CoV-2–negative crew members who did not have symptoms were quarantined in 11 hotels in Guam. All were placed in single-occupancy rooms.

A surveillance model was implemented that relied on in-person health screenings. These screenings were supplemented by self-reporting with the use of a symptom checker developed by Defense Digital Service. Health screenings and symptom-checker data were collated and analyzed each morning by 9 a.m. and again in the evening by 9 p.m. Crew members who had progressive symptoms or were deemed to have conditions potentially placing them at higher risk for poorer outcomes were followed up with additional screening. Any crew members who were determined by on-site medical providers to need closer observation or treatment were transported to Naval Hospital Guam for care. In addition to Covid-19–related health surveillance, crew members received primary care, pharmacy, and psychiatric services to ensure a complete scope of medical coverage.

On completion of prespecified periods of isolation or quarantine, all personnel were required to undergo repeat rRT-PCR testing. To be eligible for exit testing, a crew member had to remain in isolation or quarantine for a minimum of 14 days. Those in isolation were also required to be symptom-free for 3 days before exit testing. Any crew member in quarantine in whom symptoms developed was tested and moved to isolation for at least 14 additional days. All crew members were followed up for a minimum of 10 weeks, regardless of their Covid-19 status.

LABORATORY TESTING

Nasopharyngeal swab specimens were obtained from all members of the crew with the use of viral transport medium swab kits. The presence of SARS-CoV-2 infection was determined by rRT-PCR testing with the Thermo Fisher ABI 7500 or the Bio-Rad CFX96 Touch Real-Time PCR Detection System. Samples were processed with either the Qiagen QIAamp Viral RNA Mini Kit or the Roche MagNA Pure 96 instrument for automated nucleic acid extraction, and testing was performed with the Seegene Allplex 2019-nCOV assay test kit or the Centers for Disease Control

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and Prevention (CDC) emergency-use-authorization assay.[1] These assays included the detection of two targets in the nucleocapsid gene, N1 and N2. Surveillance testing for influenza-like illness was conducted with the Biofire Respiratory 2 Panel.

COLLECTION OF OUTBREAK DATA

The Navy and Marine Corps Public Health Center was tasked with providing public health support for the outbreak investigation and conducting data analysis in alignment with its core public health mission. Data were collected as part of a coordinated public health outbreak investigation conducted by the Navy to bring the outbreak under control, ensure the well-being of the crew, assess the spread and effects of SARS-CoV-2, and implement measures to return the crew to work safely. Under Navy public health support criteria, the intent of the outbreak investigation was to mitigate spread, inform decision making, gather information for use in other outbreaks, and decrease the effect on the health of the crew. This project was deemed to be nonresearch with respect to the use of human subject information and was exempt from review by the institutional review board as an emergency public health outbreak investigation.

A roster of Electronic Data Interchange Personal Identifiers for the shipboard population was matched to Defense Manpower Data Center personnel rosters from February 2020 to identify demographic information for each crew member and to confirm personal identifiers. Civilian personnel and anyone with an Electronic Data Interchange Personal Identifier that did not match with Defense Manpower Data Center were excluded from analysis. The Defense Enrollment Eligibility Reporting System was used to identify race and ethnic group for all crew members. Ages of crew members at time of the outbreak were calculated from the date of birth to March 3, 2020.

Medical surveillance data collected by the ship medical department, Naval Hospital Guam, and the joint medical task force were collated with the roster to create a data set that included dates of symptom onset, daily clinical signs and symptoms, and test results. Data from the Defense Digital Service MySymptoms symptom-tracker application were also collated into the final data set. For the purpose of this analysis, fever is defined as subjective fever reported by the crew member or a measured temperature of 100.0°F or higher. All other symptoms were reported by the crew members. Data on health-related factors were obtained from a number of existing clinical Military Health System data sources, including the Armed Forces Health Longitudinal Technology Application and Military Health System Genesis.

A confirmed case of Covid-19 was defined as one in which a nasopharyngeal swab specimen was positive for SARS-CoV-2 by rRT-PCR. A suspected case of Covid-19 was defined as one that met Council of State and Territorial Epidemiologists clinical criteria for Covid-19 without a positive test result. Confirmed cases were further classified as symptomatic (with symptom onset before the first positive laboratory test), presymptomatic (with the first positive laboratory test before subsequent symptom onset), and asymptomatic (positive laboratory test but clinical criteria never met). Patients with confirmed or suspected infection were classified as having been hospitalized for Covid-19 if the admission diagnosis suggested a Covid-19–related illness.

STATISTICAL ANALYSIS

Data collation and analysis were performed with the use of SAS software, version 9.4 (SAS Institute). Baseline characteristics among crew members who were infected and those who were not infected were compared and univariate odds ratios with 95% confidence intervals were calculated with OpenEpi (www.openepi.com). For denominators of less than 20, odds ratios were not calculated. All reported odds ratios are not adjusted for multiple comparisons.

RESULTS

TIMELINE OF THE OUTBREAK

Between March 23 and May 18, 2020, a total of 1271 crew members (26.6% of the crew) tested positive for SARS-CoV-2. An additional 60 crew members had suspected Covid-19 (Fig. 1). Of the 1271 crew members with laboratory-confirmed Covid-19, 572 (43.0%) remained asymptomatic throughout the outbreak, 293 (22.0%) were symptomatic at the time that they tested positive, and an additional 406 (30.5%) were presymptomatic at the time that they tested positive. In all, 978 (76.9%) of the 1271 crew members with labora-

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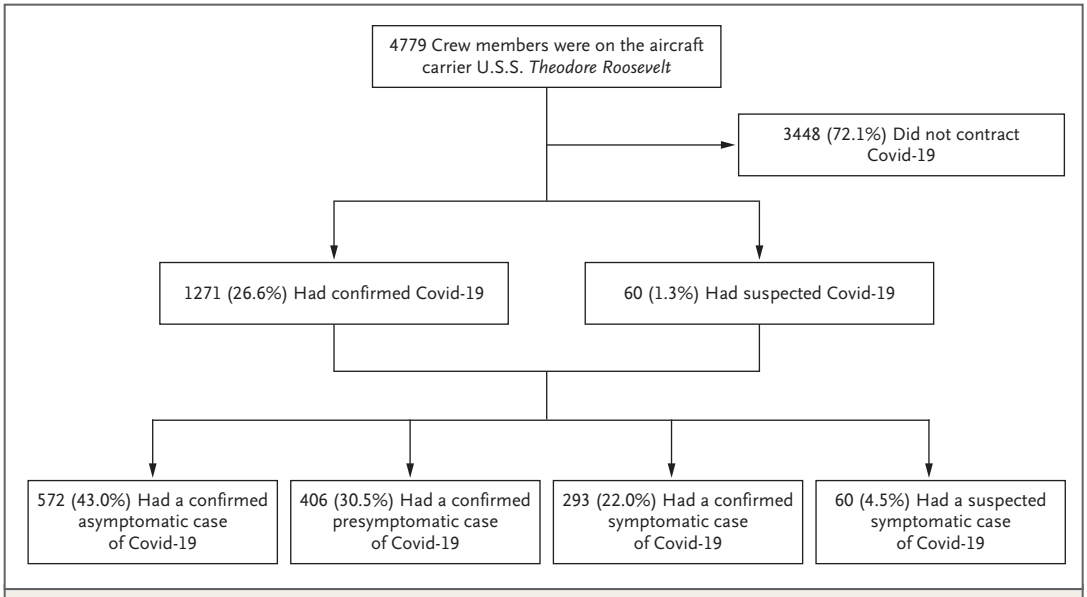

Figure 1. Distribution of Personnel According to Case Status.

A confirmed case of coronavirus disease 2019 (Covid-19) was defined as one in which a nasopharyngeal swab specimen was positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by real-time reverse-transcriptase polymerase chain reaction. A suspected case was defined as one that met Council of State and Territorial Epidemiologists clinical criteria for Covid-19 without a positive test result. Confirmed cases were further classified as symptomatic (with symptom onset before the first positive laboratory test), presymptomatic (with the first positive laboratory test before subsequent symptom onset), and asymptomatic (positive laboratory test but clinical criteria never met).

tory-confirmed Covid-19 did not have symptoms at the time that they tested positive, and 699 (55.0%) had symptoms develop at any time during the clinical course.

Testing for influenza-like illnesses had been conducted on a limited number of specimens before and after the start of the outbreak. Testing of specimens obtained from 5 crew members during the week before the outbreak identified 3 crew members who were positive for human rhinovirus or enterovirus, 1 who was positive for respiratory syncytial virus (RSV), and 1 with no pathogens detected. After the outbreak was identified on March 23, specimens from 16 crew members were tested: 10 crew members had no pathogens detected, 3 were positive for human rhinovirus or enterovirus, 2 were positive for coronavirus OC43 (not SARS-CoV-2), and 1 was positive for both human rhinovirus or enterovirus and RSV.

The outbreak epidemic curve is shown in Figure 2. In retrospect, crew members with symptomatic confirmed or suspected Covid-19 had symptoms as early as March 11, 2020, and continued to receive diagnoses up to the end of the analysis period. Epidemic curves according to sex and crew type show parallel infection rates for men and women. Although the ship docked in Guam on March 27, 2020, the outbreak continued for at least an additional 6 weeks.

CHARACTERISTICS OF THE CREW MEMBERS

The crew was predominantly young (mean age, 27 years) and male (78.3%) and was racially and ethnically diverse. At the time of deployment, all crew members were in general good health and met the U.S. Navy standards for sea duty. Ultimately, Covid-19 cases were evenly distributed across sexes, races and ethnic groups, and crew types (Table 1). Enlisted personnel (90% of the shipboard population) appeared more likely than officers to have confirmed or suspected Covid-19.

Data were analyzed to identify higher-risk work spaces. Those working in tighter spaces (e.g., reactor, engineering, supply, and weapons

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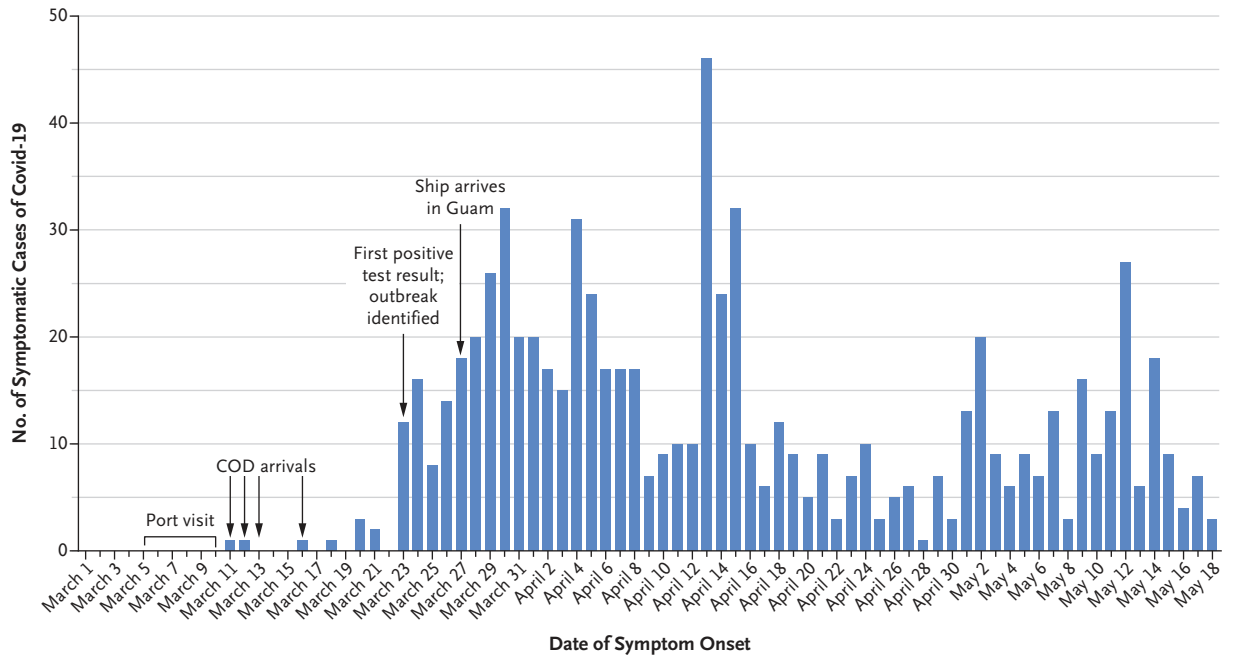

Figure 2. Numbers of Symptomatic Confirmed or Suspected Covid-19 Cases over Time.
Personnel, supplies, and mail are delivered to an aircraft carrier during carrier onboard delivery (COD).

departments) appeared more likely to have confirmed or suspected Covid-19 than those working in a combination of open-air and confined conditions (e.g., air and deck crew). Members of the medical department, who wore personal protective equipment when evaluating crew members, had a somewhat lower attack rate (16.7% [8 cases among 48 personnel) than the overall crew, despite being at highest risk as a result of exposure to patients with Covid-19 in a small space.

SYMPTOMS AND CARE

Among the crew members who had symptomatic Covid-19 (confirmed or suspected), headache was the most common symptom reported at any point during illness (occurring in 68.0%), followed by cough (59.5%), nasal or sinus congestion (43.8%), and altered sense of taste or smell (42.3%) (Fig. 3). The predominant symptoms reported at the onset of illness were cough (32.8%), headache (31.0%), and altered sense of taste or smell (24.1%). Shortness of breath at any point during illness was reported by 20.3% of the crew members with symptomatic cases, and 7.0% noted shortness of breath as an initial presenting symptom. In addition, 26.2% of the crew members with symptomatic Covid-19 reported chest pain or chest pressure at some point during their illness. Fever was reported as an initial presenting symptom by 5.3% of the crew members with symptomatic Covid-19, and fever at any point during illness was reported by 13.2%. Measured temperature readings showed that 2.8% of the crew members who had Covid-19 had a recorded temperature of 100.0°F or above, as compared with 0.3% of the crew members who did not have Covid-19. Among the crew members with Covid-19 for whom pulse oximetry data were available, approximately 0.5% had readings below 95% while breathing ambient air, with 0.08% below 94% and none below 90%.

Of the 1271 crew members who tested positive for SARS-CoV-2 plus the 60 who had suspected Covid-19, 23 (1.7%) received hospital care, for a mean of 16 days after symptom onset. Four crew members (0.3% of those with suspected or laboratory-confirmed Covid-19) were admitted to the intensive care unit, 1 of whom died from Covid-19–related cardiovascular complications. Before hospitalization, crew mem-

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Table 1. Demographic and Health Characteristics of Crew Members According to Covid-19 Status.*

Characteristic	Covid-19 Status			Univariate Odds Ratio, Covid-19 vs. No Covid-19 (95% CI)
	No Covid-19 (N=3448)	Confirmed or Suspected Covid-19 (N=1331)	Hospitalization for Covid-19 (N=23)	
Demographic characteristics				
Age — yr				
Mean	27.2	27.1	29.3	—
Range	18–59	18–53	20–46	—
Interquartile range	22–32	22–31	23–34	—
Sex — no. (%)				
Female	757 (22.0)	289 (21.7)	6 (26.1)	0.99 (0.85–1.15)
Male	2691 (78.0)	1042 (78.3)	17 (73.9)	Reference
Rank status				
Enlisted	3080 (89.3)	1231 (92.5)	23 (100.0)	1.48 (1.17–1.87)
Officer	363 (10.5)	98 (7.4)	0	Reference
Unknown	5 (0.1)	2 (0.2)	0	—
Race or ethnic group — no. (%)†				
American Indian	75 (2.2)	34 (2.6)	1 (4.3)	1.21 (0.80–1.83)
Asian or Pacific Islander	327 (9.5)	106 (8.0)	4 (17.4)	0.86 (0.68–1.10)
Black	590 (17.1)	261 (19.6)	3 (13.0)	1.18 (0.99–1.40)
Hispanic	692 (20.1)	273 (20.5)	5 (21.7)	1.05 (0.89–1.25)
White	1513 (43.9)	568 (42.7)	7 (30.4)	Reference
Other	250 (7.3)	88 (6.6)	3 (13.0)	0.94 (0.72–1.22)
Crew type‡				
Ship's crew	2086 (60.5)	786 (59.1)	13 (56.5)	Reference
Augmented crew	1288 (37.4)	501 (37.6)	9 (39.1)	1.03 (0.90–1.18)
Unknown	74 (2.1)	44 (3.3)	1 (4.3)	1.58 (1.08–2.31)
Select work centers and departments§				
Air	394 (11.4)	65 (4.9)	—	Reference
Combat support division	164 (4.8)	38 (2.9)	—	0.88 (0.58–1.33)
Deck	82 (2.4)	4 (0.3)	—	0.18 (0.07–0.52)
Engineering	137 (4.0)	67 (5.0)	—	1.85 (1.29–2.67)
Medical	40 (1.2)	8 (0.6)	—	0.76 (0.34–1.67)
Reactor	302 (8.8)	138 (10.4)	—	1.73 (1.29–2.36)
Supply	219 (6.4)	139 (10.4)	—	2.41 (1.78–3.26)
Weapons	132 (3.8)	94 (7.1)	—	2.70 (1.92–3.80)
Health characteristics				
Tobacco or nicotine user	1002 (29.1)	382 (28.7)	8 (34.8)	0.98 (0.85–1.13)
Most recent BMI¶				
Underweight or normal	1135 (32.9)	389 (29.2)	9 (39.1)	Reference
Overweight	1450 (42.1)	570 (42.8)	6 (26.1)	1.15 (0.99–1.33)
Obese	584 (16.9)	267 (20.1)	8 (34.8)	1.33 (1.11–1.61)
Unknown	279 (8.1)	105 (7.9)	0	1.10 (0.85–1.41)

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Table 1. (Continued.)

Characteristic	Covid-19 Status			Univariate Odds Ratio, Covid-19 vs. No Covid-19 (95% CI)
	No Covid-19 (N=3448)	Confirmed or Suspected Covid-19 (N=1331)	Hospitalization for Covid-19 (N=23)	
Preidentified health factors of interest‖				
Asthma	236 (6.8)	95 (7.1)	5 (21.7)	1.05 (0.82–1.34)
Cancer	35 (1.0)	10 (0.8)	0	0.74 (0.36–1.50)
Cerebrovascular diseases	2 (0.1)	0	0	—
Chronic lung disease	30 (0.9)	11 (0.8)	2 (8.7)	0.95 (0.47–1.90)
Diabetes	12 (0.3)	4 (0.3)	0	0.86 (0.28–2.68)
Hypertension	226 (6.6)	96 (7.2)	5 (21.7)	1.11 (0.87–1.42)
Immunocompromise	3 (0.1)	0	0	—
Liver disease	20 (0.6)	8 (0.6)	2 (8.7)	1.04 (0.46–2.36)
Sleep apnea	135 (3.9)	50 (3.8)	2 (8.7)	0.96 (0.69–1.33)
Tuberculosis	20 (0.6)	6 (0.5)	0	0.78 (0.31–1.94)

* Percentages may not total 100 because of rounding. Covid-19 denotes coronavirus disease 2019.
† The Defense Enrollment Eligibility Reporting System was used to identify race and ethnic group for all crew members.
‡ Augmented crew reside on the ship only at certain times when a ship is under way and provide specialized capability such as air squadrons, submarine groups, destroyer squadrons, and helicopter maritime strike squadrons.
§ Crew members in the departments of reactor, engineering, supply, weapons and in the combat support division tend to work in more confined spaces than those in the air and deck departments. Crew members in the air and deck departments tend to work in a combination of open-air and confined conditions. Medical personnel work in confined spaces but wear personal protective equipment when caring for crew members.
¶ Underweight was defined as a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of less than 18.5; normal or healthy weight, 18.5 to 24.9; overweight, 25.0 to 29.9; and obese, 30 or higher.
‖ Conditions were identified from October 1, 2017, through March 1, 2020, with the use of the following data sources: Theater Medical Data Store, Comprehensive Ambulatory/Professional Encounter Record, Standard Inpatient Data Record, Armed Forces Health Longitudinal Technology Application Clinical Data Repository, Military Health System (MHS) GENESIS, TRICARE Encounter Data, and Periodic Health Assessment.

bers with Covid-19 who became hospitalized were more likely to report cough (68%), body aches (58%), and fever (32%) than those who did not. One third of hospitalized patients reported fever before their hospitalization, as compared with 12% of nonhospitalized crew members with Covid-19. During the outbreak, as a precautionary measure, admission criteria were revised to permit hospitalization of crew members with less severe symptoms.

DISCUSSION

The epidemiology of SARS-CoV-2 infection in young, healthy populations has not been studied extensively.[2] The outbreak of Covid-19 on the U.S.S. *Theodore Roosevelt* provided an unusual opportunity to assess an outbreak in a predominantly young, healthy, working-age population. Approximately 69% of crew members were younger than 30 years of age, and no crew member was older than 65 years. All were up to date with their immunizations. Over the course of the outbreak and the subsequent response by the U.S. Navy, every crew member underwent evaluation, testing, and follow-up. This level of controlled evaluation and documentation is difficult to achieve in civilian populations.

On ships at sea, respiratory viruses such as influenza and enteric pathogens such as norovirus can spread quickly.[3,4] In the early weeks of the pandemic, several outbreaks of Covid-19 occurred on cruise ships, most notably on the *Diamond Princess*.[5,6] The medical department of a ship can be overwhelmed quickly by a major outbreak of disease, as is similarly seen with health care fa-

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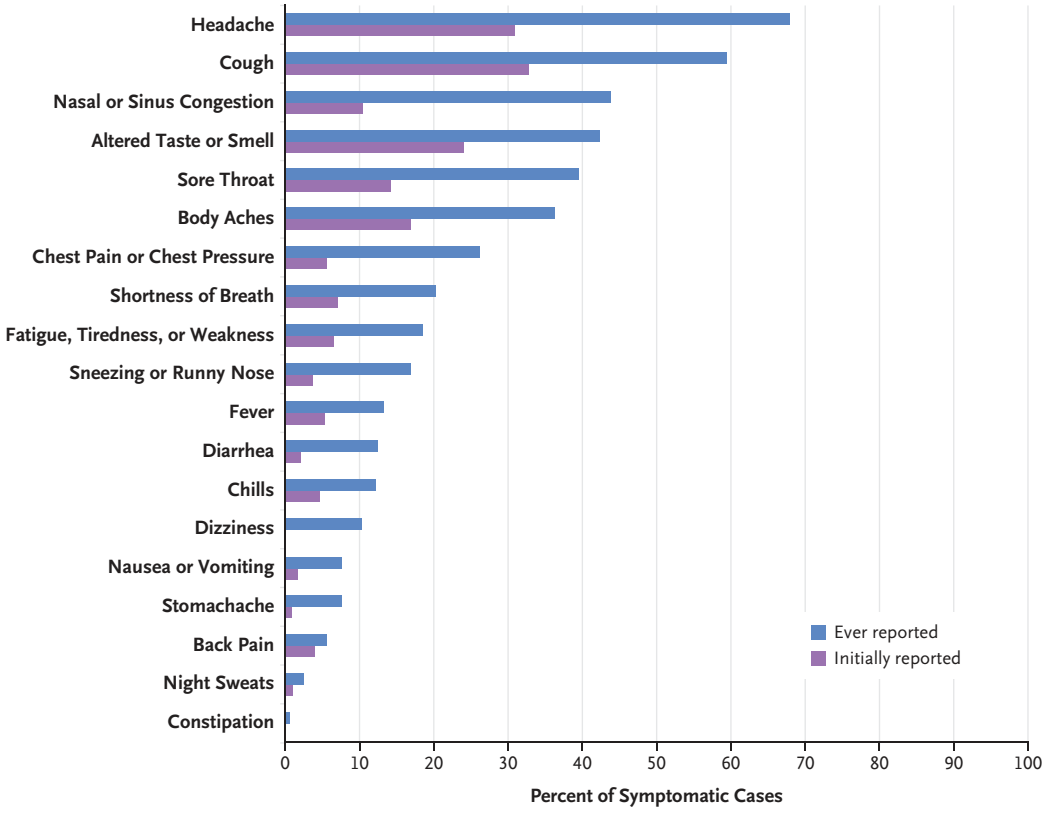

Figure 3. Distribution of Symptomatic Confirmed or Suspected Covid-19 Cases According to Symptoms.

cilities in civilian communities.[7] The shipboard environment on naval vessels is generally more confined. Typically, enlisted crew members sleep in open bays packed with dozens of tightly spaced bunks, work in densely populated areas, and congregate in gathering points such as the gyms and galleys (Figs. S1 and S2 in the Supplementary Appendix, available with the full text of this article at NEJM.org). These conditions probably facilitated the transmission of SARS-CoV-2, as evidenced by the higher likelihood of Covid-19 among enlisted crew members than among officers (Table 1).

Not surprisingly, crew members working in the engine room and other confined areas of the ship faced a higher risk of being infected than their shipmates on deck. A study conducted by the Navy and Marine Corps Public Health Center and the CDC, involving 384 volunteer U.S.S. *Theodore Roosevelt* crew members, showed similar results: those working in confined spaces had higher odds of contracting Covid-19.[8] A majority of infected crew members did not note symptoms at the time that Covid-19 was diagnosed by rRT-PCR testing. In addition, crew members with unusual or atypical symptoms may not have considered themselves to be infected with SARS-CoV-2.[9] These observations suggest that nonsymptomatic or mildly symptomatic crew members played an important role in the rapid spread of the outbreak, much as young adults with asymptomatic infection appear to contribute to spread in civilian populations.[10,11]

Although cases of serious illness occur in younger persons, they are less frequent and typically less severe than those in older persons.[9,11] In the case of the U.S.S. *Theodore Roosevelt*, few crew members were hospitalized. Certain coexisting conditions, such as hypertension, obesity, and diabetes, are associated with higher mortality.[12-14] In our findings, we noted a number of coexisting conditions among hospitalized crew members,

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including uncomplicated, mild, and medically managed asthma, lung disease (e.g., bronchitis), hypertension, and liver disease–related conditions.

Although we were able to confirm the outcomes in all infected crew members, data collection was limited by the quality of records, particularly those generated in the early days of the outbreak. Future studies involving longitudinal cohorts may provide greater insight into the epidemiology of SARS-CoV-2 infection in young adults. Our observations within a military population may not be fully generalizable to civilians. The CDC case definition for Covid-19, along with clinical criteria, changed over time (e.g., the outbreak began in March 2020, and the CDC-published case definition for Covid-19 changed in April 2020). Multiplex testing by polymerase chain reaction identified other causes of influenza-like illness on board the ship. Any effect that the case definition or other respiratory pathogens may have had on classifying a case of Covid-19 is limited, because the majority of cases were confirmed by rRT-PCR testing. Finally, the crew of the U.S.S. *Theodore Roosevelt*, like all members of the U.S. military forces, have equal access to health care. This is not true for all civilians in the United States.

Since this outbreak occurred, the U.S. Navy has incorporated lessons learned to enhance the safety and readiness of its crews. To minimize the risk of deploying with asymptomatic carriers of SARS-CoV-2 on board, the Navy has initiated several procedures to create and sustain Covid-19–free environments on its ships. Before deployment, all members of a ship's crew are placed in "restriction of movement" and insulated from community exposure for 14 days. To identify asymptomatic or presymptomatic carriers, the Navy added rRT-PCR testing at the end of the "restriction of movement" period. Navy ships have sharply reduced shore leaves at foreign ports to prevent crew members from bringing the virus on board. Since these policies (along with preventive measures of mask use, social distancing to the extent possible, small-group cohorting, strict hand hygiene, and regular cleaning of common spaces) were put in place, the Navy has deployed multiple ships without sustaining another serious outbreak. The concept of creating virus-free "bubbles" is a strategy the Navy has used and has been mirrored by the National Basketball Association and Major League Soccer to enable competition while minimizing the risk of player exposure. It is unlikely that this strategy is practical for all employers, much less the general population; however, creating bubbles or cohorts for select populations may be achievable.

Organizations seeking to safeguard their employees, customers, patients, or students may benefit from assuming that Covid-19 will be introduced into their populations and rigorously enforcing measures to minimize viral transmission by all, since persons may be unaware that they are infected.

The views expressed in this article reflect the results of research conducted by the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the U.S. government.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Severe Covid-19

David A. Berlin, M.D., Roy M. Gulick, M.D., M.P.H., and Fernando J. Martinez, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 50-year-old, previously healthy man presents to the emergency department with 2 days of worsening dyspnea. He had fever, cough, and fatigue during the week before presentation. He appears acutely ill. The body temperature is 39.5°C (103°F), heart rate 110 beats per minute, respiratory rate 24 breaths per minute, and blood pressure 130/60 mm Hg. The oxygen saturation is 87% while the patient is breathing ambient air. The white-cell count is 7300 per microliter with lymphopenia. Chest radiography shows patchy bilateral opacities in the lung parenchyma. A reverse-transcriptase–polymerase-chain-reaction assay detects the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA in a nasopharyngeal swab. How would you evaluate and manage this case?

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THE CLINICAL PROBLEM

The most common initial symptoms of coronavirus disease 2019 (Covid-19) are cough, fever, fatigue, headache, myalgias, and diarrhea.[1] Severe illness usually begins approximately 1 week after the onset of symptoms. Dyspnea is the most common symptom of severe disease and is often accompanied by hypoxemia[2,3] (Fig. 1). Progressive respiratory failure develops in many patients with severe Covid-19 soon after the onset of dyspnea and hypoxemia. These patients commonly meet the criteria for the acute respiratory distress syndrome (ARDS), which is defined as the acute onset of bilateral infiltrates, severe hypoxemia, and lung edema that is not fully explained by cardiac failure or fluid overload.[4] The majority of patients with severe Covid-19 have lymphopenia,[5] and some have thromboembolic complications[6] as well as disorders of the central or peripheral nervous system.[7] Severe Covid-19 may also lead to acute cardiac, kidney, and liver injury, in addition to cardiac arrhythmias, rhabdomyolysis, coagulopathy, and shock.[8,9] These organ failures may be associated with clinical and laboratory signs of inflammation, including high fevers, thrombocytopenia, hyperferritinemia, and elevations in C-reactive protein and interleukin-6.[10]

The diagnosis of Covid-19 can be established on the basis of a suggestive clinical history and the detection of SARS-CoV-2 RNA in respiratory secretions. Chest radiography should be performed and commonly shows bilateral consolidations or ground-glass opacities[11] (Fig. 2).

For epidemiologic purposes, severe Covid-19 in adults is defined as dyspnea, a respiratory rate of 30 or more breaths per minute, a blood oxygen saturation of 93% or less, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao_2:Fio_2) of less than 300 mm Hg, or infiltrates in more than 50%

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KEY CLINICAL POINTS

EVALUATION AND MANAGEMENT OF SEVERE COVID-19

- Patients with severe coronavirus disease 2019 (Covid-19) may become critically ill with acute respiratory distress syndrome that typically begins approximately 1 week after the onset of symptoms.
- Deciding when a patient with severe Covid-19 should receive endotracheal intubation is an essential component of care.
- After intubation, patients should receive lung-protective ventilation with plateau pressure less than or equal to 30 cm of water and with tidal volumes based on the patient's height.
- Prone positioning is a potential treatment strategy for refractory hypoxemia.
- Thrombosis and renal failure are well-recognized complications of severe Covid-19.
- Dexamethasone has been shown to reduce mortality among hospitalized patients with Covid-19 who require oxygen, particularly those receiving mechanical ventilation.
- Remdesivir was recently approved by the Food and Drug Administration for the treatment of Covid-19 in hospitalized patients, on the basis of randomized trials showing that the drug reduces time to clinical recovery; however, more data are needed to inform its role in treating severe Covid-19.

of the lung field.[12] In a large cohort of symptomatic patients with Covid-19 described early in the pandemic, 81% had mild disease, 14% had severe disease, and 5% became critically ill with organ failure; the mortality in the critically ill group was 49%.[12]

Healthy persons of any age may become critically ill with Covid-19. However, age is the most important risk factor for death or critical illness, and the risk increases with each additional decade.[13] People with chronic health conditions such as cardiovascular disease, diabetes mellitus, immunosuppression, and obesity are more likely to become critically ill from Covid-19. Severe disease is more common among men than among women. The risk is also increased among certain racial and ethnic groups such as Black and Hispanic persons in the United States.[14] The social determinants of health probably have a strong influence on the risk of severe disease.[13] A hallmark of the Covid-19 pandemic is the sudden appearance of an unprecedented number of critically ill patients in a small geographic area.[12] This can overwhelm local health care resources, resulting in shortages of trained staff, ventilators, renal-replacement therapy, and intensive care unit beds.

STRATEGIES

INITIAL STEPS

Patients with severe Covid-19 should be hospitalized for careful monitoring. Given the high risk of nosocomial spread,[3] strict infection-control procedures are needed at all times. If able, the patient should wear a surgical mask to limit the dispersion of infectious droplets.[15] Clinicians should don appropriate personal protective equipment (PPE) as defined by their local infection-prevention program, using particular caution when performing procedures that may increase the generation or dispersion of infectious aerosols. These include endotracheal intubation, extubation, bronchoscopy, airway suctioning, nebulization of medication, the use of high-flow nasal cannulae, noninvasive ventilation, and manual ventilation with a bag-mask device.[16] Current guidelines recommend that clinicians wear gowns, gloves, N95 masks, and eye protection at the least and place patients in negative-pressure rooms whenever possible during aerosol-generating procedures.[17]

Patients with severe Covid-19 have a substantial risk of prolonged critical illness and death. Therefore, at the earliest opportunity, clinicians should partner with patients by reviewing advanced directives, identifying surrogate medical decision makers, and establishing appropriate goals of care. Because infection-control measures during the pandemic may prevent families from visiting seriously ill patients, care teams should develop plans to communicate with patients' families and surrogate decision makers.

BASICS OF RESPIRATORY CARE

Patients should be monitored carefully by direct observation and pulse oximetry. Oxygen should be supplemented by the use of a nasal cannula or Venturi mask to keep the oxygen saturation of hemoglobin between 90 and 96%.[17] Deciding whether or not to intubate is a critical aspect of caring for seriously ill patients with Covid-19. Clinicians must weigh the risks of premature

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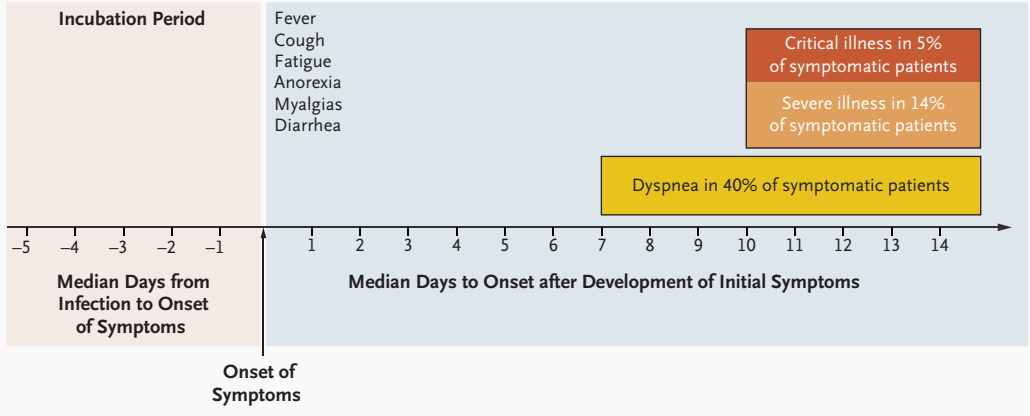

Figure 1. Timeline of Symptoms of Severe Coronavirus Disease 2019 (Covid-19).

The left border of the colored boxes shows the median time to onset of symptoms and complications. There is wide variation in the duration of symptoms and complications. Adapted from Zhou et al.[2] and the Centers for Disease Control and Prevention.[1]

intubation against the risk of sudden respiratory arrest with a chaotic emergency intubation, which exposes staff to a greater risk of infection. Signs of excessive effort in breathing, hypoxemia that is refractory to oxygen supplementation, and encephalopathy herald impending respiratory arrest and the need for urgent endotracheal intubation and mechanical ventilation. There is no single number or algorithm that determines the need for intubation, and clinicians must consider a variety of factors (Fig. 3A).

If the patient does not require intubation but remains hypoxemic, a high-flow nasal cannula can improve oxygenation and may prevent intubation in selected patients.[17,18] The use of noninvasive positive-pressure ventilation should probably be restricted to patients with Covid-19 who have respiratory insufficiency due to chronic obstructive pulmonary disease, cardiogenic pulmonary edema, or obstructive sleep apnea rather than ARDS. Patients treated with a high-flow nasal cannula or noninvasive ventilation require careful monitoring for deterioration that would indicate the need for invasive mechanical ventilation.[18]

Having awake patients turn to the prone position while they breathe high concentrations of supplemental oxygen may improve oxygenation in patients with severe Covid-19. This approach is supported by data from prospective cohorts describing its use in nonintubated patients with severe hypoxemia.[19] However, whether prone positioning can prevent intubation in patients with severe Covid-19 is unclear. Because it is difficult to provide rescue ventilation to patients who are prone, this position should be avoided in patients whose condition is rapidly deteriorating.

ENDOTRACHEAL INTUBATION

A skilled operator should perform endotracheal intubation in patients with severe Covid-19. The use of unfamiliar PPE, the risk of infection to staff, and the presence of severe hypoxemia in patients all increase the difficulty of intubation. If possible, intubation should be performed after preoxygenation and rapid-sequence induction of sedation and neuromuscular blockade. An antiviral filter should be placed in line with the airway circuit at all times. Video laryngoscopy may allow the operator to have a good view of the airway from a greater distance.[20] However, operators should choose the technique that is most likely to be successful on the first attempt. Continuous-wave capnography is the best method to confirm tracheal intubation.[20] Patients with severe Covid-19 often become hypotensive soon after intubation owing to positive-pressure ventilation and systemic vasodilation from sedatives.[20] Therefore, intravenous fluids and vasopressors should be immediately available at the time of intubation, and careful hemodynamic monitoring is essential.[20]

VENTILATOR MANAGEMENT

It is unclear whether Covid-19 is associated with a distinct form of ARDS that would benefit from

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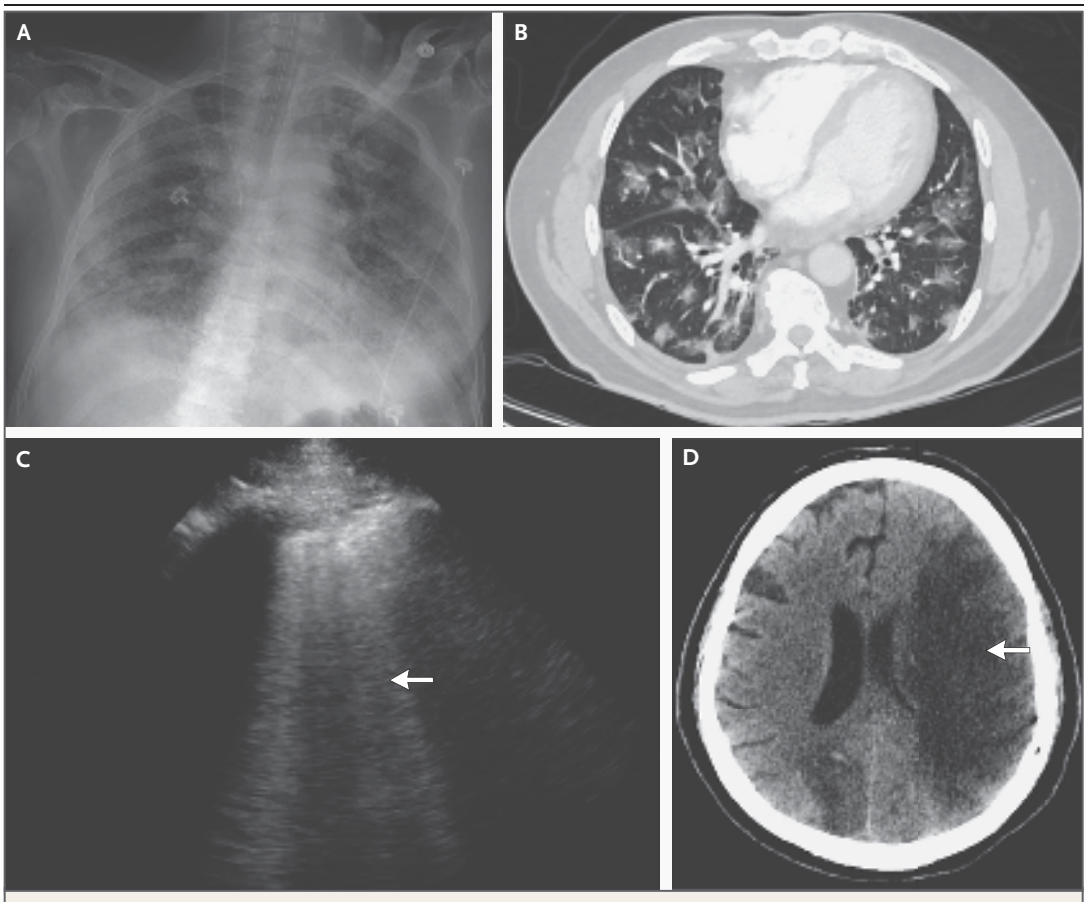

Figure 2. Radiographic and Ultrasonographic Findings of Severe Covid-19.

Chest radiography (Panel A) shows bilateral ground-glass opacities and consolidations. Computed tomography (CT) of the chest (Panel B) shows bilateral ground-glass opacities. Thoracic ultrasonography (Panel C) shows B lines (arrow); this image is courtesy of Dr. Christopher Parkhurst. CT of the head (Panel D) shows left-greater-than-right cerebral infarcts (arrow).

a new strategy of mechanical ventilation. However, most autopsies performed on patients with severe Covid-19 reveal the presence of diffuse alveolar damage, which is the hallmark of ARDS.[21] Moreover, respiratory-system compliance and gas exchange in patients with respiratory failure from severe Covid-19 are similar to those in populations enrolled in previous therapeutic trials for ARDS.[22] Therefore, clinicians should follow the treatment paradigm developed during the past two decades for ARDS (Fig. 3B).[17,18] This strategy aims to prevent ventilator-induced lung injury by avoiding alveolar overdistention, hyperoxia, and cyclical alveolar collapse.

To prevent alveolar overdistention, clinicians should limit both the tidal volume delivered by the ventilator and the maximum pressure in the alveoli at the end of inspiration. To do this, clinicians should set the ventilator to deliver a tidal volume of 6 ml per kilogram of predicted body weight; this approach is termed "lung-protective ventilation." A tidal volume up to 8 ml per kilogram of predicted body weight is allowed if the patient becomes distressed and attempts to take larger tidal volumes. A few times each day, clinicians should initiate a half-second end-inspiratory pause, which allows the pressure in the airway circuit to equilibrate between the patient and the ventilator. The pressure in the airway circuit at the end of the pause — "the plateau pressure" — approximates the alveolar pressure (relative

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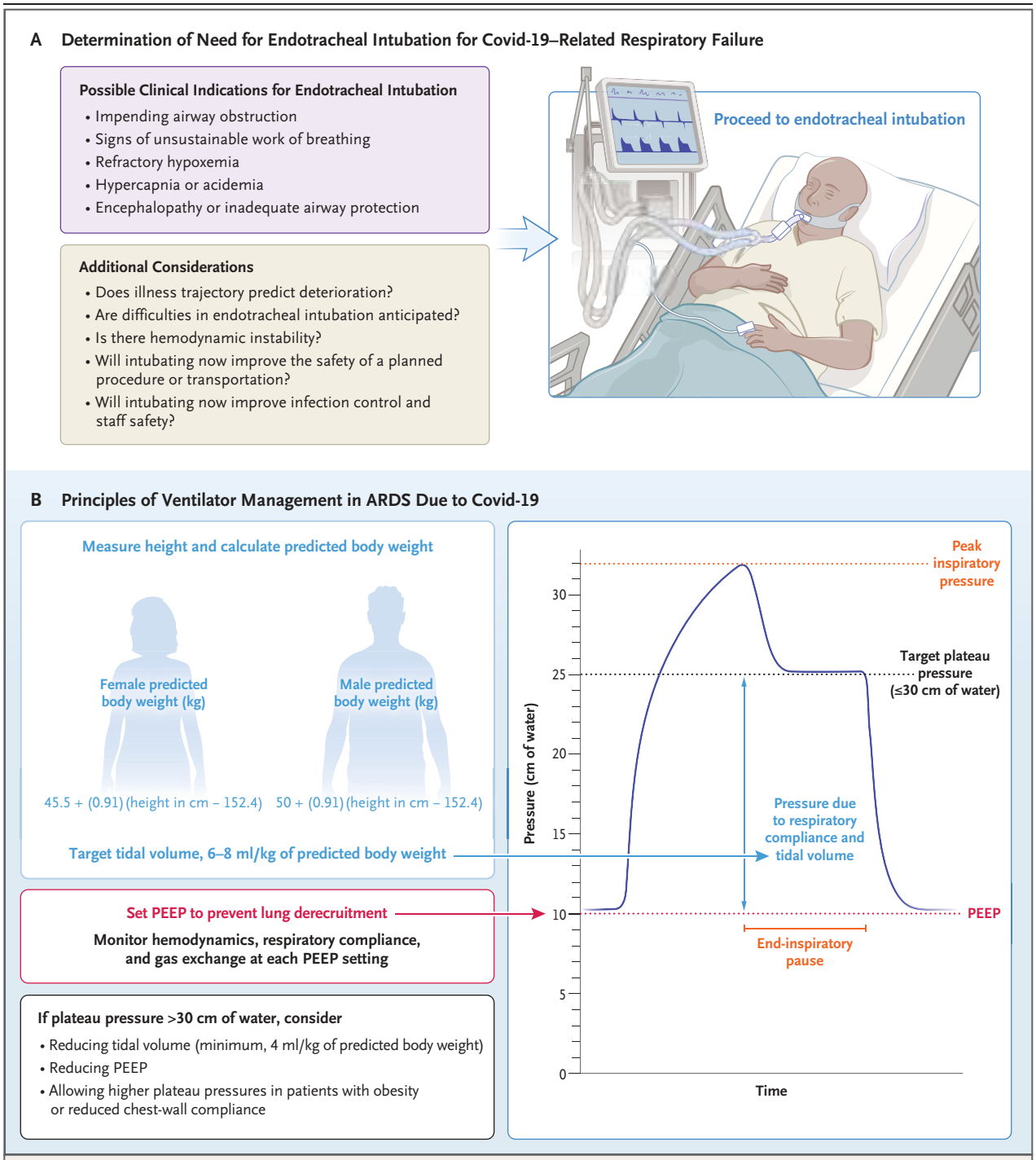

Figure 3. Invasive Mechanical Ventilation for Covid-19–Related Respiratory Failure.

As shown in Panel A, a life-threatening problem in the purple box or a combination of less severe problems in the purple and tan boxes determines the need for endotracheal intubation. In Panel B, "lung derecruitment" refers to the collapse of alveoli. All pressures are measured in the ventilator circuit and referenced to atmospheric pressure. ARDS denotes acute respiratory distress syndrome, and PEEP positive end-expiratory pressure.

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to atmospheric pressure). To prevent alveolar overdistention, the plateau pressure should not exceed 30 cm of water.[23] A higher plateau pressure without the development of ventilator-induced lung injury may be possible in patients with central obesity or noncompliant chest walls.

For patients with Covid-19–related ARDS, setting sufficient positive end-expiratory pressure (PEEP) on the ventilator may prevent alveolar collapse and facilitate the recruitment of unstable lung regions. As a result, PEEP can improve respiratory-system compliance and allow for a reduction in the F_{IO_2}. However, PEEP can reduce venous return to the heart and cause hemodynamic instability. Moreover, excessive PEEP can lead to alveolar overdistention and reduce respiratory-system compliance. No particular method of determining the appropriate level of PEEP has been shown to be superior to other methods.[17]

Sedatives and analgesics should be targeted to prevent pain, distress, and dyspnea. They can also be used to blunt the patient's respiratory drive, which improves patient synchrony with mechanical ventilation. Sedation is especially important in febrile patients with high metabolic rates who are treated with lung-protective ventilation. Neuromuscular blocking agents can be used in deeply sedated patients who continue to use their accessory muscles of ventilation and have refractory hypoxemia.[17] These agents can reduce the work of breathing, which reduces oxygen consumption and carbon dioxide production.[24] Moreover, sedatives and neuromuscular blocking agents may help reduce the risk of lung injury that may occur when patients generate strong spontaneous respiratory efforts.

REFRACTORY HYPOXEMIA

Clinicians should consider prone positioning during mechanical ventilation in patients with refractory hypoxemia (P_{aO_2}:F_{IO_2} of <150 mm Hg during respiration and F_{IO_2} of 0.6 despite appropriate PEEP). In randomized trials involving intubated patients with ARDS (not associated with Covid-19), placing the patient in the prone position for 16 hours per day has improved oxygenation and reduced mortality.[18,25] However, prone positioning of patients requires a team of at least three trained clinicians, all of whom require full PPE.[17] Inhaled pulmonary vasodilators (e.g., inhaled nitric oxide) can also improve oxygenation in refractory respiratory failure, although they do not improve survival in ARDS not associated with Covid-19.[17] Extracorporeal membrane oxygenation (ECMO) is a potential rescue strategy in patients with refractory respiratory failure. Clinicians should carefully balance possible benefits with risks (e.g., bleeding) as well as the resources available during the pandemic.[26]

THERAPY

A large, randomized clinical trial involving more than 6400 hospitalized patients with Covid-19 showed that dexamethasone significantly reduced 30-day mortality (17% reduction); benefit was limited to patients who required oxygen supplementation and appeared greater in patients receiving mechanical ventilation.[27] Consequently, dexamethasone (or potentially other glucocorticoids) is now considered the standard of care for patients with severe Covid-19.

Data from a randomized, placebo-controlled trial involving more than 1000 patients with severe Covid-19 showed that the antiviral agent remdesivir reduced time to clinical recovery; the benefit appeared greatest in patients who were receiving supplemental oxygen but were not intubated.[28] The 29-day mortality in that trial was 11.4% with remdesivir and 15.2% with placebo (hazard ratio for death, 0.73; 95% confidence interval, 0.52 to 1.03). These data support the Food and Drug Administration (FDA) approval of remdesivir for the treatment of hospitalized patients with Covid-19 in October 2020. Recent preliminary results of a large, multinational, open-label, randomized trial did not show a reduction in in-hospital mortality with use of remdesivir.[29] The combination of dexamethasone and remdesivir is increasingly used clinically, but its benefit has not been shown in randomized clinical trials. Tocilizumab, an interleukin-6 inhibitor, did not significantly reduce disease progression[30] or death in small randomized trials involving patients with severe Covid-19.[31,32]

SUPPORTIVE CARE

Patients with Covid-19 often present with volume depletion and receive isotonic-fluid resuscitation. Volume repletion helps maintain blood pressure and cardiac output during intubation and positive-pressure ventilation. After the first few days of mechanical ventilation, the goal should be to avoid hypervolemia.[33] Fever and tachypnea in patients with severe Covid-19 often

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increase insensible water loss, and careful attention must be paid to water balance. If the patient is hypotensive, the dose of vasopressor can be adjusted to maintain a mean arterial pressure of 60 to 65 mm Hg.[17] Norepinephrine is the preferred vasopressor. The presence of unexplained hemodynamic instability should prompt consideration of myocardial ischemia, myocarditis, or pulmonary embolism.

In case series, approximately 5% of patients with severe Covid-19 have received renal-replacement therapy[34]; the pathophysiology of the renal failure is currently unclear but is probably multifactorial. Because blood clotting in the circuit is common in patients with severe Covid-19,[6] the efficacy of continuous renal-replacement therapy is uncertain.

Abnormalities of the clotting cascade, such as thrombocytopenia and elevation of D-dimer levels, are common in patients with severe Covid-19 and are associated with increased mortality.[3] If there are no contraindications, patients should receive standard thromboprophylaxis (e.g., subcutaneous low-molecular-weight heparin).[35] Some case series of patients with severe Covid-19 have shown clinically significant thrombosis despite the use of thromboprophylaxis.[6] However, the benefits and risks of the routine use of more intense prophylactic anticoagulation in patients are unknown.[35]

Patients hospitalized with severe Covid-19 are often treated empirically with antibiotics.[3,9] However, bacterial coinfection is rare when immunocompetent patients first present to the hospital.[36] Antibiotics can be discontinued after a short course if signs of bacterial coinfection, such as leukocytosis and focal pulmonary infiltrates, are absent.[18] Although Covid-19 itself can cause prolonged fever,[2] clinicians should be vigilant for nosocomial infections.

Performing cardiopulmonary resuscitation in patients with Covid-19 may expose health care workers to infectious droplets and aerosols. Therefore, all the members of the resuscitation team should wear appropriate PPE before performing rescue ventilation, chest compressions, or defibrillation.[37]

Patients with Covid-19 who are receiving mechanical ventilation should receive appropriate nutrition and care to prevent constipation and injury to the skin and corneas. If the condition of a patient has stabilized, clinicians should attempt to withhold continuous sedation each day.[38] Daily awakening may be challenging because an increase in the work of breathing and the loss of synchrony with mechanical ventilation may result in distress and hypoxemia.

During the Covid-19 pandemic, an overwhelming surge of patients presenting to a hospital may temporarily require the rationing of health care resources. Local guidelines and medical ethics consultation can help clinicians navigate these difficult decisions with patients and their families.

AREAS OF UNCERTAINTY

Despite FDA approval of remdesivir for hospitalized patients with Covid-19, more data are needed to inform the role of this drug in severe Covid-19. Numerous randomized trials of many other candidate therapies, including antivirals, antibodies, and immunomodulating agents, are ongoing (Table 1).

Despite observational studies suggesting benefit of interleukin-6 inhibitors,[53,54] small, randomized clinical trials failed to show consistent benefit.[30-32] Other immunomodulating agents currently being evaluated for severe Covid-19 include passive immunotherapy with convalescent plasma, monoclonal antibodies, immunoglobulins, and interleukin-1 pathway inhibitors.[55] Pending final results of randomized trials, the risks and benefits of these approaches are also unknown. Candidate therapies for Covid-19 warrant evaluation separately in patients with established severe disease and in those with milder illness to determine whether they reduce the risk of progression to severe disease.

GUIDELINES

The recommendations in this article are largely concordant with the guidelines for severe Covid-19 from the American Thoracic Society, the Infectious Diseases Society of America, the National Institutes of Health, and the Surviving Sepsis Campaign.[17,18,56,57]

CONCLUSIONS AND RECOMMENDATIONS

For the patient described in the vignette, an important aspect of care is careful monitoring of

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Table 1. Selected Candidate Therapies for Coronavirus Disease 2019 (Covid-19).*

Class	Availability	Rationale	Clinical Data
Antiviral agents			
Hydroxychloroquine	FDA-approved for lupus, malaria, rheumatoid arthritis; FDA emergency-use authorization for certain hospitalized patients with Covid-19 was revoked	In vitro activity against SARS-CoV-2[39]	Randomized, controlled trials showed no benefit in hospitalized patients[40,41]
Lopinavir–ritonavir	FDA-approved for HIV infection	In vitro activity against SARS-CoV-2[42]	Randomized, controlled trials showed no benefit in hospitalized patients[43,44]
Remdesivir	FDA-approved for hospitalized patients with Covid-19	In vitro activity against SARS-CoV-2[42,45]	Randomized, placebo-controlled trials showed faster time to recovery with remdesivir in hospitalized patients[28,46]; preliminary results from a large, multinational, open-label randomized trial showed no mortality benefit[29]
Antibodies			
Convalescent plasma	Investigational; FDA emergency-use authorization for hospitalized patients with Covid-19	Use in other viral illnesses, including H1N1 influenza, SARS, and MERS	Small, uncontrolled cohort studies suggested benefit[47,48]; small randomized, controlled trials did not suggest benefit[49,50]; large uncontrolled study showed preliminary safety[51]; additional randomized, controlled trials in progress
Monoclonal antibodies	Investigational; FDA emergency-use authorization for nonhospitalized patients with Covid-19	Use in other viral illnesses, including Ebola and HIV	One randomized clinical trial showed that a single dose of bamlanivimab (LY-CoV555) reduced viral load in outpatients with Covid-19[52]; role in inpatients unclear
Immune-based agents			
BTK inhibitors (acalabrutinib, ibrutinib, rilzabrutinib)	FDA-approved for some hematologic cancers	Immunomodulation-targeting cytokines	Clinical trials in progress
Dexamethasone (and other glucocorticoids)	FDA-approved for multiple indications	Broad immunomodulation	Large randomized, controlled trial showed mortality benefit with dexamethasone in hospitalized patients requiring oxygen[27]
Interleukin-1 inhibitors (anakinra, canakinumab)	FDA-approved for some autoimmune diseases	Immunomodulation; activity in macrophage activation syndrome	Clinical trials in progress
Interleukin-6 inhibitors (sarilumab, siltuximab, tocilizumab)	FDA-approved for some autoimmune diseases and cytokine release syndrome (tocilizumab)	Immunomodulation; activity in cytokine release syndrome	Small randomized, controlled trials have not shown benefit[30-32]; additional clinical trials in progress
JAK inhibitors (baricitinib, ruxolitinib)	FDA-approved for rheumatoid arthritis (baricitinib) and myelofibrosis and polycythemia vera (ruxolitinib); FDA emergency-use authorization for baricitinib in combination with remdesivir for hospitalized patients with Covid-19 requiring oxygen	Broad immunomodulation	Clinical trials in progress

* Selected references are provided for rationale and clinical data. ARDS denotes acute respiratory distress syndrome, BTK Bruton's tyrosine kinase, FDA Food and Drug Administration, HIV human immunodeficiency virus, IND investigational new drug, JAK Janus kinase, MERS Middle East respiratory syndrome, SARS severe acute respiratory syndrome, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

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his respiratory status to determine whether endotracheal intubation is appropriate. If mechanical ventilation is initiated, the clinician should adhere to a lung-protective ventilation strategy by limiting the plateau pressure and tidal volumes. Deep sedation with neuromuscular blocking agents and prone positioning should be considered if refractory hypoxemia develops. Prophylactic anticoagulants should be administered to prevent thrombosis. Dexamethasone should be started, because data from a randomized clinical trial show a reduction in mortality. Although more data are needed to inform benefits of treatment with both remdesivir and dexamethasone, we would also give remdesivir given its antiviral mechanism of action and data from randomized clinical trials showing that it shortens time to clinical recovery. Rigorous adherence to infection-control practices is essential at all times. Given the high risk of complications from severe Covid-19, clinicians should work with patients and families to establish appropriate goals of care at the earliest possible time.

Given the uncertainties regarding effective treatment, clinicians should discuss available clinical trials with patients. In addition, clinicians should discuss the value of autopsies with the families of patients who do not survive.

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COVID-19 daily epidemiology update

Updated: April 19, 2021, 7 pm EST

Summary of COVID-19 cases across Canada and over time. Contains detailed data about the spread of the virus over time and in different regions of the country. Includes breakdowns by age and sex or gender. Provides an overview of hospitalizations and deaths, testing, variants of concern and exposures.

Key updates as of April 19, 2021, 7 pm EST

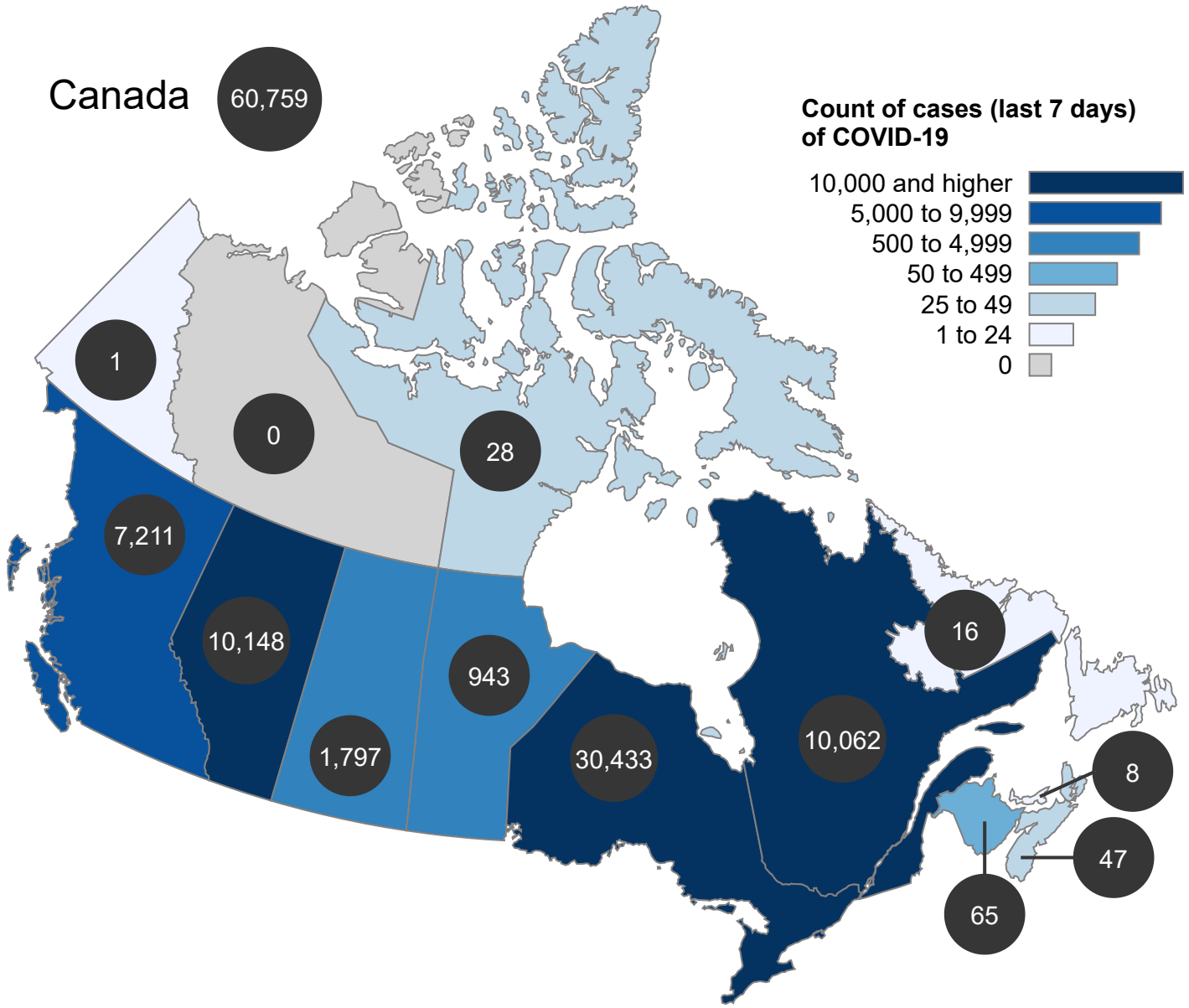
Cases today	Total cases	Active cases	Total resolved	Deaths today	Total deaths
8,317	1,131,773	88,327	1,019,779	45	23,667

Tests performed today	Total tests performed	Percent positive (total)	Tests performed per million population
105,799	30,041,115	3.9%	790,447

- We update these sections daily at 7:00 PM EST: Key updates, Current situation and National overview.
- We update these sections every Friday: Epidemic curve, Demographics, How people were exposed, and Severe illness and outcomes.
- Most cases (67.1%) and deaths (78.4%) were reported by Ontario and Quebec.
- Of the 13 jurisdictions reporting updates, no new cases were reported in 2 provinces or territories in the past 24 hours.
- Of the 13 jurisdictions reporting updates, no new deaths were reported in 9 provinces or territories in the past 24 hours.

Current situation

Figure 1a. Count of cases (last 7 days) of COVID-19, by province/territory as of April 19, 2021



The count of cases (last 7 days) of COVID-19 in **Canada** was **60,759** as of April 19, 2021.

This information is based on data from our provincial and territorial partners. It's current as of April 19, 2021, 7 pm EST. For the most up to date data for any province, territory or city, please visit their web site.

Areas in Canada with cases of COVID-19 as of April 19, 2021

	Total cases		Cases last 7 days		Active cases		Resolved††	Deaths		Deaths last 7 days		Total tests performed	
Location	**Count**	**Rate***	**Count**	**Rate***	**Count**	**Rate***	**Count**	**Count**	**Rate***	**Count**	**Rate***	**Count**	**Rate†**
Canada	**1,131,773**	**2,978**	**60,759**	**160**	**88,327**	**232**	**1,019,779**	**23,667**	**62**	**311**	**1**	**30,041,115**	**790,447**
British Columbia	120,040	2,332	7,211	140	9,583	186	108,919	1,538	30	25	0	2,372,213	460,829
Alberta	172,186	3,894	10,148	230	18,424	417	151,719	2,043	46	25	1	3,925,765	887,805
Saskatchewan	38,401	3,258	1,797	152	2,626	223	35,310	465	39	10	1	726,692	616,530
Manitoba	36,267	2,629	943	68	1,685	122	33,623	959	70	10	1	632,455	458,546
Ontario	421,442	2,860	30,433	207	42,863	291	370,844	7,735	53	168	1	13,382,023	908,240
Quebec	338,044	3,942	10,062	117	12,852	150	314,376	10,816	126	72	1	7,844,970	914,911
Newfoundland and Labrador	1,046	200	16	3	29	6	1,011	6	1	0	0	234,869	449,852
New Brunswick	1,797	230	65	8	159	20	1,605	33	4	0	0	284,651	364,248
Nova Scotia	1,822	186	47	5	63	6	1,692	67	7	1	0	466,315	476,147
Prince Edward Island	173	108	8	5	13	8	160	0	0	0	0	134,959	845,475
Yukon	76	181	1	2	2	5	73	1	2	0	0	8,799	209,241
Northwest Territories	43	95	0	0	0	0	43	0	0	0	0	16,994	376,298
Nunavut	423	1,075	28	71	28	71	391	4	10	0	0	10,334	262,598

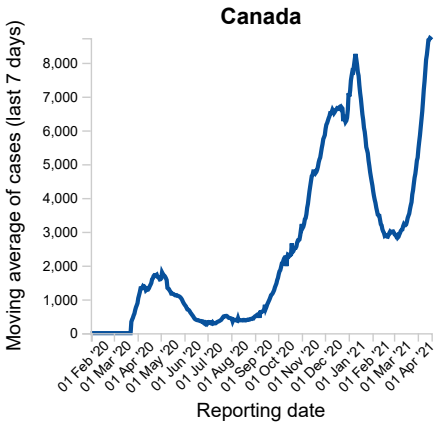
† Rate per 1,000,000 population

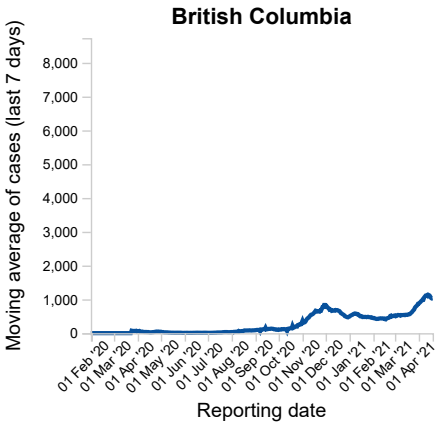
* Rate per 100,000 population

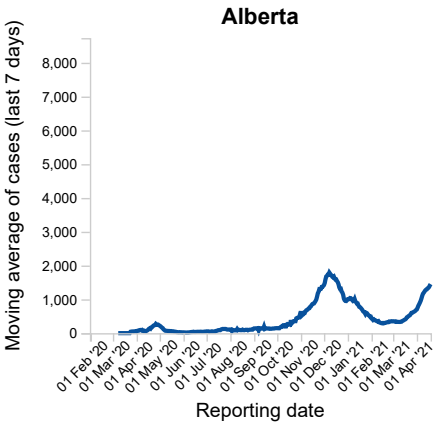
†† Recovered refers to cases that are resolved. These are people who have molecular test proof to show they had a positive COVID-19 test taken between 14 to 90 days before travel.

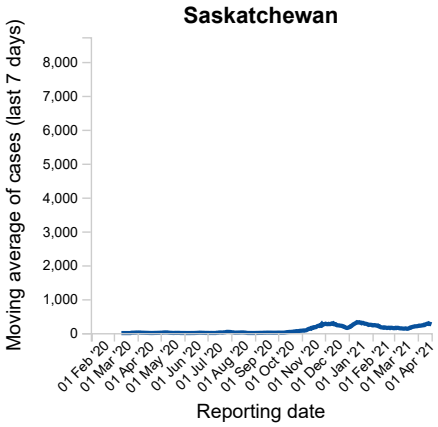
Figure 1b. Moving average of cases (last 7 days) of COVID-19 in Canada as of April 19, 2021, 7 pm EST

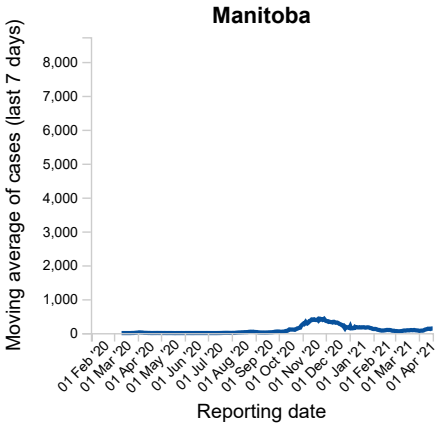
The figures below show cases over time. The range of dates (January 31st, 2020 - present date) is the same for each figure. This allows you to compare the provinces and territories on the same timescale.

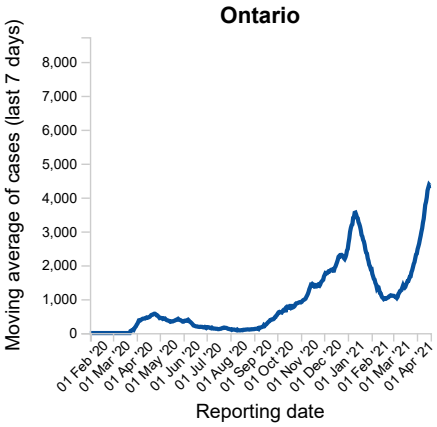


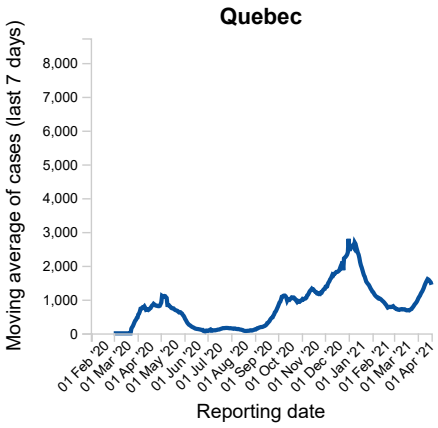


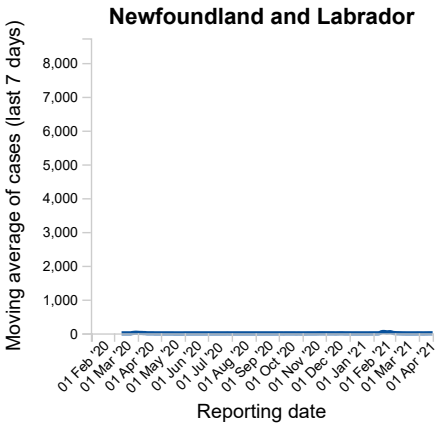


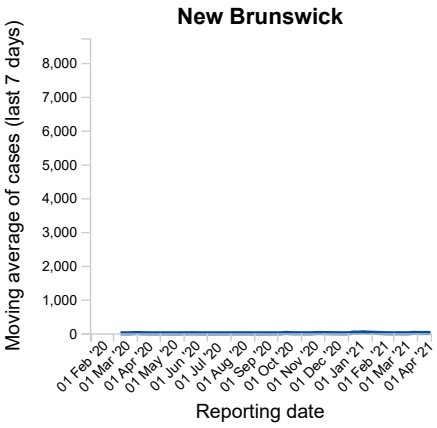


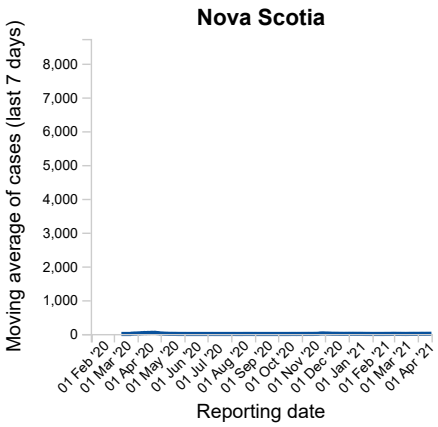


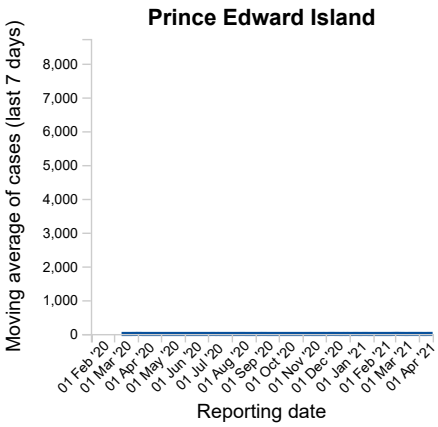


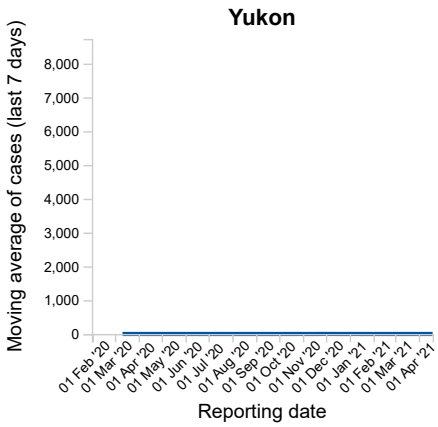


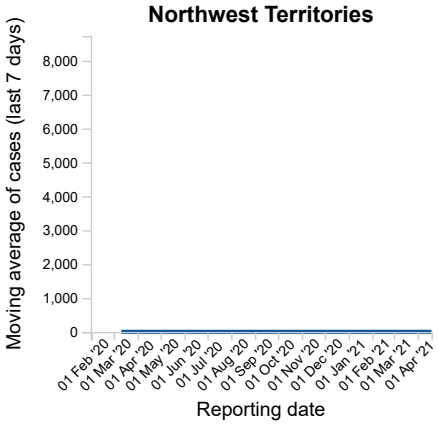


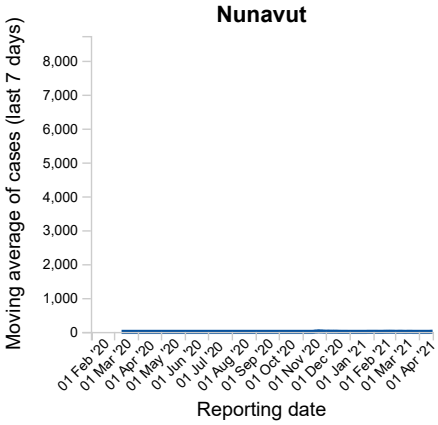












Downloadable data (in .csv format).

Note: Out of the total number of people tested, 76 were repatriated travellers, of which 13 were cases.

National overview

There have been over **30,041,115** COVID-19 tests performed in Canada or **790,447 tests per 1 million people**. Of these, **3.9%** were positive. For information about testing trends, please see the Detailed weekly epidemiological report (PDF).

Table 1. Daily* change in the number of cases, deaths and tests performed, by province or territory, as of April 19, 2021, 7 pm EST

Location	New cases	New deaths	Tests performed
Canada	**8,317**	**45**	**105,799**
British Columbia	1,000	8	10,656
Alberta	1,391	3	N/A
Saskatchewan	243	0	3,098
Manitoba	108	0	2,410
Ontario	4,447	19	53,776
Quebec	1,092	15	31,678
Newfoundland and Labrador	3	0	728
New Brunswick	9	0	1,029
Nova Scotia	15	0	2,052
Prince Edward Island	3	0	255
Yukon	0	0	11
Northwest Territories	0	0	18
Nunavut	6	0	88

* The new cases, deaths and tests reflect the difference between a province or territory's current report and their last report. Some provinces and territories do not update daily.

N/A means that no daily update was provided by the province or territory.

Variants of Concern (VOC) in Canada

All viruses, including COVID-19, change, or mutate, over time. Not all mutations are of concern. However, some changes result in variants of concern (VOC). A VOC has changes that are significant to public health. For example, they might:

- spread more easily
- cause more severe illness
- require different treatments, or
- not respond the same to current vaccines

We update VOC (Variants of concern) information daily from Sunday to Thursday at 7:00 PM EST, using publicly reported information fro the provinces and territories.

Table 2. Cumulative number of cases involving variants of concern (VOC) publicly reported, as of April 19, 2021 7:00 PM EST

Location	B.1.1.7 variant	B.1.351 variant	P.1 variant
Canada	**63,543**	**415**	**2,201**
British Columbia	3,858	71	1,810
Alberta	17,587	31	169
Saskatchewan	1,909	9	0
Manitoba	623	20	1
Ontario	36,579	104	211
Quebec	2,554	163	8
Newfoundland and Labrador	178	1	0
New Brunswick	180	4	0
Nova Scotia	63	12	1
Prince Edward Island	10	0	0
Yukon	1	0	1
Northwest Territories	1	0	0
Nunavut	0	0	0

Note: The table reports publicly available information from the provinces and territories. In case of discrepancies, the provincial or territorial data should be considered current and correct.

Detailed case information

The tables and figures below reflect detailed case information provided to the Public Health Agency of Canada (PHAC) by health authorities in the provinces and territories. This data is updated every week. It may change as we get more information about cases.

Updated: April 16, 2021, 9 am EST

Epidemic curve

As of April 16, 2021, 9 am EST, PHAC has received detailed case report data on 1,093,690 cases. Both exposure and symptom onset date were available for 1,078,119 (98.6%) cases [1].

The shaded area on the far right of Figure 2 represents lag time. This is the period of time (1 to 2 weeks) before the latest cases are reported to PHAC. This delay is a result of the time required to seek health care, get tested and receive results. It also takes time for public health authorities to gather information on cases. We update this information as it becomes available.

Figure 2. COVID-19 cases (n=1,078,119 [1]) in Canada by date of illness onset [2] as of April 16, 2021, 7 pm EST (total cases)

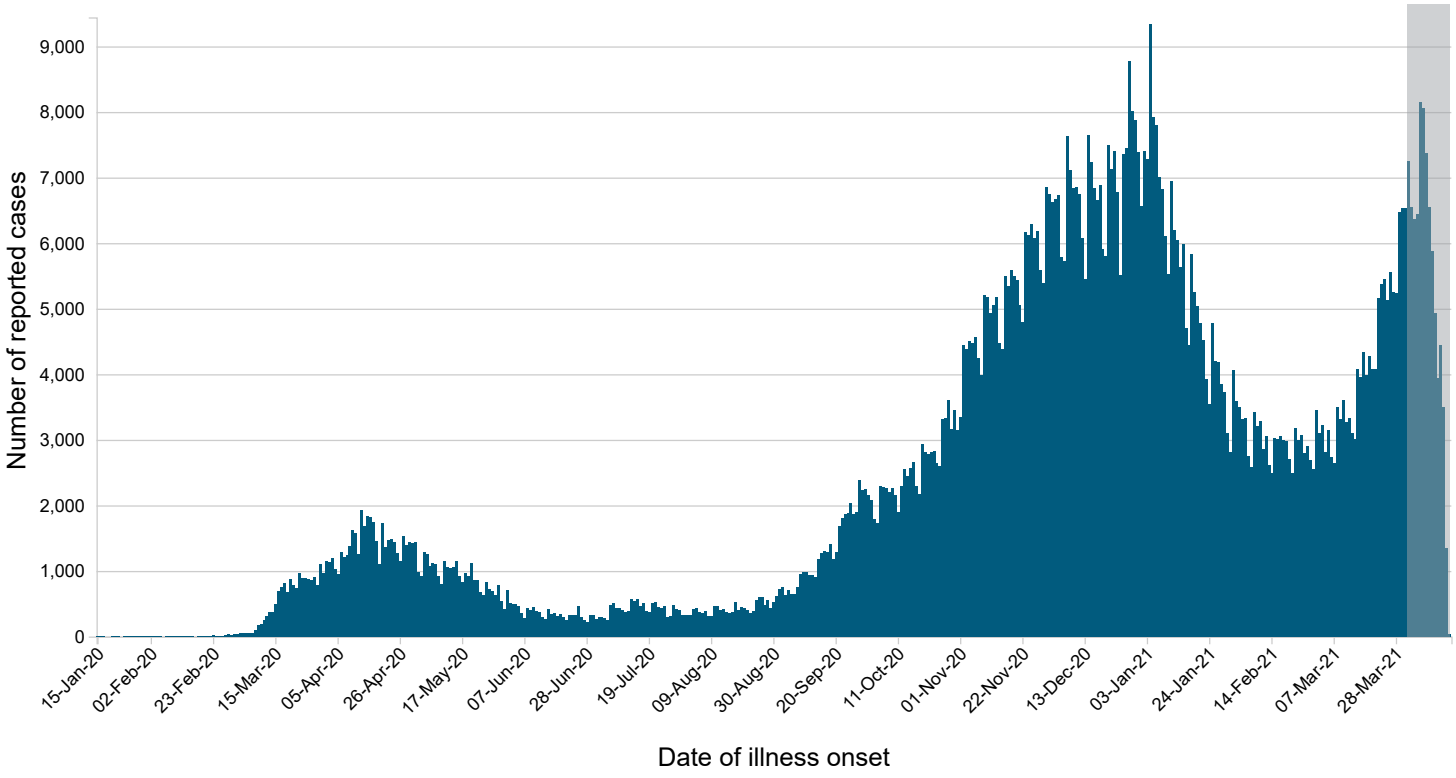


Figure 2. COVID-19 cases (n=1,078,119 [1]) in Canada by date of illness onset [2] as of April 16, 2021, 7 pm EST (by exposure)

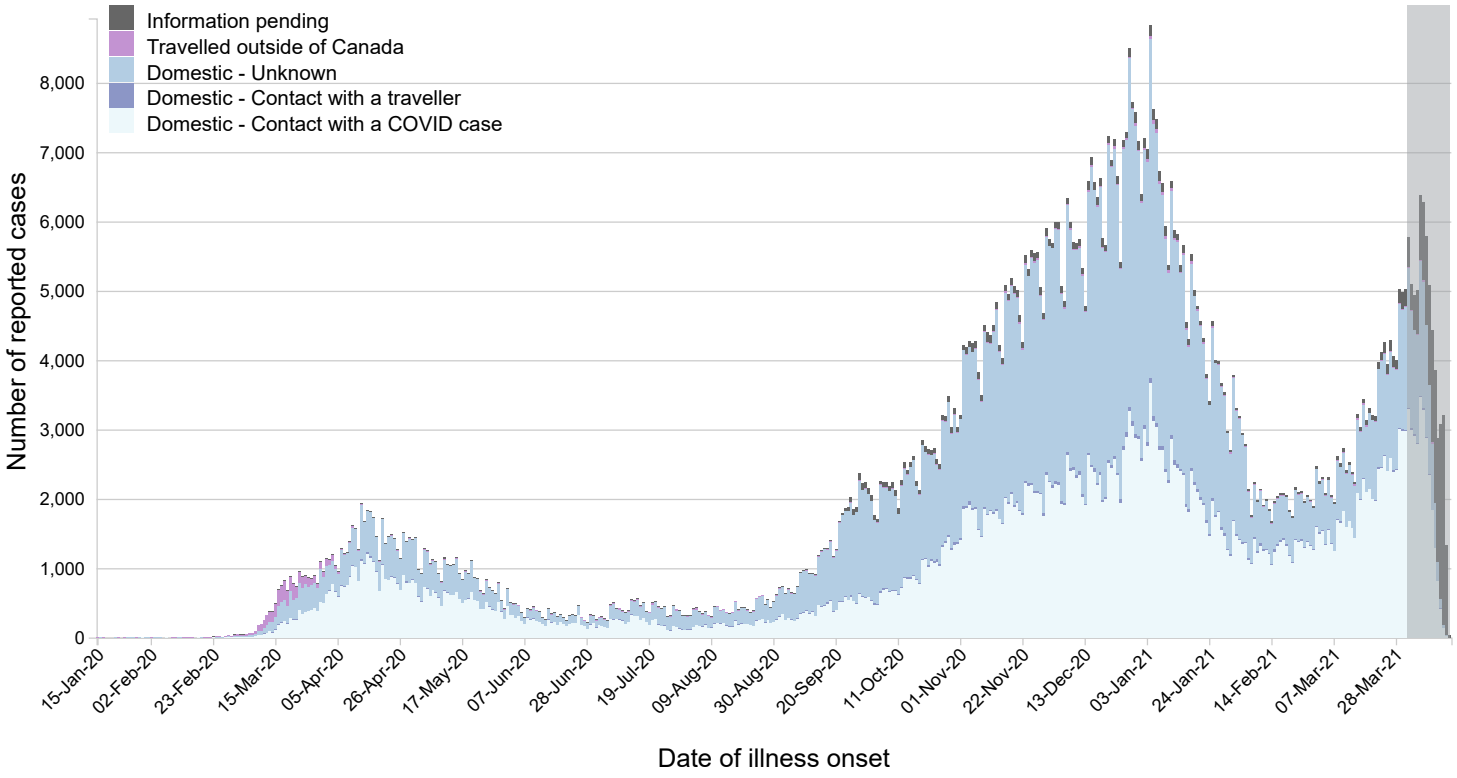


Figure 2. COVID-19 cases (n=1,077,735 [1]) in Canada by date of illness onset [2] as of April 16, 2021, 7 pm EST (by age - 10 year groups)

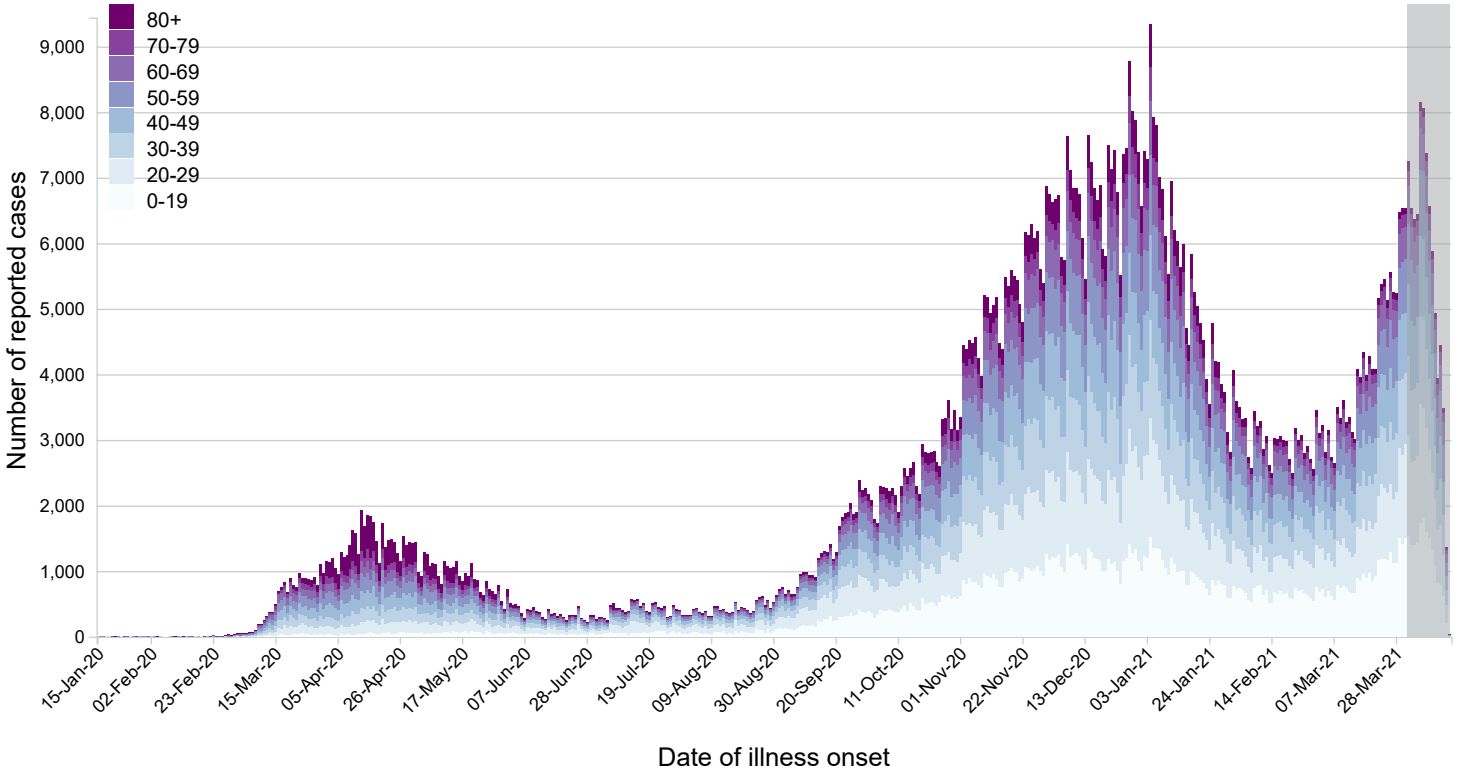
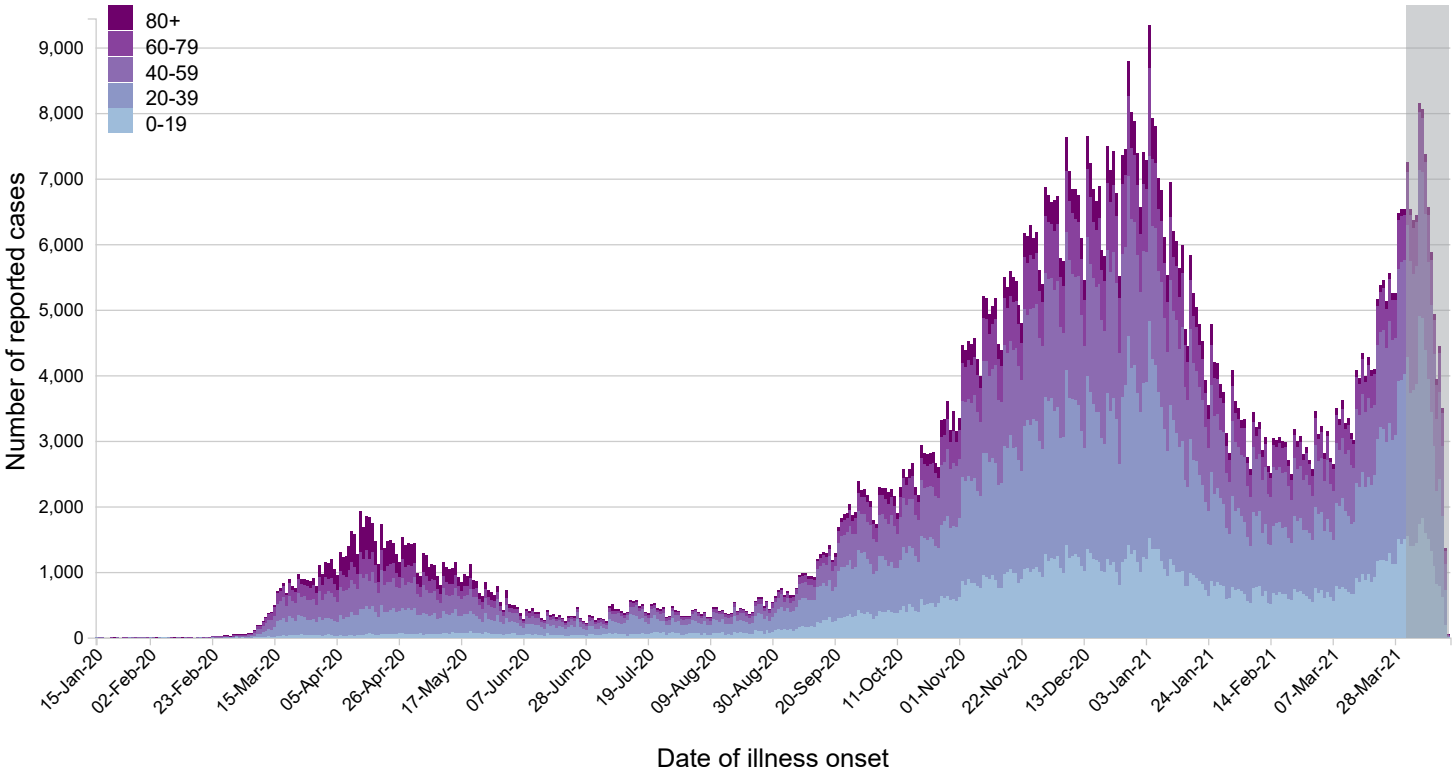


Figure 2. COVID-19 cases (n=1,077,735 [1]) in Canada by date of illness onset [2] as of April 16, 2021, 7 pm EST (by age - 20 year groups)



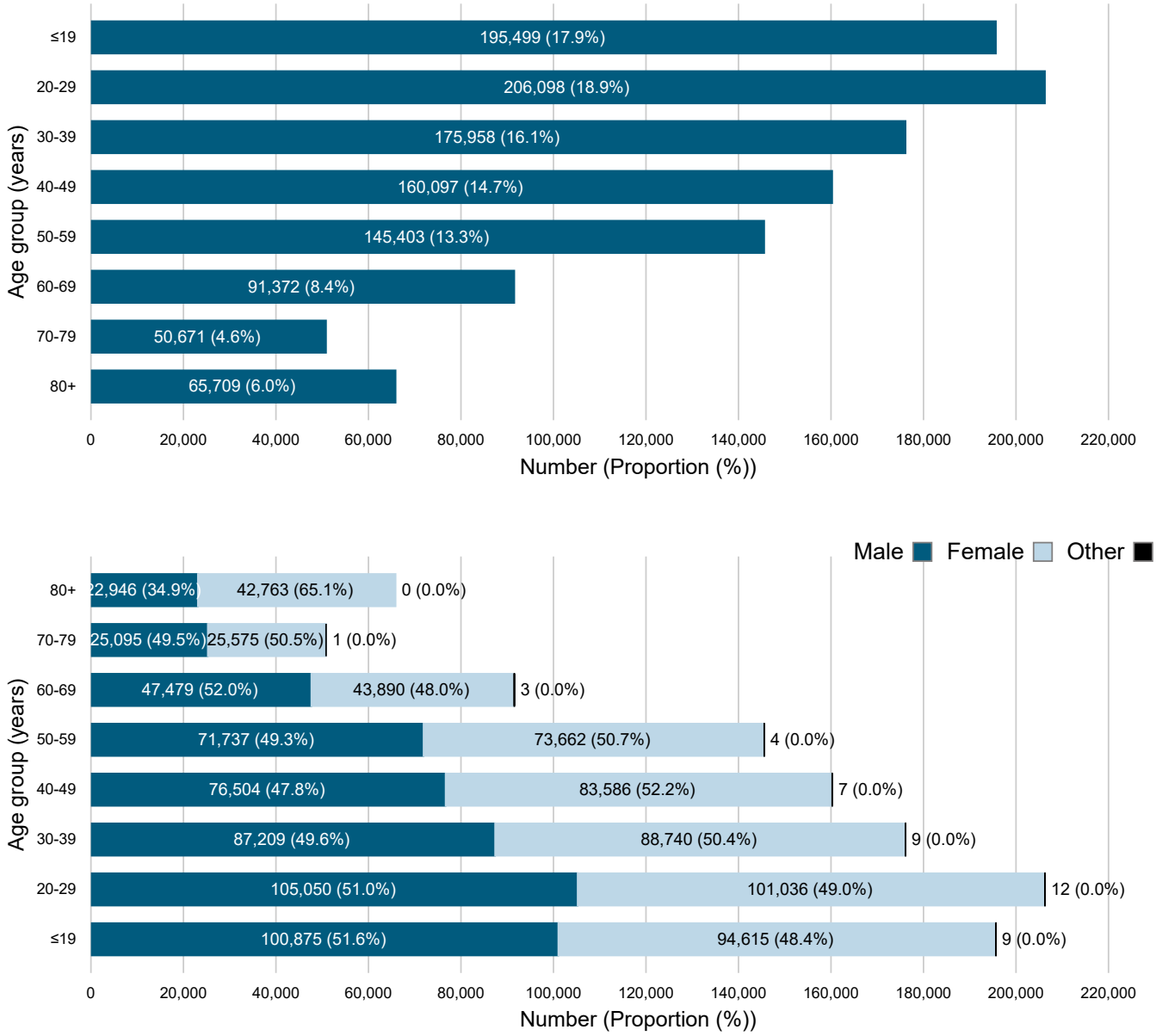
This figure may underestimate the total number of cases among returning travelers. Exposure history is not available for all cases and jurisdictions have not all consistently reported exposure history to PHAC throughout the pandemic.

Demographics

We have detailed case report data from 1,093,690 cases. We know the age of patients in 99.84% of cases, and both age and gender in 99.74% of cases.

Of the cases reported in Canada so far, about half (50.8%) were female. About one-fifth (19.0%) were 60 years old and over (Figure 3).

Figure 3. Age distribution of COVID-19 cases (n=1,091,940 [1]) in Canada as of April 16, 2021, 7 pm EST [4]



Age by gender [4] distribution of COVID-19 cases (n=1,091,940 [1]) in Canada, April 16, 2021, 7 pm EST

Age group (years)	Number of cases with case reports (percentage)	Number of male cases (percentage)	Number of female cases (percentage)	Number of other cases (percentage)
≤19	195,499 (17.9%)	100,875 (18.8%)	94,615 (17.1%)	9 (20.0%)
20-29	206,098 (18.9%)	105,050 (19.6%)	101,036 (18.2%)	12 (26.7%)
30-39	175,958 (16.1%)	87,209 (16.2%)	88,740 (16.0%)	9 (20.0%)
40-49	160,097 (14.7%)	76,504 (14.2%)	83,586 (15.1%)	7 (15.6%)
50-59	145,403 (13.3%)	71,737 (13.4%)	73,662 (13.3%)	4 (8.9%)
60-69	91,372 (8.4%)	47,479 (8.8%)	43,890 (7.9%)	3 (6.7%)
70-79	50,671 (4.6%)	25,095 (4.7%)	25,575 (4.6%)	1 (2.2%)
80+	65,709 (6.0%)	22,946 (4.3%)	42,763 (7.7%)	0 (0.0%)
Total	1,090,807 (100%)	536,895 (100%)	553,867 (100%)	45 (100%)

How people were exposed [3]

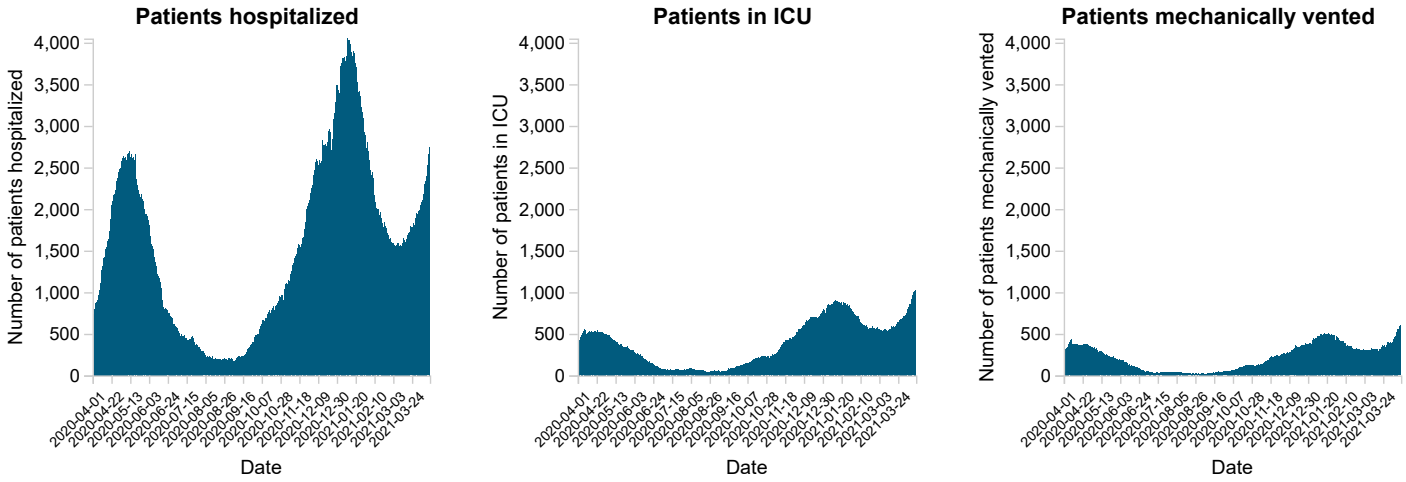
In Canada, detailed case report data were provided for 1,093,690 cases. We have exposure history for 979,763 (89.6%) cases. The probable exposure setting of these cases [1] are:

- any exposure that occurred in Canada: **937,657 (95.7%)**, including
  - from contact with a known COVID case: **446,990 (45.6%)**
  - from contact with a traveller: **7,034 (0.7%)**
  - from an unknown source: **483,633 (49.4%)**
- currently unknown (information pending): **33,491 (3.4%)**
- travelled outside of Canada: **8,615 (0.9%)**

Severe illness and outcomes

Hospital use

Figure 4. Daily number of hospital beds and ICU beds occupied by COVID-19 patients as of April 12, 2021



Between April 5, 2021 and April 12, 2021:

- the number of **hospital beds** occupied by COVID-19 patients **increased** from **2,182** to **2,741** beds.
- the number of **ICU beds** occupied by COVID-19 patients **increased** from **859** to **1,028** beds.
- the number of **COVID-19 patients who were mechanically vented increased** from **463** to **599**.

Hospitalizations and deaths to date

We have detailed case report data on 1,093,690 cases, and hospitalization status for 758,048 (69.3%) of them:

- **56,706** cases **(7.5%)** were hospitalized, of whom:
  - **10,166 (17.9%)** were admitted to the ICU
  - **1,729 (3.0%)** needed mechanical ventilation

The provinces and territories provided detailed case report forms for **23,476** deaths related to COVID-19.

Figure 5a. Age and gender [4] distribution of COVID-19 cases hospitalized in Canada as of April 16, 2021, 7 pm EST (n=56,594 [1])

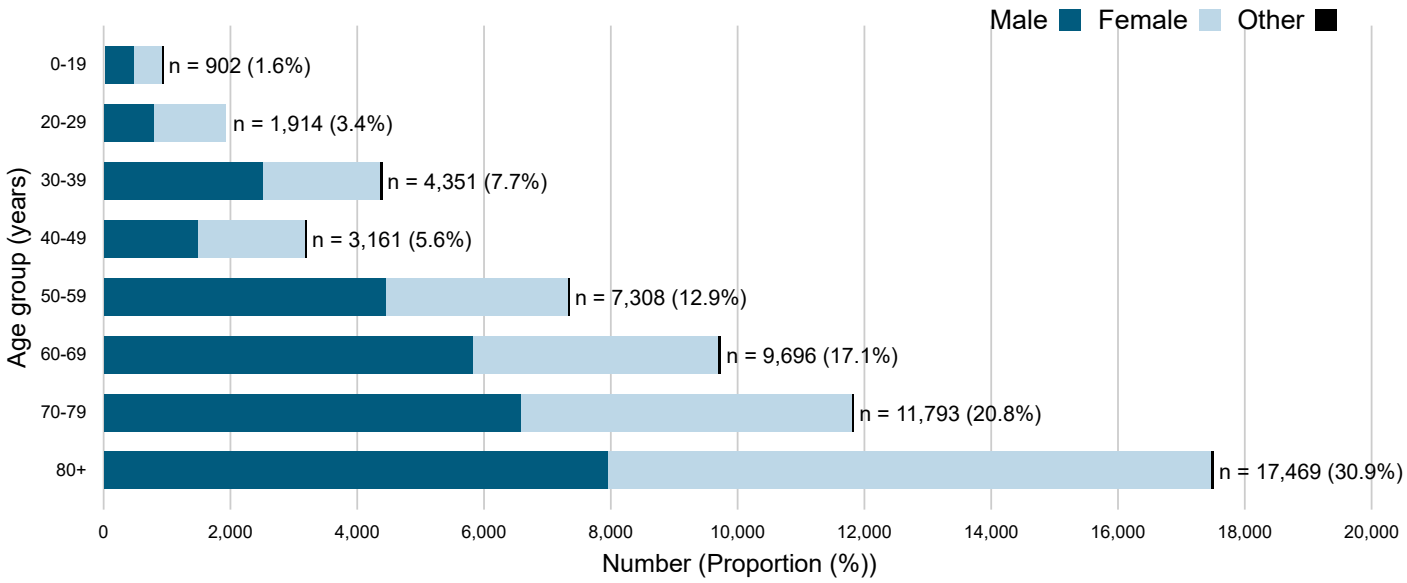


Figure 5b. Age and gender [4] distribution of COVID-19 cases admitted to ICU in Canada as of April 16, 2021, 7 pm EST (n=10,144 [1])

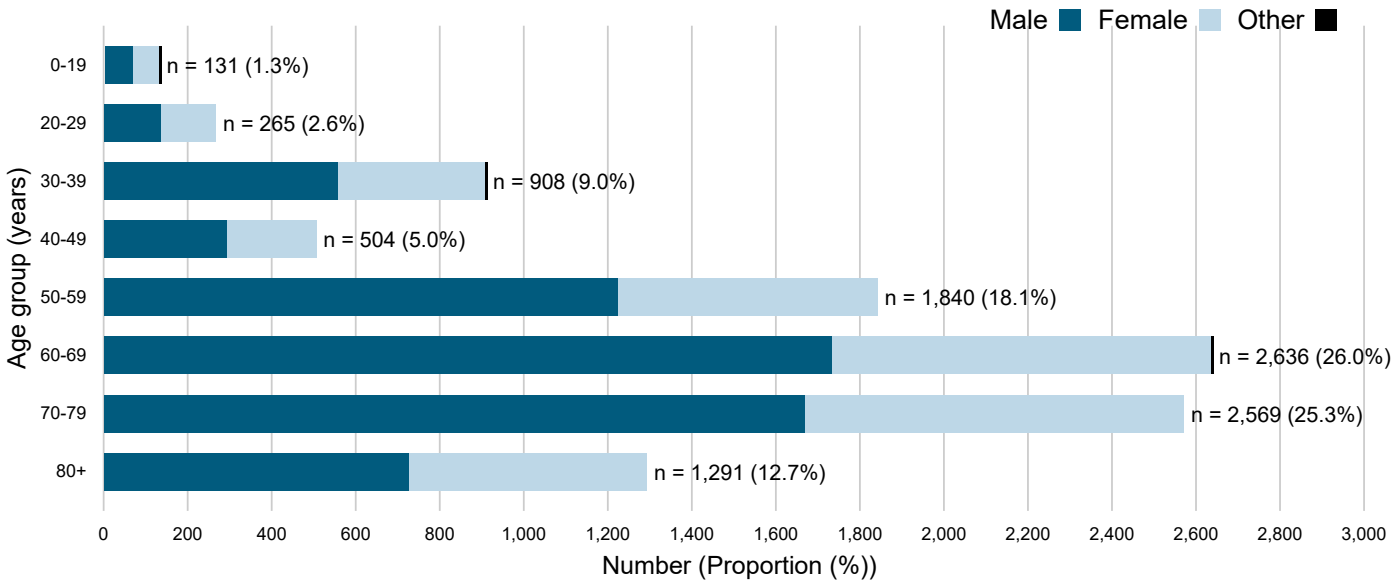
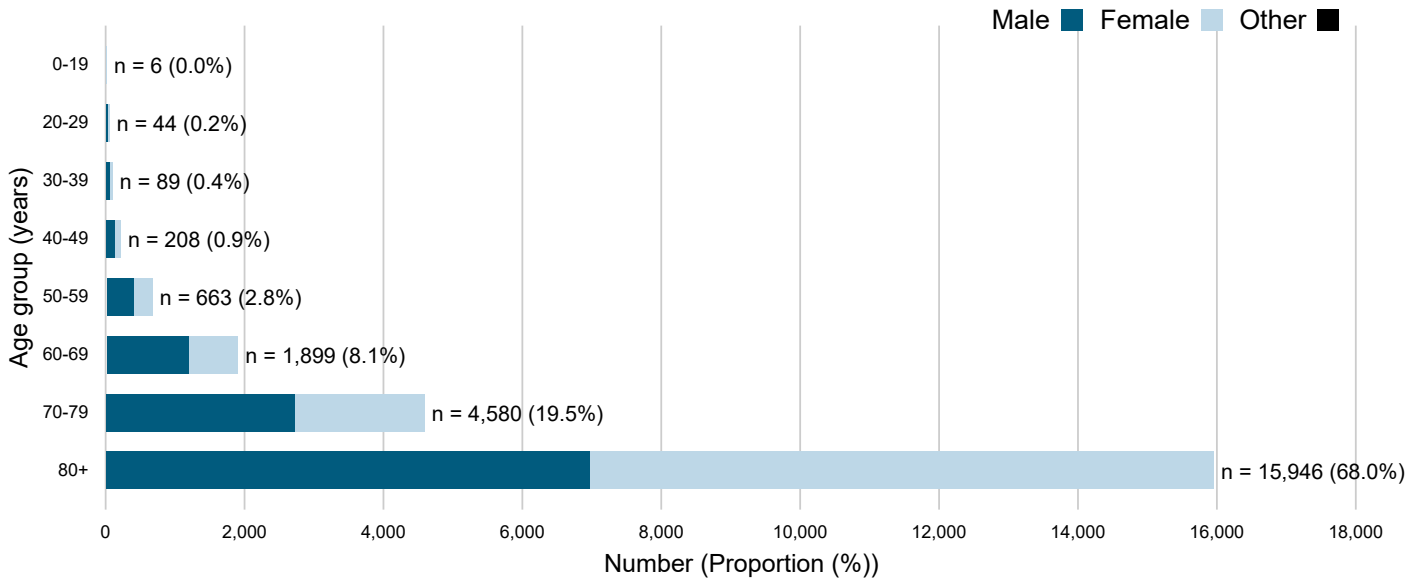


Figure 5c. Age and gender [4] distribution of COVID-19 cases deceased in Canada as of April 16, 2021, 7 pm EST (n=23,435 [1])



Data note: Figure 5 includes COVID-19 cases hospitalized, admitted to ICU, and deceased for which age and gender information were available. Therefore, some COVID-19 hospitalizations, ICU admissions, and deaths may not be included in Figure 5.

Age and gender [4] distribution of COVID-19 cases hospitalized in Canada as of April 16, 2021, 7 pm EST (n=56,594 [1])

Age group (years)	Number of cases with case reports (percentage)	Number of male cases (percentage)	Number of female cases (percentage)	Number of other cases (percentage)
0-19	902 (1.6%)	472 (0.8%)	429 (0.8%)	1 (0.0%)
20-29	1,914 (3.4%)	793 (1.4%)	1,121 (2.0%)	0 (0.0%)
30-39	4,351 (7.7%)	2,501 (4.4%)	1,846 (3.3%)	4 (0.0%)
40-49	3,161 (5.6%)	1,473 (2.6%)	1,686 (3.0%)	2 (0.0%)
50-59	7,308 (12.9%)	4,443 (7.9%)	2,863 (5.1%)	2 (0.0%)
60-69	9,696 (17.1%)	5,816 (10.3%)	3,875 (6.8%)	5 (0.0%)
70-79	11,793 (20.8%)	6,576 (11.6%)	5,216 (9.2%)	1 (0.0%)
80+	17,469 (30.9%)	7,947 (14.0%)	9,516 (16.8%)	6 (0.0%)

Age and gender [4] distribution of COVID-19 cases admitted to ICU in Canada as of April 16, 2021, 7 pm EST (n=10,144 [1])

Age group (years)	Number of cases with case reports (percentage)	Number of male cases (percentage)	Number of female cases (percentage)	Number of other cases (percentage)
0-19	131 (1.3%)	69 (0.7%)	61 (0.6%)	1 (0.0%)
20-29	265 (2.6%)	136 (1.3%)	129 (1.3%)	0 (0.0%)
30-39	908 (9.0%)	557 (5.5%)	350 (3.5%)	1 (0.0%)
40-49	504 (5.0%)	291 (2.9%)	213 (2.1%)	0 (0.0%)
50-59	1,840 (18.1%)	1,223 (12.1%)	617 (6.1%)	0 (0.0%)
60-69	2,636 (26.0%)	1,732 (17.1%)	903 (8.9%)	1 (0.0%)
70-79	2,569 (25.3%)	1,669 (16.5%)	900 (8.9%)	0 (0.0%)
80+	1,291 (12.7%)	725 (7.1%)	566 (5.6%)	0 (0.0%)

Age and gender [4] distribution of COVID-19 cases deceased in Canada as of April 16, 2021, 7 pm EST (n=23,435 [1])

Age group (years)	Number of cases with case reports (percentage)	Number of male cases (percentage)	Number of female cases (percentage)	Number of other cases (percentage)
0-19	6 (0.0%)	4 (0.0%)	2 (0.0%)	0 (0.0%)
20-29	44 (0.2%)	25 (0.0%)	19 (0.0%)	0 (0.0%)
30-39	89 (0.4%)	56 (0.1%)	33 (0.0%)	0 (0.0%)
40-49	208 (0.9%)	127 (0.2%)	81 (0.1%)	0 (0.0%)
50-59	663 (2.8%)	402 (0.6%)	261 (0.4%)	0 (0.0%)
60-69	1,899 (8.1%)	1,194 (2.5%)	705 (1.6%)	0 (0.0%)
70-79	4,580 (19.5%)	2,722 (10.8%)	1,858 (7.3%)	0 (0.0%)
80+	15,946 (68.0%)	6,974 (30.4%)	8,972 (21.0%)	0 (0.0%)

Provincial, territorial and international reporting

For more information, please refer to provincial or territorial COVID-19 webpages:

- British Columbia
- Alberta
- Saskatchewan
- Manitoba
- Ontario
- Quebec
- Newfoundland and Labrador
- New Brunswick
- Nova Scotia
- Prince Edward Island
- Yukon
- Northwest Territories
- Nunavut
- World Health Organization
- Centers for Disease Control and Prevention
- European Centre for Disease Control and Prevention

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1 This figure is based on cases for which a case report form was received by the Public Health Agency of Canada from provincial or territorial partners.

2 The shaded area represents a period of time (lag time) where it is expected that cases have occurred but have not yet been reported nationally. The earliest of the following dates were used as an estimate: Onset date, Specimen Collection Date, Laboratory Testing Date, Date Reported to Province or Territory, or Date Reported to PHAC.

3 Exposure information may not be available for all cases. Some jurisdictions haven't consistently reported to PHAC how people were exposed throughout the pandemic. As a result, this may underestimate the total number of cases by different exposures, especially among returning travelers.

4 Where available, gender data was used; when gender data was unavailable, sex data was used. Reliable data on gender diverse respondents are unavailable due to small counts.

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RESEARCH Open Access

Inverse correlation between average monthly high temperatures and COVID-19-related death rates in different geographical areas

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Abstract

Background: With the aim of providing a dynamic evaluation of the effects of basic environmental parameters on COVID-19-related death rate, we assessed the correlation between average monthly high temperatures and population density, with death/rate (monthly number of deaths/1 M people) for the months of March (start of the analysis and beginning of local epidemic in most of the Western World, except in Italy where it started in February) and April 2020 (continuation of the epidemic). Different geographical areas of the Northern Hemisphere in the United States and in Europe were selected in order to provide a wide range among the different parameters. The death rates were gathered from an available dataset. As a further control, we also included latitude, as a proxy for temperature.

Methods: Utilizing a publicly available dataset, we retrieved data for the months of March and April 2020 for 25 areas in Europe and in the US. We computed the monthly number of deaths/1 M people of confirmed COVID-19 cases and calculated the average monthly high temperatures and population density for all these areas. We determined the correlation between number of deaths/1 M people and the average monthly high temperatures, the latitude and the population density.

Results: We divided our analysis in two parts: analysis of the correlation among the different variables in the month of March and subsequent analysis in the month of April. The differences were then evaluated. In the month of March there was no statistical correlation between average monthly high temperatures of the considered geographical areas and number of deaths/1 M people. However, a statistically significant inverse correlation became significant in the month of April between average monthly high temperatures ($p = 0.0043$) and latitude ($p = 0.0253$) with number of deaths/1 M people. We also observed a statistically significant correlation between population density and number of deaths/1 M people both in the month of March ($p = 0.0297$) and in the month of April ($p = 0.0116$), when three areas extremely populated (NYC, Los Angeles and Washington DC) were included in the calculation. Once these three areas were removed, the correlation was not statistically significant ($p = 0.1695$ in the month of March, and $p = 0.7076$ in the month of April).

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Conclusions: The number of COVID-19-related deaths/1 M people was essentially the same during the month of March for all the geographical areas considered, indicating essentially that the infection was circulating quite uniformly except for Lombardy, Italy, where it started earlier. Lockdown measures were implemented between the end of March and beginning of April, except for Italy which started March 9th. We observed a strong, statistically significant inverse correlation between average monthly high temperatures with the number of deaths/1 M people. We confirmed the data by analyzing the correlation with the latitude, which can be considered a proxy for high temperature. Previous studies indicated a negative effect of high climate temperatures on Sars-COV-2 spreading. Our data indicate that social distancing measure are more successful in the presence of higher average monthly temperatures in reducing COVID-19-related death rate, and a high level of population density seems to negatively impact the effect of lockdown measures.

Keywords: SARS-CoV, SARS-CoV-2, COVID-19, Temperature, Latitude, Death rate

Background

Recently a novel, human pathogen Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged in China and its worldwide spread created a global health emergency. The World Health Organization publicly declared the SARS-CoV-2 outbreak a pandemic on March 11th 2020, and so far the virus has caused more than 200,000 deaths worldwide, strongly impacting the global economy and human habits. Different environmental conditions can affect host–pathogen interactions. In particular most respiratory viruses are sensitive to local geographical conditions like local temperature and humidity [1]. This in turn generates seasonal waves of outbreaks, by impacting viral transmission and survival [2, 3].

Some studies indicate that warm climates influences SARS-CoV-2 geographical distribution by reducing its infectivity rates [4–9], and others include additional factors, like air pollution, as responsible for increased viral spread [10].

In this study we correlate the average monthly high temperatures and the population density of different geographical areas with number of deaths/1 M people. We focused our analysis on the number of deaths/1 M people instead of number of SARS-CoV-2 RNA-positive people to avoid potential bias due to the different number of total PCR tests in the different areas considered. The areas in the Northern hemisphere were selected to provide a wide range among the different parameters, and the death rate data were gathered from an available dataset. In order to provide a dynamic correlation, the average monthly high temperatures and deaths numbers data were compared for the months of March (start of the analysis and beginning of local epidemic in most of the Western World) with the month of April. Except in Italy, which started at the beginning of March, lockdown measures were implemented between the end of March and the beginning of April in the remaining areas. By reasoning that the latitude is a proxy for temperature, as a further control we then calculated the latitude of the same areas with the number of deaths/1 M. Our data may help to understand the impact of daily temperatures on COVID-19-related death rate and modeling the containment measures according to different geographical areas, and suggest that factors other than social practices contributed to the infection of SARS-CoV-2.

Methods

Twenty-five areas located in Europe and in the United States have been selected as representative of the region/country where major outbreaks have been detected up to April 30th, 2020. We downloaded the number of deaths of confirmed COVID-19 cases of these areas [11] and we calculated the monthly number of deaths/1 M people. We then included in the dataset the average monthly high temperatures (°F) and latitude of these areas as climatic variables that can affect the spread and the lethality of COVID-19. The relationships among these variables have been analyzed with the R *tydiverse* package.

The data were obtained from the European Centre for Disease Prevention and Control (ECDC). We note that the criteria for defining death caused by or associated with COVID-19 are not homogenous internationally and therefore should be taken with caution [12, 13]. In addition, increased mortality indirectly related to COVID-19 may be indicative of sudden exhaustion of the hospital and health systems with a negative impact on the main mortality drivers (cancer, cardiovascular diseases and others). To overcome as much as possible these potential drawbacks, we selected geographical regions implementing homogenous parameters accounting for deaths related to COVID-19. More in detail, as it is standard in death reporting, Countries are asked to follow the "cause of death" classifications from the WHO's *International Classification of Diseases* guidelines [14]. In addition, National guidelines are also implemented, with the aim to better define the cause of death as related to COVID-19. Although confirmed cases are reliant on a positive

laboratory confirmation of the COVID-19 PCR test, a laboratory diagnosis may not be required for it to be listed as the cause of death. As a result, in some circumstances, depending on national guidelines, medical practitioners can record COVID-19 deaths if they think the signs and symptoms point towards this as the underlying cause.

Results

We selected several geographical areas in the Northern hemisphere of the United States and Europe, based on providing a range among the different parameters considered. The States and regions considered are outlined in Table 1. Between parenthesis we indicated the locations selected to obtain the latitudes and temperatures used for our analysis. We compared the data related to the month of March 2020. Lockdown measures were implemented between the end of March and beginning of April, except in Italy which started earlier. The death rate data were gathered as described in the Methods section.

First, we analyzed the correlation between number of deaths/1 M people and the average monthly high temperatures registered in each city considered (Fig. 1). The number of COVID-19-related deaths/1 M people was essentially the same during the month of March for all the geographical areas considered, indicating essentially that the infection was circulating quite uniformly ($p=0.2514$). In April, we observed instead a significant increase in number of deaths/1 M people in those areas where the average monthly high temperatures registered were below 65 °F (Fig. 1a). We found a statistically significant correlation between the decreased number of deaths/1 M people with the increase of the average monthly high temperatures ($p=0.0043$) (Fig. 1b). The same inverse correlation between average monthly high temperatures and COVID-19-related deaths was observed in two regions in Italy (Lombardy in the North and Sicily in the South, respectively) (Table 2). The difference was already noticeable in March, due to the early start of the epidemic, and become progressively accentuated in April (Table 2).

We confirmed these data by analyzing the correlation between the number of deaths/1 M people and the latitude, considered as a proxy for the temperature, of each area (Fig. 2a, b). In March, we don't see any statistically significant difference ($p=0.1016$), while in April, the latitude of 40° is a clear separator: in areas located above 40° the number of deaths increase significantly compared to the number of deaths in areas located below 40° ($p=0.0253$). The same inverse correlation between high latitude and COVID-19-related deaths was observed by comparing Lombardy to Sicily (Table 2).

Finally, we observed a statistically significant correlation between population density and number of deaths/1 M people in March (Fig. 3a, b) ($p=0.0297$) and April ($p=0.0116$). However, this statistical significance is due to the presence of three areas with extremely high population density: New York City, Los Angeles (CA) and Washington DC (Fig. 3c). Once these three areas were removed, the correlation was not statistically significant ($p=0.1695$ in the month of March, and $p=0.7076$ in the month of April).

In conclusion, our data indicate that there is a strong correlation between the number of deaths/1 M people

Table 1 Selected geographical areas

Location	Latitude	Average temperature March (°F)	Average temperature April (°F)
United Kingdom (London)	51.5	52.65	63.60
Belgium (Brussels)	50.84	51.16	63.80
Washington (Seattle)	47.6	50.65	60.17
Lombardy (Italy)	45.46	57.26	69.70
Massachusetts (Boston)	42.35	47.84	49.80
Michigan (Ann Harbor)	42.28	47.58	53.70
Illinois (Chicago)	41.88	47.71	56.27
Connecticut (Waterbury)	41.55	49.42	52.10
New Jersey (Newark)	40.73	54.52	57.70
New York (New York City)	40.71	53.94	56.60
Pennsylvania (Philadelphia)	39.95	56.48	59.27
Maryland (Baltimore)	39.29	59.65	61.73
Washington, D.C.	38.9	60.74	63.57
Sicily (Italy)	38.11	60.77	64.77
Malta (La Valletta)	35.93	62.77	68.53
New Mexico (Albuquerque)	35.08	62.58	71.23
California (Los Angeles)	34.05	67.74	73.40
Georgia (Atlanta)	33.74	69.00	70.77
Arizona (Phoenix)	33.44	73.55	86.45
South Carolina (Charleston)	32.77	71.48	75.60
California (San Diego)	32.71	63.90	67.40
Mississippi (Jackson)	32.3	75.13	74.37
Texas (Austin)	30.26	76.29	79.93
Louisiana (New Orleans)	29.95	78.94	80.60
Florida (Miami)	27.53	84.39	84.67

Between parenthesis are indicated the location considered for the latitude and to calculate the average monthly high temperatures

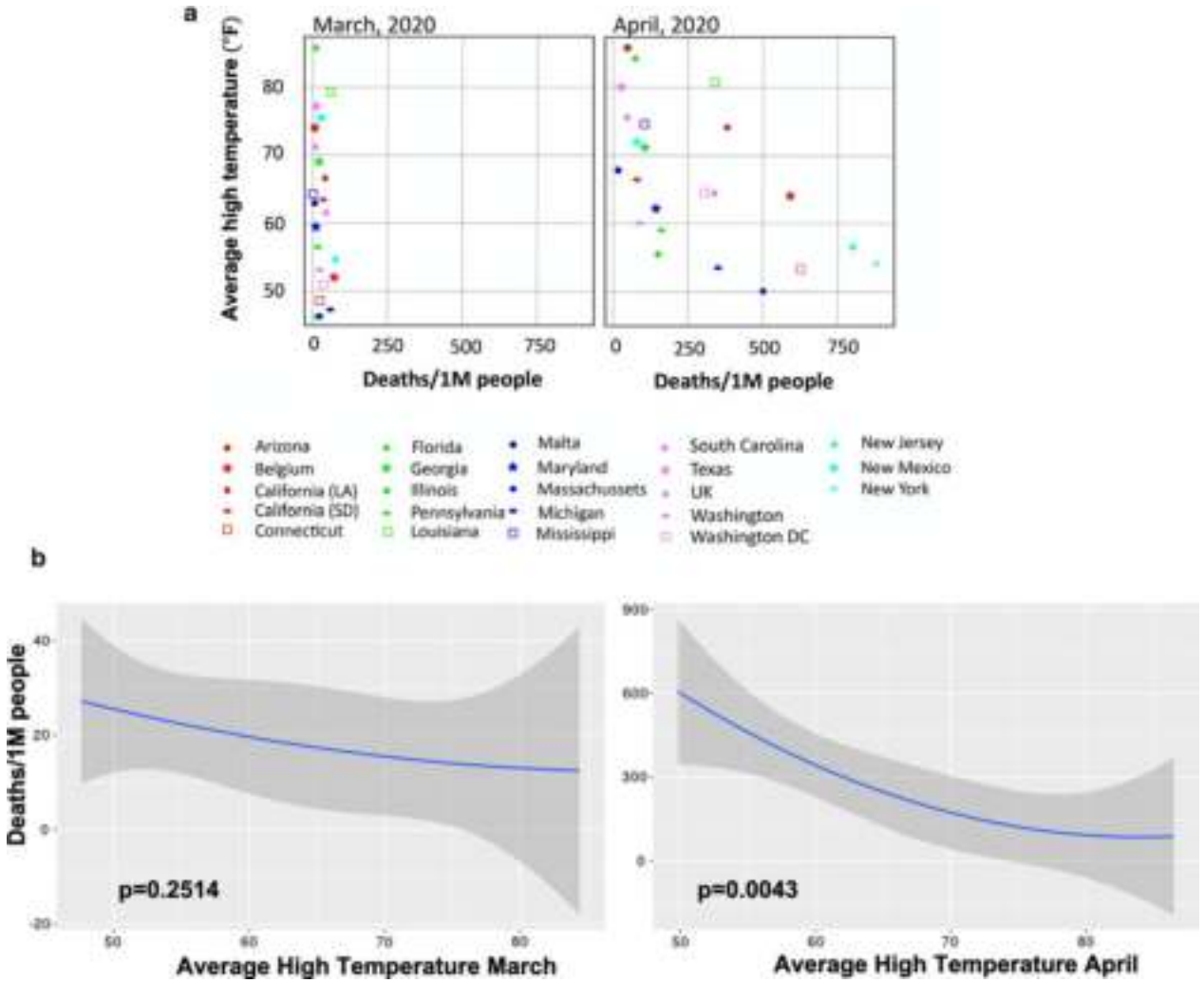

Fig. 1 Correlation between average monthly high temperatures and number of deaths/1 M people. **a** The relationship between the number of deaths/1 M people and the average monthly high temperatures (°F) for the months of March (left) and April (right) 2020 is represented for 25 areas located in Europe and in the US using scatter plots graphs. **b** The not linear correlation between these two variables is calculated using the squared transformation of the average monthly high temperatures. The p-values for each month are indicated

Table 2 Number of deaths per millions of people, average high temperatures for the months of March and April, and population density of two different Italian regions, Lombardy (North) and Sicily (South)

Location	Deaths/million of people in March	Deaths/million of people in April	Average high temperature in March (°F)	Average high temperature in April (°F)	Latitude (°)	Population density (sq ft)
Lombardy	500	700	57.26	69.70	45.46	420
Sicily	10	35	60.77	64.77	38.11	200

and climate. It is likely that social distancing measure are more successful in the presence of average monthly high temperatures in reducing COVID-19-related death rate, and high level of population density seems to reduce the effect of lockdown measures.

Discussion

We correlate the average monthly high temperatures and the population density of different geographical areas with number of deaths/1 M people. The data were analyzed for the month of March and April.

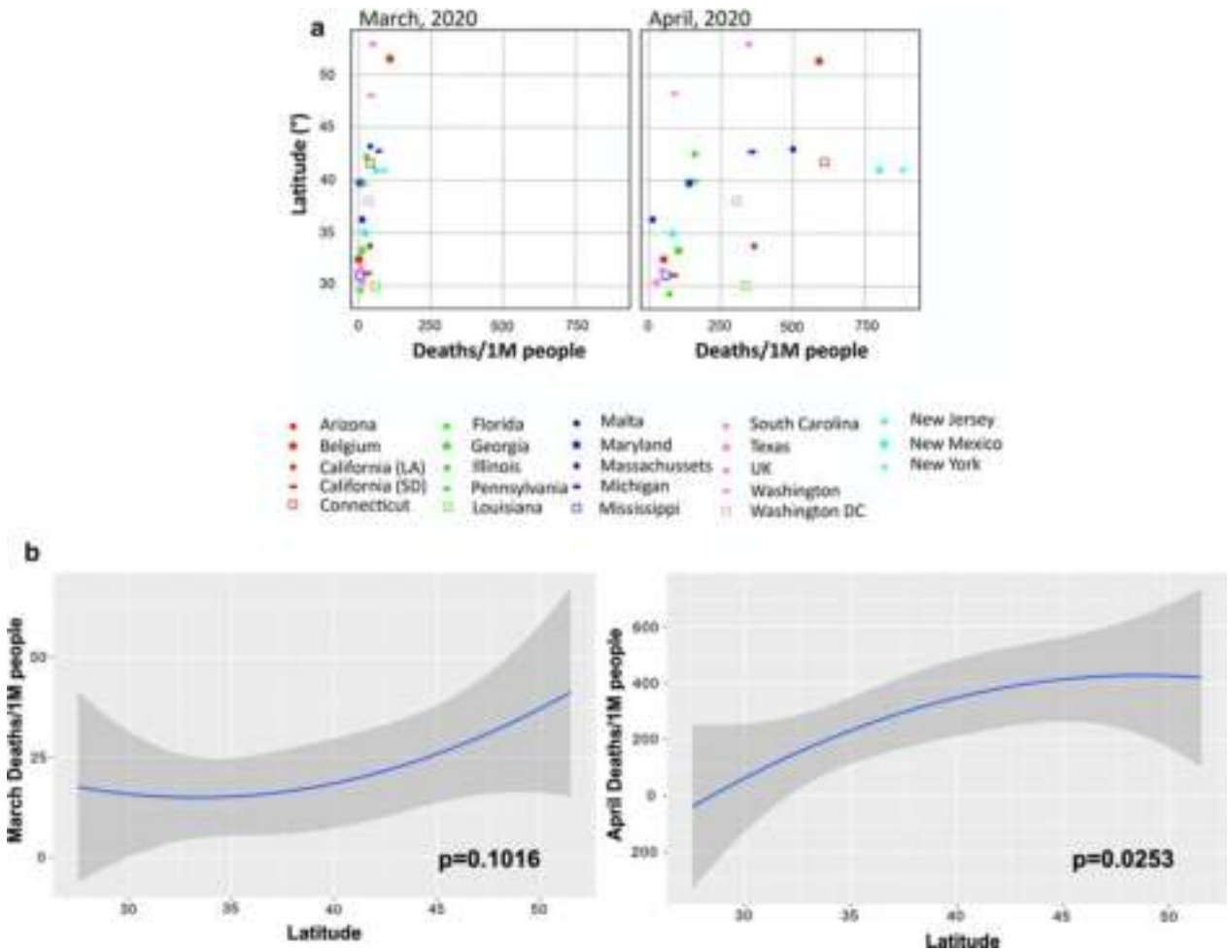

Fig. 2 Correlation between latitude and number of deaths/1 M people. **a** The relationship between the number of deaths/1 M people and the latitude (used as a proxy of the average monthly high temperatures registered) for the months of March (left) and April (right) 2020 is represented for 25 areas located in Europe and in the US using scatter plots graphs. **b** The not linear correlation between these two variables is calculated using the squared transformation of the latitudes. The p-values for each month are indicated

We did not find any correlation between temperatures and number of deaths in the month of March. On the contrary, there was a strong statistical correlation between the temperature values and number of deaths in the month of April. These data were further confirmed when we used latitude as a proxy of the temperature. It is noteworthy to remember that in all the areas considered, lockdown measures were implemented between the end of March and beginning of April (except in Lombardy and Sicily, Italy, which started earlier), and all had substantial forms of social distancing by April. Our results indicate that the areas considered started from a very similar number of deaths in the month of March, but the implementation of social distancing seems to be more successful in those areas with higher average monthly temperatures during the month of April.

We could not find a correlation between population density and number of deaths once the especially densely populated areas were removed. These data seem to indicate a possible threshold of population density as a factor contributing to virus spread.

Conclusion

Our data indicate that social distancing measures are more successful in the presence of higher daily temperature in reducing COVID-19-related death rates. On the contrary, high level of population density seems to reduce the effect of lockdown measures. Though more studies are necessary to confirm these data, we believe they help understand the impact of temperature on COVID-19-related death rate and modeling the containment measures according to different geographical areas.

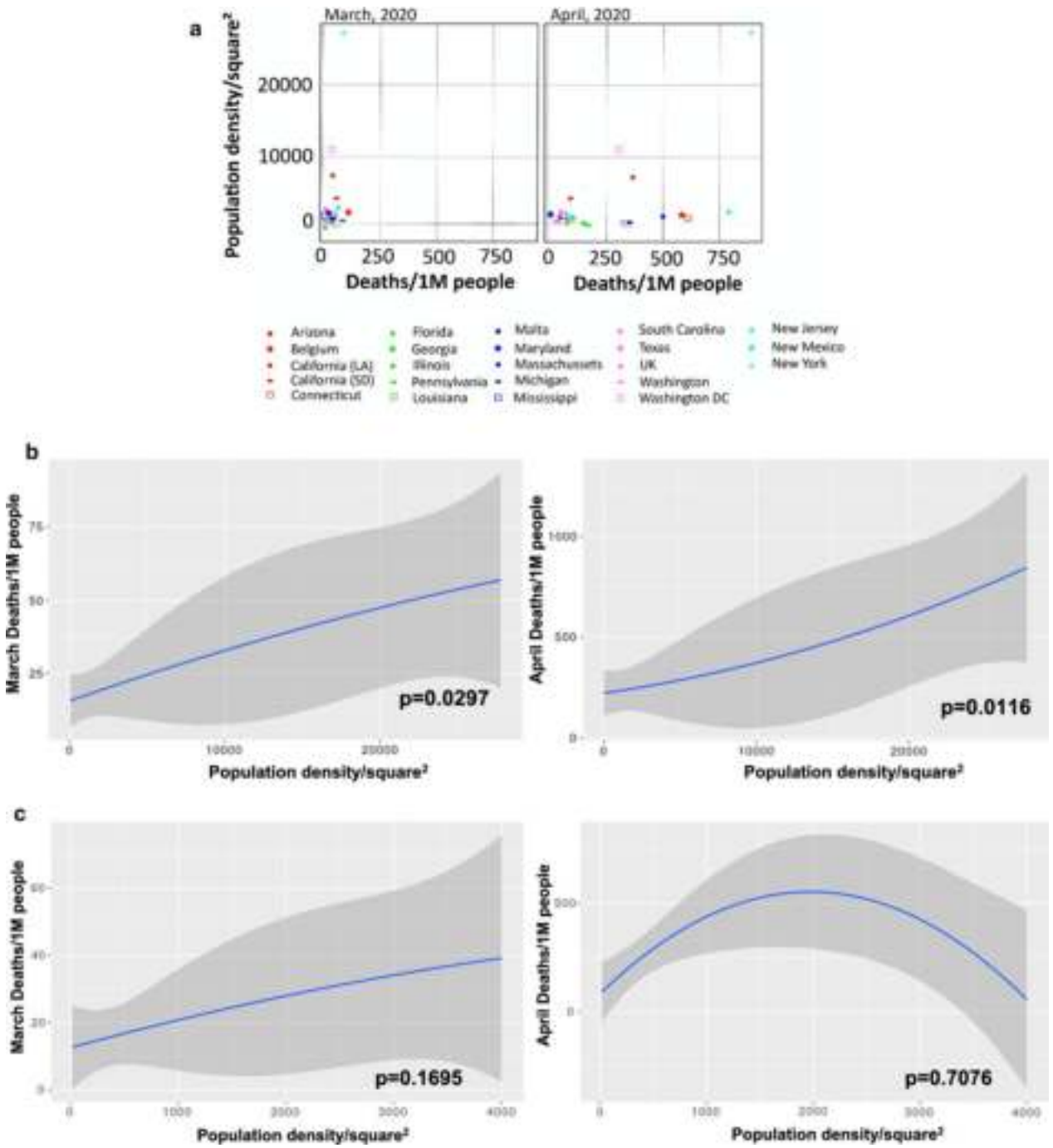

Fig. 3 Correlation between population density and number of deaths/1 M people. **a** The relationship between the number of deaths/1 M people and the population density for the months of March (left) and April (right) 2020 is represented for 25 areas located in Europe and in the US using scatter plots graphs. **b** The not linear correlation between these two variables is calculated using the squared transformation of the population density including the three highly densely populated areas (New York City, Los Angeles and Washington, DC), and **c** excluding these areas. The p-values for each month are indicated

Abbreviations

SARS-CoV: Severe acute respiratory syndrome coronavirus; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2 (COVID-19); MERS-CoV: Middle east respiratory syndrome coronavirus; WHO: World Health Organization; COVID-19: Coronavirus Disease-19.

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Authors' contributions
FB collected the data and conducted the analysis. FB, MC and DZ wrote the paper. DZ supervised the project. MP, BM, RI, RCG revised the paper. All the authors participate in the scientific discussion of these results, contributed to the final version of the project. All authors read and approved the final manuscript.

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The authors declare that they have no competing interests.

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Structural equation modeling to shed light on the controversial role of climate on the spread of SARS-CoV-2

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Climate seems to influence the spread of SARS-CoV-2, but the findings of the studies performed so far are conflicting. To overcome these issues, we performed a global scale study considering 134,871 virologic-climatic-demographic data (209 countries, first 16 weeks of the pandemic). To analyze the relation among COVID-19, population density, and climate, a theoretical path diagram was hypothesized and tested using structural equation modeling (SEM), a powerful statistical technique for the evaluation of causal assumptions. The results of the analysis showed that both climate and population density significantly influence the spread of COVID-19 ($p < 0.001$ and $p < 0.01$, respectively). Overall, climate outweighs population density (path coefficients: climate vs. incidence = 0.18, climate vs. prevalence = 0.11, population density vs. incidence = 0.04, population density vs. prevalence = 0.05). Among the climatic factors, irradiation plays the most relevant role, with a factor-loading of − 0.77, followed by temperature (− 0.56), humidity (0.52), precipitation (0.44), and pressure (0.073); for all $p < 0.001$. In conclusion, this study demonstrates that climatic factors significantly influence the spread of SARS-CoV-2. However, demographic factors, together with other determinants, can affect the transmission, and their influence may overcome the protective effect of climate, where favourable.

On March 11, 2020, the respiratory disease (COVID-19) caused by the coronavirus SARS-CoV-2, after having reached a global scale, was classified by the World Health Organization as a pandemic. Still progressing, COVID-19 has completely reshaped our world from all points of view, with dramatic social, economic, and psychological consequences.

Data provided by government and health organizations show a different distribution of the epidemic across countries[1], advocating a possible relationship between COVID-19 and climate factors. To address this issue, several studies have been carried out, but their results are mixed and conflicting, leading to deeply different conclusions[2–10].

The reasons for such contrasting findings are several. Firstly, some studies have been designed with intrinsic limitations that do not allow for a comprehensive view of the role of climate in COVID-19 spread, whether because they considered only one or few countries, without a global perspective[3,7], or due to short observation period chosen (2–8 weeks)[4,9,11], or the low number of climatic variables considered (however divergent between the various investigations)[2,5]. Secondly, none of the studies published so far have considered the role played by the demographic factors. These variables are relevant to correctly interpret the apparently inconsistent results in some areas of the globe (such as India, Brazil or USA). Thirdly, procedural unintentional biases have been made in many reports[12–16], leading to other insidious pitfalls and to the aforementioned discrepancy. One of these biases is the onset of the outbreak[12]. As the beginning of the infection did not occur simultaneously across the countries, if evaluated at the same time point, the countries whose outbreak started earlier tend to record

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higher prevalence of infection than the others. This requires a relative time scale, synchronizing the countries based on the beginning of the epidemic, prior to any statistical analysis.

Another pitfall is the single point of estimation[13,15]. Climatic conditions across countries vary considerably from region to region. Data collection limited to a restricted area (e.g. the capital city) is not representative of the whole country, and this may cause misleading results. Therefore, more data collection points within the same country should be taken into account. A further pitfall is the lag interval[11,14,16]. Incubation period, delayed testing from the onset of symptoms, as well as, late communication of test results, all contribute to a time shift between the infection exposure and the confirmation of diagnosis. Consequently, a lag time must be considered between the collection of climatic data for the analysis and the collection of COVID-19 data.

Finally, the interdependence of variables[17,18]. Climatic variables are commonly considered as stand-alone factors. Instead, they interact with each other. Therefore, an integrative and specific analysis is necessary for a comprehensive understanding of their effects, as their partial consideration could be misleading.

A comprehensive and detailed review of the existing literature about COVID-19 and climate is reported in the Supplementary Table S1.

Altogether, these questions may account for the discrepancy among the numerous studies published, leaving the debate about the relationship between climatic factors and COVID-19 still open.

Surely, knowing the factors influencing the epidemic and understanding the dynamics of its spread is strategic and crucial. This would allow us not only to limit the contagion, but also to better calibrate the containment policies, thus reducing the psychological, social, and economic repercussions. Starting from these considerations, we carried out an extensive and comprehensive analysis, based on as many as 134,871 data, using structural equation modeling (SEM), a statistical technique for testing the linear relationships between observed variables and latent variables, based on statistical data and causal qualitative hypothesis and developed by "LISREL" models, i.e. linear structural relationships[19–21]. Applied for the first time in the 70s in the field of social sciences with variables that could not be directly observed or measured, SEM later spread among the scientific community, thanks to both its flexibility and rigorous approach. One of the main advantages of SEM is the possibility to take into consideration several dependent variables simultaneously.

Flexibility and potential of this analysis were the key for the evaluation of climatic factors and their role in the outbreak of SARS-CoV-2, trying to overcome the limitations and the pitfalls above-mentioned. In addition, since COVID-19 seems to spread more widely in highly populated areas, we also investigated the influence of some socio-demographic variables (such as population density) over the incidence and prevalence of the disease.

Results

Descriptive statistics. Statistics of meteorological variables, population density, weekly incidence and prevalence of SARS-CoV-2, are summarized in Table 1. The data have been stratified by climatic zones and are relative to the first 16 weeks of infection, in the 209 countries considered in this study. From the analysis, it has emerged that there is an increasing (although apparently imperfect) trend of both incidence and prevalence from warm to cold geoclimatic areas. Low values of incidence and prevalence (both for 100,000 people) were recorded in the equatorial ($\mu \pm \sigma = 4.28 \pm 12.89$ and $\mu \pm \sigma = 11.84 \pm 35.67$, respectively) and arid zones ($\mu \pm \sigma = 10.77 \pm 34.01$ and $\mu \pm \sigma = 27.78 \pm 95.75$), areas with the hottest temperature and greater solar irradiation; while the highest values of incidence ($\mu \pm \sigma = 24.68 \pm 46.33$) and prevalence ($\mu \pm \sigma = 564.38 \pm 2986.82$) were observed in the warm temperate zone, the zone also recording the highest value of population density ($\mu \pm \sigma = 564.38 \pm 2986.82$), an important factor in virus transmission through both respiratory droplets and contact routes.

To verify the previous findings, namely that the morbidity indices (incidence and prevalence) depend on the geoclimatic zones where the countries are geographically located, the non-parametric k-sample test for median equality has been applied. The results of the test showed statistically significant differences in incidence and prevalence among the geoclimatic zones (incidence, Chi square = 309.0387 $p < 0.001$; prevalence, Chi square = 317.6152 $p < 0.001$), confirming that the transmission of the virus is indeed influenced by the climate.

To highlight and further investigate the relationship between morbidity, climatic variables, and population density, thematic world maps have also been devised (Fig. 1). For each country, the maps illustrate the following features: (a) median incidence and prevalence values of COVID-19 in the first 16 weeks of infection, (b) median values of all climatic variables (detected with a time shift of two weeks prior to the collection of virological data) in the same period, and c) population density.

From the comparison of the maps, it resulted that, with few exceptions, no evident spatial correlation seems to exist among the investigated variables. Only solar irradiation, temperature, and humidity showed an albeit modest relationship with the morbidity indices: countries with higher solar irradiation reported lower values of incidence and prevalence, while highest incidence and prevalence values were mainly recorded in areas with lower median temperatures (e.g., United States, Europe and China) and higher humidity.

To better explore the relationship between climate and incidence/prevalence of SARS-CoV-2, the bivariate correlation between these indices and all the main meteorological variables (considered individually) was investigated by means of the Spearman's rank correlation coefficient. Then, since population density represents an important factor in the transmission of the virus, the correlation between incidence/prevalence and population density was also calculated.

The results of this analysis, in agreement with the findings of thematic world maps, demonstrated only a moderate concordance between solar irradiation and temperature ($r = 0.58$; $p < 0.05$) and a significant (albeit low) negative correlation of temperature with incidence and prevalence ($r = -0.37$ and $r = -0.34$, respectively) (Table 2).

However, the weak correlations detected may have been due to the heterogeneity of the climatic conditions in the numerous countries considered. In this case, a simple bivariate regression model (such as the Spearman's rank

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Climatic zone	Variable	Mean	Std. Dev.	Min.	Max.
Cold temperate	Precipitation (mm/day)	2.61	2.68	0.00	18.15
	Humidity (%)	77.46	10.15	32.68	97.40
	Pressure (kPa)	96.97	5.93	78.87	102.70
	Temperature (°C)	5.85	6.11	−15.16	25.64
	Wind (m/s)	2.80	1.62	0.28	11.59
	Solar irradiation (MJ/m^2/day)	13.80	5.43	0.79	29.06
	Population density (n/km^2)	58.83	62.51	3.00	284.00
	Weekly incidence (per 100,000)	23.13	34.38	0.00	205.08
	Weekly prevalence (per 100,000)	74.29	133.73	0.00	856.62
Warm temperate	Precipitation (mm/day)	2.70	3.17	0.00	21.64
	Humidity (%)	74.46	11.16	23.04	97.12
	Pressure (KPa)	97.62	4.54	76.36	102.96
	Temperature (°C)	11.72	6.41	−11.21	32.64
	Wind (m/sec)	2.58	1.60	0.22	13.02
	Solar irradiation (MJ/m^2/day)	15.58	5.38	1.17	29.23
	Population density (n/km^2)	564.38	2986.82	12.00	26,337.00
	Weekly incidence (per 100,000)	24.68	46.33	0.00	342.91
	Weekly prevalence (per 100,000)	94.82	216.56	0.00	1502.94
Arid	Precipitation (mm/day)	1.58	3.76	0.00	47.56
	Humidity (%)	54.37	18.42	8.22	89.43
	Pressure (KPa)	93.93	7.99	75.22	102.37
	Temperature (°C)	19.42	8.78	−12.36	36.95
	Wind (m/sec)	2.99	1.69	0.61	16.84
	Solar irradiation (MJ/m^2/day)	20.15	4.47	4.09	30.69
	Population density (n/km^2)	113.59	328.88	2.00	2239.00
	Weekly incidence (per 100,000)	10.77	34.02	0.00	425.64
	Weekly prevalence (per 100,000)	27.78	95.75	0.00	1231.56
Equatorial	Precipitation (mm/day)	5.68	7.90	0.00	61.27
	Humidity (%)	77.07	10.00	39.34	95.85
	Pressure (KPa)	98.10	4.49	83.64	101.82
	Temperature (°C)	26.18	3.03	13.30	33.25
	Wind (m/sec)	2.69	1.66	0.25	8.16
	Solar irradiation (MJ/m^2/day)	19.54	4.32	0.77	28.37
	Population density (n/km^2)	351.20	1082.77	8.00	8358.00
	Weekly incidence (per 100,000)	4.28	12.89	0.00	115.40
	Weekly prevalence (per 100,000)	11.84	35.67	0.00	343.64

Table 1. Summary statistics of meteorological variables, *weekly incidence* and *weekly prevalence* of SARS-CoV-2, population density, by climatic zone, in the first 16 weeks of the infection, in 209 countries.

test) may be insufficient to reveal complex relationships. Therefore, a more specific analysis, in which climatic variables can be considered simultaneously and in an integrated way, is needed.

SEM analysis. To understand the intricate interactions among geoclimatic and epidemiological variables, a more consistent and suitable mathematical model, such as the multivariate regression approach of structural equation modeling (SEM), was necessary. With this statistical model it was possible to consider the integrated effects of all the meteorological variables on COVID-19 and, at the same time, to investigate the effects of population density too.

To analyze the relations among the above-mentioned variables, the theoretical path diagram reported in Fig. 2 was supposed. In this theoretical path, meteorological factors were hypothesized to be correlated to each other and linked to a variable that cannot be directly measured (*Climate*). In addition, it was assumed that *Climate* and population density are regressors on incidence and prevalence, whose covariation is expressed by an arc. Therefore, the theoretical path was then tested by SEM.

The results of the analysis showed a clear causative role of climate. For paths *Climate* → *Incidence* and *Climate* → *Prevalence*, the integrated effects of meteorological factors, measured at two-week lag and expressed by a single latent variable (*Climate*), resulted to be significantly ($p < 0.001$) linked to incidence and prevalence by a standardized positive path coefficient ($b = 0.18$ and $b = 0.11$, respectively) (Fig. 3).

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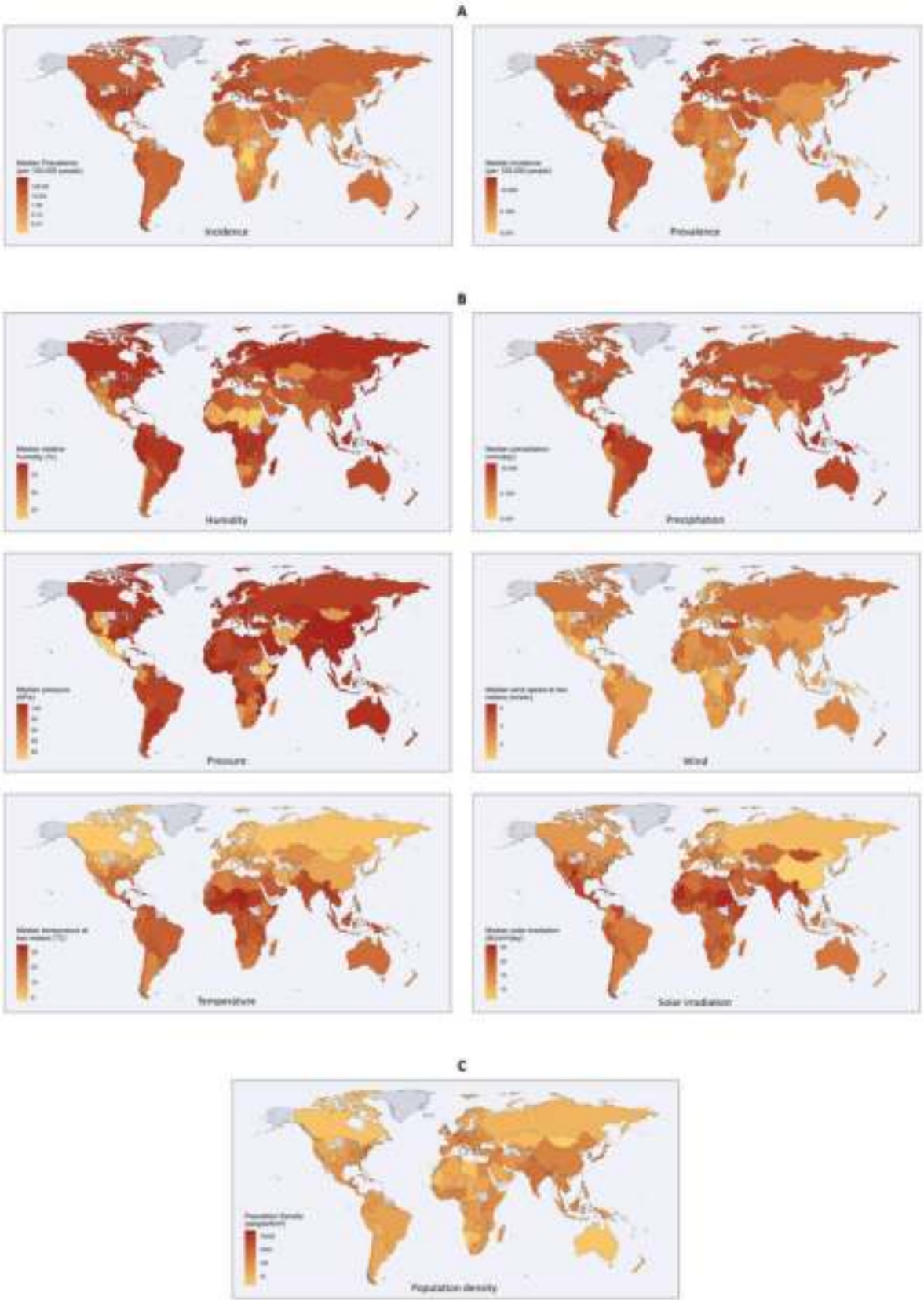

Figure 1. World countries maps. (**A**) Median values of incidence and prevalence of COVID-19. (**B**) Median values of the climatic variables. (**C**) Population density. In grey, countries not recorded. The maps were generated using R software (version 4.0.2—https://www.r-project.org/), ggplot2 library (version 3.3.2—https://CRAN.R-project.org/package=ggplot2) and Maps (version 3.3.0—https://CRAN.R-project.org/package=maps).

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	Precipitation	Humidity	Pressure	Temperature	Wind	Solar irradiation	Population density	Incidence	Prevalence
Precipitation (mm/day)	1.00								
Humidity (%)	0.55*	1.00							
Pressure (kPa)	−0.11	0.15*	1.00						
Temperature (°C)	−0.02	−0.16	0.22*	1.00					
Wind (m/s)	−0.19	−0.03	0.41*	0.09*	1.00				
Solar irradiation (MJ/m^2/day)	−0.38	−0.50	0.05*	0.58*	0.02	1.00			
Population density (n/km^2)	−0.04	0.01	0.22*	0.13*	0.05*	0.11*	1.00		
Weekly incidence (per 100,000)	0.05*	0.09*	0.07*	−0.37	−0.01	−0.15	−0.01	1.00	
Weekly prevalence (per 100,000)	0.04	0.06*	0.07*	−0.34	−0.02	−0.08	0.01	0.95*	1.00

Table 2. Spearman's rank correlation coefficient between meteorological variables, *weekly incidence* and *weekly prevalence* of SARS-CoV-2, and *population density*. *$p < 0.05$.

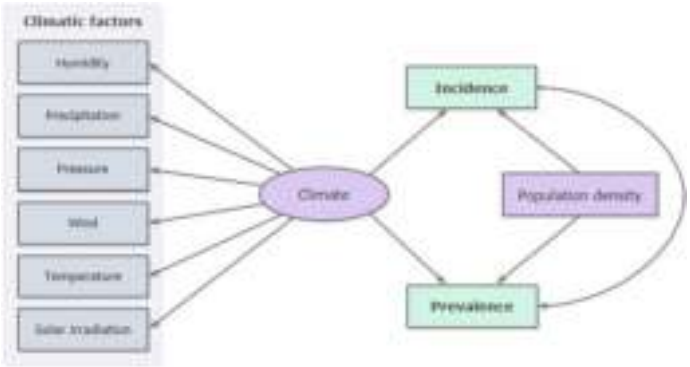

Figure 2. Theoretical path diagram used to analyze the effects of climate and population density on the spread of SARS-CoV-2. This diagram was generated using Office Power Point software, version 2010 (https://www.microsoft.com/it-it/microsoft-365/powerpoint).

In turn, the different climatic factors were found to be correlated with *Climate* in another way. Specifically, solar irradiation and temperature were negatively correlated, with a factor loading of −0.77 ($p < 0.001$) and −0.56 ($p < 0.001$), respectively. While, relative humidity, precipitation and pressure showed a positive correlation, with factor loading of 0.52, 0.44, and 0.073, (for all, $p < 0.001$). Wind was negatively correlated (−0.046) but without a significant p-value.

For paths *Population density* → *Incidence* and *Population density* → *Prevalence*, population density resulted to be linked to incidence and prevalence by standardized positive path coefficients ($b = 0.043$, $p < 0.01$ and $b = 0.051$, $p < 0.01$, respectively), although to a lesser extent than those exhibited by *Climate*. The variables, incidence and prevalence observed, being by their nature closely related, showed a high covariance between errors of 0.96 ($p < 0.001$).

An interesting outcome is given by the residual variance ($var(\varepsilon_1) = 0.97$ for incidence and $var(\varepsilon_2) = 0.98$ for prevalence). This parameter represents the effects of unmeasured factors influencing incidence and prevalence. It indicates that factors other than climate and population density affect SARS-CoV2 incidence and prevalence, but also random errors, errors in data entry, and systematic errors leading to biases in the measurement of values.

Finally, the goodness of fit of the model was tested, and the results of the evaluation showed an overall good fit (CD = 0.826, RMSEA = 0.088, SRMR = 0.078). This demonstrates that SEM adequately confirms the theoretical path diagram of Fig. 2, indicating the strength and direction of association between incidence and prevalence of SARS-CoV-2, climatic variables, and population density.

Overall, the results of the analysis demonstrated that (a) climate has a relevant impact on incidence and prevalence of SARS-CoV-2 (at least in the first 16 weeks), stronger than that exhibited by density of population;

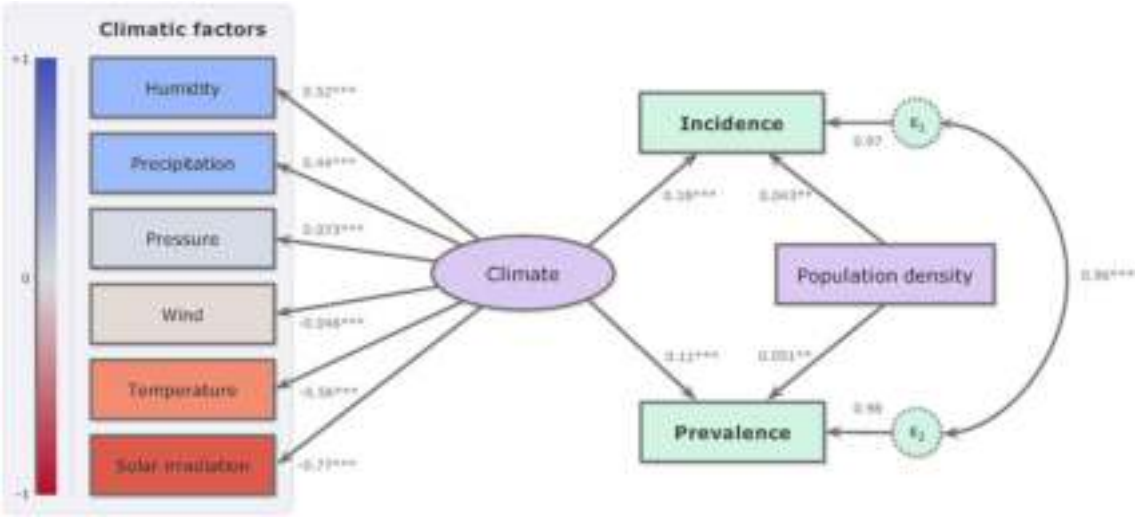

Figure 3. SEM path diagram for the effect of the climate and the population density on the spread of SARS-CoV-2. Observed variables are represented by boxes, latent variable by an ellipse, and residual terms by circles. The values on the straight arrows between latent and observed variables and those between latent and observed indicators represent the standardized path coefficients and the factors loading, respectively. The values on the straight arrows between residual terms and observed variables represent the residual variance. The diagram was generated using Office Power Point software for Microsoft 365 (https://www.microsoft.com/it-it/microsoft-365/powerpoint). ***$p < 0.001$; **$p < 0.01$.

(b) among the climatic variables, solar irradiation proved to be the most influential factor, followed (but in the opposite direction) by relative humidity, and by temperature (in the same direction of solar irradiation).

Discussion

COVID-19 pandemic represents a serious threat for people worldwide, with an alarming day-by-day increasing number of infections and death cases. Consequently, the scientific community worldwide is constantly seeking for new and useful knowledge aimed at contrasting the spread of SARS-CoV-2.

Climatic factors seem to play an important role in the epidemiology of the infection, although the results of the recent literature failed to give a unique and unequivocal knowledge on this subject.

In this paper, we have carried out an extensive and comprehensive analysis to determine the role of climate and some demographic factors in the spread of COVID-19. For this purpose, we used a particular and powerful statistical technique (the structural equation modeling), for the evaluation of causal assumptions, taking into consideration, as dependent variables, both weekly incidence and weekly prevalence.

The key objective of this study was to overcome the limitations of previous investigations. In line with this perspective, we have (a) conducted research on a global scale (on all countries in the world), (b) carried out observation over a long period of time (to our best knowledge, the longest among the studies published so far), (c) considered not some but all the main six climatic factors, (d) used a relative time scale, synchronizing the countries based on the beginning of the epidemic, (e) taken into account not a single point but multiple points of evaluation for climatic variables for each country, (f) considered a lag interval between the acquisition of climatic data and the collection of COVID-19 data for the analysis, (g) not considered the variables as stand-alone factors but taken into account their interdependence and used an integrative statistical investigation to evaluate their effects.

In light of this, the choice of SEM was very strategic. It allowed to test a complex model of relationships among climatic variables, population density and morbidity indices. Alternatively, several separate analyses, with less solid results in statistical terms, would have been required. The use of SEM has also the advantage of including, in the exploration model, variables (such as *Climate*) which cannot be directly observed. In addition, it solved the problem of the interdependence among the meteorological variables, allowing to address them in a comprehensive analysis.

Overall, this approach helped us to build a more solid analysis, yielding robust and reliable findings, highly consistent with the hypothesis that both climate and population density significantly influence the spread of COVID-19. Moreover, climate outweighs population density, and, in this context, solar irradiation, plays the most relevant role.

This is in line with the results of some epidemiological reports[10,11] and with a recent experimental investigation demonstrating that UV radiation, in very small doses, is able to inactivate SARS-CoV-2[22]. Although to a lesser extent, temperature, humidity, and precipitation also resulted to significantly influence SARS-CoV2 incidence and prevalence. Instead, the role of wind was demonstrated to be small, while that of pressure was not relevant. Overall, these findings may account for the different initial distribution of the epidemic across the countries, with the cold countries being affected more quickly and more intensely than the hot ones.

Similarly, the aforementioned results provide support to the common opinion that the climate is a determining factor in the spread of the pandemic. They also provide grounds for recent clusters of infections developed

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during the summer in different European working places, all characterized by a lack of solar irradiation and low temperature (i.e. a sausage factory in Mantova, Italy; a slaughterhouse in Gütersloh, Germany; a slaughterhouse in Tipperary, Ireland).

However, the high rates of COVID-19 observed in the last weeks in Brazil, India, and the USA seems to contradict the conclusions drawn in the present study, as this outbreak of pandemic occurred in countries with high temperature and adequate solar irradiation. However, SEM has shown that SARS-CoV-2 incidence and prevalence are influenced not only by climate but also by population density, and that factor is very high in the three countries mentioned. Therefore, if accurately interpreted, the findings of the present study may explain this apparent paradox, as well.

A puzzling result of the SEM that needs clarifications (to avoid possible misinterpretation) is the high value of residual variance (the value on the straight arrows between residual terms and dependent variable). As stated in the Methods section the residual term (the effect of which is represented by the residual variance) includes other possible variables having effects on the dependent variable. To the untrained eye, the high value of residual variances in our study (0.97 and 0.98) seems to significantly weaken the worth of the path coefficients (having lower magnitudes: 0.04–0.18). In fact, such an approach is conceptually wrong since path coefficient and residual variance are two different entities which cannot be compared to each other. Moreover, it should not be forgotten that the residual variance includes, within itself, the effects of a lot of components (various forms of errors and other causal variables), each of which may have very little relevance. So, due to its cumulative nature, residual variance may also reach high values, without, however, affecting or weakening the worth of path coefficients, whose value is confirmed by the very low p-values (<0.001 and <0.01) in our analysis. Finally, the weight that the residual terms may have in SEM can be calculated and expressed by the fit index SRMR. In the present study the value of SRMR was only 0.078, which testifies that the weight of residual terms on the tested model is irrelevant and that SEM adequately confirms the theoretical path.

In view of the causal implications of climatic factors on the spread of SARS-CoV-2, it may be tempting to identify a threshold of solar irradiation or temperature or any other climatic factor, above which the COVID-19 spread is negatively affected. This thought is deeply appealing and was also one of our main goals before collecting, analyzing and, most importantly, understanding our data. In addition, several studies had already identified a cut-off value, although with very different results[2,8,10,14,29,33–38].

However, in the case of COVID-19, considering only one climatic factor and trying to identify its threshold values, although potentially feasible, would be a constraint and, consequently, any resulting formula, would be conceptually wrong.

The correlation analyses of our study (reported in Table 2) and numerous meteorological studies incontrovertibly demonstrate that the main climatic factors (the 6 we considered) are interconnected. Therefore, focusing on single threshold values, above or below which a given event occurs, would have no mathematical or logical rationale, neither does (for example) trying to identify a threshold temperature value below which snowfall occurs. Snowfall does not depend only on temperature, but on the interaction of several atmospheric factors. Therefore, considering only the temperature will not lead to reliable forecasts since snow formation also depends on other factors (humidity, pressure, and wind). It is only through the calculation of all these variables together and the historical data collected over decades that the most likely scenarios can be identified.

Now, when it comes to SARS-CoV-2, the scenario becomes even more complex. In fact, not only is there a lack of reliable historical data on the epidemic in relation to climatic factors, but also there is the severely aggravating circumstance that, besides climatic factors, the spread of SARS-CoV-2 is influenced by countless other factors (population density, cultural habits, severity and observance of containment measures, intensity of trade and human contact, hygiene measures, etc.).

During our study, we soon realized that, due to the highly complex nature regulating the relationships between the variables, identifying a cut-off value was not feasible, precisely because too many causal variables are involved, each with a very wide range of variation. We thus decided to focus on the analysis of the relationships between climatic factors and virus spread, in order to identify the main players involved in the phenomenon and understand their effect. The magnitude and the algebraic sign of the factor loadings we calculated, led to understanding the type of correlation between each climatic variable and the latent variable Climate, identifying its strength and direction. In turn, the path coefficients linking Climate to the observed variable (incidence and prevalence) proved its correlation. Which is not negligible.

Basically, our study demonstrates that it is not possible to identify a mono-factorial threshold value to predict a reversal of COVID-19 spread. Only complex mathematical patterns (such as meteorological forecasting patterns), supported by an enormous amount of data sets (possibly also historical), may sufficiently define reliable predictability conditions.

In conclusion, the present study demonstrates that climatic factors significantly affect the spread of SARS-CoV-2 (probably and especially by influencing the air transmission through respiratory droplets). Among the variables investigated, solar irradiation proved to be the most influential factor, followed by temperature, humidity, precipitation, and, with a minimal or non-significant impact, pressure, and wind. However, demographic factors, together with other determinants, can affect the transmission (probably and especially through direct contact routes), and the influence of these can be such that they may overcome the protective effect of climate in some countries. Compared with the other studies reported in the literature, the present research has the merit of having addressed and overcome the limits of the previous investigations. To do so, however, it was necessary to use a robust mathematical model for the analysis (SEM), which required a considerable effort in terms of information needs, in order to function properly. The large amount of data used represents only a small part of the tremendous effort required, while greater effort was necessary for the selection of data and the evaluation of the criteria to be adopted for data processing. Only by respecting all these conditions, SEM could function properly and provide the results otherwise unattainable.

Methods

Data collection. Data regarding COVID-19 were collected from Johns Hopkins GitHub repository Systems Science and Engineering[23]. The information on governmental measures (school and university closures) were acquired from the UNESCO database[24]. The climatic parameters reported were taken from the dataset of the NASA Langley Research Center (LaRC) POWER Project[25] and the demographic estimates (population size, land area, population density) were obtained from the United Nations population estimates and from the World Factbook of Central Intelligence Agency (CIA)[26].

In order to evaluate the relation of COVID-19 with geo-climatic environment, the world has been divided into five geoclimatic zones, according to the updated Koppen-Geiger classification: polar, cold-temperate, warm-temperate, arid, and equatorial[27].

For SARS-Cov-2 analysis, all the UN 193 countries have been taken into account. Among these, 16 small countries, with a population below one million and a density of less than 100 people/km^2, as well as 18 countries with insufficient data on COVID-19 have been excluded. Conversely, all 50 states of the United States of America have been considered individually. Therefore, a total of 209 Countries have been included in the present study.

A total of 134,871 data were acquired from the sources mentioned above and inserted in a Microsoft Excel spreadsheet (Supplementary Table S2). Thirteen variables have been considered for the analysis and organized into the 3 groups herein reported.

1. Demographic: population size (number of people), land area (square kilometer—km^2), population density (people/km^2).
2. Climatic: climatic zone (one to five), temperature at two meters (degree Celsius—°C), solar irradiation (megajoule/square meter/day—MJ/m^2/day), relative humidity (percentage—%), wind speed at two meters (meter per second—m/s), surface pressure (kilopascal—KPa), precipitation (millimeters/day—mm/day).
3. COVID-19: date of the first confirmed case, number of new weekly cases, and number of active weekly cases.

Data processing. To ensure that the data collected met the purposes of the study, a set of specific criteria was established for the selection of the appropriate sample, and separate studies were performed to confirm the appropriateness of these choices. In particular:

1. Data on weekly new cases and active cases of SARS-CoV-2 infection were collected for a period of 16 weeks. Since the beginning of the infection did not occur simultaneously across all the countries, the data collected start from the first documented case in each country.
2. To evaluate the relationship between COVID-19 and climatic factors, matching epidemic and climatic data was found to be of importance. In each country, climatic conditions vary considerably across regions. Therefore, one to four cities, one for each of the regions most affected by COVID-19, were chosen for each country. Then, the weekly average was calculated for all the six climatic variables. Finally, the weekly means of all the cities were averaged to get the six total national weekly values. The process was repeated for all the weeks considered.
3. To evaluate the relationship between COVID-19 and climatic factors, a shift time between the collection of virologic data and the acquisition of climatic data had to be taken into consideration. In fact, the incubation period, the delay between symptom onset and testing, and the delay due to the communication of the result, contribute to a time shift between the infection exposure and the publication of the virologic data. Consequently, it is necessary to take into account a lag time between the collection of virologic data and the acquisition of climatic data for the analysis. According to the literature data[28–30], a lag time of two weeks was considered in the present study.

Data analysis. Data relative to SARS-CoV-2 were collected into a balanced panel dataset of 209 countries, starting from the first week of outbreak, until the sixteenth week. Due to data skewness (i.e. data with a non-Gaussian distribution), logarithmic transformation was applied to the analyzed variables.

The weekly incidence and prevalence of COVID-19 were calculated for each country, starting from the week of the first infection case and ending at week 16, according to the following formulas:

$$\text{Incidence} = \frac{\text{Number of new cases of Covid during week}}{\text{Population}} \times 100{,}000 \quad (1)$$

$$\text{Prevalence} = \frac{\text{Number of confirmed cases per week}}{\text{Population}} \times 100{,}000 \quad (2)$$

To verify whether the morbidity indices (incidence and prevalence) depend on the geoclimatic zones where countries are geographically located, the non-parametric k-sample test for median equality was applied and a geographic representation (thematic world map) was constructed for each of the explored variables.

To further investigate whether there is a correlation between incidence/prevalence and each climatic variable (considered individually), the Spearman rank correlation coefficient was calculated considering a two-week interval between the climatic data and the virological data. Furthermore, the correlation between incidence/prevalence and population density was also calculated.

Subsequently, on the basis of the results of the descriptive analysis, a path diagram was proposed (Fig. 2) to explore the potential relationships between meteorological variables, population density and morbidity indices.

In this theoretical path it was assumed that meteorological factors were correlated to each other and linked to an unobserved/unmeasurable variable (or latent variable), indicated by the *Climate* label. Furthermore, it was hypothesized that *Climate* (that integrates the effects of meteorological variables) and *Population Density*, were regressors of *Incidence* and *Prevalence*, assuming the following pathways: *Climate* → *Incidence*, *Climate* → *Prevalence*, *Population Density* → *Incidence*, *Population Density* → *Prevalence*. Finally, *Incidence* and *Prevalence*, being closely connected by their nature, were linked by an arc that expresses their covariance.

To test this theoretical path and convert it into a set of equations, the authors applied the SEM, a broad and flexible statistical technique for modeling causal chain of effects simultaneously. Using a confirmatory approach (hypothesis-testing), this technique, examines the relationships between observed variables and not observed (latent) variables, in turn linked to observed variables, their indicators.

The SEM graphical representation is given by a path diagram, a kind of flow-chart that uses boxes, ellipses, and circles linked via arrows. Observed variables are represented by a box, and latent variables by an ellipse. Straight single-headed arrows express causal relations and double-headed curved arrows express correlations or covariance (without a causal interpretation). The values on the straight arrows between latent and observed variables and those between latent and observed indicators, represent, respectively, the path coefficients and the factors loading (the last being the correlation coefficient for the latent and observed indicators).

The circles with short arrows pointing to dependent variables refer to residual terms ε_i. They include other possible variables that may influence dependent variables, but also random errors, errors in data entry, systematic errors leading to bias in the measurement of values. The value on the straight arrows between residual terms and dependent variables represents the residual variance (var ε_i). Two important issues of SEM that deserve to be comprehensively addressed are the path coefficient and the residual variance. The path coefficient is a basic element in the SEM model. It indicates strength and direction of the causal impact of a variable considered as a cause on another variable that is considered, instead, an effect; it is like the regression coefficient. There are two types of path coefficients: non-standardized and standardized. Both express the influence of the causal variable on the dependent variable, but the first (the non-standardized one) reflects the change in terms of unit, while the second (the standardized), changes in terms of standard deviation. For example, in path A → B, a non-standardized path coefficient of 0.20 indicates that, if variable A increases by 1-unit, variable B is be expected to increase by 0.20 unit. In the case of standardized path coefficient, if variable A increases by one standard deviation from its mean, variable B is expected to increase by 0.20 its own standard deviation from its own mean. Frequently, SEM models include more than one variable as causative factor, often with different measurement units and order of magnitude. In these cases, the use of a non-standardized path coefficient is inappropriate because the effects of these variables on the dependent variable cannot be directly compared. Instead, the standardized path coefficient, being based on a normalised parameter (the standard deviation of the mean), allows for a direct comparison of the effects of variables, regardless of their original measurements.

Since both climatic variables and population density have very different scales of measurement and order of magnitude, in the present study the standardized path coefficient was considered for the analysis.

As for the residual variance, it is worth pointing out that it includes the effects of a lot of components (errors and other variables), each of which may have very little relevance. For its cumulative nature, residual variance may also reach high values, but the actual weight that it had in SEM is expressed by the fit index SRMR (reported below).

In order to reduce the random error, observations with missing values were excluded from the SEM model processing because the interpolation approach (often used for missing data) would have introduced other sources of errors in addition to those already present and due to (a) the large number of variables considered, (b) the large number of data processed, (c) the large number of Countries from which the data were collected, and (d) the heterogeneity of the same (often very different in a number of aspects).

To evaluate the adequacy of the model, the following fit indices were considered[31]: (a) coefficient of determination (CD) (similar to the R-squared value, ranging 0–1, good fit for values close to 1); (b) root mean square error of approximation (RMSEA) (good fit for RMSEA < 0.08), and (c) standardized root mean square residual (SRMR) (adequate fit for SRMR < 0.08).

SEM was fitted by maximum likelihood estimation (MLE) method and p-value less than 0.05 was considered as statistically significant. All of the statistical analysis was performed using STATA 14.0 (STATA Corp, College Station, TX)[32], using the commands and the code reported below.

(a) Commands:

- *tsset command*, to structure in form of panel data the database containing the climate, socio-demographic and covid data of the 209 countries (for a total of 3764 records);
- *sem command*, to transform the relationships hypothesized between the variables (previously logarithmized) in a model of linear structural equations;
- *sem, standardize*, to obtain the standardized path coefficients;

(b) Code:

tsset id week_index
sem (*Climate -> L2.ln_Precipitation,*) (*Climate -> L2.ln_Humidity,*) (*Climate -> L2.ln_Pressure,*) (*Climate -> L2.ln_Temperature,*) (*Climate -> L2.ln_Wind,*) (*Climate -> L2.ln_Solar,*) (*Climate -> ln_Prevalence,*) (*Climate -> ln_Incidence,*) (*ln_Population_density -> ln_Incidence,*) (*ln_Population_density ->*

ln_Prevalence,), *covstruct*(*_lexogenous, diagonal*) *cov*(*_lexogenous*_oexogenous@0*) *latent*(*Climate*) *cov*(*e.ln_prevalence*e.ln_incidence*) *nocapslatent*
sem, standardize

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Author contributions
All authors contributed to the study conception and design. Data collection was performed by S.C., M.D.B., N.F., C.F., G.G., G.M., G.P., M.T., under the supervision of P.P.C., N.C., V.T., M.C. and R.I. The statistical analyses were chosen and performed by A.S. and F.A.T. The first draft of the manuscript was written by A.U. and A.T. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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The authors declare no competing interests.

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Article

Altitude and SARS-CoV-2 Infection in the First Pandemic Wave in Spain

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Abstract: After the first pandemic wave, a nationwide survey assessed the seroprevalence of SARS-CoV-2 antibodies in Spain and found notable differences among provinces whose causes remained unclear. This ecological study aimed to analyze the association between environmental and demographic factors and SARS-CoV-2 infection by province. The seroprevalence of SARS-CoV-2 antibodies by province was obtained from a nationwide representative survey performed in June 2020, after the first pandemic wave in Spain. Linear regression was used in the analysis. The seroprevalence of SARS-CoV-2 antibodies of the 50 provinces ranged from 0.2% to 13.6%. The altitude, which ranged from 5 to 1131 m, explained nearly half of differences in seroprevalence ($R^2 = 0.47$, $p < 0.001$). The seroprevalence in people residing in provinces above the median altitude (215 m) was three-fold higher (6.5% vs. 2.1%, $p < 0.001$). In the multivariate linear regression, the addition of population density significantly improved the predictive value of the altitude ($R^2 = 0.55$, $p < 0.001$). Every 100 m of altitude increase and 100 inhabitants/km^2 of increase in population density, the seroprevalence rose 0.84 and 0.63 percentage points, respectively. Environmental conditions related to higher altitude in winter–spring, such as lower temperatures and absolute humidity, may be relevant to SARS-CoV-2 transmission. Places with such adverse conditions may require additional efforts for pandemic control.

Keywords: SARS-CoV-2; COVID-19; altitude; seroepidemiological studies; infection transmission; population density

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1. Introduction

The first wave of the SARS-CoV-2 pandemic spread in Europe in March and April 2020, showing important geographical differences whose causes remain unclear [1]. The role of environmental and demographic conditions on SARS-CoV-2 transmission is not well known. Geographical comparisons have associated higher atmospheric temperature and humidity with lower SARS-CoV-2 transmission [2–5]. However, these studies may be affected by differences in the completeness of COVID-19 reporting in the first wave, because a high and variable percentage of cases were not confirmed [5]. Furthermore, those studies that compare countries may also be affected by the differences in the introduction of preventive interventions [6,7].

Altitude above sea level could be a potential factor related to SARS-CoV-2 transmission and COVID-19 severity [8]. Studies in Bolivia and Ecuador have suggested that physiological adaptation to hypoxia in high-altitude regions could be protective for SARS-CoV-2 infection [9,10]. However, other authors have also shown that case-fatality rate may not be reduced at high altitude [11]. Indeed, higher mortality rates attributable to COVID-19 have

been reported in areas located over 2000 m of altitude against those located below 1500 m in the United States and Mexico [12].

Several studies support the hypothesis that low temperature and low absolute humidity favor SARS-CoV-2 transmission. In Italy, a lower risk of hospitalization by COVID-19 was observed in cases in people living near the coast [13].

Spain is a mountainous and climatically diverse territory. Compared to other European countries, the altitude in Spain is higher on average and the geographical diversity is wider, resulting in a major climatic contrast. However, because the altitude range of the Spanish municipalities does not exceed 1700 m, its relevance as a cause of hypoxic effects is low.

Spain was one of the European countries first and most severely affected by COVID-19 [1,14]. Transmission increased steeply during the first half of March, and the main intervention was a lockdown implemented simultaneously in all Spanish regions on 15 March 2020 [15]. No other relevant intervention was introduced; therefore, the important geographical differences observed in COVID-19 cumulative incidence in the first pandemic wave were probably related to case reporting, and to environmental and sociodemographical factors [2–13].

This study aimed to assess the possible influence of several environmental and demographic factors on the differences in the transmission of SARS-CoV-2 among provinces in Spain.

2. Materials and Methods

This ecological study analyzed environmental and demographic factors to explain the geographical differences among provinces in the seroprevalence of SARS-CoV-2 antibodies after the first pandemic wave in Spain.

Spain is divided into 50 provinces whose capital city is usually the most populated municipality. A nationwide Seroepidemiological Survey of SARS-CoV-2 Infection was performed in a representative sample of the population [16]. The first round of this survey included a representative sample of persons of each province who were recruited from 27 April to 11 May 2020. Immunoassays were performed for the detection of IgG against SARS-CoV-2 in 51,958 persons. The seroprevalence of IgG antibodies was estimated by province [16].

Province population data by January 2020 were obtained from the National Institute for Statistics. The Geographical Institute was consulted to obtain the province extension, as well as the latitude and altitude above sea level of their respective capital city (https://www.ign.es/web/ign/portal/ane-datos-geograficos/-/datos-geograficos/datosPoblacion?tipoBusqueda=capitales, accessed date 21 January 2021). Population density was calculated as inhabitants per km^2.

The increasing part and the peak of the pandemic wave took place in March 2020, and the lockdown started on March 15 and continued up to May; therefore, the meteorological conditions in March were considered relevant to evaluate their potential effect on SARS-CoV-2 transmission. From the National Meteorological Agency, we obtained the monthly mean of each capital city for relative humidity, as well as daily maximum, minimum and mean temperatures in degrees Celsius (°C) (https://opendata.aemet.es/centrodedescargas/productosAEMET?, accessed date 21 January 2021). Absolute humidity was calculated as a function of relative humidity, mean temperature, and atmospheric pressure.

Quantitative variables were presented as the mean, standard deviation, median, and range. Means were compared by the Student's *t*-test. Categorical variables were presented as percentages and compared by χ^2. Linear regression analysis was used to test the predictive value of each variable on the seroprevalence by province. The determination coefficient (R^2) was calculated as an indicator of the proportion of the seroprevalence variability that was explained by the model. A multivariate linear regression model was fitted, starting with the most predictive variable and adding the variables that significantly

increased the predictive capacity of the model. *p*-values lower than 0.05 were considered as statistically significant. The IBM-SPSS Statistics 25 package was used for statistical analysis.

3. Results

The seroprevalence of SARS-CoV-2 IgG antibodies of the 50 Spanish provinces ranged from 0.2% to 13.6%. Variability among capital cities was considerable in altitude (ranging from 5 to 1131 m) and population density (ranging from 9 to 840 inhabitants/km^2). Very important differences were also observed in the average maximum, minimum, and mean temperatures in March 2020, as well as in average atmospheric absolute humidity (Table 1).

Table 1. Descriptive analysis of the variables considered for the 50 provinces in, Spain.

Variables Analyzed	Mean	SD	Range	Median
Seroprevalence of SARS-CoV-2 IgG, % *	4.3	3.8	0.2–13.6	2.8
Altitude above sea level, m **	370	362	5–1131	215
Latitude in degrees **	39.9	3.2	28.1–43.3	40.5
Average absolute humidity (g/m^3) **	7.3	1.3	4.9–10.6	7.3
Average of daily maximum temperatures **	17.0	2.5	12.7–22.3	16.5
Average of daily minimum temperatures **	7.0	3.6	1.0–16.1	6.6
Average of daily mean temperatures **	11.9	3.0	6.2–19.2	11.7
Population (in thousands)	943	1208	90–6747	643
Extension (km^2)	9921	4805	1980–21,766	9992
Density of population (inhabitants/km^2)	132	174	9–840	63

* Seroprevalence of SARS-CoV-2 IgG antibodies obtained by immunoassay tests from 27 April to 11 May 2020. ** Data refer to the capital city of the province. Meteorological variables were average variables of March 2020. Temperature is in degrees Celsius.

In bivariate analyses, a higher altitude, a lower absolute humidity, and lower averages of daily maximum, minimum and mean temperatures were statistically significantly associated with a higher seroprevalence in the province. Living in a province with a coast was also significantly associated with an average decrease in seroprevalence of 4.1 percentage points ($p < 0.001$; $R^2 = 0.30$) (Figure 1). However, altitude was the strongest predictive variable for the seroprevalence ($R^2 = 0.47$) (Table 2 and Figure 2).

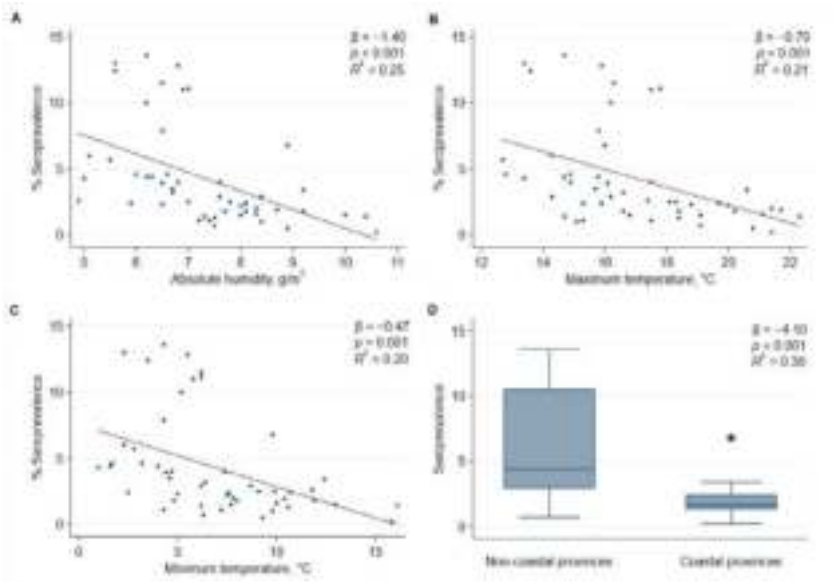

Figure 1. Bivariate association of the seroprevalence of IgG antibodies against SARS-CoV-2 as a function of four environmental parameters by province. The seroprevalence was obtained by immunoassay tests in samples collected from 27 April to 11 May 2020, in Spain. (**A**) Average of absolute humidity; (**B**) average of daily maximum temperatures; (**C**) average of daily minimum temperatures; and (**D**) box-plot of comparison between coastal and non-coastal provinces.

Table 2. Results of linear regression at the province level (n = 50) between environmental and demographic variables and the seroprevalence of IgG antibodies against SARS-CoV-2 obtained by immunoassay tests from 27 April to 11 May 2020, in Spain.

Analyses and Variables	Beta	SE	p-Value	R^2
Bivariate analyses				
Altitude above sea level (per 100 m) *	0.71	0.11	<0.001	0.47
Latitude in degrees *	0.19	0.17	0.261	0.03
Average absolute humidity (g/m^3) *	−1.40	0.35	<0.001	0.25
Average of daily maximum temperatures, °C *	−0.70	0.19	<0.001	0.21
Average of daily minimum temperatures, °C *	−0.47	0.13	0.001	0.20
Average of daily mean temperature, °C *	−0.55	0.16	0.001	0.19
Province with coast	−4.10	0.90	<0.001	0.30
Density of population (inhabitants per km^2)	−0.07	0.31	0.821	0.001
Multivariable analyses				0.55
Intercept	0.36	0.71	0.615	
Altitude above sea level (per 100 m) *	0.84	0.11	<0.001	
Density of population (inhabitants per km^2)	0.63	0.23	0.009	

* Data refer to the capital city of the province; R^2, determination coefficient. SE, standard error; We used bold case to distingish the analysis, because normal case is used to variables.

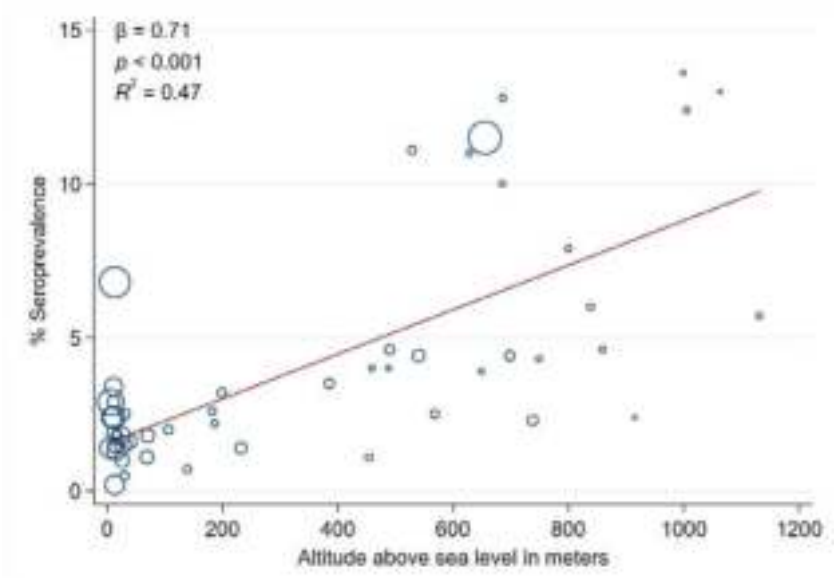

Figure 2. Linear regression analysis of the seroprevalence of IgG antibodies against SARS-CoV-2 as a function of the altitude above sea level in meters by province. The diameter of the circles is proportional to the population density. The seroprevalence was obtained by immunoassay tests in samples collected from 27 April to 11 May 2020, in Spain.

In the multivariate linear regression model, population density was the only variable that significantly improved the predictive value of the altitude (R^2 = 0.55). Each 100 m increase in altitude and 100 inhabitants/km^2 of increase in density, the seroprevalence increased by 0.84 and 0.63 percentage points, respectively (Table 2).

The 25 provinces with altitude above the median (215 m) showed a three-fold higher seroprevalence (6.5% vs. 2.1%, $p < 0.001$), lower absolute humidity (6.4 vs. 8.3 g/m^3, $p < 0.001$), and lower averages of the daily maximum, minimum and mean temperatures than the others (15.5 vs. 18.6, 4.3 vs. 9.6, 9.9 vs. 13.8 °C, respectively, $p < 0.001$) (Table 3).

Table 3. Comparison of average characteristics between provinces (n = 50) with altitude above and below the median (215 m). Spain, 2020.

Variables Analyzed	Provinces with Altitude >215 m (n = 25)		Provinces with Altitude <215 m (n = 25)		p-Value
	Mean	SD	Mean	SD	
Seroprevalence of SARS-CoV-2 IgG, % *	6.5	4.1	2.1	1.3	<0.001
Latitude in degrees **	40.8	1.7	39.0	4.0	0.043
Average absolute humidity (g/m^3) **	6.4	0.7	8.3	1.2	<0.001
Average of daily maximum temperatures, °C **	15.5	1.7	18.6	2.3	<0.001
Average of daily minimum temperatures, °C **	4.3	1.9	9.6	2.8	<0.001
Average of daily mean temperatures, °C **	9.9	1.7	13.8	2.7	<0.001
Density of population (inhabitants per km^2)	69	163	194	164	<0.001

* Seroprevalence of SARS-CoV-2 IgG antibodies obtained by immunoassay tests from 27 April to 11 May 2020. ** Data refer to the capital city of the province. Meteorological variables were average variables of March 2020.

4. Discussion

Nearly half (47%) of the important geographical differences in SARS-CoV-2 infection during the first pandemic wave in Spain may be explained by the altitude of the province of residence, and this proportion increased up to 55% when population density was also considered. The seroprevalence of SARS-CoV-2 antibodies was three-fold higher in people living in provinces with altitude above the median. The hypothesis derived from these results is that environmental factors may have a role in SARS-CoV-2 transmission greater than previously considered. More studies are needed to evaluate the role of these factors in geographical differences observed in the pandemic. These environmental conditions should be considered in the comparison of the effects of preventive interventions.

It has been suggested that geographical differences in the cumulative incidence of COVID-19 could be indicative of the success of preventive measures implemented [6,7]. However, in the first wave in Spain, a decisive part of SARS-CoV-2 transmission happened before the relevant preventive measures had been introduced, and the lockdown was implemented simultaneously in all regions. Spain has coastline almost all around the country and many mountain ranges. Some provinces in close proximity have notable altitude differences, while some distant provinces have similar altitude; this geographical pattern seems to have carried over to SARS-CoV-2 infection [16].

Bivariate analysis highlighted several environmental variables associated to the higher seroprevalence of SARS-CoV-2 antibodies, including a higher altitude, lower absolute humidity, and lower averages of daily maximum, minimum and mean temperatures, as well as living in a province with a coast. In the present study, the altitude above sea level was more predictive than any meteorological parameter. In Spain in March, those provinces with a higher altitude had, on average, lower absolute humidity, lower temperature in winter, and less sea influence, and these three factors have been related to increases in respiratory virus transmission [2–4]. Therefore, the strongest association between higher altitude and SARS-CoV-2 seroprevalence may be explained because this factor combines the effects of absolute humidity, temperature, and proximity to the coast. Environmental factors may modify the efficiency of SARS-CoV-2 transmission; however, they are not sufficient to stop the spread. Therefore, while preventive interventions are necessary for all regions [5,7,17], places with adverse conditions may have additional difficulties for the effective control of transmission and may need more strict preventive measures to achieve similar results.

Other ecological studies have evaluated the relationship between environmental factors and SARS-CoV-2 infection, and many have found an inverse relationship between air temperature and humidity and SARS-CoV-2 infection [2,12,13,18–22]. These studies have been based on COVID-19 reported cases that may be affected by differences in the completeness of reporting. In the first pandemic wave, a high percentage of cases were not confirmed, and this percentage may be different among regions and countries [5]. Furthermore, those studies that compare countries may be also affected by the differences

in the introduction of preventive interventions [6,7]. Our results are consistent with most of these studies, and additionally have the advantage of the optimal comparability among Spanish provinces because seroprevalence was assessed with the same protocol, interventions were simultaneously introduced, and social differences within the same country are probably smaller.

Studies in Latin America have not found altitude to be associated with higher transmission [16–18], but the wider altitude range and the tropical latitude make comparisons with our results difficult.

We found a lower seroprevalence of SARS-CoV-2 antibodies in provinces with a coast. This result might be consistent with the lower risk of hospitalization among COVID-19 cases in people living near the coast, which has been found in Italy [13].

The results of our bivariate analysis are consistent with worldwide and large countries' studies that did not find association between population density and SARS-CoV-2 spread [2,20]. However, a higher population density in the province was an independent predictor of SARS-CoV-2 seroprevalence when altitude was an adjusted factor. Although population density was not an important factor in COVID-19 spreading under strict lockdown policies [23], it has been also described as a relevant factor for SARS-CoV-2 transmission in less strict conditions [24–27]; therefore, some effect of population density on transmission in the period before the lockdown in Spain seems plausible.

The main strengths of this study are that Spain met special conditions in the first pandemic wave to evaluate this association, because it is an environmentally diverse territory, the lockdown was implemented simultaneously in all regions, and a nationwide survey was performed to obtain comparable estimates of the seroprevalence of SARS-CoV-2 by provinces.

This study has limitations, however. The ecological analysis may suggest a hypothesis but cannot conclude causality. Parameters of the capital city were assigned to the whole province; although, in most provinces, parameters of the capital city are a good proxy of the average conditions to which the population of the province is exposed. These results may not predict infections in further waves because a part of the population may have acquired immunity; many preventive interventions have been introduced; and the weather conditions in other months may be different. Social interaction and differences between rural and urban residence have been suggested as important factors for SARS-CoV-2 transmission; however, population density alone was not predictive for higher seroprevalence in the present study. Several potential risk factors have not been considered in the analysis, but the strong association that we found between altitude and seroprevalence is unlikely to be totally explained by confounding factors. Furthermore, because altitude is a primary factor, other environmental and social variables might act as intermediate factors explaining the association between altitude and SARS-CoV-2 infection.

5. Conclusions

In summary, important differences among Spanish provinces were observed in the seroprevalence of SARS-CoV-2 antibodies after the first pandemic wave. Nearly half of these differences may be explained by altitude. Environmental conditions related to higher altitude in winter–spring, such as the combination of low temperature and absolute humidity, may be relevant for SARS-CoV-2 transmission. A higher population density was also a predictive factor for transmission. Although spread of SARS-CoV-2 widely depends on social behaviors and preventive interventions, places with adverse environmental conditions may require additional efforts to achieve similar pandemic control.

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Diverse local epidemics reveal the distinct effects of population density, demographics, climate, depletion of susceptibles, and intervention in the first wave of COVID-19 in the United States

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The SARS-CoV-2 pandemic has caused significant mortality and morbidity worldwide, sparing almost no community. As the disease will likely remain a threat for years to come, an understanding of the precise influences of human demographics and settlement, as well as the dynamic factors of climate, susceptible depletion, and intervention, on the spread of localized epidemics will be vital for mounting an effective response. We consider the entire set of local epidemics in the United States; a broad selection of demographic, population density, and climate factors; and local mobility data, tracking social distancing interventions, to determine the key factors driving the spread and containment of the virus. Assuming first a linear model for the rate of exponential growth (or decay) in cases/mortality, we find that population-weighted density, humidity, and median age dominate the dynamics of growth and decline, once interventions are accounted for. A focus on distinct metropolitan areas suggests that some locales benefited from the timing of a nearly simultaneous nationwide shutdown, and/or the regional climate conditions in mid-March; while others suffered significant outbreaks prior to intervention. Using a first-principles model of the infection spread, we then develop predictions for the impact of the relaxation of social distancing and local climate conditions. A few regions, where a significant fraction of the population was infected, show evidence that the epidemic has partially resolved via depletion of the susceptible population (i.e., "herd immunity"), while most regions

in the United States remain overwhelmingly susceptible. These results will be important for optimal management of intervention strategies, which can be facilitated using our online dashboard.

Introduction

The new human coronavirus SARS-CoV-2 emerged in Wuhan Province, China in December 2019 (Chen et al., 2020; Li et al., 2020), reaching 10,000 confirmed cases and 200 deaths due to the disease (known as COVID-19) by the end of January this year. Although travel from China was halted by late-January, dozens of known introductions of the virus to North America occurred prior to that (Holshue et al., 2020; Kucharski et al., 2020), and dozens more known cases were imported to the US and Canada during February from Europe, the Middle East, and elsewhere. Community transmission of unknown origin was first detected in California on February 26, followed quickly by Washington State (Chu et al., 2020b), Illinois and Florida, but only on March 7 in New York City. Retrospective genomic analyses have demonstrated that case-tracing and self-quarantine efforts were effective in preventing most known imported cases from propagating (Ladner et al., 2020; Gonzalez-Reiche et al., 2020; Worobey et al., 2020), but that the eventual outbreaks on the West Coast (Worobey et al., 2020; Chu et al., 2020b; Deng et al., 2020) and New York (Gonzalez-Reiche et al., 2020) were likely seeded by unknown imports in mid-February. By early March, cross-country spread was primarily due to interstate travel rather than international imports (Fauver et al., 2020).

In mid-March 2020, nearly every region of the country saw a period of uniform exponential growth in daily confirmed cases — signifying robust community transmission — followed by a plateau in late March, likely due to social mobility reduction. The same qualitative dynamics were seen in COVID-19 mortality counts, delayed by approximately one week. Although the qualitative picture was similar across locales, the quantitative aspects of localized epidemics — including initial rate of growth, infections/deaths per capita, duration of plateau, and rapidity of resolution —were quite diverse across the country. Understanding the origins of this diversity will be key to predicting how the relaxation of social distancing, annual changes in weather, and static local demographic/population characteristics will affect the resolution of the first wave of cases, and will drive coming waves, prior to the availability of a vaccine.

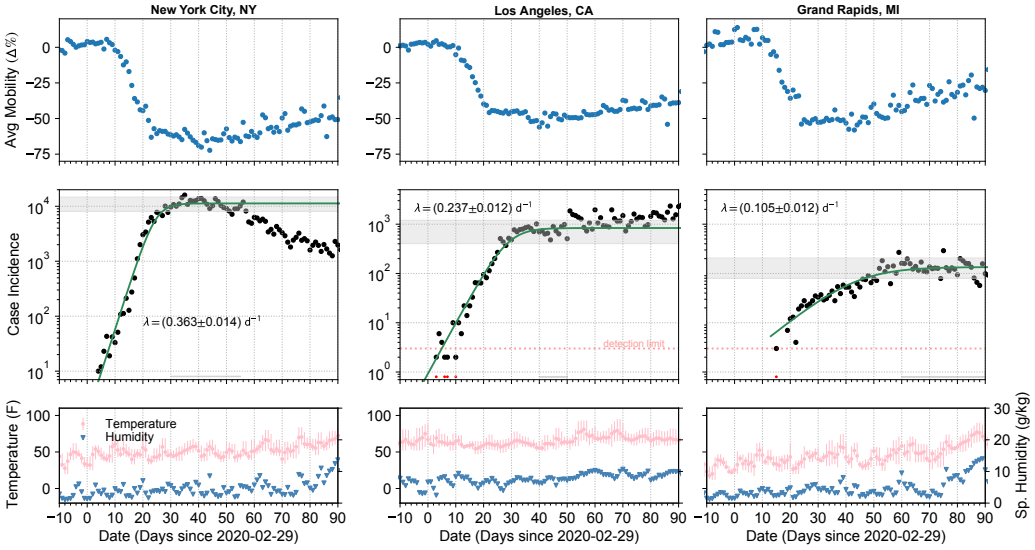
The exponential growth rate of a spreading epidemic is dependent on the biological features of the virus-host ecosystem — including the incubation time, susceptibility of target cells to infection, and persistence of the virus particle outside of the host — but, through its dependence on the transmission rate between hosts, it is also a function of external factors such as population density, air humidity, and the fraction of hosts that are susceptible. Initial studies have shown that SARS-CoV-2 has a larger rate of exponential growth (or, alternatively, a lower doubling time of cases[1]) than many other circulating human viruses (Park et al., 2020). For comparison, the pandemic influenza of 2009, which also met a largely immunologically-naive population, had a doubling time of 5–10d (Yu et al., 2012; Storms et al., 2013), while that of SARS-CoV-2 has been estimated at 2–5d (Sanche et al., 2020; Oliveiros et al., 2020) (growth rates of $\sim 0.10\mathrm{d}^{-1}$ vs. $\sim 0.25\mathrm{d}^{-1}$). It is not yet understood which factors contribute to this high level of infectiousness.

While the dynamics of an epidemic (e.g., cases over time) must be described by numerical solutions to nonlinear models, the exponential growth rate, λ, usually has a simpler dependence on external factors. Unlike case or mortality incidence numbers, the growth rate does not scale with population size. It is a directly measurable quantity from the available incidence data, unlike, e.g., the reproduction number, which requires knowledge of the serial interval distribution (Wallinga and Lipsitch, 2007; Roberts and Heesterbeek, 2007; Dushoff and Park, 2020), something that is difficult to determine empirically (Champredon and Dushoff, 2015; Nishiura, 2010). Yet, the growth rate contains the same threshold as the reproduction number ($\lambda = 0$ vs. $R_0 = 1$), between a spreading epidemic (or an unstable uninfected equilibrium) and a contracting one (or an equilibrium that is resistant to flare-ups). Thus, the growth rate is an informative direct measure on that space of underlying parameters.

In this work, we leverage the enormous data set of epidemics across the United States to evaluate the impact of demographics, population density and structure, weather, and non-pharmaceutical interventions (i.e., mobility restrictions) on the exponential rate of growth of COVID-19. Following a brief analysis of the initial spread in metropolitan regions, we expand the meaning of the exponential rate to encompass all aspects of a local epidemic — including growth, plateau and decline — and use it as a tracer of the dynamics, where its time dependence and geographic variation are dictated solely by these external variables and per capita cumulative mortality. Finally, we use the results of that linear analysis to calibrate a new nonlinear model — a renewal equation that utilizes the excursion probability of a random walk to determine the incubation period — from which we develop local predictions about the impact of social mobility relaxation, the level of herd immunity, and the potential of rebound epidemics in the Summer and Fall.

[1] The doubling time is $\ln 2$ divided by the exponential growth rate.

A



B

Variable		Mean value	Coef.	Std. Err.	t	95% CI
average growth rate, λ_{avg}			0.232	0.005	43.1	[0.220, 0.242]
avg mobility, 2wk prior	–	+2.2%	0.0063	0.0006	10.8	[0.0051,0.0074]
ln[PWD]	–	8.1	0.048	0.010	4.7	[0.028,0.069]
sp. humidity, 2wk prior	–	4.9 g/kg	-0.010	0.0027	-3.7	[-0.016, -0.005]
pop. sparsity, γ	–	0.21	-0.33	0.11	-3.0	[-0.55, -0.11]
median age	–	35.7	0.0049	0.0024	2.1	[0.0002,0.0096]

C

	med. age	mob. 2wk pr.	pop. sparsity	hum. 2wk pr.	lnpwpd	λ_{mod}	λ_{exp}	λ_{exp} err
ny_newyorkcity	0.004	0.011	0.007	0.021	0.069	0.343	0.363	0.014
il_chicago	-0.002	0.022	0.02	0.018	0.017	0.307	0.316	0.017
mi_detroit	0.008	0.044	0.019	0.02	-0.023	0.301	0.412	0.035
oh_cleveland	0.014	0.035	0.02	0.018	-0.024	0.294	0.298	0.027
pa_philadelphia	0.004	0.01	0.015	0.014	0.012	0.286	0.291	0.009
ma_boston	0.003	-0.03	0.015	0.021	0.017	0.258	0.222	0.013
ct_hartford	0.012	-0.003	0.01	0.019	-0.014	0.255	0.287	0.019
co_denver	-0.009	0.022	-0.018	0.027	-0.002	0.252	0.24	0.014
wa_seattle	-0.003	0.02	0.002	0.007	-0.006	0.252	0.223	0.019
ma_worcester	0.009	0.003	0.001	0.024	-0.02	0.248	0.237	0.026
tx_dallas	-0.015	0.027	0.011	-0.016	0.001	0.24	0.252	0.021
ga_atlanta	-0.008	0.022	0.025	-0.006	-0.025	0.24	0.242	0.019
ca_losangeles	-0.007	0.0	-0.006	-0.016	0.027	0.229	0.237	0.012
dc_washington	-0.002	-0.047	0.008	0.003	0.012	0.206	0.213	0.009
mi_grandrapids	-0.005	-0.12	-0.001	0.015	-0.038	0.083	0.105	0.012

Figure 1: *Mobility and COVID-19 incidence data examples, and the results of linear regression to extracted initial exponential growth rates, λ_{exp}, in the top 100 metropolitan regions. (A) Three example cities with different initial growth rates. Data for Google mobility (blue points), daily reported cases (black points), and weather (red and blue points, bottom) are shown with a logistic fit to cases (green line). Data at or below detection limit were excluded from fits (dates marked by red points). Thin grey bars at base of cases graphs indicate region considered "flat", with right end indicating the last point used for logistic fitting; averaging over "flat" values generates the thick grey bars to guide the eye. [See Supp. Mat. for additional information and for complete data sets for all metropolitan regions.] (B) Weighted linear regression results in fit to λ_{exp} for all metropolitan regions. (C) Effect of each variable on growth rate (i.e., $\Delta\lambda$ values) for those regions with well-estimated case and death rates; white/yellow indicates a negative effect on λ, red indicates positive.*

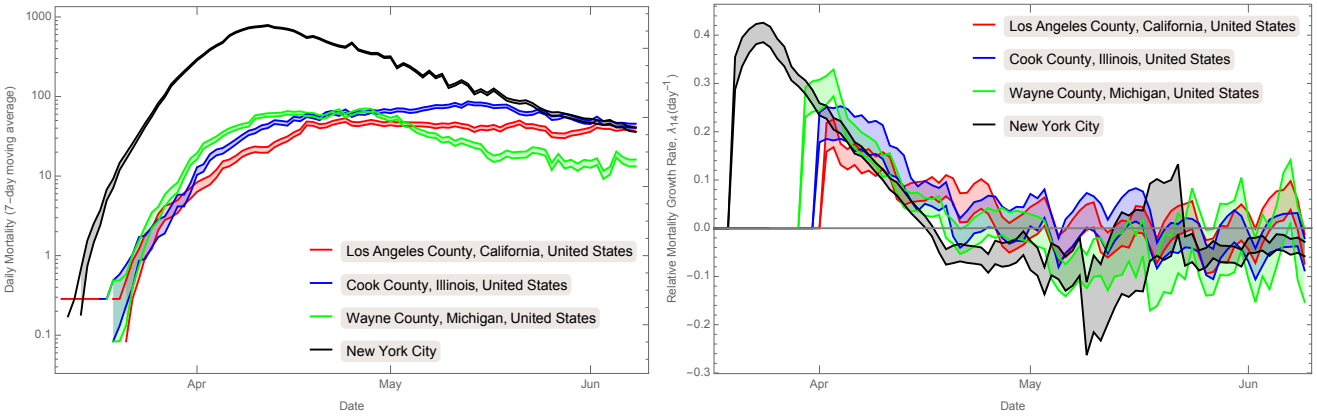


Figure 2: *COVID-19 mortality incidence (7-day rolling average, left) and exponential growth rate (λ_{14}, determined by regression of the logged mortality data over 14-day windows, right) for the four US counties with >2400 confirmed COVID-19 reported deaths (as of 8th June, 2020).*

Results

Initial growth of cases in metropolitan regions is exponential with rate depending on mobility, population, demographics, and humidity

As an initial look at COVID-19's arrival in the United States, we considered the $\sim$100 most populous metropolitan regions — using maps of population density to select compact sets of counties representing each region (see Supplementary Material) — and estimated the initial exponential growth rate of cases in each region. We performed a linear regression to a large set of demographic (sex, age, race) and population variables, along with weather and social mobility (Fitzpatrick and Karen, 2020) preceding the period of growth (Figure 1). In the best fit model ($R^2 = 0.75$, $\mathrm{BIC} = -183$), the baseline value of the initial growth rate was $\lambda = 0.21\mathrm{d}^{-1}$ (doubling time of 3.3d), with average mobility two weeks prior to growth being the most significant factor (Figure 1B). Of all variables considered, only four others were significant: population density (including both *population-weighted density* (PWD) — also called the "lived population density" because it estimates the density for the average individual (Craig, 1985)— and *population sparsity*, γ, a measure of the difference between PWD and standard population density, see Methods), $p < 0.001$ and $p = 0.006$; specific humidity two weeks prior to growth, $p = 0.001$; and median age, $p = 0.04$.

While mobility reduction certainly caused the "flattening" of case incidence in every region by late-March, our results show (Figure 1C) that it likely played a key role in reducing the *rate* of growth in Boston, Washington, DC, and Los Angeles, but was too late, with respect to the sudden appearance of the epidemic, to have such an effect in, e.g., Detroit and Cleveland. In the most extreme example, Grand Rapids, MI, seems to have benefited from a late arriving epidemic, such that its growth (with a long doubling time of 7d) occurred almost entirely post-lockdown.

Specific humidity, a measure of absolute humidity, has been previously shown to be inversely correlated with respiratory virus transmission (Lowen et al., 2007; Shaman and Kohn, 2009; Shaman, Goldstein, and Lipsitch, 2011; Kudo et al., 2019). Here, we found it to be a significant factor, but weaker than population density and mobility (Figure 1C). It could be argued that Dallas, Los Angeles, and Atlanta saw a small benefit from higher humidity at the time of the epidemic's arrival, while the dry late-winter conditions in the Midwest and Northeast were more favorable to rapid transmission of SARS-CoV-2.

Exponential growth rate of mortality as a dynamical, pan-epidemic, measure

In the remainder of this report, we consider the exponential rate of growth (or decay) in local confirmed deaths due to COVID-19. The statistics of mortality is poorer compared to reported cases, but it is much less dependent on unknown factors such as the criteria for testing, local policies, test kit availability, and asymptomatic individuals (Pearce et al., 2020). Although there is clear evidence that a large fraction of COVID-19 mortality is missed in the official counts (e.g., Leon et al., 2020; Modi et al., 2020), mortality is likely less susceptible to rapid changes in reporting, and, as long as the number of reported deaths is a monotonic function of the actual number of deaths (e.g., a constant fraction, say 50%), the sign of the exponential growth rate will be unchanged, which is the crucial measure of the success in pandemic management.

To minimize the impact of weekly changes, such as weekend reporting lulls, data dumps, and mobility changes from working days to weekends, we calculate the regression of $\ln[\mathrm{Mortality}]$ over a 14-day interval, and assign this value, $\lambda_{14}(t)$, and its standard error to the last day of the interval. Since only the data for distinct 2-week periods are independent, we multiply the regression errors by $\sqrt{14}$ to account for correlations between the daily estimates. Together with a "rolling average" of the mortality, this time-dependent measure of the exponential growth rate provides, at any day, the most up-to-date information on the progression of the epidemic (Figure 2).

In the following section, we consider a linear fit to λ_{14}, to determine the statistically-significant external (non-biological) factors influencing the dynamics of local exponential growth and decline of the epidemic. We then develop a first-principles model for λ_{14} that allows for extrapolation of these dependencies to predict the impact of future changes in social mobility and climate.

Epidemic mortality data explained by mobility, population, demographics, depletion of susceptible population and weather, throughout the first wave of COVID-19

We considered a spatio-temporal dataset containing 3933 estimates of the exponential growth measure, λ_{14}, covering the three month period of 8 March 2020 – 8 June 2020 in the 187 US counties for which information on COVID-19 mortality and all potential driving factors, below, were available (the main barrier was social mobility information, which limited us to a set of counties that included 69% of US mortality). A joint, simultaneous,

Joint Fit to All potential drivers	Estimate	Std Err	t-Statistic
Baseline Mortality Growth Rate λ_{14}	0.195	0.011	17.2
COVID Death Fraction	-59.4	6.1	-9.7
Social Mobility (2wks prior)	0.00238	0.00028	8.5
$\ln$(Population Weighted Density)-8.24	0.0412	0.0058	7.1
Social Mobility (4wks prior)	0.00122	0.00019	6.6
Population Sparsity-0.188	-0.249	0.063	-3.9
$\log$(Annual Death)-4.04	-0.0301	0.0091	-3.3
Median Age-37.47	0.0038	0.0012	3.0
People per Household-2.76	0.023	0.014	1.6
Specific Humidity (2wks prior)-5.92 g/kg	-0.0033	0.0031	-1.1
Temperature (2wks prior)-13.11 C	-0.00083	0.0013	-0.6
Temperature (4wks prior)-11.60 C	-0.00060	0.0014	-0.4
Specific Humidity (4wks prior)-5.53 g/kg	0.00058	0.0032	0.2
Joint Fit to statistically significant drivers	Estimate	Std Err	t-Statistic
Baseline Mortality Growth Rate λ_{14}	0.198	0.011	18.7
COVID Death Fraction	-56.7	5.9	-9.7
Social Mobility (2wks prior)	0.00236	0.00027	8.8
Social Mobility (4wks prior)	0.00131	0.00017	7.6
$\ln$(Population Weighted Density)-8.24	0.0413	0.0058	7.2
Population Sparsity-0.188	-0.260	0.061	-4.3
Specific Humidity (2wks prior)-5.92 g/kg	-0.0047	0.0011	-4.1
$\log$(Annual Death)-4.04	-0.0324	0.0088	-3.7
Median Age-37.48	0.0040	0.0012	3.3

Table 1: *Joint Linear Fit to $\lambda_{14}(t)$ data (Top). Any dependence with t-Statistic below 2.5σ is considered not statistically significant. Joint Linear Fit to $\lambda_{14}(t)$, including only statistically significant dependencies (Bottom). For all coefficients, the population-weighted baseline is subtracted from the linear variable.*

Parameter	Best-Fit $\pm$ Std Err	Description
$\tau = \tau_0(\text{Median Age}/26.2\text{ years})^{C_A}$		Time from exposure to contagiousness
τ_0(day)	160 ± 58	Normalization
C_A	-2.26 ± 0.95	Age dependence
d^{-1}(day)	17.6 ± 2.2	Time from exposure to quarantine/recovery
C_D	3460 ± 610	Conversion constant, $f_D \to f_I$
β: Equation (2)		Rate constant for infection
$\ln\left[k\beta_0\tau_0^{-2}(\text{m}^2/\text{day}^3)\right]$	0.37 ± 1.25	Normalization
$100C_{\mathcal{M}}$	8.08 ± 1.76	Dependence on Social Mobility
$C_{\mathcal{H}}$	-0.154 ± 0.055	Dependence on specific humidity
C_γ	-5.52 ± 2.35	Dependence on population sparsity
C_{A_D}	-1.05 ± 0.25	Dependence on total annual deaths

Table 2: *Best-fit parameters for the nonlinear model using parametrization defined in the text.*

linear fit of these data to 12 potential driving factors (Table 1) revealed only 7 factors with *independent* statistical significance. Re-fitting only to these variables returned the optimal fit for the considered factors ($\mathrm{BIC} = -5951$; $R^2 = 0.674$).

We found, not surprisingly, that higher population density, median age, and social mobility correlated with positive exponential growth, while population sparsity, specific humidity, and susceptible depletion correlated with exponentially declining mortality. Notably the coefficients for each of these quantities was in the 95% confidence intervals of those found in the analysis of metropolitan regions (and vice versa). Possibly the most surprising dependency was the negative correlation, at $\simeq -3.7\sigma$ between λ_{14} and the *total* number of annual deaths in the county. In fact, this correlation was marginally more significant than a correlation with $\log$(population), which was -3.3σ. One possible interpretation of this negative correlation is that the number of annual death is a proxy for the number of potential outbreak clusters. The larger the number of clusters, the longer it might take for the epidemic to spread across their network, which would (at least initially) slow down the onset of the epidemic.

Nonlinear model

To obtain more predictive results, we developed a mechanistic nonlinear model for infection (see Supplementary Material for details). We followed the standard analogy to chemical reaction kinetics (infection rate is proportional to the product of susceptible and infectious densities), but defined the generation interval (approximately the incubation period) through the excursion probability in a 1D random walk, modulated by an exponential rate of exit from the infected class. This approach resulted in a *renewal equation* (Heesterbeek and Dietz, 1996; Champredon and Dushoff, 2015; Champredon, Dushoff, and Earn, 2018), with a distribution of generation intervals that is more realistic than that of standard SIR/SEIR models, and which could be solved formally (in terms of the Lambert W function) for the growth rate in terms of the infection parameters:

$$\lambda = \frac{1}{2\tau}\left[\mathrm{W}\left(\sqrt{\frac{\beta\mathcal{S}\tau}{2}}\right)\right]^2 - d \qquad (1)$$

The model has four key dependencies, which we describe here, along with our assumptions about their own dependence on population, demographic, and climate variables. As mortality (on which our estimate of growth rate is based) lags infection (on which the renewal equation is based), we imposed a fixed time shift of Δt for time-dependent variables:

1. We assumed that the susceptible population, which feeds new infections and drives the growth, is actually a sub-population of the community, consisting of highly-mobile and frequently interacting individuals, and that most deaths occurred in separate sub-population of largely immobile non-interacting individuals. Under these assumptions, we found (see Supp. Mat.) that the susceptible density, $S(t)$, could be estimated from the cumulative per capita death fraction, f_D, as:

$$S(t-\Delta t) = S(0)\exp\left[-C_D\, f_D(t)\right] \quad (f_D = D_{\mathrm{tot}}/N)\ ,$$

   where D_{tot} is the cumulative mortality count, N is the initial population, and the initial density is $S(0) = k\,\mathrm{PWD}$.
2. We assumed that the logarithm of the "rate constant" for infection, β, depended linearly on social mobility, m, specific humidity, h, population sparsity, γ, and total annual death, A_D, as:

$$\begin{aligned}\ln\left[\beta\left(\mathcal{M},\mathcal{H},\gamma,A_D\right)\right] &= \ln\left[\beta_0\right] \\ &+ C_{\mathcal{M}}\left(\mathcal{M}-\bar{\mathcal{M}}\right) + C_{\mathcal{H}}\left(\mathcal{H}-\bar{\mathcal{H}}\right) \\ &+ C_{\gamma}\left(\gamma-\bar{\gamma}\right) + C_{A_D}\left(A_D-\bar{A}_D\right)\end{aligned} \qquad (2)$$

   where a barred variable represents the (population-weighted) average value over all US counties, and where the mobility and humidity factors were time-shifted with respect to the growth rate estimation window: $\mathcal{M} = m\left(t-\Delta t\right)$ and $\mathcal{H} = h\left(t-\Delta t\right)$.
3. The characteristic time scale to infectiousness, τ, is intrinsic to the biology and therefore we assumed it would depend only on the median age of the population, A. We assumed a power law dependence:

$$\tau = \tau_0\left(\frac{A}{A_0}\right)^{C_A} \qquad (3)$$

   where we fixed the pivot age, A_0, to minimize the error in τ_0.
4. The exponential rate of exit from the infected class, d, was assumed constant, since we found no significant dependence for it on other factors in our analysis of US mortality. From the properties of the Lambert W function, when the infection rate or susceptibility density approach zero — through mobility restrictions or susceptible depletion — the growth rate will tend to $\lambda \approx -d$, its minimum value.

With these parameterizations, we performed a nonlinear regression to $\lambda_{14}(t)$ using the entire set of US county mortality incidence time series (Table 2). Compared to the linear model of the previous section (Table 1b), the fit improved by 7.6σ ($\mathrm{BIC} = -6008$; $R^2 = 0.724$), despite both having 9 free parameters. Through the estimated parameter values, the model makes predictions for an

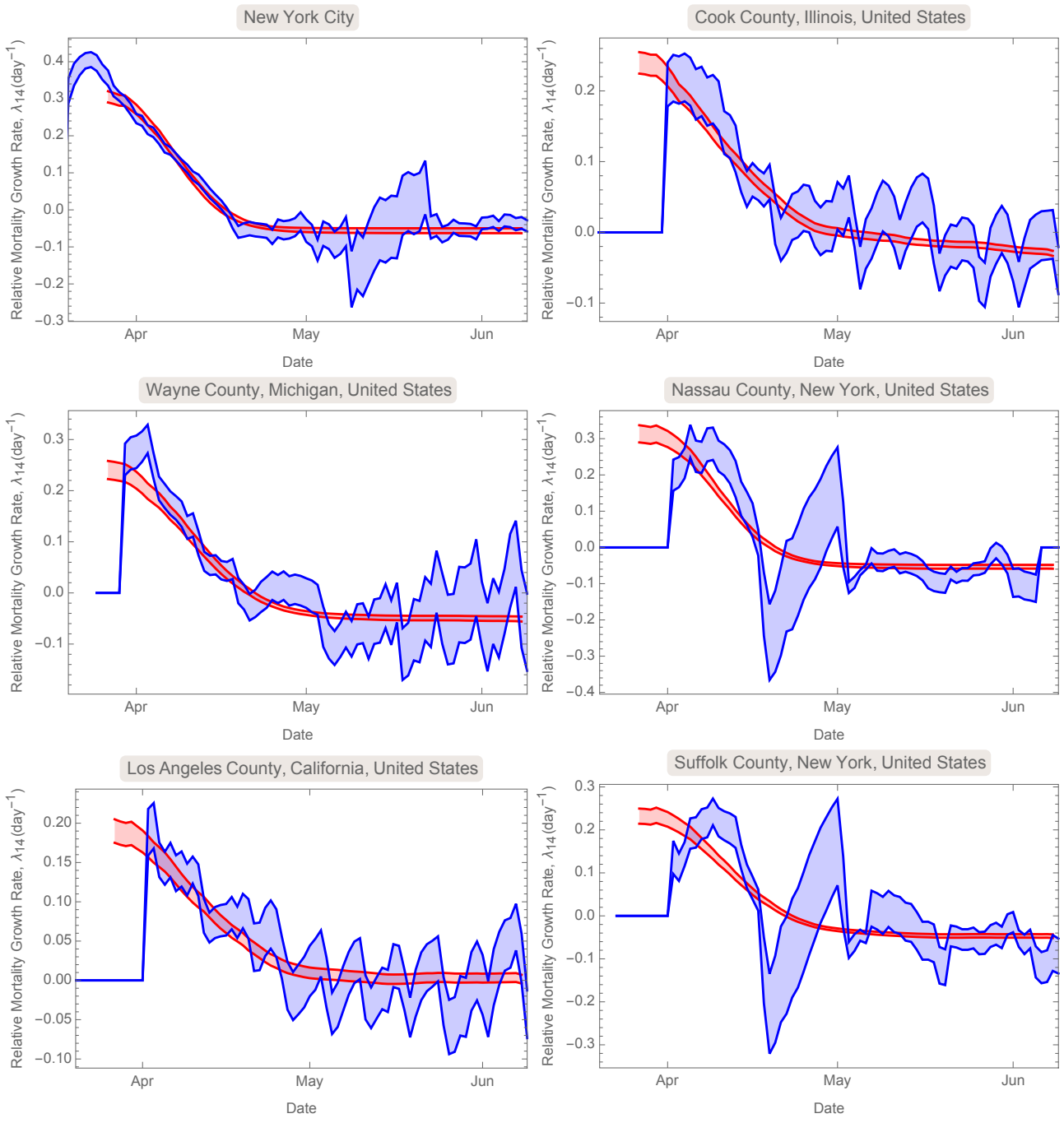


Figure 3: *Nonlinear model prediction (Eqn. 1, red) for the actual (blue) mortality growth rate, in the six counties with highest reported death. Bands show 1-σ confidence region for both the model mean and the λ_{14} value.*

individual's probability of becoming infectious, and the distributions of incubation period and generation interval, all as a function of the median age of the population (see Supplementary Material).

The model was very well fit to the mortality growth rate measurements for counties with a high mortality (Figure 3). More quantitatively, the scatter of measured growth rates around the best-fit model predictions was (on average) only 13% larger than the measurement errors, independent of the population of the county [2].

Importantly, when the model was calibrated on only a subset of the data — e.g., all but the final month for which mobility data is available — its 68% confidence prediction for the remaining data was accurate (Figure 4) given the known mobility and weather data for that final month. This suggests that the model, once calibrated on the first wave of COVID-19 infections, can make reliable predictions about the ongoing epidemic, and future waves, in the United States.

Predictions for relaxed mobility restrictions, the onset of summer, and the potential second wave

Possibly the most pressing question for the management of COVID-19 in a particular community is the combination of circumstances at which the virus fails to propagate, i.e., at which the growth rate, estimated here by λ_{14}, becomes negative (or, equivalently, the reproduction number R_t falls below one). In the absence of mobility restrictions this is informally called the threshold for "herd immunity," which is usually achieved by mass vaccination (e.g., John and Samuel, 2000; Fine, Eames, and Heymann, 2011). Without a vaccine, however, ongoing infections and death will deplete the susceptible population and thus decrease transmission. Varying the parameters of the nonlinear model individually about their Spring 2020 population-weighted mean values (Figure 5) suggests that this threshold will be very much dependent on the specific demographics, geography, and weather in the community, but it also shows that reductions in social mobility can significantly reduce transmission prior the onset of herd immunity.

To determine the threshold for herd immunity in the absence or presence of social mobility restrictions, we considered the "average US county" (i.e., a region with population-weighted average characteristics), and examined the dependence of the growth rate on the cumulative mortality. We found that in the absence of social distancing, a COVID-19 mortality rate of 0.13% (or 1300 per million population) would bring the growth rate to zero. However, changing the population density of this average county shows that the threshold can vary widely (Figure 5).

Examination of specific counties showed that the mortality level corresponding to herd immunity varies from 10 to 2500 per million people (Figure 9). At the current levels of reported COVID-19 mortality, we found that, as of June 22nd, 2020, only 128 ± 55 out of 3142 counties (inhabiting $9.4 \pm 2.1\%$ of US population) have surpassed this threshold at 68% confidence level (Figure 8). Notably, New York City, with the highest reported per capita mortality (2700 per million) has achieved mobility-independent herd immunity at the 10σ confidence level, according to the model (Figure 6). A few other large-population counties in New England, New Jersey, Michigan, Louisiana, Georgia and Mississippi that have been hard hit by the pandemic also appear to be at or close to the herd immunity threshold. This is not the case for most of the United States, however (Figure 8). Nationwide, we predict that COVID-19 herd immunity would only occur after a death toll of $340,000 \pm 61,000$, or 1058 ± 190 per million of population.

We found that the approach to the herd immunity threshold is not direct, and that social mobility restrictions and other non-pharmaceutical interventions must be applied carefully to avoid excess mortality beyond the threshold. In the absence of social distancing interventions, a typical epidemic will "overshoot" the herd immunity limit (e.g., Handel, Longini Jr, and Antia, 2007; Fung, Antia, and Handel, 2012) by up to 300%, due to ongoing infections (Figure 6). At the other extreme, a very strict "shelter in place" order would simply delay the onset of the epidemic; but if lifted (see Figures 6 and 7), the epidemic would again overshoot the herd immunity threshold. A modest level of social distancing, however — e.g., a 33% mobility reduction for the average US county — could lead to fatalities "only" at the level of herd immunity. Naturally, communities with higher population density or other risk factors (see Figure 5), would require more extreme measures to achieve the same.

Avoiding the level of mortality required for herd immunity will require long-lasting and effective non-pharmaceutical options, until a vaccine is available. The universal use of face masks has been suggested for reducing the transmission of SARS-CoV-2, with a recent meta-analysis (Chu et al., 2020a) suggesting that masks can suppress the rate of infection by a factor of 0.07–0.34 (95% CI), or equivalently $\Delta \ln(\text{transmission}) = -1.9 \pm 0.4$ (at 1σ). Using our model's dependence of the infection rate constant on mobility, this would correspond to an equivalent social mobility reduction of $\Delta\bar{\mathcal{M}}_{\rm mask} \simeq -24\% \pm 9\%$. Warmer, more humid weather has also considered a factor that could slow the epidemic (e.g., Wang et al., 2020a; Notari, 2020; Xu et

[2] See Supplementary Material for more detailed discussion of Error Diagnostics.

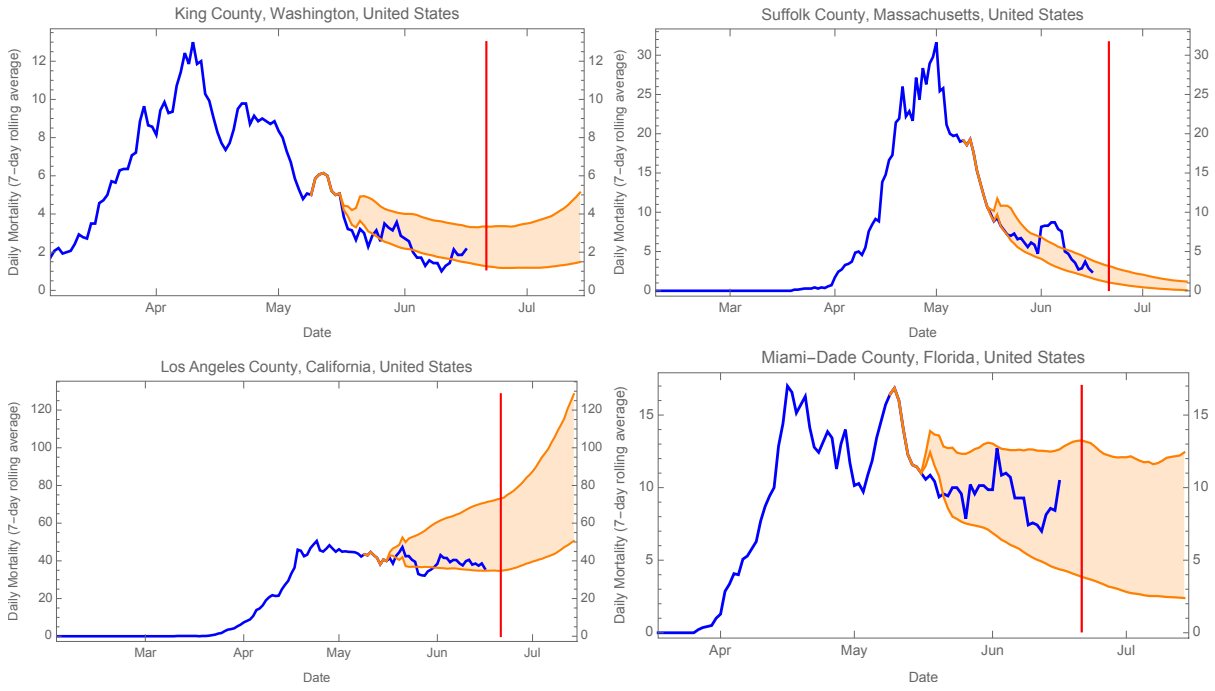


Figure 4: *Forecasts of COVID-19 mortality (orange) — based on the best-fit nonlinear model to data prior to May 16th, 2020 — versus actual reported mortality (blue) for 4 large US counties. The 68% confidence range (orange regions) were determined from 100 random 60-day long simulations (see Supplementary Methods). The vertical red lines indicate June 21st. Forecasts for most US counties can be found at our online dashboard: https://wolfr.am/COVID19Dash*

al., 2020a). Annual changes in specific humidity are $\Delta\bar{\mathcal{H}} \simeq 6\,\mathrm{g}/kg$ (Figure 10b in Supplementary Material), which can be translated in our model to an effective mobility decrease of $\Delta\bar{\mathcal{M}}_{\mathrm{summer}} \simeq -12\% \pm 5\%$. Combining these two effects could, in this simple analysis, yield a modestly effective defense for the summer months: $\Delta\bar{\mathcal{M}}_{\mathrm{mask+summer}} \simeq -37\% \pm 10\%$. Therefore, this could be a reasonable strategy for most communities to manage the COVID-19 epidemic at the aforementioned -33% level of mobility needed to arrive at herd immunity with the least excess death. More stringent measures would be required to keep mortality below that level. Of course, this general prescription would need to be fine-tuned for the specific conditions of each community.

Discussion and Conclusions

By simultaneously considering the time series of mortality incidence in every US county, and controlling for the time-varying effects of local social distancing interventions, we demonstrated for the first time a dependence of the epidemic growth of COVID-19 on population density, as well as other climate, demographic, and population factors. We further constructed a realistic, but simple, first-principles model of infection transmission that allowed us to extend our heuristic linear model of the dataset into a predictive nonlinear model, which provided a better fit to the data (with the same number of parameters), and which also accurately predicted late-time data after training on only an earlier portion of the data set. This suggests that the model is well-calibrated to predict future incidence of COVID-19, given realistic predictions/assumptions of future intervention and climate factors. We summarized some of these predictions in the final section of Results, notably that only a small fraction of US counties (with less than ten percent of the population) seem to have reached the level of herd immunity, and that relaxation of mobility restrictions without counter-measures (e.g., universal mask usage) will likely lead to increased daily mortality rates, beyond that seen in the Spring of 2020.

In any epidemiological model, the infection rate of a disease is assumed proportional to population density (Jong, Diekmann, and Heesterbeek, 1995), but, to our knowledge, its explicit effect in a real-world respiratory virus epidemic has not been demonstrated. The universal reach of the COVID-19 pandemic, and the diversity of communities affected have provided an opportunity to verify this dependence. Indeed, as we show here, it must be accounted for to see the effects of weaker drivers, such as weather and demographics. A recent study of COVID-19 in the United States, working with a similar dataset, saw no significant effect due to pop-

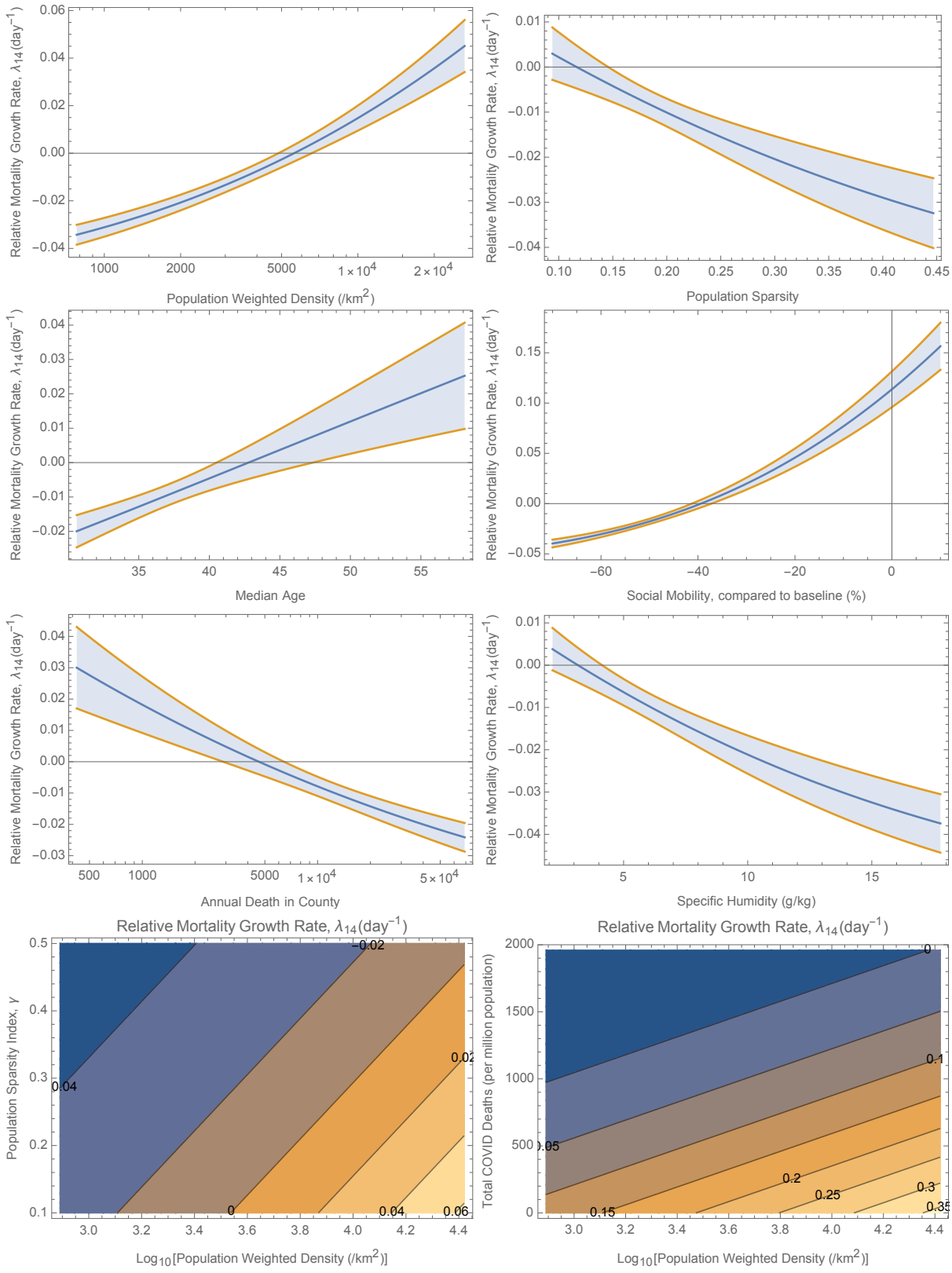


Figure 5: *Dependence and 68% confidence bands of the mortality growth rate — as specified by the nonlinear model (Eqn. 1) — on various parameters for an "average county." All parameters not being varied are fixed at their population-weighted mean values (as of 8th June, 2020): $\log_{10}$[PWD / km^{-2})] = 3.58, population sparsity = 0.188, COVID death fraction = 5.1×10^{-4} (510 deaths/million population), Median Age = 37.5 yr, log(Annual Death) = 4.04, social mobility $\bar{\mathcal{M}}$ = -44% , and specific humidity $\bar{\mathcal{H}}$=5.7 g/kg.*

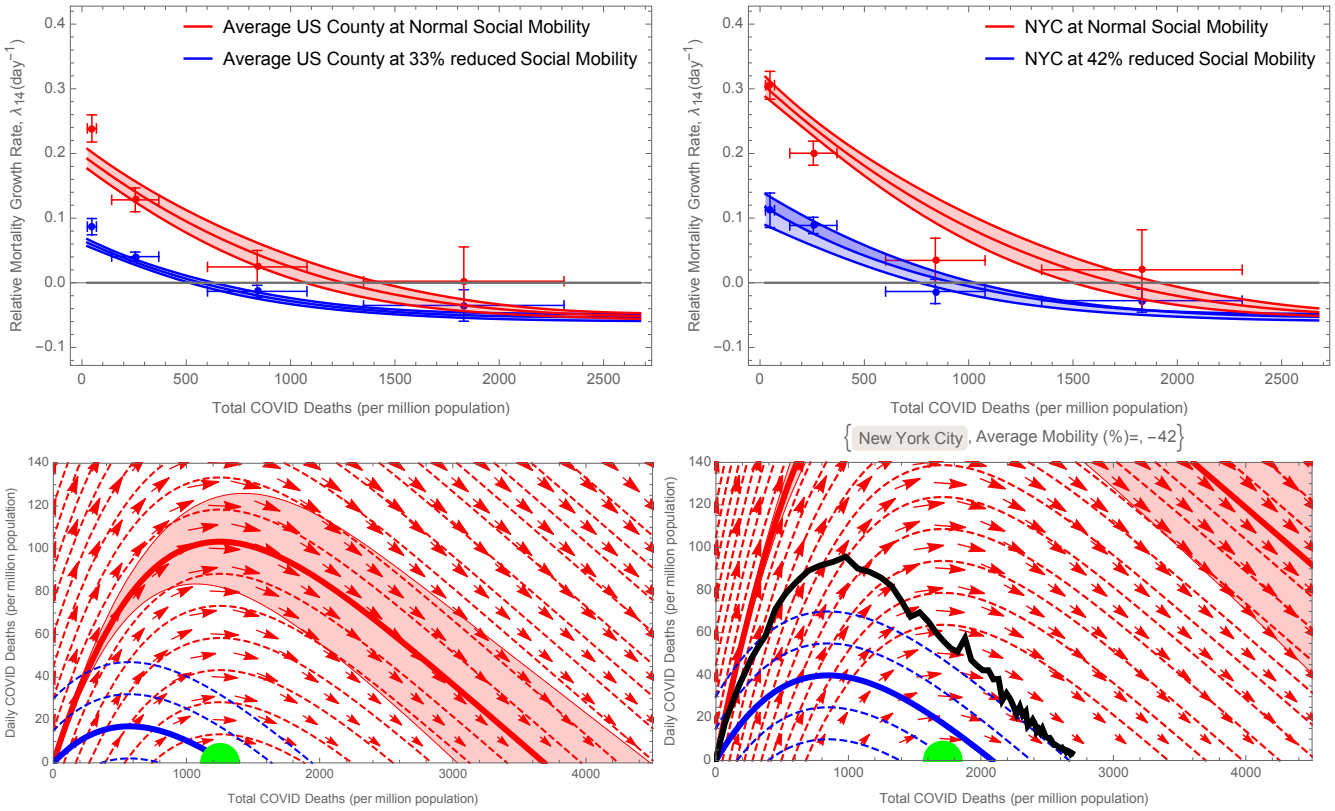


Figure 6: *Nonlinear model prediction of the exponential growth rate, λ_{14}, vs. cumulative COVID-19 mortality (top panels), assuming baseline social mobility, $\bar{\mathcal{M}} = 0$, in the "average US county" (see caption of Figure 5) on the left, and New York City, on the right. The curves show 68% predictions for the nonlinear model (Table 2), while the points with errorbars are linear fits to all the data within bins of death fraction. The threshold for "herd immunity" ($\lambda_{14} = 0$) is reached at a mortality of approximately 1300 (1700) per million for an average county (NYC), but this would be higher in counties with more unfavorable values of the drivers. The eventual mortality burden of the average county will be determined by its path through a "phase space" of Daily vs. Total Mortality (bottom panel). An epidemic without intervention (red curves, with the particular trajectory starting at zero death shown in bold) will pass the threshold for herd immunity (1300 deaths per million; note that at zero daily deaths this is a fixed point) and continue to three times that value due to ongoing infections. A modest 33% reduction in social mobility (blue curves), however, leads to mortality at "only" the herd immunity level (the green disk). The black curve on the bottom right panel shows the 7-day rolling average of reported mortality for NYC, which appears to have "overshot" the "herd immunity threshold".*

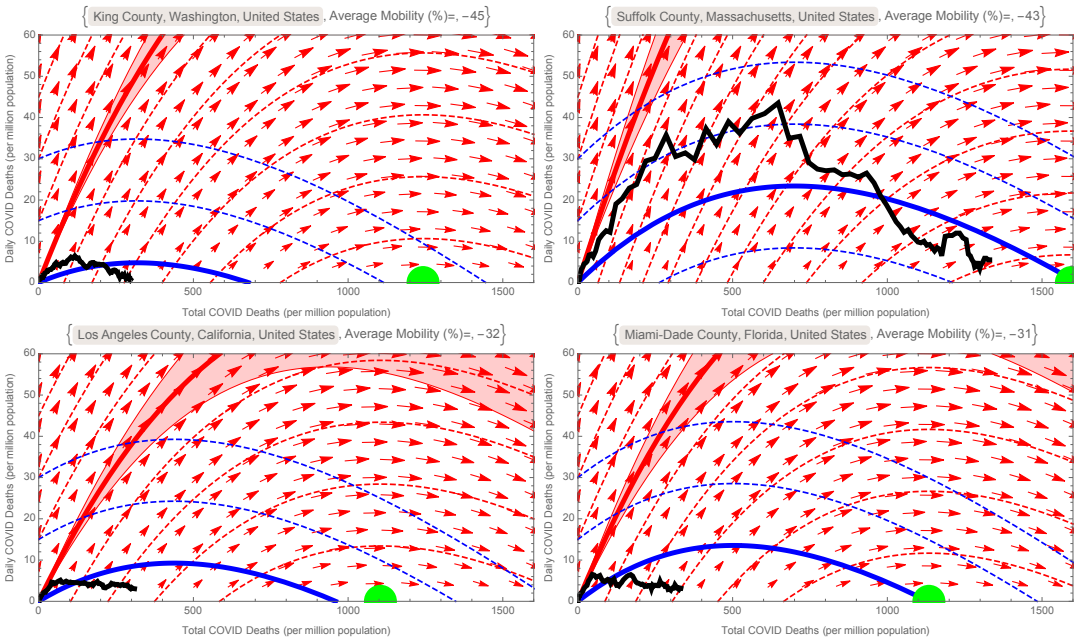


Figure 7: *Epidemic Phase Portraits for the same four counties as in Figure (4), similar to the Phase portrait in Figure (6). The blue curves are for the county's average Social Mobility during Feb. 15 through June 12, 2020, while red curves/arrows are at normal (pre-covid) social mobility. The thick black curve is the 7-day rolling average of the official reported mortality, while the green disk shows the threshold for "herd immunity".*

ulation density (Hamidi, Sabouri, and Ewing, 2020), but our analysis differs in a number of important ways. First, we have taken a dynamic approach, evaluating the time-dependence of the growth rate of mortality incidence, rather than a single static measure for each county, which allowed us to account for the changing effects of weather, mobility, and the density of susceptible individuals. Second, we have included an explicit and real-time measurement of social mobility, i.e., cell phone mobility data provided by Google (Fitzpatrick and Karen, 2020), allowing us to control for the dominant effect of intervention. Finally, and perhaps most importantly, we calculate for each county an estimate of the "lived" population density, called the population-weighted population density (PWD) (Craig, 1985), which is more meaningful than the standard population per political area. As with any population-scale measure, this serves as a proxy — here, for estimating the average rate of encounters between infectious and susceptible people — but we believe that PWD is a better proxy than standard population density, and it is becoming more prevalent, e.g., in census work (Dorling and Atkins, 1995; Wilson, 2012).

We also found a significant dependence of the mortality growth rate on specific humidity (although since temperature and humidity were highly correlated, a replacement with temperature was approximately equivalent), indicating that the disease spread more rapidly in drier (cooler) regions. There is a large body of research on the effects of temperature and humidity on the transmission of other respiratory viruses (Moriyama, Hugentobler, and Iwasaki, 2020; Kudo et al., 2019), specifically influenza (Barreca and Shimshack, 2012). Influenza was found to transmit more efficiently between guinea pigs in low relative-humidity and temperature conditions (Lowen et al., 2007), although re-analysis of this work pointed to absolute humidity (e.g., specific humidity) as the ultimate controller of transmission (Shaman and Kohn, 2009) . Although the mechanistic origin of humidity's role has not been completely clarified, theory and experiments have suggested a snowballing effect on small respiratory droplets that cause them to drop more quickly in high-humidity conditions (Tellier, 2009; Noti et al., 2013; Marr et al., 2019), along with a role for evaporation and the environmental stability of virus particles (Morawska, 2005; Marr et al., 2019). It has also been shown that the onset of the influenza season (Shaman et al., 2010; Shaman, Goldstein, and Lipsitch, 2011) — which generally occurs between late-Fall and early-Spring, but is usually quite sharply peaked for a given strain (H1N1, H3N2, or Influenza B) — and its mortality (Barreca and Shimshack, 2012) are linked to drops in absolute humidity. It is thought that humidity or temperature could be the annual periodic driver in the resonance effect causing these acute seasonal outbreaks of influenza (Dushoff et al., 2004; Tamerius et al., 2011), although other influences, such as school

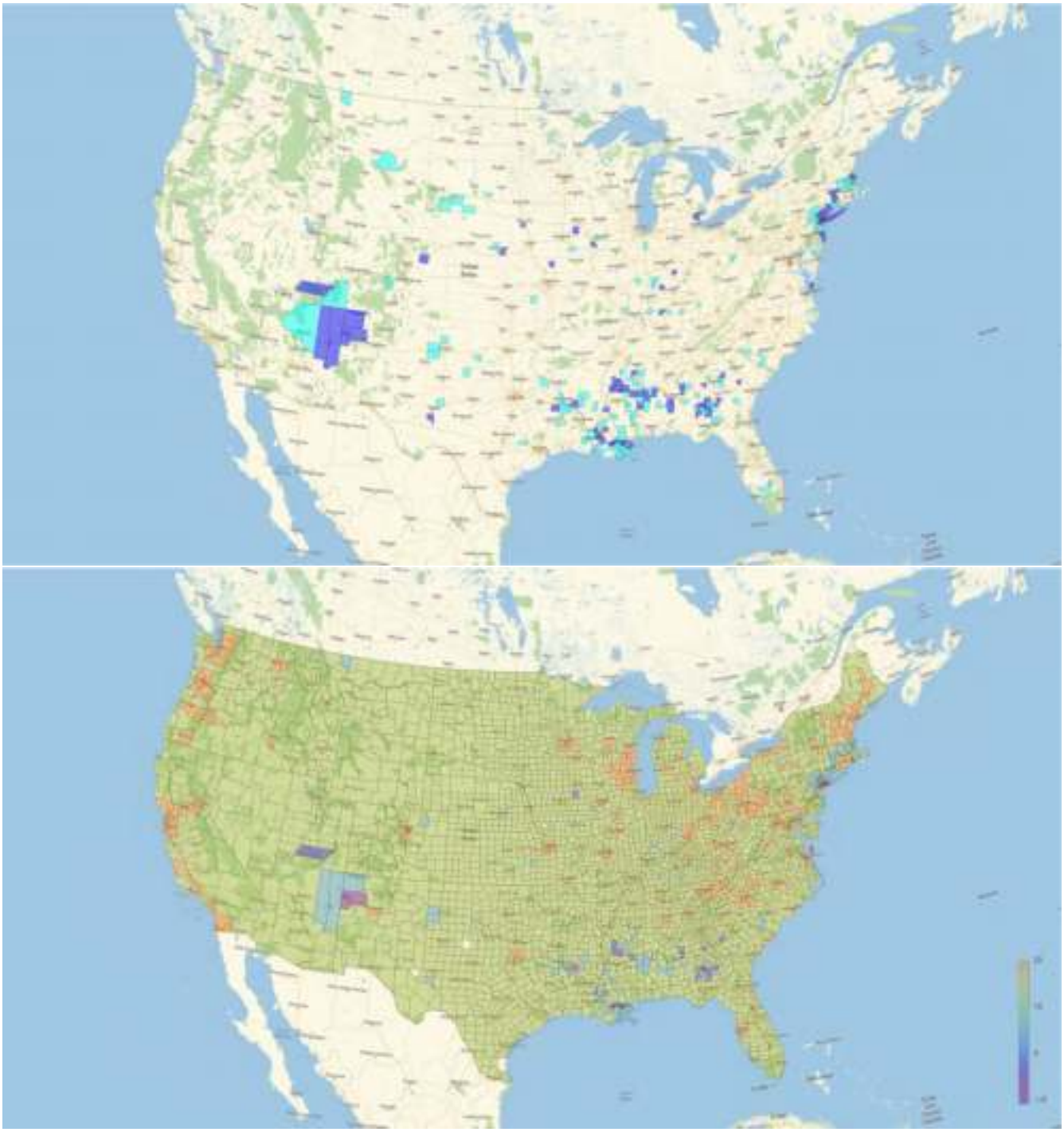


Figure 8: *Top: United States counties that have passed (blue), or are within (cyan), the threshold for "herd immunity" at the 1-σ level, as predicted by the nonlinear model. Bottom: Predicted confidence in the growth of COVID-19 outbreak (defined as predicted daily growth rate divided by its uncertainty), for all counties should they return today to their baseline (pre-COVID) social mobility. Counties that have approached the threshold of herd immunity have lower growth rates due to the depletion of susceptible individuals.*

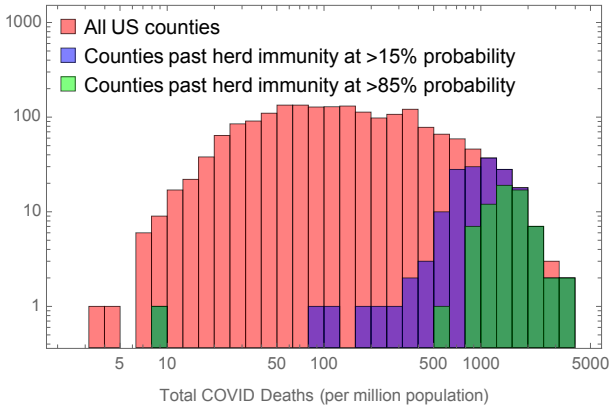


Figure 9: *Histogram of reported COVID-19 deaths per million for all US counties, showing the proportion that have passed "herd immunity" threshold, according to fit of the nonlinear model.*

openings/closings have also been implicated (Earn et al., 2012). While little is yet known about the transmission of SARS-CoV-2 specifically, other coronaviruses are known to be seasonal (Moriyama, Hugentobler, and Iwasaki, 2020; Neher et al., 2020), and there have been some preliminary reports of a dependence on weather factors (Xu et al., 2020b; Schell et al., 2020). We believe that our results represent the most definitive evidence yet for the role of weather, but emphasize that it is a weak, secondary driver, especially in the early stages of this pandemic where the susceptible fraction of the population remains large (Baker et al., 2020). Indeed, the current early-summer rebound of COVID-19 in the relatively dry and hot regions of the Southwest suggests that the disease spread will not soon be controlled by seasonality.

We developed a new model of infection in the framework of a renewal equation (see, e.g., Champredon, Dushoff, and Earn, 2018 and references therein), which we could formally solve for the exponential growth rate. The incubation period in the model was determined by a random walk through the stages of infection, yielding a non-exponential distribution of the generation interval, thus imposing more realistic delays to infectiousness than, e.g., the standard SEIR model. In this formulation, we did not make the standard compartmental model assumption that the infection of an individual induces an autonomous, sequential passage from exposure, to infectiousness, to recovery or death; indeed, the model does not explicitly account for recovered or dead individuals. This freedom allows for, e.g., a back passage from infectious to noninfectious (via the underlying random walk) and a variable rate of recovery or death. We assumed only that the exponential growth in mortality incidence matched (with delay) that of the infected incidence — the primary dynamical quantity in the renewal approach — and we let the cumulative dead count predict susceptible density — the second dynamical variable in the renewal approach — under the assumption that deaths arise from a distinct subset of the population, with lower mobility behavior than those that drive infection (see Supplementary Material). Therefore, we fitted the model to the (rolling two-week estimates of the) COVID-19 mortality incidence growth rate values, λ_{14}, for all counties and all times, and used the per capita mortality averaged over that period, f_D, to determine susceptible density. Regression to this nonlinear model was much improved over linear regression, and, once calibrated on an early portion of the county mortality incidence time series, the model accurately predicted the remaining incidence.

Because we accounted for the precise effects of social mobility in fitting our model to the actual epidemic growth and decline, we were then able to, on a county-by-county basis, "turn off" mobility restrictions and estimate the level of cumulative mortality at which SARS-CoV-2 would fail to spread even without social distancing measures, i.e., we estimated the threshold for "herd immunity." Meeting this threshold prior to the distribution of a vaccine should not be a goal of any community, because it implies substantial mortality, but the threshold is a useful benchmark to evaluate the potential for local outbreaks following the first wave of COVID-19 in Spring 2020. We found that a few counties in the United States have indeed reached herd immunity in this estimation — i.e., their predicted mortality growth rate, assuming baseline mobility, was negative — including counties in the immediate vicinity of New York City, Detroit, New Orleans, and Albany, Georgia. A number of other counties were found to be at or close to the threshold, including much of the greater New York City and Boston areas, and the Four Corners, Navajo Nation, region in the Southwest. All other regions were found to be far from the threshold for herd immunity, and therefore are susceptible to ongoing or restarted outbreaks. These determinations should be taken with caution, however. In this analysis, we estimated that the remaining fraction of susceptible individuals in the counties at or near the herd immunity threshold was in the range of 0.001% to 5% (see Supplementary Materials). This is in strong tension with initial seroprevalence studies (Rosenberg et al., 2020; Havers et al., 2020a) which placed the fraction of immune individuals in New York City at 7% in late March and 20% in late April, implying that perhaps 75% of that population remains susceptible today. We hypothesize that the pool of susceptible individuals driving the epidemic in our model is a subset of the total population — likely those with the highest mobility and geographic reach — while a different subset, with very low baseline mobility, contributes most of the mortality (see Supplementary Ma-

terial). Thus, the near total depletion of the susceptible pool we see associated with herd immunity corresponds to the highly-mobile subset, while the low-mobility subset could remain largely susceptible. One could explicitly consider such factors of population heterogeneity in a model — e.g., implementing a saturation of infectivity as a proxy for a clustering effect (Capasso and Serio, 1978; Mollison, 1985; De Boer, 2007; Farrell et al., 2019) — but we found (in results not shown) that the introduction of additional of parameters left portions of the model unidentifiable. Despite these cautions, it is interesting to note that the epidemic curves (mortality incidence over time) for those counties that we have predicted an approach to herd immunity are qualitatively different than those we have not. Specifically, the exponential rise in these counties is followed by a peak and a sharp decline — rather than the flattening seen in most regions — which is a typical feature of epidemic resolution by susceptible depletion.

At the time of this writing, in early Summer 2020, confirmed cases are again rising sharply in many locations across the United States — particularly in areas of the South and West that were spared significant mortality in the Spring wave. The horizon for an effective and fully-deployed vaccine still appears to be at least a year away. Initial studies of neutralizing antibodies in recovered COVID-19 patients, however, suggest a waning immune response after only 2–3 months, with 40% of those that were asymptomatic becoming seronegative in that time period (Long et al., 2020). Although the antiviral remdesivir (Beigel et al., 2020; Grein et al., 2020; Wang et al., 2020b) and the steroid Dexamethasone (Horby et al., 2020) have shown some promise in treating COVID-19 patients, the action of remdesivir is quite weak, and high-dose steroids can only be utilized for the most critical cases. Therefore, the management of this pandemic will likely require non-pharmaceutical intervention — including universal social distancing and mask-wearing, along with targeted closures of businesses and community gathering places — for years in the future. The analysis and prescriptive guidance we have presented here should help to target these approaches to local communities, based on their particular demographic, geographic, and climate characteristics, and can be facilitated through our online simulator dashboard. Finally, although we have focused our analysis on the United States, due to the convenience of a diverse and voluminous data set, the method and results should be applicable to any community worldwide, and we intend to extend our analysis in forthcoming work.

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Supplementary Material

Data & Methods

Datasets, Resources, Definitions

All data for cases and mortality, demographics, mobility, and weather were incorporated into the publicly-available Wolfram COVID-19 Dataset and the Wolfram|Alpha Knowledgebase (*COVID-19 Data & Resources* 2020). COVID-19 confirmed case and mortality data were obtained from both the NYTimes and Johns Hopkins University Github repositories (Johns Hopkins University, CSSE, 2020; The New York Times, 2020); the former was used for the analysis initial case data in metropolitan regions, while the average of the two data sets was used for all other analyses. In each case, daily confirmed counts were utilized. Demographic data by county, including people per household, estimated 2019 population, annual births, and annual deaths were obtained from the US Census 2019 *County Population Estimates* data set (United States Census, 2019a). Median ages were determined from the US Census 2018 *County Characteristics Resident Population Estimates* data set (United States Census, 2018). For the Median Age, Wolfram|Alpha has curated the raw data from *United States Census Bureau, American Community Survey 5-Year Estimates: B01002, the Median Age By Sex, American FactFinder*; for the People per Household and Annual Death, the source of curated data is *United States Census Bureau, State & County QuickFacts*. County outline polygons were obtained from the US Census 2019 *TIGER/Line shapefiles* database (United States Census, 2019c). Local weather data (Figure 10 was obtained from the NOAO *Global Surface Summary of the Day* (GSOD) database (National Oceanic and Atmospheric Observatory, 2020). The nearest WBAN station with daily dew point and pressure values (for calculation of specific humidity), and daily average temperature was chosen for each county or metropolitan region. Weather data was averaged over a two-week period for λ_{14}, and over a window equal to the growth period for metropolitan regions. Google's *COVID-19 Community Mobility Reports* dataset (Fitzpatrick and Karen, 2020), specifically "Workplace mobility," was used to estimate the human social mobility in each county (Figure 10).

Population-weighted population density (or, population weighted density, PWD) (Craig, 1985; Wilson, 2012; Dorling and Atkins, 1995), was calculated using the Global Human Settlement Population raster dataset (European Commission Joint Research Centre, 2019), which contains $250\,\mathrm{m}$-resolution population values worldwide, taken from census data. The value of PWD for a county — or for a set of counties, in the metropolitan region analysis — was calculated as the population-weighted average

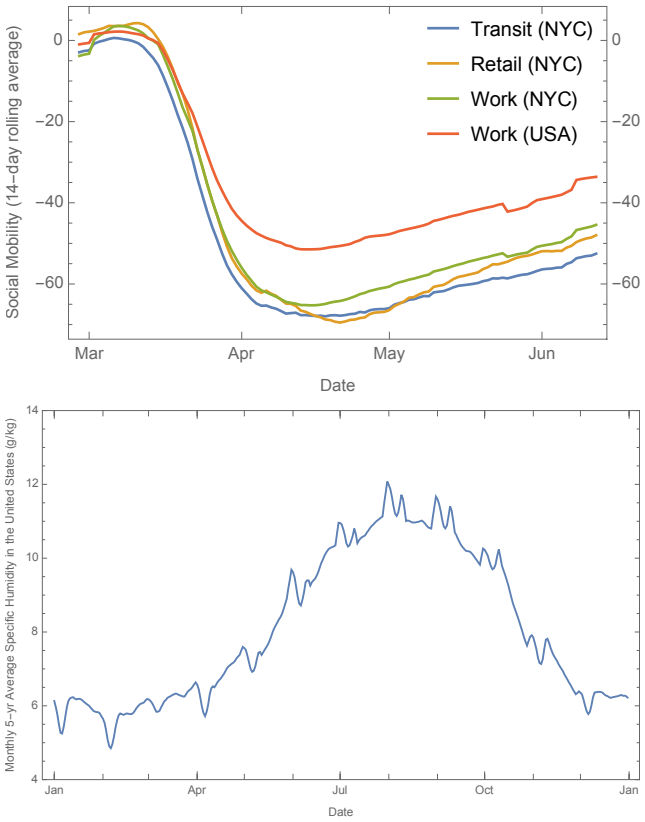

Figure 10: *(Top)(a)The 14-day rolling average of (population-weighted) social mobility (Fitzpatrick and Karen, 2020) for NYC, as well as all US counties considered here. For our analysis, we only use "work places" as an indicator, as others do not appear to show any independent correlation with $\lambda_{14}(t)$. (Bottom)(b) 28-day moving average of historical annual specific humidity in the United States (weighted-averaged by population).*

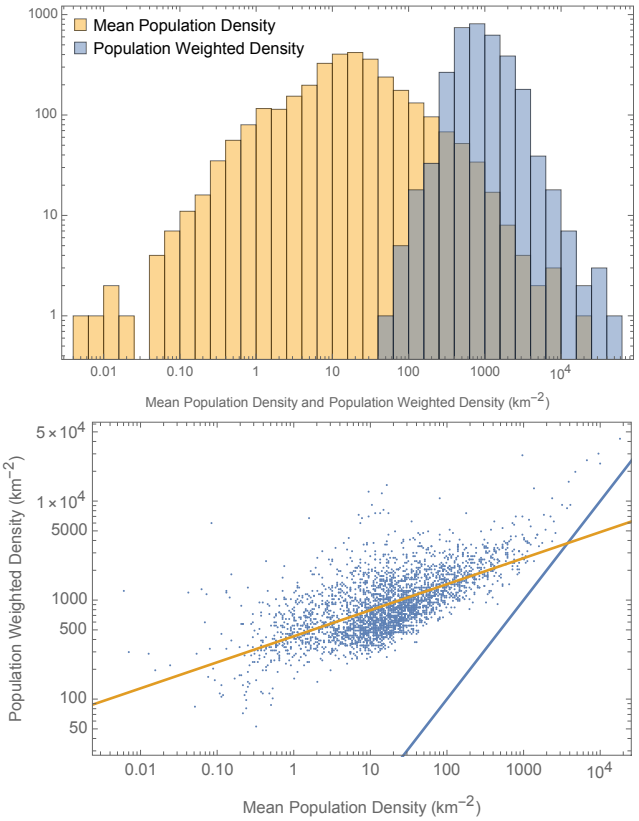

Figure 11: *Comparison of the distribution of Population Weighted Density with the Crude population density of US counties: (a)(Top): Histograms, (b)(Bottom): Relative distributions: The blue line shows the one-to-one correspondence, while the orange line is the best-fit power-law* $\mathrm{PWD}_{250}(\mathrm{km}^{-2}) \simeq 430 \times \left[D(\mathrm{km}^{-2})\right]^{1/4}$.

of density over all $(250\,\mathrm{m})^2$-area pixels contained within the region, i.e.,

$$\mathrm{PWD} = \sum_j \frac{(p_j/a_j)\,p_j}{\sum_i p_i}\,, \tag{4}$$

where p_j is the value (i.e., the population) of the jth pixel, $a_j = 0.0625\ \mathrm{km}^2$ is the area of each pixel (the GHS-POP image uses the equal-area Molleweide projection), and $\sum_i p_i$ is the total population of the region. This measure has also been called the *lived population density* because it is the population density experienced by the average person.

In high density counties, the population weighted density PWD is close to the mean density of the county $D = \mathrm{Pop}/\mathrm{Area}$, suggesting a uniform distribution of population (see Figure 11). However, in lower density counties, the mean density is much lower than the population weighted density, due to heterogeneous dense pockets of population amidst vast empty spaces outlined

by political boundaries. To represent the degree to which the population density changes across the region (county or metropolitan region) we define the *population sparsity index*, γ. Assuming that the population-weighted population density declines approximately as a power law with "pixel" area, $\mathrm{PWD}_{\sqrt{\mathrm{Area}}} \sim \mathrm{Area}^{-\gamma}$, we define:

$$\gamma = \frac{\log\left(\mathrm{PWD}_{250\,\mathrm{m}}\right) - \log(D)}{\log\left[\mathrm{Area}\right] - \log\left[(250\,\mathrm{m})^2\right]}\,. \tag{5}$$

In other words we estimate the assumed power-law decline using two data points. The distribution of γ and its correlation with county population and population density are shown in Figure (12). We can see that γ ranges from 0.09 (i.e., very uniform) for the most populous/dense counties to 0.88 (i.e. very sparse) for least populated/dense counties. For reference, the value of γ for New York City is 0.14.

Initial growth of confirmed cases for metropolitan regions

For each of the top 100 metropolitan regions (United States Census, 2019b), a logarithmic-scale population heat map, windowed from the full GHS-POP raster image, was used to select a minimal connected set of US counties enclosing the region of population enhancement. In this process, overlap and merger reduced the total number of metropolitan regions under consideration to 89.

As is discussed in the main text, nearly every metropolitan region saw, in mid-March 2020, an exponential increase of daily confirmed cases, followed by a flat/plateau period of nearly constant daily confirmed cases. In a few cases, the second phase — primarily caused by the country-wide lockdown — lasted only days or weeks (possibly signaling a depletion of the susceptible population, see discussion in main text), but for most metropolitan regions the plateau persisted for months (indeed, persists or is again increasing at the time of this writing). Thus, the initial value of the exponential growth rate, λ, of daily confirmed cases could be reliably and automatically estimated by fitting the case numbers to a logistic function

$$f_{\mathrm{logistic}}(t) = \frac{f_{\max}}{1 + \exp\left[-\lambda\,(t - t_0)\right]} \tag{6}$$

where t_0 represents the transition time from exponential growth to a constant, $f_{\max}$ is the plateau value in case numbers, and $f_{\mathrm{logistic}}(t) \propto \exp[\lambda t]$ for $t \ll t_0$. Fits were performed on the logarithm of the case numbers, yielding the maximum likelihood estimation of parameters under the assumption lognormally-distributed errors (an analysis of the fit residuals, not shown, confirmed this assumption: case number fluctuations exhibit a variance

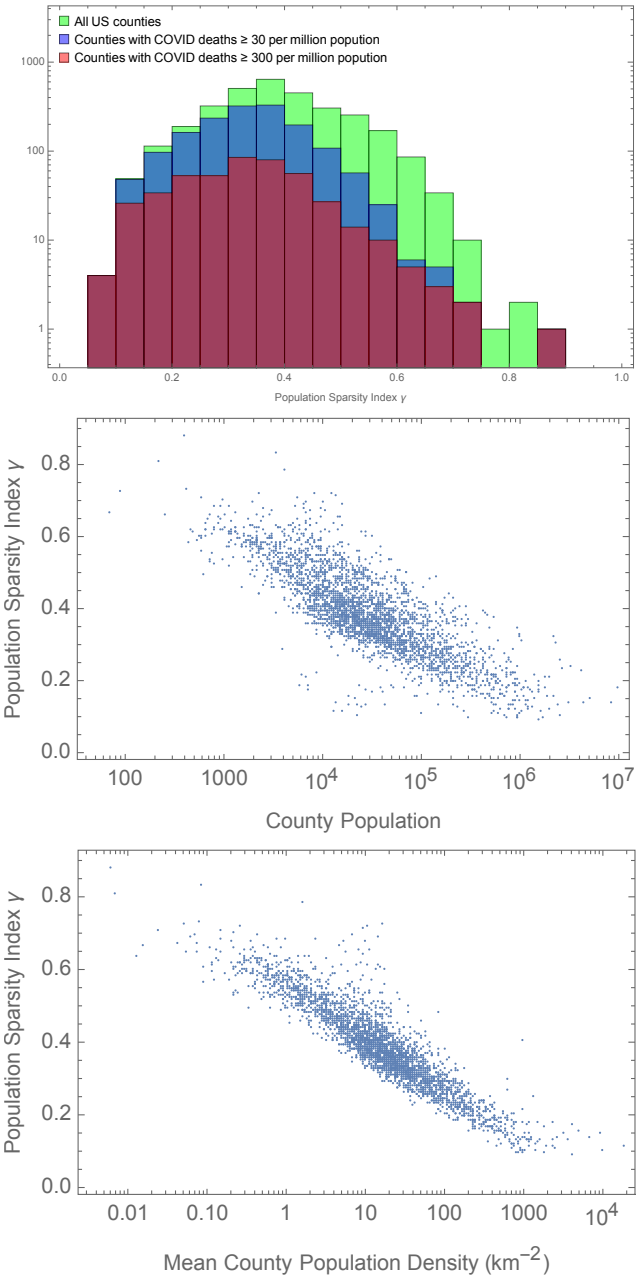

Figure 12: *(a)(Top)Distribution of Population Sparsity Index γ (b)(Middle) its correlation with total population of the county (c)(Bottom) and its average population density*

far in excess of Poisson noise, but are well modeled by a log-normal probability density function with constant width), and associated estimates of the variance in each parameter. To avoid polluting the exponential growth phase with singular early cases, a "detection limit" of 3 was imposed, and all daily case values less than or equal to that limit were ignored in fitting. The only manual intervention required for this fit was the specification of the upper limit of its range, i.e., the *end* of the plateau region, for each data set.

To analyze the effect of demographic, population, mobility, and weather variables on this initial growth rate, we perform a weighted linear regression to the lambda values (and their standard errors) of the 89 metropolitan regions.

To choose representative cities for the visual examples in Figures 1A and 1C, we performed an additional logistic fit to the mortality incidence data of each region and retained for Figure 1C only those that had (1) less than 15% error in both growth rates, and (2) $|\lambda_{\rm case} - \lambda_{\rm death}| < 0.15 d^{-1}$. This was done in an effort to specifically comment on or highlight only those cities for which the growth rate was accurately determined, and was well correlated with the more reliable measure, mortality growth, that we used for the remainder of the analysis.

Linear Dynamical Model of Mortality Data

A standard weighted least squares analysis was performed on the measured exponential growth rate, λ_{14}, as a function of demographic, mobility, population and weather variables, with weights equal to inverse root of the estimated variance.

Nonlinear Model

We construct a model where, in the standard analogy to chemical reaction kinetics, the incidence of infections per unit area at time, $i(t)$, is proportional to the product of the density of susceptible individuals, $S(t)$, and the density of infected individuals, $I(t)$. But, we allow for the rate constant for infection[3] in the encounter, β, to depend on the infected individual's "stage" of infection, C, with $C = 0$ immediately following infection. The incidence then has the form:

$$i(t) = -\dot{S}(t) = S(t) \int_0^\infty \beta(C)\, \mathcal{I}(C,t)\, \mathrm{d}C\,, \qquad (7)$$

where $\mathcal{I}(C,t)$ is the density of infected per stage at time t, and the first equality expresses that we neglect changes to the susceptible population by all means other than infection. The density of infected individuals is found by integration over the stages of infection,

$$I(t) = \int_0^\infty \mathcal{I}(C,t)\, \mathrm{d}C\,. \qquad (8)$$

If the rate constant were taken to be independent of stage, i.e., $\beta(C) = \bar{\beta}$, we would obtain the familiar expression $\dot{S}(t) = -\bar{\beta} S(t) I(t)$. We will assume spatial homogeneity and that the total density of individuals is constant and equal to $S(0)$ for a particular region, but, that the density could vary when comparing different regions.

We assume that an infected individual's evolution through the stages of infection, C, follows a Gaussian random walk in time, but modulated by an exponential rate, d, of death or recovery. Therefore we have

$$\mathcal{I}(C,t) = \int_0^\infty i(t-a)\, f_{\rm rw}\,(C;a)\, \mathrm{e}^{-d\,a}\, \mathrm{d}a \qquad (9)$$

where a is the "age" of an infection (time since infection), and the probability density function for the stage at a given age is given by

$$f_{\rm rw}\,(C;a) = \sqrt{\frac{2\tau}{\pi a}}\, \exp\left[-\frac{\tau C^2}{2a}\right]\,, \qquad (10)$$

where τ is the characteristic time scale of the random walk[4]. Integrating the expression for $\mathcal{I}(C,t)$ over all stages and taking the derivative with respect to time yields the familiar expression $\dot{I}(t) = i(t) - dI(t)$, showing that the model reduces to the SIR model if a stage-independent rate constant, $\bar{\beta}$, is assumed.

As we show here, using the random walk to specify the dependence of infection stage on time allows for both a non-exponential distribution of delays to infectiousness (which is more realistic than that of the simplest model with incubation, the SEIR model) and a formal solution for the exponential growth rate. Inserting the expression for $\mathcal{I}(t,C)$ into the incidence equation yields

$$i(t) = S(t) \int_0^\infty i(t-a) \left[\mathrm{e}^{-d\,a} \int_0^\infty \beta(C)\, f_{\rm rw}\,(C;a)\, \mathrm{d}C\right] \mathrm{d}a \qquad (11)$$

which is in the form of a *renewal equation* (Heesterbeek and Dietz, 1996; Champredon and Dushoff, 2015; Champredon, Dushoff, and Earn, 2018), with the bracketed expression being the expected infectivity of an individual with infection age a. To obtain the simplest nontrivial incubation period, we assume that $\beta(C) = \bar{\beta}\,\Theta(C-1)$ — where $\Theta(x)$ is the Heaviside step function — meaning

[3] In a physical picture of collisions, the rate constant of infection is $\beta(C) = \langle \sigma v \rangle_{\rm eff}(C)$, i.e., the scattering cross section of an encounter between a susceptible individual and an infectious individual in stage C, σ, multiplied by their relative velocity, v.

[4] More precisely: C is the absolute value of the position of a 1D random walker, taking one step every Δt, with step size drawn from a normal distribution with mean zero and variance $\Delta t/\tau$. The variance of the walker position at time t is then t/τ

that an infected individual is only infectious once they reach stage $C = 1$, and the infection rate constant is otherwise unchanging. This implies that the incidence is

$$i(t) = S(t) \int_0^\infty i(t-a)\, \bar{\beta}\, \mathcal{F}(a)\, \mathrm{d}a\,. \tag{12}$$

where

$$\begin{aligned} \mathcal{F}(a) &= \mathrm{e}^{-d\,a} \int_1^\infty f_{\mathrm{rw}}\,(C;a)\,\mathrm{d}C \\ &= \mathrm{e}^{-d\,a} \left[1 - \mathrm{erf}\left(\sqrt{\frac{\tau}{2a}}\right)\right] \end{aligned} \tag{13}$$

is the probability that an individual infected a time units ago is infectious.

If we now assume that the density of susceptibles is constant $S(t) = \bar{S}$ over some interval of time, and that the incidence grows (or decays) exponentially in that interval, $i(t) = A\mathrm{e}^{\lambda t}$, we find

$$1 = \bar{\beta}\bar{S} \int_0^\infty \exp[-a\lambda]\, \mathcal{F}(a)\, \mathrm{d}a \tag{14}$$

which, assuming $\lambda + d > 0$ (i.e., the exponential growth rate cannot go below $-d$), can be integrated to obtain

$$(\lambda + d)\, \exp\left[\sqrt{2\,(\lambda+d)\,\tau}\right] = \bar{\beta}\bar{S}\,. \tag{15}$$

This expression for $(\lambda + d)$ has a formal solution in terms of the *Lambert W-function*, with simple asymptotic forms:

$$\begin{aligned} \lambda + d &= \frac{2}{\tau}\left[\mathrm{W}\left(\sqrt{\frac{\bar{\beta}\bar{S}\tau}{2}}\right)\right]^2 \\ &\approx \begin{cases} \frac{1}{2\tau}\left\{\ln\left[\frac{2\bar{\beta}\bar{S}\tau}{\ln^2\left(\bar{\beta}\bar{S}\tau/2\right)}\right]\right\}^2 & \left(\bar{S}\bar{\beta}\tau \gg 1\right) \\ \bar{\beta}\bar{S} & \left(\bar{S}\bar{\beta}\tau \ll 1\right) \end{cases} \end{aligned} \tag{16}$$

For the early stages of the epidemic, when we can assume that the population of susceptibles is approximately constant and large, we see that the growth rate depends approximately linearly on the square of the logarithm of the density. In later stages, when either the base contact rate declines due to social distancing interventions, or the population of susceptibles decreases, we see that the exponential rate takes the value $\lambda \approx -d$.

In practice, we utilize the exact Lambert W-function expression as our "nonlinear model" for fitting λ_{14}, where we parameterize β and τ by the demographic, population, and weather variables (see main text). To estimate the susceptible density, $\bar{S}$, in this procedure we must use the reported mortality statistics. Thus far we have not specified the dynamics of death. We now make the assumption that the probability of death increases proportionally to the number of exposures an individual experiences. As we prove in a separate section, below, this implies that the susceptible density is related to the fraction of dead in the community, $f_D = D_{\mathrm{tot}}/N$ (where D_{tot} is the cumulative mortality and N is the total population), by $S(t) = S(0)\exp\left[-C_D\, f_D\right]$.

The *basic reproduction number*, R_0, and the distribution of *generation intervals*, $g(t_g)$, are defined (Champredon and Dushoff, 2015; Nishiura, 2010) through the function $\mathcal{F}(a)$:

$$g(t_g) = \frac{\bar{\beta}S(0)\,\mathcal{F}(t_g)}{R_0} \quad \text{with} \quad R_0 \stackrel{\mathrm{def}}{=} \int_0^\infty \bar{\beta}S(0)\,\mathcal{F}(t_g)\,\mathrm{d}t_g\,. \tag{17}$$

The generation interval (or, generation time), t_g, is the time between infections of an infector-infectee pair, and is often estimated from clinical data by the *serial interval*, which is the time between the start of symptoms (Britton and Scalia Tomba, 2019), and the basic reproduction number is the average number of infectees produced by a single infected individual, assuming a completely susceptible population. These quantities can be calculated exactly for our model, as

$$R_0 = \frac{\bar{\beta}S(0)}{d}\,\mathrm{e}^{-\sqrt{2d\tau}} \tag{18}$$

and

$$g(t_g) = d\,\mathrm{e}^{\sqrt{2d\tau}-dt_g} \int_1^\infty \sqrt{\frac{2\tau}{\pi t_g}}\,\exp\left[-\frac{\tau C^2}{2t_g}\right]\mathrm{d}C\,, \tag{19}$$

where the expected value and variance of the generation interval are then:

$$E\left[t_g\right] = \frac{1}{d} + \sqrt{\frac{\tau}{2d}} \quad \text{and} \quad \mathrm{Var}\left[t_g\right] = \frac{1}{d^2} + \sqrt{\frac{\tau}{8d^3}}\,. \tag{20}$$

Extended Results and Analysis

Relation between the remaining susceptible density, $S(t)$ and the death fraction, $f_D(t)$

In epidemic models the infection of susceptible individuals is typically determined by

$$\dot{S} = -\beta\, S\, I_* \tag{21}$$

where I_* is the density of infectious (contagious) individuals, and for our model, $\beta S I_*$ is the right-hand side of Eqn. 7. This can be solved, formally, as:

$$S(t) = S(0)\exp\left[-\beta \int^t I_*(s)\,\mathrm{d}s\right] \tag{22}$$

Alternatively, the susceptible density can be expressed in terms of the cumulative number of infected individuals, I_{tot}, i.e.,

$$S(t) = S(0)\left[1 - f_I(t)\right] \tag{23}$$

where $f_I(t) = I_{\rm tot}/N$, with N the total population. When fitting the exponential growth rate of mortality, $\lambda_{14}(t)$ to our nonlinear model, Eqn. (16) (see main text), we must estimate the value of the susceptible density driving growth at that time. Without any reliable information about the true infected or infectious populations, we must do so using the mortality statistics. We show here how the previous two equations can be used, along with reasonable assumptions about distinct sub-populations driving infection and death, to determine a relationship between the reported cumulative mortality (per capita) and the remaining susceptible density.

Our basic assumption is that there are two different categories of susceptible individuals underlying the dynamics of the epidemic: (A) highly mobile individuals with a large geographic reach that frequently interact with other individuals (in particular, infectious individuals) and thus drive the dynamics of infection (these could be termed "super-spreaders" (Liu, Eggo, and Kucharski, 2020)); and (B) essentially non-mobile individuals that have quite rare contacts with infectious individuals, but have a much higher probability of death once infected, and therefore make up the majority of the mortality burden. The dynamics of each susceptible population is governed by an equation of the form in Eqn. (21), with a common density of infectious individuals, I_*, but with different rate constants, $\beta_A \gg \beta_B$. From Eqn. (22), we see that the susceptible densities of the two populations are then related, at any time, by:

$$\frac{S_A(t)}{S_A(0)} = \left[\frac{S_B(t)}{S_B(0)}\right]^{\beta_A/\beta_B} . \tag{24}$$

Expressing the non-mobile population in terms of the cumulative fraction infected, we have

$$\frac{S_A(t)}{S_A(0)} = \left[1 - f_I^{(B)}(t)\right]^{\beta_A/\beta_B} , \tag{25}$$

and, assuming that the infection fatality rate (IFR) is a constant factor, $f_D(t) = \mathrm{IFR} \times f_I(t - \Delta t)$, where Δt is the delay from infection to death, we can write:

$$\frac{S_A(t)}{S_A(0)} = \left[1 - \frac{f_D^{(B)}(t + \Delta t)}{\mathrm{IFR}}\right]^{\beta_A/\beta_B} . \tag{26}$$

Finally, having assumed that the ratio of infection rates is large, we can approximate this as:

$$\frac{S_A(t - \Delta t)}{S_A(0)} \approx \exp\left[-\frac{\beta_A}{\beta_B\,\mathrm{IFR}}\, f_D^{(B)}(t)\right] \tag{27}$$

The "A" category of individuals, as defined above, are exactly those individuals driving the infection in our model (and, presumably, in the real world), and, therefore, the susceptible density S_A is exactly that which must be estimated for Eqn. (16). On the other side, with people aged 65 and over accounting for ∼80% of COVID-19 deaths, and with approximately ∼45% of deaths linked to nursing homes, the mortality statistics are clearly tracing individuals similar to category "B." Therefore, we use this relationship,

$$S(t - \Delta t) = S(0)\, \exp\left[-C_D\, f_D(t)\right] ,$$

to estimate the susceptible density in terms of the reported per capita mortality, where we assume $S(0)$ is proportional to the population weighted density (PWD).

We also considered the standard approach, in which the population is a single homogeneous group. In that case, the susceptible density could be estimated as

$$S(t) = S(0)\,[1 - f_I(t)] = S(0)\left[1 - \frac{f_D(t + \Delta t)}{\mathrm{IFR}}\right] . \tag{28}$$

In testing both models, we found that the two-component population scenario was preferred by the data at the $\sim 10\sigma$ confidence level, with the homogeneous population model failing to capture the observed dependence of the growth rate on the per capita mortality (Figure 13).

The broader implications of our assumption of two populations is that the required proportion of individuals with immunity for "herd immunity" to take effect, is lower than population with homogeneous mobility characteristics, i.e., the epidemic will slow as a significant proportion of the "super-spreader" category have been infected (category A, above), regardless of the level of infection and immunity in the rest of the population. Indeed, the effect of population heterogeneity on lowering the "herd immunity" threshold for COVID-19 was recently noted (Britton, Ball, and Trapman, 2020), and will be important in interpreting the results of randomized serology tests across the entire population (Havers et al., 2020b).

Incubation Time

The nonlinear epidemic model described above posits that the incubation of SARS-COV2 virus within an infected individual can be modelled by a stochastic random walk starting at zero, with excursions beyond ± 1 corresponding to episode(s) of infectiousness. This makes our model distinct from the standard SE^{m}I^{n}R compartmental models (see, e.g., (Champredon, Dushoff, and Earn, 2018)), where the progress of the disease is only in one direction — $E^1 \to E^2 \to \ldots \to I^1 \to I^2 \to \ldots$ — while in our model (Figure 14), the individual can jump back and forth between different stages (with the obvious exception of Death), with a constant exit rate of d for quarantine, recovery, or death. This can be described

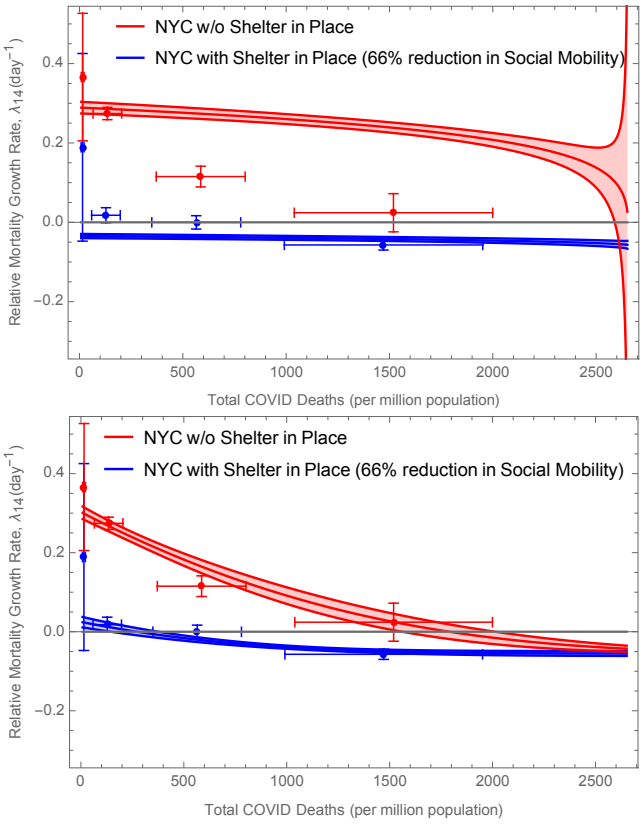

Figure 13: *Comparison of hypotheses regarding the relationship between the susceptible fraction, $S(t)/S(0)$, and the dead fraction, $f_D(t)$. A model in which deaths are suffered by a largely immobile population, while the infection is driven by a mobile category of individual (bottom) was preferred to one with a single homogenous population (top) at the 9σ confidence level. Similar to Figure 6, the points show the best-fit linear model prediction for NYC, fitted independently in different bins of mortality to population ration, while the lines show best-fit $\pm$ 1σ nonlinear models. Note that while we show the nonlinear model predictions for a county similar to NYC, we use all US data to find the best fits.*

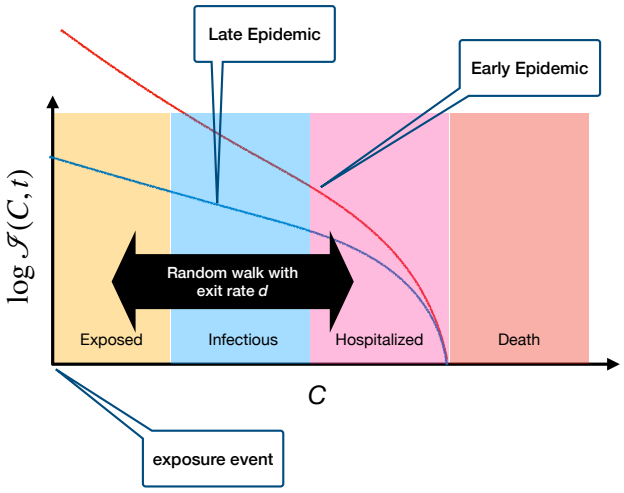

Figure 14: *The stages of COVID-19 infection, as a continuous variable C. We model the disease as a random walk, starting at $C = 0$, and a uniform exit rate (due to either quarantine or recovery). The curves show the resulting distribution in C, during the growing (early) and decaying (late) epidemic. Note that the Hospitalization and Death are not directly modelled in the Nonlinear model, as they should have a small effect on the spread of the epidemic.*

using a (leaky) diffusion equation:

$$\frac{\partial \mathcal{I}}{\partial t} = \frac{1}{2\tau}\frac{\partial^2 \mathcal{I}}{\partial C^2} - d\mathcal{I}. \tag{29}$$

Based on this picture, and the best-fit parameters to the US county mortality data (Table 2), we can infer the probabilities associated with the different stages of the disease. For example, by looking at the steady-state solutions of Equation (29), we can compute the probability that an exposed individual (who starts at $C = 0$) will ever become infectious (i.e., make it beyond $C = C_{\rm inf} = 1$):

$$P_{\rm inf} = \exp[-\sqrt{2d\tau}C_{\rm inf}], \quad \text{where} \quad C_{\rm inf} = 1, \tag{30}$$

This is plotted as a function of the median age of the community in Figure (15a). For example, for the median age of all US counties, $A = 37.4$-yr, we get:

$$P_{\rm inf}(37.4 \text{ years}) = 0.08^{+0.04}_{-0.03}\ (68\%\ \text{C.L.}), \tag{31}$$

i.e., less than 12% of exposed individuals will ever be able to infect others, although this fraction increases in older communities.

Next, we can compute the distribution of times for the onset of infectiousness, i.e., the incubation period. This can be done by using a first crossing probability of a random walk, which we did by solving Equation

(29) using a discrete Fourier series in the $(0, +1)$ interval. The resulting probability density is shown in Figure (15b), again showing a shorter incubation period in older communities.

Finally, we can compute the probability density function for the generation interval, $g(t_g)$, defined in Equation (19) (Figure 15c). This shows a similar qualitative dependence on age as the incubation period, but the median incubation period is, as expected, shorter than the generation interval for each age group. Using Eqn. (20) and our parameterization of τ, we find a mean generation interval of

$$E[t_g](37.4 \text{ years}) = 43 \pm 23 \text{ d}\,. \tag{32}$$

This estimate is much longer than those found by tracking the serial interval (time from between the start of symptoms for an infector-infectee pair) in COVID-19 patients (Ganyani et al., 2020; Nishiura, Linton, and Akhmetzhanov, 2020), which are on the order of 5–10 d. It is possible that the long tail of these distributions, generated by the slow asymptotic exponential decay at rate $d \approx 0.06 d^{-1}$, raises the mean generation interval, while a clinical study, is necessarily biased toward shorter serial intervals.

Error Diagnostics and Forecasting COVID-19 Mortality

One of the most pressing questions in any exercise in physical modelling is whether we have a good understanding of the uncertainty in the predictions of the model. While we have an estimate of the measurement uncertainties for the mortality growth rates, λ_{14}, which we discussed in the main text, we also should characterize whether the deviation of the best-fit model from the measurements are consistent with statistical errors. To evaluate this, we can look at the average of the ratio of the variance of the model residuals to that of the measurement errors, otherwise known as reduced χ^2, or χ^2_{red}. This is shown in Figure (16), demonstrating that we see no systematic error in model that is significantly bigger than statistical errors, across counties with different populations.

As another consistency check, Table (3) examines whether the parameters of the model change significantly from urban counties with large, uniform populations, to rural counties with a small and more sparse population (Figures 11-12). From counties with enough COVID mortality data, roughly those with population $\gtrsim 10^6$ inhabit half of the total population, which we chose as our threshold, separating large from small counties. We notice no statistically significant difference, and Table (3) even suggests that Fisher errors quoted here might be overestimating the true errors. This comparison brings

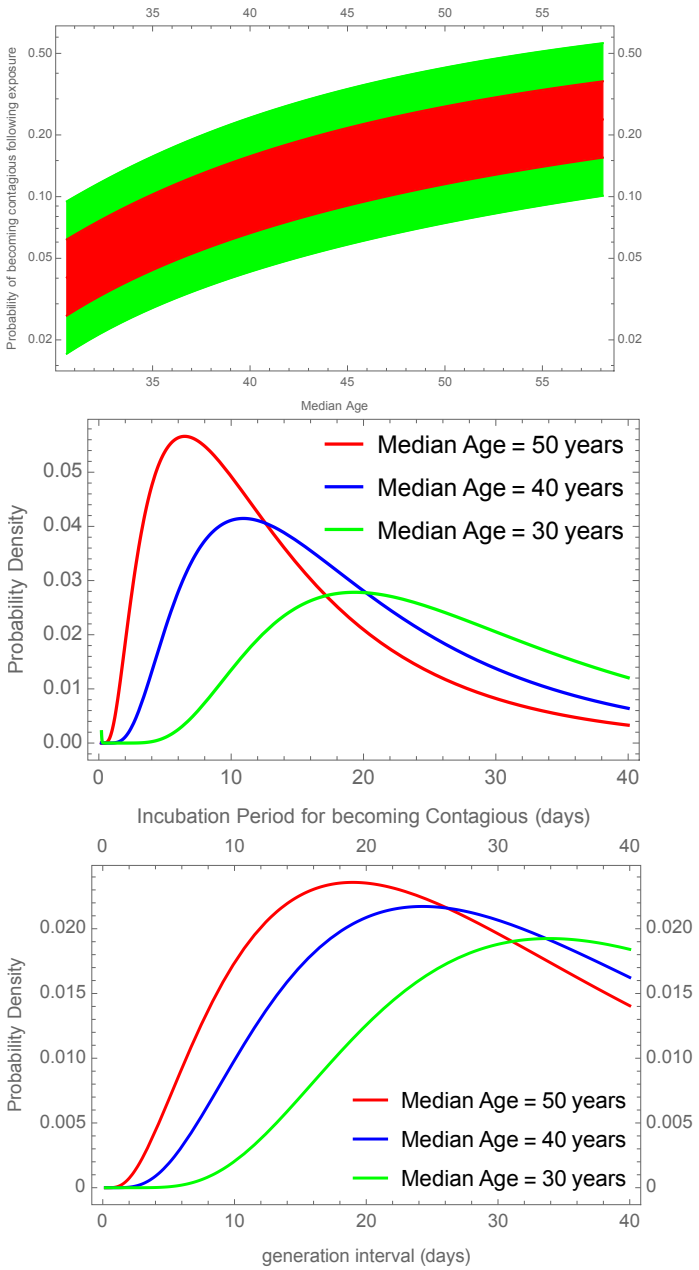

Figure 15: *(Top)(a) The probability that an individual exposed to the virus will ever become infectious. (Middle)(b) The probability distribution for incubation period for onset of virus shedding. (Bottom)(c) Distribution of the generation Interval, $g(a)$, i.e., the time from an individual's infection to them infecting another.*

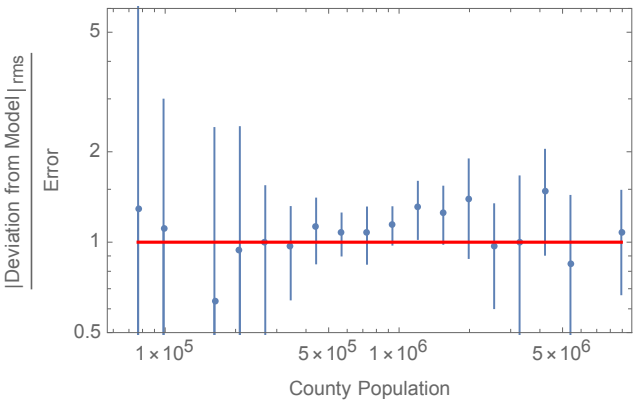

Figure 16: *Root Mean Square of the Ratio of the Simplified Nonlinear model residual to measurement errors (i.e. the $\sqrt{\chi^2_{\rm red}}$), as a function of the population of the county. We see that the residuals are consistent with measurement errors.*

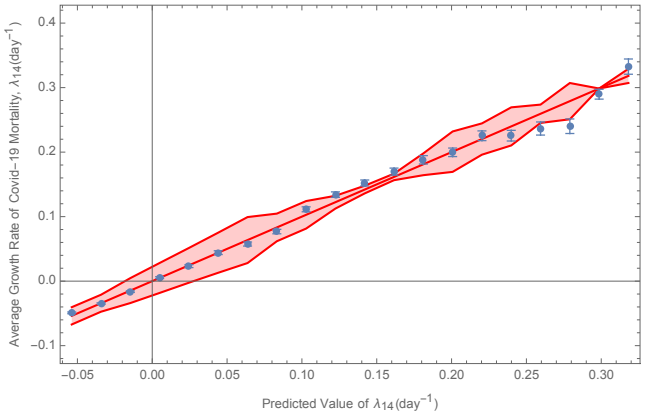

Figure 17: *Observed versus Best-Fit model prediction for bins of λ_{14}. The points show the mean of measured I_7 within each predicted bin, as well as the error on the mean. The red region shows the mean excess model error, on top of measurement uncertainties.*

further confidence in the universality of the nonlinear model across geography and demography.

On average, we find that (either county-weighted or population-weighted) $\chi^2_{\rm red} \simeq 1.28$, suggesting that the model errors are only 13% bigger than statistical errors.

We further compare the model-prediction vs measured mortality growth rate in Figure (17) for all our available data. We find that the 1-σ error in the model prediction (in excess measurement errors) is on average $\pm\sigma_{14} = \pm 0.0180$, i.e. 1.8% error in the daily mortality growth rate. This is shown in Figure (17) as the red region, which compares the model prediction with the observed mortality growth rates. We can also see that there appears to be no significant systematic deviation from the predictions, at least for $\lambda_{14} < 0.23$/day.

Given an understanding of the physical model and its uncertainties, we can provide realistic simulations to forecast the future of mortality in any community, similar to those provided in the main text (Figure 4), which can be made on-demand using our online dashboard: https://wolfr.am/COVID19Dash.

In order to perform these simulations, we follow these simple steps. To predict the daily mortality on day $t+1$, $D(t+1)$, we use the prior 13 days of $D(t)$, as well as the total mortality up to that point:

1. Use Equation (1), plugging in prior total mortality, county information, weather, mobility and parameters in Table 2 to find λ_{14}. Every simulation uses a random realization of model parameters (from their posterior fits), which remain fixed through that simulation.
2. Add the random model uncertainty to λ_{14} using:

$$\lambda_{14}(t+1) \to \lambda_{14}(t+1) + \frac{\sigma_{14}}{\sqrt{14}} \sum_{t'=t-12}^{t+1} g_{t'}, \quad (33)$$

   where $g_{t'}$s are random independent numbers drawn from a unit-variance normal distribution. This captures the model uncertainty mentioned above, while ensuring that it remains correlated across the 14 days that are used to define λ_{14}.
3. Having fixed the logarithmic slope for daily mortality λ_{14}, find the best-fit intercept and its standard error for $\ln[D(t')+1/2]$ for the preceding 13 days, i.e. $t-12 \le t' \le t$, which can then be used to find a random realization for $\ln[D(t+1)+1/2]$
4. Advance to next day and return to step 1.

Parameter	Small Counties	Large Counties	Difference/Error
$\tau_0(\mathrm{day})$	126. $\pm$ 58.9	219. $\pm$ 124.	-0.37
$d^{-1}(\mathrm{day})$	18.4 $\pm$ 3.92	18.1 $\pm$ 2.32	0.0104
$\ln\left[\beta_0\tau_0^{-2}(\mathrm{m}^2/\mathrm{day}^3)\right]$	-2.23 $\pm$ 1.57	-0.519 $\pm$ 2.1	-0.747
C_D	2743. $\pm$ 845.	4425. $\pm$ 958.	-0.323
C_A	-4.73 $\pm$ 2.31	-2.87 $\pm$ 1.75	-0.338
$100C_{\mathcal{M}}$	0.0527 $\pm$ 0.0162	0.0732 $\pm$ 0.0233	-0.227
C_γ	-1.97 $\pm$ 2.13	-8.37 $\pm$ 4.48	0.744
C_T	-0.0415 $\pm$ 0.0251	-0.0768 $\pm$ 0.0342	0.405
C_{A_D}	-1.36 $\pm$ 0.632	-0.588 $\pm$ 0.641	-0.521

Table 3: *Comparison of nonlinear model parameters between small (population < 1 million) with large (population > 1 million) counties. We see no significant statistical difference, as demonstrated by the values in the last column that remain below 1. Note that, in contrast to Table (2), we use temperature rather than specific humidity (C_T rather than $C_{\mathcal{H}}$), as the latter was not available for some small counties. Nevertheless, the parameters remain also statistically consistent with Table (2).*

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COVID-19 Deaths: Which Explanatory Variables Matter the Most?

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Summary

As Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) spreads around the World, many questions about the disease are being answered; however, many more remain poorly understood. Although the situation is rapidly evolving, with datasets being continually corrected or updated, it is crucial to understand what factors may be driving transmission through different populations. While studies are beginning to highlight specific parameters that may be playing a role, few have attempted to thoroughly estimate the relative importance of these disparate variables that likely include: climate, population demographics, and imposed state interventions. In this report, we compiled a database of more than 28 potentially explanatory variables for each of the 50 U.S. states through early May 2020. Using a combination of traditional statistical and modern machine learning approaches, we identified those variables that were the most statistically significant, and, those that were the most important. These variables were chosen to be fiduciaries of a range of possible drivers for COVID-19 deaths in the USA. We found that

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population-weighted density (PWD), some "stay at home" metrics, monthly temperature and precipitation, race/ethnicity, and chronic low-respiratory death rate, were all statistically significant. Of these, PWD and mobility metrics dominated. This suggests that the biggest impact on COVID-19 deaths was, at least initially, a function of where you lived, and not what you did. However, clearly, increasing social distancing has the net effect of (at least temporarily) reducing the effective PWD. Our results strongly support the idea that the loosening of "lock-down" orders should be tailored to the local PWD. In contrast to these variables, while still statistically significant, race/ethnicity, health, and climate effects could only account for a few percent of the variability in deaths. Where associations were anticipated but were not found, we discuss how limitations in the parameters chosen may mask a contribution that might otherwise be present.

Key words: COVID-19; Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2); Mechanistic Modeling; SEIRX.

1. Introduction

Following the first signs of its presence in December 2019 (Huang *and others*, 2020), COVID-19 has rapidly spread across the world, impacting almost every country in its wake (Dong *and others*, 2020). However, its impact has been markedly different (at least as of late May) in different locations, a consequence of factors that remain actively debated. We can categorize these factors as follows. First, imposed societal interventions, in the form of social distancing measures (e.g., "shelter in place" orders, self-isolation, school closures, etc.). Second, demographic differences in the population including age distribution, health, gender, and race of the populations. Third, climatic variability (e.g., temperature, precipitation, or humidity variations), and spatial heterogeneity in terms of the density of people that a person is typically exposed to. Fourth, environmental variability such as pollution. Fifth, virus connectivity factors, such as the likelihood

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that the disease will be imported into an area from outside. These are not mutually exclusive categories, and, indeed, we would anticipate a number of confounding variables amongst them.

Our objective in this study is to assess which of these explanatory (independent) variables are clearly important for predicting COVID-19 deaths, primarily to aid in the development of mechanistic model refinements (Riley *and others*, 2013, 2015, 2017; Ben-Nun *and others*, 2019; Turtle *and others*, 2019). Mechanistic models, as opposed to statistical or machine-learning models are typically developed by incorporating the minimum number of underlying processes necessary to describe the observations sufficiently well to answer specific questions. The types of questions being asked about COVID-19 include, but are not limited to: What impact will interventions have on the trajectory of the disease? Will weather conditions cause the disease to (at least temporarily) abate as we approach the northern summer? Which locations are likely to suffer the most severe outcomes? Which populations will likely fair better, and which will fair worse? A crucial step in answering these questions using models, then, is to understand what factors appear to matter.

In this report we assemble an illustrative dataset of parameters that capture, at least in principle, these factors. We perform several multiple-linear-regression (MLR) and machine learning (ML) analyses on the data to identify the key explanatory variables that are likely driving the variations in the number of deaths per 100,000 for the 50 contiguous U.S. states (i.e., their statistical significance). Additionally, we assess the degree to which these variables can explain the observed deaths (i.e., their importance).

2. Methodology

2.1 *Data*

Data were collected from a variety of sources, each chosen as a fiduciary of one of the factors described above. They are summarized in Table 1. Briefly, the first six parameters (retail, grocery,

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parks, transit, workplaces, and residential) were scraped from Google's Mobility Reports on April 20 (Google), and represent the fractional change (expressed as a percentage) in people's travel to these locations. Thus, a mean value of 11.38% in 'residential' represents the increase in people remaining at home since the start of "shelter in place" orders. Similarly, a decrease of 46.58% in 'retail' reflects the drop in people going to retail locations. Many of the parameters are self-explanatory, including: age, % 65 years and over (USCensus), obesity rates (LiveScience), chronic lower respiratory death rates (CDC), pollution indices (USNews), the date that a state of emergency was declared (Wikipedia), average relative annual and spring-time humidity, dew point, temperature, precipitation (Brettschneider; CurrentResults), and UV index (USEPA). However, several require further explanation.

Table 1: **List of parameters used in multiple-regression analysis, together with their basic statistical properties.** See text for detailed explanation of each parameter.

Population-weighted density (PWD) is, the average of each resident's census tract density, effectively, the density at which the average person lives. It is important to distinguish this from the average population density for a location if there is any significant heterogeneity in population density. For example, the population density of the entire U.S. is approximately 90 people per square mile. In contrast, the population-weighted density is more than 5,000 people per square mile. These data were derived from the WorldPop dataset (Worldpop).

The reported date of the first death in each state is used as a proxy for initial seeding of the virus in each state, and, by extension, a proxy for the connectivity of the state to likely sources of the disease (e.g., China, Europe, or other states).

Race parameters 1 through 4 are an attempt to identify any possible links with the underlying races/ethnicities within each state (USCensus). Specifically, they are: (1) Percent Estimate-Race alone or in combination with one or more other races-Black or African American; (2) Percent

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Estimate-Race alone or in combination with one or more other races-Asian; (3) Percent Estimate-Hispanic or Latino (of any race); and (4) Percent Estimate-One race-White (Smith, 2014).

Finally, our response (dependent) variable is the number of deaths per 100,000 (JHU). All values reported here are correct through May 10 2020. This is, of course, an ever-changing value; however, both the cumulative number of confirmed cases as well as the number of deaths per 100,000 for each state tended to maintain similar relative slopes (Figure 1), such that the results do not depend sensitively on the precise date chosen to represent the number of deaths in each state. In fact, the analysis was repeated for five different dates from April 25 through May 10 with no qualitative difference in the results, or their interpretation. It is, nevertheless, worth noting several outliers. Washington, in particular, was the first state to report an appreciable number of deaths in mid-March; however, its initial slope remained shallower than other states, and, by early April, became even flatter. The net effect of this is that in terms of relative number of deaths, from early April to early May, it exchanged position with a dozen other states. The relative positions of other states has also changed during the course of the last two months. In general, however, the changes were likely driven by a particular event that changed the evolving slope of the profile at some point. These typically occurred in the early portion of the outbreak, and the relative positions of the states in the last month has remained largely unaltered.

Fig. 1. **The variation of (Left) Cumulative number of confirmed cases per 100,000 for each state (colored arbitrarily to better separate each curve). (Right) Cumulative number of deaths per 100,000 for each state**. Data runs from 2020-03-06 through 2020-05-10.

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2.2 *Models*

Multiple regression models were analyzed using several packages in *R*, primarily relying on 'lm' (R Core Team, 2019). To identify the explanatory variables that provided the best performing model (i.e., one that lowered the prediction error), we used the 'stepAIC' function from the MASS package (Venables and Ripley, 2002). Both forward selection and backward selection (i.e., backward elimination) were performed (James *and others*, 2013). In the former, initially, no predictors are included in the model, and the algorithm iteratively adds the most contributory variables, stopping when the improvement is no longer statistically significant.

These regression techniques, however, only identify the statistical significance of the variables. To estimate the relative importance of each explanatory variable in describing the variability in deaths, we applied a number of traditional statistical and more modern machine learning (ML) approaches. Using multiple approaches is important for assessing the uncertainty that should be ascribed to a particular ordering of the variables, since different techniques rely on different metrics for importance. The techniques applied included: random forest (Liaw *and others*, 2002), Xgboost (Chen and Guestrin, 2016), relative importance (Grömping *and others*, 2006), earth (wrapper, 2019), step-wise regression (Bendel and Afifi, 1976), and DALEX (Biecek, 2018). It is important to underscore that these techniques use different definitions of what signifies"important", and, thus, we do not expect agreement between the results. Nevertheless, where the results do agree is where we can be most confident that the explanatory variable importance is significant, and where they do not, we must remain more cautious.

3. Results

When a multiple linear regression analysis was performed on the 28-parameter dataset, four explanatory variables were found to be significant: retail, average annual precipitation, average spring precipitation, and PWD (Table S1). Together, R^2 for these variables was 0.973, and thus,

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these variables are capable of explaining 97% of the variations in deaths/100,000 (n_{deaths}). We then applied a heuristic, recursive process of elimination to each of the parameters to identify those that, under a more focused analysis might raise to the point of significance. From this process, we identified five explanatory variables: retail, grocery, PWD, average spring temperature and precipitation. Thus, annual precipitation was no longer deemed to be significant, but grocery and average spring temperature now were (Table S2).

Comparison of the five most significant variables with one another showed several illuminating features (Figure S1). First, the number of deaths per 100,000 were clustered below 100 per 100,000, with New York being a significant outlier. Second, unsurprisingly, retail and grocery mobility metrics appear to be the most highly correlated of the explanatory variables. Third, the best fit curve to the number of deaths per 100,000 and PWD appears to (1) be linear, and (2) display the strongest correlation with n_{deaths}.

An analysis of the residuals suggests that Hawaii, New Mexico, and Rhode Island (observations 11, 31, and 39) deviate most (Figure S2 (left)). The fitted line through the residuals suggest the possibility that a non-linear relationship might be more appropriate, however, given the relatively high $R^2 \sim 0.9$, we suggest that this is not necessarily so. Comparing the standardized residuals against theoretical quantiles suggests that the errors are approximately normally distributed, at least for most of the states. Notably, New York (32) and Hawaii (11) (and, to a lesser extent, Rhode Island (39)) are outliers (Figure S2 (right)). To check for homoscedasticity, that is, the assumption of equal variance, we can assess whether the residuals are spread equally along the ranges of the predictors. The notable outliers are, once again, Hawaii (11), Rhode Island (39), and New York (32). Although there is variability, with the exception of New York, the standardized residuals are roughly equal to one and constant along the fitted values (Figure S3 (left)).

Finally, considering the variation of the residuals against leverages, we can estimate to what extent the outliers are influential in the regression analysis. The leverage of a particular observa-

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tion (state) is related to how much its value on the predictor variable differs from the mean of the predictor variable. We use Cook's distance as a measure of the influence of an observation, with values lying in the upper-right or lower-right being indicative of unduly influential observations. Unsurprisingly, New York (32) is clearly influential (Figure S3 (right)). Following this, Hawaii (11), and to an even lesser extent, New Jersey are leveraging the results.

In summary, based on this exploratory analysis, the strongest explanatory variable for deaths per 100,000 is PWD (Figure 2). There is a clear trend for states with increasing PWD to have higher number of deaths. There is, however, substantial scatter away from the smooth line through the data, at least in part due to the contribution(s) from some of the other explanatory variables (as well as potentially other equally, or more important variables not included). For example, it is worth noting that, geographically, the states substantially below the line are located at higher latitudes and away from either coast (N. and S. Dakota, Wyoming, Utah, Nebraska, Nevada). On the other hand, many of the states substantially above the line are from southern regions (Mississippi, Alabama, S. Carolina, Kentucky, Missouri, Louisiana). It could also be argued that this demarcation is reflective of other factors, including political affiliation, which may have modulated the timing and/or efficacy of the "shelter in place" orders. Finally, we remark that Hawaii, and to a lesser extent (because of the log-log scale) Alaska, are unique outliers in terms of unusually low deaths given their relative PWD.

Fig. 2. **The relationship between the number of deaths per 100,000 and PWD.** Each state is identified with a dot and the variability and smooth profile are shown with the dark grey region and blue line, respectively.

While the preceding analysis heuristically investigated the possible contribution of the explanatory variables in describing the variations in n_{deaths}, we next apply more robust techniques using a variety of algorithms to assess both statistical significance and importance. In these ap-

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proaches, explanatory variables are iteratively added or removed to identify the subset of variables that produce the best performing model, that is, the model with the lowest prediction error.

First, using *R*'s MASS package, we applied both forward selection, where variables were added iteratively, until the improvement is no longer statistically significant, and backward elimination, where variables are iteratively removed until the point is reached where all the variables are statistically significant (Table S3). Based on this analysis, 14 variables can account for 97% of the variability in n_{deaths}. This is approximately the same as including all 28 variables, and substantially higher than the 87.5% that we computed using our *ad hoc* approach of searching through the variables. PWD, race parameter 1, average annual temperature and precipitation, average spring precipitation are the strongest contributors.

Using the Random Forest method to assess the importance of the variables, we found (in order of importance): PWD, retail, chronic low-respiratory death rate, residential, race parameter 3, obesity rates, average spring temperature, average dew point, race parameter 1, and date of first death were the most important (Table S4). Comparing this list with the significant variables identified earlier, suggests that any subset of significant *and* important explanatory variables would include at least PWD, retail, chronic low-respiratory death rate, race parameter 1, and date of first death.

Applying the Xgboost method for ranking explanatory variables in order of their importance identified the 'retail' mobility metric as the most important variable, followed by PWD, and then two more mobility metrics (workplaces and grocery). Race parameter 1, relative humidity (afternoon), date of first death, and average spring temperature and dew point followed. Finally, Chronic low-respiratory death rate was the remaining variable but only 1% as important as the most important variable (Table S5).

The Multivariate Adaptive Regression Splines (MARS) model can also be used to rank explanatory variables. Unlike the random forest, it has been shown to be more susceptible to

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unstable explanatory variables. Nevertheless, it is a flexible technique and is included here to provide evidence for the sensitivity of our results to the technique implemented. PWD, race parameter 2, and retail captured more than 90% of the importance (Table S6), with grocery and averge annual precipitation rounding out the top-five variables.

The step-wise regression method can also be combined with the Akaike Information criteria (AIC) to identify the best model, that is, the best combination of parameters to explain the output variable. Using this approach, in order of importance, PWD, grocery, retail, average spring temperature and precipitation were all found to be important (Table S7).

Finally, we consider the DALEX package, which is, in fact, a meta-package in the sense that it can compare responses from different models to allow for direct comparison. Here, though, we apply the DALEX machinery with the random forest technique and use the 'explain' and 'variable_importance' functions to quantify their relative importance (Table S8). PWD, retail/workplaces, chronic low respiratory death rate, average relative humidity, grocery, and race parameter 1 describe most of the observed variability in n_{deaths}. The degree to which these variables contribute to the overall variations can also be visualized graphically (Figure 3). Thus, we infer that the first four variables account for most of the observations. Of these, however, average relative humidity was not found to be statistically significant in any of our analyses. Thus, while humidity was "important", it wasn't "significant".

Fig. 3. **Relative importance of explanatory variables using the DALEX method.** See text for more details.

4. Discussion

In this study, we have presented an illustrative, but not exhaustive multiple-regression analysis of 28 explanatory variables, in an attempt to identify those parameters that can best predict

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deaths per capita in U.S. states. Our results are not surprising in the sense that we would have anticipated that PWD and lockdowns, in particular, would likely explain at least some of the variations in deaths. It is also reassuring that our results support other studies highlighting the association of race/ethnicity (Yancy, 2020), climatic conditions (Sajadi *and others*, 2020), and population demographics (Flaxman *and others*, 2020*a*) with deaths. In fact, given the relative homogeneity of the U.S. population, it is somewhat remarkable that small variations from state to state would result in measurable and statistically-significant results.

Our initial dataset contained a number of other variables that were dropped from the formal analysis, primarily because, although there might be an obvious association with deaths, there was no conceivable driving mechanism (i.e., causal relationship). For example, we found that the political affiliation of each state (as measured by the results of the 2016 election) was a strong and statistically significant explanatory variable. In addition to this simply being a confounding variable for several others, such as PWD (republican states tend to be more rural) and the efficacy of lockdowns (democratic states typically implemented orders earlier and/or more stringently), its variation serves no useful role in explaining the number of deaths. Nevertheless, we emphasize the point here to highlight the dangers in over-interpreting what, based on the analysis presented here, can only be considered associations.

Making the leap from associations to causal relationships can be accomplished by mathematical models. Thus, we suggest that the results presented here can be further tested within various types of mechanistic models. Indeed, the two major associations of PWD and mobility metrics are, to varying degrees, already incorporated into models. Individual-based spatial models, for example, can explicitly account for the population-weighted density of the population as well as (at least parametrically) the mobility of people (Flaxman *and others*, 2020*b*). The significance of climate (particularly temperature, precipitation, and/or humidity) can readily be incorporated as well (Riley *and others*, 2017; Ben-Nun *and others*, 2019; Turtle *and others*, 2019).

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It is not surprising that PWD was the most important explanatory variable. It also must be recognized that this variable is related to each state's social distancing orders, with the primary difference that PWD is generally immutable, whereas social distancing can and will change over time. It may be tempting, particularly for vulnerable individuals to move to a region of lower PWD, as this will likely have a strong impact on their likelihood of dying from COVID-19. It could be argued that this should be balanced with the likelihood of the quality of healthcare being proportionately worse in more rural areas. However, based on the simple, but clear relationship between the number of deaths per 100,000 and PWD, this appears not to be the case: Regions of lower PWD are experiencing lower deaths per capita. Moreover, based on the roughly constant gradients (Figure 1(b)), this has been true for the past two months, and will likely hold for the foreseeable future.

Although it is intuitively obvious that PWD and n_{deaths} should be positively correlated in terms of causality, increases in PWD would primarily drive higher incidence, which would, in turn, result in more deaths. However, an interesting question not addressed here is whether the relationship between PWD and deaths is linear? If a disproportionate number of more vulnerable people live in higher-PWD regions, this would result in a plot of n_{deaths} versus PWD curing upwards. There is some suggestion of this in our results (Figure 2); however, such an inference is at best tentative and requires more detailed analysis, including additional datasets that are likely not yet available.

It was somewhat surprising that no significance was found for any measures of age, chronic disease, pollution, or some of the race parameters. In some cases, this is likely due to the fact that the variability was just too small to drive a signal in the results. For example, while the average obesity rate across the 50 states is 27.7%, the standard deviation is only 3.3%. In these cases, we suggest that rather than there not being contribution, we were unable to identify it because of the quality of the parameter. Indeed, several recent studies, which have focused

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specifically on a particular parameter, such as race or ethnicity, were able to identify it within smaller populations with higher heterogeneity (Raifman and Raifman, 2020). Additionally, where explanatory variables are co-linear, the explanatory capability might be absorbed by another parameter.

Equally remarkable is that small differences in race/ethnicity amongst states were statistically significant, albeit only accounting for a small fraction in the variability of the deaths. This suggests that these factors may be more important than those that were not found to be statistically significant here. Of course, this remains speculation until more definitive studies are completed.

5. Conclusions

In this study, we have applied MLR and ML analyses to a large number of potentially promising explanatory variables. We found that population-weighted density (PWD), as well as metrics for the efficacy of lock-down orders were the most significant explanatory variables in explaining the variability in the rate of deaths across U.S. states. Race/ethnicity, health, and climate effects, while statistically significant, were not as significantly important. This may reflect an intrinsic truth, or, more, more likely, is a consequence of the limitations in the data collected. Further studies with more extensive and accurate datasets (as they become available) will likely resolve these issues.

6. Software

Software in the form of R code, together with a sample input data set and complete documentation is available on request from the corresponding author (pete@predsci.com).

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Conflict of Interest: None declared.

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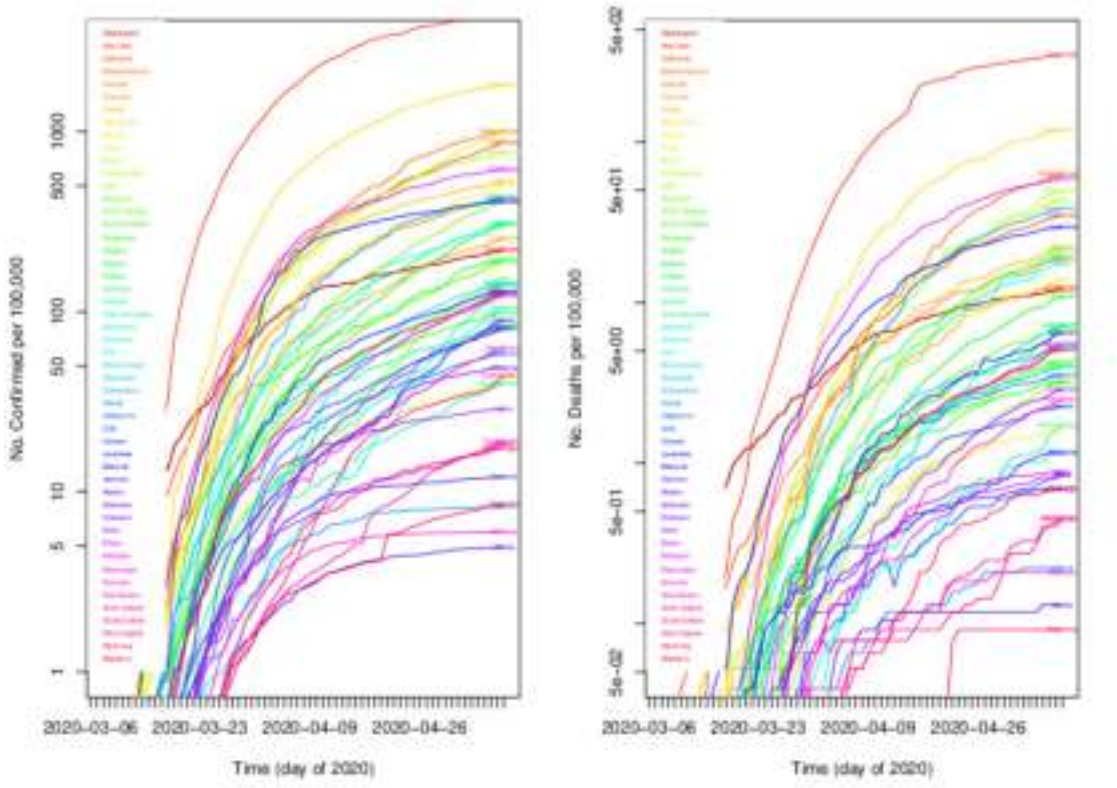

Fig. 1. **The variation of (Left) Cumulative number of confirmed cases per 100,000 for each state (colored arbitrarily to better separate each curve). (Right) Cumulative number of deaths per 100,000 for each state**. Data runs from 2020-03-06 through 2020-05-10.

Table 1. List of parameters used in multiple-regression analysis, together with their basic statistical properties. See text for detailed explanation of each parameter.

Statistic	N	Mean	St. Dev.	Min	Pctl(25)	Pctl(75)	Max
Retail	50	−46.580	6.081	−66	−50	−42.2	−36
Grocery	50	−17.380	7.982	−34	−23.8	−11	1
parks	50	16.400	42.524	−70	−6	29.8	134
Transit	50	−48.520	13.167	−76	−58	−37.5	−21
workplaces	50	−37.760	5.336	−55	−41.8	−35	−27
Residential	50	11.380	2.147	8	10	12	16
Age	50	38.616	2.328	31.000	37.325	39.600	44.900
Low indust. toxins	50	25.500	14.577	1	13.2	37.8	50
Low poll. health risk	50	25.500	14.577	1	13.2	37.8	50
Chron. low resp. death rate	50	42.790	10.520	20	34.9	48.7	64
$\geqslant$ 65 years old	50	16.506	1.926	11	15.7	17.5	21
Race param. 1	50	11.954	9.686	0.900	4.850	15.975	38.900
Race param. 2	50	5.580	8.046	1.100	2.325	5.775	56.800
Race param. 3	50	12.070	10.469	1.400	5.125	13.975	49.100
Race param. 4	50	76.164	12.881	24.300	67.825	85.000	94.300
Obesity rates	50	27.740	3.305	19.000	25.600	29.600	35.200
Av. rel. humidity	50	67.102	8.346	38.300	65.950	71.475	77.100
Av. dew point	50	41.710	9.224	26.500	34.925	46.750	65.200
Av. ann. temp. (C)	50	11.074	4.830	−3.000	7.325	14.800	21.500
Av. ann. precip. (mm)	50	941.820	371.752	241	622.5	1,216.2	1,618
State of emerg. dec.	50	−3.100	3.666	−13	−4.8	0	3
Av. spring temp.	50	10.550	4.941	−4.100	6.650	14.050	21.100
Av. spring precip.	50	82.840	34.067	20	56.8	104.5	151
Rel. hum. (morning)	50	76.280	8.593	43	73.2	81	90
rel. hum. (afternoon)	50	48.440	9.004	17	47	53.8	61
UV Index	50	7.780	2.376	1	7	9	12
Deaths/100k (n_{deaths})	50	20.769	52.440	0.092	1.313	18.250	349.854
PWD	50	3,298.370	4,113.740	694.900	1,356.450	3,561.875	28,161.500
Date of first death	50	18,341.040	6.465	18,331	18,337	18,346	18,365

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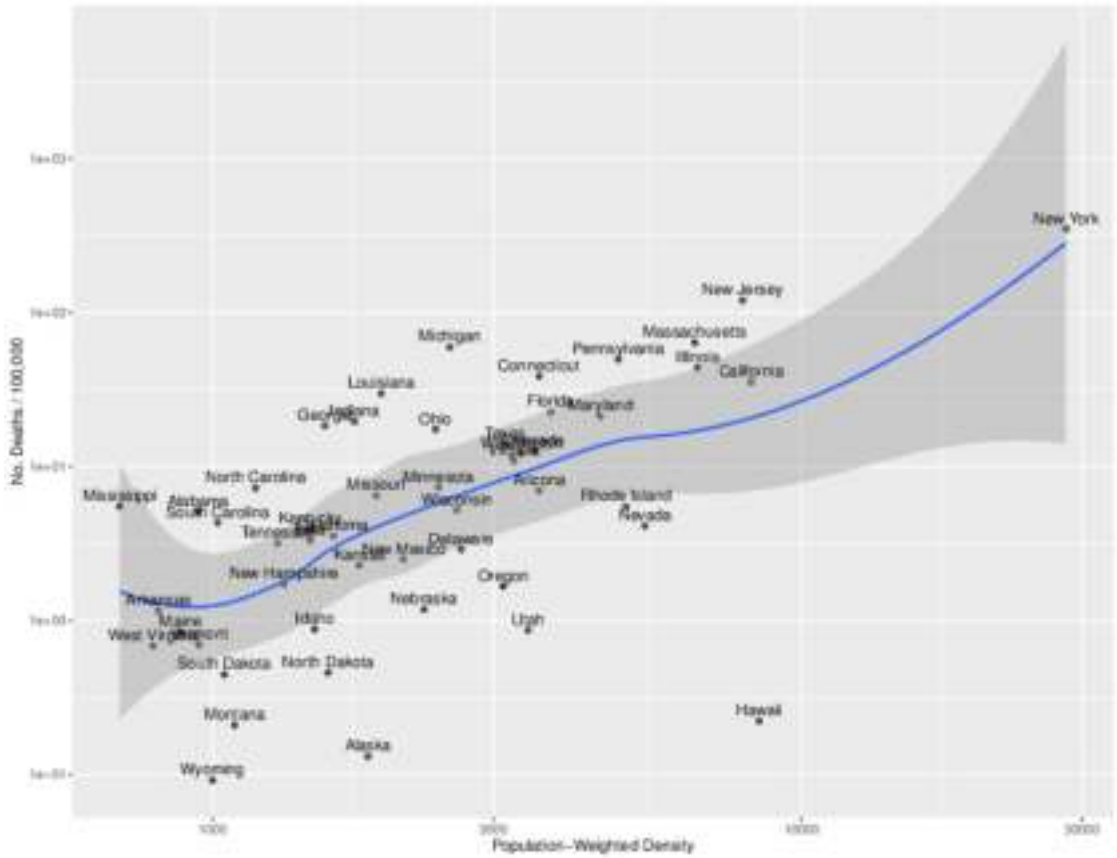

Fig. 2. **The relationship between the number of deaths per 100,000 and PWD.** Each state is identified with a dot and the variability and smooth profile are shown with the dark grey region and blue line, respectively.

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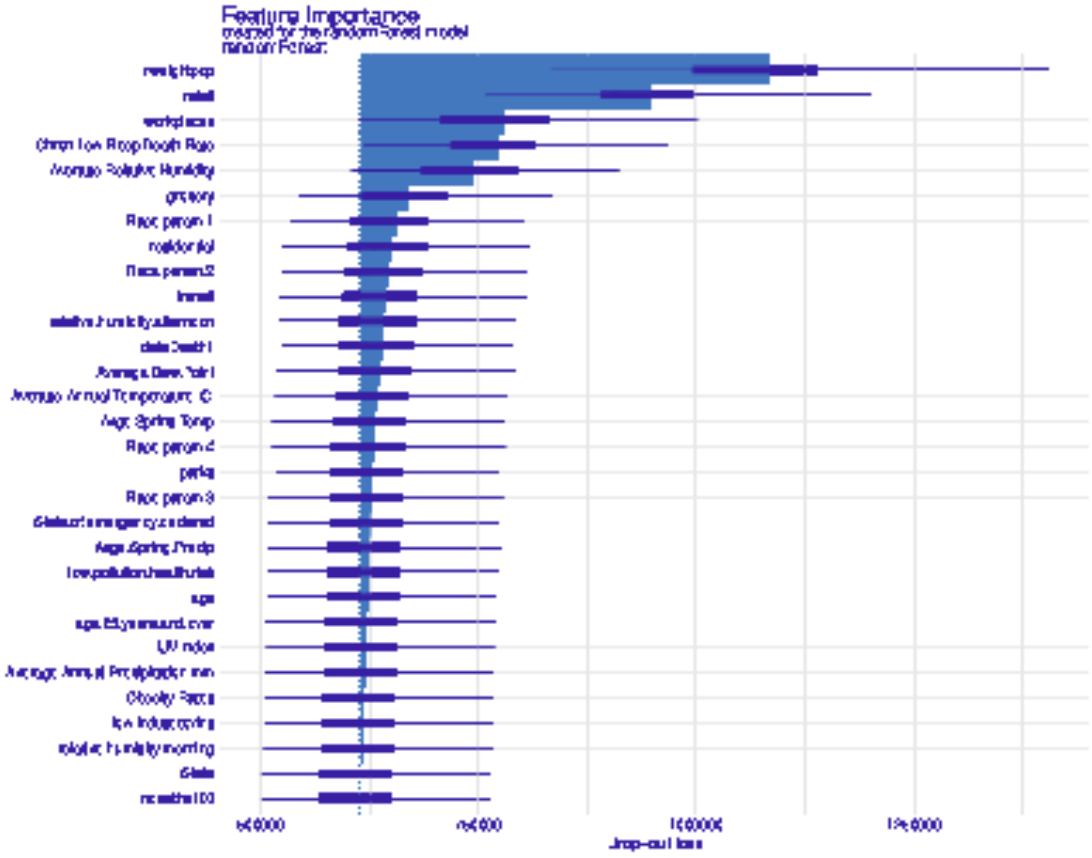

Fig. 3. **Relative importance of explanatory variables using the DALEX method.** See text for more details.

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A global-scale ecological niche model to predict SARS-CoV-2 coronavirus infection rate

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ABSTRACT

COVID-19 pandemic is a global threat to human health and economy that requires urgent prevention and monitoring strategies. Several models are under study to control the disease spread and infection rate and to detect possible factors that might favour them, with a focus on understanding the correlation between the disease and specific geophysical parameters. However, the pandemic does not present evident environmental hindrances in the infected countries. Nevertheless, a lower rate of infections has been observed in some countries, which might be related to particular population and climatic conditions.

In this paper, *infection rate* of COVID-19 is modelled globally at a 0.5° resolution, using a Maximum Entropy-based Ecological Niche Model that identifies geographical areas potentially subject to a high infection rate. The model identifies locations that could favour infection rate due to their particular geophysical (surface air temperature, precipitation, and elevation) and human-related characteristics (CO^2 and population density). It was trained by facilitating data from Italian provinces that have reported a high infection rate and subsequently tested using datasets from World countries' reports. Based on this model, a *risk index* was calculated to identify the potential World countries and regions that have a high risk of disease increment.

The distribution outputs foresee a high infection rate in many locations where real-world disease outbreaks have occurred, e.g. the Hubei province in China, and reports a high risk of disease increment in most World countries which have reported significant outbreaks (e.g. Western U.S.A.). Overall, the results suggest that a complex combination of the selected parameters might be of integral importance to understand the propagation of COVID-19 among human populations, particularly in Europe. The model and the data were distributed through Open-science Web services to maximise opportunities for re-usability regarding new data and new diseases, and also to enhance the transparency of the approach and results.

1. Introduction

The spread of the COVID-19 pandemic, caused by the SARS-CoV-2 virus, is significantly afflicting both society and the global economy, and urgently calls for the development of systems capable of monitoring and predicting the risk of infection. The modelling of SARS-CoV-2 spread is being approached with heterogeneous methodologies, ranging from pure time series analysis to ecological models using climatic parameters, especially temperature and humidity (Giuliani et al., 2020; Nickbakhsh et al., 2020; Sajadi et al., 2020; Wang et al., 2020). However, the pandemic seems to be spreading in all World cities without evident environmental hindrances. Nevertheless, some countries are experiencing a lower rate of disease cases that might be related to their particular population and climatic conditions, but the exact effect of these conditions on infection rate is still unclear (Roser et al., 2020).

Several approaches have been used to estimate the potential spatial outreach of the virus and the geophysical and climatic data that may foster disease transmission. Ecological Niche Models (ENMs) have been extensively and effectively used in this context (Costa and Peterson, 2012; Davison, 2007; Misra and Kalita, 2010; Wahlgren, 2011; Zhang et al., 2019). ENMs' aim is to predict the presence of a particular species in a geographical area by correlating species-specific occurrence records in its native habitat (presence records) with specific environmental parameters (Elith and Leathwick, 2009). The species' niche can be defined as the space within a hypervolume of numerical vectors - corresponding to environmental parameter ranges - which is correlated with the species' presence, and that fosters population persistence (*Hutchinsonian* ecological niche). Accuracy in the identification of this hypervolume can also be enhanced if the species' absence information is included in the model, as either expert-estimated or mathematically

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simulated information (Chuine and Beaubien, 2008; Coro et al., 2016; 2015b; Pearson, 2012; Peterson et al., 2011). ENMs have heterogeneous approaches and implementations, for example they can explicitly model a species' environmental preferences and physiological limits (*mechanistic models*), or they can automatically estimate the correlation between the parameter vectors and the species' presence (*correlative models*). Once the model has estimated the species' ecological niche, it can then project the niche characteristics across the native geographical area to reproduce the actual species' distribution, and subsequently extrapolate across another area (even at the global scale) to discover new potential suitable places for the species' persistence. Most ENMs that predict virus' spread use *correlative* approaches implemented as machine-learning or statistical models. These models can reach a high prediction accuracy on disease outreach because viruses and pandemics are known to be supported by particular geophysical characteristics and, potentially, by ecological and socioeconomic changes (Carlson et al., 2016; Earn et al., 2000; Morse et al., 2012; Scheffer, 2009; Scheffer and Van Nes, 2018). ENMs have been extensively used to discover these characteristics directly, or indirectly by tracing viruses' principal vectors (Fuller et al., 2013; Linden, 2006; Medley, 2010; Peterson et al., 2006; Samy et al., 2016; Signorini et al., 2014; Tachiiri et al., 2006; Valiakos et al., 2014; Walton et al., 2010; Zhu and Peterson, 2014). In particular, the Maximum Entropy model (MaxEnt) has been often used as an ENM due to its flexibility to work with both presence and presence/absence data scenarios (Coro et al., 2015b; 2013; Elith et al., 2011; Phillips et al., 2004). Also, MaxEnt can estimate the influence of each parameter on the identification of the niche, i.e. the most important parameters to understand a virus' preferred conditions. For these reasons, MaxEnt has often been used to trace the ecological niche of a virus based on pure geophysical parameters or human-related parameters (e.g. population density and urbanised area), and also to understand how climate change might foster the virus' spread (Koch et al., 2016; Miller et al., 2012; Peristeraki et al., 2006; Samy and Peterson, 2016).

In this paper, MaxEnt is used to estimate a *global-scale distribution of SARS-CoV-2 high infection rate*, and consequently of potential COVID-19 high spread rate. Differing from the other cited works, this model concentrates on infection *rate* rather than on absolute *spread* numbers. Further, the proposed model uses a complex combination of parameters to identify locations that could favour infection due to their particular geophysical- and human-related characteristics. As a result, it predicts a high probability of infection increase in many actual known infection areas, e.g. the Hubei province in China. The presented ENM is trained based on locations in Italy that have reported a high rate of new infections. Also, it facilitates geophysical (surface air temperature, precipitation, and elevation) and human-related (carbon dioxide and population density) data-vectors associated with these locations. The implemented model produces a probability map where higher values indicate a correlation with high infection rate; lower non-zero values indicate a lower correlation, and zero indicates unsuitable conditions for infection increase. A *risk index* is also calculated out of the produced probability distribution and identifies most World countries, with known high COVID-19 spread rate, as high-risk zones. Overall, the present work suggests that the involved parameters may play a key role in monitoring COVID-19 spread rate. The research question answered by the present work is: *Given the climatic, geophysical, and human-related parameters that other studies have individually correlated with a high COVID-19 infection rate, and that are publicly accessible, can we infer their overall weights and predict infection rate with high accuracy?*

This paper is organised in the following way: Section 2 describes the used data and the modelling approach and subsequently Section 3 reports performance evaluation metrics, model's parametrisation, and performance at predicting global high-infection-rate zones. Section 4 discusses results and conclusions, reporting the possible applications and future extensions of the presented model.

Table 1
Summary of all used data along with their primary sources. Details about how these data were accessed and post-processed are given in the article.

Data	Primary Source
Infection per Italian Province	Italian Civil Protection Department
World Infections	John Hopkins University
Surface Air Temperature	NASA Earth Exchange Platform
Precipitation	NASA Earth Exchange Platform
Elevation	United Stated National Geophysical Data Center
Carbon Dioxide	Copernicus Atmosphere Monitoring Service
World Population Density	Center for International Earth Science Information Network

2. Material and methods

2.1. Data

2.1.1. Data selection methodology and data availability

The methodology presented in this paper aims to be repeatable, reproducible, and re-usable for experiments on COVID-19 and other diseases. For this reason, only data which met the principles of findability, accessibility, interoperability, and re-usability were used (FAIR data). Geospatial data accessible through representational standards, published on public geospatial services, were preferred in order to maximise their usage in the implemented model and further experiments. All used data (Table 1) were post-processed and transformed into gridded raster files, and were made available through the Zenodo open-access repository (Coro, 2020a) and the Unidata Thredds service of the D4Science e-Infrastructure (Coro, 2020b) while respecting their primary sources' citation requirements. The model used an annual data set so as not to be limited to the last winter/spring season.

2.1.2. Training and test data

The Italian Civil Protection Department - the national body that deals with emergency events - publishes daily updates on the number of people infected, recovered, and mortalities from COVID-19 per region and province (Italian Civil Protection Department, 2020). Data up to the end of March 2020 (Fig. 1-a), i.e. the period of maximum infection rate in Italy, were used as a reference to identify locations with high infection rates on the basis of the derivative of the values. Among all available COVID-19 global reports, Italian data are particularly applicable to train an ENM because (i) Italy has been the first European country to be both heavily impacted by the virus and to study the virus, and (ii) infections in Italy have been reported on the basis of tens of thousands blanket tests. In Italy, a correlation between temperature and humidity increase and COVID-19 spread has been assessed (Italian Ministry of Health, 2020; Scafetta, 2020; Tuscany Regional Health Agency, 2020), in agreement with studies on other areas (Section 2.1.3). Indeed, despite the easing of the lockdown to lower levels and the consequential increase of human interactions, the disease spread has been decreasing from May 2020 (GEDI, 2020). At the end of April 2020, the Italian Prime Minister presented a plan of progressive lockdown level reduction, which also included possible regional restrictions in the case of a localised disease rate increase (Italian Government, 2020). However, significant increments were not observed and thus special regional restrictions were not applied. To better understand this phenomenon, Italy has started national projects to investigate the cause and effect relationships between the lockdown, environmental factors, and tourism, and to publish data and results under FAIR principles (CNR, 2020). Due to this range of considerations, Italy presents an optimum scenario to apply the proposed analysis. However, other countries are experiencing a high infection rate but have climatic conditions that are very different from the European ones. The identification of all these conditions would require more significant research and data collection initiatives.

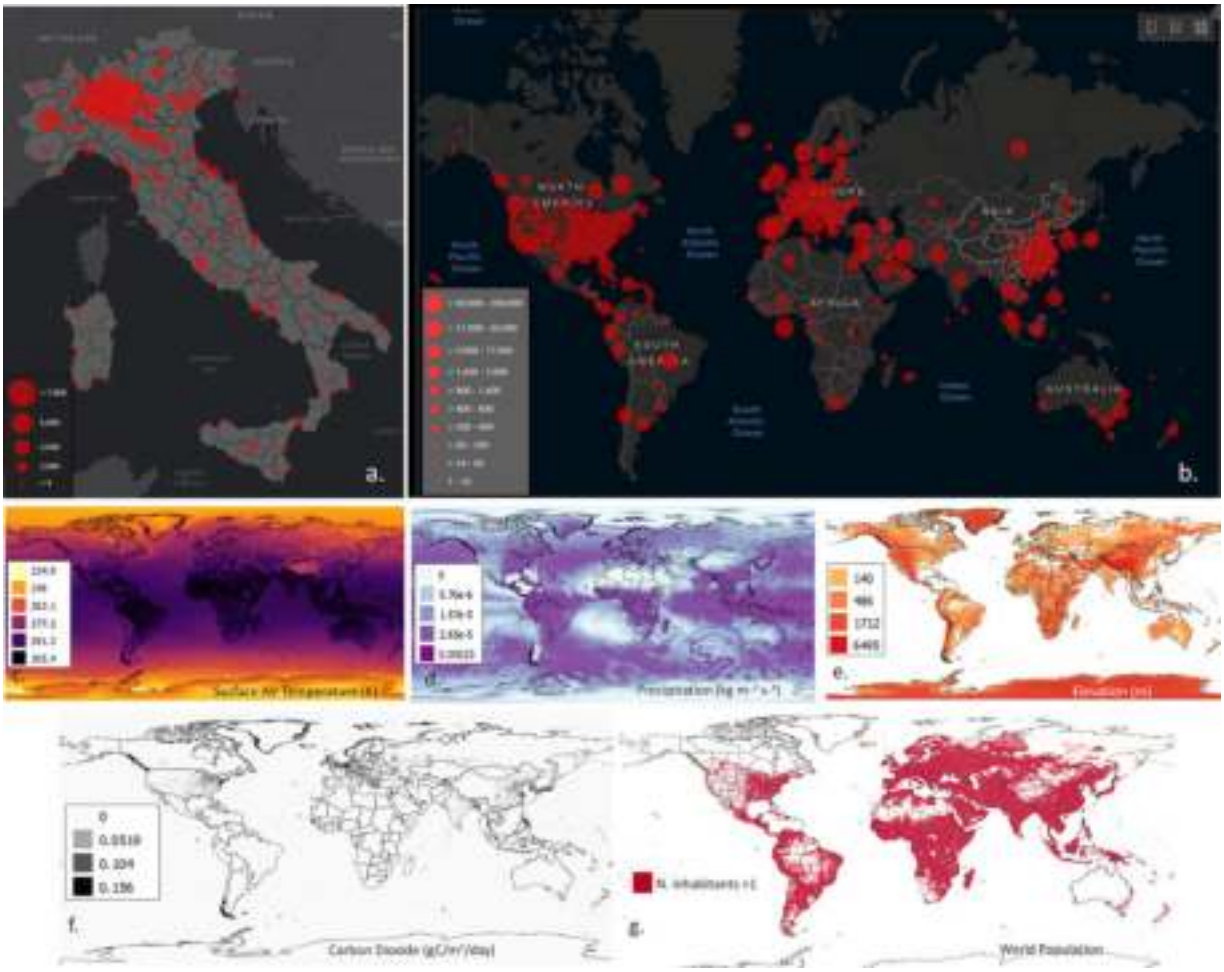

Fig. 1. Visual comparison of the global-scale data used in the presented model: (a) number of infections in Italian provinces (31 March 2020), (b) global infections (31 March 2020), (c) surface air temperature, (d) precipitation, (e) elevation, (f) carbon dioxide, (g) World population.

For the scopes of the presented experiment, Italian locations with a high virus infection rate were selected, by first calculating average rates of infected people per province and then by studying the distribution of these quantities. A total of 54 provinces was selected by applying this approach (the detailed table is available in Coro (2020a)). A Chi-squared test confirmed that the distribution of infection rates could be approximated by a log-normal distribution. Consequently, provinces with a high infection rate were identified and selected as those with infection rates over the geometric mean of the rates. These data were used as reference observations of the modelled phenomenon to train an ecological niche model. It is worth noting that using average infection *rate* instead of absolute infection *counts* helps reducing a data bias due to the number of undetected cases of infection in Italy.

John Hopkins University publishes daily updates regarding COVID-19 infections and mortality statistics by collecting reports from the World countries (Dong et al., 2020). Data are given at a national scale for most countries, and at a regional scale for other countries (e.g. China, U.S.A., and Canada) (Fig. 1-b). Unfortunately, reports from different countries are poorly comparable between them, given the different countries approaches to disease identification and monitoring (Reuters, 2020). Thus, mixing these data with Italian province data was not optimal for modelling. Nevertheless, global data were used as a reference to test the prediction performance of an aggregated *risk index* built upon the model's output (Section 2.3). To this aim, the countries/regions with the highest infection rates were selected using the same statistical analysis applied to Italian data, which resulted in 72 locations (the detailed table is available in Coro (2020a)).

2.1.3. Input parameters

Surface air Temperature and Precipitation

The NASA Earth Exchange platform hosts long-term daily forecasts between 1950 and 2100 at a 0.25° resolution for minimum and maximum surface air temperature and precipitation at the surface (NASA-NEX, 2020). Forecasts come from 20 weather models developed by the Coupled Model Intercomparison Project Phase 5 (CMIP5, 2019). The D4Science e-Infrastructure hosts these data sets averaged in time and space, for 2018 and at a 0.5° resolution as gridded NetCDF-CF files (Coro and Trumpy, 2020a). In particular, data of average surface air temperature and precipitation (Figs. 1-c and -d) were used due to their correlation with COVID-19 and similar viruses (Casanova et al., 2010; Chan et al., 2011; Chaudhuri et al., 2020; Ficetola and Rubolini, 2020; Ma et al., 2020; Oliveiros et al., 2020; Qi et al., 2020; Wang et al., 2020; Wu et al., 2020), and their general coupled involvement in virus ecological niche models (Carlson et al., 2016; Fuller et al., 2013; Patz, 1998; Valiakos et al., 2014). Additionally, precipitation was also used as a surrogate of humidity (Baskerville and Cobey, 2017; Chen et al., 2012; Masunaga, 2012). Italian provinces present a high variability of surface air temperature and precipitation. At the same elevation, there are temperature differences as high as 7° and precipitation differing of more than one order of magnitude. This variability increases the representativeness of Italian provinces as a training set.

Elevation

The United States National Geophysical Data Center (NGDC) hosts a global dataset of elevation and depth at a 0.33° resolution (ETOPO2, NOAA (2001)), which includes localised correction and integration of

satellite, ocean sounding, and land data. Elevation has been used in several ecological niche models for viruses (Miller et al., 2012; Peterson et al., 2006; Valiakos et al., 2014) and thus was included in this experiment. The D4Science e-Infrastructure hosts a FAIR ETOPO2 dataset as a gridded NetCDF-CF file (Coro and Trumpy, 2020a; 2020b) downsampled at a 0.5° resolution (Fig. 1-e).

2.1.4. Human-related parameters

The Copernicus Atmosphere Monitoring Service hosts a global-scale uniform distribution of carbon dioxide (CO^2) flux with monthly estimates (CAMS, 2019) deriving from both human and natural activity. A FAIR dataset of averaged data from January 1979 to December 2013 with a 0.5° spatial resolution is hosted by D4Science (Coro and Trumpy, 2020a) as a gridded NetCDF-CF file (Fig. 1-f). This dataset aims at combining CO^2 values preceding the higher industrialisation rate of the last decades with the natural presence of CO^2 in the soil. It summarises both natural emission and the evolution of human emission (Coro and Trumpy, 2020b). For the scope of this paper, this dataset was used as a surrogate of air pollution and human-related activity, which are generally correlated with virus spread and may foster COVID-19 spread (BBC, 2020; Clay et al., 2018; Godzinski and Suarez Castillo, 2019; Han et al., 2020; ISPRA, 2020; Lam et al., 2016; Liu et al., 2019; Tasci et al., 2018; Ye et al., 2016). Alternative parameters of CO^2, correlated with air pollution, were also tested but produced more adverse results (Section 3.2).

Population Density

Studies on complex systems' dynamics have highlighted that epidemics happen only beyond a critical threshold of population density that depends on infectivity, recovery, and mortality rates (Earn et al., 2000; Scheffer, 2009). The Center for International Earth Science Information Network openly publishes up-to-date population density data as gridded datasets with resolutions ranging from30″ to 1° (Warszawski et al., 2017). For the scopes of this paper, the Gridded Population of the World dataset - Version 4, was used at a 0.5° resolution (Fig. 1-g) to include population density factors that could be correlated with infection rate.

2.2. Modelling

The experiment presented required training of MaxEnt models with several alternative parametrisations in order to identify the model with the highest performance and the best combination of parameters (Section 2.3). To this aim, the *gCube DataMiner* cloud computing platform was used. This is an open-source system that is able to process big data and offers over 400 free-to-use processes as-a-service from multiple domains (Assante et al., 2019; Coro et al., 2015a). This platform maximises the re-usability of processes through a standard Web Processing Service (WPS) interface (Coro et al., 2017). Further, DataMiner parallelises the training of models on a network of 100 machines while choosing the best computational configuration among a range of powerful multi-core virtual machines (Ubuntu 14.04.5 LTS x86 64 with 16 virtual CPUs, 16 GB of random access memory and 100 GB of storage capacity). Additionally, the system stores all trained models and their respective parametrisations under the standard and exportable Prov-O ontological format (Lebo et al., 2013). This representation allows to recover the complete set of input/output data and metadata which enable any other authorised user to reproduce and repeat an experiment (*provenance* of the computation). The Open Science concepts of re-usability of processes, and of reproducibility and repeatability of the experiments, allow the implementation of a methodology that can, in principle, be extended to analyse other diseases (Section 4). To this aim, DataMiner hosts a MaxEnt model as-a-service (CNR, 2019; Phillips et al., 2019), which can work on textual input files (CSVs) - that include pairs of coordinates related to a certain phenomenon - and FAIR input geospatial data. The WPS interface allows (i) inclusion of this service in complex workflows through a wide range of workflow management systems which support this standard (Berthold et al., 2009; QGis, 2011; Wolstencroft et al., 2013), and (ii) re-use of the service across multiple domains (Coro et al., 2015b; 2013; Coro and Trumpy, 2020b; Coro et al., 2018).

2.2.1. Model description

MaxEnt is a machine learning model commonly used in ecological niche modelling (Baldwin, 2009; Coro et al., 2015b; 2018; Phillips et al., 2006; Phillips and Dudik, 2008; Phillips et al., 2004). It simulates a probability density function $\pi(\bar{x})$ defined on real-valued vectors of parameters $\bar{x}$ taken at locations where a species occurs in its native habitat (Coro et al., 2018; Pearson, 2012). The advantage of MaxEnt with respect to other models is that it can learn from positive examples only. Thus, it does not necessarily need absence data, which are instead automatically estimated. Considering the high-infection-rate of Italian provinces as species occurrences, the parameters associated with these areas were treated as a positive example of input vectors to train the model. One drawback of MaxEnt, is that its prediction performance is very sensitive to data quality (Elith and Leathwick, 2009), an additional consideration for using only Italian data and not combining data from other countries (Reuters, 2020).

The MaxEnt training algorithm adjusts the model's internal variables so that (i) the simulated density function $\pi(\bar{x})$ is compliant with pre-calculated mean values at training-set locations and (ii) the entropy of the density function $H = -\sum \pi(\bar{x}) \ln(\pi(\bar{x}))$ is maximum for these locations (Elith et al., 2011). MaxEnt maximises the entropy function for training locations divided by the entropy values of the parameters of random points taken in the training-set area (*background points*, Phillips et al. (2006)). The model involves a linear combination of the input parameters, whose coefficients reproduce the influence of each variable on the prediction of the training set locations (*percent contribution*). Further, the model estimates the dependency of the performance on the permutation of each parameter in the training vectors (*permutation importance*).

In this experiment, MaxEnt uses the data vectors $\bar{x}$ of Italian high-infection-rate provinces (and of *background points* in Italy) to estimate the probability density $\pi(\bar{x}) = P(high - infection - rate|\bar{x})$ that a location would foster a high infection rate. To this aim, the model estimates the ratio between the probability density $f(\bar{x})$ of the vectors across Italy and the probability density in the high-infection-rate locations $f_1(\bar{x})$. The Bayes' rule defines the relation between $P(high - infection - rate|\bar{x})$, $f(\bar{x})$, and $f_1(\bar{x})$:

$$P(high - infection - rate|\bar{x}) = \frac{f_1(\bar{x})P(high - infection - rate)}{f(\bar{x})}$$

with $P(high - infection - rate)$ being the prior distribution of high-infection-rate zones in Italy (*prevalence*), fixed to 0.5 by default (i.e. no prior assumption is given). MaxEnt hypothesises that the optimal $f_1(\bar{x})$ distribution is the closest distribution to $f(\bar{x})$, because without any training-set location there would be no expectation about certain conditions over the others (i.e. $f(\bar{x})$ is a null model for $f_1(\bar{x})$). Also, the model constraints $f_1(\bar{x})$ to reflect the observations on the training set, i.e. $f_1(\bar{x})$ should estimate high probability on parameters' values close to the parameters' means over the training set. The model uses Kullback-Leibler divergence (relative entropy) to measure the distance between the two functions:

$$d(f_1(\bar{x}), f(\bar{x})) = \sum_{\bar{x}} f_1(\bar{x}) log_2\left(\frac{f_1(\bar{x})}{f(\bar{x})}\right)$$

The aim of the training algorithm is to minimise this distance under the above constraints, which in turn maximises the entropy of the target probability density. It can be demonstrated that this characterization uniquely determines $f_1(\bar{x})$ as belonging to the following family of Gibbs distributions (Phillips et al., 2006):

$$f_1(\bar{x}) = f(\bar{x})e^{\eta(\bar{x})}$$

with $\eta(\bar{x}) = \alpha + \beta\, h(\bar{x})$; α being a normalization constant that makes $f_1(\bar{x})$ sum to 1; h being an optional transformation of the vectors $\bar{x}$ that possibly models complex relationships between parameters; β being the vector of coefficients that reports the *percent contribution* of each parameter. Thus, the ratio $f_1(\bar{x})/f(\bar{x})$ is equal to $e^{\eta(\bar{x})}$, i.e. MaxEnt needs to solve a log-linear model based on the background and training vectors to estimate the α and β parameters, which can be implemented through a penalised maximum likelihood algorithm (Phillips and Dud, 2008).

After the training phase, the parameters' *percent contribution* can be used to select the most influential parameters for the model. This potentially allows to use MaxEnt as a filter to select those parameters carrying the highest quantity of information (Coro et al., 2015b; 2013; 2018). A MaxEnt model trained on 0.5˚ resolution parameters can be reasonably used to produce probability distributions at the same resolution. Given the semantics of the selected training locations, the model produced a distribution function that could be interpreted as a global-scale probability distribution for SARS-CoV-2 high infection rate.

2.3. Evaluation metrics

The model training phase estimates the average Area Under the Curve (AUC), i.e. the integral of the Receiver Operating Characteristic (ROC) curve that plots *sensitivity* ($\frac{True\ Positives}{True\ Positives + False\ Negatives}$) against 1-*specificity* ($1 - \frac{True\ Negatives}{True\ Negative + False\ Positives}$). AUC values closer to 1 indicate high classification performance of training sites. Reference cut-off thresholds on π were also calculated during the training phase (Phillips et al., 2019) and represent (i) the value balancing *omission rate* ($\frac{False\ Negatives}{True\ Positives + False\ Negatives}$) and *sensitivity* (*balanced threshold*), (ii) the value at which *sensitivity* and *specificity* are equal, and (iii) the minimum threshold at which all training locations are correctly classified as high-infection-rate areas.

In order to numerically estimate the prediction performance of the trained model, a *risk index* was also calculated, defined as the normalised density of non-zero MaxEnt probability locations (Coro et al., 2018; McGeoch et al., 2006) for all countries/regions reported in the global dataset of infection rates (Section 2.1). High-risk zones were identified as those with a *risk index* higher than the geometric mean of the *risk* values. Accuracy on the correct identification of *high-infection-rate countries/regions* as *high-risk zones* was calculated as $\frac{n.\ of\ high-infection-rate\ areas\ identified}{overall\ n.\ of\ high-infection-rate\ areas}$. Moreover, agreement between high-risk zones' classification and high-infection-rate country/region reports was calculated using Cohen's Kappa (Cohen et al., 1960). This statistical coefficient estimates the agreement between the two classifications with respect to purely random classifications (agreement by chance). An overall interpretation of this value was assigned using Fleiss' tables (Fleiss, 1971).

3. Results

3.1. Global-scale distribution and performance

The MaxEnt model was trained using different combinations of parameters associated with Italian locations reporting a high rate of infections up to the end of March 2020 (Section 2.1). Training the model on all parameters produced the highest AUC and optimal estimates for the three model's thresholds (Table 2-a). When the model was trained with any other parameter subset, AUC resulted lower. This property indicates that all parameters bring useful information to estimate training set locations correctly. Nevertheless, the *percent contribution* and *permutation importance* of carbon dioxide, surface air temperature, and precipitation are much higher than the ones of elevation and population density (Table 3). The model using all parameters also indicates a correlation with high infection rate for particular parameter ranges (i.e. the boundaries of the niche hypervolume): CO^2 has the highest correlation around 0.03 (0.01;0.08) $g\ C\ m^{-2}\ day^{-1}$ (*moderate-high*), air temperature around 11.8 (8.0;16.0) ˚C (*moderate-low*), and precipitation around 0.3 (0.2;0.45) 10^{-4} $kg\ m^{-2}\ s^{-1}$ (*moderate*).

Table 2
Report of (a) the performance and optimal thresholds of the trained MaxEnt model, and (b) the performance of the *risk index* on the identification of global high-infection-rate countries/regions.

Model Performance - a	
AUC	0.994
Balanced omission-sensitivity threshold	0.4
Equal training sensitivity and specificity threshold	0.1
Minimum training presence threshold	0.008
Risk Index Performance - b	
Accuracy	77.25%
Kappa	0.46
Kappa Interpretation	Good

Table 3
Percent contribution and permutation importance of the parameters involved in the presented experiment, as estimated by the optimal Maximum Entropy model.

Parameter name	Percent contribution	Permutation importance (%)
Carbon Dioxide	87.2	52.8
Surface Air Temperature	7.6	40
Precipitation	5.3	6.9
Elevation	0.01	0.01
Population Density	0.01	0.2

The model was projected at the global scale to produce a global infection-rate probability distribution at a 0.5˚ resolution (Fig. 2). For each cell, this map reports the probability that the cell has suitable conditions for infection increase. Locations with a value higher than the balanced threshold ($\pi(\bar{x}) \geq 0.4$) can be classified as high-infection-rate locations, whereas the other two thresholds indicate medium infection-rate ($0.1 \leq \pi(\bar{x}) < 0.4$) and low infection-rate ($0.008 \leq \pi(\bar{x}) < 0.1$) locations. Zero probability locations indicate unsuitable areas for an infection rate increase.

As a qualitative evaluation, it can be observed that the model correctly and precisely identifies the locations of real World high infection rates, e.g. the Hubei Chinese region, Western United States, and most of Europe. Instead, wrongly classified places are, for example, Peru and Brazil, that have parameter ranges out of the niche hypervolume. The identification of the climatic/geophysical parameters fostering infection rate increase in these countries would require further research, based on a more extensive and globally shared data collection (Section 3.3).

In order to quantify the prediction accuracy of the map, the *risk index* was used to select high-risk zones and compare them with global reports of high infection rates (Fig. 3 and Table 2-b). Accuracy at predicting high-infection-rate countries/region reached 77.25%, and the overall agreement (0.46) was *good* according to Fleiss' classification. This result indicates that most countries/regions are correctly and non-randomly classified, and thus the model has extracted a correct characterisation of the actual risk of infection increase based on the considered parameters.

3.2. The weight of the CO^2 parameter

The high correlation of CO^2 with high infection rate requires a further investigation, starting from the correlation between air pollution and COVID-19 spread (Section 2.1.4). The Copernicus Atmosphere Monitoring Service provides FAIR data correlated with greenhouse gas concentration and fluxes, i.e. methane (CH_4), nitrous oxide (N_2O), and

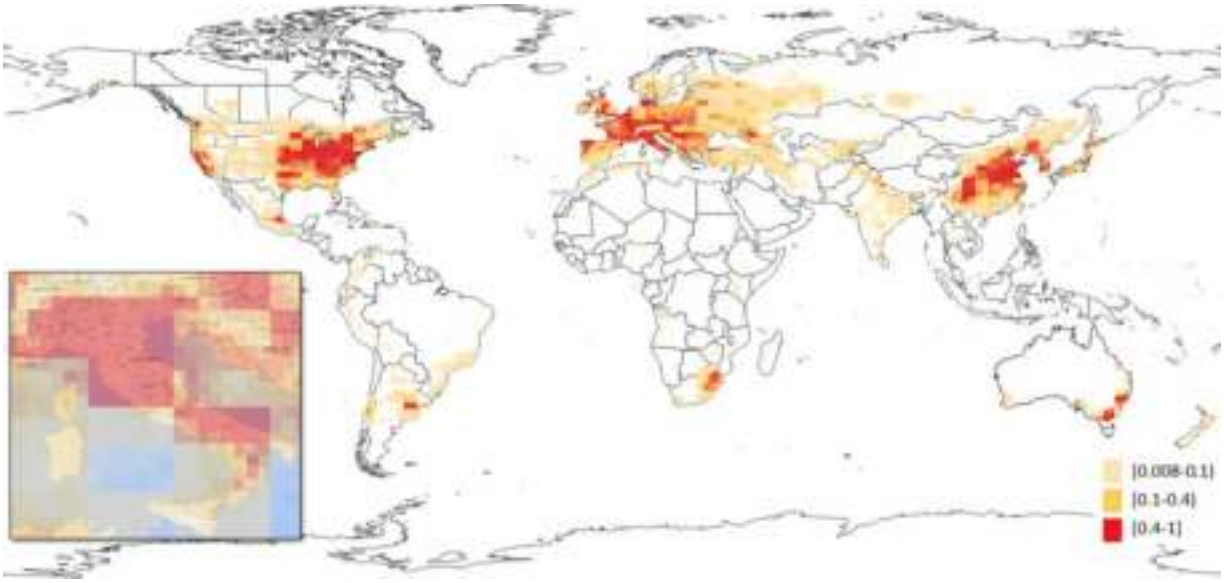

Fig. 2. Global-scale probability distribution of SARS-CoV-2 infection rate produced by the presented model, with Italy magnified at the lower-left hand side.

CO^2 (CAMS, 2020). The CH_4 and N_2O influence on prediction performance was evaluated by substituting these parameters to CO^2 in the all-parameter model (*individual* models), and then by using them together with CO^2 (*mixed* model). The aggregated data used for this analysis were published as FAIR data on Zenodo (Coro, 2020a). Executing the MaxEnt individual models revealed that CH_4 and N_2O have a much lower *percent contribution* ($\sim$ 52% for both models) to infection rate prediction than CO^2 (87.2%). Furthermore, their individual models reported a lower AUC (0.90 v.s. 0.994 of the CO^2 model). However, in these models, CH_4 and N_2O were always the parameters having the highest *percent contribution* to infection rate prediction. This property indicates that the parameters correlated with greenhouse gases concentration are of high importance for prediction accuracy, which confirms the correlation between air pollution and infection rate highlighted by other studies (Section 2.1.4). The mixed model further confirmed this result because it gained the same performance as the CO^2 individual model to predict high risk zones (77.25%). However, the mixed model reported a much higher *percent contribution* of CO^2 (85.9%) than of CH_4 (0.4%) and N_2O (0.4%). This result indicates that CH_4 and N_2O are not adding a substantially more predictive information than CO^2. Overall, this analysis indicates that CO^2 is the correct choice to represent air pollution in the experiment.

3.3. Training and input data completeness

In order to evaluate if Italian provinces were a sufficient representative training set for the reported experiment, the all-parameter MaxEnt model was executed by incrementally adding more World areas to the training set. First, the geographical areas of large cities correctly predicted by the original model were added, i.e. Madrid, London, Istanbul, Buenos Aires. This operation did not change the model's risk prediction performance (77.25%), which indicates that Italian provinces are strong representation of the correctly detected World cities. As an additional step, World city areas that were wrongly predicted by the original model were incrementally introduced, i.e. São Paulo, Lima, Santiago de Chile, Guayaquil. This process produced a continuously

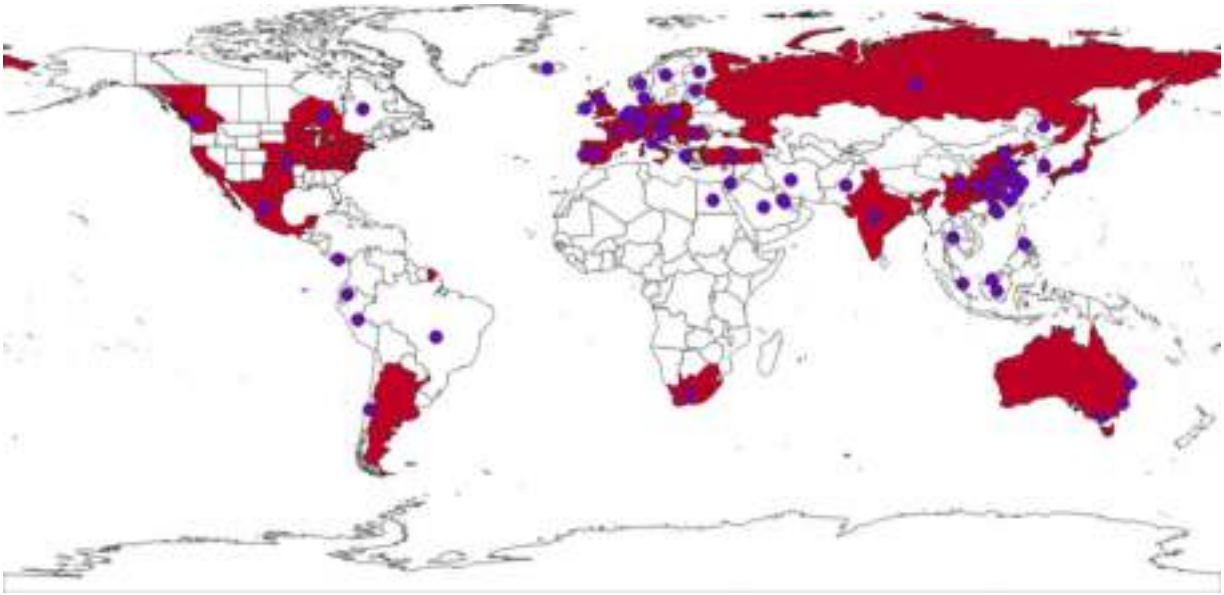

Fig. 3. Overlap between estimated high-infection-rate risk zones (coloured countries/regions) and actual reported high-infection-rate countries/regions (circles).

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decreasing AUC, also if CH_4 and N_2O were used instead of CO^2. When involving these World cities, one major effect on the parameter ranges was a change in the upper confidence limit, which increased for temperature (from 16.0 to 18.8 °C) and precipitation (from 0.45 to 0.6 10^{-4} $kg\ m^{-2}\ s^{-1}$) and the decreased for CO^2 (from 0.08 to 0.05 $g\ C\ m^{-2}\ day^{-1}$). The decreasing AUC, indicates that these ranges are not able to make the model cover all the areas of the training set. This result indicates that the used input parameters are insufficient to understand the infection rate increase in these areas, independent of the use of Italian provinces as the training set.

4. Discussion and conclusions

This paper has presented a methodology to estimate a geographical probability distribution of *high infection rate* for SARS-CoV-2, based on geophysical and human-related parameters. A *risk index* has been proposed based on this probability distribution, to identify global countries and regions that would mostly favour a high infection rate. A *good* concurrence with country-reported data and a moderate-high accuracy at predicting high-infection-rate countries/regions indicates that the model was able to identify real conditions of increased infection rate in many World areas. Generally, the model indicates a high infection rate in areas characterised by an annual moderate-high level of CO^2, moderate-low temperatures, and moderate precipitation. The most notable result is that, although the model was trained only with Italian cities, it assigns a high-infection-rate probability and a high-risk classification to most real World scenarios where a high infection rate has been actually reported. Also, the results indicate that climatic parameters such as air temperature and precipitation (or air humidity) play a critical role at defining locations that may be subject to a high infection rate. The model also indicates a temperature range which other studies have also correlated with the spread of COVID-19 (Sajadi et al., 2020). Additionally, estimated high-rates in moderate-precipitation regions might be related to reduced transmission in high-humidity zones (Wang et al., 2020). Carbon dioxide is the most influential parameter, which is correlated directly with pollution (which concurs with COVID-19 spread, Han et al. (2020)) and indirectly with population density. Correlation with population density could be one reason for the lower influence of this parameter on prediction performance. However, the fact that all parameters are necessary to achieve the optimal model performance indicates that they all contain complementary information. Thus, population density is not entirely covered by CO^2. Indeed, it affirms the complex system dynamics theory that if a population is vulnerable to a virus and its density exceeds a threshold, an epidemic will occur (Scheffer, 2009). In the case of SARS-CoV-2, the presented results indicate a likely scenario where, after this threshold, population density does not influence infection rate anymore. This observation is valid in Italy, where provinces with population densities distant of almost two orders of magnitude have reported similar infection rates for a long period (e.g. Lucca and Naples). As for elevation, the model indicates that this is not a discriminant feature, as also demonstrated by the variability in the altitudes of high-infection-rate Italian provinces. However, elevation brings some information to the model - probably related to drier weather conditions - because without this parameter the model's AUC decreases.

Currently, the complete set of parameters correlated with COVID-19 infection rate increase remains unknown. The reported results indicate that the used parameters are sufficient to predict the situation in Europe and in many World countries, however there are additional unknown factors to be investigated in the misidentified countries (e.g. Brazil, Ecuador, and Peru). The identification of all these factors is a broader question that goes beyond this paper and would require on-the-field data collection and a global-scale effort, also to make data available under FAIR principles.

The proposed Open Science-oriented methodology is quickly reusable on new infections and epidemics, for example, to predict the risk that a particular country will be subject to a high rate of cases of a new infection. Also, the results may be the basis of other models that may refine the resolution of the presented model and revise the parameters used. One fundamental step is to collect and prepare FAIR data correlated to infection rate as open-access standardised geospatial datasets. The D4Science e-Infrastructure can be used freely and openly to this aim. Moreover, the Maximum Entropy process was published as a free-to-use service (CNR, 2019) intended for global health-care systems and epidemic prevention organizations, and for possibly contributing to COVID-19 spread control.

Overall, the presented results clearly indicate and identify that the influence of geophysical, climatic, and human-related parameters on COVID-19 infection rate should be further investigated. As a future extension, the model will be enhanced by increasing the projection resolution to 0.1° on specific areas to produce regional-scale distributions. The corresponding cloud computing service will be used to (i) explore a more extensive set of parameters taken from open-access repositories, (ii) understand the importance of climatic factors with respect to human-related factors in COVID-19 infection rate, and (iii) detect seasonal trends.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at 10.1016/j.ecolmodel.2020.109187

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Investigation of the Importance of Climatic Factors in COVID-19 Worldwide Intensity

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Abstract: The transmission of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the severity of the related disease (COVID-19) are influenced by a large number of factors. This study aimed to investigate the correlation of COVID-19 case and death rates with possible causal climatological and sociodemographic factors for the March to May 2020 (first wave) period in a worldwide scale by statistically processing data for over one hundred countries. The weather parameters considered herein were air temperature, relative humidity, cumulative precipitation, and cloud cover, while sociodemographic factors included population density, median age, and government measures in response to the pandemic. The results of this study indicate that there is a statistically significant correlation between average atmospheric temperature and the COVID-19 case and death rates, with chi-square test *p*-values in the 0.001–0.02 range. Regarding sociodemographic factors, there is an even stronger dependence of the case and death rates on the population median age (p = 0.0006–0.0012). Multivariate linear regression analysis using Lasso and the forward stepwise approach revealed that the median age ranks first in importance among the examined variables, followed by the temperature and the delays in taking first governmental measures or issuing stay-at-home orders.

Keywords: COVID-19; weather; sociodemographic factors; response measures

1. Introduction

At the end of 2019, a new virus causing severe acute respiratory syndrome (SARS-CoV-2) was reported in Wuhan, China, and, due to its high human-to-human transmissibility [1], it quickly spread worldwide, resulting in the ongoing COVID-19 pandemic [2]. By the end of May 2020, which roughly signified the end of the first epidemic wave for most of the countries of the northern hemisphere, the total number of worldwide confirmed cases of COVID-19 was around six million, while the total worldwide deaths had reached 0.37 million [3], causing serious problems to the health systems of many countries.

By a simple examination of the pandemic data so far, one can easily notice the striking disparities (of orders of magnitude) in the reported confirmed case and death counts between countries (Figure 1). If certain socioeconomic indexes are considered alone, counterintuitive and irrational trends may be observed. For example, taking the Human Development Index (an index that includes the gross national income (GNI) per capita, the life expectancy, and the education level of each country) into account and comparing it with the total deaths per million of inhabitants (TDM) for the period of 3/2020–5/2020, it seems as if the countries of high development (and thus generally better health systems) are more susceptible to COVID-19 (Figure 2A). However, if we consider parameters directly associated with how aged is the population of a given country, e.g., the health index as defined by the United Nations Development Program (UNDP) or the median age (Figure 2B,C), it becomes obvious that the trend of Figure 2A can be explained, at least partly, by the fact that the populations of the more

developed countries have a comparatively larger proportion of aged persons that are, in turn, more susceptible to develop heavy illness due to the SARS-CoV-2.

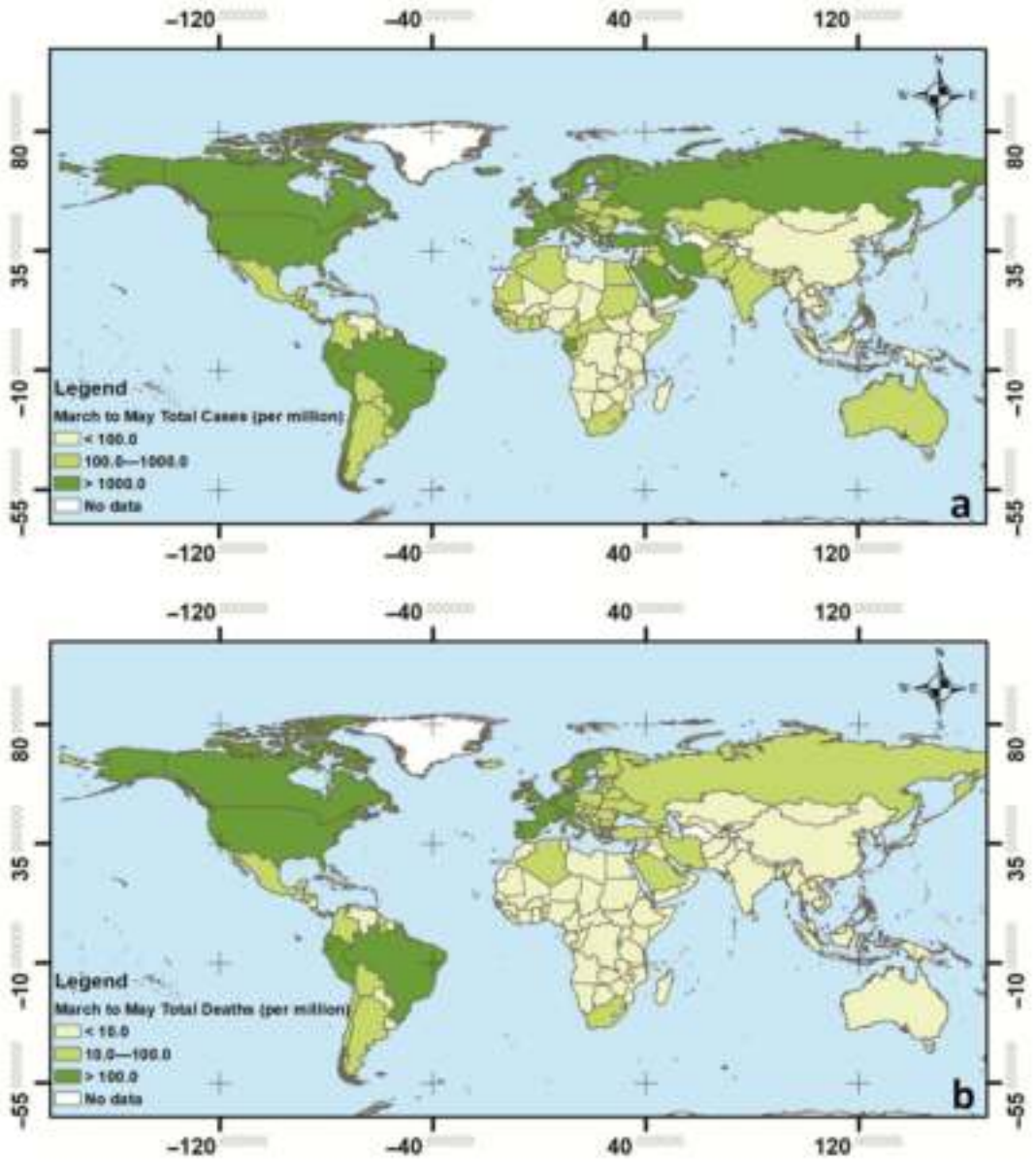

Figure 1. Worldwide distribution of (**a**) COVID-19 cases and (**b**) COVID-19-related deaths for the period of 1/3/2020–31/5/2020.

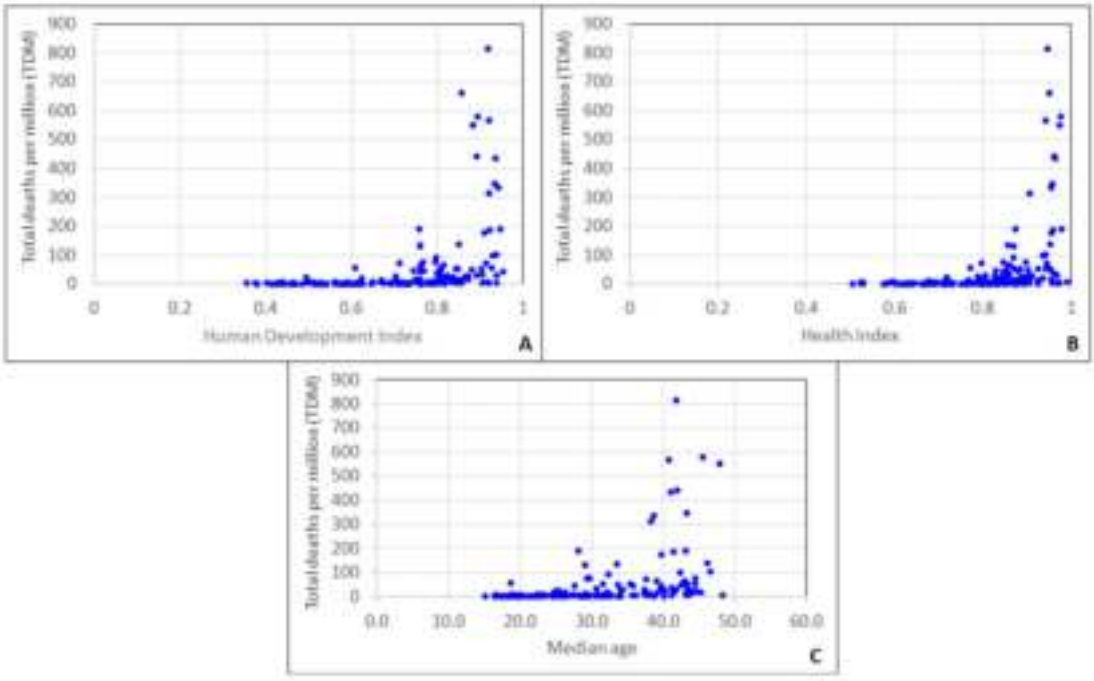

Figure 2. Variation of the total deaths per million for the period of 1/3/2020–31/5/2020 with (**A**) Human Development Index, (**B**) health index, and (**C**) median age (data for 167 countries).

The vast ranges of case and death rates observed in Figure 1 could also be partially attributed to differences in the testing rates arising from the inherent difficulties faced when dealing with a new highly transmissible pathogen (e.g., access to adequate numbers of test kits and the availability of qualified laboratories). Nonetheless, large disparities in case and death rates are observed even among countries with similar economic prosperity, age structure and social characteristics. For example, in eurozone countries (the governments of which responded alike to the pandemic), the number of deaths per million of inhabitants in the 3/2020–5/2020 period ranged from 5 to over 800, i.e., two orders of magnitude difference. Thus, it becomes evident that the pathogen's spread and impact are strongly affected by additional factors. These can be weather conditions, the promptness and mix of governmental response measures, air pollution, the volume of external travel, the frequency of use of public transportation, or other habitual and cultural/behavioral factors.

The effect of climatic factors on influenza epidemics has long being recognized [4–9]. More recently, after the onset of the new pandemic, a number of studies have been carried out to investigate the possible effect of weather on the spread of COVID-19. Some of these studies have focused on specific regions and countries, such as 122 cities in China [10], Wuhan, China [11], Mainland China [12], Jakarta, Indonesia [13], India [14,15], Iran [16], Brazil [17], Europe and United States [18], and Russia [19], while others have examined the effect of weather conditions on the pandemic at a global scale [20–41]. Smit et al. [42], who presented a comprehensive critical review of the relevant literature published in the first half of 2020, concluded that it is important for studies to include the effects of socio-economic factors and non-pharmaceutical interventions (such as government response measures) in their analysis.

This paper attempts to shed light on the degree of influence of climatic factors, namely temperature, relative humidity, precipitation, and cloud cover, on the intensity of the COVID-19 epidemic by examining the data of reported cases and deaths on a worldwide scale for the period of 3/2020–5/2020 (first wave) while simultaneously considering other important factors (social, economic, government response) that are expected to have a strong effect. First, one-to-one correlations are examined between the total numbers of deaths or cases (epidemic effects) and probable causal variables. Then, interference between causal variables is taken into account in order to reveal the actual degree of influence of the climatic factors in relation to sociodemographic ones and those related to government response.

The results of this study, which help understand the relationship between the spatial distribution of the climatic conditions and the severity of COVID-19 on a worldwide scale, could be useful to decision-making authorities for the assessment of the pandemic risk and the management of the response measures.

2. Data Collection

The epidemiological data of total cases and total deaths due to COVID-19 in each country were taken from European Commission (EC) [43], Beltekian et al. [44], and Hale et al. [45] for the period between 1/3/2020 and 31/5/2020. These were used to calculate case and death rates as the total cases per million of inhabitants (TCM) and the total deaths per million of inhabitants (TDM) due to COVID-19 using the following formulas:

$$\text{TCM} = \frac{\text{Total number of cases on } 31/5/2020 \ - \text{Total number of cases on } 1/3/2020}{\text{Country population} \times 10^{-6}} \quad (1)$$

$$\text{TDM} = \frac{\text{Total number of deaths on } 31/5/2020 \ - \text{Total number of deaths on } 1/3/2020}{\text{Country population} \times 10^{-6}} \quad (2)$$

Furthermore, data about the median age and the government response measures taken in each country to reduce the spread of the pandemic—namely the overall stringency index of the government measures and the dates of officially recorded first cases, the imposition of first measures, and the imposition of 'stay-at-home' order—were gathered from Beltekian et al. [44] and Hale et al. [45], while data on the Human Development Index (HDI), population, etc., were collected from the Global Data Lab (GDL) database originating from the United Nation Development Program and referring to the year 2018 [46].

Weather data, such as the monthly average atmospheric temperature (°C), monthly average relative humidity (%), and cumulative precipitation (mm), were collected from the Copernicus Program database [47] as raster files. These variables were estimated from climate reanalysis ERA-Interim and ERA5, depending on the source. The fraction of cloud cover, which is the proportion of a grid box covered by cloud (liquid or ice) and varies between 0 and 1, was taken from the Copernicus Program for a pressure level of 1000 hpa [48]. Then, the spatial analysis tool of the ArcGIS software (by ESRI) was employed to derive the spatial average of these variables across the entire territory of each country. After spatial averaging, the temporal average values were computed for the temperature, relative humidity, and cloud cover for the March 2020 to May 2020 period. Figure 3 presents maps showing the distribution of country average values of temperature, humidity, and cumulative precipitation.

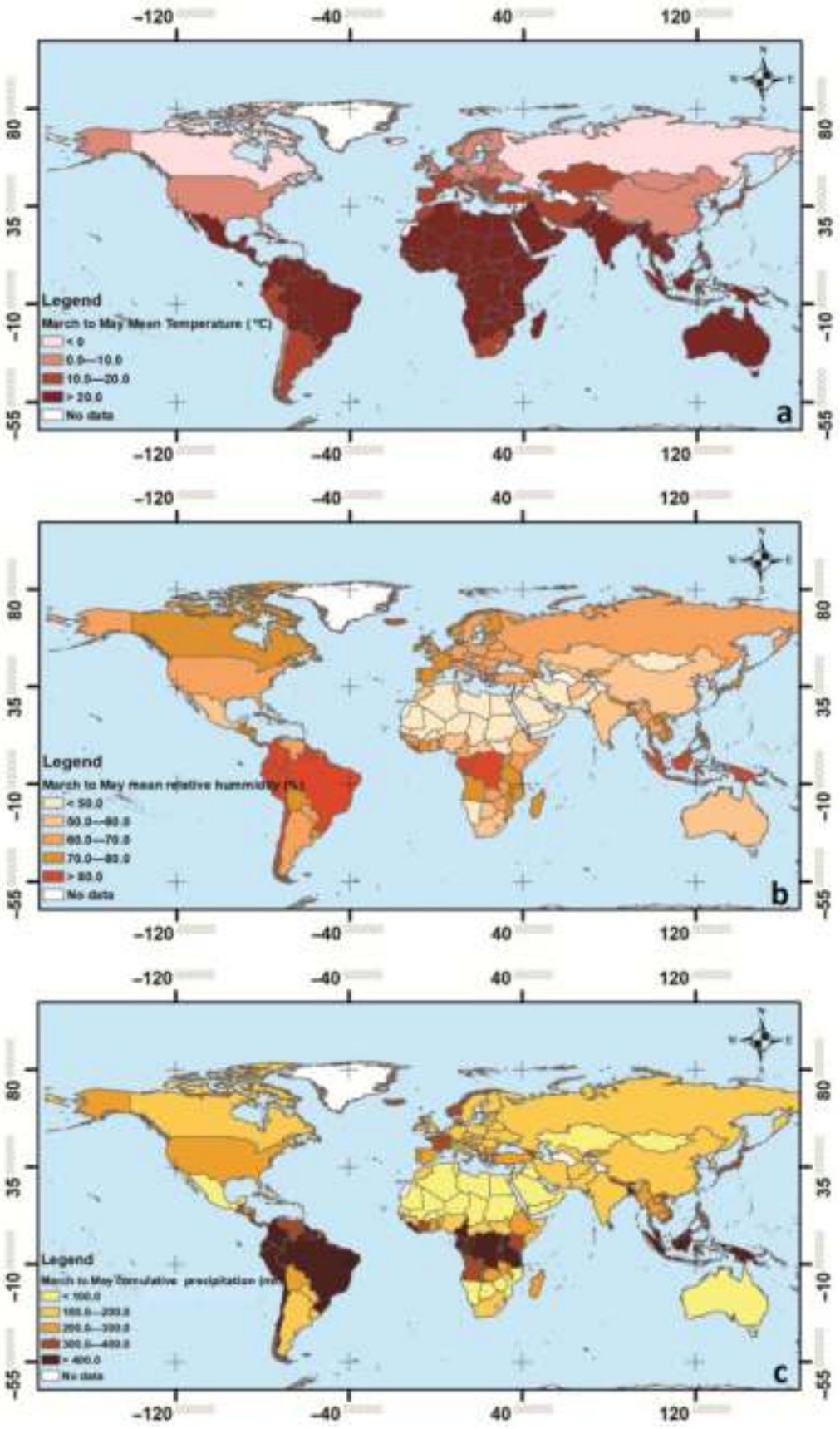

Figure 3. Worldwide distribution of (**a**) mean temperature, (**b**) mean relative humidity, and (**c**) cumulative precipitation for the period of 1/3/2020–31/5/2020.

3. Data Analysis

The collected data were divided in three groups of variables (Table 1). These were (i) the causal variables, i.e., the factors for which it was reasonable to assume that they may have an effect on the development of the pandemic; (ii) the effect variables, namely the total deaths and total cases per million of inhabitants; and (iii) the filtering variables, which were used to split and isolate datasets in order to minimize potential bias.

Table 1. Variables considered in the statistical analysis.

Effect Variables	Causal Variables	Filtering Variables
	Climatic	
	Temperature (°C)	
	Relative humidity (%)	
	Cumulative precipitation (mm)	
	Cloud cover	
Total Deaths per Million (TDM)	*Sociodemographic*	Human Development Index (HDI)
	Population density (persons/km^2)	
	Median age (years)	
Total Cases per Million (TCM)	Percentage of Population over 65 (%)	Median Age (years)
	Government response	
	Stringency IndexDelay between first case and first measures (days)	
	Delay between first case and "stay at home" order (days)	

Regarding the filtering variables, due to many differentiations among countries arising from the difficulties faced during the early stage (first wave) of the pandemic that could affect the reported epidemiological data and, thus, the TCM and the TDM (e.g., the availability of test kits and equipment, the extent and intensity of testing campaigns, and consistency in reporting of cases and deaths), it was decided to not include in the analysis the least developed countries. For this purpose, the countries were sorted with respect to their Human Development Index (HDI), and those with an HDI < 0.7 were excluded from further statistical processing. The cut-off value of 0.7 coincides with the divider considered by the United Nations Development Program (UNDP) between the "high human development" and "medium human development" classes. This choice left the dataset with an adequately large number of countries (101 from the 169 for which data were available) and still contained the full spectrum of TDM values, including all countries with TDM > 100 (Figure 1a). Given the strong dependence of the TDM on the population age (Figure 1b,c), a second group was created by isolating the countries with a median age of 35 years and larger. The second group, which numbered 55 countries, turned out to be a subgroup of the first one, i.e., all countries in it also had an HDI > 0.7. It should be stressed that both groups covered the full range of climate types, from tropical to polar.

The causal variables included climatic and sociodemographic factors, as well as factors related to the government response to the pandemic. The climatic factors examined herein, namely the temperature, relative humidity, precipitation, and cloud cover, are generally thought to have a role in influenza epidemics, a connection investigated in previous studies mentioned in the introduction. It has been observed that cold weather aggravates the spread of respiratory infections [5,49–51], while clouds block solar UV light, which decreases the survivability of viruses in the outdoor environment [52,53]. It has long been debated whether absolute humidity or relative humidity should be considered as a proper driver of the influenza seasonality [6,54,55]. Marr et al. [55] pointed out that, nowadays, it is possible to explain the mechanism of how relative humidity may influence the transmission of the influenza virus (i.e., via its role in aerosol droplet size, evaporation, and salt concentration), but a plausible mechanism explaining how absolute humidity can directly affect droplet size has not yet been established.

Regarding social structural characteristics, given the fact that COVID-19 is associated with very high mortality among the elderly, we considered the median age and the percentage of the population that is above 65 years old to quantify how aged a society is. Moreover, high population density is also thought to be a risk factor [56]. It is reasonable to assume that delays in government response are affecting the outcome of the epidemic [57,58]. We considered two types of delays: the time difference between the officially recorded first case and (i) the imposition of a "stay-at-home" order and (ii) taking the "first measures." According to Hale et al. [45], a stay-at-home order is defined as any of the following: (a) the recommendation of not leaving the house; (b) the requirement of not leaving the house except for work, daily exercise, grocery shopping, and 'essential' trips; (c) the requirement of not leaving the house but with the exceptions being much stricter (e.g., allowed to leave the house only once a week or only one person can leave at a time). The first measures varied in kind from country to country, although in most cases involved either public information/awareness campaigns, international travel restrictions, or the cancelling of public events. Finally, the Stringency Index is a composite measure that is based on nine response indicators, such as school closures, workplace closures, travel restrictions, and stay-at-home orders [44]. This index was averaged for a longer period (1/1/2020–31/5/2020) than the climatic factors because it was considered that measures taken even before the detection of first cases, such as banning travel from countries that exhibited active cases, reduced the progress of the pandemic during the 1/3/2020–31/5/2020 period.

3.1. Climatic Factors

Figure 4 plots the frequency of TDM classes (low: <10; moderate: 10–100; high: >100) and TCM classes (low: <100; moderate: 100–1000; high: >1000) for three groups of average atmospheric temperature T. The ranges of values were selected in such a way that the number of countries in each group was similar. A strong dependence of both the TDM and the TCM on temperature is apparent, as the percentage of countries with high death rates (red group) decreases as T increases, while the percentage of countries with low death rates (green group) increases with T (Figure 4a,c). Similar trends are observed for TCM (Figure 4b,d). The vast majority of countries with $T > 20$ °C experienced the pandemic to a substantially lesser degree. The p-values from χ^2 tests are also reported in the figures, with the null hypothesis being that the intensity of the epidemic (quantified by the TDM and the TCM) is independent from temperature. In all cases, the p-value is clearly less than 0.05 (the null hypothesis is rejected), suggesting a statistically significant correlation of the intensity of the epidemic with the temperature, especially in the case of the death rate. A small rise in p-values is noted when isolating the group of countries with a population median age of >35 years.

Based on Figure 5, it could be argued that there is a correlation of the TDM (and to a much lesser extent TCM) with the average relative humidity (RH). Nonetheless, the χ^2 test p-values are higher in Figure 5 than in the case of temperature, suggesting a weaker correlation between relative humidity and intensity of the epidemic. From Figure 5a,c, it appears that the percentage of countries with a TDM > 100 (red group) is elevated when RH is larger than 60%. However, the group of countries with a TDM below 10 (green group) does not show a clear decreasing course with increasing RH, as their frequency is enhanced for $RH > 70\%$. Similar observations can also be made in Figure 5b,d with respect to TCM. This can be partially attributed to the fact that many countries with an $RH > 70\%$ are located close to the equator or in the southern hemisphere, such as countries in Southeast Asia (e.g., Brunei, Indonesia, Malaysia, and Philippines) or around the Caribbean (e.g., Belize, Costa Rica, Cuba, and Jamaica), as well as New Zealand and Uruguay, and consequently had high temperatures in the examined time period. This observation suggests that RH does not influence the pandemic above a certain threshold of temperature. Most importantly, however, the epidemic severity appears to be strongly intensified if RH is in the 60–80% range provided that T is less than 15 °C, as can be better seen in Figure 6.

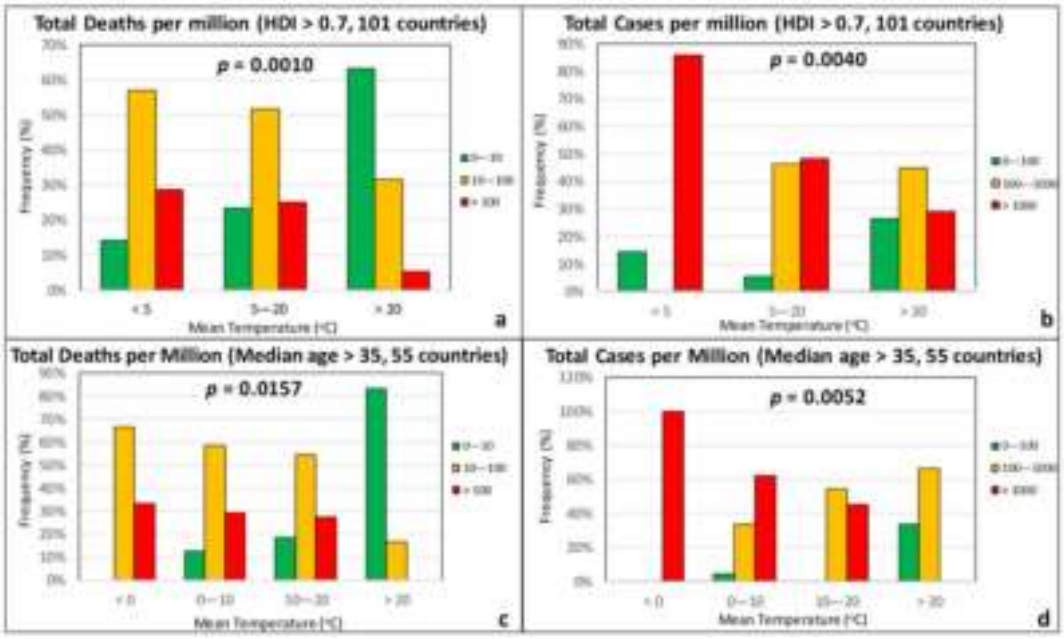

Figure 4. Frequency of total deaths per million (green: low, 0–10; orange: moderate, 10–100; red: high, >100) and total cases per million (green: low, 0–100; orange: moderate, 100–1000; red: high, >1000) as a function of the average temperature for countries with an HDI over 0.7 (**a**,**b**) and a median age over 35 years (**c**,**d**).

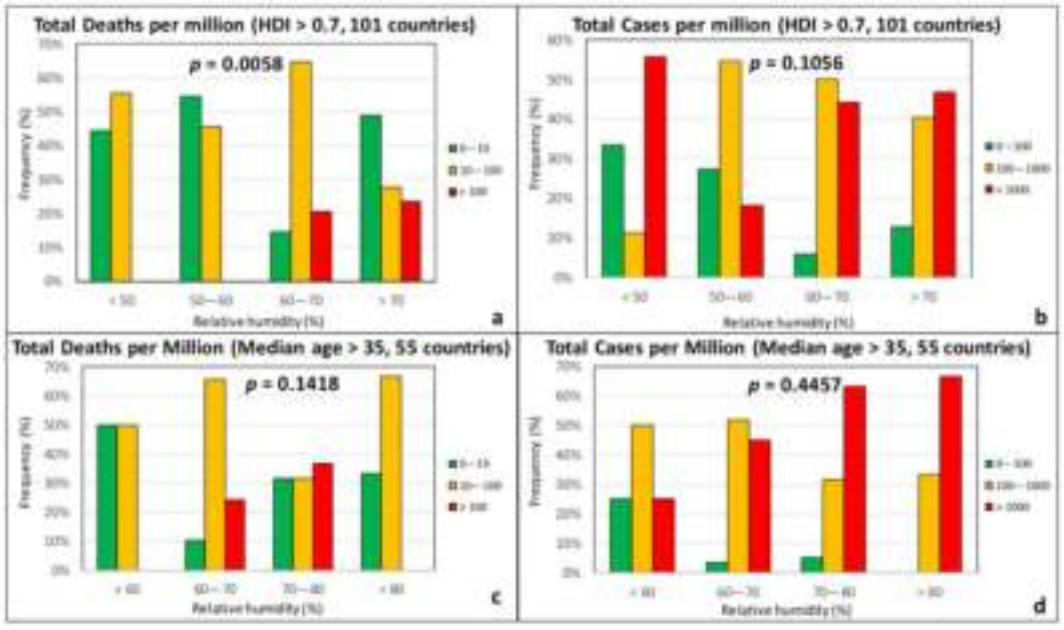

Figure 5. Frequency of total deaths per million (green: low, 0–10; orange: moderate, 10–100; red: high, >100) and total cases per million (green: low, 0–100; orange: moderate, 100–1000; red: high, >1000) as a function of the relative humidity for countries with an HDI over 0.7 (**a**,**b**) and a median age over 35 years (**c**,**d**).

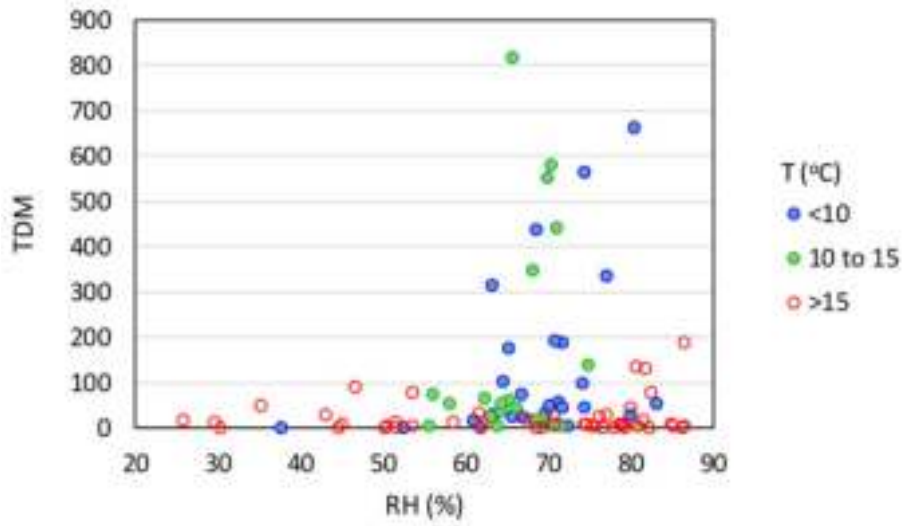

Figure 6. Total deaths per million as a function of the relative humidity and temperature (HDI > 0.7).

It is worth mentioning that studies on influenza [54,59,60] have shown that its transmissivity does not monotonically depend on *RH* if *T* lies between 10 and 25 °C, but it exhibits a local decrease ("valley") inside the range of 40–60% (in which case the virus particles become unstable) and a local peak for *RH* between 60% and 75%. For higher values of *RH*, the transmissivity decreases sharply, regardless of the temperature, as aerosol droplets take on water and increase in size, thus settling more quickly due to gravity [59].

Relative humidity, precipitation, and cloud coverage are climatic factors that are naturally related to each other. However, unlike *RH*, cumulative precipitation and cloud cover were found to correlate rather poorly with both the TDM and the TCM (Figures 7 and 8). The *p*-values in all cases are high, indicating that there is no statistically significant correlation.

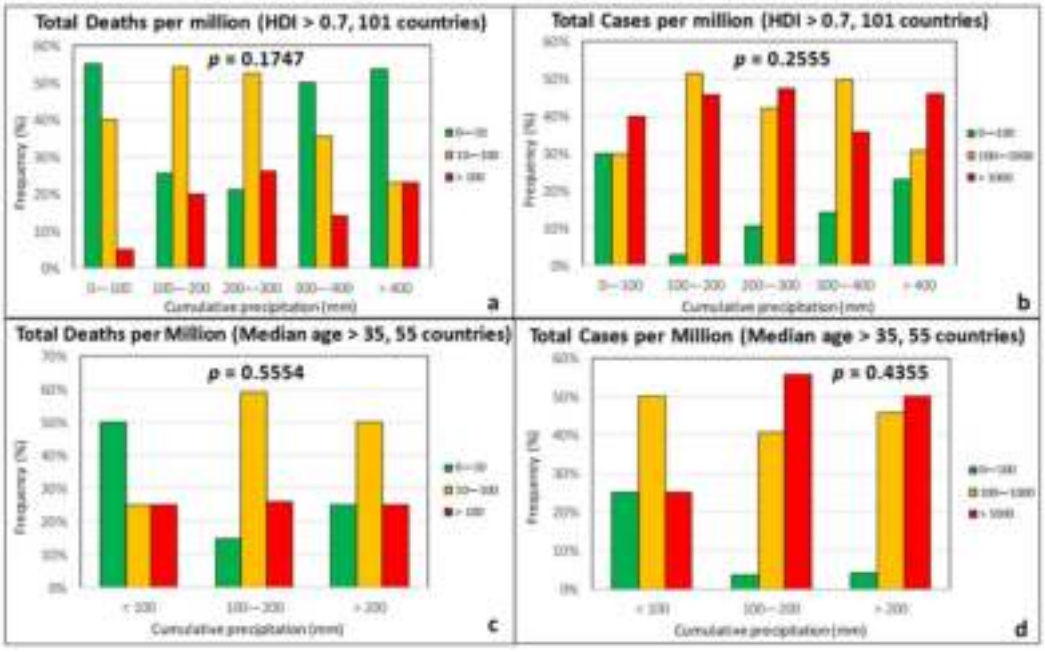

Figure 7. Frequency of total deaths per million (green: low, 0–10; orange: moderate, 10–100; red: high, >100) and total cases per million (green: low, 0–100; orange: moderate, 100–1000; red: high, >1000) as a function of the cumulative precipitation for countries with an HDI over 0.7 (**a**,**b**) and a median age over 35 years (**c**,**d**).

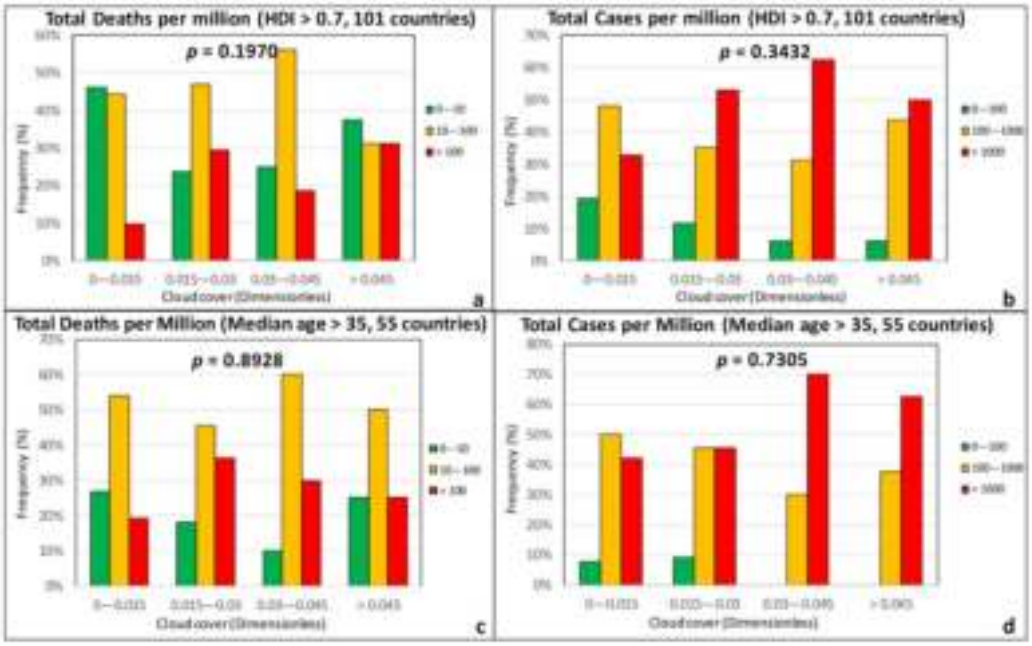

Figure 8. Frequency of total deaths per million (green: low, 0–10; orange: moderate, 10–100; red: high, >100) and total cases per million (green: low, 0–100; orange: moderate, 100–1000; red: high, >1000) as a function of the cloud cover for countries with an HDI over 0.7 (**a**,**b**) and a median age over 35 years (**c**,**d**).

3.2. Sociodemographic Factors

The contact numbers and transmission chains are larger in densely populated areas, and, thus, it would be reasonable to expect that countries with large population density would be more severely hit by the pandemic. Based on Figure 9, no specific trend can be discerned with respect to population density. This is also attested by the large *p*-values, which are in the 0.15–0.4 range. This admittedly counterintuitive observation is most likely caused by the treatment of data at a countrywide level, i.e., the population density treated herein was the total population of a country divided by its entire territorial area. For example, there are certain countries with a high TDM > 100 but with a population density below 50 inhabitants/km^2 (e.g., Brazil, Canada, and Peru). Though these countries occupy vast areas, large parts of the population are concentrated in densely populated urban centers. A more detailed spatial analysis at first or second level administrative divisions may more clearly demonstrate and accentuate the role of population density. Nonetheless, the recent epidemiologic study for COVID-19 by Hamidi et al. [61], which was done at the level of US counties, also showed weak to no dependence of the epidemic severity on population density.

Figure 10 indicates that there is a strong correlation between both the TDM and the TCM with the median age of the population, with the *p*-values being well-below 0.05. This finding is well-expected, since the rate of COVID-19 cases is known to be comparatively low among young persons [62]. Given that the death rate, in particular, increases sharply with patient age, Figure 11 shows plots of the TDM and TCM frequencies as a function of the percentage of the population aged 65 years and older. In this case, the correlation with the TDM is even stronger than in Figure 10a, while the correlation with the TCM is weaker but still statistically significant.

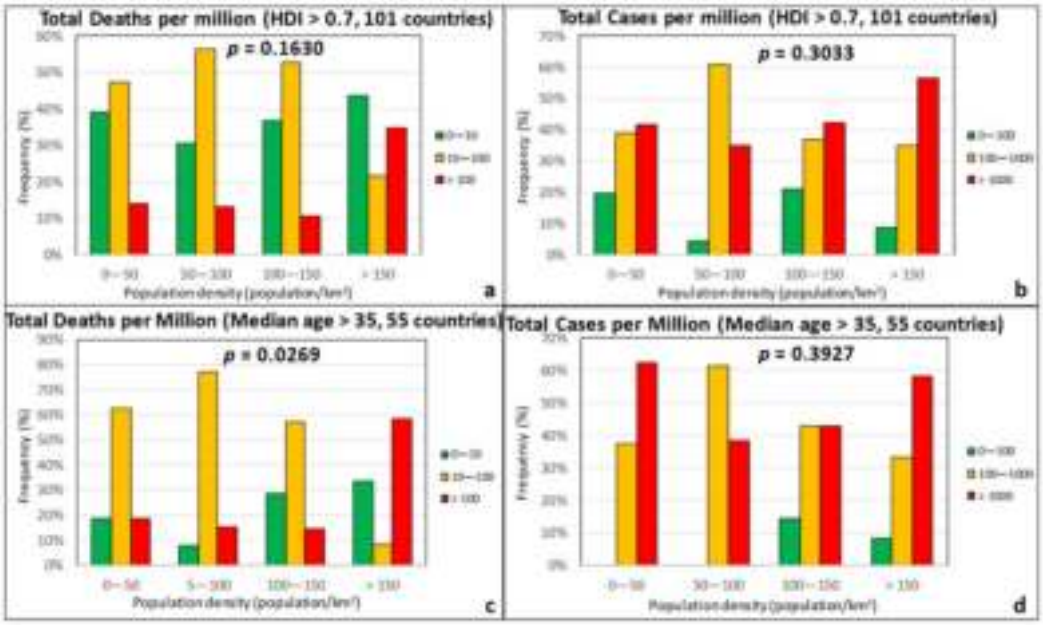

Figure 9. Frequency of total deaths per million (green: low, 0–10; orange: moderate, 10–100; red: high, >100) and total cases per million (green: low, 0–100; orange: moderate, 100–1000; red: high, >1000) as a function of the population density for countries with an HDI over 0.7 (**a**,**b**) and a median age over 35 years (**c**,**d**).

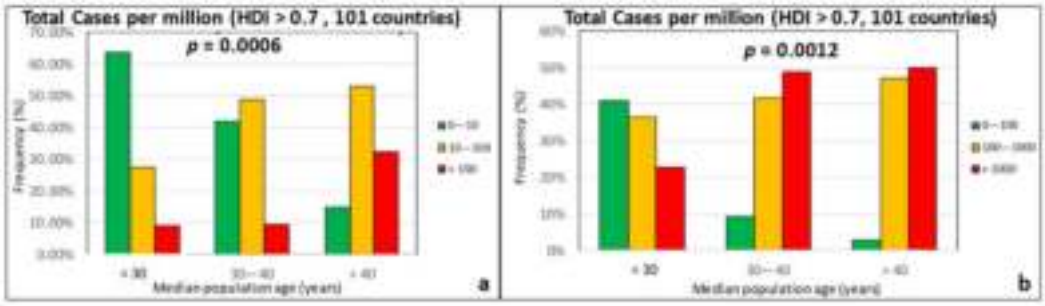

Figure 10. Frequency of (**a**) total deaths per million (green: low, 0–10; orange: moderate, 10–100; red: high, >100) and (**b**) total cases per million (green: low, 0–100; orange: moderate, 100–1000; red: high, >1000) as a function of the median age for countries with an HDI over 0.7.

Thus far, the TDM and the TCM have shown strong correlations with the average temperature and median age, with similar χ^2 test p-values. However, this does not necessarily mean that they are of similar significance. This is because of the correlation between these two causal variables. The first wave of COVID-19 unfolded during a period that was late winter and spring for the countries in the temperate zone of the northern hemisphere. Most of these countries happen also to be the most aged, while countries closer to the equator and most of the countries in the southern hemisphere have a relatively small median age. This fact is evident in Figure 12a, which plots the TDM as a function of the median age for three groups of countries separated based on the average temperature T. It can be seen that the majority of countries with $T < 15$ °C, which happen to be those most affected by COVID-19 (TDM > 100), have a median age larger than 35 years, while the opposite is true for the countries with T > 15 °C, most of which are located in South America, Africa, Middle East, and Southeast Asia. Similarly, most of the countries with average relative humidity in the 60–80% range have a median age larger than 35 years (Figure 12b). The interplay between the causal factors is addressed in Section 4, where their relative importance is examined using regression.

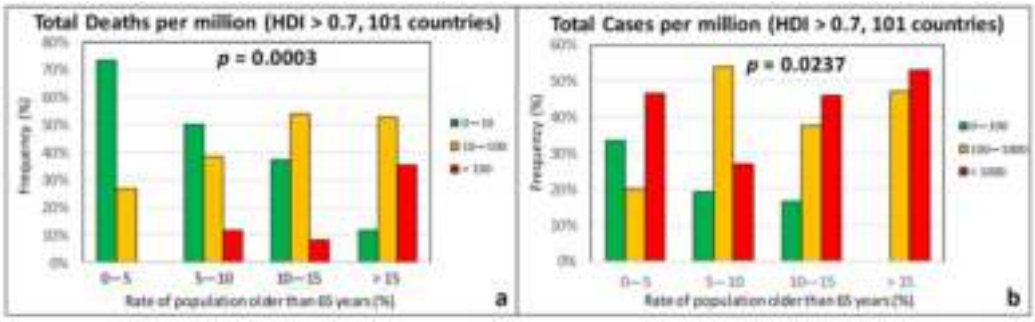

Figure 11. Frequency of (**a**) total deaths per million (green: low, 0–10; orange: moderate, 10–100; red: high, >100) and (**b**) total cases per million (green: low, 0–100; orange: moderate, 100–1000; red: high, >1000) as a function of the percentage of population with an age over 65 years for countries with an HDI over 0.7.

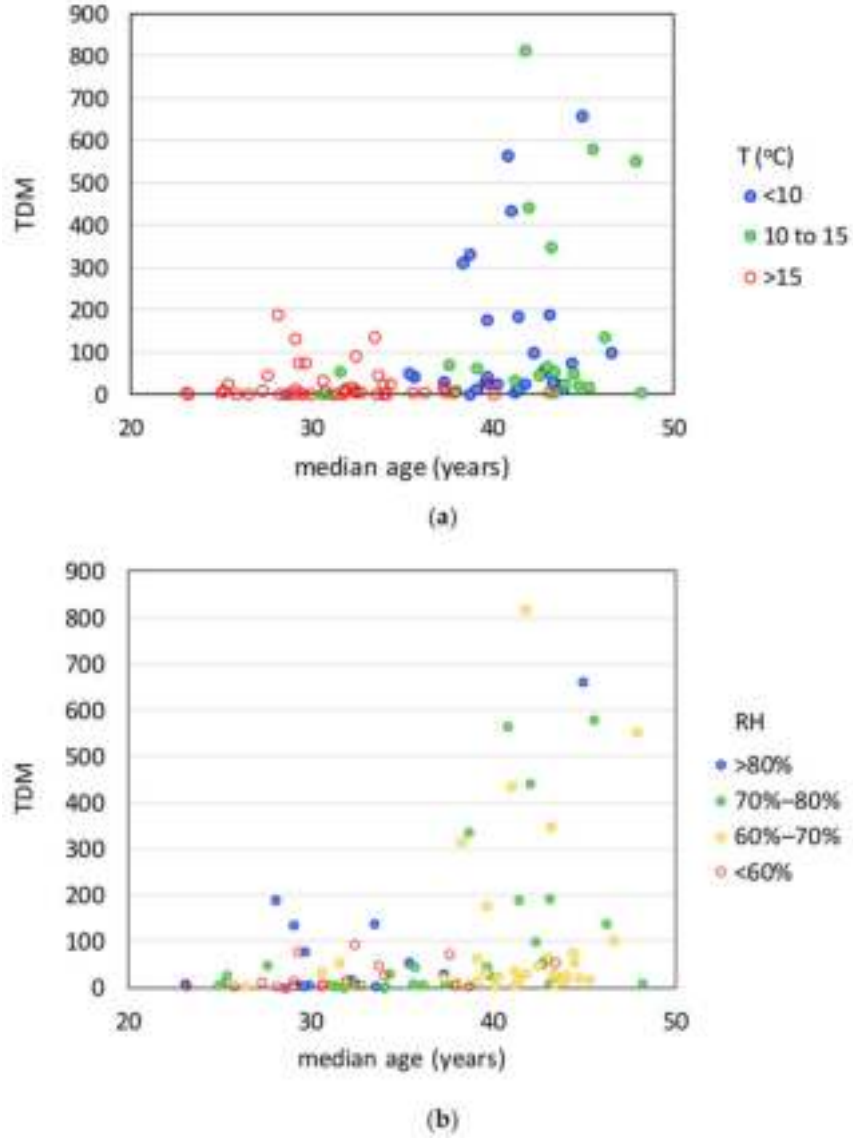

Figure 12. Total deaths per million as function of the population median age for different ranges of (**a**) temperature and (**b**) relative humidity (HDI > 0.7).

3.3. Government Response Measures

When considering the Stringency Index (SI) of the government response measures, as defined by Beltekian et al. [44], the *p*-values were found to be very high, indicating a weak correlation (Figure 13). On the contrary, the promptness of the governmental response seems to be instrumental in the containment of the epidemic. Based on Figure 14, countries that were proactive and responded by taking preventive measures one or two months before the officially recorded first case in the country ("negative" delay) experienced the first wave of COVID-19 less severely than countries that started taking the first measures after the detection of the first case.

When we isolated the countries with a median age >35 years (Figure 14b,c), the data suggested that the main role of the first governmental measures is to prevent a country from shifting from the group of moderate TDM and TCM values (orange) to the group with high values (red), while the frequency of countries that experienced the pandemic mildly is practically unaffected by the time difference between first measures and first case. Finally, according to Figure 15, the benefits of taking preventive measures early are rather independent from temperature, as a rising trend in the TDM with increasing time difference between the first measures and first case is observed in all temperature groups, especially those with $T < 15$ °C.

As seen in Figure 16, the frequency of countries that experienced the pandemic severely (TDM > 100 and TCM > 1000) increases steadily with increasing time difference between the official record of first case and the imposition of stay-at-home. With χ^2 test *p*-values generally close or well-below 0.05, the delay in issuing stay-at-home order is judged as statistically significant in limiting the intensity of the epidemic. Moreover, with only very few exceptions, countries that did not impose stay-at-home fall in the groups of moderate (orange) and high (red) death and case rates. On the other hand, the frequency of countries with low death and case rates (green group) is practically unaffected by a delay in imposing stay-at-home, even of the order of two months. This may suggest that stay-at-home is mostly effective in preventing the escalation of the impact from moderate (orange) to high (red) in countries that are more susceptible to the epidemic due to other factors.

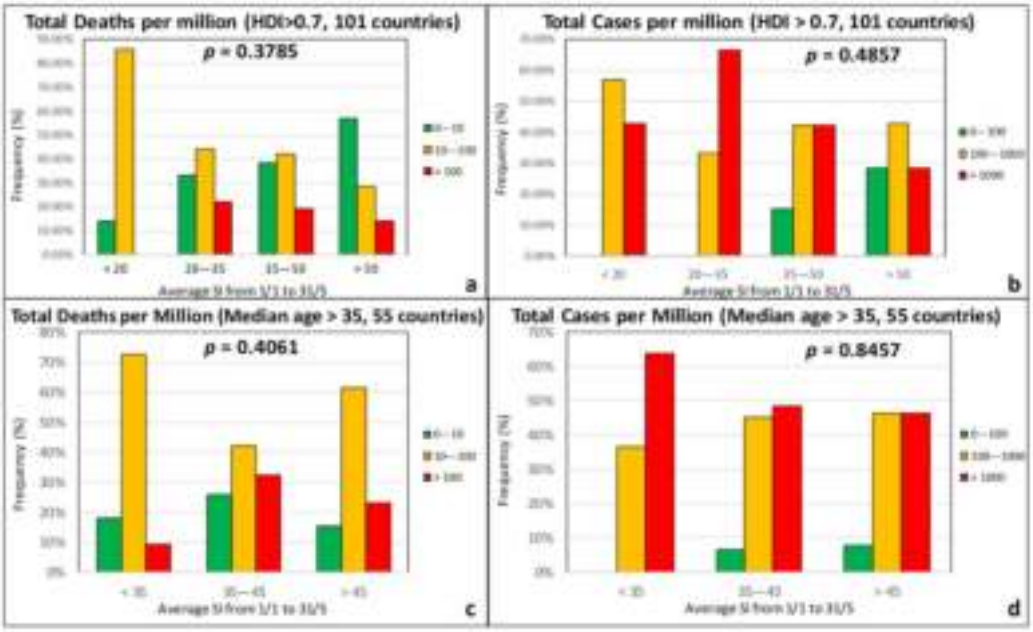

Figure 13. Frequency of total deaths per million (green: low, 0–10; orange: moderate, 10–100; red: high, >100) and total cases per million (green: low, 0–100; orange: moderate, 100–1000; red: high, >1000) as a function of the average Stringency Index for countries with an HDI over 0.7 (**a**,**b**) and a median age over 35 years (**c**,**d**).

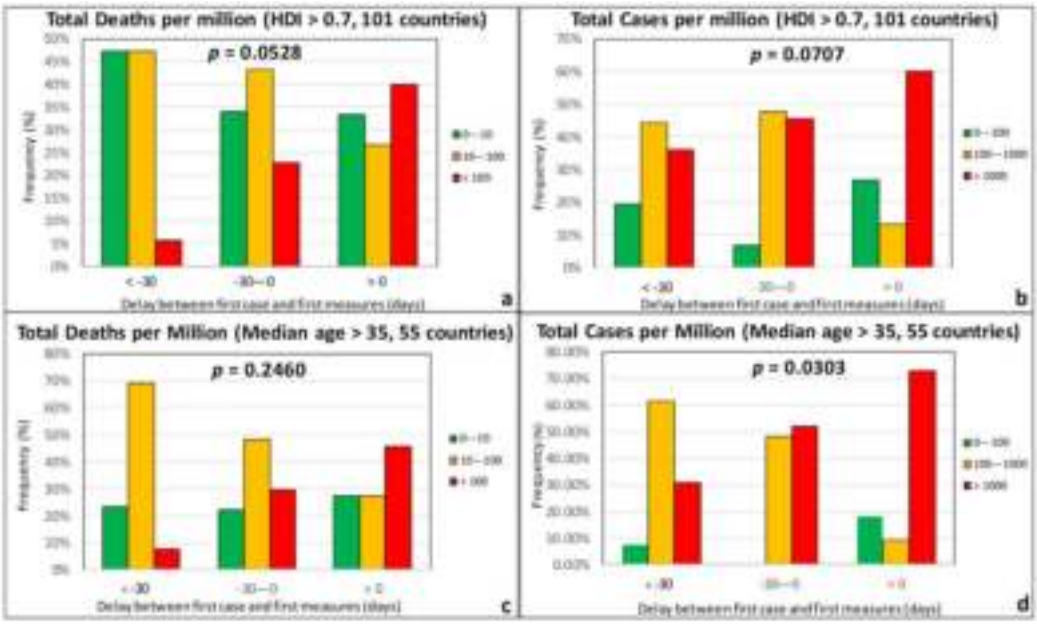

Figure 14. Frequency of total deaths per million (green: low, 0–10; orange: moderate, 10–100; red: high, >100) and total cases per million (green: low, 0–100; orange: moderate, 100–1000; red: high, >1000) as a function of the time difference between first case and first measures for countries with an HDI over 0.7 (**a**,**b**) and a median age over 35 years (**c**,**d**).

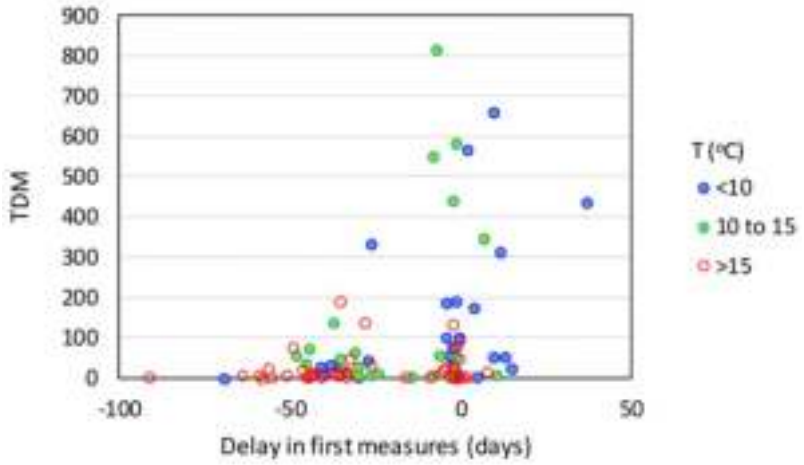

Figure 15. Total deaths per million as function of the time difference between the officially recorded first case and the first government measures for different temperature groups (HDI > 0.7).

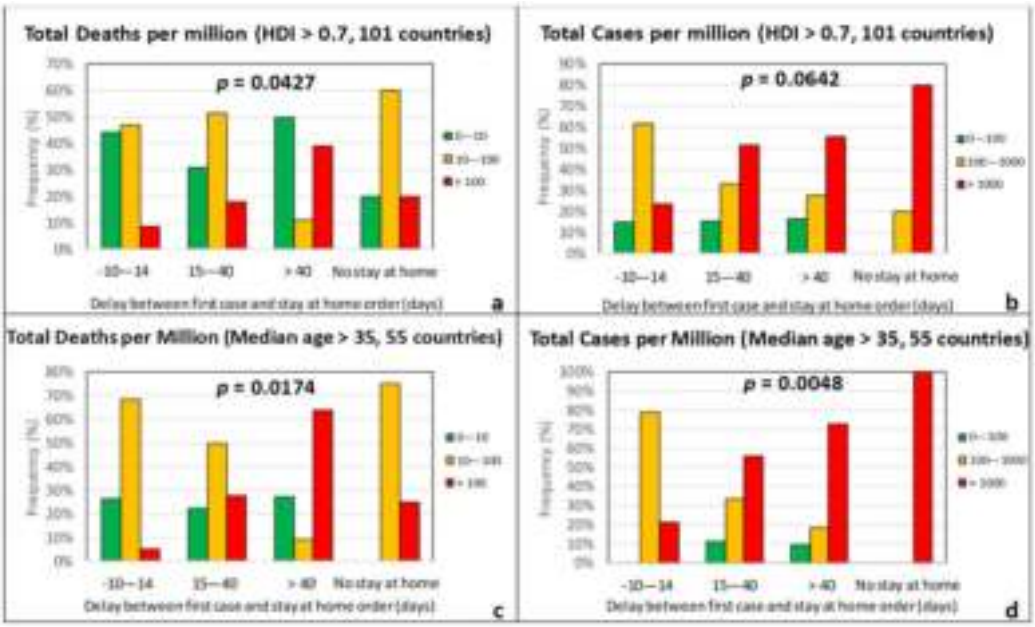

Figure 16. Frequency of total deaths per million (green: low, 0–10; orange: moderate, 10–100; red: high, >100) and total cases per million (green: low, 0–100; orange: moderate, 100–1000; red: high, >1000) as a function of the time difference between first case and the imposition of "stay-at-home" measure for countries with an HDI over 0.7 (**a**,**b**) and a median age over 35 years (**c**,**d**).

4. Multilinear Regression

4.1. Methodology

In the previous section, the epidemic effects were examined by considering each time a single causal variable, while the issue of possible interplay between certain causal variables was raised. In this section, we fit a linear equation combining all or groups of the causal variables, namely temperature, relative humidity, precipitation, cloud cover, population density, median age, government measures stringency index, delay in imposing first measures, and delay in imposing stay-at-home order. The percentage of population above 65 years old was not included in the set of variables since it exhibited a very strong correlation ($R^2 = 0.83$) with the median age. The dependent variable was set to be the TDM given that it generally exhibited the strongest correlations with the causal variables, as shown in the previous section, and is less prone to bias caused by the testing numbers. Each causal variable X_k enters the linear equation in the normalized form of $(X_k - X_{k,\min})/(X_{k,\max} - X_{k,\min})$, where $X_{k,\min}$ and $X_{k,\max}$ are the minimum and maximum values of the variable in the dataset. With this normalization, all independent variables of the equation vary from 0 to 1. Hence, the linear equation to be fitted takes the following form:

$$\begin{aligned} \mathrm{TDM} = C_0 + C_1 \frac{T - T_{\min}}{T_{\max} - T_{\min}} + C_2 \frac{RH - RH_{\min}}{RH_{\max} - RH_{\min}} + C_3 \frac{PR - PR_{\min}}{PR_{\max} - PR_{\min}} + C_4 \frac{CL - CL_{\min}}{CL_{\max} - CL_{\min}} + \\ + C_5 \frac{PD - PD_{\min}}{PD_{\max} - PD_{\min}} + C_6 \frac{MA - MA_{\min}}{MA_{\max} - MA_{\min}} + C_7 \frac{SI - SI_{\min}}{SI_{\max} - SI_{\min}} + C_8 \frac{FM - FM_{\min}}{FM_{\max} - FM_{\min}} + C_9 \frac{SH - SH_{\min}}{SH_{\max} - SH_{\min}} \end{aligned} \quad (3)$$

where T is the average temperature (°C), RH is the average relative humidity (%), PR is the cumulative precipitation (mm), CL is the average cloud cover, PD is the population density (persons/km^2), MA is the population median age, SI is the average stringency index, FM is the delay between first case and imposition of first measures (days), and SH is the delay between first case and stay-at-home order (days). To include the countries that did not impose stay-at-home in the regression analysis, their SH was calculated as the time difference between the officially recorded first case and the end of the investigated time period, i.e., 31/5/2020.

It must be stressed here that the purpose of the equation fitting was not to establish a predictive model but to discern the relative influence of the causal variables and rank them with respect to their importance. This is achieved herein using two conceptually different approaches: (i) the forward stepwise regression procedure and (ii) Lasso regression (along with its variation, the elastic net regression). The forward stepwise regression consists of performing consecutive multivariate linear regression calculations, starting with a single causal variable and adding in each step one more variable until the full set of n selected causal variables is exhausted [63,64]. With each step, the sum of squared errors (SSE) decreases. A measure of the importance of a variable k is the reduction increment in SSE induced by its inclusion in the equation (ΔSSE_k). Because ΔSSE_k depends on the order with which the variables are added to the linear model during the stepwise procedure, calculations are performed for all possible permutations of the causal variables (numbering $n!$ in total) and the average ΔSSE_k is calculated and subsequently used to rank the importance of each variable k. Moreover, it can be proven that, by normalizing ΔSSE_k with the total sum of squares SST, one can obtain the increase in the coefficient of determination R^2 caused by the inclusion of variable k in the equation ($\Delta {R^2}_k$). To perform the calculations, the above procedure was scripted in MATLAB.

Lasso regression [65] introduces in the objective function a penalty term which is the sum of the absolute values of the linear equation coefficients C_k (k = 1,2, … , n) times a user specified multiplier λ (i.e., $\lambda\Sigma|C_k|$). The elastic net regression [66] is a generalized version of Lasso in which the penalty term is a weighted average of the sum of the absolute values of the coefficients and the sum of their squares (i.e., $\lambda\alpha\Sigma|C_k| + \lambda(1-\alpha)\Sigma {C_k}^2$). If the weight factor α is set equal to 1.0, the regression is the same as the original Lasso, while as α decreases towards zero, the elastic net method tends to the ridge regression [67]. Herein, computations were performed for α = 1.0 and α = 0.9. By penalizing the presence of C_k's, these methods result in fittings that contain less non-zero coefficients (i.e., fewer causal variables than originally prescribed are effectively used) as λ is increased. Hence, a ranking of the importance of the causal variables could be obtained by repeating the regression calculations for a succession of increasing λ values. For very small λ values (negligible penalty), the fitted Equation (3) contains all nine causal variables. As λ increases, variables are successively dropped from the equation (their respective coefficients C_k became zero). The larger the λ for which C_k becomes zero (threshold value λ_T), the greater is the importance of the respective variable. The Lasso and elastic net calculations were performed using the pertinent built-in function in MATLAB.

4.2. Forward Stepwise Regression

The results of the stepwise linear regression approach are shown in Tables 2 and 3 for a selection of combinations of causal variables. The average values of the increase in R^2 due to the inclusion of each variable in the linear equation (ΔR^2) from all permutations are given in Table 2, while Table 3 shows the corresponding regression coefficients. Combination A contained all nine variables, and the number of all possible permutations in this case was 362,880. Combinations B, C, and D excluded the cloud cover, the SI, and both of them at the same time, respectively, from the equation, because, as shown the previous section, they manifested the weakest correlation with TDM. Moreover, cloud cover is naturally correlated to a certain degree with humidity and precipitation. The cloud cover and SI were left outside the equation along with other variables for the remaining combinations presented in Tables 2 and 3. Combinations E, G, I, and J contained only one of the three variables that are pertinent to atmospheric water (humidity, precipitation, and cloud cover). Finally, combinations H, I and J were set to contain only one variable pertaining to government response measures.

Table 2. Increase in coefficient of determination (ΔR^2) due to inclusion of variables in Equation (3).

Variable	Combination									
	A	B	C	D	E	F	G	H	I	J
Temperature	0.041	0.042	0.039	0.041	0.042	0.037	0.042	0.045	0.046	0.047
Relative humidity	0.009	0.010	0.007	0.008		0.010	0.007	0.008	0.008	0.007
Precipitation	0.004	0.004	0.004	0.003	0.002	0.004		0.003		
Cloud cover	0.003		0.003							
Population density	0.012	0.012	0.014	0.013	0.015		0.014	0.013	0.013	0.016
Median age	0.066	0.067	0.064	0.064	0.067	0.069	0.065	0.067	0.068	0.076
Stringency index	0.014	0.014								
Delay in first measures	0.045	0.045	0.040	0.040	0.041	0.042	0.041	0.047	0.048	
Delay in stay-at-home	0.034	0.034	0.027	0.027	0.027	0.026	0.027			0.034

Table 3. Calculated values of regression coefficients.

Variable	Coefficient	Combination									
		A	B	C	D	E	F	G	H	I	J
Temperature	C1	−108.9	−88.9	−86.7	−89.7	−93.8	−60.6	−86.8	−103.9	−99.1	−90.9
Relative humidity	C2	82.2	79.1	34.8	34.9		62.7	46.1	34.7	54.2	40.6
Precipitation	C3	13.4	−17.9	11.3	16.3	45.0	−14.8		28.1		
Cloud cover	C4	−43.5		6.6							
Population density	C5	48.8	47.5	72.9	73.3	80.3		70.3	70.3	64.9	78.9
Median age	C6	113.8	120.2	109.2	108.1	112.6	125.7	106.4	110.1	107.1	127.7
Stringency index	C7	261.0	246.9								
Delay in first measures	C8	174.2	167.7	128.5	129.2	130.9	133.9	127.5	156.0	153.6	
Delay in stay-at-home	C9	158.8	157.3	94.7	94.4	94.3	91.4	95.5			122.1
Intercept	C0	−267.7	−270.4	−52.7	−50.4	−35.3	−78.2	−54.1	−31.5	−37.5	−3.9

In all combinations, the variable with the largest ΔR^2 is clearly the median age (Table 2). The delay in imposition of first measures and the average temperature come second and third interchangeably depending on the combination, producing practically the same ΔR^2 values, while the delay in stay-at-home ranks fourth (Figure 17). The variables related to atmospheric water appear to be of small to negligible importance, with the relative humidity being the most significant among the three. The very week correlation of TDM with cumulative precipitation and cloud cover is also manifested in the sign of the corresponding regression coefficients (C_3 and C_4), which, in certain combinations, turn out to be negative. It should be noted though that the actual significance of the relative humidity could be larger, given that it most likely has a non-monotonic effect on viral transmissibility, as discussed in Section 3.1, and that a linear regression inherently cannot capture non-monotonic dependencies. The same could be argued for the precipitation and cloud cover, given that these variables are interrelated with relative humidity.

As expected, the resulting coefficient for the temperature (C_1) is negative in all combinations (Table 3), i.e., the TDM decreases with increasing average atmospheric temperature. The same would be anticipated for the coefficient for the SI (C_7). However, C_7 turns out to be consistently positive, implying that the TDM increases with the overall strictness of the government response. This counterintuitive result is probably because the SI is not purely a causal variable and can be actually considered an effect of the observed case and death rates. For example, if the epidemic in a given country escalates beyond control and overwhelms the health system, it is understandable that the government will ramp up the response and impose increasingly stricter measures in order to regain control.

The delay in issuing a stay-at-home order can also be argued to be a mixed cause/effect variable, i.e., that the delay is, to a certain extent, the outcome of how the epidemic is unfolding in a given country. For example, a state may choose not to impose stay-at-home measures at all if the case or death rates remain low due to other factors, or they may choose to impose stay-at-home measures late when certain thresholds are eventually exceeded. In case the delay in issuing a stay-at-home order was

more an effect of the death rates rather than the cause, then it would correlate negatively with the TDM and the corresponding regression coefficient (C_9) would be negative. As seen in Table 3, the resulting C_9 values are always positive and the corresponding ΔR^2 values are not negligible, suggesting that the stay-at-home measure is a factor instrumental in preventing escalation of the epidemic.

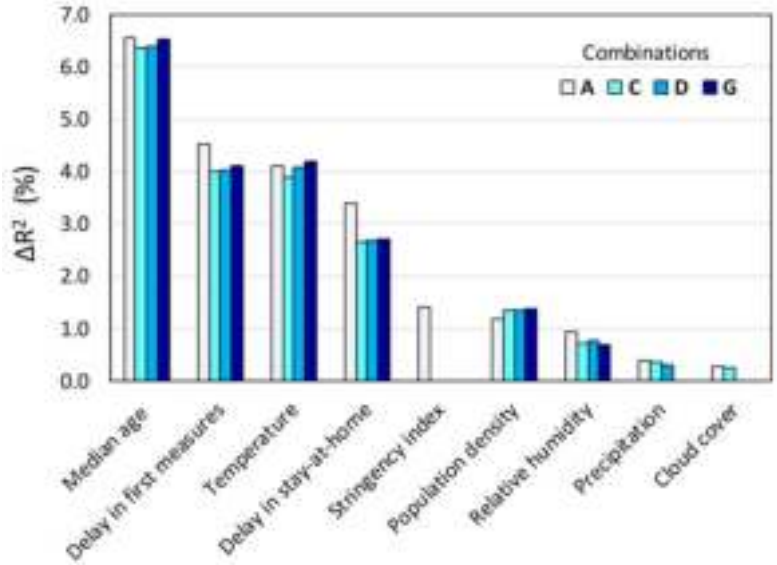

Figure 17. Rank of importance of causal variables based on stepwise regression.

This study relied on considering spatial averages across the entire territory of a country. It can be argued that such treatment may have been a source of bias in the analysis, especially in the case of large countries, as well as countries that span a wide latitude range in the temperate and arctic zones, in which case the differences in temperature (and possibly in other weather variables) are naturally large. Figure 18 shows the stepwise regression results for combination C when the six largest countries (Australia, Brazil, Canada, China, Russia, and USA) and two countries spanning a wide range of latitudes (Argentina and Chile) are removed from the dataset. It can be seen that exclusion of these countries has only a small effect on ΔR^2, and the ranking remains the same as in the case of the complete dataset.

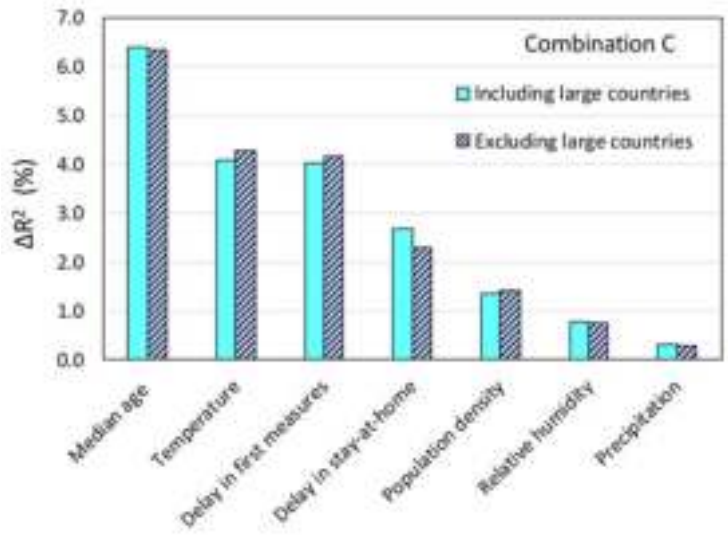

Figure 18. Effect of excluding large countries on the importance rank of causal variables resulting from stepwise regression.

4.3. Lasso and Elastic Net Regression

Figure 19 shows the variation of the coefficients C_k with increasing λ ("trace plots") from the application of Lasso regression ($\alpha = 1.0$) and elastic net regression with $\alpha = 0.9$, considering all nine causal variables of Equation (3). The λ values at which the curves reach the horizontal axis ($C_k = 0$) are the threshold λ_T values, which are plotted in Figure 20 (normalized with respect to the λ_T for the median age). It can be observed that for $\alpha = 1.0$ (Figure 19a), the curves dip more abruptly towards the horizontal axis and reach generally different λ_T values than in the case of $\alpha = 0.9$ (Figure 19b). Nonetheless, the inferred ranking of the importance of the variables is the same for both α values, with the exception of the stringency index and the cloud cover that switch places (Figure 20).

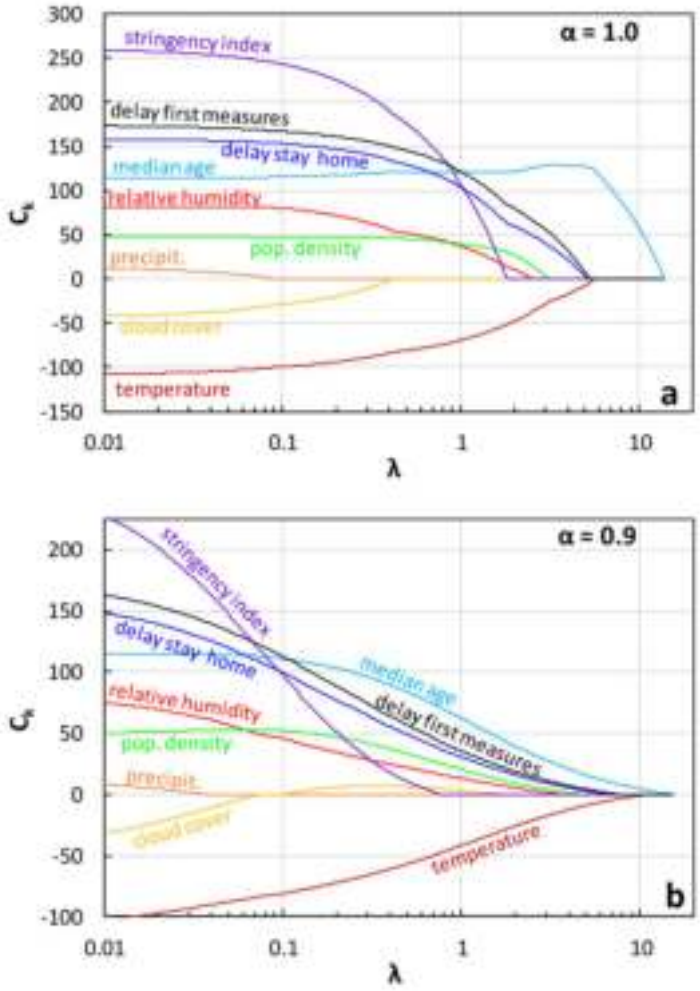

Figure 19. Trace plots of coefficients from: (**a**) Lasso regression and (**b**) elastic net regression.

The rankings from the Lasso regression and elastic net regression generally agree with that from the forward stepwise regression. As in the case of the stepwise regression results (Table 2 and Figure 17), the median age turns out to be by far the most important variable, while the variables related to atmospheric water (RH, precipitation, and cloud cover) are clearly less significant compared to the government response measures (Figure 20). Furthermore, based on the Lasso results, the temperature, the delay in taking the first measures, and the delay in imposing stay-at-home order were found to be of almost equal importance, with the temperature being only slightly ahead. The differences among them are accentuated if $\alpha = 0.9$. Figure 19 shows that the coefficient for the SI always remains positive (i.e., the severity of the epidemic increases with an increasing SI), an ambiguous outcome that, as discussed in the previous paragraph, probably stems from the fact that the stringency index is partially

an effect variable. It should be stressed here that excluding the SI from Equation (3) did not change the ranking sequence seen in Figure 20.

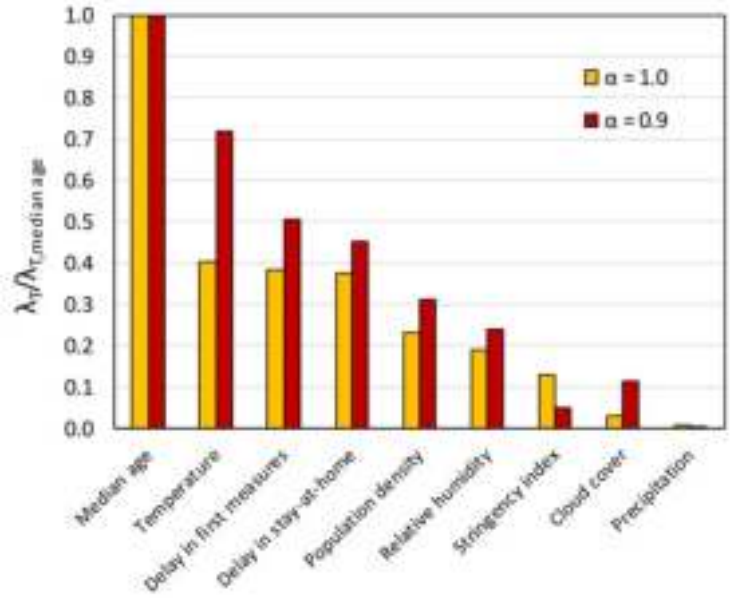

Figure 20. Rank of importance of causal variables based on Lasso and elastic net regression.

Finally, Lasso regression calculations were repeated excluding Argentina, Australia, Brazil, Canada, China, Chile, Russia, and USA in order to obtain results for a dataset in which the effect of spatial averaging across vast territories and wide range of latitudes was smaller. As seen in Figure 21, the exclusion of these countries caused insignificant changes in the λ_T, with the exception of that corresponding to the temperature, the role of which appears elevated. Despite this, the ranking of the variables remains the same as in the case of the complete dataset.

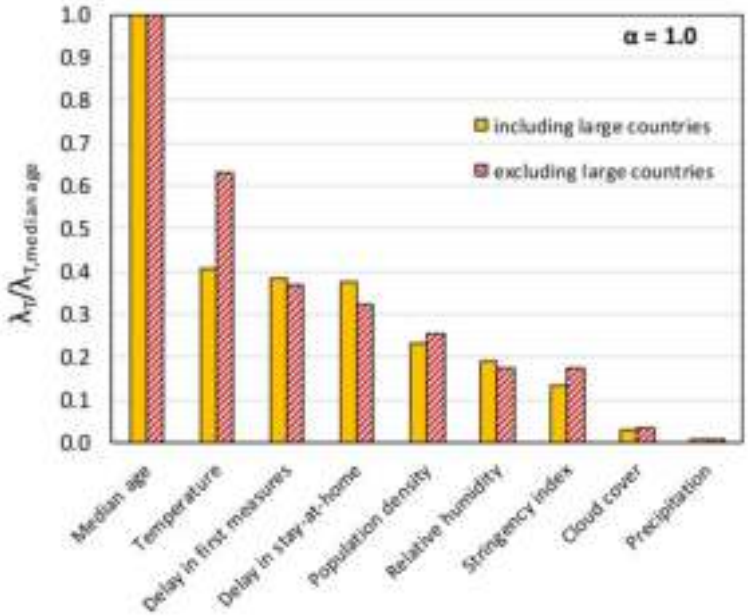

Figure 21. Effect of excluding large countries on the importance ranking of causal variables based on Lasso regression.

5. Conclusions

Due to its high human-to-human transmissibility, COVID-19 quickly spread worldwide. However, discrepancies of orders of magnitudes have been observed among the countries in terms of case and death rates. To discern the role which climatic factors play in the local epidemic intensity in conjunction with sociodemographic factors and government response measures, atmospheric data were processed in Geographic Information System (GIS) and statistically analyzed for the period of the first wave of the pandemic.

Based on the results of the present study, among the climatic variables, the average temperature showed a strong correlation with both death and case rates. Its influence appears to be of at least equal importance to the promptness of the governmental response. Relative humidity was found to have a noticeable influence that was not easily discerned, probably due to its non-monotonic character. Nonetheless, the age structure of the population clearly emerged as the most important risk factor. On the contrary, our analysis found that population density correlated rather weakly with the epidemic intensity.

With respect governments' response to COVID-19, the time difference between the first case detection in a given country and the imposition of first measures (which mainly consist of public information/awareness campaigns, international travel restrictions, and the cancelling of public events) appears to be instrumental in keeping case and death rates at moderate levels (less than 100 deaths and 1000 cases per million inhabitants). The present analysis suggests that the time difference between the occurrence of the first case and the issue of stay-at-home order also has a significant effect in preventing the escalation from moderate to high case and death rates but to a lesser degree compared to the promptness of first measures.

As final remark, it must be kept in mind that in this study, the data were treated by taking countrywide spatial averages, which had a data-smoothing effect. Future investigations relying on a more detailed, regional discretization may more clearly elucidate the role of weather on COVID-19. The temporal averaging during the span of three months may also have obscured the actual degree of the dependence of the epidemic intensity on the climatic factors. For example, the initial cold period of March 2020 (colder than the average for the entire March–May period) in countries located in the temperate zone of the northern hemisphere may have seeded large numbers of early infections that then persisted as temperatures rose in April and May to cause lower reproduction numbers R. In this case, high COVID-19 case and death rates would be paired with artificially (due to averaging) larger temperature values. Such skewing is expected to be almost absent in the case of countries in which the weather variation during this three-month period was small, such as those that are located closer to the equator.

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COVID-19 and Environmental factors. A PRISMA-compliant systematic review

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Abstract

The emergence of a novel human coronavirus, SARS-CoV-2, has become a global health concern causing severe respiratory tract infections in humans. Human-to-human transmissions have been described with incubation times between 2-10 days, facilitating its airborne spread via droplets. The impact of environmental factors on the coronavirus disease 2019 (COVID-19) outbreak is under consideration. We therefore reviewed the literature on all available information about the impact of environmental factors on human coronaviruses. Temperature, humidity and other environmental factors have been recorded as environmental drivers of the COVID-19 outbreak in China and in other countries. Higher temperatures might be positive to decrease the COVID-19 incidence. In our review, the analysis of 23 studies show evidence that high temperature and high humidity reduce the COVID-19 transmission. However, further studies concerning other environmental (namely meteorological) factors' role should be conducted in order to further prove this correlation.

As no specific therapies are available for SARS-CoV-2, early containment and prevention of further spread will be crucial to stop the ongoing outbreak and to control this novel infectious thread.

Keywords: coronaviruses, covid-19, temperature, humidity, risk factor, epidemiology, survival

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Introduction

A novel coronavirus (SARS-CoV-2) has recently emerged from China with a total of 45171 confirmed cases of pneumonia (as of February 12, 2020). Coronaviruses (CoVs) most commonly cause mild illness; but have occasionally, in recent years, led to major outbreaks of human disease. Approximately ten years after SARS, another novel, highly pathogenic CoV, in December 2019, SARS-CoV-2, a novel CoV, was identified in the City of Wuhan, Hubei Province, a major transport hub of central China. The earliest COVID-19 cases were linked to a large seafood market in Wuhan, initially suggesting a direct food source transmission pathway (Thompson 2020). Along with Severe Acute Respiratory Syndrome (SARS) coronavirus and Middle East Respiratory Syndrome (MERS) coronavirus (de Wit et al. 2016) (Peeri et al. 2020) , this is the third highly pathogenic human coronavirus that has emerged in the last two decades. In the months since the identification of the initial cases, COVID-19 has spread to 180 countries and territories and there are approximately 664,564 confirmed cases and 30,890 deaths (as of 29 March 2020).

Person-to-person transmission was confirmed as one of the main mechanisms of COVID-19 spread (Chan et al. 2020). The modes of transmission have been identified as host-to-human and human-to-human. Increased spread of SARS-CoV-2 causing COVID-19 infections worldwide has brought increased attention and fears surrounding the prevention and control of SAR-CoV-2 from both the scientific community and the general public. While many of the precautions typical for halting the spread of respiratory viruses are being implemented, other less understood transmission pathways should also be considered and addressed to reduce further spread.

The role of environment and its mediated pathways for infection by other pathogens have been a concern for decades. Substantial research into the presence, abundance, diversity, function, survival and transmission of microorganisms in the environment has taken place in recent years. There is preliminary evidence that environmentally mediated transmission may be possible; additionally, that COVID-2 could be affected by environmental factors such as seasonality,

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temperature, humidity (Tan et al. 2005) (Shaman and Kohn 2009) (Geller, Varbanov, and Duval 2012).

The aim of the review was, therefore, to summarize all available data on the impact of environmental factors on the survival of all coronaviruses including emerging SARS-CoV and MERS CoV.

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Methodology

Methodology of this systematic review and inclusion criteria were indicated in advance and recorded in *a priori* protocol in order to determine the rationale, the objectives, the eligibility and selection criteria, the search strategy and the study selection process of this systematic review. However, due to emergency of the subject and due to the pandemic awareness for COVID-19, this systematic review was not registered with PROSPERO (International Prospective Register of Systematic Reviews).

Eligibility criteria

All study design types were considered in this systematic review. Reviews were not included but screened for any information within the scope of this review. No language, publication status or publication year restrictions were imposed. As because of the COVID-19 emergency state, even not proofread publications were included in our study. All non-English studies, including Chinese, Japanese and French were translated via Google translator and were included in this systematic review. Although COVID-19 concerns years 2019 and 2020, no year of publication limit was applied, in order to exploit valuable information concerning the coronavirus relationship with environmental factors, as indicated by the past SARS and MERS lessons. All studies included, concern human coronavirus strains of various types. This systematic review was limited to studies focusing to environmental factors' impact on COVID-19. Searched experts' and researchers' opinions were not handed in this study.

The selection criteria developed a priori are described below:

- Year of publication
- Country of epidemics
- Continent of epidemics
- Environmental factor
- Assessing method

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Information sources

The search strategy and analysis process were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement for systematic reviews (Liberati et al. 2009; Page et al. 2018). Titles and abstracts of the retrieved articles were screened, while full length articles were evaluated for eligibility and were further acquired via SwetsWise Online Content. Search for articles was applied in three electronic databases: Google Scholar, PubMed & Springerlink. Google Scholar was our starting point. No unpublished information obtained. The literature search was performed from 25 to 28 of March 2020.

Search

The following terms were used to search all databases, always in combination with "coronavirus" and "COVID-19": "environmental factors", "clima", "temperature", "humidity", "absolute humidity", "relative humidity", "wind speed", "wind power", "precipitation", "rainfall". The search strategy was conducted by IPC and was peer-reviewed by AV as part of the systematic review process.

Study selection

Eligibility assessment procedure was performed in standardized and independent manner, primary by two authors (IPC and AV), to analyze and validate all relevant data to the top under discussion. Disagreements were resolved through discussion among all authors and resulted in a final consensus. After excluding records upon the eligibility criteria set, we screened all titles and abstracts of the retrieved studies, although full text review proves also to be necessary for further consideration.

Data Collection process

A data extraction sheet was developed in order to summarize the evidence of this systematic review, based on the Cochrane Consumers and Communication Review Group' data extraction

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template for included studies (Cochrane Consumers and Communication 2016). This was pilot tested on the first ten randomly selected studies and no refinement was needed. One author (IPC) extracted all proper data from the included studies and another author (AV) checked all the extracted data. No disagreements arose. In order to ascertain duplicate publications, we used the tool "check for duplicates" of Mendeley Desktop software (Version 1.19.4).

Assessment of study quality

To ascertain the validity of the included studies, two reviewers (IPC and AV) in a blind manner and independently scored the included papers' quality upon the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (Von Elm et al. 2014). Both reviewers independently scored each included paper's quality and all studies received a score that ranged from 0 to 22 points by each reviewer. Base up on a criterion included in the initial protocol of the study, the scores between the reviewers should not differ from one to another reviewer by more than 2 points. In order to generate a final score, both scores of the reviewers were averaged.

Planned methods of analysis

In order to handle data and combine the results of all the included studies, we used SPSS (Statistical Package for the Social Sciences) (IBM SPSS Statistics for Macintosh, Version 25.0 n.d.) or R software (R Development Core Team 2013).

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Results

Study selection and characteristics

The search of Google Scholar, Springerlink and PubMed provided a total of 14640, 51 and 28 articles, respectively. From the initially obtained 14719 articles, 8499 were excluded as duplicated ones upon "Check for duplicates" tool of Mendeley Desktop. The remaining 6220 articles were assessed for eligibility and a total of 6007 articles were discarded because based on a detailed evaluation of abstracts, they did not meet the eligibility criteria set and concerned: a) 2457 discussed clinical and epidemiological considerations of COVID-19, b) 813 discussed environmental factors associated with other diseases, c) 760 discussed ethical considerations od COVID-19, d) 743 discussed transmission dynamics of COVID-19, e) 655 discussed diagnostic and management outbreak investigations of COVID-19, f) 500 discussed prospects and advances in designing and developing vaccine and immuno-therapeutics of COVID-19 and g) 79 discussed socio-economic impact of COVID-19 . Of the remaining 213 articles, 124 were excluded because they did not meet the inclusion criteria. The full text of the rest 89 articles was evaluated in further detail. Finally, 23 were included for further analysis in this systematic review (Figure 1).

All 23 studies selected for this systematic review were published in 2020 and in English. 65.2% of the included studies reported China, 26.1% did not mention a certain country of epidemics, 4.3% concerned the epicentre of the disease, namely Iran, Italy, South Korea, etc. and 4.3% concerned Singapore. Upon continent of epidemics, Asia hold the leads with 69,6%, followed by Africa with 4.3%, whereas almost 21.7% did not mention specific continent and 4.3% refers to mixed continents (Asia, Europe, etc.). All included studies assessed the role of various environmental factors on transmission rates of the COVID-19.

In 24.1% of the studies, temperature was assessed for its impact on COVID-19, followed by humidity (11.1%), absolute humidity (5.6%), rainfall/precipitation (5.6%), relative humidity (5.6%), travel (5.6%), air travel (3.7%), wind speed/power (3.7%), latitude (3.7%), built

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environment (1.9%), general lockdown (1.9%), visibility (1.9%), specific humidity (1.9%), airborne dust (1.9%), air pollution (1.9%), chemical pollution (1.9%), air index (1.9%), atmospheric radiation (1.9%), cloud cover (1.9%), precipitation of the driest month (1.9%), mean temperature of the wettest quarter (1.9%), isothermality (day-to-night temperatures difference relative to the summer-to-winter annual difference) (1.9%), annual mean temperature (1.9%), mean diurnal range (1.9%), minimum temperature of the coldest month (1.9%) and precipitation of the coldest quarter (1.9%).

In order to examine the association between those environmental factors and COVID-19, most of the studies employed the review method (20.4%), followed by maximum entropy model (13%), the model (11.1%), dynamical model and ERA-5 reanalysis (9.3%), the statistical modeling Loess regression (Generalized-linear or non-linear model) (7.4%), the R proxy method (5.6%), the R reproductive number (3.7%), the One-way ANOVA followed by a post-hoc Tukey's HSD test (3.7%), the distributed lag log-linear model (3.7%), the linear regression model (3.7%), the global meta-population disease transmission model (3.7%), the Mann-Whitney U test (3.7%), the mathematical model (3.7%), the restricted cubic spline function and the generalized linear mixture model (3.7%) and the multivariate analysis (3.7%). Figure 2 displays the environmental factor assessed, combined with the assessing method and the country of epidemics it concerns. Detailed characteristics of the studies included, like author, title and year of publication, country and continent of the study, method of assessing the impact of the environmental factors and the outcome variable are described in Table 1.

Figure 2 displays the exact temperature range proposed by certain studies included in this systematic review, in which virus survival is facilitated.

Results of individual studies

Gilbert et al. used the volume of air travel concerning the flights from the infected China provinces (Guangdong, Fujan and the city Beijing) to Africa and concluded that there are 2

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identified clusters of African countries: a) those that have the higher importation risk of exposure to COVID-19, which have moderate to high capacity to face an outbreak, like Egypt, Algeria and South Africa and b) those that are at moderate risk and have high vulnerability and variable capacity (Gilbert et al. 2020). Mao et al. concluded that temperature has a non-linear dose response relationship with COVID-19 transmission, whereas there is a specific temperature range, in which virus transmission is facilitated and this might also explain the emergence of the epidemic in Wuhan city. Wang et al. suggest that regions with lower temperature records should take even stricter measures in order to prevent future outbreaks (Wang et al. 2020). Luo et al. and Poirier et al. suggest that changes in weather conditions alone, namely increase of humidity and temperature (which are usually met in spring and summer seasons) may not suffice to decrease the number of cases, if no proper public health interventions are adopted (Luo et al. 2020) (Poirier et al. 2020). Bonilla-Aldana et al. propose that temperature, rainfall and humidity may play a significant role in the virus transmission, as occurs for many zoonotic diseases (Bonilla-Aldana, Dhama, and Rodriguez-Morales 2020). Dietz et al. combined current literature and built environment and assessed its role in COVID-19 transmission, suggesting that built environment plays a significant role in the disease control and mediation and this may be taken into consideration in the building design market(Conraths et al. 2015). Oliveiros et al. regressed the doubling time of COVID-19 cases with the aid of temperature and humidity, whereas wind speed proved not be significantly associated (Oliveiros et al. 2020). Based on Shi et al. conclusions, lower and higher temperature rates may decrease the COVID-19 incidence rates and the role of absolute humidity has not yet been established (Shi et al. 2020). Lau et al. recorded an increase in the doubling time of COVID-cases and this was attributed to the lockdown measurements implemented (Lau et al. 2020). Chen et al. found out that the optimal temperature for COVID-19 is 8.07 °C, within a humidity range of 60-90% (Chen et al. 2020). Sun et al. concluded that cold and dry winter are considered as a common environmental condition conductive for COVID-19 (Sun et al. 2020). Peeri et al. attributed the increased and rapid

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COVID-19 perforation to air travel frequency and circumstances (i.e. connection flights) (Peeri et al. 2020). Gostic et al. estimated that screening during travel may miss more than half of the infected cases, as the have not developed symptoms in the time of screening (Gostic et al. 2020). Sajadi et al. reached the conclusion that temperature range of 5-11°C, combined with low specific range of 3-6g/kg and absolute humidity range of 4-7 g/kg are the optimal environmental factors for COVID-19 transmission (Sajadi, Habibzadeh, Vintzileos, Shokouhi, et al. 2020). Qu et al. linked the COVID-19 transmission with airborne dust (Qu et al. 2020). Gupta showed that for every 1°C increase above 5 °C, the temperature as factor may decrease the COVID-19 transmission rate by 10% (Gupta 2020). Cai et al. found no correlation between the daily mean temperature and the epidemic growth rate in case of Hunan or Wuhan, but insist that there is a weak correlation between the daily mean temperature and the mortality rates in both provinces (Cai et al. 2020). Chinazzi et al. assessed travel limitations practices applied in China and international scale and verified travel quarantine delayed the epidemic progression 3 to 5 days in China or more in worldwide basis (Chinazzi et al. 2020). Lee et al. reviewed Singapore's approach to COVID-19 epidemic concerning travel restrictions applied at all ports of entry (Lee, Chiew, and Khong 2020). Wang et al. propose that high temperature and high relative humidity significantly affects the COVID-19 transmission rates (J. Wang et al. 2020). Poole suggests that a climatological range of 4-12°C within an area of 25-55° latitude may enhance the COVID-19 spread (Poole 2020). Bu et al. conclude that temperature rate of 13-19°C and humidity rate of 50-80% are conducive to the virus survival (Bu et al. 2020).

Study quality

The studies included in this systematic review were scored from 17 to 19.8, upon the criteria predefined. The criteria on which studies were assessed with the minimum score were related to their not clearly addressing the following items: report of the study design and assessing method

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in the title and abstract; clearly define the participants, the interventions and the outcomes; clearly state handle of missing data and accuracy of data; generalization of the findings.

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Discussion

To the best of our knowledge, the present systematic review is the first to summarize the available evidence on the association of COVID-19 with environmental factors. Taking into consideration that the new coronavirus is a new human pathogen, which due to its outbreak in China and its rapid spread worldwide, it is important to understand reliable epidemiological information for its survival in the environment (Chen et al. 2020). Therefore, it is necessary to find prognostic predictors to distinguish high-risk areas or countries and improve the new challenging situation.

Any infectious disease origins and spread occur only when affected by certain natural and social factors through acting on the source of infection, the mode of transmission and the susceptibility of the population. The environmental factors such as meteorological factors, namely temperature and humidity proved to play a part in coronavirus outbreak besides the social factors (Jia et al. 2020). In our systematic review, overall evidence is sufficiently robust to determine the impact of temperature in virus' survival via different methods, like the effect of each 1°C increase which lowers the virus' R by 0.225 (J. Wang et al. 2020) and the doubling time of the confirmed cases which is positively correlated with temperature (Oliveiros et al. 2020). Four, studies included in this systematic review determine the exact temperature range, within which temperature is conducive to virus spread and survival. The pooled results of these 4 studies indicated that temperature range different from 4-24°C is not conducive to the survival of the coronavirus (M. Wang et al. 2020) (Sajadi, Habibzadeh, Vintzileos, Miralles-wilhelm, et al. 2020) (Poole 2020) (Bu et al. 2020). Concerning humidity, although the results in this review did not reveal robust associations between humidity and coronavirus survival and are always validated in combination with temperature, they need to be interpreted carefully given the monotonic functional relationship between humidity and temperature. In other words, if temperature was associated to COVID-19 transmission, very likely absolute humidity would play a role. Pooled results of the studies included in this systematic review show that combined

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with high temperature, absolute humidity range of 4-7 g/m^3 (Sajadi, Habibzadeh, Vintzileos, Miralles-wilhelm, et al. 2020) or specific humidity range of 3-6 g/kg (Sajadi, Habibzadeh, Vintzileos, Miralles-wilhelm, et al. 2020) or humidity of 50-80% (Sajadi, Habibzadeh, Vintzileos, Miralles-wilhelm, et al. 2020) may reduce the transmission of COVID-19. Other factors concerned, such as air index, rainfall/precipitation, wind speed, do not show to have significant impact to virus stability and survival and need to be further assessed. Although not all environmental factors and not in depth are clearly described by authors of the included studies, important associations are observed and need further investigation. Variability in the results among the studies included in our review may be attributed to i) the utilization of different types of assessing methods of each environmental factor, ii) the different qualitative characteristics of the populations used, iii) sample size, iv) duration of the study and others.

Environmental factors, characterized by lag effects and threshold effects, can target at two objects, host and virus, during infectious disease outbreak. On one hand, human activity patterns and immunity can be influenced by environmental factors. But the effect caused by environmental condition was limited during the COVID-19 outbreak, due to the absence of extreme weather and specific immunity for a newly emerging virus. On the other hand, environmental impacts on the SARS-CoV-2 are more significant than the host population because the transmission and virulence of the virus varies in different conditions. Finally, environmental impacts on transmission of virus should be characterized in the dynamic model, because infectiousness estimated in the traditional dynamic model is actually a confounding effect with environmental effect. It is necessary to take account of environmental issues based on dynamic transmission model so that the impacts could be isolated and qualified.

Apart from the he basic strengths of this review regards the study quality assessment, which was based on STROBE, its PRISMA compliance approach and the peer-review process followed.

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Limitations

Due to limited data available, other meteorological factors such as air pressure, atmospheric particles, ultraviolet, and social factors such as population movement were not included for analysis. Inclusion of such factors will provide more accurate and reliable results.

In addition, the relatively short time length of the current outbreak, combined with imperfect daily reporting practices, make our results vulnerable to changes as more data becomes available. We have assumed that travel limitations and other containment interventions have been implemented consistently across provinces and have had similar impacts (thus population mixing and contact rates are assumed to be comparable), and have ignored the fact that different places may have different reporting practices. Further improvements could incorporate data augmentation techniques that may be able to produce historical time series with likely estimates of case counts based on onset of disease rather than reporting dates. This, along with more detailed estimates of the serial interval distribution, could yield more realistic estimates of R. Finally, further experimental work needs to be conducted to better understand the mechanisms of transmission of COVID-19. Mechanistic understanding of transmission could lead to a coherent justification of our findings.

Conclusions

In summary, this review provided evidence that high temperature and high humidity reduce the COVID-19 transmission. However, further studies concerning other environmental (namely meteorological) factors' role should be conducted in order to further prove this correlation.

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Tables

Table 1 Characteristics of the studies included in this systematic review

	Author/year	Country of epidemics	Continent of epidemics	Assessing method	Environmental factor assessed
1	Gilbert et al., 2020	Not mentioned	Africa	Multivariate analysis	Air travel
2	Wang et al., 2020	China	Asia	Restricted cubic spline function & Generalized linear mixture model	Temperature
3	Luo et al., 2020	China	Asia	Estimation of a proxy for the reproductive number	Absolute humidity
4	Bonilla-Aldana et al., 2020	Not mentioned	Not mentioned	Review	Temperature Rainfall/precipitation Humidity
5	Poirier et al., 2020	Not mentioned	Not mentioned	Estimation of a proxy for the reproductive number	Temperature Humidity
6	Dietz et al., 2020	Not mentioned	Not mentioned	Review	Built environment
7	Oliveiros et al., 2020	China	Asia	Linear regression model	Temperature Humidity
8	Shi et al., 2020	China	Asia	3 Distributed lag loglinear models	Temperature Absolute humidity
9	Lau et al., 2020	China	Asia	One-way ANOVA followed by a post-hoc Tukey's HSD test	Air travel General lockdown
10	Chen et al., 2020	China	Asia	Statistical modelling: Loess regression (Generalized-linear or non-linear model)	Temperature Visibility Wind speed/power Relative humidity
11	Sun et al., 2020	China	Asia	Review	Temperature Humidity Rainfall/Precipitation
12	Gostic et al., 2020	Not mentioned	Not mentioned	Model	Travel
13	Peeri et al., 2020	Epicentre (Iran, Italy, etc.)	Epicentre (Iran, Italy, etc.)	ERA-5 reanalysis	Temperature Absolute humidity Humidity Specific humidity Latitude
14	Qu et al., 2020	Not mentioned	Not mentioned	Review	Airborne dust Air pollution Chemical pollution
15	Gupta, 2020	China	Asia	Mathematical model	Temperature
16	Cai et al.,	China	Asia	Mann-Whitney U test	Temperature
17	Chinazzi et al., 2020	China	Asia	Global metapopulation disease transmission model	Travel
18	Lee et al., 2020	Singapore	Asia	Review	Travel
19	Wang et al., 2020	China	Asia	Estimation of a proxy for the reproductive number	Temperature Relative humidity
20	Jiwei et al., 2020	China	Asia	Dynamical model	Temperature Wind speed/power Rainfall/precipitation Relative humidity Air index
21	Poole, 2020	Worldwide	Worldwide	Model	Temperature Atmospheric pollution Humidity Cloud cover Latitude
22	Bariotakis et al., 2020	Worldwide	Worldwide	Maximum entropy model	Precipitation Isothermality (day-to-night temperatures difference relative to the summer-to-winter (annual) difference) Min temperature of the coldest month Mean diurnal range Mean temperature of wettest quarter Annual mean temperature
23	Bu et al., 2020	China	Asia	Review	Temperature Humidity Rainfall/Precipitation

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Figures

Figure 1 Flow diagram of the study selection process

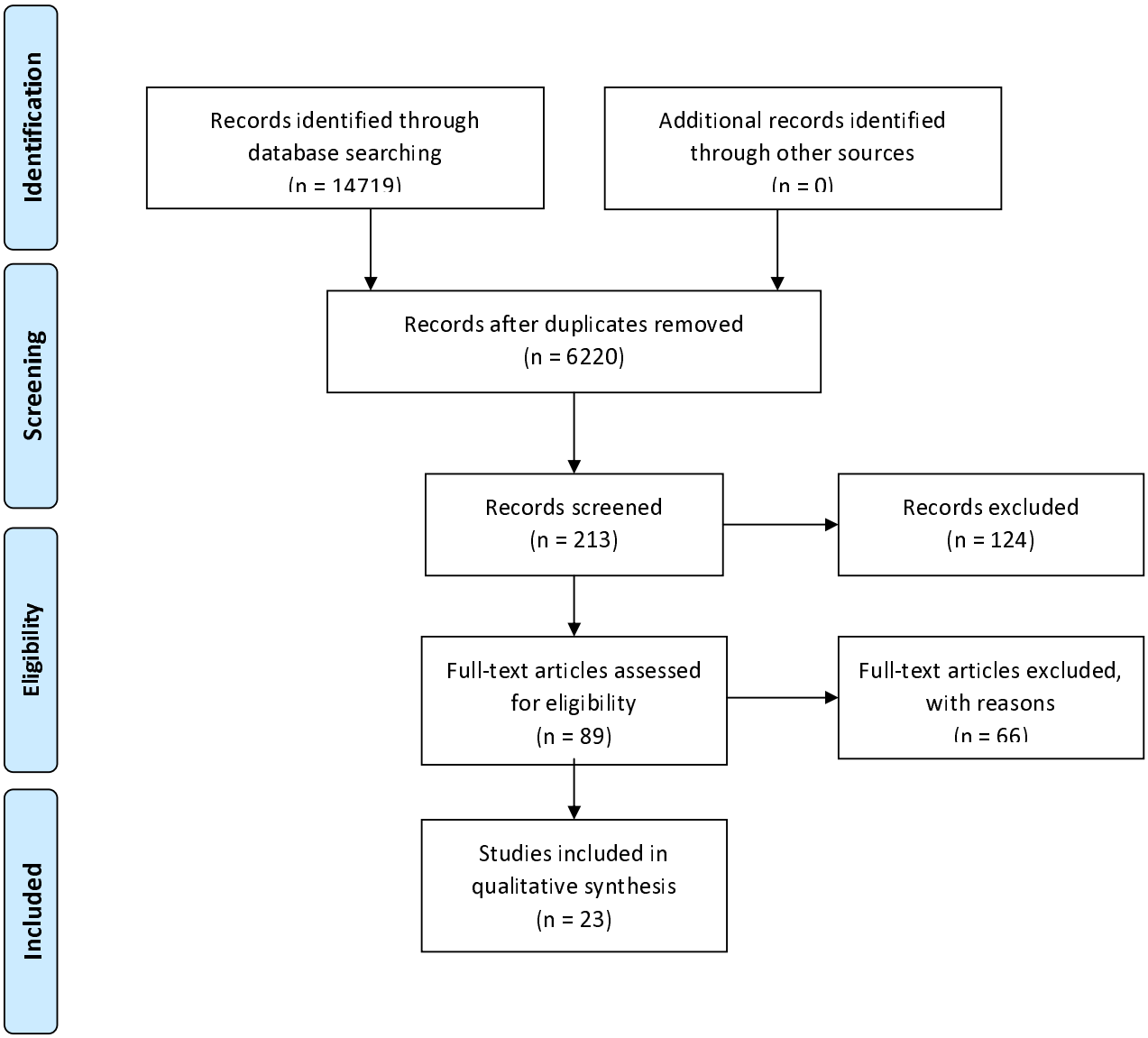

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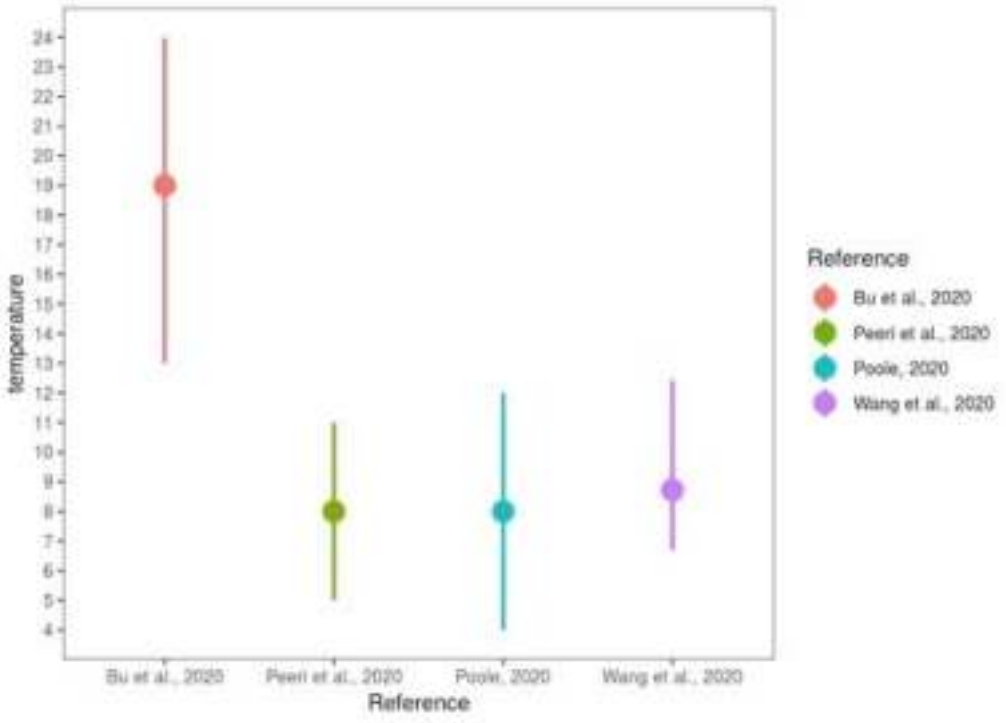
Figure 2 Temperature associated with the assessing methods the country of epidemics



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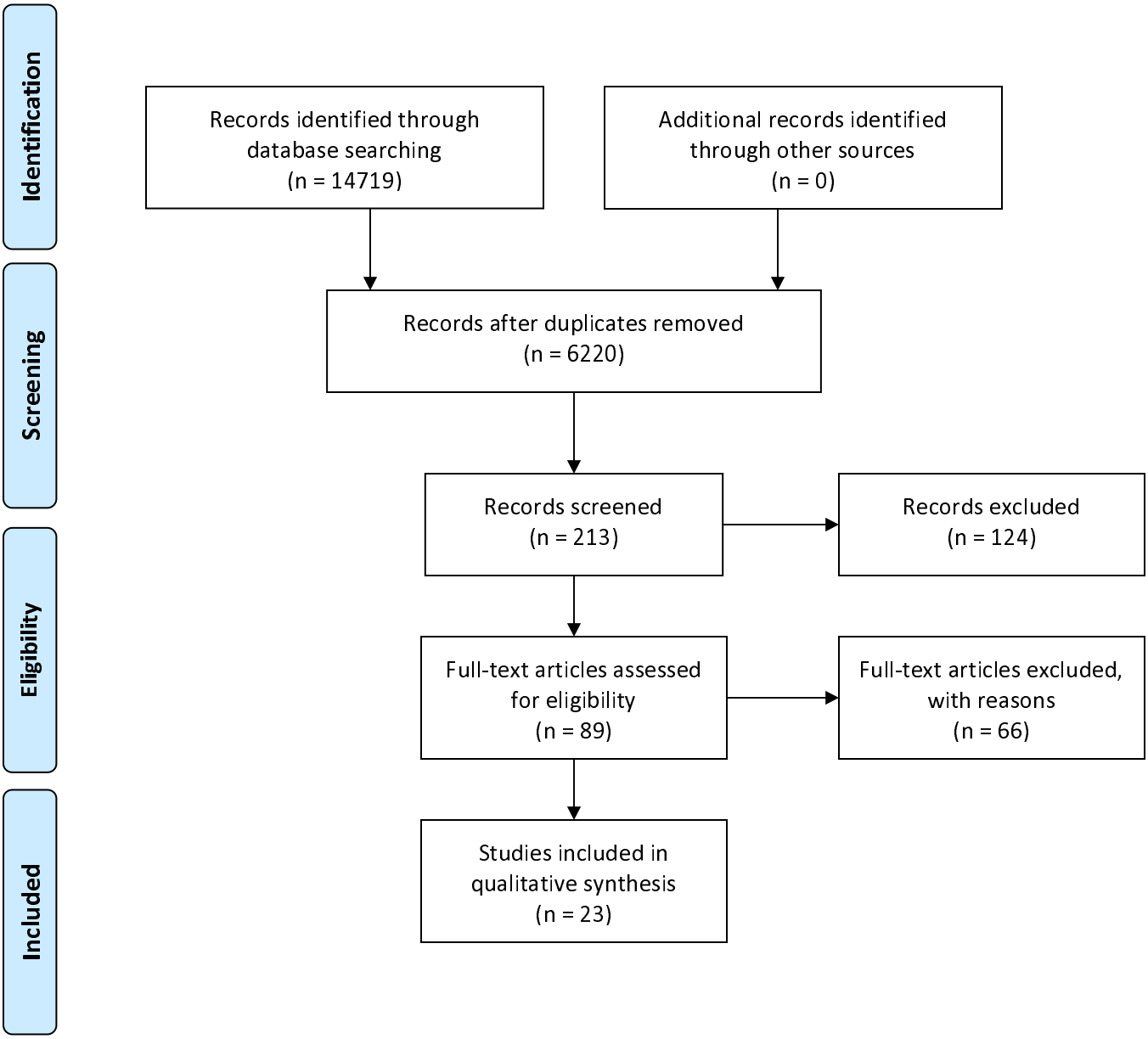

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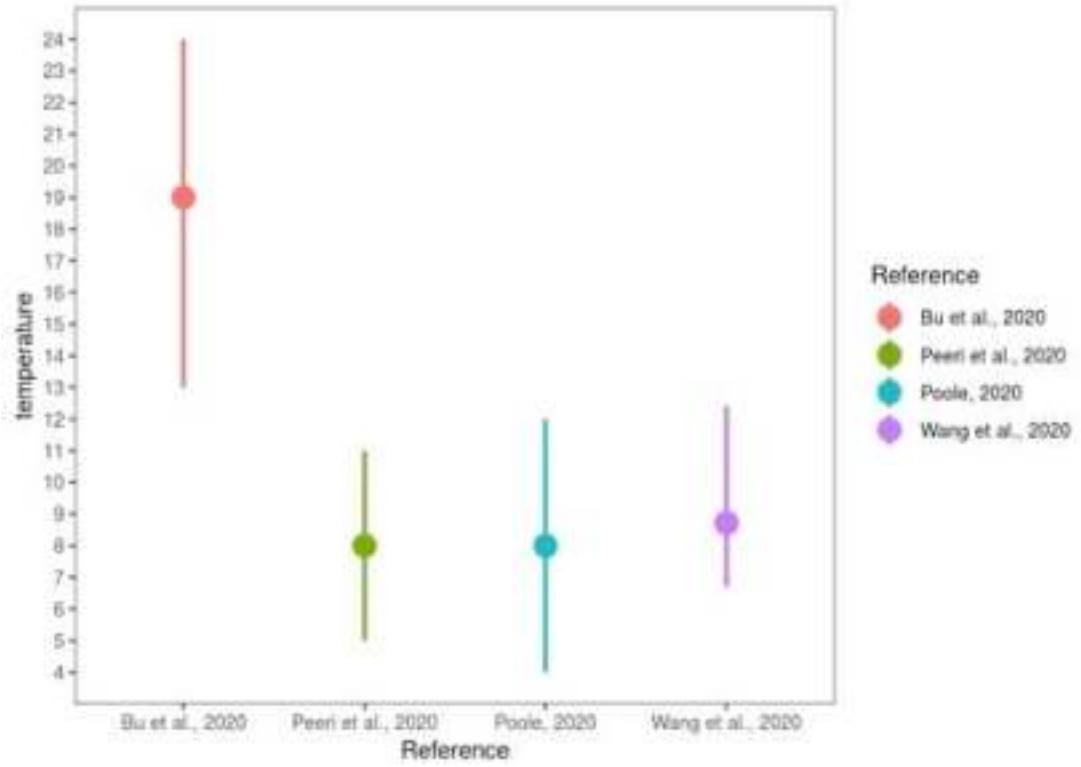
Figure 2 Environmental factors associated with the assessing methods the country of epidemics



Air transportation, population density and temperature predict the spread of COVID-19 in Brazil

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ABSTRACT

There is evidence that COVID-19, the disease caused by the betacoronavirus SARS-CoV-2, is sensitive to environmental conditions. However, such conditions often correlate with demographic and socioeconomic factors at larger spatial extents, which could confound this inference. We evaluated the effect of meteorological conditions (temperature, solar radiation, air humidity and precipitation) on 292 daily records of cumulative number of confirmed COVID-19 cases across the 27 Brazilian capital cities during the 1st month of the outbreak, while controlling for an indicator of the number of tests, the number of arriving flights, population density, proportion of elderly people and average income. Apart from increasing with time, the number of confirmed cases was mainly related to the number of arriving flights and population density, increasing with both factors. However, after accounting for these effects, the disease was shown to be temperature sensitive: there were more cases in colder cities and days, and cases accumulated faster at lower temperatures. Our best estimate indicates that a 1 °C increase in temperature has been associated with a decrease in confirmed cases of 8%. The quality of the data and unknowns limit the analysis, but the study reveals an urgent need to understand more about the environmental sensitivity of the disease to predict demands on health services in different regions and seasons.

Subjects Biogeography, Ecology, Epidemiology, Science and Medical Education
Keywords Climate, Coronavirus, Health, Pandemic

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Additional Information and Declarations can be found on page 12

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INTRODUCTION

The disease COVID-19, caused by the betacoronavirus SARS-CoV-2, has caused panic throughout the world by overwhelming medical services in many countries, leading to deaths that might have been avoided if patients had access to intensive-care units (ICUs). This has led to an unprecedented collaboration within and among countries to slow the spread of the disease, principally using social distancing (*Ebrahim et al., 2020*; *Wilder-Smith & Freedman, 2020*). While it is not clear how much present policies will reduce overall infection rates by SARS-CoV-2, there is consensus that slowing the spread of the

disease will save lives by tailoring patient demands to the capacity of health systems (*Ferguson et al., 2020*; *Walker et al., 2020*).

The strategies of social isolation applied in countries on all continents have allowed time for authorities to undertake interventions to strengthen their health systems, and one of the main actions is to estimate the number of cases of COVID-19 in each region (*Anderson et al., 2020*; *Walker et al., 2020*). This information is essential to scale the number of ICUs to the number of critically ill patients who normally require supportive lung ventilation (*Xu et al., 2020*). Brazil has a large per capita number of ICUs in comparison with Europe, but those units are not evenly spread among regions, with more ICUs per capita in southern states than in northern regions, leaving many Brazilians at large distances from the nearest ICU (*Rhodes & Moreno, 2012*). Moreover, the large demographic and socioeconomic discrepancies in the country create significant variation in susceptibility to infectious diseases (*Barreto et al., 2011*).

One of the problems in predicting the demand for hospital services is that the disease is new so that its behavior is still poorly understood, and the virus may be evolving rapidly (*Zhao et al., 2004*; *Yang et al., 2020*; *Morais et al., 2020*). Therefore, models developed in one country may give poor predictions in another. Habitat-specificity modeling suggests that SARS-CoV-2 spread may be related to environmental conditions, especially temperature and humidity (*Sajadi et al., 2020*; *Wang et al., 2020*). Further, at the host level, there is circumstantial evidence that COVID-19 is related to shortage of vitamin D, which could result from limited exposition to solar radiation (*Grant et al., 2020*). Indeed, it has been suggested that solar radiation might deactivate the virus (*Poole, 2020*). Although preliminary, these results provide a plethora of mechanistic processes linking weather and virus spread that need to be better understood.

Brazil is one of the largest countries in the world, spanning both hemispheres, with latitudes varying from 5°N to 33°S. This means that climatic conditions vary greatly and simple models that do not take into account the possible environmental sensitivity of COVID-19 might not be adequate to predict when and where there will be the greatest demand for health services in Brazil (Fig. 1). One difficulty in quantifying this sensitivity is that climate is likely to correlate with demographic and socioeconomic factors across larger spatial extents. Thus, environmental effects could be confounded unless risk factors for viral spread are taken into account, such as population density, transport connectivity and economic status (*Poole, 2020*; *Wang et al., 2020*; *Ribeiro et al., 2020*).

In an attempt to determine whether environmental variables have significant effects on the propagation of COVID-19, we modeled the daily cumulative number of confirmed cases among Brazilian capital cities in relation to meteorological variables during the 1st month of the disease in the country, while controlling for several demographic and socioeconomic factors. We used only capital cities because they are presently the only reliable sources of COVID-19 cases and represent much of the climatic variation within Brazil. Data on connectivity and frequency of cases is not presently adequate to model the spread of the disease at the municipal level, but this should be available in the future and can be used to test our hypotheses.

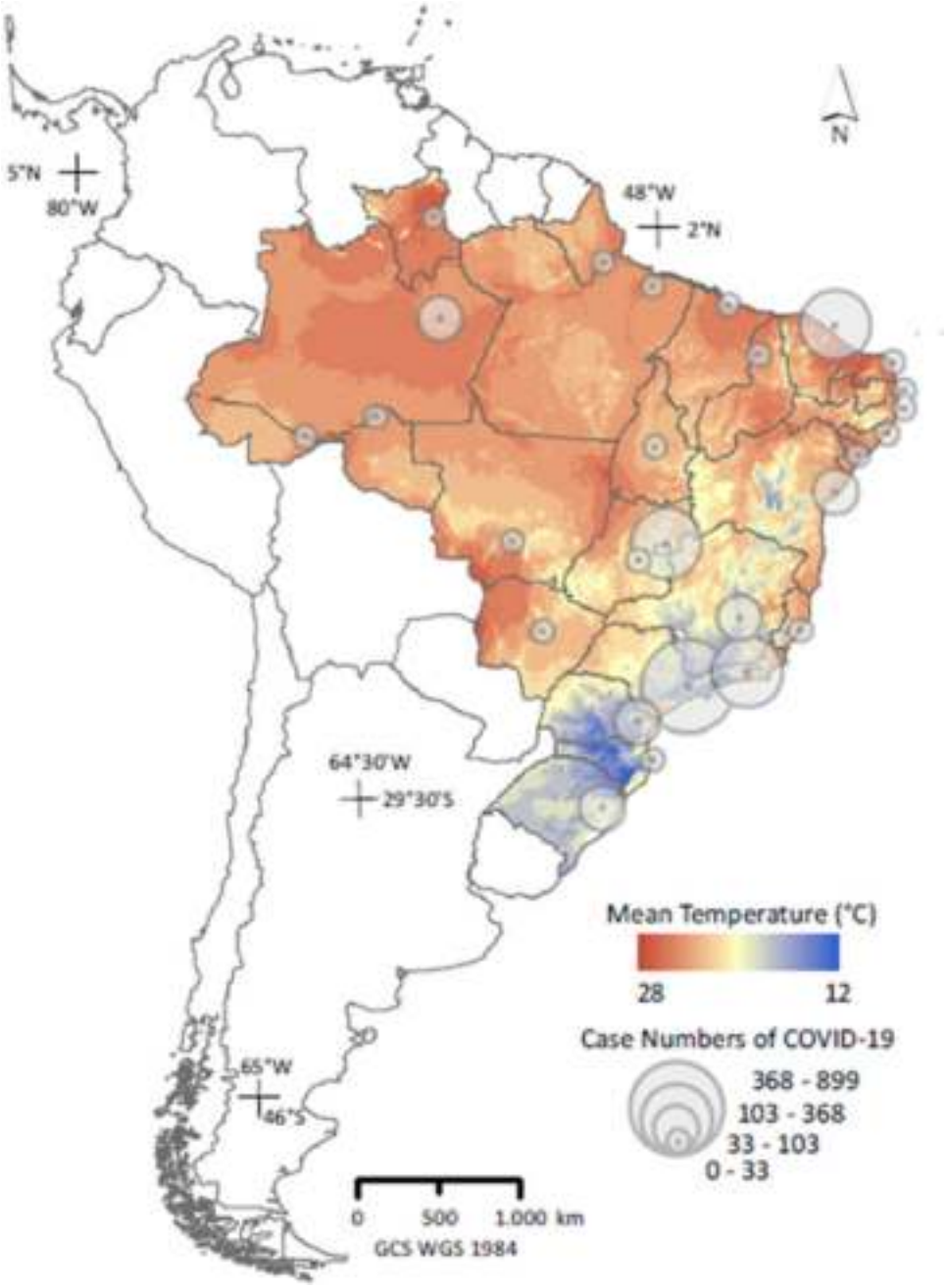

Figure 1 Distribution of counts of confirmed COVID-19 cases across capital cities in Brazil on 26 March, 2020 (n = 27); (*Secretarias de Saúde das Unidades Federativas, 2020*), superimposed on the country's thermal variability. Temperature data represent means for March over 1989–2019 (*Fick & Hijmans, 2017*), and were used only in the map; actual analyses used current, daily meteorological data. Full-size DOI: 10.7717/peerj.9322/fig-1

MATERIALS AND METHODS

We obtained daily cumulative counts of confirmed cases of COVID-19 for each of the 27 Brazilian state capital cities, as reported by State Health Secretaries and compiled by volunteers (Table S1; *Secretarias de Saúde das Unidades Federativas, 2020*).

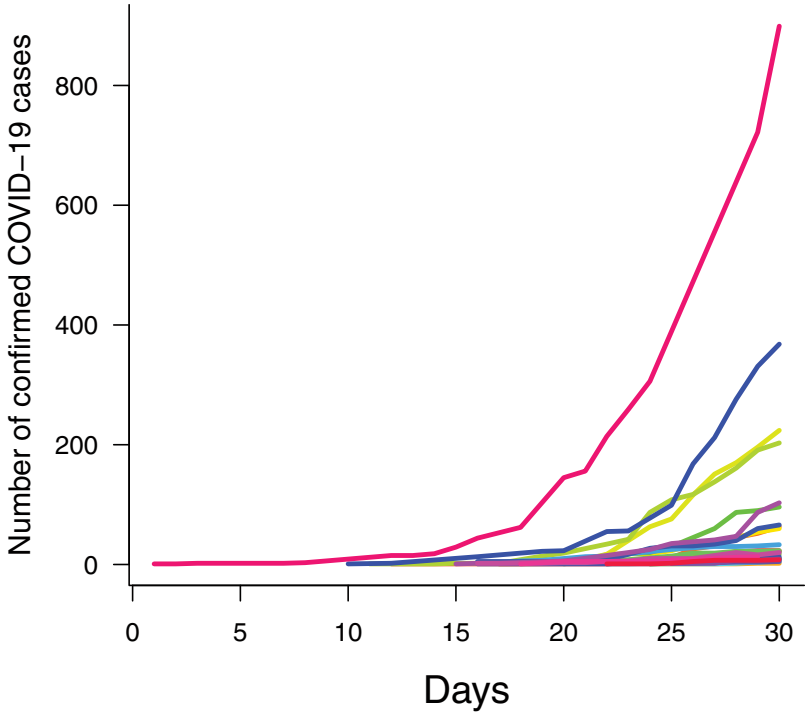

Figure 2 Daily counts of confirmed cases of COVID-2019 across Brazilian state capital cities during the first month. Exponential increase in daily counts of confirmed cases of COVID-2019 across Brazilian state capital cities (n = 292) during the first monitored month. Each line/colour represents one capital city (n = 27). Full-size DOI: 10.7717/peerj.9322/fig-2

We focused on the month since the first confirmed case, from February 26 to March 26, 2020, for which there were 292 reports on daily counts across cities.

We considered several potential predictors of the number of confirmed cases. First, it was important to account for the number of tests for COVID-19, as performing more tests tends to reveal more positive cases (*Roser et al., 2020*). The Brazilian Government has not been systematically reporting the number of performed tests, but has recommended testing of all suspected patients with severe symptoms, and the Ministry of Health reported the number of suspected cases per state until March 18, 2020. Therefore, we used the number of suspected cases per state on that date as a proxy for the number of tests, under the reasonable assumption that states with more suspected cases performed more tests.

Further, we considered the following predictors: (1) time in days, to account for the exponential growth in case numbers during this period (Fig. 2); (2) number of arriving flights in the city's metropolitan area in 2020, as airline connections can facilitate the spread of the virus (*Ribeiro et al., 2020*); (3) city population density, to account for facilitation of transmission under higher densities (*Poole, 2020*); (4) proportion of elderly people (≥60 years old) in the population, assuming that the elderly may be more likely to show severe symptoms of SARS-CoV-2 and, thus, to be diagnosed with COVID-19; (5) citizen mean income, which may affect the likelihood of people being infected by the virus, for example, due to limited access to basic sanitation or limited social isolation capabilities; (6) and the following meteorological variables: mean daily temperature (°C),

mean daily solar radiation (kJ/m^2), mean daily relative humidity (%) and mean daily precipitation (mm). The number of suspected cases and socioeconomic variables only varied across cities, whereas meteorological variables varied both between and within cities.

Data on population density, the elderly and income were obtained for the last quarter of 2019 from the Brazilian Institute for Geography and Statistics (IBGE), which samples Brazilian households quarterly for socioeconomic indicators (*Sidra, 2020*) (Table S2). Flight data were obtained from the current statistical annuary of the Brazilian Agency for Civilian Aviation (ANAC) (Table S3; *ANAC, 2020*). Hourly meteorological data were obtained from the automatic stations maintained by the Brazilian Institute for Meteorology (INMET) in the capital cities (Table S4; *INMET, 2020*).

We investigated the response of case counts to putative predictors using a Generalized Linear Mixed Model (GLMM) assuming Poisson-distributed errors and log link, and using capital-city identity as a random factor to account for autocorrelated errors within cities. This formulation induces a compound symmetry correlation structure on residuals within cities, which is mathematically equivalent to that of classical, "repeated measures" linear models (*Zuur et al., 2009*). The numbers of suspected cases and arriving flights were log-transformed to account for their highly skewed distributions, and all predictors were scaled to zero mean and unit standard deviation to facilitate parameter estimation. Consequently, estimated coefficients were scaled, thus providing a measure of predictor relative importance. Specifically, assuming a log link, a change of one unit in the scaled predictor implies a mean percent change of $(\exp(\text{coefficient}/\text{SD}) - 1) \times 100$ in the number of confirmed cases, where "coefficient" and "SD" are the predictor's model coefficient and standard deviation, respectively.

We considered time lags in the effect of meteorological conditions. Incubation time of COVID-19 averages 5 days (*Lauer et al., 2020*), and case confirmation in Brazil has taken from several days to 2 weeks due to overload of test laboratories. Therefore, the time between infection and case confirmation is likely to be longer than a week. Accordingly, we considered a set of models including all predictors but varying in the number of days meteorological predictors were lagged relative to case counts, ranging from 7 to 30 days with daily steps. Then, models were compared with Akaike's Information Criterion (AIC), a standard measure of model relative support, and the model with the lowest AIC was judged as the most supported.

Precipitation time series had missing intervals for some capital cities. Therefore, we performed two versions of the above analysis: one including all predictors but excluding days for which precipitation was lacking ($n = 269$) and another one excluding precipitation as predictor and using all counts of confirmed COVID-19 cases ($n = 292$). Because both analyses produced largely similar results, with precipitation having a negligible model coefficient (Figs. S1 and S2; Table S5), we present the analysis using the larger sample.

Lastly, we considered possible interactions between time and other predictors, assuming some factors could accelerate the temporal increase in number of confirmed cases. By definition, GLMMs assuming a log link implicitly account for interactive effects to some

degree, as log-linear models imply multiplicative effects. Still, we ran a separate GLMM which explicitly included interaction terms between time and the remaining predictors. To avoid model overparameterization, we only used the significant predictors identified in the previous analysis.

For all models, we computed the conditional predictive power (R^2_c), which indicates the variance explained jointly by predictors and the random factor, and the marginal predictive power (R^2_m), which only considers predictor effects. In these calculations, only significant predictors were retained in the model to avoid inflation of explained variance due to spurious parameters.

We acknowledge that it would be better to directly model the spread of SARS-CoV-2, but we cannot do that without making assumptions about the relationship between infection by the virus and the appearance of symptoms of the disease, which may be related to the factors that we are investigating. All analyses were performed in R 3.6.3 (*R Core Team, 2020*), with aid of packages "coronabr" (*Mortara, Sánchez-Tapia & Martins, 2020*) and "covid19br" (*Paterno, 2020*) for assessing counts of suspected cases by state, "lme4" for GLMM (*Bates et al., 2015*), "MuMIn" for AIC and R^2 calculations (*Bartoń, 2019*), and "visreg" for visualization of predictor effects (*Breheny & Burchett, 2017*).

RESULTS

There was strong support for the model whose meteorological predictors were lagged by 15 days, as indicated by its much lower AIC (Fig. 3). According to this model, the only significant predictors of the number of confirmed COVID-19 cases were time, the number of arriving flights, population density and temperature (Table 1). The number of confirmed cases increased with time (Fig. 4A), the number of arriving flights (Fig. 4B) and population density (Fig. 4C), whereas it decreased with temperature (Fig. 4D). Considering that model coefficients were scaled, comparing their values gives an indication of the relative importance of each predictor. Accordingly, time, the number of arriving flights and population density had the strongest effects (i.e., largest coefficients), followed by temperature (Table 1). Nevertheless, a change in 1 °C predicted a decrease in the number of confirmed cases by $(\exp(-0.26/3.11) - 1) \times 100 = 8\%$, independently of other factors (Table 1). Significant predictors explained 77% of the variance of daily counts of confirmed COVID-19 across capital cities in Brazil.

Explicitly accounting for interactions between time and the remaining predictors identified in the previous analysis suggested significant interactions between time and the number of arriving flights, and time and temperature, although the magnitude of the interaction coefficients was low (Table 2). On average, the temporal increase in confirmed COVID-19 cases began earlier in cities with more flights, causing a leftward shift in the relationship between confirmed cases and time (Fig. 5A). In parallel, the number of confirmed cases increased faster at lower temperatures, causing a steeper slope in the relationship between confirmed cases and time (Fig. 5B). However, these effects were relatively weak, and there was no improvement in predictive power (Table 2). Thus, the previous, simpler model captured the main patterns in the data very well.

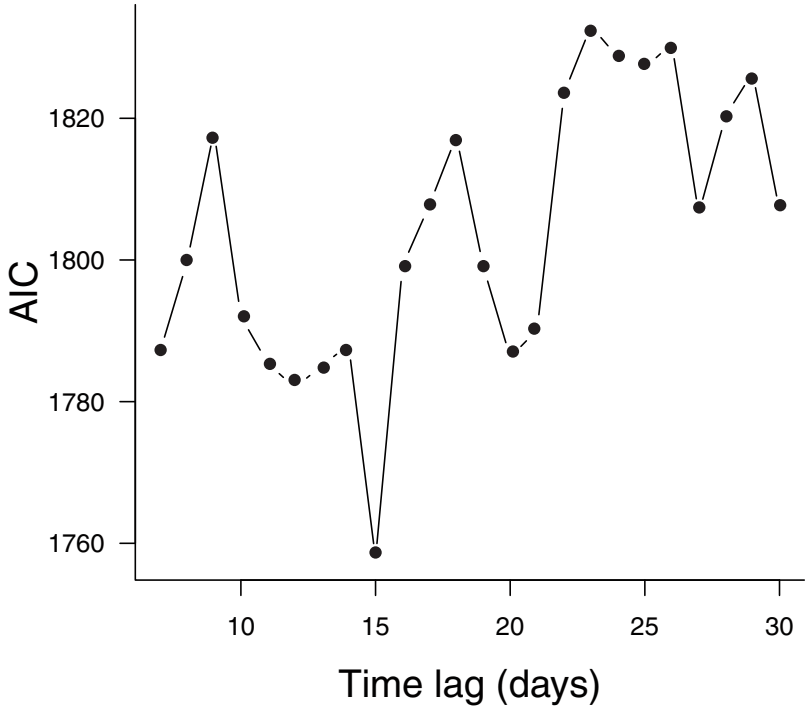

Figure 3 Models considering different time lags in meteorological predictors. Comparison of models considering different time lags in meteorological predictors using Akaike's Information Criterion (AIC). Each point represents one alternative model. Full-size DOI: 10.7717/peerj.9322/fig-3

Table 1 Results of the most supported Generalized Linear Mixed Model (GLMM) testing for independent effects on daily cumulative counts of confirmed COVID-19 across the 27 capital cities in Brazil (n = 292; R^2_c = 0.98; R^2_m = 0.77). The model assumed Poisson-distributed errors and log link, and used capital city identity as a random factor to account for autocorrelated errors of time series within cities. All predictors were scaled to zero mean and unit standard deviation. SD indicates predictor standard deviation; numbers in bold represent statistically significant effects (P < 0.05). Variables were as follows: time—time elapsed in days; Log suspected—log-transformed number of suspected COVID-19 cases in March 18, 2020; Log flights—log-transformed number of arriving flights in 2020; density—inhabitants by km^2; elderly—proportion of elderly people (≥ 60 years old); income—mean citizen income (R$); temperature—mean daily temperature (°C) with a 15-day lag; radiation—mean daily solar radiation (kJ/m^2) with a 15-day lag; humidity—mean daily air humidity (%) with a 15-day lag.

Predictor	SD	Coefficient	z	P
Intercept	–	2.17	–	–
Time	5.72	1.4	67.7	**<0.001**
Log suspected	1,399.23	0.18	0.59	0.556
Log flights	351.06	0.86	3.2	**0.001**
Density	3,087.94	0.47	2.01	**0.044**
Elderly	3.6	−0.36	−1.59	0.111
Income	787.39	0.17	0.81	0.415
Temperature	3.11	−0.26	−5.87	**<0.001**
Radiation	321.67	0.04	1.52	0.127
Humidity	10.26	0.07	1.74	0.082

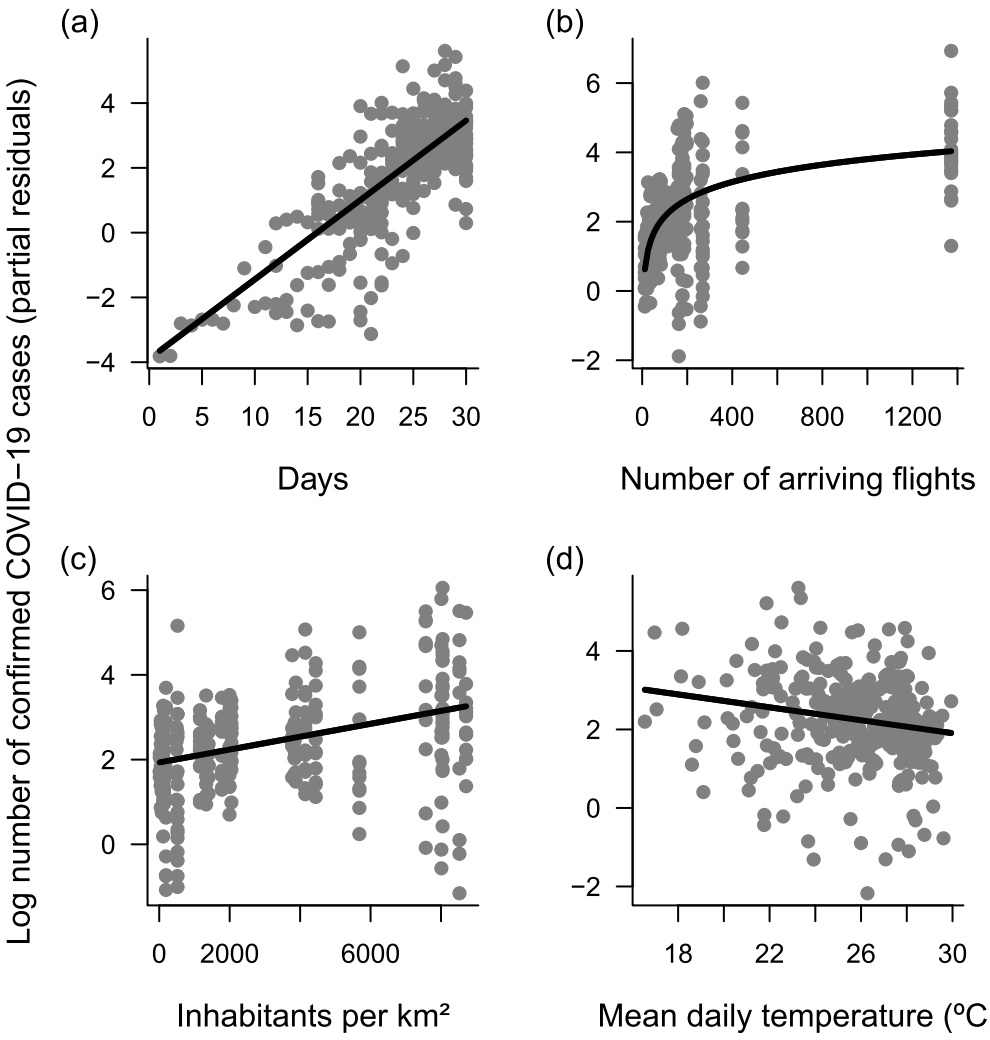

Figure 4 Response of daily cumulative counts of confirmed COVID-19 cases across the 27 Brazilian capital cities. (A) time, (B) number of arriving flights, (C) population density and (D) temperature, as indicated by the most supported Generalized Linear Mixed Model (GLMM). The model assumed Poisson-distributed errors and log link, and included capital city identity as a random factor to account for autocorrelated errors in time series within cities. Each point represents a daily observation in a given city (n = 292); lines represent predicted means. Plots use partial residuals of the response variable and thus show the effect of a given predictor while controlling the effects of remaining predictors.

Full-size DOI: 10.7717/peerj.9322/fig-4

DISCUSSION

Our results indicate that the number of confirmed COVID-19 cases in Brazil has been higher and has begun to increase earlier in cities receiving more flights, consistent with the expected role of air-transport connections in spreading the virus across the country (*Ribeiro et al., 2020*). Further, there have been more cases in cities with higher population density, consistent with the expected role of host density (*Poole, 2020*). We also have uncovered a temperature response with a lag of 15 days: there have been more confirmed cases in colder cities and days, and confirmed cases have accumulated faster under lower

Table 2 **Results of the generalized linear mixed model (GLMM) testing for interaction effects on daily cumulative counts of confirmed COVID-19 in Brazil (n = 292; R^2_c = 0.98; R^2_m = 0.77).** The model assumed Poisson-distributed errors and log link, and used capital city identity as a random factor to account for autocorrelated errors of time series within cities. Only statistically significant predictors in Table 1 were used, all of which were scaled to zero mean and unit standard deviation. SD indicates predictor standard deviation; numbers in bold represent statistically significant effects ($P < 0.05$). Variables were as follows: time–time elapsed in days; Log flights—log-transformed number of arriving flights in 2020; density—inhabitants by km^2; temperature—mean daily temperature (°C) with a 15-day lag.

Predictor	SD	Coefficient	z	P
Intercept	–	2.13	–	–
Time	5.71	1.45	46.55	**<0.001**
Log flights	1.19	0.96	4.67	**<0.001**
Density	3,057.46	0.31	1.58	0.115
Temperature	3.11	−0.30	−8.91	**<0.001**
Time × log flights	–	−0.08	−2.46	**0.014**
Time × density	–	0.01	0.47	0.641
Time × temperature	–	−0.08	−2.85	**0.004**

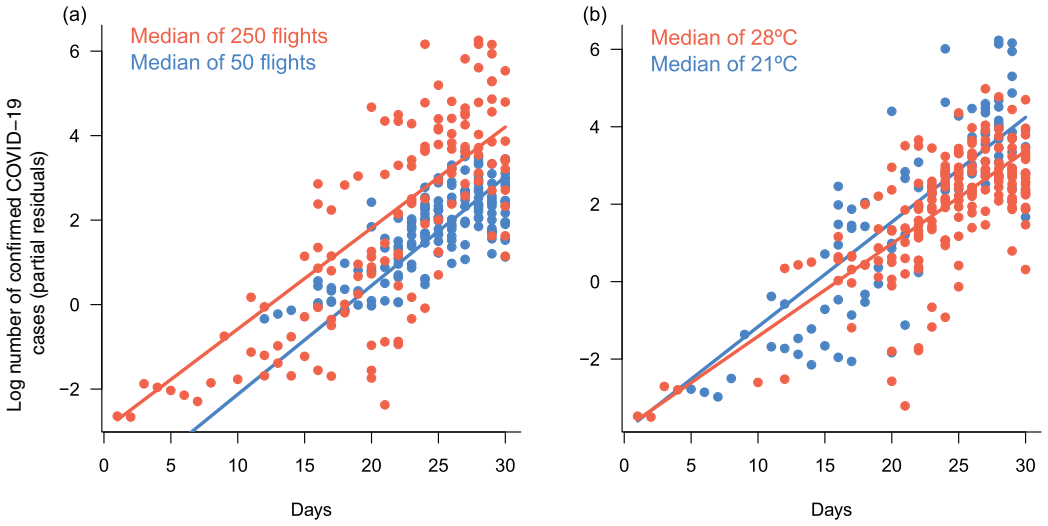

Figure 5 **Response of daily cumulative counts of confirmed COVID-19 cases in Brazil to interactive effects between time an number of arriving flights and mean daily temperature.** Response of daily cumulative counts of confirmed COVID-19 cases across the 27 Brazilian capital cities to interactive effects of (A) time and number of arriving flights, and (B) time and mean daily temperature, based on the Generalized Linear Mixed Model (GLMM) presented in Table 2. The model assumed Poisson-distributed errors and log link, and included capital city identity as a random factor to account for autocorrelated errors in time series within cities. Each point represents a daily observation in a given city (n = 292); lines represent predicted means for each group of observations, as indicated by legends. Group medians were chosen based on their respective predictor ranges (see Fig. 4). Plots use partial residuals of the response variable and thus show the effect of a given interaction while controlling the effects of remaining predictors. Full-size DOI: 10.7717/peerj.9322/fig-5

temperature days. Although correlative, these patterns were independent of several demographic and socioeconomic factors and, thus, are unlikely to be confounded by them. This is disturbing because there is little that authorities can do about this relationship,

whereas the number of arriving flights and population density can be manipulated indirectly by isolation strategies.

The temperature dependance of COVID-19 in Brazil agrees with data from China, where warmer weather also seemed to limit the spread of COVID-19 while controlling for population density and per capita GDP (*Wang et al., 2020*). It also agrees with the thermal dependance of viability and transmission demonstrated experimentally for better-studied viruses, such as influenza (*Lowen et al., 2007*) and other betacoronaviruses, for example, SARS-CoV-1 (*Chan et al., 2011*) and MERS-CoV (*Van Doremalen, Bushmaker & Munster, 2013*). While the precise mechanism underlying this pattern requires further study, it may be related to the lipid bilayer of coronaviruses, which becomes increasingly unstable as temperature increases (*Schoeman & Fielding, 2019*).

Recognizing that we are talking about the rate of spread and not necessarily final mortality rates, the information is still important for authorities trying to predict demands on health services. Our best estimate is that a rise of about 1 °C in mean daily temperature reduces the number of COVID-19 cases by about 8%, independently of other factors. Thus, for instance, our results indicate that Cuiabá, with a mean July temperature of about 23.4 °C, and Porto Alegre, with a mean July temperature of 14.9 °C, may differ up to 50% in the number of COVID-19 cases, all else being equal. It also means that the spread in Porto Alegre might be 41% lower in the middle of March (mean daily temperature of 21.3 °C) than it will be in the middle of July (mean daily temperature of 14.9). At the same time, and contrary to some suggestions (*Poole, 2020*; *Wang et al., 2020*; *Grant et al., 2020*), we found no evidence for effects of solar radiation or humidity. Perhaps such conditions are not limiting for the virus or the disease under the climatic conditions of Brazil. Also, rapid evolution of the climatic niche of SAR-Cov-2 could have a similar effect. Although the mutation rate of SARS-CoV seems to be moderate compared to that of other RNA viruses (*Zhao et al., 2004*; *Yang et al., 2020*), clustering of hundreds of worldwide SARS-CoV-2 genomes based on widely shared polymorphisms suggests 16 subtypes, all of which harbor amino acid replacements which may have phenotypic effects (*Morais et al., 2020*).

Whether the temperature effect is related to the rate of spread of SARS-CoV-2 or to the proportion of persons that suffer reportable symptoms cannot be answered with the data being provided at the moment (*Fasina, 2020*). That would require universal testing for the presence of the virus, which is not presently viable but may be a necessity in the following months. Also, one of the main difficulties we encountered was the lack of systematization of current information, since much of the data generated daily is still scattered and difficult to access. For instance, the number of tests performed, which is the key to estimate the rate of infection and the number of infected patients is not available. The large number of publications on the subject in the last 30 days shows that the scientific community is prepared for a quick response, as long as there is a systematization and transparency of information regarding the number of tests being performed, number of suspected cases, number of infected, number of deaths, etc.

Our models are necessarily simple and have limitations. Most importantly, we need city and state administrations to provide the number of performed tests on a regular basis,

so that this variable can be explicitly accounted for in the model. The data do not allow us to investigate complex nonlinear effects, which likely would require data on temperatures beyond those observed in Brazilian cities in March. Also, it is currently not possible to account for potential interactions between COVID-19 and other diseases, particularly influenza, which is seasonal. It may not be necessary to worry about this in the northern hemisphere because the peaks in COVID-19 will occur after the peaks in seasonal influenza. However, the predicted peaks in COVID-19 in the southern hemisphere will occur concomitantly with peaks in seasonal influenza (*Nelson et al., 2006*; *Viboud, Alonso & Simonsen, 2006*). The effects may just be additive, but it is not known whether the simultaneous infection will increase the severity of COVID-19 and therefore the demand for ICUs, and this interaction also could be temperature sensitive. Further, air pollution is known to increase susceptibility to viral respiratory infections (*Ciencewicki & Jaspers, 2007*), but the extent to which it affects the prevalence of COVID-19 is unclear. As COVID-19 consolidates in different cities, it will be possible to reduce uncertainties in relation to the role of temperature and other factors. Nonetheless, our models still performed well as judged by their predictive power, even when ignoring interactions between predictors.

We stress that the temperature effect does not mean that the northern, warmer regions of Brazil should expect fewer complications in their health care system, because such regions also have poorer socioeconomic and sanitary conditions (*Barreto et al., 2011*), and ICUs are concentrated in southern regions (*Rhodes & Moreno, 2012*). Although we found no evidence for an effect of income on the number of confirmed COVID-19 cases, this variable is related to the capacity of cities to respond to the pandemic. Furthermore, apart from elapsed time, the predictors with the largest standardized coefficients were the number of arriving flights and population density (Table 1). Indeed, Manaus, the largest city in Northern Brazil, was the first Brazilian city to declare the collapse of the health system early in April 2020, which is consistent with its large number of arriving flights and large population density but relatively low number of ICUs (*Rhodes & Moreno, 2012*). By contrast, although southern, colder regions have a higher density of ICUs, their situation could be aggravated if social isolation measures are not effectively adopted before and maintained throughout winter in those regions (from June to September). This should be especially important for "favelas", that is, poorer, highly populated neighborhoods with deficient infrastructure, which are presumably at high risk of infection. Thus, we do not present our results as an indication of how hospital demand should be calculated, but as a warning that models for Brazil need to take into account predicted temperatures.

CONCLUSIONS

Declared as a pandemic by the World Health Organization (WHO), the COVID-19 disease has changed human behavior and strongly affected health systems and the economy worldwide. In an extremely demanding scenario, optimizing the distribution of resources is an essential task. Brazil and other countries are starting to discuss the flexibilization of social distancing policies, as the latter could have important economic costs. However, we need to understand how and when to implement such decisions in

order to prevent new, uncontrolled disease outbreaks that may overcrowd the health care system again and generate even higher economic costs in the near future. Our results suggest that, along with arriving flights and population density, temperature should be taken into account to estimate the number of cases of COVID-19, especially with winter approaching in the southern hemisphere.

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ADDITIONAL INFORMATION AND DECLARATIONS

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Competing Interests

The authors declare that they have no competing interests.

Author Contributions

- Pedro Pequeno conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.
- Bruna Mendel conceived and designed the experiments, performed the experiments, authored or reviewed drafts of the paper, and approved the final draft.
- Clarissa Rosa conceived and designed the experiments, authored or reviewed drafts of the paper, and approved the final draft.
- Mariane Bosholn conceived and designed the experiments, authored or reviewed drafts of the paper, and approved the final draft.
- Jorge Luiz Souza conceived and designed the experiments, authored or reviewed drafts of the paper, and approved the final draft.
- Fabricio Baccaro conceived and designed the experiments, authored or reviewed drafts of the paper, and approved the final draft.
- Reinaldo Barbosa conceived and designed the experiments, authored or reviewed drafts of the paper, and approved the final draft.
- William Magnusson conceived and designed the experiments, authored or reviewed drafts of the paper, and approved the final draft.

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The following information was supplied regarding data availability:

The raw measurements are available in the Supplemental Files.

Supplemental Information

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Impact of meteorological factors on the COVID-19 transmission: A multi-city study in China

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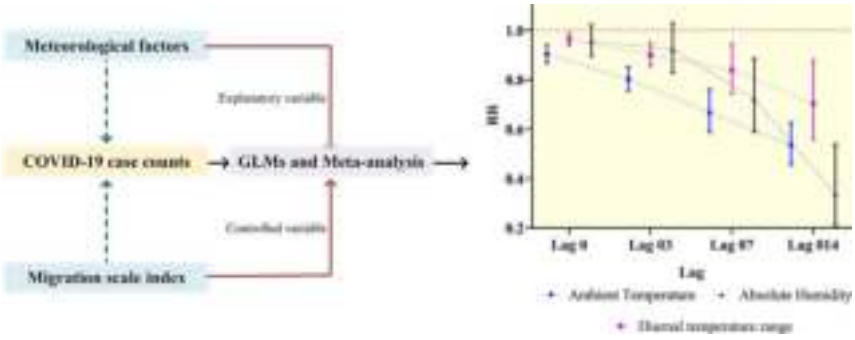
HIGHLIGHTS

- The impacts of meteorological factors on COVID-19 case counts were assessed after controlling population migration.
- The weather with low temperature, mild diurnal temperature range and low humidity likely favor the transmission of COVID-19.
- The epidemic might gradually ease partially due to rising temperatures in coming months.

GRAPHICAL ABSTRACT



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ABSTRACT

The purpose of the present study is to explore the associations between novel coronavirus disease 2019 (COVID-19) case counts and meteorological factors in 30 provincial capital cities of China. We compiled a daily dataset including confirmed case counts, ambient temperature (AT), diurnal temperature range (DTR), absolute humidity (AH) and migration scale index (MSI) for each city during the period of January 20th to March 2nd, 2020. First, we explored the associations between COVID-19 confirmed case counts, meteorological factors, and MSI using non-linear regression. Then, we conducted a two-stage analysis for 17 cities with more than 50 confirmed cases. In the first stage, generalized linear models with negative binomial distribution were fitted to estimate city-specific effects of meteorological factors on confirmed case counts. In the second stage, the meta-analysis was conducted to estimate the pooled effects. Our results showed that among 13 cities that have less than 50 confirmed cases, 9 cities locate in the Northern China with average AT below 0 °C, 12 cities had average AH below 4 g/

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Absolute humidity
Population migration

m^3, and one city (Haikou) had the highest AH (14.05 g/m^3). Those 17 cities with 50 and more cases accounted for 90.6% of all cases in our study. Each 1 °C increase in AT and DTR was related to the decline of daily confirmed case counts, and the corresponding pooled RRs were 0.80 (95% CI: 0.75, 0.85) and 0.90 (95% CI: 0.86, 0.95), respectively. For AH, the association with COVID-19 case counts were statistically significant in lag 07 and lag 014. In addition, we found the all these associations increased with accumulated time duration up to 14 days. In conclusions, meteorological factors play an independent role in the COVID-19 transmission after controlling population migration. Local weather condition with low temperature, mild diurnal temperature range and low humidity likely favor the transmission.

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1. Introduction

Wuhan, the capital city of Hubei province, China, was the first major metropolitan region suffering from the coronavirus disease 2019 (COVID-19) outbreak and the epidemic center since December, 2019 (Zhou et al., 2020). COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus. Due to the high contiguousness and wide spread, COVID-19 has officially been declared a pandemic by the World Health Organization (WHO) on March 11, 2020 (World Health Organization, 2020b). As of March 21th, more than 170 countries has reported this epidemic, with a total diagnosed cases of about 234,073 causing over 9000 deaths (World Health Organization, 2020b). Europe and the United States have gradually becoming the epicenter of the pandemic (World Health Organization, 2020c) and the world is facing great public health crisis from COVID-19, which is likely more severe than SARS in 2003.

In China, COVID-19 has spread in multiple major cities that have huge numbers of both inbound and outbound passengers (e.g., Beijing, Shanghai, and Guangzhou) (Wu et al., 2020). To block the quick spread of infection and control the severe epidemic, China has conducted strict measures by mobilizing and redistributing nationwide resources, shelter-in-place and quarantining all confirmed cases and close contacts. A study indicated that a series of control measures since January 23, 2020 in China reduced the COVID-19 epidemic size significantly, and the similar measures were expected to remain until the end of April 2020 (Yang et al., 2020). The current daily new COVID-19 cases in China have reached very low level. China has cumulatively reported more than 81,008 confirmed cases and over 3,255 deaths as of March 21, 2020 (National Health Commission of the People's Republic of China, 2020). Among all these effective strategies in controlling this epidemic, locking down Wuhan, a city of 11 million residents, was one of the most dramatic measures. It turned out that the limitation of population migration was effective in controlling epidemic diseases like COVID-19. However, the independent effect of meteorological factors on the transmission of COVID-19 has not been studied systemically while controlling population migration.

Previous studies showed that cold and dry weather is beneficial for the survival and spread of droplet-mediated viral diseases like

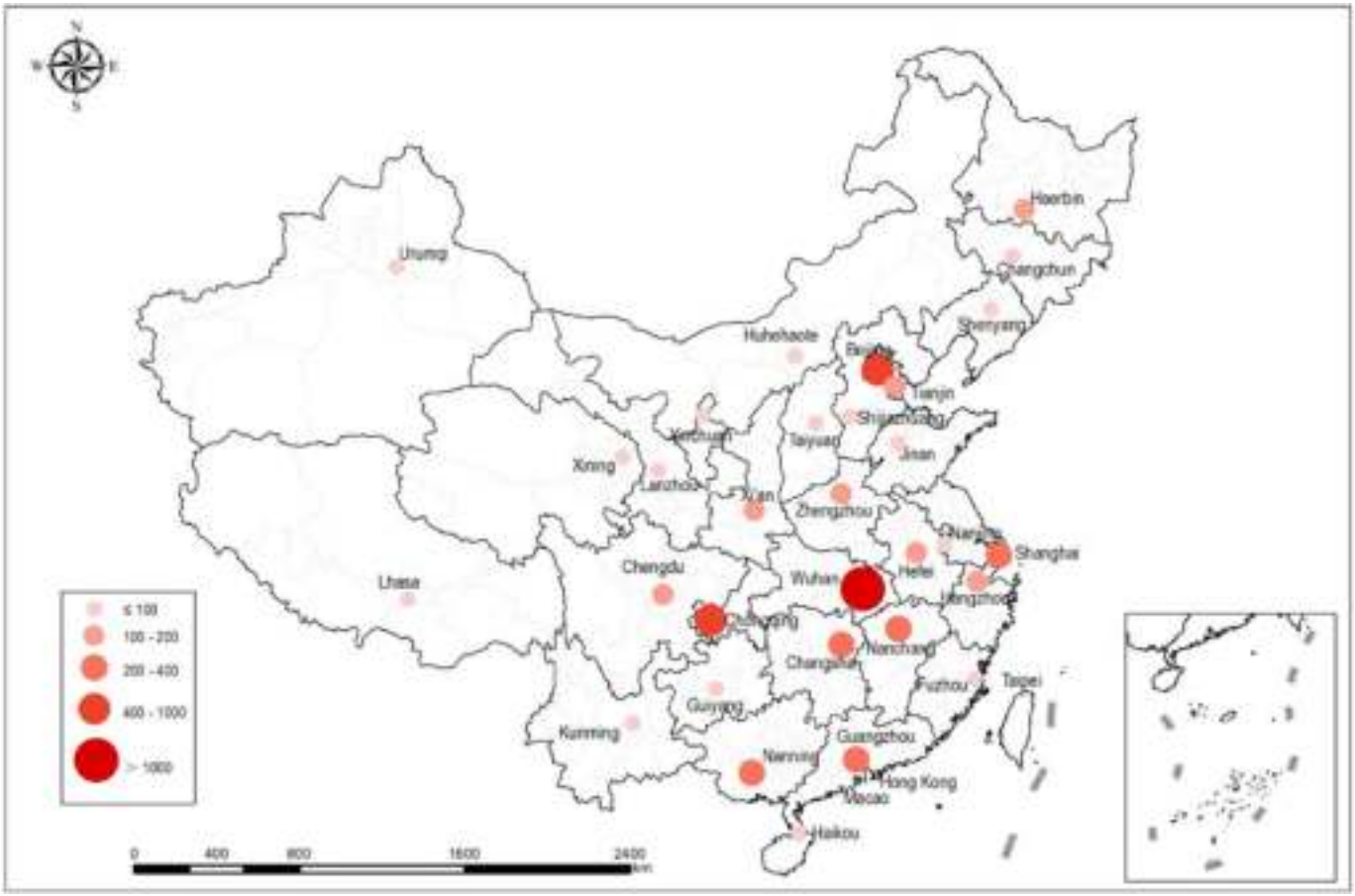

Fig. 1. Geographic patterns of COVID-19 confirmed case counts in 30 provincial capital cities of China as of March 2nd, 2020.

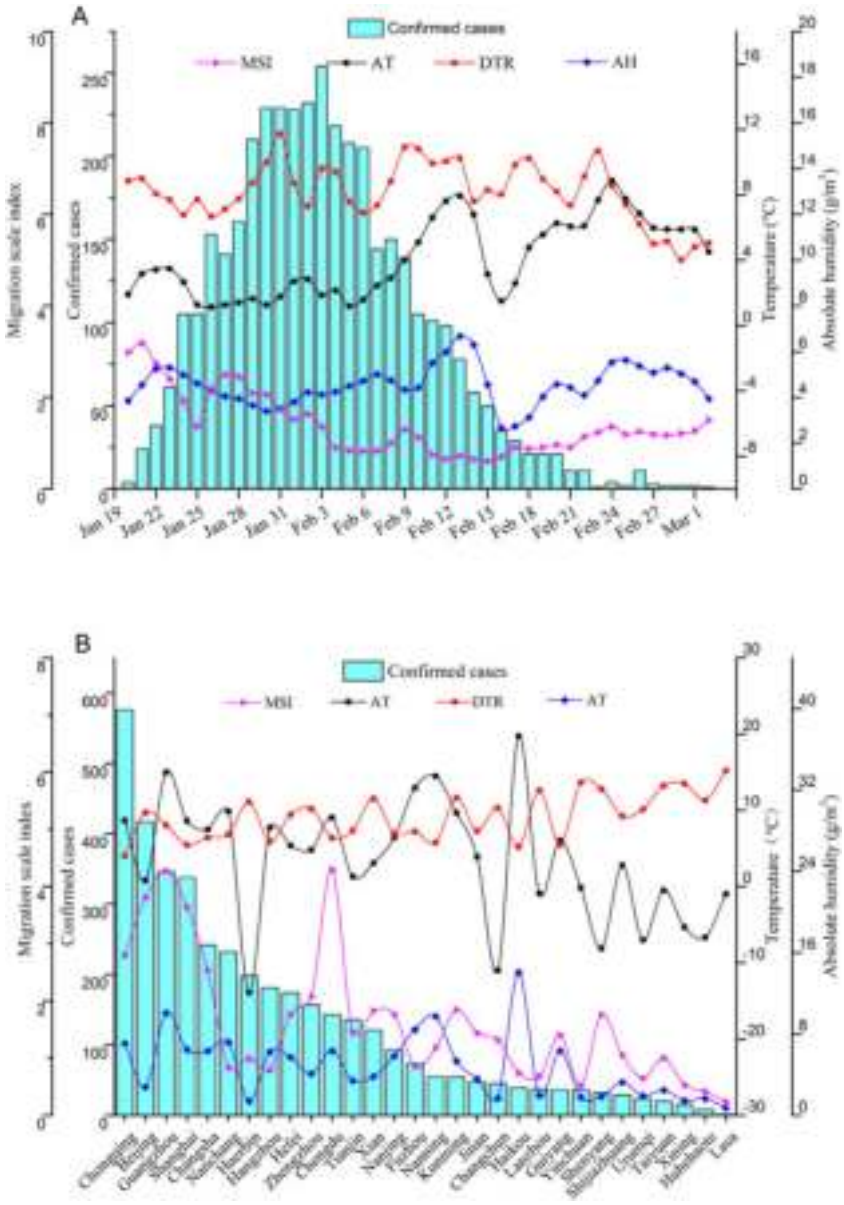

Fig. 2. Total COVID-19 case counts, average values of meteorological factors and MSI in 30 provincial capital cities of China during the period of January 20th to March 2nd 2020. Note: A: Temporal distribution; B: Regional distribution. AT: Ambient temperature; DTR: Diurnal temperature range; AH: Absolute humidity; MSI: Migration scale index.

influenza (Lowen et al., 2007; Shaman and Kohn, 2009; Li, 2011). The SARS epidemic was gradually faded with the warming weather coming, and was basically ended in July, 2003 (Tan et al., 2005; Wang et al., 2006; Cao et al., 2016), suggesting that the temperature and its variations might have affected the SARS outbreak. Some studies have suggested that the climate change might have contributed to various infectious diseases emergence and spread (Lofgren et al., 2007; Gale et al., 2010; Stott, 2016), including the SARS and COVID-19. In Korea, researchers found that the risk of influenza incidence was significantly increased with low daily temperature and low/high relative humidity (RH), but a positively correlated with diurnal temperature range (DTR) (Park et al., 2020). Absolute humidity (AH) had significant correlations with influenza viral survival and transmission rates (Shaman et al., 2010; Shaman et al., 2011). One important feature of COVID-19 epidemic is that the countries currently suffering most from the disease are most located in the regions with low temperature. Therefore, meteorological factors, such as ambient temperature (AT) and humidity, might play an important role in the spread of the disease.

Many factors might influence the COVID-19 epidemic, including social and political factors, geographical factors, climatic factors, etc. (Casadevall, 2020; Wu et al., 2020). When only considering the temperature in single-factor model in the higher-temperature group, every 1 °C increase in the minimum temperature leads to a decrease of the cumulative number of COVID-19 cases by 0.86 (Wang et al., 2020). Luo etc. reported that weather was related to the spread of COVID-19, but the increase of temperature may not necessarily lead to declines in case counts without the implementation of extensive public health interventions (Luo et al., 2020). In another study, researchers estimated that the weather variables explain 18% of the variation in disease doubling time, and the remaining 82% may be related to containment measures, general health policies, population density, transportation or cultural aspects (Oliveiros et al., 2020). Because of the human to human transmission, the migration should be considered when evaluate the effects of meteorological factors over COVID-19 transmission. However, to

Table 1
Summary of statistics for total confirmed COVID-19 case counts, MSI and meteorological factors in 30 cities during the period of January 20th to March 2nd, 2020.[a]

Cities	Counts of confirmed cases	Migration scale index	Daily average temperature (°C)	Diurnal temperature range (°C)	Absolute humidity (g/m^3)
Chongqing	576	2.80 ± 2.80	8.67 ± 1.83	4.03 ± 2.36	7.06 ± 1.15
Beijing	417	3.80 ± 3.80	0.80 ± 2.92	9.69 ± 4.54	2.75 ± 2.02
Guangzhou	346	4.27 ± 4.27	15.01 ± 3.50	8.04 ± 5.96	10.07 ± 3.33
Shanghai	338	3.64 ± 3.64	8.62 ± 2.92	5.47 ± 4.20	6.45 ± 2.18
Changsha	242	2.54 ± 2.54	7.49 ± 3.34	6.42 ± 2.47	6.33 ± 3.11
Nanchang	232	0.84 ± 0.84	9.88 ± 3.81	6.85 ± 0.77	7.17 ± 3.18
Haerbin	198	0.99 ± 0.99	−13.90 ± 5.68	11.08 ± 0.98	1.39 ± 0.89
Hangzhou	181	0.79 ± 0.79	7.72 ± 2.38	5.91 ± 2.64	6.23 ± 2.20
Hefei	174	1.76 ± 1.76	5.37 ± 3.12	9.42 ± 1.11	5.70 ± 3.54
Zhengzhou	157	2.08 ± 2.08	4.82 ± 2.73	10.20 ± 2.52	4.08 ± 2.34
Chengdu	143	4.29 ± 4.29	9.03 ± 1.75	6.39 ± 5.88	6.33 ± 1.21
Tianjin	136	1.46 ± 1.46	1.33 ± 2.96	7.35 ± 1.24	3.39 ± 2.12
Xian	121	1.83 ± 1.83	3.07 ± 2.21	11.53 ± 2.39	3.81 ± 2.02
Nanjing	93	1.76 ± 1.76	6.46 ± 2.37	6.95 ± 2.45	5.82 ± 2.99
Fuzhou	74	0.85 ± 0.85	12.94 ± 3.29	7.23 ± 0.90	8.42 ± 3.89
Nanning	55	1.18 ± 1.18	14.47 ± 3.84	5.77 ± 1.33	9.73 ± 3.77
Kunming	54	1.84 ± 1.84	9.69 ± 2.36	11.63 ± 2.83	5.34 ± 2.94
Jinan	47	1.44 ± 1.44	3.91 ± 3.28	7.28 ± 1.44	3.57 ± 3.76
Changchun	45	1.31 ± 1.31	−11.01 ± 5.92	10.32 ± 1.72	1.68 ± 1.12
Haikou	39	0.74 ± 0.74	19.73 ± 3.30	5.20 ± 0.70	14.05 ± 3.14
Lanzhou	37	0.68 ± 0.68	−0.92 ± 2.05	12.62 ± 0.86	1.95 ± 0.54
Guiyang	36	1.40 ± 1.40	6.04 ± 3.90	5.48 ± 1.32	6.35 ± 3.58
Yinchuan	36	0.52 ± 0.52	−0.15 ± 3.95	13.64 ± 0.98	1.76 ± 0.64
Shenyang	32	1.76 ± 1.76	−8.80 ± 4.36	12.77 ± 1.15	1.83 ± 0.89
Shijiazhuang	29	1.06 ± 1.06	2.77 ± 3.05	9.25 ± 1.71	3.24 ± 0.95
Urumqi	23	0.64 ± 0.64	−7.02 ± 3.77	10.12 ± 0.00	1.92 ± 0.23
Taiyuan	20	1.00 ± 1.00	−0.52 ± 2.30	13.24 ± 1.42	2.46 ± 0.67
Xining	15	0.53 ± 0.53	−5.30 ± 0.90	13.51 ± 0.65	1.45 ± 0.40
Huhehaote	8	0.41 ± 0.41	−6.65 ± 3.71	11.30 ± 0.34	1.63 ± 0.39
Lhasa	1	0.23 ± 0.23	−0.98 ± 0.55	15.20 ± 0.47	0.70 ± 0.10
Average	130.17 ± 138.60	1.62 ± 1.14	3.44 ± 7.97	9.13 ± 3.04	4.75 ± 3.14

[a] To account for the latent period of COVID-19, for each city, averaged meteorological parameters were calculated during the period of 20th to March 2nd, 2020.

our knowledge, previous studies have not controlled the population migration to examine independent effects of weather conditions on the COVID-19 transmission.

In this study, we first explored non-linear relation between COVID-19 case counts and meteorological factors. Then we used generalized linear models to examine the associations between meteorological factors and COVID-19 daily case counts in 30 provincial capitals except for Wuhan in China while controlling the population migration.

2. Methods

2.1. Data collection

Since the COVID-19 condition was much more complicated compared with other provinces due to government interventions in Hubei, like Wuhan lockdown and mass screening, we chosen to study the relationship in 30 capital cities of China. We obtained daily officially reported confirmed case counts from the Health Commission of the 30 capital cities except Wuhan during the period January 20th to March 2nd 2020 (Fig. 1). The daily meteorological data, including hourly temperature and RH, were obtained from Shanghai Meteorological Bureau and Data Center of Ministry of Ecology from January 5th to March 2nd 2020. Meanwhile, migration scale index (MSI) of the 30 cities was collected from the website of Baidu Migration (https://qianxi.baidu.com/?from=mappc). MSI reflects the population scale of moving in, and MSI of cities can be comparable. The daily average AT and DTR were calculated based on hourly data. AH was calculated according to the method used in the previous study which was measured by vapor pressure (g/m^3) (Shaman et al., 2011; Davis et al., 2016; Liu et al., 2018).

2.2. Statistical analysis

A descriptive analysis was performed to explore the city-specific characteristics of confirmed case counts, AT, DTR, AH and MSI of these 30 cities. For each city, average meteorological data were calculated based on the period of January 20th to March 2nd, 2020 to account for the lag effect and the latent period of COVID-19. Then, a second order polynomial non-linear regression models were fitted between total COVID-19 confirmed case counts and AT, DTR, AH, MSI.

We characterize the disease transmission and case distribution in the 13 cities with less than 50 confirmed cases. Then, a two-stage analysis was conducted for the other 17 cities with more than 50 cases in each city. In the first stage, because of the clustering characteristics of the disease, we adopted generalized linear models with negative binomial distribution to estimate city-specific effects. The analyses were performed with R software version 3.3.2, and the "MASS" package (MASS: Support functions and datasets for venables and Ripley's MASS, 2019) was used to fitting models. The fitted formulas were as follows:

$$\text{Log E}\,(Y_t) = \alpha + \beta_1 \text{AT} + \text{ns}\,(\text{RH}, 3) + \beta_2 \text{MSI} \quad (1)$$

$$\text{Log E}\,(Y_t) = \alpha + \beta_1 \text{DTR} + \text{ns}\,(\text{RH}, 3) + \beta_2 \text{MSI} \quad (2)$$

$$\text{Log E}\,(Y_t) = \alpha + \beta_1 \text{AH} + \beta_2 \text{MSI} \quad (3)$$

where t is the day of the observation; E(Y_t) is the expected number of daily confirmed cases on day t; α is the intercept; β is the regression coefficient. Considering the lag effects and the average latent period of COVID-19, 3-day moving average RH and 3-day moving average MSI were controlled in the models when exploring the effects of AT (1) and DTR (2). As a meteorological factor, natural cubic splines (ns) with 3 *df* was used for controlling RH. Considering the collinearity, only three-day moving average MSI were controlled in the models (3) when dealing with AH. Because of the lag effects, we evaluated the associations in lag 0, lag 03, lag 07 and lag 014 between daily confirmed case counts and these meteorological factors for each city.

In the second stage of the analysis, we conducted a random effects meta-analysis to pool estimates across city-specific associations. The

meta-analysis was performed based on STATA/SE 11.0 (StataCorp LLC, USA).

All results were expressed as the relative risk (RR) in daily confirmed case counts with 95% confidence intervals (95% CI) relative to a fixed change (1 °C or 1 g/m^3) of each factor. Statistical significance was set at p-value < 0.05.

3. Results

3.1. Descriptive analysis

As of March 2nd, 2020, a total of 3,905 cases were officially reported in 30 provincial capital cities in China. Among these cities, 17 cities had more than 50 confirmed cases, accounting for 90.6% of all cases in this study. During our study period, the daily MSI, AT, DTR and AH for these 30 cities were 1.62 ± 1.14, (3.44 ± 7.97) °C, (9.13 ± 3.04) °C and (4.76 ± 3.14) g/m^3. Strong regional differences were observed for meteorological factors and MSI.

Among the 13 cities that have less than 50 cases, 9 cities located in the Northern China with average AT below 0 °C, 12 cities had average AH below 4 g/m^3 and one city (Haikou) had the highest AH (14.05 g/m^3) (Figs. 1, 2 and Table 1). The MSI in these 13 cities were relatively lower than the remaining 17 cities that have more than 50 cases (Fig. 2).

3.2. Temporal and regional characteristics of COVID-19 transmission

The nonlinear regression analysis results (Fig. 3) suggest brief distribution characteristics between confirmed case counts and AT, DTR, AH, MSI. We found an obvious trend association between AT and the confirmed case counts, it seemed that the confirmed case number increased with temperature increasing in the range of −20 °C–20 °C. Like that, similar trend was also found between confirmed case counts and MSI. Well, we found there was an arched shape for the relationship between confirmed case counts and period-average AH, as there were more confirmed cases at the AH of around 6 g/m^3. However, the regression model showed that the confirmed cases counts declined with the increase of DTR in the range of 5 °C–15 °C.

3.3. AT, DTR and AH negatively related to the increase of COVID-19 transmission

Concerning the small sample size in those 13 cities, the fitted city-specific generalized linear models and meta-analysis were only conducted for the 17 cities with 50 and more cases to explore the associations between COVID-19 case counts and meteorological factors (Fig. 4). In city-specific analysis, significant negative associations were found in 9 cities (Beijing, Tianjin, Zhengzhou, Hangzhou, Shanghai, Xian, Nanchang, Fuzhou and Guangzhou) in lag 03. In meta-analysis, the pooled results showed that each 1 °C increase in AT was related to the decline of daily confirmed COVID-19 case counts, the corresponding overall RR was 0.80 (95% CI: 0.75, 0.85) (Fig. 4A). Each 1 °C increase in DTR was associated with decreased patients in lag 03 and the pooled RR was 0.90 (95% CI: 0.86, 0.95). In the city level, it was significant for Hangzhou, Nanchang, Fuzhou, Chengdu and Zhengzhou in lag 03 (Fig. 4B). As showed in Fig. 4C, AH had significant negative effects on confirmed case counts for 4 cities, including Guangzhou, Hangzhou, Nanchang, and Nanjing. Meta-analysis showed that each 1 g/m^3 increase in AH was significantly associated with reduced confirmed case

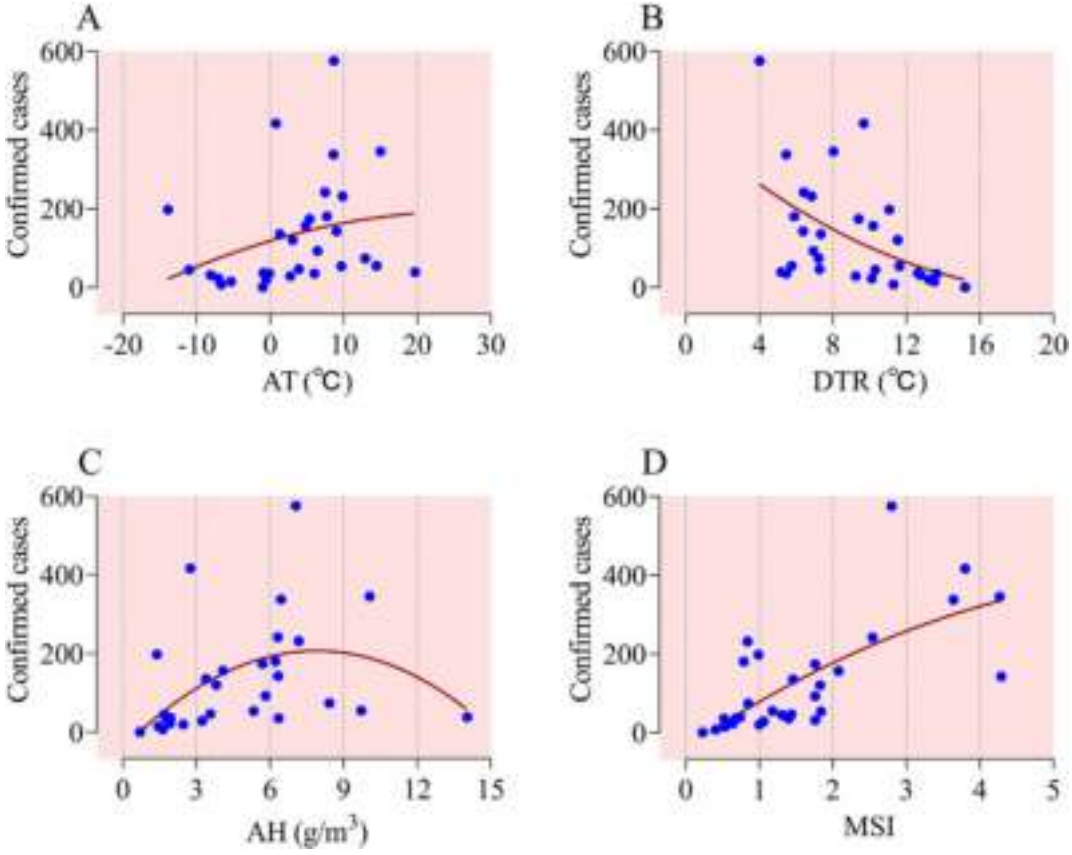

Fig. 3. Associations between COVID-19 confirmed case counts and meteorological factors, MSI in 30 provincial capital cities of China. Note: (A) AT, Curve formula: Y = 118.5 + 5.552 * X-0.1022 * X^2, R^2 = 0.08776; (B) DTR, Curve formula: Y = 408.5–40.24 * X + 0.9651* X^2, R^2 = 0.2379; (C) AH, Curve formula: Y = –40.20 + 62.59* X-3.957 * X^2, R^2 = 0.2291; (D) MSI: Y = –38.21 + 125.7 * X-8.973 * X^2, R^2 = 0.4953. The brown lines in figures represent second order polynomial curves. The blue dots represent the 30 cities. AT: Ambient temperature; DTR: Diurnal temperature range; AH: Absolute humidity; MSI: Migration scale index.

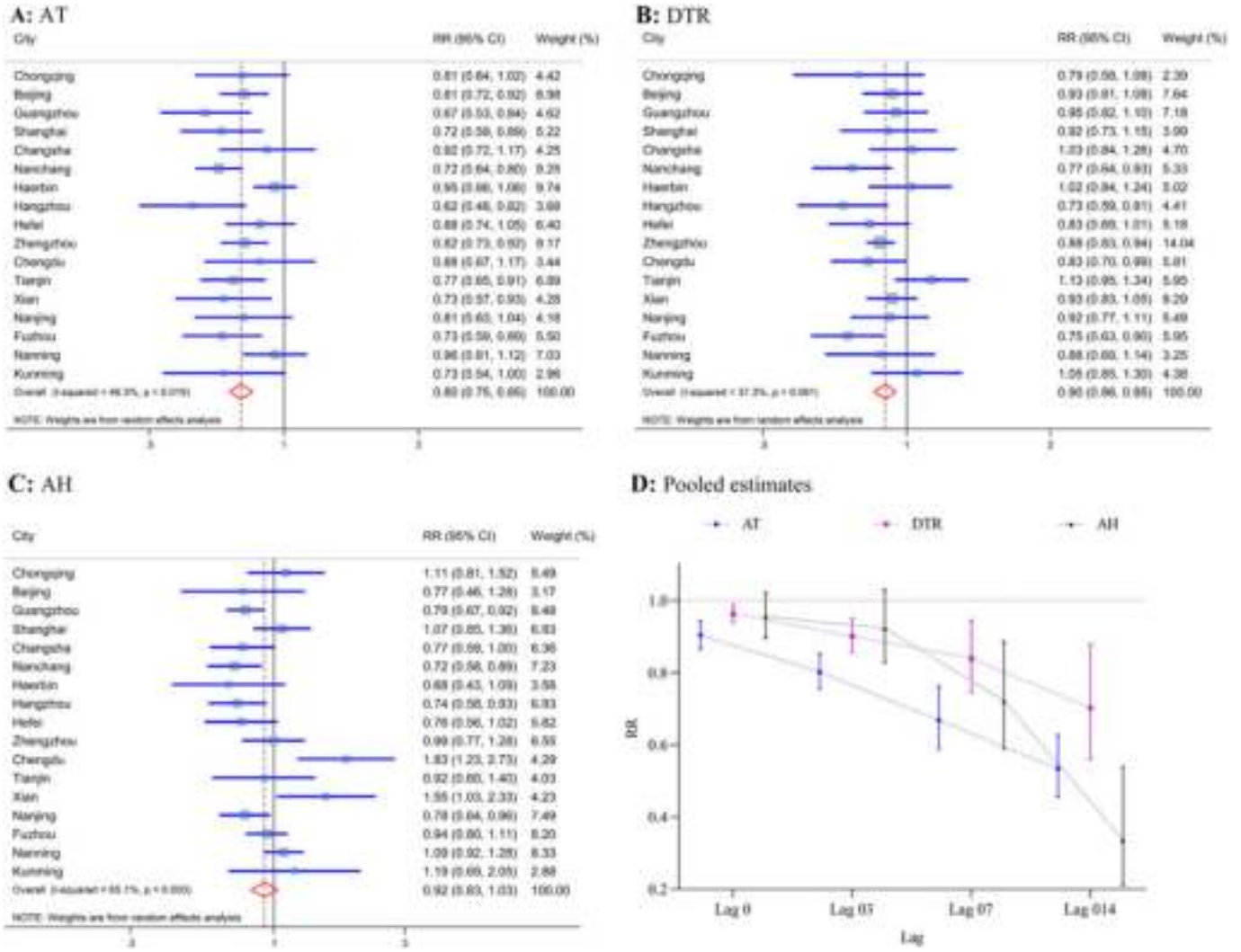

Fig.ure 4. Meta-analysis for effects of meteorological factors on COVID-19 case counts in 17cities during the period of January 20th to March 2nd 2020. Note: (A) AT; (B) DTR; (C) AH; (D) Pooled estimates in lag 0, lag 03, lag 07 and lag 014. The associations of COVID-19 case counts with AT, AH and DTR in each city was evaluated by fitting generalized linear models respectively (Lag 03). The meta-analysis was conducted to combine the city-specific results. AT: Ambient Temperature; DTR: Diurnal Temperature Range; AH, Absolute Humidity.

counts for 17 cities cities in lag 07, lag 014 and the combined RR was 0.72 (95% CI: 0.59, 0.89) and 0.33 (95% CI: 0.21, 0.54).

Fig. 4D showed associations between confirmed case counts and AT, DTR and AH in lag 0, lag 03, lag 07 and lag 014. The pooled effects of AT, DTR and AH became stronger with the increase of cumulative lag days.

4. Discussions

As of March 2nd, China has reported 80, 302 COVID-19 cases. This is the first study to examine the impact of meteorological factors on COVID-19 after controlling population migration. Our results indicated that COVID-19 transmission may be affected by meteorological factors, and a weather with low temperature, mild diurnal temperature range and low humidity likely favor its transmission.

Our findings on the impact of meteorological conditions over the transmission of COVID-19 are consistent with previous studies on the transmission of SARS or other infectious diseases (Tan et al., 2005; Lin et al., 2006; Liu et al., 2018; Park et al., 2020). Some studies suggested that global climate change might be accompanied by the changes to the outbreak of infectious diseases (Bezirtzoglou et al., 2011; Anwar et al., 2019; Casadevall, 2020). As we know, viruses are completely dependent on their hosts for replication and survival. It is possible that as virus has adapted to gradually higher global AT, some new and previously unknown infectious diseases are likely to emerge and spread (Casadevall, 2020), such as SARS-CoV and Ebola virus, and poses a threat to human health. The emergence and spread of novel coronavirus since December 2019 might be related to the ongoing climate change. In winter and spring, a decrease in resistance to respiratory diseases in a colder environment for population might be easier to accelerate the spread velocity. Lin etc. showed that in days with a lower air temperature during the epidemic, the risk of increased daily incidence of SARS was 18.18-fold (95% CI: 5.6, 58.8) higher than in days with a higher temperature (Lin et al., 2006). Tan etc. found a close association between temperature, its variations and the SARS outbreak in the four cities in China, suggesting that SARS more likely outbreaks in spring (Tan et al., 2005). Consistent with these results, we also found that each 1 °C increase in AT was related to the decline of daily confirmed case counts, the corresponding overall RR was 0.80 (95% CI: 0.75, 0.85). In addition, Lambrechts etc. has found that a large DTR might impede dengue virus infection of the mosquito midgut and reduce transmission risks compared to a small DTR or constant temperature. Intensity of dengue virus transmission can be influenced by the specific combination of mean and range in temperature fluctuations (Lambrechts et al., 2011). In our study, each 1 °C increase in DTR was associated with decreased

patients in lag 03 and the pooled RR was 0.90 (95% CI: 0.86, 0.95). This suggests that novel coronavirus might be also more suited to survive in an environment with small DTR or constant temperature.

AH is an indicator describing the mass of water vapor per volume of air (g/m^3). Shaman et al. found that 50% of influenza virus transmission variability and 90% of influenza virus survival variability could be explained by AH variation, whereas, only 12% and 36% could be explained by relative humidity (Shaman and Kohn, 2009), and the epidemic influenza typically peaks in the winter when low AH maximizes R0 (Shaman et al., 2011). A previous study found that AH was one of most important weather parameters in predicting heat-related mortality among a spectrum of weather parameters (Zhang et al., 2014). These studies indicated that AH may be a better indicator of humidity in acute health effects. The COVID-19 outbreak in China happened in winter and early spring with lower AH. Our results indicated that there might exist an optimum low humidity for COVID-19 to spread. Because those 12 cities with AH below 4 g/m^3 confirmed fewer case counts than other cities. For the 17 cities with more than 50 cases, results showed that every 1 g/m^3 increase in AH was significantly associated with declined confirmed case counts in lag 07, lag 014 and the combined RR was 0.72 (95% CI: 0.59, 0.89) and 0.33 (95% CI: 0.21, 0.54). Consistent with our results, Liu et al. has explored the effects of AH on H7N9 infection risks in China and found significantly higher effects of low AH on risks of H7N9 infection (Liu et al., 2018). Possible explanation is that low AH might increase the stability of coronavirus and favor its transmission like influenza did (Lowen et al., 2007). Our results are somewhat different from a previous study about early COVID-19 outbreak, which reported that the changes in temperature and humidity as spring and summer months arriving might not lead to decline of confirmed case counts without the implementation of extensive public health interventions (Luo et al., 2020). Although public health control measures play a major role in controlling pandemic like COVID-19, our results indicate an independent role of weather conditions on the transmission. Unlike this study, we used data over a longer period and controlled the population migration in our models. Therefore, we are optimistic that this epidemic will be faded to a large degree in the coming warmer season with the enforcement of public health interventions in China.

As we know, the COVID-19 in China firstly confirmed in Wuhan and a considerable proportion of confirmed cases in other cities of China were imported from Wuhan, which may confuse the relation of meteorological environment and COVID-19. However, we controlled its effect with MSI and estimated a significant association between the meteorological environment and COVID-19 transmission. The most important environmental implication is that, AT, DTR and AH are critical factor for COVID-19 transmission, which also deserve to be better studied in other regions during this pandemic.

In conclusions, our study implicates that meteorological factors play an independent role in the COVID-19 transmission. A weather with low temperature, mild diurnal temperature range and low humidity favors the transmission. This study indicates that the epidemic might gradually ease as a result of rising temperatures in coming months as well as the implementation of public health control measures.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Influence of population density, temperature, and absolute humidity on spread and decay durations of COVID-19: A comparative study of scenarios in China, England, Germany, and Japan

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ABSTRACT

In this study, we analyzed the spread and decay durations of the COVID-19 pandemic in several cities of China, England, Germany, and Japan, where the first wave has undergone decay. Differences in medical and health insurance systems, as well as in regional policies incommoded the comparison of the spread and decay in different cities and countries. The spread and decay durations in the cities of the four studied countries were reordered and calculated based on an asymmetric bell-shaped model. We acquired the values of the ambient temperature, absolute humidity, and population density to perform multivariable analysis. We found a significant correlation ($p < 0.05$) of the spread and decay durations with population density in the four analyzed countries. Specifically, spread duration showed a high correlation with population density and absolute humidity ($p < 0.05$), whereas decay duration demonstrated the highest correlation with population density, absolute humidity, and maximum temperature ($p < 0.05$). The effect of population density was almost nonexistent in China because of the implemented strict lockdown. Our findings will be useful in policy setting and governmental actions in the next pandemic, as well as in the next waves of COVID-19.

1. Introduction

The outbreak of the coronavirus disease (COVID-19) has been reported worldwide, and it has reached more than 200 countries [1,2]. Numerous studies on COVID-19 have investigated meteorological factors, clinical factors, and public health interventions that affect infection and morbidity [3–6]. Commonly, the morbidity and mortality rates of COVID-19 differ by one or more orders of magnitude in each country. Some hypotheses for this observation have been presented but remain controversial, such as the effects of the Bacillus Calmette–Guérin vaccine [7,8], age structure [9,10], and race [11,12].

Another factor that policies should consider is the duration of the lockdown [13–15]. However, proper comparison is not straightforward because of various cofactors, such as human behavior and regional policies; a similar problem occurs with the determination of the morbidity and mortality rates.

During the constraint, the public was stressed because of the lack of information on potential risk factors. Several restrictions negatively impact different life aspects, including employment rate and education progress. Therefore, it is important to determine which social and environmental factors may influence the morbidity and mortality rates in different societies. Thus, the analysis of COVID-19 data will ensure the appropriate policy setting and governmental actions during the pandemic. The establishment of effective policies is closely related to the available medical resources and the required duration of restrictions (e.g., city lockdown). Different lockdown and restriction measures have been applied worldwide. A summary of the lockdown policies in China, England, Germany, and Japan is listed in Appendix.

Among the other cofactors, ambient temperature and humidity have been extensively investigated worldwide [16,17]. Ma et al. [18] discussed the effects of the ambient temperature on mortality in Wuhan, China. Liu et al. [19] and Xie and Zhu [20] discussed the effects of the

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ambient temperature and absolute humidity on the number of confirmed cases in Chinese cities. Tosepu et al. [21] discussed the effect of weather on the number of confirmed cases in Jakarta, Indonesia. Briz-Redón and Serrano-Aroca [22] performed a spatiotemporal analysis of temperature during the early evolution of COVID-19 in Spain. A similar analysis was conducted using data from Oslo, Norway [23]. Furthermore, recent studies have evaluated the effects of temperature and relative humidity on the morbidity rates in Brazil [24,25]. A numerical study on the spread of COVID-19 in Croatia has also been reported [26]. Studies using global data have discussed how temperature and humidity are correlated with the infection and fatality rates of COVID-19 [27,28]. However, the timeframe of the spread in each country may be different and difficult to define.

Our previous study [29] conducted with data from Japan suggested that the population density, which is somewhat indicative of social distancing, was more significant than the meteorological factors. The effect of population density on the morbidity rate was also discussed in a case study of Iran [30]. These studies suggested that several cofactors introduce uncertainty. When discussing the effects of policies, a multi-city analysis representing different countries may be imperative. In multi-country analyses, the number of conducted tests may add uncertainty because this number depends on medical resources and regional

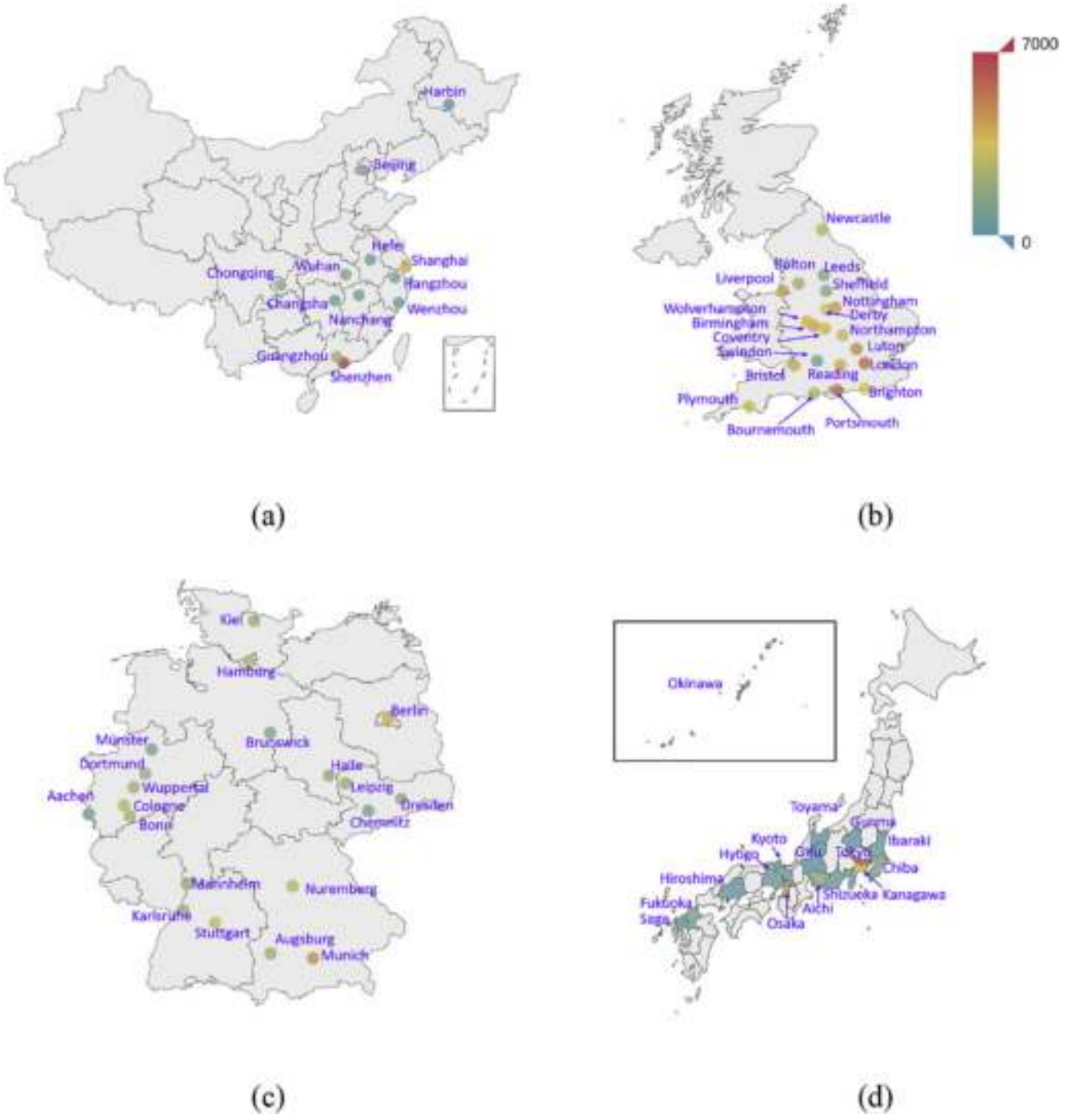

Fig. 1. Map of studied cities or prefectures and population density (people per km^2) in color scales in (a) China, (b) England, (c) Germany, and (d) Japan.

policies.

Unlike the morbidity and mortality rates, the duration of the pandemic may be less affected by different factors; e.g., it may not depend on the available medical resources. The understanding of the pandemic durations will be helpful for developing protection policies and governmental actions, to soften the potential damages to economy and social fabrics. In our recent study on 19 Japanese prefectures [31], the duration of the pandemic was discussed for the first time, and population density, absolute humidity, and temperature were found to be well-correlated in the spread stage. Conversely, the decay stage was predominantly affected by population density. The case study of COVID-19 in Japan provided insights into several environmental factors owing to the consistency and uniformity in data recording, healthcare quality, and social behavior. One open question is whether the findings obtained for one country can be applied globally.

The purpose of this novel study was to evaluate the effects of population density and meteorological factors on the pattern of spread and decay durations in cities or prefectures in four countries, including China, England, Germany, and Japan. To the best of our knowledge, a multi-country analysis focusing on the population, temperature and humidity factors of the COVID-19 duration has been hardly explored.

2. Material and methods

2.1. Study population

Data were collected for cities or prefectures from four countries, China, England, Germany and Japan, where medical resources collapse was not experienced (except for Wuhan, China). In our previous study [31], the correlation of population and meteorological factors with the spread and decay durations in Japan was studied. China is the first country reported the COVID-19 cases and imposed strict lockdown policies. England and German implemented restriction policies from March. The restrictions in all four countries have been eased before June. Moreover, the choice of the countries also depended on the data availability, the public accessibility of the statistics in city or prefecture level in the four countries allows the analyses to consider the effect of population and meteorological factors in fine resolution.

First, we selected the primate cities of each country, or those in which the pandemic began (Fig. 1). Wuhan was the first and most significant pandemic location in China. Data for municipalities directly under the central government and provincial capitals were collected. Those with a maximum daily increase in cases (7-day average) of less than 10 were excluded from the analysis. Wenzhou exhibited the largest daily increase outside Hubei Province, and it was also included. In England and Germany, we initially selected the cities with the highest population. However, several cities were excluded from the analysis if their daily case curves contained multiple peaks and did not decrease to 10% of the maximum 7-day average because the curves diverged from the bell-shaped model used. Finally, 20 cities in England and Germany were included in the analysis. In Japan, 16 prefectures had more than 10 confirmed daily positive cases; the data for these prefectures were included in the analysis.

2.2. Data sources

Three datasets were utilized in this study (shown in Table 1). The first dataset was the number of confirmed positive cases in each city. The data of the cities in China were collected from the dataset "China COVID-19 Daily Cases with Basemap" [32]. The data of the cities in England and Germany were collected from the referenced webpage [33] and NPGEO Corona Hub [34], respectively. The data of the prefectures in Japan were obtained from Toyo Keizai Online [35] and are based on a report by the Ministry of Health, Labour and Welfare [36]. The last date of data was June 23. Before June, the policies concerning the emergency in the four countries were eased. The number of confirmed positives may be influenced by the day of the week and latency, which is affected by the doctors' judgment. Therefore, we considered a moving average over 7 days (± 3 days in addition to the corresponding day) to reduce the effect of potential singularities.

The second dataset was population and population density in each city, as shown in Table 1. The population data of China were collected from the Statistical Yearbook for each municipality or province. The population data of England were collected from the Office for National Statistics [37]. The population data of Germany were collected from the Statistical Offices of the Federal Government and the Federal States [38]. The data of the prefectures in Japan were obtained from the Statistics Bureau of Japan [39].

The third dataset focused on weather information. The maximum and minimum temperature and relative humidity in China, England, and Germany were obtained from the National Centers for Environmental Information [40]. The weather data of each Japan prefecture were obtained from the Japan Meteorological Agency [41] during the time of the pandemic. The absolute humidity was derived from the relative humidity and ambient temperature data. The meteorological factors for the selected cities are shown in Table S1.

2.3. Outcome variables

In our previous study [31], the number of days required for spreading from 10 to 90% and those for decaying from 90% to 10% of the peak of the confirmed positives (7-day average), namely the spread duration (D_S) and decay duration (D_D), were established as metrics for evaluation of the time span of the pandemic outbreak. An illustration of the definition of the spread and decay durations are shown in Fig. 2 a). Fig. 2 b) shows the relationship between the two durations, *K*-means clustering ($n = 2$) was first applied to separate the data into two major groups. The red group mainly contained cities in China and Japan, whereas the green group contained cities in England and Germany. In the latter clustering, Birmingham and Wolverhampton (England), Berlin and Stuttgart (Germany), and Aichi and Saga (Japan) were excluded as outliers because they were not in the clustering circle. This tendency might have been caused by an overlap of repetitive smaller waves or cluster infections, which do not follow the theoretical spread curves. For example, dual peaks were observed in Aichi during the spread and decay stages.

2.4. Statistical analysis

Statistical analysis was then conducted to determine the correlation between different factors and the spread and decay durations. A multivariable analysis using linear regression was then conducted with the following model:

$$y = \beta_0 + \beta_1 \cdot PD + \beta_2 \cdot AH + \beta_3 \cdot T_{min} + \beta_4 \cdot T_{max} + \beta_5 \cdot T_{avg} + \epsilon \quad (1)$$

where β_0 is intercept, $\beta_1 - \beta_5$ are regression coefficients, ϵ is residual, y is the output variable i.e. D_S or D_D. In the equation, y linearly depends on a combination of independent variables of population density and meteorological factors. Statistical significance was accepted at $p < 0.05$, with test of null hypothesis that $\beta_i = 0$, $i = 1, \ldots, 5$.

3. Results

Fig. 3 shows the dependence of the spread and decay durations on the population density (also see Table S2). The overall correlation of the spread durations with the population densities of four countries was statistically significant ($p < 0.0001$); however, only Japan exhibited a statistical significance ($p < 0.05$) when each country was considered individually. A similar tendency was observed for the decay duration; the correlation with the population density was statistically significant ($p < 0.0001$) when data from all countries were included in the

Table 1

P: population (thousand persons); *PD*: population density (people per km^2); T_{ss}, T_{se}, D_s: starting date, termination date, and duration of the spread stage, respectively; T_{ds}, T_{de}, D_d: starting date, termination date, and duration of the decay stage (days), respectively for the COVID-19 pandemic (2020) in different cities/prefectures in (a) China, (b) England, (c) Germany, and (d) Japan.

(a)	*P*	*PD*	T_{ss}	T_{se}	D_s	T_{ds}	T_{de}	D_d
Beijing	21,536	1312	17-Jan	28-Jan	12	2-Feb	17-Feb	16
Changsha	8155	690	22-Jan	30-Jan	9	4-Feb	16-Feb	13
Chongqing	8190	1260	20-Jan	30-Jan	11	4-Feb	21-Feb	18
Guangzhou	15,306	2059	23-Jan	30-Jan	8	5-Feb	14-Feb	10
Hangzhou	9806	582	21-Jan	29-Jan	9	1-Feb	14-Feb	14
Harbin	9515	179	24-Jan	2-Feb	10	10-Feb	20-Feb	11
Hefei	8087	707	21-Jan	4-Feb	15	7-Feb	17-Feb	11
Nanchang	5546	749	24-Jan	30-Jan	7	3-Feb	17-Feb	15
Shanghai	24,238	3823	16-Jan	26-Jan	11	1-Feb	14-Feb	14
Shenzhen	13,027	6484	22-Jan	30-Jan	9	4-Feb	16-Feb	13
Wenzhou	9300	768	23-Jan	29-Jan	7	5-Feb	14-Feb	10
Wuhan	11,081	1293	25-Jan	6-Feb	13	13-Feb	24-Feb	12
(b)	*P*	*PD*	T_{ss}	T_{se}	D_s	T_{ds}	T_{de}	D_d
Birmingham	1142	4264	14-Mar	27-Mar	14	3-Apr	25-May	53
Bolton	288	2057	23-Mar	5-Apr	14	13-Apr	23-May	41
Bournemouth	395	2451	22-Mar	6-Apr	16	16-Apr	12-May	27
Brighton	291	3514	15-Mar	3-Apr	20	16-Apr	8-May	23
Bristol	463	4213	15-Mar	7-Apr	24	18-Apr	13-May	26
Coventry	372	3766	8-Mar	28-Mar	14	5-Apr	22-May	39
Derby	257	3297	13-Mar	29-Mar	17	2-Apr	19-May	48
Leeds	793	1438	19-Mar	7-Apr	20	25-Apr	25-May	31
Liverpool	498	4455	18-Mar	3-Apr	17	9-Apr	18-May	40
London	8962	5712	7-Mar	25-Mar	19	4-Apr	6-May	33
Luton	213	4915	17-Mar	4-Apr	19	10-Apr	7-May	28
Newcastle	303	2631	17-Mar	31-Mar	15	10-Apr	10-May	31
Northampton	225	2781	19-Mar	1-Apr	14	8-Apr	22-Apr	15
Nottingham	333	4462	12-Mar	2-Apr	22	8-Apr	27-May	50
Plymouth	262	3283	15-Mar	11-Apr	28	23-Apr	21-May	29
Portsmouth	215	5339	12-Mar	5-Apr	25	13-Apr	9-May	27
Reading	162	4004	22-Mar	12-Apr	22	16-Apr	18-May	23
Sheffield	585	1590	15-Mar	27-Mar	13	4-Apr	17-May	44
Swindon	222	966	21-Mar	7-Apr	18	15-Apr	20-May	36
Wolverhampton	263	3793	9-Mar	18-Apr	41	27-Apr	6-Jun	41
(c)	*P*	*PD*	T_{ss}	T_{se}	D_s	T_{ds}	T_{de}	D_d
Aachen (District)	557	788	3-Mar	21-Mar	19	3-Apr	2-May	30
Augsburg	297	2020	12-Mar	24-Mar	13	29-Mar	30-Apr	33
Berlin	3669	4118	9-Mar	23-Mar	15	1-Apr	24-May	54
Bonn	330	2337	8-Mar	21-Mar	14	5-Apr	9-May	35
Brunswick	249	1298	16-Mar	28-Mar	13	1-Apr	18-Apr	18
Chemnitz	246	1115	13-Mar	28-Mar	16	31-Mar	19-Apr	20
Cologne	1088	2685	9-Mar	16-Mar	8	1-Apr	6-May	36
Dortmund	588	2096	13-Mar	3-Apr	22	5-Apr	8-May	34
Dresden	557	1693	10-Mar	22-Mar	13	30-Mar	8-May	40
Halle (Saale)	239	1768	13-Mar	26-Mar	14	1-Apr	2-May	32
Hamburg	1847	2446	9-Mar	20-Mar	12	28-Mar	2-May	36
Karlsruhe	312	1799	10-Mar	24-Mar	15	6-Apr	10-May	35
Kiel	247	2081	13-Mar	25-Mar	13	1-Apr	7-May	37
Leipzig	593	1995	9-Mar	21-Mar	13	3-Apr	11-May	39
Mannheim	311	2143	9-Mar	24-Mar	16	6-Apr	5-May	30
Munich	1484	4781	11-Mar	26-Mar	16	31-Mar	14-May	45
Münster	315	1041	12-Mar	17-Mar	6	26-Mar	16-Apr	22
Nuremberg	518	2780	15-Mar	3-Apr	20	8-Apr	9-May	32
Stuttgart	636	3067	8-Mar	16-Mar	9	30-Mar	18-May	50
Wuppertal	355	2109	14-Mar	4-Apr	22	10-Apr	17-May	38
(d)	*P*	*PD*	T_{ss}	T_{se}	D_s	T_{ds}	T_{de}	D_d
Aichi	7552	1460	22-Feb	30-Mar	38	1-Apr	27-Apr	27
Chiba	6259	1217	19-Mar	2-Apr	15	13-Apr	5-May	23
Fukuoka	5104	1025	22-Mar	1-Apr	11	9-Apr	27-Apr	19
Gifu	1987	187	25-Mar	4-Apr	11	6-Apr	17-Apr	12
Gunma	1942	305	25-Mar	5-Apr	12	9-Apr	22-Apr	14
Hiroshima	2804	331	26-Mar	6-Apr	12	10-Apr	27-Apr	18
Hyogo	5466	650	19-Mar	4-Apr	17	7-Apr	4-May	28
Ibaraki	2860	470	16-Mar	28-Mar	13	8-Apr	23-Apr	16
Kanagawa	9198	3808	19-Mar	3-Apr	16	11-Apr	19-May	39
Kyoto	2583	560	16-Mar	2-Apr	18	5-Apr	9-May	35
Okinawa	1453	638	28-Mar	3-Apr	7	10-Apr	25-Apr	16
Osaka	8809	4631	18-Mar	6-Apr	20	13-Apr	6-May	24
Saga	815	334	23-Mar	15-Apr	24	22-Apr	1-May	10
Shizuoka	3644	468	25-Mar	3-Apr	10	6-Apr	27-Apr	22

(*continued on next page*)

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Table 1 (*continued*)

(d)	*P*	*PD*	T_{ss}	T_{se}	D_s	T_{ds}	T_{de}	D_d
Tokyo	13,921	6355	17-Mar	3-Apr	18	10-Apr	7-May	28
Toyama	1044	246	1-Apr	13-Apr	13	18-Apr	30-Apr	13

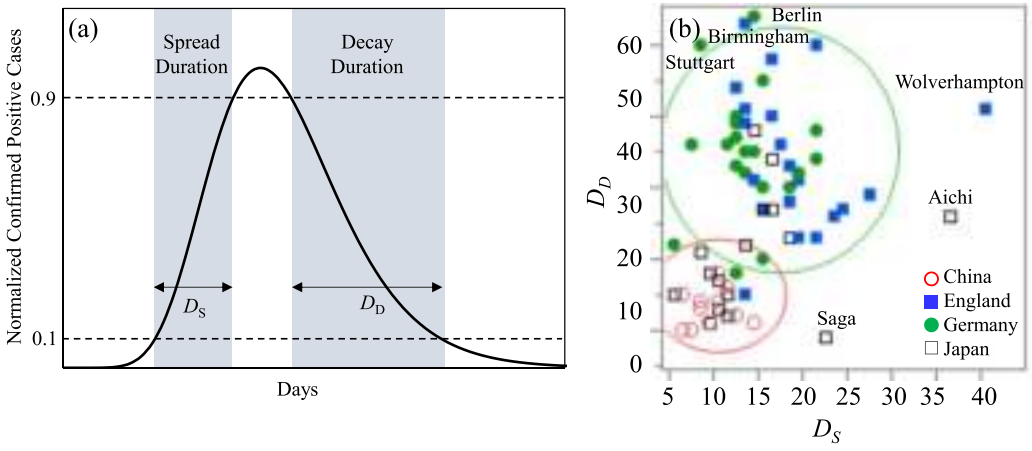

Fig. 2. (a) Definition of the spread (D_S) and decay durations (D_D) in days along the curve of daily normalized confirmed positive cases of COVID-19 [31]. (b) Relationship between D_S and D_D in days. The red and green ellipses mainly contain cities in China and Japan and those in England and Germany. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

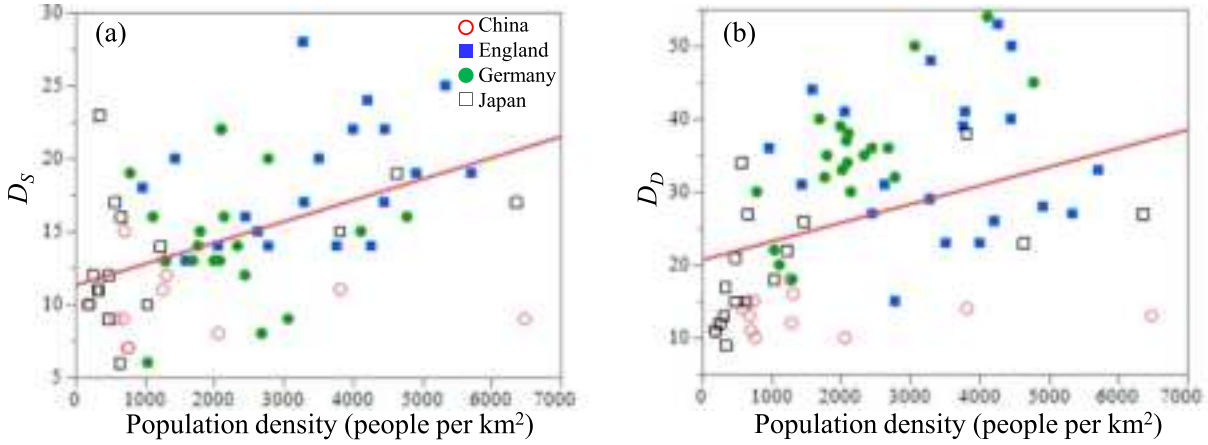

Fig. 3. Relationship of (a) spread and (b) decay durations (D_S and D_D, respectively) with population density.

evaluation. However, only Germany ($p < 0.005$) exhibited statistically significant correlations. The durations of the spread and decay stages were not influenced by the population density in China.

A multivariable analysis was conducted to investigate the relationship between the spread and decay durations of the pandemic with the absolute humidity and ambient temperature measured during the corresponding periods, as well as with the population density. As shown in Fig. 4 and Table 2, the duration of the spread period was characterized with respect to population density and absolute humidity, and the decay period was characterized with respect to population density, absolute humidity, and daily maximum temperature ($p < 0.0001$ for both the spread and decay durations). The maximum temperature was related to the maximum absolute humidity. Thus, multicollinearity was evaluated based on the variance inflation factors (VIFs). We used the threshold value of the VIF to differentiate between low and high contributions, which is commonly taken as 10 [42]. The higher the maximum temperature and absolute humidity, the shorter the spread and decay periods in the analysis of the four countries. The contributions of the population density were 64% and 28% in the spread and decay durations, respectively, and the remaining proportions were explained by the absolute humidity and temperature.

The decay duration in Germany exhibited statistical significances with population density, average temperature, and absolute humidity, the spread duration in England with population density and daily minimum temperature, and the spread period in Japan with population density and absolute humidity. The *p*-value of the decay period in Japan with respect to the daily maximum temperature was 0.063. As listed in Table 2, the residual spread and decay durations were 2.77 days and 6.60 days for all four countries, whereas the average residuals were 2.18 days and 3.84 days for the individual countries, respectively. The effect of population density was nonexistent in China, as shown in Fig. 3.

4. Discussion and conclusion

Understanding the potential risks during the pandemic is essential for managing medical resources. Furthermore, a model that can be used to estimate the potential spread and decay durations of the pandemic enables the implementation of evidence-based government policies.

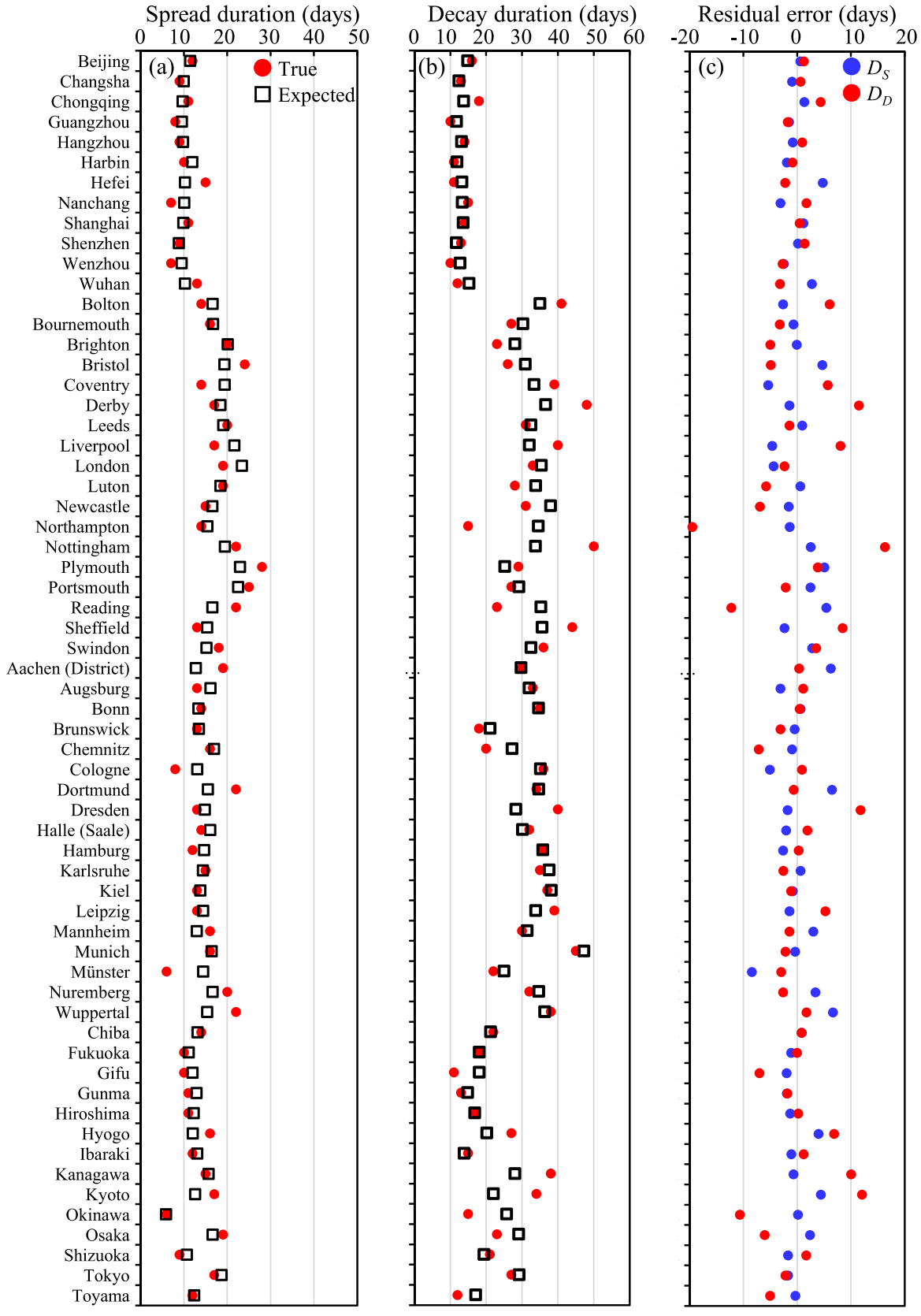

Fig. 4. Multivariable analysis with the variables listed in Table 2(b) for each country. The number of days of (a) spread duration, (b) decay duration, and (c) residual error.

Table 2
Multivariable analysis for spread (D_S) and decay (D_D) durations for (a) all countries and (b) individual countries. *PD* represents the population density. T_{ave}, T_{max}, and T_{min} represent the daily average, maximum, and minimum temperatures, respectively. *AH* represents the daily average absolute humidity values.

(a)	Variables	R^2	adj. R^2	*p*-value	VIF	Residual
D_S	PD, AH	0.32	0.30	<0.0001	1.00	2.77
D_D	PD, T_{max}, AH	0.35	0.32	<0.0001	1.74	6.60
(b)	Variables	R^2	adj. R^2	*p*-value	VIF	Residual
China						
D_S	AH	0.12	0.03	0.27	1.00	1.79
D_D	T_{max}, AH	0.21	0.03	0.35	7.88	1.78
England						
D_S	PD, T_{min}	0.39	0.30	<0.05	1.12	2.45
D_D	AH	0.12	0.06	0.16	1.00	6.34
Germany						
D_S	T_{min}	0.10	0.04	0.20	1.00	2.71
D_D	PD, T_{ave}, AH	0.68	0.61	<0.001	2.44	2.37
Japan						
D_S	PD, AH	0.66	0.60	<0.005	1.02	1.47
D_D	PD, T_{max}	0.40	0.29	0.06	1.20	4.10

This may reduce the potential damage to the economy, education, and various daily activities that have suffered during the lockdown restrictions. This study presented a data analysis of how meteorological factors and population density are correlated to the spread and decay durations of the COVID-19 pandemic in four countries, in some cities of which, the first wave has already decayed. Specifically, both durations exhibited a high correlation with the population density. Longer durations were expected in cities with higher population densities, implicitly suggesting the importance of social distancing [43]. This has been confirmed in cities of England and Germany, which was observed in Japan [31]. The opposite tendency found in China can be explained by the fact that the strict lockdown imposed social distancing despite the high population density.

Direct evaluation of the polices across different countries is difficult, owing to the differences in the testing rates, public response, culture etc. From the collected dataset and the analysis, the effect of policy may be implicitly inferred. In China, short durations and insignificant correlations of durations with population and meteorological factors were observed owing to the broadly strict lockdown policies. In England, mixed signals (such as "herd immunity") was sent out in the beginning, and criticism appeared for the government of not acting quickly in March. In Germany, in the beginning of the pandemic, the government responded with actions such as contact tracing and testing, followed by prohibition of gathering with strict punishment for violation. The multivariable regression analysis revealed significant correlations between spread duration and factors in UK, but not in Germany. The opposite trend observed for decay duration. In Japan, unlike many other countries where city lockdowns were enforced, citizens self-isolated during this state of emergency; stronger correlations for spread and decay durations observed. From these finding, it may be suggested that the strict restriction and its implementation may be related to less correlation of the durations of the pandemic waves with the population and meteorological factors.

Both temperature and absolute humidity were less correlated with the durations than with the population density. This study conducted a multivariable analysis considering population density, maximum and minimum temperature, and absolute humidity. The adjusted R^2 values were 0.30 and 0.32 for the durations of the spread and decay stages, respectively, and they were statistically significant. The spreading and decay durations were sufficiently estimated from the multivariable analysis; the residual spread and decay durations were 2.77 days and 6.60 days for all countries, whereas the average residuals were 2.18 days and 3.84 days for the individual countries. This suggested that we can estimate the durations based on these parameters. One limitation of the analysis in this study is that the daily-increase curves in some cities diverge from the bell-shape used for defining the spread and decay durations, owing to the repetitive sub waves and cluster infections.

In conclusion, the durations of the spread and decay stages of the COVID-19 pandemic were correlated with absolute humidity, temperature, and population density in four countries that did not experience a collapse of their medical systems. The contributions of these factors were different in each country, which could be attributed to regional policies. Although the morbidity and mortality rates differed by one to two orders of magnitude, these parameters were sufficient to estimate the durations. The higher population density tends to lead to prolonged spread and decay durations, while less correlations with the population and meteorological factors. The contribution rate of population density for multivariable are 30–50% in each country. The tendency of shortening duration with higher temperature and humidity reported by [31] was not clearly observed in Germany and England. These durations were affected by the policies and human behavior. With strict lockdown policies imposed (China), durations are shortened and their correlations with the population density and meteorological factor become insignificant. These findings will be useful in policy setting and governmental actions, such as determining the necessary shutdown length. This factor should be considered in another potential pandemic or next waves of COVID-19, in addition to the results of the multi-city comparison.

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Authors' contributions

Conceptualization: YD, AH & ER. Data curation: YD, DA, SK, Formal analysis: YD, DA & SK. Investigation: SK, JG & AH. Methodology: YD, SK, ER & AH. Project administration: AH & ER. Resources. Software. Supervision: AH & ER. Validation: YD, DA & SK. Visualization: SK & YD. Roles/Writing: DA, YD, ER & AH. Writing, review & editing: All.

Declaration of Competing Interest

The authors declare no competing interests.

Appendix A. Policies in different countries

The rapid spread of the virus in China in early 2020 lead several countries to adopt drastic measures at different scales. China [44] enforced a strict lockdown, which started in Wuhan and expanded to the whole province. On February 10, Beijing and Shanghai, two of China's largest cities, restricted the movement of residents and vehicles, made wearing masks compulsory, and shut down leisure and other non-essential community services [45].

The first transmission of COVID-19 in England was confirmed in February. Initially, the government decided not to shut down large gatherings or introduce restrictions. On March 20, the Prime Minister announced in a television broadcast that all pubs, cafes, restaurants, bars, and gyms were to close. On March 23, a nationwide lockdown was announced. At this point, there were 2433 confirmed cases in London. The closure of pubs, restaurants, and indoor sports and leisure facilities was imposed via the Health Protection (Coronavirus, Business Closure) (England) Regulations 2020 [46]. On May 10, plans to ease lockdown restrictions were announced [47].

In Germany, authorities shut down schools and stopped major sports events on March 13, 2020, which was closely followed by further decisions regarding restaurants, shops, and other services [48]. The government banned gatherings in churches, mosques, and synagogues, and ordered the closure of non-essential shops, playgrounds, and schools. Moreover, regional trains were curtailed in an effort to reduce travel. On

May 6, Chancellor announced steps to ease the coronavirus lockdown in Germany [49].

In Japan, a state of emergency was declared nationwide on April 16 after being implemented to only seven prefectures on April 7 [50]. During this state of emergency, people self-contained voluntarily instead of a government-enforced lockdown of the prefectures. This state of emergency was discontinued on May 23.

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.onehlt.2020.100203.

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Influence of Absolute Humidity, Temperature and Population Density on COVID-19 Spread and Decay Durations: Multi-Prefecture Study in Japan

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Abstract: This study analyzed the spread and decay durations of the COVID-19 pandemic in different prefectures of Japan. During the pandemic, affordable healthcare was widely available in Japan and the medical system did not suffer a collapse, making accurate comparisons between prefectures possible. For the 16 prefectures included in this study that had daily maximum confirmed cases exceeding ten, the number of daily confirmed cases follow bell-shape or log-normal distribution in most prefectures. A good correlation was observed between the spread and decay durations. However, some exceptions were observed in areas where travelers returned from foreign countries, which were defined as the origins of infection clusters. Excluding these prefectures, the population density was shown to be a major factor, affecting the spread and decay patterns, with $R^2 = 0.39$ ($p < 0.05$) and 0.42 ($p < 0.05$), respectively, approximately corresponding to social distancing. The maximum absolute humidity was found to affect the decay duration normalized by the population density ($R^2 > 0.36$, $p < 0.05$). Our findings indicate that the estimated pandemic spread duration, based on the multivariate analysis of maximum absolute humidity, ambient temperature, and population density (adjusted $R^2 = 0.53$, p-value < 0.05), could prove useful for intervention planning during potential future pandemics, including a second COVID-19 outbreak.

Keywords: COVID-19; temperature; absolute humidity; population density; spread and decay durations

1. Introduction

Outbreaks of the infectious coronavirus disease of 2019 (COVID-19) have been reported worldwide [1,2]. In response, numerous studies on COVID-19 have been conducted on different aspects, including disease prevention, control, diagnosis, causes, and epidemiology [3]. A state of emergency was declared in 7 of Japan's 47 prefectures on 7 April 2020. This state of emergency was extended nationwide on 16 April and ended on 25 May 2020. During this state of emergency, people voluntarily self-isolated and no government-enforced lockdown of the prefectures (districts) was implemented.

Many epidemic modeling approaches exist [4] and various mathematical models have been used to demonstrate different aspects related to COVID-19, including serial intervals [5], transmission in China [6], and case studies in Wuhan, China [7], Italy [8], and Spain [9]. Comparisons among different countries have also been made [10] and the importance of different models in developing policies has

been discussed in [11]. Regarding the COVID-19 spread in Italy, a multivariate analysis study was conducted to evaluate the effect of different environmental factors on confirmed positive cases [12]. Three regions in Italy with high national infection rates were considered. In a time-series analysis, different factors were evaluated within each region. Strong correlations were found with different environmental factors, such as the average temperature, humidity, and wind speed. Although this study addressed how these factors were correlated with confirmed COVID-19 cases, it does not discuss their influence on disease spread and decay durations. However, it does provide a parameter fitting model based on local data within each region. Being able to estimate the duration of the epidemic in different prefectures would be useful for developing lockdown policies.

The duration and morbidity rates of COVID-19, however, are not easy to compare because different co-factors affect them. The number of polymerase chain reaction (PCR) tests, a simple and cost-effective test conducted in Japan was limited because of its reliability; therefore, chest computed tomography imaging was performed to obtain highly accurate diagnoses [13]. In addition, to avoid nosocomial infections and medical resource shortages, it was suggested that people with symptoms (e.g., fever > 37.5 °C for no more than four consecutive days) stay home and not seek immediate medical attention unless they had been in close contact with infected people or had recently visited a foreign country. Some patients have been reported to be asymptomatic [14], making the statistical study of COVID-19 more complex.

The statistics of confirmed deaths and COVID-19 positive patients are being updated every day in each prefecture of Japan. Furthermore, the Japanese medical system did not collapse during the outbreak, and the health insurance system provides COVID-19 medical care for free. However, the percentage of positive coronavirus tests ranges from 2.2 to 34.8% (Table 1) throughout Japan, making morbidity estimations in different areas more challenging. Assuming that the criteria for conducting a test are the same in each prefecture, the estimation of the epidemic duration provides a useful parameter.

Table 1. Population, area, and population density data of 19 prefectures where daily maximum cases of COVID-19 exceeded 10. Total cases of COVID-19 and mean percentages of the positive test cases are also listed.

	Population (×1000)	Population Density (People Per km^2)	Total Cases (Through 25 May)	Daily Max Cases	Percentage of Positive Test Results (%)
Tokyo	13,921	6354.8	5170	206	34.8
Kanagawa *	9198	3807.5	1336	94	14.7
Saitama *	7350	1932.0	1000	56	5.2
Chiba *	6259	1217.4	904	70	6.4
Ibaragi	2860	470.4	168	28	3.7
Gunma	1942	304.6	149	44	4.2
Shizuoka	3644	467.9	75	18	2.2
Aichi	7552	1460.0	507	21	5.2
Gifu **	1987	187.3	150	18	4.4
Ishikawa	1138	271.7	296	20	11.2
Toyama	1044	245.6	227	21	7.3
Osaka	8809	4631.0	1781	108	6.1
Hyogo ***	5466	650.4	699	57	6.4
Kyoto ***	2583	560.1	358	20	4.6
Shiga ***	1414	352.0	100	12	5.7
Hiroshima	2804	331.1	167	51	2.5
Fukuoka	5104	1024.8	672	108	5.7
Saga ****	815	333.6	47	11	3.4
Okinawa	1453	637.5	81	17	2.9

* Kanagawa, Saitama, and Chiba are considered adjacent prefectures of Tokyo. ** Gifu is considered an adjacent prefecture of Aichi. *** Hyogo, Kyoto, and Shiga are considered adjacent prefectures of Osaka. **** Saga is considered an adjacent prefecture of Fukuoka.

Environmental co-factors potentially influencing COVID-19 morbidity, including ambient temperature, absolute humidity, and air pollution, have been studied [15–22]. However, neither these studies nor the above-mentioned modeling studies have considered the impact of population density and ambient conditions on both the spread and decay duration [23]. In fact, the durations were not discussed at all. The necessity of population density scaling in epidemic transmission models has been suggested for infectious diseases in general [24], indicating that the factors characterizing the spread and decay durations might be different. Recent studies have confirmed the effect of temperature and relative humidity on morbidity rates in Brazil [22,25] and the morbidity/mortality rates in Japan [26]. Studies with wider scopes include global data analysis—discussion on how temperature and humidity are correlated with the infection and fatality rates of the COVID-19 pandemic [27,28]. Both studies focus on the morbidity and mortality rates in their respective study area and globally, but neither of them discusses the effect of environmental factors on the duration of COVID-19, which is an essential factor for policymaking. Its effect on the mortality and morbidity rates is still controversial; for example, no correlation with weather data was found in a study of 122 cities in China [19], whereas a correlation was reported in [15]. A report highlighting the duration of the pandemic spread may lead to better management of medical resources and protective gear, which is a well-known life-threatening factor during the evolution of COVID-19.

In this study, we evaluate the effect of different ambient conditions and population densities on the spread and decay durations of COVID-19 in different prefectures of Japan. To the best of our knowledge, this is the first study to discuss the effect of environmental factors during COVID-19 in Japan. Japan provides an interesting case study for environmental factors, because medical services and social reactions are similar nationwide and high-quality data were properly recorded.

2. Materials and Methods

2.1. Data Source

Three datasets were utilized in this study. The first dataset contains the number of confirmed positive cases in each prefecture that was obtained from Toyo Keizai Online [29] and is based on a report by the Ministry of Health, Labour and Welfare [30].

Because the state of emergency was terminated on 25 May 2020, this study utilized data from 15 March 2020, to that date. COVID-19 started spreading in mid-February in the Aichi Prefecture, which is the only prefecture where the spread started earlier than 15 March. As such, additional data were obtained from the Aichi Prefecture website [31] and included in this study.

The second dataset consists of population and prefecture area data that were obtained from the Statistics Bureau of Japan [32] (Table 1). Several prefectures are classified as geographically adjacent to primary prefectures (Tokyo, Osaka, Aichi, and Fukuoka; Table 1). In adjacent prefectures, several people were found to commute to the primary prefectures, thus potentially affecting the prefecture data, and should, therefore, not be neglected.

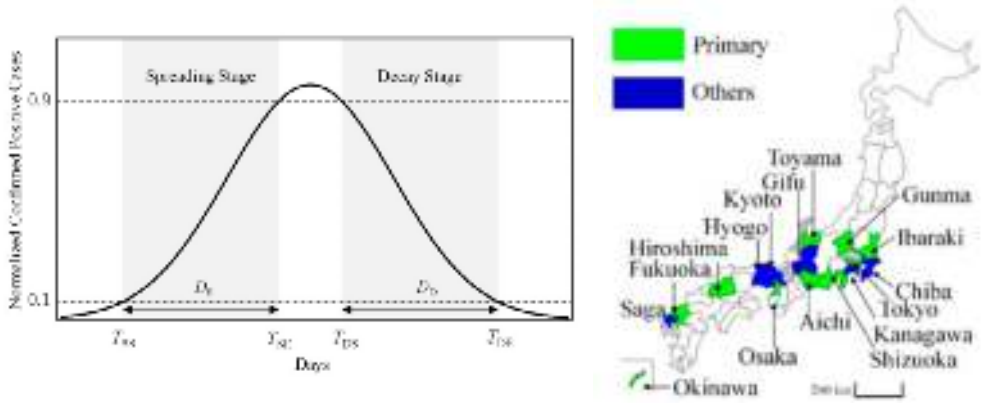
The third dataset contains weather data obtained from the Japan Meteorological Agency for each prefecture during the time of the pandemic. The absolute humidity was derived from the relative humidity and ambient temperature data [33].

2.2. Data Processing

The number of confirmed positive tests may be influenced by diagnostic data, based on Japanese guidelines, serial intervals, and latency, which is affected by each doctor's judgment; therefore, the moving average over 7 days (± 3 days in addition to the corresponding day) was considered to reduce the effect of potential singularities. This duration was used in the trajectory analysis of COVID-19 as well [34], also considering its incubation time (mean value of 5.1 days) [35]. Additional small peaks were still observed, which were attributed to clusters of patients (e.g., nosocomial infections, nursing home patients, and people returning from foreign countries). Similar to other countries, the number

of confirmed positives may depend on the day of the week (see [34]); in general, the number of tests conducted on weekends is lower than on weekdays.

This tendency prevents the direct fitting of the observed cases for comparison with a computational model (typically expressed as a bell-shape or a log-normal distribution, similar to the trend in theoretical models [36,37]). Therefore, our study introduces the criteria of days required for spreading from 10% to 90% and for decaying from 90% to 10% of the peak [38] of the confirmed positives (7-day average [34]), as metrics for the evaluation, as shown in Figure 1a. This metric is particularly useful for cases where the noise effect should not be neglected. A limitation of this metric is that a certain minimum number of samples is needed because if the number of samples is small, one or two new patients would significantly influence the results. Therefore, as a pre-processing step, prefecture data were excluded if the daily maximum number of confirmed positive cases was less than 10. In addition, the percentage of morbidity/mortality in nosocomial infections and nursing home patients should not be significant. In Ishikawa, however, 75% of the confirmed deaths were nosocomial infections. Two prefectures (Saitama and Shiga) were excluded from the analysis due to a lack of humidity data, which are essential for discussing the effect of ambient conditions on the spread and decay durations (see the data source in the next subsection). Based on this criterion, 16 prefectures met the minimum number of confirmed positive cases, as shown in Figure 1b.



(**a**) (**b**)

Figure 1. (**a**) Proposed definition of the spread and decay durations along the curve of the COVID-19 pandemic, which has been applied to the 7-day moving average of original data. Time parameters extracted from the definition are T_{SS} (start of spread), T_{SE} (end of spread), T_{DS} (start of decay), T_{DE} (end of decay), D_S (spread duration), and D_D (decay duration). (**b**) Map of Japan with 16 prefectures under study classified as primary prefectures and adjacent prefectures (others).

2.3. Statistics

A statistical analysis was conducted to determine the correlation between different factors and both the spread and decay periods of the pandemic using the software JMP (SAS Institute, Cary, NC, USA). To assist the pairwise correlations, we calculated the Spearman's rank correlation between the spread and decay durations normalized to the population density and different environmental parameters. The correlation matrix with partial correlation probabilities was also calculated. Subsequently, a multivariate analysis using linear regression was conducted using the same software. Statistical significance was accepted at $p < 0.05$.

3. Results

Table 2 lists the starting and terminating dates of the spread and decay stages (using moving averages) as well as the date of the peak value of daily confirmed cases (without averaging) observed for each prefecture. Figure 2 shows the time-series of the confirmed new positive cases for the spread and decay durations based on the data presented in Table 2.

Table 2. Starting and terminating dates of the spread and decay stages of the COVID-19 pandemic and the date (year 2020) when the highest daily peak value of confirmed cases was reported.

	T_{SS}	T_{SE}	Daily Peak *	T_{DS}	T_{DE}	D_S	D_D
Tokyo	17-Mar	3-Apr	17-Apr	10-Apr	7-May	17	27
Kanagawa	19-Mar	3-Apr	10-Apr	11-Apr	19-May	15	38
Chiba	19-Mar	2-Apr	17-Apr	13-Apr	5-May	14	22
Ibaraki	16-Mar	28-Mar	3-Apr	8-Apr	23-Apr	12	15
Gunma	25-Mar	5-Apr	11-Apr	9-Apr	22-Apr	11	13
Shizuoka	25-Mar	3-Apr	10-Apr	6-Apr	27-Apr	9	21
Aichi	22-Feb	30-Mar	4-Apr	1-Apr	27-Apr	37	26
Gifu	25-Mar	4-Apr	8-Apr	6-Apr	17-Apr	10	11
Toyama	1-Apr	13-Apr	17-Apr	18-Apr	30-Apr	12	12
Osaka	18-Mar	6-Apr	14-Apr	13-Apr	6-May	19	23
Hyogo	19-Mar	4-Apr	9-Apr	7-Apr	4-May	16	27
Kyoto	16-Mar	2-Apr	7-Apr	5-Apr	9-May	17	34
Hiroshima	26-Mar	6-Apr	12-Apr	10-Apr	27-Apr	11	17
Fukuoka	22-Mar	1-Apr	11-Apr	9-Apr	27-Apr	10	18
Saga	23-Mar	15-Apr	19-Apr	22-Apr	1-May	23	9
Okinawa	28-Mar	3-Apr	7-Apr	10-Apr	25-Apr	6	15

* Moving average is not applicable for daily peak values.

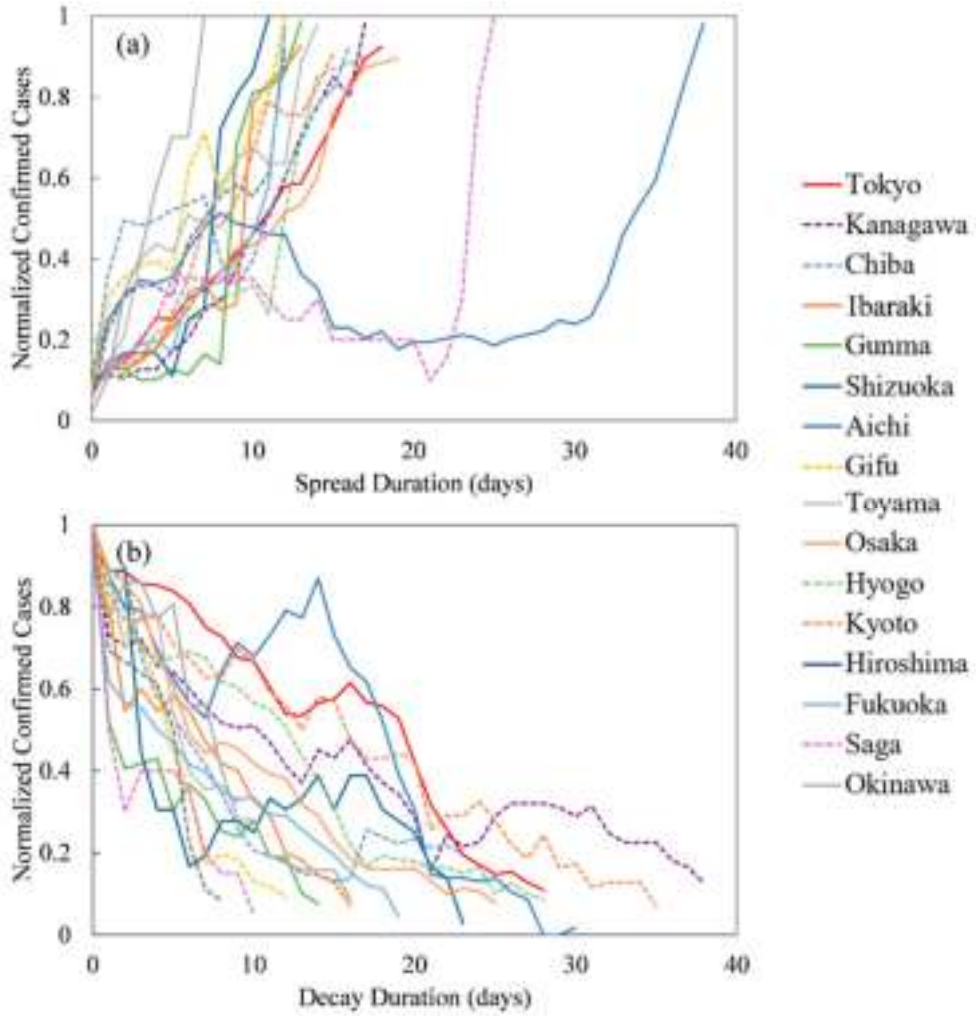


Figure 2. (**a**) Spread and (**b**) decay durations (in days) of 16 prefectures in Japan. Dashed lines represent the prefectures that are adjacent to primary prefectures (Tokyo, Osaka, Aichi, and Fukuoka).

As shown in Figure 2a, the number of normalized confirmed cases increased in most prefectures, and multiple peaks are observed in some prefectures. In Aichi, the start of the spread period, T_{SS}, was three weeks earlier than in the other studied prefectures (Table 2), and in mid-March, when traveling residents returned home from foreign countries in response to a call from the Japanese government, two large peaks are visible in the spread graph. A similar tendency is observed in Saga, while in Chiba, and Gifu, only small peaks are observed.

As shown in Figure 2b, which illustrates the pandemic decay timeline, the number of normalized confirmed cases decreased over time in most prefectures. Similar to Figure 2a, multiple peaks are observed in some prefectures, including Kanagawa and Hyogo. In Aichi, the second peak, whose magnitude is approximately 0.9 times the maximum value, occurred on 15 April 2020, and was caused by travelers returning from foreign countries [39].

Figure 3 illustrates the relationship between the durations of the spread and decay stages. These relationships are separated into two groups based on hierarchical clustering. The red group consists of metropolitan regions with a relatively high population density compared to the more rural blue group. Hereafter, the Aichi and Saga are considered to be outliers. Based on Figure 3, we hypothesize that population density is an important factor, and further investigation is required.

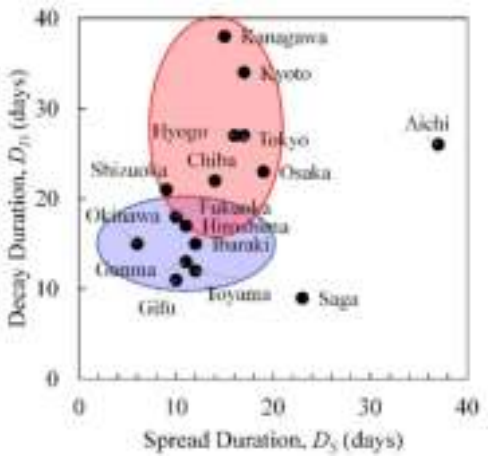


Figure 3. Relationship between the durations of spread and decay (in days). The red ellipse highlights prefectures with relatively high population densities, while the blue ellipse highlights those with lower population densities.

Figure 4 shows the relationship between the spread and decay durations (D_S and D_D) and the population density. The data of Aichi and Saga prefectures were excluded due to their outlier status. The resulting curves confirm the correlation between the spread and decay durations and the population density. The coefficients of determination of the spread and decay stages are 0.390 and 0.424 ($p < 0.05$), respectively.

For environmental factors, the mean daily temperature and humidity values listed in Table 3 were obtained for the two durations listed in Table 2. Figure 5 shows the effect of the ambient parameters on the spread and decay durations. The daily mean, maximum, and diurnal change values were selected based on previous studies on the influenza virus [40,41] and suggest that the temperature and humidity variations are likely correlated with the COVID-19 mortality rate [15]. As seen in Figure 5, such a correlation was observed for the data analyzed in this study. If the adjacent prefectures and those prefectures with multiple peaks in the curves are excluded, a mild correlation is observed for the maximum absolute humidity ($R^2 > 0.2$) with the spread and decay durations (see also Table 4). In both cases, including and excluding adjacent prefectures, the maximum absolute humidity is the parameter that correlates significantly with duration. A brief discussion on how maximum ambient temperature and maximum absolute humidity are correlated can be found in Appendix A.

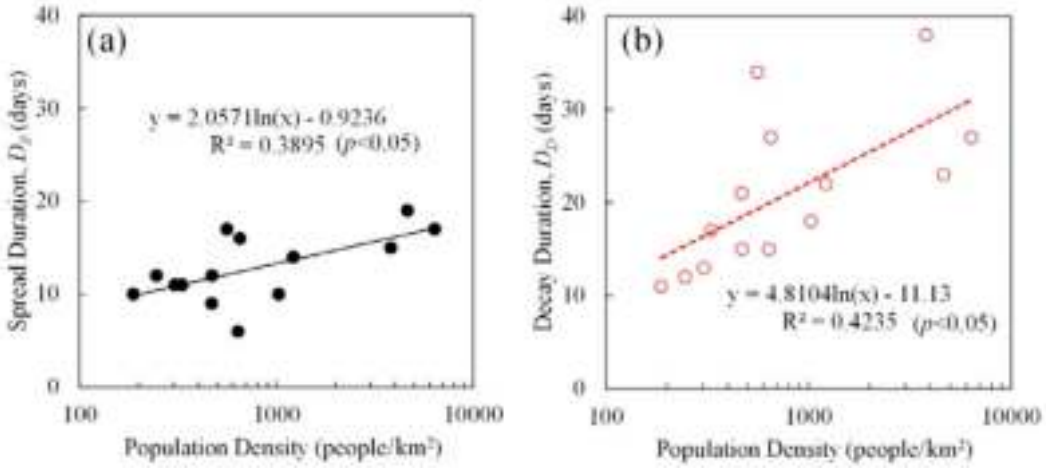


Figure 4. Relationship of the (**a**) spread and (**b**) decay durations (D_S and D_D) with population density.

Table 3. Daily average, maximum and minimum temperature, and absolute humidity values. The values are averaged during the spread and decay stages as listed in Table 2. T_{ave}, T_{max}, and T_{min} represent the daily average, maximum, and minimum temperatures, respectively. H_{ave}, H_{max}, and H_{min} represent the daily average, maximum, and minimum absolute humidity values, respectively.

	D_S						D_D					
	T_{ave}	T_{max}	T_{min}	H_{ave}	H_{max}	H_{min}	T_{ave}	T_{max}	T_{min}	H_{ave}	H_{max}	H_{min}
Tokyo	11.7	16.7	6.7	6.4	9.3	4.5	14.4	19.2	9.9	8.6	10.7	6.7
Kanagawa	12.4	16.7	8.0	6.8	9.7	4.7	16.6	20.7	13.0	9.8	11.7	7.7
Chiba	12.4	16.1	8.1	6.6	9.5	4.6	15.1	19.1	11.2	8.4	10.3	6.4
Ibaragi	10.3	17.1	3.4	5.7	8.5	3.7	10.8	15.6	6.4	6.5	8.2	4.9
Gunma	10.6	15.3	5.4	5.7	7.5	4.6	11.5	16.3	7.2	6.3	8.4	4.9
Shizuoka	13.1	16.6	9.3	8.6	10.6	6.6	14.3	18.7	10.0	7.1	8.9	5.4
Aichi	10.1	14.8	6.0	5.9	7.9	4.4	13.0	18.3	8.6	6.5	8.4	4.9
Gifu	12.0	16.4	7.7	6.7	8.4	4.9	12.6	18.2	7.7	5.1	6.6	3.6
Toyama	9.7	14.6	5.2	6.3	7.7	4.7	12.1	17.6	7.7	7.5	9.1	5.8
Osaka	12.7	17.0	8.9	6.7	8.9	5.1	16.2	20.6	12.3	8.1	10.2	6.3
Hyogo	12.7	16.4	9.1	7.2	9.6	5.3	15.5	19.0	12.4	8.1	9.5	6.0
Kyoto	11.5	16.6	6.8	6.4	8.6	4.7	14.7	20.1	10.0	7.1	9.0	5.3
Hiroshima	12.4	16.2	8.6	6.5	8.5	5.0	13.2	17.4	9.2	5.6	7.4	4.2
Fukuoka	14.2	17.5	11.3	8.8	11.0	6.9	14.0	17.5	10.9	7.3	9.4	5.7
Saga	13.4	17.9	9.0	7.3	9.1	5.5	14.9	20.1	9.8	7.1	8.6	5.4
Okinawa	21.3	24.0	18.8	14.7	17.4	12.4	19.8	22.1	17.6	11.8	14.1	10.0

Table 4. Spearman's rank correlation coefficients and *p*-values for spread and decay durations normalized by population density.

	Ds/Density		Dd/Density	
	ρ	*p*-Value	ρ	*p*-Value
T_{ave}	−0.526	0.05	−0.459	0.099
T_{max}	−0.659	<0.05	−0.385	0.175
T_{min}	−0.415	0.140	−0.465	0.094
T_{diff}	0.227	0.435	0.487	0.078
H_{ave}	−0.494	0.061	−0.716	<0.05
H_{max}	−0.737	<0.05	−0.741	<0.05
H_{min}	−0.130	0.657	−0.733	<0.05
H_{diff}	−0.760	<0.05	−0.718	<0.05

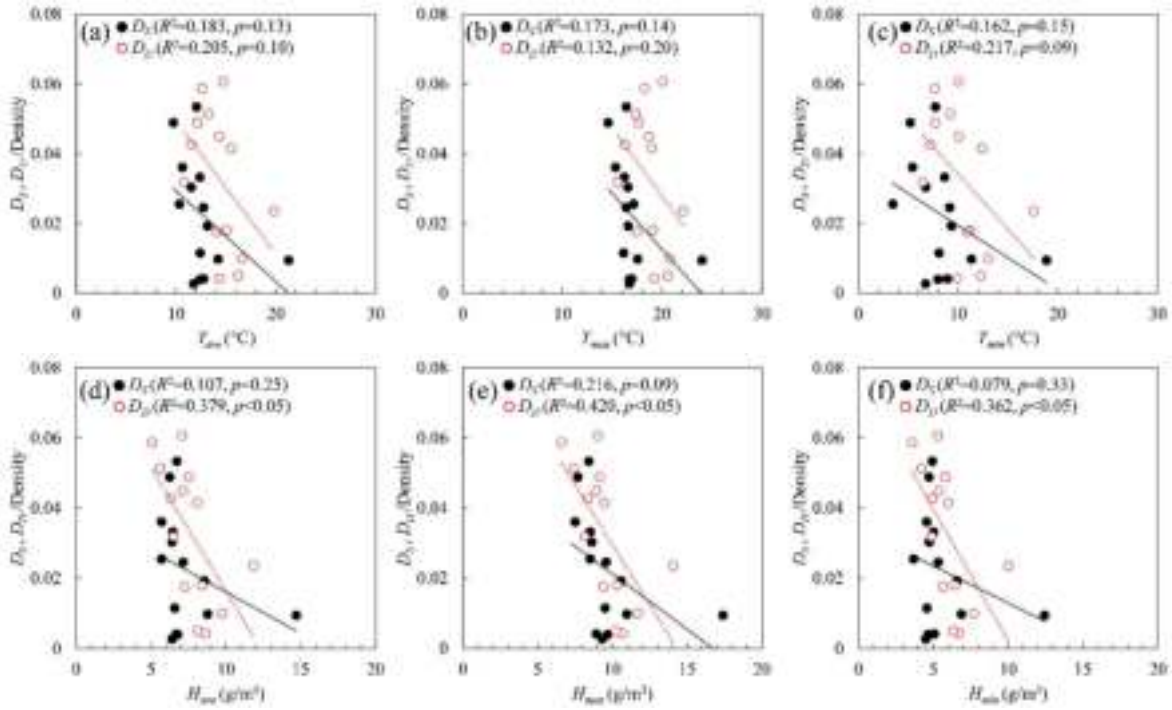


Figure 5. Relationship of the spread and decay durations (D_S and D_D) with (**a**) daily average temperature (T_{ave}), (**b**) daily maximum temperature (T_{max}), (**c**) daily minimum temperature (T_{min}), (**d**) daily average absolute humidity (H_{ave}), (**e**) daily maximum absolute humidity (H_{max}), and (**f**) daily minimum absolute humidity (H_{min}).

A multivariate correlation analysis was conducted to examine the relationship between the daily maximum temperature and absolute humidity values measured during the study period (pandemic spread and decay) and the population density (Figure 6). The data of Aichi and Saga prefectures were excluded due to their outlier status. The results yield adjusted R^2 values of 0.53($p < 0.05$) and 0.24($p = 0.130$) in the spread and decay stages, respectively, indicating variability within some prefectures, as shown in Table 5. The standardized partial regression coefficients of population density, daily maximum temperature, and absolute humidity are 0.611, 0.203, and −0.682, respectively, for the spread duration, while they are 0.388, 0.544, and −0.219, respectively, for the decay duration (Figure 6).

Table 5. Coefficients of determination R^2, adjusted R^2 values and p-values for the multivariate linear regression.

	R^2	adj. R^2	p-Value
D_S	0.641	0.533	<0.05
D_D	0.416	0.240	0.130

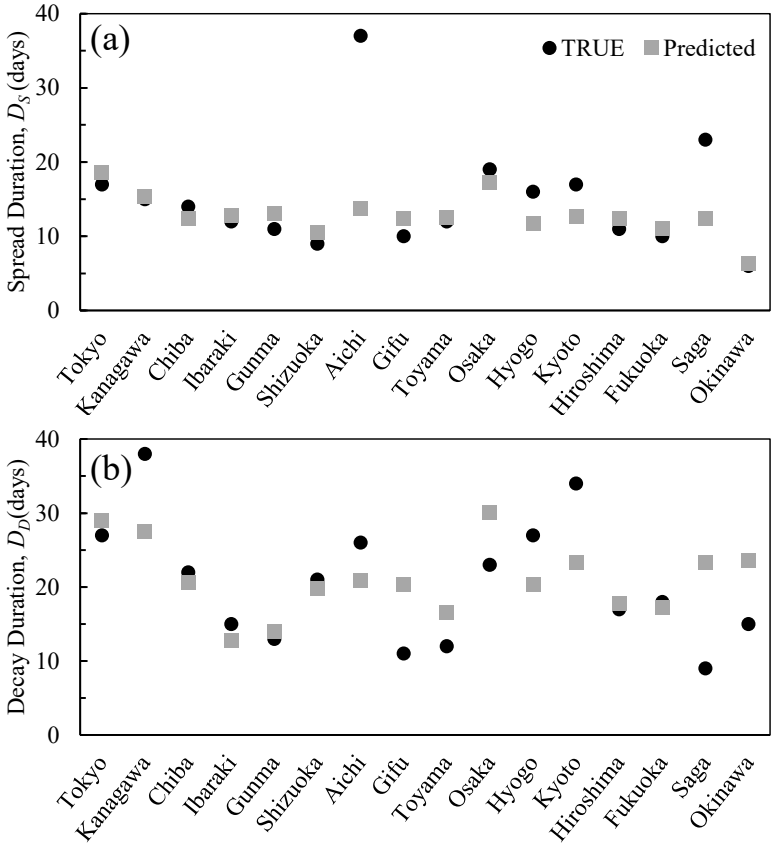


Figure 6. Multivariate regression (population density, maximum temperature, and absolute humidity) results for (**a**) spread and (**b**) decay periods.

4. Discussion

The effect of temperature and humidity on morbidity and mortality has long been investigated in research on health problems caused by different environmental factors (e.g., [42,43]). Even for COVID-19, as reviewed in the introduction, their influence has been discussed extensively in different countries. A case study of COVID-19 in Japan highlights the environmental factors in view of the consistency of data recording, healthcare quality, and social response to the outbreak of the disease. The limitation of data, which is partly attributable to different policies in Japan, as in Section 2, is one factor hampering the analysis of available COVID-19 data. A further challenge is the large variation in data reliability, consistency, and uniformity.

In this study, the durations of the spread and decay stages were evaluated, for the first time, to assist with the setting of policies and action plans. Although the results obtained in this study cannot be directly implemented in all cases, it provides valuable insight into how environmental factors influence the transmission phase during a pandemic in a more general framework.

The COVID-19 spread and decay durations of 16 prefectures in Japan that had a daily maximum of confirmed positive cases exceeding 10 were compared. A definition of the metrics for both durations from 10–90% of the normalized confirmed cases has been introduced. Normalization was performed to avoid potential differences in the absolute number of cases reported among prefectures due to different regulations. One difficulty in handling the data was the lower number of cases in Japan compared to most other countries; for example, the number is one to two orders of magnitude smaller than that of most European countries (e.g., see [34]). As mentioned above, a time-series analysis of COVID-19 cases in Japan is not feasible due to the Japanese COVID-19 policy combined with the incubation period.

The results of this study show that the number of confirmed cases generally increased and then decreased, forming bell-shaped or log-normal curves [36,37]. However, significant dual peaks are

observed in Aichi and Saga during the spread stage and in Aichi, Saga and Tokyo during the decay stage. According to reports of each prefecture, this is mainly caused by patient clusters, which are attributed to nosocomial infections, nursing home patients, and travelers returning from foreign countries. In Aichi, at least one peak is caused predominantly by individuals who returned from foreign countries. The duration of such peaks is relatively short compared to the prefecture durations and generally shorter than the estimated ones. The total spread and decay durations in Aichi were shorter than 20 days for the first bell-shaped curve, whereas the estimated duration from the multivariate analysis was 35 days and thus may not be considered as a second outbreak. If the duration defining threshold is changed (e.g., 0.05. to 0.95), the tendency does not change for distributions following a bell-shape and the duration increases by 30%. However, some differences are apparent in prefectures where small peaks (i.e., cluster infections) are observed. In general, such prefectures have been excluded or treated separately, thus not influencing our conclusions.

Most noteworthy is the evaluation of the effect of population density on the spread and decay durations. The results for the primary prefectures show a good correlation between these parameters, indicating that population density functions as a rough proxy for social distancing [44]. Our data indicate that it significantly influences the formation of the bell-shape of the curve describing the pandemic. By normalizing our data using population density, we found good correlations between the temperature and absolute humidity, and the identified durations. This is surprising because the ambient conditions in the real world vary significantly with time (e.g., [45–47]). Regarding ambient condition parameters, the daily maximum absolute humidity had the greatest effect.

The parameters obtained with multivariate linear regression analysis were applied for the predictions: adjusted R^2 values are 0.53 ($p < 0.05$) and 0.24 ($p = 0.13$) for the spread and decay durations, respectively; that is, the decay duration is not statistically significant. The small peaks observed in the prefectures adjacent to the primary prefectures (Figure 2b) could be the potential reason for this.

This demonstrates that in adjacent prefectures the influence of the primary prefectures may not be neglected because residents commuting between the prefectures influence the spread and/or decay durations. For example, Hyogo prefectural governor decided to match the end of state emergency with that in Osaka; they are adjacent with each other.

Therefore, additional constraints were defined to exclude prefectures located adjacent to primary prefectures to avoid the influence of infections caused by neighboring major pandemic clusters. A set of nine prefectures demonstrated a strong correlation of the average absolute humidity and population density, yielding adjusted R^2 values of 0.896 ($p < 0.05$) and 0.681 ($p < 0.05$) in the spread and decay stages, respectively.

The importance of absolute humidity was suggested in previous studies on the morbidity/mortality rate of the influenza virus [48,49] and also in a preliminary study of COVID-19 [22]. Note that the differences in other parameters, including maximum and average temperatures, and average absolute humidity, show comparable correlations. In [22] the role of the ambient parameters could not be adequately constrained, and controversies and inconsistencies remained (see the review in "Introduction").

A straightforward comparison of our findings with those of different countries is not feasible because the data is measured based on different closure policies, testing rates, validation measures, etc., which would introduce several biases. Further factors influencing data accuracy are lockdown restrictions, social distancing, and public response. Recently, the effect of air-conditioning units on COVID-19 transmission has also been suggested [50]. This case study on the pandemic duration in Japan nevertheless provides a highly consistent result that may lead to a better understanding of this correlation.

5. Conclusions

This study investigates the correlation of the durations of the spread and decay stages of COVID-19 with ambient conditions and population density in 16 prefectures of Japan. Although the number of

cases reported in Japan is limited, the uniformity of the data provides a fairly consistent conclusion; the population density is dominant, and higher absolute humidity and temperature may result in shorter durations. Some exceptions exist, especially in prefectures where travelers returned from foreign countries. In addition, the durations in adjacent prefectures were influenced by the primary prefectures (e.g., Tokyo, Osaka, Aichi, and Fukuoka), resulting in longer durations. For a potential pandemic, especially a potential second wave of COVID-19, this factor should be considered as well as the multi-city comparison for developing different protection policies.

Author Contributions: Conceptualization, A.H.; Data curation, E.A.R. and S.K.; Formal analysis, S.K., J.G.-T. and A.H.; Investigation, E.A.R., S.K. and J.G.-T.; Methodology, A.H.; Project Administration, A.H.; Resources, E.A.R.; Software, E.A.R. and S.K.; Validation, E.A.R.; Visualization, S.K.; Writing—original draft, A.H.; Writing—review and editing, E.A.R., S.K., J.G.-T. and A.H. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

The relationship between the different ambient condition metrics and morbidity is often discussed (e.g., [51]). For the COVID-19 duration analyzed in this study, the correlation between the maximum temperature and maximum absolute humidity in the spread duration presented in Figure A1 are significant ($p < 0.05$). The duration of COVID-19 was generally limited to two months; thus, the metrics considered in the discussion of Figure 6 are correlated unlike the discussion of their annual impact on influenza (e.g., [49]).

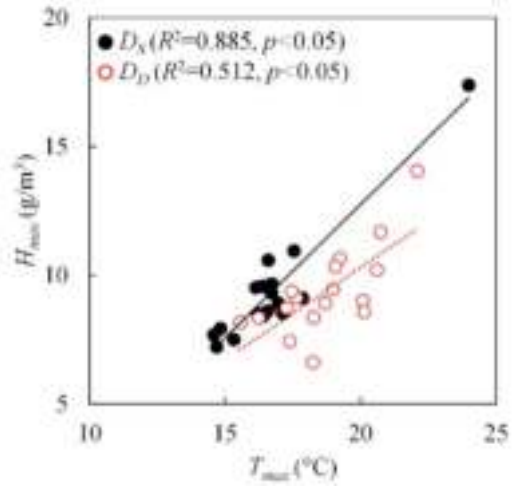

Figure A1. Relationship between maximum humidity and maximum temperature.

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Is coronavirus disease (COVID-19) seasonal? A critical analysis of empirical and epidemiological studies at global and local scales

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ABSTRACT

Coronavirus disease (COVID-19) has infected more than 50 million people and killed more than one million, worldwide, during less than a year course. COVID-19, which has already become the worst pandemic in the last 100 years, is still spreading worldwide. Since the beginning of the outbreak, it has been of particular interest to understand whether COVID-19 is seasonal; the finding might help for better planning and preparation for the fight against the disease. Over the past 12 months, numerous empirical and epidemiological studies have been performed to define the distinct diffusion patterns of COVID-19. Thereby, a wealth of data has accumulated on the relationship between various seasonal meteorological factors and COVID-19 transmissibility at global and local scales. In this review, we aimed to discuss whether COVID-19 exhibits any seasonal features in a global and local perspective by collecting and providing summaries of the findings from empirical and epidemiological studies on the COVID-19 pandemic during its first seasonal cycle.

1. Introduction

Seasonality is a common feature of viral infections in humans and various animals (Dowell and Ho, 2004; Moriyama et al., 2020). For example, while human influenza virus, coronaviruses (HCoVs), and orthopneumoviruses exhibit an annual increase in incidence during winter (Shaman and Kohn, 2009), some non-polio enteroviruses have seasonal peaks in summer (Pons-Salort et al., 2018). As common HCoVs show seasonality, it is plausible to believe that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a member of the same family, could also exhibit seasonal features (Killerby et al., 2018; Ye et al., 2020).

SARS-CoV-2, the virus that causes coronavirus disease (COVID-19), was first identified in Wuhan, China, in December 2019. Since then, the virus has rapidly spread worldwide. As of November 9, 2020, more than 50,000,000 confirmed cases with more than 1,250,000 deaths have been reported (case fatality rate [CFR] of approximately 2.5%). During the first months of the outbreak, COVID-19 has shown an interesting diffusion pattern, as the transmission was restricted to a certain range of latitude, temperature, and humidity (Sajadi et al., 2020; Sarmadi et al., 2020). As COVID-19 is a novel disease, it has been challenging so far to corroborate its seasonality because of its short existence. However, statistical data on SARS-CoV-2 transmission have accumulated over the past 12 months, and this new information could provide clues that may explain the distinct diffusion patterns of COVID-19 in the pandemic.

The restricted pattern of spread of COVID-19 has been of great interest. This is because identifying the cause of the disparate diffusion pattern could prove useful in predicting how the COVID-19 situation might unfold. Although vaccine administrations have already begun, there have been reports of new variants of SARS-CoV-2, against which the already developed vaccines may be ineffective (Callaway, 2021). Furthermore, how long the antibody response will be sustained following a natural infection with SARS-CoV-2 is questionable as recent studies suggest that the humoral immunity against SARS-CoV-2 may be short-lived (Anna et al., 2020; Ibarrondo et al., 2020). In line with this, it was recently found that naturally infected individuals, especially those with mild symptoms, are prone to a reinfection (Ibarrondo et al., 2020; Seow et al., 2020). In fact, mounting evidence suggests that COVID-19 has the potential to become a seasonal illness like seasonal influenza (Lavine et al., 2021). This emphasizes the importance of understanding the transmission patterns of SARS-CoV-2, that is, whether it is a seasonal virus. While human-to-human interactions play a great role in viral diffusion, temperature and humidity can still alter human behavioral

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Nonstandard abbreviations used:

AH	absolute humidity
CFR	case fatality rate
CI	confidence interval
COVID-19	coronavirus disease
GAM	generalized additive model
HCoV	human coronavirus
LAC	Latin America and the Caribbean
LR	linear regression
RBM	receptor binding motif
RH	relative humidity
RRR	ratios of rate ratios
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SEIR	Susceptible-Exposed-Infectious-Recovered
SH	specific humidity

patterns, immune system functioning/response, and viral survivability in the external environment; these all ultimately contribute to high SARS-CoV-2 transmission (Al Huraimel et al., 2020; Bontempi et al., 2020; Bontempi, 2020, 2021; Courtemanche et al., 2020; Tammes, 2020). If the development of new vaccines will be constantly required, as with the yearly flu vaccine, establishing whether COVID-19 has seasonality will play a crucial role in future planning of vaccine development.

Here, we aimed to provide a synthesized summary of the findings of empirical and epidemiological studies on the impact of seasonal meteorological factors (e.g., temperature; absolute [AH], relative [RH], and specific humidity [SH]; precipitation; solar radiation/ultraviolet [UV]; wind speed; latitude; and air pollution) on COVID-19 transmissibility during the first seasonal cycle of the pandemic. Of note, we explicitly evaluated the findings of global and local studies separately; this is because sample size and regional disparities may have impacted the findings. By "global study", we refer to cross-country analysis with a dataset comprising data from 50 or more countries. Conversely, by definition, "local study" refers to cross-category analysis in a single country or cross-country analysis with a dataset of fewer than 50 countries.

2. Temperature forms an inverse relationship with the global transmission of SARS-CoV-2

Since the first COVID-19 case was reported in December 2019, the disease has now completed a full seasonal cycle. Between the time when COVID-19 transitioned from being an epidemic to being declared a real pandemic of global significance, regions with higher temperatures (>20°C) still reported lower numbers of COVID-19 cases than those with lower temperatures. Notably, 90% of SARS-CoV-2 transmission occurred within temperatures ranging between 3°C and 17°C in February and March 2020 (Bukhari and Jameel, 2020). Interestingly, the first few countries and cities with a rapid spread of COVID-19 (Italy, Iran, South Korea, and the US cities such as New York and Washington) exhibited a climate similar to the original hotspots of SARS-CoV-2 (Hubei and Hunan) with average temperatures between 3°C and 10°C (Bukhari and Jameel, 2020). In line with these observations, cities with substantial community spread (≥10 deaths as of March 10, 2020) showed average temperatures between 5°C and 11°C, which is indicative of a direct relationship between temperature and the transmission of SARS-CoV-2 (Sajadi et al., 2020). Comprehensively, the preferential distribution of SARS-CoV-2 globally is along the inverse latitudinal gradients (Bajaj and Arya, 2020); SARS-CoV-2 initially spread less prominently around the equator, but more prominently in regions with moderate and cold climates. Overall, these descriptive analyses from the early studies on COVID-19 raised the possibility that SARS-CoV-2 could be temperature-sensitive.

In congruence with these observations, empirical and epidemiological studies have corroborated an inverse relationship between temperature and global distribution of COVID-19 (Table 1). Correlation studies reported that the average temperature is negatively associated with both the proportion of deaths ($r = -0.5$, $p < 0.01$) and cases ($r = -0.5$, $p < 0.01$) per 10^5 population (Sarmadi et al., 2020). Pearson correlation analysis in another study revealed that average temperature negatively correlates with the attack rate, a similar concept as the CFR in terms of infectivity ($r = -0.36$, $p = 0.02$) (Hassan et al., 2020). This result is consistent with that of a study that used Spearman correlation analysis (Bezabih et al., 2020).

A simple linear regression (LR) model found that the air temperature at 2 m above the surface (2 m temperature) forms an inverse relationship with the log of the total number of cases in 50 different countries ($R^2 = 0.26$, $p < 0.001$) (Sajadi et al., 2020). In another simple LR analysis, average high temperature was reciprocally related to both total deaths ($\beta = -0.0377$, $R^2 = 0.4192$) and total cases per million population ($\beta = -0.0037$, $R^2 = 0.5875$) (Iqbal et al., 2020). A stepwise LR model fitted with R_0 displayed a negative relationship between temperature and SARS-CoV-2 infectivity (Metelmann et al., 2020). Fitting a simple LR on the exponential spread rate with the average temperature again exhibited a decreasing slope ($\beta = -0.0035$, $R^2 = 0.18$) (Notari, 2021). Equivalently, in studies using multiple meteorological variables, temperature showed a negative relationship with the total number of cases of SARS-CoV-2 infection ($\beta = -6.40$, $p < 0.01$) (Sobral et al., 2020). Accordingly, the Gutenberg-Richter law equation showed that a 1 °C increase in temperature results in decreased number of COVID-19 infections by 13–16 cases per day (Sil and Kumar, 2020). In addition, a generalized additive model (GAM), with a penalized spline function on the time variable, resulted in a negative trend between average temperature and the number of daily new cases in 166 countries ($\beta = -2.85\%$, $p < 0.01$) (Wu et al., 2020b). In accordance with all these studies, a micro-analysis of 9 locations across the globe (Italy, the United Kingdom, France, Sweden, Iran, the USA, South Korea, and Australia) showed a similar pattern, where regions with higher atmospheric temperature exhibited higher growth rates in the daily number of new cases with a median lag of 10 days (Rouen et al., 2020).

Whereas there was also a small number of studies showing no correlation between temperature and COVID-19 transmissibility (Islam et al., 2020; Jamil et al., 2020; Jüni et al., 2020) (Table 1), most studies showed an inverse relationship between temperature and the transmission of SARS-CoV-2 (Fig. 1).

3. Consistent with the global data, temperature forms an inverse relationship with local transmission of SARS-CoV-2

As COVID-19 was first reported in Wuhan, China, initial research regarding the effects of meteorological factors on SARS-Cov-2 transmission was heavily based toward China. Analysis of data collected from multiple Chinese provinces between December 2019 and February 2020 revealed that temperature and COVID-19 infection rates formed a negative relationship (Jiang et al., 2020; Wang et al., 2020). A parameterization analysis revealed that Chinese provinces with temperatures ranging from −9.41 to −13.87 °C experienced higher SARS-Cov-2 transmission rates (Lin et al., 2020a). Pearson correlation analyses on data collected from 31 Chinese provinces identified 14 provinces with a significant correlation ($p < 0.05$). Out of those 14 provinces, 12 showed a negative correlation between daily temperature and the number of infected cases (Rahman et al., 2020). A group of studies reported that with regression and correlation analysis, increment in temperature resulted in a decrease in the daily number of confirmed cases (Li et al., 2020a, 2020b; Liu et al., 2020b; Luo et al., 2020; Rouen et al., 2020; Oliveiros et al., 2020; Qi et al., 2020; Xie and Zhu, 2020). Several other studies analyzed variables from the Susceptible-Exposed-Infectious-Recovered (SEIR)

Table 1
The impact of temperature on the transmissibility of COVID-19.

Relation	Country	Statistical method used	Ref.
Negative	Global (≥50 countries)	Mapping to Köppen's climate	Bajaj and Arya (2020)
		Spearman correlation	Bezabih et al. (2020)
		Simple LR model; Pearson correlation	Hassan et al. (2020)
		Simple LR model	Iqbal et al. (2020)
		Multivariate LR model	Luo et al. (2020)
		Stepwise LR model	Metelmann et al. (2020)
		Simple LR model	Notari (2021)
		Mann-Whitney test; LR model	Sajadi et al. (2020)
		Pearson correlation	Sarmadi et al. (2020)
		Gutenberg–Richter law model	Sil and Kumar (2020)
		Uni/Multivariate LR model (by panel data strategy)	Sobral et al. (2020)
		GAM	Wu et al. (2020b)
	Brazil	GAM; Polynomial regression model	Prata et al. (2020)
		Shapiro-Wilk test; Spearman correlation	Rosario et al. (2020)
	China	SEIR model with simple LR model; Pearson correlation	Guo et al. (2020)
		Multivariate Poisson regression model	Jiang et al. (2020)
		Simple LR model	Li et al. (2020a)
		Spearman correlation	Li et al. (2020b)
		Mechanism-based parameterization model with spatial correlation and exponential regression model	Lin et al. (2020a)
		Multivariant regression model	Lin et al. (2020b)
		Meta-analysis with generalized linear models	Liu et al. (2020b)
		Stepwise LR model	Metelmann et al. (2020)
		Combination of linear and exponential models	Oliveiros et al. (2020)
		GAM	Qi et al. (2020)
		Spearman correlation	Rahman et al. (2020)
	Europe	Uni/Multivariate LR model (by panel data strategy)	Ozyigit (2020)
	Europe; USA	Polynomial regression model	Benedetti et al. (2020)
	LAC	Spearman correlation	Bolaño-Ortiz et al. (2020)
	Mexico	Spearman correlation; clustering	Méndez-Arriaga (2020)
	Spain	Polynomial regression model	Sanchez-Lorenzo et al. (2021)
	Turkey	Spearman correlation	Sahin (2020)
	USA	Gaussian function model; Pearson correlation	Scafetta (2020)
		Negative binomial regression model (with generalized estimating equations)	Sehra et al. (2020)
	Worldwide (5 countries)	Multivariate LR model	Luo et al. (2020)
	Worldwide (9 countries)	Micro-correlation with Spearman correlation	Rouen et al. (2020)
Positive	Brazil	Canonical correlation	Auler et al. (2020)
	China	Simple LR model; Spearman correlation	Yao et al. (2020a)
		GAM	Xie and Zhu (2020)
	India	Spearman correlation	Das and Chatterjee (2020)
		GAM	Gupta et al. (2020)
		Spearman correlation	Mangla et al. (2020)
	Norway	Spearman correlation	Menebo (2020)
	Singapore	Spearman/Kendall correlation	Pani et al. (2020)
	USA	Spearman/Kendall correlation	Bashir et al. (2020)
No	Global (≥50 countries)	Multilevel mixed-effects regression model	Islam et al. (2020)
		Gaussian function model	Jamil et al. (2020)
		Weighted random-effects regression model	Jüni et al. (2020)
	China	Multivariate LR model	Yao et al. (2020b)
	South Africa	Pearson correlation	Chetty et al. (2020)
	Spain	Spatiotemporal latent Gaussian model	Briz-Redón and Serrano-Aroca (2020)
	USA	Maxent model	Harbert et al. (2020)
		Negative binomial mixed model	Wu et al. (2020a)

model with regression analysis and showed that the transmission rate was negatively related to temperature (Guo et al., 2020; Lin et al., 2020b). Similarly, a stepwise LR model, used to analyze data collected up to May 2020, when the COVID-19 spread was largely under control in China, displayed a negative relationship between the temperature and COVID-19 infectivity (Metelmann et al., 2020).

Studies showed that the acceleration of transmission dynamics of COVID-19 throughout Europe had a strong association with temperature (Benedetti et al., 2020; Ozyigit, 2020; Sanchez-Lorenzo et al., 2021). A simple LR analysis of the relationship between average temperature and COVID-19 case growth in EU-15 area countries (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, and the United Kingdom) following each country's 100th reported case, confirmed the coefficient for temperature effect on the COVID-19 case growth rate as −0.009 ($p < 0.01$). Therefore, a 0.9% decrease in SARS-CoV-2 transmission was expected following a 1 °C increase in the average temperature (Ozyigit, 2020). A model analysis of 25 locations from Europe and the USA suggested that the average monthly high temperature is inversely associated with COVID-19 deaths per million population (Benedetti et al., 2020). For Spain, an exponential regression model indicated that the temperature of a region (between 5°C and 11°C) determined the total number of cases and deaths due to COVID-19 (Sanchez-Lorenzo et al., 2021).

For Brazil, the dose-response relationship shown by a GAM suggested that temperature and the total number of daily cumulative confirmed cases of COVID-19 forms a negative relationship (Prata et al., 2020). Each 1°C rise in temperature led to a decrease in the cumulative daily number of COVID-19 confirmed cases by 5.18%. Likewise, Spearman correlation test results demonstrated that the average and maximum temperatures correlated negatively ($p < 0.01$) with the number of COVID-19 cases (Rosario et al., 2020). Not only in Brazil, but also in Latin America and the Caribbean (LAC), a negative relationship was shown between temperature and COVID-19 cases (Bolaño-Ortiz et al., 2020).

In the USA, from January 20, 2020, COVID-19 spread across its states at exponential rates (Holshue et al., 2020). In the US, states with maximum daily temperature above 52 °F (11 °C) showed an inverse relationship with the rate of new cases (incidence rate ratio = 0.85, 95% confidence interval (CI) = [0.76, 0.96], $p = 0.009$) (Sehra et al., 2020). A Gaussian function model demonstrated that deaths per million population in the largest cities of each state in the US peaked between 4 °C and 12 °C (Scafetta, 2020). Similar results were obtained in Mexico, where high temperatures established harsh conditions for SARS-CoV-2 survival and led to lower local transmission ratio and confirmed cases for a month (Méndez-Arriaga, 2020).

Although most data indicated an inverse association of viral spread with temperature, few findings were inconsistent with these. From March to April 2020, New York City experienced increasing new COVID-

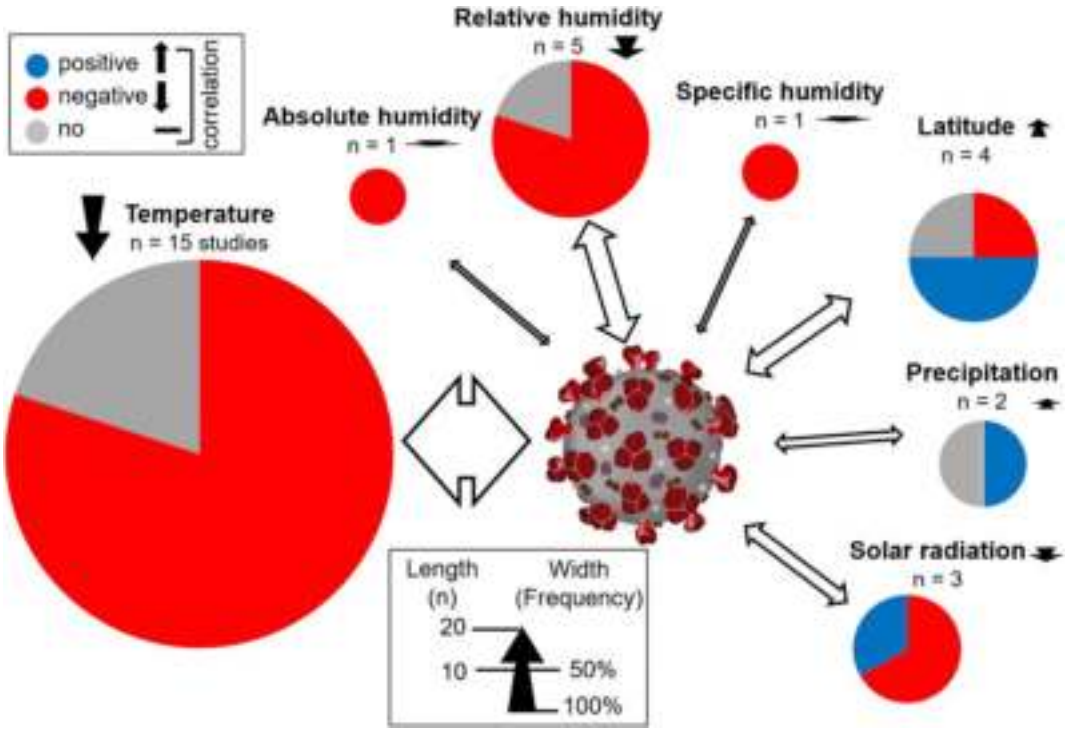

Fig. 1. The impact of meteorological factors on COVID-19 incidence at global scopes.

19 confirmed cases and mortality rates along with increasing city temperatures that ranged between 0°C and 18°C (Bashir et al., 2020). Similarly, Brazil and China also reported a positive relationship between temperature and the number of COVID-19 cases. Five state capitals in Brazil showed a higher case rate at elevated temperatures (Auler et al., 2020). As for China, 112 cities located on the northeast side of mainland China as well as 31 major cities across China followed the positively associated tendency (Xie and Zhu, 2020; Yao et al., 2020a). Besides, positive correlation between temperature and COVID-19 was observed in India, Norway and Singapore studies (Das and Chatterjee, 2020; Gupta et al., 2020; Mangla et al., 2020; Menebo, 2020; Pani et al., 2020). Notably, although SARS-CoV-2 first spread in the temperate zone (Chennakesavulu and Reddy, 2020; Huang et al., 2020; Sajadi et al., 2020; Sarmadi et al., 2020), India and Singapore are located outside the temperate zone, while Norway is at the most northern edge of the temperate zone. Interestingly, some studies also reported no correlation between temperature and the local transmission of SARS-CoV-2 (Briz-Redón and Serrano-Aroca, 2020; Chetty et al., 2020; Harbert et al., 2020; Wu et al., 2020a; Yao et al., 2020b) (Table 1).

Nevertheless, in the analysis of the association of temperature with

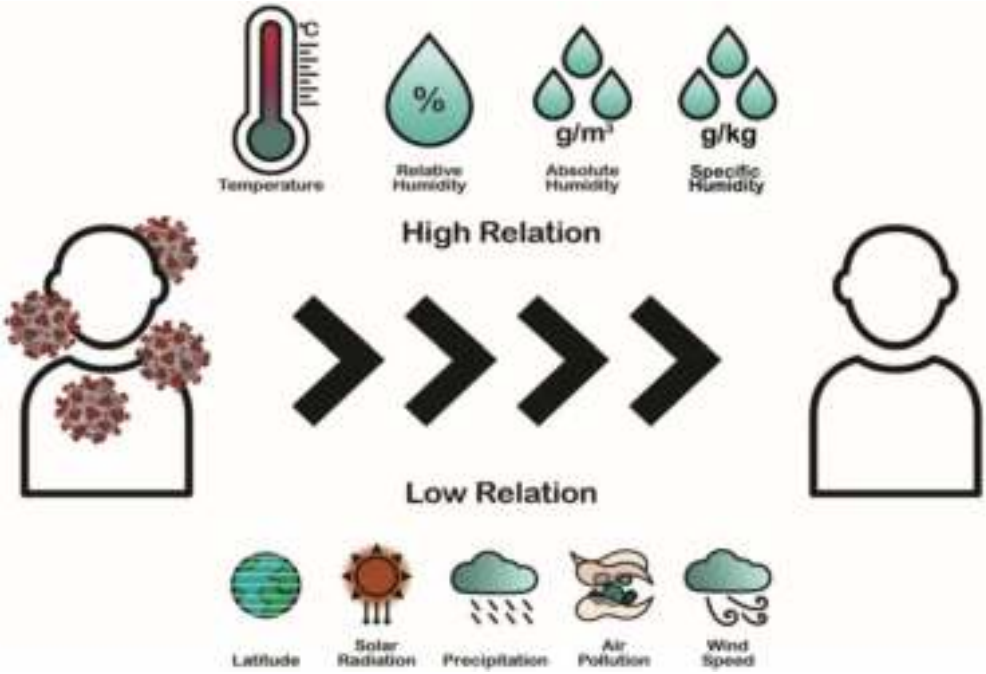

Fig. 2. Meteorological factors highly related with COVID-19 incidence at global scopes.

the local transmission of SARS-CoV-2, most studies reported, overall, an inverse relationship (Table 1 and Fig. 2). This is consistent with the general pattern observed for the global transmission of SARS-CoV-2 (Table 1).

4. Humidity tends to negatively correlate with the global transmission of SARS-CoV-2

Humidity, which is the concentration of water vapor present in the air is a decisive factor that determines the formation and size of aerosol droplets, which the virus can use as a medium to infect new hosts. Thus, humidity is an important meteorological variable that could affect the transmission of SARS-CoV-2 (Harper, 1961; Yang and Marr, 2011).

Pearson correlation analysis showed that RH is negatively correlated with the log of cases per million population ($r_H = -0.23$ with $P_{151}[-1 \leq r \leq r_H] = 0.2\%$) and the log of deaths per million population ($r_H = -0.31$, $P_{151}[-1 \leq r \leq r_H] \leq 0.01\%$) (Scafetta, 2020). When the effect of RH on daily new cases and daily new deaths was log-linearly analyzed using a GAM, a 1% increase in RH was associated with a 0.85% (95% Cl = [0.51%, 1.19%]) reduction in the daily new cases and a 0.51% (95% Cl = [0.34%, 0.67%]) reduction in daily new deaths (Wu et al., 2020b). A weighted random-effects regression analysis was concluded and showed that the epidemic growth of COVID-19 was reciprocally associated with both RH (ratios of rate ratios [RRR] per 10% = 0.91, 95% CI = [0.85, 0.96]) and AH (RRR per 5 g/m^3 = 0.92, 95% CI = [0.85, 0.96]) (Jüni et al., 2020). Congruently, studies using a LR model revealed a negative correlation between humidity and SARS-CoV-2 transmission (Metelmann et al., 2020; Sajadi et al., 2020). Only one study showed no correlation of humidity with global transmission of SARS-CoV-2 at all (Islam et al., 2020) (Table 2).

Overall, a fairly unequivocal effect of humidity on the global transmission of SARS-CoV-2 is observed (Table 2). Mounting evidence suggests that humidity negatively affects the global transmission of SARS-CoV-2 (Fig. 1).

5. Humidity may be a lesser determinant factor for local transmission of SARS-CoV-2

Till date, some studies have shown that humidity is negatively associated with SARS-CoV-2 transmission in China. In four major cities of China, RH correlated negatively with the reproductive rate (R_0) of SARS-CoV-2 ($r = -0.391$, $p = 0.000$) (Guo et al., 2020). Similar patterns were reported for AH, because a 1 g/m^3 increase in AH resulted in a decrease of 0.92 in the overall relative risk in 17 capital cities of China (Liu and Zhang, 2020).

Besides China, in some countries such as Spain, Italy, Turkey, LAC, and India, RH and SH were found to be inversely associated with local COVID-19 cases (Table 2). A polynomial regression analysis of cumulative data showed that SH is negatively associated with SARS-CoV-2 transmission in Spain (Sanchez-Lorenzo et al., 2021). A Pearson correlation analysis of regions in Italy revealed that RH is negatively correlated with the log of deaths per million population ($r_H = -0.37$, $P_{20}[-1 \leq r \leq rH] = 5.4\%$) (Scafetta, 2020). The same study showed, using a Gaussian function model, that states in the US with RH levels between 60 and 75% were the most affected by COVID-19, accounting for 80% of deaths in the USA. Studies that analyzed the association of humidity with COVID-19 cases using Spearman correlation analysis also drew consistent results. In New Delhi, RH was negatively associated with the number of daily COVID-19 infections between March 4 and June 24, 2020 ($r_s = -0.63$, $p < 0.05$) (Mangla et al., 2020). In addition, the number of COVID-19 infections was found to be negatively associated with SH in India (Gupta et al., 2020). In agreement, analysis of the data collected from 9 cities in Turkey between March 10 and April 5, 2020, revealed a negative relationship between RH and SARS-CoV-2 transmission ($r_s = -0.317$) (Şahin, 2020).

Contrarily, other studies indicated that humidity has no or a positive effect on the transmission of SARS-CoV-2 in China. In 31 Chinese provinces, a negative relationship between RH and doubling time of cumulative COVID-19 cases was shown; meaning that RH was positively associated with the rate of local COVID-19 progression (Oliveiros et al., 2020). Another analysis of data from 16 Chinese provinces concluded that RH and SARS-CoV-2 transmission rates have no significant spatial correlation ($R = -0.17$, $p = 0.48$) (Lin et al., 2020a). Similarly, multiple other studies did not find a significant association between RH and SARS-CoV-2 transmission in China (Li et al., 2020b; Metelmann et al., 2020; Rahman et al., 2020; Yao et al., 2020b).

Humidity was also observed to have a positive relationship with local SARS-CoV-2 transmission rates in the USA, Singapore, and the Netherlands (Table 2). When the relationship between RH and SARS-CoV-2 transmission in the USA was investigated using a distributed lag non-linear model with data collected from California, high RH was a

Table 2
The impact of humidity on the transmissibility of COVID-19.

Relation	Country	Statistical method used	Ref.
Absolute humidity (AH)			
Negative	Global (≥50 countries)	Weighted random-effects regression	Jüni et al. (2020)
	China	Meta-analysis with generalized linear models	Liu et al. (2020b)
Positive	Netherlands	Pearson correlation; Spearman correlation; spatiotemporal model	Ravelli and Gonzales Martinez (2020)
	Singapore	Spearman/Kendall correlation test	Pani et al. (2020)
	Worldwide (5 countries)	Multivariate LR model	Luo et al. (2020)
Relative humidity (RH)			
Negative	Global (≥50 countries)	Weighted random-effects regression	Jüni et al. (2020)
		Multivariate LR model	Metelmann et al. (2020)
		Pearson correlation	Scafetta (2020)
		GAM	Wu et al. (2020b)
	China	SEIR model with simple LR model; Pearson correlation	Guo et al. (2020)
		GAM	Qi et al. (2020)
	India	Spearman correlation	Mangla et al. (2020)
	Turkey	Spearman correlation	Şahin (2020)
Positive	China	Multivariate Poisson regression models	Jiang et al. (2020)
		Combination of linear and exponential regression models	Oliveiros et al. (2020)
		Simple LR model; Spearman correlation	Yao et al. (2020a)
	Singapore	Spearman and Kendall rank correlation tests	Pani et al. (2020)
	USA	Distributed lag non-linear model	Fang et al. (2020)
No	Global (≥50 countries)	Multilevel mixed-effects regression model	Islam et al. (2020)
	Brazil	Spearman correlation	Rosario et al. (2020)
	China	Spearman rank correlation	Li et al. (2020b)
		Mechanism-based parameterization model with spatial correlation and exponential regression	Lin et al. (2020a)
		Stepwise LR model	Metelmann et al. (2020)
		Spearman correlation	Rahman et al. (2020)
		Multivariate regression	Yao et al. (2020b)
	USA	Negative binomial mixed models	Wu et al. (2020a)
Specific humidity (SH)			
Negative	Global (≥50 countries)	Simple LR	Sajadi et al. (2020)
	India	GAM	Gupta et al. (2020)
	Spain	Polynomial regression analysis	Sanchez-Lorenzo et al. (2021)

risk factor; RH of around 98% was related to an increased risk of SARS-CoV-2 transmission (RR = 1.703, 95% CI = [1.049, 2.765]) (Fang et al., 2020). In Singapore, both RH and AH were positively correlated to new COVID-19 cases, when analyzed using Spearman (RH: $r_s = 0.21$, $p < 0.05$; AH: $r_s = 0.59$, $p < 0.01$) and Kendall rank correlation analyses (RH: $\tau = 0.15$, $p < 0.05$; AH: $\tau = 0.45$, $p < 0.001$) (Pani et al., 2020). The average RH was 91% and the average AH was 22 g/m^3 over the period of the data collection. In the Netherlands, from March to July 2020, a spatiotemporal disease model affirmed that SH was strongly correlated with the number of daily COVID-19 cases ($r = 0.701$, $p = 0.000$; $r_s = 0.838$, $p = 0.000$) (Ravelli and Gonzales Martinez, 2020).

Overall, humidity may be a lesser determinant factor for local SARS-CoV-2 transmission (Fig. 3). Nevertheless, we cannot exclude the possibility that these inconsistent findings in the relationship between humidity and local transmission of SARS-CoV-2 may be attributed to sample size differences. Further studies are needed to clearly address the relationship between (absolute, relative, and specific) humidity and COVID-19 transmissibility.

6. Other meteorological factors related to SARS-CoV-2 transmission: Air pollution, wind speed, latitude, precipitation and solar radiation

Air pollution, wind speed, latitude, precipitation, and solar radiation are influential factors in determining seasonality in other respiratory viral infections (Domingo et al., 2020; du Prel et al., 2009; Price et al., 2019). However, whether there is a link between COVID-19 transmissibility and the aforementioned meteorological factors remains unclear (Table 3). As compared to temperature or humidity, fewer results are published regarding their possible contribution to SARS-CoV-2 transmission (Table 3). Additionally, the studies included in this review did not report cohesive results to indicate a distinct relationship between each of the factors and the transmission of SARS-CoV-2 (Figs. 2 and 3).

7. Discussion

Meteorological factors play a vital role in the transmissibility of HCoVs. In general, human and animal CoVs show a much higher persistence under low temperature and low RH (Aboubakr et al., 2020). Similarly, the spread of SARS-CoV-2 could be seasonally associated with the colder months. This phenomenon may be closely related to the increased persistence of airborne aerosols under a low temperature and low humidity environment, which increase the chance of infection of a new host (Harper, 1961). The amount of water vapor that a unit of air can hold diminishes at lower temperatures, and a reduction in the size of aerosol droplets occurs at lower humidity due to evaporation (Yang and Marr, 2011).

Higher persistence of SARS-CoV-2 resulting from low temperature could also be explained by the effects of temperatures on the structure of viruses. In high-temperature environments, the order of phospholipids in the viral envelope is disrupted, thus hindering the stability of the viral envelope (Polozov et al., 2008). Higher infectivity in low-temperature conditions could also be attributed to the changes in the receptor-binding motif (RBM) conformation. At temperatures between 10 and 30°C, the RBM is in an open conformation, which is more favorable for host cell receptor recognition and binding (Rath and Kumar, 2020).

It is also evident that meteorological factors have a strong impact on host susceptibility (Dowell, 2001; Fisman, 2007). A typical example would be the effects of temperature and humidity on the mucosal layer lining of the host respiratory tract (Moriyama et al., 2020). Prior studies found that both lower temperature and humidity trigger mucus hypersecretion, which impede the appropriate removal of viruses or foreign substances by the host mucociliary mechanisms, leading to increased virion stability in the host upper respiratory mucosa (Lowen et al., 2007;

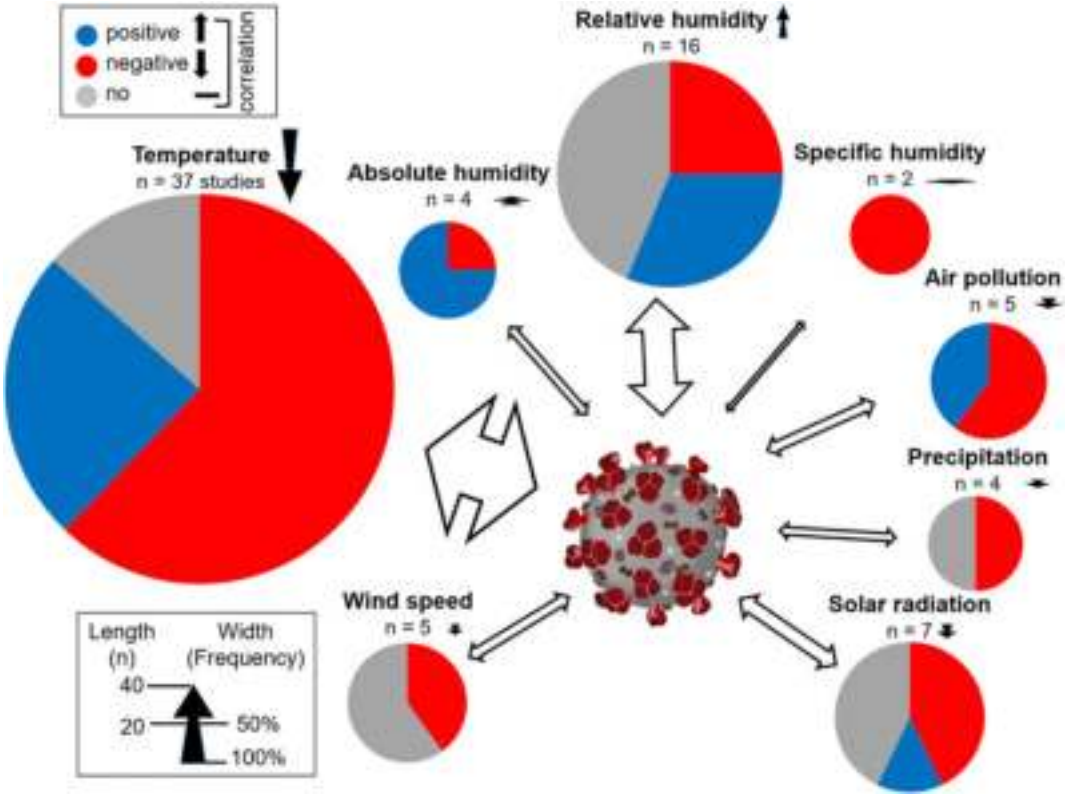

Fig. 3. The impact of meteorological factors on COVID-19 incidence at local scopes.

Table 3
The impact of other meteorological factors (w/o temperature, humidity) on the transmissibility of COVID-19.

Relation	Country	Statistical method used	Ref.
Air pollution			
Negative	China	Simple LR model; Spearman correlation	Yao et al. (2020a)
	India	GAM	Das and Chatterjee (2020)
	USA	Spearman correlation; Kendall correlation	Bashir et al. (2020)
Positive	China	Simple LR model	Li et al. (2020a)
	USA	Negative binomial mixed models	Wu et al. (2020a)
Latitude			
Negative	Global (≥50 countries)	Stepwise LR model	Metelmann et al. (2020)
Positive		Spearman correlation	Bezabih et al. (2020)
		Pearson correlation	Sarmadi et al. (2020)
No		Weighted random-effects regression	Jüni et al. (2020)
Precipitation			
Negative	India	GAM	Gupta et al. (2020)
	Norway	Spearman correlation	Menebo (2020)
Positive	Global (≥50 countries)	Multivariate LR model (by panel data strategy)	Sobral et al. (2020)
No	Global (≥50 countries)	Spearman correlation	Bezabih et al. (2020)
	Brazil	Spearman correlation	Rosario et al. (2020)
	India	Spearman correlation	Mangla et al. (2020)
Solar radiation/UV			
Negative	Global (≥50 countries)	Simple LR model	Iqbal et al. (2020)
		Stepwise LR model	Metelmann et al. (2020)
	Brazil	Spearman correlation	Rosario et al. (2020)
	China	LR model	Li et al. (2020a)
	India	Spearman correlation	Das and Chatterjee (2020)
Positive	Global (≥50 countries)	Multivariate LR model (by panel data strategy)	Sobral et al. (2020)
	India	GAM	Gupta et al. (2020)
No	China	Stepwise LR model	Metelmann et al. (2020)
		Multivariate LR model	Yao et al. (2020b)
	USA	Spearman correlation	Harbert et al. (2020)
Wind speed			
Negative	Brazil	Spearman correlation	Rosario et al. (2020)
	Singapore	Spearman/Kendall correlation test	Pani et al. (2020)
No	India	Spearman correlation	Mangla et al. (2020)
	Norway	Spearman correlation	Menebo (2020)
	USA	Spearman correlation	Harbert et al. (2020)

Tian and Wen, 2015; Wise et al., 2018). Reduced humidity also damages epithelial cell integrity and impairs the re-epithelialization process, allowing easier opportunities for the transmission of infection (Kudo et al., 2019). Furthermore, decreased body temperature is linked with lower expression of interferon-stimulated genes that are actively involved in the primary antiviral defense mechanisms (Foxman et al., 2015; Ivashkiv and Donlin, 2014).

Factors such as solar radiation may alter the seasonal perceptions of the human body by inducing changes in the melatonin mediated circadian rhythm (Nelson and Drazen, 1999). Such shifts in the seasonal perception leads to fluctuations in certain gene expression levels (Dopico et al., 2015; Goldinger et al., 2015). About 147 genes in our immune system are affected by meteorological changes; they are also associated with the processes involving B-cell receptor signaling, Fc receptor-gamma-associated processes, lysosomes, chemokine signaling, and phagosomes (Dopico et al., 2015). The same study proposed that the immune system-related genes are observed in a higher inflammatory status during winter months. This raises the likelihood of cardiovascular, autoimmune, and neurological diseases, further leading to human immune system susceptibility to viral infection.

Population density is another possible contributing factor to a high SARS-CoV-2 transmission rate (Diao et al., 2021; Li et al., 2018; Randolph and Barreiro, 2020; Sil and Kumar, 2020; Tarwater and Martin, 2001). A positive correlation between the population density of an area and the transmission rate has also been observed for viruses other than SARS-CoV-2, emphasizing the importance of taking population density into account when studying the seasonality of SARS-CoV-2 (Vanden Broecke et al., 2019). Mounting evidence suggests that population density has a high impact on the spread of COVID-19 by affecting contact rates (de Lusignan et al., 2020; Han et al., 2021; Kodera et al., 2020; Rocklöv and Sjödin, 2020; Tammes, 2020). The differences in the targeted region's population density could be a possible reason for the contradictory reports on the effect of various meteorological factors. Studies that collected data from cities with higher population densities reported a positive relationship between meteorological factors and SARS-CoV-2 transmission and vice versa (Bashir et al., 2020; Das and Chatterjee, 2020; Menebo, 2020; Pedrosa, 2020). Besides population density, variability in population behavior, air pollution, sewage, natural water has been proposed as other factors that may contribute to the different transmission rates of SARS-CoV-2 (Al Huraimel et al., 2020; Bontempi et al., 2020; Bontempi, 2020, 2021; Courtemanche et al., 2020; Liu et al., 2020a; Tammes, 2020). Behavioral measures such as wearing of masks have been proven to effectively prevent the spread of other known viruses like the influenza virus (Greenhalgh et al., 2020; Liu and Zhang, 2020). Such results indicate that other social factors should be considered when looking into the possible seasonality of COVID-19.

It is important to mention that this review could not have avoided a few methodological limitations. Firstly, most studies included in this review only considered the effects of meteorological factors on SARS-CoV-2 transmission, while neglecting the effects of factors that are dependent on human-to-human interaction. Such factors include social and economic factors such as population density, population behavior, lockdown policies and telecommuting. Certainly, there is a consensus on the fact that virus transmission is mainly caused by human-to-human interaction. Thus, any analysis claiming to find strong correlations without considering human-to-human interaction cannot establish a definite causal explanation (Bontempi, 2020). Secondly, each study included different types of data and utilized different methods in their analysis; these could possibly bring about contradictory findings amongst studies. For example, while some researchers used the absolute number of confirmed/death cases in their analysis, others employed a wide range of metrics such as the number of cumulative confirmed/death cases, R_0 and incidence rate. Coupled with the disparity in the use of a consistent metric of viral transmission, the variability in data collection, data screening approaches and statistical procedures renders the comparison amongst studies as an arduous task. This is especially true when comparing studies from a wide range of locations, where elements other than meteorological factors such as socioeconomic, geographic factors and spatiotemporal patterns are involved in the COVID-19 contagion. Indeed, considering the aforementioned limitations, we are not making a hasty claim that meteorological conditions are the only causative factors or the dominant factor of SARS-CoV-2 transmission. However, we conclude that a clear pattern can be observed, which is an inverse forcing of temperature and humidity on the spread of COVID-19 on a global scale.

8. Conclusion

Several empirical and epidemiological studies have indicated that temperature and humidity are the most significant factors affecting SARS-CoV-2 transmission. Studies collectively agree with the inverse forcing of temperature and humidity (AH, RH, and SH) on the global transmission of SARS-CoV-2. These general tendencies observed for SARS-CoV-2 transmission is consistent with the survivability of other HCoVs in various environmental conditions. Based on the studies presented here, COVID-19 appears to be temperature-sensitive and, therefore, seasonal. Along with the other meteorological factors, such as air pollution, wind speed, etc., analyses on local regions drew ambiguous conclusions on the effect of humidity on SARS-CoV-2 transmission. These discrepancies could be the product of other social and biological factors, such as population density, population behavior, social distancing, and host susceptibility. Nevertheless, as the coronavirus pandemic has just completed a full seasonal cycle, further studies are desirable to corroborate the negative correlation of AH, RH, and SH with the SARS-Cov transmissibility at local scales, if possible, with increased sizes of datasets.

Credit roles

Woo Seok Byun, Investigation, Validation, Writing – original draft, Writing – review & editing. Sin Woo Heo, Investigation, Writing – original draft, Writing – review & editing. Gunhee Jo, Investigation, Writing – original draft. Jae Won Kim, Conceptualization, Investigation, Writing – original draft. Sarang Kim, Investigation, Writing – original draft. Sujie Lee, Investigation, Writing – original draft. Hye Eun Park, Investigation, Writing – original draft, Writing – review & editing. Jea-Hyun Baek, Conceptualization, Writing – original draft, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Research Letter

Research Letter

The spread rate of SARS-CoV-2 is strongly associated with population density

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The novel severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) emerged in December 2019 and made a huge impact on human society. Different countries and regions have made different policies in control and prevention of the spread of SARS-CoV-2. It is known that the spread rate of a virus, i.e. SARS-CoV-2, heavily depends on population density.[1] Besides, population density has large impacts on the basic reproduction number (R_0) of SARS-COV-2.[2] It is also observed that patients in high-transmission areas have a higher incidence of severe coronavirus disease outcomes when compared with patients in low-transmission areas.[3] To this end, this study investigates the spread rates of SARS-CoV-2 in different regions with different population densities.

We calculated the spread rates of SARS-CoV-2 in different regions of the USA. The counties of the USA are categorized into four regions: the first region consisting of counties with a population density <50 persons/km^2, and the second, third and fourth regions consisting of counties with population densities between 50 and 200, between 200 and 800, and >800 persons/km^2. In this way, the population of the USA is roughly evenly categorized into the four regions, which include 72.3, 91.2, 102.2 and 61.3 million persons, respectively.

The spread rates of SARS-CoV-2 are calculated for each of the four regions. The calculations are based on the data collected by the data hub at the Johns Hopkins University from 1 March 2020 to 30 June 2020.[4] The spread rate of SARS-CoV-2 in a region is defined as the average number of new deaths in last 7 days per 1 million persons as follows:

$$\text{Rate} = \frac{\#\text{of new deaths in last 7 days}}{7} * \frac{1\,000\,000}{\text{Population}}$$

The rates are normalized to a million persons to ensure they are comparable among different regions with different populations. We employ the number of new deaths rather than the number of new infections because the latter number is very inaccurate due to two reasons. First, many people have little or no symptom after infection of SARS-CoV-2,[5] these people are not likely included in the number of infections. Second, number of infections heavily depends on the sufficiency of test facilities and reagents. When more tests are performed, the number of infections gets larger.

By analysis of the spread rates of SARS-CoV-2 in different regions, we have two observations. First, SARS-CoV-2 has higher spread rates in regions with high population densities than regions with low population densities. Before mid-April, when the spread rates of SARS-CoV-2 achieve maximal values for the four regions, the spread rate of SARS-CoV-2 in region 4 is higher than the spread rate in region 3, followed by the spread rates in region 2, which exceeds the spread rates in region 1 (Figure 1). On average, the spread rates in region 4 are 8.0 times as the spread rates in region 1 before 15 April 2020. Similarly, the spread rates in region 3 and region 2 are 3.9 and 1.7 times as the spread rates in region 1 before 15 April 2020. We note that SARS-CoV-2 achieves the maximal spread rates around mid-April in the four regions. However, control and prevention measures are adopted as early as 22 March 2020 when the residents of New York were required to stay home.[6] It was reported that the median time from illness onset to death is 18.5 days for SARS-CoV-2 infection.[7] Since the spread rate in this study is defined on number of new death, the spread rates achieve the maximal values at least 18.5 days after the control and prevention measures are adopted.

Second, we note that the control and prevention measures for SARS-CoV-2 have better effects in regions with high population density. From mid-April (11 April–20 April) to June (20 June–30 June), the spread rate of SARS-CoV-2 in region 4 is reduced to 8.1%. However, the spread rates of SARS-CoV-2 in regions 3,

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Figure 1. The spread rates of SARS-CoV-2 in four regions from 1 March 2020 to 30 June 2020. The four regions are categorized by population density from low to high.

2 and 1 are reduced to 46.1, 73.3 and 100.6%, respectively, in the same time period. In other words, the control and prevention measures have very significant effects in region 4 (counties with very high population densities), i.e. the spread rate of SARS-CoV-2 is reduced for >10 times. On the other hand, the control and prevention measures have almost no effect in region 1 (counties with very low population densities), i.e. the spread rate of SARS-CoV-2 retains at the same level. In addition, the control and prevention measures have limited effect to reduce the spread rate of SARS-CoV-2 for region 3 as well.

Since region 1 and region 2 account for 50% of the population of the USA, it is worthy of discussion that should a standard control and prevention measure be made or how to make multiple-layer control and prevention measures, which are flexible for different regions. This study has proved that the spread rate of SARS-CoV-2 is strongly associated with population density, and diversified control and prevention measures should be made for different regions according to population density.

Authors' contribution

K.C. conceived and designed the study and drafted the manuscript, and Z.-H.L. collected and analysed data.

Conflict of interest

None declared.

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Estimating and explaining the spread of COVID-19 at the county level in the USA

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The basic reproduction number, R_0, determines the rate of spread of a communicable disease and therefore gives fundamental information needed to plan public health interventions. Using mortality records, we estimated the rate of spread of COVID-19 among 160 counties and county-aggregates in the USA at the start of the epidemic. We show that most of the high among-county variance is explained by four factors ($R^2 = 0.70$): the timing of outbreak, population size, population density, and spatial location. For predictions of future spread, population density and spatial location are important, and for the latter we show that SARS-CoV-2 strains containing the G614 mutation to the spike gene are associated with higher rates of spread. Finally, the high predictability of R_0 allows extending estimates to all 3109 counties in the conterminous 48 states. The high variation of R_0 argues for public health policies enacted at the county level for controlling COVID-19.

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The basic reproduction number, R_0, is the number of secondary infections produced per primary infection of a disease in a susceptible population, and it is a fundamental metric in epidemiology that gauges, among other factors, the initial rate of disease spread during an epidemic[1]. While R_0 depends in part on the biological properties of the pathogen, it also depends on properties of the host population, such as the contact rate between individuals[1,2]. Estimates of R_0 are required for designing public health interventions for infectious diseases such as COVID-19: for example, R_0 determines in large part the proportion of a population that must be vaccinated to control a disease[3,4]. Because R_0 at the start of an epidemic measures the spread rate under "normal" conditions without interventions, these initial R_0 values can inform policies to allow life to get "back to normal."

The estimates of R_0 before intervention determine the intensity with which public health interventions must be applied, and the risk and magnitude of potential resurgent outbreaks. In these contexts, R_0 is a reference against which the success or failure of public interventions can be assessed. Using R_0 estimates to design public health policies is predicated on the assumption that the R_0 values at the start of the epidemic reflect properties of the infective agent and population, and therefore predict the potential rate of spread of the disease. Estimates of R_0, however, might not predict future risks if (i) they are measured after perceived risks have generated government actions or pre-emptive personal measures to reduce the spread rate[5–7], (ii) they are driven by stochastic events, such as super-spreading[8,9], or (iii) they are driven by social or environmental conditions that are likely to change between the time of initial epidemic and the future time for which public health interventions are designed[10,11]. To address these potential limitations for using R_0 to design public health policies and future risks of spread, we investigated possible underlying causes for variation in estimates of R_0 among counties: if the causes are unlikely to change in the future, then so too are values of R_0 unlikely to change.

Policies to manage for COVID-19 in the USA are set by a mix of jurisdictions from state to local levels. We estimated R_0 at the county level both to match policymaking and to account for possibly large variation in R_0 among counties. To estimate R_0, we performed the analyses on the number of daily COVID-19 deaths[12]. We used death count rather than infection case reports, because we suspected that the proportion of reported deaths due to COVID-19 is less sensitive to variation in testing rates and methods. We recognize that some deaths due to COVID-19 will go unreported (e.g., the growing evidence from "excess deaths"[13,14]) and that different counties and states may use different criteria for determining the cause of death as COVID-19. Nonetheless, due to the mathematical structure of our estimation procedure, unreported deaths due to COVID-19 and differences among counties in reporting criteria will have little effect on our estimates of R_0; specifically, the estimates of R_0 for a given county will not change provided the proportion of unreported deaths in a county does not change through time. We analyzed data for counties that had at least 100 reported cumulative deaths by 23 May, 2020 ("Methods"), and for other counties we aggregated data within the same state, including deaths whose county was unknown. This led to 160 final time series representing counties in 39 states and the District of Columbia, of which 36 were aggregated at the state level. Some states, even after aggregating data from all counties, did not reach the 100-threshold of cumulative deaths, and therefore the spread rate for these states was not estimated.

We found high variance in the spread rate of COVID-19 among counties, most of which is explained by four factors: the timing of the county-level outbreak, population size, population density, and spatial location. Population density is likely an indicator of the average contact rate among people, and its explanatory power in the statistical model makes it an important predictor of future spread. Spatial location is also important, and we show that some of the effect of spatial location could be caused by differences among strains of SARS-CoV-2 that dominated in different parts of the USA. Using the statistical model, we estimated R_0 at the county level for the entire conterminous USA, giving information to design public health policies for controlling COVID-19.

Results

Estimates of the spread rate. Before estimating R_0, we first estimated the rate of spread of the virus-caused COVID-19 as the rate of increase of the daily death counts, r_0. Although this approach is not typically used in epidemiological studies, it has the advantage of being statistically robust even when the data (death counts) are few, and it makes the minimum number of assumptions that could affect the estimates in unexpected ways (Supplementary Methods: Overview of Statistical Methods). We applied a time-varying autoregressive state-space model to each time series of death counts[15,16]. In contrast to other models of COVID-19 epidemics[17–19], we do not incorporate the transmission process and the daily time course of transmission, but instead we estimate the time-varying exponential change in the number of deaths per day, $r(t)$[20]. Detailed simulation analyses (Supplementary Methods: Simulation model) showed that estimates of $r(t)$ generally lagged behind the true values. Therefore, we analyzed the time series in forward and reverse directions, and averaged to get the estimates of r_0 at the start of the time series (Supplementary Fig. 1); this approach counterbalances the lag in the forward direction with the lag in the backward direction, thereby reducing the lag effect. The model was fit accounting for greater uncertainty when mortality counts were low, and confidence intervals of the estimates were obtained from parametric bootstrapping which is the most robust approach for low counts. Thus, our strategy was to use a parsimonious model to give robust estimates of r_0 even for counties that had experienced relatively few deaths, and then calculate R_0 from r_0 after the fitting process using well-established methods[21].

Our r_0 estimates ranged from close to zero for several counties to 0.33 for New York City (five boroughs); the latter implies that the number of deaths increases by a factor of $e^{0.33} = 1.39$ per day. There were highly statistically significant differences between upper and lower estimates (Fig. 1). Although our time series approach allowed us to estimate r_0 at the start of even small epidemics, we anticipated two factors that could potentially affect our estimates of r_0 that are not likely to be useful in explaining future spread rates. The first factor is the timing of the onset of county-level epidemic: 35% of the local outbreaks started after the declaration of COVID-19 as a pandemic by the WHO on 11 March, 2020[22]. Therefore, we anticipated estimates of r_0 to decrease with the Julian date of outbreak onset due to changes in human behaviors caused by public awareness about COVID-19[7]. Because our goal was to estimate disease spread under "normal" conditions, we wanted to factor out the effect of timing. We used the second factor, the size of the population encompassed by the time series, to factor out statistical bias from the time series analyses. Simulation studies showed that estimates for time series with low death counts were downward biased (Supplementary Fig. 2). Because for a given spread rate $r(t)$ the total number of deaths in a time series should be proportional to the population size, we used population size as a covariate to remove bias. In addition to these two factors that we do not think have strong predictive value for the future rate of spread, we also anticipated effects of population density and spatial autocorrelation. Therefore, we regressed r_0 against outbreak onset, population size,

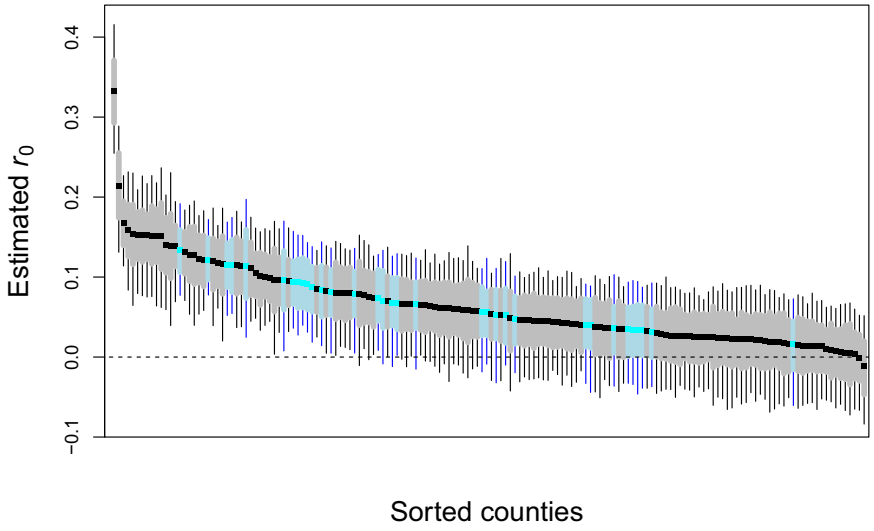

Fig. 1 Estimates of initial spread rate, r_0. The figure shows r_0 point estimates (in black), sorted by magnitude, for 124 counties (gray) and 36 county-aggregates (blue), with 66% (bars) and 95% (whiskers) bootstrapped confidence intervals.

and population density, and included spatially autocorrelated error terms.

Explaining variation in r_0. The regression analysis showed highly significant effects of all four factors (Table 1), and each factor had a substantial partial R^2_{pred}[23]. The overall R^2_{pred} was 0.70, so most of the county-to-county variance was explained. We calculated corrected r_0 values, factoring out outbreak onset and population size, by standardizing the r_0 values to 11 March 2020, and to the most populous county (for which the estimates of r_0 are likely best). Counties with low to medium population density never had high corrected r_0 values, suggesting that population density sets an upper limit on the rate of spread of COVID-19 (Fig. 2a), in agreement with expectations and published results[1,24]. Nonetheless, despite the unequivocal statistical effect of population density ($P < 10^{-8}$, Table 1), the explanatory power was not high in comparison to the entire model (partial $R^2_{pred} = 0.14$), probably because population density at the scale of counties will be only roughly related to contact rates among people. The contact rates will likely depend on a wide variety of additional factors, such as transmission through social gatherings, colleges, and nursing homes.

Spatial autocorrelation had strong power in explaining variation in r_0 among counties (partial $R^2_{pred} = 0.48$, Table 1) and occurred at the scale of hundreds of kilometers (Fig. 2b). This spatial autocorrelation might reflect differences in public responses to COVID-19 across the USA not captured by the variable in the regression model for outbreak onset. For example, Seattle, WA, reported the first positive case in the USA, on 15 January 2020, and there was a public response before deaths were recorded[25]. In contrast, the response in New York City was delayed, even though the outbreak occurred later than in Seattle[26]. Spatial autocorrelation could also be caused by movement of infected individuals. However, movement would only lead to autocorrelation in our regression analysis if many of the reported deaths were of people infected outside the county; while some deaths were likely caused by infections from outside counties, privacy restrictions on case data make these data hard to obtain, and we assume that such deaths are a small proportion of the total. A further possibility is that spatial variation in the rate of spread of COVID-19 reflects spatial variation in the occurrence of different genetic strains of SARS-CoV-2.

To investigate whether spatial autocorrelation could potentially be caused by different strains of SARS-CoV-2 differing in transmissibility, we analyzed publicly available information about genomic sequences from the GISAID metadata[27]. Scientific debate has focused on the role of the G614 mutation in the spike protein gene (D614G) to increase the rate of transmission of SARS-CoV-2[28]. We, therefore, asked whether the proportion of strains containing the G614 mutation was associated with higher rates of COVID-19 spread. Because the genomic samples are only located to the state level, we performed the analysis accordingly, for each state selecting the r_0 from the county or county-aggregate with the highest number of deaths (and hence being most likely represented in the genomic samples). We further restricted genomic samples to those collected within 30 days following the outbreak onset we used to select the data for time-series analyses, and we required at least five genomic samples per state. This data handling resulted in 28 states available for analysis. We again used our regression model (Eq. 3), now including the proportion of strains having the G614 mutation instead of spatial location. The proportion of samples containing the G614 mutation had a positive effect on r_0 ($P = 0.016$, Table S1). The low proportion of strains containing the G614 mutation in the Pacific Northwest and the Southeast were associated with lower values of r_0 (Fig. 3).

Before analyzing the full GISAID data, we analyzed a subset from Nextstrain[29] naïvely, without engaging the specific hypothesis that the G614 mutation increased transmission. This naïve analysis

Table 1 Factors explaining the initial spread rate of COVID-19 for 160 county and county-aggregates in the USA.

	Coefficient	SE	t	P	partial R^2_{pred}
Onset	−0.0019	0.0004	−4.59	10^{-4}	0.11
Log(size)	0.0247	0.0028	8.92	$<10^{-8}$	0.36
Density$^{1/4}$	0.025	0.0028	8.92	$<10^{-8}$	0.14
Space	Range = 5.71 Nugget = 0.33		$\chi^2_2 = 73$	$<10^{-8}$	0.48

Results of the regression of the estimates of the initial spread rate, r_0, against (i) the date of outbreak onset, (ii) total population size and (iii) population density, in which (iv) spatial autocorrelation is incorporated into the residual error. Transforms of population size and density were selected to best-fit the data and satisfy linearity assumptions. The coefficient column contains the estimate of the regression parameters with their associated t-tests; spatial autocorrelation is characterized by a range and nugget for regional and local sources of variation, and their joint significance is given by a likelihood ratio test. For the overall model, $R^2_{pred} = 0.70$, and the residual standard error is 1.19.

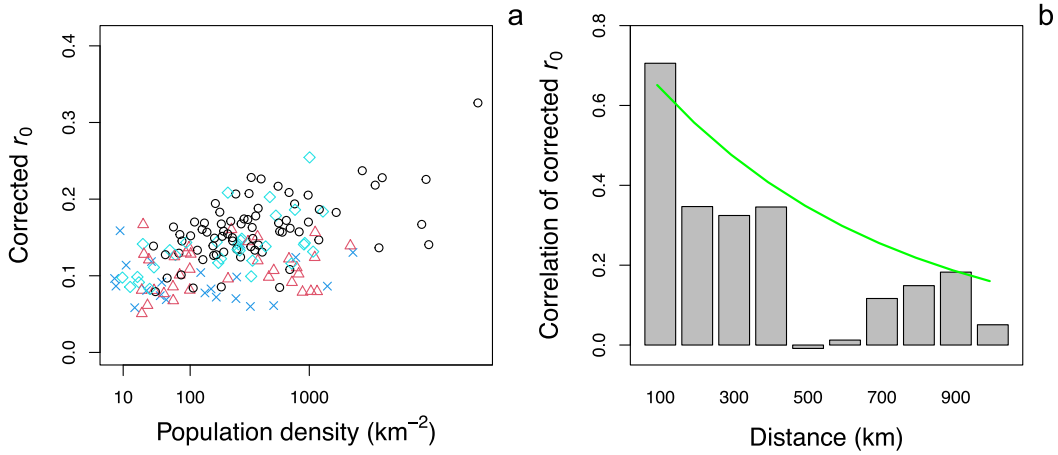

Fig. 2 Estimates of initial spread rates, r_0, after correcting for the effects of outbreak onset and population size. a Effect of population density: Northeast, black circles; Midwest, cyan diamonds; South, blue x's; West, red triangles. **b** Effect of spatial proximity depicted by computing correlations in bins representing 0–100 km, 100–200 km, etc. The line gives the spatial autocorrelation of the residuals from the fitted regression (Eq. 3).

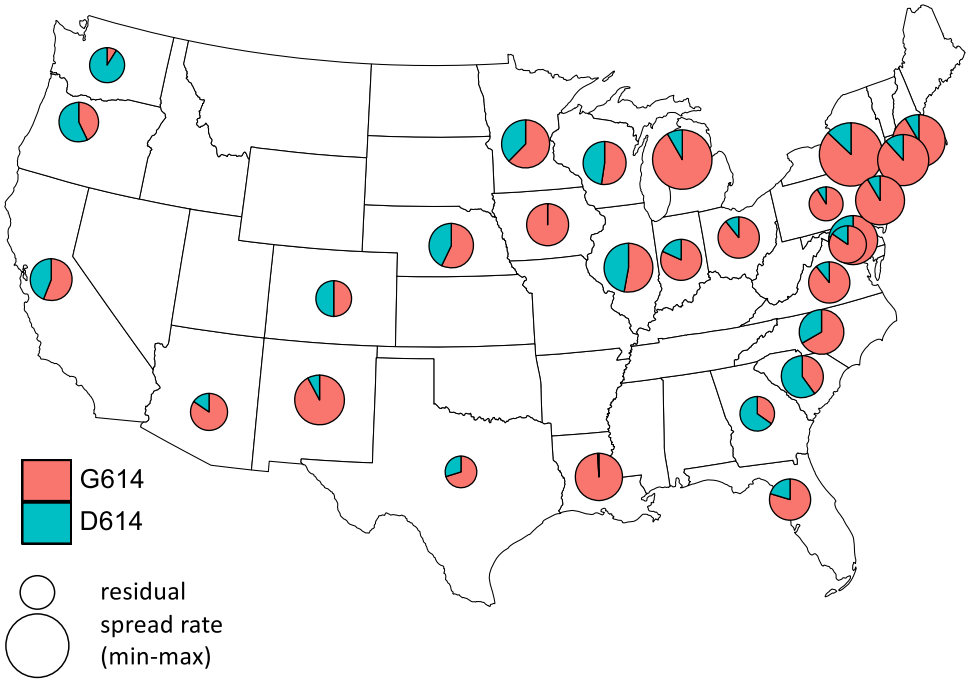

Fig. 3 Spatial distribution of strains of SARS-CoV-2 having the G614 mutation in the spike gene at the outbreak onset among states. Pie charts give the proportion of samples in states collected within 30 days following the outbreak onset that are in the G clades (red)[27]. The size of the pie is proportional to the residual values of r_0 after removing the effects of the timing of outbreak onset, population size represented by the time series, and population density. For each state, we used the estimate of r_0 corresponding to the county or county-aggregate that had the greatest number of deaths.

considered strains from Nextstrain clades 19A, 19B, 20A, 20B, and 20C; clades 19A and 19B do not contain the G614 mutation, but the other clades do. We found that the proportion of samples within clade 19B had a negative effect on r_0 ($P = 0.019$, Supplementary Table 2). Strain 19A, however, did not have a negative effect on r_0. This suggests possible differences among strains separate from or in addition to the G614 mutation[30]. A consensus on the potential impact of SARS-CoV-2 mutations is still lacking[28]: some studies present evidence for a differential pathogenicity and transmissibility[31,32], while others conclude that mutations might be mostly neutral or even reduce transmissibility[33]. Because our analyses only associate strains with spread rates, they give no information about possible mechanisms explaining differences among strains. Nonetheless, our analyses are suggestive of the potential link between viral genomic variation and its impact on transmission and mortality[34].

To check whether there are other factors that might explain variation in our estimates of r_0 among counties, we investigated additional population characteristics[35–42] that might be expected to affect the initial spread rate of COVID-19: (i) proportion of the population over 65, (ii) adult obesity, (iii) diabetes, (iv) education, (v) income, (vi) poverty, (vii) economic equality, (viii) race, and (ix) political leaning (Supplementary Table 3). The first three characteristics likely affect morbidity[43], although it is not clear how higher morbidity could affect the spread rate. The remaining characteristics might affect health outcomes and responses to public health interventions; for example, education, income, and poverty might all affect the need for individuals to work in jobs

that expose them to greater risks of infection. Nonetheless, because we focused on the early spread of COVID-19, we anticipated that these characteristics would have minimal effects. Despite the potential for all nine characteristics to affect estimates of r_0, we found that none was a statistically significant predictor of r_0 when taking the four main factors into account (all $P > 0.1$). We also repeated the main analyses (without the nine additional characteristics) on estimates of $r(t)$ after COVID-19 was broadly established in the USA (5 May 2020, assuming an average time between infection and death of 18 days) (Supplementary Table 4). The R^2_{pred} was 0.40, largely driven by a large positive effect of the date of outbreak onset. The absence of significant effects of the nine additional population characteristics on r_0, and the lower explanatory power of the model on $r(t)$ at the end of the time series, underscore the importance of population density and spatial autocorrelation in predicting county-level values of r_0.

Extrapolating R_0 to all counties. In the regression model (Table 1), the standard deviation of the residuals was 1.19 times higher than the average standard error of the estimates of r_0. This implies that the uncertainty of an estimate of r_0 from the regression is only slightly higher than the uncertainty in the estimate of r_0 from the time series itself; the fixed terms (ignoring spatial autocorrelation) in the regression model explain 71% ($= 1/1.19^2$) of the explainable variance in r_0. Therefore, using estimates from death count time series from other counties will give estimates of r_0 for a focal county (lacking reliable estimates) that are almost as precise as the estimate from the county's time series. We used the regression to extrapolate values of R_0 for all 3109 counties in the conterminous USA (Fig. 4, Supplementary Data 1). The high predictability of r_0, and hence R_0, from the regression is seen in the comparison between R_0 calculated from the raw estimates of r_0 (Fig. 4a) and R_0 calculated from the corrected r_0 values (Fig. 4b). Extrapolation from the regression model makes it possible not only to get refined estimates for the counties that were aggregated in the time-series analyses; it also gives estimates for counties within states with so few deaths that county-aggregates could not be analyzed (Fig. 4c, d). The end product is a map of estimated R_0 values for the conterminous USA (Fig. 4e).

Discussion

It is widely understood that different states and counties in the USA, and different countries in the world, have experienced COVID-19 epidemics differently. Our analyses have put numbers on these differences in the USA. The large differences argue for public health interventions to be designed at the county level. For example, the vaccination coverage in the most densely populated area, New York City, needed to prevent future outbreaks of COVID-19 will be much greater than for sparsely populated counties. Therefore, once vaccines are broadly available to the public, they should be distributed first to counties with high R_0 to have the greatest impact in reducing community spread. Similarly, if non-pharmaceutical public health interventions have to be increased during resurgent outbreaks, then counties with higher R_0 values will require stronger interventions. As a final example, county-level R_0 values can be used to assess the practicality of contact-tracing of infections, which become impractical when R_0 is high[44,45].

Estimating county-level values of R_0 at the start of the epidemic faces statistical challenges that our analyses have tried to address. We used death counts, rather than cases reported from testing, because particularly at the start of the epidemic, testing was limited and heterogeneous among states and counties. Nonetheless, death counts are not perfect, because different criteria could be used by different counties to ascribe deaths to SARS-CoV-2. Furthermore, evidence suggests that "excess deaths" have occurred in comparison to historical data[13] and that these excess deaths are likely due to the mis-attribution to causes other than SARS-CoV-2. Nonetheless, we estimated R_0 from the spread rate of the disease (Eq. 1), which depends on the change in the number of recorded deaths from one day to the next. This change in death counts should be insensitive to the criteria used to ascribe death to SARS-CoV-2, and although there are undoubtedly mistakes and omissions, our statistical methods account for this measurement error.

We present our county-level estimates of R_0 as preliminary guides for policy planning, while recognizing the myriad other epidemiological factors (such as mobility[46–48]) and political factors (such as legal jurisdictions[49]) that must shape public health decisions[3,50–52]. Although we have emphasized the high predictability of R_0 among counties in the USA, our estimates of R_0 will be under-estimates for some regions if there are changes in the transmissibility of strains (Fig. 3). This uncertainty underscores the need for more information about strain differences affecting SARS-CoV-2 transmission[28,30].

We recognize the importance of following the day-to-day changes in death and case rates, and short-term projections used to anticipate hospital needs and modify public policies[53–55]. Looking back to the initial spread rates, however, gives a window into the future and what public health policies will be needed when COVID-19 is endemic.

Methods

Data selection and handling: death data. For mortality due to COVID-19, we used time series provided by the New York Times[12]. We selected the New York Times dataset because it is rigorously curated. We analyzed separately only counties that had records of 100 or more deaths by 23 May, 2020. The threshold of 100 was a balance between including more counties and obtaining reliable estimates of $r(t)$. Preliminary simulations showed that time series with low numbers of deaths would bias $r(t)$ estimates (Supplementary Fig. 2). However, we did not want to use the maximum daily number of deaths as a selection criterion, because this could lead to selection of counties based on data from a single day. It would also involve some circularity, because the information obtained, $r(t)$, would be directly related to the criterion used to select datasets. Therefore, we used the threshold of 100 cumulative deaths. The District of Columbia was treated as a county. Also, because the New York Times dataset aggregated the five boroughs of New York City, we treated them as a single county. For counties with fewer than 100 deaths, we aggregated mortality to the state level to create a single time series. For thirteen states (AK, DE, HI, ID, ME, MT, ND, NH, SD, UT, VM, WV, and WY), the aggregated time series did not contain 100 or more deaths and were therefore not analyzed.

Data selection and handling: explanatory county-level variables. County-level variables were collected from several public data sources[36–42]. We selected socio-economic variables a priori in part to represent a broad set of population characteristics.

Time series analysis: time series model. We used a time-varying autoregressive model[15,56] designed explicitly to estimate the rate of increase of a variable using nonlinear, state-dependent error terms[16]. We assume in our analyses that the susceptible proportion of the population represented by a time series is close to one, and therefore there is no decrease in the infection rate caused by a pool of individuals who were infected, recovered, and were then immune to further infection.

The model is

$$x(t) = r(t-1) + x(t-1) \quad (1a)$$

$$r(t) = r(t-1) + \omega_r(t) \quad (1b)$$

$$D(t) = \exp(x(t) + \phi(t)) \quad (1c)$$

Here, $x(t)$ is the unobserved, log-transformed value of daily deaths at time t, and $D(t)$ is the observed count that depends on the observation uncertainty described by the random variable $\phi(t)$. Because a few of the datasets that we analyzed had zeros, we replaced zeros with 0.5 before log-transformation. The model assumes that the death count increases exponentially at rate $r(t)$, where the latent state variable $r(t)$ changes through time as a random walk with $\omega_r(t) \sim N(0, \sigma^2_r)$. We assume that the count data follow a quasi-Poisson distribution. Thus, the expectation of counts at time t is $\exp(x(t))$, and the variance is proportional to this expectation.

We fit the model using the extended Kalman filter to compute the maximum likelihood[57,58]. In addition to the parameters σ^2_r and σ^2_ϕ, we estimated the initial

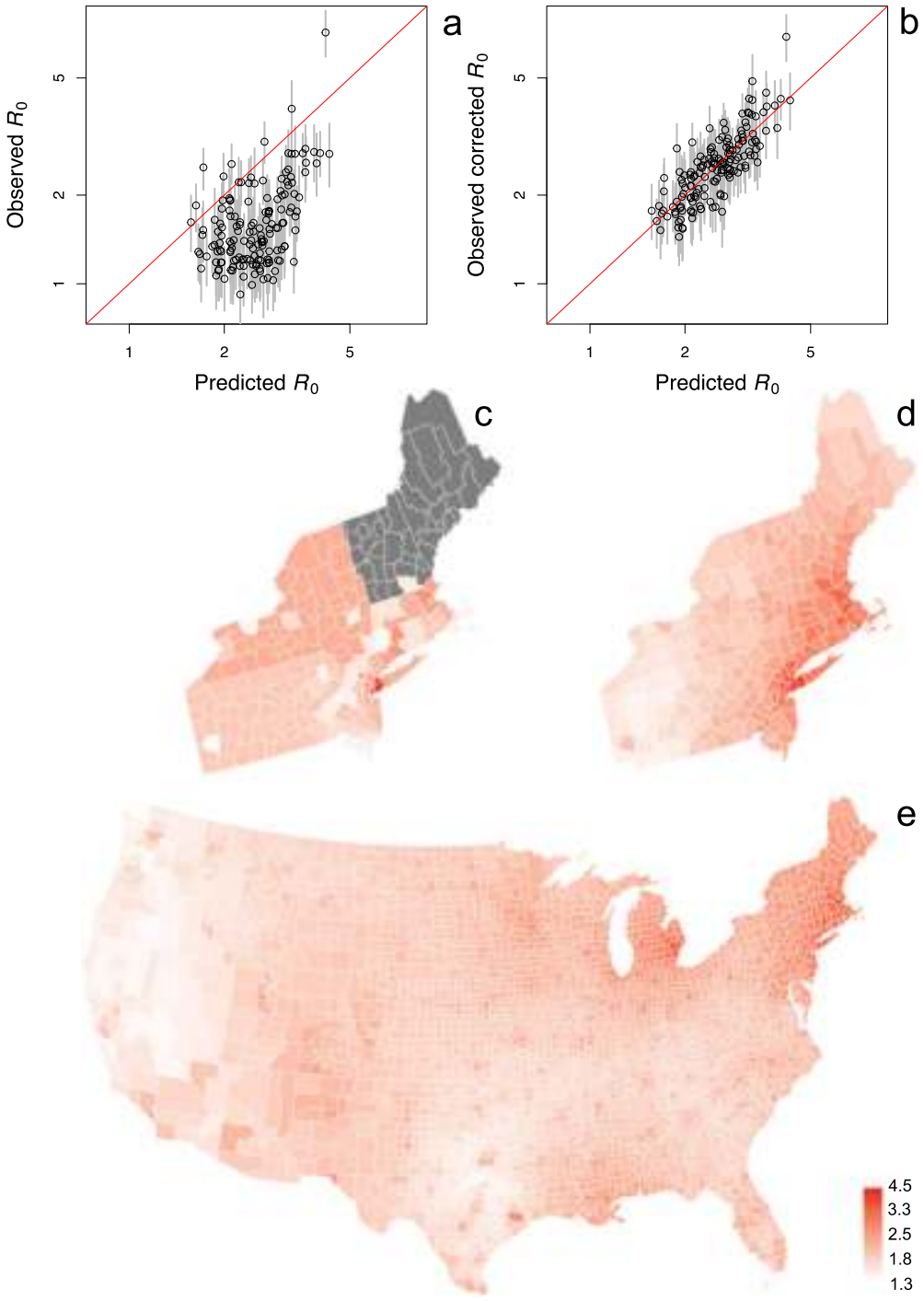

Fig. 4 Prediction of R_0 values for all 3109 counties in the conterminous USA. a, **b** Raw and corrected estimates of R_0 for 160 counties and county-aggregates. The predicted R_0 values are obtained from the regression model, with corrections to standardize values to an outbreak onset of 11 March 2020, and a population size equal to the most populous county. Comparing the raw estimates of R_0 (**a**) and the corrected R_0 values (**b**) shows the predictive power of the regression analysis. We thus used the regression model to predict R_0 for all counties. **c**, **d** To illustrate the prediction process for the northeastern states, the raw estimates (**c**) are all the same for county-aggregates and could not be made for some states (gray). In contrast, the predictability of R_0 in the regression model allows for better estimates (**d**). **e** This makes it possible to extend estimates of R_0 to all 3109 counties in the conterminous USA.

value of $r(t)$ at the start of the time series, r_0, and the initial value of $x(t)$, x_0. The estimation also requires terms for the variances in x_0 and r_0, which we assumed were zero and σ^2_r, respectively. In the validation using simulated data (Supplementary Methods: Simulation model), we found that the estimation process tended to absorb σ^2_r to zero too often. To eliminate this absorption to zero, we imposed a minimum of 0.02 on σ^2_r.

Time series analysis: parametric bootstrapping. To generate approximate confidence intervals for the time-varying estimates of $r(t)$ (Eq. 1b), we used a parametric bootstrap designed to simulate datasets with the same characteristics as the real data that are then refit using the autoregressive model. We used bootstrapping to obtain confidence intervals, because an initial simulation study showed that standard methods, such as obtaining the variance of $r(t)$ from the Kalman filter, were too

conservative (the confidence intervals too narrow) when the number of counts was small. Furthermore, parametric bootstrapping can reveal bias and other features of a model, such as the lags we found during model fitting (Supplementary Fig. 1a, b).

Changes in $r(t)$ consist of unbiased day-to-day variation and the biased deviations that lead to longer-term changes in $r(t)$. The bootstrap treats the day-to-day variation as a random variable while preserving the biased deviations that generate longer-term changes in $r(t)$. Specifically, the bootstrap was performed by calculating the differences between successive estimates of $r(t)$, $\Delta r(t) = r(t) - r(t\text{-}1)$, and then standardizing to remove the bias, $\Delta r_s(t) = \Delta r(t) - \mathrm{E}[\Delta r(t)]$, where E[] denotes the expected value. The sequence $\Delta r_s(t)$ was fit using an autoregressive time-series model with time lag 1, AR(1), to preserve any shorter-term autocorrelation in the data. For the bootstrap, a new time series was simulated from this AR(1) model, $\Delta\rho(t)$, and then standardized, $\Delta\rho_s(t) = \Delta\rho(t) - \mathrm{E}[\Delta\rho(t)]$. The simulated time series for the spread rate was constructed as $\rho(t) = r(t) + \Delta\rho_s(t)/2^{1/2}$, where dividing by $2^{1/2}$ accounts for the fact that $\Delta\rho_s(t)$ was calculated from the difference between successive values of $r(t)$. A new time series of count data, $\xi(t)$, was then generated using equation 1 with the parameters from fitting the data. Finally, the statistical model was fit to the reconstructed $\xi(t)$. In this refitting, we fixed the variance in $r(t)$, σ^2_r, to the same value as estimated from the data. Therefore, the bootstrap confidence intervals are conditional of the estimate of σ^2_r.

Time series analysis: calculating R_0. We derived estimates of $R(t)$ directly from $r(t)$ using the Dublin-Lotka equation[21] from demography. This equation is derived from a convolution of the distribution of births under the assumption of exponential population growth. In our case, the "birth" of COVID-19 is the secondary infection of susceptible hosts leading to death, and the assumption of exponential population growth is equivalent to assuming that the initial rate of spread of the disease is exponential, as is the case in equation 1. Thus,

$$R(t) = 1/\sum\nolimits_{\tau} \mathrm{e}^{-r(t)}\tau p(\tau) \tag{2}$$

where $p(\tau)$ is the distribution of the proportion of secondary infections caused by a primary infection that occurred τ days previously. We used the distribution of $p(\tau)$ from Li et al.[59] that had an average serial interval of $T_0 = 7.5$ days; smaller or larger values of T_0, and greater or lesser variance in $p(\tau)$, will decrease or increase $R(t)$ but will not change the pattern in $R(t)$ through time. Note that the uncertainty in the distribution of serial times for COVID-19 is a major reason why we focus on estimating r_0, rather than R_0: the estimates of r_0 are not contingent on time distributions that are poorly known. Computing $R(t)$ from $r(t)$ also does not depend on the mean or variance in time between secondary infection and death. We report values of $R(t)$ at dates that are offset by 18 days, the average length of time between initial infection and death given by Zhou et al.[60].

Time series analysis: Initial date of the time series. Many time series consisted of initial periods containing zeros that were uninformative. As the initial date for the time series, we chose the day on which the estimated daily death count exceeded 1. To estimate the daily death count, we fit a Generalized Additive Mixed Model (GAMM) to the death data while accounting for autocorrelation and greater measurement error at low counts using the R package mgcv[61]. We used this procedure, rather than using a threshold of the raw death count, because the raw death count will include variability due to sampling small numbers of deaths. Applying the GAMM to "smooth" over the variation in count data gives a well-justified method for standardizing the initial dates for each time series.

Time series analysis: validation. We performed extensive simulations to validate the time-series analysis approach (Supplementary Methods: Simulation model).

Regression analysis for r_0. We applied a Generalized Least Squares (GLS) regression model to explain the variation in estimates of r_0 from the 160 county and county-aggregate time series:

$$r_0 = b_0 + b_1 start.date + b_2 log(pop.size) + b_3 pop.den^{0.25} + \varepsilon \tag{3}$$

where *start.date* is the Julian date of the start of the time series, log(*pop.size*) and $pop.den^{0.25}$ are the log-transformed population size and 0.25 power-transformed population density of the county or county-aggregate, respectively, and ε is a multivariate Gaussian random variable with covariance matrix $\sigma^2\mathbf{\Sigma}$. We used the transforms log(*pop.size*) and $pop.den^{0.25}$ to account for nonlinear relationships with r_0; these transforms give the highest maximum likelihood of the overall regression. The covariance matrix contains a spatial correlation matrix of the form $\mathbf{C} = u\mathbf{I} + (1\text{–}u)\mathbf{S}(g)$ where u is the nugget and $\mathbf{S}(g)$ contains elements $\exp(-d_{ij}/g)$, where d_{ij} is the distance between spatial locations and g is the range[62]. To incorporate differences in the precision of the estimates of r_0 among time series, we weighted by the vector of their standard errors, **s**, so that $\mathbf{\Sigma} = \mathrm{diag}(\mathbf{s}) * \mathbf{C} * \mathrm{diag}(\mathbf{s})$, where * denotes matrix multiplication. With this weighting, the overall scaling term for the variance, σ^2, will equal 1 if the residual variance of the regression model matches the square of the standard errors of the estimates of r_0 from the time series. We fit the regression model with the function gls() in the R package nlme[63].

To make predictions for new values of r_0, we used the relationship

$$\hat{e}_i = \bar{e} + \mathbf{v_i} * \mathbf{V}^{-1}(\epsilon_i - \bar{e}) \tag{4}$$

where ε_i is the GLS residual for data i, $\hat{e}_i$ is the predicted residual, $\bar{e}$ is the mean of the GLS residuals, **V** is the covariance matrix for data other than i, and $\mathbf{v_i}$ is a row vector containing the covariances between data i and the other data in the dataset[64]. This equation was used for three purposes. First, we used it to compute R^2_{pred} for the regression model by removing each data point, recomputing $\hat{e}_i$, and using these values to compute the predicted residual variance[23]. Second, we used it to obtain predicted values of r_0, and subsequently R_0, for the 160 counties and county-aggregates for which r_0 was also estimated from time series. Third, we used equation (4) to obtain predicted values of r_0, and hence predicted R_0, for all other counties. We also calculated the variance of the estimates from[64]

$$\hat{v}_i = \sigma^2 - \mathbf{v_i} * \mathbf{V}^{-1} * v_i^{\mathbf{t}} \tag{5}$$

Predicted values of R_0 were mapped using the R package usmap[65].

Regression analysis for SARS-CoV-2 effects on r_0. The GISAID metadata[27] for SARS-CoV-2 contains the clade and state-level location for strains in the USA; strains G, GH, and GR contain the G614 mutation. For each state, we limited the SARS-CoV-2 genomes to those collected no more than 30 days following the onset of outbreak that we used as the starting point for the time series from which we estimated r_0; from these genomes (totaling 5290 from all states), we calculated the proportion that had the G614 mutation. We limited the analyses to the 28 states that had five or more genome samples. For each state, we selected the estimates of r_0 from the county or county-aggregate representing the greatest number of deaths. We fit these estimates of r_0 with the weighted Least Squares (LS) model as in equation (3) with additional variables for strain. Figure 3 was constructed using the R packages usmap[65] and scatterpie[66].

Statistics and reproducibility. The statistics for this study are summarized in the preceding sections of the "Methods". No experiments were conducted, so experimental reproducibility is not an issue. Nonetheless, we repeated analyses using alternative datasets giving county-level characteristics, and also an alternative dataset on SARS-CoV-2 strains (Supplementary Methods: Analysis of Nextstrain metadata of SARS-CoV-2 strains), and all of the conclusions were the same.

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The data that support the findings of this study are available on Figshare[67].

Code availability

R code for the analyses is available on Figshare[67].

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Author contributions

A.R.I and C.B. designed the study, and A.R.I. led the analyses and writing of the manuscript.

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RESEARCH ARTICLE

Population density and basic reproductive number of COVID-19 across United States counties

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Abstract

The basic reproductive number (R_0) is a function of contact rates among individuals, transmission probability, and duration of infectiousness. We sought to determine the association between population density and R_0 of SARS-CoV-2 across U.S. counties. We conducted a cross-sectional analysis using linear mixed models with random intercept and fixed slopes to assess the association of population density and R_0, and controlled for state-level effects using random intercepts. We also assessed whether the association was differential across county-level main mode of transportation percentage as a proxy for transportation accessibility, and adjusted for median household income. The median R_0 among the United States counties was 1.66 (IQR: 1.35–2.11). A population density threshold of 22 people/km^2 was needed to sustain an outbreak. Counties with greater population density have greater rates of transmission of SARS-CoV-2, likely due to increased contact rates in areas with greater density. An increase in one unit of log population density increased R_0 by 0.16 (95% CI: 0.13 to 0.19). This association remained when adjusted for main mode of transportation and household income. The effect of population density on R_0 was not modified by transportation mode. Our findings suggest that dense areas increase contact rates necessary for disease transmission. SARS-CoV-2 R_0 estimates need to consider this geographic variability for proper planning and resource allocation, particularly as epidemics newly emerge and old outbreaks resurge.

Introduction

The COVID-19 pandemic has infected millions of people globally, and there are over 400 thousand reported deaths and 7 million confirmed cases of COVID-19 worldwide [1]. Transmission of airborne and directly transmitted pathogens, such as SARS-CoV-2 (the causative

available publicly (link: https://github.com/nytimes/covid-19-data/blob/master/us-counties.csv).

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agent of COVID-19), have been previously shown to be density-dependent [2–4]. Population density facilitates transmission of disease via close person-to-person contact [5–8], and may support sustained disease transmission due to increased contact rates [9–11]. Large urban areas have more opportunities for disease transmission, and hotspots of SARS-CoV-2 have been mostly concentrated in cities [12].

The basic reproductive number (R_0) describes the contagiousness and transmissibility of pathogens, and is a function of contact rates among individuals, transmission probability (probability of transmission per contact), and duration of infectiousness [13]. This is in contrast with the time-varying reproductive number (R_t), defined as the number of people in a population who were infected by an infectious individual at a given point in time, which reflects the changing levels of immunity in the population and the impact of control measures limiting transmission [14]. Control measures include implementation of non-pharmaceutical interventions (NPIs), such as face coverings and social distancing. Thus, R_0 estimates of COVID-19 are not exclusively determined by the pathogen, and variability in R_0 depends on local sociobehavioral and environmental settings, including population density [12].

During the initial phase of the outbreak, or the exponential growth period, we hypothesize that spatial heterogeneity in R_0 occurs primarily due to geographic variability in contact rates, since transmission probability and duration of infectiousness remain constant across settings. During this time frame, transmission probabilities across localities are equivalent, because exponential growth occurs prior to the implementation of NPIs which affect likelihood of transmission during contact. Moreover, contact networks are also affected by transportation systems that facilitate disease spread due to increased interconnectivity and mobility between different geographic areas [15, 16]; thus, we also hypothesize that the association of population density and R_0 may be differential depending on transportation accessibility, and areas that lack access to efficient modes of transportation would not have the same SARS-CoV-2 growth rate, even in high density areas.

In the current COVID-19 pandemic, evidence of the association of population density and disease transmission have been conflicting [17–20]. The estimation of differential R_0 using these area-level factors can assist in more accurate predictions of the rate of spread of SARS--CoV-2 in geographic settings with potential resurgence, where cases have been steadily increasing. In this study, we examine the association of population density with R_0 of COVID-19 across United States counties.

Methods

Data

We obtained publicly available daily COVID-19 cases among United States counties from the New York Times [21]. For each county, we assumed that the exponential growth period began one week prior to the second daily increase in cases. We assumed that the period of exponential growth lasted approximately 18 days, as previous research have shown the COVID-19 exponential period to be around 20–24 days in New York City [22]. These assumptions calibrated the period of exponential growth accordingly and created reasonable curves that approximated exponential growth across the counties for case data (Fig A in S1 Appendix). The algorithm ensured that the virus had taken hold in the area and allowed a sufficient number of days to estimate the exponential growth rate, as R_0 cannot be estimated accurately with sparse data, since it would be uncertain if the county was experiencing a sustained outbreak with community transmission. We restricted our analyses to counties that met a certain threshold of cumulative case counts at the end of the exponential growth period, but including counties with less than 25 cases included daily incidence counts that were insufficient to

calculate R_0 and yielded computational errors. Our final analytic sample included counties with 25 cases or greater at the end of the exponential growth period.

Data on the primary mode of transportation to work and median household income were obtained from the most recent 5-year American Community Survey (ACS) 2014–2018 survey estimates from the United States Census Bureau [23]. Main commuting mode was operationalized as the total percentage of people that use private transportation to work, such as those that own private vehicles (car, truck, van, motorcycle) or use a private taxi. Private transportation is a proxy for transportation accessibility in each county, as we hypothesize that areas that that lack efficient modes of transportation may not have as fast of COVID-19 exponential growth, and we want to assess whether the effect of density on R_0 would differ due to ease of transportation accessibility. Population and land area were obtained from the 2010 census, and density was calculated by population divided by total square km. All census data were extracted using the R package *tidycensus* [24].

Statistical analysis

We first compared the densities of counties included in the final analytical sample to those that did not have sufficient case counts with a two-sample Wilcoxon test. R_0 was estimated from the exponential growth rate method developed by Wallinga and Lipstich [25] and implemented by the R package *R0* [26], assuming a generation interval with a gamma distribution of mean 4.7 and standard deviation of 2.9 [27]. We then conducted a cross-sectional analysis using linear mixed models with random intercepts for each state and fixed slopes for the counties to assess the association of population density and R_0. The linear mixed models allow the intercept to vary among states, which accounts for non-independence among counties within each state, potentially due to variable resource allocation and differing health systems across states.

We also adjusted for county-level main mode of transportation to work percentage and median household income to control for any potential confounding between the association of density and R_0. Therefore, we fit 4 models with R_0 as the outcome and the following factors as covariates: Model 1: population density; Model 2: population density and the percent of individuals reporting private transportation as their main mode of transportation to work; Model 3: population density and the percent of individuals reporting private transportation, and median household income; Model 4: population density, percent of individuals reporting private transportation, median household income, and the interaction of private transportation use with population density. The associated linear mixed model equation for model 4 is

$$\begin{aligned} Y_{ij} = {} & \beta_{0j} + \beta_{1j} ln(density 1\ unit\ increase)_{ij} + \beta_{2j} \%private\ transportation_{ij} \\ & + \beta_{3j} median\ household\ income_{ij} + \beta_{4j} \%private\ transportation_{ij} \\ & * median\ household\ income_{ij} + e_{ij} \end{aligned}$$

where $\beta_{0j} = \gamma_{00} + u_{0j}$, for the i-th county for the j-th state

Sensitivity analyses

We conducted three sensitivity analyses to address the limitations of our approach and assess the robustness of our results. First, we conducted a sensitivity analysis using death counts from the New York Times [21] to estimate R_0 to limit bias due to differential availability of testing by geographic location. We used the same exponential period as the cases, but with a lag of 14 days to account for the delays from symptom onset to deaths of cases [28–30]. Moreover, the analysis of deaths was restricted to counties with greater than 10 deaths and more than 5 daily

increases in incident deaths, in order to appropriately estimate R_0 in counties with sufficient death counts. The daily death data created curves that approximated exponential growth across the counties (Fig B in S1 Appendix). Second, we excluded counties within a radius of 15 miles, the average commuting miles in the United States [31], from counties with densities greater than the 75th percentile. Removing these adjacent counties would demonstrate the extent of biases due to individuals commuting from surrounding counties to cities. If cases are imported from more densely population (i.e. cities) to less dense counties, we could potentially be biasing our estimates downwards. Lastly, we conducted an analysis excluding influential counties with a Cook's distance measure over 4/N for each model. Cook's distance is a commonly used indicator of influence, which measures the extent data points impact the regression parameter estimates [32]. Our sensitivity analysis excluding influential counties ensures that our findings were not driven by these highly influential observations, and that the association holds for other counties.

All analyses was conducted in R version 4.0.0 [33]. The figure and removal of adjacent counties in the sensitivity analyses were done with ArcGIS [34].

Results

The United States has 3,221 counties and county equivalents. When restricting to counties with greater than 25 cases, 1,151 (35.73%) counties were included (Fig 1). The median R_0 among the counties was 1.66 (IQR: 1.35–2.11). The median start and end of the exponential growth period was March 25, 2020 and April 9, 2020 respectively, and differed for each county depending on the start of disease transmission. The median density in counties included and not included in the analysis were 53.8 people/km^2 (IQR: 21.24–144.05) and 11.3 people/km^2 (IQR: 3. 56–23.88) respectively, and the difference was statistically significant ($p < 0.0001$). A

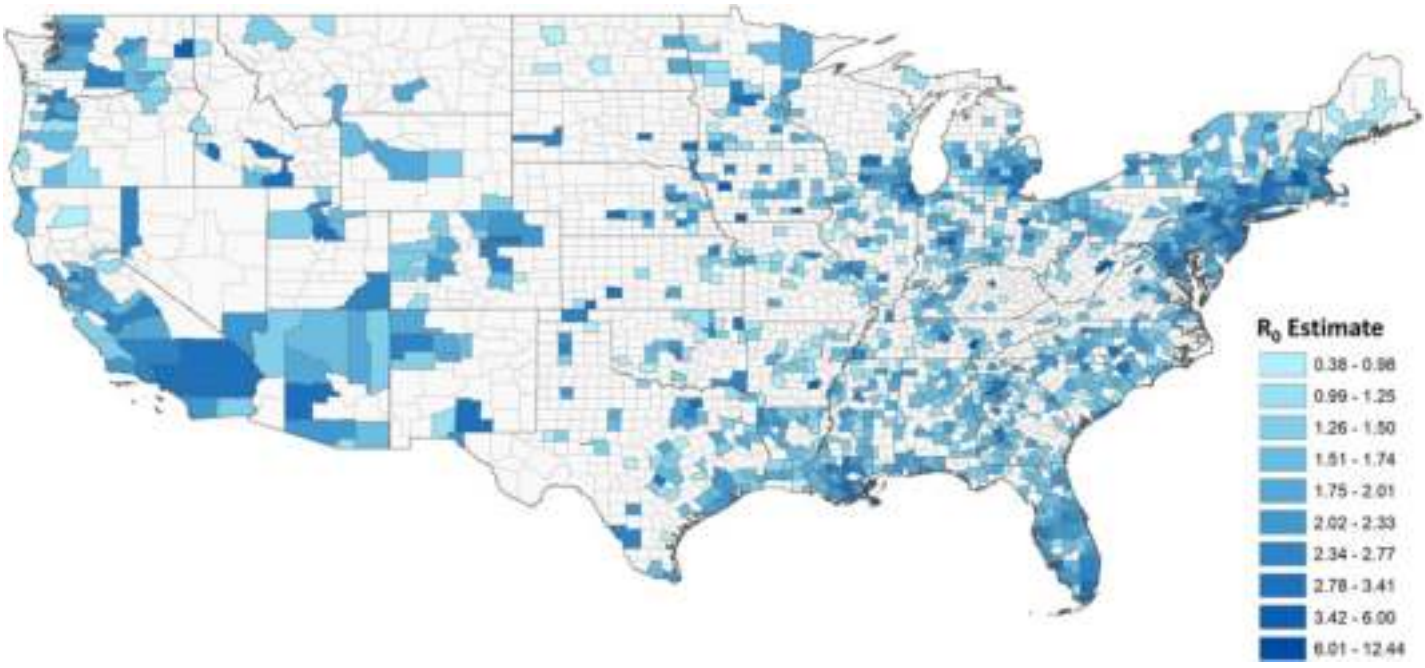

Fig 1. Basic reproductive number (R_0) estimates across United States counties. Larger R_0 indicates greater transmission during the initial phase of the outbreak, or the exponential growth period. We restricted calculation of R_0 to counties with greater than 25 cases at the end of the exponential growth period (n = 1,151), as R_0 cannot be estimated accurately with sparse data and it would be uncertain if the county was experiencing a sustained outbreak with community transmission.

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population density threshold of approximately 22 people/km^2 was needed to sustain an outbreak (Fig 2).

An increase in one unit of log population density increased R_0 by 0.16 (95% CI = 0.13 to 0.19) (Model 1; Table 1), or the doubling of population density increased the R_0 on average by 0.11 (95% CI = 0.09 to 0.13). When adjusted for percent of private transportation and median household income, the association of log population density and R_0 remained unchanged (Model 3; Table 1). There was no significant interaction, and the effect of population density on R_0 was the same among counties with a larger percentage with private vehicles as their transportation to work, but was no longer significant (Model 4; Table 1). Therefore, model 4 should be not be interpreted, since the interaction does not contribute to the model and only serves to decrease the precision (larger confidence intervals) of the measures of association of interest. R_0 decreased by 0.12 (95% CI = -0.02 to -0.04) with an 10% increase in private transportation as the main commute mode, accounting for population density and median household income (Model 3; Table 1).

In all three sensitivity analyses, population density remained positively associated with R_0, demonstrating the robustness of our main analysis. First, death data was used to calculate R_0 from 301 counties. The median R_0 among the counties that had sufficient death counts was 1.40 (IQR: 1.05–1.78). The unadjusted association between population density and R_0 remained consistent (β = 0.18, 95% CI = 0.14 to 0.23) (Model 1a; Table 2), and there were no significant interactions (Model 4a; Table 2). Next, there were 288 counties above the 75th percentile, and 414 counties that were within 15 miles of these counties high-density counties. We removed these 414 counties from the sample, and using the subsample of 737 counties, our findings remained consistent (Table 2). Influential counties were also not driving the

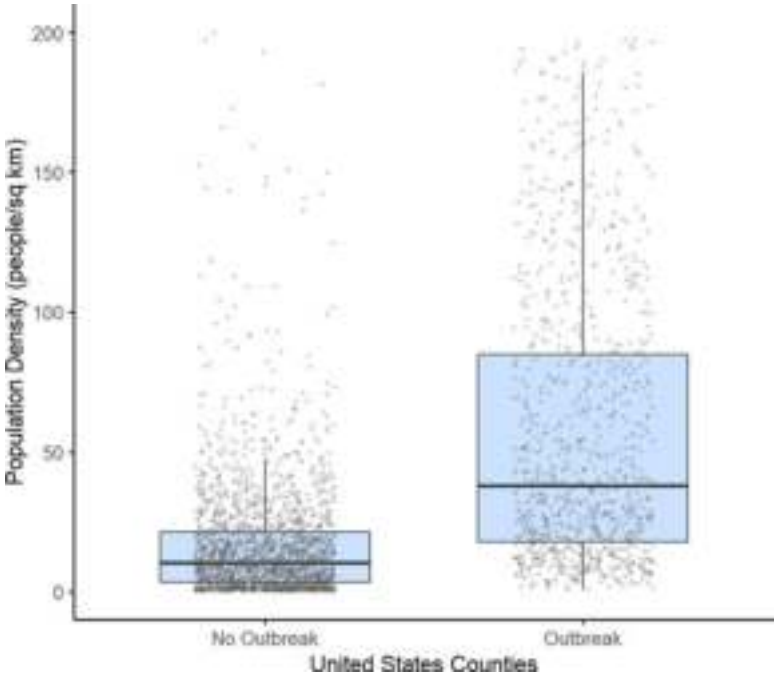

Fig 2. Population density threshold required to establish a sustained outbreak in United States counties. A population density of approximately 22 people/km^2 was needed to sustain an outbreak, which is approximately equal to the lower IQR of the counties with established COVID-19 outbreaks [median = 53.8 population/km^2; IQR = 21.24, 144.05], and a slightly less than the upper IQR of the counties with no COVID-19 outbreaks [median = 11.3 population/km^2; IQR = 3.56, 23.88]. The grey circles represent the individual county population densities.

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Table 1. Linear mixed models (random intercept, fixed slope) evaluating the association between population density and basic reproductive number (R_0) among United States counties.

	Model 1	Model 2	Model 3	Model 4
Log of population density	**0.16*** (0.13–0.19)**	**0.15*** (0.12, 0.18)**	**0.15*** (0.12, 0.18)**	0.20 (-0.06, 0.47)
Percent of private transportation (10%)		**-0.12*** (-0.19, -0.04)**	**-0.12** (-0.2, -0.04)**	-0.08 (-0.27, 0.11)
Median household income ($10,000)			0.00 (-0.03, 0.03)	0.00 (-0.03, 0.03)
Interaction of population density and transportation				-0.01 (-0.04, 0.02)

pvalue

* < 0.05

** < 0.01

*** < 0.001.

Model 1- unadjusted association of population density and R_0.

Model 2 –association of population density adjusted for the percent of individuals reporting private transportation.

Model 3 –association of population density, percent of individuals reporting private transportation, and median household income.

Model 4 –association of population density, percent of individuals reporting private transportation, median household income, and the interaction of population density and transportation.

Estimates for each model is a slope (beta) with a null of 0; a positive slope indicates that an increase in the log of population density increases R_0 by the beta estimate for the log of population density. The interaction term indicates that the association of population density and R_0 differs depending on the percentage of people using the private transportation for work.

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Table 2. Sensitivity analysis of linear mixed models (random intercept, fixed slope) using (a) deaths only, (b) removing counties within 15 miles of high-density counties, and (c) removing high influence counties.

	Model 1	Model 2	Model 3	Model 4
Deaths only				
Log of population density	**0.18*** (0.14, 0.23)**	**0.14*** (0.09, 0.19)**	**0.12*** (0.07, 0.17)**	**0.48* (0.01, 0.94)**
Percent of private transportation (10%)		**-0.16** (-0.26, -0.06)**	**-0.15** (-0.24, -0.05)**	0.14 (-0.24, 0.53)
Median household income ($10,000)			**0.06** (0.03, 0.1)**	**0.07*** (0.03, 0.11)**
Interaction of population density and transportation				-0.04 (-0.09, 0.01)
No counties adjacent to high density counties				
Log of population density	**0.17*** (0.14, 0.2)**	**0.17*** (0.13, 0.2)**	**0.16*** (0.13, 0.2)**	0.02 (-0.13, 0.17)
Percent of private transportation (10%)		0.01 (-0.07, 0.1)	-0.01 (-0.12, 0.1)	-0.12 (-0.28, 0.03)
Median household income ($10,000)			0.02 (-0.03, 0.06)	0.01 (-0.03, 0.05)
Interaction of population density and transportation				0.03 (0, 0.06)
Removing high influence counties				
Log of population density	**0.18*** (0.15, 0.2)**	**0.18*** (0.16, 0.21)**	**0.18*** (0.15, 0.2)**	**0.38* (0.04, 0.72)**
Percent of private transportation (10%)		-0.01 (-0.09, 0.07)	-0.02 (-0.1, 0.07)	0.09 (-0.1, 0.29)
Median household income ($10,000)			0 (-0.03, 0.02)	0 (-0.02, 0.03)
Interaction of population density and transportation				-0.02 (-0.06, 0.02)

pvalue

* < 0.05

** < 0.01

*** < 0.001.

Model 1– unadjusted association of population density and R_0.

Model 2 –association of population density adjusted for the percent of individuals reporting private transportation.

Model 3 –association of population density, percent of individuals reporting private transportation, and median household income.

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association of population density and R_0, and our results remained robust (Table 2). For the two sensitivity analyses excluding counties adjacent to highly dense counties and excluding high influence counties, however, the association of private transportation usage and R_0 did not remain (Models 2a, 3a, 2b, 3b; Table 2).

Discussion

Our findings show that the basic reproductive number (R_0) is associated with population density, even when percent of individuals that use private transportation and median income were accounted for. In these settings, greater population density may potentially facilitate interactions between susceptible and infectious individuals in densely-populated networks, which sustain continued transmission and spread of COVID-19. Moreover, we see that population density continues to have an important impact on disease transmission regardless of transportation accessibility and median income, suggesting that the opportunity for effective contacts are mostly driven by crowding in denser areas, increasing the contact rates necessary for disease spread. However, we did not see that density-dependence is differential across transportation accessibility, as demonstrated by the non-significant interaction of population density and transportation. Our findings are consistent with previous research that have demonstrated a strong relationship between population density and other infectious diseases [4, 6, 7, 9, 35]. In the current SARS--CoV-2 pandemic, recent literature has been conflicting, where some research also suggests a density-dependence of COVID-19 transmission [17, 36] and other measures of the severity of the outbreak [19, 37], while other research suggests that there are other factors that can better explain the pandemic [18, 38]. However, to our knowledge, our results are one of the first to show that population density is an important driver of COVID-19 transmission, even in areas where residents rely more on private modes of transportation. Moreover, even though transmission is less in lower density areas (i.e. rural areas), rural settings may eventually disproportionately be more vulnerable to COVID-19 morbidity and mortality. Individuals in rural areas are generally older, have more underlying conditions, have less access to care, and have fewer ICU beds, ventilators, and facilities needed for severe COVID-19 treatment [39–42]. Further research is needed on the overall burden of COVID-19 across the spectrum of population density.

Geographic estimates of R_0 of SARS-CoV-2 need to take into account the specific area's population density, since the R_0 estimate is dependent on both the pathogenicity of the virus as well as environmental influences. In countries where cases are only on the starting to climb, such as countries in Latin America and Southern Africa [1, 43], or there is a resurgence of cases, such as India, Iraq, and Israel [44], area-specific density can assist in predictions of R_0, which is important because epidemiological forecasts and predictive models are sensitive to small changes in R_0 inputs. Accurate estimation of R_0 consequently leads to more precise approximations of the epidemic size, so that governments can appropriately allocate resources and coordinate mitigation strategies. Moreover, as cities and states reopen in the United States, and if there is a second-wave of infections, areas with higher density accessibility will likely have greater SARS-CoV-2 resurgence.

Our study has a number of limitations. While we demonstrate that population density is associated with R_0, the estimation of R_0 can be biased depending on the data and assumptions adopted. However, our main aim in this analysis was to evaluate the association between population density and R_0, and not to accurately estimate R_0. Thus, any biases in estimation of R_0 due to underlying assumptions would likely be non-differential across counties, and would still yield similar results. In addition, we estimated R_0 based on the number of reported cases; therefore, the incidence of COVID-19 across US counties may be underestimated at varying rates due to differential testing. Testing data at the county-level currently do not exist, and we

were unable to adjust for the number of tests performed. Confounding of true epidemic growth by increase in testing could also be a potential constraint to the robustness of the analysis. To mitigate this limitation, we included a random intercept term to adjust for state-level effects, and thus differential testing across states were accounted by our model. Differential testing by local governments within states are less likely to strongly impact our findings, as most funding and budgets for COVID-19 is distributed at the state-level [45, 46]. We also conducted a sensitivity analysis using death data which demonstrates the robustness of our findings. Furthermore, we utilized a number of assumptions based on previous findings to calibrate the exponential growth period, which ensured that the virus had taken hold and allowed a sufficient number of days and case counts to estimate exponential growth. There are potential for biases in our method; for example, there is the possibility that some NPIs were introduced in the initial outbreak stage of COVID-19 in some counties; however, if this was the case, then case counts and subsequently R_0 would even higher than we calculated, and thus our associations of density and R_0 was underestimated. However, we implemented numerous ways to limit the biases. The exponential growth period was restricted to approximately 14 days at the start of the epidemic, where we would expect limited increases in testing and thus would not affect R_0 substantially. Moreover, we plotted the calibrated exponential growth curves of all the counties included in our analysis, which gave us reasonable curves that approximated exponential growth for case and death data. Another limitation is that we had to only include counties that had sufficient case data in order to accurately estimate R_0; however, if we included all counties, the true association between population density and R_0 would likely be greater than what we report in our analysis given our findings that the counties excluded in the analysis had a significantly lower density and expected very low R_0 due to lack of cases. Another limitation is that our model also assumes homogenous mixing, which may can be an oversimplification of the heterogeneity in contact patterns within populations [4, 47]. However, previous research has shown that population structure only changes R_0 estimates slightly [48], and assumptions of well-mixed populations are valid in small-to-medium spatial scales [17]. Moreover, our method loses spatial granularity in assessing R_0 in counties, especially in counties with spatially heterogenous clustering. The aim of our study, however, was to provide a generalizable estimate of the association between population density and R_0, in order to appropriately estimate potential for disease transmission, rather than a microspatial estimate that may not be generalizable to other settings. Finally, an important confounder that we were unable to adjust for is the number of importations of SARS-CoV-2 in these counties, as more urbanized areas are more likely to have links with countries and other states where the virus could have originated from. Even so, we still see that once an area is seeded with COVID-19, the growth rate is greater in denser areas during the time period prior to implementation of NPIs.

Conclusions

Counties with greater population density have greater rates of transmission of SARS-CoV-2, likely due to increased contact rates in areas with greater population density. Population density affects the network of contacts necessary for disease transmission, and SARS-CoV-2 R_0 estimates need to consider this variability for proper planning and resource allocation, particularly as epidemics newly emerge and old outbreaks resurge.

Supporting information

S1 Appendix. Population density and basic reproductive number of COVID-19 across United States counties.
(DOCX)

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The Geography of the Covid-19 Pandemic: A Data-Driven Approach to Exploring Geographical Driving Forces

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Abstract: The Covid-19 pandemic emerged and evolved so quickly that societies were not able to respond quickly enough, mainly due to the nature of the Covid-19 virus' rate of spread and also the largely open societies that we live in. While we have been willingly moving towards open societies and reducing movement barriers, there is a need to be prepared for minimizing the openness of society on occasions such as large pandemics, which are low probability events with massive impacts. Certainly, similar to many phenomena, the Covid-19 pandemic has shown us its own geography presenting its emergence and evolving patterns as well as taking advantage of our geographical settings for escalating its spread. Hence, this study aims at presenting a data-driven approach for exploring the spatio-temporal patterns of the pandemic over a regional scale, i.e., Europe and a country scale, i.e., Denmark, and also what geographical variables potentially contribute to expediting its spread. We used official regional infection rates, points of interest, temperature and air pollution data for monitoring the pandemic's spread across Europe and also applied geospatial methods such as spatial autocorrelation and space-time autocorrelation to extract relevant indicators that could explain the dynamics of the pandemic. Furthermore, we applied statistical methods, e.g., ordinary least squares, geographically weighted regression, as well as machine learning methods, e.g., random forest for exploring the potential correlation between the chosen underlying factors and the pandemic spread. Our findings indicate that population density, amenities such as cafes and bars, and pollution levels are the most influential explanatory variables while pollution levels can be explicitly used to monitor lockdown measures and infection rates at country level. The choice of data and methods used in this study along with the achieved results and presented discussions can empower health authorities and decision makers with an interactive decision support tool, which can be useful for imposing geographically varying lockdowns and protectives measures using historical data.

Keywords: machine learning; public health; Covid-19 pandemic; spatio-temporal analysis; spatial autocorrelation

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1. Introduction

According to the World Health Organization (WHO), there have been more than 79.2 million confirmed cases of Covid-19 globally and 1.7 million people are reported to have died hereof by the end of 2020 [1]. The Covid-19 pandemic has had and will continue to have life-changing effects on our lives around the world. Therefore, there is an urgent need for interdisciplinary studies to support health authorities and decisions makers with data-driven approaches for more effective recommendations and regulations for better management of such situations [2,3]. The Covid-19 outbreak has proven to be largely associated with geography, geographical information, and the geographical constellation of our cityscapes, land use information and transportation means, among others [4,5]. While epidemiologists and virologists and medics are trying to develop the right medicines, vaccines and medical solutions, an investigation of the geographical patterns of the pandemic and their relationship with geographical space with respect to

the outbreak's characteristics such as outbreak hot spots and cold spots, proximity of relevant urban elements, e.g., bars and restaurants, can help decision makers to impose more effective protective measures. These analyses help them to understand the nature and magnitude and severity of outbreak up to a certain timeframe and plan the future actions according to the historical development of the outbreak. Once such knowledge is gained, they can optimize daily societal activities more efficiently while lowering the infection risk. Thus, the aim of this study is to propose a data-driven approach for harvesting open geographic data (socio-economic data, biophysical data, mobility network, climatological data) released by open data initiatives and earth observation missions in order to (a) extract meaningful information about the geography of the pandemic such as hot- and cold spots in a temporal manner, i.e., weekly basis, that allow us to identify regions that have been constantly exposed to high infection rates or wise versa, (b) uncover the relationship between the outbreak and its geographical dimension. To do so, an application of statistical models and machine learning techniques will be tested allowing to explore what geographical settings support the outbreak. Finally, we will present appropriate open-source geospatial tools for achieving the aforementioned outputs.

The reminder of the paper is structured as follows: The introduction is followed by a literature review in Section 1.1. The data and methods used in the study will be presented in Section 2, while Section 3 presents our results. Section 4 presents discussions on our results and leads to conclusive remarks.

1.1. Related Work

Since the Covid-19 virus spread throughout the world causing a global pandemic, several studies have been conducted on the causes and factors that are essential to the spread of the virus. In this section, we present the state of the art on the studies focusing on geographic features and their correlation to the spread of virus together with machine learning techniques used in prediction spread and infection rates. The early studies related to the geography of Covid-19 focused on mapping the space and time of proven incidences and also to correlate these to geographic factors such as climate indicators and measures population density, population composition and human travel patterns. For instance, a study by Kim, Sun, and Castro [6] found a strong spatial autocorrelation and with the use of space-time scan identified clusters of Covid-19. Their findings proved that the disease initially spread in the densely and heavy populated capital region and over time moved to more distant regions of the country, furthermore single events of large spread and counter measures of these showed a space-time ripple effect in decreasing infection rates, which is also confirmed by the study of Giachino, et al. [7].

Investigating how climate indicators affect the spread, Briz-Redón and Serrano-Aroca [8] found no significant correlation between spring temperatures of Spain and Covid-19 cases, whereas Malki et al. [9] found Covid-19 was positively correlated to temperature and humidity, but also that these factors alone are not sufficient alone to predict infection rates. Briz-Redón and Serrano-Aroca [8] found that population density and number of visitors to a city had high correlations ($p > 0.85$) to infection rates, and Sannigrahi et al. [10] also found that total population, population income and poverty rates are strongly correlated to infection rates ($p = 0.75, 0.68, 0.69$ respectively). Mollalo, Behzad and Rivera [11] investigated demographic data across the United States and found that income inequality, household income, percentage of nurses and percentage of female black population, to be the most relevant explanatory demographic variables of countrywide infection numbers.

Studying the very first wave of Covid-19 in Wuhan China, Kraemer et al. [12] showed that by using positioning data of citizens, future infection hotspots can be accurately predicted. The study found an $R^2 = 0.89$ between people travelling out of Wuhan and towards nearby cities and hereby causing spread of virus. Likewise, Kapoor et al. [13] was able to predict next-day cases within a single county in the United States with very high accuracy (RMSLE = 0.0109); this was done by plotting mobility data of people's

movement between counties on a graph neural network. It has, however, proven difficult for researchers to use geographic variables to predict the spread of virus through machine learning techniques. Wang et al. [14] were able to predict and forecast infection rates during the first wave of the pandemic in the spring of 2020 using a logistic growth model with a s-shaped curve, but they also found that the nature of the pandemic in the long term cannot be fitted to such a curve, and thus concluded that such a model can only poorly account for the fluctuations of infection seen over time. Besides being capable of predicting infection rates, studying them with machine learning techniques can provide knowledge about the importance and relationship between the included variables. Using machine learning, Gupta and Gharehgozli [15] showed that population density and pollution levels are closely correlated to virus spread.

Pollution levels and air-quality have indeed been seen to also change rapidly over the course of the pandemic, mainly due to the measures imposed on citizens' ability to move and travel, and restrictions imposed on how businesses to run. Bao and Zhang [16] studied pollution levels across 44 Chinese cities, and found that across all pollution measures, the general Air Quality Index increased by 7.76% while the pollution indicators of SO_2, $PM_{2.5}$, PM_{10}, NO_2 and CO decreased by 6.76%, 5.93%, 13.66%, 24.67% and 4.58%, respectively. Collivignarelli et al. [17] similarly found that the early lockdown measures imposed in Milan (Italy) caused nitrogen dioxide and nitrogen oxide levels to fall by 61% and 74%, respectively, during the time of the lockdown.

Since the beginning of the Covid-19 pandemic, studies has been made to find factors that impact the spread of the virus, and we have presented some of the most relevant within the field of geographical analysis. Based on these, we aimed to implement novel techniques to map the spread of the virus within the European Union across space and time, examine explanatory variables and use them to predict infection rates. By including variables used in different studies presented, we can gain a deeper understanding of geographic driving factors in the Covid-19 pandemic. Within the geographic medium, our study additionally adds points of interest (POIs) data as a new set of variables that reflects the location of social hubs within urban areas. With the findings of the significant changes in pollution levels over the pandemic, these will also be included, allowing us to further investigate the correlation and explanatory factors between a large set of indicators for climate, pollution, population density, and POIs and the infection rate of Covid-19.

2. Data and Methods

2.1. Data

Covid-19 data was obtained from the European Centre for Disease Prevention and Control (ECDC), an agency under the European Union. The ECDC tracks and publish Covid-19 case numbers for the whole globe on a country level, within the European Union Covid-19 infection rates are also published at subnational regional levels. The dataset used is the *"Data on the weekly subnational 14-day notification rate of new COVID-19 cases"*, which contains weekly infection rates since week 13 (effectively week 14, since the data is based on bi-weekly reports) for each of the European subnational regions.

The subnational regions should be in accordance with the European Nomenclature of territorial units for statistics (NUTS) Regions, but it varies from country to country as per on what NUTS level the data is being recorded at. It has therefore been necessary to create a shapefile that consists of both NUTS 2 and NUTS 3 regions, and manually validate that each region matches the NUTS code provided by ECDC. This does, inevitably, results in countries being divided in an uneven amount of regions, with countries towards east such as Hungary, Estonia, Romania reporting cases at a municipal level, and the larger central European countries such as Germany, France, Spain reporting at a larger regional level. Cases reported in Wales UK, could not be identified at either NUTS 2 or 3 level, so the case data for Wales has been averaged in to a single region. The Covid-19 infection rate for each region are summed to a total infection rate covering the period of week 13 to week 45 (23 March 2020—8 November 2020), these can be seen in Figure 1.

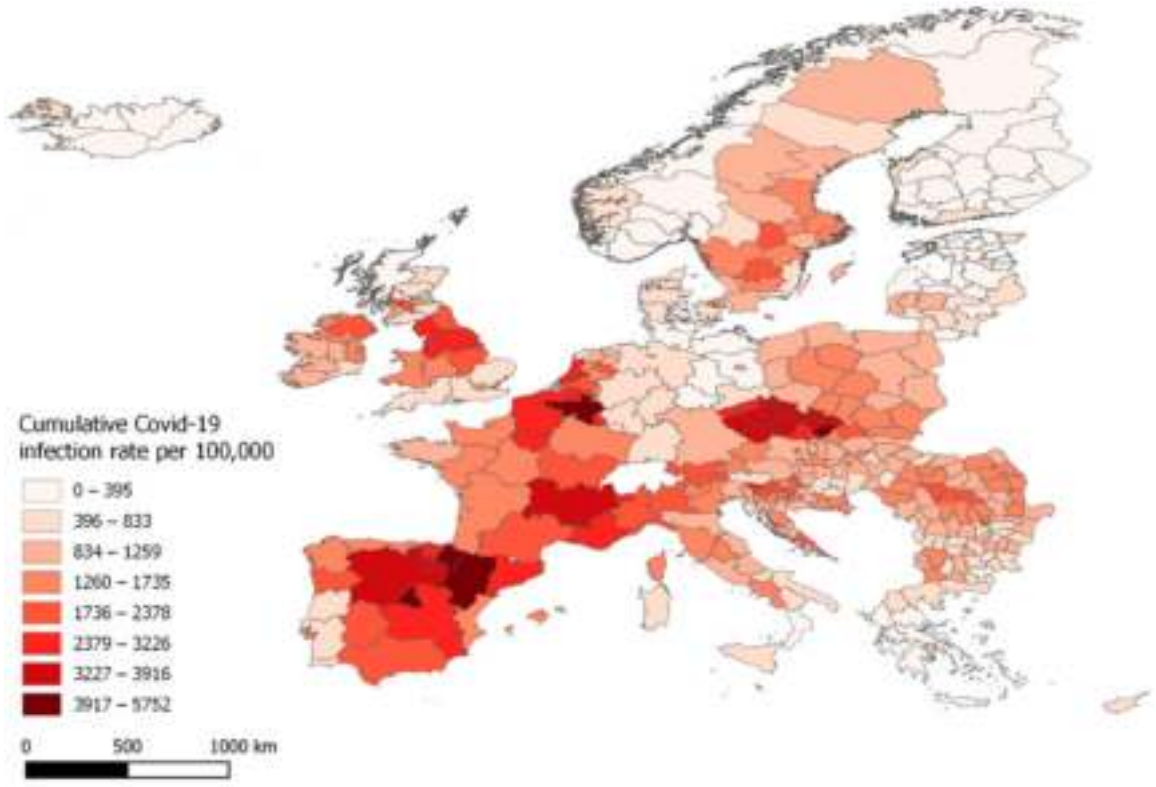

Figure 1. Cumulative Covid-19 infection rates per 100,000 inhabitant, from 23 March until 8 November 2020.

POI data was gathered from OpenStreetMap (OSM), where all amenities for each country was collected through the overpass API and merged into a complete amenity point dataset. The number of amenities within each region were counted per capita by the 10 most abundant amenity types, i.e., restaurants, bars, cafés, gas stations, etc.

The amenities contained in OSM are crowdsourced data, which naturally raises the question of data quality. Since the amenity data is implemented as counts within the individual European regions, only the quality of completeness of the amenities are of concern. The quality of positional accuracy of points is not a cause for concern when working on a European scale. Unfortunately, completeness of amenities in the European countries was mostly studied a decade ago when the use and data contained in OSM was rising [18,19], and since then, most studies on accuracies of OSM amenities has been made with the focus of positional accuracy, and not completeness. A recent study on completeness of road and OSM's POIs data in Europe found general high levels of quality in amenities and road data across major European cities [20]. The overall quality of OSM data in developed countries around the world is generally at a very high level [21], providing data in comparable quality to those of official data sources [22]. Places that has a high degree of tourism, i.e., most major European cities, also has a high completeness of the mapped amenities, whereas the data quality in rural areas remains to be tested [20].

Daily surface temperatures are available from Copernicus Climate Change Services (C3S) who monitor temperatures from ground stations across Europe. The daily mean temperature of 2019 was downloaded from the E-OBS database as a 0.1 degree regular gridded raster, and averaged in to an annual mean temperature. The annual mean temperature for each region is derived by using zonal statistics.

The Copernicus Atmosphere Monitoring Service (CAMS) monitors a set of variables related to air-quality and pollution levels across Europe, and distributes these as 0.1 degree rasters. Based on availability and documented cause for each pollutant, we chose "Non-methane VOCs" (volatile organic compounds), "Particulate matter < 2.5 μm ($PM_{2.5}$)", "Nitrogen dioxide" and "Particulate matter < 10 μm (PM_{10})" as indicators for air-quality and pollution levels. The four indicator data sets were downloaded as daily levels in the

period of February through October for both 2019 and 2020 and the average year over year difference was calculated for each indicator and through zonal statistics transferred to the study regions.

The results is a data set covering 401 European regions with total Covid-19 infections a dependent variable (x0) and 17 independent geographic variables. All variables are listed in Table 1.

Table 1. Regions, Covid Infection rates and related variables.

Variable	Argument
Total infected [dependent variable]	X0
Population Density	X1
Restaurants per cap.	X2
Cafes per cap.	X3
Fast Food Places per cap.	X4
Pubs per cap.	X5
Bars per cap.	X6
Gas Stations per cap.	X7
Schools per cap.	X8
Doctors' Offices per cap.	X9
Kinder gardens per cap.	X10
Annual mean temperature	X11
Nitrogen dioxide, year-over-year change	X12
Particulate matter < 2.5 μm ($PM_{2.5}$, year-over-year change	X13
Non-methane VOCs (volatile organic compounds), year-over-year change	X14
Particulate matter < 10 μm (PM_{10}), year-over-year change	X15

2.2. Methods

2.2.1. Exploratory Data Analysis

Initially, an exploratory data analysis is carried out using the global Moran's I statistics to determine spatial autocorrelation. The Moran's statistic is a measure of how a variable of a region is correlated variable values of its surrounding regions, under the assumption that variable values are normally distributed across space. Moran's I follows a normal distribution curve and tests whether clustering is appearing by calculating a z-score and *p*-values, which are measures for standard deviation values and level of significance. Moran's I is a product of these values ranging from −1 to 1, where −1 is clustering of dissimilar values, 0 is perfect distribution of values and 1 is clustering of similar values and hereby showing spatial autocorrelation [23]. A predefined measure of neighbors are set, and each individual regions and its surrounding areas are tested for spatial autocorrelation against the complete data set. We used the *k* nearest neighbors to define neighborhoods, with differentiated k values for the two scales of the study. For the European spatial autocorrelation analysis we set $k = 6$ and for the Danish one we set $k = 4$.

The result of the analysis is grouped into four categories: hotspot, coldspot, doughnuts and diamonds. The hot- and coldspots are showing clusters of high infection rates and clusters of low infection rates, and the doughnuts and diamonds are showing regions with low infection rates surrounded by high infection rates and regions with high infection rates surrounded by low infection rates.

The data for the analysis are the total infection rates for each region gathered by accumulating the bi-weekly infection rates since week 14. The spatial autocorrelation is therefore a measure of clusters over the pandemic as a whole.

2.2.2. Space Time Patterns

As an addition to the exploratory data analysis, an emerging hotspot analyses was made based on the results of spatial autocorrelation. The emerging hotspot analysis is a method that utilize a three-dimensional data set to locate clusters through both time and space. By doing a spatial autocorrelation analysis for each time slot of the available data (34 weeks) and adding these as layers on top of each other, it is possible to analyze how hot and coldspots change in space over time. The analysis was carried out as an extension to the spatial autocorrelation analysis done with the Pysal library in Python where we implemented space time patterns categorization inspired by the Esri tool for the same purpose [24]. The analysis look for 13 different scenarios for each region, these are seen in Table 2. The standard implementation of space time categories include an upper time interval threshold (t_{max}) of 90% and a lower time interval threshold (t_{min}) at opposite l0% in some of the categories. To better account for the changes in infection clustering in space it was decided to do multiple analysis with t_{max} and t_{min} at 75%, 25% and 55%, 45% for those categories.

Table 2. Regions, Covid Infection rates and related variables (modified from [24]).

Space Time Category	Definition (t_{max} = 90%, t_{min} = 10%)
New Hotspot	Region identified as hotspot in the last time step that has not been a hotspot before
Sporadic Hotspot	Region identified as a hot spot at least once but in less than 10% of the time steps that also has not been a cold spot
Oscillating Hotspot	Region identified as hotspot in the last time step and been a hotspot in less than 90% of the time steps that also been a coldspot at least once
Historical Hotspot	Region that is not identified as hot spot in the last time step but has been a hot spot in more than 90% of the time steps
Intensifying Hotspot	Region identified as a hotspot in the last time step that has also been a hotspot in more than 90% of the time steps
Persistent Hotspot	Region identified as a hotspot in at least 90% of the time steps
New Coldspot	Region identified as a coldspot in the last time step that has not been a coldspot before
Sporadic Coldspot	Region identified as a coldspot at least once but in less than 10% of the time steps that also has not been a hotspot
Oscillating Coldspot	Region identified as a cold spot in the last time step and been a coldspot in less than 90% of the time steps that also been a hotspot at least once
Historical Coldspot	Region that is not identified as coldspot in the last time step but has been a coldspot in more than 90% of the time steps
Intensifying Coldspot	Region identified as a coldspot in the last time step that has also been a coldspot in more than 90% of the time steps
Persistent Coldspot	Region identified as a coldspot in at least 90% of the time steps
Not Significant	None of the above

The classifications are based on assessments of the results of spatial autocorrelation outputs stacked as layers through time, and these are then categorized by looking through the layers vertically. This is considered a simplified emerging hot spot analysis, as the analyses of the individual layers does include the layers above or below.

2.2.3. Statistical Models: OLS & Geographically Weighted Regression

OLS

The ordinary least squares is a global regression model that seeks to investigate the relationship between a dependent variables (indicators) and a number of independent variables. The model is explained by the following equation [25]:

$$y = \beta_0 + B_1 X_1 + \beta_2 X_2 + \cdots \beta_n X_n + \varepsilon \quad (1)$$

where y is the dependent variable, in our case Covid-19 infection rates, β is the ordinary least squares estimated coefficients and ε is the residuals of the predicted values. The OLS is a global model since the equation assume the relationship between the dependent variable and the indicators to be constant for the whole data set. This is however a simplification of the investigated relationship, as this will often vary from location to location.

GWR

The geographically weighted regression (GWR) model is a similar regression model with the addition of adding geography to the equation by estimating local coefficients for local areas. GWR is thereby a local OLS model that varies over space. GWR is described by the OLS equation with the addition of coordinates for each location [25]:

$$y = \beta_0(u_i, v_i) + B_1(u_i, v_i) X_1 + \beta_2(u_i, v_i) X_2 + \cdots \beta_n(u_i, v_i) X_n + \varepsilon \quad (2)$$

The local regression area is defined by a spatial kernel function and a bandwidth that can be defined as either distance (fixed bandwidth) or a neighborhood size (adaptive bandwidth). Only areas that are within the kernel are included in the GWR model. We used an adaptive bandwidth size defined by automatic model calibration and a Bi-square kernel.

GWR is capable of mapping how variable relationships vary across space and hereby to tell which variables best describes the variation seen in the dependent variable at different regions. We included all the variables seen in Table 1 in the GWR analysis. The model is evaluated by mapping local R^2 values, variables coefficients and model residuals.

2.2.4. Machine Learning Prediction

The geographic variables collected are a mix of static elements and dynamic climatic indicators. The population density, amenity counts and annual temperatures are elements that both reflects the geography and cityscapes, while at the same time, also tells something about the culture and local habits of the people living in a certain area. Meanwhile the air quality and pollution indicators are variables that change on the short term as a direct consequence of the level of activity and movement of people within a region. The year over year change should be a good indicator of how far from normal the activity level in a region has been, and thereby reflect the different lockdown policies implemented in the different countries and regions, a measure that elsewise is difficult to quantify.

By incorporating all these values in a prediction model, we aim at reflecting different aspects of geography, culture and level of activity in the regions across Europe. However, with lockdown measures being one of the key components in preventing the spread of virus, a pan European prediction model that does not directly include lockdown measures is very unlikely to outperform a model that does include such measures.

We therefore aim at carrying out the prediction at different levels of scale, with the broadest being all the 401 European regions where cases are reported. Narrowing down, the prediction is performed on the identified hot- and cold spots identified in the spatial autocorrelation analysis, reflecting the clusters of regions who did worst and best in terms of total Covid-19 infections. Lastly, the prediction is carried at a municipal level for the country Denmark, where the implemented policies have almost been uniform since the beginning of the pandemic.

We chose three different prediction models, all capable of predicting quantity values, and set out to predict the infection rate based on the 16 independent variables. The predictors of choice are random forest regressor [26], lasso regression [27] and support vector regression (SVR) [28,29]. The models were each chosen because they are widely used in similar prediction tasks.

3. Results

By November 2020, all European countries were affected by the Covid-19 pandemic, but the infection rates varied greatly between the individual countries and regions. Belgium, Spain and the Czech Republic are over the course of the whole period the countries with the highest infection rates. The regions of Wallone and Brussels in Belgium are the two worst hit, with total infection rates of 11,504 and 10,832 per 100,000 population. Iceland and Finland are the two countries with least infected regions. Five out of six regions in Iceland have less than 100 infected per capita and its capital region have had a total of 115 infected per 100,000 population. In Figure 2, bi-weekly infection rates for the included regions are visualized at three different weeks of 2020.

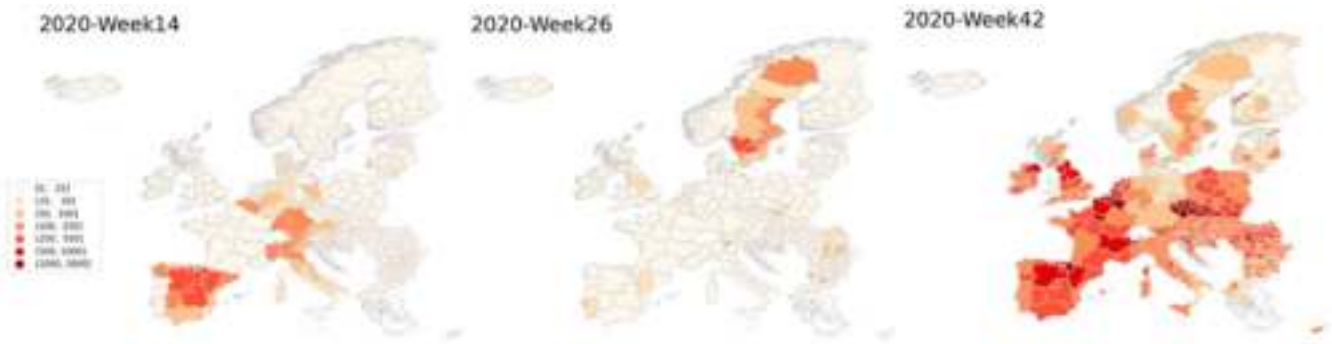

Figure 2. Bi-weekly infection rates at week 14, week 26 and week 42.

Over the whole time period of March to November, peak infection rates has occurred at different countries. In the spring of 2020 northern Italy and Spain were the worst affected, whereas in the summer Sweden was the only country with overall high infections, in the fall of 2020 the majority of countries were seeing surges in infections far higher than those observed in the spring.

3.1. Spatial Autocorrelation, EU and DK

The spatial autocorrelation analysis was carried out at the levels of all European Regions and for the municipalities in Denmark. The analysis covers a period of 32 weeks, from the start of April until start of November 2020, for which the infection rates has been accumulated.

The spatial autocorrelation analysis seen in Figure 3 successfully identified clusters of hot- and coldspots together while also locating some doughnuts and diamonds. For Europe as a whole it is clear that the identified hotspots over the whole pandemic is the majority of Spain, France and Belgium and some parts of The Netherlands, the Czech Republic is also identified as a hotspot resulting in the surrounding regions of south Germany and Poland being doughnuts, i.e., low infection areas surrounded by high infected areas. Low infection areas, coldspots, are seen to mostly in the Nordic regions of Norway, Finland, the Baltic countries and Iceland, while Greece and Cyprus are the only southern regions reporting low infection rates.

For the municipalities of Denmark, high-infection areas are centered around the capital region of Copenhagen and its surrounding municipalities. High infection rates are also seen in the second largest city of Denmark, Aarhus, as this is identified as a diamond, i.e., having high infection rates while its surrounding municipalities have not seen similar high rates. The coldspot are seen to be the less populated areas of southern Denmark and

central-north Jutland. The third largest city of Denmark, Odense in central Fyn, are within the large cold spot towards south and hereby not having significant higher infection rates than its surrounding municipalities.

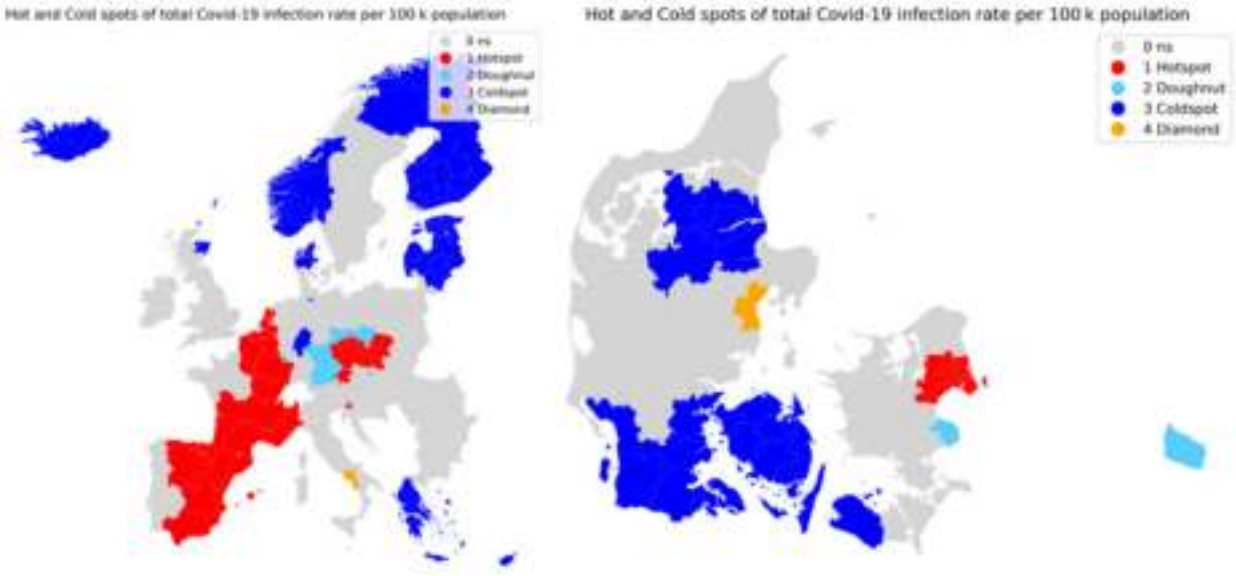

Figure 3. Hot and cold spots of total accumulated Covid-19 cases in the EU regions (left) and the municipalities of Denmark (right).

As the spatial autocorrelation is based on accumulated infection rates, it does not show how infection rates has fluctuated over time in the individual regions, for this purpose we can assess the results of emerging hotspot analysis.

3.2. Space Time Patterns—Emerging Hotspot Analysis

The emerging hotspot analysis is a product of spatial autocorrelation over time, where each classification bin is a measure of how many times a regions has been either a hot- or coldspot or having no significance. As described in Section 2.2.2, two analyses are carried out each with a different threshold for how many times a region must be of a category that falls under one of the space time pattern categories.

3.2.1. Emerging Hotspots—Europe

In Figure 4, the results of the emerging hotspot analysis for the EU regions are seen. Both at the 90% time interval setting and the 70% time interval setting, the majority of regions are seen to fall under the 'not significant' class, meaning that they did fall under any of the categories specified in Table 2. At the 90%-time interval map, new hotspots are seen to appear in northern Italy, parts of Austria (including Vienna), Croatia and the capital region of Poland. The sounding regions, that is mostly Austria and Croatia, are classified as oscillating hotspots, which are new hotspots that has in fact been a coldspot at an earlier time. Oscillating coldspots are centered on Ireland, Northern Ireland and some regions in Scotland, while some regions in Finland are seen to be intensifying coldspots which are regions that has generally have low infection rates and keep on doing so.

As seen in Figure 5, when lowering the time setting from 90% to 75%, more regions are expectedly classified in to the hot and coldspot categories. Especially the sporadic hot and coldspots are seen to be greater in number, with most of Romania, eastern France and northern Italy covered, and also Luxembourg, Wales and parts of The Netherlands (including its capital region) being sporadic hotspots. Sporadic coldspots are also seen to be greater in number, covering northern Germany, southern Denmark, eastern Hungary and Poland, and southern Italy. A larger part of Finland and all of Iceland is now classified as intensifying hotspots, and the regions of and around Ireland not changing their classification.

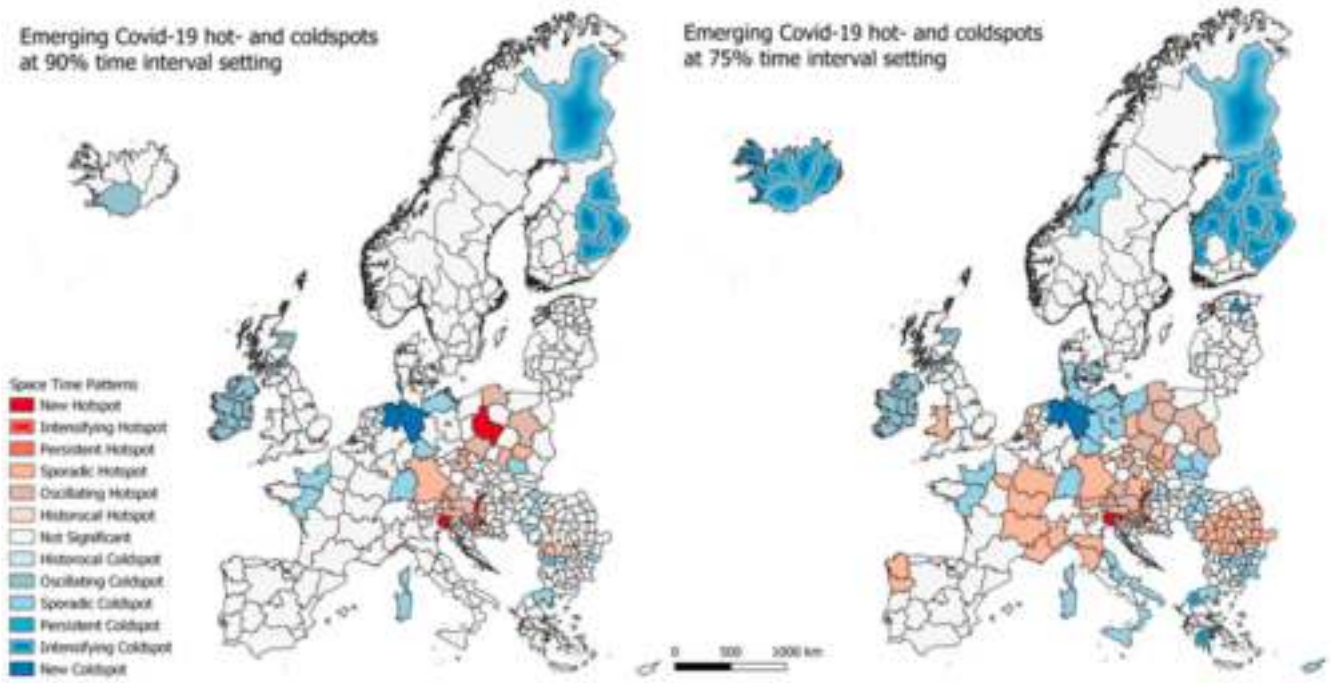

Figure 4. Emerging hotspot results for total cumulative infection rates from week 13 to week 45 in Europe at 90% (left) and 75% (right) time interval setting.

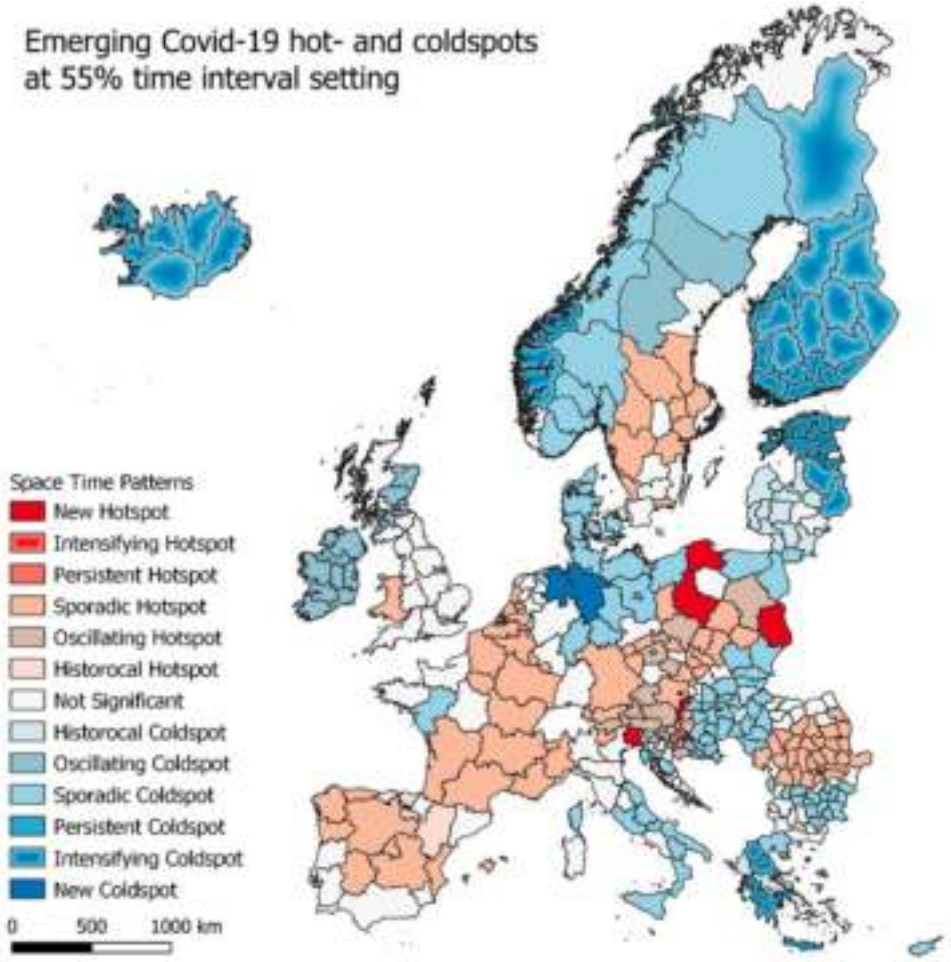

Figure 5. Emerging hotspot results for total cumulative infection rates from week 13 to week 45 at 55% time interval setting.

3.2.2. Emerging Hotspots—Denmark

A similar emerging hotspot analysis was carried out for the municipalities of Denmark, the results are seen in Figure 6. Interestingly, only the sporadic coldspots are seen to be greater in number when the time interval threshold is lowered from 90% to 75%. At the lower threshold, these sporadic coldspots covers large parts of mid- and western Jutland together with the municipalities towards south for the islands Lolland and Falster. For both the analysis, the outcome is otherwise roughly the same. In close proximity to Copenhagen, we see four oscillating hotspots and going a bit further away from the capital we see the sporadic hotspots. The oscillating coldspots are meanwhile seen to be at the opposite end of the country, in the very north of Jutland, where the 4th largest city of Denmark, Aalborg in also placed. Interestingly, neither the capital of the second and third largest cities of Denmark are categorized as any kind of hotspot. In Figures 7 and 8, the emerging hotspot analysis is implemented on a monthly basis, showing in which parts of the country infection rates where increasing and decreasing at the given times.

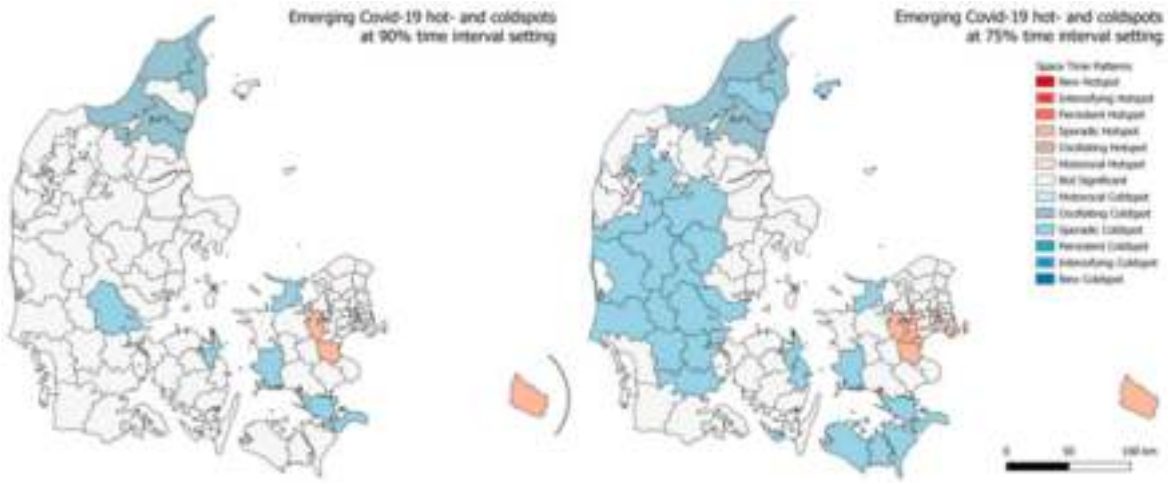

Figure 6. Emerging hotspot results for total cumulative infection rates from week 13 to week 45 in Denmark at 90% (left) and 75% (right) time interval setting.

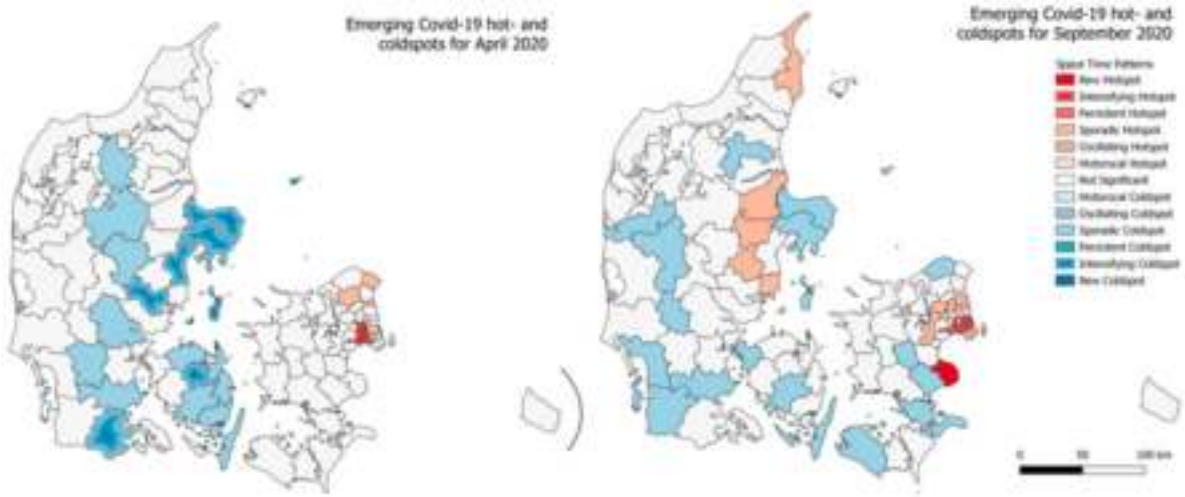

Figure 7. Emerging hotspot results for total cumulative infection rates in Denmark for April 2020 (left) and September 2020 (right) at 75% time interval setting.

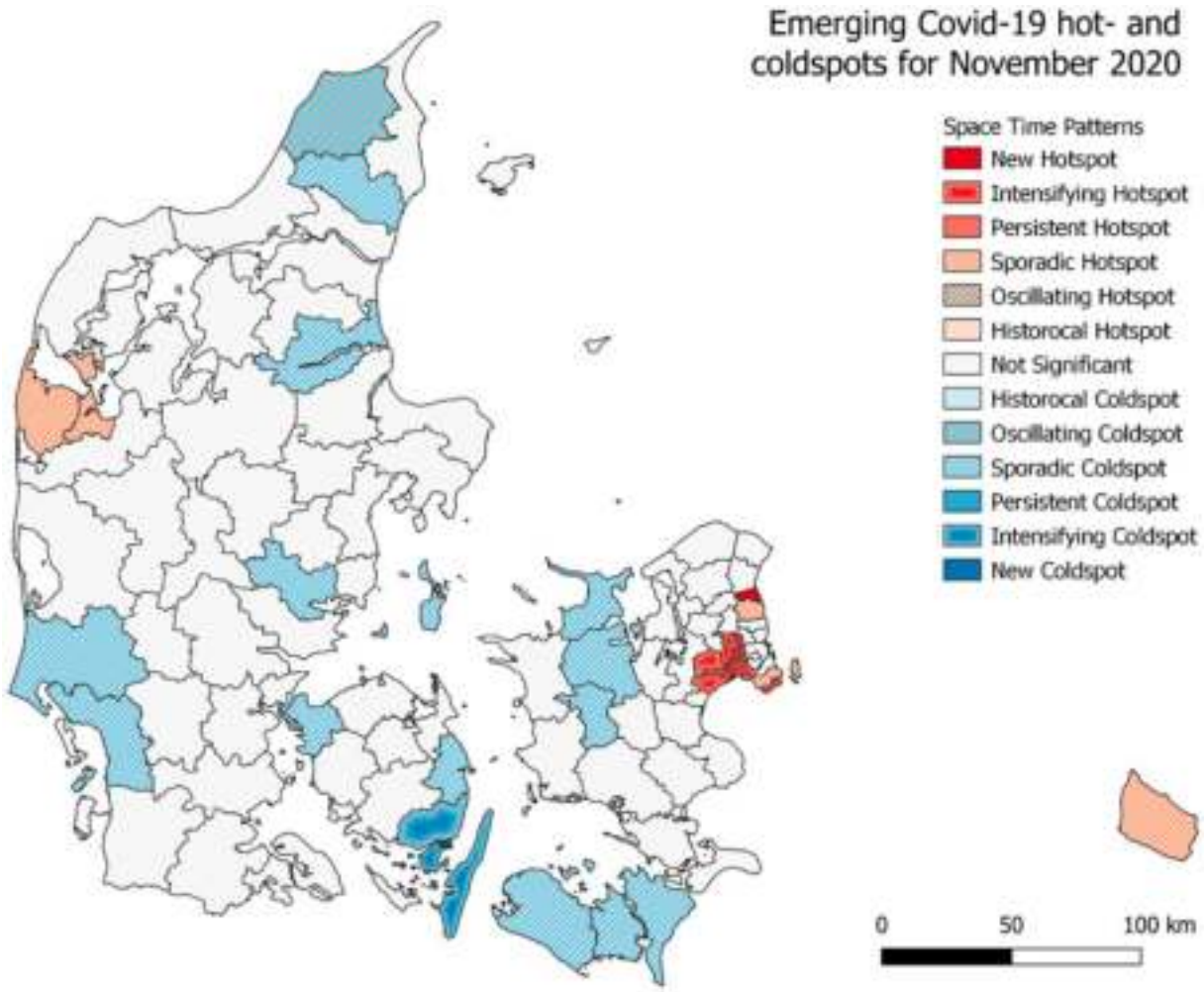

Figure 8. Emerging hotspot results for total cumulative infection rates in Denmark for November 2020 at 75% time interval setting.

3.3. Geographically Weighted Regression—EU

The GWR model was used to analyze how the 16 variables affected the total infection rate over the 401 European regions, the results consist of both the global regression model (OLS) and as local regression model. An automatic calibrated adaptive bi-square kernel [25] was used, with a bandwidth size of 104. See the global result statistics in Table 3 and local regression model results in Table 4.

Table 3. The global regression model (OLS) and the local regression model (GWR) results.

Model	Res Sum Squares	AIC	AICc	R^2	Adjusted R^2
OLS	219.230	927.850	931.448	0.453	0.432
GWR	66.922	654.585	752.719	0.833	0.765

Table 4. Variable statistics for OLS and GWR model. Est = Estimate, SE = Standard Error.

Variable	OLS		*p*-Value	GWR			
	Est	SE		STD	Min	Median	Max
X0	0.000	0.038	1.000	0.380	−0.909	−0.010	0.805
X1	0.111	0.043	0.009	0.137	−0.110	0.113	0.676
X2	0.109	0.063	0.084	0.222	−0.246	0.167	1.122
X3	−0.264	0.056	0.000	0.412	−1.612	−0.184	0.279
X4	0.007	0.049	0.893	0.306	−0.784	0.119	0.683
X5	−0.071	0.045	0.116	0.197	−0.761	−0.113	0.487
X6	0.195	0.054	0.000	0.359	−0.598	0.112	1.312
X7	0.011	0.051	0.828	0.441	−0.629	−0.018	1.487
X8	0.048	0.046	0.297	0.208	−0.568	−0.028	0.355
X9	−0.102	0.044	0.021	0.306	−1.074	−0.200	1.349
X10	−0.087	0.045	0.056	0.225	−0.610	0.010	0.780
X11	−0.134	0.052	0.010	0.322	−1.135	−0.280	0.640
X12	−0.115	0.049	0.019	0.353	−1.257	−0.022	0.794
X13	0.144	0.057	0.011	0.298	−0.997	0.039	0.500
X14	0.506	0.050	0.000	0.279	−0.124	0.372	0.956
X15	−0.142	0.050	0.004	0.376	−0.697	−0.069	1.360

Comparing the global regression model (OLS) with the local regression model (GWR) in Table 3, the residual sum of squares is seen to drop significantly from 219 to 66, and the AIC dropped from 931 to 752. The adjusted R^2 value almost got a twofold increase from 0.432 to 0.765, indicating that the GWR model is able to account for 76.5% of the variation in Covid-19 infections. These results confirm the superiority of GWR in a case where we expect spatial variably in the relationship between the variables [30]. We can further investigate the statistics results for each of the variables included in the model, these are shown in Table 4.

Inspecting the *p*-values of the individual variables in Table 4, the five variables having the greatest significance (*p*-value) on the dependent variable are X1 (Population Density), X3 (Cafes), X6 (Bars), X14 (Non-methane VOC) and X15 (PM_{10}). The mapped coefficients for these five variables are shown in Figure 9. In the mapped coefficients, a similar pattern is seen between café and PM_{10} levels that the variables are of most influence in central Scandinavia, i.e., central Norway and Sweden, Denmark and Northern Germany. The other three variables do to some degree also share the same pattern, with the greatest influence on Covid-19 infection rates seen in eastern Europe, France, and to some degree Scandinavia and Italy.

X14 (Non-methane VOC) and X15 (PM_{10}) are both measures of air pollution, so these could be expected to have similar estimate coefficients, whereas the coefficients calculated in the OLS model in Table 4 show that X14 is positive and X15 is negative. The mapped coefficients in Figure 9 shows that the variable coefficients geographically are very different from each other, and similarly in Figure 10 where the two variables are seen to have significance in areas directly opposite to each other. Even though X14 and X15 are measures of air pollution, they each represent different emission sources and thus, do not follow the same geographic pattern.

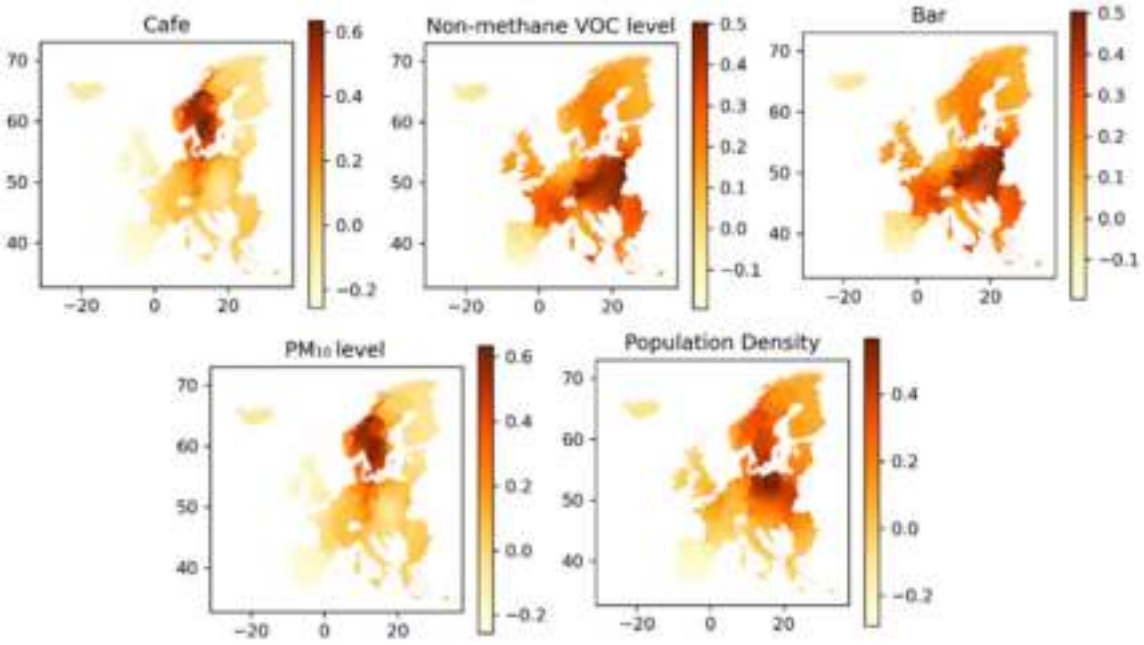

Figure 9. The coefficients of the 5 most significant variables in explaining total Covid-19 infections.

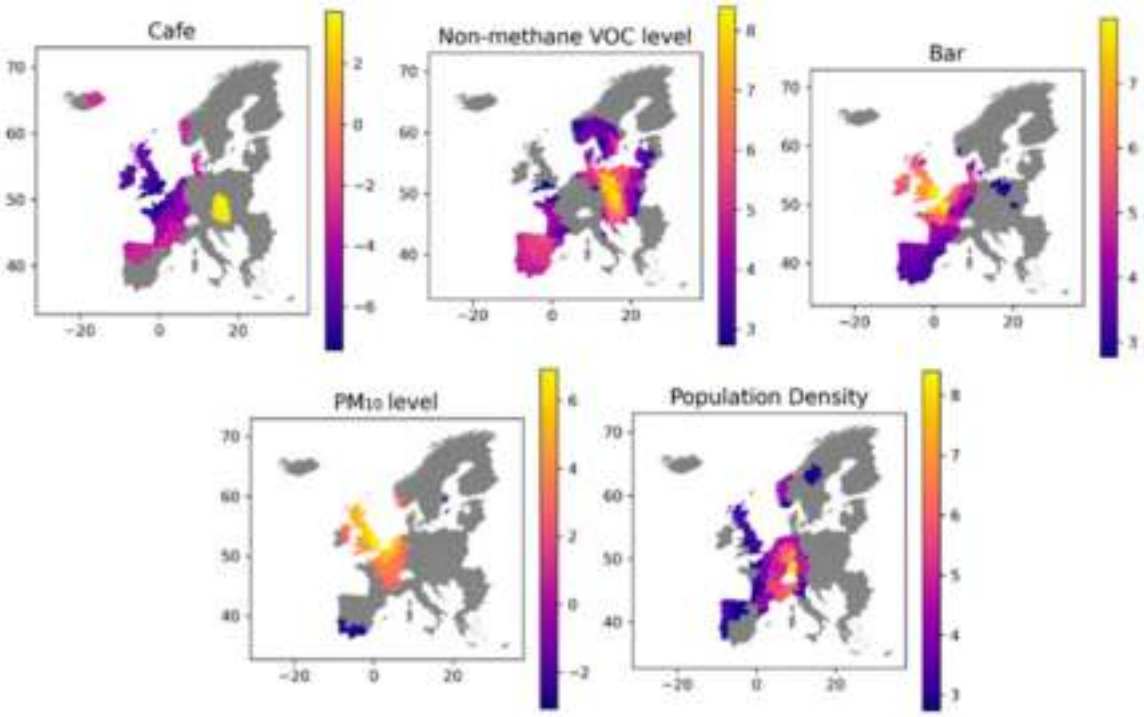

Figure 10. The significance of the 5 most significant variables in explaining total Covid-19 infections.

The charts in Figure 10 are showing in which regions each variable is having a significance towards the infection rate, this can both be a positive (high rates) and negative (low rates) impact on the rate. In the regions coloured in grey the variable did show any significance toward infection rates.

The population density is seen to have an overall positive effect on infection rates, with the greatest effect seen in the central European regions, covering Germany, France, Belgium, The Netherlands and England. Looking at cafes as bars, they seem to have effect in roughly the same area of western Europe, but interestingly each of these variables are affecting infection rates in opposite directions. Areas with a high number of bars per capita

are having high infection rates, where the opposite is the case with cafes per capita in roughly the same areas. Since the two pollution level indicators, Non-methane VOC and PM_{10}, are measured as year-over-year changes, higher values equal to a higher percentage yearly change. While we see the pollution indicators having impact at different geographic regions, the impact of them is highly positive. This indicates that regions that did not have a decrease in their pollution levels also had high Covid-19 infection numbers.

Figure 11 shows the geographic distribution of the condition numbers, local R^2 values, and standardized residuals. The condition number checks for redundancy in the variables used in the local regression task, and values above 30 are a cause for concern and results within these regions are not to be trusted [31]. For the most part, the condition numbers do not cause reasons for concern except at the very red regions of Romania and Greece. The levels here are in fact so high that the model output is not of any use in these regions. The R^2 values are indicators of how well the model can fit the regression locally. The highest R^2 values are in the regions around East Germany, Poland and Czech Republic, together with some parts of Scandinavia and Spain. The lowest R^2 values are seen in Italy, parts of France and the North of Romania. Lastly the residuals are mapped to investigate if these appear to be clustered, to have a properly fitted model the residual should be evenly distributed in space. The residual map in Figure 11 does not indicate any spatial clustering of residuals.

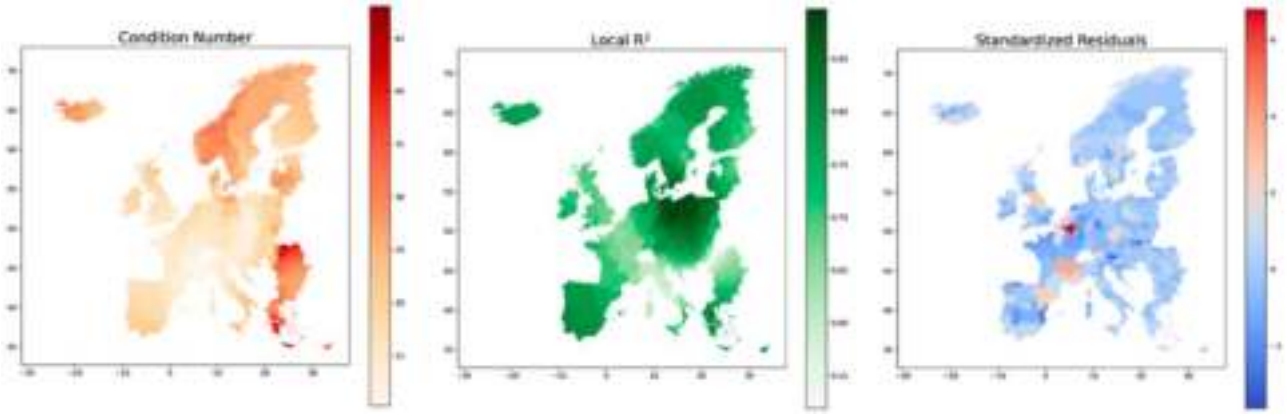

Figure 11. Geographic distribution of Condition Number, Local R^2 values and Standardized Residuals for the GWR model of total Covid-19 infections.

3.4. Machine Learning Prediction

The machine learning prediction aimed at predicting the total infection rate for the included regions based on the variables described in Section 2.1 and Table 1. We tested three different models at four different scale levels, ranging from all of Europe, to selected regions of Europe and down to the individual municipalities of Denmark. All data included in the model are normalized and split into training and test data at a ratio of 70/30. The models are evaluated using the accuracy and mean absolute error (MAE) metrics, the accuracy should be as high as possible and MAE as low as possible. All models across all regions are ran over 10 iterations each and the evaluation scores are the average of the result of each iteration. The results of the models are seen in Table 5.

Across the included prediction models, the random forest is the best performing in both accuracy and MAE. The random forest prediction of all European regions is seen to have an accuracy of 52%, where, when only including the hot- and cold-spots, the same predictor is achieving 76% accuracy. The latter is of course a selection of the regions performing best and worst in terms of infection number, so a higher accuracy is expected here. However, the lowest MAE of all predictions is seen to be the pan European random forest prediction. The random forest prediction for the municipalities of Denmark showed 61% accuracy and a MAE of 0.095. This is finest level of scale for the predictions and also within a single country, so the policies for infection counter-measures are much more uniform across the regions.

Table 5. Machine Learning Prediction Results, MAE = Mean Absolute Error.

Area	Nr. of Regions	Model	Accuracy	MAE
Europe	401	Random Forest	**52%**	**0.079**
		Lasso	36%	0.153
		Support Vector Regression	51%	0.151
Europe—Hot- & Coldspots	128	Random Forest	**76%**	**0.099**
		Lasso	74%	0.285
		Support Vector Regression	73%	0.256
Europe—Hotspots	56	Random Forest	19%	**0.177**
		Lasso	- %	0.217
		Support Vector Regression	- %	0.221
Denmark	98	Random Forest	**61%**	**0.095**
		Lasso	35%	0.233
		Support Vector Regression	41%	0.232

Numbers marked in bold are the best achieved accuracy measures for the given area.

The importance of the 10 most significant variables in the random forest pan Europe prediction is shown in the plot in Figure 12. It is clear that the year over year change of Non-methane VOCs are by far the most importance variable in this model, secondly comes population density, a variable that is also expected to be of significance importance to the spread of the virus. These variables are the only ones with a significance greater than 10%, and following them comes gas stations and other measures for air quality and pollution levels. This is according well to the results found in the geographic weighted regression models, where both Non-methane VOC and Population density showed great significance in explaining total infection rates.

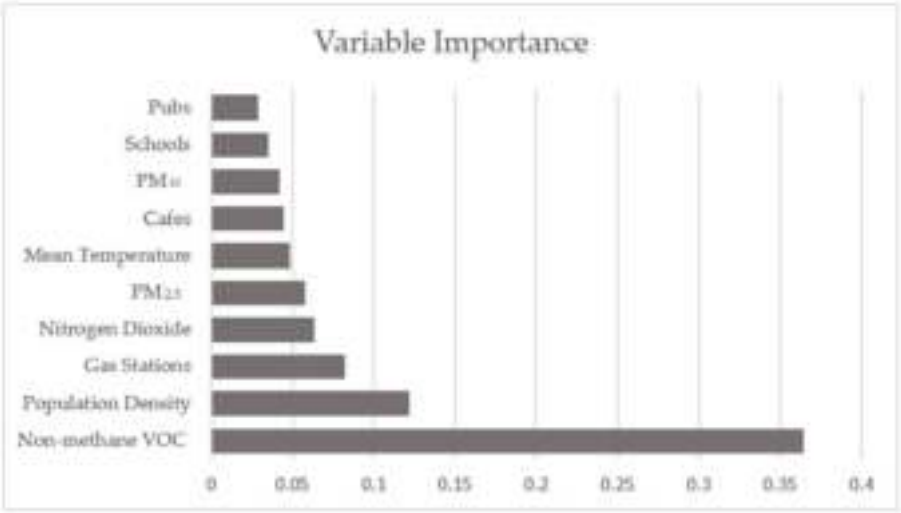

Figure 12. Variable Importance for Random Forest Regression of all EU regions.

4. Discussion

Throughout the paper, we have presented and implemented a number of tools that can be used to help understand how the spread of Covid-19 has evolved over time, where it is currently most active and what are the factors that affect this spread. For the most part of 2020 and continuing into 2021, Europe has been severely hit by the global pandemic with the first wave seen in the spring of 2020 followed by a summer with generally low infection rates and into the fall and winter of 2020 where the second, and in many cases, even more severe wave of infection raging over Europe. By the end of 2020, no country in Europe has remained safe and unaffected by the virus.

Our spatial autocorrelation analysis identified the central European regions as the hotspot of the total pandemic, and the more isolated and less populated Nordic regions

as cold spots. This finding confirms our general understanding of how viruses spread, where densely populated and interconnected areas are at higher risk for a fast spread of pandemic [32,33]. As this analysis does not reflect the spread of virus over time, we used the finding of the spatial autocorrelation in an emerging hotspot analysis. This analysis is a powerful tool in mapping the pandemic in its current status and still factoring in how the individual regions have been affected in the past. The analysis can be implemented at many different scales of time and can hereby be used to study the spread of virus over long periods of time and down to monthly or even bi-weekly status of individual regions. The emerging hotspot maps are great tools for authorities to help deciding on where measures must be tightened or relieved while also serving as a great communication tool for the citizens to understand the basis of such decisions.

Our further analysis revolves around investigating what geographic factors affects the infection rate of Covid-19 in Europe, for this purpose we carried out a geographically weighted regression analysis. We found that the number of bars and cafes are significantly correlated to infection rates, confirming that places for social aggregation serve as infection source. Further analysis could be done at finer scales, to provide more in-depth knowledge of how the virus spread locally throughout cities and hereby help decision making regarding if such places should have restrictions imposed. Furthermore, we found that the air-quality and pollution indicators of Non-methane VOC and PM_{10} levels are also correlated with infection rates. This proves as an indication towards the level of activity in the society as lockdown measures expectedly have an effect on pollution levels [16], and indeed regions that had lower reduction in pollution levels have higher infection rates. Moreover, the GWR analysis showed a positive correlation between population density and infection rates, a finding that confirms the hypothesis that population density is associated with higher Covid-19 infection rates [15,34–37].

Finally, we implemented all the variables in a machine learning framework including random forest, support vector regression and lasso with the goal of assessing the predictability of infection rate solely based on the included variable features. Our pan European model was able to predict the infection rate with 52% accuracy and the single country model of Denmark resulted in 61% accuracy. A key component in predicting infection rates is naturally to which degree a country has introduced lockdown measures, a variable that is difficult to quantify and that was not introduced in the model. To achieve better prediction results, such a variable is highly recommended to include in the future works. The variable importance showed that pollution measures have a great importance in the prediction and given the fact that pollution levels and lockdown measures are closely correlated, we suggest that future research use pollution measures as one potential proxy of countrywide lockdowns. Certainly, while moving towards electric vehicles and renewable energies, such a proxy will not function. Actual levels of lockdown could also be quantified, but that is a challenging task since policies and their implementation are subject to human interpretation and behaviour. Due to the fact of dissimilar policies implemented, we found that implementing a single model across multiple countries is challenging, this is further concluded by result of the same model performing 10% better within a single country, i.e., Denmark, where policies are more uniform. This is largely due to a number of reasons such as (a) dissimilar number of COVID tests per capita rooted in the cost of Covid-19 tests from being free of charge (e.g., Denmark) or expensive (e.g., Greece, Romania), (b) not applying a universal standard for reporting infection numbers, (c) diversity of geodemographic distribution across each country, (d) dissimilar health services across Europe and, (e) wide diversity of cultures, behavioural factors, dominant background health issues in Europe.

5. Conclusions

This study presented a series of useful geospatial methods for studying the geography of Covid-19 and what factors facilitate the pandemic's spread. We located European hot- and cold spots of infection rates and used this to further investigate and visualize how individual regions and municipalities have progressed over time. The emerging

hot spot analysis is especially a powerful tool in understanding and visualizing where case numbers are rising and falling and hereby contribute to decision-making and raise understanding in the general public. We further examined the drivers of the pandemic through a pan European statistical GWR model and in a machine learning environment. The GWR model shows the most significant points of interest in explaining infection rates, while also showing that population density and air pollution are also strong explanatory factors. Our machine learning model, i.e., the random forest method, reached prediction accuracies of 52% and 61% for Europe and Denmark and confirmed that pollution data can be used as a relevant variable in predicting infections. In order to develop better prediction models in the future, we suggest including further variables that reflects lockdown levels of individual regions over time. Such a variable could be made from close examination of adopted policies, but could as well be derived from pollution levels.

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Data Availability Statement: All the data and codes used in this study are shared at https://github.com/jimjoker/Covid-19_geographic_analysis (accessed on 1 March 2021).

Conflicts of Interest: The authors declare no conflict of interest.

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Predictors of the Aggregate of COVID-19 Cases and Its Case-Fatality: A Global Investigation Involving 120 Countries

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Abstract

Objective: Since the identification of COVID-19 in December 2019 as a pandemic, over 4500 research papers were published with the term "COVID-19" contained in its title. Many of these reports on the COVID-19 pandemic suggested that the coronavirus was associated with more serious chronic diseases and mortality particularly in patients with chronic diseases regardless of country and age. Therefore, there is a need to understand how common comorbidities and other factors are associated with the risk of death due to COVID-19 infection. Our investigation aims at exploring this relationship. Specifically, our analysis aimed to explore the relationship between the total number of COVID-19 cases and mortality associated with COVID-19 infection accounting for other risk factors. **Methods**: Due to the presence of over dispersion, the Negative Binomial Regression is used to model the aggregate number of COVID-19 cases. Case-fatality associated with this infection is modeled as an outcome variable using machine learning predictive multivariable regression. The data we used are the COVID-19 cases and associated deaths from the start of the pandemic up to December 02-2020, the day Pfizer was granted approval for their new COVID-19 vaccine. **Results**: Our analysis found significant regional variation in case fatality. Moreover, the aggregate number of cases had several risk factors including chronic kidney disease, population density and the percentage of gross domestic product spent on healthcare. **The Conclusions**: There are important regional variations in COVID-19 case fatality. We identified three factors to be significantly correlated with case fatality.

Keywords

Intraclass Correlation Coefficient, Hierarchical Data Structure, Negative Binomial Regression, Data Splitting, Mixed Effects Linear Regression Model

1. Introduction

Coronavirus disease 2019 (COVID-19) is now a considered a pandemic by the World Health Organization. The main objective of this study is to report on the association between regional case fatality of COVID-19, kidney diseases mortality, diabetes, population density and the Gross Domestic Product (GPD). This cross-sectional historical data was constructed by combining data from several sources [1]-[6].

The above sited data sources were accessed on December 2-2020. We included in the study the cumulative number of COVID-19 cases and the associated death counts by country as of December 2-2020. We excluded countries that had cumulative count less than 10,000 cases. The data base has 120 countries, and we divided them into regions according to the classification given in data source number 2, resulting in 15 regions. This classification is shown in **Table 1**. This table has in the first column the names of the countries, the second column is the name of the region they belong to, within brackets, the number of countries in that region, and the third column is a code given to each region.

Basically, we have two outcome variables of interest: 1) The aggregate number of cases per country over the period ending December 2-2020 (AC). 2) The COVID-19 Case Fatality (CF). This is calculated as:

AC = Count of COVID-19 cases analyzed at the regional level.

CF = Count of deaths attributed to COVID-19/(Count of COVID-19 cases) × 100,000.

This paper has three objectives. Firstly, we quantify the degree between regions variation in both AC and CF. The second objective is to identify the important factors associated with AC and CF. We use machine learning algorithm to build a regression models with the entire data set divided into learning set and validation test to quantify the predictive accuracy of the constructed models.

2. Selected Risk Factors

2.1. Chronic Kidney Diseases

Chronic Kidney Disease (CKD) is an important contributor to morbidity and mortality from noncommunicable diseases, and this disease should be actively addressed to meet the UN's Sustainable Development Goal target to reduce premature mortality from non-communicable diseases by a third by 2030 [2]. We extracted the CKD prevalence and the associated mortality from the countries listed in table. The rationale was that there are many published articles

Table 1. Countries and the corresponding Regional classification as given in https://doi.org/10.1016/s0140-6736(20)30045-3.

Countries	Region name	Region Code
Peru, Ecuador, Bolivia	Andean. Latin (3)	10
Kazakhstan, Georgia, Armenia, Azerbaijan, Kyrgyzstan, Uzbekistan, Tajikistan	Central Asia (7)	2
Czechia, Romania, Hungary, Serbia, Bulgaria, Croatia, Slovakia, Bosnia, Slovenia, North-Macedonia, Albania, Montenegro	Central Europe (12)	5
Brazil, Columbia, Mexico, Panama, Costa Rica, Guatemala, Honduras, Venezuela Paraguay, El-Salvador.	Central Latin America (10)	11
Dominican Republic, Puerto Rico, Jamaica	Caribbean (3)	9
Ethiopia, Kenya, Uganda, Zambia, Madagascar. Mozambique, Angola, French Guinea.	CESSA (8)	13
Indonesia, Philippine, China, Myanmar, Malaysia, Sri Lanka, French Polynesia, Maldives.	East Asia (8)	1
Russia, Poland, Ukraine Belarus, Lithuania, Latvia, Estonia	East Europe (7)	6
Japan, Singapore, Republic Korea, Australia.	HIAP (4)	4
Iran, Iraq, Turkey,	MENA (20)	12
Morocco, Saudi Arabia, Israel, Jordan, United Arab, Kuwait, Qatar, Lebanon, Oman, Egypt, Occupied Palestine, Tunisia, Bahrain, Algeria, Libya, Afghanistan, Sudan.		
India, Bangladesh, Pakistan, Nepal.	South Asia (4)	3
Chile, Argentina, Uruguay	South Latin America (3)	8
South Africa, Namibia, Zimbabwe	SSSA (3)	15
USA, France, Spain, UK, Italy, Germany, Belgium, Netherland	West Europe and North America (20)	7
Canada, Switzerland, Portugal, Austria, Sweden, Greece, Denmark, Ireland, Norway, Luxemburg, Finland, Cyprus.		
Mali, Nigeria, Ghana, Cameroon, Ivory Coast	WSSA (8)	14
Senegal, Guinea, Cape Verde		

CSSA = Central Sub-Saharan-Africa, MENA = Middle East and North Africa, HIAP = High Income Asian Pacific, WSSA = Western Sub-Saharan-Africa, SSSA = Southern Sub-Saharan Africa.

highlighting the importance of CKD as a possible risk factor for COVID-19 mortality.

A recent meta-analysis [7] outlined several reasons urging investigators to emphasize the importance of CKD during the COVID-19 infection. It was also noted in [7] that CKD has not attracted enough awareness due to its inconspicuous course, especially in the early stage. Both diabetes and hypertension are the leading causes of CKD in all developed countries and many developing countries, and the long-term or advanced CKD usually increases the risk of car-

diovascular diseases. To be noted, these conditions accompanying CKD are all risk factors that exacerbate the COVID-19 patients. The present study highlights the importance of CKD as a risk factor for COVID-19 mortality. Some reports either did not include information on CKD or failed to state the definition of CKD used in the study. By contrast, the study by Williamson *et al.* [8] includes data for three subgroups with CKD. These data also demonstrate that patients with severe forms of CKD have a very high risk of COVID-19 mortality, which is even higher than that of other known high-risk groups, including patients with hypertension, obesity, chronic heart disease or lung disease [9] [10] [11]. The CKD data indicate that these patients deserve special attention with regard to COVID-19.

2.2. Population Density

Two studies [12] [13] utilized data from Japan suggested that the population density, which is somewhat indicative of social distancing, was a significant factor associated with COVID-19 infection. The effect of population density on the morbidity rate was also discussed in a case study of Iran [14]. These studies suggested that several cofactors introduce uncertainty. When discussing the effects of policies, a multi-city analysis representing different countries may be imperative. In multi-country analyses, the number of conducted tests may add uncertainty because this number depends on medical and economic resources for each country.

2.3. Diabetes

A recent population-based study from Italy [15] documented that the presence of comorbidities, including diabetes, were associated with a more severe course of COVID-19 and a higher fatality rate. Other studies from the most affected countries, including China, United States and Italy, seem to indicate that prevalence of diabetes among patients affected by COVID-19 is not higher than that observed in the general population, thus suggesting that diabetes is not a risk factor for SARS-CoV-2 infection. However, a large body of evidence demonstrate that diabetes is a risk factor for disease progression towards critical illness, development of acute respiratory distress syndrome, need for mechanical ventilation or admission to intensive care unit, and ultimately death. The mechanisms underlying the relationship between COVID-19 and diabetes remain to be elucidated. In particular, it is still unresolved whether is diabetes per se, especially if poorly controlled, or rather the various comorbidities/complications associated with it that predispose patients with COVID-19 to a worse prognosis. In fact, conditions that cluster with diabetes in the context of the metabolic syndrome, such as obesity and hypertension, or complicated chronic hyperglycemia, such as cardiovascular disease and chronic kidney disease, have also been associated with poor prognosis in these individuals and the available studies have not consistently shown that diabetes predict disease severity independently of them [15].

The estimated global prevalence was 9.3% in 2019 with an upward trend [16] [17]. In the USA alone, more than 34 million adults had known or undiagnosed diabetes in 2018 [18]. In 2017, diabetes was listed as the underlying or contributing cause of death on 270,702 death certificates, which corresponds to a crude rate of 83.1 per 100,000 persons [18]. Infectious diseases are more frequent and can be associated with worse outcomes in patients with diabetes [19]. Therefore, it is not surprising that diabetes has been considered as a possible risk factor or a predictor for worse outcomes in patients with coronavirus disease 2019 (COVID-19) [20] [21] [22]. COVID-19 rapidly reached the level of a pandemic and has caused more than 850,000 deaths worldwide within a few months despite unprecedented mitigation measures [23]. The strength of the association between diabetes and COVID-19 has been investigated in observational cohorts around the world. We aimed to systematically review and conduct a meta-analysis of the available observational studies reporting the effect of diabetes on mortality among hospitalized patients with COVID-19.

We obtained the data of global prevalence of diabetes by country from [24]. The rationale behind including diabetes in the data base of or study is to explore the strength of the country level diabetes prevalence with the CF outcome variable.

2.4. Gross Domestic Product (GDP) and the Percentage of Spending on Health Care (PHSC)

A recent article [25] analyzed data from 88 countries included as a covariate the percentage of government spending on healthcare. This factor is an indicative of the level of preparedness of the healthcare system to face urgent crisis such as the one caused by the COVID-19 pandemic. The authors showed that there is a significant relationship between an increase in health care spending and reduction in the COVID-19 case fatality. The finding that countries with strong healthcare capacity had fewer deaths per confirmed case was unsurprising. In this sense, the [25] study confirms previous research on the association of overall mortality (all causes) and healthcare funding [26].

3. Data Analysis

We divided the data analysis into two sections. In the first section univariate and descriptive statistics are produced with graphics. We also explore the extent of regional variability for the parameters of interest. This is measured by comparing the between regional variation to the within regional variations. A widely used statistic in this regard is the "Intraclass Correlation Coefficient" (ICCC). In the second stage we first identify the risk factors associated with the outcome of interest. Factors that are significantly correlated with the outcome of interest are used in a multivariate analysis model. The model that we used identifies regions as random effects. Using predictive analytic machine learning regression approach to evaluate the joint effect of the selected covariates on the outcome of

interest is done by splitting the data into training data (70% of the entire data) and validation or test set (the remaining 30% of the data).

3.1. Descriptive Measures (Table 2)

The lowest average population density is in region 4, or, HIAP (47267.5 ± 51256.458).

The highest average population density is in region 7, or, West Europe (2628158.14 ± 6383767.55).

The histogram of population density is shown in Figure 1.

In Table 3 we present the summary statistics for the aggregate number of COVID-19 cases.

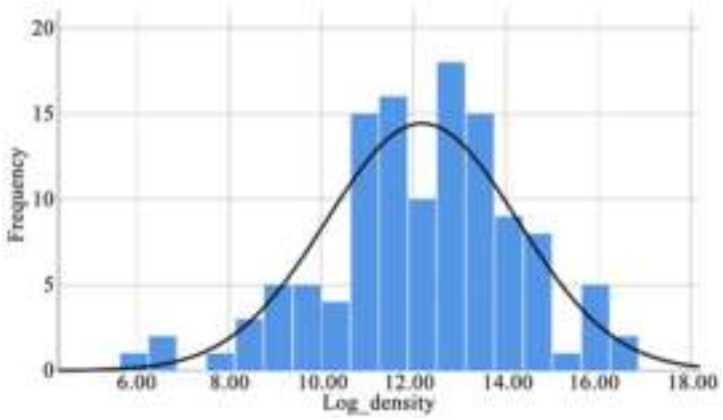

Figure 1. Histogram of log-population density.

Table 2. Summary measures of population density.

region	n	Mean	Std. Deviation
1	7	1,861,024.86	3,518,931.634
2	7	528,770.57	978,243.226
3	4	1,116,063.25	1,488,519.088
4	4	2,042,718.50	3,769,584.918
5	12	71,242.50	61,214.452
6	7	2,628,158.14	6,383,767.547
7	20	1,148,782.75	2,924,033.825
8	2	1,768,251.00	1,431,394.843
9	4	47,267.50	52,156.458
10	3	886,879.33	536,486.935
11	10	1,331,402.60	2,603,264.787
12	20	1,278,450.40	2,620,104.048
13	8	674,711.75	394,170.103
14	8	455,876.25	416,606.224
15	3	812,469.67	415,296.062
Total	119	1,078,510.29	2,576,968.860

Table 3. Summary measures of the aggregate number of COVID-19 cases by region.

region	n	Mean	Std. Deviation
1	7	181,340.86	214,429.947
2	7	105,576.43	55,184.339
3	4	2,650,841.50	4,566,745.811
4	4	68,670.75	57,557.320
5	12	175,681.33	163,726.359
6	7	619,801.86	858,270.813
7	20	1,230,523.65	2,938,619.513
8	2	988,698.50	616,363.061
9	4	55,656.50	62,874.115
10	3	434,431.00	458,961.374
11	10	953,104.00	1,947,275.831
12	20	233,409.90	230,576.529
13	8	36,655.00	38,224.367
14	8	39,255.13	34,628.880
15	3	272,281.33	450,353.611
Total	119	530,003.45	1,619,102.721

From Figure 2 we can see that the distribution of the number of cases is highly skewed to the right and the data in Table 1 shows that the variance is much larger than the mean, a phenomenon known as "over dispersion".

In Table 4 we present the mean, standard deviations of CF as defined above. The largest mean CF is in Andean Latin America (5626.36 ± 1685), while the smallest mean number of CF is in Central Asia (1199.95 ± 402.64).

The large variations in CF can better be depicted from the boxplot of the data as shown by the boxplot as given in Figure 3.

It appears from the above boxplot (Figure 3) that there is considerable variation in the distribution of CF. One way to stabilize this variation is to employ a specific transformation. We selected the logarithmic transformation, so that the dependent variable of interest is Y = Log (CF). The histogram of this new outcome variable Y is given in Figure 4. The Q-Q plot of Y is given in Figure 5 and it shows the closeness of the distribution of Y to that of the normal distribution.

The primary predictor of interest is CKD case fatality (Table 5).

As can be seen from Figure 6, there is great amount of variation among the 15 regions with respect to CKD case fatality. The next covariate we examine is the percent of GDP spending on healthcare. The summary measures are shown in Table 6, with the histogram given in Figure 7.

The above histogram (Figure 7) is quite symmetric apart from an extreme outlier. We shall not employ any transformation on this variable.

In Table 7 we present the summary measures of the diabetes prevalence for each of the 15 regions in the data.

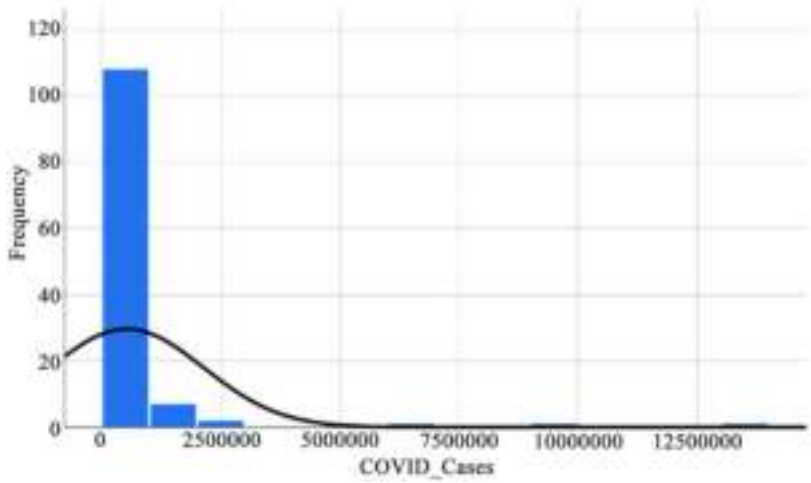

Figure 2. Histogram of the number of COVID-19 cases.

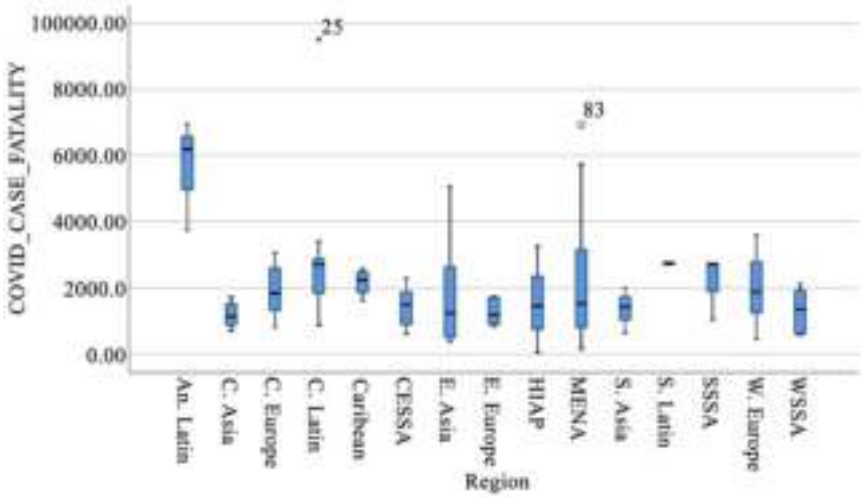

Figure 3. Boxplot of COVID-19 case fatality by region.

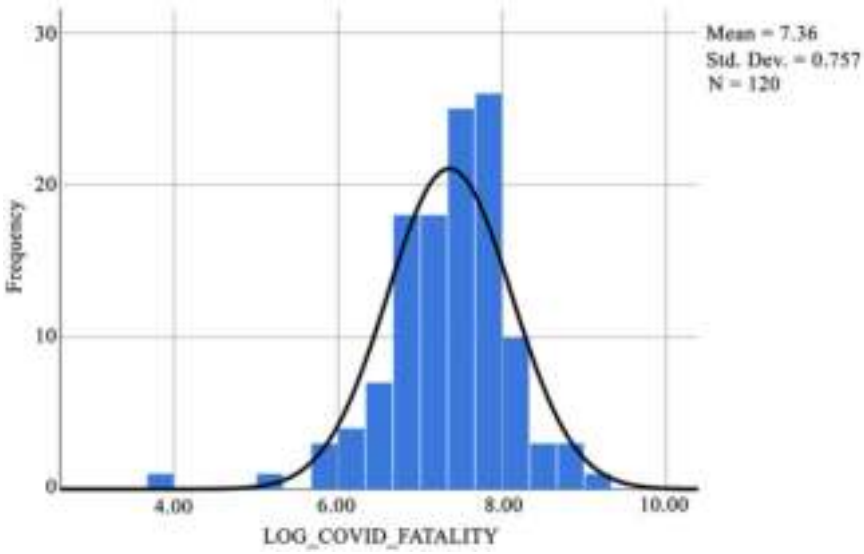

Figure 4. Histogram of Y = Log COVID-19 case fatality.

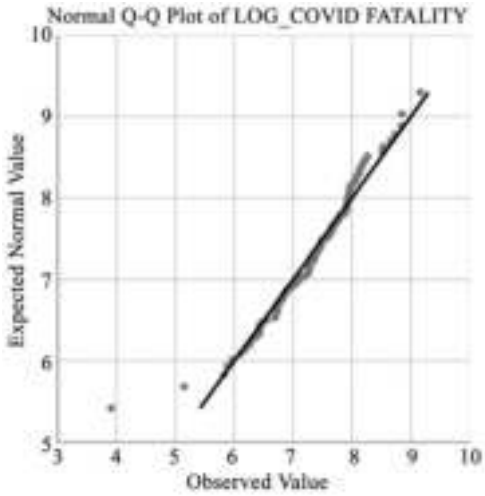

Figure 5. Q-Q plot of the logarithm of COVID-19 case fatality.

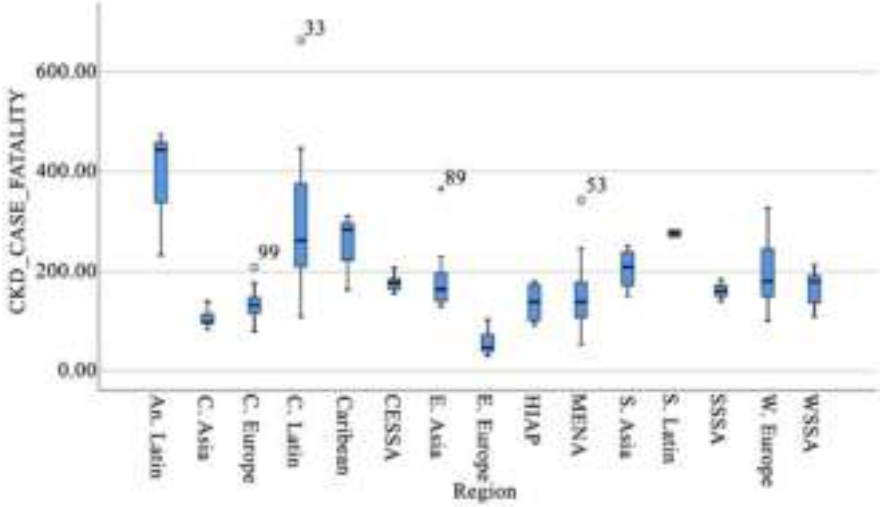

Figure 6. Boxplot for the CKD case fatality.

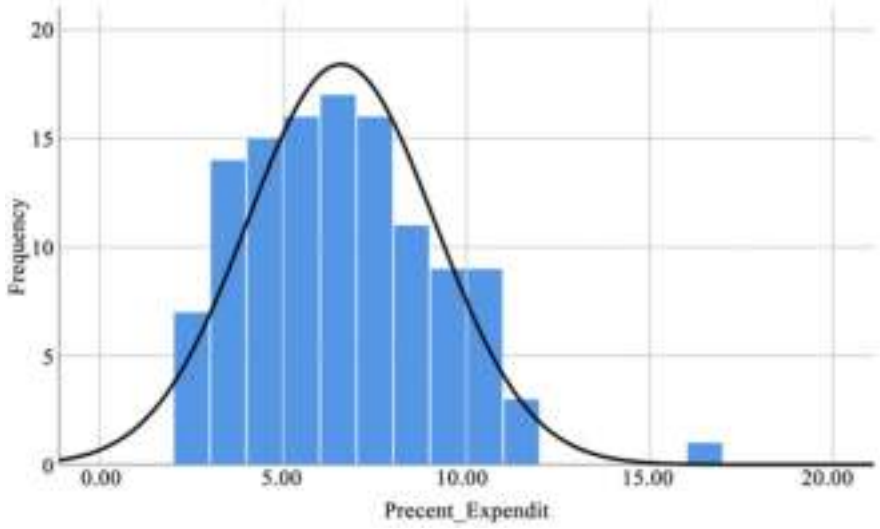

Figure 7. Histogram of the distribution of percentage of GDP on healthcare.

Table 4. COVID_CASE_FATALITY = (COVID death count/COVID Cases) × 100,000.

Region	No. Countries	Mean	Std. Deviation	Std. Error
E. Asia-1	7	1953.2808	1723.40851	651.38719
C.l Asia-2	7	1199.9530	402.63886	152.18318
S. Asia-3	4	1388.4963	562.42803	281.21402
HIAP-4	4	1557.8282	1311.68261	655.84130
C.Euro-5	12	1907.2677	781.13785	225.49507
E.Euro-6	7	1290.2332	426.50378	161.20328
W.Euro7	20	2021.0526	927.78022	207.45796
S.L.A -8	2	2754.8536	51.00766	36.06786
Caribb-9	4	2179.4770	427.92517	213.96259
A. L.A-10	3	5626.3620	1684.96910	972.81736
C. Lat-11	10	3009.9215	2415.83335	763.95358
Mena-12	20	2195.6513	1917.32557	428.72703
Cessa-13	8	1436.8359	589.94954	208.57866
Wssa-14	8	1319.0813	683.02871	241.48712
Sssa-15	3	2173.6344	969.30033	559.62581
Total	119	2015.8405	1466.14430	134.40123

Table 5. CKD_CASE_FATALITY (2017).

Code	Region (n)	Mean	Std. Deviation	Std. Error
1	E. Asia 7	190.6910	83.79775	31.67257
2	C. Asia 7	106.2960	19.44093	7.34798
3	S. Asia 4	205.0174	43.44818	21.72409
4	HIAP 4	137.6728	42.52006	21.26003
5	C. Eur. 12	134.3351	34.96087	10.09233
6	E. Eur. 7	58.2134	26.27258	9.93010
7	W. Eur.20	198.4845	67.26280	15.04042
8	SLA. 2	275.6629	9.04869	6.39839
9	Caribb. 4	259.9511	65.95979	32.97990
10	And. Lat.3	383.4160	132.26184	76.36141
11	CLA. 10	306.2912	159.77184	50.52429
12	MENA 20	149.4680	66.97740	14.97660
13	CESSA 8	177.1631	16.48127	5.82701
14	WSSA 8	167.5075	37.65762	13.31398
15	SSSA 3	161.9803	21.72116	12.54072
Total	119	180.4692	95.11304	8.71900

Table 6. Percent of GDP spending on healthcare (2018).

Code	Region(n)	Mean	Std. Deviation
1	E. Asia 7	4.9057	2.14183
2	C. Asia 7	6.0900	2.42986
3	S. Asia 4	3.7300	1.49457
4	HIAP 4	8.0625	2.77191
5	C. Euro.12	7.2317	1.17092
6	E. Euro. 7	6.3514	0.77802
7	W. Euro 20	9.8350	2.37384
8	SLA 2	9.3800	0.33941
9	Caribb.4	4.3950	1.76847
10	ALA 3	6.5600	1.46738
11	CLA 10	6.7430	1.58911
12	MENA19	5.7611	1.91436
13	CESSA 7	5.0629	1.88558
14	WSSA 8	4.0038	0.60512
15	SSSA 3	6.9867	1.96128
Total	117	6.6104	2.54257

Table 7. Diabetes prevalence worldwide by region (2019).

Code	Region	Mean	Std. Deviation	Std. Error
E. Asia	6	8.9833	4.45260	1.81777
C. Asia	7	6.1143	0.20354	0.07693
S. Asia	4	11.6750	5.63996	2.81998
HAIP	4	5.9000	0.66833	0.33417
C. Eur	12	7.4917	1.45943	0.42130
E. Eur	7	5.8286	2.27502	0.85988
W. Eur	20	6.3700	2.22429	0.49737
SLA	2	7.2500	1.90919	1.35000
Carrib.	4	10.7500	3.09031	1.54515
ALA	3	6.3000	0.70000	0.40415
CLA	10	9.0800	1.96344	0.62090
MENA	20	11.9650	3.95012	0.88327
CESSA	8	5.5750	5.03920	1.78163
WSSA	8	2.9500	1.25584	0.44401
SSSA	3	6.3333	5.67656	3.27736
Total	118	7.7864	3.89396	0.35847

The lowest diabetes prevalence is in WSSA (2.95), while the highest is in MENA region (11.965).

3.2. Detection of Regional Clustering

In this section we shall quantify the degree of clustering for any continuous variable.

We assume that we have k regions and that the individual units within each region are the countries as indicated in Table 1. To articulate this concept, we first assume that the quantity of interest measured in the j^{th} country within the i^{th} *region,* y_{ij} is modelled as

$$y_{ij} = \mu + \tau_i + e_{ij} \tag{3.1}$$

where;

τ_i = random regional effect and represents the collective effects of all regional level unmeasured covariates.

e_{ij} = the country within region deviation from the overall mean of the i^{th} *region*

μ is the grand mean of all measurements in the population. It is assumed that the region effects $\{\tau_i\}$ are normally and identically distributed with mean 0 and variance σ_τ^2, the errors $\{e_{ij}\}$ are normally and identically distributed with mean 0 and variance σ_ϵ^2, and the $\{\tau_i\}$ and $\{e_{ij}\}$ are independent. For this model the ICCC, which may be interpreted as the correlation ρ between any two countries belonging to the same region, is defined as:

$$\rho = \frac{\sigma_\tau^2}{\sigma_\tau^2 + \sigma_\epsilon^2} \tag{3.2}$$

It is seen by definition that the ICCC is defined as non-negative in this model, a plausible assumption for the application of interest here. We also note that the variance components σ_τ^2, and σ_ϵ^2 can be estimated from the one-way ANOVA mean squares (see; Shoukri, page 47) [27] given in expectation by

$$E(\text{MSB}) = \sigma_\epsilon^2 + n_0\sigma_\tau^2 \tag{3.3}$$

$$E(\text{MSW}) = \sigma_\epsilon^2 \tag{3.4}$$

The ANOVA estimator of ρ is then given by

$$\hat{\rho}_0 = \frac{\text{MSB} - \text{MSW}}{\text{MSB} + (n_0 - 1)\text{MSW}} \tag{3.5}$$

where MSB and MSW are, obtained from the usual ANOVA table, with corresponding sums of squares

$$\text{SSB} = \sum_{i=1}^{k} n_i (\bar{y}_i - \bar{y})^2$$

$$\text{SSW} = \sum_{i=1}^{k} \sum_{j=1}^{n_i} (y_{ij} - \bar{y}_i)^2,$$

where

$$N = \sum_{i=1}^{k} n_i \quad \text{and} \quad n_0 = \frac{1}{k-1}\left[N - \sum_{i=1}^{k} n_i^2 / N\right].$$

$$\text{MSB} = \text{SSB}/(k-1), \text{ and } \text{MSW} = \text{SSW}/(N-k).$$

Using the delta method, and to the first order of approximation, the variance of $\hat{\rho}_0$ [27] is given by:

$$\operatorname{var}\left(\hat{\rho}_0\right)=\frac{2\left(1-\rho\right)^2\left(1+\left(n_0-1\right)\rho\right)^2}{n_0^2\left(k-1\right)\left(1-\frac{k}{N}\right)} \tag{3.6}$$

In our data, $k = 15$, $N = 120$, and $n_0 = 7.47$.

We now start screening for the potential risk factors using bivariate correlation analysis. **Table 8** provides the Pearson's correlations and the associated p-values. Significant factors (p-value < 0.05) are candidate for entry into the multivariate model. **Table 9** accounts for the regional clustering effect. The clustering parameter (Intra Class Correlation Coefficient) affects the standard errors by a quantity known as the "*Design Effect*" or DEFF. The effect of the clustering is that the standard errors must be multiplied by the corresponding DEFF when we desire to construct confidence limits on the mean of the variable of interest.

It should be noted that the general definition of the "Design Effect" or DEFF is $\left(1+\left(n_0-1\right)\rho\right)^{1/2}$, that is when reporting the standard errors of the means in **Tables 3-6** the standard error reported in these tables must be multiplied by the corresponding DEFF. We note that the between regions variations is quite significant for all the parameters in **Table 8**, except for the COVID-19 cases where the ICCC is quite low for that parameter. This means that there is a large amount of variability between countries within regions with respect to the COVID-19 cases.

Table 8. Bivariate correlations between variables in the data set.

Variable 1	Variable 2	Pearson's correlation	p-value
Log-COVID Case Fatality	Log-CKD Case Fatality (2017)	0.347	0.00001
Log-COVID Case Fatality	Log-Density (2019)	0.567	0.00001
Log-COVID Case Fatality	% of GDP spent on Healthcare (2018)	0.203	0.028
Log-COVID Case Fatality			
Log-COVID Case Fatality	Prevalence of Diabetes (2019)	0.002	0.979
COVID-19 cases	Log (pop. Density)	0.429	0.00001
COVID-19 cases	CKD count	0.508	0.00001
COVID-19 cases	% spending on healthcare	0.331	0.00001

Table 9. Regional clustering of variables of interest. DEFF = $(1 + 6.47 * \text{ICCC})^{1/2}$.

Variable	ICCC	SE	DEFF
1. COVID-19 Cases	0.022	0.060	1.14*
2. COVID Case Fatality	0.190	0.098	1.47
3. CKD Case fatality (2017)	0.461	0.116	2
4. % of GDP spent on Healthcare (2018)	0.480	0.120	1.91
5. Diabetes (2019)	0.410	0.116	2.03

*No regional clustering.

In the next section we develop multiple regression models relating the target outcome variables; COVID-19 cases, and COVID-19 case fatality using the significant predictors.

4. Multivariate Regression Analyses

4.1. Negative Binomial Regression Model (NBRM)

From Table 9, the outcome variable, the number of COVID-19 cases does not exhibit regional clustering. That is one can safely ignore the region as a predictor. However, this variable (which is an integer variable) exhibits large amount of over dispersion, (the variance is much larger than the mean). The commonly used regression models of counts in the presence of over dispersion are constructed using the Negative Binomial Regression Model (NBRM) [28]. For this model we selected number of COVID-19 case as the dependent variable, and the three risk factors that are, in the univariate screening step for potential predictors, significantly correlated with it as shown in Table 8. It is interesting to see that in the NBRM multiple regression model the three covariates are jointly significantly associated the number of COVID-19 cases. The results are shown in Table 10. For this type of models, the "Scaled Deviance" is taken as a measure of goodness of fit of the NBRM. An optimal model should have a scaled deviance very close to unity. The scaled deviance for our model is 1.417. In our opinion this value is not substantially higher than unity, and the results based on the NBRM are quite useful. As the brilliant statistician ***George Box*** once said: *All models are wrong, some of them are useful.*

4.2. Linear Mixed Effects Modeling of COVID-19 Case Fatality

Before we proceed with the data analysis of COVID-19 Case fatality we should emphasize the hierarchical structure of the data. Basically, the data have two levels; the higher level consists of regions and the lower level consists of countries nested within regions. The results of the fitted model are summarized in Table 11 and Table 12. In Table 11 we have the results of the F-statistic to test the significance of all effects. In Table 12, we have the estimated regression coefficients.

Table 10. Results of the negative binomial regression of the aggregate number of COVID-19 cases.

Parameter	Regression coefficient estimate	Standard Error	p-value
Intercept	7.844	0.5027	0.00001
CKD-Count-2017	3.53E−8	9.9415E−9	0.00001
Percent spending on healthcare	0.198	0.0360	0.00001
Log-Population density	0.253	0.0505	0.00001

Dependent variable: COVID cases. Model: (Intercept), CKD_COUNT_2017, Percent-expenditure on healthcare.

Table 11. Dependent variable: LOG_COVID_FATALITY. The type III sums of squares.

Source		Type III Sum of Squares	df	Mean Square	F	p-value.
Intercept	Hypothesis	36.342	1	36.342	127.026	0.000
	Error	31.073	108.611	0.286		
Region	Hypothesis	11.433	14	0.817	2.952	0.001
	Error	27.669	100	0.277		
Log-population density	Hypothesis	17.269	1	17.269	62.411	0.000
	Error	27.669	100	0.277		
GDP_PER_CAPITA	Hypothesis	1.821	1	1.821	6.582	0.012
	Error	27.669	100	0.277		
CKD_CASE_FATALITY	Hypothesis	1.136	1	1.136	4.106	0.045
	Error	27.669	100	0.277		

Table 12. Dependent variable: LOG_COVID_FATALITY.

Parameter	B	Std. Error	t	p-value
Intercept	4.203	0.411	10.226	0.000
[Region = An.Latin]	1.026	0.394	2.603	0.011
[Region = C.Asia]	0.155	0.276	0.562	0.575
[Region = C.Europe]	0.899	0.246	3.655	0.000
[Region = C.Latin]	0.553	0.273	2.024	0.046
[Region = Caribean]	1.044	0.335	3.114	0.002
[Region = CESSA]	−0.048	0.264	−0.181	0.856
[Region = E.Asia]	0.143	0.274	0.522	0.603
[Region = E.Europe]	0.321	0.286	1.125	0.263
[Region = HIAP]	0.267	0.370	0.721	0.473
[Region = MENA]	0.435	0.226	1.923	0.057
[Region = S.Asia]	−0.111	0.324	−0.342	0.733
[Region = S.Latin]	0.258	0.573	0.450	0.654
[Region = SSA]	0.339	0.358	0.948	0.345
[Region = W.Europe]	0.994	0.302	3.292	0.001
[Region = WSSA]	0[a]			
Log_density	0.212	0.027	7.900	0.000
GDP_PER_CAPITA	−1.001E−5	3.904E−6	−2.565	0.012
CKD_CASE_FATALITY	0.001	0.001	2.026	0.045

All risk factors we included in the model are deemed significant, except diabetes which was not significant neither in the univariate screening stage nor in the multiple regression model. In Note that in Table 12, the region WSSA was

selected as the reference category when the computer program created dummy variables for the 15 regions.

Now the model-based prediction for the random effects model the correlation between observed and predicted outcome is R = 0.765, which is quite high. Moreover, we found no association between the model-based predictions and the residuals indicating that no model assumptions have been violated.

5. Conclusions

The data that we analyzed are two-levels or hierarchical. We used R software [29] and the commercial software SPSS version 25 [30] for the data analyses. The univariate analyses showed that there is strong regional clustering of CKD, population density and percentage of GDP spending on health care. But the variability between regions in the COVID-19 cases was significantly lower than the variability with regions.

The analyses in this paper targeted two important outcome variables. The first is the aggregate number of COVID-19 cases. The NBRM found that CKD count, population density, and the percentage of GDP spent on healthcare were the most significant risk factors associated with this outcome. The second outcome variable is the COVID-19 case-fatality. The predictive analytic procedure showed that regional effect, log-population density, per-capita GDP, and CKD case fatality are the most important predictors of this outcome. The analysis showed that neither diabetes, nor the percentage of GDP spending on healthcare is significant predictors of COVID-19 case fatality.

Since the analyses in this paper are ecological, the conclusions should not be applied at the within region country level. By contrast, there may be several regional area-level environmental factors that we were not able to explore that may explain the correlation we see between regional level prevalence of health-related risk factors and case fatality of COVID-19.

Since these data did not include within country individual subjects' information on the health status of the case patients, conclusions cannot be drawn about within countries individual risk factors. However, this analysis suggests that there are important regional-level variations in COVID-19 infections that are correlated with variations in other chronic conditions, suggesting that the factors that influence health disparities may also be operating on the distribution of COVID-19.

Furthermore, there presently are limitations with overall infection count data. The analyses were conducted with data only in the first wave of the COVID-19 pandemic in the world. This fact may explain the associations observed with both CKD and population density, rather than indicators of who is being infected, and these data continue to reflect those countries with the most severe outcomes after infection. Finally, the implementation of restrictions on travel and in-person activities may also impact overall rates of COVID-19 during this first wave. It should also be noted that several new strains of the virus have

emerged near the end of 2020. Therefore, new and more comprehensive data on the new variant of the COVID virus through the winter of 2021 may clarify the association with other comorbid conditions.

In summary, these analyses found that countries within the fifteen regions estimated CKD case fatality and population density were significant ecologic predictors of case fatality of COVID-19.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Association of Social Distancing, Population Density, and Temperature With the Instantaneous Reproduction Number of SARS-CoV-2 in Counties Across the United States

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Abstract

IMPORTANCE Local variation in the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) across the United States has not been well studied.

OBJECTIVE To examine the association of county-level factors with variation in the SARS-CoV-2 reproduction number over time.

DESIGN, SETTING, AND PARTICIPANTS This cohort study included 211 counties, representing state capitals and cities with at least 100 000 residents and including 178 892 208 US residents, in 46 states and the District of Columbia between February 25, 2020, and April 23, 2020.

EXPOSURES Social distancing, measured by percentage change in visits to nonessential businesses; population density; and daily wet-bulb temperatures.

MAIN OUTCOMES AND MEASURES Instantaneous reproduction number (R_t), or cases generated by each incident case at a given time, estimated from daily case incidence data.

RESULTS The 211 counties contained 178 892 208 of 326 289 971 US residents (54.8%). Median (interquartile range) population density was 1022.7 (471.2-1846.0) people per square mile. The mean (SD) peak reduction in visits to nonessential business between April 6 and April 19, as the country was sheltering in place, was 68.7% (7.9%). Median (interquartile range) daily wet-bulb temperatures were 7.5 (3.8-12.8) °C. Median (interquartile range) case incidence and fatality rates per 100 000 people were approximately 10 times higher for the top decile of densely populated counties (1185.2 [313.2-1891.2] cases; 43.7 [10.4-106.7] deaths) than for counties in the lowest density quartile (121.4 [87.8-175.4] cases; 4.2 [1.9-8.0] deaths). Mean (SD) R_t in the first 2 weeks was 5.7 (2.5) in the top decile compared with 3.1 (1.2) in the lowest quartile. In multivariable analysis, a 50% decrease in visits to nonessential businesses was associated with a 45% decrease in R_t (95% CI, 43%-49%). From a relative R_t at 0 °C of 2.13 (95% CI, 1.89-2.40), relative R_t decreased to a minimum as temperatures warmed to 11 °C, increased between 11 and 20 °C (1.61; 95% CI, 1.42-1.84) and then declined again at temperatures greater than 20 °C. With a 70% reduction in visits to nonessential business, 202 counties (95.7%) were estimated to fall below a threshold R_t of 1.0, including 17 of 21 counties (81.0%) in the top density decile and 52 of 53 counties (98.1%) in the lowest density quartile.[2]

CONCLUSIONS AND RELEVANCE In this cohort study, social distancing, lower population density, and temperate weather were associated with a decreased R_t for SARS-CoV-2 in counties across the United States. These associations could inform selective public policy planning in communities during the coronavirus disease 2019 pandemic.

Key Points

Question How is the instantaneous reproduction number of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) associated with social distancing, wet-bulb temperature, and population density in counties across the United States?

Findings In this cohort study of 211 counties in 46 states, social distancing, temperate weather, and lower population density were associated with a decrease in the instantaneous reproduction number of SARS-CoV-2. Of these county-specific factors, social distancing appeared to have the most substantial association with a reduction in SARS-CoV-2 transmission.

Meaning In this study, the instantaneous reproduction number of SARS-CoV-2 varied substantially among counties; the associations between the reproduction number and county-specific factors could inform policies to reduce SARS-CoV-2 transmission in selective and heterogeneous communities.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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Introduction

Coronavirus disease 2019 (COVID-19) is the result of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus has caused a pandemic resulting in more than 3.2 million cases of COVID-19 by May 1, 2020, with more than 236 000 deaths worldwide. By the same date, there were more than 1 million individuals with COVID-19 in the United States, resulting in more than 64 000 deaths. The rapid evolution of this pandemic led to the widespread implementation of social distancing measures across most of the United States and the world.

The transmissibility of SARS-CoV-2, like other viral pathogens, is estimated by the reproduction number (R). An infectious pathogen's R value represents the number of people that will be infected by an individual who has the infection. An R value that exceeds 1 will result in increasing numbers of incident cases as each individual with the infection transmits it to more than 1 other individual. When the R value is below 1, the transmission of that pathogen will eventually cease as each patient will transmit infection to less than 1 person. Therefore, the R value is an important measure to estimate when attempting to predict the evolution of an outbreak. It is often assumed that R is constant for each pathogen; however, R most certainly varies by location and by time, which is referred to as the instantaneous R (R_t).[1-3] At the individual level, variation in R_t is likely dependent on being in environments where exposure risk is high or of intense duration, such as among high-exposure workers in health care or mass transit settings or for families in densely crowded living conditions. At the community level, variation in R_t may also include population density (as a proxy for increased likelihood of crowded conditions), temperature and/or humidity (given their effects on viral propagation), policies such as social distancing, and the number of susceptible individuals.

Models that rely on fixed assumptions for R_t are unlikely to capture local heterogeneity in transmission. Our objective was to examine how time-varying changes in social distancing and weather within counties of different population densities might be associated with changing R_t values across counties in the United States. Understanding how these time-varying factors might influence the R_t of SARS-CoV-2 could allow policy makers to implement targeted interventions to decrease R_t in heterogeneous communities.

Methods

Using publicly deidentified data, this study was determined to be exempt from institutional review board review[4] and informed consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.[5]

Setting and Participants

We selected 211 counties, representing 178 892 208 of 326 289 971 US residents (54.8%), based on the following characteristics: had at least 1 case of COVID-19 as of February 25, 2020, and either contained at least 1 city with population exceeding 100 000 residents or the state capital. For states with no counties containing a city with 100 000 persons, the most populated county in that state was selected. We excluded counties with average daily case rates of less than 5 and counties with fewer than 3 days with daily case rates of more than 5 during the analysis period of February 25 to April 23, 2020. We considered time-0 for each county to be the date on which they achieved the minimum threshold of disease activity. A total of 211 counties, representing 46 states and the District of Columbia, met these criteria.

Outcome

The outcome was the estimated R_t of SARS-CoV-2 in each county. Daily incident case counts of COVID-19 aggregated at the county level were obtained from the *New York Times*.[6]

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Exposures

There were 3 a priori exposure variables: social distancing practice, population density, and daily mean wet-bulb temperatures. Social distancing was measured using a data set of daily cellular telephone movement, provided by Unacast, that allows comparison of the association of social distancing policies with individuals' movement within a county.[7,8] Based on an a priori assumption and confirmed by preliminary analyses that included cellular telephone measurement of overall distance traveled, we used a social distancing variable that measured percentage change in visits to nonessential businesses (eg, restaurants, hair salons) within each county compared with visits in a 4-week baseline period between February 10 and March 8, 2020. We used a rolling average of the percentage of visits 3 to 14 days before time-0, based on the lag observed between change in social distancing and mean R_t estimates across the counties (eFigure 1 in the Supplement) and on an incubation period of at least 3 days.[9]

Population density of each county was obtained from US Census data and is expressed as number of people per square mile. Log transformation was performed to achieve a normal distribution because of substantial skewedness in density for the largest cities.

It has been demonstrated that humidity and temperature both play a role in the seasonality of influenza; viral transmission is most efficient at lower humidity and temperature. It is proposed that colder, drier air damages respiratory mucosa and thickens secretions, impairing the protective capacity of mucociliary clearance, and that higher humidity physically limits the distance respiratory droplets can travel.[10,11] For this reason, the primary weather variable we used was wet-bulb temperature, a metric that captures the complex thermodynamic relationship of temperature and humidity, has been shown to predict human health events with more precision than temperature and humidity separately, and avoids the associated problem of collinearity.[12,13] Wet-bulb temperatures were obtained from the National Oceanic and Atmospheric Administration Local Climatological Data.

Covariates

County-level covariates that may confound the association between the exposures of interest and R_t were considered and included demographic factors (eg, age distribution, insurance status, and socioeconomic status) and health-related factors associated with COVID-19 severity (eg, proportion of individuals with hypertension, obesity, or diabetes and proportion of individuals who smoke).[14] Demographic and health characteristics were abstracted from the US Census, American Community Survey, Behavioral Risk Factor Surveillance System, Esri Business Analyst, and Multi-Resolution Land Characteristics Consortium.[15-18]

From 70 covariates, we examined the correlation between each pair of factors and calculated the variance inflation factor to quantify multicollinearity among variables (eFigure 2 in the Supplement). Among highly correlated variables, we chose covariates based on their potential association with viral transmission and/or the probability of an individual with infection becoming symptomatic and obtaining a diagnostic test. The final covariates included proportion of residents older than 65 years, with incomes less than 200% of the poverty level, and with diabetes. Variables for obesity, smoking, and uninsured population were removed because of collinearity with other variables.

Statistical Analysis

Our analysis followed a 2-step procedure. First, we calculated the R_t for SARS-CoV-2 using the method of Cori et al[1] with a moving average window of 3 days. This method has been applied in the dynamic estimation of R_t from Wuhan, China.[19] The generation time of SARS-CoV-2 was assumed to follow a γ distribution, with mean (SD) of 7.5 (3.4) days according to a previous epidemiological survey of the first 425 cases in Wuhan, China.[9] In the early days of a county's outbreak, when the ratio of cases to tests was unstable, kernel smoothing with a box kernel and bandwidth of 7 days was performed to account for the likelihood that cases from prior days would accumulate when testing capacity increased.[20,21] We stopped smoothing 1 day after the county's ratio of daily cases to tests

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first fell in the interval of 5% to 90% or after March 20, 2020, whichever came first, to avoid overprocessing the data.

Next, we fit a hierarchical linear mixed-effects model with random intercepts for each county and metropolitan area to evaluate the association between exposures and R_t after a log transformation, adjusting for covariates. Population density was standardized after log transformation because of the highly skewed distribution. Temperature associations were estimated using a distributed lag nonlinear model, which considers bidimensional exposure-lag response associations between wet-bulb temperature and log(R_t).[22-24] We considered a lag period of 4 days to 14 days before case identification to reflect the incubation period of SARS-CoV-2 and to reduce bias introduced by daily weather affecting an individual's decision to seek a test. The final cross-basis term included natural cubic splines defined by 3 internal knots at the 10th, 75th, and 90th percentile of temperature ranges observed during the period, corresponding to 1 °C, 13 °C, and 19 °C, and 2 knots in the lag dimension at 7 and 11 days. The number and placement of spline knots were based on an a priori assumption of a relatively simple association between temperature and SARS-CoV-2 transmission and on minimization of the Akaike information criterion. The temperature knots permitted flexibility in the model nonlinearity at higher and lower temperatures, within the moderate range used in this study.[25] We included an interaction term between population density and temperature, assuming that temperatures would influence transmissibility differently in densely populated counties.[26] The relative change in R_t was expressed as the cumulative exposure response relative to 11 °C. Interactions between population density and social distancing were included in the linear mixed-effects model, given the hypothesis that the association of social distancing with the R_t might be greater in highly dense areas. We also controlled for potential time effect using a cubic polynomial of days in outbreak. Statistical significance of the associations was determined using the maximum likelihood ratio test at the nominal level of $P < .05$. All tests were 2-tailed.

We ran 3 sensitivity analyses. First, the model was re-estimated every 2 weeks (a total of 3 times) during a period of 1 month, checking for stability in estimates of associations for primary covariates. Second, the model fit was evaluated by calculating in-sample R^2 in a randomly selected 70% of counties over 100 replicates. Finally, to address concerns regarding potential bias owing to the exclusion of counties with later outbreaks or with less overall population density, we relaxed our inclusion criteria to permit counties with active outbreaks and a total population of at least 100 000 residents (as opposed to having cities with at least 100 000 residents), and we re-estimated the associations of social distancing and wet-bulb temperatures with R_t during the study period. Given concerns regarding limited representation of temperatures at the upper and lower ranges across counties of different population density, we did not include interaction terms between population density and temperature. Analyses were performed with R version 3.6.0 (R Project for Statistical Computing) using the EpiEstim and dlnm packages.[27]

Results

Geographic locations and characteristics of the 211 counties are demonstrated in **Figure 1** and **Table 1**. The 211 counties contained 178 892 208 of 326 289 971 US residents (54.8%). County median (interquartile range [IQR]) population density was 1022.7 (471.2-1846.0) people per square mile, with skewing of the top decile of 21 counties to a median (IQR) of 8916.0 (5381.1-14 475.6) people per square mile. The mean (SD) reduction in visits by people to nonessential business by mid-April was 68.7% (7.9%). Median (IQR) daily wet-bulb temperatures were 7.5 (3.8-12.8) °C. The 21 counties in the top decile for population density had the highest median (IQR) incident case and fatality rate per 100 000 people (1185.2 [313.2-1891.2] cases; 43.7 [10.4-106.7]), nearly 10 times the estimates in the lowest quartile (121.4 [87.8-175.4] cases; 4.2 (1.9-8.0) deaths). Mean (SD) R in the first 2 weeks was 5.7 (2.5) in the top decile compared with 3.1 (1.2) in the lowest quartile. The mean (SD) change in visits to nonessential businesses from April 6 to April 19 was higher among counties in the top decile (−77.9% [7.9%]) compared with those in the lowest quartile (−66.3% [7.8%]). The top decile of

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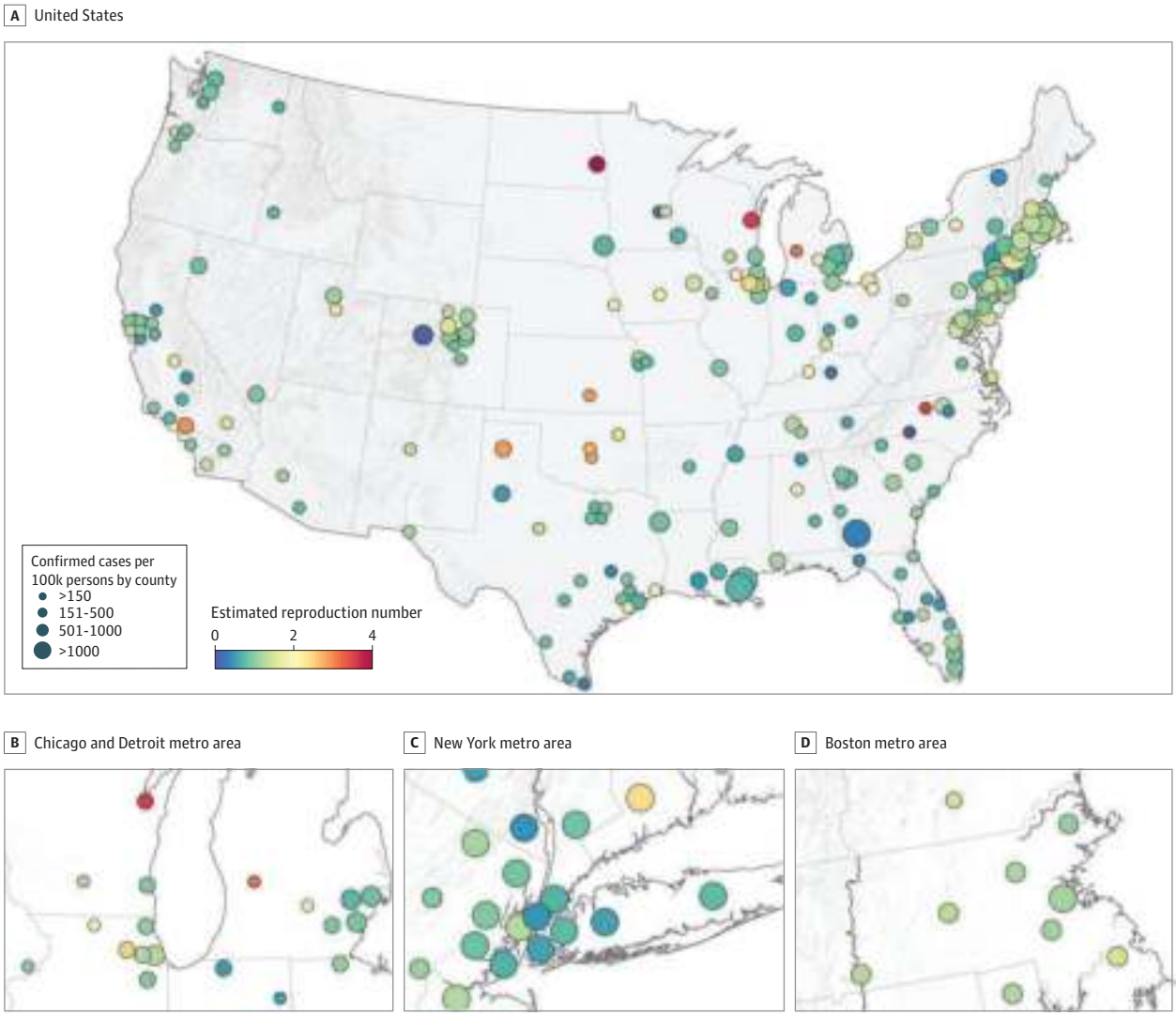
counties also experienced colder median (IQR) temperatures during the analysis period compared with the counties in the lowest quartile (5.9 [3.4-8.4] °C vs 7.9 [3.1-12.7] °C).

We estimated R_t over a total of 6588 county-days for the 211 counties; 17 outlier county days were removed because of an extremely low estimate of R_t at low case thresholds (ie, $R_t < 0.05$). The estimated R_t by county varied greatly, but it tended to be highest earlier the epidemic, reaching a peak R_t of 7.8 before declining later in the period (eFigure 1 in the Supplement). Adjusting for county-level covariates, social distancing, population density, and temperature were associated with R_t (**Table 2**). The estimated R_t in the context of a 50% decrease in visits to nonessential businesses was 54% (95% CI, 51%-57%; $P < .001$) of the R_t in the setting of normal visit intensity, corresponding to a 46% decrease in the overall R_t. Compared with counties in the bottom quartile of population density, the 21 counties in the top decile of density had a 15% increase (95% CI, 9%-22%; $P < .001$) in relative R_t.

The nonlinear association of lagged temperature between 4 and 14 days is reported in Table 2 and **Figure 2**. Compared with the minimum estimated R_t at 11 °C, relative R_t increased across the coldest temperatures to a relative R_t at 0 °C of 2.13 (95% CI, 1.89-2.40). A smaller peak of the relative

Figure 1. Location and Estimated Instantaneous Reproduction Number of Severe Acute Respiratory Syndrome Coronavirus 2 as of April 26, 2020, in 211 Counties in the United States



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R_t to 1.61 (95% CI, 1.41-1.84) was estimated at 20 °C, before declining again at higher temperatures. These findings were robust to the addition of 183 less densely populated counties with at least 100 000 residents (eTable and eFigure 3 in the Supplement).

The standardized association of social distancing, population density, and temperature on R_t, appears in **Figure 3**. Assuming social distancing of 35% (ie, halfway between estimates during the US shelter-in-place phase and normal activity), 2 counties (0.9%) were estimated to have a R_t less than 1.0 at 2 °C, and 114 counties (54.0%) were estimated to have a R_t of less than 1.0 at 11 °C. When visits to nonessential businesses were reduced to the national mean of 70%, the number of counties estimated to have R_t less than 1.0 increased to 63 (29.9%) and 202 (95.7%) at 2 °C and 11 °C, respectively. At this 70% reduction in visits to nonessential businesses, 28 and 52 of 53 counties

Table 1. Population Characteristics in an Analysis of Instantaneous R for Severe Acute Respiratory Syndrome Coronavirus 2 by Population Density for 211 Counties Across the United States

Characteristic[a]	Population density					
	<25th Percentile (n = 53)	25th-50th Percentile (n = 53)	50th-75th Percentile (n = 53)	75th-90th Percentile (n = 31)	>90th Percentile (n = 21)	All (N = 211)
Population density, median (IQR), people per square mile	298.4 (164.2-376.1)	662.7 (539.1-826.8)	1368.7 (1211.4-1584.9)	2395.4 (2151.2-2860.6)	8916.0 (5381.8-14 475.6)	1022.7 (471.2-1846.0)
Hypertension, mean (SD), % of population	29.4 (5.3)	31.6 (3.9)	31.2 (3.1)	31.5 (3.8)	29.3 (3.5)	30.7 (4.2)
Diabetes, mean (SD), % of population	9.2 (2.3)	10.1 (1.8)	10.0 (1.3)	10.3 (1.5)	10.1 (1.5)	9.9 (1.8)
Regular smoking, mean (SD), % of population[b]	16.5 (2.4)	16.9 (2.3)	16.3 (2.6)	16.6 (2.7)	15.9 (2.5)	16.5 (2.5)
BMI >30, mean (SD), % of population	29.6 (4.5)	30.9 (3.5)	30.2 (3.5)	31.1 (3.8)	28.2 (4.1)	30.1 (3.9)
Age, median (IQR), % of population						
<18 y	23.9 (22.1-25.7)	23.4 (21.6-24.8)	22.3 (21.4-23.8)	23.1 (22.1-24.1)	20.9 (18.3-22.2)	22.7 (21.4-24.5)
18-34 y	24.5 (23.1-26.4)	23.7 (22.0-26.1)	23.3 (21.3-25.0)	24.4 (22.7-25.9)	28.3 (23.8-30.6)	24.1 (22.3-26.2)
35-64 y	37.1 (35.5-38.6)	38.1 (36.5-39.8)	39.5 (38.1-41.0)	38.9 (37.6-40.3)	38.8 (37.1-40.6)	38.4 (36.9-40.1)
≥65 y	13.8 (11.9-14.8)	13.5 (12.6-15.2)	14.7 (12.8-16.2)	13.5 (11.8-14.7)	13.2 (11.9-14.8)	13.8 (12.4-15.4)
Low income, mean (SD), % of population[c]	33.2 (9.8)	31.5 (8.6)	27.0 (8.8)	30.4 (8.5)	31.2 (10.2)	30.6 (9.3)
Uninsured, mean (SD), % of population	9.6 (4.7)	9.5 (5.4)	8.2 (4.1)	9.4 (4.4)	8.5 (3.1)	9.1 (4.6)
Change in visits to nonessential businesses, mean (SD), %[d]						
February 24 to March 8	-2.4 (7.0)	-2.5 (6.1)	-3.0 (5.7)	-3.1 (6.1)	-2.8 (6.3)	-2.7 (6.3)
April 6 to April 19	-66.3 (7.8)	-65.3 (7.3)	-69.2 (6.8)	-71.3 (5.8)	-77.9 (5.2)	-68.7 (7.9)
Daily wet-bulb temperature, median (IQR), °C[e]	7.9 (3.1-12.7)	8.2 (4.1-14.8)	8.2 (4.2-14.5)	7.8 (3.9-13.7)	5.9 (3.4-8.4)	7.5 (3.8-12.8)
R in the first 2 weeks, mean (SD)	3.1 (1.2)	3.1 (1.1)	3.6 (1.1)	4.0 (1.6)	5.7 (2.5)	3.6 (1.6)
Cases per 100 000 people on April 26, median (IQR), No.	121.4 (87.8-175.4)	126.7 (79.3-180.3)	196.0 (73.1-530.4)	206.6 (110.5-483.2)	1185.2 (313.2-1891.2)	154.7 (87.9-350.6)
Deaths per 100 000 people on April 26, median (IQR), No.	4.2 (1.9-8.0)	4.2 (2.3-7.5)	5.6 (2.3-28.6)	8.9 (4.1-21.9)	43.7 (10.4-106.7)	5.8 (2.5-16.3)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; R, reproduction number.

[a] All characteristics were obtained from the American Community Survey (2018) except health data, which were obtained from the US Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System (2017); social distancing, which were obtained from Unacast (2020); and wet-bulb temperature, which were obtained from the National Oceanic and Atmospheric Administration (2020).

[b] Regular smoking was defined as adult respondents who reported smoking at least 100 cigarettes in their life and currently smoking at least some days.

[c] Low income was defined as incomes of less than 200% of the poverty level.

[d] Visits to nonessential businesses obtained from Unacast, calculated as the change from mean nonessential business visits during matching days of the week before March 9, 2020.

[e] Daily wet-bulb temperatures were calculated by averaging the hourly recordings from weather stations that contribute to the National Oceanic and Atmospheric Administration Local Climatological Data.

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(52.8% and 98.1%, respectively) in the lowest quartile of density achieved this threshold at 2 °C and 11 °C, respectively, compared with 0 and 17 of 21 counties (81.0%) in the top decile at the same temperatures.

No significant interactions were observed for population density and social distancing. Model estimates were stable over time. The overall R^2 of the mixed-effects model was 0.53 based on the covariate associations; the addition of random county and metropolitan area intercepts increased the R^2 to 0.64. Distribution of the in-sample R^2 in a randomly selected 70% of counties over 100 replicates revealed good model fit (eFigure 4 in the Supplement).

Discussion

In this analysis of 211 US counties, change in social distancing, population density, and wet-bulb daily temperature were associated with the rate of SARS-CoV-2 transmission within a county, as measured by estimated R_t. Our analysis indicates that of these 3 factors, implementation of social distancing has been the most significant in reducing transmission. In addition, the mitigating association of increased social distancing and moderate increases in wet-bulb daily temperature were most

Table 2. Ratios of R_t for Social Distancing and Population Density in 211 United States Counties Between February 25 and April 23, 2020

Variable	R_t ratio estimates with 95% CIs[a]			*P* value
Visits to nonessential businesses, compared with no change[b]	Reduce 25%	Reduce 50%	Reduce 75%	NA
	0.73 (0.71-0.75)	0.54 (0.51-0.57)	0.40 (0.36-0.43)	<.001
Population density, compared with 25th percentile[c]	50th percentile	75th percentile	90th percentile	NA
	1.05 (1.03-1.07)	1.09 (1.05-1.14)	1.15 (1.09-1.22)	<.001
Wet-bulb temperature	0 °C	5 °C	20 °C	NA
	2.13 (1.89-2.40)	1.38 (1.27- 1.50)	1.61 (1.41-1.84)	<.001

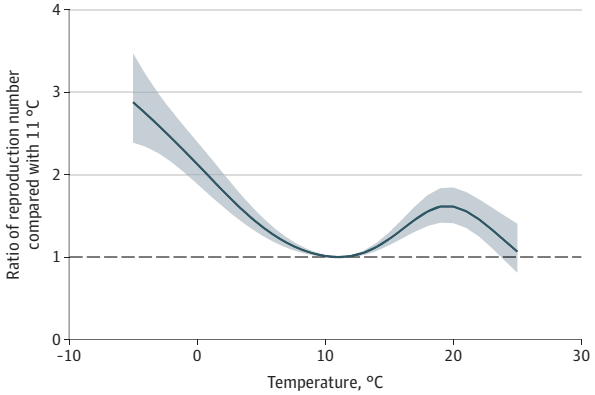
Abbreviations: NA, not applicable; R_t, instantaneous reproduction number.

[a] Estimates and variation obtained through mixed-effects linear models using a log transformed R_t, log population density, and distributed lag nonlinear models to estimate temperature effects. Postestimation was performed to convert variables into meaningful units of change. Ratios of R_t are compared with the reference groups, adjusting for proportion of residents older than 65 years, with incomes less than 200% of the poverty level, and with diabetes. Marginal R^2 was 0.50; conditional R^2 was 0.61.

[b] Visits to nonessential businesses obtained from Unacast. The referent value was the average visits to nonessential business before March 9, 2020.

[c] Population density was categorized at the 25th, 50th, 75th, and 90th percentiles, which corresponded to 471, 1022, 1846, and 3951 people per square mile.

Figure 2. Cumulative Lagged Temperature Dependence of the Instantaneous Reproduction Number of Severe Acute Respiratory Syndrome Coronavirus 2 in 211 US Counties



Cumulative exposure-response association between mean daily wet-bulb temperatures and instantaneous reproduction number using a lag period of 4 to 14 days before case identification. The line represents the estimated instantaneous reproduction number at each point along the temperature range compared with 11 °C. The shaded areas represent the 95% CIs. The wet-bulb temperature range for the counties included in the analysis was −9 °C to 25 °C.

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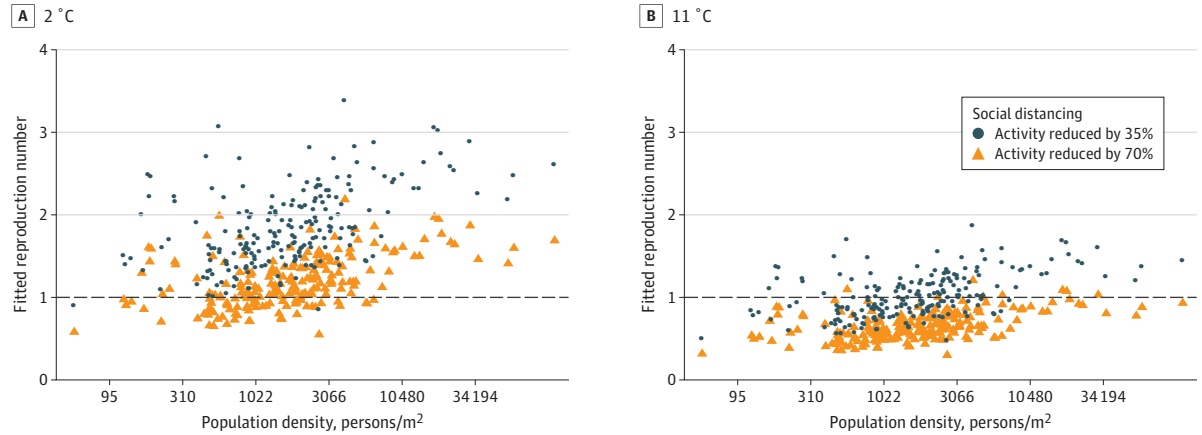
dramatic in counties with higher population density, which had high R_t values, consistent with higher R estimates from around the world.[28]

The underlying mechanism for the associations of social distancing and population density on the estimated R_t for SARS-CoV-2 is likely associated with increased droplet transmission and potentially airborne transmission when individuals are in closer proximity to each other.[29,30] However, the association of population density with COVID-19 outcomes may not be limited to transmission. The densest counties also had the highest number of deaths per 100 000 people. The association of more severe disease in higher density areas is hypothesized to be associated with the inoculum effect. The inoculum effect suggests that individuals exposed to a higher viral load at the time of infection will have more severe illness; this is supported by epidemiologic studies for other viruses,[31,32] in particular for SARS-CoV-1.[33-35] These data support the concept that during a pandemic, people living in highly dense counties are more likely to transmit SARS-CoV-2 and to be exposed to higher inoculums of SARS-CoV-2. This translates not only to more cases of COVID-19 but also to a higher case fatality rate. Data assessing the inoculum effect for SARS-CoV-2 are needed to confirm this hypothesis.

Our analysis, which used well-established methods developed to examine the association of temperature with human health, is also among the first to consider the association of temperature and humidity with SARS-CoV-2 transmission.[22,25] We found that combined temperature and humidity associations (proxied by wet-bulb temperatures) were nonlinear with the R_t and insufficient alone to mitigate R_t values below 1 in the absence of considerable social distancing. The nonlinear associations we observed were such that R_t ratios decreased, as hypothesized, when wet-bulb temperatures increased to 11 °C. Beyond 11 °C, there was a modest increase in relative R_t ratios before the ratios began declining again at higher temperatures.

The nonlinear associations we observed, particularly within the temperate range, are consistent with the inverse relationship of temperature and transmission in animal models for influenza and other coronaviruses.[10,36] Those studies also found that higher humidity was associated with increased viability and transmission of influenza through fomites, even as aerosol transmission was mitigated with warming temperatures. If SARS-CoV-2 has similar properties to influenza at higher humidity, it could explain our association of wet-bulb temperatures higher than 11 °C with a modest increase in R_t.

Figure 3. The Association of Social Distancing, Population Density, and Temperature With the Instantaneous Reproduction Number of Severe Acute Respiratory Syndrome Coronavirus 2 in 211 US Counties



Each point represents the fitted instantaneous reproduction number of an individual county at 2 °C (A) and 11 °C (B), adjusted for the proportion of residents older than 65 years, with incomes less than 200% of poverty level, and with diabetes. Different levels of social distancing are shown for a 35% reduction and 70% reduction in visits to nonessential businesses.

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Beyond the direct association of temperature and humidity with virus stability, viability, and propagation, it is also possible that changes in temperature and humidity alter human activity. For example, at higher temperatures people may be more likely to congregate in public locations, such as beaches and festivals. Therefore, an increase in R_t at higher temperatures could also be explained in part by a decrease in social distancing not measured by our social distancing variable. Regardless of the etiology, we remain cautious in interpreting the association of higher temperature and humidity with R_t beyond the temperate range we observed in this analysis. The coming months will allow for additional assessment of R_t during more prolonged periods of higher temperature and humidity. These additional observations will help to confirm or refute the attenuated associations at higher temperatures observed in this study.

To date, projections of COVID-19 outcomes have considered large areas, such as countries, provinces, and US states. These models have provided useful information to set expectations for deaths in the United States, to identify potential gaps in health services, such as intensive care unit beds and ventilators, and to guide initial wide-ranging social distancing recommendations from federal and state governments. Our county-level analysis has allowed us to better examine relevant contributions of social distancing, population density, and seasonal weather changes on a given county's R_t. This approach gives valuable information on risk of transmission to inform area-specific public policy decisions. It will be important to examine whether the introduction of these associations to models can accurately estimate the likelihood of viral transmission in the future, given that these factors will continue to change. To the degree that predictive modeling efforts are successful, it may demonstrate some validity of using this approach, which incorporates random effects for counties alongside seasonal changes to inform future epidemics.

Limitations

There are always limitations in observational studies. Generalizability remains a concern, particularly given our focus on larger counties. The 45% of US residents not captured in our analysis were residing in smaller, rural counties, and as such, our models are not applicable to these areas. It is reassuring that the inclusion of an additional 183 more geographically dispersed and less densely populated counties replicated our findings. Second, temperature associations we observed might have been confounded by time period in the analysis, given that outbreaks occurred during spring in parallel with changing weather. However, the addition of time to the model did not appreciably change our results. Third, increases in testing capacity might have biased the models by inflating the total cases reported within each county. It is possible that differences in diagnostic test availability could contribute to the variation detected by the random effects across counties. However, our estimate of R_t depended on the rate of change of cases, rather than on the absolute number of cases, and during the period in which this analysis was conducted, test positivity rates, a proxy for testing capacity, were flat.[37] Furthermore, we smoothed early outbreak case incidences to account for early limited access to diagnostic tests. We intentionally did not include testing capacity as a covariate, so as not to overfit the model (eg, controlling for a factor that was also associated with rising viral transmission itself). Fourth, as the random county and metropolitan area intercepts explained additional variation, there are likely other unmeasured county factors that we did not capture. Our proxy for social distancing used cellular telephone records and may not have captured all movement and gathering within a county; it requires further validation as a proxy for the distancing associations we were measuring. Other unmeasured factors might include commuter automobile traffic, public transportation usage, and domestic and international flights, which had decreased during the study period. It is clear that early local epidemics were seeded by international travel that contributed to early transmission in some locations.[38] Further investigation will be needed as communities reopen to examine the association of these additional time-varying factors with risk of SARS-CoV-2 transmission.

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Conclusions

The results of this study suggest that social distancing, population density, and daily weather may account for variation in the R_t for SARS-COv-2 across the United States. These results may guide policy decisions for managing this pandemic more selectively at the local level throughout the country.

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SUPPLEMENT.

eFigure 1. Average Instantaneous Reproduction Number (R_t) Superimposed on Scatter of Social Distancing Over Time Across 211 United States Counties
eFigure 2. Correlation Matrix of Potential Covariates
eFigure 3. Additional 183 US Counties Included in a Robustness Analysis of Weather and Social Distancing Effects on the Instantaneous Reproduction Number (R_t)
eFigure 4. In-Sample R^2 Obtained From 100 Replicates of Random 70% Samples of 211 United States Counties
eTable. Comparison of Characteristics Between Original 211 and Additional 183 United States Counties Included in a Robustness Analysis of Weather and Social Distancing Effects on the Instantaneous Reproduction Number (R_t)

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Prevalence of SARS-CoV-2 antibodies in a large nationwide sample of patients on dialysis in the USA: a cross-sectional study

Shuchi Anand, Maria Montez-Rath, Jialin Han, Julie Bozeman, Russell Kerschmann, Paul Beyer, Julie Parsonnet, Glenn M Chertow

Summary

Background Many patients receiving dialysis in the USA share the socioeconomic characteristics of underserved communities, and undergo routine monthly laboratory testing, facilitating a practical, unbiased, and repeatable assessment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seroprevalence.

Methods For this cross-sectional study, in partnership with a central laboratory that receives samples from approximately 1300 dialysis facilities across the USA, we tested the remainder plasma of 28 503 randomly selected adult patients receiving dialysis in July, 2020, using a spike protein receptor binding domain total antibody chemiluminescence assay (100% sensitivity, 99·8% specificity). We extracted data on age, sex, race and ethnicity, and residence and facility ZIP codes from the anonymised electronic health records, linking patient-level residence data with cumulative and daily cases and deaths per 100 000 population and with nasal swab test positivity rates. We standardised prevalence estimates according to the overall US dialysis and adult population, and present estimates for four prespecified strata (age, sex, region, and race and ethnicity).

Findings The sampled population had similar age, sex, and race and ethnicity distribution to the US dialysis population, with a higher proportion of older people, men, and people living in majority Black and Hispanic neighbourhoods than in the US adult population. Seroprevalence of SARS-CoV-2 was 8·0% (95% CI 7·7–8·4) in the sample, 8·3% (8·0–8·6) when standardised to the US dialysis population, and 9·3% (8·8–9·9) when standardised to the US adult population. When standardised to the US dialysis population, seroprevalence ranged from 3·5% (3·1–3·9) in the west to 27·2% (25·9–28·5) in the northeast. Comparing seroprevalent and case counts per 100 000 population, we found that 9·2% (8·7–9·8) of seropositive patients were diagnosed. When compared with other measures of SARS-CoV-2 spread, seroprevalence correlated best with deaths per 100 000 population (Spearman's ρ=0·77). Residents of non-Hispanic Black and Hispanic neighbourhoods experienced higher odds of seropositivity (odds ratio 3·9 [95% CI 3·4–4·6] and 2·3 [1·9–2·6], respectively) compared with residents of predominantly non-Hispanic white neighbourhoods. Residents of neighbourhoods in the highest population density quintile experienced increased odds of seropositivity (10·3 [8·7–12·2]) compared with residents of the lowest density quintile. County mobility restrictions that reduced workplace visits by at least 5% in early March, 2020, were associated with lower odds of seropositivity in July, 2020 (0·4 [0·3–0·5]) when compared with a reduction of less than 5%.

Interpretation During the first wave of the COVID-19 pandemic, fewer than 10% of the US adult population formed antibodies against SARS-CoV-2, and fewer than 10% of those with antibodies were diagnosed. Public health efforts to limit SARS-CoV-2 spread need to especially target racial and ethnic minority and densely populated communities.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus stimulates a rapid antibody response in people with symptomatic[1–5] and asymptomatic[2,6,7] infection. Seroprevalence of SARS-CoV-2 antibodies in a population thus serves as a reasonable measure of exposure and spread. Seroprevalence surveys in the USA, however, have been restricted to single hotspots[8–10] or under-represented high-risk or vulnerable populations.[9,11] Moreover, these studies face challenges to timely repetition and longitudinal follow-up, limiting their utility for surveillance.[8–10]

Patients receiving dialysis might be considered an ideal sentinel population in which to study the evolution of the COVID-19 public health crisis. Patients receiving dialysis in the USA undergo routine monthly laboratory studies to gauge the effectiveness of therapy and to screen for associated complications. In haemodialysis, regular access to the bloodstream abrogates the need for phlebotomy to acquire blood samples. Risk factors for acquisition of SARS-CoV-2 and for severe COVID-19, including advanced age, non-white race, poverty, and diabetes, are the rule rather than the exception in the US dialysis population.[12]

Research in context

Evidence before this study

Measuring the seroprevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies provides a comprehensive assessment of its community spread. Community seroprevalence surveys require considerable infrastructure and expense, and face implementation challenges during the COVID-19 pandemic due to restricted outreach in the worst-affected communities. Of the two largest seroprevalence surveys in the USA, one was limited only to New York state (n=15 101) and used convenience sampling at grocery stores. A second survey used remainder plasma from people visiting commercial laboratories in six cities (n=11 933), but lacked details on race and ethnicity and other community-level risk factors.

Added value of this study

We tested the remainder plasma of 28 503 patients receiving dialysis throughout the USA, using a chemiluminescence assay with high sensitivity and specificity. To our knowledge, we provide the first nationally representative estimate of SARS-CoV-2 seroprevalence in the US dialysis and US adult population, and estimates for differences in seroprevalence by neighbourhood race and ethnicity, poverty, population density, and mobility restriction. We also evaluate which of the existing measures of COVID-19 incidence most closely correlate with seroprevalence. Most importantly, we show that as patients receiving dialysis have monthly blood draws, without fail and without bias, and are a population with increased representation of racial and ethnic minorities, repeated cross-sectional analyses of seroprevalence within this sentinel population can be implemented as a practical and unbiased surveillance strategy in the USA.

Implications of all the available evidence

Similar to data from other highly affected countries and regions (eg, Spain and Wuhan, China), despite the intense strain on resources and unprecedented excess mortality being experienced in the USA during the COVID-19 pandemic, fewer than 10% of US adults had formed antibodies to SARS-CoV-2 as of July, 2020. There was significant regional variation from less than 5% prevalence in the west to more than 25% in the northeast. Public health efforts to curb the spread of the virus need to continue, with focus on some of the highest-risk communities that we identified, such as majority Black and Hispanic neighbourhoods, poorer neighbourhoods, and densely populated metropolitan areas. A surveillance strategy relying on monthly testing of remainder plasma of patients receiving dialysis can produce unbiased estimates of SARS-CoV-2 spread inclusive of hard-to-reach, disadvantaged populations in the USA. Such surveillance can inform disease trends, resource allocation, and effectiveness of community interventions during the COVID-19 pandemic.

Testing remainder plasma from monthly samples obtained for routine care of patients on dialysis for SARS-CoV-2 antibodies therefore represents a practical approach to a population-representative surveillance strategy,[13] informing risks faced by a susceptible population while ensuring representation from racial and ethnic minorities. In addition, seroprevalence surveys in patients receiving dialysis can be linked to patient-level and community-level data to enable evaluation and quantification of differences in SARS-CoV-2 prevalence by demographic and neighbourhood strata, and thus facilitate effective mitigation strategies targeting the highest-risk individuals and communities.

In partnership with a commercial clinical laboratory, we tested seroprevalence of SARS-CoV-2 antibodies in a randomly selected representative sample of patients. Our goal was to provide a nationwide estimate of exposure to SARS-CoV-2 during the first wave of COVID-19 in the USA, up to July, 2020, with stratification by region, age, sex, and race and ethnicity. We also harnessed population data on SARS-CoV-2 cases and deaths and percentage testing positive using nasal swab testing to assess how seroprevalence estimates correlated with other epidemiological measures of COVID-19 incidence. Finally, to inform preventive strategies for the high-risk dialysis population as well as the general population, we investigated community-level correlates for seropositivity.

Methods

Study design and participants

We did a cross-sectional analysis of adult (≥18 years) patients undergoing monthly laboratory testing at Ascend Clinical using samples obtained for routine clinical care that otherwise would have been discarded. Ascend Clinical is a commercial clinical laboratory based in Redwood City, California, that receives samples from a nationwide network of around 1300 dialysis facilities, serving approximately 65 000 patients. We randomly selected patients from the patient list on June 15, 2020, for seroprevalence testing to be done in July, 2020, using implicit stratification by region, age, sex, and race and ethnicity followed by systematic sampling with fractional polynomials.[14] After sample selection and processing, Ascend Clinical sent anonymised data on patient age, sex, race and ethnicity, and residence and facility ZIP codes to Stanford University investigators for analyses. Stanford University investigators further linked patient geographical information (ZIP code) to census data and publicly available COVID-19 burden and community mobility data. The study received expedited approval from the Stanford University of Medicine Institutional Review Board; informed consent was waived.

Procedures

We used the US Food and Drug Administration-approved Siemens Healthineers SARS-CoV-2 spike protein receptor

binding domain (S1RBD) total antibody (immunoglobulin) chemiluminescence assay, which has 100% sensitivity (≥14 days after a positive PCR test) and 99·8% specificity.[5] We chose this assay on the basis of its Emergency Use Authorization in June, 2020, in the context that S1RBD is also the target of vaccine development efforts.[15] Sample processing is detailed in the appendix (p 3).

We linked patient-level residence data with cumulative and daily cases and deaths per 100 000 population as compiled on a county level by the Center for Systems Science and Engineering at Johns Hopkins University[16] and with nasal swab test positivity rates, as compiled on a state level by the Covid Tracking Project.[17] For Utah, we followed the Utah Department of Health groupings of several smaller counties and extracted data directly.[18] New York City data are not available by county within the Johns Hopkins University dataset; therefore, we directly extracted data from the New York City Dashboard.[19] For county-level mobility restrictions, we used Google Mobility Data that report an average percentage change in the number of workplace visits over the period March 1–15, 2020, before the implementation of shelter-in-place restrictions in the majority of the country. Percentage changes in the Google Mobility data are indexed to a corresponding weekday (eg, Tuesdays are matched to Tuesdays) from Jan 3 to Feb 6, 2020.[20]

We also linked patient-level residence data with ZIP code tabulation area (ZCTA) data from the 2018 American Community Survey (ACS) 5-year estimates[21] to ascertain patient neighbourhood proportion living below the poverty level and race and ethnicity mix, and with American Census Bureau 2010 estimates[22] to ascertain population density. We defined ZCTA majority race and ethnicity as Hispanic, non-Hispanic Black, or non-Hispanic white if the population in the ZCTA was at least 60% Hispanic, non-Hispanic Black, or non-Hispanic white, respectively; where this was not the case, if the Hispanic and Black population combined was at least 60% of the population, the ZCTA majority was defined as Hispanic and Black, otherwise as other. For urban versus rural ZCTA status, we used the 2010 Rural Urban Commuting Area codes by census tract, categorising a ZCTA as dense urban, metropolitan, micropolitan, or small town or rural area if more than 50% of the population in the ZCTA was living in one of these area codes.[23]

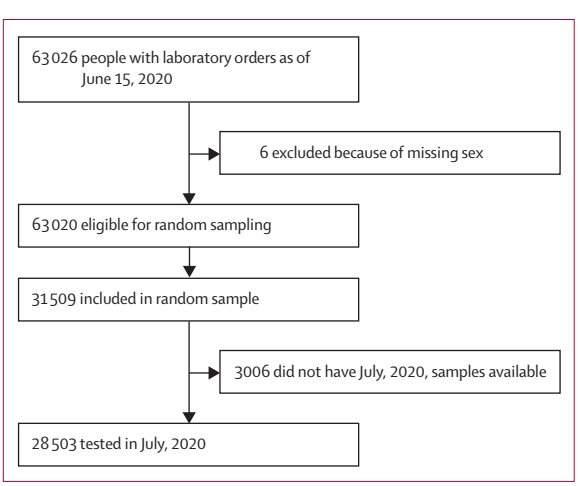

Figure 1: **Patient sampling and analytic cohort**

See **Online** for appendix

Statistical analysis

We assumed a nationwide prevalence of SARS-CoV-2 antibody of 5%.[8,24] To generate prevalence estimates for patients on dialysis using preselected regional strata with precision within 0·5%, a sample of 27 364 was required (appendix p 2). Based on previous trends, we expected 15% of selected samples to be unavailable in July, 2020, due to death, move to other facilities, or other reasons for missing laboratory data (eg, hospitalisation or non-adherence). Accounting for this potential dropout, we randomly selected 31 509 patients.

We present prevalence estimates with 95% CIs in our sample, standardised to the US adult dialysis population and to the US adult population. For the US adult dialysis

	Selected sample (n=28 503)	US adult dialysis population (n=499 150)	US adult population (n=253 815 197)
Age, years			
18–44	3303 (11·6%)	60 540 (12·1%)	117 499 477 (46·3%)
45–64	11 541 (40·5%)	207 022 (41·5%)	83 892 606 (33·1%)
65–79	10 220 (35·9%)	174 341 (34·9%)	39 949 825 (15·7%)
≥80	3439 (12·1%)	57 247 (11·5%)	12 473 289 (4·9%)
Sex			
Female	12 155 (42·6%)	213 869 (42·8%)	130 236 328 (51·3%)
Male	16 348 (57·4%)	285 281 (57·2%)	123 578 869 (48·7%)
Race and ethnicity*†			
Hispanic	3187 (11·2%)	87 611 (17·6%)	60 861 275 (18·7%)
Non-Hispanic white	6533 (22·9%)	203 421 (40·8%)	197 202 727 (60·4%)
Non-Hispanic Black	4894 (17·2%)	173 190 (34·7%)	39 717 152 (12·2%)
Other	2479 (8·7%)	34 928 (7·0%)	28 493 202 (8·7%)
Unknown	11 410 (40·0%)	0	0
ZCTA majority race and ethnicity*‡			
Non-Hispanic white	8733 (30·6%)	206 678 (41·4%)	189 968 192 (58·2%)
Non-Hispanic Black	2585 (9·1%)	54 999 (11·0%)	12 550 083 (3·8%)
Hispanic	4568 (16·0%)	52 953 (10·6%)	26 310 796 (8·1%)
Hispanic and Black	2878 (10·1%)	43 396 (8·7%)	17 238 911 (5·3%)
Other	9737 (34·2%)	140 781 (28·2%)	80 206 374 (24·6%)
Region			
Northeast	4536 (15·9%)	78 619 (15·8%)	44 519 465 (17·5%)
South	10 939 (38·4%)	214 974 (43·1%)	96 250 597 (37·9%)
Midwest	3763 (13·2%)	94 490 (18·9%)	52 876 708 (20·8%)
West	9265 (32·5%)	111 067 (22·3%)	60 168 427 (23·7%)

US adult population given is for 2018 and US adult patients dialysis population as of Jan 1, 2017. ZCTA=ZIP code tabulation area. *Computed for total US 2018 population (n=326 274 356). †When excluding people with unknown race and ethnicity, the proportions were 18·6% Hispanic, 38·2% non-Hispanic white, 28·6% non-Hispanic Black, and 14·5% non-Hispanic other. ‡343 people in the US Renal Data System and two people in the sample populations were missing data on ZCTA majority race and ethnicity due to missing ZIP code.

Table 1: **Comparison of sampled population, US adult dialysis population, and US adult population**

For the **United States Renal Data System database** see https://www.usrds.org

population, we used the distribution of all adults receiving maintenance dialysis, excluding those living in the territories, on Jan 1, 2017, identified through the United States Renal Data System database. For the US adult population, we used 2018 ACS 1-year estimates.[21] Based on the test sensitivity range obtained by Schnurra and colleagues in their external validation,[25] we also provide test characteristic-adjusted sample population estimates, ranging sensitivity from 85% to 98%.[10] To compute the percentage of estimated seroprevalent cases that were likely to be diagnosed cases,[10,26] we compared the estimated seroprevalent cases per 100 000 adult population with Johns Hopkins University estimates of cumulative diagnosed cases per 100 000 US adult population as of June 15, 2020.

To standardise estimates, we assigned weights to each person based on their membership to each of 32 strata of census regions (northeast, south, midwest, and west), age (18–44, 45–64, 65–79, and ≥80 years), and sex. We defined post-stratification weights as the proportion of each stratum represented in the US dialysis population or US adult population divided by the analogous proportion in the sample.[27–29] We then computed weighted frequencies and 95% CIs according to four prespecified strata (region, age, sex, and race and ethnicity) with differences evaluated using Rao-Scott χ^2 tests.[30,31] Due to the missingness of race and ethnicity data in the electronic health records, we used the additional measure of ZCTA race and ethnicity distribution with categories adapted from Moore and colleages.[32,33]

Next, we correlated five measures of COVID-19 incidence—cumulative cases on June 15, 2020 (or first available date between June 15 and June 30, 2020); cumulative deaths on June 30, 2020 (or last available date between June 15 and June 30, 2020); 15-day averages of daily cases and daily deaths; and percentage testing positive on nasal swab tests between June 15 and June 30, 2020—with SARS-CoV-2 seroprevalence in patients on dialysis in July, 2020. To do this, we first collapsed all measures to a state level and then assessed the Spearman's correlation coefficient ρ for the association of each measure with seroprevalence. Because of the high density of Ascend Clinical facilities in New York, Texas, and California, we also chose those states to present county-level correlations.

Finally, using logistic regression, we determined the age-adjusted and sex-adjusted correlates of seropositivity for patient ZCTA race and ethnicity distribution, percentage living below poverty level, rural or urban classification, population density, and county mobility restriction.

We assumed statistical significance at $\alpha<0{\cdot}05$. All statistical analyses were done with SAS Enterprise Guide (version 7.1) and Stata (version 15.1).

	Unweighted sample		Standardised to US adult dialysis population*	
	Count	Seropositive	Seropositive	Seropositive people per 100 000 population†
Age, years‡				
18–44	291	8·8% (7·9–9·9)	8·9% (8·0–10·0)	8921
45–64	958	8·3% (7·8–8·8)	8·6% (8·1–9·2)	8632
65–79	807	7·9% (7·4–8·5)	7·9% (7·4–8·5)	7934
≥80	236	6·9% (6·0–7·8)	7·3% (6·5–8·3)	7337
Sex				
Female	970	8·0% (7·5–8·5)	8·2% (7·7–8·7)	8162
Male	1322	8·1% (7·7–8·5)	8·4% (7·9–8·8)	8359
Race and ethnicity§				
Hispanic	201	6·3% (5·5–7·2)	6·3% (5·5–7·3)	3808
Non-Hispanic Black	467	9·5% (8·7–10·4)	9·3% (8·5–10·1)	5004
Non-Hispanic white	229	3·5% (3·1–4·0)	3·4% (3·0–3·9)	1991
Other	103	4·2% (3·4–5·0)	4·9% (4·1–5·9)	4796
Unknown	1292	11·3% (10·7–12·0)	11·8% (11·1–12·4)	..
ZCTA majority race and ethnicity§				
Hispanic	412	9·0% (8·2–10·0)	9·4% (8·5–10·3)	13 387
Non-Hispanic Black	380	14·7% (13·3–16·3)	14·1% (12·9–15·5)	13 575
Hispanic and Black	420	14·6% (13·3–16·1)	14·5% (13·2–15·9)	17 333
Non-Hispanic white	367	4·2% (3·8–4·7)	4·3% (3·8–4·7)	3438
Integrated	713	7·3% (6·8–7·9)	8·0% (7·4–8·6)	8610
Region§				
Northeast	1231	27·1% (25·7–28·7)	27·2% (25·9–28·5)	27 207
South	474	4·3% (4·0–4·7)	4·4% (4·0–4·8)	4358
Midwest	265	7·0% (6·2–7·9)	7·1% (6·3–7·9)	7062
West	322	3·5% (3·1–3·9)	3·5% (3·1–3·9)	3487
Overall	2292	8·0% (7·7–8·4)	8·3% (8·0–8·6)	8275

SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. ZCTA=ZIP code tabulation area. *Standardised to the US dialysis population using all adults receiving dialysis for the treatment of end-stage kidney disease on Jan 1, 2017, identified through the United States Renal Data System database (n=499 150). †Seropositivity per 100 000 people calculated as (standardised count/category count) × 100 000. ‡Different at $\alpha<0{\cdot}05$ by the Rao-Scott χ^2 test. §Different at $\alpha<0{\cdot}0001$ by the Rao-Scott χ^2 test.

Table 2: **Seroprevalence of SARS-CoV-2 antibodies in patients receiving dialysis in the USA**

Role of the funding source

Ascend Clinical Laboratories supported the remainder plasma testing for SARS-CoV-2 antibodies. SA, MM-R, and JH had complete access to all data in the study and SA, MM-R, JH, JP, and GMC were responsible for the decision to submit for publication.

Results

Of the 31 509 people selected for testing on June 15, 2020, 28 503 were tested in July, 2020 (figure 1), with 25 217 (88·5%) tested in the first 2 weeks (appendix p 4). The sampling was representative of the US dialysis patient distribution by age, sex, race and ethnicity (when excluding patients without race and ethnicity data), and region, except sampled patients were less likely to be non-Hispanic Black (table 1). Compared with the US adult population, our sampled patient population was older, had more men, and was more likely to be non-Hispanic Black and living in non-white neighbourhoods

	Seropositivity standardised to US adult population*	Seropositive people per 100 000 population†
Age, years‡		
18–44	9·8% (8·7–10·9)	9006
45–64	9·5% (8·9–10·1)	9516
65–79	8·3% (7·8–8·9)	8315
≥80	7·4% (6·5–8·5)	7436
Sex		
Female	9·3% (8·6–10·2)	9022
Male	9·3% (8·6–10·0)	8954
Race and ethnicity§		
Hispanic	8·0% (6·6–9·6)	3526
Non-Hispanic Black	9·9% (8·7–11·3)	12035
Non-Hispanic white	4·3% (3·5–5·2)	1102
Other	5·7% (4·2–7·7)	3342
Unknown	12·5% (11·6–13·5)	..
ZCTA majority race and ethnicity§		
Hispanic	11·3% (9·8–12·9)	16041
Non-Hispanic Black	13·9% (12·1–16·0)	31061
Hispanic and Black	16·3% (14·3–18·5)	24923
Non-Hispanic white	4·8% (4·1–5·5)	1919
Other	8·9% (8·0–9·8)	8423
Region§		
Northeast	27·6% (25·7–29·7)	26697
South	5·1% (4·5–5·7)	4894
Midwest	7·4% (6·3–8·8)	7157
West	4·2% (3·6–4·9)	4048
Overall	9·3% (8·8–9·9)	8989

ZCTA=ZIP code tabulation area. *Standardised to the US population using American Community Survey 2018 data. †Seropositivity per 100 000 people calculated as (standardised count/category count) × 100 000. ‡Different at α<0·05 by the Rao-Scott χ^2 test. §Different at α<0·0001 by the Rao-Scott χ^2 test.

Table 3: **Seroprevalence estimates for the US adult population**

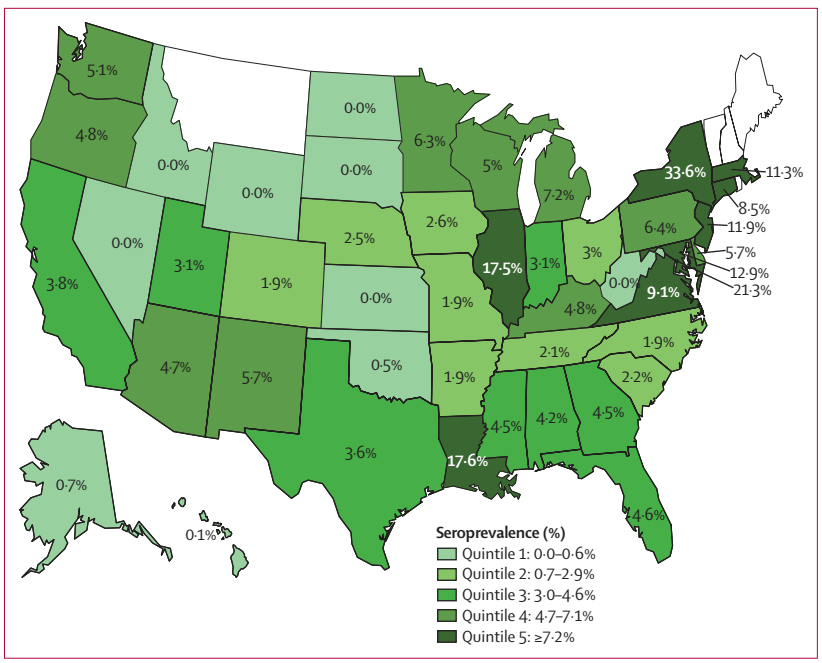

Figure 2: **Prevalence of SARS-CoV-2 antibodies in sampled population, by state**
Bolded borders represent states with more than 100 patients in the sample. The median number of patients sampled by state was 176 (IQR 83–536). States in white were not sampled. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

(table 1). A greater proportion of our sampled population and the US dialysis population lived in the west, and a lower proportion lived in the midwest, compared with the US adult population. Patients in our sample lived in 46 states and in 1013 (32%) of 3141 US counties (appendix p 6).

Overall, sample seroprevalence was 8·0% (95% CI 7·7–8·4). Accounting for the externally validated test sensitivity,[25] seroprevalence ranged from 8·2% (7·9–8·5) to 9·4% (9·1–9·8) in our sampled population (appendix p 7). When standardised to the US dialysis population, seroprevalence was 8·3% (8·0–8·6), with high regional variation in seroprevalence (ranging from 3·5% [3·1–3·9] in the west to 27·2% [25·9–28·5] in the northeast; table 2). Seroprevalence was similar by sex and modestly lower in people aged 80 years or older compared with those aged 45–64 years (table 2). Differences in seroprevalence by race and ethnicity were similar using both our patient-level (electronic health record) and neighbourhood-level (ZCTA majority race and ethnicity) measures, with non-Hispanic Black patients having the highest seropositivity, followed by Hispanic patients, and non-Hispanic white patients having the lowest.

We estimated the SARS-CoV-2 standardised seroprevalence in the US population to be 9·3% (95% CI 8·8–9·9; table 3). Based on the Johns Hopkins University cumulative case data as of June 15, 2020, the prevalence of (nasal swab) diagnosed cases was 826 per 100 000 US adult population, compared with our estimate of 8989 seropositive people per 100 000 population, meaning that 9·2% (8·7–9·8) of seropositive people were diagnosed.

Using data from our sampled population, variation by state was high, ranging from 0·0% in seven states to 33·6% (31·7–35·6) in New York, with the highest regional variation occurring in the northeast (figure 2; appendix pp 8–9). When comparing state seroprevalence against cumulative cases and deaths per 100 000 population, deaths correlated best (ρ=0·66 for cases *vs* 0·77 for deaths; figure 3). The percentage of people testing positive by nasal swab test and 15-day average of daily deaths in the latter half of June, 2020, showed a weaker correlation (ρ=0·58 and 0·66, respectively), whereas 15-day average of daily cases did not correlate with seroprevalence (ρ=–0·14). On a county level in California, New York, and Texas, there was even more heterogeneity in the correlation between seroprevalence and other disease measures (ρ≤0·51 for all correlations for all three states' county-level data; appendix p 10).

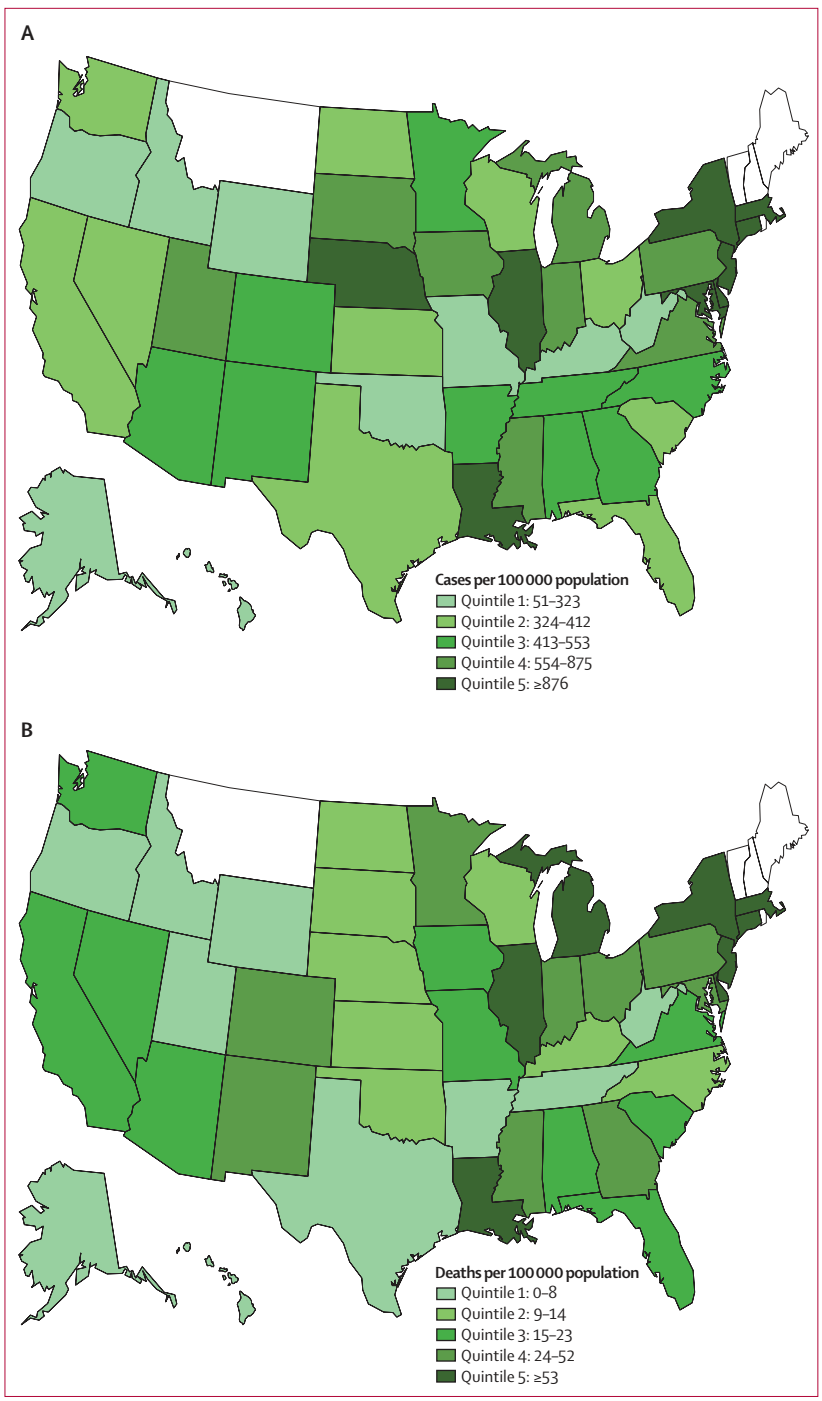

Figure 3: **Cumulative cases (A) and cumulative deaths (B) per 100 000 population, by state**
Data are in the US population as of June 15 (A) and June 30 (B), 2020.[16,18,19,21] States in white were not included in the sample.

Likelihood of SARS-CoV-2 seropositivity was lower among older people (odds ratio 0·8 [95% CI 0·7–0·9] for people aged 80 years or older *vs* people aged 45–64 years), but did not differ by sex (1·0 [0·9–1·1] for women *vs* men). In age-adjusted and sex-adjusted models, neighbourhood racial and ethnic distribution, poverty level, dense urbanisation, population density, and percentage change in workplace visits in early March, 2020, were all strongly associated with seropositivity (figure 4).

Discussion

In our analysis of seroprevalence of SARS-CoV-2 spike protein receptor binding antibodies from a nationwide representative sample of patients receiving dialysis, we find that despite the USA contemporaneously leading the world in the numbers of diagnosed cases, overall, fewer than 10% of US adults had evidence of seroconversion in July, 2020. A vast majority of US adults, including people receiving dialysis who are among the highest risk for mortality upon contracting SARS-CoV-2,[34] do not have evidence of exposure or immune response. Furthermore, we find increased likelihood of SARS-CoV-2 seropositivity in residents of predominantly Black and Hispanic neighbourhoods (two to three times higher), poorer areas (two times higher), and the most densely populated areas (ten times higher). Early reduction in community mobility in March, 2020, was associated with 60% lower likelihood of individual-level seroconversion by July that year.

Unlike most published estimates of SARS-CoV-2 seroprevalence from the USA,[8,10,11] patients included in our study sample had antibodies measured from blood collected as part of routine medical care. Thus, our prevalence estimates should not be subject to selection bias due to presence versus absence of symptoms, availability of testing materials, local or regional testing strategies, geography, income, educational attainment, language proficiency, immigration status, mobility, anxiety, fear, or other factors. Moreover, since end-stage kidney disease qualifies affected patients for Medicare insurance, and since end-stage kidney disease disproportionately affects Black, Hispanic, and other disadvantaged populations,[12,35,36] we are able to determine—with a high level of precision—differences in seroprevalence among patient groups within and across regions of the USA. Of the two larger seroprevalence surveys published from the USA thus far, one was confined to New York state (n=15 101), employed a convenience sampling technique at grocery stores, and relied on a microsphere immunoassay with lower sensitivity.[10] The second, the Centers for Disease Control and Prevention (CDC) Six Sites study (n=11 933), used remainder plasma from people getting testing for undefined clinical indications, and did not have detailed sociodemographic information about the tested people.[11]

Uncertainty exists as to whether seroprevalence estimates in the dialysis population can be extrapolated to the US population more broadly. A recent analysis of SARS-CoV-2 IgG antibodies in two dialysis units in London, UK, reported seroprevalence of 36%, higher than in healthy blood donors (15%) but lower than in healthcare workers (45%) sampled within a similar time frame.[37] Our data might overestimate overall seroprevalence in

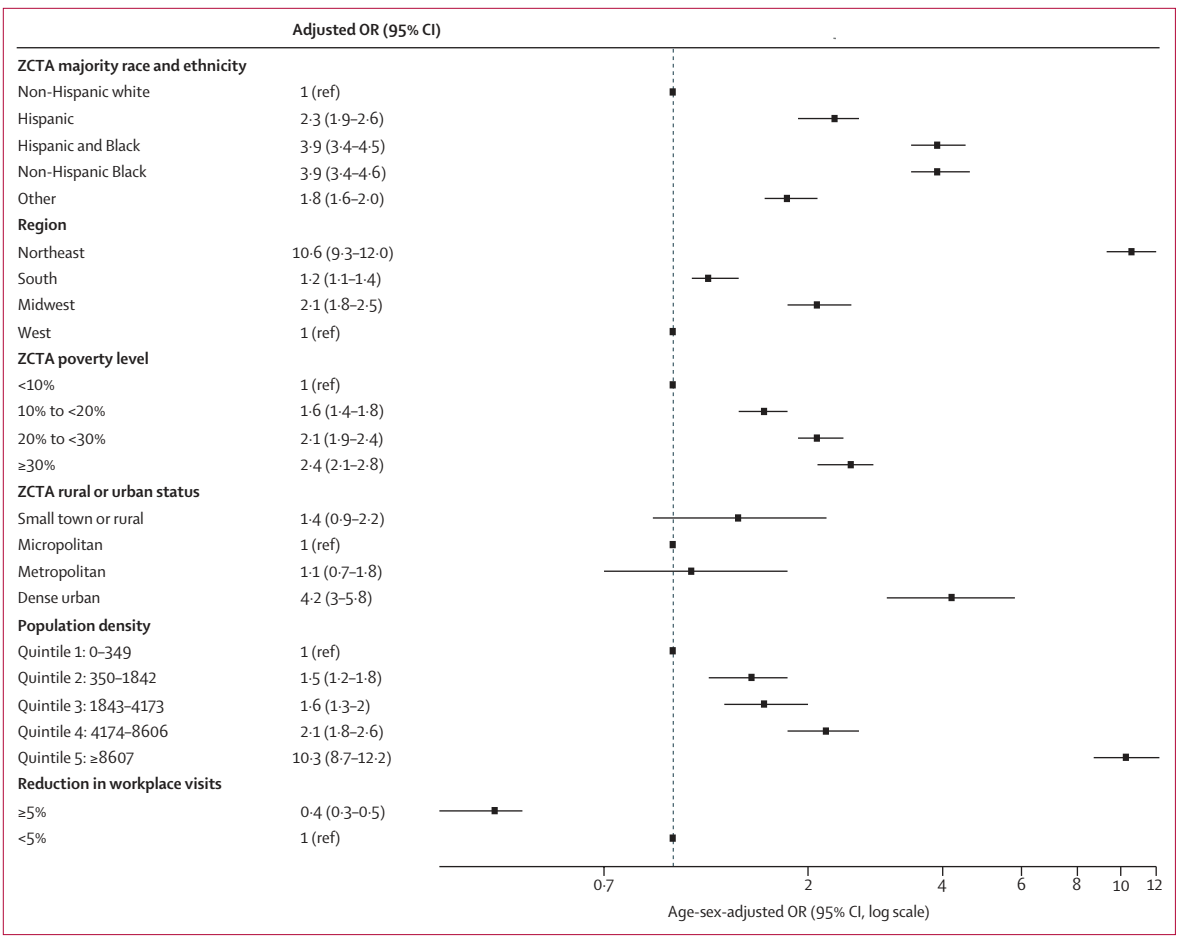

***Figure 4*: Forest plot for odds of SARS-CoV-2 seropositivity**
All variables are at a neighbourhood (ie, ZCTA) level, except for reduction in workplace visits, which is at a county level, and are modelled separately, accounting for age and sex. Poverty level is defined as percentage of people living below the federal poverty level in the ZCTA. Population density quintiles are derived from the ZCTA (median 2884 people per square mile [IQR 603–6800]). Reductions in workplace visits were measured during the first 2 weeks of March, 2020, compared with a baseline in January–February, 2020. OR=odds ratio. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. ZCTA=ZIP code tabulation area.

the general population since patients on dialysis are disproportionately from racial and ethnic minorities;[38,39] for example, Black Americans have a nearly four-times higher risk of end-stage kidney disease than white Americans.[12] Moreover, the process of undergoing in-centre haemodialysis might include the use of public or non-public shared transportation to and from the facility, and 10–12 h of care delivered in indoor facilities.

Conversely, these data might underestimate overall seroprevalence in the general population. Patients receiving dialysis are less likely to be employed[40] and more likely to restrict their mobility and social activity due to advanced age and frailty;[41] therefore, they might have fewer opportunities to acquire the infection, particularly from asymptomatic individuals. Extrapolating from multiple prospective hepatitis B immunisation studies—in which 50–75% of vaccinated patients receiving dialysis mounted a response compared with 95% or more people from the general population—patients receiving dialysis might mount a weaker immune response and thus be less likely to seroconvert.[42] Finally, patients receiving dialysis might have been more likely to die or have been hospitalised due to complications of SARS-CoV-2 infection. If so, these patients would not have been present for testing in the dialysis facilities, creating a survival bias and yielding lower estimates of exposure.

Nonetheless, the ten-times difference we observed between diagnosed cases per 100 000 population and our estimates of seropositive people per 100 000 has been similarly reported in studies from New York,[10] the CDC Six Sites study,[11] and in a population-representative analysis from Geneva.[26] Thus, our findings comport with other seroprevalence estimates. We confirm that as in other studies from COVID-19 hotspots,[1,26,43] a minority of the population has evidence of exposure and immune response, and a vast majority, including people at high risk for mortality (ie, the population on dialysis), remain vulnerable. In fact, even if the seroprevalence estimates derived from the US dialysis population overestimated true seroprevalence in the overall US adult population,

our data nonetheless support that fewer than 10% of the US population has seroconverted as of July, 2020, and herd immunity remains out of reach, as has been the conclusion from large international surveys from the UK[44] and Spain,[1] where intense outbreaks of COVID-19 occurred during the spring and summer of 2020.

Furthermore, the seroprevalence differences captured by region, age, sex, and community-level risk factors (ie, internal comparisons) are expected to be similar in the US dialysis and US general adult population. Our study provides convincing evidence that the COVID-19 pandemic has dramatically amplified existing health disparities. Data from the CDC highlighting SARS-CoV-2 health disparities evaluate hospitalisations and deaths by race and ethnicity,[45,46] calling into question whether Black and Hispanic populations are experiencing more severe illness versus facing higher likelihoods of exposure. Some US state dashboards also report higher cumulative cases among Black and Hispanic people compared with non-Hispanic white people,[47] but none have as precisely quantified differences on a national level.

Neighbourhood poverty and population density were also highly correlated with seroprevalence, with a possible threshold effect for population density, such that there was a ten-times higher risk in the highest density ZCTAs (>8607 people per square mile). Population density is recognised as a crucial factor, driving the spread in metropolitan areas, in confined spaces (eg, the *Diamond Princess* cruise ship), large gatherings (eg, the New Orleans' Mardi Gras),[48,49] and in populous regions across the world.[50] Rocklöv and Sjödin suggest that the basic reproduction number (R_0) of SARS-CoV-2 increases linearly with population density.[51] Our data also show slightly lower likelihood of seropositivity among older people, as was seen in a recent report from Geneva[26] and attributed to better adherence to physical distancing measures by the authors. A higher competing risk from hospitalisations or mortality after SARS-CoV-2 exposure might be a larger contributing factor in the observed lower seroprevalence in older compared with younger age groups.

In addition to providing an overall estimate of SARS-CoV-2 seroprevalence and quantifying differences by patient and community characteristics, our study puts forth a viable surveillance strategy for SARS-CoV-2 spread in the USA. WHO and other experts[13,52] advocate for repeated cross-sectional analyses of seroprevalence as a disease tracking system able to most completely measure the true incidence of SARS-CoV-2, since these can more likely capture incidence of exposure in both symptomatic and asymptomatic individuals. In fact, we observed substantial heterogeneity in the correlation between seroprevalence and other measures of SARS-CoV-2 that are currently being used—with the exception of deaths per 100 000, which are a late outcome[53]—supporting the use of rapidly instituted seroprevalence surveys as a complementary surveillance tool. Additional public health implications of seroprevalence surveys include assessing testing adequacy. For example, in states where the difference between seropositive and diagnosed cases is decreasing over time, testing capacity is likely to be increasing. Furthermore, following seroconversion rates over time can presage hospitalisations and intensive care unit stays, since the time between exposure and seroconversion is relatively short (median 10 days),[26] and can therefore facilitate resource allocation. Finally, as we show by assessing community mobility restrictions, seroprevalence surveys can measure the effects of interventions to treat or prevent infection with SARS-CoV-2.[13] Repeated serological surveys, if done in a community setting, would require extensive resources and yet remain subject to selection bias. However recurring monthly testing of remainder plasma of randomly selected sets of people—as is practically feasible in patients receiving dialysis—can serve as a representative surveillance system in the USA, with minimal phlebotomy or infrastructure requirement, and as our data show, include traditionally under-represented and socially disadvantaged groups.

This analysis has numerous strengths. We used a highly specific and sensitive immunoassay, one which has been robustly linked to SARS-CoV-2 exposure.[13,25,54,55] The study sample was highly representative of the US dialysis population and, as noted, we used remainder plasma from specimens used in routine clinical care. The sample size and sampling scheme allowed us to estimate with precision prevalence across several patient characteristics. Moreover, linking to US Census and other publicly available data sources assembled during the pandemic provides valuable context when considering the implications of these data to the general population. There are also several important limitations. As noted previously, it is plausible that seroprevalence estimates from the US dialysis population overestimate seroprevalence in the US adult population. We do not have patient-level data on symptoms nor nasal swab testing results, and thus cannot test whether the likelihood of seroconversion differs in patients receiving dialysis from generally healthy adults, although preliminary data from London, UK, suggest no differences.[37] We also do not have patient-level data on health status, employment status, income, household size, living space, and other sociodemographic factors, and so relied on neighbourhood proxies for some of these domains. Dialysis units are more often located in urban areas, and thus we have under-representation of rural areas. Finally, while large, our study was designed for precise regional, not state-level or county-level, estimates.

In conclusion, we present SARS-CoV-2 seroprevalence data in a broadly representative sample of patients receiving dialysis across the USA and show striking differences in seroprevalence by several patient characteristics, with higher seroprevalence in younger patients, Black and Hispanic patients, and patients living in poorer and majority-minority neighbourhoods. These data can help to

inform surveillance and management strategies during the next phase of the pandemic. Serial sampling of dialysis remainder plasma should be used to determine trends in disease prevalence and the effect of various strategies being implemented around the USA to reduce the burden of COVID-19 on the general population.

Contributors

SA assisted with data cleaning and analysis planning, and manuscript writing. MM-R developed the analysis plan, generated census data tables, supervised data analysis, and contributed to manuscript writing. JH undertook data cleaning and analysis, including linkage to external data and figure generation, and contributed to manuscript writing. JB undertook sample processing and data preparation and contributed to manuscript writing. RK selected seroprevalence testing, supervised sample processing, and contributed to manuscript writing. PB co-conceived the study, secured seroprevalence testing, and supervised sample processing and data preparation. JP supervised the study analysis plan, identified relevant external data, contributed to data interpretation, and supervised manuscript writing. GMC co-conceived the study, supervised the study analysis plan, and co-wrote the manuscript.

Declaration of interests

JB, RK and PB are employed by Ascend Clinical Laboratories. GMC is on the Board of Directors of Satellite Healthcare, a not-for-profit dialysis organisation. All remaining authors declare no competing interests.

Data sharing

De-identified cross-sectional data from the analysis can be made available after authors' review of request and might require compilation of specific categories (eg, at the older age groups) to protect patient privacy.

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The COVID-19 pandemic as experienced by the individual

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Abstract

The ongoing COVID-19 pandemic has progressed with varying degrees of intensity in individual countries, suggesting it is important to analyse factors that vary between them. We study measures of 'population-weighted density', which capture density as perceived by a randomly chosen individual. These measures of population density can significantly explain variation in the initial rate of spread of COVID-19 between countries within Europe. However, such measures do not explain differences on a global scale, particularly when considering countries in East Asia, or looking later into the epidemics. Therefore, to control for country-level differences in response to COVID-19 we consider the cross-cultural measure of individualism proposed by Hofstede. This score can significantly explain variation in the size of epidemics across Europe, North America, and East Asia. Using both our measure of population-weighted density and the Hofstede score we can significantly explain half the variation in the current size of epidemics across Europe and North America. By controlling for country-level responses to the virus and population density, our analysis of the global incidence of COVID-19 can help focus attention on epidemic control measures that are effective for individual countries.

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1 Introduction

Since the onset of the COVID-19 pandemic in December 2019, over a million people have died of the disease worldwide [41]. Given the vast human and economic cost, considerable effort has been given to understanding and modelling epidemics by the media and scientific community [37, 6]. At this early stage, the media in particular have performed the role of disseminating mortality data between and within countries, often through data visualizations.

Such visualizations [37] are informally used to assess the responses and interventions of various Governments, or the quality of their health services, and have therefore put pressure on governments to allocate resources based on apparent differences between the performance of countries. We caution against making such judgements based on raw data alone without controlling for factors that may impact the rate of spread of COVID-19 and the severity of any outbreak. These factors may include: demographic variables such as age and ethnicity, pre-existing medical conditions, patterns of mobility (i.e., travel), and cultural factors such as voluntary mask wearing, household age profile, or patterns of social contact. These factors exist independently of the quality of any specific Government coronavirus response, and more formal analysis is beginning to emerge that suggests they are important for the apparent severity of epidemics between countries [3].

Any assessment of a COVID-19 epidemic in any country must be carried out carefully, in the context of these factors. It will be a major statistical exercise to do this properly, considering interactions rigorously. In this article, we make a minor early contribution to such an audit by considering one demographic factor, population density, while controlling for cross-cultural differences that may impact country-level responses to the virus.

Population density plays a significant role in emerging infectious diseases [16, 39, 22]. The basic reproduction number (R_0) for a zoonotic pathogen not yet fully adapted for human-to-human transmission may in fact require sufficiently many interactions, facilitated by population density, for an outbreak to occur [17]. This need for a sufficient density of people susceptible to infection was apparent to those first modelling infectious disease outbreaks nearly 100 years ago ([18]). Contemporary modelling of influenza pandemics have utilised this framework, and subsequently employed it to model COVID-19 epidemics ([5, 6]). Of note in these models is the use of the standard measure of population density (total number of people divided by area) applied to relatively high resolution population data (square kilometre). This prompted us to consider two questions: does weighting high resolution population data by the local density experienced by an average individual improve its ability to predict epidemic growth, and could such a methodology be used to explain the dynamics of epidemics between countries?

Regardless of what demographic variables are chosen to compare COVID-19 epidemics between countries, the same problem will be encountered: individual countries and their governments have responded differently to the virus. Public health interventions have

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included: testing, contact tracing, and isolation of positive cases and their contacts; restricting public gatherings, physical distancing, mandated face mask wearing, and closures of schools and nonessential businesses [13]. It is noticeable that such measures appear to have been more effective in East Asian countries than Europe and North America; for example, China has reduced cases by 90% but Italy and the USA have not replicated this performance [29, 26]. This may be partly due to the speed with which control measures have been instigated; and in particularly, when the strongest measure, lockdowns, have been ordered [1, 9]. Any analysis that attempts to compare country-level COVID-19 epidemics will need to control for these differences. The Oxford COVID-19 Government Response Tracker collates these country-level responses into a 'Stringency index' [12]; however, whether these government responses are derived from a more fundamental difference in cultural responses to infectious diseases has not been currently explored.

It has been hypothesised that pathogen exposure puts selection pressure on animals to modify their behaviour, which in humans has been labelled the 'pathogen-stress hypothesis' [8, 7, 21]. Fincher et al. [8] hypothesised that historical pathogen prevalence could explain variation in cross-cultural measures of individualism and collectivism. In particular, historical and contemporary pathogen prevalence was significantly negatively correlated with, for example, the cross-cultural measure of individualism proposed by Hofstede [15], which captures to what extent a country values individual freedom over collective benefit. This axis between individualism and collectivism has been shown to be particularly stark between Western and East Asian countries, with the former more individualistic and the latter more collectivist. Interestingly, countries with high individualism scores also have a greater susceptibility to zoonotic disease outbreaks [21]. Whether these observations can be replicated for the current COVID-19 pandemic and used to control for country-level responses is currently an unanswered question.

We have used publicly available data to examine whether population density can explain the burden of COVID-19 disease between countries. We first explore two methods for rationalising the 'lived density' experienced by an average individual. High resolution population data from the WorldPop data set has allowed us to calculate two measures of population-weighted density (PWD) for multiple countries across East Asia, Europe, North America, and US states. We investigate whether these PWD measures can explain the initial and current stages of the ongoing COVID-19 pandemic. Finally, we examine whether the Hofstede cross-cultural measure of individualism can account for variance between the current size of COVID-19 epidemics, and subsequently use both PWD and the Hofstede score to explain the current size of COVID-19 epidemics across a range of countries. This analysis provides a rationale for controlling two important variables, population density and country-level responses, when comparing epidemics between countries.

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2 Methods

2.1 COVID-19 mortality data

We use two sets of data in this paper to measure the extent of COVID-19 in a region, firstly a measure that captures the rate of spread early on, and secondly a measure that captures the size of the epidemic after a period of time has passed.

The first measure examines the rate of spread early in the epidemic by choosing a relatively small threshold value of deaths, and then comparing the number of deaths that have occurred a fixed number of days later. For concreteness, we choose these numbers to be 5 and 5: that is, our metric is "number of deaths that have occurred 5 days after deaths hit 5". In the sense of the classical SIR model [18], we anticipate that this is a phase of unrestricted exponential growth, where we seek to compare the growth exponent. Since this measure seeks to capture the early rate of spread, we do not believe it is appropriate to normalize these figures by total population size, since this corresponds to a situation of a limited number of small localized outbreaks which have not spread to the whole country.

Clearly the choice of these numbers is somewhat arbitrary: we want to choose a threshold that is large enough that daily numbers are not affected too much by random fluctuations, and to wait a long enough period for random daily effects to cancel out. However, waiting too long means that the numbers can be affected by Government actions such as lockdowns. Further, waiting for deaths to hit too high a level may exclude some smaller countries. Some experimentation has shown that our results are robust to the choice of parameters.

An alternative method would be to study the rate of growth of cases. However, such comparison risk being distorted by the significant variation between availability of tests in different countries early in the pandemic.

Our second measure is to consider total deaths per million 120 days after the 1st clinically confirmed case. We are therefore measuring epidemics at a comparable stage of their duration.

The data on COVID-19 deaths itself was obtained online. Data for European countries was taken from [31], which is itself based on ECDC data. Data for US states was downloaded from [23]. Data for East Asian countries was also taken from [31].

2.2 Population data

We studied 30 European countries, using figures of standard population density ρ_S (see Results for notation) taken from Wikipedia [40], and using the values of the non-empty lived density ρ_N for each country calculated by Rae from Eurostat data, and stated in [28]. Some extremely small countries (where the size of the COVID-19 outbreak was too small

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to achieve the threshold discussed above) were excluded from the comparison.

Additionally, we used WorldPop population count data [35] to calculate the population-weighted density ρ_W for these countries, using the formula (3). As described in [32, 34] WorldPop distribution datasets are produced by disaggregating administrative-unit based official population estimates into grid cells having a resolution of 3 arc seconds (approximately 100m at the equator) before summarizing them at 30 arc seconds (approximately 1km at the equator). To ensure comparability between countries, 2019 gridded country-based population estimates were adjusted to match the corresponding UNPD country total estimates [38].

We tabulate the resulting values ρ_N, ρ_W, ρ_S and $V = \rho_W/\rho_S$ in Appendix A for completeness. Additionally, in Appendix B we consider a range of other countries of interest and provide values of their standard population density ρ_S (again taken from Wikipedia [40]) and population-weighted density ρ_W calculated from WorldPop data [35] in the same way.

We studied the 50 US States, using figures of standard population density ρ_S taken from Wikipedia, and calculating the population-weighted density ρ_W ourselves, again based on WorldPop data. Values of ρ_N were not available for US states, but since we found a stronger relationship between rate of spread in Europe with ρ_W than with ρ_N (see Figures 3 and 4), in any case we prefer to focus on ρ_W. We tabulate the density values for US states in Appendix C for completeness.

2.3 Hofstede individualism score

We used the values of this measure for a range of countries calculated from questionnaires and tabulated in [15, Table 4.1].

2.4 Nomenclature of regions analysed, data processing and availability

Global regions analysed were: Western/West (Europe, USA, Canada, Israel); East Asia and Oceania (Australia and New Zealand). Countries are listed in appendices A and B

Fits for normal or lognormal (base 10) distributions were generated using a maximum likelihood approach, and the likelihoods compared for statistically significant differences (see [2, Section 6.7.2]). It was observed that the initial rate of spread of COVID-19 and later deaths per million associated with it followed a lognormal distribution, and this was used for regression analysis. The antilog is presented on graphs to aid interpretation. All data is available at: `https://github.com/ptrckgrlnd/COVID-PWD-and-Individualism`

3 Results

3.1 Lived density, or population density as experienced by a random individual

First we motivate and define the various measures of population density that we use in this paper.

Example 3.1. *Consider three countries, each with 100,000 people and an area of 100km^2, and consider the population of each square kilometre grid square. As illustrated in Figure 1:*

1. *Averagia has a uniform spread of population, with 1,000 people living in each grid square.*
2. *Builtupia has ten towns, each consisting of 10,000 people living in a single square kilometre, and the remaining land is uninhabited.*
3. *Citia has one city, where 100,000 people live in a single square kilometre, and the remaining land is uninhabited.*

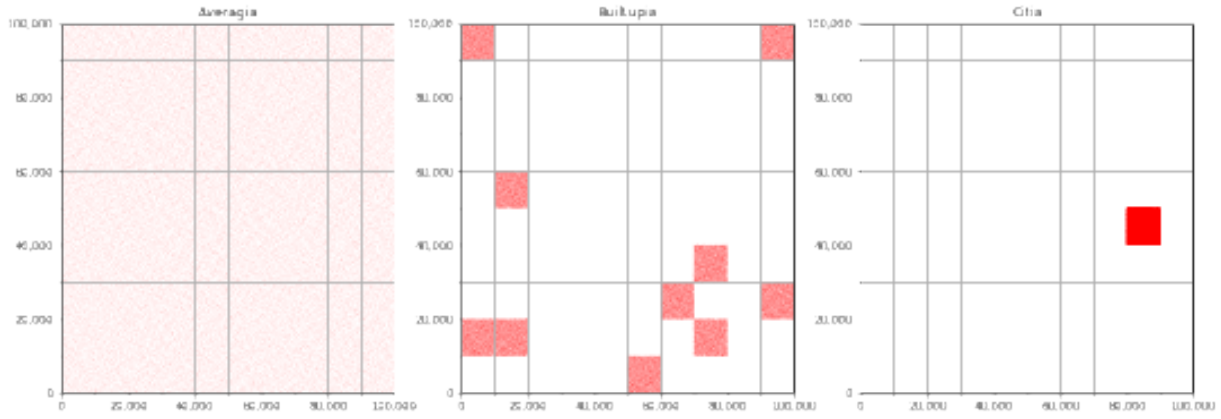

Figure 1: Schematic diagram of population in Averagia, Builtupia and Citia – see Example 3.1.

Since each standard population density is 100000/100 = 1000 people/km^2, we might naively say that each country is equally crowded. However, if we consider the lived experience of a person in each country, it is clear that in everyday life residents of Citia would have daily encounters with more people than in Builtupia, who in turn would have daily encounters with more people than Averagia. Since daily encounters are likely to cause infection events, it seems natural to imagine that COVID-19 would spread more rapidly in

Citia than in Builtupia, and in turn faster in Builtupia than in Averagia. We would like to use a measure of population density that captures this, and here define two such measures.

We will consider a region of total area A, divided into M subareas of area $A_1, \ldots, A_M$ respectively. We will write n_i for the population of the ith subarea, and write $n = \sum_{i=1}^{M} n_i$ for the total population of the region.

Definition 3.2. *In this notation, the* standard population density *is*

$$\rho_S = \frac{n}{A} = \frac{\sum_{i=1}^{M} n_i}{\sum_{i=1}^{M} A_i}. \tag{1}$$

Definition 3.3. *We will refer to the* non-empty lived density *[28] as the same expression normalized by the total area where some people live. That is, we write S for the set of regions with non-zero population, and consider*

$$\rho_N = \frac{\sum_{i \in S} n_i}{\sum_{i \in S} A_i}. \tag{2}$$

Note that in comparison with the expression (1) given for ρ_S, the numerator is unchanged here, since removing terms which are zero does not affect the value of a sum. Indeed, if each subarea contains at least one person then the non-empty lived density ρ_N coincides with the standard population density ρ_S.

Definition 3.4. *We will refer to the* population-weighted density *[4] as the sum*

$$\rho_W = \frac{1}{n} \sum_{i=1}^{M} \frac{n_i^2}{A_i} = \sum_{i=1}^{M} \left(\frac{n_i}{n}\right) \left(\frac{n_i}{A_i}\right). \tag{3}$$

We can think of this as a quadratic measure because if each subarea has $A_i = 1$ then it becomes $\rho_W = \left(\sum_{i=1}^{M} n_i^2\right)/n$. Note that the form of this quantity is somewhat reminiscent of the Herfindahl–Hirschman Index, which is used in economics to measure diversity of market share (see [14] for a history of this quantity).

Remark 3.5. *As described for example in [25]:*

1. *We can think of this population-weighted density ρ_W as follows: select an individual uniformly at random from the population (with probability n_i/n this will be someone from subarea i). Then n_i/A_i is the density of their local subarea. Hence, assuming the subareas are small enough to be reasonably homogeneous, this measure represents the expected local density, sampling by person.*

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2. *In contrast, the standard population density corresponds to sampling by area. That is, pick a point uniformly in the region (with probability A_i/A this will be a point in subarea i). Then according to this distribution, the expected local density will be*

$$\sum_{i=1}^{M} \left(\frac{A_i}{A}\right)\left(\frac{n_i}{A_i}\right) = \frac{n}{A}, \tag{4}$$

the standard population density ρ_S.

We return to Example 3.1, where recall that each country had standard population density $\rho_S = 1000$. Considering the square kilometre grid squares as the subareas, note that that the non-empty lived density ρ_N of Averagia, Builtuipia and Citia is $100000/100 = 1000$ people/km^2, $100000/10 = 10000$ people/km^2 and $100000/1 = 100000$ people/km^2 respectively. In fact, calculation shows that the same three values hold for the population-weighted density ρ_W in these cases (though this will not be true in general). For example, for Builtupia, there are 10 non-zero terms in the sum of $\left(\frac{n_i}{n}\right)\left(\frac{n_i}{A_i}\right)$, each equal to $(1/10)(10000/1)$, giving 10000 overall.

Notice that ρ_S, ρ_N and ρ_W are all measured in the same units, namely people/km^2, meaning that it is legitimate to compare them. It turns out that the three measures are always ordered in the same way for every region:

Lemma 3.6. *For any region, the three measures satisfy*

$$\rho_S \leq \rho_N \leq \rho_W,$$

with equality in the first inequality if and only if all the areas have non-zero population, and with equality in the second inequality if and only if all the areas of non-zero population have the same density.

Proof. The fact that $\rho_S \leq \rho_N$ is clear, since the two expressions both have the same numerator n, but the non-empty lived density has a smaller denominator since the sum is taken over a smaller range. Clearly, equality holds if and only if the denominators are equal.

The fact that $\rho_N \leq \rho_W$ is more subtle, but can be proved using the Cauchy-Schwarz inequality. Recall that we write S for the set of areas of non-zero population, then use the fact that

$$n^2 = \left(\sum_{i\in S} \frac{n_i}{\sqrt{A_i}}\sqrt{A_i}\right)^2 \leq \left(\sum_{i\in S} \frac{n_i^2}{A_i}\right)\left(\sum_{i\in S} A_i\right) = (n\rho_W)\left(\sum_{i\in S} A_i\right), \tag{5}$$

and rearrange, using the fact that the value of ρ_W is unchanged if we restrict to a sum over $i \in S$ (since terms with $n_i = 0$ do not contribute to the sum). Equality holds if and only if each populated subarea has the same density, that is if n_i/A_i does not depend on i for each $i \in S$. □

Indeed, a version of the same argument shows that if we partition a subarea into smaller subareas (by obtaining more finely grained population and area data) then the population-weighted density ρ_W does not decrease, and will strictly increase unless all the new subareas have the same density. In other words, the maximum value of ρ_W for a region is obtained by breaking it into small homogeneous subareas.

Definition 3.7. *For a given region we define the* variability coefficient $V = \rho_W/\rho_S$. *Note that this is a dimension-free quantity.*

From Lemma 3.6, we know that $V \geq 1$ for any region. This ratio measures the extent to which population is evenly distributed in a region; returning to the toy Example 3.1, notice that Averagia has $V = 1$, Builtupia has $V = 10$ and Citia has $V = 100$. These values may help calibrate our understanding of the values of V observed for actual regions.

3.2 Population density analysis of Western countries

First, since we have values for all three measures ρ_S, ρ_N and ρ_W for a range of European countries, we compare how well each measure explains the rate of spread of COVID-19.

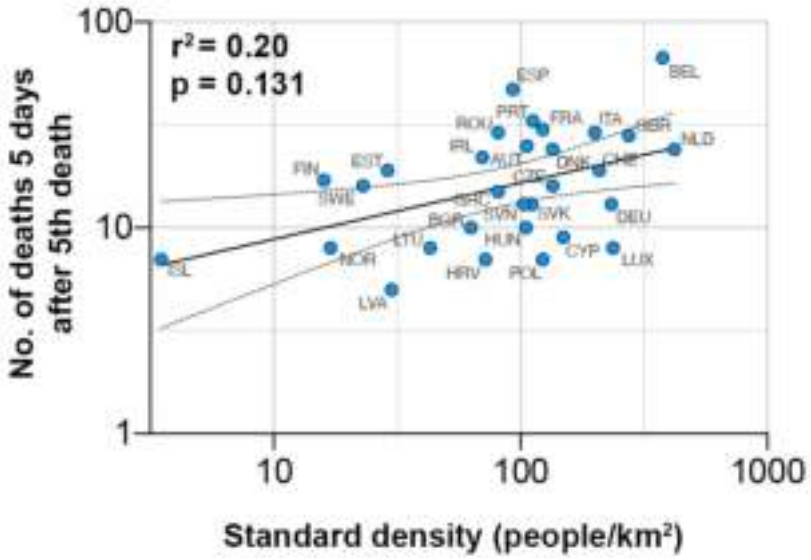


Figure 2: Simple linear regression analysis of rate of COVID-19 spread against standard population density ρ_S for European countries. Both axes are on a log scale. $n = 30$, dashed lines represent 95% CI.

In Figure 2 we plot the correlation between the rate of COVID-19 spread and the standard population density ρ_S for European countries. However, the r^2 of 0.20 is relatively

low and the p-value of 0.131 means a lack of statistical significance. In contrast, for the rate of spread and the respective lived density measures, the effect is stronger than for the corresponding plot for ρ_S. In Figure 3 we see a significant correlation between rate of spread and ρ_N for Europe ($r^2 = 0.26$ and $p < 0.004$), and in Figure 4 we see an even stronger effect in terms of ρ_W ($r^2 = 0.53$ and $p < 0.0001$). Therefore, we conclude that in each case using non-standard measures of population density reveals statistically significant effects compared with those arising from the standard population density ρ_S. It appears that the population-weighted measure ρ_W is of the most value in this sense, explaining over half the variation in the rate of spread of COVID-19 across Europe.

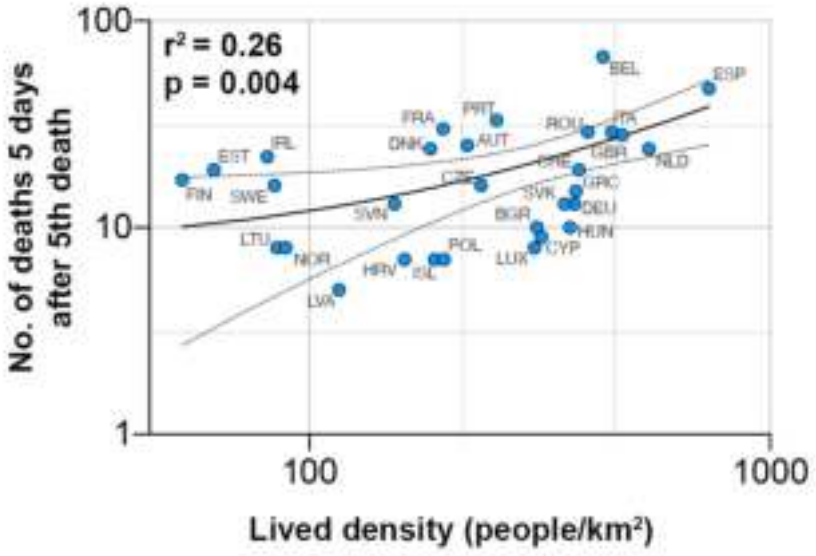


Figure 3: Simple linear regression analysis of rate of COVID-19 spread against non-empty lived population density ρ_N for European countries. Both axes are on a log scale. $n = 30$, dashed lines represent 95% CI.

Having established that ρ_W works well to explain the variation in rates of spread among European countries, we can perform a similar analysis for a wider range of countries.

First, we add the United States, Canada and Israel to the range of countries considered, to emphasise that the correlation observed is not restricted to European countries. As before, the standard density ρ_S does not explain a significant fraction of the correlation, achieving $r^2 = 0.13, p = 0.0378$ (figure not shown here for brevity).

However, in Figure 5, we show that adding these further countries still leaves a good fit between ρ_W and the number of deaths 5 days after the 5th death. Further, we show that this early rate of spread is crucial in determining the ultimate scale of the epidemic, by shading each point according to the number of deaths per million 120 days after the 1st case. It is striking that generally the countries with the highest final death tolls are positioned to the right-hand side of the graph, indicating that they are typically those with

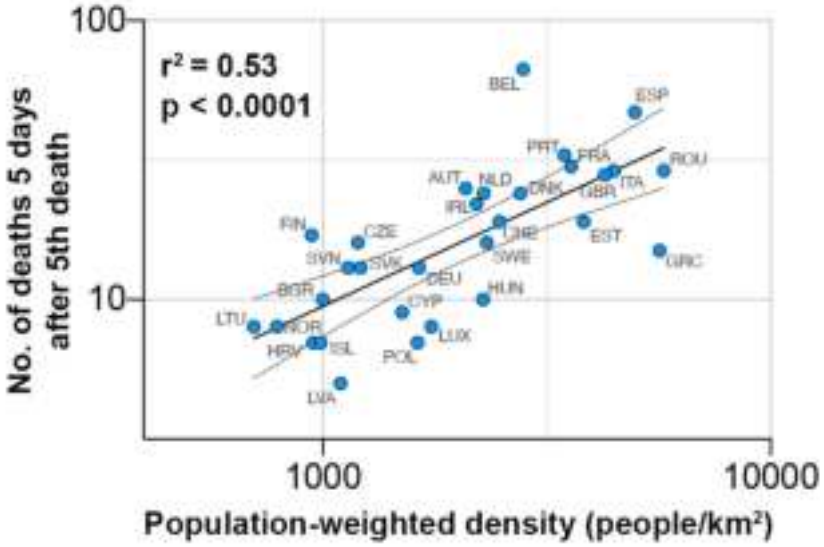


Figure 4: Simple linear regression analysis of rate of COVID-19 spread against population-weighted density ρ_W for European countries. Both axes are on a log scale. $n = 30$, dashed lines represent 95% CI.

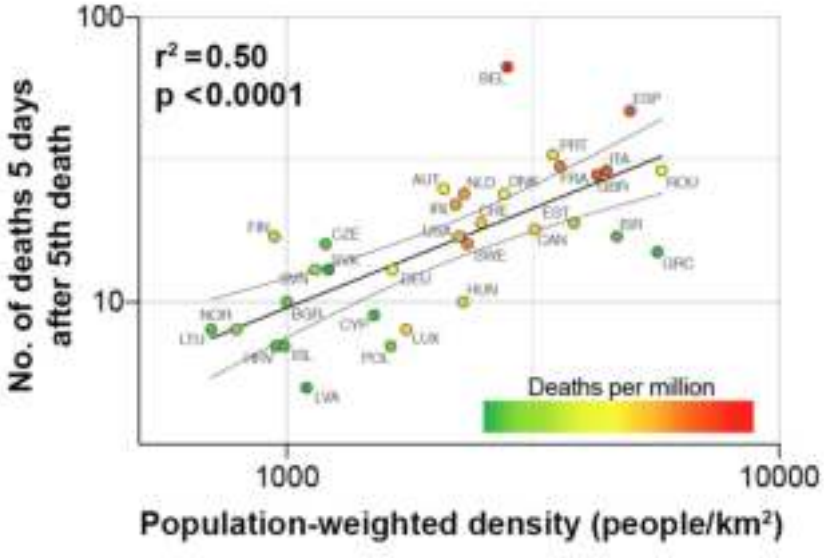
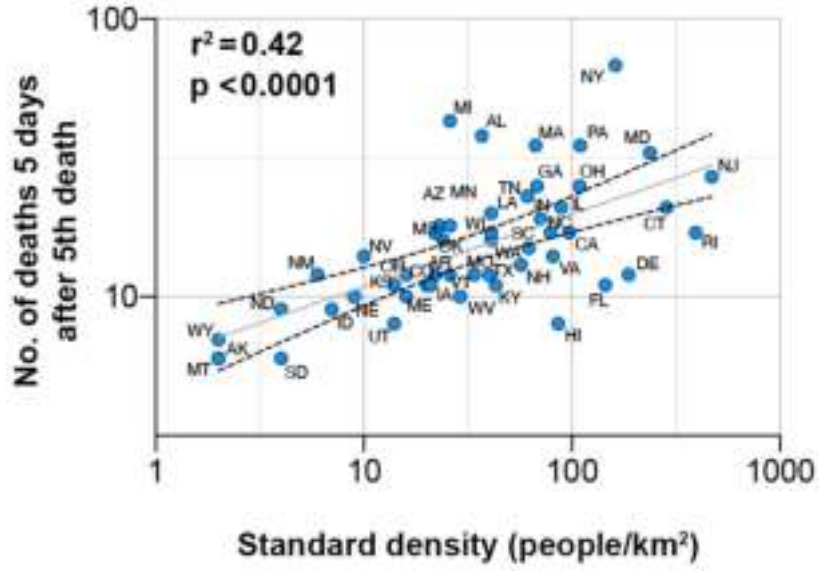


Figure 5: Simple linear regression analysis of rate of COVID-19 spread against population-weighted density ρ_W for a range of Western countries. Plot is on a log-log scale. $n = 33$, dashed lines represent 95% CI. Deaths per million are 120 days after the 1st confirmed case for each country.

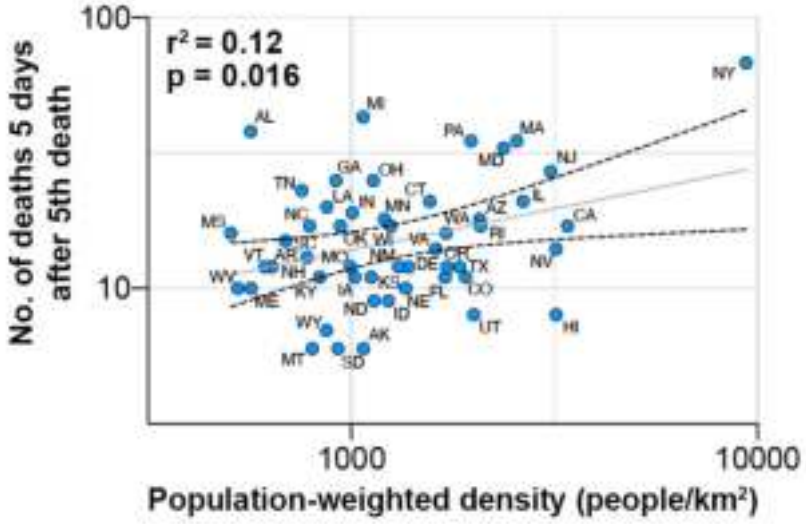
large population-weighted densities.

3.3 Limitations of population density: US states

Next, we perform a similar analysis for the US states, to confirm analysis of [30] who found a statistically significant effect for population-weighted density ρ_W.



a)



b)

Figure 6: Simple linear regression analysis for US states of rate of COVID-19 spread against a) standard density ρ_S b) population-weighted density ρ_W. Plots are on a log-log scale. $n = 50$, dashed lines represent 95% CI.

As shown in Figure 6, the population-weighted density does indeed provide a statistically significant effect ($r^2 = 0.12$, $p = 0.016$). However it is striking that in this case, in contrast to the case of European countries, the standard density ρ_S explains more of the

variation ($r^2 = 0.42$, $p < 0.0001$).

In particular, we can observe from Figure 6 that there is surprisingly little variability in the values of ρ_W calculated. For example, even extremely sparsely-populated states such as Alaska and Wyoming (with standard density $\rho_S \leq 2$) have a population-weighted density ρ_W between 800 and 1100, comparable with denser states such as Georgia ($\rho_S = 68$) and Indiana ($\rho_S = 71$).

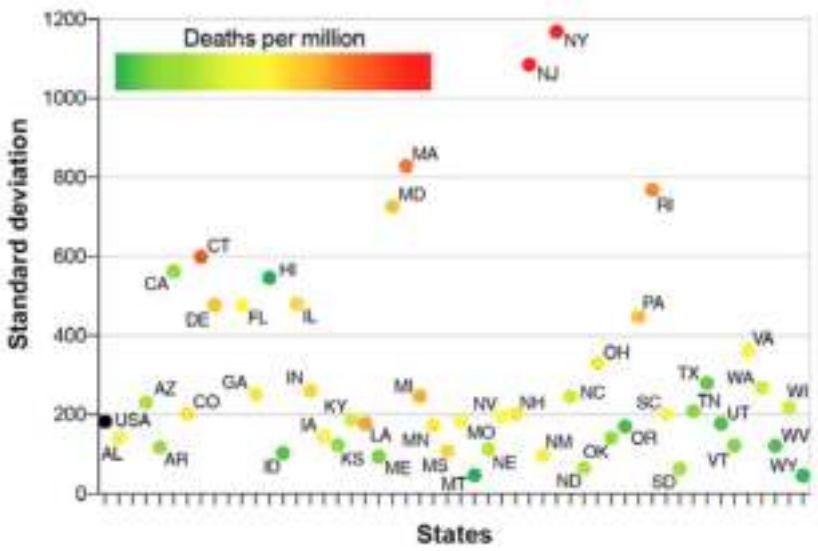


Figure 7: Values of standard deviation observed for US states, shaded according to the deaths per million 120 days after the 1st confirmed case in each state

We can understand this better by studying the standard deviation of the population values n_i within grid squares in a state. If the squares all have area of one square kilometer, then calculation in the spirit of Remark 3.5 shows that since the expected value of n_i is ρ_S, the variance of n_i satisfies

$$\mathrm{Var}(n_i) = \rho_S \rho_W - \rho_S^2,$$

so that the standard deviation is $\rho_S \sqrt{V - 1}$, meaning it captures a combination of standard density and variability.

In Figure 7 we plot the values of standard deviation for each state in alphabetical order, with points shaded according to their deaths per million 120 days after the first confirmed case in each state. It is striking to observe that high values of this standard deviation measure correctly identify the states with highest numbers of deaths - with the majority, however, having similar values for standard deviation and deaths per million.

3.4 The Hofstede measure of individualism can control for country-level differences in the response to COVID-19

Population-weighted density could not explain variation in the early or late stages of COVID-19 epidemics between multiple East Asian countries (data not shown). However, population-weighted density was able to significantly explain the number of deaths per million 120 days after the 1st confirmed case across a global collection of countries including both Western and East Asian countries but the variance explained was relatively low ($r^2 = 0.14$, $p = 0.0075$). This lack of explanatory power for population density (either ρ_S or ρ_W) is particularly noticeable as multiple East Asian countries have very high population densities. For example, Singapore with a population-weighted density of 21,925 and Hong Kong with 46,301 are far in excess of any Western country. As both pre- and peri-pandemic responses to new and emerging infectious diseases could be affected by cultural differences we investigated the explanatory power of the Hofstede individualism score, which has been correlated with historical pathogen exposure [8, 7, 21]

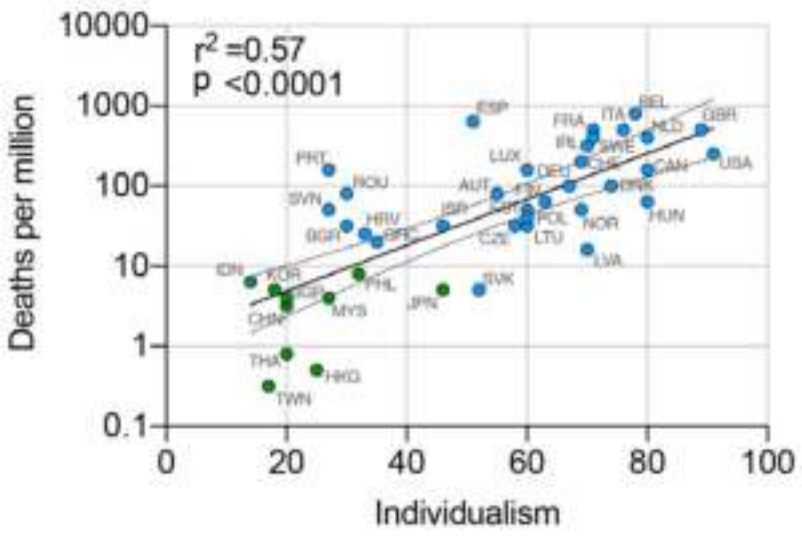


Figure 8: Simple linear regression analysis shows the Hofstede measure of individualism explains the global variation in deaths per million 120 days after the 1st confirmed COVID-19 case (green = Asian countries, blue = Western). $n = 41$, dashed lines represent 95% CI.

As can be seen in Figure 8, the Hofstede measure of individualism significantly explains variation in the number of deaths 120 days after the 1st clinically confirmed COVID-19 case across multiple Western and East Asian countries.

One possible criticism of the individualism measure in this context is that the green and blue points are somewhat separated in Figure 8, and so this score may be serving as a

proxy for other factors that give the difference between Western and East Asian countries. However, we observed that the Hofstede individualism score can control for country-level responses when examining the role of population density in explaining variation in COVID-19 epidemic sizes across Western countries late in the ongoing pandemic. For example, Figure 9 shows that individualism can improve the fit of deaths per million across Western countries. A multiple linear regression based on both population-weighted density ρ_W and the Hofstede individualism score shows that both these variables are statistically significant in this context, and together give $R^2 = 0.46$ when considering deaths per million 120 days after the 1st confirmed COVID-19 case (which is considerably higher than the $r^2 = 0.27$ achieved in this context by ρ_W alone).

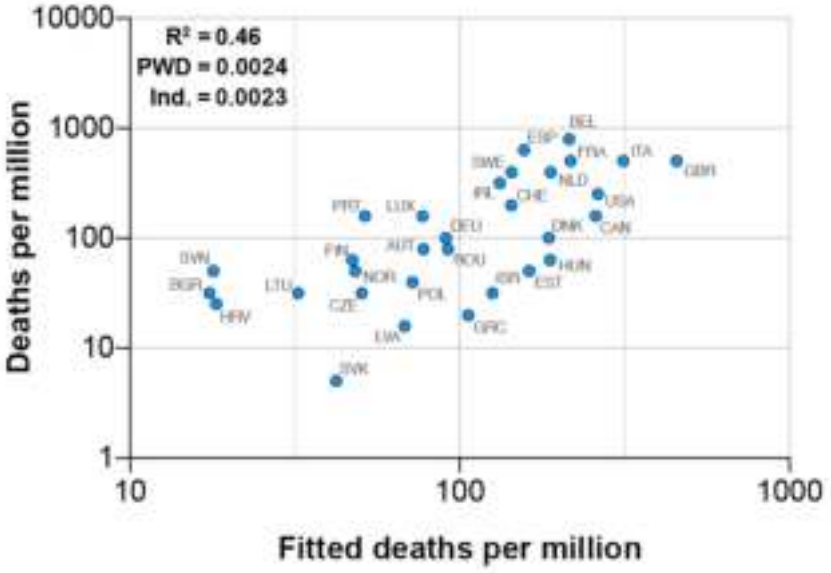


Figure 9: Multiple linear regression between deaths per million 120 days after the 1st confirmed COVID-19 case and a combination of the Hofstede individualism score (Ind) and population-weighted density ρ_W (PWD) for Western countries. $n = 33$.

4 Discussion

Country-level comparisons have been used to assess government responses to the COVID-19 pandemic. For these comparisons to be useful, they must be done using carefully controlled analysis. This study is an early contribution to this effort which focuses on population density. We find that the initial rate of spread of COVID-19 across Western countries can be readily explained by their population-weighted density. PWD does not appear to be as crucial for the spread of COVID-19 in East Asia, or for explaining the size of current epidemics recorded across multiple countries. However, controlling for country-level responses using the Hofstede cross-cultural measure of individualism allows a substantial

proportion of the variance in the size of current COVID-19 epidemics across Western countries to be explained.

PWD can be seen to more readily explain the initial rate of COVID-19 spread by examining individual countries as plotted in Figure 4. For example, Spain has one of the quickest rates of COVID-19 spread yet its standard population density $\rho_S = 93$ people/km^2 is relatively low; in contrast, Spain has one of the highest lived non-empty population densities in Europe, with a value of $\rho_N = 737$ people/km^2, and one of the highest PWD, with $\rho_W = 4980$ people/km^2. As discussed in detail in [28], much of Spain is unpopulated, with very high density populations in Barcelona and Madrid. As a result, other than three very small countries (Monaco, Andorra and Malta, not studied here because of the size of their epidemics), Spain is one of the most densely populated countries in Europe, which our measure of population density captures.

Also of note, are countries whose rate of spread is as predicted by their PWD despite popular perception about their relative performance. For example, Germany has a population-weighted density $\rho_W = 1641$ people/km^2 — lower than Sweden or Ireland (see Appendix A) — reflecting the fact that its population is fairly evenly distributed across the country (giving its relatively low value $V = 7$). Considering Germany's PWD, it may be unnecessary to postulate the existence of an 'immunological dark matter' to explain the current size of its epidemic [33]. In fact, from Figure 4 the European country which stands out for having a significantly slower spread than expected is Greece, which has a very high population-weighted density. This may be due to its high stringency national response [12], which is particularly interesting as it has one of the lowest Hofstede individualism scores within Europe [15, Table 4.1].

Our observation that standard population density ρ_S but not PWD ρ_W predicts the rate of COVID-19 spread across US states was unexpected. We can observe from Figure 6b that there is surprisingly little variability in the values of ρ_W calculated. The fit observed in Figure 6a due to standard population density ρ_S comes through sparsely-populated states such as Alaska and Wyoming, with the remainder of the states forming a relatively homogenous cluster. It is striking that New York, the state with the fastest rate of spread, has a significantly higher value of ρ_W than any other state, whereas is not an outlier in terms of ρ_S, indicating the importance of ρ_W in this context. These observations combined suggest that the lived population density experienced by many Americans is similar; this hypothesis is supported by the observation that the standard deviations for population density within US states as plotted in Figure 7 are also similar. It may be possible that other factors such as mobility (i.e., travel between states) affect the rate of COVID-19 spread within the USA; as has been observed, for example, in China [19]. Although, for epidemic management, there is still value in observing that US states with the highest PWD, like New York, are, as predicted, those with quickest rate of COVID-19 spread. For the USA as a whole, the Hofstede measure of individualism was found to accurately predict its current epidemic size relative to other less individualistic countries. Why might this cross-cultural axis between individualism and collectivism explain variation in COVID-19?

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As argued by Fincher and Thornhill [7], collectivism has a two-fold benefit in protecting societies against pathogens. The first is greater attention to in-group vs out-group members, which can limit contact with out-group members either in general or during disease outbreaks; and the second is increased social pressure to conform to group priorities over individual rights. These are culture-wide attitudes and we hypothesise that the Hofstede score can be used as a proxy for both government-level responses and everyday social pressure to perform prosocial behaviour. At the level of government, these differences in cultural values may have impacted how quickly and strongly control measures were put in place to limit the spread of COVID19 [12]. For example, limiting travel within and between countries for both nationals and non-nationals, widespread population surveillance to identify infected individuals and their contacts, and quarantining infected individuals and anyone they have come into contact with; in contrast, in more individualistic countries governments have been slow to restrict individual rights and less comprehensive [12, 13]. At the level of everyday individual conduct the ability of a society to enforce prosocial behaviour (e.g., symptom vigilance and self isolation, mask wearing, hand hygiene) may impact the probability of outbreaks; for example, where they are dependent on superspreader events [20].

We have focused on population density as a default, stable variable that may impact differences in the dynamics of epidemics between countries. What other variables might also play a role?

Advanced age is a risk factor for severe disease and mortality following infection with SARS-CoV-2 [24, 42]. Considering immunosenescence and 'inflamm-aging' are known features of advanced age, it is possible that industrialised countries with aging populations may have sufficient densities of immunocompromised people to promote outbreaks of zoonotic pathogens initially ill adapted to human-to-human transmission [10, 11, 39]). And in terms of country comparisons, age has been a factor impacting relative differences in mortality [3].

At the country-level and in the absence of physical distancing measures, mobility has a significant impact on the spread of COVID-19 ([19]). The degree to which this factor has impacted the international spread of COVID-19 has yet to be formally investigated. However, two countries noticeably absent from our analysis may give possible insight to this question. Although Australia and New Zealand only marginally reduce the variance explained for the initial rate of spread of COVID-19 amongst Western countries ($r^2 = 0.47$, $p < 0.0001$), these two highly individualistic countries are outliers in the global comparison of deaths per million using the Hofstede score ($r^2 = 0.41$, $p < 0.0001$). Compared to the UK, for example, AUZ and NZ have 4-fold and 10-fold less international arrivals, respectively, per year [36]. Therefore, it may be the case that the international connectivity of countries such as the UK has played an important role in the size of its epidemic [27].

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5 Conclusion

This study attempts to robustly control one demographic variable, population density, so that relative differences in the spread of COVID-19 between countries can be compared. By highlighting where and when this factor has contributed to the spread of COVID-19, we believe this study can contribute to the discussion about which epidemic control measures are suitable for which countries. In general, shielding immunocompromised people living at relatively high density, for example the elderly in care facilities, should be essential. Other control measures exist over different time-scales. For example, in the short-term highly internationally connected countries such as the UK and USA should limit travel. However, in the long-term these two countries, as well as others across the West, should discuss democratically how to respond to new and emerging infectious diseases rapidly while preserving individual rights. As the prospect of a second wave of COVID-19 is likely [43], both the short and long term, however, are now and soon.

Acknowledgments

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A Table of densities for European Countries

Country	Non-empty ρ_N	Population-weighted ρ_W	Standard ρ_S	Variability $V = \rho_W/\rho_S$
Austria	220	2084	106	20
Belgium	434	2804	376	7
Bulgaria	312	1000	63	16
Croatia	161	952	72	13
Cyprus	319	1504	149	10
Czechia	236	1198	135	9
Denmark	183	2761	135	20
Estonia	62	3827	29	132
Finland	53	944	16	59
France	195	3590	123	29
Germany	376	1641	233	7
Greece	379	5654	81	70
Hungary	368	2280	105	22
Iceland	187	989	3.5	283
Ireland	81	2203	70	31
Italy	453	4460	200	22
Latvia	116	1096	30	37
Lithuania	85	702	43	16
Luxembourg	308	1750	237	7
Netherlands	546	2289	420	5
Norway	89	791	17	47
Poland	196	1627	123	13
Portugal	255	3469	112	31
Romania	402	5771	81	71
Slovakia	358	1215	111	11
Slovenia	153	1140	103	11
Spain	737	4980	93	54
Sweden	84	2246	23	98
Switzerland	385	2479	208	12
UK	478	4265	274	16

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B Table of densities for other selected countries

Country	Population-weighted ρ_W	Standard ρ_S	Variability $V = \rho_W/\rho_S$
Australia	2273	3.2	758
Canada	3188	4	797
China	7098	146	49
Hong Kong	46301	6781	7
Israel	4678	417	11
Japan	5338	333	16
Malaysia	2745	99	28
New Zealand	2030	19	107
Philippines	9254	362	26
Singapore	21925	7894	3
South Korea	9265	516	18
Indonesia	3447	141	24
Taiwan	10602	652	16
Thailand	2832	130	22
USA	2241	34	66

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C Table of densities for US States

State	Population-weighted ρ_W	Standard ρ_S	Variability $V = \rho_W/\rho_S$
AL	566	37	15.3
AK	1072	0.5	2144.6
AZ	2070	23	90.0
AR	639	22	29.0
CA	3409	97	35.1
CO	1913	20	95.7
CT	1562	286	5.5
DE	1385	187	7.4
FL	1705	145	11.8
GA	919	68	13.5
HI	3198	86	37.2
ID	1236	7	176.6
IL	2650	89	29.8
IN	1007	71	14.2
IA	1020	21	48.6
KS	1120	14	80.0
KY	838	43	19.5
LA	872	41	21.3
ME	567	16	35.4
MD	2372	238	10.0
MA	2557	336	7.6
MI	1070	67	16.0
MN	1208	26	46.5
MS	507	24	21.1
MO	997	34	29.3
MT	803	2	401.5
NE	1363	9	151.5
NV	3194	10	319.4
NH	779	57	13.7
NJ	3102	470	6.6
NM	1310	6	218.4
NY	9371	162	57.8
NC	790	79	10.0
ND	1139	4	284.6

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State	Population-weighted ρ_W	Standard ρ_S	Variability V
OH	1134	109	10.4
OK	941	22	42.8
OR	1724	16	107.7
PA	1973	110	17.9
RI	2083	394	5.3
SC	690	62	11.1
SD	928	4	232.0
TN	757	61	12.4
TX	1848	40	46.2
UT	2004	14	143.1
VT	614	26	23.6
VA	1617	81	20.0
WA	1713	41	41.8
WV	526	29	18.1
WI	1253	41	30.6
WY	871	2	435.4

0441

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SARS-CoV-2 in Italy: Population Density correlates with Morbidity and Mortality

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SARS-CoV-2 in Italy: Population Density correlates with Morbidity and Mortality

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Running Head: COVID-19 in Italy: Morbidity and Mortality

Keywords: COVID-19; Population density; Medical Supplies; Morbidity; Case-Fatality Rate

Summary

Since the beginning of the SARS-CoV-2/COVID-19 epidemic in China, elderly and multimorbid subjects showed a higher mortality rate. However, other factors could influence the mortality and the spread of contagion such as the population density. An archival research based on the Italian data stratified by region was performed in order to quantify the association between the population density, ageing index, number of positive cases, number of deaths, case-fatality rate, and medical equipment (gloves, masks, and ventilators). Results showed a significant positive linear relationship between the population density and cases, deaths, and case-fatality rate. No correlation with the ageing index was shown. Furthermore, we found a significant positive correlation between the number of medical supplies and population density, cases, and deaths. However, the medical supplies did not show any correlation with the case-fatality rate. Taken together, these findings suggest that the population density and the lack of medical equipment are key factors explaining morbidity and mortality of COVID-19 in Italy.

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On 31 December 2019, a cluster of pneumonia of unknown etiology was found in the city of Wuhan, Hubei Province. Twenty-seven patients presented with fever, cough, shortness of breath, and bilateral lung infiltrates (1). On 9 January 2020, the causative agent of pneumonia was identified: a new coronavirus, provisionally named 2019-nCoV and later renamed as SARS-CoV-2 by the International Committee on Taxonomy of Viruses (1). By that moment, the infectious disease is commonly referred to as COVID-19 (COronaVIrus Disease 19). There are many hypotheses about the genesis of SARS-CoV-2/COVID-19. Although some of them are quite inventive, the zoonotic spillover appears the most reliable and comprehensive explanation. It takes into account a wide range of factors associated with the ignition and maintenance of the infection, including ecological, anthropological, and epidemiological determinants of pathogen exposure (2).

From the clinical standpoint, it was immediately clear that mortality was higher in elderly and multimorbid individuals: the first death occurred in a 61-years-old patient with abdominal tumor and chronic liver disease (3). This evidence has been further supported by the Italian epidemiological data (4). Out of a total of 73780 cases, the deaths are 6801 with a significant increase of the disease severity in patients aged over 69 years, as shown by the case-fatality rate (CFR), i.e., the proportion of deceased patients among the total number of positive cases. In particular, the highest number of deaths (5105, pairs to approximately 75%) has been recorded in patients aged between 70 and 89 years. The median age of deceased patients is 79 years, whereas it is 63 years in the whole cohort of positive cases (5). The presence of concomitant chronic pathologies has been observed in 710 patients who died, with three or more associated diseases in 50% of cases (5). Sex also appears to be a significant risk factor since the CFR is higher in men than women regardless of age (male = 11.4%, female = 6.5%) (4). However, the effect of the population density (PD) on the spread of contagion and mortality rate should not be overlooked.

In order to quantify the relationship between the impact of COVID-19 on the Italian population and the demographic/epidemiological data available for each region (4, 6–8), we carried out an explorative "archival" analysis by crossing the PD (i.e., number of inhabitants per Km^2), the

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ageing index (AI, i.e., the number of elders per 100 persons younger than 15 years old), the number of positive cases, the number of deaths, the CFR, and the number of the main medical supplies (MS) distributed around the country (i.e., gloves, masks, and ventilators). For this purpose, we used a non-parametric Spearman's correlation analysis (r_{rho}). The significance threshold was fixed at $\alpha < 0.05$. The descriptive statistics for each Italian region are reported in Table 1.

A significant and moderate correlation emerged between the PD and the number of cases ($r_{rho} = 0.67$, $p = .001$), deaths ($r_{rho} = 0.69$, $p = .001$), and CFR ($r_{rho} = 0.47$, $p = .03$) (Fig. 1). The housing density reasonably increases the speed with which the virus spreads since a greater number of social contacts enhances the likelihood of transmission. However, no correlation between the AI and the number of cases ($r_{rho} = -0.16$, $p = .50$), deaths ($r_{rho} = -0.04$, $p = .85$), and CFR ($r_{rho} = 0.13$, $p = .57$) was found (Fig. 2). This suggests that the areas mainly inhabited by elderly are not necessarily the most affected by the disease. For instance, the Molise and the Friuli Venezia Giulia regions have an overlapping AI, but the CFR is higher in the former. Furthermore, Lombardy is the Italian region hardest hit by the COVID-19, with the highest CFR and a weak-to-moderate AI. Liguria is the fourth region in terms of CFR, despite being the "oldest" territory as shown by the highest AI (Table 1).

What do we know about sex and multimorbidity? Based on the data released by the Italian National Institute of Statistics (ISTAT) for biennium 2018–2019 (9), 49.2% of the over-65s and 66.6% of the over-75s reported at least two serious chronic diseases. Interestingly, the percentage of multimorbidity was higher in women (over-65s = 54.5%, over-75s = 72.9%) compared to men (over-65s = 43%, over-75s = 57.6%) (9). These data would tend to suggest that elderly multimorbid women should be more affected by the infection. The Italian experience is telling us exactly the opposite, namely, women are less affected by the COVID-19 compared to men both in terms of total cases and mortality (4). A partial explanation for this evidence may be arise from the lower immune reactions observed in males compared to females in both the innate and acquired immunity responses (10).

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As concerns the MS, results showed a significant moderate correlation between the PD and the number of gloves ($r_{rho} = 0.49$, $p = .03$), masks ($r_{rho} = 0.63$, $p = .003$), and ventilators ($r_{rho} = 0.56$, $p = .01$). Furthermore, a strong linear association was found i) between the number of positive cases and MS (gloves, $r_{rho} = 0.89$, $p = .0001$; masks, $r_{rho} = 0.76$, $p = .0001$; ventilators, $r_{rho} = 0.90$, $p = .0001$), and ii) between the number of deaths and MS (gloves, $r_{rho} = 0.84$, $p = .0001$; masks, $r_{rho} = 0.69$, $p = .001$; ventilators, $r_{rho} = 0.81$, $p = .0001$) (Fig 1). As previously discussed, the most densely-populated regions are also the most affected by the outbreak; consequently, they need increased resources to deal with the emergency. However, the MS showed no correlation with the CFR (gloves, $r_{rho} = 0.28$, $p = .23$; masks, $r_{rho} = 0.31$, $p = .18$; ventilators, $r_{rho} = 0.25$, $p = .29$) (Fig. 2). This finding is quite interesting, since the number of the available MS may have not been sufficiently large in terms of both primary prevention (i.e., gloves and masks) and management of patients with severe respiratory failure (i.e., ventilators).

Among other factors influencing the vulnerability to COVID-19, a recent "position" paper of the Italian Society of Environmental Medicine (SIMA) explored the role exercised by the atmospheric particulate matter (PM) (11). The PM could act as a carrier for many contaminants including viruses. Since high concentrations of PM_{10} (diameter < 10 mμ) were recorded in some provinces of Northern Italy at the beginning of the epidemic, PM may have exerted a "boost" action in these territories. Conversely, such a phenomenon was not observed in other areas of the peninsula (11). Beyond this hypothesis, inhalation of PM can certainly act as irritative stimulus for the respiratory tree; indeed, it is associated with increased respiratory morbidity (12). It should also be recalled that COVID-19, as all infectious diseases, is the result of the interaction between the virulence of the infective agent and the individual vulnerability. In this perspective, the genomic epidemiology could help to better define many aspects of the pandemic, i.e., the genetic diversity, the reliability of diagnostic methods, and the design of appropriate therapies and potential vaccines (13).

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The main limitation of the present study is ascribable to its nature of ecological study; we used only regional aggregated-level data. In this vein, further studies using individual-level data are needed to confirm our hypothesis. Based on the examination of demographical and epidemiological data, we suggest that PD, in addition to age, multimorbidity, and lack of medical equipment, is one of the key factors explaining morbidity and mortality of COVID-19 in Italy. Consequently, the restrictive measures including the social distancing and quarantine remain the most effective, pending a vaccine or targeted therapies.

Conflict of interest

None to declare.

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Table 1. Descriptive statistics for each region (Data updated to 26 March 2020)

Region	PD (Inhab/Km^2)	AI (%)	Total cases	Total deaths	Cases per 1000 pop	Deaths per 1000 pop	CFR (%)	Gloves[a]	Masks[b]	Ventilators[c]
Abruzzo	121	191.8	824	12	0.62	0.01	1.45	155000	515410	5
Basilicata	56	193.2	10	0	0.01	-	-	41500	288621	2
Calabria	128	163.3	223	6	0.11	0.00	2.69	45000	288395	3
Campania	424	129.8	1151	40	0.19	0.01	3.47	140000	1368024	10
Emilia Romagna	199	182.6	10008	1068	2.24	0.23	10.67	698000	4740809	158
Friuli Venezia Giulia	153	217.2	918	66	0.75	0.05	7.18	244500	569120	3
Lazio	341	162.6	1817	88	0.30	0.01	4.84	158000	1474007	15
Liguria	286	255.8	1695	180	1.09	0.11	10.61	202000	870540	56
Lombardia	422	165.5	34907	4484	3.46	0.44	12.84	3142000	4223495	346
Marche	162	196.2	3011	97	1.97	0.06	3.22	393500	-	63
Molise	69	217.5	73	8	0.23	0.02	10.95	35500	101544	-
Piemonte	172	205.9	5111	194	1.17	0.04	3.79	821500	4005452	84
Puglia	206	168.6	1165	61	0.28	0.01	5.23	152000	622450	14
Sardegna	68	212.0	292	13	0.17	0.01	4.45	100000	307237	-
Sicilia	194	153.7	458	15	0.09	0.00	3.27	80000	927750	-

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Toscana	162	204.6	2247	59	0.60	0.01	2.62	370600	2579780	28
Trentino-Alto Adige	79	138.5	2126	92	1.98	0.08	4.32	161300	1278620	17
Umbria	104	204.2	409	11	0.46	0.01	2.68	308000	950393	20
Valle d'Aosta	39	181.6	400	6	3.18	0.04	1.50	55000	324060	5
Veneto	267	172.1	6935	301	1.41	0.06	4.34	317000	3781863	177

PD, Population Density; Inhab, Inhabitants; AI, Ageing Index; pop, population; CFR, Case-Fatality Rate

([a]) Latex Gloves EN420 and EN374

([b]) Surgical Face Mask, Non-Surgical Face Masks, Masks FFP2 and FFP3

([c]) Lung Ventilators for Intensive Care Unit (compressed air), Lung Ventilators for Sub-Intensive Care Unit (turbine)

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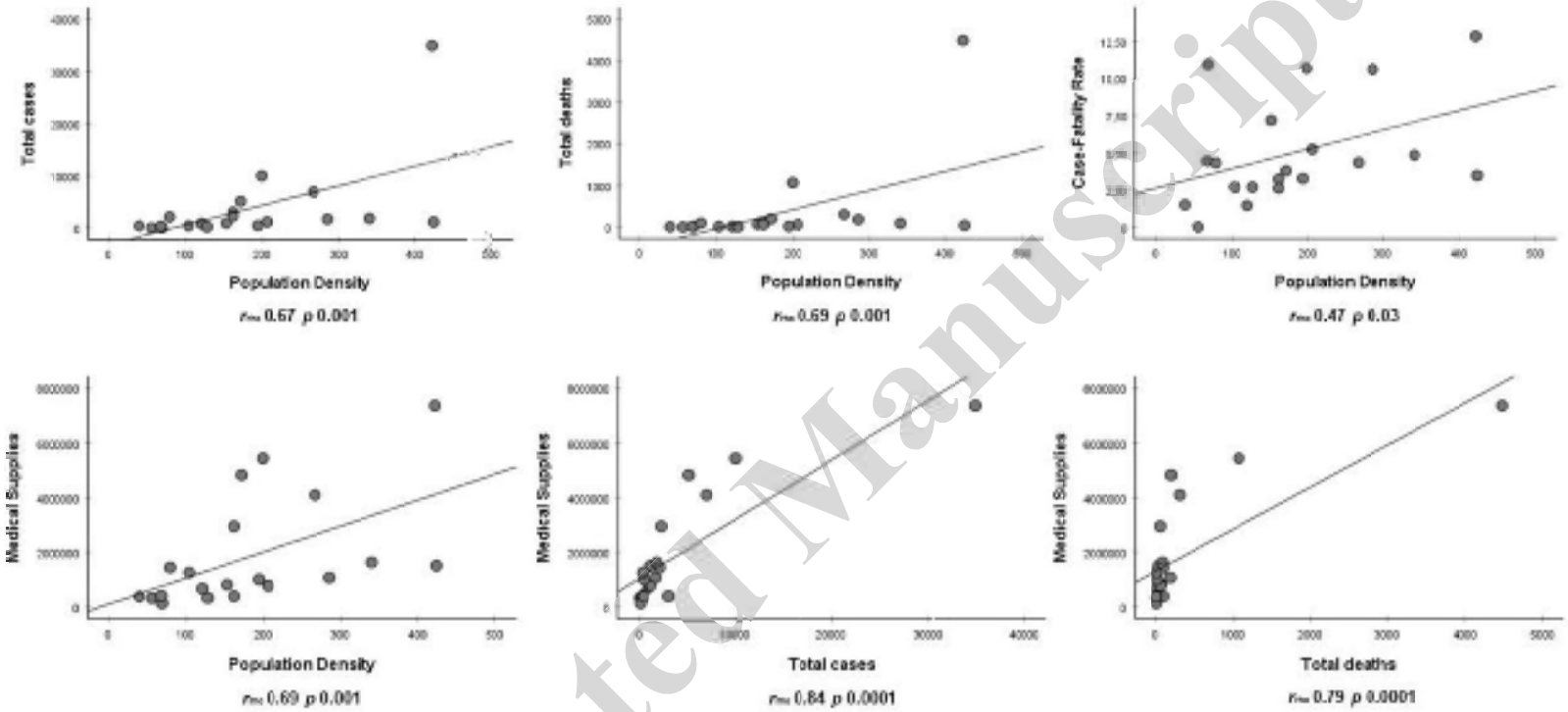

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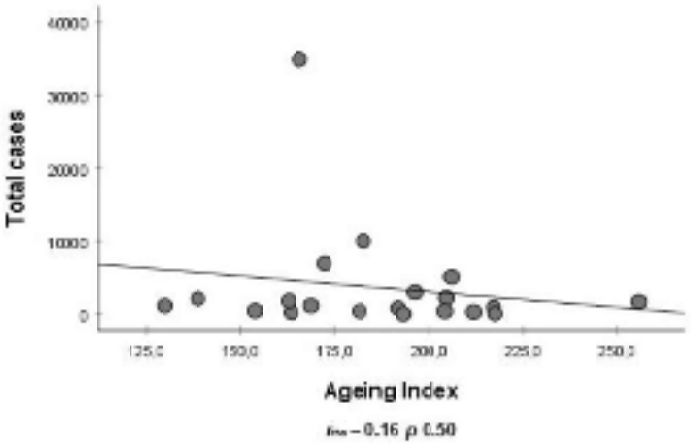

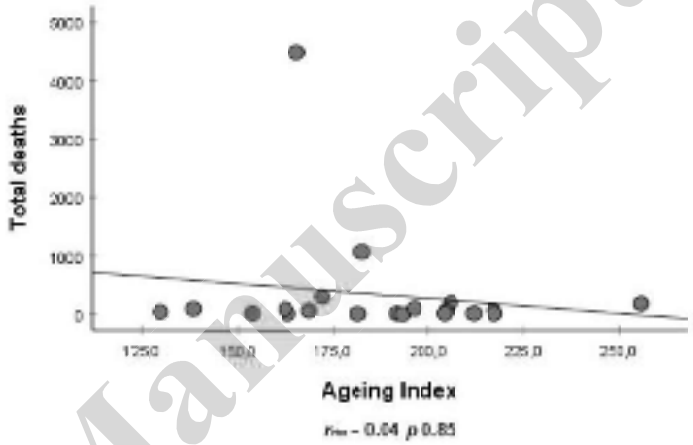

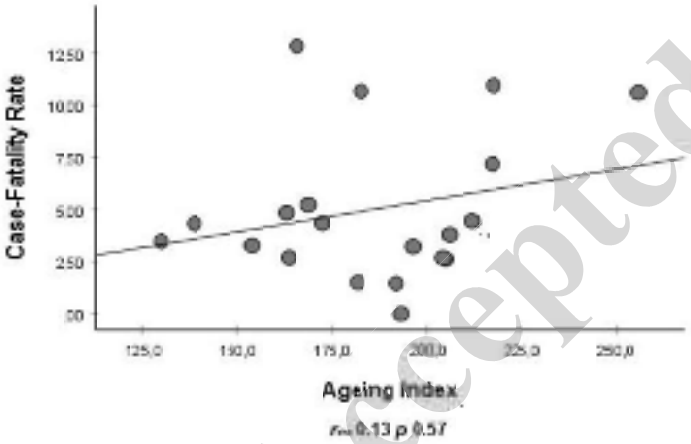

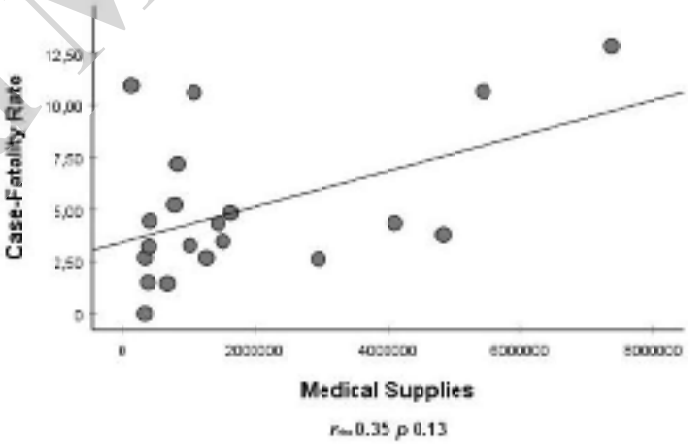

Accepted Manuscript

Seroprevalence of SARS-CoV-2 in slums versus non-slums in Mumbai, India

Estimating seroprevalence is crucial for controlling the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There are few published serosurveys in low-income and middle-income countries, which comprise over two-thirds of confirmed cases of COVID-19.[1] India has 6·1 million confirmed cases—a fifth of the worldwide total. Socioeconomic disparities and population density might drive disease dynamics in megacities that account for a large share of India's cases. To address these issues, we estimated prevalence in six slum and non-slum communities across three wards (one each from the three zones) of Mumbai, India.

This study was approved by the Indian Government and Institutional Review Boards at participating institutions (appendix p 1). On the basis of power calculations to estimate a 1·5 percentage-point difference in prevalence in a two-sided test with 95% CI in each study site, we aimed to test a total of 8870 individuals from both slum and non-slum communities across three wards: 2249 from Matunga, 1622 from Chembur West, and 576 from Dahisar (appendix p 11). We confined sampling between June 29 and July 19, 2020, to ensure that prevalence did not change substantially during the study. Individuals aged 12 years or older were eligible; those who did not consent or had contraindications to venipuncture were excluded.

Working in eight of the largest slums per ward, we divided each slum into areas covering roughly 400 homes. We sampled 100 homes per area, starting from the centroid of each area and selecting every fourth home. We divided the non-slum areas of each ward into cells of equal size so that sampling 100 persons per cell would meet our target sample size for that ward. Starting from a building at the centre of each cell, we obtained consent from resident associations to recruit one household per floor. We sampled adjacent buildings this way until the target was met or the study period ended.

Surveyors sought voluntary consent from one person per household, rotating through a list of eight demographic groups (female and male participants from four age strata) across households. Our final sample is a function of the population distribution across groups and consent rate per group.

We collected data on household demographics and 5 mL of blood from participants via venipuncture. Samples were tested for IgG antibodies to the nucleocapsid via chemiluminescence by use of Abbott Diagnostics Architect test (Abbott, IL, USA), for which sensitivity ranged from 90·0% (95% CI 74·4–96·5)[2] to 96·9% (89·5–99·5)[3] and specificity from 100·0% (95·4–100·0)[2] to 99·9%.[3]

We estimated the proportion of tests that were positive using Abbott's recommended cutoff (1·4) and score CIs. We used binomial regression of test results on indicators for age and sex to estimate demographic correlates of positive tests. By use of weights that matched the demographic distribution in samples and their respective sites, we calculated age-weighted and sex-weighted proportions. We used data from India's 2011 Census to aggregate adjusted proportions to the slum and non-slum level across wards. We derived adjusted seroprevalence from adjusted proportions using the Rogan–Gladen[4] correction for imperfect test accuracy, assuming low and high estimates of sensitivity and associated specificity. CIs for adjusted proportions are adjusted Wald intervals and those for seroprevalence are unadjusted Wald intervals; statistical comparisons employ Wald tests. We examined sensitivity to the cutoff recommended by Abbott by plotting the distribution of underlying IgG scores and estimated proportions under different cutoffs. We mapped the proportion of positive tests to location using latitude and longitude rounded to 4 significant digits. We analysed 4202 samples from slums and 2702 samples from non-slums (appendix pp 11–13).

Consent rates in slums were comparable with other studies.[1] For instance, in slums in Matunga, we recruited 45·6% of households visited. Based on field notes, over half of the households not sampled were due to homes being empty rather than non-consent. Recruitment fell short of sample-size targets in non-slum areas due to low consent rates. However, such rates cannot be quantified because we do not have information on the number of flats per building.

The proportions of positive tests by age and sex in different sites (appendix p 9) show markedly higher proportions in slums than in non-slums. Regression estimates (appendix p 14) suggest that unadjusted positive proportions were higher among women than among men (slums p<0·001; non-slums p<0·001). Intriguingly, although proportions of positive tests among individuals aged older than 60 years were lower in non-slums (*vs* age 12–24 years; p<0·0223), it was higher in slums (*vs* age 25–39 years; p<0·001).

Reweighting our sample to account for population demographics (appendix p 12) and population in each ward showed that 54·1% of samples in slums and 16·1% of those in non-slums tested positive (appendix p 8)—a significant difference (p<0·001). Our estimates of adjusted seroprevalence are higher in slums (means ranging from 55·1% to 61·4%) than in non-slums (mean ranging from 12·0% to 18·9%) across wards (appendix p 8). Underlying IgG scores are higher and the positive rate is more sensitive to the manufacturer's recommended cutoff in slums than in non-slums (appendix pp 16–17).

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See Online for appendix

Mapping our estimates to locations (appendix p 10) showed sharp differences over distances as little as 100 m. Our estimates of seroprevalence suggest a high reproductive rate of SARS-CoV-2 in slums. Combined with reported COVID-19 cases and numbers of death in sampled wards, our findings suggest a high asymptomatic spread of the infection and an infection fatality rate of 0·076% in slums and 0·263% in non-slums. The higher prevalence in slums could be driven by population density, lower adherence to distancing measures, and poorer hygiene. This stark variation in prevalence within wards also highlights the importance of geographic variation for epidemiological modelling[5] and policy discussions of herd immunity. Although moderate consent rates might bias our estimates of proportions of positive tests, the unadjusted age-weighted and sex-weighted proportions are not significantly different (appendix p 15).

JS reports to the Municipal Corporation of Greater Mumbai. All other authors declare no competing interests. The author list is provided in alphabetical order on first name basis.

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SHORT COMMUNICATION

Impact of population density on Covid-19 infected and mortality rate in India

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Abstract
The Covid-19 is a highly contagious disease which becomes a serious global health concern. The residents living in areas with high population density, such as big or metropolitan cities, have a higher probability to come into close contact with others and consequently any contagious disease is expected to spread rapidly in dense areas. However, recently, after analyzing Covid-19 cases in the USA researchers at the Johns Hopkins Bloomberg School of Public Health, London school of economics, and IZA—Institute of Labour Economics conclude that the spread of Covid-19 is not linked with population density. Here, we investigate the influence of population density on Covid-19 spread and related mortality in the context of India. After a detailed correlation and regression analysis of infection and mortality rates due to Covid-19 at the district level, we find moderate association between Covid-19 spread and population density.

Keywords Covid-19 · Infection and mortality rate · Population density · India

Introduction

The emergence and continuous spreading of the highly contagious disease Covid-19 leads the World in a very distressing stage. The disease has severe adverse effects on the world economy, as well as on many aspects of human lives like employment, education, physical and mental health of individuals, etc.

In the absence of any precise medicine for the treatment of Covid-19 or any effective vaccine to prevent it, several efforts are made, based on the available pandemic data, in modeling the Covid-19 cases to understand the dynamics of infections (Chen et al. 2020a, b; Roy et al. 2020; Rahman et al. 2020) and subsequently forecasting about the future course of the pandemic for scheming strategies to quickly contain the spreading of the infections by other means like physical distancing, lockdown, etc.

The modeling of transmission of any infectious disease relies on several factors associated with the disease. A number of studies suggest that Covid-19 infection is associated with meteorological factors such as temperature, humidity, wind speed, etc. In particular, below 3 °C, the number of COVID-19 infections in China is found to have a positive linear association with average temperature (Zhu and Xie 2020). A similar correlation between temperature and Covid-19 cases is also found in several Countries and cities, like India (Gupta et al. 2020), Indonesia (Tosepu et al. 2020), Turkey (Şahin 2020), New York (USA) (Bashir et al. 2020), as well as on a worldwide scale (Chen et al. 2020a).

Since coronavirus (SARS-COV-2) transmits via human contact (Chan et al. 2020; Li et al. 2020), the common perception is that Covid-19 spreads rapidly in dense areas, whereas the probability of getting infected is low in areas with low population density. However, after analyzing Covid-19 infection and death rates of 913 urban counties in the USA, a recent investigation by researchers at the Johns Hopkins Bloomberg School of Public Health claims that the infection rate is not linked with population density, whereas death rate is inversely related to population density (Hamidi et al. 2020) except for metropolitan areas where higher infection and higher mortality rates have been noted. The inverse mortality relation with density has been attributed by the authors on the availability of better healthcare

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systems at higher density locations. A very recent study by the researchers from the London school of economics and IZA—Institute of Labour Economics, based on urban Covid-19 cases in the USA, concluded that the timing of the outbreak depends on population density with denser regions leading an early breakout, but both Covid-19 infection and death rates are unrelated with urban population density (Carozzi et al. 2020).

India is a large country with a total population of more than 1.3 billion. It has diverse demographic features. As of 10th September 2020, India is the second maximum Covid-19 affected country by the total number of infected people after the USA. The Covid-19 pandemic situation in India thus allows us to cross-check the recent findings (Hamidi et al. 2020; Carozzi et al. 2020) on the impact of population density on Covid-19 spread and related mortality. Probably the first study on the impact of population density (along with several other geographical factors) on the spread of Covid-19 was done by Gupta et al. (2020) in the context of India, but their analysis was based on the Covid-19 data of Indian states up to the 27th April 2020 when total reported Covid-19 cases was only 29,458 and they considered population density at the state level only.

In India, a major part of total infections and mortality have, at least apparently, been attributed to metropolitan cities such as Mumbai, Delhi, Bangalore, Ahmedabad, Chennai, and Kolkata. The infection and death rates appear to be much lower at remote districts. However, because of the large population of the metropolitan cities, the total infections and mortality are normally higher in those places. Moreover, a strong presence of media reported the Covid-19 cases in metropolitan cities in greater detail which might give a false impression that only these cities are dominantly contributing Covid-19 infection and related death.

To have a concrete and reliable idea on the issue in the present work, a detailed analysis of Covid-19-infected and death cases as a function of population density of Indian districts are performed. So far there is no established model about the role of population density on the spread of highly contagious diseases. The findings of the impact of population density on mortality during the 1918 influenza pandemic are debatable. A few researchers find no link between population density and death in 1918 influenza (Chowell et al. 2008; Nishiura and Chowell 2008), whereas a few others claim for a significant positive correlation (Garrett 2010). The Covid-19 pandemic allows us to study the issue in more detail and reliably. The issue is also important in the connection to planning of future towns/cities.

Our findings suggest that till 10th September 2020, Covid-19 infections and mortality in India are moderately correlated with population density; on the average, both the infected and the death cases are higher for large population density.

Data used

India, the seventh largest country of the world, is a federal union of twenty-eight (28) states and eight (8) union territories at present. The states and union territories are further divided into districts for administrative convenience. At present, there are total of 718 districts in India.

The district-wise Covid-19 cumulative infection and death cases data were taken from the daily bulletins of the Ministry of Health and Family Welfares of Government of India (https://www.mohfw.gov.in/) and the State Governments (such as https://www.wbhealth.gov.in/pages/corona/bulletin, (West Bengal), https://dgmhup.gov.in/en/covidteamreport, (Uttar Pradesh) https://arogya.maharashtra.gov.in/1175/Novel--Corona-Virus, (Maharashtra) https://stopcorona.tn.gov.in/daily-bulletin/, (Tamil Nadu), https://hmfw.ap.gov.in/covid_19_dailybulletins.aspx (Andhra Pradesh etc.). The daily compiled data from the Central and all the State Government bulletins are also available at api.covid19india.org. We use the data till 10th September, 2020.

The updated corona infected and death data are not available for a few districts such as the districts of Delhi, Goa, and Andaman and Nicobar. Besides that, the cumulative infected and mortality data for districts of Telangana are not reported**.** We, therefore, could not include those districts in our analysis.

For the district-wise total population and population density, we have used the census 2011 data of the Government of India which are given at https://censusindia.gov.in/. A few new districts have been created since 2011 by splitting, rearranging some districts. For such cases, we have taken the population and density data from the web site of the concerned districts though we could not include all such districts because of lack of data on the district website. We finally consider a total of 600 districts of India in our analysis.

Methodology

Our primary objective is to explore whether any correlation between Covid-19-infected and mortality cases in India with population density exists or not and if yes, we shall consider modeling between the Covid-19 infection and mortality rate in India (dependent variables) with population density (independent variable).

The computation of the correlation coefficient is the most commonly adopted approach for judging statistical relationship between two variables which essentially measures the degree of (linear) association (Bewick et al. 2003; Kutner et al. 2005).

For a set of n pair of observations x_i and y_i (i varies from 1 to n), the (Pearson) correlation coefficient is defined by

$$r = \frac{\mathrm{Cov}(x, y)}{\sigma_x \sigma_y} \tag{1}$$

where $\mathrm{Cov}(x,y) \left(\equiv \frac{1}{n} \sum_{i=1}^{n} \left(x_i - \bar{x} \right) \left(y_i - \bar{y} \right) \right)$ denotes the cross-covariance of the two variables and σ_i $(i = x,y)$ is the standard deviation.

It is important to examine whether the association is genuine or not which can be done by considering the null hypothesis test. We shall apply the F test, which compares variances of the two variables and the t-test for the purpose and estimate the p value which essentially gives the probability that the results from the sample data occurred by chance.

We shall also consider linear regression analysis to model the relationship between the infection/mortality rate and population density. The linear regression relies on the relation

$$y_i = a x_i + b + \varepsilon_i, \tag{2}$$

where x and y are the independent and the dependent variables, respectively, a is the slope, b is the intercept on the y-axis, and ε is the error with zero mean value. In the present work, population density is the independent variable, while the infection/mortality rate is the dependent variable. Since the infection/mortality rate must vanish when population density is zero, we have opted $b = 0$. However, non-zero b is also considered for completeness of the analysis which incorporates the option that the behavior of $y(x)$ is non-linear near the origin. Using the method of least squares, we estimate the parameters a^e and b^e from the data. So for a given x_j the model estimated y_j^e will be

$$y_j^e = a^e x_i + b^e. \tag{3}$$

The coefficient of determination (R^2) quantifies the amount of variability in dependent variable explained by the model and is defined by the relation

$$R^2 = \frac{\mathrm{SST}}{\mathrm{SSE}} - 1, \tag{4}$$

where SSE is the sum of squared errors (squared residuals) $\mathrm{SSE} = \sum_{i=1}^{n} \left(\left(y_i - y_i^e \right) \right)^2$ and SST is the sum of squared variation in dependent variable about its mean $\mathrm{SST} = \sum_{i=1}^{n} \left(\left(y_i - \bar{y}_i \right) \right)^2$. With the increase in number of regressors, the value of R^2 always increases. For a meaningful measure of goodness of model fit, adjusted R^2 is used instead of considering the number of explanatory variables in the model. Microsoft MS Excel software has been exploited to compute the mentioned concerned parameters from the data.

Results and discussion

The first case of COVID-19 was reported in India on 30th January 2020. By 10th September 2020, the total 4,559,727 people are infected in India by coronavirus out of which 3,539,983 have recovered, while it is fatal for 76,304 Indians.

Many of the Indian states are quite large and populous. We first address the states separately, but restrict our analysis only to scatter diagram. Since the population of different districts are vastly different, we have considered the total infected and death cases per one million people for each of the districts. Here, we shall show the results for four major states—West Bengal, Maharashtra, Uttar Pradesh, and Tamil Nadu, which are from the East, West, North, and South parts of the country, respectively. The scatter plot of the total (cumulative) infected and death cases per one million people against population density for the stated states are depicted in Fig. 1. It is found that the infection and death rate are higher in metropolitan cities having huge population density in all the cases except Uttar Pradesh where no districts have very large population density. On the other hand, it is noticed that Covid-19 spread and related death are low in districts with low population density. The situation is not very clear in districts with moderate density; the data points spread all over the graphical area with a slight trend to rise of infection and death with density.

Next we consider India as a whole. The scatter plots of the total (cumulative) infected and death cases per one million people against population density for 600 districts of the country are shown in Fig. 2a. Though there are large fluctuations, particularly in the mid population density regions, overall, there is a tendency that both infection and death cases rise with population density.

We estimate the correlation coefficients considering infection and mortality rates as the dependent variables and population density as the independent variable which are found as 0.49 (for infection) and 0.59 (mortality), respectively, indicating moderate positive correlation. For the significance test, the p values are computed which are found very small ($\sim 10^{-37}$ for infection rate and even smaller for mortality rate), less than any sensible significant level, and hence the null hypothesis (no correlation) is rejected.

Subsequently, we express the variation of the infection and mortality rates with population density through Eq. (3). The least-square fitting gives $a^e{}_{\mathrm{infec}} = 1.26 \pm 0.09$ and $b^e{}_{\mathrm{infec}} = 2070 \pm 170$ and $a^e{}_{\mathrm{mort}} = 0.04 \pm 0.002$ and $b^e{}_{\mathrm{mort}} = 13.2 \pm 4.3$. We also force the straight line to pass through the origin since the infection/mortality rate should be zero when population density vanishes. It is found that

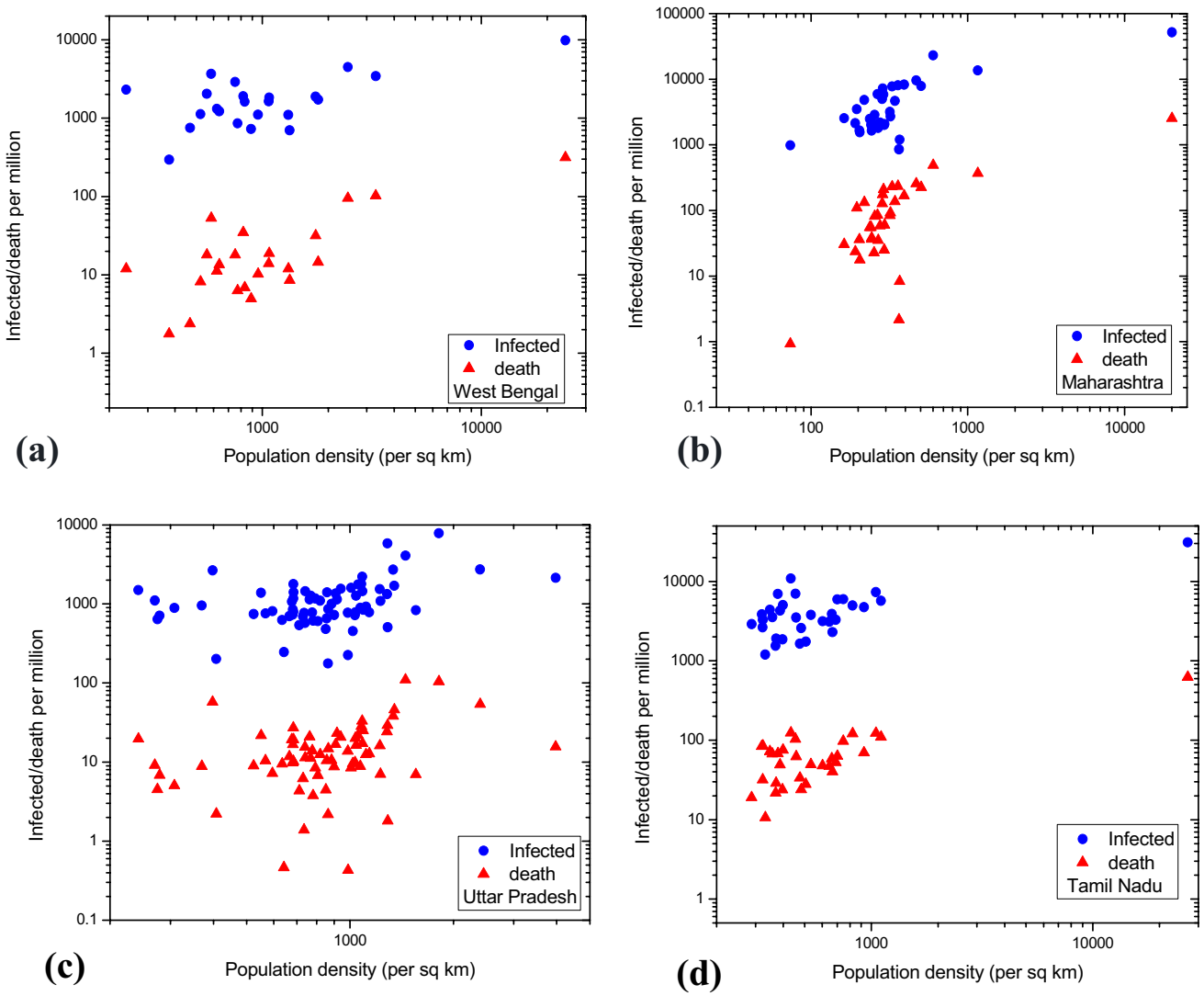

Fig. 1 Variation of infected and death rate due to Covid-19 with population density of districts of **a** West Bengal, **b** Maharashtra, **c** Uttar Pradesh, and **d** Tamil Nadu

the correlation coefficients are higher and p values are lower in no intercept cases. The linear fit of mortality rate against population density passing through the origin gives the adjusted R^2 around 41% that decreases to 23% when megacities are excluded in the fitting. It is found that the power- law relation does not describe the data well; it gives much lower R^2 compared to that of the linear fit.

The correlation between population density and infected/death cases is revealed when we consider small bins in population density and corresponding average infection/death cases are taken. In the dataset of districts of India, the population density per square km is found to vary from 3 to 26,903. We bin the population density in log scale with varying widths; particularly, larger bin widths at high population density are considered so as to have at least a reasonable count of districts (at least 3) in each bin. The results are shown in Fig. 3. A linear (proportional) fit describes both the infection and mortality data well.

To verify the claim of researchers that denser regions led an early breakout, we plot the same Covid-19 infection/death variation with population density in Fig. 2b, but for the data till 5th July 2020. It appears that with the time the number of infection and death cases are increased, but the overall trend remains mostly unaltered at least till 10th September, 2020.

In the present analysis, we have considered population density obtained by dividing the total population of a district by its total area which implicitly assumes a uniform spatial distribution of populations within a district. The Covid-19 spread and death cases are also considered as uniform. Such assumptions lead to some uncertainty in estimating the correlation between Covid-19 spread and population density. For instance, the population density in the Darjeeling district

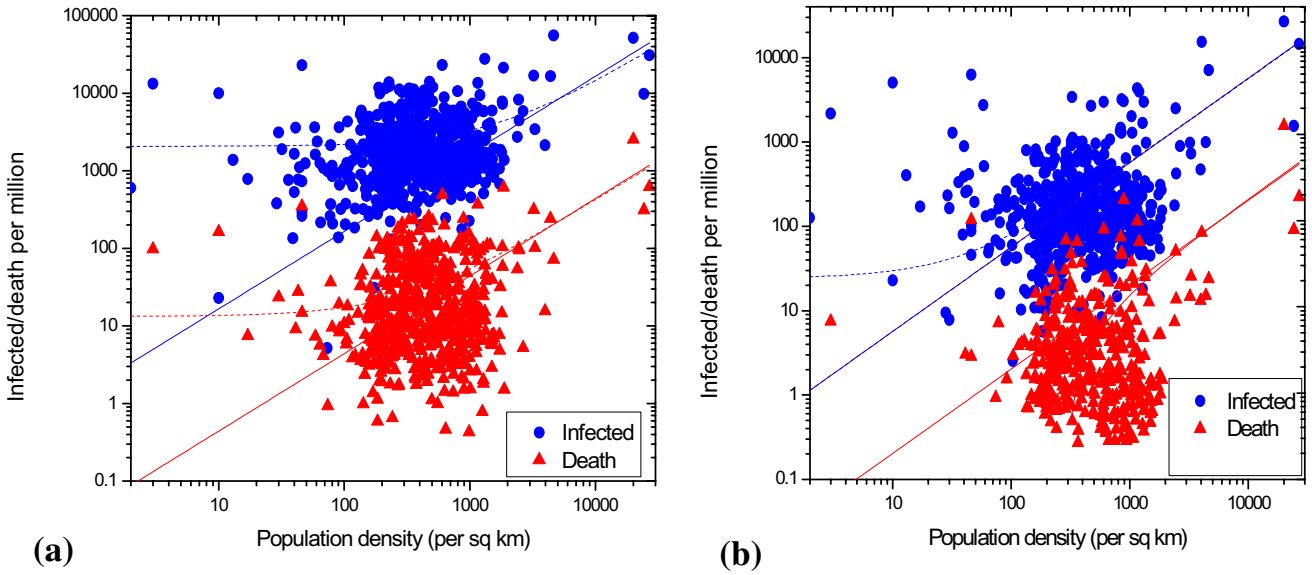

Fig. 2 Same as Fig. 1 but for the whole India, **a** up to 10th September 2020, **b** till 5th July2020. The solid and dash lines describe the linear fit of the data with zero and non-zero intercepts, respectively

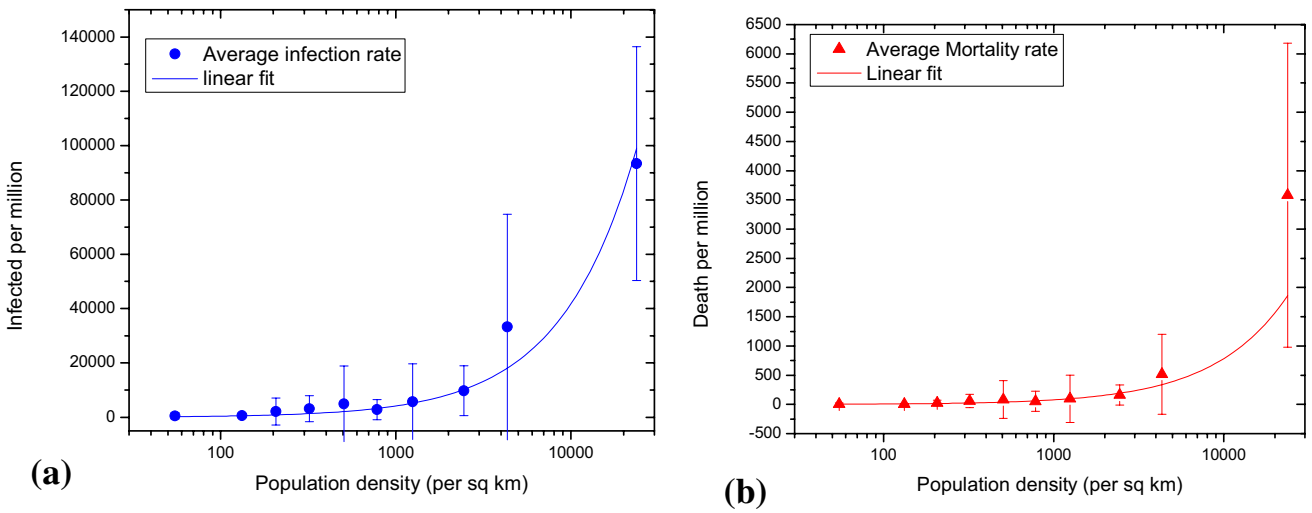

Fig. 3 Variation of averaged infected and death rate due to Covid-19 with population density for the whole country

of West Bengal is among the lowest in the state though the infection and mortality cases are relatively high in the district. This is because of Siliguri, which is one of the congested cities of the state, falls in the Darjeeling district. Most of the infection and mortality cases in the Darjeeling district (and also in the Jalpaiguri district which jurisdiction wise contain a part of Siliguri) are from Siliguri, whereas the major geographical part of the Darjeeling district is the hill area where population density is quite low and thereby the resulting population density of the district is on the lower side. Further study is needed to overcome the stated issues, say by considering the weighted population mean which is a measure of average "experienced" density or considering sub-division as a basic unit for the study. However, the limited availability of necessary data in the public domain is a major hindrance to such improvements.

The R^2 value of the relation between infection/mortality rate and population density is found moderate, not very high, which implies that only a part of the infection/mortality rate due to Covid-19 can be explained in terms of population density. This can be understood by the facts that the Covid-19 spread and related mortality in a district may depend on various other factors including geographical features, economic conditions, prevailing health conditions, genetic

Table 1 Correlation coefficients and p values

Data	Infection				Mortality			
	Linear fit		Linear fit with no intercept		Linear fit		Linear fit with no intercept	
	r	p	r	p	r	p	r	p
Up to 10th September 2020	0.49	0.0000	0.58	0.0000	0.59	0.0000	0.64	0.0000
Up to 5th July 2020	0.65	0.0000	0.67	0.0000	0.57	0.0000	0.57	0.0000

factors, health infrastructure, policies adopted by the regulating authorities, the average age of the residents of the districts, number of testing, etc. It is already known that Covid-19 has a larger impact on the older population (and population with comorbidity). The share of the older population is not the same in all the districts, neither the total testing number. However, there is no prevailing straightforward and unambiguous method of entangling different probable dependent factors. More research on these aspects are necessary to address the stated issues.

Conclusion

In conclusion, the present analysis indicates a positive correlation between Covid-19 infection and related mortality with population density as revealed from the correlation and R^2 analysis, in contrast to the findings by the researchers at the Johns Hopkins Bloomberg School of Public Health, London school of economics, and IZA—Institute of Labor Economics**,** based on US data. The significance of the correlation is found high from the p values which strongly indicate that the null hypothesis is false in the present case, at least till now.

There is a vast difference in the living conditions of people in the USA and in India which may be responsible for the different behavior of the infected/mortality cases due to Covid-19 with population density in the two countries. The (large) density in India is reflected through the pressing of people against each other in the street, public vehicles, trains, queue for ration, etc. The average area occupied by a family for living in cities of India is also much smaller. The Covid-19 cases were found higher in metropolitan cities even in the USA (Hamidi et al. 2020). So containing a highly infectious disease like Covid-19 is a serious challenge for the country like India unless by any means (maybe by mutation also) the coronavirus (SARS-COV-2) is transformed to a non-lethal variety or an effective vaccine/medicine is discovered (Tables 1, 2).

Table 2 Adjusted R^2 in Linear fitting of Infection and death rate

Data	Infection		Mortality	
	Linear fit	Linear fit with no intercept	Linear fit	Linear fit with no intercept
Up to 10th September 2020	0.24	0.33	0.35	0.41
Up to 5th July 2020	0.42	0.45	0.32	0.32
Up to 10th September 2020 but excluding the megacities	0.11	0.38	0.32	0.23
Up to 5th July 2020 but excluding the megacities	0.11	0.22	0.03	0.12

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Data availability We have taken the district-wise Covid-19 cumulative infection and death cases data from the bulletins of Government of India (https://www.mohfw.gov.in/) which is also given at api.covid19india.org.)

Compliance with ethical standards

Conflict of interest There is no conflict of interest between the authors.

Consent for publication Yes.

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COVID-19 among the inhabitants of the slums in the city of Buenos Aires: a population-based study

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ABSTRACT

Objective To summarise the unfolding of the COVID-19 epidemic among slum dwellers and different social strata in the city of Buenos Aires during the first 20 weeks after the first reported case.

Design Observational study using a time-series analysis. Natural experiment in a big city.

Setting Population of the city of Buenos Aires and the integrated health reporting system records of positive RT-PCR for COVID-19 tests.

Participants Records from the Argentine Integrated Health Reporting System for all persons with suspected and RT-PCR-confirmed diagnosis of COVID-19 between 31 January and 14 July 2020.

Outcomes To estimate the effects of living in a slum on the standardised incidence rate of COVID-19, corrected Poisson regression models were used. Additionally, the impact of socioeconomic status was performed using an ecological analysis at the community level.

Results A total of 114 052 people were tested for symptoms related with COVID-19. Of these, 39 039 (34.2%) were RT-PCR positive. The incidence rates for COVID-19 towards the end of the 20th week were 160 (155 to 165) per 100 000 people among the inhabitants who did not reside in the slums (n=2 841 997) and 708 (674 to 642) among slums dwellers (n=233 749). Compared with the better-off socioeconomic quintile (1.00), there was a linear gradient on incidence rates: 1.36 (1.25 to 1.46), 1.61 (1.49 to 1.74), 1.86 (1.72 to 2.01), 2.94 (2.74 to 3.16) from Q2 to Q5, respectively. Slum dwellers were associated with an incidence rate of 14.3 (13.4 to 15.4).

Conclusions The distribution of the epidemic is socially conditioned. Slum dwellers are at a much higher risk than the rest of the community. Slum dwellers should not be considered just another risk category but an entirely different reality that requires policies tailored to their needs.

Strengths and limitations of this study

- The main strength of the study is that it included all the reported cases of COVID-19 (confirmed by RT-PCR) in the city of Buenos Aires.
- The demographic databases used in this study allow the ecological characterisation of the characteristics of the different neighbourhoods of the city and the slums.
- As it happens in administrative and case-report databases, there may have been classification errors. This could have been the case of people whose postal address did not allow an appropriate characterisation. These data were corrected manually.
- The ecological characterisation of the city's neighbourhoods can be considered reductionist, as it does not incorporate individual data but rather population aggregates. However, the attributes of the neighbourhoods are usually strong indicators of health outcomes.
- The results show internal consistency in terms of increasing gradients between indicators of deprivation and incidence rates.

INTRODUCTION

The COVID-19 pandemic is a major public health challenge. However, this threat is not evenly distributed neither among nations nor within countries.[1–6] Argentina in general, and the city of Buenos Aires in particular, constitute a model case study of the inequities in the distribution of the pandemic due to the presence of two phenomena characteristic of much of the south of the world: the fragmentation of the healthcare systems between public and private systems, and on the other hand, the concentration of extreme poverty that are the inhabitants of the slums.[7] The slums represent the extreme stratum of urban poverty and constitute a case of special vulnerability due to their overcrowded housing conditions and lack of basic resources that make it difficult to comply with social distancing measures.[8 9]

Although there is interest from the international community[10] about what might be expected from the development of the pandemic in these social groups, so far there are no reports of this topic in the literature. Latin America is currently one of the continents most affected by the epidemic and is also the continent with the greatest social inequality.[11 12]

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Around 3 million people live in the city of Buenos Aires, of which between 7% and 10% have a residence in a slum.[13] Argentina behaved more restrictively than its neighbours and on 20 March established a strict lockdown strategy. Additionally, starting from the 13th week, a strategy of active search of cases in slums and vulnerable communities was established. This study reports the development of the COVID-19 epidemic in Buenos Aires with particular emphasis on the social distribution of the infection among the different socioeconomic strata of the city and slum dwellers, using a time-series analyses.

METHODS

All persons who meet the definition of suspected case for COVID-19 infection are systematically reported in the Argentine Integrated Health Information System (SISA). The report includes detailed demographic information including age, gender, place of residence and social security, as well as the description of the healthcare provider. The system also has clinical information that includes the date of onset of symptoms, clinical features and outcomes of cases describing whether the person was hospitalised or required critical care. This dataset is updated daily in order to qualify the status of active or closed case as well as information on the vital status of each person. The present manuscript includes all the people registered into the SISA database from 31 January to 14 July 2020 in CABA. Due to the fact that it takes about a week to update the database with the laboratory results, this analysis reports all data reported up to 7 July 2020. Although the first confirmed case of COVID-19 in Argentina was reported on 2 March 2020 in a 43-year-old person who had returned from a trip in an endemic circulation area, 13 suspected cases were tested before this first confirmed case. During the period analysed in the manuscript, the two kits that were mostly used for assessments were the RealStar SARS-CoV-2 RTPCR Kit 1.0 (Altona diagnostics, Germany) which has reported a sensitivity of 97.8% and specificity of 97.3%. To a lesser extent, the GeneFinder COVID-19 Plus RealAmp Kit was used, which has a reported sensitivity of 97.4% and specificity of 100%.

Slums

The definition of slum was made according to the address provided by each person to the health personnel involved in the identification of cases. Although the definition of slum is not universal, in the city of Buenos Aires it is defined as an unplanned settlement characterised by a high population density and consisting of precarious housing with high levels of unsatisfied basic needs. The cartography of the city's communes as well as the location of the slums can be consulted on the city's government website (https://www.estadisticaciudad.gob.ar/eyc/?p=45322) and https://www.buenosaires.gob.ar/areas/educacion/dirinv/pdf/villas_nht_y_nuevos_asentamientos.pdf). There are 38 mapped slums in the city, 6 of the 38 slums are home to almost 50% of the total slum population (Villa 1-11-14, n=26 000; Villa 15, n=20 000; Villa 20, n=20 000; Villa 21–24, n=30 000; Villa 31, n=45 000; Villa R Bueno, n=5000). However, this analysis describes the epidemiological situation in all the slums of the city.

Data analysis

All persons tested for suspected case of COVID-19 residing in CABA were included in the analysis. The characteristics of patients with either confirmed or ruled-out COVID-19 infection are described using numbers and percentage for categorical attributes, and means and SD for numerical variables with normal distributions. The differences between groups of interest were tested using the X^2 test for discrete variables and the T or Wilcoxon-Mann-Whitney test for numerical variables with normal and abnormal distribution, respectively. In order to determine independent variables that are associated with a positive real-time quantitative RT-PCR for SARS-CoV-2, a multiple logistic regression was settled. Results are reported using the central estimator and the 95% CI.

The calculation of incidence rates of COVID-19 infection per 100 000 people was made by age groups (eight groups of 10 years each and a group of people ≥80 years) considering population census figures. The total number of people living in slums was considered to be 7.6% of the total population of CABA projected to year 2020. The composition by age groups within the slum was taken from the census that the government of CABA made on the biggest slum in CABA (Villa 31, n=40 000). The composition of the different age strata outside the slums was taken from the national census.

In order to estimate the effects of living in a slum on incidence rate of COVID-19, Poisson regression models were used. Age strata were the independent variable, while the incidence rate of COVID-19 infection was the dependent variable.

In order to evaluate the effect that socioeconomic differences have on the incidence rates of COVID-19 infection regardless of the slums, an ecological analysis was carried out taking into account the social and economic indicators of each of the 15 communes of the city (average population per commune=188 685±27 456). The economic, social and demographic characterisation of each one of the communes arises from the national census that is not carried out in the slums and therefore is an indicator of the conditions of the communes without considering the slums that are located in each commune. Additionally, the government of the city of Buenos Aires maintains up-to-date statistics that measure various indicators of deprivation at the level of each of the 15 communes. These include the average income of a family, the type of employment and economic activity, the years of education (both as a categorical or continuous variable), the type of medical insurance (public and private) and the housing conditions. For the purposes of this paper, each commune was scored on the basis of each of these domains. This score was subsequently divided

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into quintiles, which were used as an index of deprivation (with the higher values indicating greater deprivation). The quintiles were introduced into all risk models by adjusting for the average age of each commune.

The incidence rate for COVID-19 of each of the communes arises from the notification of cases in people with domiciles outside the slums. The denominator of each of the communes results from the census estimates for 2020 by subtracting the number of people living in the slum in each of the communes.

Socioeconomic condition was characterised based on the degree of unsatisfied basic needs (UBNs) at the level of each of the 15 communes of CABA. In order to estimate the effects of UBN, Poisson regression models were used. Quintiles of UBN were the independent variable, while the incidence rate from COVID-19 infection was the dependent variables. To evaluate the presence of differential effects of potential demographic differences between departments, age and gender composition were added to the models. Results are presented as incidence rate ratio (IRR) which is defined as the incidence rate among slum dwellers divided by the incidence rate of those people not living in a slum.

All analyses were two-tailed, and a p value of <0.05 was considered statistically significant. Statistical computations were conducted using R V.3.6.1 for Windows (R Foundation for Statistical Computing, Vienna).

Patient and public involvement

Patients and the public were not directly involved in the present study.

RESULTS

From the first reported case, a total of 114 052 people were tested for symptoms related with COVID-19. Of these, 39 039 (34.2%) were RT-PCR positive.

The infection began to spread outside the slums with a rapid increase until week 5 of the series, when the policy of social distancing began. In fact, since the introduction of restrictive measures to the circulation, the behaviour of the epidemic had a flattened curve from week 5 to 11 (table 1 and figure 1A). On the other hand, the viral circulation started in the fifth week in the slums with a very fast growth that was nuanced from the beginning of active search strategies ('DetecAR') of cases (table 1 and figure 1B). The demographic characteristics of slum dwellers and non-slum dwellers are presented in table 2.

In a regression model that takes into account demographic factors (age and gender), self-reported comorbidities (hypertension, diabetes), obesity and health financing, living in a slum was associated with a higher probability of having COVID-19 disease (2.38 (2.31 to 2.46), p<0.0001).

Table 1 Number of tests and percentage of positivity per week among slum dwellers and non-slum dwellers

		Residents not living in a slum								Slum residents							
Week	Ending	Assays	Test/M	Positive	%	Age	SD	Men	%	Assays	Test/M	Positive	%	Age	SD	Men	%
1	2/5	4	1	0	0	33.8	5.3	1	25	0	0	0	0	—	—	0	0
2	3/3	17	6	1	5.9	38.3	14.5	10	58.8	0	0	0	0	—	—	0	0
3	3/10	86	30	12	14	44.5	19.9	43	50	0	0	0	0	—	—	0	0
4	3/17	299	105	57	19.1	37.9	19.4	135	45.2	8	34	0	0	37	18	5	62.5
5	3/24	480	169	155	32.3	43.3	21.1	252	52.5	8	34	1	12.5	23.9	18	5	62.5
6	3/31	854	301	156	18.3	51.1	23.6	433	50.7	31	133	8	25.8	40.5	25.2	17	54.8
7	4/7	1621	570	172	10.6	44.8	24	814	50.2	124	530	15	12.1	28.3	19.5	59	47.6
8	4/14	1634	575	106	6.5	45.3	24.4	808	49.4	138	590	16	11.6	31	22	72	52.2
9	4/21	2303	810	157	6.8	46.2	24.1	1111	48.2	193	826	34	17.6	32.2	19.8	93	48.2
10	4/28	2392	842	236	9.9	48	25.7	1096	45.8	322	1378	136	42.2	29.8	18.1	147	45.7
11	5/5	2453	863	142	5.8	47.9	25.4	1153	47	440	1882	247	56.1	29.5	17.2	211	48
12	5/12	2719	957	337	12.4	47.3	25	1293	47.6	1039	4445	705	67.9	31.3	18.2	537	51.7
13	5/19	3475	1223	542	15.6	47	25.1	1630	46.9	1661	7106	1070	64.4	29.7	18	739	44.5
14	5/26	4715	1659	1034	21.9	43.3	23.5	2215	47	2819	12060	1569	55.7	28.7	17.3	1364	48.4
15	6/2	5335	1877	1361	25.5	44.1	23.4	2324	43.6	2859	12231	1428	49.9	28.2	17.7	1352	47.3
16	6/9	5997	2110	1758	29.3	43.7	23.2	2826	47.1	2859	12231	1447	50.6	28.9	18.1	1367	47.8
17	6/16	7262	2555	2405	33.1	43.8	23.1	3262	44.9	3479	14883	1692	48.6	29	17.2	1629	46.8
18	6/23	9630	3389	3466	36	42.9	22	4466	46.4	4226	18079	2099	49.7	30	17.8	2097	49.6
19	6/30	10202	3590	3639	35.7	41.8	21.7	4742	46.5	4713	20163	2255	47.8	28.6	17.5	2266	48.1
20	7/7	11477	4038	4548	39.6	42.9	22.4	5342	46.5	3595	15380	1656	46.1	29.8	18.2	1769	49.2
21	7/14	10459	3680	3450	33	44.3	22.3	4840	46.3	2124	9087	927	43.6	30.3	18.2	1022	48.1

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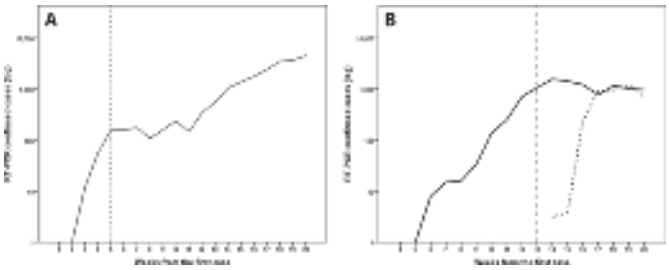

Figure 1 Evolution of the COVID-19 RT-PCR curve in people living outside the slums (A) and between resident slums (B).

COVID-19 incidence rate

The incidence rate for COVID-19 in the city of Buenos Aires towards the end of the 20th week was 201.7 (196.7 to 206.73) per 100 000 people. This rate was significantly different among people living in slums compared with those who did not. The incidence rates of COVID-19 infection were 160.0 (155.4 to 164.7) per 100 000 people among the inhabitants who did not reside in the slums (n=2 841 997) and 708.4 (674.5 to 742.5) among those who had a residence in the slum (233 749) (IRR 11.08 (10.51 to 11.68), p<0.0001) (table 3).

This difference was present in all age groups at the end of the 20th week (table 4 and figure 2).

Socioeconomic status of communes and COVID-19 incidence rate

The distribution of the incidence rate for COVID-19 was related to the level of unsatisfied basic needs for each of the city's neighbourhoods. Excluding the slums, compared with those communes with better social and economic situation (1.00), the progressive deprivation quintiles were associated with a higher probability of infection 1.36 (1.25 to 146); 1.61 (1.49 to 1.74); 1.86 (1.73 to 2.01) and 2.94 (2.74 to 3.16) for quintiles 2–5, respectively. The inclusion of slums, on the other hand, carries a risk of 14.4 (13.4 to 15.4) (table 5).

Table 2 Demographic and clinical presentation characteristics among slum dwellers and non-slum dwellers

	Non-slum residents	Slum residents	
n	23 734	15 305	P value
Gender—female, n (%)	11 824 (49.8)	7740 (50.6)	<0.0001
Gender—male, n (%)	11 803 (49.7)	7522 (49.1)	
None declared, n (%)	107 (0.4)	43 (0.3)	
Mean age (SD)	43.9 (22.2)	30.9 (17.6)	<0.0001
Age 0–39 years, n (%)	11 400 (48.0)	10 731 (70.1)	<0.0001
Age 40–59 years, n (%)	6834 (28.8)	3626 (23.6)	
Age ≥60 years, n (%)	5485 (23.1)	943 (6.2)	
Declared diseases and conditions			
Asthma, n (%)	603 (2.5)	540 (3.5)	<0.0001
Diabetes, n (%)	858 (3.6)	566 (3.7)	0.669
COPD, n (%)	277 (1.2)	34 (0.2)	<0.0001
Hypertension, n (%)	1960 (8.3)	680 (4.4)	<0.0001
Chronic heart failure, n (%)	332 (1.4)	57 (0.4)	<0.0001
Obesity (≥30 BMI), n (%)	640 (2.7)	485 (3.2)	0.006
Current smoker, n (%)	732 (3.1)	622 (4.1)	<0.0001

BMI, body mass index; COPD, chronic obstructive pulmonary disease.

Table 3 Weekly incidence rates between residents outside and inside the slums

	Residents not living in a slum			Slum residents		
Week	Incidence rate	Lower 95% CI	Upper 95% CI	Incidence rate	Lower 95% CI	Upper 95% CI
1	0.0	0.0	0.0	0.0	0.0	0.0
2	0.0	0.0	0.1	0.0	0.0	0.0
3	0.4	0.2	0.7	0.0	0.0	0.0
4	2.0	1.5	2.5	0.0	0.0	0.0
5	5.5	4.6	6.3	0.4	0.4	1.3
6	5.5	4.6	6.4	3.4	1.1	5.8
7	6.1	5.2	7.0	6.4	3.2	9.7
8	3.7	3.0	4.4	6.8	3.5	10.2
9	5.5	4.7	6.4	14.6	9.7	19.4
10	8.3	7.2	9.4	58.2	48.4	68.0
11	5.0	4.2	5.8	105.7	92.5	118.8
12	11.9	10.6	13.1	301.6	279.4	323.8
13	19.1	17.5	20.7	457.8	430.4	485.1
14	36.4	34.2	38.6	671.2	638.1	704.3
15	47.9	45.4	50.4	610.9	579.3	642.5
16	61.9	59.0	64.8	619.0	587.2	650.8
17	84.6	81.2	88.0	723.9	689.5	758.2
18	122.0	117.9	126.0	898.0	859.7	936.2
19	128.0	123.9	132.2	964.7	925.1	1004.3
20	160.0	155.0	165.0	708.0	674.0	742.0
21	121.4	117.4	125.4	396.6	371.1	422.1

OUTCOMES

Hospitalisations

A total of 11 671 people were hospitalised. Among these, 5116 (43.8%) were admitted to a public hospital and approximately half of these (2350%–46.2%) were slum dwellers.

Of those hospitalised persons, those with residence in a slum were significantly younger (35.6±20.8 years) than those living out of slum (50.0±23.9 years, (p<0.0001)). Despite this, the requirement for intensive care assistance was similar (225/3193 (7.0%)) among people with residence in the slum and 575/8478 (6.8%) among people outside the slums.

Mortality

Of the 39 039 patients who tested positive for COVID-19, at the time of this analysis, a total of 729 people (1.86%) died, of whom 150 (20.6%) resided in a slum.

In age-corrected and sex-corrected regression models including comorbidities (asthma, diabetes, chronic lung disease, hypertension, heart failure, renal failure), obesity

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Table 4 Incidence rates at week 20 among residents in and out of slums by age group

Age group	Residents not living in a slum			Slum residents					
	Incidence rate	Lower 95% CI	Upper 95% CI	Incidence rate	Lower 95% CI	Upper 95% CI	IRR	Lower 95% CI	Upper 95% CI
0–9	60.5	52.6	68.4	346.9	298.1	395.8	5.689	4.333	7.468
10–19	76.5	67.5	85.5	522.6	456.3	589.0	6.882	5.41	8.753
20–29	193.0	179.0	207.0	627.8	563.2	692.4	3.254	2.769	3.823
30–39	208.3	194.6	222.0	860.9	768.1	953.6	4.139	3.558	4.816
40–49	194.9	181.2	208.7	1156.5	1012.8	1300.2	5.933	5.098	6.905
50–59	188.9	173.4	204.4	1618.3	1379.8	1856.8	8.561	7.364	9.953
60–69	143.3	129.1	157.6	2110.7	1634.9	2586.5	14.762	12.462	17.487
70–79	153.1	136.1	170.2	2224.1	1378.8	3069.5	14.536	12.34	17.123
≥80	291.8	263.1	320.4	7265.0	3939.2	10590.7	24.88	22.133	27.968

IRR, incidence rate ratio.

and current smoker living in a slum were associated with an increased risk of dying (2.40 (1.95 to 2.95), p<0.0001).

DISCUSSION

Twenty weeks after the first case was reported in the city of Buenos Aires, the COVID-19 pandemic is focusing on the city's most economically vulnerable social groups. Although slum dwellers represent 7% of the city's population, they contribute 40% of the cases. However, absolute numbers do not accurately reflect the amount of inequitable distribution. Age-adjusted stratified incidence rates differ in astronomical proportions. For each age range, the minimum difference is a magnitude of 3 times; and for groups of people over 50 years, the differences exceed the range of 14 times more. These differences also extend to mortality, where slum dwellers, despite being younger, have higher mortality. Beyond the metrics that characterise slums, it is important to consider that

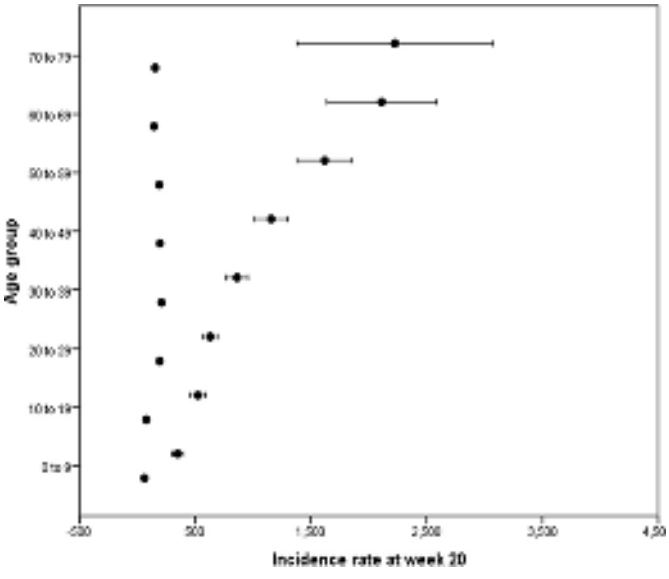

Figure 2 Difference in incidence rates by age group in week 20 between inhabitants with and without residence in the slums.

half of the households in slums do not have sewage disposal, those one-third are critically overcrowded and that one in four does not have main water. Eighty per cent of adults over 25 years of age have not completed secondary education.

The most recent estimates for slum populations suggest that nearly 900 million people live in slums in the developing world, and it is estimated that by 2030, about 2 out of 5 billion of the world's people will live in slums located mostly in big cities.[8 9] Despite this, health in slums can be considered poorly studied. Moreover, slums are not identified as a determinant of health in the Global Burden of Disease report.

This report actually shows that slum residents cannot be considered an extension of urban poverty or a mere risk category. Slums constitute an individual reality with its own identity and a dynamism that can only be managed as such. The health strategies in the city of Buenos Aires were in fact not an extension of the approach to the problem in the rest of the city. The active search for suspicious cases and an intensive testing plan resulted in a flattening of the slum curve. Although the positivity rate remains high, the progression of the epidemic could only be contained by a non-passive strategy. The slums, although more concentrated in the south of the city, are distributed throughout the city. In fact,

Table 5 Social gradient in the distribution of incidence rates between the different neighbourhoods of the city and the slums

SES quintiles	IRR	Lower 95% CI	Upper 95% CI	P value
1	1			
2	1.358	1.259	1.465	<0.0001
3	1.611	1.492	1.741	<0.0001
4	1.865	1.729	2.012	<0.0001
5	2.943	2.738	3.162	<0.0001
Slum	14.375	13.413	15.407	<0.0001

IRR, incidence rate ratio; SES, socioeconomic status.

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the largest conglomerate is located in close proximity to one of the city's most affluent neighbourhoods. Therefore, it is not the geographical distribution but the social conditions that determine the results.

In the rest of the city where the majority of the population lives, it is also observed that the distribution of the infection is socially conditioned. This phenomenon was described in other large cities such as New York or Chicago[1–5] where there is a disproportionate representation of cases between the black and Latino communities.

Although previous theoretical models elegantly documented that an eventual pandemic similar to that of 1918 would have events concentrated in the poor world[14] with more than 95% of the victims among the most disadvantaged social groups, the verification of this asymmetry in a concrete reality and in short times is one more example that the inequality of the world of a century ago is still in force.

Despite mathematical models describing what could theoretically happen in the developing world,[15–17] this is—to the best of our knowledge—the first concrete communication of the evolving of the pandemic among slum dwellers in a large city. The rigorousness of the health information system in Argentina contributes enormously to the description of this phenomenon. It is possible that countries with a similar or greater disease burden than Argentina may not be able to complete a survey of these characteristics due to fragmented or incomplete reporting systems. Although incidence rates cannot be extrapolated to other settings, the underlying concept is one of international relevance.

This analysis finds associations between place of residence and population incidence rates and does not give or pretend to give a mechanistic explanation of why these differences occur. Many factors can be related to these findings. The overcrowding of slums and the lack of basic services must certainly play a role in the impossibility of achieving adequate social distance. But not only material deprivation plays a role. Fear of losing a job due to absenteeism may mean that consultations for symptoms may be delayed among slum dwellers. In any case it is important to investigate these reasons and in no way to prejudge or give rise to a stigmatisation that is a well-described phenomenon and should be avoided.[18]

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Population density index and its use for distribution of Covid-19: A case study using Turkish data

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ABSTRACT

Since March 2020, many countries around the world have been experiencing a large outbreak of a novel coronavirus (2019-nCoV). Because there is a higher rate of contact between humans in cities with higher population weighted densities, Covid-19 spreads faster in these areas. In this study, we examined the relationship between population weighted density and the spread of Covid-19. Using data from Turkey, we calculated the elasticity of Covid-19 spread with respect to population weighted density to be 0.67 after controlling for other factors. In addition to the density, the proportion of people over 65, the per capita GDP, and the number of total health care workers in each city positively contributed to the case numbers, while education level and temperature had a negative effect. We suggested a policy measure on how to transfer health care workers from different areas to the areas with a possibility of wide spread.
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1. Introduction

An ongoing outbreak of a novel coronavirus (2019-nCov) was identified only a few days after the World Health Organization (WHO) was alerted about a cluster of pneumonia of unknown aetiology in the city of Wuhan, China on 31 December 2019 [1]. The outbreak appears to have started from a single zoonotic transmission event or multiple zoonotic transmission events at a wet market in Wuhan where game animals and meat were sold [2] and is quickly approaching 25 million confirmed cases worldwide [3].

The start date for the epidemic, total cases, and fatalities were different for each country. The country with the highest number of cases as of August 28, 2020 is the United States, with more than 6 million confirmed cases, followed by Brazil and India. There were more than 3.5 million confirmed cases in Europe. In all of these regions, crowded cities are the epicenters for the disease [4]. What sets these cities apart from rural areas are their high population densities. Population weighted density can be described as a weighted average of density across the tracts, where tracts are not weighted by land area but by population [5].

Density is one of the most fundamental characteristics of an urban area [6]. However, raw population density, simply population divided by count, is not a good measure of the density at which the population lives [5]. Los Angeles is actually denser than New York, but it is hemmed in by mountains, limiting how far the commuting zone can reach. However, according to population weighted density, an average New Yorker lives in a census tract with more than 12,400 people within a kilometer square. That is three times more than the density of Los Angeles County [7]. The population weighted density of several of European cities, such as Barcelona (24,600), Madrid (18,600), Valencia (17,300) and Paris (13,300) are much higher than New York City. The population weighted density of Rome (8,900), Berlin (8,200) and London(8,000) is also relatively high [8].

Especially in pandemies such as coronavirus, where human contact is the main reason for spread, population- weighted densities are better measure than conventional densities, because the variation in density across the subareas matters more than the density in total area. Before New York City placed restrictions on its residents in order to combat disease spread, the number of cases in New York City was close to 20 times the number of cases in Los Angeles County [4].

The aim for this paper was first to derive population weighted density for the cities in Turkey and the districts for its major three cities in 2020. Then using the data points in April 2020, we analyzed the relationship with the density and the spread of coronavirus in

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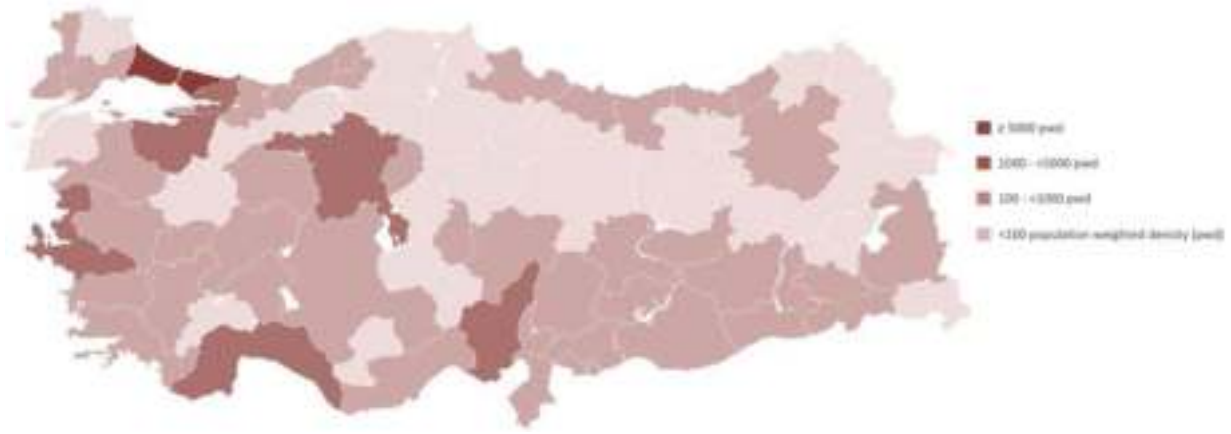

Fig. 1. Population Weighted Density Map for Turkey.

those cities controlling for cities' education level, wealth, health care force, temperature, and demographics. We suggest that, in conjunction with information about a cities' number of health care workers and fatality statistics in August 2020, population weighted density can also inform us on how to mobilize each region health care force from low spread risk areas to high spread risk areas.

2. Population weighted density in Turkey

Let D be the density of the urban area, which is the total population, P divided by the total area A:

$$D = \frac{P}{A}$$

Let p_i is the population and a_i is the area of subareas, by definition $P = \sum p_i$ and $A = \sum a_i$. Therefore the density for each areas is $d_i = \frac{p_i}{a_i}$. Population-weighted density D_p is the mean of the subareas densities weighted by the population of the subareas:

$$D_p = \frac{1}{P}\sum p_i d_i.$$

Ottensmann [9] showed that the difference between population-weighted density and conventional density is a simple function of the variance in density across the census subareas and conventional density. Craig [5] suggested the amount of differences will depend on the variation in density across the subareas. We would expect similar results for the areas that have been defined in such a ways that they do not include sparsely settled territory. In the USA, this measure has been part of the national statistics since 2010, but it has not been used yet in Turkey.

By using population values from the Turkish Statistical Institution and area values from several websites that use Google Earth, we calculated population weighted density for each city in Turkey [10].

Istanbul, with a population of more than 15 million, was ranked as the first city according to population weighted density. On average, residents in Istanbul live with 16, 757 people around their 1 km^2. Istanbul population weighted density is lower than Barcelona, Madrid and Valencia. However, it is higher than Paris population density and almost double that of London. Fig. 1 shows a map of Turkey with respect to the population weighted density of each of its regions.

Izmir was the second dense population in Turkey according to population weighted index, although it is in third place when it comes to population and raw density. Ankara was the third dense population, although according to raw density it was as eighth (Table A1). For the three major cities, we also calculated population density of the each district (Tables A2–A4) as well as their corresponding population weighted density maps. For our knowledge, this was the first time the population weighted densities are calculated for Turkey and these three cities (Fig. A1).

3. Method

Turkey's Health Ministry has released only limited data on the spread of the virus and announced the number of Covid-19 cases in individual cities on two occasions, on April 1 st and April 4th [11]. As of August 28, 2020, there were more than 265,000 cases in Turkey and Istanbul accounted for almost 60 percent of confirmed cases of Covid-19. Izmir and Ankara have been declared growing hot spots, as was predicted by population weighted density.

For each city, we calculated the difference in the case numbers to proxy for the spread of the disease in each city. There was a strong positive relationship between population weighted density and and the spread of the disease (Fig. 2). Correlation coefficient was calculated as 0.97 with $p - value < 0.0001$.

Risk factors including education and wealth of each city, number of health care workers, proportion of male population to female population, and proportion of people over 65 years old were available from the Turkish Statistical Institution. For each city we calculated the average temperature in Celcius since 1941 and use it as an additional regressor to control for the effect of temperature on spread of the disease [12].

To determine the relationship between these variables and our outcome variable, corona spread, we consider the following model:

$$y_j = \beta_o + \beta_1 x_{1_j} \ldots + \beta_k x_{kj} + u_j,$$

where j indexes m cities. All of our variables are at the city level. The spread, our outcomes variable, defined as log of differences in case numbers in a given city measured two different time period. However, note that estimating the model on individuals and clustering standard errors by city would yield the same coefficients and standard errors as estimating city means using analytic weights and standard errors robust to heteroskedasticity.

The coefficient $[(k+1)\times 1]$ matrix β can be obtained

$$\hat{\beta} = (\tilde{X}'\tilde{X})^{-1}\tilde{X}'\tilde{y},$$

where $\tilde{X}$ and $\tilde{y}$ obtained by multiplying each row of $[n \times (k+1)]$ matrix X and row of $[n \times 1]$ matrix $\boldsymbol{y}$ by $\sqrt{w_j}$, w_j being the number

Fig. 2. Relationship between Population Weighted Density and the Disease Spread.

of individuals contributing to the average. For standard errors, the variance-covariance matrix can be calculated as

$$\sum = \frac{1}{(m-(k+1))}\tilde{\hat{u}}\prime\tilde{\hat{u}}(\tilde{X}\prime\tilde{X})^{-1}$$

where $\tilde{\hat{u}}$ is equal to row of $[n \times 1]$ matrix $\hat{u}$ multiplied by $\sqrt{w_j}$ [13].

The variables such as population weighted density, total health care workers, and city's per capita GDP in logarithmic form allowed us to measure elasticity. The other explanatory variables were used as level forms, thus providing semi-elasticity measures.

4. Results

On average, a person in Turkey lives with 3,868 people within 1 km^2. The average education level is around 7.5 years and 9.12 % of the population is 65 years old and over. There is a slightly higher male population than female population and the per capita income is $9,745. There are about 1.9 doctors, 2.37 nurses and 2.22 other health care workers per 1000 people in Turkey (Table 1).

Pandemics spread through the movement of and interaction between infected people, and these interactions occur more frequently in places with high population weighted densities. Therefore, it has been assumed that during pandemics such as Covid-19, density is associated with higher rates of transmission, infection, and mortality [14,15]. After controlling for other factors, weighted regression yield that the elasticity of population weighted density with respect to the growth of coronaspread is calculated as 0.67 (Table 2). 1 % increase in population-weighted-density increased the growth of the disease spread by .67 %.

For each district in Istanbul, we measured percentage changes in expected cases relative to the district with the average population density. We choose Besiktas district as a reference since population weighted density for district is approximately equal to the density of Istanbul as a whole. For example, Avcilar district's population weighted density is around 10 % higher than Kadikoy, so the growth of Covid-19 cases for Avcilar will be 6.7 % higher than Kadikoy (Fig. 3).

As expected, there were significant associations between socioeconomic factors and the growth of the spread. As is consistent with the literature, cities with higher-than-average education levels had significantly lower Covid-19 infection rates. This trend can be explained by the facts that people with higher education levels have a better understanding of the virus and take shelter-in-place restrictions more seriously. They are also more likely to be able to work from home [16].

The proportion of the population aged 65 years and older was also positively associated with the growth rate in cases. Each percentage point increased the growth rate by 11 %. This may be due to the fact that people aged 65 years and older have weaker immune systems than the rest of the population [17].

Since the higher health care workers in the city is related with the higher number of testing, we found strong positive correlation between total number of health care workers and the spread of the disease. Cities with 1 % higher health care workers were associated with .84 % higher disease spread. These findings are consistent with previous studies in the US that found statewide testing is the most significant predictor of the county infection rate [18].

Wang et al. previously demonstrated that an increase in temperature reduces the transmission of Covid-19 [19]. We found similar results in Turkey. The cities with higher temperature had lower spread rate. An additional 1 °C decreased the spread rate by 16 %.

Since Turkey did not restrict the working population to leave their houses, cities with higher per capita GDP were associated with higher number of cases. A 1 % point increase in GDP in the cities was associated with a 1.12 % increase in the growth rate of the cases. Gangemi et al. also found a strong significant relationship between GDP and Covid-19 case numbers in their analysis using the indicators from the World Bank [20].

Table 1
City Characteristics.

Demographics	N	Mean	STD	Weighted Mean	Weighted STD
Number of Cities	81				
Population-Weighted-Density		543	1918	3868	6327
Education Level (years)		6.96	.71	7.42	0.96
Temperature(Celcius)		6.70	3.53	7.82	3.02
Doctors		1877	4200	9347	12252
Nurses		2340	4269	9994	12477
Other Health Care Workers		2197	3506	8415	9840
65 and over age		% 10.53	3.58	9.12	3.02
Per capita Income		$7,249	$2,570	$9,745	$4,210
Proportion of Male to Female		1.02	.037	1.01	.02

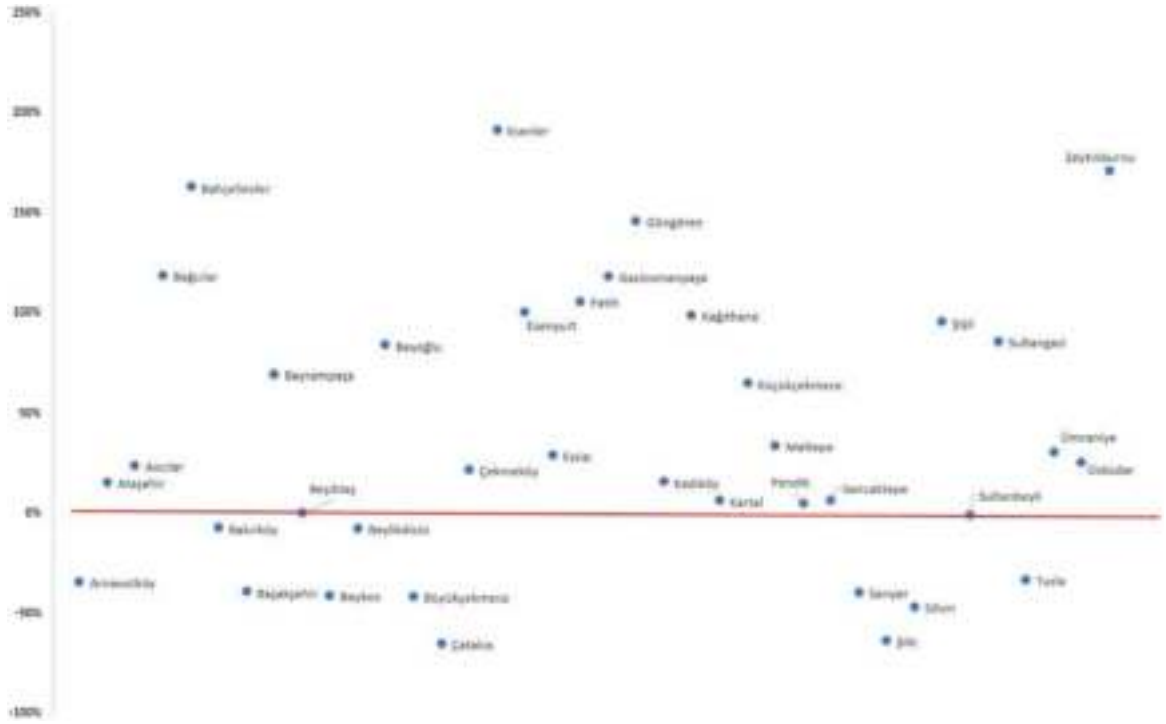

Fig. 3. The Expected Percentage increase in district cases in Istanbul relative to Istanbul average.

Table 2
Weighted Regression to Explain Log of Differences in Cases.

Variables	Coefficient	Std. Err.	P>|t|
Log (Population-Weighted-Density)	0.67	0.15	0.001
Education	−0.45	0.16	0.007
Log (Total Health Care Workers)	0.85	0.18	0.001
Temperature	−0.16	0.03	0.001
65 and over age	.11	.04	0.005
Log (per capita GDP)	1.12	0.45	0.02
Proportion of Male to Female	4.86	4.08	0.238

The proportion of male population to female population was not associated with growth rate of the cases. Although the coefficient was positive, i.e. the cities with higher male to female population had higher cases, the variable was not significant. (p = 0.238) (Table 2). A recent study has shown that men and women have the same prevalence for Covid-19, although men who have tested positive for Covid-19 are more at risk for worse outcomes and death, independent of age [21].

Newly published research on the rate of Covid-19 spread in the US has also provided insight on which factors affect disease spread. The researchers examined data from January 20, 2020 through May 25, 2020 from 913 different metropolitan US counties. They used a regression model and took into account factors such as population size, education level, and demographic variables including age, race, and health care infrastructure (e.g. ICU bed capacity). In so doing, the authors of the study concluded that a higher county population, a higher proportion of people aged 60 and above, a lower proportion of college educated individuals, and a higher proportion of African Americans were all associated with a greater infection rate of Covid-19 [18].

5. Discussion

In epidemiological terms, ẗflattening the curveëfers to the implementation of measures that slow the rate at which people are infected by the virus, thus lessening the burden on medical professionals and the health care system. The ćurveëfers to the projected number of people who will come into contact with COVID-19 over a period of time. As more people contract the virus, the infection curve rises. If it rises too quickly, then the health care system risks becoming overloaded, which can lead to hospitals running out of the supplies they need to help infected people recover.

How many people a given patient is likely to infect is defined by the reproductive number. Decreasing this number is the ultimate goal in fighting the pandemic. If it is less than one, then group of infected people would be generating less infection, the curve

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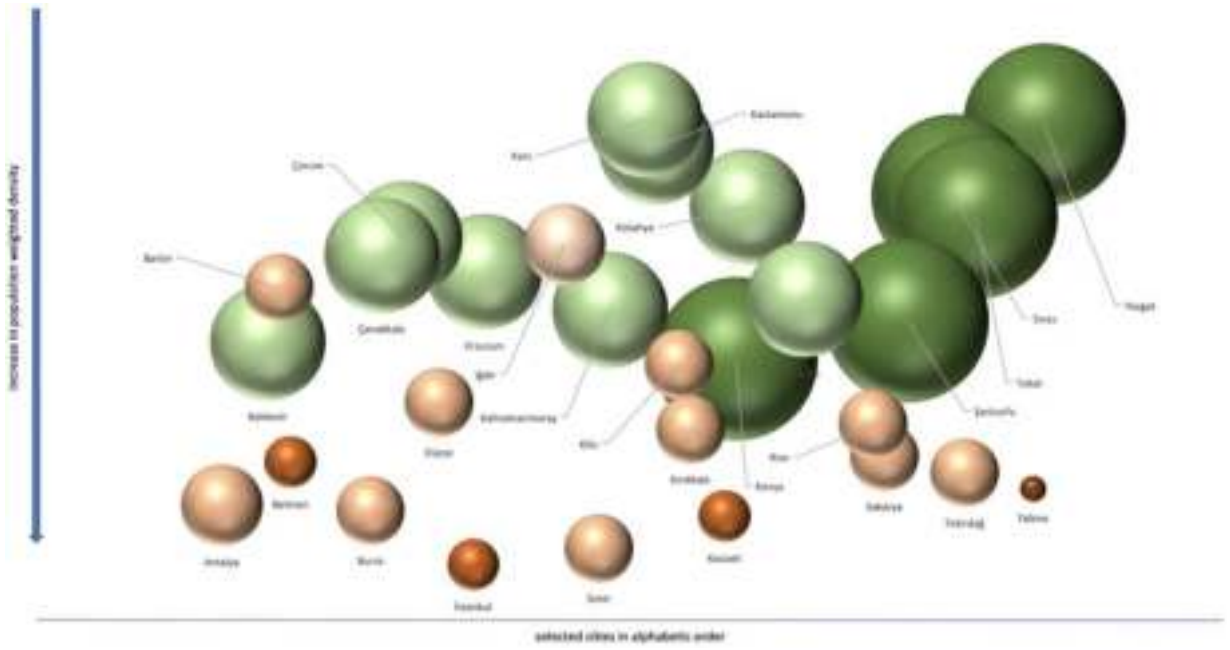

Fig. 4. Possible Health Care Workers Transfer Among the Cities during the outbreak. Size of each bubble is proportional to the ratio of health care workers divided by population weighted density.

would flatten, and eventually die down. The reproductive number has four components: *duration, opportunity, transmission probability* and *susceptibility* [22]. The multiplication of each component gives the reproductive number. *Duration* here refers to the duration of infectivity, not duration of symptoms, as some patients may remain symptomatic even after viral recovery [23]. *Opportunity* is a measure of how many people you come into contact with for every day you're infections. *Transmission probability* is a measure of the chance the infection will get across during an interaction and *susceptibility* is a measure of the chance the person at the other end of the interaction will pick up the infection and became infectious themself.

Population Weighted Density increases the *opportunity* component of reproductive number and increases the probability of speeding up the curve. The faster the infection curve rises, the quicker the local health care system gets overloaded beyond its capacity to treat people. More and more new patients may be forced to go without ICU beds, and more and more hospitals may run out of the basic supplies they need to respond to the outbreak.

From a policy-planning perspective, population weighted density can give a very clear objective: paying attention to the areas with highest population weighted density. In 2009, the H1N1 pandemic persisted for relatively longer periods of time in areas of Taiwan that had higher population densities [24]. There was a positive and significant relationship between the death rate from the 1918 influenza pandemic and the state-level population density in the United States [25].

Many countries have initially implemented measures in the hope of slowing the Covid-19 spread. These measures include social distancing, placing restrictions on domestic travel, and implementing a curfew. Although these measures were initially successful, June saw the beginning of quarantine fatigue caused by the profound burden of extreme social distancing and economic hardship as well as forced reopening of shuttered business, resulting in an increase spread. Governments around the world fear that the combination of the coming influenza season and Covid-19 will flood hospitals with patients. Many countries are responding to this imminent issue by augmenting hospital capacity, including constructing temporary hospitals within large spaces such as convention centers. The most effective of these temporary measures would be constructed near the areas with highest population weighted densities.

For any health care system to perform well it depends on the availability of a sufficient number of skilled health care workers. Furthermore, it is crucial that these health workers be mobile, since urban areas are first to experience spikes in Covid-19 cases. For example, in the first months of the Covid-19 epidemic, health care workers flew from San Francisco to New York City, where there was a higher need for services [26]. If such mobility is available, we suggest that attention to population weighted density can direct how this transfer might be done. We graphed the cities in Turkey with low risk spread (proxied by low population density) with a high number of health care workers (Fig. 4). The big green cities like Yozgat, Sivas, Tokat are the cities with low population weighted density with relatively high number of health care workers, and the brown small cities like Istanbul, Batman, Kocaeli and Yalova are the ones with high population weighted density with relatively low number health care workers. Possible transfer of health care workers can be done from cities marked by big green bubbles to cities marked by small brown bubbles. Note that healthcare workers are one major resource in the health systems, but for treating patients with Covid it would not be enough to shift workers without providing/shifting other care resources such as beds, reanimation equipment.

Population weighted density can also be used as a tool to evaluate the success of fighting with pandemic. We compiled the death data from 8 different cities in Turkey. These were the only 8 cities that make the death data available on a daily basis online [27]. We graphed the series of daily death since March 25, 2020 (two weeks after the first corona virus case) until August 30, 2020 for last three years (Fig. A2). The total deaths are directly linked with the coronavirus as well as those from other causes such as stroke, heart disease, and cancer. Turkey's total count of coronavirus cases only includes cases that have been confirmed with a positive test result and does not include cases that have been clinically diagnosed with no test. The total number of deaths indicate fatalities

Table 3
Ascending Ranking of Increase in Death between March 15 to August 30, 2020 relative to average of last three years, controlling for population weighted density.

Cities	Population Weighted Density (Ranking) (A)	Excess Death (B)	B/A	Population Density (C)	B/C
Kocaeli	1916(4)	237	0.12	541	0.44
Istanbul	16757 (1)	4771	0.28	2987	1.60
Bursa	1903 (5)	757	0.40	293	2.58
Denizli	433(19)	213	0.49	89	2.39
Malatya	260 (26)	221	0.85	68	3.25
Sakarya	535 (15)	1116	2.08	213	5.24
Kahramanmaras	129 (42)	363	2.81	80	4.54
Konya	165 (33)	795	4.81	57	13.95

that have coincided with the onset of the outbreak, though they are not necessarily attributed solely to the coronavirus.

For eight cities we selected, we calculated the increase amount of death relative to average of last three years. We then divided this number with population weighted density to determine, controlling for the density, the proportion death per density measure (Table 3). Consistent with previous research, cities with higher population densities tend to have lower death rates, possibly they enjoyed a higher level of development including better health care systems. The recent analysis found that after controlling for factors such as metropolitan size, education, race and age, doubling the activity density was associated with an 11.3 percent lower death rate [18].

6. Conclusions

The impact of population density on the rate of spread of emerging highly contagious infectious diseases has rarely been studied. The current Covid-19 pandemic allows us to investigate these relationships. Our study uses a regression model to study the impact of population weighted density on Covid-19 spread in Turkey while controlling for key compounding. We found that population weighted density is one of the most significant predictors of infection rates. However, counties with higher densities have significantly lower virus-related mortality rates, possibly due to superior health care systems.

Most of the data is preliminary during the outbreak and the data that we can use in Turkey is limited. We were able to update our analysis for the death statistics by August 30th. However, the Turkish ministry of health has not published case numbers by cities after April 2, 2020. Because of this, the results in Table 2 have not been updated beyond April 2, 2020. However, our results were consistent with the previous research [14,16–21]. Additionally, we are unable to measure the number of patients with underlying conditions in each city, which would decrease the survival rate of each of these regions. We have seen death toll raise in a cities like Zonguldak where most of the population suffers from chronic lung diseases due to work conditions in the minings located in the city. We have used the death statistics to measure the success of dealing with the outbreak, but any death statistics in the midst of pandemic are tricky to pin down and must be considered preliminary. We have seen most of the countries are improving their death statistics, which they now acknowledge incomplete.

In order to control and manage the outbreak, our analysis suggests that population weighted density can be a useful tool. According to previous research, there are many advantages of compact development. It is associated with with open space preservation, higher innovation and overall economic productivity, greater social capital, less likelihood of obesity and related chronic diseases and increased overall life expectancy [28–32]. However, compact development can be big ënemyïn the coronavirus fight [15]. High density means that people in those areas live very differently from other people. Those who live or work in or near the city shop and commute differently: they are far more likely to walk or take public transit than the rest of the people. The disease spreads faster in the areas with high population weighted areas then elsewhere simply because there is so much human contact.

At this stage, particular attention should be given to the prevention of spreading in the highest dense areas directed by population weighted density. The concept of flattening the curveültimately assumes that the same number of people will contract the coronavirus whether or not the curve is steep or flattened. If the curve is flattened, however, there is less stress placed upon the health care system, which results in better health care access for those who are sick.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgments

None.

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RESEARCH Open Access

Population density, a factor in the spread of COVID-19 in Algeria: statistic study

Nadjat Kadi* and Mounia Khelfaoui

Abstract

Background: Since November 2019, the world has suffered the disastrous consequences of the COVID-19 pandemic. No country has been spared either socially or economically. Given the inevitability of the spread of this virus, researches have been active to understand and to counteract the factors that anticipate its spread. In this research, we endorse population density as a catalyst factor for the proliferation of COVID-19 in Algeria. We are interested in the relationship between population density and the spread of COVID-19 in Algerian cities. The latter is characterized by a disparity in the concentration of the population according to the geographic location of each.

Results: The cluster analysis allowed us to isolate the groups of cities with the highest numbers of COVID-19 infected cases and the highest population densities. The regression models obtained suggest that there is a strong correlation between the population density and the number of COVID-19 infections in Algeria. This finding is verified by the correlation coefficients. Thus, it is estimated that population density has a positive effect on the spread of COVID-19 in the Algerian context during the study period.

Conclusions: The spread of COVID-19 in Algeria is increasing as the population density increases. Once this factor has been demonstrated, the fight against the proliferation of the virus can be thwarted by measures to raise public awareness of social distancing in public places namely supermarkets, markets, and cafes.

Keywords: COVID-19, Population density, Cluster analysis, Correlation, Simple regression analysis, Algeria

Background

Throughout history, humanity has encountered many epidemics that have forever transformed the social, economic, and architectural life of societies. The primary objective of these transformations is to curb the disease transmission within the population. Investigating the factors that cause this epidemic is the priority of the scientific community and epidemiologists considering the catastrophic human deaths and socio-economic effects on the population. Since November 2019, the world has been confronted to the COVID-19 epidemic commonly known as COVID-19. At the time of writing this article, COVID-19 caused 436,682 deaths and more than 8 million infected cases. The virus has spread to 213 countries according to the World Health Organization. A priori, people's proximity is the first advanced factor to explain the transmissibility of pandemic viruses. Several research studies have been questioned on the link between the density of the territories and the current epidemic and which have concluded that the relation is positive in most of the time (Bouda-Olga 2020). As well, a study of European countries and the United States of America (USA) deduced that population density has a small but substantial effect on the rate of spread of the virus. She goes on to argue that there is a significant correlation of R^2 = 0.23 in Europe and R^2 = 0.39 in the USA (Babbit et al. 2020). Conversely, other analyses presume that the density of the population is not at issue and cannot be a determining factor in the proliferation of COVID-19. They present some cities like Singapore, Seoul, Shanghai, and New York as a counter-example because of their consequent population densities, and whose number of infections caused by COVID-19 is no different from that of cities with low urban density. Similarly, an empirical study in China on data collected for 284 Chinese cities, the results

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do not corroborate the idea that density is a key determinant of the risk of transmission of COVID-19. On either hand, the most afflicted cities are those with a relatively low density of between 5000 and 10,000 inhabitants per km^2 (Fang and Wahba 2020).

Between supporter and opponent, the density of the population cannot be discounted in the research of the factors of propagation of the diseases and each country must focus on this element and all the related variables. For this, we propose research on the effect of population density on the spread of COVID-19 in Algeria. The choice of this factor is not fortuitous as long as the first instruction to avoid contamination by this virus is social distancing.

Methods

- We calculate the population density for each city: it is the number of individuals or inhabitants occupying an area of 1 km^2 (inhabitants/km^2);
- To respond to the question of the study, we opted for cluster analysis and more precisely the hierarchical cluster method (Cornich 2007) in two cases:

1. To group the cities according to the COVID-19 infection rate in order to provide an idea of the spread of the disease and to make comparisons between the contamination rates of the different cities of Algeria;
2. Create clusters of cities according to the rate of COVID-19 infection and population density to allow comparisons between communities with the highest and lowest rates.

- We find the Pearson correlation coefficient (Schneider et al. 2010) and the coefficient of determination to determine the strength and the nature of the relationship between population density and the number of infected cases, through data for 48 cities, then according to geographic regions (coast, highlands, and the south);
- We construct a simple linear model (Schneider et al. 2010) to illustrate the impact of population density on the number of cases of COVID-19 infection over a period from 02 March 2020 to 10 June 2020. The linear model is as follows:

$Y = B + aX$

Such as:

Y is the dependent variable that represents the number of cases of COVID-19 infection

X is the independent variable that represents population density (inhabitants/km^2)

B is the constant

Then we deduce two models:

- Model 1: We use data from all cities to evaluate the relationship and degree of impact of population density on the spread of COVID-19 in Algeria;
- Model 2: In order to prove that population density is a factor in the spread of the virus in Algeria, we use data from cities that belong to the coastal region (which has 25 cities) whose population density is the highest (most of the Algerian population is concentrated on the coast).

We will use the IBM SPSS Statistics 25 to apply these statistical methods analysis.

Data

Algeria is divided into 48 cities called Wilayas dispatched over an area of 2,381,741 km^2 (World population prospects 2020), constituting three major regions: coastal cities, high plateau cities, and southern cities. The population density of each region is respectively 274 inhabitants/km^2, 70.6 inhabitants/km^2, and 2 inhabitants/km^2 (National Statistics Office of Algeria (ONS) 2008). In addition, the coastal region contains 25 cities, the high plateau region is composed of 14, and the Sahara region consists of 9 cities (Ministry of Interior 2016).

Description of the various data included in the study:

- The population of each city: the data used are extracted from the last population census in Algeria for the year 2008 (National Statistics Office of Algeria (ONS) 2008);
- The area of each city: data from the interior ministry (Ministry of Interior 2016);
- Number of cases infected with the COVID-19 virus from the beginning of the epidemic in Algeria from 02 March 2020 to 10 June 2020 from the Ministry of Health, Population and Hospital Reform (Ministry of Health and hospital reform of Algeria 2020).

Results

Until researching the relationship between population density and the spread of COVID-19 in Algeria, we propose to give an idea of the classification of cities by number of cases infected with the virus.

Classification of cities according to cases of COVID-19 infection in Algeria

The use of the classification method in data analysis has allowed us to classify cities according to the degree of

cases infected with the virus in the study period. The results obtained are shown in Fig. 1.

Figure 1 shows that the study population of 48 cities was divided into four groups, namely:

- The first group: contains the 36 cities with an average of 105 infected cases;
- The second group: includes 8 cities (Constantine, Tipaza, Aindefla, Bejaia, Ouaragla, Telemcen, Bordj-Bouariridj, Medea), with an average of 332 infected cases;
- The third group: comprises the cities of Setif and Oran, with an average of 679 infected cases;
- The fourth group: includes the cities of Algiers and Blida, with an average of 1227 infected cases.

The cluster method enabled us to classify cities by cases of COVID-19 and population density for the study period. The results are illustrated in Fig. 2.

Figure 2 shows that the study population of 48 cities was divided into four groups, namely:

- First group: contains the 44 cities with an average population density estimated at 127.64 inhabitants/km^2 and an average number of COVID-19 cases estimated at 146 cases;

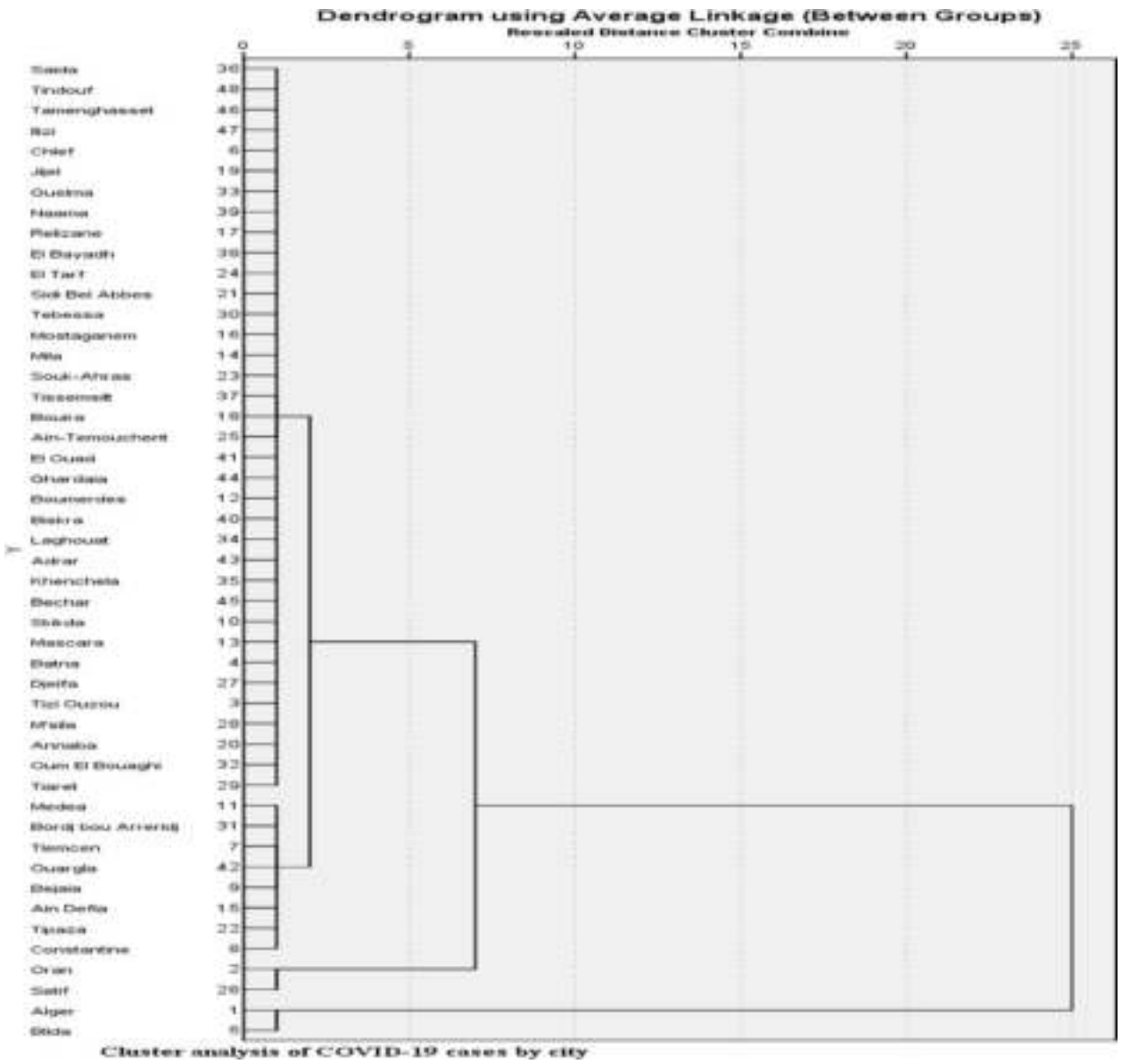

Fig. 1 Cluster analysis of COVID-19 cases by city

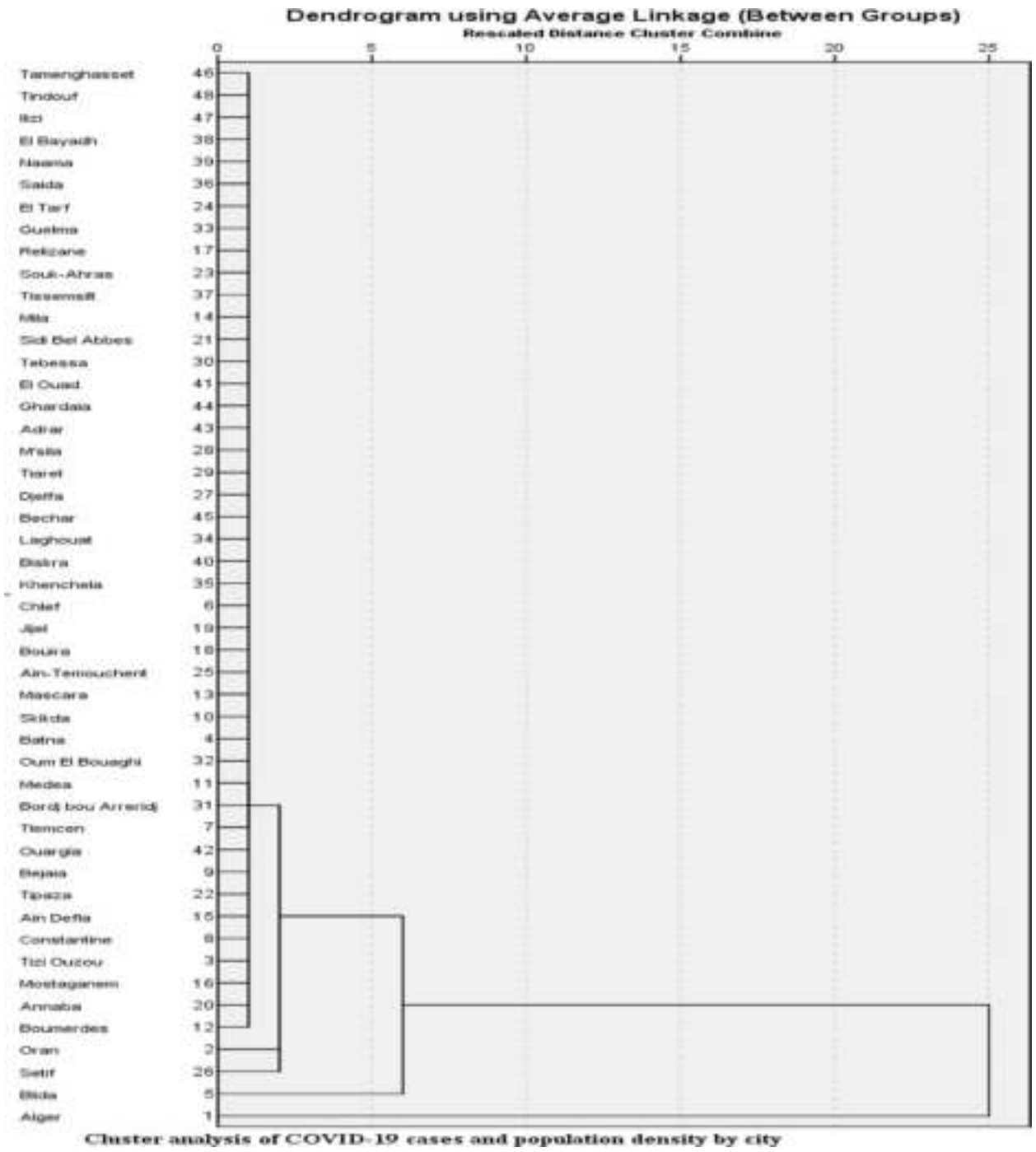

Fig. 2 Cluster analysis of COVID-19 cases and population density by city

Table 1 Correlation coefficients between population density and the COVID-19 cases

Population density (inhabitants/km2)	Geographical regions	COVID-19 cases (Coronavirus)	
		R	R^2
	All the cities	0.711	0.505
	Coastal region	0.729	0.531
	Highland region	0.482	0.232
	Southern region	0.202	0.041

- The second group: includes the cities of Oran and Constantine with an average population density of 407.325 (inhabitants/km2) and an average of 679 infected cases;
- The third group: comprises one city of Blida an estimated population density of 636.79 (inhabitants/km2) and 1288 cases of COVID-19;
- The fourth group: includes one city of Alger with an estimated population density of 2511.05 (inhabitants/km2) and 1166 cases of COVID-19.

Correlation between population density and COVID-19 cases

The cluster method has allowed us to isolate the city groups characterized by a high population density number of COVID-19 cases and those with lower population density and cases of COVID-19.

So, can we say there is a relation between population density and COVID-19 spread?

Indeed, we note from Table 1 the existence of a strong relation between the two variables estimated at 0.711. The population density explains the spread of COVID-19 in Algeria at a rate of 50.50%. The rest of the contamination is explained by other factors: sanitary, social, and economic. It is also noted that this relation differs

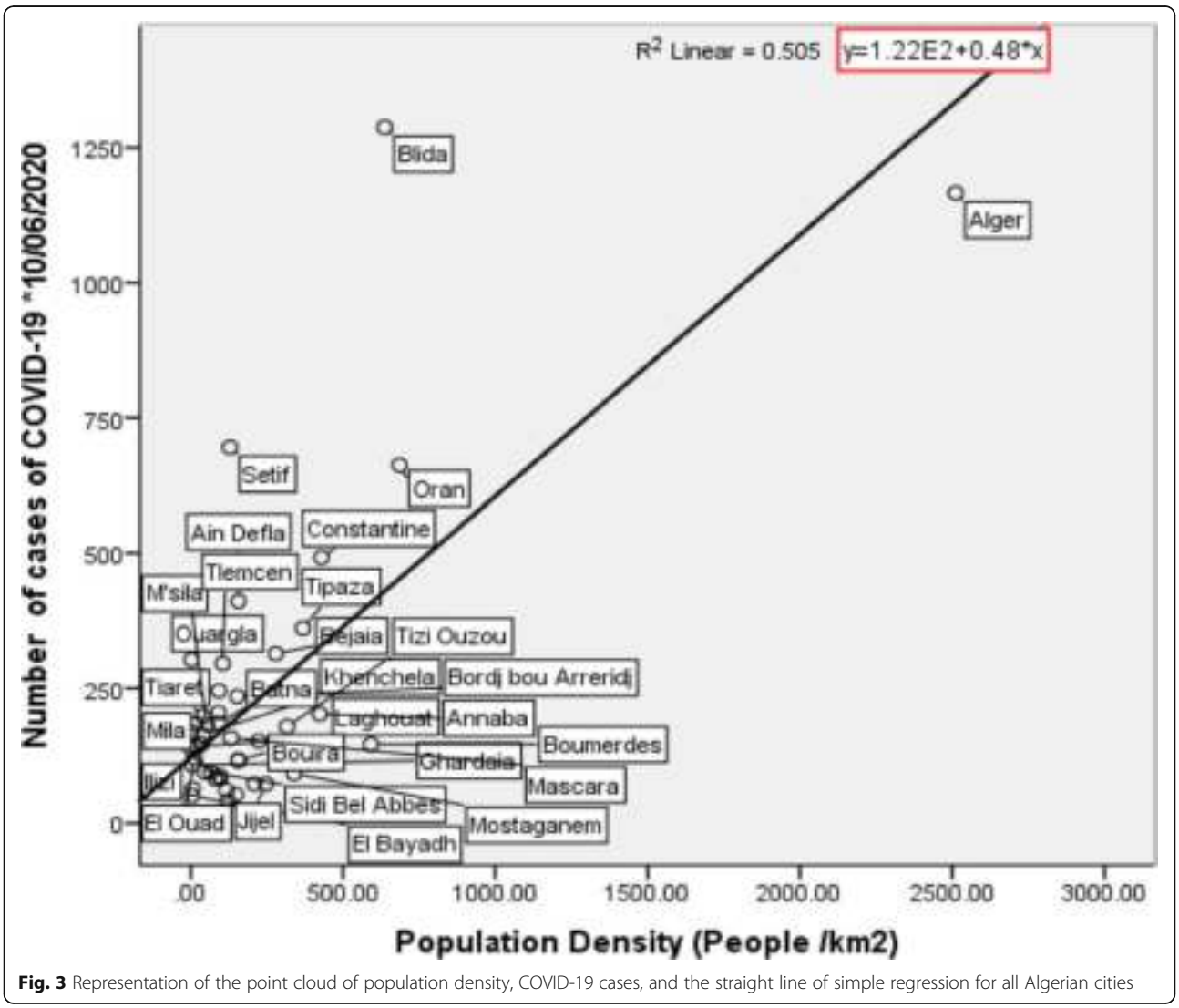

Fig. 3 Representation of the point cloud of population density, COVID-19 cases, and the straight line of simple regression for all Algerian cities

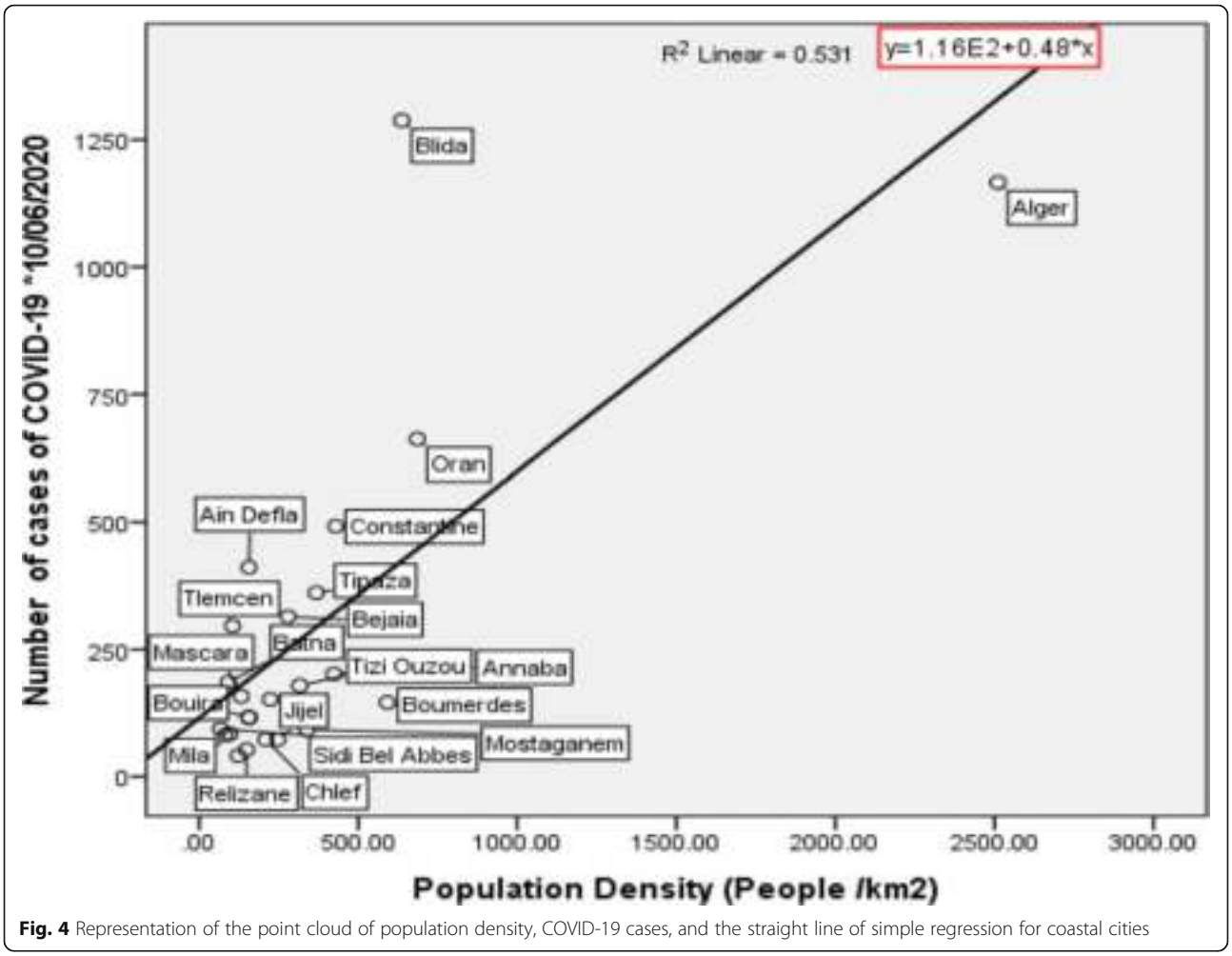

Fig. 4 Representation of the point cloud of population density, COVID-19 cases, and the straight line of simple regression for coastal cities

from one region to another. It is significantly strong in the coastal region (R^2 = 0.531), marginally less strong in the high plateau region (R^2 = 0.232), and relatively low in the southern region (R^2 = 0.041).

The degree of influence of population density on the propagation of the COVID-19 in Algeria

In order to explain the degree of influence of population density on the spread of COVID-19 in Algeria, two clouds of points were created. The first concerns population density and cases of COVID-19 for all Algerian cities (Fig. 3). The second refers exclusively to coastal cities (Fig. 4).

Through Fig. 3, we note that is a significant effect at the significance level of 5% of the population density on the increase in infections with COVID-19 because each time the population density increases by 1 individual/km2, there is an increase in the number of cases of COVID-19 estimated at 0.48 for all Algerian cities (48 cities).

We note also through Fig. 4 that is a significant effect at the significance level of 5% of the population density on the increase in infections with COVID-19 because each time the population density increases by 1 individual/km2, there is an increase in the number of cases of COVID-19 estimated at 0.48 for coastal cities.

Discussion

We note from the taxonomic analysis (Figs. 1 and 2) that the big Algerian cities (Algiers, Blida, Oran, and Setif) with a high population density are the most affected by the COVID-19 epidemic compared to the less populated cities. Also, the correlation coefficient indicates the existence of a strong correlation between population density and the number of cases of COVID-19 in the coastal region, compared with that of the highlands which is less important.

As for the southern region, the relationship between population density and COVID-19 spread is much lesser.

We found that population density has a positive effect on increasing the number of cases of COVID-19 virus. As population density increases, the number of infections increases, especially in coastal regions (Figs. 3 and 4).

Conclusion

We deduce from this study that we carried out on the spread of the Covid-19 virus in Algeria over the period 02 March 2020 to 10 June 2020 that the higher the population density, the closer there is people in public places, which will increase the spread of the current virus.

Therefore, we recommend through this study to take into account the population density factor and to provide all necessary measures to protect against the spread of the virus in Algeria and highlight the cities that have a high population density. Also, increase awareness of social distance within the population realizing adequately that it is a very difficult task in our society; it is accustomed to the proximity inherited by ancestral traditions.

Abbreviations

R: Correlation coefficient; R^2: Coefficient of determination

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Authors' contributions

All authors wrote, read, and approved the final manuscript.

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Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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The spread of 2019-nCoV in China was primarily driven by population density. Comment on "Association between short-term exposure to air pollution and COVID-19 infection: Evidence from China" by Zhu et al.

Keywords:
Novel coronavirus
2019-nCoV
COVID-19
Population density
Demography
Air pollution

1. Introduction and background

The outbreak of the coronavirus pandemic (Cheng and Shan, 2020) has stimulated a multitude of studies on the topic over just a few months. Yet a few of them go beyond the clinical scope and try to deal with other epidemiological aspects. However, both the earlier literature on other viruses and some recent studies on the novel coronavirus have examined the likely relationship between socio-economic and environmental conditions and the diffusion of pandemics. In particular, those studies point to the role potentially played by weather conditions (Iqbal et al., 2020; Sobral et al., 2020), transportation (Adda, 2016; Jia et al., 2020), economic activity (Sarmadi et al., 2020), and air pollution (Coccia, 2020; Conticini et al., 2020). As far as the latter aspect is concerned, it is worth noting that pollution emissions are already known to be associated with respiratory viral infections (Becker and Soukup, 1999; Ciencewicki and Jaspers, 2007; Cui et al., 2003; Horne et al., 2018; Mehta et al., 2013; Xu et al., 2016; Ye et al., 2016). Recently, an article published in the journal *Science of the Total Environment* has supported the "Association between short-term exposure to air pollution and COVID-19 infection" (Zhu et al., 2020) based on an analysis of 120 Chinese cities using a generalized additive model. The authors find "significantly positive associations of $PM_{2.5}$, PM_{10}, CO, NO_2 and O_3 with COVID-19 confirmed cases" (p. 3).

In this note, we show that the results of the study mentioned above may be affected by the issue of *spurious correlation* due to the omission of a common factor, namely, population density. Far be it from us deny that air pollution - and other factors as well - may have amplified the spread of the pandemic. The issue lies in the fact that, except for weather conditions, the concurrent factors suggested so far - i.e., transportation volumes, economic activity, and air pollution - are anthropic in nature. Thus, they all depend on the extent of human activities: the larger the population is, the higher the transportation volumes, economic activity, air pollution, and virus infections are (Fig. 1). Accordingly, when it comes to measuring the actual effect of anthropogenic causes on the pandemic, normalizing by population size and controlling for population density (Coccia, 2020) is by no means an option. Under the above framework, we consider alternative modeling, whose data covers almost all Chinese provinces and their socio-economic variables, relativized by the population size. Further, we also consider environmental variables that may explain the infection rate. Our main aim is to raise questions about future directions of the research on ecological and socio-economic aspects of 2019-nCoV.

2. Materials and method

2.1. Outline of the problem

To show how the issue of *spurious correlation* may affect the relationship between virus contamination (Y) and air pollution (X) though population (Pop), we consider data of people infected by COVID-19 and the level of sulfur dioxide (SO2) emissions in the provinces of China (details about variables, study area, and data sources are provided in the next sub-sections). The scatterplot of X and Y and the fitting line show a positive relationship (Fig. 2, left panel). However, when turning to consider the variables expressed as per capita data - $RY=Y/Pop$ and $RX = X/Pop$ - a negative relationship can be found (Fig. 2, right panel). The above issues can also be detected by comparing the simple correlation coefficient $\rho_{XY} = +0.33$ and the *partial* correlation coefficient $\rho_{XY|Pop} = -0.45$, which changes in sign and size. The previous example shows that the *net* relationship between several phenomena may be quite different from the *gross* one, the latter being possibly inflated by latent variables. That implies the need to consider all the potential factors that determine the health status of a society.

2.2. Nomenclature

As far as the dependent variables are concerned, let us denote by *Cov* the total number of confirmed cases of 2019-nCoV, and by *RCov* the incidence rate of the infection, namely, the number of cases per 100 thousand inhabitants.

The first set of covariates is as follows:

- *Pop* is the population size;
- *Den* is the population density, namely, the ratio between population and area in km^2;
- *Grp* is the gross regional product;
- *Pr* stands for the yearly average precipitation;
- *Th* indicates the annual average maximum temperature;
- *SO2* is the levels of sulfur dioxide emissions;
- *Iwg* stands for the emissions of industrial waste gases.

The second set of covariates includes the variables that depend on human activity and are hence normalized by population:

- $RGrp = Grp/Pop$ is the per capita gross regional product;
- $RSO2 = SO2/Pop$ stands for the per capita emissions of sulfur dioxide;
- $RIwg = Iwg/Pop$ indicates the emissions of industrial waste gases in per capita values.

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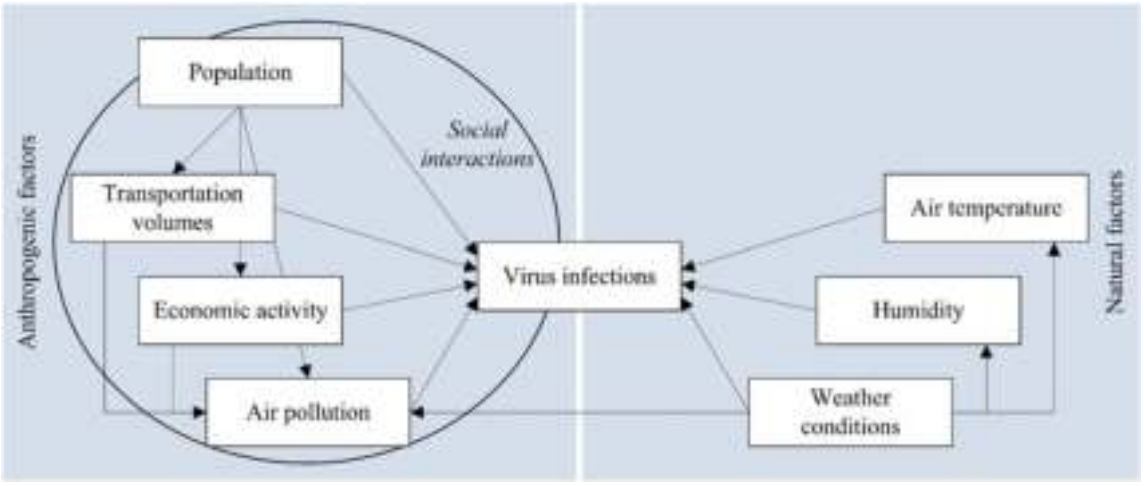

Fig. 1. Interactions between anthropogenic factors, natural factors, and virus infections.

2.3. Study area and data sources

This study focuses on 28 mainland Chinese provinces, autonomous regions, and municipalities outside Hubei province. Tibet and Guizhou are excluded due to missing data.

Data concerning the cumulative confirmed cases of the 2019-nCoV as of March 22, 2020 (Fig. 3) - irrespective of whether they resulted in deaths, and regardless of the number of people that have recovered from the virus - is collected from the Coronavirus Resource Center of the Johns Hopkins University (Dong et al., 2020).

Demographic and economic variables are derived from the annual publication of the National Bureau of Statistics of China (National Bureau of Statistics of China, 2019). Information about precipitation and temperature is gathered from Current Results,[1] based on data conveyed by the China Meteorological Administration and the World Meteorological Organization.

Data about pollution emissions are taken from the paper "The Pollution state in 31 Provinces and Regions in China" (Yang and Yang, 2011). Although outdated, those values are assumed to be a fair proxy of current emissions in Chinese provinces.

2.4. Analytical models

To study the relationships between dependent and independent variables, we use the spatial autoregressive (SAR) models (Copiello and Grillenzoni, 2017; Elhorst, 2010) with exogenous predictors:

$$Cov_i = \alpha + \rho\,\overline{Cov}_{i-1} + \beta_0 Pop_i + \beta_1 Den_i + \beta_2 Grp_i + \beta_3\ Pr_i + \beta_4 Th_i + \beta_5 SO2_i + \beta_6 Iwg_i + e_i,\ e_i \sim \mathrm{IN}(0,\sigma_e^2) \quad (1)$$

$$RCov_i = \alpha + \rho\,\overline{RCov}_{i-1} + \beta_1 Den_i + \beta_2 RGrp_i + \beta_3\ Pr_i + \beta_4 Th_i + \beta_5 RSO2_i + \beta_6 RIwg_i + u_i,\ u_i \sim \mathrm{IN}(0,\sigma_u^2) \quad (2)$$

where i is the province index, α, β_j, and ρ are the coefficients, and e_i and u_i are residuals, which are expected to be independent and normally (IN) distributed, with mean zero and constant variance. It is worth noting that the model of Eq. (2) differs from the model of Eq. (1) because the variables which directly depend on human activity are normalized by population in the latter.

In the models of Eqs. (1) and (2), ρ is the spatial autocorrelation coefficient; hence, $\overline{Cov}_{i-1}$ and $\overline{RCov}_{i-1}$ are *spatially lagged* dependent variables (i.e., the mean values of Cov_{ji} and $RCov_{ji}$ in the j provinces contiguous to the ith area). These lagged terms aim to identify whether the analyzed phenomenon has a spatial pattern accordingly to Tobler's (1970) first law of geography, namely, that "everything is related to everything else, but near things are more related than distant things" (p. 236).

In order to satisfy the assumption of homoscedasticity (i.e., σ^2 independent of i), all variables are transformed with natural logarithms (ln).

The core of the analysis is represented by statistical significance and sign (+ or -) of the estimated coefficients β_j. In particular, the differences in the β_j of in the models of Eqs. (1)–(2) is a symptom of *spurious correlation* between epidemic and environmental variables.

3. Results and discussion

The estimates of the models of Eqs. (1) and (2) are provided in Tables 1 and 2 (see also Figs. 4 and 5). In general, they are satisfactory as they fulfill the standard assumptions of regression, namely, normal residuals, absence of outliers and multicollinearity, and good fitting. Specifically, the hypothesis H_0: $e_i, u_i \sim \mathrm{IN}(0,\sigma^2)$ is accepted with low $Chi^2(2)$ statistics: 2.8637 (p-value 0.2389) for *Cov*, and 0.7412 (p-value 0.6903) for *RCov*. The explanatory variables are not affected by multicollinearity according to the low Variance Inflation Factors (VIFs ≤2.5, suggested in Allison, 1999). The adjusted R^2 are 0.7124 for *Cov*, and 0.4906 for *RCov*.

The coefficients of the spatially lagged terms are not significant, meaning the absence of spatial correlation in the data. However, that may depend on the high level of spatial aggregation of provincial data, which involves suitable local policies to control the epidemic. For example, movement restrictions should be better adopted at the national level, at least, provided the national borders are not porous.

As regards the analysis of the explanatory variables, in the model with *Cov* (the absolute number of confirmed cases), the average maximum temperature *Th* plays a significant role. Apart from indirect effects - namely, the higher is the temperature, the higher is the level of social interactions, and so the spread of the infection - the positive coefficient of *Th* stimulates other interpretations. Assuming that the novel coronavirus was already circulating before December 2019, it could imply that the recent global outbreak is also related to the mild weather conditions experienced in February 2020 (Masters, 2020). That contrasts with the expectation that the epidemic will spread less easily and more slowly during spring and summer as temperatures get warmer, as also suggested in other articles published in the journal *Science of the Total Environment* (Ma et al., 2020; Xie and Zhu, 2020). However, it has to be

[1] See https://www.currentresults.com/Weather/China/average-yearly-precipitation.php (last accessed 22.06.2020)

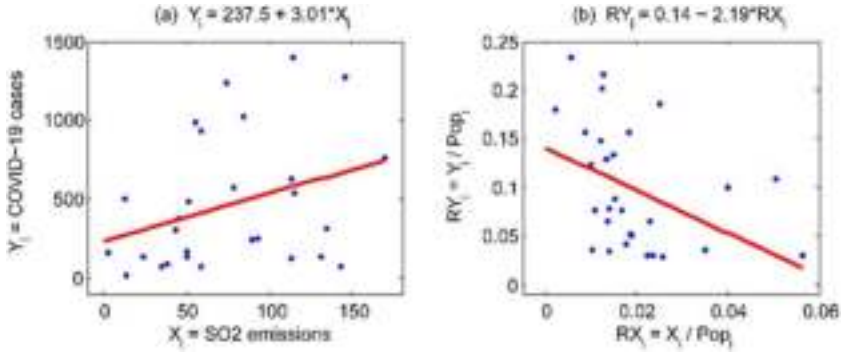

Fig. 2. Scatterplots and fitting lines of COVID-19 cases and SO2 emissions in Chinese provinces, given the population size.

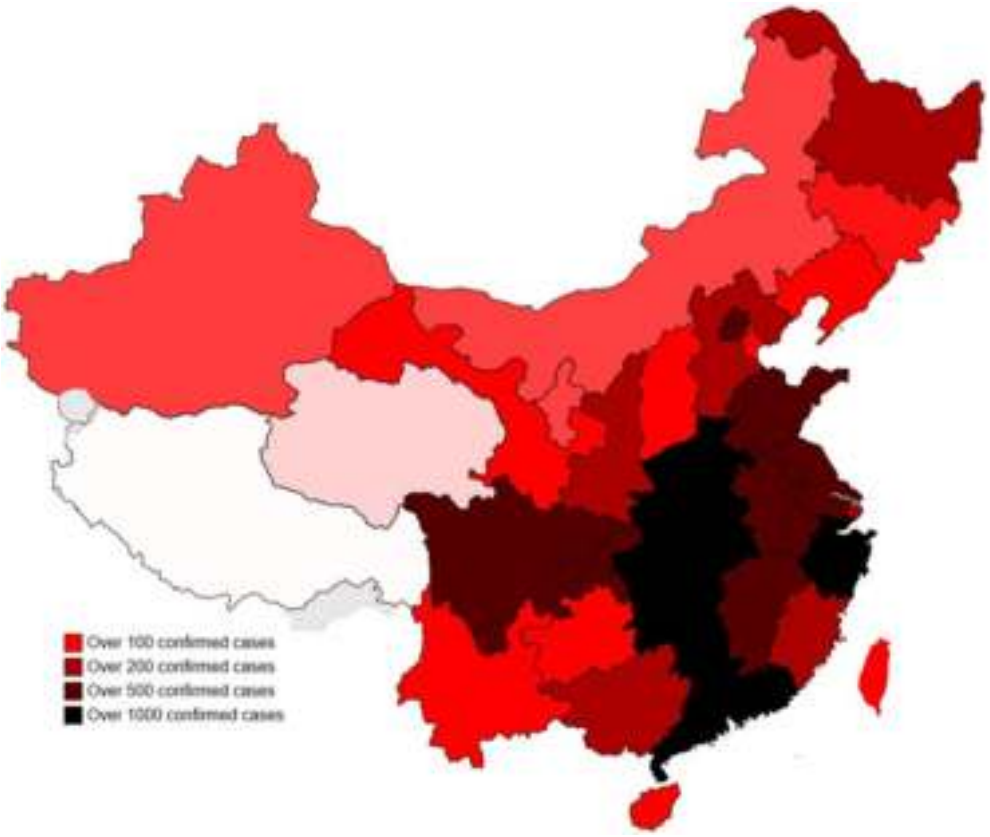

Fig. 3. Chinese provinces by COVID-19 overall confirmed cases as of March 22, 2020.
(Source: https://github.com/globalcitizen/2019-wuhan-coronavirus-data, last accessed 22.06.2020.)

considered that the incidence rate of the infection - adjusted for population density and other factors - has been found to be inversely associated with warmer and drier weather conditions (Byass, 2020).

Another significant covariate of the overall confirmed cases is the gross regional product *Grp*, which takes on a positive sign. Incidentally, that predictor is significantly correlated with some of the variables representing air pollution (*SO2*: ρ 0.5516, *p*-value 0.0023; *Iwg*: ρ 0.5412, p-value 0.0029). Apparently, this finding confirms the association found in the study authored by Zhu et al. (2020). Nevertheless, it is a trivial result. It has to be expected that the

Table 1
Results of the estimation of the model of Eq. (1) for the overall confirmed cases of 2019-nCoV.

Dependent: *Cov*					
Predictor	Coefficient	Std. err.	t-Stat[1]	p-Value	VIF
const	−5.997	1.256	−4.773***	0.0001	–
Grp	0.889	0.110	8.078***	0.0000	1.085
Th	0.966	0.274	3.532***	0.0016	1.085

Cov: total number of confirmed cases of 2019-nCoV. *Grp*: gross regional product. *Th*: annual average maximum temperature. [1] Significance levels: * 0.1; ** 0.05; *** 0.01.

Table 2
Results of the estimation of the model of Eq. (2) for the incidence rate of 2019-nCoV.

Dependent: *RCov*					
Predictor	Coefficient	Std. err.	t-Stat[1]	p-Value	VIF
const	−1.241	0.367	−3.378***	0.0024	–
Den	0.286	0.047	6.056***	0.0000	1.022
RIwg	−0.528	0.180	−2.941***	0.0069	1.022

RCov: number of cases of 2019-nCoV per 100 thousand inhabitants. *Den*: population density. *RIwg*: per capita emissions of industrial waste gases.
[1] Significance levels: * 0.1; ** 0.05; *** 0.01.

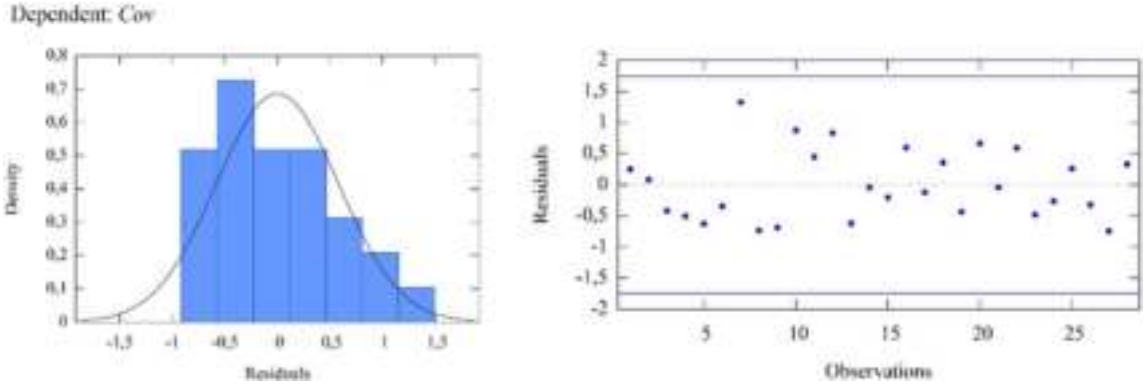

Fig. 4. Normal distribution (left panel) and .95 Confidence intervals (right panel) of the residuals for the model of Eq. (1).

overall confirmed cases are higher in the most populated areas, which are usually also the most industrialized and wealthy, and, as a consequence, the most polluted ones.

The problem is much more evident when turning to the analysis of the predictors of the incidence rate *RCov*. Population density is a significant driver of the number of cases per 100,000 population. That is in keeping with earlier literature (Amuakwa-Mensah et al., 2017), as well as with recent studies focusing on how population size and population density affect both the current and future spread of COVID-19 disease (Jahangiri et al., 2020; Rocklöv and Sjödin, 2020; Zhang et al., 2020). That might explain why, to date, the epidemic has hit so hard several highly densely populated areas around the world: Lombardy region in Italy, North Rhine-Westphalia in Germany, Madrid metropolitan area as far as Spain is concerned, New York in the United States, San Paulo in Brazil, and so forth.

That is actually the issue with the finding presented by Zhu et al. (2020), namely, that the authors missed normalizing by population the number of novel coronavirus cases before testing the relationship with air pollution and other covariates. The authors state that their generalized additive model also includes "city fixed effects … to control for time-invariant city characteristics such as population size and density" (p. 2). Unfortunately, the results are not reported in full detail, so it is unknown the role played by those fixed effects, as well as how the same fixed effects interact with the variables measuring the pollutants. Hence, there remains an open question: would the COVID-pollution relationship be confirmed using the incidence rate, instead of the number of confirmed cases, as the dependent variable?

Furthermore, in the model of Eq. (2), the level of emissions of industrial waste gas *Iwg* is another significant predictor of the number of cases per 100,000 population. Nevertheless, it takes on a negative sign, which leaves room for doubt about the hypothesis that air pollution has actually played a role in the spread of 2019-nCoV.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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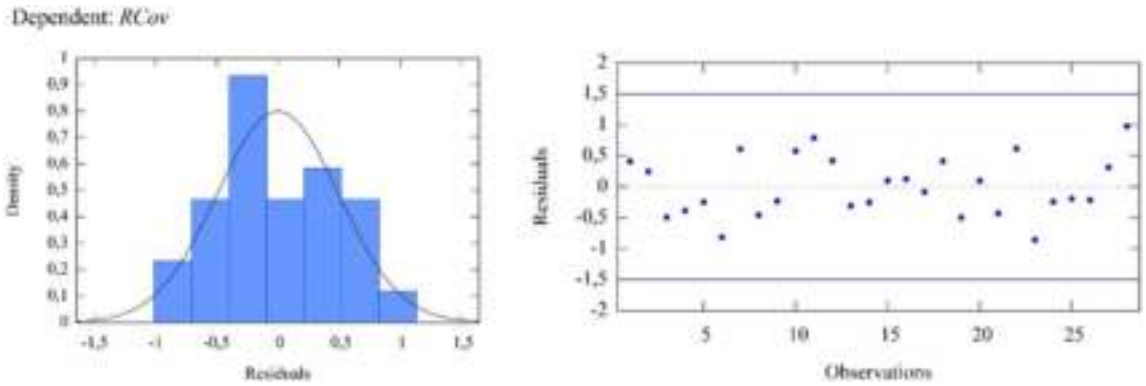

Fig. 5. Normal distribution (left panel) and .95 Confidence intervals (right panel) of the residuals for the model of Eq. (2).

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Article

Factors associated with COVID-19-related death using OpenSAFELY

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Coronavirus disease 2019 (COVID-19) has rapidly affected mortality worldwide[1]. There is unprecedented urgency to understand who is most at risk of severe outcomes, and this requires new approaches for the timely analysis of large datasets. Working on behalf of NHS England, we created OpenSAFELY—a secure health analytics platform that covers 40% of all patients in England and holds patient data within the existing data centre of a major vendor of primary care electronic health records. Here we used OpenSAFELY to examine factors associated with COVID-19-related death. Primary care records of 17,278,392 adults were pseudonymously linked to 10,926 COVID-19-related deaths. COVID-19-related death was associated with: being male (hazard ratio (HR) 1.59 (95% confidence interval 1.53–1.65)); greater age and deprivation (both with a strong gradient); diabetes; severe asthma; and various other medical conditions. Compared with people of white ethnicity, Black and South Asian people were at higher risk, even after adjustment for other factors (HR 1.48 (1.29–1.69) and 1.45 (1.32–1.58), respectively). We have quantified a range of clinical factors associated with COVID-19-related death in one of the largest cohort studies on this topic so far. More patient records are rapidly being added to OpenSAFELY, we will update and extend our results regularly.

On 11 March 2020, the World Health Organization (WHO) characterized COVID-19—which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—as a pandemic, after 118,000 cases and 4,291 deaths were reported in 114 countries[2]. As of 6 May 2020 (the date of latest data availability for this study), cases had reached over 3.5 million globally, with more than 240,000 deaths attributed to the virus[1]. On the same day in the UK, there had been 206,715 confirmed cases of COVID-19, and 30,615 COVID-19-related deaths[3].

Age and gender are well-established risk factors for severe COVID-19 outcomes: over 90% of the COVID-19-related deaths in the UK have been in people over 60, and 60% in men[4]. Various pre-existing conditions have also been associated with increased risk. For example, the Chinese Center for Disease Control and Prevention reported in a study of 44,672 individuals (1,023 deaths) that cardiovascular disease, hypertension, diabetes, respiratory disease and cancers were associated with an increased risk of death[5]; however, correction for relationships with age was not possible. A UK cross-sectional survey of 16,749 patients who were hospitalized with COVID-19 showed that the risk of death was higher for patients with cardiac, pulmonary and kidney disease, as well as cancer, dementia and obesity (HRs of 1.19–1.39 after correction for age and sex)[6]. Obesity was associated with treatment escalation in a French intensive care cohort[7] ($n = 124$) and a New York hospital presentation cohort[8] ($n = 3,615$). The risks associated with smoking are unclear[9–11]. People from Black and minority ethnic groups are at increased risk of poor outcomes from COVID-19, for reasons that are unclear[12,13].

Patient care is typically managed through electronic health records, which are commonly used in research. However traditional approaches to the analysis of electronic health records rely on intermittent extracts of small samples of historic data. Evaluating a rapidly arising novel cause of death requires a new approach. We therefore set out to deliver a secure analytics platform inside the data centre of major electronic health records vendors, running across the full, linked and pseudonymized electronic health records of a very large population of NHS patients, to determine factors that are associated with COVID-19-related death in England.

Associations with COVID-19-related death

In total, 17,278,392 adults were included (Fig. 1; cohort description in Table 1). Eleven per cent of individuals (1,851,868) had ethnicity recorded as mixed, South Asian, Black or other (hereafter referred to

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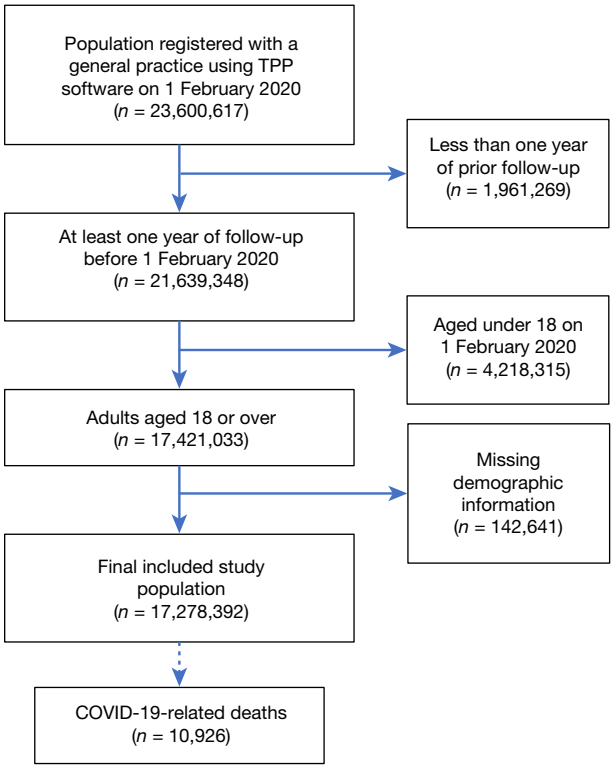

Fig. 1 | Flow diagram of the cohort. The diagram shows the numbers of individuals (*n*) excluded at different stages and the identification of cases for the main end points.

as Black and minority ethnic, BAME). There were missing data for body mass index (3,751,769; 22%), smoking status (720,923; 4%), ethnicity (4,560,113; 26%) and blood pressure (1,715,095; 10%). COVID-19-related death was recorded in linked death registration data for 10,926 of the study population.

The overall cumulative incidence of COVID-19-related death 90 days after the start of the study was less than 0.01% in those aged 18–39 years, rising to 0.67% and 0.44% in men and women, respectively, aged 80 years or over (Fig. 2).

Associations between patient-level factors and risk of COVID-19-related death are shown in Table 2 and Fig. 3. Increasing age was strongly associated with risk, with people aged 80 or over having a more than 20-fold-increased risk compared to 50–59-year-olds (fully adjusted HR 20.60; 95% confidence interval (CI) 18.70–22.68). With age fitted as a flexible spline, an approximately log-linear relationship was observed (Extended Data Fig. 1). Men had a higher risk than women (fully adjusted HR 1.59 (1.53–1.65)). These findings are consistent with patterns observed in smaller studies worldwide and in the UK[14].

People from all BAME groups were at higher risk than those of white ethnicity. When adjusted only for age and sex, hazard ratios ranged from 1.62–1.88 for Black and South Asian individuals and people of mixed ethnicities, compared to white people, decreasing to 1.43–1.48 after adjustment for all included factors (results for more detailed categories are shown in Extended Data Table 1). BAME ethnicity has previously been found to be associated with an increased risk of COVID-19 infection and poor outcomes[12,13,15]. Our findings show that only a small part of the excess risk is explained by a higher prevalence of medical problems such as cardiovascular disease or diabetes among BAME people, or by higher levels of deprivation.

We found a consistent pattern of increasing risk with greater deprivation, with the most deprived quintile having a hazard ratio of 1.79 compared to the least deprived, consistent with recent national statistics[16]. Again, very little of this increased risk was explained by pre-existing disease or clinical factors, suggesting that other social factors have an important role.

Increasing risks were seen with increasing obesity (fully adjusted HR 1.92 (1.72–2.13) for a body mass index (BMI; kg m^{-2}) of over 40), and most comorbidities were associated with a higher risk of COVID-19-related death, including diabetes (greater hazard ratio for those with a recently measured glycated haemoglobin (HbA1c) level of at least 58 mmol mol^{-1}), severe asthma (defined as asthma with recent use of an oral corticosteroid), respiratory disease, chronic heart disease, liver disease, stroke, dementia, other neurological diseases, reduced kidney function (greater hazard ratio associated with a lower estimated glomerular filtration rate; eGFR), autoimmune diseases (rheumatoid arthritis, lupus or psoriasis) and other immunosuppressive conditions (Table 2). Those with a recent (that is, in the last five years) history of haematological malignancy had an at least 2.5-fold increased risk, which decreased slightly after five years. For other cancers, hazard ratios were smaller and increased risks were associated mainly with recent diagnoses. A history of dialysis or end-stage renal failure was associated with increased risk when added in a secondary analysis (HR 3.69 (3.09–4.39)). These findings largely concur with other data, including the UK international severe acute respiratory and emerging infection consortium (ISARIC) study of hospitalized UK patients with COVID-19—which indicated an increased risk of death with cardiac, pulmonary and kidney disease, malignancy, obesity and dementia[6]—and a large Chinese study that, although lacking correction for age, suggested that cardiovascular disease, hypertension, diabetes, respiratory disease and cancers are associated with increased mortality[5]. Our results showing that severe asthma is associated with a higher risk are notable, as early data suggested that asthma was under-represented in patients with COVID-19 who were hospitalized or had severe outcomes[17,18].

Post hoc analyses of smoking and hypertension

Both current and former smoking were associated with a higher risk in models that were adjusted for age and sex only, but in the fully adjusted model current smoking was associated with a lower risk (fully adjusted HR 0.89 (0.82–0.97)), which concurs with the lower than expected prevalence of smoking that was observed in previous studies among patients with COVID-19 in China[10], France[11] and the United States[19]. We investigated this in more depth post hoc by adding covariates individually to the age, sex and smoking model, and found that the change in hazard ratio was driven largely by adjustment for chronic respiratory disease (HR 0.98 (0.90–1.06) after adjustment). This and other comorbidities could be consequences of smoking, highlighting that the fully adjusted smoking hazard ratio cannot be interpreted causally owing to the inclusion of factors that are likely to mediate smoking effects. We therefore then fitted a model adjusted for demographic factors only (age, sex, deprivation and ethnicity), which showed a non-significant positive hazard ratio for current smoking (HR 1.07 (0.98–1.18)). This does not support any postulated protective effect of nicotine[9,20], but suggests that any increased risk with current smoking is likely to be small and will need to be clarified as the epidemic progresses and more data accumulate.

We similarly investigated the change in the hypertension hazard ratio (from 1.09 (1.05–1.14) adjusted for age and sex, to 0.89 (0.85–0.93) with all covariates included), and found that diabetes and obesity were principally responsible for this reduction (HR 0.97 (0.92–1.01) adjusted for age, sex, diabetes and obesity). Given the strong association between blood pressure and age we then examined the interaction between these variables; this revealed strong evidence of interaction ($P < 0.001$), with hypertension associated with a higher risk up to the age of 70 years and a lower risk above the age of 70 (adjusted HRs 3.10 (1.69–5.70), 2.73 (1.96–3.81), 2.07 (1.73–2.47), 1.32 (1.17–1.50), 0.94 (0.86–1.02) and 0.73 (0.69–0.78) for ages 18–39, 40–49, 50–59, 60–69, 70–79 and 80 or over, respectively). The reasons for the inverse association

Table 1 | Cohort description with number of COVID-19 deaths by patient characteristics

Characteristic	Category	Number of individuals (column %)	Number of COVID-19-related deaths (% within stratum)
Total		17,278,392 (100.0)	10,926 (0.06)
Age	18–39	5,914,384 (34.2)	54 (0.00)
	40–49	2,849,984 (16.5)	140 (0.00)
	50–59	3,051,110 (17.7)	522 (0.02)
	60–69	2,392,392 (13.8)	1,101 (0.05)
	70–79	1,938,842 (11.2)	2,635 (0.14)
	80+	1,131,680 (6.5)	6,474 (0.57)
Sex	Female	8,647,989 (50.1)	4,764 (0.06)
	Male	8,630,403 (49.9)	6,162 (0.07)
BMI (kg m^{-2})	<18.5	310,721 (1.8)	522 (0.17)
	18.5–24.9	4,763,150 (27.6)	3,364 (0.07)
	25–29.9	4,682,906 (27.1)	3,068 (0.07)
	30–34.9 (obese class I)	2,384,406 (13.8)	1,813 (0.08)
	35–39.9 (obese class II)	922,398 (5.3)	762 (0.08)
	≥40 (obese class III)	463,042 (2.7)	379 (0.08)
	Missing	3,751,769 (21.7)	1,018 (0.03)
Smoking	Never	7,924,739 (45.9)	3,598 (0.05)
	Former	5,690,966 (32.9)	6,531 (0.11)
	Current	2,941,764 (17.0)	708 (0.02)
	Missing	720,923 (4.2)	89 (0.01)
Ethnicity	White	10,866,411 (62.9)	7,119 (0.07)
	Mixed	169,697 (1.0)	62 (0.04)
	South Asian	1,022,130 (5.9)	608 (0.06)
	Black	339,909 (2.0)	250 (0.07)
	Other	320,132 (1.9)	110 (0.03)
	Missing	4,560,113 (26.4)	2,777 (0.06)
IMD quintile	1 (least deprived)	3,497,154 (20.2)	1,908 (0.05)
	2	3,476,668 (20.1)	2,030 (0.06)
	3	3,483,668 (20.2)	2,114 (0.06)
	4	3,480,459 (20.1)	2,388 (0.07)
	5 (most deprived)	3,340,443 (19.3)	2,486 (0.07)
Blood pressure	Normal	3,804,148 (22.0)	2,487 (0.07)
	Elevated	2,482,710 (14.4)	1,899 (0.08)
	High stage 1	5,548,198 (32.1)	3,281 (0.06)
	High stage 2	3,728,241 (21.6)	3,229 (0.09)
	Missing	1,715,095 (9.9)	30 (0.00)
High blood pressure or diagnosed hypertension		5,925,492 (34.3)	8,049 (0.14)
Respiratory disease excluding asthma		703,917 (4.1)	2,240 (0.32)
Asthma[a]	With no recent OCS use	2,454,403 (14.2)	1,211 (0.05)
	With recent OCS use	291,670 (1.7)	335 (0.11)
Chronic heart disease		1,167,455 (6.8)	3,811 (0.33)
Diabetes[b]	With HbA1c < 58 mmol mol^{-1}	1,038,082 (6.0)	2,391 (0.23)
	With HbA1c ≥ 58 mmol mol^{-1}	486,491 (2.8)	1,254 (0.26)
	With no recent HbA1c measure	193,993 (1.1)	444 (0.23)
Cancer (non-haematological)	Diagnosed <1 year ago	79,964 (0.5)	220 (0.28)
	Diagnosed 1–4.9 years ago	234,186 (1.4)	449 (0.19)
	Diagnosed ≥5 years ago	542,320 (3.1)	1,125 (0.21)
Haematological malignancy	Diagnosed <1 year ago	8,704 (0.1)	43 (0.49)
	Diagnosed 1–4.9 years ago	27,742 (0.2)	120 (0.43)
	Diagnosed ≥5 years ago	63,460 (0.4)	173 (0.27)

Continued

Characteristic	Category	Number of individuals (column %)	Number of COVID-19-related deaths (% within stratum)
Reduced kidney function[c]	eGFR 30–60	1,007,383 (5.8)	3,987 (0.40)
	eGFR < 30	78,093 (0.5)	864 (1.11)
Kidney dialysis		23,978 (0.1)	192 (0.80)
Liver disease		100,017 (0.6)	181 (0.18)
Stroke or dementia		390,002 (2.3)	2,423 (0.62)
Other neurological disease		170,448 (1.0)	665 (0.39)
Organ transplant		20,001 (0.1)	69 (0.34)
Asplenia		27,917 (0.2)	40 (0.14)
Rheumatoid arthritis, lupus or psoriasis		878,475 (5.1)	962 (0.11)
Other immunosuppressive condition		44,504 (0.3)	52 (0.12)

IMD, index of multiple deprivation.

[a]For oral corticosteroid (OCS) use, 'recent' refers to <1 year before baseline.

[b]Classification by HbA1c is based on measurements within 15 months of baseline.

[c]eGFR is measured in ml min^{-1} per 1.73 m^2 and taken from the most recent serum creatinine measurement.

between hypertension and mortality in older individuals are unclear and warrant further investigation, including detailed examination of frailty, comorbidity and drug exposures in this age group.

Model checking and sensitivity analyses

The average C-statistic—a measure of the model's ability to distinguish between patients who experience COVID-19-related deaths and those who do not, ranging from 0 (no ability) to 1 (perfect ability)—was 0.93. Results were similar when missing data were handled using analysis of complete records only, or using multiple imputation (sensitivity analyses; Extended Data Table 2). Non-proportional hazards were detected in the primary model ($P < 0.001$). A sensitivity analysis with earlier administrative censoring at 6 April 2020—before which mortality should not have been affected by the social distancing policies that were introduced in the UK in late March—showed no evidence of non-proportional hazards ($P = 0.83$). Hazard ratios were similar but somewhat larger in magnitude for some covariates, whereas the association with increasing deprivation appeared to be smaller (Extended Data Table 2).

Discussion

This secure analytics platform operating across NHS patient records of over 17 million adults and 6 million children was used to identify, quantify and analyse factors associated with COVID-19-related death in one of the largest cohort studies on this topic conducted by any country so far. Most comorbidities were associated with increased risk, including cardiovascular disease, diabetes, respiratory disease (including severe asthma), obesity, a history of haematological malignancy or recent other cancer, kidney, liver and neurological diseases, and autoimmune conditions. South Asian and Black people had a substantially higher risk of COVID-19-related death than white people, and this was only partly attributable to comorbidities, deprivation or other factors. A strong association between deprivation and risk was also only partly explained by comorbidities or other factors.

Our analyses provide a preliminary picture of how key demographic characteristics and a range of comorbidities—which were a priori selected as being of interest in COVID-19—are jointly associated with poor outcomes. These initial results may be used to inform the development of prognostic models. We caution against interpreting our estimates as causal effects. For example, the fully adjusted smoking hazard ratio does not capture the causal effect of smoking, owing to the inclusion of comorbidities that are likely to mediate any effect of smoking on COVID-19-related death (for example, chronic obstructive pulmonary disease). Our study has highlighted a need for carefully designed analyses that specifically focus on the causal effect of smoking on COVID-19-related death. Similarly, there is a need for analyses exploring the causal relationships that underlie the associations observed between hypertension and COVID-19-related death.

Strengths and weaknesses

The greatest strengths of this study are its size and the speed at which it was conducted. By building a secure analytics platform across routinely collected live clinical data stored in situ, we have produced timely results from the current NHS records of approximately 40% of the English population. The large scale of the study allows more precision—on rarer exposures and on multiple factors—and rapid detection of important signals. Our platform will expand to provide updated analyses over time. Another strength is our use of open methods: we pre-specified our analysis plan and shared our full analytic code and codelists for review and reuse. We ascertained patient demographics, medications and comorbidities from full pseudonymized longitudinal primary care records, which provide substantially more detail than data that are recorded on admission to hospital, and which take into account the total population rather than the selected subset of individuals who present at hospitals. We censored deaths from other causes using data from the UK Office for National Statistics (ONS). Analyses were stratified by area to account for known geographical differences in the incidence of COVID-19.

The study also has some important limitations. In our outcome definition, we included clinically suspected (non-laboratory-confirmed) cases of COVID-19, because testing has not always been carried out, especially in older patients in care homes. However, this may have

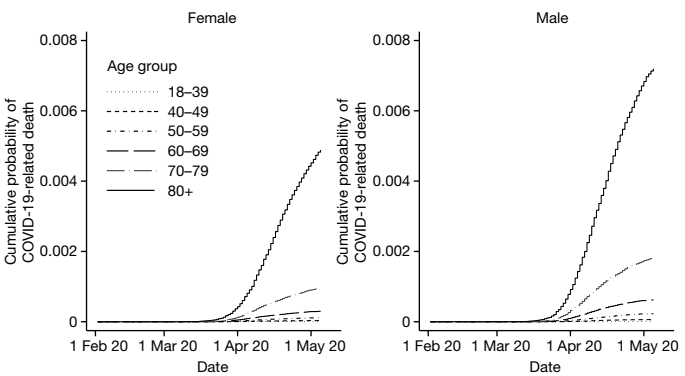

Fig. 2 | Kaplan–Meier plots for COVID-19-related death. Plots show COVID-19-related death over time by age and sex.

Table 2 | Hazard ratios and 95% confidence intervals for COVID-19-related death

Characteristic	Category	COVID-19 death HR (95% CI)	
		Adjusted for age and sex	Fully adjusted
Age	18–39	0.05 (0.04–0.07)	0.06 (0.04–0.08)
	40–49	0.28 (0.23–0.33)	0.30 (0.25–0.36)
	50–59	1.00 (ref)	1.00 (ref)
	60–69	2.79 (2.52–3.10)	2.40 (2.16–2.66)
	70–79	8.62 (7.84–9.46)	6.07 (5.51–6.69)
	80+	38.29 (35.02–41.87)	20.60 (18.70–22.68)
Sex	Female	1.00 (ref)	1.00 (ref)
	Male	1.78 (1.71–1.85)	1.59 (1.53–1.65)
BMI (kg m^{-2})	Not obese	1.00 (ref)	1.00 (ref)
	30–34.9 (obese class I)	1.23 (1.17–1.30)	1.05 (1.00–1.11)
	35–39.9 (obese class II)	1.81 (1.68–1.95)	1.40 (1.30–1.52)
	≥40 (obese class III)	2.66 (2.39–2.95)	1.92 (1.72–2.13)
Smoking	Never	1.00 (ref)	1.00 (ref)
	Former	1.43 (1.37–1.49)	1.19 (1.14–1.24)
	Current	1.14 (1.05–1.23)	0.89 (0.82–0.97)
Ethnicity[a]	White	1.00 (ref)	1.00 (ref)
	Mixed	1.62 (1.26–2.08)	1.43 (1.11–1.84)
	South Asian	1.69 (1.54–1.84)	1.45 (1.32–1.58)
	Black	1.88 (1.65–2.14)	1.48 (1.29–1.69)
	Other	1.37 (1.13–1.65)	1.33 (1.10–1.61)
IMD quintile	1 (least deprived)	1.00 (ref)	1.00 (ref)
	2	1.16 (1.08–1.23)	1.12 (1.05–1.19)
	3	1.31 (1.23–1.40)	1.22 (1.15–1.30)
	4	1.69 (1.59–1.79)	1.51 (1.42–1.61)
	5 (most deprived)	2.11 (1.98–2.25)	1.79 (1.68–1.91)
Blood pressure	Normal	1.00 (ref)	1.00 (ref)
	High blood pressure or diagnosed hypertension	1.09 (1.05–1.14)	0.89 (0.85–0.93)
Respiratory disease excluding asthma		1.95 (1.86–2.04)	1.63 (1.55–1.71)
Asthma[b] (versus none)	With no recent OCS use	1.13 (1.07–1.20)	0.99 (0.93–1.05)
	With recent OCS use	1.55 (1.39–1.73)	1.13 (1.01–1.26)
Chronic heart disease		1.57 (1.51–1.64)	1.17 (1.12–1.22)
Diabetes[c] (versus none)	With HbA1c < 58 mmol mol^{-1}	1.58 (1.51–1.66)	1.31 (1.24–1.37)
	With HbA1c ≥ 58 mmol mol^{-1}	2.61 (2.46–2.77)	1.95 (1.83–2.08)
	With no recent HbA1c measure	2.27 (2.06–2.50)	1.90 (1.72–2.09)
Cancer (non-haematological, versus none)	Diagnosed <1 year ago	1.81 (1.58–2.07)	1.72 (1.50–1.96)
	Diagnosed 1–4.9 years ago	1.20 (1.10–1.32)	1.15 (1.05–1.27)
	Diagnosed ≥5 years ago	0.99 (0.93–1.06)	0.96 (0.91–1.03)
Haematological malignancy (versus none)	Diagnosed <1 year ago	3.02 (2.24–4.08)	2.80 (2.08–3.78)
	Diagnosed 1–4.9 years ago	2.56 (2.14–3.06)	2.46 (2.06–2.95)
	Diagnosed ≥5 years ago	1.70 (1.46–1.98)	1.61 (1.39–1.87)
Reduced kidney function[d] (versus none)	eGFR 30–60	1.56 (1.49–1.63)	1.33 (1.28–1.40)
	eGFR < 30	3.48 (3.23–3.75)	2.52 (2.33–2.72)
Liver disease		2.39 (2.06–2.77)	1.75 (1.51–2.03)
Stroke or dementia		2.57 (2.46–2.70)	2.16 (2.06–2.27)
Other neurological disease		3.08 (2.85–3.33)	2.58 (2.38–2.79)
Organ transplant		6.00 (4.73–7.61)	3.53 (2.77–4.49)
Asplenia		1.62 (1.19–2.21)	1.34 (0.98–1.83)
Rheumatoid arthritis, lupus or psoriasis		1.30 (1.21–1.38)	1.19 (1.11–1.27)
Other immunosuppressive condition		2.75 (2.10–3.62)	2.21 (1.68–2.90)

Models were adjusted for age using a four-knot cubic spline for age, except for estimation of age-group hazard ratios. Ref, reference group; 95% CI, 95% confidence interval.

[a]Ethnicity hazard ratios were estimated from a model restricted to those with recorded ethnicity.

[b]For OCS use, 'recent' refers to during the year before baseline.

[c]Classification by HbA1c is based on measurements within 15 months of baseline.

[d]eGFR is measured in ml min^{-1} per 1.73 m^2 and taken from the most recent serum creatinine measurement.

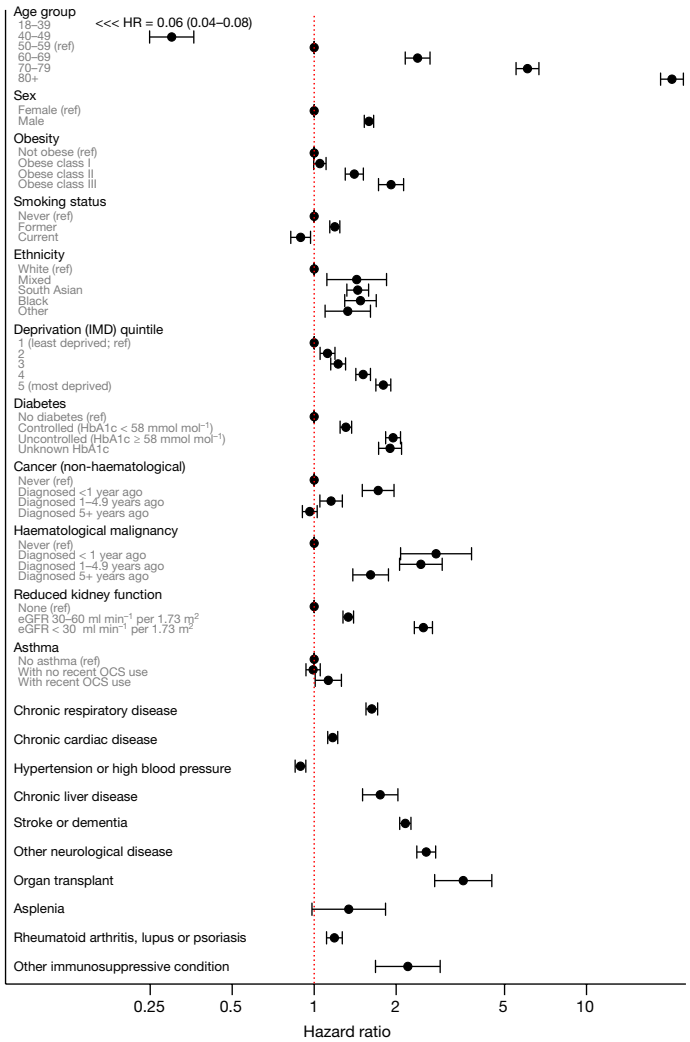

Fig. 3 | Estimated hazard ratios for each patient characteristic from a multivariable Cox model. Hazard ratios are shown on a log scale. Error bars represent the limits of the 95% confidence interval for the hazard ratio. IMD, index of multiple deprivation; obese class I, BMI 30–34.9; obese class II, BMI 35–39.9; obese class III, BMI ≥ 40; OCS, oral corticosteroid; ref, reference group. All hazard ratios are adjusted for all other factors listed other than ethnicity. Ethnicity estimates are from a separate model among those individuals for whom complete ethnicity data were available, and are fully adjusted for other covariates. Total n = 17,278,392 for the non-ethnicity models, and 12,718,279 for the ethnicity model.

resulted in some patients being incorrectly identified as having COVID-19. In addition, some COVID-19-related deaths may have been misclassified as non-COVID-19, particularly in the early stages of the pandemic; however, this inaccuracy is likely to have reduced quickly as the number of deaths increased, and a degree of outcome underascertainment—providing it is unrelated to patient characteristics—should not have biased our hazard ratios. Owing to the rarity of the outcome, the associations observed will be driven primarily by the profile of patient characteristics in the included cases. Our findings reflect both an individual's risk of infection and their risk of dying once infected. We will consider more detailed patient trajectories in future research within the OpenSAFELY platform.

Our large population may not be fully representative. We include only 17% of general practices in London—where many of the earlier cases of COVID-19 occurred—owing to the substantial geographical variation in the choice of electronic health record system. The user interface of electronic health records can affect prescribing of certain medicines[21–23], so it is possible that coding varies between systems.

Primary care records are detailed and longitudinal, but can be incomplete for data on patient characteristics. Ethnicity was missing for approximately 26% of patients, but was broadly representative[24]; there were also missing data on obesity and smoking. Sensitivity analyses found that our estimates were robust to our assumptions around missing data.

Non-proportional hazards could be due to very large numbers or unmeasured covariates. However, rapid changes in social behaviours (social distancing, shielding) and changes in the burden of infection may also have affected patient groups differentially. The larger hazard ratios seen for several covariates in a sensitivity analysis with earlier censoring (soon after social distancing and shielding policies were introduced) are consistent with patients who are more at risk being more compliant with these policies. By contrast, the risk associated with deprivation may have increased over time. Further analyses will explore the changes before and after the implementation of national initiatives around COVID-19.

Policy implications and interpretation

The UK has a policy of recommending shielding (staying at home at all times and avoiding any face-to-face contact) for groups who are identified as being extremely vulnerable to COVID-19 on the basis of pre-existing medical conditions[25]. We were able to evaluate the association between most of these conditions and death from COVID-19, and we confirmed the increased mortality risks, supporting the targeted use of additional protection measures for people in these groups. We have demonstrated that only a small part of the substantially increased risks of COVID-19-related death among BAME groups and among people living in more-deprived areas can be attributed to existing disease. Improved strategies to protect people in these groups are urgently needed[26]. These might include the specific consideration of BAME groups in shielding guidelines and workplace policies. Studies are needed to investigate the interplay of additional factors that we were unable to examine, including employment, access to personal protective equipment and the related risk of exposure to infection, and household density.

The UK has an unusually large volume of very detailed longitudinal patient data, especially through primary care, and we believe the UK has a responsibility to the global community to make good use of this data. OpenSAFELY demonstrates—on a very large scale—that this can be done securely, transparently and rapidly. We will enhance the OpenSAFELY platform to further inform the global response to the COVID-19 emergency.

Future research

The underlying causes of the higher risk of COVID-19-related death among BAME individuals, and among people from deprived areas, require further investigation. We would suggest collecting data on occupational exposure and living conditions as first steps. The statistical power offered by our approach means that associations with less-common factors can be robustly assessed in more detail and at the earliest possible date as the pandemic progresses. We will therefore update our findings and address smaller risk groups as new cases arise over time. The open source reusable codebase on OpenSAFELY supports the rapid, secure and collaborative development of new analyses; we are currently conducting expedited studies on the effects of various medical treatments and population interventions on the risk of COVID-19 infection, admission to intensive care units and death, alongside other observational analyses. OpenSAFELY is rapidly scalable for the incorporation of more NHS patient records, and new sources of data are progressing.

In conclusion, we have generated early insights into factors associated with COVID-19-related death using the detailed primary care

records of 17 million NHS patients, while maintaining privacy, in the context of a global health emergency.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-020-2521-4.

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Methods

Study design

We conducted a cohort study using national primary care electronic health record data linked to data on COVID-19-related deaths (see 'Data source'). The cohort study began on 1 February 2020, which was chosen as a date several weeks before the first reported COVID-19-related deaths and the day after the second laboratory-confirmed case[27]; and ended on 6 May 2020. The cohort study examines risk among the general population rather than in a population infected with SARS-COV-2. Therefore, all patients were included irrespective of any SARS-COV-2 test results. No randomization was undertaken. Outcome assessment was undertaken as part of routine health care, therefore no blinding of any sort was attempted. However, study investigators had no involvement in outcome assessment.

Data source

We used patient data from general practice (GP) records managed by the GP software provider The Phoenix Partnership (TPP), linked to death data from the ONS. ONS data include information on all deaths, including COVID-19-related death (defined as a COVID-19 ICD-10 code mentioned anywhere on the death certificate) and non-COVID-19 death, which was used for censoring.

The data were accessed, linked and analysed using OpenSAFELY, a new data analytics platform that was created to address urgent questions relating to the epidemiology and treatment of COVID-19 in England. OpenSAFELY provides a secure software interface that allows detailed pseudonymized primary care patient records to be analysed in near-real time where they already reside—hosted within the highly secure data centre of the electronic health records vendor—to minimize the reidentification risks when data are transported off-site; other smaller datasets are linked to these data within the same environment using a matching pseudonym derived from the NHS number. More information can be found at https://opensafely.org/.

The dataset that was analysed with OpenSAFELY is based on around 24 million currently registered patients (approximately 40% of the English population) from GP surgeries using the TPP SystmOne electronic health record system. SystmOne is a secure centralized electronic health records system that has been used in English clinical practice since 1998; it records data entered (in real time) by GPs and practice staff during routine primary care. The system is accredited under the NHS-approved systems framework for general practice[28,29]. Data extracted from TPP SystmOne have previously been used in medical research, as part of the ResearchOne dataset[30,31]. From these electronic health records a pseudonymized dataset was created for OpenSAFELY that consisted of 20 billion rows of structured data; including, for example, the diagnoses, medications, physiological parameters and prior investigations of pseudonymized patients (Extended Data Fig. 2, level 1). All OpenSAFELY data processing took place on TPP's servers; external data providers securely transferred pseudoymized data (such as COVID-19-related death from ONS) for linkage to OpenSAFELY (Extended Data Fig. 2, level 2); and study definitions developed in Python on GitHub were pulled into the OpenSAFELY infrastructure and used to create a study dataset of one row per patient (Extended Data Fig. 2, level 3). Statistical code was developed using synthetic data and used to analyse the study dataset; this included code to check data ranges, to check consistency of data columns and to produce descriptive statistics for comparison with expected disease prevalences to ensure validity, as well as code to fit our analysis models. Only two authors (K.B. and A.J.W.) accessed OpenSAFELY to run code; no pseudonymized patient-level data were ever removed from TPP infrastructure; and only aggregated, anonymous, manually checked study results were released for publication (Extended Data Fig. 2, level 4), All code for data management and analysis is archived online (see 'Code availability').

Study population and observation period

Our study population consisted of all adults (males and females 18 years and above) currently registered as active patients in a TPP GP surgery in England on 1 February 2020. To be included in the study, participants were required to have at least one year of prior follow-up in the GP practice to ensure that baseline patient characteristics could be adequately captured, and to have recorded sex, age and deprivation[32] (see 'Covariates'). Patients were observed from 1 February 2020 and were followed until the first of either their death date (whether COVID-19-related or due to other causes) or the study end date, 6 May 2020. For this analysis, ONS death data were available to 11 May 2020, but we used an earlier censor date to allow for delays in reporting of the last few days of available data.

Outcomes

The outcome was COVID-19-related death; this was ascertained from ONS death certificate data in which the COVID related ICD-10 codes U071 or U072 were present in the record.

Covariates

Characteristics included: health conditions listed in UK guidance on 'higher risk' groups[33]; other common conditions that may cause immunodeficiency inherently or through medication (cancer and common autoimmune conditions); and emerging risk factors for severe outcomes among COVID-19 cases (such as raised blood pressure).

Age, sex, BMI (kg m^{-2}) and smoking status were included. Where categorized, age groups were: 18–39, 40–49, 50–59, 60–69, 70–79 and 80+ years. BMI was ascertained from weight measurements within the last 10 years, restricted to those taken when the patient was over 16 years old. Obesity was grouped using categories derived from the WHO classification of BMI: no evidence of obesity, BMI < 30; obese class I, BMI 30–34.9; obese class II, BMI 35–39.9; and obese class III, BMI 40+. Smoking status was grouped into current-, former- and never-smokers.

The following comorbidities were also considered: asthma, other chronic respiratory disease, chronic heart disease, diabetes mellitus, chronic liver disease, chronic neurological diseases, common autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus or psoriasis), solid organ transplant, asplenia, other immunosuppressive conditions, cancer, evidence of reduced kidney function, and raised blood pressure or a diagnosis of hypertension.

Disease groupings followed national guidance on risk of influenza infection[34], therefore 'chronic respiratory disease (other than asthma)' included chronic obstructive pulmonary disease, fibrosing lung disease, bronchiectasis or cystic fibrosis; and 'chronic heart disease' included chronic heart failure, ischaemic heart disease, and severe valve or congenital heart disease likely to require lifelong follow-up. Chronic neurological conditions were separated into diseases with a probable cardiovascular aetiology (stroke, transient ischaemic attack, dementia) and conditions in which respiratory function may be compromised, such as motor neurone disease, myasthenia gravis, multiple sclerosis, Parkinson's disease, cerebral palsy, quadriplegia or hemiplegia and progressive cerebellar disease. Asplenia included splenectomy or a spleen dysfunction, including sickle cell disease. Other immunosuppressive conditions included human immunodeficiency virus (HIV) or a condition inducing permanent immunodeficiency ever diagnosed, or aplastic anaemia or temporary immunodeficiency recorded within the last year. Haematological malignancies were considered separately from other cancers to reflect the immunosuppression associated with haematological malignancies and their treatment. Kidney function was ascertained from the most recent serum creatinine measurement, where available, and was converted into the eGFR using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation[35], with reduced kidney function grouped into eGFR 30–59.9 or <30 ml min^{-1} per 1.73 m^2. History of kidney dialysis or end-stage renal failure was

separately explored in a secondary analysis. Raised blood pressure was defined as either a previous coded diagnosis of hypertension or the most recent recording indicating systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg.

Asthma was grouped by use of oral corticosteroids as an indication of severity. Diabetes was grouped according to the most recent Hba1c measurement within the last 15 months (Hba1c < 58 mmol mol^{-1}; Hba1c ≥ 58 mmol mol^{-1}; or no recent measure available). Cancer was grouped by time since the first diagnosis (within the last year; between 1 and 4.9 years ago; more than 5 years ago).

Other covariates that were considered as potential upstream factors were deprivation and ethnicity. Deprivation was measured by the index of multiple deprivation (IMD, in quintiles, with higher values indicating greater deprivation), derived from the patient's postcode at lower super output area level for a high degree of precision. Ethnicity was grouped into white, Black, South Asian, mixed, or other. In sensitivity analyses, a more detailed grouping of ethnicity was explored. The Sustainability and Transformation Partnership (STP, an NHS administrative region) of the patient's general practice was included as an additional adjustment for geographical variation in infection rates across the country.

Information on all covariates was obtained from primary care records by searching TPP SystmOne records for specific coded data. TPP SystmOne allows users to work with the SNOMED-CT clinical terminology, using a GP subset of SNOMED-CT codes. This subset maps on to the native Read version 3 (CTV3) clinical coding system on which SystmOne is built. Medicines are entered or prescribed in a format compliant with the NHS Dictionary of Medicines and Devices (dm+d)[36], a local UK extension library of SNOMED. Codelists for particular underlying conditions and medicines were compiled from a variety of sources. These include British National Formulary (BNF) codes from OpenPrescribing.net, published codelists for asthma[37–39], immunosuppression[40–42], psoriasis[43], systemic lupus erythematosus[44], rheumatoid arthritis[45,46] and cancer[47,48], and Read Code 2 lists designed specifically to describe groups who are at increased risk of influenza infection[18]. Read Code 2 lists were added to with SNOMED codes and cross-checked against NHS Quality and Outcomes Framework (QOF) registers, then translated into CTV3 with manual curation. Decisions on every codelist were documented and the final lists were reviewed by at least two authors. Detailed information on compilation and sources for every individual codelist is available at https://codelists.opensafely.org/ and the lists are available for inspection and reuse by the broader research community.

Statistical analysis

Patient numbers are depicted in a flowchart (Fig. 1). The Kaplan–Meier failure function was estimated by age group and sex. For each patient characteristic, a Cox proportional hazards model was fitted, with days in study as the timescale, stratified by geographical area (STP), and adjusted for sex and age modelled using restricted cubic splines. Violations of the proportional hazards assumption were explored by testing for a zero slope in the scaled Schoenfeld residuals. All patient characteristics, including age (again modelled as a spline), sex, BMI, smoking, IMD quintile, and comorbidities listed above were then included in a single multivariable Cox proportional hazards model, stratified by STP. Hazard ratios from the age-and-sex adjusted and fully adjusted models are reported with 95% confidence intervals. Models were also refitted with age group fitted as a categorical variable to obtain hazard ratios by age group.

In the primary analysis, those with missing BMI were assumed to be non-obese and those with missing smoking information were assumed to be non-smokers on the assumption that both obesity and smoking would be likely to be recorded if present. A sensitivity analysis was run among those with complete BMI and smoking data only. Ethnicity was omitted from the main multivariable model owing data being missing for 26% of individuals; hazard ratios for ethnicity were therefore obtained from a separate model among individuals with complete ethnicity data only. Hazard ratios for other patient characteristics, adjusted for ethnicity, were also obtained from this model and are presented in the sensitivity analyses to allow assessment of whether estimates were distorted by ethnicity in the primary model. We conducted an additional sensitivity analysis using a population-calibrated imputation approach to handle missing ethnicity[49,50], with marginal proportions of each ethnicity group within each of nine broad geographical regions of England (East, East Midlands, London, North East, North West, South East, South West, West Midlands, Yorkshire and The Humber) taken from Annual Population Survey (APS) data (pooled 2014–2016)[51]. Five imputed datasets were created with estimated hazard ratios combined using Rubin's rules.

The C-statistic was calculated as a measure of model discrimination. Owing to computational time, this was estimated by randomly sampling 5,000 patients with and without the outcome and calculating the C-statistic using the random sample, repeating this 10 times and taking the average C-statistic. Weights were applied to account for the sampling[56].

All *P* values presented are two-sided.

Information governance and ethics

NHS England is the data controller; TPP is the data processor; and the key researchers on OpenSAFELY are acting on behalf of NHS England. This implementation of OpenSAFELY is hosted within the TPP environment, which is accredited to the ISO 27001 information security standard and is NHS IG Toolkit compliant[52,53]; patient data have been pseudonymized for analysis and linkage using industry standard cryptographic hashing techniques; all pseudonymized datasets transmitted for linkage onto OpenSAFELY are encrypted; access to the platform is through a virtual private network (VPN) connection, restricted to a small group of researchers, their specific machine and IP address; the researchers hold contracts with NHS England and only access the platform to initiate database queries and statistical models; all database activity is logged; and only aggregate statistical outputs leave the platform environment following best practice for anonymization of results such as statistical disclosure control for low cell counts[54]. The OpenSAFELY research platform adheres to the data protection principles of the UK Data Protection Act 2018 and the EU General Data Protection Regulation (GDPR) 2016. In March 2020, the Secretary of State for Health and Social Care used powers under the UK Health Service (Control of Patient Information) Regulations 2002 (COPI) to require organizations to process confidential patient information for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the COVID-19 outbreak and incidents of exposure[55]. Together, these provide the legal bases to link patient datasets on the OpenSAFELY platform. GP practices, from which the primary care data are obtained, are required to share relevant health information to support the public health response to the pandemic, and have been informed of the OpenSAFELY analytics platform. This study was approved by the Health Research Authority (REC reference 20/LO/0651) and by the London School of Hygiene and Tropical Medicine (LSHTM) ethics board (reference 21863). No further ethical or research governance approval was required by the University of Oxford but copies of the approval documents were reviewed and held on record. Guarantor: B.G. and L.S.

Patient and public involvement

Patients were not formally involved in developing this specific study design. We have developed a publicly available website (https://opensafely.org/) that allows any patient or member of the public to contact us regarding this study or the broader OpenSAFELY project. This feedback will be used to refine and prioritize our OpenSAFELY activities.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this paper.

Data availability

All data were linked, stored and analysed securely within the OpenSAFELY platform (https://opensafely.org/). Detailed pseudonymized patient data are potentially reidentifiable and therefore not shared. We rapidly delivered the OpenSAFELY data analysis platform without prior funding to deliver timely analyses on urgent research questions in the context of the global COVID-19 health emergency: now that the platform is established we are developing a formal process for external users to request access in collaboration with NHS England. Details of this process will be published shortly on the OpenSAFELY website.

Code availability

Data management was performed using Python 3.8 and SQL, with analysis carried out using Stata 16.1 and Python. All code is shared openly for review and reuse under an MIT open license. All code for data management and analysis is archived online at https://github.com/opensafely/risk-factors-research. All clinical and medicines codelists are openly available for inspection and reuse at https://codelists.opensafely.org/.

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Author contributions B.G. conceived the platform and the approach; B.G. and L.S. led the project overall and are guarantors; S.B. led the software; E.J.W and K.B. led the statistical analysis; C.E.M. and A.J.W. led on codelists and implementation; and A.M. led on information governance. Contributions are as follows: data curation, C.B., J.P., J.C., S.H., S.B., D.E., P.I. and C.E.M.; analysis, E.J.W., K.B., A.J.W. and C.E.M.; funding acquisition, B.G. and L.S.; information governance, A.M., B.G., C.B. and J.P.; methodology, E.J.W., K.B., A.J.W., B.G., L.S., C.B., J.P., J.C., S.H., S.B., D.E., P.I., C.E.M., R.G., D.H. and R.P.; disease category conceptualization and codelists, C.E.M., A.J.W., P.I., S.B., D.E., C.B., J.C., J.P., S.H., H.J.C., K.B., S.B., A.M., B.M., L.T., I.J.D., H.I.M., R.M. and H.F.; ethics approval, H.J.C., E.J.W., L.S. and B.G.; project administration, C.E.M., H.J.C., C.B., S.B., A.M., L.S. and B.G.; resources, B.G., L.S. and F.H.; software, S.B., D.E., P.I., A.J.W., C.E.M., C.B., F.H., J.C. and S.H.; supervision, B.G., L.S. and S.B.; writing (original draft), H.J.C., E.J.W., K.B., B.M., C.E.M., A.M., B.G. and L.S.; and writing (review and editing), C.B., C.E.M., H.J.C., E.J.W., K.B., S.B., A.M., B.M., L.T., I.J.D., H.I.M., R.M., A.J.W. and S.J.W.E. All authors were involved in design and conceptual development and reviewed and approved the final manuscript.

Competing interests All authors have completed the International Committee of Medical Journal Editors (ICMJE) uniform disclosure form at www.icmje.org/coi_disclosure.pdf. C.B., J.P., F.H., J.C. and S.H. are employees of TPP. A.M. was interim Chief Medical Officer of NHS Digital April–Sept 2019 (left NHS Digital at the end of January 2020) and Digital Clinical Champion NHS England 2014–2015. All other authors have no competing interests.

Additional information

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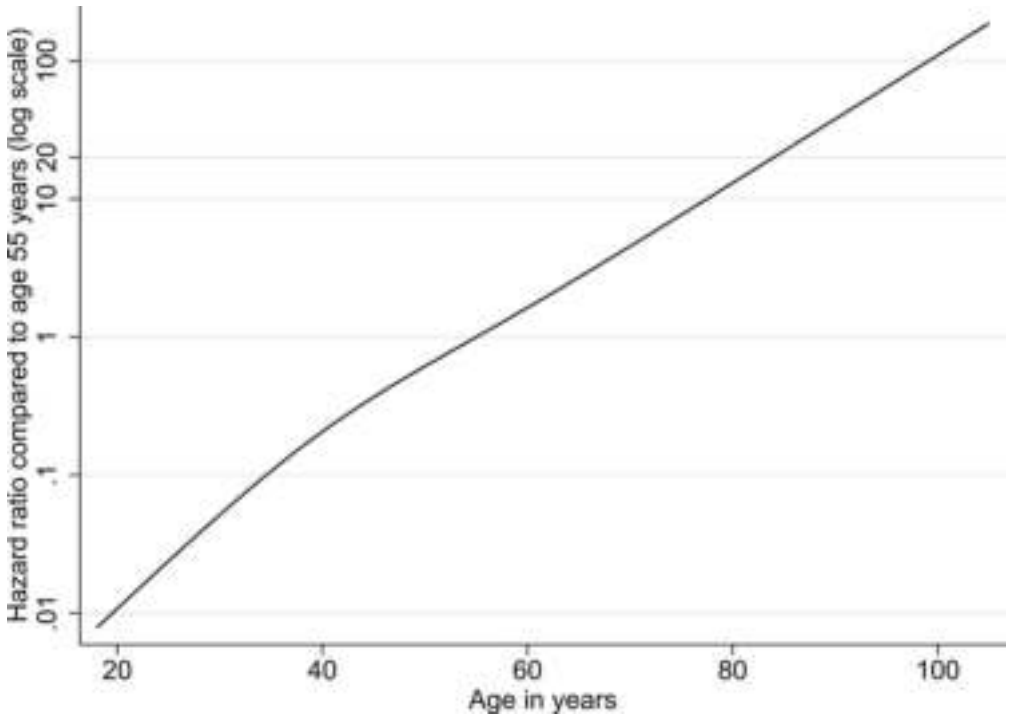
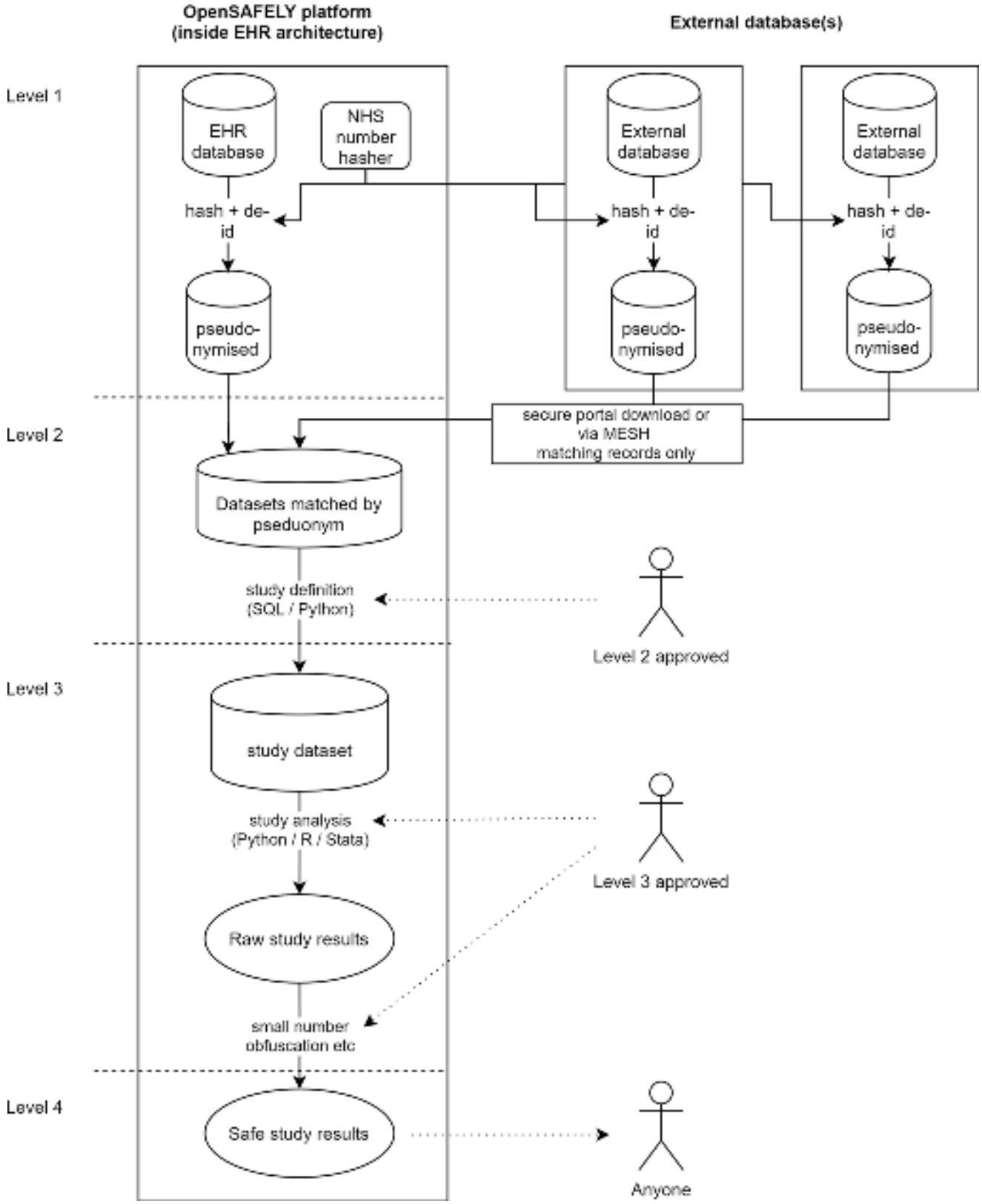


Extended Data Fig. 1 | Estimated log-transformed hazard ratio by age in years. From the primary fully adjusted model containing a four-knot cubic spline for age, and adjusted for all covariates listed in Table 2 except for ethnicity.



Extended Data Fig. 2 | Illustration of data flows in the OpenSAFELY platform. Overview of the architecture of the OpenSAFELY platform. EHR, electronic health record.

Extended Data Table 1 | Adjusted hazard ratios for detailed ethnicity categories

Ethnicity	Fully adjusted hazard ratio*	95% CI
British or mixed British	1.00	(ref)
Irish	1.16	(0.96-1.41)
Other White	0.87	(0.79-0.97)
Mixed ethnicity	1.42	(1.11-1.83)
Indian or British Indian	1.40	(1.23-1.59)
Pakistani or British Pakistani	1.24	(1.06-1.46)
Bangladeshi or British Bangladeshi	1.84	(1.36-2.49)
Other Asian	1.73	(1.44-2.09)
Caribbean	1.28	(1.07-1.53)
African	1.77	(1.41-2.22)
Other Black	1.73	(1.24-2.40)
Chinese	1.22	(0.81-1.85)
Other	1.35	(1.09-1.67)

Estimated from a model restricted to those with recorded ethnicity, adjusted for age (using a four-knot cubic spline for age), sex, BMI, smoking, IMD quintile, hypertension or high blood pressure, asthma, chronic heart disease, diabetes, non-haematological cancer, haematological malignancy, reduced kidney function, liver disease, stroke or dementia, other neurological disease, organ transplant, asplenia, rheumatoid arthritis, lupus or psoriasis, and other immunosuppressive condition. All categorizations are as in the primary analysis.

Extended Data Table 2 | Hazard ratios and 95% confidence intervals in sensitivity analyses

		Fully adjusted HR and 95% CI				
Characteristic	**Category**	**Primary analysis**	**Early censoring at 6/4/2020**	**Restricted to those with complete BMI /smoking**	**Adjusted for ethnicity in those where recorded**	**Adjusted for ethnicity using multiple imputation**
N outcome events in analysis		10926	2816	9880	8149	
Age	18-<40	0.06 (0.04-0.08)	0.07 (0.04-0.12)	0.07 (0.05-0.10)	0.07 (0.05-0.09)	0.06 (0.04-0.07)
	40-<50	0.30 (0.25-0.36)	0.33 (0.23-0.46)	0.30 (0.25-0.37)	0.29 (0.24-0.36)	0.29 (0.24-0.35)
	50-<60	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	60-<70	2.40 (2.16-2.66)	2.55 (2.11-3.08)	2.38 (2.13-2.66)	2.37 (2.11-2.67)	2.43 (2.19-2.70)
	70-<80	6.07 (5.51-6.69)	5.84 (4.88-6.98)	5.96 (5.37-6.61)	6.05 (5.42-6.76)	6.24 (5.66-6.87)
	80+	20.60 (18.70-22.68)	14.66 (12.23-17.58)	19.96 (18.00-22.14)	20.19 (18.08-22.54)	21.19 (19.23-23.34)
Sex	Female	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Male	1.59 (1.53-1.65)	1.89 (1.75-2.05)	1.65 (1.58-1.72)	1.54 (1.47-1.61)	1.57 (1.52-1.64)
BMI	Not obese	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	
	30-34.9kg/m2 (Obese class I)	1.05 (1.00-1.11)	1.30 (1.16-1.43)	1.07 (1.02-1.13)	1.05 (0.99-1.11)	1.06 (1.00-1.11)
	35-39.9kg/m2 (Obese class II)	1.40 (1.30-1.52)	1.57 (1.36-1.81)	1.45 (1.34-1.57)	1.41 (1.30-1.54)	1.42 (1.32-1.54)
	≥40 kg/m2 (Obese class III)	1.92 (1.72-2.13)	2.70 (2.26-3.21)	1.99 (1.79-2.21)	1.92 (1.70-2.17)	1.96 (1.76-2.18)
Smoking	Never	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Former	1.19 (1.14-1.24)	1.27 (1.17-1.39)	1.18 (1.13-1.24)	1.22 (1.16-1.29)	1.23 (1.18-1.29)
	Current	0.89 (0.82-0.97)	0.93 (0.79-1.09)	0.91 (0.83-0.99)	0.93 (0.84-1.02)	0.93 (0.85-1.01)
Ethnicity[a]	White	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Mixed	1.43 (1.11-1.84)	1.01 (0.60-1.72)	1.38 (1.05-1.80)	1.43 (1.11-1.84)	1.44 (1.06-1.95)
	South Asian	1.45 (1.32-1.58)	1.63 (1.38-1.91)	1.51 (1.38-1.66)	1.45 (1.32-1.58)	1.48 (1.33-1.65)
	Black	1.48 (1.29-1.69)	1.76 (1.41-2.19)	1.47 (1.28-1.69)	1.48 (1.29-1.69)	1.53 (1.32-1.77)
	Other	1.33 (1.10-1.61)	1.84 (1.37-2.47)	1.40 (1.15-1.71)	1.33 (1.10-1.61)	1.34 (1.12-1.61)
IMD quintile	1 (least deprived)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	2	1.12 (1.05-1.19)	0.96 (0.85-1.08)	1.12 (1.05-1.19)	1.16 (1.08-1.25)	1.12 (1.05-1.19)
	3	1.22 (1.15-1.30)	1.00 (0.88-1.12)	1.23 (1.15-1.31)	1.26 (1.17-1.36)	1.21 (1.14-1.29)
	4	1.51 (1.42-1.61)	1.26 (1.11-1.41)	1.51 (1.42-1.61)	1.54 (1.43-1.66)	1.48 (1.39-1.57)
	5 (most deprived)	1.79 (1.68-1.91)	1.41 (1.25-1.60)	1.80 (1.68-1.93)	1.77 (1.64-1.91)	1.72 (1.61-1.84)
Blood pressure	Normal	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	High bp or diagnosed hyper-tension	0.89 (0.85-0.93)	0.95 (0.87-1.04)	0.88 (0.84-0.92)	0.91 (0.86-0.96)	0.89 (0.85-0.93)
Respiratory disease ex asthma		1.63 (1.55-1.71)	1.86 (1.69-2.04)	1.59 (1.51-1.67)	1.65 (1.56-1.75)	1.64 (1.56-1.72)
Asthma (vs none)[b]	With no recent OCS use	0.99 (0.93-1.05)	1.08 (0.96-1.20)	0.97 (0.91-1.04)	0.94 (0.87-1.00)	0.98 (0.93-1.05)
	With recent OCS use	1.13 (1.01-1.26)	1.38 (1.13-1.67)	1.09 (0.97-1.22)	1.08 (0.95-1.23)	1.11 (0.99-1.24)
Chronic heart disease		1.17 (1.12-1.22)	1.37 (1.26-1.48)	1.16 (1.11-1.22)	1.16 (1.11-1.22)	1.17 (1.12-1.22)
Diabetes (vs none)[c]	With HbA1c<58 mmol/mol	1.31 (1.24-1.37)	1.39 (1.26-1.52)	1.29 (1.23-1.36)	1.28 (1.21-1.36)	1.27 (1.21-1.33)
	WithHbA1c>=58 mmol/mol	1.95 (1.83-2.08)	2.33 (2.08-2.61)	1.90 (1.79-2.02)	1.86 (1.73-2.00)	1.87 (1.76-1.99)
	With no recent HbA1c measure	1.90 (1.72-2.09)	1.71 (1.40-2.08)	1.92 (1.74-2.12)	1.86 (1.67-2.08)	1.84 (1.67-2.02)
Cancer (non-haematological, vs none)	Diagnosed < 1 year ago	1.72 (1.50-1.96)	1.66 (1.27-2.16)	1.68 (1.46-1.94)	1.67 (1.43-1.96)	1.74 (1.52-1.99)
	Diagnosed 1-4.9 years ago	1.15 (1.05-1.27)	1.34 (1.13-1.60)	1.16 (1.05-1.28)	1.21 (1.09-1.35)	1.17 (1.06-1.28)
	Diagnosed ≥5 years ago	0.96 (0.91-1.03)	0.92 (0.81-1.04)	0.97 (0.91-1.03)	0.98 (0.92-1.06)	0.97 (0.92-1.04)
Haematological malignancy (vs none)	Diagnosed < 1 year ago	2.60 (2.08-3.78)	2.20 (1.14-4.24)	2.86 (2.10-3.88)	2.33 (1.60-3.41)	2.81 (2.08-3.79)
	Diagnosed 1-4.9 years ago	2.46 (2.06-2.95)	3.49 (2.61-4.68)	2.40 (1.99-2.90)	2.53 (2.05-3.11)	2.48 (2.07-2.97)
	Diagnosed ≥5 years ago	1.61 (1.39-1.87)	1.45 (1.06-1.97)	1.61 (1.38-1.89)	1.55 (1.30-1.85)	1.63 (1.40-1.89)
Reduced kidney function[d]	Estimated GFR 30-60	1.33 (1.28-1.40)	1.49 (1.36-1.63)	1.33 (1.27-1.39)	1.37 (1.30-1.44)	1.33 (1.27-1.39)
	Estimated GFR <30	2.52 (2.33-2.72)	2.98 (2.57-3.45)	2.47 (2.28-2.68)	2.50 (2.29-2.74)	2.50 (2.31-2.70)
Liver disease		1.75 (1.51-2.03)	1.92 (1.48-2.49)	1.69 (1.44-1.97)	1.75 (1.48-2.07)	1.75 (1.51-2.03)
Stroke/dementia		2.16 (2.06-2.27)	1.74 (1.58-1.93)	2.12 (2.01-2.22)	2.16 (2.05-2.28)	2.16 (2.06-2.27)
Other neurological disease		2.58 (2.38-2.79)	2.26 (1.91-2.68)	2.50 (2.30-2.73)	2.53 (2.31-2.77)	2.58 (2.38-2.80)
Organ transplant		3.53 (2.77-4.49)	2.55 (1.59-4.10)	3.70 (2.89-4.73)	3.45 (2.62-4.54)	3.46 (2.74-4.44)
Asplenia		1.34 (0.98-1.83)	1.87 (1.12-3.11)	1.29 (0.93-1.80)	1.34 (0.94-1.92)	1.33 (0.96-1.82)
Rheumatoid/Lupus/ Psoriasis		1.19 (1.11-1.27)	1.29 (1.14-1.46)	1.17 (1.09-1.25)	1.15 (1.07-1.24)	1.20 (1.12-1.28)
Other immunosuppressive condition		2.21 (1.68-2.90)	2.60 (1.65-4.09)	2.11 (1.58-2.83)	2.24 (1.66-3.03)	1.67 (1.31-2.11)

Models were adjusted for age using a four-knot cubic spline for age, except for estimation of age-group hazard ratios.

[a]Ethnicity hazard ratios in the primary analysis were estimated from a model restricted to those with recorded ethnicity.

[b]For OCS use, 'recent' refers to <1 year before baseline.

[c]HbA1c classification is based on the most recent measurement in the 15 months prior to baseline.

[d]eGFR is measured in ml min^{-1} per 1.73 m^2 and taken from the most recent serum creatinine measurement.

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Reporting Summary

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Data were collected using TPP SystmOne software (14th May maintenance release), for the purpose of direct clinical care. Data management was performed using Python 3.8 and SQL. All code for data management and analysis is archived online at https://github.com/opensafely/risk-factors-research.
Data analysis	Analysis was carried out using Stata 16.1 / Python 3.8. All code for data management and analysis is archived at https://github.com/opensafely/risk-factors-research.

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All data were linked, stored and analysed securely within the OpenSAFELY platform https://opensafely.org/. All code is shared openly for review and re-use under MIT open license. Detailed pseudonymised patient data is potentially re-identifiable and therefore not shared. All clinical and medicines codelists are openly available for inspection and reuse at https://codelists.opensafely.org/.

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Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	We conducted a quantitative cohort study using national primary care electronic health record data linked to COVID-19 death data.
Research sample	We used patient data from general practice (GP) records managed by the GP software provider The Phoenix Partnership (TPP), linked to Office for National Statistics (ONS) death data. The sample of patients represents approximately 40% of the population of England, spread geographically across the whole country.
Sampling strategy	Our study population consisted of all adults (males and females 18 years and above) currently registered as active patients in a TPP general practice in England on 1st February 2020. To be included in the study, participants were required to have at least 1 year of prior follow-up in the GP practice to ensure that baseline patient characteristics could be adequately captured, and to have recorded sex, age, and deprivation (see covariates, below).
Data collection	Data were collected by clinicians (e.g. doctors, nurses) and administrative staff, for the purpose of direct clinical care. This was carried out on computers using TPP SystmOne software. The researchers were not present for data collection into the TPP database. Data were then queried from the TPP database by the researchers, to create the study dataset. This was carried out using Python 3.8 and SQL software (available here https://github.com/opensafely/risk-factors-research). This study did not have an experimental condition or hypothesis.
Timing	Patients were observed from the 1st of February 2020 and were followed until the first of either their death date (whether COVID-19 related or due to other causes) or the study end date, 6th May 2020.
Data exclusions	To be included in the study, participants were required to have at least 1 year of prior follow-up in the GP practice to ensure that baseline patient characteristics could be adequately captured, and to have recorded sex, age, and deprivation. The total number of excluded patients was 6,322,225.
Non-participation	No participants dropped out.
Randomization	Participants were not allocated into experimental groups.

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Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
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☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	See above
Recruitment	This study uses data gathered during routine medical practice. We selected all patients except those <18 years old, anyone without a recorded sex, age, or deprivation score, and anyone without a year of prior follow-up (to ensure that baseline patient characteristics could be adequately captured). These inclusive criteria mean that bias is minimised.

Ethics oversight	This study was approved by the Health Research Authority (REC reference 20/LO/0651) and by the LSHTM Ethics Board (reference 21863). In March 2020, the Secretary of State for Health and Social Care used powers under the UK Health Service (Control of Patient Information) Regulations 2002 (COPI) to require organisations to process confidential patient information for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the COVID-19 outbreak and incidents of exposure. Taken together, these provide the legal bases to link patient datasets on the OpenSAFELY platform and set aside the requirement for patient consent for COVID-19 related public health research. GP practices, from which the primary care data is obtained, are required to share relevant health information to support the public health response to the pandemic, and have been informed of the OpenSAFELY analytics platform.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Estimates of the severity of coronavirus disease 2019: a model-based analysis

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Summary

Background In the face of rapidly changing data, a range of case fatality ratio estimates for coronavirus disease 2019 (COVID-19) have been produced that differ substantially in magnitude. We aimed to provide robust estimates, accounting for censoring and ascertainment biases.

Methods We collected individual-case data for patients who died from COVID-19 in Hubei, mainland China (reported by national and provincial health commissions to Feb 8, 2020), and for cases outside of mainland China (from government or ministry of health websites and media reports for 37 countries, as well as Hong Kong and Macau, until Feb 25, 2020). These individual-case data were used to estimate the time between onset of symptoms and outcome (death or discharge from hospital). We next obtained age-stratified estimates of the case fatality ratio by relating the aggregate distribution of cases to the observed cumulative deaths in China, assuming a constant attack rate by age and adjusting for demography and age-based and location-based under-ascertainment. We also estimated the case fatality ratio from individual line-list data on 1334 cases identified outside of mainland China. Using data on the prevalence of PCR-confirmed cases in international residents repatriated from China, we obtained age-stratified estimates of the infection fatality ratio. Furthermore, data on age-stratified severity in a subset of 3665 cases from China were used to estimate the proportion of infected individuals who are likely to require hospitalisation.

Findings Using data on 24 deaths that occurred in mainland China and 165 recoveries outside of China, we estimated the mean duration from onset of symptoms to death to be 17·8 days (95% credible interval [CrI] 16·9–19·2) and to hospital discharge to be 24·7 days (22·9–28·1). In all laboratory confirmed and clinically diagnosed cases from mainland China (n=70 117), we estimated a crude case fatality ratio (adjusted for censoring) of 3·67% (95% CrI 3·56–3·80). However, after further adjusting for demography and under-ascertainment, we obtained a best estimate of the case fatality ratio in China of 1·38% (1·23–1·53), with substantially higher ratios in older age groups (0·32% [0·27–0·38] in those aged <60 years *vs* 6·4% [5·7–7·2] in those aged ≥60 years), up to 13·4% (11·2–15·9) in those aged 80 years or older. Estimates of case fatality ratio from international cases stratified by age were consistent with those from China (parametric estimate 1·4% [0·4–3·5] in those aged <60 years [n=360] and 4·5% [1·8–11·1] in those aged ≥60 years [n=151]). Our estimated overall infection fatality ratio for China was 0·66% (0·39–1·33), with an increasing profile with age. Similarly, estimates of the proportion of infected individuals likely to be hospitalised increased with age up to a maximum of 18·4% (11·0–37·6) in those aged 80 years or older.

Interpretation These early estimates give an indication of the fatality ratio across the spectrum of COVID-19 disease and show a strong age gradient in risk of death.

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Introduction

As of March 25, 2020, 414 179 cases and 18 440 deaths due to coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), had been reported worldwide.[1] The epidemic began in mainland China, with a geographical focus in the city of Wuhan, Hubei. However, on Feb 26, 2020, the rate of increase in cases became greater in the rest of the world than inside China. Substantial outbreaks are occurring in Italy (69 176 cases), the USA (51 914 cases), and Iran (24 811 cases), and geographical expansion of the epidemic continues.

Clinical studies of hospitalised patients have shown that, at onset of COVID-19, patients frequently show symptoms associated with viral pneumonia, most commonly fever, cough, sore throat, myalgia, and fatigue.[2–6] The case definition adopted in China and elsewhere includes further stratification of cases as severe (defined as tachypnoea [≥30 breaths per min], oxygen saturation ≤93% at rest, or PaO_2/FiO_2 ratio <300 mm Hg) and critical (respiratory

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Research in context

Evidence before this study

We searched PubMed, medRxiv, bioRxiv, arXiv, SSRN, Research Square, Virological, and Wellcome Open Research for peer-reviewed articles, preprints, and research reports on the severity of coronavirus disease 2019 (COVID-19), using the search terms "coronavirus", "2019-nCoV", and similar terms, and "fatality", up to March 6, 2020. Several studies have estimated the case fatality ratio (the percentage of individuals with symptomatic or confirmed disease who die from the disease) and infection fatality ratio (the percentage of all infected individuals who die from the disease, including those with mild disease) of COVID-19 using a range of different statistical and modelling methods. Studies done solely in hospitalised patients report the highest fatality ratios (8–28%), representing the outcome for the most severely ill patients. Estimates of the population-level case fatality ratio from all case reports are in the range of 2–8%. Estimates of the infection fatality ratio averaged across all age-groups range from 0·2% to 1·6%, while estimates of the infection fatality ratio in the oldest age group (≥80 years) range from 8% to 36%. None of the identified studies had adjusted for differences in the denominator populations to obtain estimates that could be applied across populations. No other studies have estimated the proportion of infected individuals who will require hospitalisation.

Added value of this study

By synthesising data from across a range of surveillance settings, we obtained estimates of the age-stratified case fatality ratio and infection fatality ratio that take into account the different denominator populations in the datasets. Our underlying assumption, that attack rates (ie, the probability of becoming infected) do not vary substantially by age, is consistent with previous studies for respiratory infections. Under this assumption, differences in age patterns among cases in Wuhan versus those elsewhere in China would probably due to under-ascertainment of cases, given the different surveillance systems in place. Our results are consistent with this hypothesis, with cases in Wuhan seen in older individuals, who would have been identified through attendance at hospital, whereas cases elsewhere in China being younger overall, which would be explained by the policy of testing those with a travel history to Wuhan. After correcting for these biases, we found that estimates of the case fatality ratio from China are consistent with those obtained from early international cases. Our age-stratified estimates of the infection fatality ratio can be applied to any demography to give an estimate of the infection fatality ratio in older and younger populations. These estimates can be combined with estimates of the infection attack rate (approximately 80% for an unmitigated epidemic) to give rough projections of scale. Similarly, our estimates of the proportion of infections requiring hospitalisation can be combined with the infection attack rate to forecast health-care requirements.

Implications of all the available evidence

Our estimates of the case fatality ratio for COVID-19, although lower than some of the crude estimates made to date, are substantially higher than for recent influenza pandemics (eg, H1N1 influenza in 2009). With the rapid geographical spread observed to date, COVID-19 therefore represents a major global health threat in the coming weeks and months. Our estimate of the proportion of infected individuals requiring hospitalisation, when combined with likely infection attack rates (around 50–80%), show that even the most advanced health-care systems are likely to be overwhelmed. These estimates are therefore crucial to enable countries around the world to best prepare as the global pandemic continues to unfold.

failure requiring mechanical ventilation, septic shock, or other organ dysfunction or failure that requires intensive care).[7] According to the report from the WHO–China Joint Mission on COVID-19, 80% of the 55 924 patients with laboratory-confirmed COVID-19 in China to Feb 20, 2020, had mild-to-moderate disease, including both non-pneumonia and pneumonia cases, while 13·8% developed severe disease and 6·1% developed to a critical stage requiring intensive care.[8] In a study of clinical progression in 1099 patients,[4] those at highest risk for severe disease and death included people over the age of 60 years and those with underlying conditions, including hypertension, diabetes, cardiovascular disease, chronic respiratory disease, and cancer.

Assessing the severity of COVID-19 is crucial to determine the appropriateness of mitigation strategies and to enable planning for health-care needs as epidemics unfold. However, crude case fatality ratios obtained by dividing the number of deaths by the number of cases can be misleading.[9,10] First, there can be a period of 2–3 weeks between a person developing symptoms, the case subsequently being detected and reported, and observation of the final clinical outcome. During a growing epidemic, the final clinical outcome of most of the reported cases is typically unknown. Simply dividing the cumulative reported number of deaths by the cumulative number of reported cases will therefore underestimate the true case fatality ratio early in an epidemic.[9–11] This effect was observed in past epidemics of respiratory pathogens, including severe acute respiratory syndrome (SARS)[12] and H1N1[9] influenza, and as such is widely recognised. Thus, many of the estimates of the case fatality ratio that have been obtained to date for COVID-19 correct for this effect.[13–16] Additionally, however, during the exponential growth phase of an epidemic, the observed time lags between the onset of symptoms and outcome (recovery or death) are censored, and naive estimates of the observed times from symptom onset to outcome provide biased estimates of the actual distributions. Ignoring this effect tends to bias the estimated

case fatality ratio downwards during the early growth phase of an epidemic.

Second, surveillance of a newly emerged pathogen is typically biased towards detecting clinically severe cases, especially at the start of an epidemic when diagnostic capacity is low (figure 1). Estimates of the case fatality ratio can thus be biased upwards until the extent of clinically milder disease is determined.[9] Data from the epicentre of the outbreak in Wuhan have primarily been obtained through hospital surveillance and, thus, are likely to represent patients with moderate or severe illness, with atypical pneumonia or acute respiratory distress being used to define suspected cases eligible for testing.[7] In these individuals, clinical outcomes are likely to be more severe, so any estimates of the case fatality ratio will be higher. Elsewhere in mainland China and the rest of the world, countries and administrative regions alert to the risk of infection being imported via travel initially instituted surveillance for COVID-19 with a broader set of clinical criteria for defining a suspected case. These criteria typically included a combination of symptoms (eg, cough and fever) combined with recent travel history to the affected region (Wuhan, or Hubei province)[2,17]. Such surveillance is likely to detect clinically mild cases but, by initially restricting testing to those with a travel history or link, might have missed other symptomatic cases.

Here we attempt to adjust for these biases in data sources to obtain estimates of the case fatality ratio (proportion of all cases that will eventually lead to death) and infection fatality ratio (the proportion of all infections that will eventually lead to death) using both individual-level case report data and aggregate case and death counts from mainland China, from Hong Kong and Macau, and international case reports. By adjusting for both underlying demography and potential under-ascertainment at different levels of the severity pyramid (figure 1), these estimates should be broadly applicable across a range of settings to inform health planning while more detailed case data accrue.

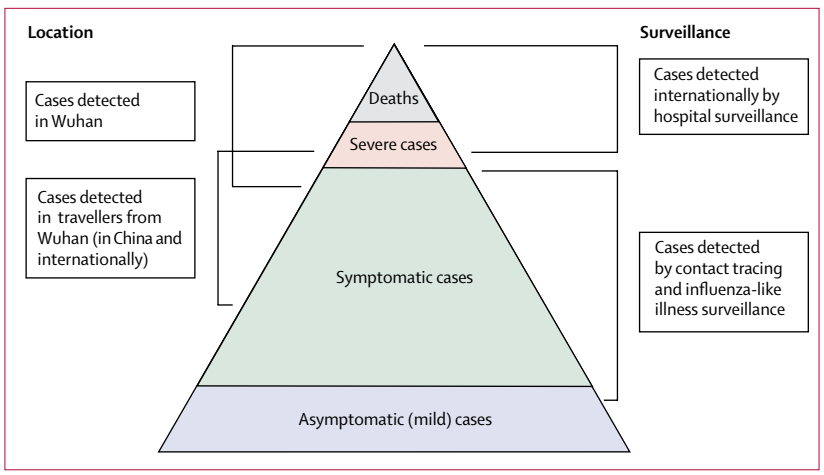

Figure 1: **Spectrum of COVID-19 cases**
At the top of the pyramid, those meeting the WHO case criteria for severe or critical cases are likely to be identified in the hospital setting, presenting with atypical viral pneumonia. These cases will have been identified in mainland China and among those categorised internationally as local transmission. Many more cases are likely to be symptomatic (ie, with fever, cough, or myalgia), but might not require hospitalisation. These cases will have been identified through links to international travel to high-risk areas and through contact-tracing of contacts of confirmed cases. They might also be identified through population surveillance of, for example, influenza-like illness. The bottom part of the pyramid represents mild (and possibly asymptomatic) cases. These cases might be identified through contact tracing and subsequently via serological testing.

Methods

Individual-level data on early deaths from mainland China

We identified information on the characteristics of 48 patients who died from COVID-19 in Hubei, reported by the National Health Commission and the Hubei Province Health Commission website up to Feb 8, 2020. We recorded the following data elements, where available: sex, age, date of symptom onset, date of hospitalisation, and date of death. Of the 48 cases, neither the date of symptom onset nor the date of report was available for 13 cases. We also removed eight cases with onset before Jan 1, 2020, or death before Jan 21, 2020, and three deaths after Jan 28, 2020, which were the dates consistent with reliable reporting of onset and death in this setting, respectively, considering the onset-to-death times (including early onsets creates a bias towards long onset-to-death times, reflecting under-ascertainment of deaths early on). This left 24 deaths, which we used to estimate the onset-to-death distribution.

Individual-level data on cases outside mainland China

We collated data on 2010 cases reported in 37 countries and two special administrative regions of China (Hong Kong and Macau), from government or ministry of health websites and media reports, until Feb 25, 2020. We recorded the following information where available: country or administrative region in which the case was detected, whether the infection was acquired in China or abroad, date of travel, date of symptom onset, date of hospitalisation, date of confirmation, date of recovery, and date of death. We used data from 165 recovered individuals with reported recovery dates and reported or imputed onset dates to estimate the onset-to-recovery distribution, after excluding 26 recoveries without appropriate information on dates of recovery, report, or locality. We used data on 1334 international cases to obtain estimates of the case fatality ratio, not including cases without dates of report.

Data on aggregate cases and deaths in mainland China

Data on 70 117 PCR-confirmed and clinically diagnosed cases by date of onset in Wuhan and elsewhere in China from Jan 1 to Feb 11, 2020, were extracted from the WHO–China Joint Mission report.[8] Over this period a total of 1023 deaths were reported across China, with these data available disaggregated into 10-year age bands between 0–9 years and 70–79 years old, and a further age

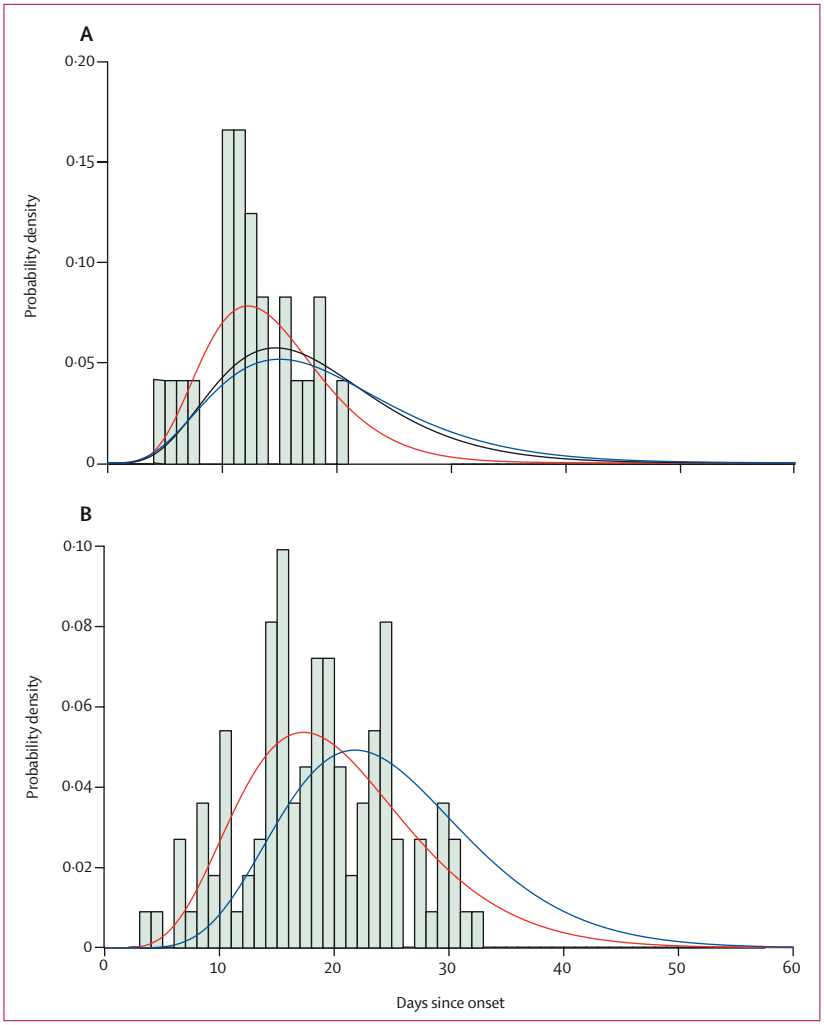

***Figure 2*: Onset-to-death and onset-to-recovery distributions**
(A) Onset-to-death data from 24 cases in mainland China early in the epidemic. (B) Onset-to-recovery data from 169 cases outside of mainland China. Red lines show the best fit (posterior mode) gamma distributions, uncorrected for epidemic growth, which are biased towards shorter durations. Blue lines show the same distributions corrected for epidemic growth. The black line (panel A) shows the posterior estimate of the onset-to-death distribution following fitting to the aggregate case data.

For the **data and code used in this study** see https://github.com/mrc-ide/COVID19_CFR_submission

See Online for appendix

band for those aged 80 years or older.[7] Using collated data on daily reported deaths obtained each day from the National Health Commission regional websites, we estimated that 74% of deaths occurred in Wuhan and the remainder outside Wuhan. Additionally, the most recent available cumulative estimates (March 3, 2020) of 80 304 confirmed cases and 2946 deaths within China were extracted from the WHO COVID-19 Situation Report (number 43).[1]

An earlier (now withdrawn) preprint of a subset of these cases up to Jan 26, 2020 reported the age distribution of cases categorised by severity for 3665 cases.[18] Under the China case definition, a severe case is defined as tachypnoea (≥30 breaths per min) or oxygen saturation 93% or higher at rest, or PaO_2/FiO_2 ratio less than 300 mm Hg.[7] Assuming severe cases to require hospitalisation (as opposed to all of the patients who were hospitalised in China, some of whom will have been hospitalised to reduce onward transmission), we used the proportion of severe cases by age in these patients to estimate the proportion of cases and infections requiring hospitalisation.

Data on infection in repatriated international Wuhan residents

Data on infection prevalence in repatriated expatriates returning to their home countries were obtained from government or ministry of health websites and media reports. To match to the incidence reported in Wuhan on Jan 30, 2020, we used data from six flights that departed between Jan 30 and Feb 1, 2020, inclusive.

Data on cases and deaths on the *Diamond Princess* cruise ship

In early February 2020 a cruise liner named the *Diamond Princess* was quarantined after a disembarked passenger tested positive for the virus. Subsequently all 3711 passengers on board were tested over the next month. We extracted data on the ages of passengers onboard on Feb 5, 2020, the dates of positive test reports, which were available for 657 out of 712 PCR-confirmed cases, and the dates of ten deaths among these cases from the reports of the Japan Ministry of Health, Labour and Welfare[19] and international media.

Demographic data

Age-stratified population data for 2018 were obtained from the National Bureau of Statistics of China.[20] According to these data, the population of Wuhan in 2018 was approximately 11 million people.

Statistical analysis overview

All analyses were done with R software (version 3.6.2), with Bayesian Marko-Chain Monte Carlo via the package drjacoby (version 1.0.0).[21] Data and code are available online at GitHub.

Estimation of time intervals between symptom onset and outcome

In estimating time intervals between symptom onset and outcome, it was necessary to account for the fact that, during a growing epidemic, a higher proportion of the cases will have been infected recently (appendix p 7).Therefore, we re-parameterised a gamma model to account for exponential growth using a growth rate of 0·14 per day, obtained from the early case onset data (appendix p 6). Using Bayesian methods, we fitted gamma distributions to the data on time from onset to death and onset to recovery, conditional on having observed the final outcome. Missing onset dates were imputed on the basis of dates of report, where available.

	Deaths	Laboratory-confirmed cases*	Case fatality ratio			Infection fatality ratio†
			Crude	Adjusted for censoring	Adjusted for censoring, demography, and under-ascertainment‡	
Overall	1023	44 672	2·29% (2·15–2·43)	3·67% (3·56–3·80)	1·38% (1·23–1·53)	0·657% (0·389–1·33)
Age group, years						
0–9	0	416	0·000% (0·000–0·883)	0·0954% (0·0110–1·34)	0·00260% (0·000312–0·0382)	0·00161% (0·000185–0·0249)
10–19	1	549	0·182% (0·00461–1·01)	0·352% (0·0663–1·74)	0·0148% (0·00288–0·0759)	0·00695% (0·00149–0·0502)
20–29	7	3619	0·193% (0·0778–0·398)	0·296% (0·158–0·662)	0·0600% (0·0317–0·132)	0·0309% (0·0138–0·0923)
30–39	18	7600	0·237% (0·140–0·374)	0·348% (0·241–0·577)	0·146% (0·103–0·255)	0·0844% (0·0408–0·185)
40–49	38	8571	0·443% (0·314–0·608)	0·711% (0·521–0·966)	0·295% (0·221–0·422)	0·161% (0·0764–0·323)
50–59	130	10 008	1·30% (1·09–1·54)	2·06% (1·74–2·43)	1·25% (1·03–1·55)	0·595% (0·344–1·28)
60–69	309	8583	3·60% (3·22–4·02)	5·79% (5·20–6·34)	3·99% (3·41–4·55)	1·93% (1·11–3·89)
70–79	312	3918	7·96% (7·13–8·86)	12·7% (11·5–13·9)	8·61% (7·48–9·99)	4·28% (2·45–8·44)
≥80	208	1408	14·8% (13·0–16·7)	23·3% (20·3–26·7)	13·4% (11·2–15·9)	7·80% (3·80–13·3)
Age category (binary), years						
<60	194	30 763	0·631% (0·545–0·726)	1·01% (0·900–1·17)	0·318% (0·274–0·378)	0·145% (0·0883–0·317)
≥60	829	13 909	5·96% (5·57–6·37)	9·49% (9·11–9·95)	6·38% (5·70–7·17)	3·28% (1·82–6·18)

Crude case fatality ratios are presented as mean (95% confidence interval). All other fatality ratios are presented as posterior mode (95% credible interval). Estimates are shown to three significant figures. Cases and deaths are aggregate numbers reported from Jan 1 to Feb 11, 2020.[8] Crude case fatality ratios are calculated as the number of deaths divided by the number of laboratory-confirmed cases. Our estimates also include clinically diagnosed cases (a scaling of 1·31 applied across all age-groups, as the breakdown by age was not reported for clinically diagnosed cases), which gives larger denominators and thus lower case fatality ratios than if only laboratory-confirmed cases were included. *Values do not include the clinically diagnosed cases included in our estimates. †Obtained by combining estimates of case fatality ratios with information on infection prevalence obtained from those returning home on repatriation flights. ‡Accounts for the underlying demography in Wuhan and elsewhere in China and corrects for under-ascertainment.

Table 1: **Estimates of case fatality ratio and infection fatality ratio obtained from aggregate time series of cases in mainland China**

Estimation of case fatality ratio, infection fatality ratio, and proportion hospitalised from aggregated case data

Estimates of the distribution of times from onset-to-death were used to project the expected cumulative number of deaths given the onsets observed in Wuhan and outside Wuhan, assuming a uniform attack rate across age groups. Using the age-distribution of the population, we obtained an estimate of the expected number of infections in each age group. Under-ascertainment was estimated in and outside of Wuhan by comparing the number of observed cases by age to this expected distribution, assuming perfect ascertainment in the 50–59 age group as this group had the highest number of detected cases relative to population size. We also did a sensitivity analysis assuming a differential attack rate by age (appendix p 9). For Wuhan, we added scaling to account for further under-ascertainment compared with outside of Wuhan. These steps gave us the expected age-distribution of cases.

For a given onset-to-death distribution, we obtained a modelled estimate of the cumulative number of deaths by age under an age-dependent case fatality ratio (fitted relative to the case fatality ratio in the oldest age group, which represented the highest crude case fatality ratio). This estimate was compared with the observed deaths by age using a Poisson likelihood. These data were then jointly fitted alongside the most recent age-aggregated cumulative deaths and cases in mainland China. Given that the numbers of observed cases and deaths have dropped substantially following a peak in late January, the ratio of current cumulative cases to current number of deaths, once corrected for under-ascertainment, should provide a good estimate of the final case fatality ratio.[11]

To estimate the infection fatality ratio we fitted to data on infection prevalence from international Wuhan residents who were repatriated to their home countries. Our age-stratified case fatality ratio and infection fatality ratio model was jointly fitted to the case data and infection prevalence data with use of Bayesian methods, using our previous estimate of the onset-to-death distribution as a prior. Full mathematical details are provided in the appendix (p 8).

Assuming a uniform attack rate by age groups, we used the demography-adjusted under-ascertainment rates calculated above to obtain an estimate of the proportion of infected individuals who would require hospitalisation.

To independently validate our infection fatality ratio estimate, we analysed data from the outbreak on the *Diamond Princess* cruise liner taking the dates of reported positive tests as a proxy for onset date. We calculated the expected proportion of deaths observed until March 25, 2020, given the onset times and estimated onset-to-death distribution (appendix p 13).

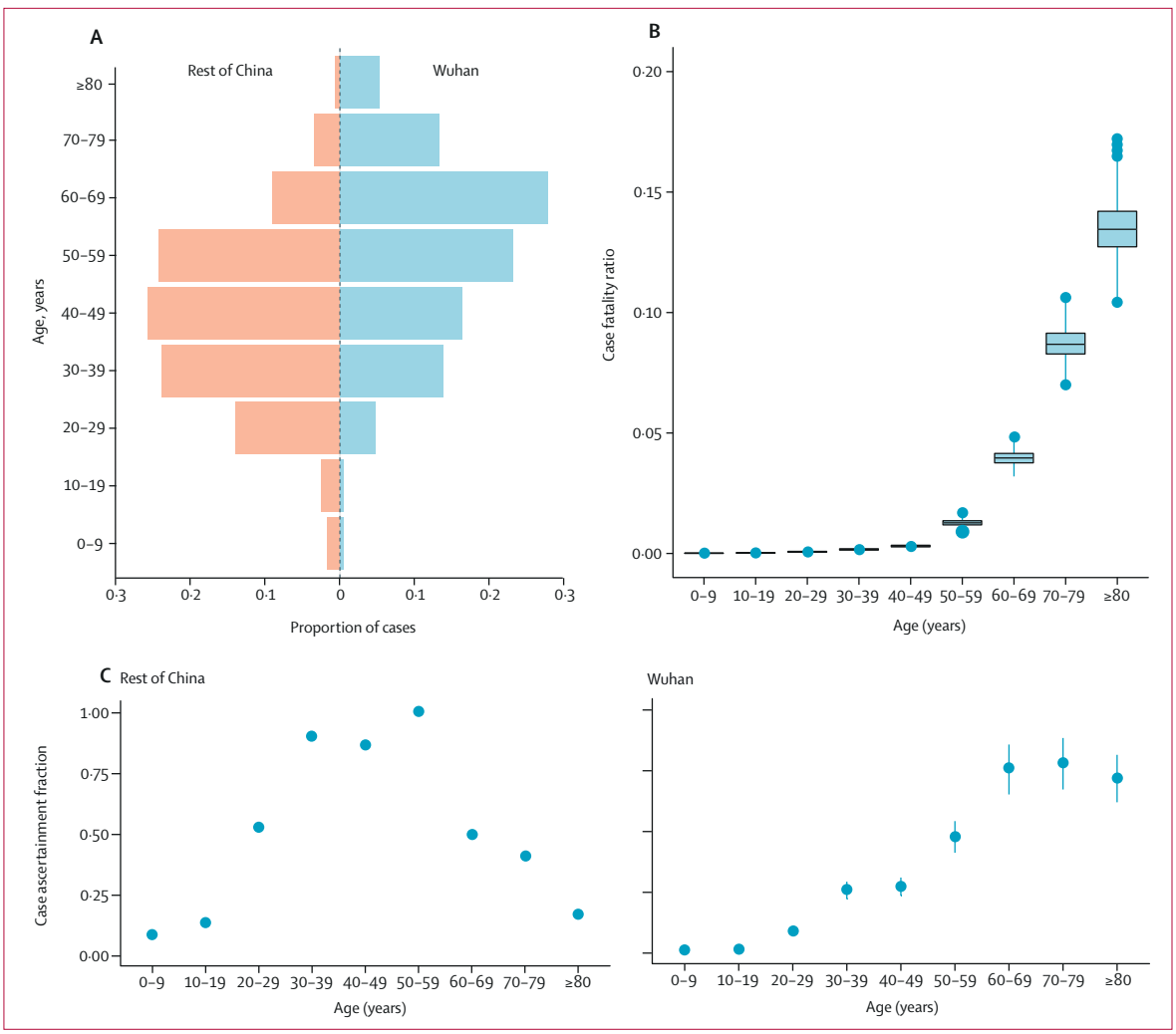

Figure 3: **Estimates of case fatality ratio by age, obtained from aggregate data from mainland China**
(A) Age-distribution of cases in Wuhan and elsewhere in China. (B) Estimates of the case fatality ratio by age group, adjusted for demography and under-ascertainment. Boxes represent median (central horizontal line) and IQR, vertical lines represent 1·5 × IQR, and individual points represent any estimates outside of this range. (C) Estimated proportions of cases ascertained in the rest of China and in Wuhan relative to the 50–59 years age group elsewhere in China. Error bars represent 95% CrIs.

Estimation of case fatality ratio from individual case data

We used parametric and non-parametric methods[11,22] to estimate the case fatality ratio in cases reported outside of mainland China using individual-level data. Cases in which the outcome was unknown were treated as censored observations. For parametric and non-parametric analyses, missing onset dates were multiply imputed using information on the onset-to-report distribution, and unreported recoveries were imputed using onset-to-outcome distributions and country summary data. The parametric models were fitted to the data using Bayesian methods (appendix p 12).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In the subset of 24 deaths from COVID-19 that occurred in mainland China early in the epidemic, with correction for bias introduced by the growth of the epidemic, we estimated the mean time from onset to death to be 18·8 days (95% credible interval [CrI] 15·7–49·7; figure 2) with a coefficient of variation of 0·45 (95% CrI 0·29–0·54). With the small number of observations in these data and given that they were from early in the epidemic, we could not rule out many deaths occurring with longer times from onset to death, hence the high upper limit of the credible interval. However, given that

	Parametric		Non-parametric	
	n	Case fatality ratio	n	Case fatality ratio
Overall	585	2·7% (1·4–4·7)	1334	4·1% (2·1–7·8)
Travel versus local transmission				
Travellers to mainland China	203	1·1% (0·4–4·1)	208	2·4% (0·6–8·5)
Local transmission	382	3·6% (1·9–7·2)	387	3·8% (1·7–8·2)
Age group, years				
<60	360	1·4% (0·4–3·5)	449	1·5% (0·6–3·9)
≥60	151	4·5% (1·8–11·1)	181	12·8% (4·1–33·5)

Parametric estimates are presented as posterior mode (95% credible interval), and were obtained using the gamma-distributed estimates of onset-to-death and onset-to-recovery. Non-parametric estimates are presented as maximum likelihood estimate (95% confidence interval) and were obtained using a modified Kaplan-Meier method.[11,23] Note that due to missing data on age and travel status, numbers in the stratified analysis are lower than for the overall analysis. In addition, the parametric method requires a correction for the epidemic growth rate, and these estimates were therefore obtained from the subset of data for which the travel or local transmission and age was known.

Table 2: **Estimates of case fatality ratio obtained from individual-level data on cases identified outside of mainland China**

	Severe cases	All cases	Proportion of infected individuals hospitalised
0–9 years	0	13	0·00% (0·00–0·00)
10–19 years	1	50	0·0408% (0·0243–0·0832)
20–29 years	49	437	1·04% (0·622–2·13)
30–39 years	124	733	3·43% (2·04–7·00)
40–49 years	154	743	4·25% (2·53–8·68)
50–59 years	222	790	8·16% (4·86–16·7)
60–69 years	201	560	11·8% (7·01–24·0)
70–79 years	133	263	16·6% (9·87–33·8)
≥80 years	51	76	18·4% (11·0–37·6)

Proportions of infected individuals hospitalised are presented as posterior mode (95% credible interval) and are adjusted for under-ascertainment and corrected for demography. Estimates are shown to three signficant figures. We assumed, based on severity classification from a UK context, that cases defined as severe would be hospitalised.

Table 3: **Estimates of the proportion of all infections that would lead to hospitalisation, obtained from a subset of cases reported in mainland China[18]**

the epidemic in China has since declined, our posterior estimate of the mean time from onset to death, informed by the analysis of aggregated data from China, is more precise (mean 17·8 days [16·9–19·2]; figure 2).

Using data on the outcomes of 169 cases reported outside of mainland China, we estimated a mean onset-to-recovery time of 24·7 days (95% CrI 22·9–28·1) and coefficient of variation of 0·35 (0·31–0·39; figure 2). Both these onset-to-outcome estimates are consistent with a separate study in China.[23]

Case fatality ratios were estimated from aggregate data on cases and deaths in mainland China (table 1). A large proportion of the cases, including all of those early in the epidemic, were reported in Wuhan, where the local health system was quickly overwhelmed. As a result, the age distribution of cases reported in Wuhan differed to that in the rest of China (figure 3A). Reported cases in Wuhan were more frequent in older age groups, perhaps reflecting higher severity (and therefore prioritisation for hospitalisation in Wuhan), while cases outside of Wuhan might also show a bias in terms of the relationship between age and travel. Adjusting for differences in underlying demography and assuming no overall difference in the attack rate by age, we estimated high under-ascertainment of cases in younger age groups both inside and outside of Wuhan (figure 3C, D). Furthermore, we estimated a higher level of under-ascertainment overall in Wuhan compared with outside of Wuhan (figure 3C). Accounting for this under-ascertainment, we estimated the highest case fatality ratio (13·4% [11·2–15·9%]) in the 80 years and older age group (figure 3B, table 1), with lower case fatality ratios associated with lower age groups, and the lowest in the 0–9 years age group (0·00260% [0·000312–0·0382]).

In cases reported outside of mainland China, we estimated an overall modal case fatality ratio of 2·7% (95% CrI 1·4–4·7) using the parametric model (table 2). In those who reported travel to mainland China (and would therefore have been detected in the surveillance system), we estimated an overall modal case fatality ratio of 1·1% (0·4–4·1), and in those without any reported travel to China (therefore detected either through contact tracing or through hospital surveillance), we estimated a case fatality ratio of 3·6% (1·9–7·2) using the parametric model. The estimated case fatality ratio was lower in those aged under 60 years of age (1·4% [0·4–3·5]) compared with those aged 60 years and over (4·5% [1·8–11·1]). Similar estimates were obtained using non-parametric methods (table 2).

In international Wuhan residents repatriated on six flights, we estimated a prevalence of infection of 0·87% (95% CI 0·32–1·9; six of 689). Adjusting for demography and under-ascertainment, we estimate an infection fatality ratio of 0·66% (95% CrI 0·39–1·33). As for the case fatality ratio, this is strongly age-dependent, with estimates rising steeply from age 50 years upwards (table 1). The demography-adjusted and under-ascertainment-adjusted proportion of infected individuals requiring hospitalisation ranges from 1·1% in the 20–29 years age group up to 18·4% in those 80 years and older (table 3). Using these age-stratified infection fatality ratio estimates, we estimate the infection fatality ratio in the *Diamond Princess* population to be 2·9%. Given the delay from onset of symptoms to death, we would expect 97% of these deaths to have occurred by March 25, 2020, giving an estimate of the current infection fatality ratio of 2·8%, compared with the empirical estimate of 1·4% (95% CI 0·7–2·6; ten of 712).

Discussion

From an extensive analysis of data from different regions of the world, our best estimate at the current time for the

case fatality ratio of COVID-19 in China is 1·38% (95% CrI 1·23–1·53). Although this value remains lower than estimates for other coronaviruses, including SARS[24] and Middle East respiratory syndrome (MERS),[25] it is substantially higher than estimates from the 2009 H1N1 influenza pandemic.[26,27] Our estimate of an infection fatality ratio of 0·66% in China was informed by PCR testing of international Wuhan residents returning on repatriation flights. This value was consistent with the infection fatality ratio observed in passengers on the *Diamond Princess* cruise ship up to March 5, 2020, although it is slightly above the upper 95% confidence limit of the age-adjusted infection fatality ratio observed by March 25 (of 712 confirmed cases, 601 have been discharged, ten have died, and 11 remain in a critical condition). This difference might be due to repatriation flight data slightly underestimating milder infections, or due to cruise passengers having better outcomes because of a potentially higher-than-average quality of health care.

Our estimates of the probability of requiring hospitalisation assume that only severe cases require hospitalisation. This assumption is clearly different from the pattern of hospitalisation that occurred in China, where hospitalisation was also used to ensure case isolation. Mortality can also be expected to vary with the underlying health of specific populations, given that the risks associated with COVID-19 will be heavily influenced by the presence of underlying comorbidities.

Our estimate of the case fatality ratio is substantially lower than the crude case fatality ratio obtained from China based on the cases and deaths observed to date, which is currently 3·67%, as well as many of the estimates currently in the literature. The principle reason for this difference is that the crude estimate does not take into account the severity of cases. For example, various estimates have been made from patient populations ranging from those with generally milder symptoms (for example international travellers detected through screening of travel history)[13] through to those identified in the hospital setting.[14,15]

It is clear from the data that have emerged from China that case fatality ratio increases substantially with age. Our results suggest a very low fatality ratio in those under the age of 20 years. As there are very few cases in this age group, it remains unclear whether this reflects a low risk of death or a difference in susceptibility, although early results indicate young people are not at lower risk of infection than adults.[28] Serological testing in this age group will be crucial in the coming weeks to understand the significance of this age group in driving population transmission. The estimated increase in severity with age is clearly reflected in case reports, in which the mean age tends to be in the range of 50–60 years. Different surveillance systems will pick up a different age case mix, and we find that those with milder symptoms detected through a history of travel are younger on average than those detected through hospital surveillance. Our correction for this surveillance bias therefore allows us to obtain estimates that can be applied to different case mixes and demographic population structures. However, it should be noted that this correction is applicable under the assumption of a uniform infection attack rate (ie, exposure) across the population. We also assumed perfect case ascertainment outside of Wuhan in the age group with the most cases relative to their population size (50–59-year-olds); however, if many cases were missed, the case fatality ratio and infection fatality ratio estimates might be lower. In the absence of random population surveys of infection prevalence, our adjustment from case fatality ratio to infection fatality ratio relied on repatriation flight data, which was not age specific. The reported proportion of infected individuals who were asymptomatic on the *Diamond Princess* did not vary considerably by age, supporting this approach, but future larger representative population prevalence surveys and seroprevalence surveys will inform such estimates further.

Much of the data informing global estimates of the case fatality ratio at present are from the early outbreak in Wuhan. Given that the health system in this city was quickly overwhelmed, our estimates suggest that there is substantial under-ascertainment of cases in the younger age groups (who we estimate to have milder disease) by comparison with elsewhere in mainland China. This under-ascertainment is the main factor driving the difference between our estimate of the crude case fatality ratio from China (3·67%) and our best estimate of the overall case fatality ratio (1·38%). The case fatality ratio is likely to be strongly influenced by the availability of health-care facilities. However surprisingly, although health-care availability in Wuhan was stretched, our estimates from international cases are of a similar magnitude, suggesting relatively little difference in health outcome. Finally, as clinical knowledge of this new disease accrues, it is possible that outcomes will improve. It will therefore be important to revise these estimates as epidemics unfold.

The world is currently experiencing the early stages of a global pandemic. Although China has succeeded in containing the disease spread for 2 months, such containment is unlikely to be achievable in most countries. Thus, much of the world will experience very large community epidemics of COVID-19 over the coming weeks and months. Our estimates of the underlying infection fatality ratio of this virus will inform assessments of health effects likely to be experienced in different countries, and thus decisions around appropriate mitigation policies to be adopted.

Contributors

NMF and ACG conceived the study with input from RV, LCO, ID, PW, and CW. RV, LCO, and ID led the analysis of individual-case data for the international cases and estimation of the onset-to-outcome distributions, with input from CAD, ACG, and NMF. RV, PW, CW, and PGTW led the analysis of the China data, with input from ACG and NMF. NI coordinated management of the team, including the data collation and processing.

NI and GC-D undertook the extraction of the international case data. HT undertook the extraction of flight repatriation data, with input from NI and AD. HF led the extraction of the China mainland data from national and regional websites with input from HW, YW, and XX. JTG developed the code for the non-parametric model. ACG produced the first draft of the manuscript. All authors contributed to the final draft.

Declaration of interests

LCO reports grants from WHO outside of the submitted work. CAD reports grants from the UK Medical Research Council and from the National Institute for Health Research during the conduct of the study. NMF reports grants from the UK Medical Research Council and the UK National Institute for Health Research during the conduct of the study, and grants from Gavi, the Vaccine Alliance, Janssen Pharmaceuticals, and the Bill and Melinda Gates Foundation outside of the submitted work. All other authors declare no competing interests.

Data sharing

All data and code used in this study are available in a GitHub repository.

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For the **GitHub repository for this study** see https://github.com/mrc-ide/COVID19_CFR_submission

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Population-level COVID-19 mortality risk for non-elderly individuals overall and for non-elderly individuals without underlying diseases in pandemic epicenters

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ABSTRACT

Objective: To provide estimates of the relative rate of COVID-19 death in people <65 years old versus older individuals in the general population, the absolute risk of COVID-19 death at the population level during the first epidemic wave, and the proportion of COVID-19 deaths in non-elderly people without underlying diseases in epicenters of the pandemic.

Eligible data: Cross-sectional survey of countries and US states with at least 800 COVID-19 deaths as of April 24, 2020 and with information on the number of deaths in people with age <65. Data were available for 14 countries (Belgium, Canada, France, Germany, India, Ireland, Italy, Mexico, Netherlands, Portugal, Spain, Sweden, Switzerland, UK) and 13 US states (California, Connecticut, Florida, Georgia, Illinois, Indiana, Louisiana, Maryland, Massachusetts, Michigan, New Jersey, New York, Pennsylvania). We also examined available data on COVID-19 deaths in people with age <65 and no underlying diseases.

Main outcome measures: Proportion of COVID-19 deaths in people <65 years old; relative mortality rate of COVID-19 death in people <65 versus ≥65 years old; absolute risk of COVID-19 death in people <65 and in those ≥80 years old in the general population as of June 17, 2020; absolute COVID-19 mortality rate expressed as equivalent of mortality rate from driving a motor vehicle.

Results: Individuals with age <65 account for 4.5–11.2% of all COVID-19 deaths in European countries and Canada, 8.3–22.7% in the US locations, and were the majority in India and Mexico. People <65 years old had 30- to 100-fold lower risk of COVID-19 death than those ≥65 years old in 11 European countries and Canada, 16- to 52-fold lower risk in US locations, and less than 10-fold in India and Mexico. The absolute risk of COVID-19 death as of June 17, 2020 for people <65 years old in high-income countries ranged from 10 (Germany) to 349 per million (New Jersey) and it was 5 per million in India and 96 per million in Mexico. The absolute risk of COVID-19 death for people ≥80 years old ranged from 0.6 (Florida) to 17.5 per thousand (Connecticut). The COVID-19 mortality rate in people <65 years old during the period of fatalities from the epidemic was equivalent to the mortality rate from driving between 4 and 82 miles per day for 13 countries and 5 states, and was higher (equivalent to the mortality rate from driving 106–483 miles per day) for 8 other states and the UK. People <65 years old without underlying predisposing conditions accounted for only 0.7–3.6% of all COVID-19 deaths in France, Italy, Netherlands, Sweden, Georgia, and New York City and 17.7% in Mexico.

Conclusions: People <65 years old have very small risks of COVID-19 death even in pandemic epicenters and deaths for people <65 years without underlying predisposing conditions are remarkably uncommon. Strategies focusing specifically on protecting high-risk elderly individuals should be considered in managing the pandemic.

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1. Introduction

As the coronavirus disease 2019 (COVID-19) pandemic has spread widely around the globe (Fauci et al., 2020; Gates, 2020), estimates about its eventual impact in terms of total number of deaths have varied widely, as they are mostly based on mathematical models with various speculative assumptions. It is crucial to estimate how much smaller the risk of death is among non-elderly people (<65 years old) as opposed to older individuals and how frequent deaths are in people who are <65 years old and have no underlying predisposing diseases. Media have capitalized on stories of young healthy individuals with severe, fatal outcomes. However, exaggeration should be avoided in responding to the pandemic (Ioannidis, 2020a). Accurate estimates of mortality rate at different age groups have important implications. Deaths of young, healthy people contribute far more quality-adjusted life-years lost than deaths in elderly individuals with pre-existing morbidity. Knowledge of COVID-19 mortality rates for people <65 years old at the population level can help guide different management strategies for the pandemic. People <65 years old represent the lion's share of the workforce.

Here, we used data from 14 countries and 13 states in the USA that have been epicenters of the pandemic with a large number of deaths and where data were available for deaths according to age stratification. We aimed to evaluate the relative mortality rate in people <65 years old versus older individuals in the general population, to provide estimates of absolute risk of COVID-19 death in these epicenters during the first epidemic wave, and to understand what proportion of COVID-19 deaths occur in people <65 years old and without underlying diseases.

2. Methods

We considered data from publicly reported situational reports of countries and US states or major cities that had already been major epicenters of the pandemic as of late April, 2020; thus epidemic waves are likely to be mostly completed almost two months later (by mid-June, 2020). Eligibility criteria included: (1) at least 800 deaths accumulated as of April 24, 2020 (so as to qualify for an early hotbed of the epidemic and to have a meaningful amount of data to analyze); and (2) information available on death counts per age strata, allowing to calculate numbers of deaths in people with age <65 or, alternatively, at least in people with age <60.

Different dates for extractions are listed throughout the manuscript, depending on data availability; Supplementary Table 1 provides all the dates of collection of the various COVID-19-related data.

For each of the eligible geographical locations, we extracted information from the most up-to-date situational reports as of May 23, 2020 (countries) or May 24, 2020 (US locations) focusing on total number of deaths with available age stratification, and number of deaths in age <65 (or, if not available, number of deaths in age <60 and in age 60–69), and ≥65. Information was extracted independently in duplicate by two authors (JI, CA) and discrepancies were resolved. Whenever information was unavailable for the desirable <65 years cut-off, we contacted the respective authorities issuing the situational report. For secondary analyses, we also extracted information on deaths in the more granular age subgroups of <40, 40–64, 65–79, and ≥80.

One author (DC-I) downloaded information on the proportion of the population in each eligible location for each age group. We used census information from populationpyramid.net/world/2019 for countries and from https://worldpopulationreview.com for the US states.

We calculated the population-level relative mortality rate of COVID-19 death for an individual <65 years old as compared with an individual ≥65 years old for each eligible country and US state/city. This we calculated as the ratio of absolute risks (COVID-19 deaths with age <65/population with age <65 in the respective age-pyramid) divided by (COVID-19 deaths with age ≥65/population with age ≥65 in the respective age-pyramid). Inverting this relative mortality rate shows how many fold lower the risk of COVID-19 death is for an individual <65 years old as compared with an individual ≥65 years old.

We also calculated the absolute risk of dying with COVID-19 during the first epidemic wave for a person <65 years old in each eligible country and state by dividing the number of COVID-19 deaths (updated as of the end of day June 17, 2020) in this age group by the census population in this age group. Certainly, the number of deaths will increase and there is some uncertainty about the total projected number of deaths in each of these locations when this epidemic wave has passed, and all deaths have been counted. With the exception of India and Mexico, all other locations had largely completed the epidemic wave as of June 17 (for a visualization see Supplementary Fig. 1) – at least the first wave, since it remains unknown whether they may be any second waves. We also documented for each country and state the peak 7-day moving up to June 17, 2020. We used a 7-day moving frame, because there is some unavoidable noise fluctuation in death counts every day, plus for several countries and states there may be worse reporting delays for deaths during the weekend days. We used the actual date that deaths occurred for these estimates, but, whenever this was unavailable, we used the date of death reporting.

The magnitude of COVID-19 mortality rates is difficult to grasp, especially when population-level risks are small. Therefore, we converted the absolute risks of COVID-19 death into equivalents of mortality rate by a well-known, almost ubiquitous activity (Ioannidis, 2013), driving/travelling by motor vehicle. We used estimates from the International Transport Forum Road Safety Annual Report 2018 for the number of road deaths per billion vehicle miles driven for each European country (OECD, 2020). For Spain, Italy, Portugal, and Mexico there were only data available for number of road fatalities per 100,000 inhabitants and for India we found similar data from Wikipedia. Since road deaths per 100,000 inhabitants tend to correlate reasonably well with road deaths per billion vehicle miles in Europe, we used for Italy and Portugal the same road deaths per billion miles as for Belgium, since Italy and Portugal have the same road deaths per 100,000 inhabitants as Belgium. Similarly, we used for Spain the same road deaths per billion miles as Germany. For Mexico and India, their road fatalities per 100,000 inhabitants were close to the USA values and we used the USA value road deaths per billion miles with adjustment for the difference. For USA locations, we used the state-specific data provided for 2018 by the Insurance Institute for Highway Safety (Insurance Institute for Highway safety, 2020). In other words, for each location we identified the distance that one has to travel by motor vehicle to expose oneself to the same hazard as the absolute COVID-19 mortality rate observed until June 17, 2020. We then divided the estimated miles travelled by the number of days that have passed since the first COVID-19 death was recorded in each location and until June 17, 2020. The result transforms the average risk of COVID-19 death per day during the period where COVID-19 deaths occur into an equivalent of miles travelled by car per day. The longer the distance, the higher the risk. Of note, for a typical death curve, e.g. as documented in Wuhan (Du et al., 2020), the miles travelled per day estimate may be overestimated, if the covered fatality period extends beyond the peak of the curve (as is the case in all high-income locations that we analyzed), and may be underestimated otherwise – this situation may apply to India and Mexico.

Finally, we sought information from the situational reports and from personal communications with the respective health authorities on how many COVID-19 deaths had been documented in people <65 years old who had no underlying predisposing conditions. Predisposing conditions for worse outcome in COVID-19 may include (Guan et al., 2020; Wang et al., 2020a; World Health Organization, 2020) cardiovascular disease, hypertension, diabetes, chronic obstructive pulmonary disease and severe asthma, kidney failure, severe liver disease, immunodeficiency, and malignancy. We followed the data collection principles of each national and state organization on how underlying conditions were defined. Data were readily available in published reports or public datasets for France (Santé publique France, 2020), Mexico (Secretaría de Salud, 2020), Georgia (Georgia Department of Public Health, 2020) and

New York City (New York City Health, 2020). We contacted all other national agencies and state departments of health when we could find contact information and thus we obtained additional such data according to the presence or not of underlying conditions from the Italian COVID-19 team (personal communication, Luigi Palmieri), from the Dutch COVID-19 team (personal communication, Susan van den Hof), and from the Swedish National Board of Health and Welfare (personal communication, Erik Wahlström) (Socialstyrelsen, 2020). We encourage other organizations to send us similar data, as they become available, so that they can be incorporated in further updates. We avoided performing a formal meta-analysis, since these data are using different definitions of eligible comorbidities and data collection methods.

3. Results

3.1. Eligible data

Eighteen countries (Belgium, Brazil, Canada, China, France, Germany, India, Iran, Ireland, Italy, Mexico, Netherlands, Portugal, Spain, Sweden, Switzerland, Turkey, United Kingdom) and 13 US states (California, Connecticut, Florida, Georgia, Illinois, Indiana, Louisiana, Maryland, Massachusetts, Michigan, New Jersey, New York, Pennsylvania) fulfilled the first eligibility criterion and of those, 14 countries (Belgium, Canada, France, Germany, India, Ireland, Italy, Mexico, Netherlands, Portugal, Spain, Sweden, Switzerland, United Kingdom) as well as all 13 states had some available data on required age categories so that they could be included in our analysis. (Santé publique France, 2020; Secretaría de Salud, 2020; Georgia Department of Public Health, 2020, Sciensano: the Belgian Institute for Health, 2020; Public Health Agency of Canada, 2020; Robert Koch Institut, 2020; Ministry of Health and Family Welfare, 2020; Health Protection Surveillance Centre/Lárionad Faire um Chosaint Sláinte, 2020; Epidemiology for public health/Istituto Superiore di Sanità, 2020; Rijksinstituut voor Volksgezondheid en Milieu – RIVM, 2020; Serviço Nacional de Saúde/Direção-Geral da Saúde, 2020; Centro de Coordinación de Alertas y Emergencias Sanitarias, 2020; Folkhälsomyndigheten, 2020; Bundesamt für Gesundheit BAG, 2020; Office for National Statistics, 2020; State of California, 2020; State of Connecticut, 2020; Florida Department of Health Open Data, 2020; Illinois Department of Public Health, 2020; Indiana State Department of Health, 2020; Louisiana Department of Health/Office of Public Health, 2020; Maryland Department of Health, 2020; Massachusetts Department of Public Health/Executive office of Health and Human Services, 2020; State of Michigan, 2020; New Jersey Department of Health, 2020; New York State Department of Health, 2020; Pennsylvania Department of Health/Bureau of Health Statistics and Registries, 2020)

3.2. Deaths with age stratification

Age distribution of COVID-19 deaths are shown in Fig. 1 and detailed in Table 1 (raw data in Supplementary Table 2). Individuals with age <65 accounted for only 4.5–11.2% of all COVID-19 deaths in all European countries and Canada. Among the 13 US locations, the proportion of deaths contributed by individuals <65 ranged from 8.3 to 22.7% of all deaths. Conversely, in Mexico and India, they were the majority.

Individuals with age <40 accounted for <1.3% of all COVID-19 deaths in European countries and Canada and 0.4–2.3% in the US states, but were a much larger proportion in Mexico and India. Individuals 80 years or older accounted for the large majority of deaths (half to four-fifths or more) in Europe (except Ireland) and Canada, while in the US there was wider variability across states (range, 39–63%). In Mexico, they accounted for only 8.3% of deaths (no data on India).

3.3. Relative rate of dying with COVID-19 for individuals <65 years old versus older individuals at the population level

As shown in Fig. 2 (raw data in Supplementary Tables 3–4), the percentage of the population <65 years old varied from 75.18% to 86.31% in high-income countries' locations and exceeded 90% in India and Mexico. People <65 years old had overall a 30- to 100-fold lower risk of COVID-19 death than those ≥65 years old in European countries and Canada, for the US locations, the relative mortality rate was somewhat smaller (16–52-fold), while for Mexico and India the relative mortality rate was less than 10-fold.

3.4. Absolute risk of death with COVID-19 at the population level

Table 2 shows the estimates of the absolute risk of dying with COVID-19 at the population level for people <65 years old and for those ≥80 years old as of June 17. For these estimates we used the total number of deaths as of the close of day June 17, 2020 (for sources see Supplementary Table 5), and not just those where age information was available (as in Table 1). Also shown is the 7-day moving period that had the largest number of deaths. As shown, with the exception of India and Mexico, the peak period was already long before June 17, suggesting

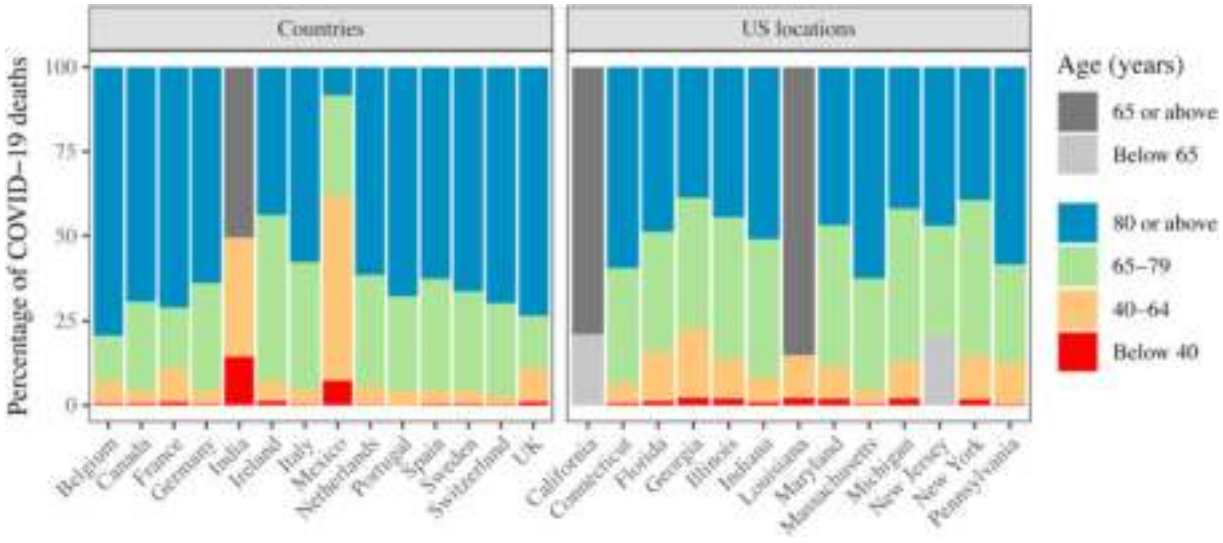

Fig. 1. Proportion of COVID-19 deaths by specific age group category. For detailed numbers, and deviations from age category cutoffs (when data were not provided for these exact age-categories), see Table 1.

Table 1
Proportion of COVID-19 deaths in specific age groups.

Location (date report)	Total deaths[a]	% of deaths age <40 among total deaths	% of deaths age 40–64 among total deaths	% of deaths age 65–79 among total deaths	% of age ≥80 among total deaths	% of deathsage <65 among total deaths
Countries						
Belgium (May 22)	6579	0.5[b]	6.7[c]	13.5[d]	79.2[e]	7.2
Canada (May 22)	2305	0.6	3.9[f]	26.3[g]	69.2	4.5
France (May 18)	17488	1.0[b]	10.2[c]	17.7[d]	70.6[e]	11.2
Germany (May 23)	8211	0.4	4.2[f]	31.3[g]	63.7	4.5 [7.6][h]
India (May 21)	3435	14.4[b]	35.1[i]	ND	ND	49.5[h]
Ireland (May 20)	1330	1.3[b]	6.1[c]	48.8[j]	43.8[k]	7.4
Italy (May 20)	31017	0.3	4.4[f]	37.6[g]	57.7	3.6 [7.1][h]
Mexico (May 24)	7394	7.3	54.7	29.6	8.3	62.1
Netherlands (May 22)	5788	0.2	5.6	32.7	61.5	5.8
Portugal (May 22)	1302	0.1	4.2[f]	28.2[g]	67.6	4.2 [7.2][h]
Spain (May 22)	20552	0.5	4.3[f]	32.6[g]	62.7	4.7 [7.7][h]
Sweden (May 22)	3992	0.5	4.0[f]	29.3[g]	66.1	4.5 [6.9][h]
Switzerland (May 23)	1640	0.3	2.4[f]	27.7[g]	69.6	2.7 [5.1][h]
UK (May 8)	41020	1.1[b]	10.1[c]	15.4[d]	73.4[e]	11.2
US locations						
California (May 22)	3708	ND	ND	ND	ND	21.0
Connecticut (May 22)	3674	0.7	5.6[f]	34.2[g]	59.5	6.1 [10.3][h]
Florida (May 24)	2316	1.3	14.6	35.3	48.8	15.9
Georgia (May 24)	1821	2.3	20.5	38.6	38.7	22.7
Illinois (May 24)	4856	2.0	11.8[f]	41.7[g]	44.4	13.9 [19.8][h]
Indiana (May 23)	1824	1.0	7.5[f]	40.5[g]	50.9	8.5 [13.8][h]
Louisiana (May 24)	2567	2.2	12.7[f]	ND	ND	14.9 [21.0][h]
Maryland (May 24)	2103	2.0	9.8[f]	41.5[g]	46.8	11.8 [17.1][h]
Massachusetts (May 24)	6372	0.4	4.5[f]	32.5[g]	62.6	4.9 [8.3][h]
Michigan (May 23)	5228	2.0	11.0[f]	45.0[g]	42.0	13.0 [19.0][h]
New Jersey (May 22)	11133	ND	ND	32.5	47.0	20.5
New York (May 23)	23382	1.8	13.1[f]	45.7[g]	39.4	14.9 [21.4][h]
Pennsylvania (May 21)	4980	0.4	12.2	29.0	58.4	12.6

The proportions of deaths across different categories may change if late-occurring or late-reported deaths have a different age distribution. This may be an issue specifically for Mexico and India where the epidemic wave was still far from mature at the time of data collection. As of June 26, 2020, no updated age-group death data could be found for India, but such updated data were available for Mexico, and the age distribution had not changed much, e.g. 58.3% of deaths were in people with age <65 years. ND: no data.

[a] Using deaths' data with available information on age.
[b] Group <45 years (not available for <40 years).
[c] Group 45–64 years (not available for 40–64 years).
[d] Group 65–74 years (not available for 65–79 years).
[e] Group ≥75 years (not available for ≥80 years).
[f] Group 40–59 years (not available for 45–64 years).
[g] Group 60–79 years (not available for 65–79 years).
[h] Group <60 years [the number shown in brackets is the approximated estimate for age <65 assuming that a third of the deaths in the 60–69 bracket are in <65 years old people, as suggested by other countries where data are available on 5-year age intervals].
[i] Group 45–59 years (not available for 45–64 years).
[j] Group 65–84 years (not available for 65–79 years).
[k] Group ≥85 years (not available for ≥80 years).

that the epidemic fatality waves had already reached substantial maturity as of June 17. Visual perusal (Supplementary Fig. 1) also agrees that these epidemic waves are practically complete. The absolute risk of death for people <65 years old in high-income countries ranged widely from 10 per million in Germany to 349 per million in New Jersey. Connecticut, Illinois, Louisiana, Massachusetts, Michigan, New Jersey, and New York had an absolute risk of death exceeding 100 per million. The risk was 5 per million in India (data on <60 years old) and 96 per million in Mexico.

The absolute risk of death for people ≥80 years old in high-income countries ranged from approximately 0.6 in a thousand in Florida to 17.5 in a thousand in Connecticut. For middle-income countries, it was 0.8 in a thousand in Mexico as of June 17 (no data for India).

Table 3 shows the conversion of the absolute risk of COVID-19 death as of June 17 into the equivalent mortality rate from motor vehicle travelled miles. The distances (corresponding to equivalent mortality rates) ranged from driving a total of 416 miles to 47773 miles. Dividing by the number of days since the first documented COVID-19 death, the average daily risk of COVID-19 death for an individual <65 years old in 11 of the 12 European countries or Canada is equivalent to driving between 12 and 82 miles per day during this period (94–126 days). California, Florida, Georgia, Indiana, and Pennsylvania are also in the same range of daily risk over 92–151 days. Conversely, the risk is higher in the UK and in the other 8 states in the USA (driving 106–483 miles per day) for the 92–111 days during which they have witnessed COVID-19 deaths. In India it was only 4 miles per day and in Mexico it was 79 miles per day.

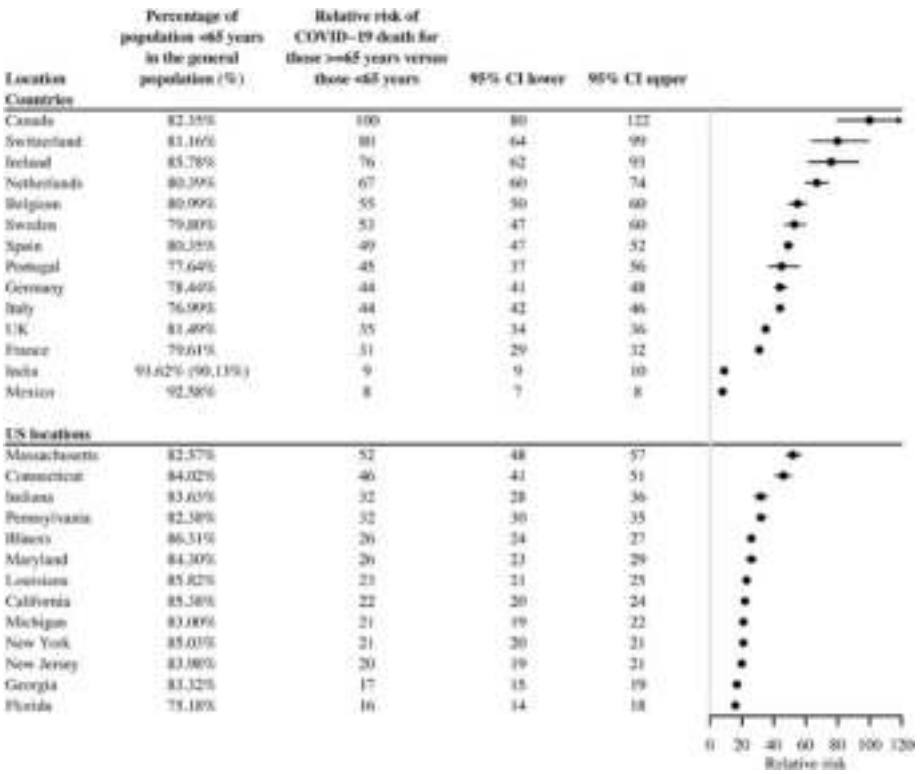

Fig. 2. Age distribution in the general population and relative mortality rate (relative risk of dying from COVID-19) for age ≥65 versus <65. For India, the value in parenthesis is for the group <60 years old, and relative mortality rate is given for ≥60 versus <60 years.

3.5. COVID-19 deaths in individuals <65 years old without underlying conditions

Data on deaths in patients <65 years old without any underlying conditions (comorbidities) were available for France, Italy, Mexico, Netherlands, Sweden, Georgia, and New York City. As shown in Table 4, the proportion of these deaths ranged from 0.7 to 3.6% of all COVID-19 deaths with the exception of Mexico that had a much higher percentage (17.7%). Excluding Mexico, the highest proportions were in France, Sweden, and Georgia. France data were based on deaths for which electronic death certificates were available, and completeness of death certificate information is unknown (Santé publique France, 2020). Data on Sweden were based on death counts that included also probable deaths without laboratory confirmation; moreover, only cardiovascular disease, hypertension, diabetes, and pulmonary disease were counted as comorbidities in this assessment, so it is possible that additional patients may have had other comorbidities (Socialstyrelsen, 2020).

The lowest percentage (0.65% of all COVID-19 deaths) was seen in New York City. Similarly low percentages (0.7% of all COVID-19 deaths) were seen in Italy and Netherlands based on more detailed medical chart review. In Italy, this review is done on a subset of the deaths (n = 917 as of April 2). In the Netherlands, information on underlying diseases is sought since April 10th only for those who died <70 years of age.

4. Discussion

The evaluation of data from 14 countries and 13 US locations that are epicenters of the COVID-19 pandemic shows that non-elderly people <65 years old represent a small fraction (4.5–11.2%) of all COVID-19 deaths in European countries and Canada and between 8.3% and 22.7% of all COVID-19 deaths in 13 US locations, even though this age group represents the majority of the general population. Conversely, in Mexico and India, most COVID-19 deaths occurred in the <65 age group. Overall, the risk of death is 15-100-fold lower in non-elderly people <65 years old than in older individuals in high-income countries and US states, but less than 10-fold lower in India and Mexico. The age-dependent risk gradient is modestly sharper in European countries and Canada versus most of the US locations. Regardless, the absolute risk of death in the non-elderly population is consistently very low even in these pandemic hotbeds. As of June 17, 2020, only 5 to 349 per million people in this age group have died with a COVID-19 diagnosis and the epidemic wave is practically complete in Europe and North America. Moreover, the vast majority of deaths in this age group occur in the age group 40–65 that comprises 37–48% of the population in the 0–65 years old bracket.

Unless there is a further peak of deaths downstream, the total risk of death for the entire epidemic wave in these locations may not be much larger than what has been documented as of June 17 (with the exception of Mexico and India), assuming a fairly symmetric epidemic wave, as in the case of Wuhan (World Health Organization, 2020). The risk observed in this first wave cannot be extrapolated to any future second wave, which is unknown whether it will exist and, if so, how high it might be.

For the whole COVID-19 fatality season to-date (starting with the date the first death was documented in each location), the average daily risk of dying from coronavirus for a person <65 years old is equivalent to the risk of dying driving a distance of 4–82 miles by car per day during that COVID-19 fatality season in 18 of the 27 hotbeds and 106–483 miles per day in the other 9 hotbeds (UK and 8 USA locations). For many hotbeds, the risk of death is in the same level roughly as dying from a car accident during daily commute, although it can be higher in the locations that are most hit. For example, the average commute is 31.5 miles per day for Americans according to the American Driving Survey (Kim et al., 2019) and 16.9 miles per day round trip in Sweden (Swedish National Mediation Office, 2019). The highest daily risk of COVID-19 death (in New Jersey) corresponds roughly to the risk of dying in a traffic accident while travelling daily from Manhattan to Washington, DC round trip for these 99 days of COVID-19 fatalities-period. We

Table 2
COVID-19 deaths, peak 7-day period for deaths, population count and absolute risk of COVID-19 death for age groups <65 (per million) and ≥80 (per thousand).

Location	Day of first documented COVID-19 death[a]	Peak 7-day COVID-19 death count as of June 17	Total COVID-19 deaths as of June 17 (n)[b]	Risk for people <65 (per million)	Risk for people ≥80 (per thousand)
Countries					
Belgium	Mar 10	Apr 7–13	9675	75	ND
Canada	Mar 9	Apr 30-May 6	8213	12	3.5
France	Feb 14	Apr 2–8	29575	64	ND
Germany	Mar 9	Apr 12–18	8830	10	1.0
India	Mar 12	June 11–17	11903	5[c]	ND
Ireland	Mar 11	Apr 19–25	1449	25	ND
Italy	Feb 22	Mar 27-Apr 2	33168	50	4.3
Mexico	Mar 19	June 3–9	18310	96	0.8
Netherlands	Mar 6	Mar 30-Apr 5	6074	26	4.6
Portugal	Mar 16	Apr 7–13	1523	14	1.5
Spain	Feb 13	Mar 27-Apr 2	27136	55	5.9
Sweden	Mar 10	Apr 9–15	5041	44	6.4
Switzerland	Mar 5	Apr 2–8	1678	12	2.6
UK	Feb 28	Apr 7–13	42153	86	ND
US locations					
California	Feb 6	Apr 18–24	5208	32	ND
Connecticut	Mar 17	Apr 20–26	4219	145	17.5
Florida	Mar 6	May 5–11	3018	29	0.6
Georgia	Mar 12	Apr 16–22	2575	65	1.4
Illinois	Mar 17	May 5–11	6485	117	8.8
Indiana	Mar 15	Apr 21–27	2289	56	3.3
Louisiana	Mar 14	Apr 5–11	2950	155	ND
Maryland	Mar 17	Apr 24–30	2866	96	4.6
Massachusetts	Mar 18	Apr 18–24	7734	111	11.3
Michigan	Mar 18	Apr 10–16	5792	132	5.0
New Jersey	Mar 11	Apr 15–21	12769	349	14.2
New York	Mar 14	Apr 7–13	24629	319	14.6
Pennsylvania	Mar 18	Apr 29-May 5	6319	75	5.8

Peak 7-day period of deaths is based on data as of June 17 (June 14 for Ireland and June 15 for Italy) and thus higher peaks and/or a second wave cannot be fully excluded. For France, Germany, Ireland, Italy, Portugal, Spain, Michigan, New Jersey, and New York only date of deaths reported were available, not actual date of death. ND: no data to allow calculation.

[a] Based on official reports or news articles, but cannot exclude earlier COVID-19 deaths that went undetected.

[b] Sources for total death counts are available in Supplementary Table 5.

[c] For India: risk for people <60 years (per million) since <65 was not available.

Table 3
Absolute risk of COVID-19 death expressed as equivalent of mortality rate from associated with motor vehicle driving over given distances.

Location	Road deaths per billion miles Travelled	Risk of COVID-19 death for <65 year old people as total miles travelled equivalent until June 17	Days with COVID-19 deaths (as of June 17)	Risk of COVID-19 death for <65 year old people as miles travelled per day equivalent
Countries				
Belgium	11.7	6388	100	64
Canada	8.2	1453	101	14
France	9.3	6888	125	55
Germany	6.8	1511	101	15
India	11.5[a]	416	98	4[b]
Ireland	6.1	4179	95	44
Italy	11.7[a]	4302	115	37
Mexico	13.4[a]	7178	91	79
Netherlands	7.6	3375	104	32
Portugal	11.7[a]	1171	94	12
Spain	6.8[a]	8143	126	65
Sweden	5.3	8211	100	82
Switzerland	5.1	2417	105	23
UK	5.5	15608	111	141
US locations				
California	10.2	3146	151	21
Connecticut	9.3	15632	93	168
Florida	14.1	2057	104	20
Georgia	11.4	5741	98	59
Illinois	9.6	12235	93	132
Indiana	10.5	5339	93	57
Louisiana	15.3	10155	96	106
Maryland	8.4	11390	93	122
Massachusetts	5.4	20601	92	224
Michigan	9.5	13889	92	151
New Jersey	7.3	47773	99	483
New York	7.6	42007	96	438
Pennsylvania	11.7	6449	92	70

[a] Approximation (see Methods, we welcome provision of any more precise estimates).

[b] For India: risk for people <60 years since <65 was not available.

Table 4
COVID-19 deaths in individuals <65 years old without underlying conditions.

Location (date report)	Deaths: total; age <65 (n)	Deaths assessed for comorbidities: total; age <65 (n)	Deaths with age <65 without comorbidities (n)	Percentage of deaths in age <65 without comorbidities[a]
Countries				
France (June 23)	29720; 2080	11071; 1071	307	2.0%
Italy (April 2)	12550; 1135	917; ND	6	0.7%
Mexico (June 26)	25779; 15035	25638; 14947	4535	17.7%
Netherlands (April 25)	4409; 257	2730; 204	23	0.7%
Sweden (June 24)	5082; 300	5082; 300	121	2.4%
US locations				
Georgia (June 26)	2770; 609	2089; 482	114	3.6%
New York City (June 26)	17753; 4681	15694; 4215	104	0.7%

ND: no data available.

[a] In the estimation, it is assumed that among deaths in patients <65, the presence of comorbidities is equally frequent in the patients whose medical records have not been assessed and in those whose medical records have been assessed.

provide raw data for diverse age groups (<40, 40–65, 65–80, >80), so that one can calculate risks in these age groups as well. People who are 40–65 years old may have about double the risk of the overall <65 age stratum, while those 40 years old or younger have almost no risk at all of dying. Moreover, females may have approximately 2-times lower risk than males (Williamson et al., 2020).

These risk estimates correspond to the main epicenters of the pandemic that accounted for almost 300,000 of the COVID-19 deaths as of June 17, 2020 and (with the exception of India and Mexico) exceeded 100 deaths per million inhabitants. The majority of countries around the world and the majority of states and cities in the USA have much lower fatality rates; in these places, the risk of death from COVID-19 this season for people <65 years old may typically be similar or even smaller to the risk of dying from a car accident during daily commute. We acknowledge that we cannot make any statement about the occurrence and magnitude of any second wave (e.g. in the fall/winter or next spring), but even for influenza the magnitude of the 2020–2021 wave is largely unpredictable.

The absolute mortality rate in an age group depends on the proportion of people infected and on the infection fatality rate in that age group. The proportion of people infected depends on the natural spread of the virus and the impact of preventive measures taken. The relative mortality rate between different age groups depends mostly on the difference in the infection fatality rate of these age groups and may also be modulated if preventive measures are taken that decrease exposure and spread in one age group more than in another. Most seroprevalence studies to-date suggest fairly similar rates of spread of the virus in different ae groups. But some exceptions may exist (Ioannidis, 2020b).

We should acknowledge that the risk estimates presented in our analysis integrate the composite effects of all the measures taken by the authorities in each location. Population-level mortality rates would have been different if no measure to limit disease transmission was taken. Absolute risks may be shaped by these preventive measures, although we have no "control" data to see what the risk would have been if some of these measures had not been taken or if different measures had been adopted. It is also likely that in most of the examined epicenters most of the preventive measures (e.g. lockdowns) were probably implemented horizontally, in the whole population, without substantial differences between age groups. If so, the relative population-level mortality rates (comparing young with elderly) may be more stable than absolute risk estimates. Nevertheless if specific measures focus more on protecting specific age-groups (e.g. focusing more on specifically protecting the elderly in the future), mortality rates in different age groups may change by different amounts and this may thus affect also the relative mortality rate estimates.

We should also acknowledge that most of the epicenters considered in this analysis are high-income countries with generally high life expectancy. For lower-income countries, the proportion of deaths among younger age strata appears substantially larger. This may reflect differences in life expectancy and age pyramids. For example, in India, life expectancy is almost a decade less than in the USA and almost 15 years less than in Switzerland, making octogenarians and nonagenarians few in relative terms. The overall population level mortality rate across all age groups is much lower compared with the other epicenters we analyzed; thus the absolute population risk of death for non-elderly individuals in India is extremely low. For Mexico, the proportion of elderly people is higher than India but still very low (<8% above 65).

Some caveats about the data need to be discussed. Even though mortality is an unambiguous endpoint, attribution of death to a specific cause is often challenging and definitions of "COVID-19 death" vary across countries and sometimes even change within countries over time. For example, the presented age-stratified data on Canada do not seem to include deaths that happened outside the hospitals. Different countries and US locations differ on the threshold of including deaths at care homes. For example, in Belgium, 53% of deaths come from care homes, but 94% of them have not had laboratory confirmation (Rankin et al., 2020). Several US locations have also started counting also "probable" deaths without any COVID-19 laboratory confirmation, a debatable practice at best. On the other hand, this may be defended as a justified approach since in some locations testing was not available or not performed. Overall, some COVID-19 deaths may be missed, and others may be overcounted. Different death tallies are derived by different sites, e.g. CDC (Centers for Disease Control and Prevention, 2020a) and the popular Worldometer site. (Worldometer.info) Arbitration and proper calibration of death counts may need to await careful, in depth medical chart review and autopsy efforts. Under- and over-counting may be responsible for some of the heterogeneity observed in risk estimates.

We should also acknowledge that we focused on mortality risk and not on hospitalizations. Empirical experience shows that COVID-19 has the potential to overwhelm specific hospitals (e.g. Lombardy, Queens or Bronx), especially in settings where hospitals run close to maximum capacity even under regular circumstances, and when they serve high risk populations in cities with high population density and major congregations in mass events. Therefore, hospital preparedness is essential, regardless of whether the risk of death is very low in the general population. Similarly, work modeling hospital bed needs is useful. However, for understanding the risk of individuals from the general population, the analogy against deaths by motor vehicle accidents is still relevant, since motor vehicle accidents also result in many more people who require hospitalizations and who suffer major injuries beyond the numbers of those who die.

The mortality rate estimates that we calculated may also be corroborated by the perusal of patterns of excess mortality in the general population during the period of COVID-19 fatalities. For example, data from 24 European countries (EUROMOMO, 2020) show that in the 11 weeks between week 10 and week 21 in 2020, the excess of deaths increased by 13780 deaths in the <65 years age category and by 152418 deaths in the older age category. Therefore, the excess deaths in the <65 years category accounted for 8.3% of the total excess, a number very compatible with the 4.5–11.2% figure observed in the 11 European countries that we analyzed. However, one should be cautious in this comparison, because changes in other causes of deaths may also affect the magnitude of the overall excess during this period. In fact, there is concern that COVID-19 measures may have taken a toll on other causes of death, e.g. people with heart attacks may fear for coming to hospitals for treatment (Krumholtz, 2020; Metzler et al., 2020).

The large majority of the deaths in non-elderly individuals occur in patients who have underlying diseases. Based on existing data to-date (Guan et al., 2020; Wang et al., 2020a; World Health Organization, 2020), cardiovascular disease, hypertension, chronic obstructive pulmonary disease and severe asthma, diabetes, kidney failure, severe liver disease, immunodeficiency, and malignancy may confer an increased risk of adverse outcome. Individuals with these diseases should consider that their risk may be higher than average and rigorous prognostic models need to be developed to estimate with accuracy this increased risk. In non-elderly populations, the more prevalent of these conditions is cardiovascular disease and hypertension, with prevalence of approximately 10% in the 20–39 age group and 38% in the 40–59 age group in the USA (Yazdanyar and Newman, 2009) and similarly high percentages in many other countries. We encourage public health authorities to start reporting systematically data separately on each of the major comorbidities according to age strata. Some data are available for the prevalence of these conditions across all age groups of COVID-19 deaths. Data from the UK from the OpenSafely study suggest that hypertension alone does not increase the risk of death, while uncontrolled diabetes, controlled diabetes, severe asthma, and chronic heart disease increases the risk 2.36-, 1.50-, 1.27- and 1.25 -fold (Williamson et al., 2020).

We could retrieve data from 7 locations on the COVID-19 mortality of people who were both <65 years old and had no underlying diseases. Consistently, the data suggest that these deaths are remarkably uncommon in high-income countries, although their exact percentage contribution to all COVID-19 deaths varies modestly across locations

(0.7–3.6%). It is likely that much of this variability may reflect differences on how underlying conditions are captured. We also caution that some people with no recorded comorbidities may have had some underlying diseases, but these where not reported in a crisis setting, or these conditions may have been undiagnosed. Overall, this further strengthens the notion that for healthy non-elderly people, the risk of dying from COVID-19 in the first half of 2020 was very small. This is in stark contrast with many news stories that focus on the demise of young people and the panic and horror that these widely reverberated stories are causing (Hundreds of young America, 2020; WHO says, 2020). Conversely, the available data from Mexico suggest that one out of six deaths were in people <65 and without underlying conditions (Secretaría de Salud, 2020). This may primarily reflect a different age-pyramid, although additional reasons might be deleterious effects of deprivation, lower access to health services, or higher rates of undiagnosed conditions in lower-income countries. It is very important for authorities in all countries and US locations to report carefully curated data on comorbidities and related death rates.

Another interesting observation is the higher share of deaths in the <65 years old group in most of the US locations as opposed to the European countries. This pattern requires further investigation, but it may reflect unfavorable socioeconomic circumstances for victims of COVID-19 in the USA. It is important to study in more detail the socioeconomic profile of the COVID-19 victims, but preliminary data show that deaths cluster in areas with high levels of poverty and underprivileged populations and ethnic/racial minorities are over-represented among the victims (Centers for Disease Control and Prevention, 2020b). Some mostly low-wage occupations, including essential jobs, also may be prone to more exposure risk than other jobs where working remotely is feasible. COVID-19 may thus be yet another disease with a profile dependent on inequalities and generating even more inequalities. The difference in the proportion of deaths in people <65 years old across different US locations may be due to chance, or may reflect genuine differences in the proportion of deaths occurring in nursing homes and/or the proportion of deaths occurring in younger populations of disadvantaged people, differences in reporting of COVID-19 deaths, or other unclear reasons. Of interest, influenza deaths seem to have a similar difference in age distribution between the USA and European countries like Italy: a larger proportion of influenza deaths in the USA tend to be in the <65 age group (Estimated Influenza, 2018), as compared with Italy (Rosano et al., 2019). Of course, a major difference between influenza and COVID-19 is that the latter typically does not cause deaths in otherwise healthy children, in contrast to influenza (Wang et al., 2020b).

The vast majority of COVID-19 victims are elderly people and in all European countries analyzed as well as Canada and most US locations, more than half and up to three quarters are at least 80 years old. The median age of death for COVID-19 tends to be similar or slightly smaller than the life expectancy of the population in each respective location. In several locations, large clusters of deaths come from nursing home facilities. Data from European countries suggest that 42–57% of all deaths have happened in care homes (Booth, 2020) and many deaths in the US have also occurred in nursing homes (Nursing Homes and Assisted, 2020). Moreover, the differentiation between dying "with" SARS-CoV-2 versus dying "from" SARS-CoV-2 may be difficult to make, and the vast majority of patients with COVID-19 have comorbidities and these could also contribute to the fatal outcome or may be even more important than SARS-CoV-2 in causing the death (Boccia et al., 2020). Nursing homes and hospitalized patients (nosocomial infection) appear to account for a lion's share of COVID-19 mortality. Overall, the loss of quality-adjusted life-years from COVID-19 may be much smaller than a crude reading of the number of deaths might suggest, once these features are accounted for.

The data that we have compiled allow to estimate also absolute risks of death in the highest risk group, i.e. elderly individuals ≥80 years old in these hot epicenters of the pandemic. These are markedly higher than the risks of death in individuals <65 years old. However, the absolute risk of death even in this highest age category to-date barely reach up to 1.75% in the most hit location and in several locations it is lower than 1 in a thousand. Nevertheless, these risks are clearly high enough to warrant high alert. They suggest that, no matter what strategy is selected for addressing COVID-19 in the current or future epidemic waves should include special emphasis in protecting very elderly individuals.

Knowledge of relative and absolute risks for different population strata are instrumental for carefully choosing next steps. Lockdowns have been implemented in many countries and this was a fully justified initial "better safe than sorry" approach in the absence of good data. However, long-term lockdowns may have major adverse consequences for health (suicides, domestic violence, worsening mental health, cardiovascular disease, loss of health insurance from unemployment, and famine, to name a few) and also creating new major issues for society at large (Krumholtz, 2020; COVID's Other casualties, 2020; Docherty et al., 2020; Sud et al., 2020; Moser et al., 2020; Parmet and Sinha, 2020). Lockdowns originally aimed to save the health care system, but as patients avoid coming to the hospitals for common, treatable problems (De filippo et al., 2020), deaths may rise from non-treatment; also hospitals face an emerging crisis also leading to their demise. It is even argued that lockdowns may be even harmful as a response to COVID-19 itself, if they broaden rather than flatten the epidemic curve (Wittkowski, 2020). Information from seroprevalence and universal screening studies suggest that the frequency of infections is much larger than the documented cases and thus the overall infection fatality rate is likely to be much lower than previously thought (Ioannidis, 2020b; Bendavid et al., 2020; Shakiba et al., 2020; Iwata et al., 2020). It seems that the majority of infections are either asymptomatic or mildly symptomatic and thus do not come to medical attention (Gudbjartsson et al., 2020). These data also suggest that the infection fatality rate may be close to that of a severe influenza season (<0.2%) when the health system does not collapse and when massive nosocomial infections and nursing home spread are averted. Conversely, high infection fatality rates are seen when hospitals are overrun, and when there are massive death loads from nosocomial-infected hospitalized patients and nursing home residents. Therefore, the finding of very low risk in the vast majority of the general population has major implications for strategic next steps in managing the COVID-19 pandemic. Tailored measures that maintain social life and the economy functional to avoid potentially even deaths from socioeconomic disruption, plus effective protection of select high-risk individuals (in particular in hospitals and nursing homes) may be a sensible option. Draconian measures of hygiene and infection control and universal, repeated testing of personnel in hospital and care facilities may achieve drastic reductions in deaths. Concurrently, the vast majority of the population may be reassured that their risks are very low.

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Data sharing

All data used are in the manuscript and its supplements.

Declaration of competing interest

None.

CRediT authorship contribution statement

John P.A. Ioannidis: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Project administration. **Cathrine Axfors:** Conceptualization, Software, Formal analysis, Investigation, Data curation, Writing - review & editing. **Despina G. Contopoulos-Ioannidis:** Conceptualization, Methodology, Investigation, Data curation, Writing - review & editing.

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Appendix A. Supplementary data

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Canadian Motor Vehicle Traffic Collision Statistics: 2018

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Introduction

Transport Canada's National Collision Database (NCDB) contains data on all reportable motor vehicle collisions in Canada that the provinces and territories provide each year.

The federal, provincial, and territorial governments in Canada work to improve road safety to reduce the number of fatalities and serious injuries and to have the safest roads in the world. The year 2018 saw an increase in the number of fatalities and injuries, however serious injuries went down. 2018 marked the sixth consecutive year with a fatality count below 2,000 and remains among the lowest counts for all three of these casualty groups since these data were first collected by Transport Canada in the early 1970's.

- In 2018, the number of motor vehicle fatalities was 1,922; up 3.6% from 2017 (1,856).
- The number of serious injuries decreased to 9,494 in 2018; down 6.1% from 2017 (10,107).
- The number of fatalities per 100,000 population increased slightly to 5.2 in 2018 (from 5.0 in 2017), yet is still the second lowest on record.
- The number of fatalities per billion vehicle kilometres travelled slightly increased to 4.9 in 2018 (from 4.8 in 2017); also the second lowest recorded

Collisions and Casualties - 1999-2018

	Collisions		Victims		
Year	Fatal [1]	Personal Injury [2]	Fatalities [3]	Serious Injuries [4]	Injuries [5] (Total)
1999	2,632	148,683	2,980	16,187	218,457
2000	2,548	153,290	2,904	15,581	222,848
2001	2,415	149,023	2,758	15,296	216,542
2002	2,583	153,832	2,921	15,894	222,665
2003	2,487	150,493	2,777	15,110	216,123
2004	2,438	145,150	2,735	15,572	206,104
2005	2,551	145,559	2,898	15,792	204,701
2006	2,586	142,517	2,871	16,044	199,976
2007	2,455	138,615	2,753	14,410	192,745
2008	2,193	127,571	2,431	12,851	176,394
2009	2,007	123,449	2,216	11,955	170,770

Year	Collisions		Victims		
	Fatal [1]	Personal Injury [2]	Fatalities [3]	Serious Injuries [4]	Injuries [5] (Total)
2010	2,021	123,615	2,238	11,796	172,081
2011	1,849	122,350	2,023	10,940	167,741
2012	1,848	122,834 [r]	2,075	11,104	166,727 [r]
2013	1,772	120,371	1,951 [r]	10,662 [r]	164,525
2014	1,675 [r]	114,618 [r]	1,841 [r]	10,445 [r]	156,558 [r]
2015	1,695 [r]	117,846 [r]	1,889 [r]	10,855 [r]	161,061 [r]
2016	1,737 [r]	116,534 [r]	1,899 [r]	10,564 [r]	158,791 [r]
2017	1,694 [r]	112,714 [r]	1,856 [r]	10,107 [r]	152,772 [r]
2018	1,743	108,371	1,922	9,494	152,847

Footnotes

1 "Fatal collisions" include all reported motor vehicle crashes that resulted in at least one death, where death occurred within 30 days of the collision, except in Quebec before 2007 (eight days).

2 "Personal injury collisions" include all reported motor vehicle crashes which resulted in at least one injury but not death within 30 days of the collision, except in Quebec before 2007 (eight days).

3 "Fatalities" include all those who died as a result of a reported traffic collision within 30 days of its occurrence, except in Quebec before 2007 (eight days).

4 "Serious Injuries" include persons admitted to hospital for treatment or observation. Serious injuries were estimated from 1999 to 2018 because several jurisdictions under-reported these numbers.

5 "Total Injuries" include all reported severities of injuries ranging from minimal to serious.

r Revised.

Fatalities and Injuries by Age Group - 2018

Age Group (yrs)	Fatalities	Serious Injuries	Injuries (Total)
0 - 4	19	141	2,975
5 - 14	36	277	5,952
15 - 19	124	752	12,700
20 - 24	204	1,022	17,064
25 - 34	303	1,667	28,819
35 - 44	250	1,273	23,269
45 - 54	255	1,303	22,159
55 - 64	287	1,184	18,808
65 +	430	1,306	17,378

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Age Group (yrs)	Fatalities	Serious Injuries	Injuries (Total)
Not stated	14	101	3,723
Total	**1,922**	**9,026**	**152,847**

Fatalities by Road User Class 2014-2018

Road User Class	2014	2015	2016	2017	2018
# Drivers	907 [r]	908 [r]	875 [r]	957 [r]	960
% Drivers	49.3 [r]	48.1 [r]	46.1 [r]	51.6 [r]	49.9
# Passengers	342 [r]	356 [r]	338 [r]	317 [r]	340
% Passengers	18.6 [r]	18.8 [r]	17.8 [r]	17.1 [r]	17.7
# Pedestrians	304 [r]	299 [r]	355 [r]	302 [r]	332
% Pedestrians	16.5 [r]	15.8	18.7 [r]	16.3 [r]	17.3
# Bicyclists	42	49	49 [r]	40 [r]	44
% Bicyclists	2.3	2.6	2.6 [r]	2.2 [r]	2.3
# Motorcyclists [*]	191 [r]	211 [r]	214 [r]	197 [r]	200
% Motorcyclists	10.4 [r]	11.2 [r]	11.3 [r]	10.6 [r]	10.4
# Not stated/Other	55 [r]	66 [r]	68 [r]	43 [r]	46
% Not stated/Other	3.0 [r]	3.5 [r]	3.6 [r]	2.3 [r]	2.4
# Total	**1,841 [r]**	**1,889 [r]**	**1,899 [r]**	**1,856 [r]**	**1,922**
% Total	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

Footnotes

* Includes moped riders.

r Revised.

Fatalities 1999-2018

Year	Fatalities
1999	2,980
2000	2,904
2001	2,758
2002	2,921
2003	2,777
2004	2,735
2005	2,898
2006	2,871
2007	2,753
2008	2,431
2009	2,216
2010	2,238
2011	2,023
2012	2,075
2013	1,951 r

Year	Fatalities
2014	1,841 [r]
2015	1,889 [r]
2016	1,899 [r]
2017	1,856 [r]
2018	1,922

Fatality Rate (per 10,000 motor vehicles registered)

Year	Fatality Rate
1999	1.70
2000	1.62
2001	1.52
2002	1.57
2003	1.47
2004	1.43
2005	1.50
2006	1.43
2007	1.34
2008	1.15
2009	1.04
2010	1.02
2011	0.91

Year	Fatality Rate
2012	0.93
2013	0.85
2014	0.78 r
2015	0.79
2016	0.78
2017	0.76 r
2018	0.77

Footnote

r Revised.

Casualty Rates - 2018

	Per 100,000 Population [1]		Per Billion Vehicle-Kilometres [2]		Per 100,000 Licensed Drivers	
	Fatalities	Injuries	Fatalities	Injuries	Fatalities	Injuries
Canada	5.2	412.4	4.9	391.1	7.2	575.0
NL	7.4	517.0	7.2	498.9	6.6	460.8
PE	9.8	424.2	9.6	415.6	13.2	573.8

	Per 100,000 Population [1]		Per Billion Vehicle-Kilometres [2]		Per 100,000 Licensed Drivers	
	Fatalities	Injuries	Fatalities	Injuries	Fatalities	Injuries
NS	7.8	747.8	6.3	603.5	10.2	978.9
NB	6.5	348.3	5.6	301.1	9.0	484.3
QC	4.3	418.9	4.5	444.1	6.4	622.1
ON	4.2	356.9	4.1	347.4	5.8	491.3
MB	5.2	891.7	4.6	791.6	7.6	1,310.0
SK	11.0	361.9	8.6	284.0	15.8	517.5
AB	6.8	396.9	4.5	265.8	9.0	530.0
BC	5.6	393.4	6.9	477.5	8.0	555.7
YT	15.7	444.5	10.1	284.5	24.1	681.1
NT	4.5	224.5	4.7	235.8	7.6	382.5
NU	5.2	65.1	48.8	609.8	74.2	928.0

Footnotes

1 Statistics Canada, Annual Demographic Estimates: Canada, Provinces and Territories, 2019, Catalogue No. 91-215-X.

2 Statistics Canada, 'Canadian Vehicle Survey', Catalogue No. 53-223-XIE.

Notes: Vehicle kilometres travelled data were not available for 2018 so they were estimated using average yearly change for the years 2015-2017

Data for Ontario and Alberta are preliminary for 2018. Data for New Brunswick were estimated.

Changes in how traffic collision reports are collected in Manitoba resulted in an increased number of injuries of a minimal nature being captured in 2018.

Newfoundland and Labrador data reflects information contained in the Vehicle Collision Reports received and processed as of June 1, 2019.

Rate-based data in smaller jurisdictions have a high level of fluctuation due to their small sample size.

Percentage of Fatalities and Serious Injuries by Road User Class - 2018

Road User Class	Fatalities	Serious Injuries
Drivers	49.9	46.9
Passengers	17.7	19.0
Pedestrians	17.3	15.5
Bicyclists	2.3	4.0
Motorcyclists *	10.4	12.1
Not Stated/Other	2.4	2.5
Total	**100.0**	**100.0**

Footnote

* Includes moped riders.

Percentage of Driver and Passenger Fatalities and Serious Injuries Where Victims Were Not Using Seat Belts 2014-2018

Drivers

	2014	2015	2016	2017	2018
Fatalities	26.2	28.7	29.6	27.4	29.4
Serious Injuries	11.8	10.4	9.8	10.6	10.8

Passengers

	2014	2015	2016	2017	2018
Fatalities	33.2	27.6	25.6	31.1	32.1
Serious Injuries	17.7	17.4	15.4	16.9	18.4

Note: "Serious Injuries" include victims admitted to hospital for treatment or observation.

Number of Collisions By Location - 2018

Location	Fatal	Personal Injury

Location	Fatal	Personal Injury
Urban [1]	767	79,349
Rural [2]	952	26,458
Not stated	24	2,564
Total	**1,743**	**108,371**

Footnotes

1 Urban includes:

a. metropolitan roads and streets and other urban areas, or
b. a speed limit at the collision site of 60 km/h or less.

2 Rural includes:

a. primary or secondary highways, as well as local roads, or
b. a speed limit at the collision site exceeding 60 km/h.

Note: In Alberta, New Brunswick, Manitoba, and Saskatchewan, "urban" includes any area within the corporate boundaries of a city, town, village or hamlet. "Rural" includes any area outside of what is defined as “Urban”.

Percentage of Driver and Passenger Fatalities and Serious Injuries by Age Group - 2018

	Fatalities	Serious Injuries

Age Group (yrs)	Drivers	Fatalities Passengers	Drivers	Serious Injuries Passengers

Age Group (yrs)	Drivers	Passengers	Drivers	Passengers
0 - 4	0.0	3.5	0.1	4.3
5 - 14	0.0	6.7	0.1	7.8
15 - 19	5.3	11.1	6.9	14.0
20 - 24	11.2	13.5	10.9	13.6
25 - 34	17.8	17.8	20.5	16.8
35 - 44	14.8	8.5	16.9	9.3
45 - 54	14.8	9.1	16.4	9.2
55 - 64	15.5	10.5	13.9	9.4
65 +	20.6	17.8	14.2	12.5
Not Stated	0.0	1.5	0.1	3.1
Total	**100.0**	**100.0**	**100.0**	**100.0**

Number of Licensed Drivers by Gender and by Age - 2018

Age Group (yrs)	Males	Females	Total
< 16	27,978	24,400	52,378
16 - 19	595,997	550,424	1,146,421
20 - 24	1,038,827	939,866	1,978,693
25 - 34	2,355,211	2,244,570	4,599,781

Age Group (yrs)	Males	Females	Total
35 - 44	2,310,446	2,260,037	4,570,483
45 - 54	2,337,348	2,242,405	4,579,752
55 - 64	2,408,462	2,290,010	4,698,472
65 +	2,596,983	2,359,949	4,956,932
Not Stated	81	81	162
Total	**13,671,332**	**12,911,741**	**26,583,073**

Licensed Drivers and Motor Vehicle Registrations by Type of Vehicle 1999-2018 (in thousands)

	Licensed Drivers [1]	Light-Duty Vehicles [2]	Commercial Vehicles [3]	Motorcycles [4]
1999	20,934	16,538	722	274
2000	20,593	16,832	739	311
2001	20,879	17,055	729	318
2002	21,163	17,543	724	350
2003	21,436	17,755	740	373
2004	21,673	17,920	752	409
2005	21,937	18,124	786	443
2006	22,278	18,739	841	485
2007	22,606	19,199	872	522
2008	22,972	19,613	907	567

	Licensed Drivers [1]	Light-Duty Vehicles [2]	Commercial Vehicles [3]	Motorcycles [4]
2009	23,198	19,877	915	595
2010	23,541	20,268	964	616
2011	23,831	20,608	1,008	631
2012	24,147	20,652	1,053	661
2013	24,630	21,262	1,072	672
2014	24,914	21,730	1,121	688
2015	25,273	22,068	1,147	709
2016	25,580	22,410	1,144	716
2017	26,004	22,678	1,168	721
2018	26,583	23,137	1,194	730

Footnotes

1 Excludes temporary permits prior to 1999.

2 Pre-1999, these registrations include passenger automobiles. From 1999, light-duty vehicles include passenger type vehicles (automobiles, passenger vans), light trucks and vans (less than 4 500 kg).

3	Pre-1999, these registrations include trucks, buses and other commercial vehicles, such as vans. From 1999, these registrations include commercial vehicles (trucks and buses) greater than 4 500 kg.
4	Includes mopeds.

Source: the motor vehicle registration data are from Statistics Canada, CANSIM, Table 405-0004. From 1999 the licensed driver data were provided by each jurisdiction.

> Note: A reduced level of police reporting in British Columbia since 2008 has affected the British Columbia totals and, to a lesser extent, national totals reported in this publication.

To find out more about national road safety programs or initiatives, call Transport Canada toll free at 1-800-333-0371 or e-mail us at mvs-sa@tc.gc.ca.

You can also visit our web site at www.tc.gc.ca/motor-vehicle-safety or the Canadian Council of Motor Transport Administrators' web site at www.ccmta.ca.

More detailed motor vehicle collision data can be queried using the National Collision Database (NCDB) On-Line tool located at www.tc.gc.ca/vehicleCollisions.

> **Did you find this information helpful?**

Transport Canada is closely monitoring the COVID-19 situation. In response, we have issued some **transportation-related measures and guidance**. Please check if any of these measures apply to you.

You may experience longer than usual wait times or partial service interruptions. If you cannot get through, please **contact us by email**.

For information on COVID-19 updates, please visit **Canada.ca/coronavirus**.

Date modified:
2020-12-01

Check for updates

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Asymptomatic transmission of covid-19

What we know, and what we don't

Allyson M Pollock, [1] James Lancaster[2]

The UK's £100bn "Operation Moonshot" to roll out mass testing for covid-19 to cities and universities around the country raises two key questions. How infectious are people who test positive but have no symptoms? And, what is their contribution to transmission of live virus?

Unusually in disease management, a positive test result is the sole criterion for a covid-19 case. Normally, a test is a support for clinical diagnosis, not a substitute. This lack of clinical oversight means we know very little about the proportions of people with positive results who are truly asymptomatic throughout the course of their infection and the proportions who are paucisymptomatic (subclinical), presymptomatic (go on to develop symptoms later), or post-infection (with viral RNA fragments still detectable from an earlier infection).

Earlier estimates that 80% of infections are asymptomatic were too high and have since been revised down to between 17% and 20% of people with infections.[1 2] Studies estimating this proportion are limited by heterogeneity in case definitions, incomplete symptom assessment, and inadequate retrospective and prospective follow-up of symptoms, however.[3] Around 49% of people initially defined as asymptomatic go on to develop symptoms.[4 5]

It's also unclear to what extent people with no symptoms transmit SARS-CoV-2. The only test for live virus is viral culture. PCR and lateral flow tests do not distinguish live virus. No test of infection or infectiousness is currently available for routine use.[6-8] As things stand, a person who tests positive with any kind of test may or may not have an active infection with live virus, and may or may not be infectious.[9]

The relations between viral load, viral shedding, infection, infectiousness, and duration of infectiousness are not well understood. In a recent systematic review, no study was able to culture live virus from symptomatic participants after the ninth day of illness, despite persistently high viral loads in quantitative PCR diagnostic tests. However, cycle threshold (Ct) values from PCR tests are not direct measures of viral load and are subject to error.[10]

While viral load seems to be similar in people with and without symptoms, the presence of RNA does not necessarily represent transmissible live virus. The duration of viral RNA shedding (interval between first and last positive PCR result for any sample) is shorter in people who remain asymptomatic, so they are probably less infectious than people who develop symptoms.[11]

Viral culture studies suggest that people with SARS-CoV-2 can become infectious one to two days before the onset of symptoms and continue to be infectious up to seven days thereafter; viable virus is relatively short lived.[7] Symptomatic and presymptomatic transmission have a greater role in the spread of SARS-CoV-2 than truly asymptomatic transmission.[1 2 12 13]

The transmission rates to contacts within a specific group (secondary attack rate) may be 3-25 times lower for people who are asymptomatic than for those with symptoms.[1 12 14 15] A city-wide prevalence study of almost 10 million people in Wuhan found no evidence of asymptomatic transmission.[16] Coughing, which is a prominent symptom of covid-19, may result in far more viral particles being shed than talking and breathing, so people with symptomatic infections are more contagious, irrespective of close contact.[17] On the other hand, asymptomatic and presymptomatic people may have more contacts than symptomatic people (who are isolating), underlining the importance of hand washing and social distancing measures for everyone.

Missed opportunity

By failing to integrate testing into clinical care, we have missed an important opportunity to better understand the role of asymptomatic infection in transmission. Given the variation in prevalence and testing strategies by region, the proportions of people with positive and negative test results should be published alongside the purpose of the testing strategy and the population tested (screening healthy populations in schools, universities, and health and social care, or testing people with symptoms). Government regulations on recording the age, ethnicity, sex, and place of residence of people with positive results must also be followed.[18]

Searching for people who are asymptomatic yet infectious is like searching for needles that appear and reappear transiently in haystacks, particularly when rates are falling.[19] Mass testing risks the harmful diversion of scarce resources. A further concern is the use of inadequately evaluated tests as screening tools in healthy populations.[20]

The UK's testing strategy needs to be reset in line with the Scientific Advisory Group for Emergencies' recommendation that "Prioritising rapid testing of symptomatic people is likely to have a greater impact on identifying positive cases and reducing transmission than frequent testing of asymptomatic people in an outbreak area."[21]

Testing should be reintegrated into clinical care with clinical and public health oversight and case definitions based on clinical diagnosis. Carefully designed prospective studies of cases and contacts are needed to estimate transmission rates by people

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with and without symptoms. These should include careful investigations of outbreaks—for example, testing all contacts of people with a clear history of exposure, especially in high risk environments such as nursing homes, prisons, and other institutional settings.

Coronavirus infection surveys by the Office for National Statistics[22] and the REACT survey[23] could be expanded to include clinical follow-up of participants combined with tests of viral load and viral cultures. The absence of strong evidence that asymptomatic people are a driver of transmission is another good reason for pausing the roll out of mass testing in schools, universities, and communities.

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PLOS MEDICINE

RESEARCH ARTICLE

Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta-analysis

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Data Availability Statement: The file listing all included studies and files used for all analyses are available from the Harvard Dataverse database.

Abstract

Background

There is disagreement about the level of asymptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We conducted a living systematic review and meta-analysis to address three questions: (1) Amongst people who become infected with SARS-CoV-2, what proportion does not experience symptoms at all during their infection? (2) Amongst people with SARS-CoV-2 infection who are asymptomatic when diagnosed, what proportion will develop symptoms later? (3) What proportion of SARS-CoV-2 transmission is accounted for by people who are either asymptomatic throughout infection or presymptomatic?

Methods and findings

We searched PubMed, Embase, bioRxiv, and medRxiv using a database of SARS-CoV-2 literature that is updated daily, on 25 March 2020, 20 April 2020, and 10 June 2020. Studies of people with SARS-CoV-2 diagnosed by reverse transcriptase PCR (RT-PCR) that documented follow-up and symptom status at the beginning and end of follow-up or modelling studies were included. One reviewer extracted data and a second verified the extraction, with disagreement resolved by discussion or a third reviewer. Risk of bias in empirical studies was assessed with an adapted checklist for case series, and the relevance and credibility of modelling studies were assessed using a published checklist. We included a total of 94 studies. The overall estimate of the proportion of people who become infected with SARS-CoV-2 and remain asymptomatic throughout infection was 20% (95% confidence interval [CI] 17–25) with a prediction interval of 3%–67% in 79 studies that addressed this review question. There was some evidence that biases in the selection of participants influence the estimate. In seven studies of defined populations screened for SARS-CoV-2 and then

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Competing interests: I have read the journal's policy and the authors of this manuscript have the following competing interests: GS has participated in two scientific meetings for Merck and Biogen. NL is a member of the PLOS Medicine editorial board.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; CrI, credibility interval; E, number of secondary transmission events; F, female; GI, generation interval; IQR, interquartile range; M, male; NR, not reported; RT-PCR, reverse transcriptase PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; USA, United States of America.

followed, 31% (95% CI 26%–37%, prediction interval 24%–38%) remained asymptomatic. The proportion of people that is presymptomatic could not be summarised, owing to heterogeneity. The secondary attack rate was lower in contacts of people with asymptomatic infection than those with symptomatic infection (relative risk 0.35, 95% CI 0.10–1.27). Modelling studies fit to data found a higher proportion of all SARS-CoV-2 infections resulting from transmission from presymptomatic individuals than from asymptomatic individuals. Limitations of the review include that most included studies were not designed to estimate the proportion of asymptomatic SARS-CoV-2 infections and were at risk of selection biases; we did not consider the possible impact of false negative RT-PCR results, which would underestimate the proportion of asymptomatic infections; and the database does not include all sources.

Conclusions

The findings of this living systematic review suggest that most people who become infected with SARS-CoV-2 will not remain asymptomatic throughout the course of the infection. The contribution of presymptomatic and asymptomatic infections to overall SARS-CoV-2 transmission means that combination prevention measures, with enhanced hand hygiene, masks, testing tracing, and isolation strategies and social distancing, will continue to be needed.

Author summary

Why was this study done?

- The proportion of people who will remain asymptomatic throughout the course of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), is not known.
- Studies that assess people at just one time point will overestimate the proportion of true asymptomatic infection because those who go on to develop COVID-19 symptoms will be wrongly classified as asymptomatic rather than presymptomatic.
- The amount, and infectiousness, of asymptomatic SARS-CoV-2 infection will determine what kind of measures will prevent transmission most effectively.

What did the researchers do and find?

- We did a living systematic review through 10 June 2020, using automated workflows that speed up the review processes and allow the review to be updated when relevant new evidence becomes available.
- Overall, in 79 studies in a range of different settings, 20% (95% confidence interval [CI] 17%–25%, prediction interval 3%–67%) of people with SARS-CoV-2 infection remained asymptomatic during follow-up, but biases in study designs limit the certainty of this estimate.
- In seven studies of defined populations screened for SARS-CoV-2 and then followed, 31% (95% CI 26%–37%, prediction interval 24%–38%) remained asymptomatic.

- We found some evidence that SARS-CoV-2 infection in contacts of people with asymptomatic infection is less likely than in contacts of people with symptomatic infection (relative risk 0.35, 95% CI 0.10–1.27).

What do these findings mean?

- The findings of this living systematic review suggest that most people who become infected with SARS-CoV-2 will not remain asymptomatic throughout the course of infection.
- Future studies should be designed specifically to determine the true proportion of asymptomatic SARS-CoV-2 infections, using methods to minimise biases in the selection of study participants and ascertainment of symptom status during follow-up.
- The contribution of presymptomatic and asymptomatic infections to overall SARS-CoV-2 transmission means that combination prevention measures, with enhanced hand hygiene, masks, testing tracing, and isolation strategies and social distancing, will continue to be needed.

Introduction

There is ongoing discussion about the level of asymptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The authors of a narrative review report a range of proportions of participants positive for SARS-CoV-2 but asymptomatic in different studies from 6% to 96% [1]. The discrepancy results, in part, from the interpretation of studies that report a proportion of asymptomatic people with SARS-CoV-2 detected at a single point. The studies cited include both people who will remain asymptomatic throughout and those, known as presymptomatic, who will develop symptoms of coronavirus disease 2019 (COVID-19) if followed up [2]. The full spectrum and distribution of COVID-19, from completely asymptomatic, to mild and nonspecific symptoms, viral pneumonia, respiratory distress syndrome, and death, are not yet known [3]. Without follow-up, however, the proportions of asymptomatic and presymptomatic infections cannot be determined.

Accurate estimates of the proportions of true asymptomatic and presymptomatic infections are needed urgently because their contribution to overall SARS-CoV-2 transmission at the population level will determine the appropriate balance of control measures [3]. If the predominant route of transmission is from people who have symptoms, then strategies should focus on testing, followed by isolation of infected individuals and quarantine of their contacts. If, however, most transmission is from people without symptoms, social distancing measures that reduce contact with people who might be infectious should be prioritised, enhanced by active case-finding through testing of asymptomatic people.

The objectives of this study were to address three questions: (1) Amongst people who become infected with SARS-CoV-2, what proportion do not experience symptoms at all during their infection? (2) Amongst people with SARS-CoV-2 infection who are asymptomatic when diagnosed, what proportion will develop symptoms later? (3) What proportion of SARS-CoV-2 transmission is accounted for by people who are either asymptomatic throughout infection or presymptomatic?

Methods

We conducted a living systematic review, a systematic review that provides an online summary of findings and is updated when relevant new evidence becomes available [4]. The review follows a published protocol (https://osf.io/9ewys/), which describes in detail the methods used to speed up review tasks [5] and to assess relevant evidence rapidly during a public health emergency [6]. The first two versions of the review have been published as preprints [7,8]. We report our findings according to the statement on preferred reporting items for systematic reviews and meta-analyses (S1 PRISMA Checklist) [9]. Ethics committee review was not required for this study. Box 1 shows our definitions of symptoms, asymptomatic infection, and presymptomatic status. We use the term asymptomatic SARS-CoV-2 infection for people without symptoms of COVID-19 who remain asymptomatic throughout the course of infection. We use the term presymptomatic for people who do not have symptoms of COVID-19 when enrolled in a study but who develop symptoms during adequate follow-up.

Box 1. Definitions of symptoms and symptom status in a person with SARS-CoV-2 infections

Symptoms: symptoms that a person experiences and reports. We used the authors' definitions. We searched included manuscripts for an explicit statement that the study participant did not report symptoms that they experienced. Some authors defined 'asymptomatic' as an absence of self-reported symptoms. We did not include clinical signs observed or elicited on examination.

Asymptomatic infection: a person with laboratory-confirmed SARS-CoV-2 infection, who has no symptoms, according to the authors' report, at the time of first clinical assessment and had no symptoms at the end of follow-up. The end of follow-up was defined as any of the following: virological cure, with one or more negative reverse transcriptase PCR (RT-PCR) test results; follow-up for 14 days or more after the last possible exposure to an index case; follow-up for 7 days or more after the first RT-PCR positive result.

Presymptomatic: a person with laboratory-confirmed SARS-CoV-2 infection, who has no symptoms, according to the authors' report, at the time of first clinical assessment but who developed symptoms by the end of follow-up. The end of follow-up was defined as any of the following: virological cure, with one or more negative RT-PCR test results; follow-up for 14 days or more after the last possible exposure to an index case; follow-up for 7 days or more after the first RT-PCR positive result.

Information sources and search

We conducted the first search on 25 March 2020 and updated it on 20 April and 10 June 2020. We searched the COVID-19 living evidence database [10], which is generated using automated workflow processes [5] to (1) provide daily updates of searches of four electronic databases (Medline PubMed, Ovid Embase, bioRxiv, and medRxiv), using medical subject headings and free-text keywords for SARS-CoV-2 infection and COVID-19; (2) de-duplicate the records; (3) tag records that are preprints; and (4) allow searches of titles and abstracts using Boolean operators. We used the search function to identify studies of asymptomatic or presymptomatic SARS-CoV-2 infection using a search string of medical subject headings and free-text

keywords (S1 Text). We also examined articles suggested by experts and the reference lists of retrieved mathematical modelling studies and systematic reviews. Reports from this living rapid systematic review will be updated at 3-monthly intervals, with continuously updated searches.

Eligibility criteria

We included studies in any language of people with SARS-CoV-2 diagnosed by RT-PCR that documented follow-up and symptom status at the beginning and end of follow-up or investigated the contribution to SARS-CoV-2 transmission of asymptomatic or presymptomatic infection. We included contact-tracing investigations, case series, cohort studies, case-control studies, and statistical and mathematical modelling studies. We excluded the following study types: case reports of a single patient and case series in which participants were not enrolled consecutively. When multiple records included data from the same study population, we linked the records and extracted data from the most complete report.

Study selection and data extraction

Reviewers worked in pairs to screen records using an application programming interface in the electronic data capture system (REDCap, Vanderbilt University, Nashville, TN, USA). One reviewer selected potentially eligible studies and a second reviewer verified all included and excluded studies. We reported the identification, exclusion, and inclusion of studies in a flowchart (S1 Fig). The reviewers determined which of the three review questions each study addressed, using the definitions in Box 1. One reviewer extracted data using a pre-piloted extraction form in REDCap, and a second reviewer verified the extracted data using the query system. A third reviewer adjudicated on disagreements that could not be resolved by discussion. We contacted study authors for clarification when the study description was insufficient to reach a decision on inclusion or if reported data in the manuscript were internally inconsistent. The extracted variables included, but were not limited to, study design, country and/or region, study setting, population, age, primary outcomes, and length of follow-up. From empirical studies, we extracted raw numbers of individuals with any outcome and its relevant denominator. From statistical and mathematical modelling studies, we extracted proportions and uncertainty intervals reported by the authors.

The primary outcomes for each review question were (1) proportion with asymptomatic SARS-CoV-2 infection who did not experience symptoms at all during follow-up; (2) proportion with SARS-CoV-2 infections who did not have symptoms at the time of testing but developed symptoms during follow-up; (3) estimated proportion (with uncertainty interval) of SARS-CoV-2 transmission accounted for by people who are asymptomatic or presymptomatic. A secondary outcome for review question 3 was the secondary attack rate from asymptomatic or presymptomatic index cases.

Risk of bias in included studies

Two authors independently assessed the risk of bias. A third reviewer resolved disagreements. For observational epidemiological studies, we adapted the Joanna Briggs Institute Critical Appraisal Checklist for Case Series [11]. The adapted tool included items about inclusion criteria, measurement of asymptomatic status, follow-up of course of disease, and statistical analysis. We added items about selection biases affecting the study population from a tool for the assessment of risk of bias in prevalence studies [12]. For mathematical modelling studies, we used a checklist for assessing relevance and credibility [13].

Synthesis of the evidence

We used the 'metaprop' and 'metabin' functions from the 'meta' package (version 4.11–0) [14] in R (version 3.5.1) to display the study findings in forest plots and synthesise their findings. The 95% confidence intervals (CIs) for each study are estimated using the Clopper-Pearson method [15]. We examined heterogeneity visually in forest plots. We stratified studies according to the methods used to identify people with asymptomatic SARS-CoV-2 infection and the study setting. To synthesise proportions from comparable studies, in terms of design and population, we used stratified random-effects meta-analysis. For the stratified and overall summary estimates, we calculated prediction intervals, to represent the likely range of proportions that would be obtained in subsequent studies conducted in similar settings [16]. We calculated the secondary attack rate as the number of cases among contacts as a proportion of all close contacts ascertained. We did not account for potential clustering of contacts because the included studies did not report the size of clusters. We compared the secondary attack rate from asymptomatic or presymptomatic index cases with that from symptomatic cases. If there were no events in a group, we added 0.5 to each cell in the 2 × 2 table. We used random-effects meta-analysis with the Mantel-Haenszel method to estimate a summary risk ratio (with 95% CI).

Results

The living evidence database contained a total of 25,538 records about SARS-CoV-2 or COVID-19 by 10 June 2020. The searches for studies about asymptomatic or presymptomatic SARS-CoV-2 on 25 March, 20 April, and 10 June resulted in 89, 230, and 688 records for screening (S1 Fig). In the first version of the review [7], 11 articles were eligible for inclusion [17–27], version 2 [8] identified another 26 eligible records [28–53], and version 3 identified another 61 eligible records [54–114]. After excluding four articles for which more recent data became available in a subsequent version [25,29,30,35], the total number of articles included was 94 (S1 Table) [17–24,26–28,31–34,36–114]. The types of evidence changed across the three versions of the review (S1 Table). In the first version, six of 11 studies were contact investigations of single-family clusters with a total of 39 people. In the next versions, study designs included larger investigations of contacts and outbreaks, screening of defined groups, and studies of hospitalised adults and children. Across all three review versions, data from 79 empirical observational studies were collected in 19 countries or territories (Tables 1 and 2) and included 6,832 people with SARS-CoV-2 infection. Forty-seven of the studies, including 3,802 infected people, were done in China (S2 Table). At the time of their inclusion in the review, 23 of the included records were preprints; six of these had been published in peer-reviewed journals by 17 July 2020 [19,20,27,81,82,106].

Proportion of people with asymptomatic SARS-CoV-2 infection

We included 79 studies that reported empirical data about 6,616 people with SARS-CoV-2 infection (1,287 defined as having asymptomatic infection) [17,18,21–23,26–28,31,32,34,36,39–45,47–50,52–54,56–62,64,66–68,70–77,79–90,92–112,114] and one statistical modelling study [24] (Table 1). The sex distribution of the people with asymptomatic infection was reported in 41/79 studies, and the median age was reported in 35/79 studies (Table 1). The results of the studies were heterogeneous (S2 Fig). We defined seven strata, according to the method of selection of asymptomatic status and study settings. Study findings within some of these strata were more consistent (Fig 1). We considered the statistical modelling study of passengers on the *Diamond Princess* cruise ship passengers [24] separately, because of the different

Table 1. Characteristics of studies reporting on proportion of asymptomatic SARS-CoV-2 infections.

Author	Country, location	Total SARS-CoV-2, *n*	Asymptomatic SARS-CoV-2, *n*	Sex of asymptomatic people	Age of asymptomatic people, years, median	Follow-up method[a]
Contact investigation, single						
Tong, ZD [44]	China, Zhejiang	5	3	2 F, 3 M	28 IQR 12–41	1, 3
Huang, R [74]	China, Suqian	2	1	1 F, 0 M	54	3
Jiang, XL [76]	China, Shandong	8	3	3 F, 0 M	35 IQR 0–53	3
Jiang, X [75]	China, Chongqing	3	1	1 F, 0 M	8	2
Liao, J [22]	China, Chongqing	12	3	NR	NR	1, 2
Hu, Z [21]	China, Nanjing	4	1	0 F, 1 M	64	2, 3
Luo, SH [23]	China, Anhui	4	1	1 F, 0 M	50	1, 2, 3
Chan, JF [18]	China, Guangdong	5	1	0 F, 1 M	10	1
Ye, F [49]	China, Sichuan	5	1	0 F, 1 M	28	1, 2
Bai, Y [17]	China, Anyang	6	1	1 F, 0 M	20	1
Luo, Y [85]	China, Wuhan	6	5	NR	37 IQR 7–62	1
Zhang, J [50]	China, Wuhan and Beijing	5	2	1 F, 1 M	NR	2
Zhang, B [110]	China, Guangdong	7	2	0 F, 2 M	13.5 IQR 13–14	3
Huang, L [73]	China, Gansu	7	2	2 F, 0 M	44 IQR 38.5–49.5	2
Qian, G [26]	China, Zhejiang	8	2	1 F, 1 M	30.5 IQR 1–60	1, 2
Gao, Y [70]	China, Wuxi	15	6	3 F, 3 M	50 IQR 48–51	1, 2
Contact investigation, aggregated						
Hijnen, D [72]	Germany	11	1	0 F, 1 M	49	1
Brandstetter, S [62]	Germany	36	2	NR	NR	2
Zhang, W2 [111]	China, Guiyang	12	4	NR	NR	1, 2, 3
Cheng, HY [66]	Taiwan	22	4	NR	NR	1
Wang, Z [47]	China, Wuhan	47	4	NR	NR	1
Wu, J [105]	China, Zhuhai	83	8	NR	NR	1, 2
Luo, L [36]	China, Guangzhou	129	8	NR	NR	1, 2, 3
Bi, Q [60]	China, Shenzhen	87	17	NR	NR	2, 3
Yang, R [108]	China, Wuhan	78	33	22 F, 11 M	37 IQR 26–45	3
Outbreak investigation						
Danis, K [32]	France	13	1	NR	NR	1, 2
Böhmer, MM [61]	Germany	16	1	NR	NR	1
Roxby, AC [94]	USA	6	3	NR	NR	1
Yang, N [48]	China, Xiaoshan	10	2	1 F, 1 M	NR	1, 2
Schwierzeck, V [95]	Germany	12	2	NR	NR	2
Arons, MM [58]	USA	47	3	NR	NR	2
Park, SY [90]	South Korea	97	4	NR	NR	2
Dora, AV [68]	USA	19	6	0 F, 6 M	75 IQR 72–75	3
Tian, S [43]	China, Shandong	24	7	NR	NR	3
Solbach, W [97]	Germany	97	10	NR	NR	2
Graham, N [71]	United Kingdom	126	46	NR	NR	2

(*Continued*)

Table 1. (Continued)

Author	Country, location	Total SARS-CoV-2, *n*	Asymptomatic SARS-CoV-2, *n*	Sex of asymptomatic people	Age of asymptomatic people, years, median	Follow-up method[a]
Pham, TQ [100]	Vietnam	208	89	NR	31 IQR 23–45	2
Screening of defined population						
Hoehl, S [34]	Germany	2	1	0 F, 1 M	58	2
Chang, L [31]	China, Wuhan	4	2	0 F, 2 M	45 IQR 37–53	2
Arima, Y [28]	Japan	12	4	NR	NR	1, 2
Rivett, L [93]	United Kingdom	30	5	NR	NR	2
Treibel, TA [101]	United Kingdom	44	12	NR	NR	2
Lavezzo, E [81]	Italy	73	29	NR	NR	2
Lombardi, A [82]	Italy	138	41	NR	NR	3
Hospitalised adults						
Pongpirul, WA [39]	Thailand	11	1	1 F, 0 M	66	2, 3
Zou, L [53]	China, Zhuhai	18	1	1 M, 0 M	26	1
Qiu, C [92]	China, Hunan	104	5	NR	NR	2
Zhou, R [114]	China, Guangdong	31	9	NR	NR	3
Chang, MC [64]	South Korea	139	10	4 F, 6 M	NR	1, 2
Zhou, X [52]	China, Shanghai	328	10	NR	NR	1, 2, 3
Angelo Vaira, L [57]	Italy	345	10	NR	NR	3
Wang, X [45]	China, Wuhan	1012	14	NR	NR	1, 2
Wong, J [103]	Brunei	138	16	NR	NR	2, 3
Xu, T [107]	China, Jiangsu	342	15	5 F, 10 M	27 IQR 17–36	2, 3
London, V [83]	USA	68	22	22 F, 0 M	30.5 IQR 24.5–34.8	2
Tabata, S [27]	Japan[b]	104	33	18 F, 15 M	70 IQR 57–75	2
Andrikopoulou, M [56]	USA	158	46	46 F, 0 M	NR	1, 2
Noh, JY [89]	South Korea	199	53	NR	NR	3
Kumar, R [80]	India, New Delhi	231	108	18 F, 90 M	NR	2, 3
Hospitalised children						
See, KC [41]	Malaysia	4	1	0 F, 1 M	9	1, 2, 3
Tan, YP [42]	China, Changsha	10	2	1 F, 1 M	8	2, 3
Tan, X [99]	China, Changsha	13	2	2 F, 0 M	5 IQR 2–8	1, 2, 3
Melgosa, M [87]	Spain	16	3	NR	NR	1, 2
Wu, HP [104]	China, Jiangxi	23	3	NR	NR	3
Song, W [98]	China, Hubei	16	8	3 F, 5 M	11 IQR 7–12	1, 2
Bai, K [59]	China, Chongqing	25	8	NR	NR	3
Xu, H [106]	China, Guizhou	32	11	4 F, 7 M	NR	1, 2
Qiu, H [40]	China, Zhejiang	36	10	NR	NR	1, 2, 3
Lu, Y [84]	China, Wuhan	110	29	12 F, 17 M	7 IQR 6–11	2, 3
Hospitalised adults and children						
Merza, MA [88]	Iraqi Kurdistan	15	6	NR	NR	2, 3
Yongchen, Z [109]	China, Jiangsu	21	5	2 F, 3 M	25 IQR 14–54	1, 2, 3

(*Continued*)

Table 1. (Continued)

Author	Country, location	Total SARS-CoV-2, *n*	Asymptomatic SARS-CoV-2, *n*	Sex of asymptomatic people	Age of asymptomatic people, years, median	Follow-up method[a]
Ma, Y [86]	China, Shandong	47	11	5 F, 6 M	23 IQR NR	2
Kim, SE [77]	South Korea	71	10	6 F, 4 M	31 IQR 21–55	2
Choe, PG [67]	South Korea	113	15	17 F, 8 M	NR	3
Sharma, AK [96]	India, Jaipur	234	215	NR	NR	1, 2, 3
Zhang, W3 [112]	China, Guiyang	137	26	12 F, 14 M	24 IQR 12–36	1, 2
Alshami, AA [54]	Saudi Arabia	128	69	36 F, 33 M	NR	2, 3
Kong, W [79]	China, Sichuan	473	45	NR	NR	1, 2
Wang, Y2 [102]	China, Chongqing	279	63	29 F, 34 M	39 IQR 27–53	3

[a]Follow-up according to protocol (1: 14 days after last possible exposure; 2: 7 days after diagnosis; 3: until negative RT-PCR result).

[b]People of different nationalities taken from *Diamond Princess* cruise ship to a hospital in Japan.

Abbreviations: F, female; IQR, interquartile range; M, male; NR, not reported; RT-PCR, reverse transcriptase PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; USA, United States of America

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method of analysis and overlap with the study population reported by Tabata and colleagues [27].

The main risks of bias across all categories of empirical studies were in the selection and enrolment of people with asymptomatic infection and mismeasurement of asymptomatic status because of absent or incomplete definitions (S3 Fig). Sources of bias specific to studies in particular settings are discussed with the relevant results.

The overall estimate of the proportion of people who become infected with SARS-CoV-2 and remain asymptomatic throughout the course of infection was 20% (95% CI 17%–25%, 79 studies), with a prediction interval of 3%–67% (Fig 1). One statistical modelling study was based on data from all 634 passengers from the *Diamond Princess* cruise ship with RT-PCR positive test results [24]. The authors adjusted for the proportion of people who would develop symptoms (right censoring) in a Bayesian framework to estimate that, if all were followed up until the end of the incubation period, the probability of asymptomatic infections would be 17.9% (95% credibility interval [CrI] 15.5%–20.2%).

The summary estimates of the proportion of people with asymptomatic SARS-CoV-2 infection differed according to study setting, although prediction intervals for all groups overlapped. The first three strata in Fig 1 involve studies that reported on different types of contact investigation, which start with an identified COVID-19 case. The studies reporting on single-family clusters (21 estimates from 16 studies in China, $n = 102$ people with SARS-CoV-2) all included at least one asymptomatic person [17,18,21–23,26,44,49,50,70,73–76,85,110]. The summary estimate was 34% (95% CI 26%–44%, prediction interval 25%–45%). In nine studies that reported on close contacts of infected individuals and aggregated data from clusters of both asymptomatic and symptomatic people with SARS-CoV-2 the summary estimate was 14% (95% CI 8%–23%, prediction interval 2%–53%) [36,47,60,62,66,72,105,108,111]. We included 12 studies ($n = 675$ people) that reported on outbreak investigations arising from a single symptomatic person or from the country's first imported cases of people with COVID-19 [32,43,48,58,61,68,71,90,94,95,97,100]. Four of the outbreaks involved nursing homes [58,68,71,94] and four involved occupational settings [43,61,90,95]. The summary estimate of

Table 2. Characteristics of studies that measured the proportion of people with SARS-CoV-2 infection that develops symptoms.

Author	Country, location	Total asymptomatic SARS-CoV-2, *n*	Develop symptoms after testing, *n*	Sex of asymptomatic people at time of testing	Age of asymptomatic people at time of testing, years, median	Follow-up method[a]
Contact investigation, single						
Ye, F [49]	China, Sichuan	3	2	0 F, 3 M	28 IQR 23–50	1, 2
Zhang, B [110]	China, Guangdong	4	2	0 F, 4 M	34 IQR 33–35	3
Huang, L [73]	China, Gansu	4	2	3 F, 1 M	44.5 IQR 34.50–54.25	2
Jiang, XL [76]	China, Shandong	5	2	3 F, 2 M	35 IQR 35–37	3
Hu, Z [21]	China, Nanjing	24	5	NR	NR	2, 3
Contact investigation, aggregated						
Zhang, W2 [111]	China, Guangzhou	12	8	NR	NR	1, 2, 3
Outbreak investigation						
Schwierzeck, V [95]	Germany	6	4	NR	NR	2
Park, SY [90]	South Korea	8	4	NR	NR	2
Arons, MM [58]	USA	27	24	NR	NR	2
Dora, AV [68]	USA	14	8	0 F, 14 M	NR	3
Graham, N [71]	United Kingdom	54	8	NR	NR	1
Screening of defined population						
Hoehl, S [34]	Germany	2	1	1 F, 1 M	51	2
Rivett, L [93]	United Kingdom	6	1	NR	NR	2
Chang, L [31]	China, Wuhan	4	2	1 F, 3 M	39.5 IQR 29–47.5	2
Arima, Y [28]	Japan	5	2	NR	NR	1, 2
Lytras, T [37]	Greece	39	4	NR	NR	2
Lavezzo, E [81]	Italy	39	10	NR	NR	2
Hospitalised adults						
Al-Shamsi, HO [55]	United Arab Emirates	7	7	5 F, 2 M	51.6 IQR 40–76	3
Luo, SH [23]	China, Anhui	8	7	NR	NR	1, 2, 3
Zhou, X [52]	China, Shanghai	13	3	7 F, 6 M	NR	2, 3
Zhou, R [114]	China, Guangdong	31	22	NR	NR	3
Wang, X [45]	China, Wuhan	30	16	NR	NR	1, 2
Tabata, S [27]	Cruise Ship	43	10	24 F, 19 M	69 IQR 60.5–75	2
Wang, Y1 [46]	China, Shenzhen	55	43	NR	49 IQR 2–69	3
Meng, H [38]	China, Wuhan	58	16	NR	NR	2
Andrikopoulou, M [56]	USA	63	16	63 F, 0 M	NR	1, 2
Zhang, Z [113]	China, Shenzhen	56	33	33 F, 23 M	NR	2, 3
Wong, J [103]	Brunei	138	42	NR	NR	2, 3
Hospitalised children						

(*Continued*)

Table 2. (Continued)

Author	Country, location	Total asymptomatic SARS-CoV-2, *n*	Develop symptoms after testing, *n*	Sex of asymptomatic people at time of testing	Age of asymptomatic people at time of testing, years, median	Follow-up method[a]
See, KC [41]	Malaysia	2	1	0 F, 2 M	5 IQR 1–9	1, 2, 3
Hospitalised adults and children						
Kim, SE [77]	South Korea	13	3	7 F, 6 M	31 IQR 20.5–51.5	2
Choe, PG [67]	South Korea	54	39	32 F, 22 M	NR	3
Kong, W [79]	China, Sichuan	62	17	NR	NR	1

[a]Follow-up according to protocol (1: 14 days after possible exposure; 2: 7 days after diagnosis; 3: until one or more negative RT-PCR result).

[b]People of different nationalities taken from *Diamond Princess* cruise ship to a hospital in Japan.

[c]Until hospital discharge or negative RT-PCR.

Abbreviations: F, female; IQR, interquartile range; M, male; NR, not reported; RT-PCR, reverse transcriptase PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; USA, United States of America

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the proportion of asymptomatic SARS-CoV-2 infections was 18% (95% CI 10%–28%, prediction interval 2%–64%).

In seven studies, people with SARS-CoV-2 infection were detected through screening of all people in defined populations who were potentially exposed (303 infected people amongst 10,090 screened) [28,31,34,81,82,93,101]. The screened populations included healthcare workers [82,93,101]; people evacuated from a setting where SARS-CoV-2 transmission was confirmed, irrespective of symptom status [28,34]; the whole population of one village in Italy [81]; and blood donors [31]. In these studies, the summary estimate of the proportion asymptomatic was 31% (95% CI 26%–37%, prediction interval 24%–38%). There is a risk of selection bias in studies of certain groups, such as healthcare workers and blood donors, because people with symptoms are excluded [31,82,93,101], or from nonresponders in population-based screening [81]. Retrospective symptom ascertainment could also increase the proportion determined asymptomatic [81,82,101].

The remaining studies, in hospital settings, included adult patients only (15 studies, $n = 3{,}228$) [27,39,45,52,53,56,57,64,80,83,89,92,103,107,114], children only (10 studies, $n = 285$) [40–42,59,84,87,98,99,104,106], or adults and children (10 studies, $n = 1{,}518$) [54,67,77,79,86,88,96,102,109,112] (Table 1, Fig 1). The types of hospital and clinical severity of patients differed, including settings in which anyone with SARS-CoV-2 infection was admitted for isolation and traditional hospitals.

Proportion of presymptomatic SARS-CoV-2 infections

We included 31 studies in which the people with no symptoms of COVID-19 at enrolment were followed up, and the proportion that develops symptoms is defined as presymptomatic (Table 2, Fig 2) [21,27,28,31,34,37,38,41,45,46,49,52,55,56,58,67,68,71,73,76,77,79,81,90,93,95,103,110,111,113,114]. Four studies addressed only this review question [37,38,55,113]. The findings from the 31 studies were heterogeneous (S4 Fig), even when categorised according to the method of selection of asymptomatic participants, and we did not estimate a summary measure (Fig 2).

Additional analyses

We investigated heterogeneity in the estimates of the proportion of asymptomatic SARS-CoV-2 infections in subgroup analyses that were not specified in the original protocol. In studies of

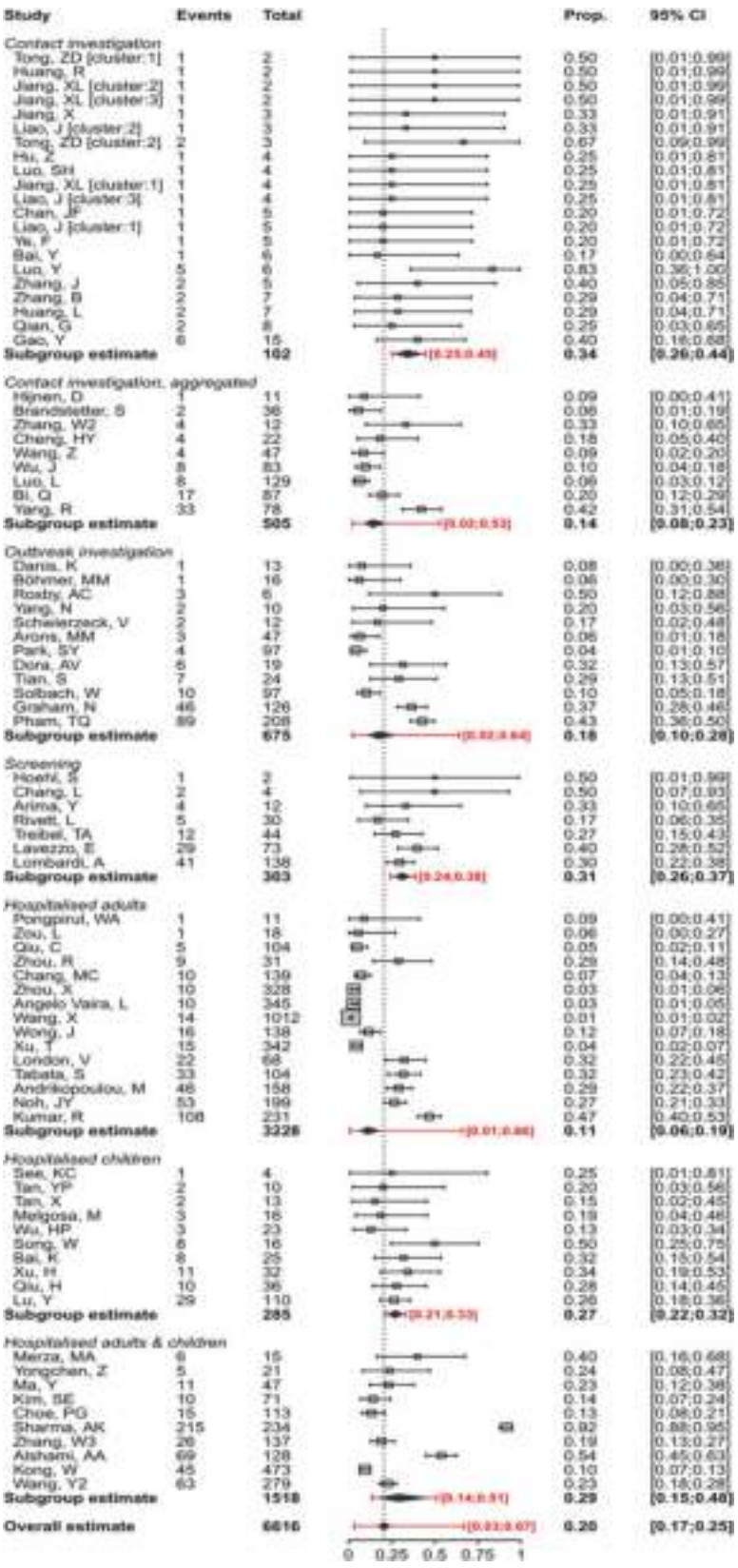
Study
Events
Total
Prop.
95% CI
Contact investigation
Tong, ZD [cluster:1] 1 2 0.50 [0.01;0.99]
Huang, R 1 2 0.50 [0.01;0.99]
Jiang, XL [cluster:2] 1 2 0.50 [0.01;0.99]
Jiang, XL [cluster:3] 1 2 0.50 [0.01;0.99]
Jiang, X 1 3 0.33 [0.01;0.91]
Liao, J [cluster:2] 1 3 0.33 [0.01;0.91]
Tong, ZD [cluster:2] 2 3 0.67 [0.09;0.99]
Hu, Z 1 4 0.25 [0.01;0.81]
Luo, SH 1 4 0.25 [0.01;0.81]
Jiang, XL [cluster:1] 1 4 0.25 [0.01;0.81]
Liao, J [cluster:3] 1 4 0.25 [0.01;0.81]
Chan, JF 1 5 0.20 [0.01;0.72]
Liao, J [cluster:1] 1 5 0.20 [0.01;0.72]
Ye, F 1 5 0.20 [0.01;0.72]
Bai, Y 1 6 0.17 [0.00;0.64]
Luo, Y 5 6 0.83 [0.36;1.00]
Zhang, J 2 5 0.40 [0.05;0.85]
Zhang, B 2 7 0.29 [0.04;0.71]
Huang, L 2 7 0.29 [0.04;0.71]
Qian, G 2 8 0.25 [0.03;0.65]
Gao, Y 6 15 0.40 [0.16;0.68]
Subgroup estimate 102 0.34 [0.26;0.44]
Contact investigation, aggregated
Hijnen, D 1 11 0.09 [0.00;0.41]
Brandstetter, S 2 36 0.06 [0.01;0.19]
Zhang, W2 4 12 0.33 [0.10;0.65]
Cheng, HY 4 22 0.18 [0.05;0.40]
Wang, Z 4 47 0.09 [0.02;0.20]
Wu, J 8 83 0.10 [0.04;0.18]
Luo, L 8 129 0.06 [0.03;0.12]
Bi, Q 17 87 0.20 [0.12;0.29]
Yang, R 33 78 0.42 [0.31;0.54]
Subgroup estimate 505 0.14 [0.08;0.23]
Outbreak investigation
Danis, K 1 13 0.08 [0.00;0.36]
Böhmer, MM 1 16 0.06 [0.00;0.30]
Rosby, AC 3 6 0.50 [0.12;0.88]
Yang, N 2 10 0.20 [0.03;0.56]
Schwierzeck, V 2 12 0.17 [0.02;0.48]
Arons, MM 3 47 0.06 [0.01;0.18]
Park, SY 4 97 0.04 [0.01;0.10]
Dora, AV 6 19 0.32 [0.13;0.57]
Tian, S 7 24 0.29 [0.13;0.51]
Solbach, W 10 97 0.10 [0.05;0.18]
Graham, N 46 126 0.37 [0.28;0.46]
Pham, TQ 89 208 0.43 [0.36;0.50]
Subgroup estimate 675 0.18 [0.10;0.28]
Screening
Hoehl, S 1 2 0.50 [0.01;0.99]
Chang, L 2 4 0.50 [0.07;0.93]
Arima, Y 4 12 0.33 [0.10;0.65]
Rivett, L 5 30 0.17 [0.06;0.35]
Treibel, TA 12 44 0.27 [0.15;0.43]
Lavezzo, E 29 73 0.40 [0.28;0.52]
Lombardi, A 41 138 0.30 [0.22;0.38]
Subgroup estimate 303 0.31 [0.26;0.37]
Hospitalised adults
Pongpirul, WA 1 11 0.09 [0.00;0.41]
Zou, L 1 18 0.06 [0.00;0.27]
Qiu, C 5 104 0.05 [0.02;0.11]
Zhou, R 9 31 0.29 [0.14;0.48]
Chang, MC 10 139 0.07 [0.04;0.13]
Zhou, X 10 328 0.03 [0.01;0.06]
Angelo Vaira, L 10 345 0.03 [0.01;0.05]
Wang, X 14 1012 0.01 [0.01;0.02]
Wong, J 16 138 0.12 [0.07;0.18]
Xu, T 15 342 0.04 [0.02;0.07]
London, V 22 68 0.32 [0.22;0.45]
Tabata, S 33 104 0.32 [0.23;0.42]
Andrikopoulou, M 46 158 0.29 [0.22;0.37]
Noh, JY 53 199 0.27 [0.21;0.33]
Kumar, R 108 231 0.47 [0.40;0.53]
Subgroup estimate 3228 0.11 [0.06;0.19]
Hospitalised children
See, KC 1 4 0.25 [0.01;0.81]
Tan, YP 2 10 0.20 [0.03;0.56]
Tan, X 2 13 0.15 [0.02;0.45]
Melgosa, M 3 16 0.19 [0.04;0.46]
Wu, HP 3 23 0.13 [0.03;0.34]
Song, W 8 16 0.50 [0.25;0.75]
Bai, K 8 25 0.32 [0.15;0.54]
Xu, H 11 32 0.34 [0.19;0.53]
Qiu, H 10 36 0.28 [0.14;0.45]
Lu, Y 29 110 0.26 [0.18;0.36]
Subgroup estimate 285 0.27 [0.22;0.32]
Hospitalised adults & children
Merza, MA 6 15 0.40 [0.16;0.68]
Yongchen, Z 5 21 0.24 [0.08;0.47]
Ma, Y 11 47 0.23 [0.12;0.38]
Kim, SE 10 71 0.14 [0.07;0.24]
Choe, PG 15 113 0.13 [0.08;0.21]
Sharma, AK 215 234 0.92 [0.88;0.95]
Zhang, W3 26 137 0.19 [0.13;0.27]
Alshami, AA 69 128 0.54 [0.45;0.63]
Kong, W 45 473 0.10 [0.07;0.13]
Wang, Y2 63 279 0.23 [0.18;0.28]
Subgroup estimate 1518 0.29 [0.15;0.48]
Overall estimate 6616 0.20 [0.17;0.25]
0
0.25
0.5
0.75
1

Fig 1. Forest plot of proportion ('Prop.') of people with asymptomatic SARS-CoV-2 infection, stratified by setting. In the setting 'Contact investigations', in which more than one cluster was reported, clusters are annotated with '[cluster]'. The diamond shows the summary estimate and its 95% CI. The red bar and red text show the prediction interval. CI, confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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hospitalised children, the point estimate was higher (27%, 95% CI 22%–32%, 10 studies) than in adults (11%, 95% CI 6%–19%, 15 studies) (Fig 1). The proportion of asymptomatic SARS--CoV-2 infection estimated in studies of hospitalised patients (35 studies, 19%, 95% CI 14%–25%) was similar to that in all other settings (44 studies, 22%, 95% CI 17%–29%, S5 Fig). To examine publication status, we conducted a sensitivity analysis, omitting studies that were identified as preprints at the time of data extraction (S6 Fig). The estimate of the proportion of asymptomatic infection in all settings (18%, 95% CI 14%–22%) and setting-specific estimates were very similar to the main analysis.

Contribution of asymptomatic and presymptomatic infection to SARS-CoV-2 to transmission

Five of the studies that conducted detailed contact investigations provided enough data to calculate a secondary attack rate according to the symptom status of the index cases (Fig 3) [36,65,66,90,111]. The summary risk ratio for asymptomatic compared with symptomatic was 0.35 (95% CI 0.1–1.27) and for presymptomatic compared with symptomatic people was 0.63 (95% CI 0.18–2.26) [66,90]. The risk of bias in ascertainment of contacts was judged to be low in all studies.

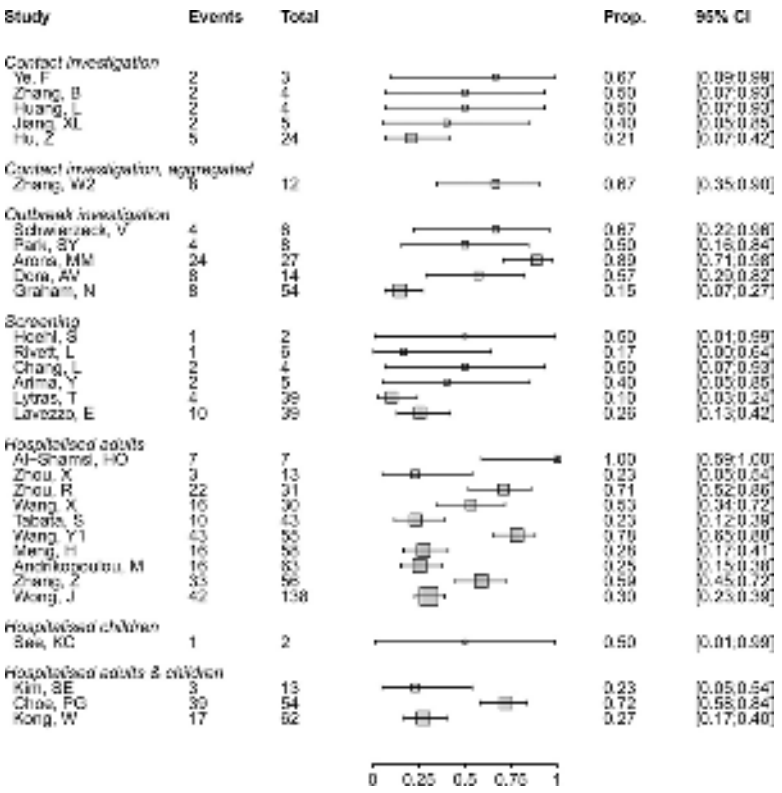

Fig 2. Forest plot of proportion ('Prop.') of people with presymptomatic SARS-CoV-2 infection, stratified by setting. CI, confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

https://doi.org/10.1371/journal.pmed.1003346.g002

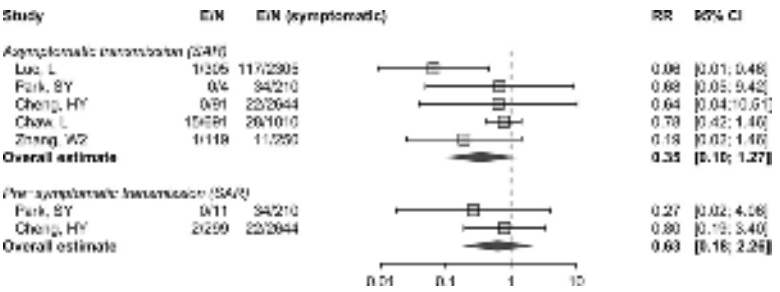

Fig 3. Forest plot of the RR and 95% CI of the SAR, comparing infections in contacts of asymptomatic and presymptomatic index cases with infections in contacts of symptomatic cases. The RR is on a logarithmic scale. CI, confidence interval; E, number of secondary transmission events; N, number of close contacts; RR, risk ratio; SAR, secondary attack rate.

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We included eight mathematical modelling studies (Fig 4) [19,20,33,51,63,69,78,91]. The models in five studies were informed by analysis of data from contact investigations in China, South Korea, Singapore, and the *Diamond Princess* cruise ship, using data to estimate the serial interval or generation time [19,20,33,69,78], and in three studies the authors used previously published estimates [51,63,91].

Estimates of the contributions of both asymptomatic and presymptomatic infections SARS-CoV-2 transmission were very heterogeneous. In two studies, the contributions to SARS-CoV-2 transmission of asymptomatic infection were estimated to be 6% (95% CrI 0%–57%) [19] and 69% (95% CrI 20%–85%) [69] (Fig 4). The estimates have large uncertainty intervals and the disparate predictions result from differences in the proportion of asymptomatic infections and relative infectiousness of asymptomatic infection. Ferretti and colleagues provide an interactive web application [19] that shows how these parameters affect the model results.

Models of the contribution of presymptomatic transmission used different assumptions about the durations and distributions of infection parameters such as incubation period,

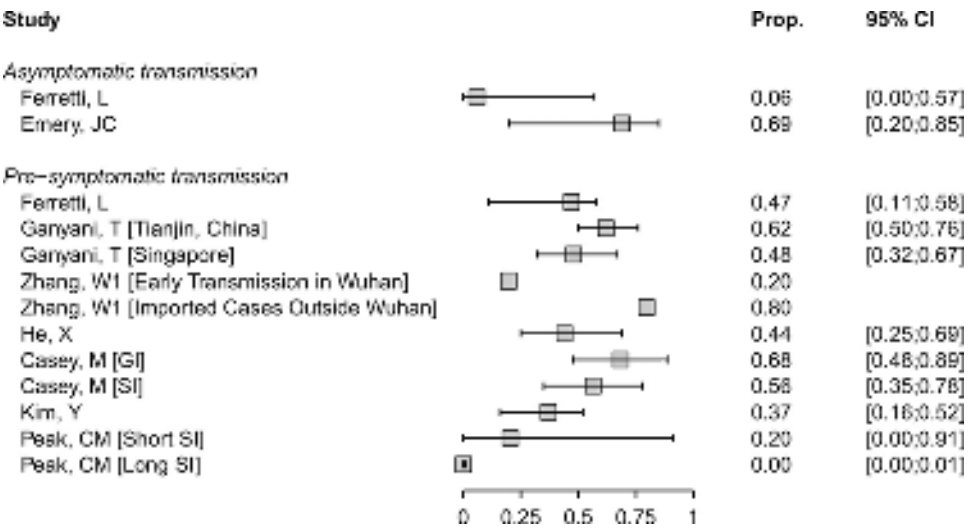

Fig 4. Forest plot of proportion ('Prop.') of SARS-CoV-2 infection resulting from asymptomatic or presymptomatic transmission. For studies that report outcomes in multiple settings, these are annotated in brackets. CI, confidence interval; GI, generation interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SI, serial interval.

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generation time, and serial interval [19,20,33,51,63,78,91]. In models that accounted for uncertainty appropriately, most estimates of the proportion of transmission resulting from people with SARS-CoV-2 who are presymptomatic ranged from 20% to 70%. In one study that estimated a contribution of <1% [91], the model-fitted serial interval was longer than observed in empirical studies [115]. The credibility of most modelling studies was limited by the absence of external validation. The data to which the models were fitted were generally from small samples (S7 Fig).

Discussion

Summary of main findings

The summary proportion of SARS-CoV-2 that is asymptomatic throughout the course of infection was estimated, across all study settings, to be 20% (95% CI 17%–25%, 79 studies), with a prediction interval of 3%–67%. In studies that identified SARS-CoV-2 infection through screening of defined populations, the proportion of asymptomatic infections was 31% (95% CI 26%–37%, 7 studies). In 31 studies reporting on people who are presymptomatic but who go on to develop symptoms, the results were too heterogeneous to combine. The secondary attack rate from asymptomatic infections may be lower than that from symptomatic infections (relative risk 0.35, 95% CI 0.1–1.27). Modelling studies estimated a wide range of the proportion of all SARS-CoV-2 infections that result from transmission from asymptomatic and presymptomatic individuals.

Strengths and weaknesses

A strength of this review is that we used clear definitions and separated review questions to distinguish between SARS-CoV-2 infections that remain asymptomatic throughout their course from those that become symptomatic and to separate proportions of people with infection from their contribution to transmission in a population. This living systematic review uses methods to minimise bias whilst increasing the speed of the review process [5,6] and will be updated regularly. We only included studies that provided information about follow-up through the course of infection, which allowed reliable assessment about the proportion of asymptomatic people in different settings. In the statistical synthesis of proportions, we used a method that accounts for the binary nature of the data and avoids the normality approximation (weighted logistic regression).

Limitations of the review are that most included studies were not designed to estimate the proportion of asymptomatic SARS-CoV-2 infection and definitions of asymptomatic status were often incomplete or absent. The risks of bias, particularly those affecting selection of participants, differed between studies and could result in both underestimation and overestimation of the true proportion of asymptomatic infections. Also, we did not consider the possible impact of false negative RT-PCR results, which might be more likely to occur in asymptomatic infections [116] and would underestimate the proportion of asymptomatic infections [117]. The four databases that we searched are not comprehensive, but they cover the majority of publications and we do not believe that we have missed studies that would change our conclusions.

Comparison with other reviews

We found narrative reviews that reported wide ranges (5%–96%) of infections that might be asymptomatic [1,118]. These reviews presented cross-sectional studies alongside longitudinal studies and did not distinguish between asymptomatic and presymptomatic infection. We found three systematic reviews, which reported similar summary estimates from meta-analysis

of studies published up to May [119–121]. In two reviews, authors applied inclusion criteria to reduce the risks of selection bias, with summary estimates of 11% (95% CI 4%–18%, 6 studies) [120] and 15% (95% CI 12%–18%, 9 studies) [121]. Our review includes all these studies, mostly in the categories of aggregated contact or outbreak investigations, with compatible summary estimates (Fig 1). We categorised one report [81] with other studies in which a defined population was screened. The summary estimate in the third systematic review (16%, 95% CI 10%–23%, 41 studies) [119] was similar to that of other systematic reviews, despite inclusion of studies with no information about follow-up. In comparison with other reviews, rather than restricting inclusion, we give a comprehensive overview of studies with adequate follow-up, with assessment of risks of bias and exploration of heterogeneity (S2–S7 Figs). The three versions of this review to date have shown how types of evidence change over time, from single-family investigations to large screening studies (S1 Table).

Interpretation

The findings from systematic reviews, including ours [119–121], do not support the claim that a large majority of SARS-CoV-2 infections are asymptomatic [122]. We estimated that, across all study settings, the proportion of SARS-CoV-2 infections that are asymptomatic throughout the course of infection is 20% (95% CI 17%–25%). The wider prediction interval reflects the heterogeneity between studies and indicates that future studies with similar study designs and in similar settings will estimate a proportion of asymptomatic infections from 3% to 67%. Studies that detect SARS-CoV-2 through screening of defined populations irrespective of infection status at enrolment should be less affected by selection biases. In this group of studies, the estimated proportion of asymptomatic infection was 31% (95% CI 26%–37%, prediction interval 24%–38%). This estimate suggests that other studies might have had an overrepresentation of participants diagnosed because of symptoms, but there were also potential selection biases in screening studies that might have overestimated the proportion of asymptomatic infections. Our knowledge to date is based on data collected during the acute phase of an international public health emergency, mostly for other purposes. To estimate the true proportion of asymptomatic SARS-CoV-2 infections, researchers need to design prospective longitudinal studies with clear definitions, methods that minimise selection and measurement biases, and transparent reporting. Serological tests, in combination with virological diagnostic methods, might improve ascertainment of SARS-CoV-2 infection in asymptomatic populations. Prospective documentation of symptom status would be required, and improvements in the performance of serological tests are still needed [123].

Our review adds to information about the relative contributions of asymptomatic and presymptomatic infection to overall SARS-CoV-2 transmission. Since all people infected with SARS-CoV-2 are initially asymptomatic, the proportion that will go on to develop symptoms can be derived by subtraction from the estimated proportion with true asymptomatic infections; from our review, we would estimate this fraction to be 80% (95% CI 75%–83%). Since SARS-CoV-2 can be transmitted a few days before the onset of symptoms [124], presymptomatic transmission likely contributes substantially to overall SARS-CoV-2 epidemics. The analysis of secondary attack rates provides some evidence of lower infectiousness of people with asymptomatic than symptomatic infection (Fig 3) [36,65,66,90,111], but more studies are needed to quantify this association more precisely. If both the proportion and transmissibility of asymptomatic infection are relatively low, people with asymptomatic SARS-CoV-2 infection should account for a smaller proportion of overall transmission than presymptomatic individuals. This is consistent with the findings of the only mathematical modelling study in our review that explored this question [19]. Uncertainties in estimates of the true proportion and

the relative infectiousness of asymptomatic SARS-Cov-2 infection and other infection parameters contributed to heterogeneous predictions about the proportion of presymptomatic transmission [20,33,51,63,78,91].

Implications and unanswered questions

Integration of evidence from epidemiological, clinical, and laboratory studies will help to clarify the relative infectiousness of asymptomatic SARS-CoV-2. Studies using viral culture as well as RNA detection are needed, since RT-PCR defined viral loads appear to be broadly similar in asymptomatic and symptomatic people [116,125]. Age might play a role as children appear more likely than adults to have an asymptomatic course of infection (Fig 1) [126]; age was poorly reported in studies included in this review (Table 1).

SARS-CoV-2 transmission from people who are either asymptomatic or presymptomatic has implications for prevention. Social distancing measures will need to be sustained at some level because droplet transmission from close contact with people with asymptomatic and presymptomatic infection occurs. Easing of restrictions will, however, only be possible with wide access to testing, contact tracing, and rapid isolation of infected individuals. Quarantine of close contacts is also essential to prevent onward transmission during asymptomatic or presymptomatic periods of those that have become infected. Digital, proximity tracing could supplement classical contact tracing to speed up detection of contacts to interrupt transmission during the presymptomatic phase if shown to be effective [19,127]. The findings of this systematic review of publications early in the pandemic suggests that most SARS-CoV-2 infections are not asymptomatic throughout the course of infection. The contribution of presymptomatic and asymptomatic infections to overall SARS-CoV-2 transmission means that combination prevention measures, with enhanced hand and respiratory hygiene, testing tracing, and isolation strategies and social distancing, will continue to be needed.

Supporting information

S1 PRISMA Checklist.
(DOCX)

S1 Text. Search strings.
(DOCX)

S1 Fig. Flowchart.
(PDF)

S2 Fig. Review question 1, forest plot of included studies, by study precision.
(PDF)

S3 Fig. Risk of bias in studies included in review question 1 and review question 2.
(PDF)

S4 Fig. Review question 2, forest plot of included studies, by study precision.
(PDF)

S5 Fig. Review question 1, subgroup analysis comparing studies of hospitalised patients with all other settings.
(PDF)

S6 Fig. Review question 1, sensitivity analysis, omitting studies that were preprints at the time of literature search.
(PDF)

S7 Fig. Assessment of credibility of mathematical modelling studies.
(PDF)

S1 Table. Types of study included in successive versions of the living systematic review, as of 10 June 2020.
(DOCX)

S2 Table. Location of studies contributing data to review questions 1 and 2.
(DOCX)

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ORIGINAL ARTICLE

Estimating the extent of asymptomatic COVID-19 and its potential for community transmission: Systematic review and meta-analysis

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BACKGROUND: Knowing the prevalence of true asymptomatic coronavirus disease 2019 (COVID-19) cases is critical for designing mitigation measures against the pandemic. We aimed to synthesize all available research on asymptomatic cases and transmission rates. **METHODS:** We searched PubMed, Embase, Cochrane COVID-19 trials, and Europe PMC for primary studies on asymptomatic prevalence in which (1) the sample frame includes at-risk populations and (2) follow-up was sufficient to identify pre-symptomatic cases. Meta-analysis used fixed-effects and random-effects models. We assessed risk of bias by combination of questions adapted from risk of bias tools for prevalence and diagnostic accuracy studies. **RESULTS:** We screened 2,454 articles and included 13 low risk-of-bias studies from seven countries that tested 21,708 at-risk people, of which 663 were positive and 111 asymptomatic. Diagnosis in all studies was confirmed using a real-time reverse transcriptase–polymerase chain reaction test. The asymptomatic proportion ranged from 4% to 41%. Meta-analysis (fixed effects) found that the proportion of asymptomatic cases was 17% (95% CI 14% to 20%) overall and higher in aged care (20%; 95% CI 14% to 27%) than in non-aged care (16%; 95% CI 13% to 20%). The relative risk (RR) of asymptomatic transmission was 42% lower than that for symptomatic transmission (combined RR 0.58; 95% CI 0.34 to 0.99, $p = 0.047$). **CONCLUSIONS:** Our one-in-six estimate of the prevalence of asymptomatic COVID-19 cases and asymptomatic transmission rates is lower than those of many highly publicized studies but still sufficient to warrant policy attention. Further robust epidemiological evidence is urgently needed, including in subpopulations such as children, to better understand how asymptomatic cases contribute to the pandemic.

KEYWORDS: emerging or re-emerging diseases, epidemiology, evidence-based medicine, public health policy

HISTORIQUE : Il est essentiel de connaître la prévalence des véritables cas asymptomatiques de maladie à coronavirus 2019 (COVID-19) pour concevoir des mesures d'atténuation de la pandémie. Les chercheurs ont voulu synthétiser toutes les recherches disponibles sur les cas asymptomatiques et les taux de transmission. **MÉTHODOLOGIE :** Les chercheurs ont fouillé les bases de données PubMed, Embase, Cochrane pour trouver les études sur la COVID-19, et Europe PMC pour colliger les études primaires sur la prévalence des cas asymptomatiques dans lesquelles 1) le cadre d'échantillonnage incluait une population à risque et 2) le suivi était suffisant pour dépister les cas présymptomatiques. La méta-analyse a fait appel à des modèles d'effets fixes et d'effets aléatoires. Nous avons évalué le risque de biais par une combinaison de questions adaptées d'outils sur les risques de biais des études de prévalence et de précision diagnostique. **RÉSULTATS :** Les chercheurs ont extrait 2 454 articles, dont 13 études à faible risque de biais de sept pays dans lesquelles 21 708 personnes à risque ont subi le test de dépistage, soit 663 cas positifs et 111 cas asymptomatiques. Dans toutes les études, le diagnostic a été confirmé au moyen du test d'amplification en chaîne par polymérase après transcriptase inverse en temps réel. La proportion de cas asymptomatiques se situait entre 4 % et 41 %. La méta-analyse (à effets fixes) a établi que la proportion de cas asymptomatiques s'élevait à 17 % (IC à 95 %, 14 % à 20 %) dans l'ensemble, mais qu'elles étaient plus élevées dans les soins aux aînés (20 %; IC à 95 %, 14 % à 27 %) qu'auprès du reste de la population (16 %; IC à 95 %, 13 % à 20 %). Le risque relatif [RR] de transmission de cas asymptomatiques était plus faible de 42 % que celui de cas symptomatiques (RR combiné de 0,58; IC à 95 %, 0,34 à 0.99, p = 0,047). **CONCLUSIONS :** L'évaluation de la prévalence d'un sixième de cas asymptomatiques de COVID-19 et de taux de transmission de cas asymptomatiques est inférieure à celle de nombreuses études hautement publicisées, mais suffit tout de même pour justifier l'intérêt de la santé publique. D'autres données épidémiologiques solides s'imposent de toute urgence, y compris dans des sous-populations comme les enfants, pour mieux comprendre l'effet des cas asymptomatiques sur la pandémie.

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MOTS-CLÉS : épidémiologie, maladie émergente ou réémergente, médecine fondée sur des données probantes, politique de santé publique

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INTRODUCTION

Asymptomatic cases of any infection are of considerable concern for public health policies to manage epidemics. Such asymptomatic cases complicate the tracking of an epidemic and prevent reliable estimates of transmission, tracing, and tracking strategies for containing an epidemic through isolation and quarantine. This has been a significant concern in the current coronavirus disease 2019 (COVID-19) pandemic (1).

The possibility of asymptomatic transmission of COVID-19 cases was first raised by a case report in China in which a traveller from Wuhan was presumed to have transmitted the infection to five other family members in other locations while she remained asymptomatic for the entire 21-day follow-up period (2). Subsequently, other reports confirmed not only the possibility of such transmission but began quantifying the potential proportions. For example, the outbreak on the Diamond Princess cruise ship included a substantial proportion of asymptomatic cases after widespread testing of those on board the ship (3). An early rapid review by the Centre for Evidence-Based Medicine in Oxford, United Kingdom, found that the estimated proportion of asymptomatic COVID-19 cases ranged from 5% to 80% (4). However, many of the identified studies were either poorly executed or poorly documented, making the validity of these estimates questionable.

We therefore sought to identify all studies that had attempted to estimate the proportion of asymptomatic COVID-19 cases, select those with low risk of bias, and synthesize them to provide an overall estimate and potential range. We also aimed to estimate the rate of forward transmission from asymptomatic cases if sufficient data were found.

METHODS

We conducted a systematic review and meta-analysis using enhanced processes with an initial report completed within 2 weeks and daily short team meetings to review progress, plan the next actions, and resolve discrepancies and other obstacles (5). We also used locally developed open access automation tools and programs such as the Polyglot Search Translator, SearchRefiner, and the SRA Helper to design, refine, and convert our search strategy for all the databases we searched and to speed up the screening process (6). We searched the PROSPERO database to rule out the existence of a similar review and PubMed, Embase, and Cochrane COVID-19 trials for published studies and Europe PMC for pre-prints from January 2020 to July 20, 2020. A search string composed of MeSH terms and words was developed in PubMed and was translated to be run in other databases using the Polyglot Search Translator. The search strategies for all databases are presented in Supplemental Appendix 1. We also conducted forward and backward citation searches of the included studies in the Scopus citation database.

We restricted publication types to reports of primary data collection released in full (including pre-prints) with sufficient details to enable a risk-of-bias assessment, and we contacted authors for clarifications on follow-up times and sampling frames. We anticipated that cross-sectional prevalence surveys with follow-up and cohort studies would be the bulk of eligible reports. No restrictions on language were imposed. We excluded studies for the following reasons: sampling frame in part determined by presence or absence of symptoms; no or unclear follow-up; no data on asymptomatic cases; single case study or small cluster; modelling or simulation studies (but sources of real data were checked for possible inclusion); non–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) studies; antiviral treatment studies; and study protocols, guidelines, editorials, or historical accounts without data to calculate primary outcomes.

Participants

We included studies of people of any age in which all those at risk of contracting SARS-CoV-2 were tested regardless of presence or absence of symptoms; diagnosis was confirmed by a positive result on a real-time reverse transcriptase–polymerase chain reaction (RT-PCR), and all cases had a follow-up period of at least 7 days to distinguish asymptomatic cases from pre-symptomatic cases (Figure 1).

Outcomes

Our primary outcome was the proportion of all people with SARS-Cov-2 infection who were completely asymptomatic at the time of the test and throughout the follow-up period, where the denominator included all tested individuals in the

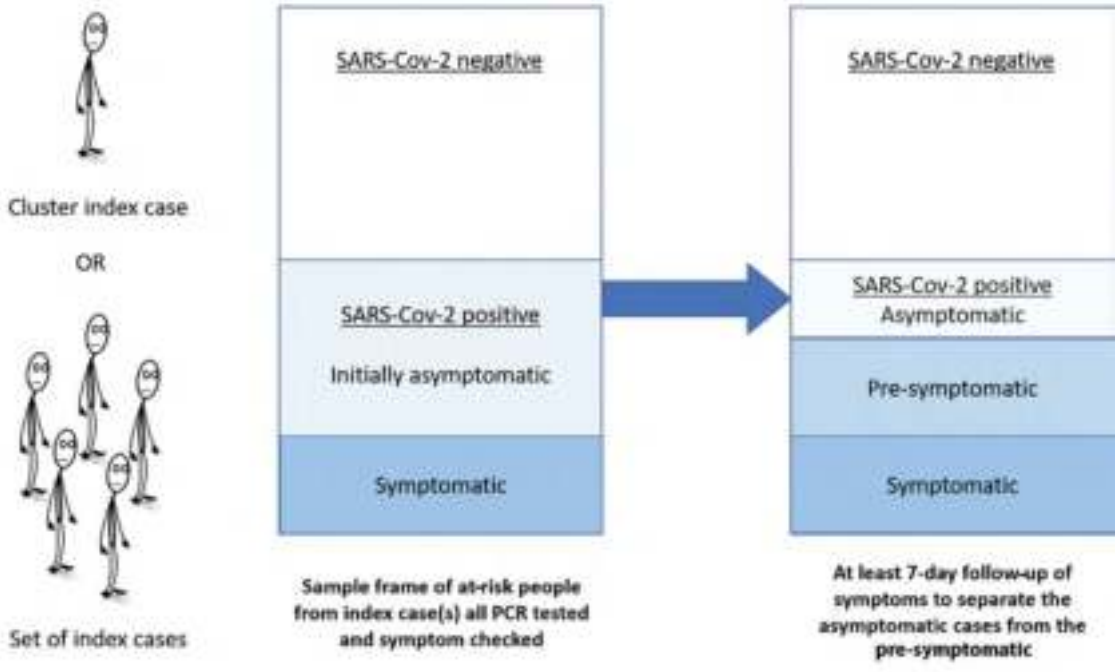

Figure 1: Depiction of ideal study flow and criteria used for study inclusion: (1) sample frame of at-risk people and (2) adequate follow-up on symptoms
SARS-Cov-2 = Severe acute respiratory syndrome coronavirus 2; PCR = Polymerase chain reaction

study sample whose result was positive, and the numerator included those who tested positive and had no symptoms. Our secondary outcome was estimate of onward transmission of the infection from asymptomatic cases.

Study selection and screening

Two authors (OB and MC) independently screened titles, abstracts, and full texts according to eligibility criteria. All discrepancies were resolved via group discussion with the other authors. Reasons for exclusion were documented for all full-text articles deemed ineligible (Supplemental Appendix 2); see the Preferred Reporting Information for Systematic Reviews and Meta-Analyses diagram (Figure 2).

Data extraction

Three authors (OB, MC, KB) used a Microsoft Excel spreadsheet to extract the following information:

1. Methods: study authors, year of publication, country, publication type, duration of study, duration of follow-up
2. Participants: sample size, age (mean or median, range), setting (community, province, aged care facility, hospital, screening clinic), presence or absence of symptoms, test results
3. History of illness and diagnosis: type of test; numerator (number of asymptomatic); denominator (sampling frame); mildly symptomatic or symptomatic subjects; and number or proportion of people infected by the asymptomatic case.
4. Case definitions were as follows:
   - Asymptomatic: confirmed via any testing specified earlier with report of no symptoms for the duration of sufficient follow-up to differentiate from pre-symptomatic cases.
   - Exposure: contact with a confirmed case or potential contact with another pre-symptomatic person (e.g., came from an endemic area or linked with an infected traveller).

The World Health Organization recommends that "for confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after the date on which the sample was taken which led to confirmation" (7, p.11).

Risk-of-bias assessment

Three authors (OB, MC, KB) assessed the risk of bias of potentially includable studies. We used a combination of risk-of-bias tools for prevalence studies and diagnostic accuracy and adapted the key signaling questions on sampling frame, ascertainment of infectious disease status, acceptability of methods to identify denominators, case

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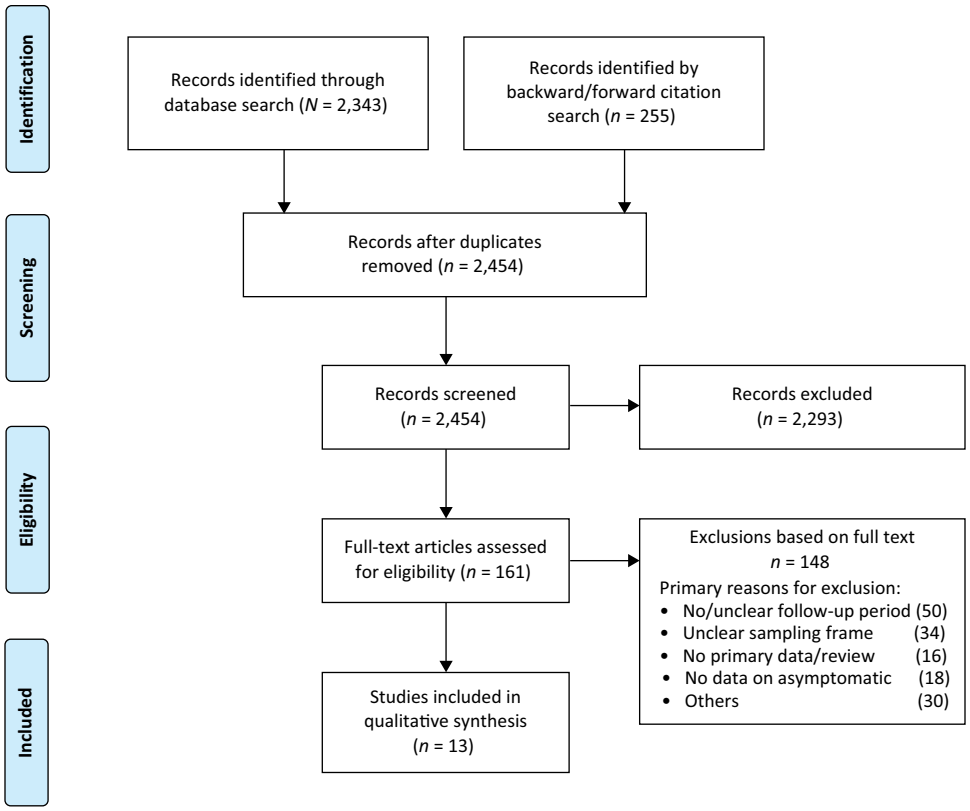

Figure 2: Screening and selection of articles

definition of *asymptomatic* for the numerator, and length of follow-up, as shown in Table 2 and in Supplemental Appendix 3 in full (8,9).

Data analysis

We estimated the proportion of COVID-19 cases who were asymptomatic for each included study population, assuming a binomial distribution and calculating exact Clopper–Pearson confidence intervals. We then pooled data from all included studies using (1) fixed-effects meta-analysis and (2) random-effects meta-analysis. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC); the FREQ procedure was used for individual studies and the fixed-effects meta-analysis; the NLMIXED procedure was used for the random-effects meta-analysis.

We also meta-analyzed the forward transmission rates from asymptomatic and symptomatic cases when there were sufficient data and report the pooled RR comparing the two. We planned to undertake subgroup analysis for age (between studies, and within studies when age was reported separately for asymptomatic and symptomatic cases). Because the analysis included only studies deemed to be of high quality on items 1 and 2 after risk-of-bias appraisal, no sensitivity analysis of high- versus low-quality studies was undertaken. Instead, we did a sensitivity analysis in which we omitted studies with a follow-up duration of less than 14 days.

RESULTS

A total of 2,454 articles were screened for title and abstract, and 161 full-text articles were assessed for inclusion (Figure 2). Major reasons for exclusion were inadequate sampling frame and insufficient follow-up time to accurately classify the asymptomatic cases. The full list of excluded studies with reasons is presented in Supplemental Appendix 2. Thirteen articles—nine published and four preprints—from seven countries (China, $n = 4$; United States, $n = 4$; Taiwan, $n = 1$; Brunei, $n = 1$; Korea, $n = 1$; France, $n = 1$; and Italy, $n = 1$) that tested 21,708 close contacts of at least 849 confirmed COVID-19 cases, of which 663 were positive and 111 were asymptomatic, met the eligibility criteria for the estimation of the primary outcome (10–22).

The sampling frames of the selected studies included residents of skilled nursing facilities (SNFs; 10, 12, 15, 19, 20); high-risk close contacts of confirmed COVID-19 cases

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Table 1: Characteristics of included studies (*N* = 13)

Study (country) and publication status	Study population (sampling frame)	Sample size and age	Diagnostic testing and frequency	Length of follow-up for asymptomatic cases
Roxby et al (20) (United States) Published	Residents of independent and assisted living communities (Facility 1) in Seattle after two confirmed cases between 5 and 9 Mar	*N* = 79; mean age of cohort 86 y	Nasal swab, RT-PCR, twice, 1 wk apart	7 d
Patel et al (19) (United States) Published	Residents and staff of skilled nursing facility in Illinois on 15 Mar	*N* = 126; median age of cases 82 y.	Nasal swab, RT-PCR, once	30 d
Dora et al (15) (United States) Published	Residents of skilled nursing facility in Veterans Affairs Greater Los Angeles Healthcare System between 29 Mar and 23 Apr	*N* = 99; median age of cohort 75 y.	Nasal swab, RT-PCR, repeated every 10 d	At least 14 d
Blain et al (12) (France) Published	Nursing home residents in France tested weekly since early Mar	*N* = 79; mean age 86 y	Nasal swab, RT-PCR, repeated weekly	6 wk
Arons et al (10) (United States) Published	Residents of skilled nursing facility (Facility A) in Seattle after a confirmed case on 1 Mar	*N* = 86; mean age of cohort 77 y, mean age of cases 79 y.	Nasal swab, RT-PCR, twice, 1 wk apart	7 d
Zhang et al (22) (China) Published	Close contacts of confirmed cases between 28 Jan and 15 Mar in Guangzhou, China	*N* = 369; median age 35 y.	Nasal swab, RT-PCR, at least twice	14 d
Tian et al (21) (China) Preprint	Close contacts (coworkers, family members, customers) of a confirmed supermarket employee (super-spreader) in Liaocheng, China.	*N* ≃ 8,000; mean age of cases 48 y	Nasal swab, RT-PCR, repeated every 2 days	16±6.15 d
Cheng et al (14) (Taiwan) Published	High-risk close contacts (household members, HCWs) of first 100 cases in Taiwan	*N* = 849; mean age of cohort 42 y, mean age of cases 41 y	Nasal swab, RT-PCR, repeated during 14 d quarantine	14 d
Lavezzo et al (16) (Italy) Published	Majority of population of Italian town of Vò after a COVID-19 death on 21 Feb.	*N* = 2,812; mean age of cohort 47 y, mean age of cases 58 y	Nasal swab, RT-PCR, twice, 7–14 d apart	7–14 d
Bi et al (11) (China) Published	Close contacts of cases confirmed before 9 Feb in Shenzhen, China	*N* = 1,286; mean age of cohort 38 y, mean age of cases 43 y	Nasal swab, RT-PCR, repeated during 14 d quarantine	95% followed up for ≥12 d
Chaw et al (13) (Brunei) Preprint	Bruneian attendants of a religious event in Malaysia, where a confirmed case was present	*N* = 1,830; mean age of cohort 31 y, mean age of cases 33 y	Nasal swab, RT-PCR, repeated weekly	14 d

(*Continued*)

Table 1: Characteristics of included studies (*N* = 13) (*Continued*)

Study (country) and publication status	Study population (sampling frame)	Sample size and age	Diagnostic testing and frequency	Length of follow-up for asymptomatic cases
Luo et al (17) (China) Preprint	Close contacts of 347 confirmed COVID-19 patients identified between 13 Jan and 6 Mar in Guangzhou, China	*N* = 4,950; mean age of cohort 38 y, mean age of cases 44 y	Nasal swab, RT-PCR, repeated every 2 d	14 d
Park et al (18) (Korea) Published	Employees, residents, and visitors of a commercial and residential building where a confirmed case worked	*N* = 1,143; mean age of cohort 38 y	Nasal swab, RT-PCR, repeated during 14 d quarantine	14 d

RT-PCR = Reverse transcriptase–polymerase chain reaction; HCWs = Health care workers; COVID-19 = Coronavirus disease 2019

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(11, 13, 14, 17, 18, 21); and a whole district surveillance program in Italy (16). The demographic characteristics (Table 1) indicate that most of the tested individuals were adults, with a mean age of more than 75 years in the five SNF studies and a mean age of more than 31 years in the non-aged care studies. The proportions of children and young people (0–20 years) ranged from 6% to 23.5%.

Diagnosis in all studies was confirmed via RT-PCR and in two cases was supplemented with radiological evidence (17, 21). Testing of individuals in the study sample varied across settings but was generally very high: all contacts regardless of symptoms (11, 13, 14, 17, 18, 21), more than 97% of SNF residents (10, 12, 15, 19, 20), and 85.9% of an entire town (16). The length of follow-up for monitored individuals in the SNF studies ranged from 7 to 30 days (10, 12, 15, 19, 20); 14 days for the Bruneian (13), Taiwanese (14), Korean (18), and Chinese close contacts (17, 22); 7–14 days in the Italian community (16); 12 days for 95% of all contacts in the Shenzhen community surveillance (11); and a mean of 16 (SD 6) days in Liaocheng, China (21).

The proportion of asymptomatic cases in the 13 included studies ranged from 4% (95% CI 1% to 10%) in Korea (18) to 40% in Vò, Italy (16) and in an aged care facility in the United States (20). Combining data from all 13 studies, we estimate that 17% of cases were asymptomatic (fixed effects 95% CI 14% to 20%;); for the eight non-aged care studies, 16% (95% CI 13% to 19%); and for the five studies of SNFs, 20% (95% CI 14% to 27%) (Figure 3). The corresponding estimated proportions in the random-effects meta-analysis were, overall, 18% (95% CI 9% to 26%); non-aged care, 16% (95% CI 7% to 26%); and aged care, 21% (95% CI 5% to 36%). The 95% prediction interval was 4% to 52%. In the sensitivity analysis, which omitted studies in which length of follow-up was less than 14 days (10, 11, 16, 20), the overall estimate was modestly lower at 15% (fixed-effects 95% CI 12% to 18%) or 17% (random-effects 95% CI 8 to 26%). Heterogeneity as expressed by I^2 was 84%.

Five studies reported data on secondary infection transmission from asymptomatic cases (Table 2). The asymptomatic transmission rates ranged from none to 2.2%, whereas symptomatic transmission rates ranged between 0.8% and 15.4%. Cycle threshold from real-time RT-PCR assays or the viral load did not differ between asymptomatic and symptomatic individuals in three of the studies (10, 14, 16). Overall, the RR of asymptomatic transmission was 42% lower than that of symptomatic transmission (pooled RR 0.58, fixed-effects 95% CI 0.335 to 0.994, $p = 0.047$; RR 0.38, random-effects 95% CI 0.13 to 1.083, $p = 0.07$; $I^2 = 43.4\%$).

Risk of bias of included studies

Table 3 summarizes the overall risk-of-bias assessment of the nine included studies (the full list of risk-of-bias questions is in Supplemental Appendix 3). All of the studies were evaluated as low risk of bias for the sampling frame and length of follow-up domains (domains 1 and 5), which were part of the inclusion criteria. Two studies had potential non-response bias because not all of the eligible participants were tested (14% [463/3,275] of the target population was not tested in the Lavezzo et al study [16]) or results were not reported for all tested participants (87/98 cases were reported in the Bi et al study [11]; domain 2). Four studies either had not tested the study population at least twice during the follow-up period or had not provided clear information on testing (11, 13, 14, 21) (domain 3). Nine studies did not explicitly state the asymptomatic case definition they adhered to or had additional bias because of a high percentage of people in the SNFs with severe cognitive impairment (10–12, 14–16, 19–21) (domain 4).

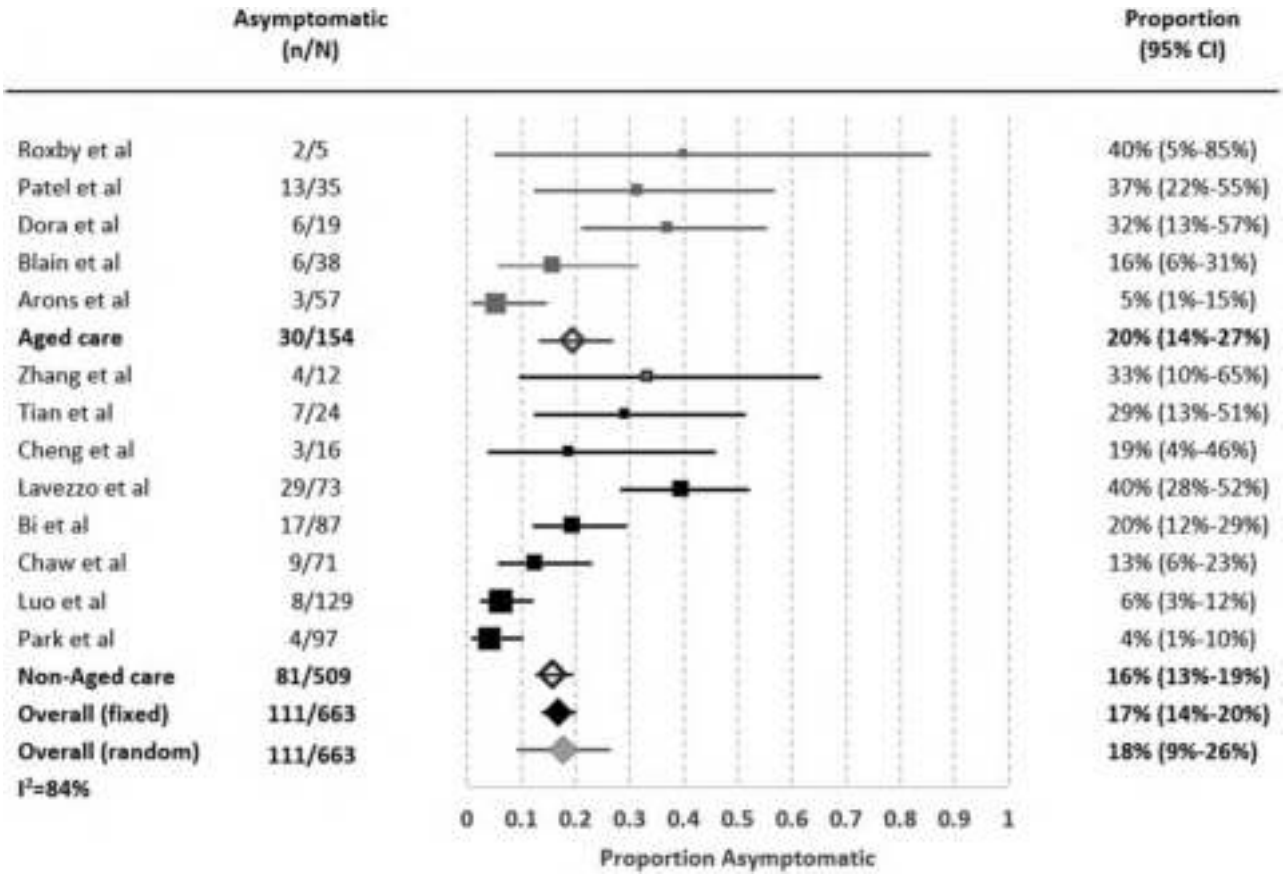

Figure 3: Pooled estimates of proportion of asymptomatic carriers by subpopulations
N = Positive cases; n = Asymptomatic cases

Table 2: Comparison of secondary transmission rates

	No./*N* (%)		
Study	Asymptomatic transmission rate	Symptomatic transmission rate	Relative risk
Zhang et al (22)	1/119 (0.8)	11/250 (4.4)	0.2
Cheng et al (14)	0/91 (0)	22/2644 (0.8)	0.66
Chaw et al (13)	15/691 (2.2)	28/1010 (2.8)	0.78
Luo et al (17)	1/305 (0.3)	117/2305 (5.1)	0.06
Park et al (18)	0/4 (0)	34/221 (15.4)	0.72

Excluded studies

Several well-publicized studies did not meet our inclusion criteria. The outbreak on the Diamond Princess cruise ship involved 3,711 passengers, of whom more than 600 acquired COVID-19 (3). Many of the positive cases were relocated to medical facilities in Japan without details of their clinical progression. To correct for the lack of follow-up, Mizumoto et al applied a statistical adjustment for the right censoring and estimated that 17.9% (95% CI 15.5% to 20.2%) of positive cases were asymptomatic.

An open-invitation screening of the Icelandic population suggested that around 0.8% of the population were SARS-CoV-2 positive, with half classified as (initially) asymptomatic (2). However, because there was no follow-up, we cannot separate asymptomatic from pre-symptomatic individuals. Moreover, the study excluded symptomatic people undergoing

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Table 3: Risk of bias in 13 included studies*

Included Studies	Risk-of-bias assessment questions				
	1. Was the sampling frame a true or close representation of the target population?	2. Was the likelihood of non-response bias among those at risk of infection minimal?	3. Is the reference standard used likely to correctly classify all SARS-CoV-2 infections?	4. Was an acceptable case definition used in the study?	5. Was the length of follow-up to define case definition appropriate?
Roxby et al	☺	☺	☺	😐	☺
Patel et al	☺	☺	☺	😐	☺
Dora et al	☺	☺	☺	😐	☺
Blain et al	☺	☺	☺	😐	☺
Arons et al	☺	☺	☺	😐	☺
Zhang et al	☺	☺	☺	☺	☺
Tian et al	☺	☺	😐	😐	☺
Chen et al	☺	☺	😐	😐	☺
Lavezzo et al	☺	😐	☺	😐	☺
Bi et al	☺	😐	😐	😐	☺
Chaw et al	☺	☺	😐	☺	☺
Luo et al	☺	☺	☺	☺	☺
Park et al	☺	☺	☺	☺	☺

SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; Green smiley face = Low risk; Yellow straight face = moderate or unclear risk

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targeted testing, which impeded estimation of an overall asymptomatic rate.

A study of 215 pregnant women in New York identified 33 SARS-CoV-2–positive women (23). On admission to the delivery unit, 4 of the 33 positive cases were symptomatic and 3 became symptomatic before postpartum discharge, suggesting an asymptomatic rate of 79% (26/33). However, the 2 days of follow-up were insufficient to meet our inclusion criteria.

A case report of a pre-symptomatic Chinese businessman transmitting COVID-19 to a German business partner was also excluded because despite three other people acquiring the infection from the infected German source, none of them was asymptomatic at follow-up (24). A 5-day point-prevalence testing of adults living in homeless shelters in Boston found 147 positive cases, of which the majority had mild or no symptoms (25). We excluded this study because no numeric estimate was included of those who were truly asymptomatic, and there was no follow-up assessment.

Two studies examined people repatriated from overseas to their home countries by plane. Neither study was clear on whether symptomatic people could board the plane and be included, and if they were excluded, the asymptomatic rates would be overestimated. A study of 565 Japanese citizens repatriated from China (26) found 13 positives—4 asymptomatic and 9 symptomatic, based on screening on arrival. Another study of 383 Greek citizens repatriated from the United Kingdom, Spain, and Turkey (27) found 40 asymptomatic positive people on arrival, 4 of whom later self-reported symptoms. Again, the likely initial exclusion of symptomatic people and the lack of comprehensive follow-up would both result in overestimation of the asymptomatic rates.

DISCUSSION

Principal findings

Although the rate of asymptomatic COVID-19 cases has received considerable attention, we found only 13 studies that provided an adequate sample frame and follow-up to ascertain a valid estimate of the proportion of asymptomatic cases. The combined estimate of the asymptomatic proportion was 17% (95% CI 14% to 20%) but had considerable heterogeneity (I^2 = 84%) and a 95% prediction interval that ranged from 4% to 52%. There was no clear difference in the proportions between aged care and non-aged care studies. Only 5 of the

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13 studies provided data on transmission rates from asymptomatic cases. The transmission risk from asymptomatic cases appeared to be lower than that of symptomatic cases, but there was considerable uncertainty in the extent of this (RR 0.58; 95% CI 0.335 to 0.994, $p = 0.047$).

Strengths and weaknesses of the study

Strengths of our systematic review include achieving full methodological rigor within a much shorter time frame than traditional reviews using enhanced processes and automation tools (5). We also critically assessed the risk of bias of all full-text articles we screened to include studies with the least risk of bias in sampling frame and length of follow-up domains to be able to differentiate between asymptomatic and pre-symptomatic cases.

Our findings have several limitations. First, our search focused on published and pre-print articles, and we may have missed some public health reports that are either unpublished or only available on organisational websites. Second, the design and reporting of most of the studies had a number of important deficits that could affect their inclusion or our estimates. These deficits include poor reporting of the sample frame, testing and symptom check, and follow-up processes. Such reporting would have been considerably aided by including a flow chart of cases (as Lavezzo et al [16] did) with identification, testing, and follow-up, including missing data. A further important limitation was the poor reporting of symptoms, which was often simply dichotomised into symptomatic versus asymptomatic without clear definitions and details of possible mild symptoms. The included studies did not report sufficient data to examine the impact of age and underlying comorbidities on the asymptomatic rate. Finally, all included studies relied on RT-qPCR; hence, some cases might have been missed because of false-negative results, especially when study participants were only tested once (28). If the tests missed more asymptomatic cases, then the true proportion of asymptomatic cases could be higher than our estimates. However, false-positive results, which may occur when people without symptoms are tested in low-prevalence settings, would mean the true prevalence of asymptomatic cases was lower than our estimates.

Strengths and weaknesses compared with other studies

Several other non-systematic and systematic reviews have examined the proportion of asymptomatic cases. The non-systematic reviews estimated asymptomatic rates as between 5% and 80% (4, 29). However, they included only early cross-sectional reports and did not critically appraise the study design, nor did they attempt to pool the most valid studies. Five other systematic reviews reported pooled estimates of asymptomatic rate as between 8% and 16% (30–34). However, these reviews included studies that we excluded because of high risk of bias in the sampling frame. Ongoing monitoring for new studies is warranted but should include robust methodological assessment, including ensuring included studies have a sufficient follow-up period to differentiate the asymptomatic from the pre-symptomatic cases. Our review currently also has a more recent search date than other reviews and includes sensitivity analysis by length of follow-up time. Our estimate of risk of transmission by asymptomatic cases was comparable to those reported in two other empirical reviews by Buitrago-Garcia et al (RR 0.35) and Koh et al (RR 0.39) (32, 34).

Meaning of the study

Estimates of the proportion of the cases that are asymptomatic and the risk of transmission are vital parameters for modelling studies. Our estimates of the proportion of asymptomatic cases and their risk of transmission suggest that asymptomatic spread is unlikely to be a major driver of clusters or community transmission of infection, but the extent of transmission risk for pre-symptomatic and minor symptomatic cases remains unknown. The generalisability of the overall estimate is unclear, and we observed considerable variation across the included studies, which had different settings, countries, and study design, reflected in the reasonably wide prediction interval.

Unanswered questions and future research

Many unanswered questions about asymptomatic cases remain. Only one of the more recent studies we included tested patients for immunoglobulin G antibodies to determine seroconversion among elderly individuals. Without repeated and widespread RT-PCR and antibody tests, it is difficult to accurately estimate the prevalence of COVID-19 infection and inform our infection prevention strategies (35). The role of viral load and virus shedding dynamics in asymptomatic and symptomatic cases will further help answer the question of forward transmission and disease length and severity. Other unknowns include whether there is a difference in the proportion of cases that are asymptomatic according to age (particularly children versus adults), sex, or underlying comorbidities, and whether asymptomatic cases develop long-term immunity to new infections. For most studies, the PCR (positive) cases were traced from the index cases, and the testing was carried out mostly at the beginning of the pandemic wave for the locale. So, for this review of inception cohorts, people with long-term persistent positive testing were unlikely to be misclassified as asymptomatic. The issue of persistent PCR positivity after a person has recovered from infection might be of concern to more recent studies conducted at some time after the first wave of the pandemic. In such

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studies, researchers will need to ask about history of illness compatible with COVID-19 even if this occurred months ago, and PCR testing could be supplemented by other tests such as viral culture and anti-SARS-CoV-2 antibody tests.

Our recommendations for future research also include improved clearer reporting of methods, sampling frames, case definition of *asymptomatic,* extent of contact tracing, duration of follow-up periods, presentation of age distribution of asymptomatic cases, and separation of pre-symptomatic and mild cases from asymptomatic cases in results tables. Most studies used a limited definition of asymptomatic COVID-19 case, which could lead to mixing paucisymptomatic cases with asymptomatic cases. If that were a common issue, then the true prevalence of asymptomatic cases would be even lower than the current estimates. A reliable estimate of the proportion of asymptomatic cases and the burden of disease is imperative in understanding the infection transmission capacity of asymptomatic cases to inform public health measures for these individuals who, according to our findings, appear to pose lower risk of transmission. Until we have further immunological and epidemiological evidence, we advise that the importance of asymptomatic cases for driving the spread of pandemic to be considered with caution.

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RESEARCH ARTICLE

What do we know about SARS-CoV-2 transmission? A systematic review and meta-analysis of the secondary attack rate and associated risk factors

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Abstract

Introduction

Current SARS-CoV-2 containment measures rely on controlling viral transmission. Effective prioritization can be determined by understanding SARS-CoV-2 transmission dynamics. We conducted a systematic review and meta-analyses of the secondary attack rate (SAR) in household and healthcare settings. We also examined whether household transmission differed by symptom status of index case, adult and children, and relationship to index case.

Methods

We searched PubMed, medRxiv, and bioRxiv databases between January 1 and July 25, 2020. High-quality studies presenting original data for calculating point estimates and 95% confidence intervals (CI) were included. Random effects models were constructed to pool SAR in household and healthcare settings. Publication bias was assessed by funnel plots and Egger's meta-regression test.

Results

43 studies met the inclusion criteria for household SAR, 18 for healthcare SAR, and 17 for other settings. The pooled household SAR was 18.1% (95% CI: 15.7%, 20.6%), with significant heterogeneity across studies ranging from 3.9% to 54.9%. SAR of symptomatic index cases was higher than asymptomatic cases (RR: 3.23; 95% CI: 1.46, 7.14). Adults showed higher susceptibility to infection than children (RR: 1.71; 95% CI: 1.35, 2.17). Spouses of index cases were more likely to be infected compared to other household contacts (RR: 2.39; 95% CI: 1.79, 3.19). In healthcare settings, SAR was estimated at 0.7% (95% CI: 0.4%, 1.0%).

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Discussion

While aggressive contact tracing strategies may be appropriate early in an outbreak, as it progresses, measures should transition to account for setting-specific transmission risk. Quarantine may need to cover entire communities while tracing shifts to identifying transmission hotspots and vulnerable populations. Where possible, confirmed cases should be isolated away from the household.

Introduction

The COVID-19 pandemic continues to escalate. Modeling studies have enhanced understanding of SARS-CoV-2 transmission dynamics and initial phylogenetic analysis of closely related viruses suggest highly linked person-to-person spread of SARS-CoV-2 originating from mid-November to early December 2019 [1–3].

There are no known effective therapeutics or vaccines [4, 5]. As such, containment measures rely on the capacity to control viral transmission from person-to-person, such as case isolation, contact tracing and quarantine, and physical distancing [6]. Effective prioritization of these measures can be determined by understanding SARS-CoV-2 transmission patterns.

There is an abundance of literature on the biological mode of transmission of coronaviruses: through exhaled droplets, aerosol at close proximity, fomites, and possibly through fecal-oral contamination [7, 8]. However, few observational studies have assessed transmission patterns in populations, and what determines whether the infection is contained or spreads. Previous theoretical work by Fraser et al. proposed three transmission-related criteria that impact on outbreak control: (i) viral transmissibility; (ii) disease generation time; and (iii) the proportion of transmission occurring prior to symptoms [9].

To better understand SARS-CoV-2 transmission, we conducted a systematic review and meta-analyses of publicly available studies to estimate the secondary attack rate (SAR) in various settings. We also examined whether household transmission differed by symptom status of index case, adult and children (< 18 years old), and relationship to index case.

Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Definition

SAR is defined as the probability that an exposed susceptible person develops disease caused by an infected person [10]. It is calculated by dividing the number of exposed close contacts who tested positive (numerator) by the total number of exposed close contacts of the index case (denominator).

Search strategy and inclusion criteria

We performed a literature search of published journal articles in PubMed and pre-print articles in medRxiv and bioRxiv from January 1, 2020 using the search terms ("SARS-CoV-2" OR "COVID-19") AND ("attack rate" OR "contact tracing" OR "close contacts"). The last search date was on July 25, 2020. All studies that were written in English or have an abstract in English were included.

Studies reporting SAR were included if they: (i) presented original data for SAR estimation, such as from a contact tracing investigation; (ii) reported a numerator and denominator of close contacts, or at least two of numerator, denominator, and SAR; (iii) specified a particular setting; and (iv) cases were confirmed positive with SARS-CoV-2 through reverse transcription polymerase chain reaction (RT-PCR) test. Point-testing or prevalence studies to measure cumulative incidence of infection in a setting were excluded from the meta-analyses as the source of infection could not be traced, but we discussed some of these studies where relevant.

Data extraction and quality assessment

The articles were initially screened by title and abstract, and subsequently by review of selected full-text articles. Three reviewers selected the studies independently using predetermined inclusion criteria and differences in opinions were resolved through consensus. Data were obtained directly from the reports, but when not explicitly stated, we derived the data from tables, charts, or supplementary materials. The following data were extracted from each included study: surname of first author; study design; location of study; number of index cases; total number of close contacts; number of close contacts tested positive for SARS-CoV-2; setting type; symptom of index case; age group of secondary cases; and relationship of secondary cases to index case.

The quality of the studies was independently assessed by three reviewers based on the UK National Institute for Clinical Excellence guidelines [11]. The evaluation is based on a set of eight criteria. Differences in assessments were resolved through consensus. Studies with a score greater than 4 (out of 8) were considered to be of high quality and thus included in the meta-analyses [12].

Statistical analysis

Point estimates and 95% confidence intervals (CI) were calculated. CIs were estimated using a Normal approximation but in studies with a small number of secondary cases (< 5) a binomial approximation was used. Meta-analyses were performed using random-effects DerSimonian-Laird model [13]. We also estimated risk ratios to examine SAR differences by symptom status of the index case, age of close contacts, and relationship of household contacts. The I^2 statistic was used as a measure of heterogeneity, with higher values signifying greater degree of variation [14]. Publication bias was assessed by funnel plots and Egger's meta-regression test [15]. A p-value of <0.05 was considered as statistically significant. Statistical analysis was done in STATA 14 using the package metan, metafunnel, and metabias [16–18].

Results

A total of 663 records were identified from the databases (Fig 1). After screening by title and abstract, we included 118 studies and after a detailed assessment based on the inclusion criteria and quality assessment, 57 studies were included in the meta-analyses. A majority of the included studies focused on transmission in households. In non-household settings, most studies were conducted in healthcare settings. As such, our systematic review and meta-analyses focused on SAR in household and healthcare settings, but we also discussed the SAR in other settings.

Household SAR

We identified 43 studies that allowed direct estimation of the SAR in households (Table 1). Thirty-five studies were published articles (five in Chinese language, two in Korean language)

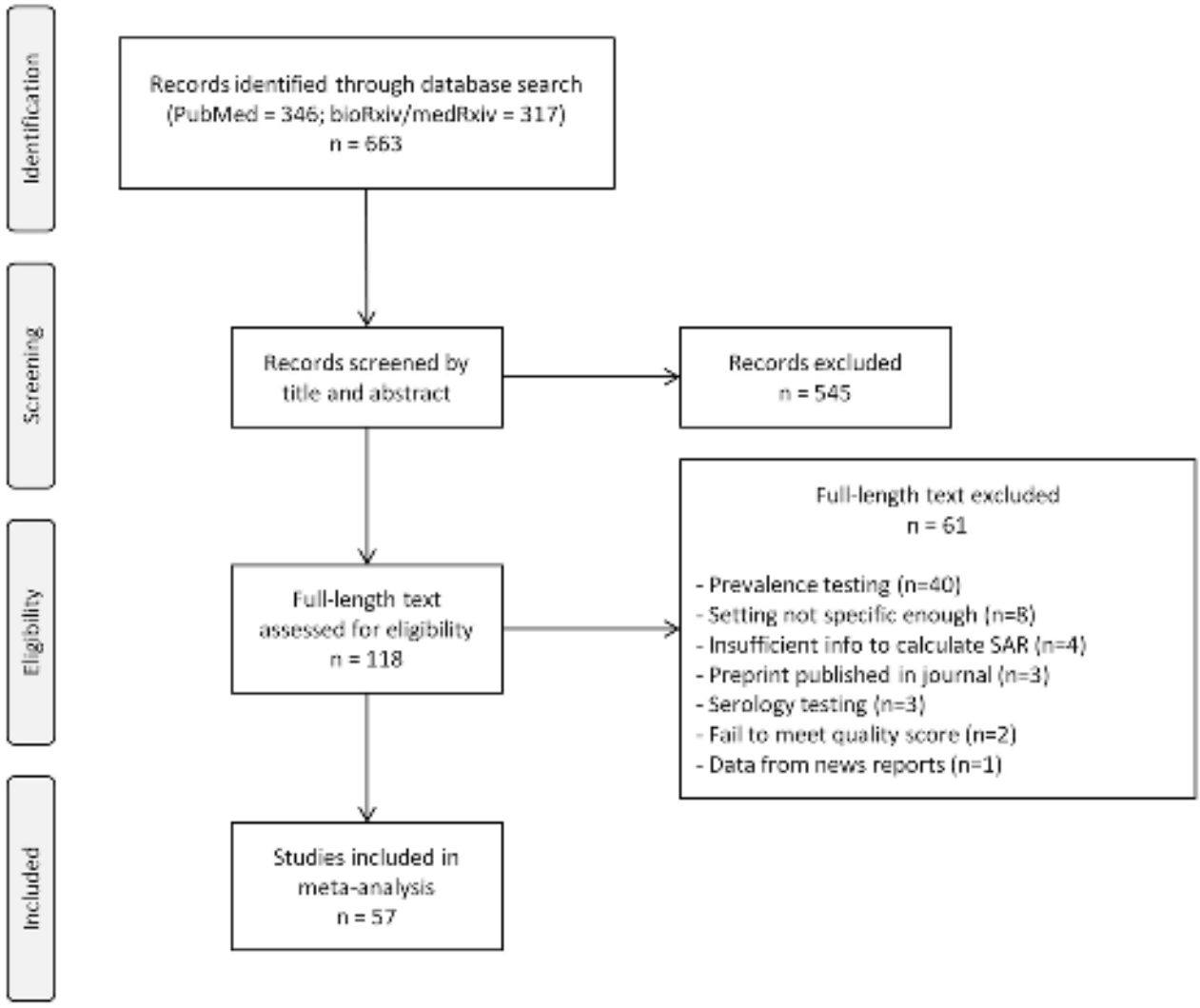

Fig 1. Flow chart of search strategy and study selection for the secondary attack rate (SAR).

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and eight were pre-prints. About half of the studies were in China (22 in mainland China, 1 in Hong Kong, 1 in Taiwan), five in South Korea, four in the United States, two in Israel, and the others were in Australia, Brunei, Canada, Germany, India, Italy, Singapore, and Spain.

Index cases were confirmed positive cases identified or suspected to have been first exposed to the SARS-CoV-2 virus within the household, generally based on the timing of symptom onset and epidemiological link. Some studies identified close contacts through active surveillance systems while in others they were identified following an outbreak investigation. Testing protocols of close contacts also differed; all close contacts were tested regardless of symptoms in most studies, but only symptomatic contacts were tested in five studies.

There was variation in the definition of household contacts; most included only those who resided with the index case, some studies expanded this to include others who spent at least a night in the same residence or a specified duration of at least 24 hours of living together, while others included family members or close relatives.

Table 1. Description of studies included in the review and analysis of household secondary attack rate (SAR).

Study, location	Description of study	Definition of close contact	Household SAR (%)	No. of index cases	Additional comments	Quality score
Wang et al., Beijing, China [19]	Retrospective study of households	Lived with primary case in a house for 4 days before and for more than 24 hours after the primary case developed illness related to COVID-19	77/335 (23.0%)	41		6
Wang et al., Beijing, China [20]	Summary of contact investigations	Family members or relatives	111/714 (15.5%)	585		7
Liu et al., Guangdong, China [21]	Retrospective study of different exposure settings	Spouse and family members	330/2441 (13.5%)	1361		7
Jing et al., Guangzhou, China [22]	Retrospective study of households	Lived in the same residential address	93/542 (17.2%)	215		6
Luo et al., Guangzhou, China [23]	Prospective study of different modes of contact	Lived in the same household	96/946 (10.1%)	347		7
Zhang et al., Guangzhou, China [24]	Retrospective study of pre-symptomatic transmission in different exposure settings	Lived in the same household	10/62 (16.1%)	38		6
Wu et al., Hangzhou, China [25]	Retrospective study of different exposure settings	Lived in the same household	50/280 (17.9%)	144		5
Li et al., Hubei, China [26]	Retrospective study of households	Lived in the same residence for at least 24 hours	64/392 (16.3%)	105		6
Zhang et al., Hunan, China [27]	Retrospective study of different exposure settings	Lived in the same household	339/617 (54.9%)	136		6
Zhang et al., Liaocheng, China [28]	Retrospective study of a supermarket cluster	Family members	12/93 (12.9%)	25		5
Deng et al., Nanchang, China [29]	Retrospective study of different exposure settings	Lived in the same household	20/201 (10.0%)	27		5
Chen et al., Ningbo, China [30]	Prospective study of different exposure settings	Lived in the same household	37/279 (13.3%)	187		6
Xin et al., Qingdao, China [31]	Prospective study of households	Family members in the same house	19/106 (17.9%)	31		7
Bi et al., Shenzhen, China [32]	Retrospective study of cases identified through symptomatic surveillance and contact tracing	Shared a room, apartment, or other sleeping arrangement	77/686 (11.2%)	391		6
Wei et al., Shenzhen, China [33]	Retrospective study of households	Lived in the same household, including visiting period	21/66 (31.8%)	60		5
Dong et al., Tianjin, China [34]	Retrospective study of households	Family members	53/259 (20.5%)	135		5
Wang et al., Wuhan, China [35]	Retrospective study of household transmission by healthcare workers	Family members	10/43 (23.3%)	25		5
Wang et al., Wuhan, China [36]	Retrospective study of households	Lived in the same household	47/155 (30.3%)	85	Only close contacts with symptoms tested; 51 contacts without symptoms assumed negative	5
Yu et al., Wuhan, China [37]	Retrospective study of different exposure settings	Family members	143/1396 (10.2%)	560		5
Hua et al., Zhejiang, China [38]	Retrospective study of households	Family members	151/835 (18.1%)	n/a		7
Sun et al., Zhejiang, China [39]	Retrospective study of family clusters	Family members	189/598 (31.6%)	148		5
Wu et al., Zhuhai, China [40]	Retrospective study of households	Spent at least one night in the house after symptom onset of the index case	48/148 (32.4%)	35		6

(*Continued*)

Table 1. (Continued)

Study, location	Description of study	Definition of close contact	Household SAR (%)	No. of index cases	Additional comments	Quality score
Kwok et al., Hong Kong, China [41]	Retrospective study of cases and close contacts	Provided care or stayed at the same place while the index case was ill	24/206 (11.7%)	53		6
Cheng et al., Taiwan, China [42]	Prospective study of different exposure settings and different exposure time windows	Lived in the same household	10/151 (6.6%)	100	Only close contacts with symptoms tested	7
Draper et al., Northern Territory, Australia [43]	Retrospective study in different exposure settings	Lived in the same household	2/51 (3.9%)	28	Only close contacts with symptoms tested	6
Chaw et al., Brunei [44]	Retrospective study in different exposure settings	Lived in the same household	28/264 (10.6%)	19		5
Schwartz et al., Ontario, Canada [45]	Retrospective study of household transmission by healthcare workers	Lived in the same residential address	391/3986 (9.8%)	n/a		6
Böhmer et al., Bavaria, Germany [46]	Analysis of contact investigation	Shared living space	2/20 (10%)	1		6
Laxminarayan et al., Tamil Nadu, India [47]	Retrospective study of different exposure settings	Lived in the same household	380/4066 (9.3%)	997		7
Boscolo-Rizzo et al., Treviso, Italy [48]	Retrospective study of adult household contacts of mildly symptomatic cases	Lived in the same household	54/121 (44.6%)	179	Only 121 out of 296 close contacts tested	5
Dattner et al., Bnei Brak, Israel [49]	Summary of contact investigations	Lived in the same household	981/2824 (34.7%)	529		6
Somekh et al., Bnei Brak, Israel [50]	Analysis of contact investigation	Lived in the same household	36/94 (38.3%)	n/a		5
Yung et al., Singapore [51]	Retrospective study of paediatric household contacts	Lived in the same household	13/213 (6.1%)	223		6
Lee et al., Busan, South Korea [52]	Analysis of contact investigation of asymptomatic index cases	Lived in the same household	1/23 (4.3%)	10		5
Son et al., Busan, South Korea [53]	Summary of contact investigations	Lived in the same household	16/196 (8.2%)	108		6
Park et al., Seoul, South Korea [54]	Retrospective study of a call center cluster	Lived in the same household	34/225 (15.1%)	97		6
Korea CDC, South Korea [55]	Summary of contact investigations	Lived in the same household	9/119 (7.6%)	30		5
Park et al., South Korea [56]	Summary of contact investigations	Lived in the same household	1248/10592 (11.8%)	5706		7
Arnedo-Pena et al., Castellon, Spain [57]	Retrospective study of households	Lived in the same household	83/745 (11.1%)	347		6
Rosenberg et al., New York State, United States [58]	Retrospective study of different exposure settings	Lived in the same residential address	131/343 (38.2%)	229		6
Dawson et al., Wisconsin, United States [59]	Retrospective study of households	Lived in the same household	16/64 (25%)	26		5
Yousaf et al., Wisconsin and Utah, United States [60]	Retrospective study of households	Lived in the same household	47/195 (24.1%)	n/a		6

(*Continued*)

Table 1. (Continued)

Study, location	Description of study	Definition of close contact	Household SAR (%)	No. of index cases	Additional comments	Quality score
Burke et al., United States [61]	Analysis of contact investigation	Family members or friends who spent at least one night in the same residence during the presumed infectious period of the index case	2/15 (13.3%)	9	Only close contacts with symptoms tested	6

Note: Index cases as defined in the respective study, generally determined based on the timing of symptom onset and epidemiological link.

https://doi.org/10.1371/journal.pone.0240205.t001

Only three studies differentiated the symptom status of index cases into pre-symptomatic and symptomatic. Fourteen studies had information on age groups that allowed differentiation by children and adults. Seven studies reported SAR by the relationship of close contacts of index cases.

From these 43 studies, we estimated household SAR and conducted subgroup analyses by stratifying according to location, definition of close contact, testing protocol, and publication status. We also examined whether SAR differed by symptom status of index case, child/adult infection, and relationship of close contacts of index cases.

Fig 2 summarizes the estimated SARs. The pooled household SAR is 18.1% (95% CI: 15.7%, 20.6%) with significant heterogeneity ($p < 0.001$). Household SAR ranged from 3.9% in Australia (Northern Territory) to more than 30% in some studies in China (Hunan, Shenzhen, Wuhan, Zhejiang, Zhuhai), Israel (Bnei Brak), Italy (Treviso), and the United States (New York).

Stratified household SAR

The household SAR from studies in mainland China (20.1%; 95% CI: 16.2%, 23.9%) was not significantly higher than other countries and areas (16.0%; 95% CI: 12.6%, 19.5%) (S1 Fig in S1 Materials). There was no significant difference in SAR in terms of the definition of household close contacts, whether they were based on living in the same household (18.2%; 95% CI: 15.3%, 21.2%) or based on relationships such as family and close relatives (17.8%; 95% CI: 13.8%, 21.8%) (S2 Fig in S1 Materials). Difference in testing protocols—whether testing was done for all contacts regardless of symptoms (18.0%; 95% CI: 15.4%, 20.5%) or symptomatic contacts only (19.8%; 95% CI: 4.6%, 35.0%)—also did not show a significant difference in household SAR (S3 Fig in S1 Materials).

The household SAR for published studies (18.7%; 95% CI: 16.0%, 21.4%) was not significantly higher than preprints (15.6%; 95% CI: 8.7%, 22.4%) (S4 Fig in S1 Materials). Funnel plot and Egger's meta-regression test also did not indicate the presence of publication bias (S5 Fig and S1 Table in S1 Materials).

Risk factors of household transmission

The risk of transmission varies by the symptom status of the index case. Based on three studies with available data, household SAR of symptomatic index cases were significantly higher than asymptomatic and pre-symptomatic cases, with a relative risk (RR) of 3.23 (95% CI: 1.46, 7.14) (Fig 3). In all three studies, the household SAR of symptomatic index cases (20.0%; 95% CI: 11.4%, 28.6%) was higher than those of asymptomatic ones (4.7%; 95% CI: 1.1%, 8.3%) (Fig 4).

SAR from 14 studies showed that close contacts who were adults were more likely to be infected compared to children (< 18 years old), with a relative risk of 1.71 (95% CI: 1.35, 2.17)

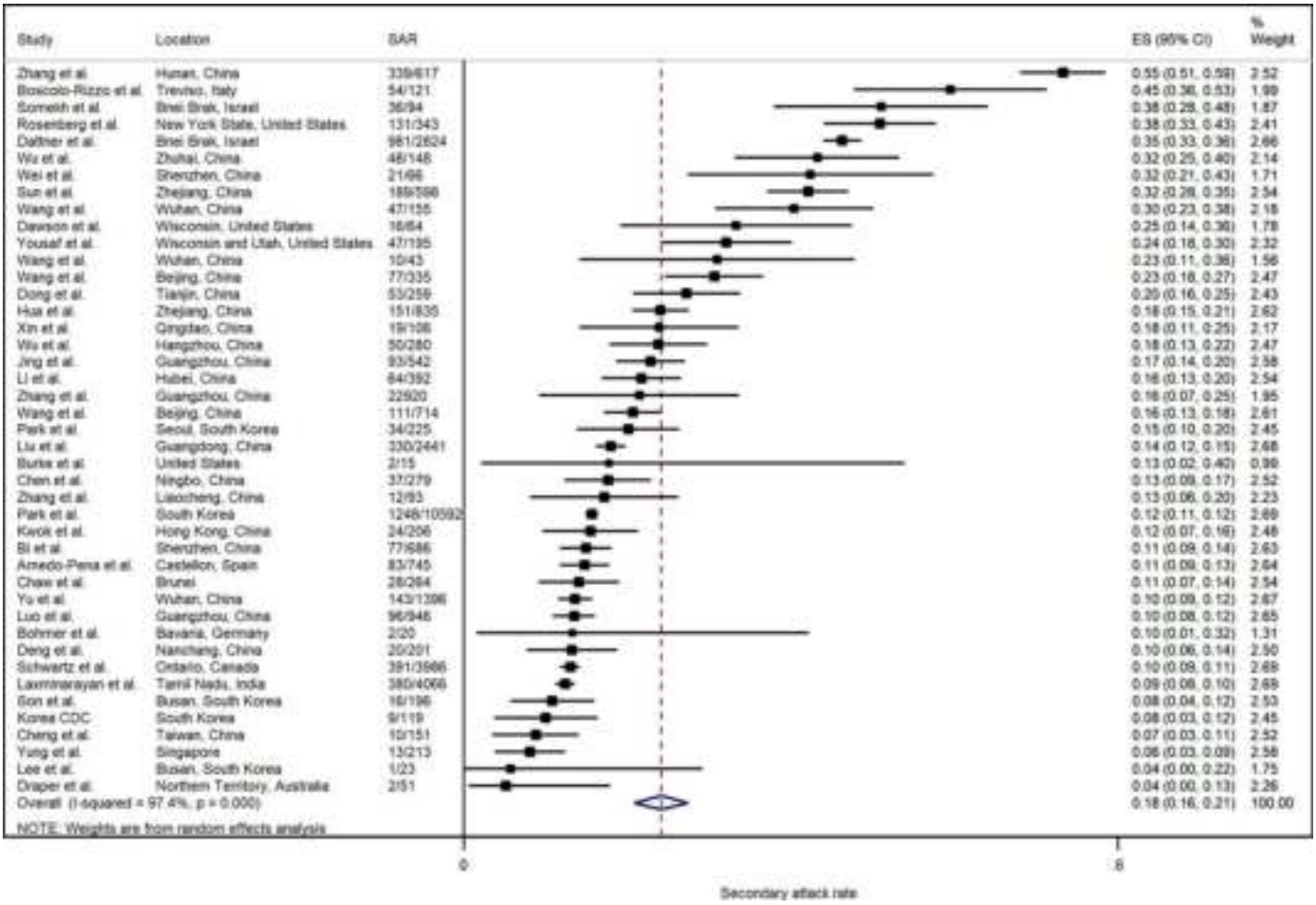

Fig 2. Forest plot of household secondary attack rates (SAR). ES is the estimated SAR, with 95% confidence intervals (CI). I-squared is the percentage of between-study heterogeneity that is attributable to variability in the true effect, rather than sampling variation.

https://doi.org/10.1371/journal.pone.0240205.g002

(Fig 5). However, there was considerable heterogeneity among the included studies. In three studies, infection in adults was marginally lower than in children, but overall, the household SAR in adults (33.3%; 95% CI: 24.4%, 42.1%) was significantly higher than that in children (16.9%; 95% CI: 10.9%, 22.9%) (Fig 6).

Spouse relationship to index case from seven studies indicated a significantly higher risk of infection (RR: 2.39; 95% CI: 1.79, 3.19) compared to other household members (Fig 7). In all seven studies, the SAR to spouses (37.5%; 95% CI: 22.2%, 52.7%) was higher than to other household contacts (16.3%; 95% CI: 10.6%, 22.1%) (Fig 8). However, there was considerable heterogeneity among the included studies.

Healthcare SAR

There are fewer SAR studies in non-household settings. We identified 18 studies that allowed direct estimation of the SAR in healthcare settings where transmission was determined to arise from an infected patient (Table 2). Nine of the studies covered multiple settings while the other nine studies focused solely on transmission in healthcare settings.

Sixteen studies were published articles (two in Chinese language) and two were pre-prints. Nine studies were in China, four in the United States, and the others were in Germany, India,

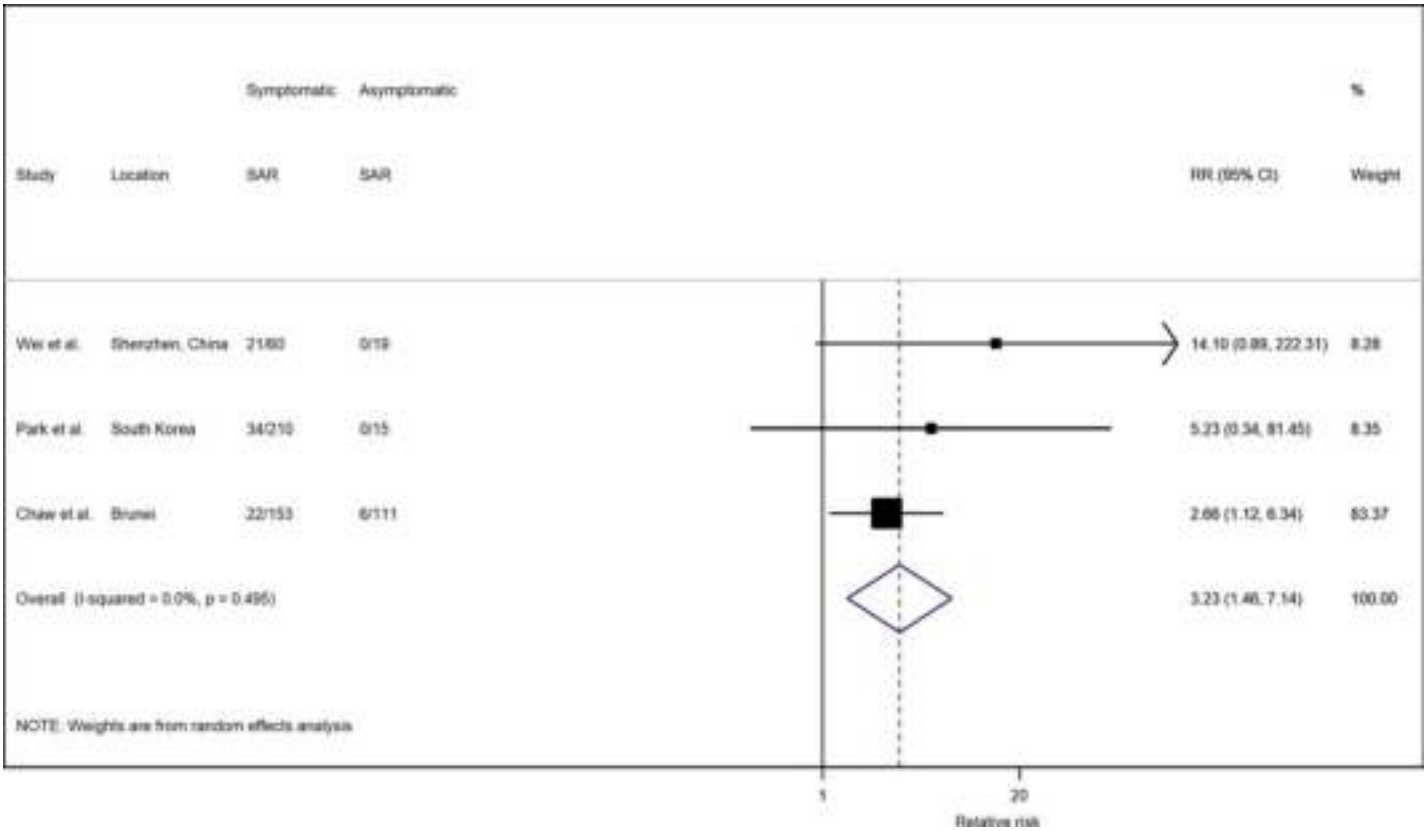

Fig 3. Forest plot of household transmission risk by symptom status of index case. RR is the estimated risk ratio, with 95% confidence intervals (CI). I-squared is the percentage of between-study heterogeneity that is attributable to variability in the true effect, rather than sampling variation.

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Japan, Singapore, and Switzerland. All close contacts were tested regardless of symptoms except for four studies where testing was done only on symptomatic contacts. There was minor variation in the definition of healthcare contacts; most included healthcare workers and patients that were exposed to the index case, although a few studies were more specific in indicating close contact as those without personal protective equipment (PPE) or within a certain distance from the index case.

Fig 9 summarizes the estimated SARs. The pooled healthcare SAR was 0.7% (95% CI: 0.4%, 1.0%). Heterogeneity was not significant (p = 0.690). The SAR in healthcare settings in most studies was generally low (< 2%), except for a study in Wuhan that indicated 2 of 5 (40%) healthcare personnel were infected [37]. A study in California that tested symptomatic contacts only [68] had a relatively high healthcare SAR (7.0%), but overall there was no significant difference according to testing protocols (S6 Fig in S1 Materials).

SAR in other non-household settings

We found 17 studies that allowed estimation of SAR in settings or by contact type other than household and healthcare: relatives outside the household; meal; travel; social; workplace; school; religious gathering; business meeting; choir; and chalet (Table 3). Due to the limited number of studies in each of these settings, unclear or imprecise definitions of close contacts, and the large variation in SAR across the settings, we did not estimate a pooled SAR. Instead, we reported the SAR to highlight potential high-risk settings.

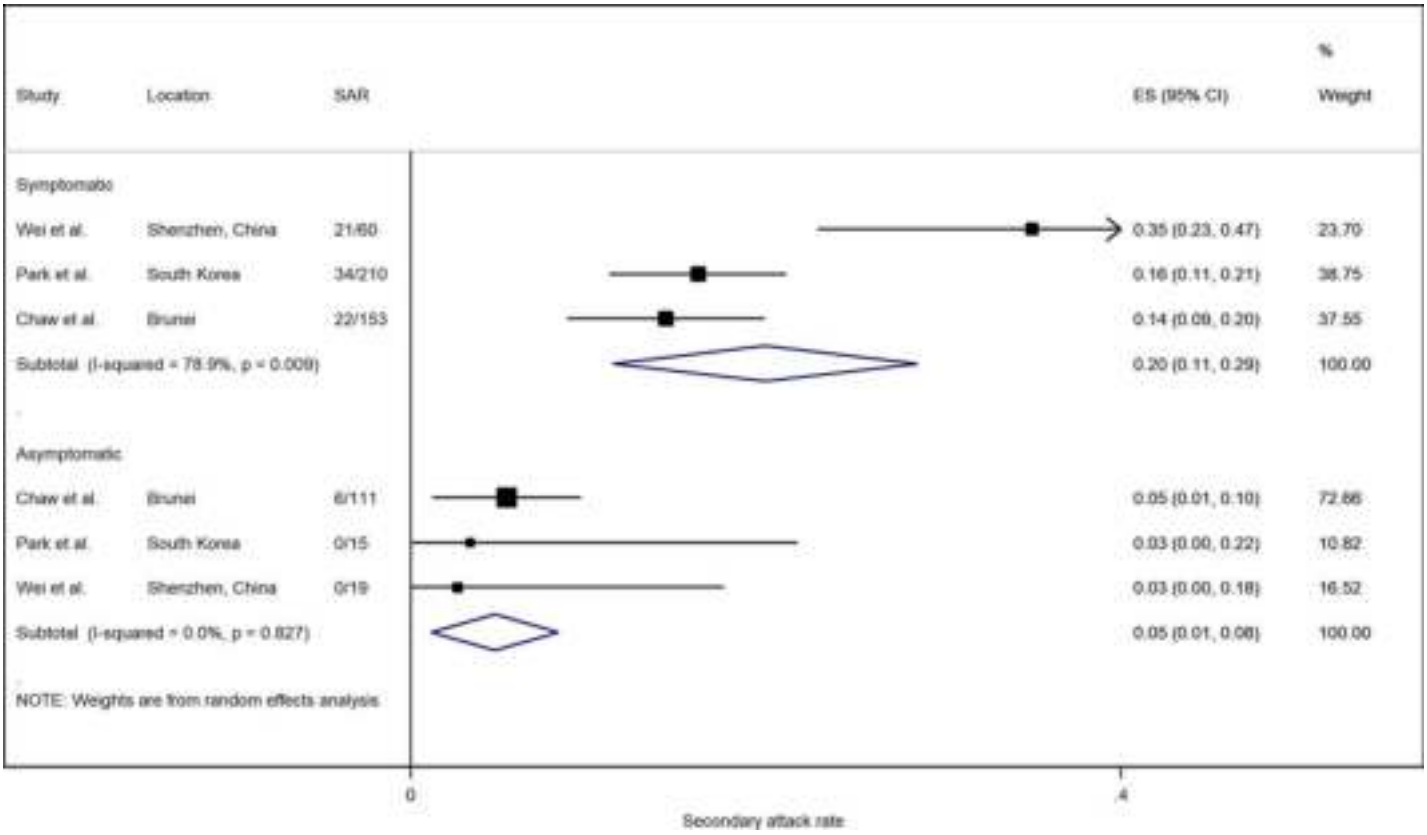

Fig 4. Forest plot of household secondary attack rates (SAR) by symptom status of index case. ES is the estimated SAR, with 95% confidence intervals (CI). I-squared is the percentage of between-study heterogeneity that is attributable to variability in the true effect, rather than sampling variation.

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High SARs were observed in a meeting (84.6%), a chalet (73.3%), and at choirs (70.4%, 53.3%). In other settings, relatively high SARs were reported in eating (38.8%, 28.6%) and traveling (80.8%, 46.6%) with a case, as well as a study evaluating a religious event (14.8%). SARs were much lower in encounters with relatives (3.5% to 6.6%), social contacts (0.9% to 2.2%), and at workplace or school (0% to 5.3%).

Discussion

Summary of key findings

We estimated household SAR at 18.1% (95% CI: 15.7%, 20.6%), with significant heterogeneity across studies ranging from 3.9% to 54.9%. Symptomatic persons in households had a significantly higher risk of infecting others compared to asymptomatic ones (RR: 3.23; 95% CI: 1.46, 7.14). Adults in households had a significantly higher risk of infection relative to children (RR: 1.71; 95% CI: 1.35, 2.17). Spouses of index cases were more likely to be infected when compared to other household contacts (RR: 2.39; 95% CI: 1.79, 3.19). In healthcare settings, SAR was estimated at 0.6% (95% CI: 0.4%, 0.9%).

Secondary attack rate

We used SAR across various settings as a measure of viral transmissibility. While a number of studies have estimated the basic reproductive number (R0) at 2–4, [77–80] in isolation it is a

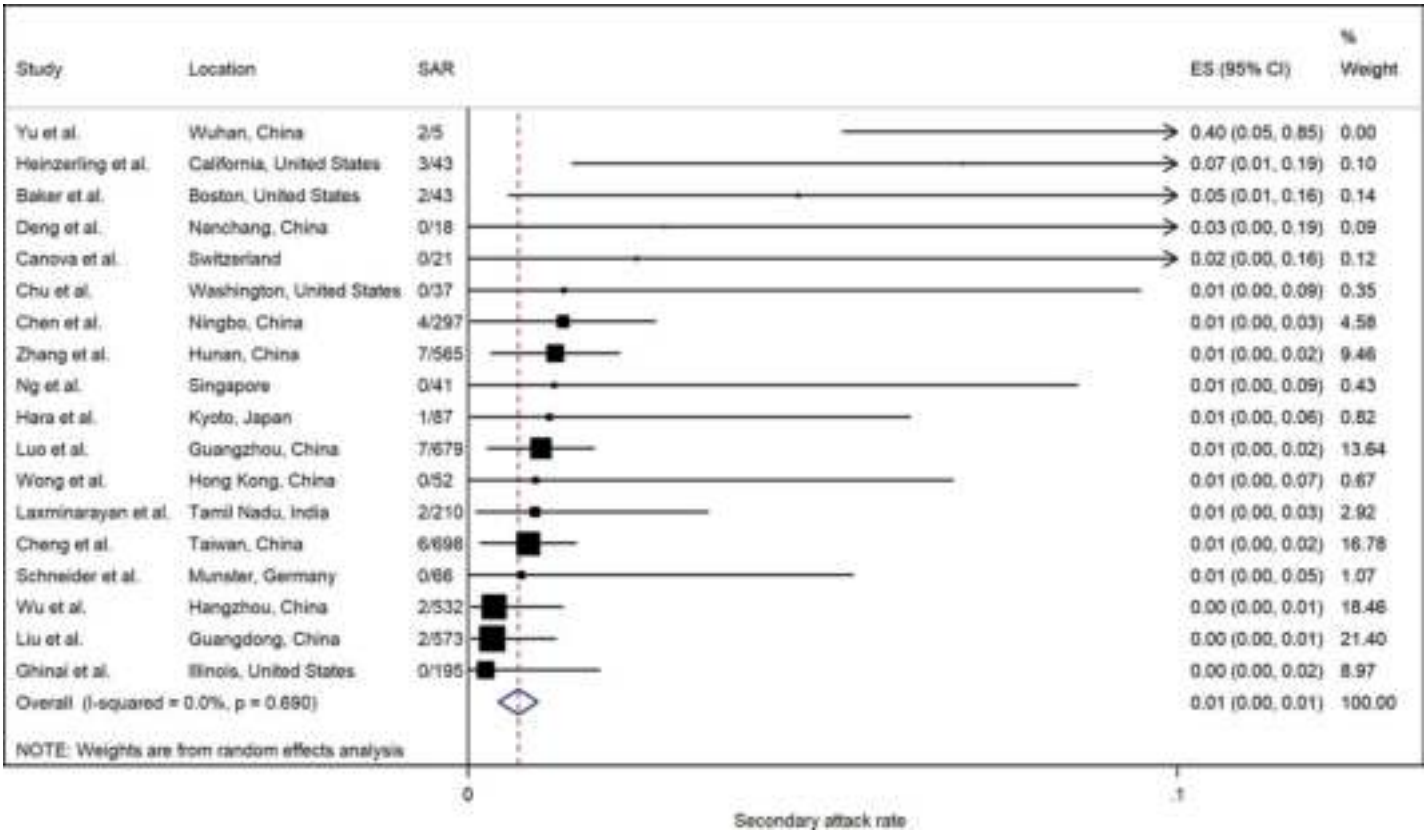

Fig 5. Forest plot of household transmission risk by adult and children close contact. RR is the estimated risk ratio, with 95% confidence intervals (CI). I-squared is the percentage of between-study heterogeneity that is attributable to variability in the true effect, rather than sampling variation.

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suboptimal gauge of infectious disease dynamics as it does not account for variability in specific situations and settings [81, 82].

Significant heterogeneity in SAR across different settings is unsurprising given that SAR depends not only on the causative agent but also on socio-demographic, environmental, and behavioral factors in study populations [83]. Variation in methods for case ascertainment and subsequent detection of infected cases among contacts likely contributed to the heterogeneity across studies.

Household SAR was estimated at 18.1%. Reports suggest that familial transmission account for the majority of transmissions [36, 84]. The household is thought to be a fundamental unit of SARS-CoV-2 transmission because of the high frequency and intensity of contacts that occur between family members, and because transmission has continued in places with movement restriction [44]. We found that household SAR was higher than the upper range of estimates of the household SAR for the 2009 H1N1 pandemic influenza (5–15%) [85–87], and also higher than that observed for both SARS (5–10%) [88–90] and MERS (4–5%) [91, 92]. This suggests relatively higher SARS-CoV-2 transmissibility in the household setting, when compared to that of H1N1 and MERS viruses. SARS-CoV-2 also has a higher R0 when compared to MERS-CoV and SARS-CoV-1 [93]. This finding highlights the necessity of swift case isolation, immediate tracing, and quarantine of household contacts [94].

The highest household SARs were observed in mainland China, Israel, Italy, and the United States—countries with sustained outbreaks—whereas SARs were generally lower in countries and areas that have done relatively well in outbreak control, such as Brunei, Hong Kong, South

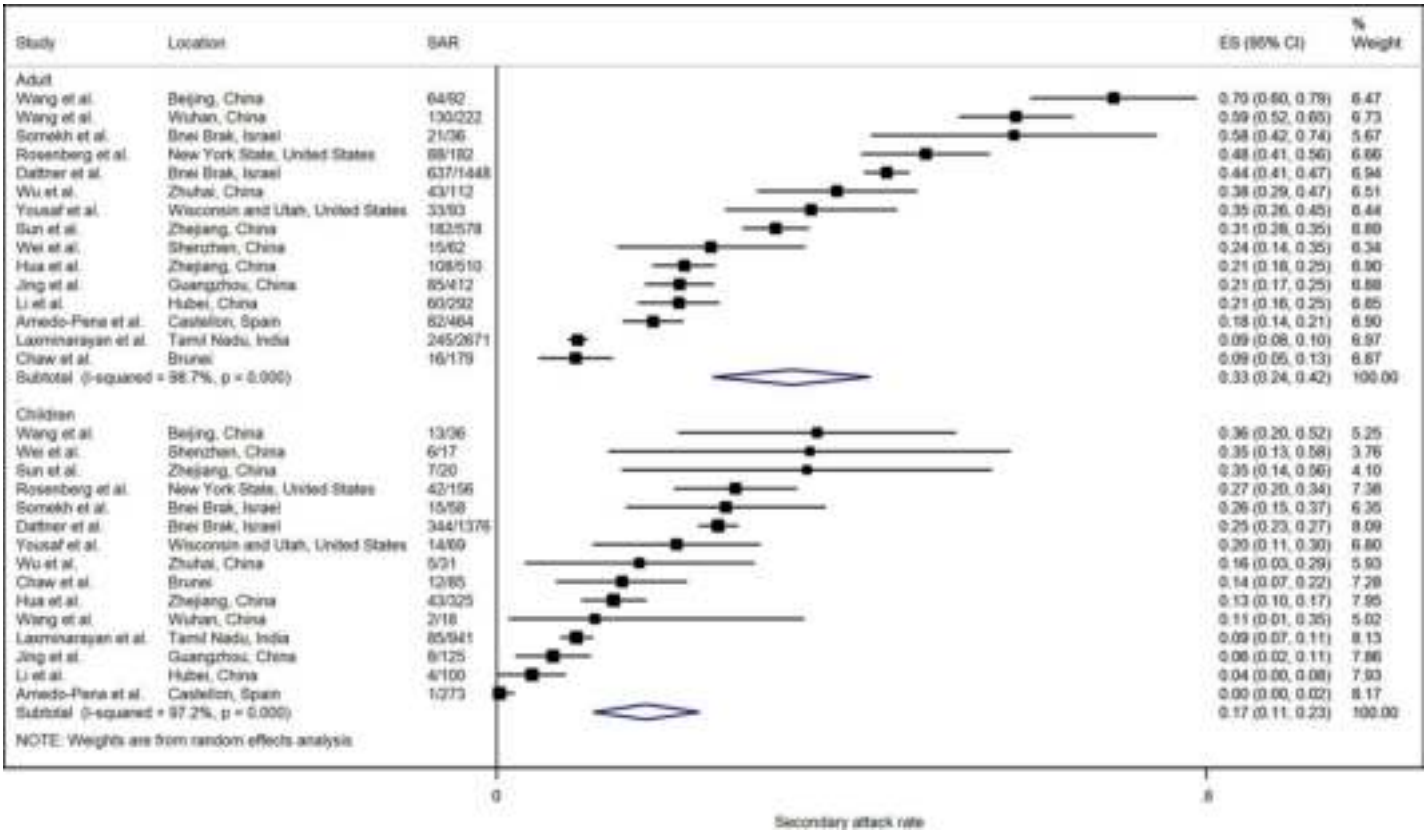

Fig 6. Forest plot of household secondary attack rates (SAR) by adult and children close contact. ES is the estimated SAR, with 95% confidence intervals (CI). I-squared is the percentage of between-study heterogeneity that is attributable to variability in the true effect, rather than sampling variation.

https://doi.org/10.1371/journal.pone.0240205.g006

Korea, and Taiwan. Outside sources of infection are likely to be higher in countries with sustained community transmission, and as such without accounting for these, the household SARs are likely to be overestimated. Nonetheless, the potential for high transmission in households is clearly evident.

Healthcare workers who provide care to hospitalized patients could be at high risk of infection, particularly those without adequate PPE due to delayed diagnosis of COVID-19. We quantified this risk and found that SARs in healthcare settings in most studies were low (< 2%). An exception is a study in Wuhan, which reported that 2 out of 5 (40%) medical personnel were infected [37]. The authors attributed the high SAR to inadequate acknowledgment of pathogens, misclassification of patients with COVID-19 as ordinary fever cases, and shortage of PPE during the early stage (late December 2019 to early January 2020) when the outbreak was still not well understood.

The generally low SAR in non-household settings may mask variation between setting types. Some studies reported significantly higher SAR in mass gatherings and other enclosed settings with potential for prolonged physical contact, such as at a meeting in Germany (84.6%) [75], a ski chalet in France (73.3%) [71], at a choir in France (70.4%) [72], during meals in China (38.8%) [40], and during travel in India (80.8%) [47]. In contrast, SAR in workplace, school, and social settings ranged between 0–5%, suggesting a gradation of risk outside the household.

Our meta-analyses excluded studies that solely reported attack rates (AR) without identification of an index case and their transmission generations within the cluster. However, such

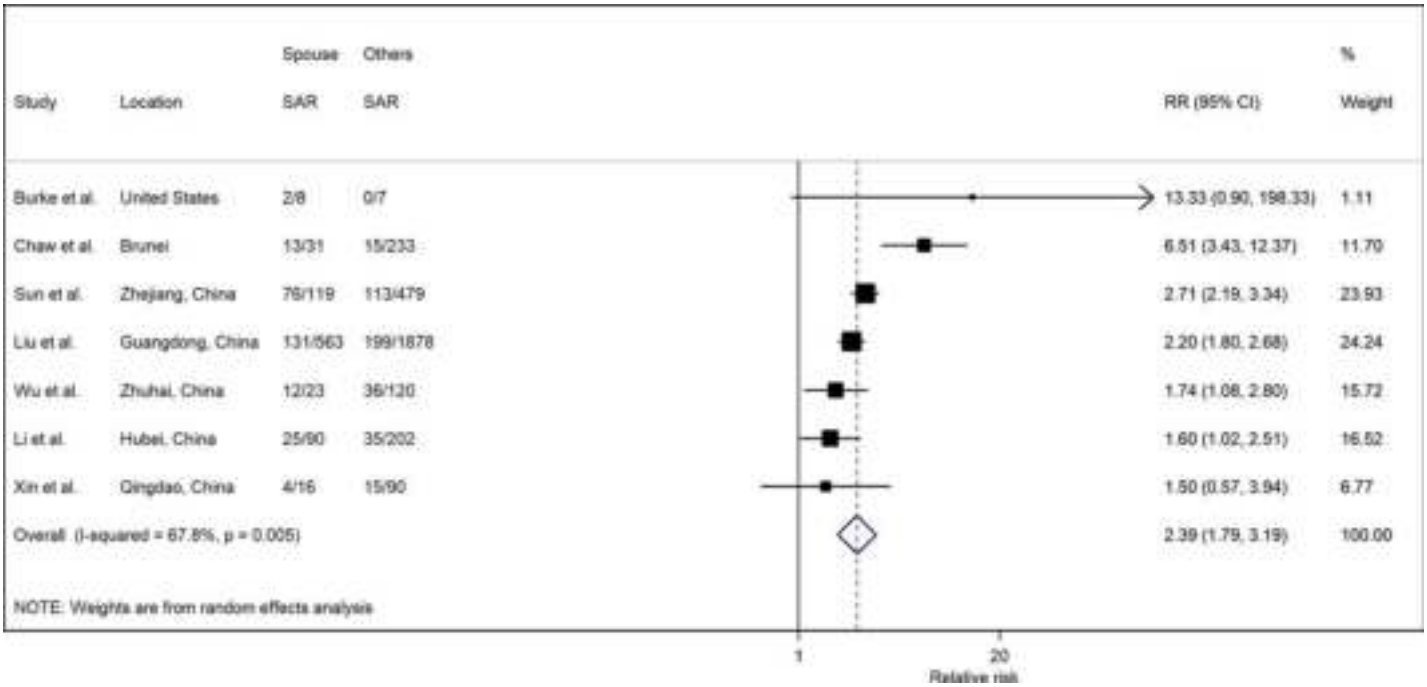

Fig 7. Forest plot of household transmission risk by relationship to index case. RR is the estimated risk ratio, with 95% confidence intervals (CI). I-squared is the percentage of between-study heterogeneity that is attributable to variability in the true effect, rather than sampling variation.

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studies may be important in understanding the role of super-spreading events (SSEs) in driving SARS-CoV-2 transmission [82]. Specific settings where high ARs (> 20%) have been observed were in a correctional and detention facility in Louisiana (72.4%) [95], nursing homes in California (70.3%) [96] and the United Kingdom (40.3%) [97], in cruise ships (59%) [98], a call centre in South Korea (43.5%) [54], a church in Arkansas (38%) [99], among college students during a spring break trip in Mexico (32.8%) [100], a homeless shelter in Boston (36%) [101], a fitness dance class in South Korea (26.3%) [102], and a wedding in Jordan (21.7%) [103] (S2 Table in S1 Materials). High ARs have also been reported in healthcare settings in Mexico City (31.9%) [104] and the United Kingdom (27.7%) [105].

Reflecting on the high SAR in households and high AR in numerous non-household settings, we suggest that several common environmental factors could potentially account for the rapid person-to-person transmission observed: closed environments, population density, and shared eating environments. This is supported by environmental sampling studies [106] and from ecological observations on the declining incidence of COVID-19 cases in areas with restrictions placed on indoor mass gatherings [107].

There are implications for mass gatherings, particularly as countries begin to relax physical distancing measures. Non-household residential settings such as long-term care facilities, dormitories, and detention facilities pose specific challenges where additional prevention measures merit consideration, including staff screening, enhanced testing, and strict visitor policies [108].

Certainly, across all settings, the longer the duration and the greater the degree of physical contact with an index case, the higher the risk of transmission. However, we find that the risk model for transmission of SARS-CoV-2 is nuanced—while the highest risk of transmission is in crowded and enclosed settings, casual social interaction in some public settings have a lower risk. In addition, as the pandemic progresses and concern with physical distancing measures

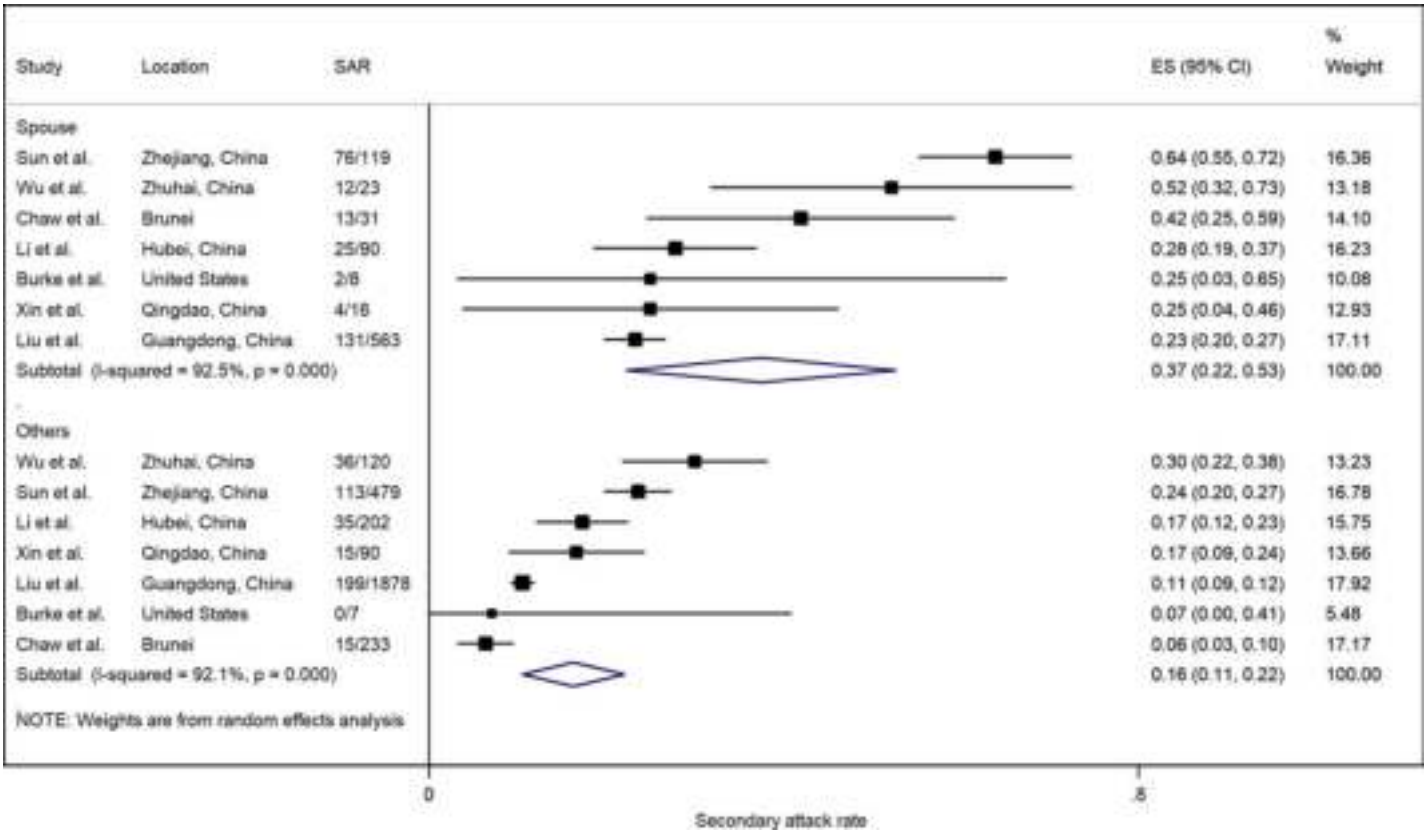

Fig 8. Forest plot of household secondary attack rates (SAR) by relationship to index case. ES is the estimated SAR, with 95% confidence intervals (CI). I-squared is the percentage of between-study heterogeneity that is attributable to variability in the true effect, rather than sampling variation.

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(so-called "quarantine fatigue") gain momentum [109], public communications surrounding these measures should convey this continuum of risk based on the transmission dynamics across different settings, supporting sustainable longer-term behavior changes.

SARS-CoV-2 transmission in children

For many infectious diseases, such as seasonal and pandemic influenza, children are known be drivers of transmission within households and communities [110]. Case series data on SARS--CoV-2 suggests that children are less likely to be affected than adults. A national analysis of the first 72,314 cases in China reported only 2.1% of all cases were children aged 0–19 years old [111]. Other population-wide studies show similarly low proportions [56, 112, 113].

To better understand their relative susceptibility to infection, we compared the SAR between adults and children and found that adults were at 1.7 times higher risk of infection than children. The lower rate of susceptibility in children could be explained by differences in symptomatic infection rates and subsequent issues with case ascertainment [114].

The literature surrounding infectivity in children was scarce. In household transmission studies, children were usually identified through contact tracing of adult cases, although a number of case reports documented transmission from children to adults [115]. There is also insufficient knowledge on transmissibility of SARS-CoV-2 from children to other children. In addition, age may be important to determine dynamics of interactions among children but inadequate data hampered our efforts at risk stratification by age.

Table 2. Description of studies included in the review and analysis of healthcare secondary attack rate (SAR).

Study, location	Description of study	Definition of close contact	Healthcare SAR (%)	No. of index cases	Additional comments	Quality score
Liu et al., Guangdong, China [21]	Retrospective study of different exposure settings	Healthcare workers exposed to case	2/573 (0.3%)	1361		7
Luo et al., Guangzhou, China [23]	Prospective study of different modes of contact	Medical staff who provide direct care, family members or others who have similar close contact with case, such as visiting or staying at the same hospital ward	7/679 (1.0%)	347		7
Wu et al., Hangzhou, China [25]	Retrospective study of different exposure settings	Healthcare provided or other patient	2/532 (0.4%)	144		5
Zhang et al., Hunan, China [27]	Retrospective study of different exposure settings	Diagnosed, treated, or nursed a case	7/565 (1.2%)	136		6
Deng et al., Nanchang, China [29]	Retrospective study of different exposure settings	Had medical services at the same time or shared wards	0/18 (0%)	27		5
Chen et al., Ningbo, China [30]	Prospective study of different exposure settings	Healthcare workers exposed to case	4/297 (1.3%)	187		6
Yu et al., Wuhan, China [37]	Retrospective study of different exposure settings	Doctors and patients exposed to case	2/5 (40%)	560		5
Wong et al., Hong Kong, China [62]	Retrospective study of healthcare setting	Patient or staff who stayed or worked in the same ward as the index patient	0/52 (0%)	1	Only 52 of 120 contacts tested; the rest were asymptomatic	5
Cheng et al., Taiwan, China [42]	Prospective study of different exposure settings and different exposure time windows	Within 2m without appropriate PPE and without a minimal requirement of exposure time	6/698 (0.9%)	100	Only close contacts with symptoms tested	7
Schneider et al., Munster, Germany [63]	Retrospective study of healthcare setting	Healthcare workers exposed to infected patient	0/66 (0%)	1		5
Laxminarayan et al., Tamil Nadu, India [47]	Retrospective study of different exposure settings	Healthcare workers exposed to case	2/210 (1.0%)	11		7
Hara et al., Kyoto, Japan [64]	Retrospective study of healthcare setting	Patients exposed to an infected healthcare worker	1/87 (1.1%)	1		5
Ng et al., Singapore [65]	Retrospective study of healthcare setting	Exposed to aerosol-generating procedures for at least 10 minutes at a distance of less than 2 meters from the infected patient	0/41 (0%)	1		5
Canova et al., Switzerland [66]	Analysis of contact investigation	Healthcare workers with unprotected contact with the case	0/21 (0%)	1		6
Baker et al., Boston, United States [67]	Retrospective study of healthcare setting	Provided care to infected patient	2/44 (4.5%)	1	7 healthcare workers not tested, and assumed negative	5
Heinzerling et al., California, United States [68]	Retrospective study of healthcare setting	Symptomatic healthcare workers exposed to infected patient	3/43 (7.0%)	1	121 healthcare workers exposed, but only those with symptoms tested	5
Ghinai et al., Illinois, United States [69]	Analysis of contact investigation	People who reported or were identified to have potential exposure on or after the date of symptom onset of the case	0/195 (0%)	1	Only persons under investigation and selected asymptomatic healthcare personnel tested	5
Chu et al., Washington, United States [70]	Retrospective study of healthcare setting	Face-to-face interaction with infected patient without full personal protective equipment (PPE)	0/37 (0%)	1		5

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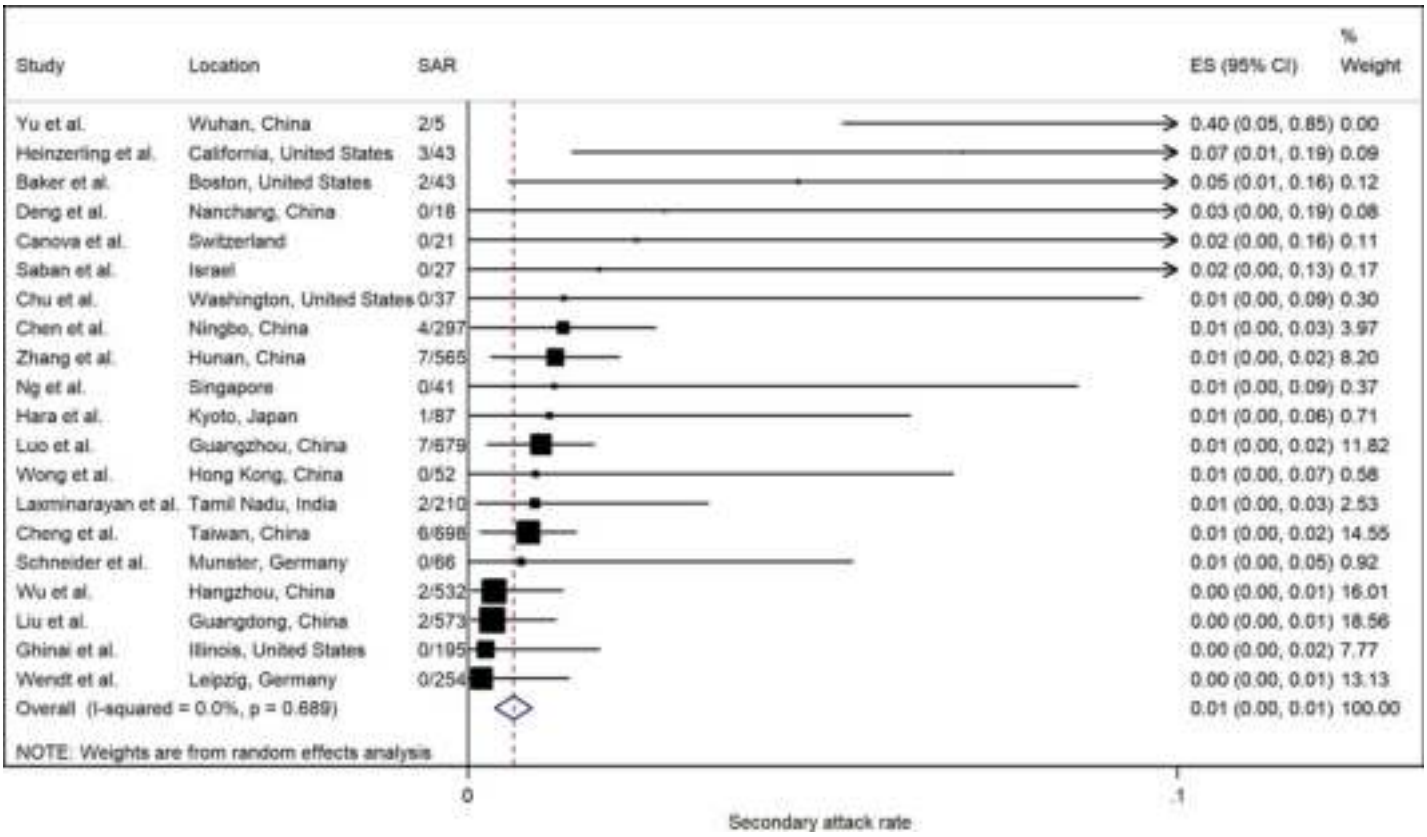

Fig 9. Forest plot of secondary attack rates (SAR) in healthcare settings. ES is the estimated SAR, with 95% confidence intervals (CI). I-squared is the percentage of between-study heterogeneity that is attributable to variability in the true effect, rather than sampling variation.

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While there are important unknowns with respect to SARS-CoV-2 in children, these early findings may assist health authorities in determining proportionate thresholds for school closures in future waves of the pandemic.

Strengths and limitations

Our analysis has important limitations. The studies selected were based on field investigation; variability was noted with respect to the study design, the number of individuals assessed, clinical definitions, the extent to which confirmatory laboratory tests were used, the methods of clinical data collection, and the duration of follow-up. Studies have different definitions of household and contacts and are subject to recall and observer bias [116]. Moreover, without accounting for outside sources of infection, setting-specific SARs are likely to be overestimated [83]. In fact, none of the reviewed studies addressed the composition of secondary vs. community infections when estimating the SAR or used viral sequencing to confirm homology between the strains infecting the index and secondary cases in the household.

All SAR studies were retrospective transmission studies based on contact tracing datasets where the index case determination or the direction of transmission may be uncertain, particularly as a substantial proportion of cases was asymptomatic or mild. An additional challenge concerns the timing of recruitment of cases and their contacts during the course of an epidemic. Studies conducted in early stages can provide timely SAR estimates; however, this may be influenced by behavioral factors and other non-pharmaceutical interventions (e.g. community quarantine) that could have altered over the course of the epidemic [83].

Table 3. Studies of secondary attack rate (SAR) in settings outside household and healthcare.

Study	Location	Setting	SAR (%)
Danis et al. [71]	French Alps	Chalet	11/15 (73.3%)
Charlotte [72]	France	Choir	19/27 (70.4%)
Hamner et al. [73]	Washington, United States	Choir	32/60 (53.3%)
Wu et al. [40]	Zhuhai, China	Meal	40/103 (38.8%)
Shen et al. [74]	Zhejiang, China	Meal	2/7 (28.6%)
Deng et al. [29]	Changsha, China	Meal	17/160 (10.6%)
Bi et al. [32]	Shenzhen, China	Meal	61/707 (8.6%)
Chen et al. [30]	Ningbo, China	Meal	52/724 (7.2%)
Hijnen et al. [75]	Munich, Germany	Meeting	11/13 (84.6%)
Cheng et al. [42]	Taiwan, China	Non-household family	5/76 (6.6%)
Liu et al. [21]	Guangdong, China	Non-household family	132/2266 (5.8%)
Chaw et al. [44]	Brunei	Non-household family	5/144 (3.5%)
Chaw et al. [44]	Brunei	Religious	8/54 (14.8%)
Wang et al. [20]	Beijing, China	Social	75/3363 (2.2%)
Zhang et al. [24]	Guangzhou, China	Social	1/66 (1.5%)
Liu et al. [21]	Guangdong, China	Social	41/3344 (1.2%)
Chaw et al. [44]	Brunei	Social	4/445 (0.9%)
Laxminarayan et al. [47]	Tamil Nadu, India	Travel	63/78 (80.8%)
Wu et al. [40]	Zhuhai, China	Travel	34/73 (46.6%)
Chen et al. [30]	Ningbo, China	Travel	28/235 (11.9%)
Zhang et al. [24]	Hunan, China	Travel	22/304 (7.2%)
Bi et al. [32]	Shenzhen, China	Travel	18/318 (5.7%)
Draper et al. [43]	Northern Territory, Australia	Travel	2/46 (4.3%)
Liu et al. [21]	Guangdong, China	Travel	10/2778 (0.4%)
Luo et al. [23]	Guangzhou, China	Travel	3/2358 (0.1%)
Deng et al. [29]	Changsha, China	Travel	0/17 (0%)
Danis et al. [71]	French Alps	School	0/112 (0%)
Heavey et al. [76]	Ireland	School	0/1025 (0%)
Deng et al. [29]	Changsha, China	Workplace	5/94 (5.3%)
Zhang et al. [24]	Guangzhou, China	Workplace	0/119 (0%)
Chen et al. [30]	Ningbo, China	Workplace/school	1/47 (2.1%)
Chaw et al. [44]	Brunei	Workplace/school	6/848 (0.7%)

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The major strength of our study is that it comprehensively covers publicly available studies on SARS-CoV-2 transmission-related dynamics with regards to settings and associated risk factors, thus allowing a better understanding and identification of the key drivers of transmission.

Conclusion

Our estimates of SAR across various settings demonstrate the challenges in controlling SARS--CoV-2 transmission. Overall, these findings suggest that aggressive contact-tracing strategies based on suspect cases may be appropriate early in an outbreak. However, as the outbreak progresses, control measures should transition to a combination of approaches that account for setting-specific transmission risk. Given the high SARs observed in households and other residential settings, physical distancing measures may need to cover entire communities such as dormitories, workplaces, or other institutional settings, while contact tracing should shift to

identifying hotspots of transmission and vulnerable populations. Where possible, confirmed cases should be isolated away from the household.

Supporting information

S1 Checklist. PRISMA 2009 checklist.
(DOC)

S1 Materials.
(PDF)

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Supervision: Justin Wong.

Validation: Justin Wong.

Visualization: Wee Chian Koh.

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Defining the role of asymptomatic and pre-symptomatic SARS-CoV-2 transmission – a living systematic review

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Defining the role of asymptomatic and pre-symptomatic SARS-CoV-2 transmission – a living systematic review

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Key words: COVID-19, asymptomatic, transmission, SARS-CoV-2, secondary attack rate

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Abstract:

Background Reports suggest that asymptomatic individuals (those with no symptoms at all throughout infection) with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are infectious, but the extent of transmission based on symptom status requires further study.

Purpose This living review aims to critically appraise available data about secondary attack rates from people with asymptomatic, pre-symptomatic and symptomatic SARS-CoV-2 infection.

Data sources Medline, EMBASE, China Academic Journals full-text database (CNKI), and pre-print servers were searched from 30 December 2019 to 3 July 2020 using relevant MESH terms.

Study selection Studies that report on contact tracing of index cases with SARS-CoV-2 infection in either English or Chinese were included.

Data extraction Two authors independently extracted data and assessed study quality and risk of bias. We calculated the secondary attack rate as the number of contacts with SARS-CoV-2, divided by the number of contacts tested.

Data synthesis Of 927 studies identified, 80 were included. Summary secondary attack rate estimates were 1% (95% CI: 0%-2%) with a prediction interval of 0-10% for asymptomatic index cases in 10 studies, 7% (95% CI: 3%-11%) with a prediction interval of 1- 40% for pre-symptomatic cases in 11 studies and 6% (95% CI: 5%-8%) with a prediction interval of 5- 38% for symptomatic index cases in 40 studies. The highest secondary attack rates were found in contacts who lived in the same household as the index case. Other activities associated with transmission were group activities such as sharing meals or playing board games with the index case, regardless of the disease status of the index case.

Limitations We excluded some studies because the index case or number of contacts were unclear.

Conclusion Asymptomatic patients can transmit SARS-CoV-2 to others, but our findings indicate that such individuals are responsible for fewer secondary infections than people with symptoms.

Systematic review registration PROSPERO CRD42020188168

Funding: No funding was received

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Introduction:

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) demonstrates efficient transmission in populations without effective public health interventions; basic reproduction numbers (R_0) values range between 2-3 [1]. While asymptomatic transmission has been described as the "Achilles' heel" of control efforts during this pandemic, the extent to which transmission of SARS-CoV-2 by people without symptoms drives this pandemic remains uncertain [2]. SARS-CoV-2 infection that is asymptomatic at the time of laboratory testing is widely reported [3]; however, studies that follow infected people over time suggest that many infections are not asymptomatic throughout the entire disease course, and a large proportion of these individuals ultimately develop a diverse range of symptoms [4-7]. For instance, Sugano et al. reported a detailed cluster outbreak in music clubs in Japan, where asymptomatic cases reported also included pre-symptomatic cases [8]. A living systematic review of studies published up to 10 June 2020 estimated that 20% (95% CI 17 to 25%) of people who become infected with SARS-CoV-2 remain asymptomatic throughout infection [7].

One of the barriers to understanding the role of asymptomatic transmission is the lack of consistency in case definitions [9]. While symptom severity exists on a spectrum, individuals infected with SARS-CoV-2 can be miscategorized as asymptomatic, when they have milder or atypical symptoms leading to overestimation of the proportion without symptoms [3, 10]. For instance, in a detailed study of SARS-CoV-2 infections in Iceland where individuals deemed at high risk for COVID-19 including those with a consistent syndrome were screened in a targeted manner, and other individuals were tested via a population screening mechanism, more than a third in the second group reported symptoms potentially consistent with COVID-19 [3]. However, it is increasingly becoming clear that some individuals experience more diverse symptoms, including taste and smell disturbance or myalgia, either for the entire course of illness or preceding respiratory symptoms. These symptoms can be so mild and insidious that they do not limit patients' daily activities [4, 11]. The situation is further complicated by subjective patient perception and differences between studies in the elicitation and reporting of symptoms.

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There are reports describing asymptomatic individuals with SARS-CoV-2 who are infectious [12] and who have infected one or more contacts [13], but the extent and significance of asymptomatic transmission requires further understanding. The aim of this review is to summarize the available evidence about secondary attack rates (defined as the probability that an infected individual will transmit the disease to a susceptible individual) amongst the contacts of individuals with SARS-CoV-2 with different symptom status to provide information about how contagious they are, and their role in driving the pandemic.

Methods:

Systematic review was registered in PROSPERO on 8 June 2020 (CRD42020188168) and will be updated 4-6 months according to the availability of new evidence as a living systematic review [14]. The larger review aims to answer transmission dynamics of SARS-CoV-2. The analysis in this report addresses one of the review questions; to identify secondary attack rate based on symptom status.

Definitions

We defined “asymptomatic” as an individual with laboratory-confirmed SARS-CoV-2 infection but without symptoms throughout their entire course of infection, or after 14 days of follow up; “paucisymptomatic” as an individual with laboratory-confirmed SARS-CoV-2 infection with mild symptoms, and “pre-symptomatic” as an individual who reports no symptoms at the time of the initial positive test result, but who subsequently develops symptoms attributable to COVID-19. We used these definitions to categorize the index cases. Secondary attack rate was defined as the number of new SARS-CoV-2 infection cases among susceptible contacts of primary cases divided by the total number of susceptible contacts.

Search Strategy

We retrieved articles about transmission of SARS-CoV-2 infection through systematic searches of eight databases: Medline, EMBASE, Europe PMC, Web of Science, SCOPUS, Chinese database (CNKI), and preprint servers (MedRxiv, BioRxiv) using relevant Medical Subject

Headings (MeSH) terms (Supplementary material). The initial search was completed from 30 December 2019 to 21 May 2020, searches were repeated on 8 June 2020 and 3 July 2020, owing to the rapidly increasing numbers of studies.

Study Selection

Studies were eligible if they met the inclusion criteria: (1) report on Coronavirus disease 2019 (COVID-19) or SARS-CoV-2 infection and (2) report an outbreak investigation or contact tracing study. Exclusion criteria were: (1) review articles; (2) observational studies providing only the proportion of individuals infected; (3) studies that do not indicate the number of contacts or secondary infections; and (4) reports in media sources. We also manually screened the references of the included original studies and reviews to identify additional eligible studies.

Data Extraction

Two authors (XQ and AIN) independently reviewed reports by title and abstract for relevance, with at least 20% of all reports being screened in duplicate to ensure consistency. Two authors then independently read the full text report of all studies not excluded by title and abstract, to consider eligibility for inclusion. Any disagreements regarding study inclusion were resolved through discussion with a third author (MC). Data were extracted onto a standardized form. From each study, the following variables were extracted: the name of the first author, year of publication, country, sample size, details of index cases (categorised as asymptomatic, pre-symptomatic and symptomatic); event details such as environment, transmission details; number of contacts, number of secondary cases. If these data were not reported, we contacted authors to request them and checked with the authors about all symptoms that they sought.

Risk of bias in included studies

Two authors (XQ and AIN) independently assessed completeness of reporting and risks of bias, using an adapted version of the Joanna Briggs Institute Critical Appraisal Checklist for Case Series (Supplementary material). Any disagreements were resolved through discussion with a third author (MC).

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Data synthesis and statistical analysis

The studies are summarized in text and table form, descriptive statistics were completed for key outcome measures. Secondary attack rates were computed from raw data in each study, dividing the number of infected contacts of primary cases by the total number of susceptible exposed contacts. A pooled analysis was carried out to generate summary estimates for the secondary attack rate in each subgroup analyzed (asymptomatic, pre-symptomatic and symptomatic index cases), in the framework of a random effect model. The Freeman – Tukey double-arcsine variance-stabilizing transformation was used to combine data, due to its advantage over log and logit transformations which did not allow to compute the proportion in the presence of zero event counts [15]. Secondary attack rates are presented as a proportion along with 95% CIs in forest plots. Heterogeneity between study estimates was gauged by means of the Cochran's Q and I^2 statistic: an I^2 value above 75% indicates high heterogeneity [16]. Moreover, a 95% prediction interval is displayed in the forest plots, which is an index of dispersion, providing information on how widely the true effect size varies. It can also provide the range of values in which a future observation will fall [17]. Analyses were performed though the software MetaXL version 5.3 (Ersatz, EpiGear International, Sunrise Beach, Australia) [18].

Results:

The systematic search identified 927 potentially relevant articles and 789 records were screened after removal of duplicates. Of 187 articles retrieved for full-text review and assessed for eligibility, 80 studies were included in the systematic review, and among those we identified 69 studies that indicated the symptom status of index case(s). In this analysis, we excluded 11 studies that reported asymptomatic and symptomatic index cases together or no symptom status of the index case was available. We re-classified three studies from asymptomatic to pre-symptomatic as the index cases developed symptoms later during the disease course after reviewing the details and contacting the authors [19-21]. The number of selected papers at each step of the screening and eligibility are reported in the flow diagram (Figure 1).

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Summary of secondary attack rates of asymptomatic index cases

Ten studies were included in the quantitative analysis (Table 1) [6, 13, 22-29]. Summary secondary attach rate estimate was 1% (95% CI: 0%-2%) with a prediction interval ranged of 0-10% (Figure 2). All except one tested all close contacts for SARS-CoV-2, regardless of symptoms [26]. Cheng et al. only tested symptomatic cases, but they also tested high risk populations regardless of symptoms including the household and hospital contacts [26]. Six studies reported on household contacts, two studies included hospital contacts and two studies included non-household close contacts.

Three studies identified no secondary cases after following up 17, 91 and 455 close contacts of asymptomatic index cases (asymptomatic secondary attack rate of 0%) [24-26]. Of those, two studies demonstrated higher symptomatic secondary attack rates; Cheng et al. demonstrated that mild cases had a secondary attack rate of 3.8% (95% CI 1.1, 12.8%) and severe cases had 4% (95% CI 1.0, 15.8%) secondary attack rate [26], while Park et al. showing household symptomatic secondary attack rate of 16.2% (95% CI 11.6, 22.0%) [24]. In another study, 305 contacts of 8 asymptomatic cases were followed up, identifying one secondary case (secondary attack rate 0.3% (95% CI 0.0, 1.8%) [28]. In the same study, attack rates from index cases with mild, moderate and severe diseases were 3.3%, 5.6% and 6.2%, respectively. Zhang et al. followed up 119 close contacts of 12 asymptomatic index cases and identified one secondary case, an asymptomatic secondary attack rate of 0.8% (95% CI 0.0, 4.6). In the same study, the secondary attack rate was 3.5% (95% CI 1.5-8.0) for those with mild, 5.7% (95% CI 2.5, 12.8%) for those with moderate, and 4.5% (95% CI 0.8, 21.8%) for those with severe symptoms [6]. In this study, close contacts that lived with an index case had 12 times the risk of infection as those who did not live with the index case (RR 12.5 - 95% CI 1.6, 100.8) and those who had frequent contact with an index case-patient, and those who had more than 5 contacts had 29 times the risk of infection as those with fewer contacts (RR 29.0 - 95% CI 3.6, 232.3). Two studies indicated an asymptomatic secondary attack rate of 1% and 1.9% [22, 23]. Chaw et al. reported asymptomatic and pre-symptomatic contacts together. The authors clarified that 3 asymptomatic index cases and their 106 close contacts were followed up, leading to 3 secondary cases, a

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secondary attack rate of 2.8% (95% CI 0.06, 8.0%). In this study, the overall secondary attack rate was 10.6% in the household setting, which was higher for symptomatic cases (14.4%, 95% CI 8·8, 19·9%) than that of asymptomatic cases and for non-household contacts 0.7 (95% CI 0.1, 1,3) [13]. Zeng et al. conducted the largest contact tracing study, following up 753 close contacts of asymptomatic index cases and identified one secondary case, an asymptomatic secondary attack rate of 0.13% (95% CI 0.0, 0.7%) [27].

Summary of pre-symptomatic secondary attack rates

Sixteen papers reported either outbreak investigations or contact tracing studies reporting transmission from an index case during the pre-symptomatic period [13, 19, 21, 26, 30-40] (Table 2). Of those, eleven studies were included in the quantitative analysis. The summary SAR estimate was 7% (95% CI: 3%-11%) with a prediction interval of 1 to 40% (Figure 3). These studies followed up 22 to 585 close contacts whose initial exposure occurred before symptom onset of the index case. Even in studies that followed up large numbers of people, including community contacts, the majority of secondary cases identified were from the same household or among friend gatherings. In these studies, having meals together, or playing cards with the index case were exposure activities associated with transmission. The remaining one study reported an outbreak in a restaurant [40] and four studies exclusively reported family cluster outbreaks [30, 32, 33, 39]; these investigations did not test contacts outside the household, and it is challenging to truly differentiate transmission during the pre-symptomatic period from symptomatic transmission in the household setting (Supplementary Figure 1).

Summary of symptomatic secondary attack rates

Forty-six papers reported either outbreak investigations or contact tracing studies reporting transmission from symptomatic index case(s). Of those, 40 reported contact tracing studies reported secondary attack rates ranging from 0% to 38.89% [13, 24, 27, 28, 38, 41-75] and 6 reported outbreak investigation [76-80] (Supplementary Table 1). 40 contact tracing studies with 44 observations were included in the quantitative analysis (Figure 4). The summary estimate of SAR from symptomatic index subjects was 6% (95% CI: 5%-8%) with a prediction interval of 5-

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38%. Of those, 9 studies reported less than 1% secondary attack rates, 2 of those were in healthcare setting, 2 included outdoor interaction, 4 included non-household contacts. Higher frequency of contacts and household contacts were reported to be higher risk than non-household contacts.

Quality assessment

All papers included a clear definition of symptomatic and asymptomatic cases, number of secondary cases and number of contacts. The majority of studies identified index cases with a clear diagnosis, had an acceptable case definition and sufficiently followed up close contacts (for a minimum of 14 days). However, in some studies the definition of close contact and setting of transmission was not provided. In addition, it was unclear in four reports whether all potential close contacts were included, therefore, the direction of bias is uncertain. We summarized the quality assessment in Supplementary Table 2.

Discussion:

This systematic review provides comprehensive data on secondary attack rates based on symptom status of the index case(s). While asymptomatic patients can transmit the virus to others [81], the findings from ten studies in this review found summary secondary attack rates of 1% with a prediction interval of 0-10% for asymptomatic index cases compared with secondary attack rates of 6% with a prediction interval of 5-38% in symptomatic cases and 7% with a prediction interval of 1-40% in pre-symptomatic case. These findings suggest that individuals who are asymptomatic throughout the disease course are responsible for fewer secondary infections than symptomatic and pre-symptomatic cases. Most transmission events were associated with living with the index case or group activities such as sharing meals and playing board games.

Given the importance of transmission heterogeneity in propagating the pandemic, it is important that we learn about the various factors that contribute to transmission. According to modelling and contact tracing studies, around 80% of secondary infections can be linked to 20% of cases

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259 which distinguishes SARS-CoV-2 from seasonal influenza, although a similar pattern was also
260 observed in SARS-CoV and MERS-CoV [82-84]. While there are multiple factors (environmental
261 factors, contact patterns and socioeconomic inequalities) that contribute to this heterogeneity,
262 some evidence starting to emerge about the influence of individual's infectiousness on
263 transmission dynamics. In this systematic review, we found that index cases with symptoms had
264 a higher secondary attack rate compared with truly asymptomatic index cases. While there is a
265 need to better understand this difference, it may be due to shorter duration of infectiousness. In a
266 living systematic review including of studies published up to 6 June 2020, we found that cases
267 with asymptomatic people had a shorter duration of RNA shedding than symptomatic individuals
268 [85]. Asymptomatic patients may therefore be contagious but for a shorter duration than
269 symptomatic people; this might contribute to lower transmission to their contacts. However, we
270 do not yet know the relative importance of behavioral factors by the host versus environmental
271 factors in determining transmission risk. It is not known whether the size of the cluster of
272 secondary infections would be different according to index case symptom status in a high-risk
273 environment with no mitigation measures in place.
274
275 Modelling studies suggest that it is not possible to have widespread infection without substantial
276 pre-symptomatic transmission. Viral load dynamics of SARS-CoV-2 derived from confirmed
277 cases suggest that peak viral loads are detected at the start of symptom onset up to day 5 of
278 illness, indicating highest infectiousness occurs just before or within the first few days after
279 symptom onset [85]. So far, several contact tracing studies emphasize that the highest risk of
280 transmission occurs during the prodromal phase or early in the disease course [64, 86]. For
281 instance, in a prospective contact tracing study of 100 confirmed cases of COVID-19 and 2761
282 close contacts, no secondary cases were identified when the exposure occurred more than 5
283 days after the symptom onset [26]. Our findings therefore have important implications from a
284 public health perspective. In settings such as nursing homes, homeless shelters, prisons, cruise
285 ships and meat-packing plants in which many people spend prolong period of time together in
286 the same environment including sleeping, dining and sharing common facilities, and where
287 several outbreaks have been documented, pre-symptomatic transmission may contribute

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288 substantially to transmission [87, 88]. In these settings, when infection develops, most patients
289 are already inside the facility with high viral loads that increase the risk of onward transmission.
290 This highlights the importance of mitigation measures and surveillance in these settings to
291 identify those patients early in the disease course to prevent onward transmission inside the
292 facility.
293
294 This systematic review has several strengths. Firstly, this is a living systematic review examining
295 the transmission of SARS-CoV-2 through contact tracing and outbreak investigation studies.
296 Secondly, we only included studies with clear case definitions, which indicated the number of
297 contacts and secondary cases. We excluded studies in which the index case was unclear, or the
298 numbers of contacts were not provided. The estimates from individual studies are also subject to
299 limitations, such as imprecision resulting from small study size, and multiple sources of bias in
300 the estimation of the true secondary attack rate, which are detailed in this paper [89]. Moreover,
301 while the number of index cases could influence the confidence interval estimation for secondary
302 attack rate due to heterogeneity among index cases, we have constructed a prediction interval to
303 yield conservative confidence interval estimates.
304
305 We identified two other systematic reviews that investigated asymptomatic transmission, with
306 different research questions, which results in different search terms and studies retrieved. One
307 living systematic review, which included studies published up to 10 June 2020, identified five
308 studies that directly compared secondary attack rates between asymptomatic and symptomatic
309 index cases; all were included in our review [7]. This study only included studies that provided
310 data to allow relative risks to be estimated. The summary risk ratios for asymptomatic versus
311 symptomatic (0.35, 95% CI 0.10, 1.27) and pre-symptomatic versus symptomatic (0.63, 95% CI
312 0.18, 2.26) are consistent with our findings. The second review estimated only household
313 secondary attack rates and included studies published up to 29 July 2020 [90]. Of three studies
314 that included asymptomatic index cases, two were included in our review. We excluded one of
315 the studies because the number of contacts of asymptomatic index cases was not specified; we
316 have not yet received details of the study after contacting the authors. Advantages of our review

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over these two studies are inclusion of studies published in Chinese, search terms that aimed to capture studies specifically estimating secondary attack rates.

In summary, whilst asymptomatic transmission is a major concern for SARS-CoV-2 community spread, secondary attack rates from those who remain asymptomatic throughout their course of infection are low suggesting limited infectiousness. Although it is difficult to estimate the proportion of pre-symptomatic transmission, these patients are likely to be highly infectious just before and around the time of symptom onset and appear to transmit efficiently, particularly within households. Given these results, in the context of limited resources, approaches should be targeted predominantly on identifying and immediately isolating patients with prodromal or mild symptoms and their contacts, which may avert a significant number of community transmission clusters [91]. Future clinical studies should incorporate clear definitions and assess a broad range of symptoms associated with COVID-19, include longitudinal follow up of patients, and calculate secondary attack rates for a wider range of settings and populations [9].

Conflict of Interest: The authors declare that there is no conflict of interest

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Contribution statement:

X Qiu: investigation, data curation, writing – original draft; A Nergiz: investigation, data curation, writing – review and editing; A. E. Maraolo: methodology, formal analysis, writing – original draft;

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I. Bogoch and N. Low: interpretation, writing – review and editing; M. Cevik: conceptualisation, methodology, investigation, writing – original draft, supervision.

Figure legends:

Figure 1: Flowchart describing the study design process

Figure 2: Secondary attack rates from asymptomatic index cases to their contacts

Figure 3: Secondary attack rates from pre-symptomatic index cases to their contacts

Figure 4: Secondary attack rates from symptomatic index cases to their contacts

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354 **Table 1: Transmission from truly asymptomatic index cases**

	Index Cases	Environment	Number of contacts	Number of Secondary cases	Asymptomatic SAR (95% CI)	Symptomatic SAR (95% CI)
Chaw et al. * [13]	3	Household Non-household	106	3	2.8% (0.06, 8.0)	14.4% (8.8, 19.9) 0.7% (0.01, 1.3)
Chen Y et al. [29]	30	Household Non-household	146	6	4.1% (1.7, 9.1)	6.3% (5.3, 7.5)
Cheng et al.[26]	9	Non-household	91	0	0% (0.0, 4.1)	Mild 3.76 (1.1-12.8) Severe 3.99 (1.0-15.8)
Gao et al.[25]	1	Household and healthcare	455	0	0% (0.0, 0.08)	
Jiang et al.[22]	3	Household	195	2	1% (0.1, 3.7)	
Luo et al. [28]	8	Household and non-household	305	1	0.33% (0.0, 1.8) OR (0.29 (0.04, 2.2))	Mild 3.3% (OR 0.48 (0.28, 0.82) Mod 5.6% (OR 1.0) Sev 6.2% (OR 1.19 (0.7, 2.1)
Mandić-Rajčević et al.[23]	1	Healthcare	53	1	1.9% (0.0,10.0)	
Park et al.[24]	4	Household	17	0	0% (0.0, 19.5)	16.2 % (11.6,22.0)
Zeng et al. [27]		All contacts	753	1	0.13% (0.0, 0.7)	2.02% (1.8, 2.3)
Zhang et al.[6]	12	Household	119	1	0.8% (0.0, 4.6)	Mild 3.5% (1.5, 8.0) Mod 5.7% (2.5, 12.8) Severe 4.5% (0.8, 21.8)

Transmission dynamics and secondary attack rates

355 Abbreviations: CI, confidence interval; OR, odds ratio; SAR, secondary attack rate; sev, severe * authors contacted for more details

Index Cases	Environment	Number of contacts	Number of Secondary cases	Pre-symptomatic SAR (95% CI)	Secondary cases

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356 **Table 2: Transmission during pre-symptomatic period**

Transmission dynamics and secondary attack rates

Contract-tracing						
Chaw et al.* [13]	7	Household and non-household	585	15	2.56% (1.4, 4.2)	
Cheng et al.[26]	NR	Household and non-household	299	2	0.7% (0.1, 2.4)	
Hong L et al.[31]	41	Household and non-household	197	24	12.2% (8.0, 17.6)	Friends, family, card playing partners
Huang et al.[19]	1	Friends	22	7	31.8% (13.0, 54.9)	Shared meal with index
Pang et al. [34]	1	Household and non-household	103	6	5.8% (2.2, 12.2)	Living together or sharing meal
Park et al. [24]	4	Household	11	0	0% (0.0, 2.8)	
Pung R et al. [38]	2	Religious gathering	142	3	2.1% (0.5, 6.5)	
Qian et al. [35]	1	Household and non-household	137	10	7.3% (3.6, 13.0)	Living together or sharing meal
Yang et al. [36]	2	Household and non-household	123	6	4.9% (1.8, 10.3)	All secondary cases lived together
Ye et al. [21]	1	Family	44	4	9.1% (2.5, 21.4)	Extended family
Zhao et al [37]	1	Friends	15	4	26.7% (7.8, 55.1)	Meal and Mahjong game gathering
Outbreak investigation						
Chen M et al.[30]	1	Household	3	2	66.7% (9.4, 99.2)	Family cluster outbreak
Li P et al.[32]	1	Household	5	4	80% (28.4, 99.5)	Family cluster outbreak
Lu J et al [40]	1	Restaurant	82	9	11% (5.9, 19.6)	
Jiang Y et al [39]	1	Household	7	3	42.9% (11.8, 79.8)	Family cluster outbreak
Qian G et al. [33]	2	Household	4	3	75% (10.4, 99.4)	Family cluster outbreak

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Abbreviations: CI, confidence interval; SAR, secondary attack rate

* authors contacted for more details

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Figure 1. Flowchart describing inclusion and exclusion of studies at each stage of the review

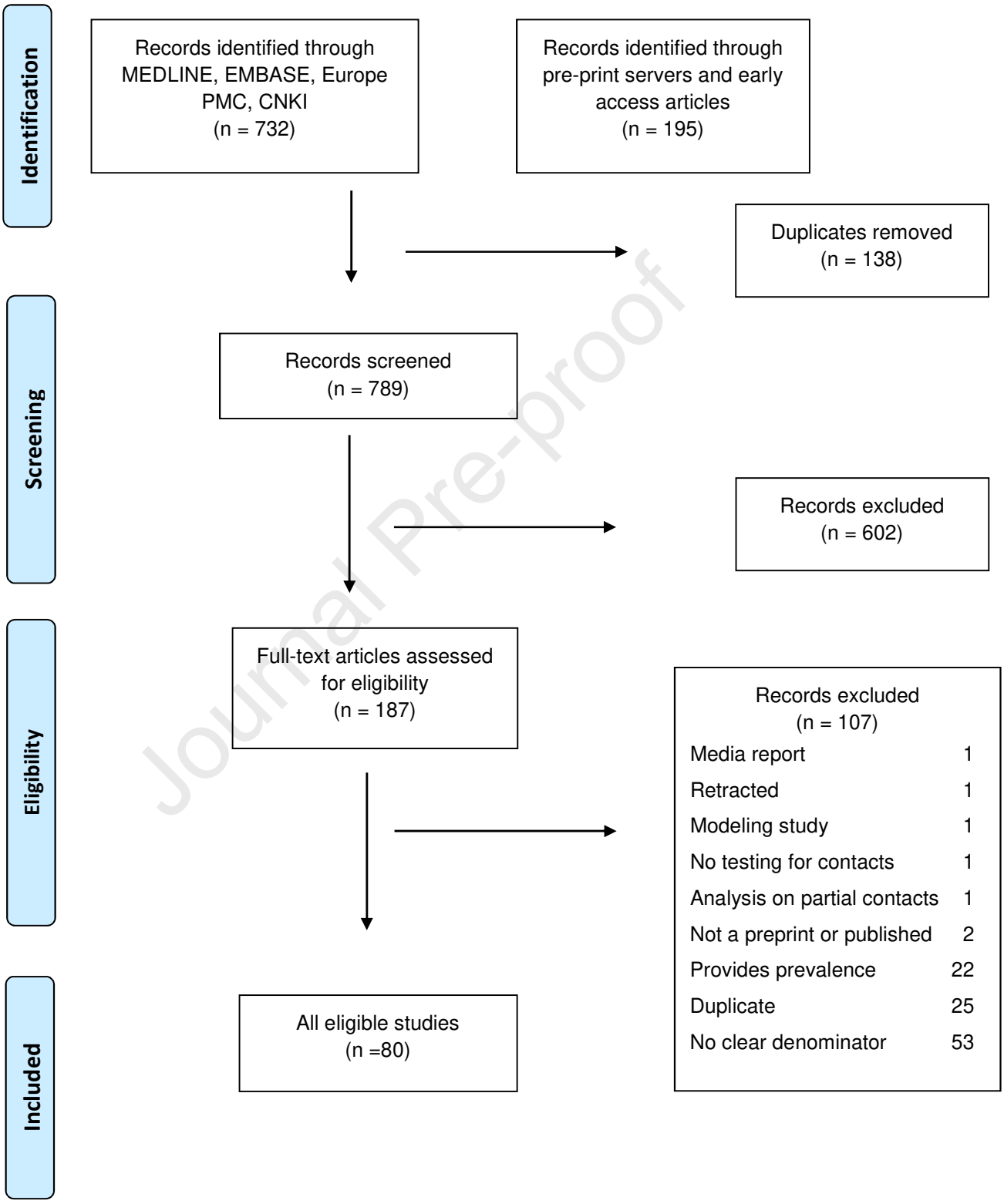

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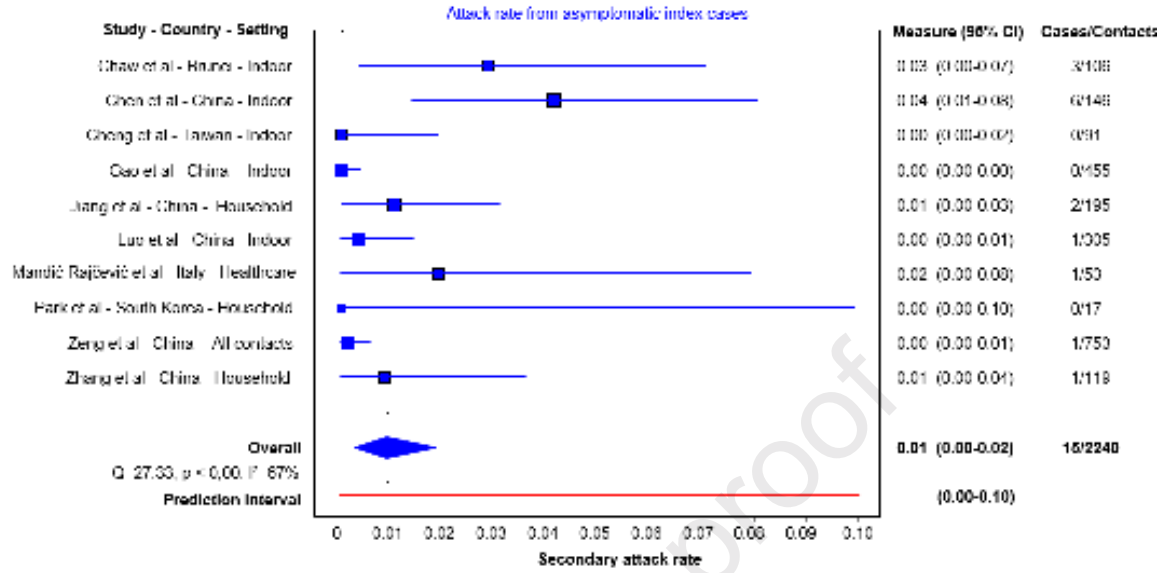
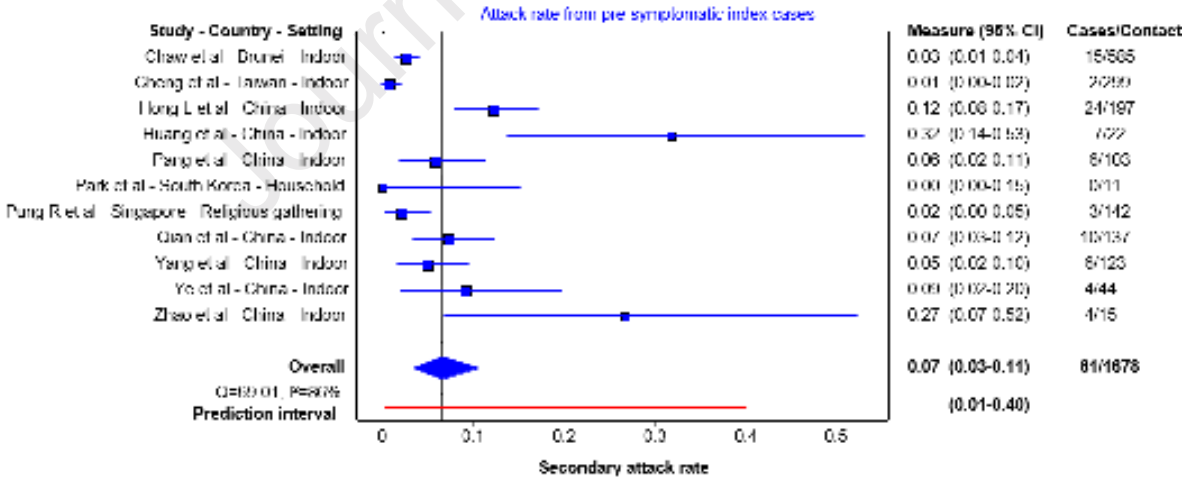
Figure 2: Secondary attack rates from asymptomatic index cases to their contacts



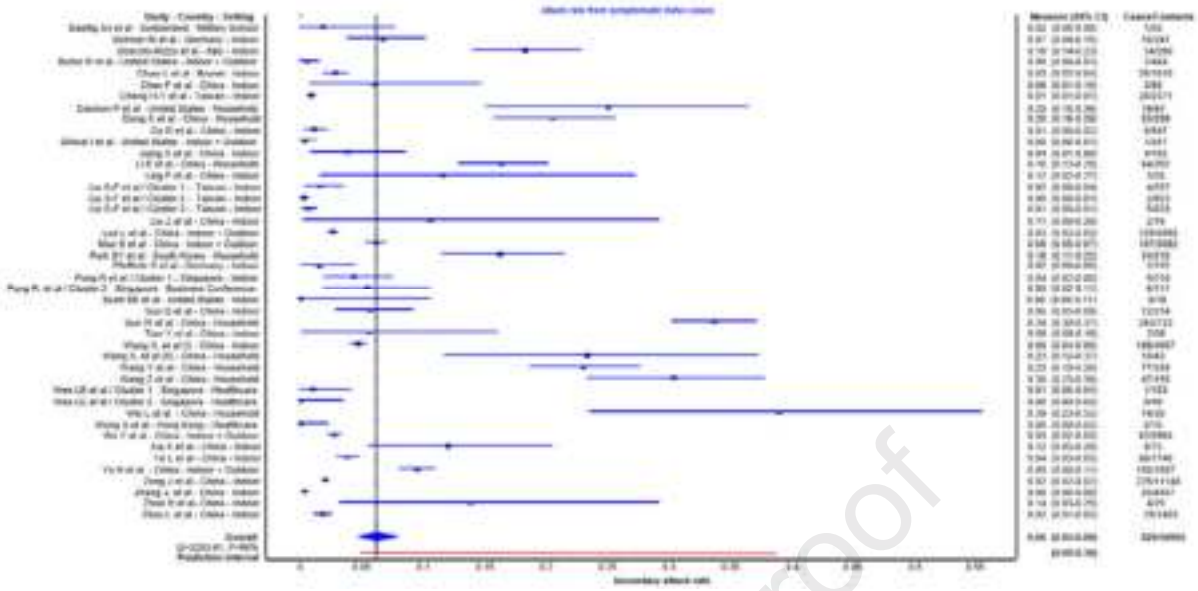
For each study the secondary attack rate is reported with its 95% CI.
A prediction interval at the bottom of the forest is depicted.

Figure 3: Secondary attack rates from pre-symptomatic index cases to their contacts



For each study the secondary attack rate is reported with its 95% CI.
A prediction interval at the bottom of the forest is depicted.

Figure 4: Secondary attack rates from symptomatic index cases to their contacts



For each study the secondary attack rate is reported with its 95% CI.
A prediction interval at the bottom of the forest is depicted.

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Post-lockdown SARS-CoV-2 nucleic acid screening in nearly ten million residents of Wuhan, China

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Stringent COVID-19 control measures were imposed in Wuhan between January 23 and April 8, 2020. Estimates of the prevalence of infection following the release of restrictions could inform post-lockdown pandemic management. Here, we describe a city-wide SARS-CoV-2 nucleic acid screening programme between May 14 and June 1, 2020 in Wuhan. All city residents aged six years or older were eligible and 9,899,828 (92.9%) participated. No new symptomatic cases and 300 asymptomatic cases (detection rate 0.303/10,000, 95% CI 0.270–0.339/10,000) were identified. There were no positive tests amongst 1,174 close contacts of asymptomatic cases. 107 of 34,424 previously recovered COVID-19 patients tested positive again (re-positive rate 0.31%, 95% CI 0.423–0.574%). The prevalence of SARS-CoV-2 infection in Wuhan was therefore very low five to eight weeks after the end of lockdown.

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The Coronavirus Disease 2019 (COVID-19) was first reported in December 2019, and was classified as a pandemic by the World Health Organization on March 11, 2020[1]. Following strict lockdown measures, the COVID-19 epidemic was generally under control in China, and the whole country has progressed into a post-lockdown phase. In this phase, countries face new problems and challenges, including how to accurately assess the post-lockdown risk of the COVID-19 epidemic, how to avoid new waves of COVID-19 outbreaks, and how to facilitate the resumption of economy and normal social life. As the city most severely affected by COVID-19 in China, Wuhan had been under lockdown measures from January 23 until April 8, 2020. During the first 2 months after city's reopening, there were only a few sporadic COVID-19 cases in Wuhan (six newly confirmed cases from April 8 to May 10, 2020[2]). However, there was still concern about the risk of COVID-19 in Wuhan, which seriously affected the resumption of industrial production and social services, and hampered the normal lives of residents. In order to ascertain the current status of the COVID-19 epidemic, the city government of Wuhan carried out a comprehensive citywide nucleic acid screening of SARS-CoV-2 infection from May 14, 2020 to June 1, 2020.

The citywide screening of SARS-CoV-2 infection in Wuhan is a mass screening programme in post-lockdown settings, and provided invaluable experiences or lessons with international relevance as more countries and cities around the world entering the post-lockdown phase. In this study, we report the organisation process, detailed technical methods used, and results of this citywide nucleic acid screening.

Results

There were 10,652,513 eligible people aged ≥6 years in Wuhan (94.1% of the total population). The nucleic acid screening was completed in 19 days (from May 14, 2020 to Jun 1, 2020), and tested a total of 9,899,828 persons from the 10,652,513 eligible people (participation rate, 92.9%). Of the 9899,828 participants, 9,865,404 had no previous diagnosis of COVID-19, and 34,424 were recovered COVID-19 patients.

The screening of the 9,865,404 participants without a history of COVID-19 found no newly confirmed COVID-19 cases, and identified 300 asymptomatic positive cases with a detection rate of 0.303 (95% CI 0.270–0.339)/10,000. The median age-stratified Ct-values of the asymptomatic cases were shown in Supplementary Table 1. Of the 300 asymptomatic positive cases, two cases came from one family and another two were from another family. There were no previously confirmed COVID-19 patients in these two families. A total of 1174 close contacts of the asymptomatic positive cases were traced, and they all tested negative for the COVID-19. There were 34,424 previously recovered COVID-19 cases who participated in the screening. Of the 34,424 participants with a history of COVID-19, 107 tested positive again, giving a repositive rate of 0.310% (95% CI 0.423–0.574%).

Virus cultures were negative for all asymptomatic positive and repositive cases, indicating no "viable virus" in positive cases detected in this study.

All asymptomatic positive cases, repositive cases and their close contacts were isolated for at least 2 weeks until the results of nucleic acid testing were negative. None of detected positive cases or their close contacts became symptomatic or newly confirmed with COVID-19 during the isolation period. In this screening programme, single and mixed testing was performed, respectively, for 76.7% and 23.3% of the collected samples. The asymptomatic positive rates were 0.321 (95% CI 0.282–0.364)/10,000 and 0.243 (95% CI 0.183–0.315)/10,000, respectively.

The 300 asymptomatic positive persons aged from 10 to 89 years, included 132 males (0.256/10,000) and 168 females (0.355/10,000). The asymptomatic positive rate was the lowest in children or adolescents aged 17 and below (0.124/10,000), and the highest among the elderly aged 60 years and above (0.442/10,000) (Table 1). The asymptomatic positive rate in females (0.355/10,000) was higher than that in males (0.256/10,000).

The asymptomatic positive cases were mainly domestic and unemployed residents (24.3%), retired older adults (21.3%), and public service workers (11.7%) (Fig. 1).

The asymptomatic positive rate in urban districts was on average 0.456/10,000, ranging from 0.317/10,000 in Hongshan to 0.807/10,000 in Wuchang district. A lower rate of asymptomatic positive cases was found in suburban districts (0.132/10,000), ranging from 0.047/10,000 in Xinzhou to 0.237/10,000 in Jiangan district (Fig. 2).

Among the 7280 residential communities in Wuhan, asymptomatic positive cases were identified in 265 (3.6%) communities (only one case detected in 246 communities), while no asymptomatic positive cases were found in other 96.4% communities.

Testing of antibody against SARS-CoV-2 virus was positive IgG (+) in 190 of the 300 asymptomatic cases, indicating that 63.3% (95% CI 57.6–68.8%) of asymptomatic positive cases were actually infected. The proportion of asymptomatic positive cases with both IgM (−) and IgG (−) was 36.7% (95% CI: 31.2–42.4%; $n = 110$), indicating the possibility of infection window or false positive results of the nucleic acid testing (Table 2).

Higher detection rates of asymptomatic infected persons were in Wuchang, Qingshan and Qiaokou districts, and the prevalence of previously confirmed COVID-19 cases were 68.243/10,000, 53.767/10,000, and 100.047/10,000, respectively, in the three districts. Figure 3 shows that districts with a high detection rate of asymptomatic positive persons generally had a high prevalence of confirmed COVID-19 cases ($r_s = 0.729$, $P = 0.002$).

Discussion

The citywide nucleic acid screening of SARS-CoV-2 infection in Wuhan recruited nearly 10 million people, and found no newly confirmed cases with COVID-19. The detection rate of asymptomatic positive cases was very low, and there was no evidence of transmission from asymptomatic positive persons to traced close contacts. There were no asymptomatic positive cases in 96.4% of the residential communities.

Previous studies have shown that asymptomatic individuals infected with SARS-CoV-2 virus were infectious[3], and might subsequently become symptomatic[4]. Compared with symptomatic patients, asymptomatic infected persons generally have low quantity of viral loads and a short duration of viral shedding, which decrease the transmission risk of SARS-CoV-2[5]. In the present study, virus culture was carried out on samples from asymptomatic positive cases, and found no viable SARS-CoV-2 virus. All close contacts of the asymptomatic positive cases tested negative, indicating that the asymptomatic positive cases detected in this study were unlikely to be infectious.

There was a low repositive rate in recovered COVID-19 patients in Wuhan. Results of virus culturing and contract tracing found no evidence that repositive cases in recovered COVID-19 patients were infectious, which is consistent with evidence from other sources. A study in Korea found no confirmed COVID-19 cases by monitoring 790 contacts of 285 repositive cases[6]. The official surveillance of recovered COVID-19 patients in China also revealed no evidence on the infectiousness of repositive cases[7]. Considering the strong force of infection of COVID-19[8–10], it is expected that the number of confirmed cases is associated with the risk of being infected in communities. We

Table 1 Characteristics of asymptomatic positive individuals.

	Total (%)	Asymptomatic positive persons (%)	Detection rate per 10,000 (95% CI)	*P* value
Total	9,899,828 (100.0)	300 (100.0)	0.303 (0.270–0.339)	
Sex				
Male	5,162,960 (52.2)	132 (44.0)	0.256 (0.214–0.303)	0.005
Female	4,736,868 (47.8)	168 (56.0)	0.355 (0.303–0.413	
Age (years old)				
≤17	969,014 (9.8)	12 (4.0)	0.124 (0.064–0.216)	<0.001
18–44	4,448,230 (44.9)	104 (34.7)	0.234 (0.191–0.283)	
45–59	2,492,943 (25.2)	96 (32.0)	0.385 (0.312–0.470)	
≥60	1,989,641 (20.1)	88 (29.3)	0.442 (0.355–0.545)	
Administrative Districts in Wuhan				
Wuchang	904,636 (9.1)	73 (24.3)	0.807 (0.633–1.015)	<0.001
Qingshan	414,312 (4.2)	23 (7.7)	0.555 (0.352–0.833)	
Qiaokou	583,440 (5.9)	32 (10.7)	0.548 (0.375–0.774)	
Hanyang	717,429 (7.2)	29 (9.7)	0.404 (0.271–0.581)	
Jianghan	524,224 (5.3)	19 (6.3)	0.362 (0.218–0.566)	
Hongshan	1,103,079 (11.1)	35 (11.7)	0.317 (0.221–0.441)	
East Lake High-tech Development Area	782,987 (7.9)	19 (6.3)	0.243 (0.146–0.379)	
Jiangan	800,440 (8.1)	19 (6.3)	0.237 (0.143–0.371)	
Caidian	503,595 (5.1)	11 (3.7)	0.218 (0.109–0.391)	
Jiangxia	671,248 (6.8)	14 (4.7)	0.209 (0.114–0.350)	
Huangpi	979,920 (9.9)	14 (4.7)	0.143 (0.078–0.240)	
Hannan	417,022 (4.2)	4 (1.3)	0.096 (0.026–0.246)	
Dongxihu	777,204 (7.9)	5 (1.7)	0.064 (0.021–0.150)	
Xinzhou	634,408 (6.4)	3 (1.0)	0.047 (0.010–0.138)	
East Lake Scenic Area of Wuhan	85,884 (0.9)	0 (0.0)	0.000 (0.000–0.430)	

χ^2 test was used to assess the association between the detection rate of asymptomatic cases increased and sex and age. Urban districts of Wuhan includes Wuchang, Qingshan, Qiaokou, Hanyang, Jiangan, Jianghan, and Hongshan; Suburban districts of Wuhan includes Hannan, Caidian, Dongxihu, Xinzhou, Jiangxia, Huangpi, East Lake High-tech Development Area, and East Lake Scenic Area of Wuhan.

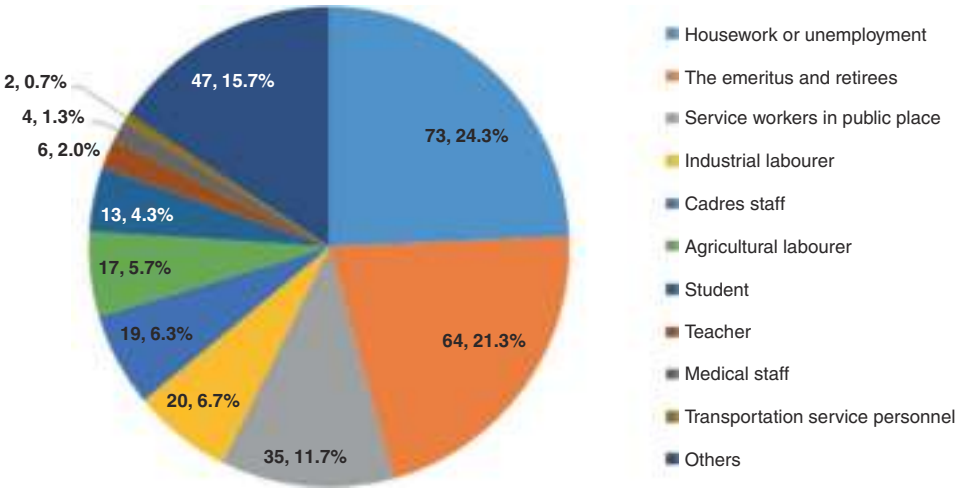

Fig. 1 The occupation distribution of asymptomatic positive cases (%). Note: Others included the self-employed, military personnel, and so on. (Source data are provided as s Source Data file.).

found that asymptomatic positive rates in different districts of Wuhan were correlated with the prevalence of previously confirmed cases. This is in line with the temporal and spatial evolution (especially the long-tailed characteristic) of infectious diseases[11].

Existing laboratory virus culture and genetic studies[9,10] showed that the virulence of SARS-CoV-2 virus may be weakening over time, and the newly infected persons were more likely to be asymptomatic and with a lower viral load than earlier infected cases. With the centralized isolation and treatment of all COVID-19 cases during the lockdown period in Wuhan, the risk of residents being infected in the community has been greatly reduced. When susceptible residents are exposed to a low dose of virus, they may tend to be asymptomatic as a result of their own immunity. Serological antibody testing in the current study found that at least 63% of asymptomatic positive cases were actually infected with SARS-CoV-2 virus. Nonetheless, it is too early to be complacent, because of the existence of asymptomatic positive cases and high level of susceptibility in residents in Wuhan. Public health measures for the prevention and control of COVID-19 epidemic, including wearing masks, keeping safe social distancing in Wuhan should be sustained. Especially, vulnerable populations with weakened immunity or co-morbidities, or both, should continue to be appropriately shielded.

Findings from this study show that COVID-19 was well controlled in Wuhan at the time of the screening programme. After two months since the screening programme (by August 9, 2020), there were no newly confirmed COVID-19 cases in Wuhan.

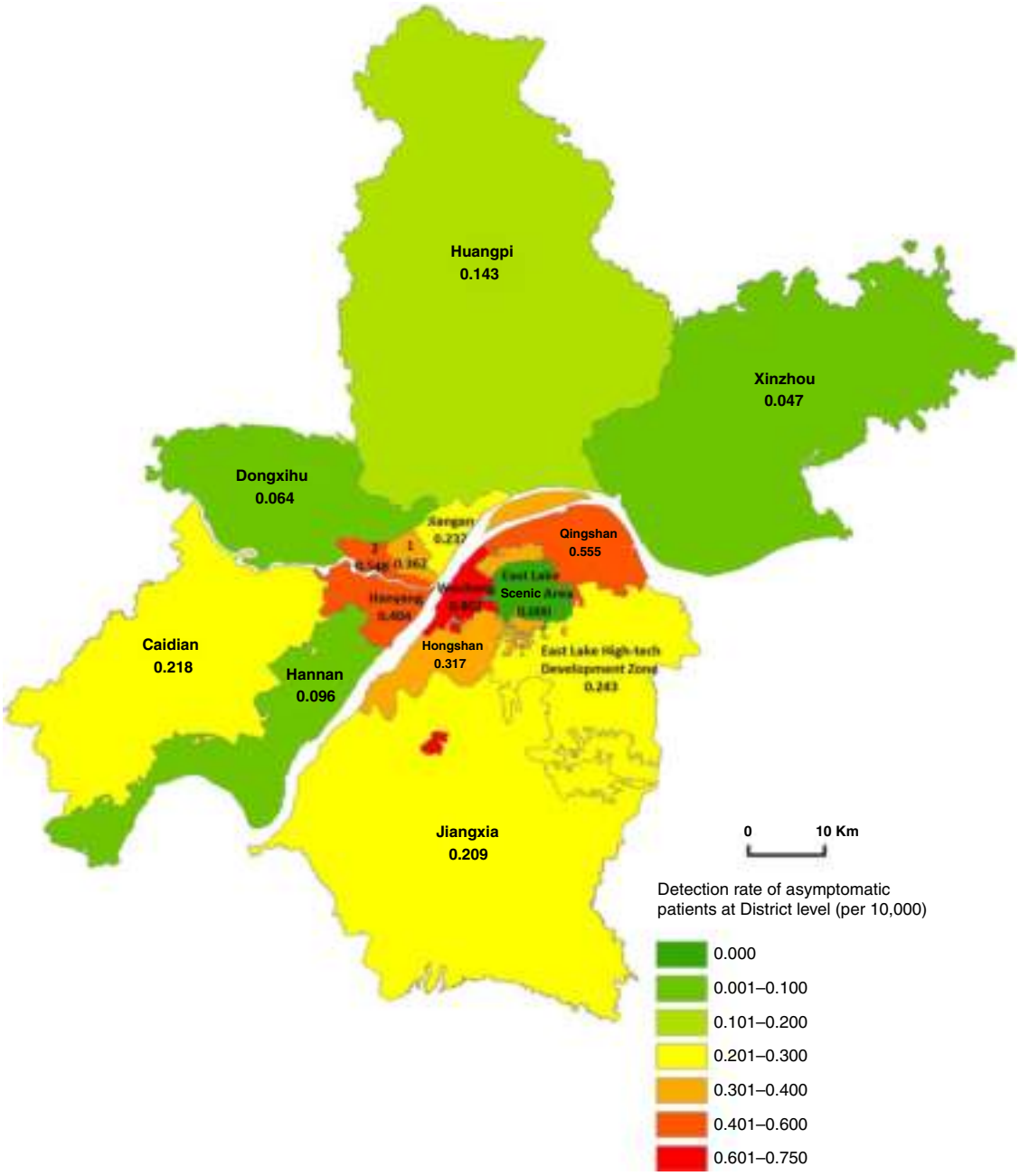

Fig. 2 The geographic distribution of the detection rate of asymptomatic positive cases. Note: 1 represents Jianghan district; 2 represents Qiaokou district. (Source data are provided as s Source Data file.).

Table 2 Results of the detection of antibody in 300 asymptomatic positive persons.

IgM Results	IgG	Asymptomatic positive persons	% (95% CI)
−	+	161	53.7 (47.8–59.4)
−	−	110	36.7 (31.2–42.4)
+	+	29	9.7 (6.6–13.6)
+	−	0	0.0 (0.0–1.2)

"−" indicates negative; "+" indicates positive.

Further testing of SARS-CoV-2 in samples collected from market environment settings in Wuhan were conducted, and found no positive results after checking a total of 52,312 samples from 1795 market setting during June 13 to July 2, 2020[12].

This study has several limitations that need to be discussed. First, this was a cross-sectional screening programme, and we are unable to assess the changes over time in asymptomatic positive and reoperative results. Second, although a positive result of nucleic acid testing reveals the existence of the viral RNAs, some false negative results were likely to have occurred, in particular due to the relatively low level of virus loads in asymptomatic infected individuals, inadequate collection of samples, and limited accuracy of the testing technology[13]. Although the screening programme provided no direct evidence on the sensitivity and specificity of the testing method used, a meta-analysis reported a

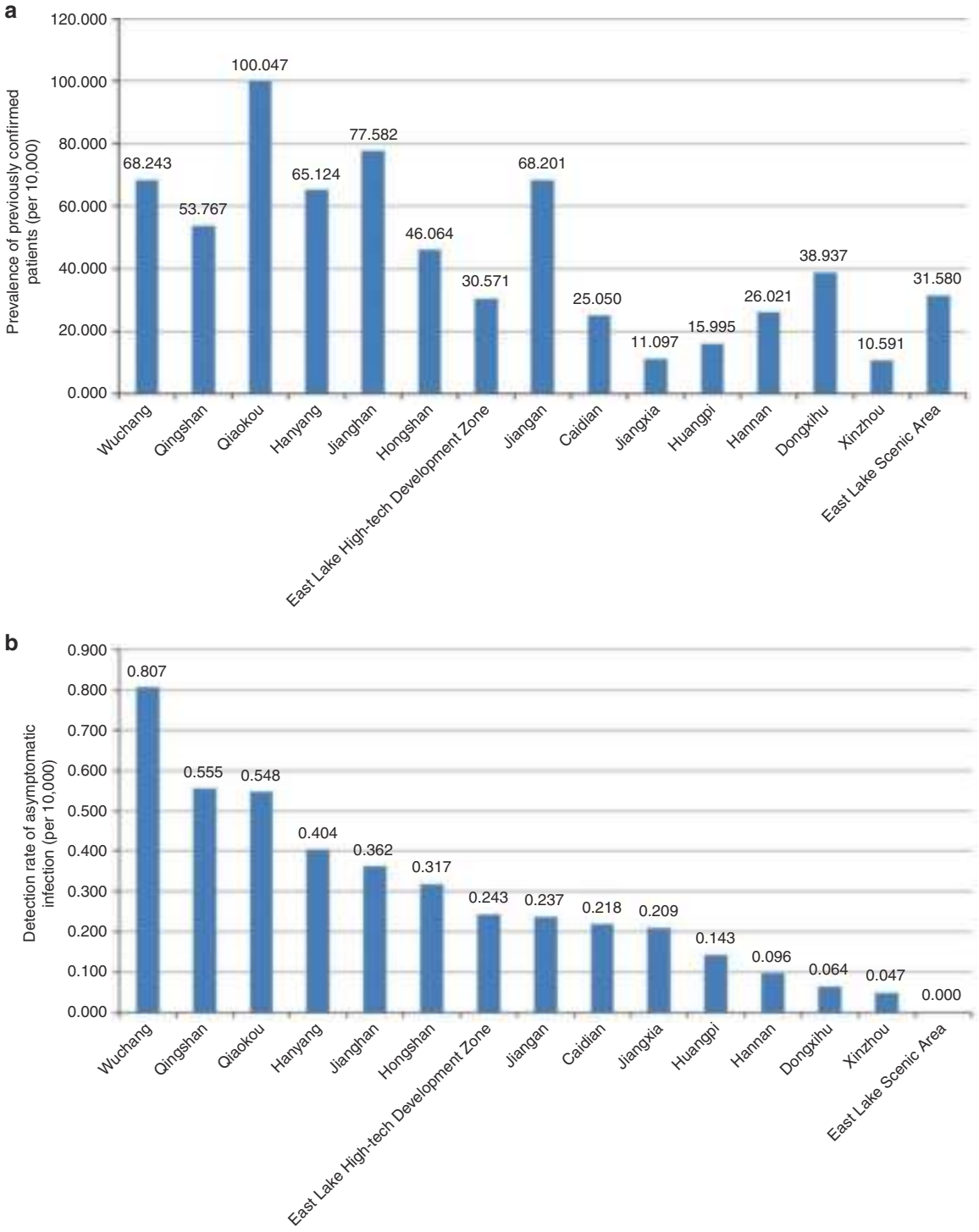

Fig. 3 The prevalence of previously confirmed patients and the detection rate of asymptomatic positive cases of COVID-19 in each district in Wuhan. **a** The prevalence of previously confirmed patients of COVID-19 in each district in Wuhan. **b** The detection rate of asymptomatic positive cases of COVID-19 in each district in Wuhan. (Source data are provided as s Source Data file.).

pooled sensitivity of 73% (95% CI 68–78%) for nasopharayngeal and throat swab testing of COVID-19[14]. Testing kits used in the screening programme were publicly purchased by the government and these kits have been widely used in China and other countries. Multiple measures were taken to possibly minimise false negative results in the screening programme. For example, standard training was provided to health works for sample collection to ensure the sample quality. The experiment procedures, including specimen collection, extraction, PCR, were according to official guidelines (Supplementary Note 1). For the real-time RT-PCR assay, two target genes were simultaneously tested. Even so, false negative results remained possible, particularly in any mass screening programmes. However, even if test sensitivity was as low as 50%, then the actual prevalence would be twice as high as reported in this study, but would still be very low. Around 7.1% of eligible residents did not participate in the citywide nucleic acid screening and the screening programme did not collect detailed data on reasons for nonparticipation, which is a limitation of this

study. Although there were no official statistics, a large number of migrant workers and university students left Wuhan before the lockdown, joining their families in other cities or provinces for traditional Chinese New Year. Therefore, it is likely that most nonparticipants were not in Wuhan at the time of the screening. The main objective of the screening programme was to assess the risk of COVID-19 epidemic in residents who were actually living in the post-lockdown Wuhan. Therefore, the estimated positive rates are unlikely to be materially influenced by nonparticipation of residents who were not in Wuhan or some residents who did not participate in the screening for other reasons. Moreover, people who left Wuhan were the target population for monitoring in other provinces and cities and were required to take nucleic acid testing. Although there was no official statistics showing the positive rate of nucleic acid testing in this population, there was no report that shown a higher positive rate of nucleic acid testing than our findings.

In summary, the detection rate of asymptomatic positive cases in the post-lockdown Wuhan was very low (0.303/10,000), and there was no evidence that the identified asymptomatic positive cases were infectious. These findings enabled decision makers to adjust prevention and control strategies in the post-lockdown period. Further studies are required to fully evaluate the impacts and cost-effectiveness of the citywide screening of SARS-CoV-2 infections on population's health, health behaviours, economy, and society.

Methods

Study population and ethical approvals. Wuhan has about 11 million residents in total, with seven urban and eight suburban districts. Residents are living in 7280 residential communities (or residential enclosures, "xiao-qu" in Chinese), and each residential community could be physically isolated from other communities for preventing transmission of COVID-19.

The screening programme recruited residents (including recovered COVID-19 patients) currently living in Wuhan who were aged ≥6 years (5,162,960 males, 52.2%). All participants provided written or verbal informed consent after reading a statement that explained the purpose of the testing. For participants who aged 6–17 years old, consent was obtained from their parents or guardians. The study protocol for an evaluation of the programme based on anonymized screening data was approved by the Ethics Committee of the Tongji Medical College Institutional Review Board, Huazhong University of Science and Technology, Wuhan, China (No. IROG0003571).

Organizational guarantee and community mobilization. A citywide nucleic acid screening group was formed, with specialized task teams contributing to comprehensive coordination, technical guidance, quality control, participation invitation, information management, communication, and supervision of the screening. The city government invested 900 million yuan (RMB) in the testing programme. From 14 May to 1 June 2020, in the peak time, up to 2907 sample collection sites were functioning at the same time in Wuhan. Each sample collection site had an assigned sample collection group, including several health professionals (staffed according to the number of communities' residents), 2–4 community managers, 1–2 police officers, and 1–2 inspectors. The sampling sites were set up based on the number and accessibility of local residents. Local community workers were responsible for a safe and orderly sampling process to minimise the waiting time. In addition, mobile sampling teams were formed by primary health care professionals and volunteers to conduct door-to-door sampling for residents who had physical difficulties or were unable to walk.

About 50,000 health professionals (mainly doctors and nurses from community health centers) and more than 280,000 person-times of community workers and volunteers contributed to sample collection, transport of equipment and samples collected, arrangement of participation process, and maintaining order of sampling sites. Public information communication and participant invitation were implemented through mass media, mobile messages, WeChat groups, and residential community broadcasts, so as to increase residents' awareness and the participation.

Acquisition, preservation, and transport of samples. All sampling personnel received standard training for the collection of oropharyngeal swab samples. To minimise the risk of cross-infection, the sampling process strictly followed a disinfection process and environmental ventilation were ensured. The collected samples were stored in a virus preservation solution or immersed in isotonic saline, tissue culture solution, or phosphate buffer (Supplementary note 1). Then, all samples were sent to testing institutions within 4 h using delivery boxes for biological samples refrigerated with dry ice to guarantee the stability of nucleic acid samples.

Technical methods for laboratory testing of collected samples. A total of 63 nucleic acid testing laboratories, 1451 laboratory workers and 701 testing equipment were involved in the nucleic acid testing. Received samples were stored at 4 °C and tested within 24 h of collection. Any samples that could not be tested within 24 h were stored at −70 °C or below (Supplementary note 1). In addition to "single testing" (i.e., separate testing of a single sample), "mixed testing" was also performed for 23% of the collected samples to increase efficiency, in which five samples were mixed in equal amounts, and tested in the same test tube. If a mixed testing was positive for COVID-19, all individual samples were separately retested within 24 h[15].

Details regarding technical methods for sequencing and virus culture were provided in Supplementary note 1. Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay method was used for the nucleic acid testing. We simultaneously amplified and tested the two target genes: open reading frame 1ab (ORF1ab) and nucleocapsid protein (N) (Supplementary Note 1). A cycle threshold value (Ct-value) less than 37 was defined as a positive result, and no Ct-value or a Ct-value of 40 or more was defined as a negative result. For Ct-values ranging from 37 to 40, the sample was retested. If the retest result remained less than 40 and the amplification curve had obvious peak, the sample was classified as positive; otherwise, it was reported as being negative. These diagnostic criteria were based on China's official recommendations[16].

For asymptomatic positive cases, virus culture was carried out in biosafety level-3 laboratories. The colloidal gold antibody test was also performed for asymptomatic positive cases (Supplementary note 1). All testing results were double entered into a specifically designed database, and managed by the Big Data and Investigation Group of the COVID-19 Prevention and Control Centre in Wuhan, which was established to collect and manage data relevant to the COVID-19 epidemic.

Participant data collection and management. Before sample collection, residents electronically (using a specifically designed smartphone application) self-uploaded their personal information, including ID number, name, sex, age, and place of residence. Then, the electronic machine system generated a unique personal barcode and stuck it on the sample tube to ensure the match between the sample and the participant. Then trained staff interviewed each individual regarding the history of COVID-19 and previous nucleic acid testing. There was a database of confirmed COVID-19 cases in Wuhan, which can be used to validate the self-reported previous COVID-19 infection. All information was entered into a central database. The testing results were continually uploaded to the central database by testing institutions. Contact tracing investigations were conducted on participants who tested positive for SARS-CoV-2, to track and manage their close contacts. The pre-existing unique identification code for each resident was used as the programme's identification number, to ensure information accuracy during the whole process of screening, from sampling, nucleic acid testing, result reporting, the isolation of detected positive cases, and tracing of close contacts of positive cases. All screening information was kept strictly confidential and was not allowed to be disclosed or used for other purposes other than clinical and public health management. Personal information of asymptomatic positive cases was only disclosed to designated medical institutions and community health centres for the purpose of medical isolation and identification of close contacts. Researcher was blind to the study hypothesis during data collection.

Biological security guarantee. Nucleic acid testing was performed in biosafety level-2 (BSL-2) laboratories, and virus culture was conducted in biosafety level-3 laboratories. Sampling and testing personnel adopted the personal protective measures according to the standard of biosafety level-3 laboratories. Participating laboratories implemented control measures to guarantee biological safety in accordance with relevant regulations[17].

Result query and feedback. Two to three days after sample collection, participants could inquire about their test results using WeChat or Alipay application by their unique ID numbers. The results included text descriptions of nucleic acid testing and coloured health codes. A green coloured health code refers to a negative result, and a red coloured health code indicates a positive result.

Definition and management of identified confirmed cases and close contacts. In this study, all confirmed COVID-19 cases were diagnosed by designated medical institutions according to National Guidelines for the Prevention and Control of COVID-19 (Supplementary Note 2). Asymptomatic positive cases referred to individuals who had a positive result during screening, and they had neither a history of COVID-19 diagnosis, nor any clinical symptoms at the time of the nucleic acid testing. Close contacts were individuals who closely contacted with an asymptomatic positive person since 2 days before the nucleic acid sampling[16]. Repositive cases refer to individuals who recovered from previously confirmed COVID-19 disease and had a positive testing again in the screening programme. All repositive cases, asymptomatic positive persons, and their close contacts were

isolated for at least 2 weeks in designated hotels managed by primary health care professionals, and they were released from isolation only if two consecutive nucleic acid tests were negative.

Statistical analysis. Detection rate of asymptomatic positive or repositive cases was calculated by dividing the number of individuals with a positive result of nucleic acid testing by the number of participants tested. Because of extremely low detection rates, we calculated 95% confidence intervals of estimated proportions using Pearson–Klopper exact method, implemented through R package "binom" version 1.1-1[18]. SPSS version 22.0 was used for other statistical analyses. We analyzed the distribution of asymptomatic positive cases and assessed the Spearman correlation between the asymptomatic positive rate and the prevalence of previously confirmed COVID-19 cases in different districts of Wuhan. Differences in asymptomatic positive rates by sex and age groups were assessed using the χ^2 test. ArcGIS 10.0 was used to draw a geographic distribution map of asymptomatic positive cases. A value of $P < 0.05$ (two-tailed) was considered statistically significant.

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

Detailed data directly used to generate each figure or table of this study are available within the article, Supplementary Information and source data are provided with this paper.

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Author contributions

S.Y.C., C.W., X.X.Y., and Z.X.L. conceived the study. C.W., Y.C.H., T.T.W., K.L., H.B.X., and X.S. participated in the acquisition of data. S.B.W. and J.G. were responsible for the on-site specimen collection, laboratory testing quality evaluation, and control. Y.C.H., T.T.W., and L.Q.L. analyzed the data. H.J., Y.H.G., and F.J.S. gave advice on methodology. Q.F.T. and C.Z.L. investigated the responses to the citywide nucleic acid testing among residents lived in outside of Wuhan city. S.Y.C., Y.G., C.W., and X.X.Y. drafted the manuscript, Y.G., M.B., and F.J.S. revised the manuscript, and M.B., C.Z.L., and F.J.S. critically commented and edited the manuscript. All authors read and approved the final manuscript. Z.X.L. is the guarantor of this study.

Competing interests

The authors declare no competing interests.

Additional information

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Contact Tracing Assessment of COVID-19 Transmission Dynamics in Taiwan and Risk at Different Exposure Periods Before and After Symptom Onset

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IMPORTANCE The dynamics of coronavirus disease 2019 (COVID-19) transmissibility are yet to be fully understood. Better understanding of the transmission dynamics is important for the development and evaluation of effective control policies.

OBJECTIVE To delineate the transmission dynamics of COVID-19 and evaluate the transmission risk at different exposure window periods before and after symptom onset.

DESIGN, SETTING, AND PARTICIPANTS This prospective case-ascertained study in Taiwan included laboratory-confirmed cases of COVID-19 and their contacts. The study period was from January 15 to March 18, 2020. All close contacts were quarantined at home for 14 days after their last exposure to the index case. During the quarantine period, any relevant symptoms (fever, cough, or other respiratory symptoms) of contacts triggered a COVID-19 test. The final follow-up date was April 2, 2020.

MAIN OUTCOMES AND MEASURES Secondary clinical attack rate (considering symptomatic cases only) for different exposure time windows of the index cases and for different exposure settings (such as household, family, and health care).

RESULTS We enrolled 100 confirmed patients, with a median age of 44 years (range, 11-88 years), including 44 men and 56 women. Among their 2761 close contacts, there were 22 paired index-secondary cases. The overall secondary clinical attack rate was 0.7% (95% CI, 0.4%-1.0%). The attack rate was higher among the 1818 contacts whose exposure to index cases started within 5 days of symptom onset (1.0% [95% CI, 0.6%-1.6%]) compared with those who were exposed later (0 cases from 852 contacts; 95% CI, 0%-0.4%). The 299 contacts with exclusive presymptomatic exposures were also at risk (attack rate, 0.7% [95% CI, 0.2%-2.4%]). The attack rate was higher among household (4.6% [95% CI, 2.3%-9.3%]) and nonhousehold (5.3% [95% CI, 2.1%-12.8%]) family contacts than that in health care or other settings. The attack rates were higher among those aged 40 to 59 years (1.1% [95% CI, 0.6%-2.1%]) and those aged 60 years and older (0.9% [95% CI, 0.3%-2.6%]).

CONCLUSIONS AND RELEVANCE In this study, high transmissibility of COVID-19 before and immediately after symptom onset suggests that finding and isolating symptomatic patients alone may not suffice to contain the epidemic, and more generalized measures may be required, such as social distancing.

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Author Audio Interview

Supplemental content

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The coronavirus disease 2019 (COVID-19) outbreak that originated in Wuhan, China, spread to more than 100 countries within 2 months of when the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in January 2020.[1,2] Following the Wuhan lockdown and other extreme social-distancing measures conducted by the Chinese government, several countries with widespread outbreaks implemented similar measures, including shutting down entire cities or communities, banning international or domestic travel, conducting border control with symptom screening, and implementing isolation and quarantine.

The unknown epidemiologic characteristics and transmission dynamics of a novel pathogen, such as SARS-CoV-2, complicate the development and evaluation of effective control policies.[3] The serial interval of COVID-19, defined as the interval between the symptom onset of the index case and that of the secondary case, was found to be short (4-5 days) and was similar to the estimated incubation period.[4] The short serial interval of COVID-19 and results from viral shedding studies suggested that most transmission occurred near or even before the time of symptom onset.[4-6] On the other hand, prolonged viral shedding raised concerns about prolonged infectiousness of patients and the need for extended isolation. A few preliminary contact-tracing studies showed that the highest-risk exposure setting of COVID-19 transmission was the household.[7-9] Nevertheless, it is not known when and how long a patient with COVID-19 should be isolated or whether close contacts should be quarantined. Additional information is needed about the transmission risk at different time points before and after symptom onset and with different types of exposures, such as through the household or a health care facility.

In Taiwan, the first COVID-19 case was confirmed on January 21, 2020.[10] With proactive containment efforts and comprehensive contact tracing, the number of COVID-19 cases remained low, as compared with other countries that had widespread outbreaks.[11,12] Using the contact tracing data in Taiwan, we aimed to delineate the transmission dynamics of COVID-19, evaluate the infection risk at different exposure windows, and estimate the infectious period.

Key Points

Question What is the transmissibility of coronavirus disease 2019 (COVID-19) to close contacts?

Findings In this case-ascertained study of 100 cases of confirmed COVID-19 and 2761 close contacts, the overall secondary clinical attack rate was 0.7%. The attack rate was higher among contacts whose exposure to the index case started within 5 days of symptom onset than those who were exposed later.

Meaning High transmissibility of COVID-19 before and immediately after symptom onset suggests that finding and isolating symptomatic patients alone may not suffice to interrupt transmission, and that more generalized measures might be required, such as social distancing.

Methods

Study Population

On January 15, 2020, in response to the outbreak in Wuhan, the Taiwan Centers for Disease Control (Taiwan CDC) made COVID-19 a notifiable disease. We conducted a prospective case-ascertained study that enrolled all the initial 100 confirmed cases in Taiwan between January 15 and March 18, 2020, and their close contacts. All contacts were followed up until 14 days after the last exposure to the index case. The last follow-up date was April 2, 2020.

The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[13] Information was collected according to the pronouncement of the Central Epidemic Command Center and in accordance with Article 17 of the Communicable Disease Control Act.[14] As part of the public health response functions of the Central Epidemic Command Center for surveillance purposes, institutional review board approval of this study and informed consent were waived. Prior to analysis, the data were deidentified.

Ascertainment of Cases

A confirmed case met the criteria of notification for COVID-19 in Taiwan and tested positive by real-time reverse transcriptase–polymerase chain reaction (RT-PCR) test.[15] Detailed information, including demographic and clinical data, was reported to the National Notifiable Disease Surveillance System.[16] The investigation team determined the clinical severity of the confirmed patients following the World Health Organization (WHO) interim guidance.[17]

Contact Tracing for COVID-19

When a patient was laboratory-confirmed to have SARS-CoV-2 infection, a thorough epidemiological investigation, including contact tracing, was implemented by the outbreak investigation team of the Taiwan CDC and local health authorities. The period of investigation started at the date at symptom onset (and could be extended to up to 4 days before symptom onset when epidemiologically indicated) and ended at the date at COVID-19 confirmation. For asymptomatic confirmed cases, the period of investigation was based on the date at confirmation (instead of date at onset) and was determined according to epidemiological investigation. The definition of a close contact was a person who did not wear appropriate personal protection equipment (PPE) while having face-to-face contact with a confirmed case for more than 15 minutes during the investigation period. A contact was listed as a household contact if he or she lived in the same household with the index case. Those listed as family contacts were family members not living in the same household.

For health care settings, medical staff, hospital workers, and other patients in the same setting were included; close contact was defined by contacting an index case within 2 m without appropriate PPE and without a minimal requirement of exposure time. Whether the PPE was regarded as "appropriate" depended on the exposure setting and the procedures performed. For example, for physicians who performed aerosol-generating procedures, such as intubation, an N95 respirator

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Table 1. Characteristics of the 2761 Close Contacts by Different Exposure Settings

	Exposure, No. (%)			
	Household (n = 151)	Family (n = 76)	Health care (n = 698)	Others (n = 1836)[a]
Age, median (range), y	33 (1-96)	45 (0-88)	39 (0-92)	35 (0-89)
Age group, y				
0-19	24 (16)	14 (18)	29 (4)	214 (12)
20-39	55 (36)	16 (21)	281 (40)	809 (44)
40-59	38 (25)	24 (32)	175 (25)	557 (30)
≥60	26 (17)	11 (14)	119 (17)	175 (10)
Unknown	8 (5)	11 (14)	94 (13)	81 (4)
Sex				
Female	70 (46)	41 (54)	454 (65)	872 (47)
Male	81 (54)	30 (39)	228 (33)	816 (44)
Unknown	0	5 (7)	16 (2)	148 (8)
Time from onset to exposure, median (range), d[b]	−4 (−4 to 9)	6 (−4 to 26)	1 (−4 to 23)	2 (−4 to 26)
Time from onset to exposure, d[b]				
<0	100 (66)	10 (13)	236 (34)	389 (21)
0-3	39 (26)	15 (20)	150 (21)	663 (36)
4-5	6 (4)	6 (8)	38 (5)	166 (9)
6-7	4 (3)	10 (13)	17 (2)	88 (5)
8-9	2 (1)	3 (4)	110 (16)	334 (18)
>9	0	24 (32)	146 (21)	114 (6)
Unknown	0	8 (11)	1 (0.1)	82 (5)

[a] Others include friends, airline crew members and passengers, and other casual contacts.

[b] Defined as the elapsed time between the date at symptom onset of the index case and the first date at exposure. For example, people from the group "<0 days" had their first contact with the index case before the case had any symptoms.

was required. For such procedures, a surgical mask would not be appropriate PPE. Accordingly, the medical staff would be listed as a close contact.

All close contacts were quarantined at home for 14 days after their last exposure to the index case. During the quarantine period, any relevant symptoms (fever, cough, or other respiratory symptoms) of close contacts would trigger RT-PCR testing for COVID-19. For high-risk populations, including household and hospital contacts, RT-PCR was performed regardless of symptoms. Essentially, these high-risk contacts were tested once when they were listed as a close contact. If the initial COVID-19 test result was negative, further testing would only be performed if a close contact developed symptoms during quarantine. The Taiwan CDC used an electronic tracing system (Infectious Disease Contact Tracing Platform and Management System) to follow and record the daily health status of those quarantined contacts.[18] The information collected included age, sex, the index case, date at exposure, and the exposure setting.

Data Processing and Analysis

Paired data of index case and close contacts were extracted from the contact tracing database and outbreak investigation reports. For a family cluster, the index case was determined based on the temporality of symptom onset and review of the epidemiological link. A secondary case was excluded from the paired data if the beginning of exposure was after symptom onset of the secondary case (only applied when the secondary case was symptomatic). For health care contacts, the date at exposure would be the date at admission of the case if the exact date at exposure was not recorded.

Incubation period and serial interval were estimated using the contact tracing data in Taiwan and publicly available data sets globally (eMethods in the Supplement). We used the Bayesian hierarchical model to increase the stability in small-sample estimation. The exposure window period was defined as the period between the first and last day of reported exposure to the index case based on contact investigation. Following the WHO, we defined the secondary clinical attack rate as the ratio of symptomatic confirmed cases among the close contacts.[19] We analyzed the dynamic change of secondary clinical attack rate in relation to symptom onset of the index case (days <0, 0-3, 4-5, 6-7, 8-9, or >9).

The percentage of missing information was small (7.0% for age, 6.1% for sex, and 3.3% for time from onset to exposure; **Table 1**). In the univariable analysis of secondary clinical attack rate by different exposure characteristics (eg, age), close contacts with missing information in that particular exposure attribute were excluded. All statistical tests were 2-sided with an α level of .05. All confidence intervals (CIs) were 95%. R software (R Foundation for Statistical Computing) and RStan (Stan Development Team) were used for data management and analysis.

Results

As of March 18, 2020, there were 100 patients with laboratory-confirmed COVID-19 in Taiwan, including 10 clusters of patients and 9 asymptomatic patients. The median age of the 100 patients was 44 years old (range, 11-88 years); 44 were men and 56 were women. Of the 2761 close contacts that were identi-

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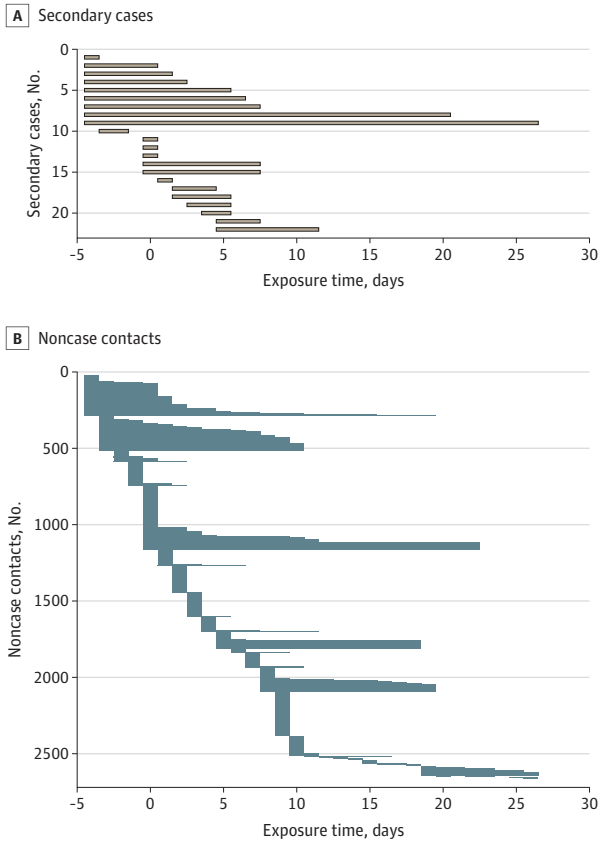
fied, 5.5% were household contacts, 2.8% were nonhousehold family contacts, and 25.3% were health care contacts (Table 1). Through contact tracing, 23 secondary cases were found. One of the 23 cases was excluded from subsequent transmission-pair analysis because the documented day at exposure occurred after symptom onset of the secondary case. None of the 9 asymptomatic case patients transmitted a secondary case. Using the data on the 22 paired cases, we estimated that the median incubation period was 4.1 days (95% credible interval [CrI], 0.4-15.8), and the median serial interval was 4.1 days (95% CrI, 0.1-27.8) (eTables 1-5 and eFigures 1-5 in the Supplement).

Among the 2761 close contacts, 22 secondary cases of COVID-19 infection (including 4 asymptomatic infections) were detected, with an infection risk of 0.8% (95% CI, 0.5%-1.2%). The secondary clinical attack rate was 18 of 2761, or 0.7% (95% CI, 0.4%-1.0%). **Figure 1** shows the exposure window of all contacts. All of the 22 secondary cases had their first exposure before the sixth day of the index case's symptom onset. By comparison, only 68% of noncase contacts had their first exposure before day 6 (Table 1). The secondary clinical attack rate was higher among those whose initial exposure to the index case was within 5 days of symptom onset than those who were exposed after day 6 (zero transmission of 852 contacts [95% CI, 0%-0.4%]) (**Table 2** and **Figure 2**A). The 735 contacts whose initial exposure occurred before symptom onset of the index case were also at risk, with a secondary clinical attack rate of 1.0% (95% CI, 0.5%-2.0%). A subgroup of 299 contacts with exclusive presymptomatic exposures were also at risk (secondary clinical attack rate, 0.7% [95% CI, 0.2%-2.4%]).

The secondary clinical attack rate was 4.6% (95% CI, 2.3%-9.3%) among 151 household contacts and 5.3% (95% CI, 2.1%-12.8%) in 76 nonhousehold family contacts (Table 2). The high attack rate from early exposure remained when the analysis was restricted to household and nonhousehold family contacts (**Table 3** and Figure 2B). The attack rates were higher among those aged 40 to 59 years (1.1% [95% CI, 0.6%-2.1%]) and those aged 60 years and older (0.9% [95% CI, 0.3%-2.6%]). The 786 close contacts of the 6 confirmed cases presenting with severe disease were at a higher risk compared with the 1097 close contacts of the 56 cases presenting with mild disease (risk ratio, 3.76 [95% CI, 1.10-12.76] and 3.99 [95% CI, 1.00-15.84] for severe pneumonia and acute respiratory distress syndrome/sepsis, respectively). Among the 91 close contacts of the 9 asymptomatic cases, no secondary transmission was observed. The secondary attack rate among contacts of cases with infection acquired in Taiwan was higher than that among contacts of cases with infection acquired outside of Taiwan (Table 2).

Figure 1. Exposure Window Period Among Secondary Cases and Noncase Contacts



The exposure time was defined as the period from the first day of exposure to the index case to the last day of exposure. Time zero indicates the day of symptom onset of the index case.

Discussion

Our analysis of close contacts to confirmed COVID-19 cases revealed a relatively short infectious period of COVID-19 and a higher transmission risk around the time of symptom onset of the index case, followed by a lower transmission risk at the later stage of disease. The observed decreasing transmission risk over time for COVID-19 was in striking contrast to the transmission pattern of severe acute respiratory syndrome (SARS), in which the transmission risk remained low until after day 5 of symptom onset in the index cases.[20] Our study and the study by Nishiura et al[4] revealed a short serial interval of COVID-19, with a median of 4 to 5 days. In contrast, the mean serial interval of SARS was estimated to be 8.4 days in Singapore.[20] The present contact tracing analysis suggested that the shorter serial interval of COVID-19 was due to the combination of early-stage transmission and a short period of infectiousness.

The observed pattern of the secondary clinical attack rate over time was also consistent with the quantitative data of the SARS-CoV-2 viral shedding in upper respiratory specimens, which has been found in China to be a high viral load around the time of symptom onset, followed by a gradual decrease in viral shedding to a low level after 10 days.[5] The viral load was similar among asymptomatic, minimally symptomatic, and symptomatic patients. Another virological study in patients with COVID-19 in Germany also found no viable isolates of the virus after the first week of symptoms.[21] Our findings agree with the virological data on high transmissibility of COVID-19 in the first week after the onset of symptoms and decreased risk afterwards.[21] We also documented and quantified the

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Table 2. Secondary Clinical Attack Rate for COVID-19 Among the 2761 Close Contacts by Different Exposure Settings, Times, and Characteristics

	No. of secondary cases (asymptomatic case)	No. of contacts	Secondary clinical attack rate, % (95% CI)	Risk ratio (95% CI)
Exposure setting				
Household	10 (3)	151	4.6 (2.3-9.3)	1 [Reference]
Nonhousehold family	5 (1)	76	5.3 (2.1-12.8)	1.14 (0.34-3.76)
Health care	6 (0)	698	0.9 (0.4-1.9)	0.19 (0.06-0.54)
Others[a]	1 (0)	1836	0.1 (0-0.3)	0.01 (0-0.09)
Time from onset to exposure, d[b]				
<0	10 (3)	735	1.0 (0.5-2.0)	1 [Reference]
0-3	9 (1)	867	0.9 (0.5-1.8)	0.97 (0.35-2.66)
4-5	3 (0)	216	1.4 (0.5-4.0)	1.46 (0.38-5.59)
6-7	0	119	0 (0-3.1)	0
8-9	0	449	0 (0-0.9)	0
>9	0	284	0 (0-1.3)	0
Exclusively presymptomatic exposure[c]				
No	20 (4)	2371	0.7 (0.4-1.1)	1 [Reference]
Yes	2 (0)	299	0.7 (0.2-2.4)	0.99 (0.23-4.29)
Age of close contacts, y				
0-19	1 (1)	281	0 (0-1.4)	0
20-39	8 (2)	1161	0.5 (0.2- 1.1)	1 [Reference]
40-59	10 (1)	794	1.1 (0.6-2.1)	2.19 (0.78-6.14)
≥60	3 (0)	331	0.9 (0.3-2.6)	1.75 (0.44-6.97)
Source of index case				
Local	18 (3)	967	1.6 (1.0-2.5)	1 [Reference]
Imported	4 (1)	1794	0.2 (0.1-0.5)	0.11 (0.03-0.37)
Clinical severity of index case				
Asymptomatic	0	91	0 (0-4.1)	0
Mild illness	4 (0)	1097	0.4 (0.1-0.9)	1 [Reference]
Pneumonia				
Mild	5 (2)	761	0.4 (0.1-1.2)	1.08 (0.24-4.82)
Severe	7 (0)	511	1.4 (0.7-2.8)	3.76 (1.10-12.76)
ARDS/sepsis	6 (2)	275	1.5 (0.6-3.7)	3.99 (1.00-15.84)

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019.

[a] Others include friends, airline crew members and passengers, and other casual contacts.

[b] Defined as the elapsed time between the date at symptom onset of the index case and the first date at exposure. For example, people from the group "<0 days" had their first contact with the index case before the case had any symptoms.

[c] All the reported exposures occurred during the presymptomatic period of the index case.

transmission potential of COVID-19 in a subgroup of contacts whose exposure occurred exclusively during the presymptomatic period of the index case. Our analysis revealed a similar clinical attack rate between the contacts who only had presymptomatic exposure and those who had postsymptomatic exposure.

To summarize the evidence, the decreasing risk for secondary infection over time in our study, the observed short serial interval, and the trend of decreasing viral shedding and viability after symptom onset strongly suggested high transmissibility of the disease near or even before the day of symptom onset. Because the onset of overt clinical symptoms, such as fever, dyspnea, and signs of pneumonia, usually occurred 5 to 7 days after initial symptom onset, the infection might well have been transmitted at or before the time of detection.[22,23] This characteristic makes containment efforts challenging. In a modeling study, Hellewell et al[24] found that the possibility of controlling COVID-19 through isolation and contact tracing decreased with increasing proportion of transmission that occurred before symptom onset. The findings of this modeling study, when viewed in the context of our findings, might help to explain the difficult situation in such areas and countries as China, South Korea, Iran, and Italy. Aggressive social distancing and proactive contact tracing might be necessary to block the transmission chain of COVID-19 and to keep presumptive patients away from susceptible populations with a high risk for severe disease.

The observed short duration of infectiousness with lower risk of transmission 1 week after symptom onset has important implications for redirecting the efforts to control COVID-19. Given the nonspecific and mostly mild symptoms of COVID-19 at presentation, patients are often identified and hospitalized at a later stage of disease when the transmissibility of infection has started to decrease. In this case, hospitalization would not be helpful for isolation and reducing transmission, and should be only for patients whose clinical course is sufficiently severe. When the number of confirmed cases rapidly increases, home care for patients with mild illness may be

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Figure 2. Number of Contacts, Secondary Cases, and Secondary Clinical Attack Rate by the Time of First Exposure

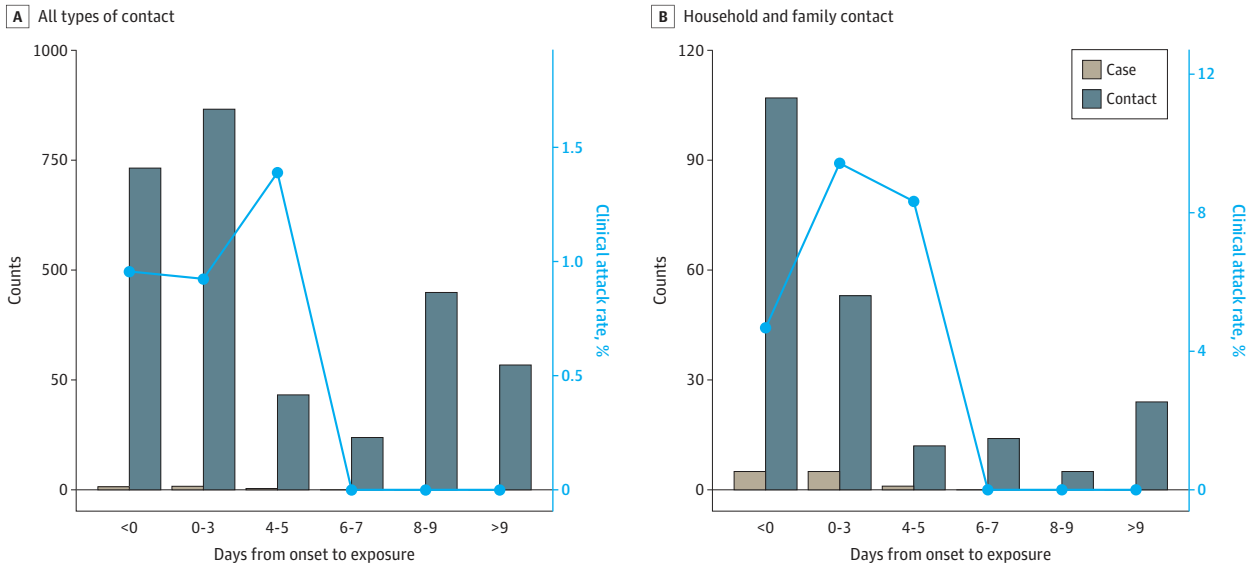

Table 3. Risk for Symptomatic COVID-19 Infection Among the 2761 Close Contacts, Simultaneously Stratified by Exposure Setting and Time From Symptom Onset of the Index Case to First Day of Exposure

First day of exposure, d	Household		Nonhousehold family		Health care		Others[a]	
	Case/contact, No.	Attack rate, % (95% CI)[b]	Case/contact, No.	Attack rate, % (95% CI)[b]	Case/contact, No.	Attack rate, % (95% CI)[b]	Case/contact, No.	Attack rate, % (95% CI)[b]
<0	4/100	4.0 (1.6-9.8)	1/10	10.0 (1.8-40.4)	2/236	0.8 (0.2-3.0)	0/389	0 (0-1.0)
0-3	2/39	5.1 (1.4-16.9)	3/15	20.0 (7.0-45.2)	3/150	2.0 (0.7-5.7)	0/663	0 (0-0.6)
4-5	1/6	16.7 (3.0-56.4)	0/6	0 (0-39.0)	1/38	2.6 (0.5-13.5)	1/166	0.6 (0.1-3.3)
6-7	0/4	0 (0-49.0)	0/10	0 (0-27.8)	0/17	0 (0-18.4)	0/88	0 (0-4.2)
8-9	0/2	0 (0-65.7)	0/3	0 (0-56.1)	0/110	0 (0-3.3)	0/334	0 (0-1.1)
>9	0/0	NC	0/24	0 (0-13.8)	0/146	0 (0-2.6)	0/114	0 (0-3.3)

Abbreviations: COVID-19, coronavirus disease 2019; NC, not calculable.

[a] Others include friends, airline crew members and passengers, and other casual contacts.

[b] Secondary clinical attack rate.

preferred.[25] In Taiwan (where patients with COVID-19 have been routinely hospitalized), the most prolonged duration of hospital isolation for the 100 confirmed cases was more than 2 months. If every patient with mild illness is to be isolated in the hospital or other isolation facilities for such a prolonged period during a large epidemic, the health care system would soon be overwhelmed, and the case-fatality rate may increase, as observed in Wuhan.[26,27] Similarly, better understanding of the potential duration of transmission could help direct containment strategies. For example, contact tracing could focus on the contacts near or even before symptom onset of the index cases when the number of index cases or contacts is too large for all contacts to be traced, given the available resources.

Several patients in our study were initially considered to have pneumonia of unknown etiology and had multiple contacts in the health care setting before being diagnosed. However, the number of health care contacts that led to nosocomial transmission was low. Besides the basic PPE used by medical staffs, this finding might be due to the late admissions of these patients and their lower risk of transmitting COVID-19 by the time of hospitalization. This pattern is compatible with the observations in China and Hong Kong. In China, the number of nosocomial infections might be lower than reported because some health care workers acquired infections in their households rather than in the health care faciltiy.[9] In Hong Kong, most hospitalization was also delayed to at least 5 days after disease onset.[28] In closed settings such as a hospital or a cruise ship,[29,30] fomite transmission might play an important role, amplifying the risk of transmission and making the temporality of transmission less identifiable.[30-32] Better understanding of the dynamic change of transmissibility of COVID-19 over time and how health care workers are most likely to be infected could allow for better targeting of control measures, including the use of appropriate PPE.

In the contact tracing cohort, we observed a relatively low transmission rate of COVID-19. During the study period (January to early March 2020), the major containment measures in Taiwan were travel alerts with restriction to affected countries (principally China), home quarantine for travelers entering Taiwan, and comprehensive contact tracing for confirmed cases.[11] In response to a possible shortage of face masks,

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the government proactively initiated a name-based rationing system for mask purchase and boosted the production of face masks to ensure the availability for both N95 respirators and face masks to both health care professionals and the general public. A general recommendation on social distancing from the government was not in place, but spontaneous behavioral changes that reduced community mobility were observed.[33]

Limitations

Our study has limitations. First, we did not completely examine contacts before the symptom onset of the index cases. Therefore, we might have underestimated the importance of early transmission. Thus, the actual contribution of early transmission to new infections could be greater than our estimates suggests. Our findings agree with the recommendation from the WHO to use 4 days before symptom onset as the starting date for contact tracing.[19] This modification may help to further understand the pattern of early transmission in COVID-19. Second, we could not completely separate out the effect of close household contact and early contact given the strong correlation of the 2. The increased transmissibility in the early stage of COVID-19 may be partially attributed to the effect of household and nonhousehold family contacts rather than increased infectiousness at the early stage. When we stratified by type of exposure, however, the pattern of early transmission remained.

Conclusions

In summary, the findings of this study suggest that most transmission of COVID-19 occurred at the very early stage of the disease or even before the onset of symptoms, and the secondary clinical attack rate among contacts decreased over time as symptoms developed and progressed. The pattern of high transmissibility near and before symptom onset and the likely short infectious period of the virus could inform control strategies for COVID-19, as well as additional studies to fully elucidate the transmission dynamics of the virus.

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Editor's Note

Contact Tracing, Testing, and Control of COVID-19—Learning From Taiwan

Robert Steinbrook, MD

Taiwan is a country of about 24 million people, 81 miles off the coast of mainland China. As of late April 2020, Taiwan had about 330 confirmed cases of coronavirus disease 2019 (COVID-19) and 6 deaths. By comparison, the US had about 1 million confirmed cases of COVID-19, and 60 000 deaths.

In this issue of *JAMA Internal Medicine*, there is a remarkable report from Taiwan on the use of contact tracing and virologic polymerase chain reaction testing to assess the transmission dynamics of COVID-19 in the country's initial 100 confirmed cases.[1] Among 2761 close contacts of the 100 cases, confirmed between January 15 and March 18, 2020, Cheng et al report that there were 22 paired-index secondary cases and an overall secondary clinical attack rate of 0.7% (95% CI, 0.4%-1.0%).[1]

Related article page 1156 and 1262

The study has important messages for the control of COVID-19 throughout the world. First, people with COVID-19 were found to be most infectious to others before and within 5 days of symptom onset. Within 5 days of symptom onset, the attack rate was 1.0% (95% CI, 0.6%-1.5%). With exclusive presymptomatic exposures, the attack rate was 0.7% (95% CI, 0.2%-2.4%), and with exposures 6 days or more after symptom onset, there were 0 cases from 852 contacts (95% CI, 0%-0.4%).[1]

These findings underscore the pressing public health need for accurate and comprehensive contact tracing and testing. Testing only those people who are symptomatic will miss many infections and render contact tracing less effective. The finding that asymptomatic people and those with minimal or fewer symptoms early in infection are those most likely to transmit COVID-19 strongly argues for maintaining social distancing and

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Household Transmission of SARS-CoV-2
A Systematic Review and Meta-analysis

Zachary J. Madewell, PhD; Yang Yang, PhD; Ira M. Longini Jr, PhD; M. Elizabeth Halloran, MD, DSc; Natalie E. Dean, PhD

Abstract

IMPORTANCE Crowded indoor environments, such as households, are high-risk settings for the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

OBJECTIVES To examine evidence for household transmission of SARS-CoV-2, disaggregated by several covariates, and to compare it with other coronaviruses.

DATA SOURCE PubMed, searched through October 19, 2020. Search terms included *SARS-CoV-2* or *COVID-19* with *secondary attack rate*, *household*, *close contacts*, *contact transmission*, *contact attack rate*, or *family transmission*.

STUDY SELECTION All articles with original data for estimating household secondary attack rate were included. Case reports focusing on individual households and studies of close contacts that did not report secondary attack rates for household members were excluded.

DATA EXTRACTION AND SYNTHESIS Meta-analyses were done using a restricted maximum-likelihood estimator model to yield a point estimate and 95% CI for secondary attack rate for each subgroup analyzed, with a random effect for each study. To make comparisons across exposure types, study was treated as a random effect, and exposure type was a fixed moderator. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline was followed.

MAIN OUTCOMES AND MEASURES Secondary attack rate for SARS-CoV-2, disaggregated by covariates (ie, household or family contact, index case symptom status, adult or child contacts, contact sex, relationship to index case, adult or child index cases, index case sex, number of contacts in household) and for other coronaviruses.

RESULTS A total of 54 relevant studies with 77 758 participants reporting household secondary transmission were identified. Estimated household secondary attack rate was 16.6% (95% CI, 14.0%-19.3%), higher than secondary attack rates for SARS-CoV (7.5%; 95% CI, 4.8%-10.7%) and MERS-CoV (4.7%; 95% CI, 0.9%-10.7%). Household secondary attack rates were increased from symptomatic index cases (18.0%; 95% CI, 14.2%-22.1%) than from asymptomatic index cases (0.7%; 95% CI, 0%-4.9%), to adult contacts (28.3%; 95% CI, 20.2%-37.1%) than to child contacts (16.8%; 95% CI, 12.3%-21.7%), to spouses (37.8%; 95% CI, 25.8%-50.5%) than to other family contacts (17.8%; 95% CI, 11.7%-24.8%), and in households with 1 contact (41.5%; 95% CI, 31.7%-51.7%) than in households with 3 or more contacts (22.8%; 95% CI, 13.6%-33.5%).

(continued)

Key Points

Question What is the household secondary attack rate for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)?

Findings In this meta-analysis of 54 studies with 77 758 participants, the estimated overall household secondary attack rate was 16.6%, higher than observed secondary attack rates for SARS-CoV and Middle East respiratory syndrome coronavirus. Controlling for differences across studies, secondary attack rates were higher in households from symptomatic index cases than asymptomatic index cases, to adult contacts than to child contacts, to spouses than to other family contacts, and in households with 1 contact than households with 3 or more contacts.

Meaning These findings suggest that households are and will continue to be important venues for transmission, even in areas where community transmission is reduced.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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Abstract (continued)

CONCLUSIONS AND RELEVANCE The findings of this study suggest that given that individuals with suspected or confirmed infections are being referred to isolate at home, households will continue to be a significant venue for transmission of SARS-CoV-2.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is spread via direct or indirect contact with infected people via infected respiratory droplets or saliva, fomites, or aerosols.[1,2] Crowded indoor environments with sustained close contact and conversations, such as households, are a particularly high-risk setting.[3]

The World Health Organization China Joint Mission reported human-to-human transmission in China largely occurred within families, accounting for 78% to 85% of clusters in Guangdong and Sichuan provinces.[4] Stay-at-home orders reduced human mobility by 35% to 63% in the United States,[5] 63% in the United Kingdom,[6] and 54% in Wuhan,[7] relative to normal conditions, which concomitantly increased time at home. Modeling studies demonstrated that household transmission had a greater relative contribution to the basic reproductive number after social distancing (30%-55%) than before social distancing (5%-35%).[8] While current US Centers for Disease Control and Prevention recommendations are to maintain 6 feet of distance from a sick household member, this may be difficult to achieve in practice and not be fully effective.[9]

The household secondary attack rate characterizes virus transmissibility. Studies can collect detailed data on type, timing, and duration of contacts and identify risk factors associated with infectiousness of index cases and susceptibility of contacts. Our objective was to estimate the secondary attack rate of SARS-CoV-2 in households and determine factors that modify this parameter. We also estimated the proportion of households with index cases that had any secondary transmission. Furthermore, we compared the SARS-CoV-2 household secondary attack rate with that of other severe viruses and with that to close contacts for studies that reported the secondary attack rate for both close and household contacts.

Methods

Definitions

We estimated the transmissibility of SARS-CoV-2 within the household or family by the empirical secondary attack rate by dividing the number of new infections among contacts by the total number of contacts. Household contacts include anyone living in the same residence as the index case. Family contacts include the family members of index cases, including individuals who live outside the index case's household. Close contact definitions varied by study and included physical proximity to an index case, exceeding a minimum contact time, and/or not wearing effective protection around index cases before the index case was tested.

Search Strategy

Following Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline, we searched PubMed using terms including *SARS-CoV-2* or *COVID-19* with *secondary attack rate*, *household*, *close contacts*, *contact transmission*, *contact attack rate*, or *family transmission* (eTable 1 in the Supplement) with no restrictions on language, study design, time, or place of publication. The last search was conducted October 19, 2020.

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Eligibility Criteria

Eligibility criteria are described in eAppendix 1 in the Supplement. All articles with original data for estimating household secondary attack rate were included. Case reports focusing on individual households and studies of close contacts that did not report secondary attack rates for household members were excluded.

Data Extraction

One of us (Z.J.M.) extracted data from each study. Details appear in eAppendix 2 in the Supplement.

Evaluation of Study Quality and Risk of Bias

To assess the methodological quality and risk of bias of included studies of SARS-CoV-2, we used the same modified version of the Newcastle-Ottawa quality assessment scale for observational studies used by Fung et al.[10,11] Studies received as many as 9 points based on participant selection (4 points), study comparability (1 point), and outcome of interest (4 points). Studies were classified as having high (≤3 points), moderate (4-6 points), and low (≥7 points) risk of bias. One of us (Z.J.M.) evaluated the study quality and assigned the quality grades.

Statistical Analysis

Meta-analyses were done using a restricted maximum-likelihood estimator model to yield Freeman-Tukey double arcsine–transformed point estimates and 95% CI for secondary attack rate for each subgroup analyzed, with a random effect for each study.[12] For comparisons across covariates (ie, household or family, index case symptom status, adult or child contacts, contact sex, relationship to index case, adult or child index cases, index case sex, number of household contacts, study location, universal or symptomatic testing, dates of study) and comparisons with close contacts and other viruses, study was treated as a random effect, and the covariate was a fixed moderator. Variables had to have been collected in at least 3 studies to be included in meta-analyses. The Cochran Q test and I^2 statistic are reported as measures of heterogeneity. I^2 values of 25%, 50%, and 75% indicated low, moderate, and high heterogeneity, respectively.[13] Stastistical significance was set at a 2-tailed $\alpha = .05$. All analyses were done in R version 4.0.2 using the package metafor (R Project for Statistical Computing).[14,15]

When at least 10 studies were available, we used funnel plots, Begg correlation, and Egger test to evaluate publication bias, with significance set at $P < .10$.[16,17] If we detected publication bias, we used the Duval and Tweedie trim-and-fill approach for adjustment.[18]

Results

We identified 54 relevant published studies that reported household secondary transmission, with 77 758 participants (eTable 1 in the Supplement).[19-72] A total of 16 of 54 studies (29.6%) were at high risk of bias, 27 (50.0%) were moderate, and 11 (20.4%) were low (eTable 2 in the Supplement). Lower quality was attributed to studies with 1 or fewer test per contact (35 studies [64.8%]), small sample sizes (31 [57.4%]), and secondary attack rate not disaggregated by covariates (28 [51.9%]).

A description of index case identification period and methods and symptom status is provided in eTable 3 in the Supplement. Most studies did not describe how co-primary index cases were handled or whether secondary infections could have been acquired from outside the household, both of which can inflate the empirical secondary attack rate. Testing and monitoring strategies varied between studies, often reflecting variations in local testing guidelines implemented as part of contact tracing (eTable 4 and eAppendix 3 in the Supplement).

Figure 1 summarizes secondary attack rates for 44 studies[19-26,28-30,32-36,38-45,47-57,59,61-63,65-67,69,70] of household contacts and 10 of family contacts.[26,31,37,45,58,60,65,68,71,72] Estimated mean secondary attack rate for household contacts was 16.4% (95% CI, 13.4%-19.6%) and family contacts was 17.4% (95% CI, 12.7%-22.5%). One study[40]

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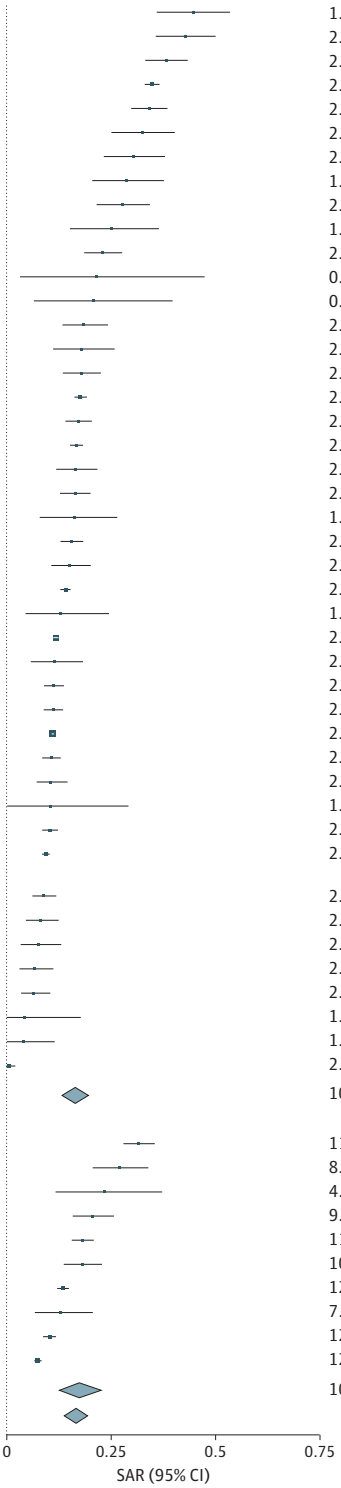
Figure 1. Secondary Attack Rates (SAR) of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) for Household Contacts and Family Contacts

Source	Location	Participants, No.	Participants with SARS-CoV-2 infection, No.	SAR (95% CI)	Weight, %
Household contacts					
Boscolo-Rizzo et al,[24] 2020	Treviso Province, Italy	121	54	0.45 (0.36-0.54)	1.93
Patel et al,[53] 2020	London, UK	185	79	0.43 (0.36-0.50)	2.17
Rosenberg et al,[55] 2020	New York, US	343	131	0.38 (0.33-0.43)	2.43
Dattner et al,[29] 2020	Bnei Brak, Israel	2824	981	0.35 (0.33-0.37)	2.77
Lopez Bernal et al,[47] 2020	UK	472	161	0.34 (0.30-0.38)	2.54
Wu et al,[65] 2020	Zhuhai, China	148	48	0.32 (0.25-0.40)	2.08
Wang et al,[61] 2020	Wuhan, China	155	47	0.30 (0.23-0.38)	2.12
Teherani et al,[59] 2020	Atlanta, US	108	31	0.29 (0.21-0.38)	1.92
Lewis et al,[44] 2020	Utah and Wisconsin, US	188	52	0.28 (0.21-0.34)	2.23
Dawson et al,[30] 2020	Wisconsin, US	64	16	0.25 (0.15-0.36)	1.61
Wang et al,[63] 2020	Beijing, China	335	77	0.23 (0.19-0.28)	2.47
Han,[35] 2020	South Korea	14	3	0.21 (0.03-0.47)	0.66
Böhmer et al,[23] 2020	Bavaria, Germany	24	5	0.21 (0.07-0.40)	0.97
Bae et al,[21] 2020	Cheonan, South Korea	200	37	0.18 (0.13-0.24)	2.32
Xin et al,[67] 2020	Qingdao Muncipal, China	106	19	0.18 (0.11-0.26)	2.01
Wu et al,[66] 2020	Hangzhou, China	280	50	0.18 (0.14-0.23)	2.45
Hu et al,[36] 2020	Hunan, China	2771	491	0.18 (0.16-0.19)	2.78
Jing et al,[39] 2020	Guangzhou, China	542	93	0.17 (0.14-0.20)	2.62
Lyngse et al,[49] 2020	Denmark	2226	371	0.17 (0.15-0.18)	2.77
Doung-ngern et al,[32] 2020	Thailand	230	38	0.17 (0.12-0.22)	2.39
Li et al,[45] 2020	Wuhan, China	392	64	0.16 (0.13-0.20)	2.55
Zhang et al,[70] 2020	China	62	10	0.16 (0.08-0.26)	1.70
Wang et al,[62] 2020	Beijing, China	714	111	0.16 (0.13-0.18)	2.67
Park et al,[52] 2020	Seoul, South Korea	225	34	0.15 (0.11-0.20)	2.39
Fateh-Moghadam et al,[34] 2020	Trento, Italy	3546	500	0.14 (0.13-0.15)	2.79
Islam and Noman,[38] 2020	Chattogram, Bangladesh	46	6	0.13 (0.05-0.25)	1.55
Park et al,[51] 2020	South Korea	10 592	1248	0.12 (0.11-0.12)	2.81
Phiriyasart et al,[54] 2020	Pattani Province, Thailand	106	12	0.11 (0.06-0.18)	2.11
Bi et al,[22] 2020	Shenzhen, China	686	77	0.11 (0.09-0.14)	2.68
Arnedo-Pena et al,[20] 2020	Castellon, Spain	745	83	0.11 (0.09-0.14)	2.69
Adamik et al,[19] 2020	Poland	32 023	3553	0.11 (0.11-0.11)	2.82
Malheiro et al,[50] 2020	Eastern Porto, Portugal	780	83	0.11 (0.09-0.13)	2.70
Chaw et al,[26] 2020	Brunei	264	28	0.11 (0.07-0.15)	2.49
Burke,[25] 2020	US	19	2	0.11 (0.00-0.29)	1.00
Luo et al,[48] 2020	Guangzhou, China	1015	105	0.10 (0.09-0.12)	2.73
Laxminarayan et al,[42] 2020	Tamil Nadu and Andhra Pradesh, India	4065	380	0.09 (0.08-0.10)	2.80
Shah et al,[56] 2020	Gujarat, India	386	34	0.09 (0.06-0.12)	2.61
Son et al,[57] 2020	Busan, South Korea	196	16	0.08 (0.05-0.12)	2.44
Korea CDC,[41] 2020	South Korea	119	9	0.08 (0.03-0.13)	2.26
Cheng et al,[28] 2020	Taiwan	151	10	0.07 (0.03-0.11)	2.38
Yung et al,[69] 2020	Singapore	200	13	0.06 (0.03-0.10)	2.48
Lee et al,[43] 2020	Busan, South Korea	23	1	0.04 (0.00-0.18)	1.42
Draper et al,[33] 2020	Northern Territory, Australia	51	2	0.04 (0.00-0.11)	1.98
Kim et al,[40] 2020	South Korea	208	1	0.00 (0.00-0.02)	2.72
Subgroup estimate				0.164 (0.134-0.196)	100
Family contacts					
Sun et al,[58] 2020	Zhejiang Province, China	598	189	0.32 (0.28-0.35)	11.05
van der Hoek et al,[60] 2020	Netherlands	174	47	0.27 (0.21-0.34)	8.54
Wang et al,[64] 2020	Wuhan, China	43	10	0.23 (0.12-0.37)	4.42
Dong et al,[31] 2020	Tianjin, China	259	53	0.20 (0.16-0.26)	9.78
Hua et al,[37] 2020	Zhejiang Province, China	835	151	0.18 (0.16-0.21)	11.66
Chen et al,[27] 2020	Ningbo, China	272	49	0.18 (0.14-0.23)	10.00
Liu et al,[46] 2020	Guangdong Province, China	2441	330	0.14 (0.12-0.15)	12.35
Zhang et al,[71] 2020	Liaocheng, China	93	12	0.13 (0.07-0.21)	7.53
Yu et al,[68] 2020	Wuhan, China	1396	143	0.10 (0.09-0.12)	12.17
Zhuang et al,[72] 2020	Guangdong Province, China	3697	276	0.07 (0.07-0.08)	12.51
Subgroup estimate				0.174 (0.127-0.225)	100
Combined estimate[a]				0.166 (0.140-0.193)	



Point sizes are an inverse function of the precision of the estimates, and bars correspond to 95% CIs. CDC indicates Centers for Disease Control and Prevention.

[a] Weights for the combined estimate are available in eTable 8 in the Supplement.

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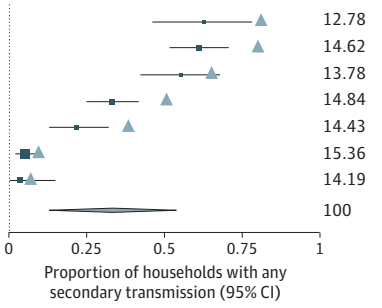
restricted index cases to children (age <18 years), resulting in a substantially lower secondary attack rate of 0.5%. Excluding this outlier, the combined secondary attack rate for household and family contacts was 17.1% (95%, 14.6%-19.7%). Secondary attack rates for household and family contacts were more than 3 times higher than for close contacts (4.8%; 95% CI, 3.4%-6.5%; $P < .001$) (eFigure 2 in the Supplement). Significant heterogeneity was found among studies of household ($I^2 = 96.9\%$; $P < .001$), family ($I^2 = 93.0\%$; $P < .001$), and close ($I^2 = 97.0\%$; $P < .001$) contacts. No significant publication bias was observed for studies of household, family, or close contacts (eFigure 3 in the Supplement). Secondary attack rates were not significantly different when restricting to 38 studies[19,20,22,23,26-31,34-40,42,44-51,54-57,60,62,63,65,67-69,72] with low or moderate risk of bias (15.6%; 95%, 12.8%-18.5%) (eFigure 4 in the Supplement). There were no significant differences in secondary attack rates between 21 studies in China[22,27,31,36,37,39,45,46,48,58,61-68,70-72] and 33 studies from other countries[19-21,23-26,28-30,32-35,38,40-44,47,49-57,59,60,69] (eFigure 5 in the Supplement), 18 studies that tested symptomatic contacts[19-21,24,25,28,29,33,34,41,47,50,53,56,58,59,61,64] and 33 studies that reported testing all contacts[22,23,26,27,30,31,35-40,42-46,48,49,51,52,54,55,57,60,63,65-67,69-72] (eFigure 6 in the Supplement), and 16 early studies[22,23,25,31,37,39,45,58,61,63-66,68,71,72] (January-February) and 20 later studies[19,24,26,29,30,32-35,38,42,44,50,53-56,59,60,69] (March-July) (eFigure 7 in the Supplement).

To study the transmissibility of asymptomatic SARS-CoV-2 index cases, eFigure 8 in the Supplement summarizes 27 studies[19-21,23-26,30,32-34,44,45,47,50,52-54,56,59-61,63,64,68,69,72] reporting household secondary attack rates from symptomatic index cases and 4 studies[26,43,44,52] from asymptomatic or presymptomatic index cases. Estimated mean household secondary attack rate from symptomatic index cases (18.0%; 95% CI, 14.2%-22.1%) was significantly higher than from asymptomatic or presymptomatic index cases (0.7%; 95% CI, 0%-4.9%; $P < .001$), although there were few studies in the latter group. These findings are consistent with other household studies[28,70] reporting asymptomatic index cases as having limited role in household transmission.

There is evidence for clustering of SARS-CoV-2 infections within households, with some households having many secondary infections while many others have none.[73-75] For example, 1 study[55] reported that 26 of 103 (25.2%) households had all members test positive. This is consistent with observation of overdispersion in the number of secondary cases per index case across a range of settings.[3] While most studies reported only the average number of secondary infections per index case, some also reported transmission by household.[44,55,56,63,65,69] **Figure 2** summarizes the proportion of households with any secondary transmission. Using an empirical analysis based on secondary attack rates and mean number of contacts per household, we found the proportion of

Figure 2. Mean Number of Contacts per Household, Secondary Attack Rate (SAR) of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and Proportion of Households Reporting Any Secondary Transmission From Index Cases

Source	Location	Mean contacts	Contacts		Households		Proportion of households with any secondary transmission (95% CI)	Weight, %
			Total	Infected	Total	Infected		
Wu et al,[65] 2020	Zhuhai, China	4.229	148	48	35	22	0.63 (0.46-0.78)	12.78
Rosenberg et al,[55] 2020	New York, US	3.330	343	131	103	63	0.61 (0.52-0.70)	14.62
Lewis et al,[44] 2020	Utah and Wisconsin, US	3.241	188	52	58	32	0.55 (0.42-0.68)	13.78
Wang et al,[63] 2020	Beijing, China	2.702	335	77	124	41	0.33 (0.25-0.42)	14.84
Shah et al,[56] 2020	Gujarat, India	5.216	386	34	74	16	0.22 (0.13-0.32)	14.43
Yung et al,[69] 2020	Singapore	1.493	200	13	134	7	0.05 (0.02-0.10)	15.36
Draper et al,[33] 2020	Northern Territory, Australia	1.821	51	2	28	1	0.04 (0.00-0.15)	14.19
Model estimate							0.317 (0.134-0.534)	100



The expected proportion of households with any secondary transmission (represented by the triangles) was calculated as proportion with at least 1 secondary infection in a household = $1 - (1 - SAR)^n$, where n is the mean number of contacts for that study (eTable 5 in the Supplement). Point sizes are an inverse function of the precision of the estimates, and bars correspond to 95% CIs.

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households with any secondary transmission was lower than expected in a setting with no clustering (eg, most transmission is not characterized by a minority of infected individuals) (eTable 5 in the Supplement). Ideally, future studies will assess this formally by fitting a β binomial to quantify overdispersion in the full data.

A number of studies examined factors associated with susceptibility of household contacts to infection (eTable 6 in the Supplement). Age was the most examined covariate, with most studies[20,29,36-39,45,46,48,49,55,63,65,68] reporting lower secondary transmission of SARS-CoV-2 to child contacts than adult contacts. In 5 studies,[20,36,39,48,49] individuals older than 60 years were most susceptible to SARS-CoV-2 infection. Contact age was not associated with susceptibility in 9 studies,[26,28,32,44,47,58,66,67,70] although these were typically less powered to detect a difference. **Figure 3** summarizes 15 studies[22,26,29,37,39,42,44,45,47,49,55,59,60,63,65] reporting separate secondary attack rates to children and adult contacts. The estimated mean household secondary attack rate was significantly higher to adult contacts (28.3%; 95% CI, 20.2%-37.1%) than to child contacts (16.8%; 95% CI, 12.3%-21.7%; $P < .001$). Significant heterogeneity was found among studies of adult ($I^2 = 96.8\%$; $P < .001$) and child contacts ($I^2 = 78.9\%$; $P < .001$). Begg ($P = .03$) and Egger ($P = .03$) tests were statistically significant for studies of adult but not child contacts (eFigure 9 in the Supplement). One study of adults[63] had a high secondary attack rate in the forest plot. Excluding this study improved the funnel plot symmetry and resulted in a secondary attack rate to adult contacts of 26.3% (95% CI, 19.3%-33.2%).

The second most examined factor was sex of exposed contacts, which was not associated with susceptibility for most studies[20,22,26,32,36,39,44,45,47-49,58,65-67,70] except 3.[38,46,68] eFigure 10 in the Supplement summarizes results from 11 studies[20,39,42,44,45,47,49,58,65,67,69] reporting household secondary attack rates by contact sex. Estimated mean household secondary attack rate to female contacts (20.7%; 95% CI, 15.0%-26.9%) was not significantly different than to male contacts (17.7%; 95% CI, 12.4%-23.8%). Significant heterogeneity was found among studies of female contacts ($I^2 = 87.4\%$; $P < .001$) and male contacts ($I^2 = 87.7\%$; $P < .001$). Moderate asymmetry was observed in the funnel plots, which was significant for studies of female contacts from Egger test ($P = .07$) but not male contacts (eFigure 11 in the Supplement). However, imputation of an adjusted effect size using the trim-and-fill method did not significantly change the secondary attack rate to female contacts (19.7%; 95% CI, 13.9%-25.6%).

Spouse relationship to index case was associated with secondary infection in 4 studies[26,45,46,58] of 6 in which this was examined.[65,67] Infection risk was highest for spouses, followed by nonspouse family members and other relatives, which were all higher than other contacts.[46] **Figure 4** summarizes results from 7 studies[26,44-46,58,65,67] reporting household secondary attack rates by relationship. Estimated mean household secondary attack rate to spouses (37.8%; 95% CI, 25.8%-50.5%) was significantly higher than to other contacts (17.8%; 95% CI, 11.7%-24.8%). Significant heterogeneity was found among studies of spouses ($I^2 = 78.6\%$; $P < .001$) and other relationships ($I^2 = 83.5\%$; $P < .001$).

Several studies examined factors associated with infectiousness of index cases. Older index case age was associated with increased secondary infections in 3 studies[20,47,67] of 9 in which this was examined.[22,36,39,44,63,65] eFigure 12 in the Supplement summarizes results from 3 studies[42,44,51] reporting household secondary attack rates by index case age. Estimated mean household secondary attack rate from adults (15.2%; 95% CI, 6.2%-27.4%) was not significantly different than that from children (7.9%; 95% CI, 1.7%-16.8%). Index case sex was associated with transmission in 3 studies[42,44,67] of 9 in which this was examined.[20,36,45,47,63,65] eFigure 13 in the Supplement summarizes results from 7 studies[20,42,44,45,65,67,69] reporting household secondary attack rates by index case sex. Estimated mean household secondary attack rate from female contacts (16.6%; 95% CI, 11.2%-22.8%) was not significantly different than from male contacts (16.4%; 95% CI, 9.0%-25.5%).

Critically severe index case symptoms was associated with higher infectiousness in 6 studies[20,38,46-48,67] of 9 in which this was examined.[44,63,70] Index case cough was associated with

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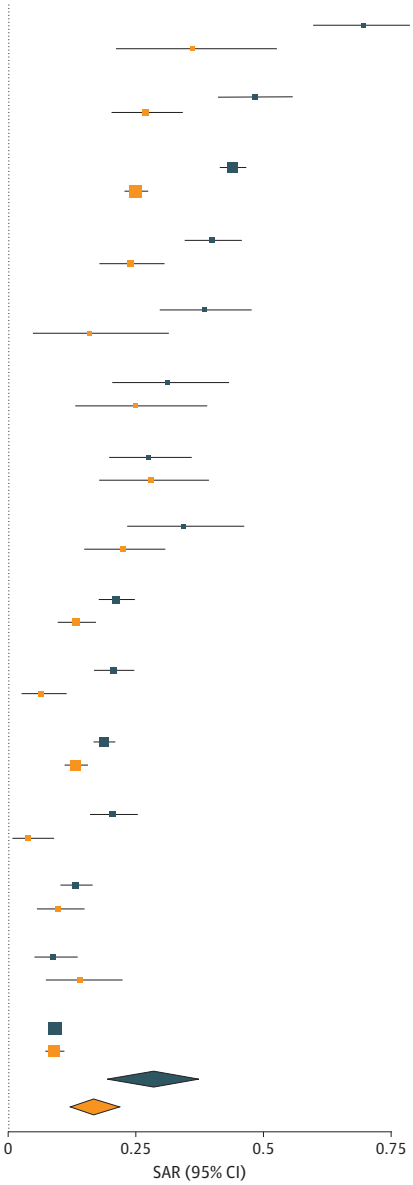
infectivity in 2 studies [20,65] of 8 in which this was examined[45-48,63,67] (eAppendix 4 in the Supplement).

Contact frequency with the index case was associated with higher odds of infection, specifically at least 5 contacts during 2 days before the index case was confirmed,[70] at least 4 contacts and 1 to 3 contacts,[63] or frequent contact within 1 meter.[22,67,68] Smaller households were associated with transmission in 4 studies[20,39,47,49] of 7 in which this was examined.[55,63,65] **Figure 5** summarizes results from 6 studies[20,47,49,55,61,65] reporting household secondary attack rates by number of

Figure 3. Secondary Attack Rates (SAR) of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) for Adult (≥18 Years) and Child (<18 Years) Household and Family Contacts

Source	Location	Participants, No.	Participants with SARS-CoV-2 infection, No.	SAR (95% CI)	Weight, %
Wang et al,[63] 2020	Beijing, China				
Adults		92	64	0.70 (0.60-0.79)	6.07
Children		36	13	0.36 (0.21-0.53)	2.81
Rosenberg et al,[55] 2020	New York, US				
Adults		182	88	0.48 (0.41-0.56)	6.57
Children		156	42	0.27 (0.20-0.34)	6.65
Dattner et al,[29] 2020	Bnei Brak, Israel				
Adults		1448	637	0.44 (0.41-0.47)	7.21
Children		1376	344	0.25 (0.23-0.27)	9.92
Lopez Bernal et al,[47] 2020	UK				
Adults		297	119	0.40 (0.35-0.46)	6.85
Children		175	42	0.24 (0.18-0.31)	7.01
Wu et al,[65] 2020	Zhuhai, China				
Adults		112	43	0.38 (0.30-0.48)	6.20
Children		31	5	0.16 (0.05-0.31)	3.05
Teherani et al,[59] 2020	Atlanta, US				
Adults		64	20	0.31 (0.20-0.43)	5.64
Children		44	11	0.25 (0.13-0.39)	3.48
Lewis et al,[44] 2020	Utah and Wisconsin, US				
Adults		120	33	0.28 (0.20-0.36)	6.34
Children		68	19	0.28 (0.18-0.39)	4.46
van der Hoek et al,[60] 2020[a]	Netherlands				
Adults		67	23	0.34 (0.23-0.46)	5.66
Children		107	24	0.22 (0.15-0.31)	5.84
Hua et al,[37] 2020[a]	Zhejiang Province, China				
Adults		510	108	0.21 (0.18-0.25)	7.08
Children		325	43	0.13 (0.10-0.17)	8.69
Jing et al,[39] 2020	Guangzhou, China				
Adults		412	85	0.21 (0.17-0.25)	7.03
Children		125	8	0.06 (0.03-0.11)	7.51
Lyngse et al,[49] 2020	Denmark				
Adults		1367	257	0.19 (0.17-0.21)	7.22
Children		859	114	0.13 (0.11-0.16)	9.76
Li et al,[45] 2020	Wuhan, China				
Adults		292	60	0.21 (0.16-0.25)	6.92
Children		100	4	0.04 (0.01-0.09)	7.51
Bi et al,[22] 2020	Shenzhen, China				
Adults		462	61	0.13 (0.10-0.16)	7.09
Children		163	16	0.10 (0.06-0.15)	7.66
Chaw et al,[26] 2020	Brunei				
Adults		179	16	0.09 (0.05-0.14)	6.86
Children		85	12	0.14 (0.07-0.22)	5.71
Laxminarayan et al,[42] 2020	Tamil Nadu and Andhra Pradesh, India				
Adults		2671	245	0.09 (0.08-0.10)	7.28
Children		941	85	0.09 (0.07-0.11)	9.93
Adults estimate				0.283 (0.202-0.371)	100
Children estimate				0.168 (0.123-0.217)	100



Point sizes are an inverse function of the precision of the estimates and bars correspond to 95% CIs.

[a] Study of family contacts.

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contacts in the household. Estimated mean household secondary attack rate for households with 1 contact (41.5%; 95% CI, 31.7%-51.7%) was significantly higher than households with at least 3 contacts (22.8%; 95% CI, 13.6%-33.5%; $P < .001$) but not different than households with 2 contacts (38.6%; 95% CI, 17.9%-61.6%). There was significant heterogeneity in secondary attack rates between studies with 1 contact ($I^2 = 52.9\%$; $P = .049$), 2 contacts ($I^2 = 93.6\%$; $P < .001$), or 3 or more contacts ($I^2 = 91.6\%$; $P < .001$). Information was not available on household crowding (eg, number of people per room).

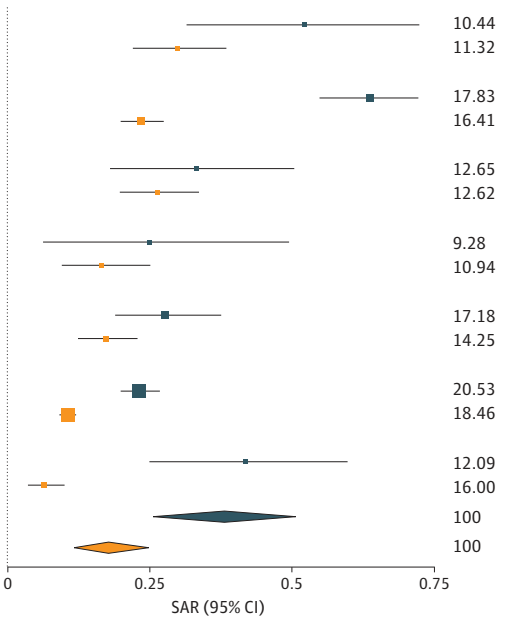
eFigure 14 in the Supplement summarizes 7 studies[76-82] reporting household secondary attack rates for SARS-CoV, and 7 studies[83-89] for Middle East respiratory syndrome coronavirus (MERS-CoV). Estimated mean household secondary attack rate was 7.5% (95% CI, 4.8%-10.7%) for SARS-CoV and 4.7% (95% CI, 0.9%-10.7%) for MERS-CoV (eTable 7 in the Supplement), both lower than the household secondary attack rate of 16.6% for SARS-CoV-2 in this study ($P < .001$). The SARS-CoV-2 secondary attack rate was also higher than secondary attack rates reported for HCoV-NL63 (0-12.6%), HCoV-OC43 (10.6-13.2%), HCoV-229E (7.2-14.9%), and HCoV-HKU1 (8.6%).[90-92] Household secondary attack rates for SARS-CoV-2 were within the mid-range of household secondary attack rates reported for influenza, which ranged from 1% to 38% based on polymerase chain reaction–confirmed infection.[93]

Discussion

We synthesized the available evidence on household studies of SARS-CoV-2. The combined household and family secondary attack rate was 16.6% (95% CI, 14.0%-19.3%), although with significant heterogeneity between studies. This point estimate is higher than previously observed

Figure 4. Secondary Attack Rates (SAR) of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) for Household and Family Contacts by Relationship to Index Case

Source	Location	Participants, No.	Participants with SARS-CoV-2 infection, No.	SAR (95% CI)	Weight, %
Wu et al,[65] 2020	Zhuhai, China				
Spouse		23	12	0.52 (0.32-0.72)	10.44
Other		120	36	0.30 (0.22-0.39)	11.32
Sun et al,[58] 2020[a]	Zhejiang Province, China				
Spouse		119	76	0.64 (0.55-0.72)	17.83
Other		479	113	0.24 (0.20-0.28)	16.41
Lewis et al,[44] 2020	Utah and Wisconsin, US				
Spouse		33	11	0.33 (0.18-0.50)	12.65
Other		155	41	0.26 (0.20-0.34)	12.62
Xin et al,[67] 2020	Qingdao Municipal, China				
Spouse		16	4	0.25 (0.06-0.50)	9.28
Other		90	15	0.17 (0.10-0.25)	10.94
Li et al,[45] 2020	Wuhan, China				
Spouse		90	25	0.28 (0.19-0.38)	17.18
Other		202	35	0.17 (0.12-0.23)	14.25
Liu et al,[46] 2020	Guangdong Province, China				
Spouse		563	131	0.23 (0.20-0.27)	20.53
Other		1878	199	0.11 (0.09-0.12)	18.46
Chaw et al,[26] 2020	Brunei				
Spouse		31	13	0.42 (0.25-0.60)	12.09
Other		233	15	0.06 (0.04-0.10)	16.00
Spouse estimate				0.378 (0.258-0.505)	100
Other estimate				0.178 (0.117-0.248)	100



Point sizes are an inverse function of the precision of the estimates and bars correspond to 95% CIs.

[a] Study of family contacts.

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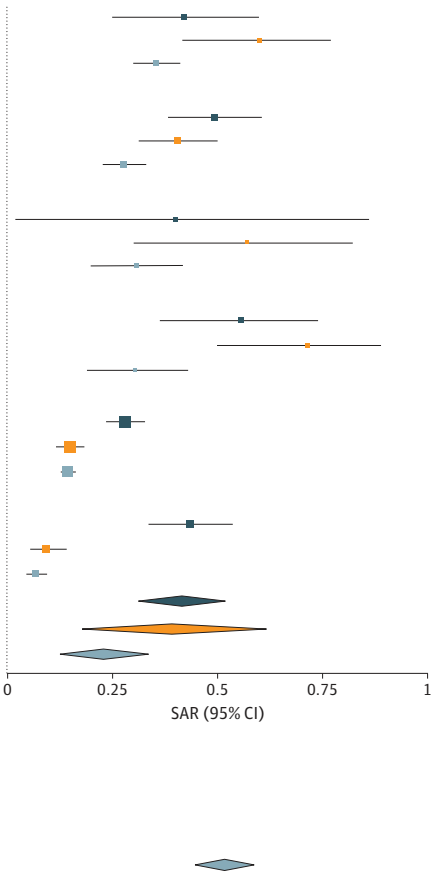
secondary attack rates for SARS-CoV and MERS-CoV. Households are favorable environments for transmission. They are what are known as 3Cs environments, as they are closed spaces, where family members may crowd and be in close contact with conversation.[94] There may be reduced use of personal protective equipment relative to other settings.

That secondary attack rates were not significantly different between household and family contacts may indicate that most family contacts are in the same household as index cases. Household and family contacts are at higher risk than other types of close contacts, and risks are not equal within households. Spouses were at higher risk than other family contacts, which may explain why the secondary attack rate was higher in households with 1 vs 3 or greater contacts. Spouse relationship to the index case was also a significant risk factor observed in studies of SARS-CoV and H1N1.[82,95] This may reflect intimacy, sleeping in the same room, or longer or more direct exposure to index cases. Further investigation is required to determine whether sexual contact is a transmission route. Although not directly assessed, household crowding (eg, number of people per room) may be more important for SARS-CoV-2 transmission than the total number of people per household, as has been demonstrated for influenza.[96-98]

The finding that secondary attack rates were higher to adult contacts than to child contacts is consistent with empirical and modeling studies.[99,100] Lower infection rates in children may be

Figure 5. Secondary Attack Rates (SAR) of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by the Number of People Living in the Same Household as the Index Case

Source	Location	Participants, No.	Participants with SARS-CoV-2 infection, No.	SAR (95% CI)	Weight, %
Rosenberg et al,[55] 2020	New York, US				
1 Contact		31	13	0.42 (0.25-0.60)	12.20
2 Contacts		30	18	0.60 (0.42-0.77)	15.53
≥3 Contacts		282	100	0.35 (0.30-0.41)	17.35
Lopez Bernal et al,[47] 2020	UK				
1 Contact		77	38	0.49 (0.38-0.61)	20.20
2 Contacts		106	43	0.41 (0.31-0.50)	18.49
≥3 Contacts		289	80	0.28 (0.23-0.33)	17.54
Wu et al,[65] 2020	Zhuhai, China				
1 Contact		5	2	0.40 (0.02-0.86)	2.74
2 Contacts		14	8	0.57 (0.30-0.82)	12.32
≥3 Contacts		124	38	0.31 (0.23-0.39)	15.12
Wang et al,[61] 2020	Wuhan, China				
1 Contact		27	15	0.56 (0.36-0.74)	11.05
2 Contacts		21	15	0.71 (0.50-0.89)	14.50
≥3 Contacts		56	17	0.30 (0.19-0.43)	11.75
Lyngse et al,[49] 2020	Denmark				
1 Contact		368	103	0.28 (0.24-0.33)	31.92
2 Contacts		432	64	0.15 (0.12-0.18)	19.72
≥3 Contacts		1426	204	0.14 (0.13-0.16)	19.42
Arnedo-Pena et al,[20] 2020	Castellon, Spain				
1 Contact		92	40	0.43 (0.33-0.54)	21.89
2 Contacts		173	16	0.09 (0.05-0.14)	19.43
≥3 Contacts		397	27	0.07 (0.05-0.10)	18.82
1 Contact estimate				0.415 (0.317-0.517)	100
2 Contacts estimate				0.386 (0.179-0.616)	100
≥3 Contacts estimate				0.228 (0.136-0.335)	100



Point sizes are an inverse function of the precision of the estimates, and bars correspond to 95% CIs.

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attributed to asymptomatic or mild disease, reduced susceptibility from cross-immunity from other coronaviruses,[101] and low case ascertainment,[102] but the difference persisted in studies in which all contacts were tested regardless of symptoms. Higher transmission rates to adults may be influenced by spousal transmission. Given the increased risk to spousal contacts, future studies might compare child contacts and nonspouse adult contacts to ascertain whether this difference persists. Limited data suggest children have not played a substantive role in household transmission of SARS-CoV-2.[40,103-105] However, a study in South Korea of 10 592 household contacts noted relatively high transmission from index cases who were aged 10 to 19 years.[51] Although children seem to be at reduced risk for symptomatic disease, it is still unclear whether they shed virus similarly to adults.[106]

We did not find associations between household contact or index case sex and secondary transmission. The World Health Organization reports roughly even distribution of SARS-CoV-2 infections between women and men worldwide, with higher mortality in men.[107]

We found significantly higher secondary attack rates from symptomatic index cases than asymptomatic or presymptomatic index cases, although less data were available on the latter. The lack of substantial transmission from observed asymptomatic index cases is notable. However, presymptomatic transmission does occur, with some studies reporting the timing of peak infectiousness at approximately the period of symptom onset.[108,109] In countries where infected individuals were isolated outside the home, this could further alter the timing of secondary infections by limiting contacts after illness onset.[110]

Household secondary attack rates were higher for SARS-CoV-2 than SARS-CoV and MERS-CoV, which may be attributed to structural differences in spike proteins,[111] higher basic reproductive rates,[112] and higher viral loads in the nose and throat at the time of symptom onset.[113] Symptoms associated with MERS-CoV and SARS-CoV often require hospitalization, which increases nosocomial transmission, whereas less severe symptoms of SARS-CoV-2 facilitate community transmission.[113] Similarly, presymptomatic transmission was not observed for MERS-CoV or SARS-CoV.[114,115]

Limitations

Our study had several limitations. The most notable is the large amount of unexplained heterogeneity across studies. This is likely attributable to variability in study definitions of index cases and household contacts, frequency and type of testing, sociodemographic factors, household characteristics (eg, density, air ventilation), and local policies (eg, centralized isolation). Rates of community transmission also varied across locations. Given that studies cannot always rule out infections from outside of the home (eg, nonhousehold contacts), household transmission may be overestimated. For this reason, we excluded studies that used antibody tests to diagnose household contacts. Furthermore, many analyses ignored tertiary transmission within the household, classifying all subsequent cases as secondary to the index case. Eighteen studies[19-21,24,25,28,29,33,34,41,47,50,53,56,58,59,61,64] involved testing only symptomatic household contacts, which would miss asymptomatic or subclinical infections, although secondary attack rate estimates were similar across studies testing all vs only symptomatic contacts.

Important questions remain regarding household spread of SARS-CoV-2. Chief among them is the infectiousness of children to their household contacts and the infectiousness of asymptomatic, mildly ill, and severely ill index cases. This study did not provide additional elucidation of factors influencing intergenerational spread. People unable to work at home may have greater risk of SARS-CoV-2 exposure, which may increase transmission risk to other household members. There may be overdispersion in the number of secondary infections per index case, which could be caused by variations in viral shedding, household ventilation, or other factors.

Conclusions

The findings of this study suggest that households are and will continue to be important venues for transmission, even where community transmission is reduced. Prevention strategies, such as

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increased mask-wearing at home, improved ventilation, voluntary isolation at external facilities, and targeted antiviral prophylaxis, should be further explored.

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GLOBAL INFLUENZA PROGRAMME

Non-pharmaceutical public health measures for mitigating the risk and impact of epidemic and pandemic influenza

Annex: Report of systematic literature reviews

World Health Organization

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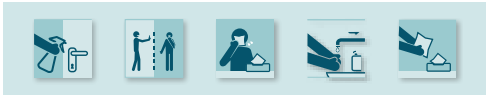

Non-pharmaceutical public health measures for mitigating the risk and impact of epidemic and pandemic influenza

Annex: Report of systematic literature reviews

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Abbreviations and acronyms

ACH	air changes per hour
CI	confidence interval
EDR	excess death rate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ILI	influenza-like illness
ITIS	infrared thermal image scanner
NPI	non-pharmaceutical intervention
PCR	polymerase chain reaction
PICTs	Pacific Island Countries and Territories
RCT	randomized controlled trial
RNA	ribonucleic acid
RR	risk ratio
SC	school closure
UV	ultraviolet
WC	workplace closure
WHO	World Health Organization

Glossary

Contact tracing	Identification and follow-up of persons who may have come into contact with an infected person.
Closure	Halting the operation of an institution or business.
Isolation	Separation or confinement of a person who has or is suspected of having influenza virus infection, to prevent further infections.
Non-pharmaceutical /non-pharmacological interventions	Interventions that do not include pharmacological measures such as vaccines and antiviral drugs.
Personal protective measures	Measures to reduce personal risk of infection, such as hand washing and face masks.
Quarantine	Separation or restriction of the movement of persons who may be infected, based either on exposure to other infected people or on a history of travel to affected areas.
Movement restriction	Limitation on the movements of a person who has or is suspected of having an infection

EXECUTIVE SUMMARY

New influenza A viruses emerge in humans from time to time, causing global pandemics. The most recent influenza pandemic began in 2009 with the influenza A(H1N1)pdm09 virus. Public health measures against pandemic influenza include vaccines, antiviral drugs and non-pharmaceutical measures. Given that vaccines against novel pandemic strains are unlikely to be available in the early months of an influenza pandemic, and antiviral drugs are in short supply in many locations, non-pharmaceutical public health measures are often some of the most accessible interventions for community mitigation of a pandemic. Non-pharmaceutical interventions (NPIs) also have an important role in mitigating interpandemic influenza epidemics, which occur each winter in temperate locations and at varying times of the year in tropical and subtropical locations. These measures could reduce individuals' risk of infection, delay the epidemic peak, reduce the "height" of the epidemic peak, and spread cases over a long time period; each of these outcomes would contribute to reducing the overall impact of a pandemic or epidemic.

Here, we systematically review and evaluate the evidence base on the effectiveness and impact of community mitigation measures for pandemic and interpandemic influenza. This evidence base will contribute to updated public health guidelines for community mitigation measures for influenza. The scope of this review includes evidence on the effectiveness of interventions such as personal protective measures, environmental measures, social distancing measures, and travel-related measures. Consideration is also given to the feasibility of each intervention, including potential ethical issues.

We found that there is a limited evidence base on the effectiveness of non-pharmaceutical community mitigation measures. There are a number of high-quality randomized controlled trials demonstrating that personal measures (e.g. hand hygiene and face masks) have at best a small effect on transmission, with the caveat that higher compliance in a severe pandemic might improve efficacy. However, there are few randomized trials for other NPIs, and much of the evidence base is from observational studies and computer simulations. School closures can reduce transmission, but would need to be carefully timed to achieve mitigation objectives, while there may be ethical issues to consider. Travel-related measures are unlikely to be successful in most locations because current screening tools such as thermal scanners cannot identify presymptomatic and asymptomatic infections, and travel restrictions and travel bans are likely to have prohibitive economic consequences.

INTRODUCTION

Non-pharmacological interventions (NPIs) are often the most accessible interventions when a new pandemic influenza virus emerges and begins to spread, because of limited availability of antiviral drugs and delays in the availability of vaccines against the pandemic strain (1). These community mitigation measures may be able to slow the spread of infections in the community, delaying the peak in infections, reducing the size of the peak and spreading infections over a longer period of time (Fig. 1) (*2, 3*). Each of these consequences should contribute to reducing the overall impact of the epidemic or pandemic. Given that in some locations there could be limited surge capacity in hospitals (and particularly in intensive care beds), spreading infections over a longer time period could save lives, even if the total number of infections remained the same.

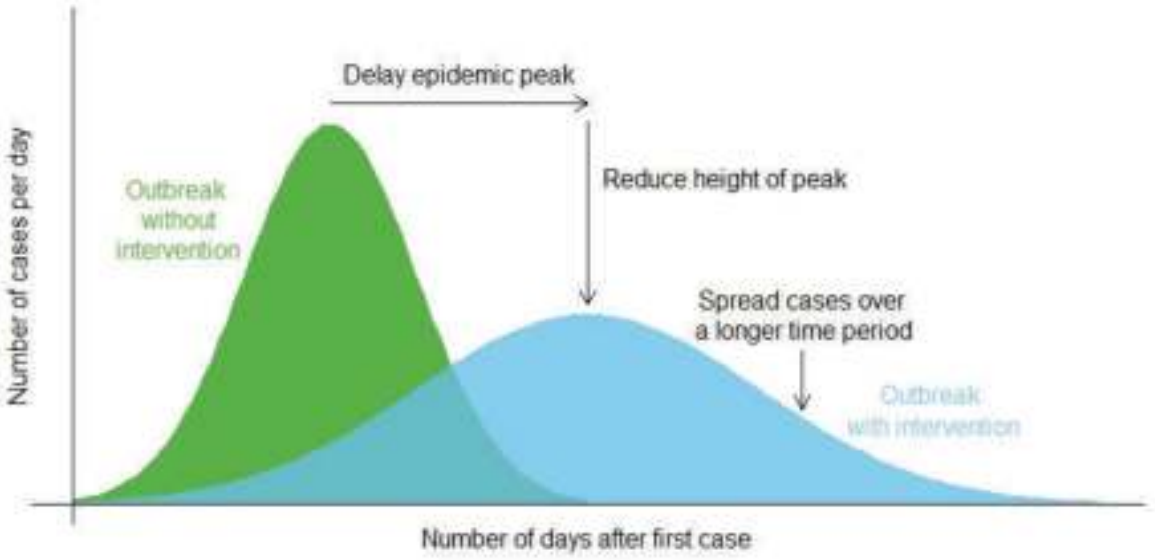

Fig. 1. Intended impact of non-pharmaceutical interventions on an influenza epidemic or pandemic by reducing person-to-person transmission

NPIs in non-health care settings usually focus on: reducing transmission by personal or environmental protective measures (e.g. hand hygiene); reducing the spread in the community populations (e.g. isolating and treating patients; closing schools and cancelling mass gatherings); limiting the international spread on travelling (e.g. travel screening and restriction); and public advice to the community (*4*). A number of health authorities have recently updated their reviews and guidelines on NPIs, including the United States (US) Centers for Disease Control and Prevention (CDC) (*2*), the European Centre for Disease Prevention and Control (*3*), the Australian Government Department of Health (*5*), the United Kingdom Department of Health (*6*), the Singapore Ministry of Health (*7*) and the Government of New Zealand (*8*).

This review examines the evidence base on each of the NPIs in community settings. While our focus is on the effectiveness of NPIs for mitigation of an influenza pandemic, the same measures may also be used in interpandemic influenza epidemics, which occur each winter in temperate locations and at varying times of the year in tropical and subtropical locations. In addition to NPIs in community settings, health authorities may also intervene in health care settings and systems, for example by establishing special influenza outpatient clinics, improving triage and isolation in hospitals, and cancelling non-essential surgeries. Health care system interventions are outside the scope of the present review of community mitigation measures.

The list of community mitigation measures is shown below. For each of the 18 listed NPIs, we first determined whether any systematic review had been published within the past 5 years (i.e. since January 2014), If there was a recently published review, we conducted a systematic review limited to studies published more recently than that review (starting from 1 year prior to the publication date), and updated that existing review. If we could not identify a systematic review of the NPI within the past 5 years, we conducted a full systematic review for the NPI. For the review of peer-reviewed articles, two independent reviewers screened all titles of studies identified by the search strategy for each of the NPIs, then reviewed the abstracts of the potentially relevant studies. If the studies described that NPI and its effectiveness against influenza transmission, the reviewers read the full-length text and extracted relevant data. Further discussion with a third reviewer was held if a consensus was not reached. We also evaluated the methodological quality of each of the studies using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (*9*), based on the question of whether NPIs can reduce influenza transmission in the community. The quality of evidence was ranked for each study as high, moderate, low or very low, based on its risk of bias, consistency, directness, precision of the results and publication bias. Hence, we set the highest priority on randomized controlled trials (RCTs), then on observational studies and finally on simulation studies. If RCTs were reported, as a general principle we did not review observational studies or simulation studies, and if observational studies were reported, as a general principle we did not review simulation studies.

This report describes the evidence base on the effectiveness of each NPI. The specific targets of the evidence include but are not limited to reducing transmission, delaying the peak of the epidemic, spreading out infections over a longer time period, and reducing the total number of infections. This review of the evidence base will support the development of guidance on the use of NPIs for community mitigation. The NPIs reviewed in this report are listed below.

LIST OF NON-PHARMACEUTICAL PUBLIC HEALTH MEASURES

NPI	DEFINITION
Personal protective measures	**Personal hygiene measures to reduce the risk of acquiring or spreading respiratory infections.**
1. Hand hygiene	A personal measure aiming to reduce influenza transmission via direct or indirect contact by washing hands with soap and water or alcohol-based hand cleaners.
2. Respiratory etiquette	A personal measure aiming to reduce influenza transmission via respiratory droplets by covering nose and mouth with disposable tissues while coughing or sneezing.
3. Face masks	A personal measure aiming to reduce influenza transmission by wearing face mask of different types, including home-made masks, surgical and medical masks, or respirators with higher filtration rates. Masks can be worn by symptomatic or exposed persons to reduce onwards transmission (source control), or by uninfected persons in the community to reduce their risk of infection.

LIST OF NON-PHARMACEUTICAL PUBLIC HEALTH MEASURES

NPI	DEFINITION
Environmental measures	**Environmental hygiene measures to reduce the risk of acquiring or spreading influenza within an area.**
4. Surface and object cleaning	Routine cleaning of frequently used surfaces and objects to reduce influenza transmission.
5. Other environmental measures	Other measures to reduce risk of influenza transmission through the environment.
Social distancing measures	**Social measures to reduce the risk of acquiring or spreading respiratory infections in various community settings (e.g. homes, workplaces, schools, health care settings etc.)**
6. Contact tracing	The identification and follow-up of persons who may have come into contact with an infected person, usually in combination with quarantine of identified contacts.
7. Isolation of sick individuals	Reduction in virus transmission from an ill person to others by confining symptomatic individuals for a defined period either in a special facility or at home.
8. Quarantine of exposed individuals	Isolation of individuals who contacted a person with proven or suspected influenza, or travel history to an affected area, for a defined period after last exposure. Quarantined cases may be isolated.
9. School closure	Closure of schools either when virus transmission is observed in the school or community, or an early planned closure of schools before influenza transmission initiates.
10. Workplace closure	Closure of workplaces when virus transmission is observed in the workplace, or an early planned closure of workplaces before influenza transmission initiates.
11. Workplace measures	Measures to reduce influenza transmission in the workplace, or on the way to and from work, by decreasing frequency and length of social interactions.
12. Avoiding crowding	Measures to reduce influenza transmission in crowded areas (e.g. large meetings, conferences, and religious pilgrimages, national and international events).
Travel-related measures	**Measures including the provision of travel health advice, screening of travellers and restriction of travellers.**
13. Travel advice	Official government travel advice with legal and economic implications.
14. Entry and exit screening	Screening travellers for influenza symptoms to reduce the number of infectious individuals entering or leaving a country with infection, respectively, in order to delay the international spread of infection.

LIST OF NON-PHARMACEUTICAL PUBLIC HEALTH MEASURES

NPI	DEFINITION
15. Internal travel restrictions	Prevent or limit influenza transmission by restricting travel within a country.
16. Border closures	Prevent influenza entering a country by restricting travel to or from an affected area, in order to delay the international spread of infection.

SUPPORTING EVIDENCE FOR NPIS

Search strategy

Systematic reviews of NPIs were conducted using four databases (PubMed, EMBASE, MEDLINE and Cochrane Library) and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy for each topic is given below.

MEASURES	SEARCH TERMS
1. Hand hygiene	#1: "hand hygiene" OR "hand washing" OR "handwashing" OR "hand-washing" OR "hand-wash" OR "hand wash" OR "handwash" OR "hand sanitize" OR "hand sanitizers" OR "hand sanitizer" OR "hand rub" OR "handrub" OR "hand rubbing" OR "hand cleansing" OR "hand cleans" OR "hand cleanser" OR "hand disinfectant" OR "hand disinfectants" OR "hand disinfection" OR "hand soap" OR "hand wipe" #2: "influenza" OR "flu" #3: #1 AND #2
2. Respiratory etiquette	#1: "respiratory hygiene" OR "cough etiquette" OR "respiratory etiquette" #2: "influenza" OR "flu" #3: #1 AND #2
3. Face masks	#1: "facemask" OR "facemasks" OR "mask" OR "masks" OR "respirator" OR "respirators" #2: "influenza" OR "flu" #3: #1 AND 2
4. Surface and object cleaning	#1: "surface" OR "surfaces" OR "object" OR "objects" OR "fomite" OR "fomites" OR "environment" OR "environmental" #2: "clean" OR "cleans" OR "cleaning" OR "cleanse" OR "cleansing" OR "disinfect" OR "disinfects" OR "disinfection" OR "disinfecting" OR "wipe" OR "wipes" OR "sanitize" OR "sanitizes" OR "sanitizing" OR "sanitation" OR "sterilize" OR "sterilizes" OR "sterilizing" OR "sterilization" OR "sterilise" OR "sterilises" OR "sterilising" OR "sterilisation" OR "decontaminate" OR "decontaminates" OR "decontaminating" OR "decontamination" #3: "influenza" OR "flu" #4: #1 AND #2 AND #3

MEASURES	SEARCH TERMS
5. Other environmental measures	UV light #1: "ultraviolet" OR "UVGI" OR "UV" OR "UVC" OR "far-UVC" OR "UV-C" #2: "influenza" OR "flu" #3: #1 AND #2 Ventilation and humidity #1: "ventilation" OR "temperature" OR "humidity" OR "environment" #2: "indoor" OR "room" #3: "influenza" OR "flu" #4: #1 AND #2 AND #3
6. Contact tracing	#1: "contact tracing" OR "trace contact" OR "trace contacts" OR "identify contact" OR "identify contacts" OR "case detection" OR "detect cases" OR "case finding" OR "find cases" OR "early detection" #2: "influenza" OR "flu" #3: #1 AND #2
7. Isolation of sick individuals	#1: "patient isolation" OR "case isolation" OR "voluntary isolation" OR "home isolation" OR "social isolation" OR "self-isolation" #2: "influenza" OR "flu" #3: #1 AND #2
8. Quarantine of exposed individuals	#1: "quarantine" #2: "influenza" OR "flu" #3: #1 AND #2
9. School closure	#1: "school closure" OR "class dismissal" OR "school holiday" OR "community mitigation" OR "social distancing" #2: "influenza" OR "flu" #3: #1 AND #2
10. Workplace closure	#1: "workplace" OR "work site" OR "business" OR "organization" OR "office" #2: "closure" OR "close" #3: "influenza" OR "flu" #4: #1 AND #2 AND #3
11. Workplace measures	#1: "telework" OR "leave" OR "social mixing" OR "social distancing" OR "community mitigation" OR "non-pharmaceutical" OR "nonpharmaceutical" #2: "influenza" OR "flu" #3: #1 AND #2
12. Avoiding crowding	#1: "event" OR "meeting" OR "sport" OR "concert" OR "pilgrimage" OR "park" OR "conference" OR "mass" OR "public" OR "community" OR "large" OR "general" OR "church" #2: "gather*" OR "crowd*" #3: "influenza" OR "flu" #4: #1 AND #2 AND #3

MEASURES	SEARCH TERMS
13. Travel advice	#1: "travel" OR "traveler" OR "travelers" OR "traveller" OR "travellers" #2: "advice" OR "restrict" OR "restriction" OR "prohibit" OR "prohibition" #3: "influenza" OR "flu" #4: #1 AND #2 AND #3
14. Entry and exit screening	#1: "travel" OR "traveler" OR "travelers" OR "traveller" OR "travellers" #2: "screen" OR "screening" OR "entry screening" OR "exit screening" OR "entry-exit screening" OR "mass screening" OR "border screening" OR "detect" OR "detecting" OR "detection" #3: "influenza" OR "flu" #4: #1 AND #2 AND #3
15. Internal travel restriction	#1: "travel" OR "traveler" OR "travelers" OR "traveller" OR "travellers" #2: "domestic" OR "internal" #3: "restrict" OR "restriction" OR "prohibit" OR "prohibition" OR "limit" OR "limitation" OR "control" #4: "influenza" OR "flu" #5: #1 AND #2 AND #3 AND #4
16. Border closure	#1: "travel" OR "traveler" OR "travelers" OR "traveller" OR "travellers" #2: "border" OR "international" #3: "restrict" OR "restriction" OR "prohibit" OR "prohibition" OR "limit" OR "limitation" OR "control" OR "closure" #4: influenza" OR "flu" #5: #1 AND #2 AND #3 AND #4

1. PERSONAL PROTECTIVE MEASURES

1.1. Hand hygiene

Terminology
The definitions of relevant hand hygiene practices and products, and common terminology, are shown in Table 1 below.

Table 1. Definitions of hand hygiene terms

TERM	DEFINITION
Hand hygiene practices	
Hand hygiene	A general term referring to any action of hand cleansing, e.g. handwashing, antiseptic handwash, antiseptic hand rub, or surgical hand antisepsis (*10, 11*)
Hand cleansing	Action of performing hand hygiene for the purpose of physically or mechanically removing dirt, organic material, and/or microorganisms (*10*)
Handwashing	Washing hands with plain or antimicrobial soap and water (*10*)
Antiseptic handwashing	Washing hands with soap and water, or other detergents containing an antiseptic agent (*10*)
Antiseptic handrubbing (or handrubbing)	Applying an antiseptic handrub to all surfaces of the hands to reduce or inhibit the growth of microorganisms without the need for an exogenous source of water and requiring no rinsing or drying with towels or other devices (*10, 11*)
Hand disinfection	Hand disinfection is extensively used as a term in some parts of the world and can refer to antiseptic handwash, antiseptic handrubbing, hand antisepsis / decontamination / degerming, handwashing with an antimicrobial soap and water, hygienic hand antisepsis, or hygienic handrub (*10*)
Hand hygiene products	
Alcohol-based (hand) rub (or hand sanitizer)	An alcohol-containing preparation (liquid, gel or foam) designed for application to the hands to inactivate microorganisms and/or temporarily suppress their growth. Such preparations may contain one or more types of alcohol, other active ingredients with excipients, and humectants (*10*)

TERM	DEFINITION
Antimicrobial (medicated) soap	Soap (detergent) containing an antiseptic agent at a concentration sufficient to inactivate microorganisms and/or temporarily suppress their growth. The detergent activity of such soaps may also dislodge transient microorganisms or other contaminants from the skin to facilitate their subsequent removal by water (*10*)
Antiseptic hand wipe	A piece of fabric or paper pre-wetted with an antiseptic used for wiping hands to inactivate and/or remove microbial contamination. They may be considered as an alternative to washing hands with non-antimicrobial soap and water but, because they are not as effective at reducing bacterial counts on health care workers' hands as alcohol-based handrubs or washing hands with an antimicrobial soap and water, they are not a substitute for using an alcohol-based handrub or antimicrobial soap (*10*)
Plain soap	Plain soap refers to detergents that do not contain antimicrobial agents or contain low concentrations of antimicrobial agents that are effective solely as preservatives (*11*)
Other	
Visibly soiled hands	Hands showing visible dirt or visibly contaminated with proteinaceous material, blood, or other body fluids (e.g. faecal material or urine) (*11*)

Methods

We conducted a review of systematic reviews. PubMed, Medline, EMBASE and CENTRAL were searched for reviews until 1 August 2018. Review selection criteria were systematic reviews within 5 years studying the effect of hand hygiene interventions on prevention of laboratory-confirmed influenza in non-health care settings, regardless of language.

After identifying the most recent published systematic review (see below), we updated the search done in that published review in the same four databases through to 14 August 2018 using the same search terms. Study selection criteria were RCTs comparing the effect of hand hygiene interventions with no intervention in laboratory-confirmed influenza prevention in community settings. Study participants or clusters of participants were assigned prospectively into intervention and control groups using random allocation. A community setting was defined as an open setting without confinement or special care for the patients. Articles describing any hand hygiene related interventions were included. No language limits were applied.

Because of the availability of a reasonable number of randomized trials of hand hygiene, we did not extend the search to observational studies, but we did note the findings from earlier systematic reviews of observational studies of hand hygiene (*12-14*).

After data extraction, quality assessment of the evidence was done for included studies based on the GRADE framework. The research question was to study the effect of hand hygiene intervention on laboratory-confirmed influenza prevention.

Two independent reviewers (ZX and ES) reviewed retrieved titles and subsequent relevant abstracts independently. Titles or abstracts with any one of the reviewers' decision to include were included in next step. After title and abstract screening, two reviewers reviewed the full text based on the selection criteria. Data extraction and evidence quality assessment were also done by the reviewers. If a consensus was not reached, further discussion was held or opinion was obtained from the third independent reviewer.

Risk ratios (RRs) and their 95% confidence intervals (95% CIs) were calculated to estimate the effect of hand hygiene intervention on prevention of laboratory-confirmed influenza. Heterogeneity of each pooled and subgroup analysis was assessed by I2 statistics. The overall effect of each pooled and subgroup analysis was estimated by fixed-effect model. If the heterogeneity was high (I2 ≥ 75%), we did not estimate an overall pooled effect.

Results

We identified 225 reviews through the database search with our search terms, of which 172 reviews were screened out during by title and abstract screening. 46 reviews were excluded after full-text assessment that were not systematic reviews, not within the past 5 years, not based on RCTs, or had no hand hygiene intervention or no laboratory-confirmed influenza outcome. In total, seven reviews were included in our analysis, from which we identified nine eligible articles. The most recent systematic review and meta-analysis was published in 2014; it reviewed and analysed RCTs to study the effect of hand hygiene on the prevention of laboratory-confirmed influenza (*15*). The process of identifying these review articles is shown in Fig. 2.

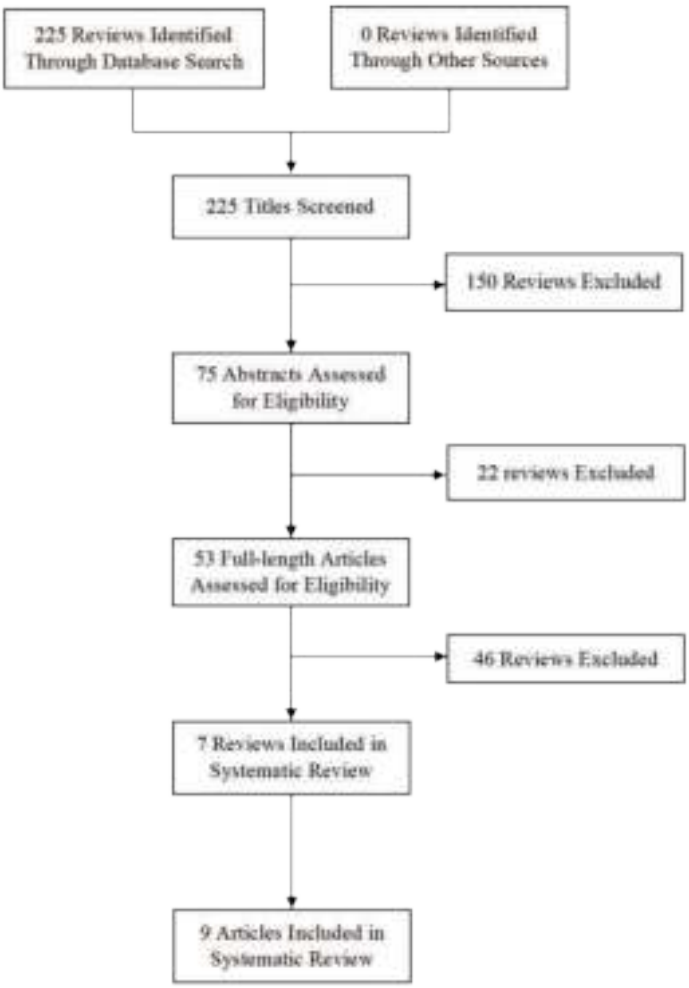

Fig. 2. The flow chart of hand hygiene review selection

In the additional search to update the systematic review by Wong et al. (*15*) that was published in 2014, 352 articles were identified from 1 January 2013 to 14 August 2018. At total of 319 articles were excluded in the title and abstract screening. 30 articles were excluded that were not RCTs, not done outside of health care settings, did not have a hand hygiene intervention or did not have a laboratory-confirmed influenza outcome. Three additional articles were identified since the publication of the review by Wong et al. (*15*). In total, 12 articles (11 studies; Azman et al. (*16*) and Stebbins et al. (*17*) were the same project during the same period but studied different questions) were included in our systematic review and 11 articles (10 studies; Levy et al. (*18*) only had household level secondary infection data but no individual level data) were included in the meta-analysis. The article selection flow is shown in Fig. 2.

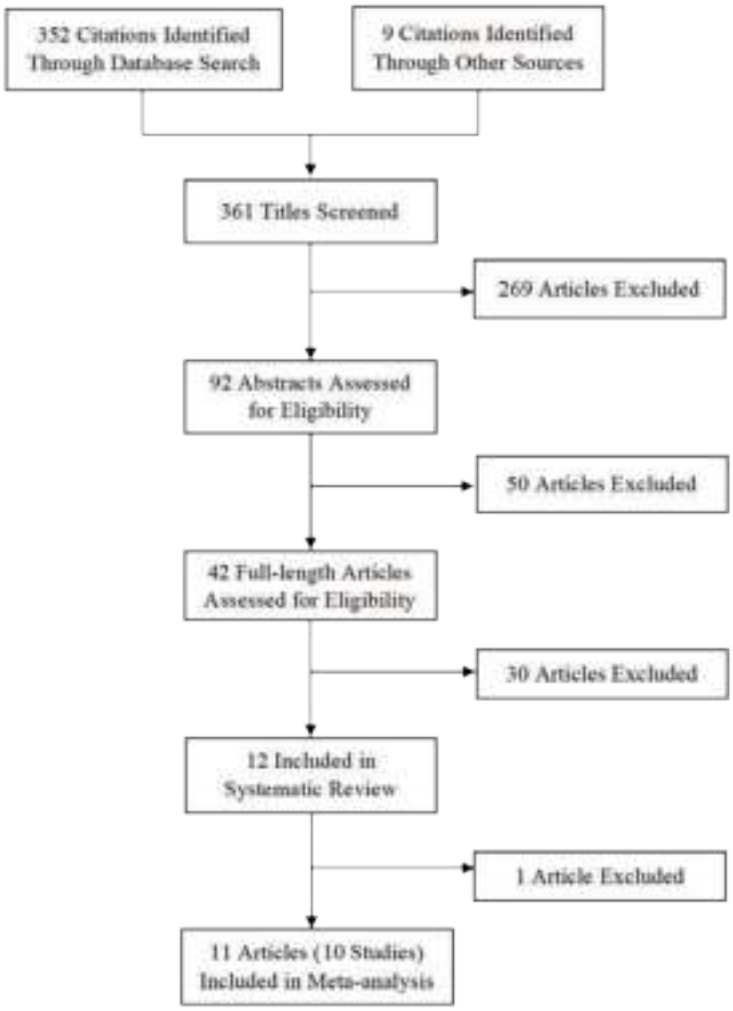

Fig. 3. The flow chart of hand hygiene article selection

Table 2. Basic characteristics of included studies

CHARACTERISTICS	NO. OF STUDIES (%)
Country	
Developed	7 (64)
Developing	4 (36)
Setting	
Household	7 (64)
Elementary school	2 (18)
University residential hall	2 (18)
Transmission mode	
Primary	5 (45)
Secondary	6 (55)
Intervention evaluated[a]	
Hand sanitizer and education	3 (20)
Hand sanitizer, soap and education	1 (7)
Hand sanitizer and face mask	3 (20)
Hand sanitizer, face mask and education	2 (13)
Soap	3 (20)
Soap and education	1 (7)
Soap and face mask	2 (13)
Outcome assessed	
Laboratory-confirmed influenza	11 (100)

[a] More than one intervention for some studies.

Among the 11 included studies, 7 studies were in household settings, two in elementary schools and two in university residential halls. Included study information is shown in Table 2, and detailed study description and evidence quality assessment are shown in Table 3. The evidence profile for the outcomes is summarized in Table 4.

In the pooled analysis, hand hygiene with face mask (RR = 0.91, 95% CI: 0.73–1.13, p = 0.39, I2 = 35%) did not have a statistically significant protective effect in non-health care settings (Fig. 4) *(19-24)*. Some published studies noted that poor adherence to hand hygiene may lead to underestimation of the true effect of the intervention (*19, 21, 22*).

The relative importance of transmission modes of influenza may vary in different settings. In school settings, no total effect was generated due to high heterogeneity (Fig. 5) (*17, 25*). In a study in the United States of America (USA), there was no significant effect of hand hygiene with a point estimate of the risk ratio close to 1, whereas a large trial in Egypt reported a reduction of more than 50% in influenza cases in the intervention group.

Hand hygiene with face mask intervention contributed to 52% relative risk reduction (RR = 0.48, 95% CI: 0.21–1.08, p = 0.08, marginally significant, I2 = 0%) of laboratory-confirmed influenza infection in university residential hall (Fig. 6) (*20, 23*).

The efficacy of hand hygiene with or without face mask was insignificant (RR = 1.05, 95% CI: 0.86–1.27, p = 0.65, I2 = 57%) in household setting in the analysis (Fig. 7) (*19, 21, 22, 24, 26, 27*). Although the pooled analysis did not identify a significant effect of hand hygiene overall, some household transmission studies reported that implementing hand hygiene intervention earlier after onset in the index case might be more effective in preventing secondary cases in the household (*19, 24*).

Experimental studies found that influenza virus could not survive long on human hands (*28, 29*). Viable influenza virus could be transmitted from contaminated surfaces to human hands by rubbing (*30*). Simmerman cultured live influenza virus from a finger swab sample from a laboratory-confirmed influenza patient (*31*). This evidence suggested the biological plausibility of indirect contact transmission via contaminated hands of influenza. Experimental studies also claimed that hand hygiene practice (e.g. handwashing with water and soap, and handrubbing with alcohol-based handrub) is effective to inactivate or reduce viable influenza virus on human hands (*32-34*). These results highlighted the importance of hand hygiene and suggested that hand hygiene may be initiative to prevent influenza transmission.

Ethical considerations

There are no major ethical issues. Alcohol-based handrub might be not available in some locations due to religious objections, such as the situation of incompliance of hand hygiene recommendation among Muslim health care workers (35). Skin irritation by alcohol handrub is possible, although the irritant potential of alcohol-based handrub is very low (*36*). Low adherence to hand hygiene intervention was observed in some studies (*19, 21, 22, 26*).

Knowledge gaps

Our review identified 10 RCTs of hand hygiene against laboratory-confirmed influenza. The pooled estimate of the effectiveness of hand hygiene in household settings was close to the null, with a fairly narrow confidence interval (Fig. 7), and future studies are unlikely to move the pooled estimate far from the null even if individual trials done in the future show protective efficacy of hand hygiene. In schools, there are only two published trials, and there is a clear need for additional studies to resolve the discrepancy between those two studies from the USA and Egypt (*17, 25*), one of which showed a considerable effect of hand hygiene (Fig. 5).

A more basic knowledge gap is on mechanisms of person-to-person transmission of influenza, including virus survival on hands and different types of surfaces, and the potential for contact transmission to occur in different locations and with different environmental conditions. Randomized trials of hand hygiene can contribute to determining modes of influenza transmission because hand hygiene would primarily act against one specific mode of transmission (indirect contact) but not other modes (respiratory droplets of varying sizes) (*37*).

Table 3. Description of studies included in the review of hand hygiene

STUDY	STUDY DESIGN	STUDY PERIOD	POPULATION & SETTING	TRANSMISSION MODE	INTERVENTION	OUTCOME & FINDING	QUALITY OF EVIDENCE
Azman AS, 2013 (*16*)	Cluster-RCT School level	2007–2008 influenza season	3360 students from 10 elementary schools in Pittsburgh, USA	Primary and secondary	Hand sanitizer, soap and education	The primary transmission outcome refers to Stebbins, S. 2011; no significant difference in secondary ILI attack rate between intervention group and control group	Moderate
Levy JW, 2014 (*18*)	Cluster-RCT Household level	2009–2010	191 households with index children recruited from a public paediatric hospital in Bangkok, Thailand	Secondary	Handwashing; handwashing and face mask	Less secondary influenza infections in households in the intervention group than control group, but not statistically significant; handwashing reduces surface influenza RNA contamination	Moderate
Ram PK, 2015 (*27*)	Cluster-RCT Household level	2009–2010	384 households with index case-patients recruited from a hospital in Kishoregoni, Bangladesh	Secondary	Handwashing with soap and education	Handwashing promotion did not prevent secondary influenza infection in household setting	Moderate
Aiello AE, 2010 (*20*)	Cluster-RCT University residence hall level	2006–2007 influenza season	1297 participants recruited from7 residential halls in Michigan, USA	Primary	Hand sanitizer and face mask; face mask	The laboratory-confirmed influenza protective effect of intervention is not significant; but the intervention is significant in ILI reduction	Moderate
Aiello AE, 2012 (*23*)	Cluster-RCT University residence hall level	2007–2008 influenza season	1111 participants recruited from 5 residential halls in Michigan, USA	Primary	Hand sanitizer and face mask; face mask	Reductions in the rates of influenza in the intervention groups, but not significant; significant reduction in the rates of ILI	High
Cowling BJ, 2008 (*26*)	Cluster-RCT Household level	2007	198 households with index subjects recruited from outpatient clinics in Hong Kong SAR, China	Secondary	Hand sanitizer and education; face mask and education	No significant difference between intervention groups and control group in laboratory-confirmed influenza and clinical secondary attack rate	Moderate

STUDY	STUDY DESIGN	STUDY PERIOD	POPULATION & SETTING	TRANSMISSION MODE	INTERVENTION	OUTCOME & FINDING	QUALITY OF EVIDENCE
Cowling BJ, 2009 (*19*)	Cluster-RCT Household level	2008	259 households with index subjects recruited from outpatient clinics in Hong Kong SAR, China	Secondary	Hand sanitizer and education; hand sanitizer, face mask and education	Hand hygiene and face mask intervention prevent influenza transmission, but not statistically significant; among the households implementing interventions within 36 hours symptom onset of index cases, the interventions significantly reduce influenza transmission	Moderate
Larson EL, 2010 (*21*)	Cluster-RCT Household level	2006–2008	509 households were recruited in New York, USA	Primary	Hand sanitizer and education; hand sanitizer, face mask and education	There is no detectable benefit of hand hygiene, face mask and education intervention on influenza prevention	Moderate
Simmerman JM, 2011 (*22*)	Cluster-RCT Household level	2008–2009	442 households with index children recruited from a public paediatric hospital in Bangkok, Thailand	Secondary	Handwashing; handwashing and face mask	Hand hygiene and face mask intervention did not reduce influenza transmission	Moderate
Stebbins S, 2011 (*17*)	Cluster-RCT School level	2007–2008 influenza season	3360 students from 10 elementary schools in Pittsburgh, USA	Primary	Hand sanitizer, soap and education	"WHACK the Flu" programme did not reduce laboratory-confirmed influenza infection, but reduced absence episodes and laboratory-confirmed influenza A	Moderate
Suess T, 2011 (*24*)	Cluster-RCT Household level	2009–2010 pandemic season 2010–2011 influenza season	84 households with one influenza positive index case were recruited by general practitioners or paediatricians in Berlin, Germany	Secondary	Hand sanitizer and face mask; face mask	The interventions could reduce influenza transmission in household setting when implemented early and use properly	Moderate
Talaat M, 2011 (*25*)	Cluster-RCT School level	2008	44 451 students were enrolled from 60 elementary schools in Cairo, Egypt	Primary	Handwashing	Hand hygiene campaign effectively reduced different kinds of infectious disease, including laboratory-confirmed influenza	Moderate

ILI: influenza-like illness; RCT: randomized controlled trial; RNA: ribonucleic acid; SAR: Special Administrative Region; USA: United States of America.

Table 4. Grade evidence profile for hand hygiene

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hand hygiene with or without face mask	versus control	Risk ratio	Quality	Importance
Effect of hand hygiene intervention on prevention of laboratory-confirmed influenza											
10	Randomized trial [1]	No serious risk of bias [2,3,4]	Serious [5]	No serious indirectness [6]	Serious [7]	Strong association [8]	434/6442 (6.7%)	504/5392 (9.3%)	Risk ratio cannot be generated because of high heterogeneity	Moderate	Important

1 All studies were randomized trials.
2 All studies were cluster-RCTs at household, school and university residence level.
3 Five studies reported blinding of study staff including clinical staff, laboratory staff or recruiting physicians. Subjects of all studies were not blinded due to the nature of the study design.
4 Allocation concealment was adequate in all trials. Three studies used block randomization and seven studies used simple randomization.
5 High heterogeneity was observed in the pooled analysis (I2 > 50%).
6 Laboratory-confirmed influenza was the outcome for all studies.
7 Cowling B.J. 2008 and Suess T. 2011 reported insufficient number of participants. Cowling B.J. 2009 reported insufficient statistical power. Larson E.L. 2010 reported lower rate of illness was found compared to initial assumption. Simmerman J.M. 2011 reported did not reach the recruitment target. Talaat M. 2011 reported low rate of testing of students who were absent due to ILI.
8 Aiello AE (2012), rated as high-quality study, showed a large effect in favouring hand hygiene intervention – RR = 0.4.

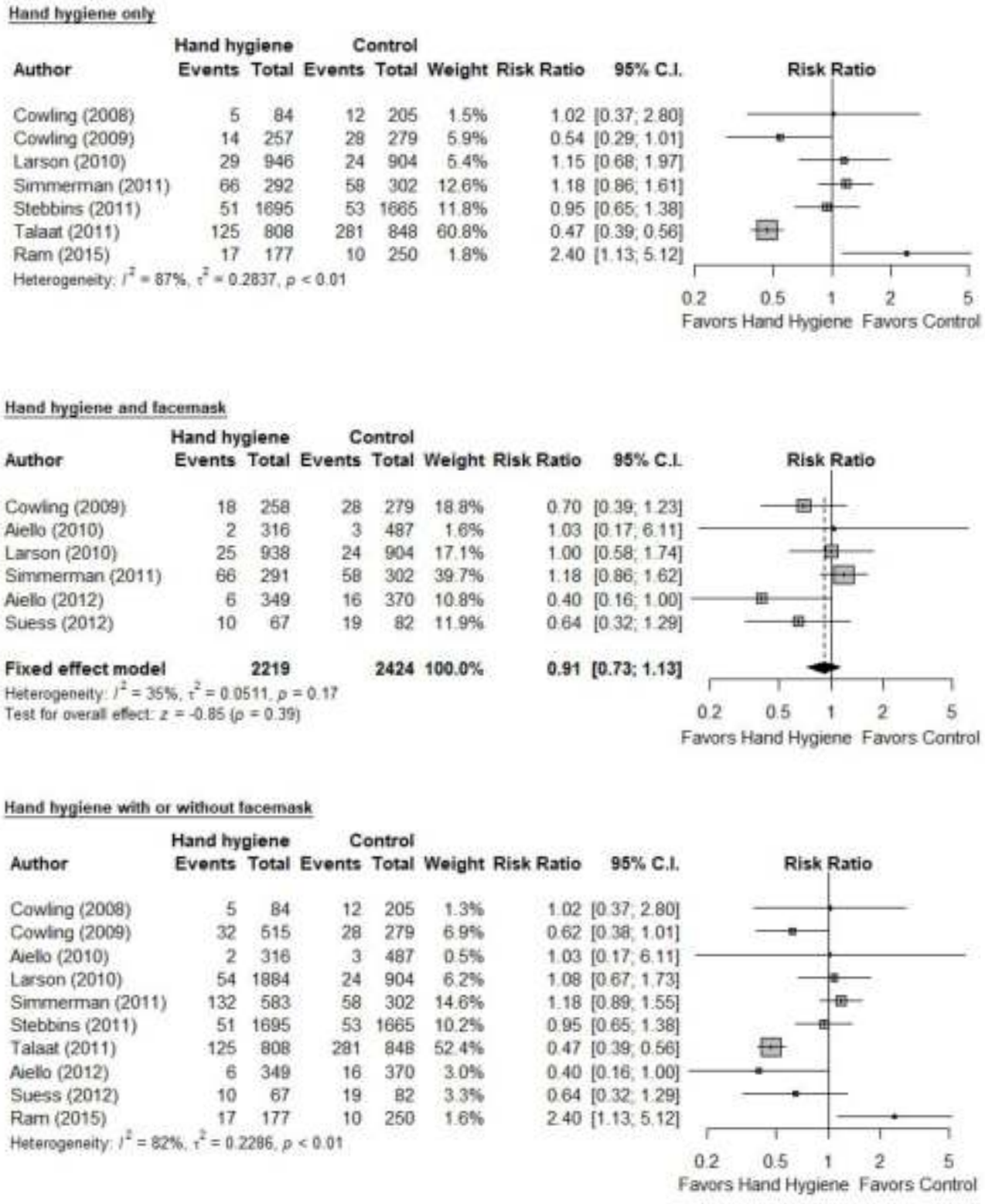

Fig. 4. Risk ratios for the effect of hand hygiene interventions with or without face mask on laboratory-confirmed influenza (pooled analysis)

Note: Total effect would not be estimated when heterogeneity is high (I2 ≥75%).

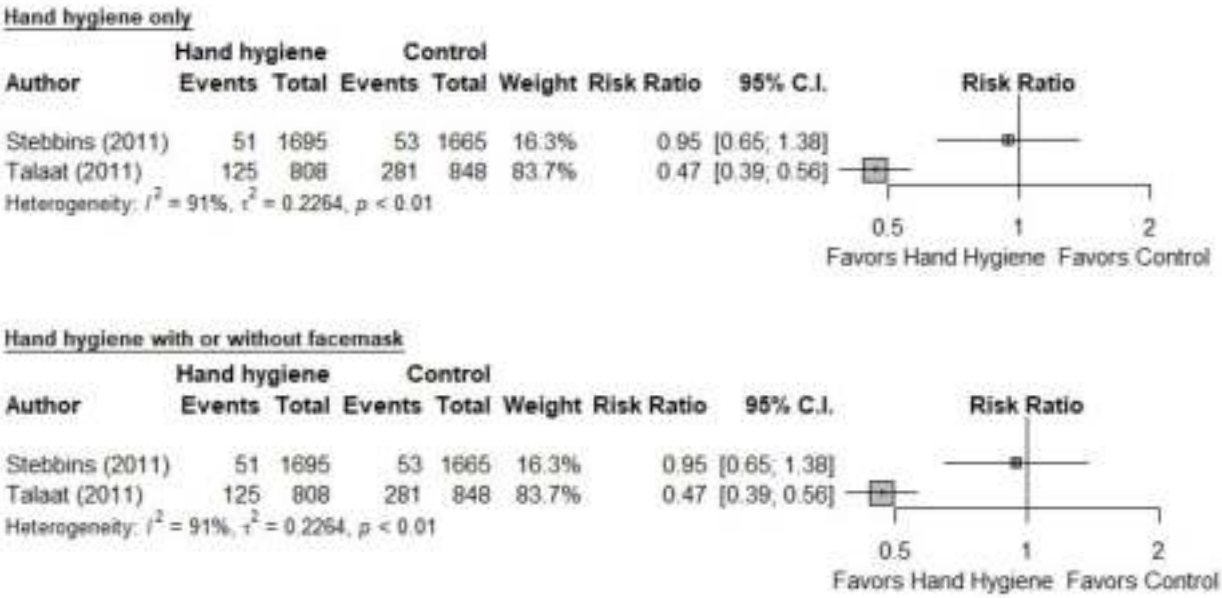

Fig. 5. Risk ratios for the effect of hand hygiene interventions with or without face mask on laboratory-confirmed influenza in elementary school setting

Note: Total effect would not be estimated when heterogeneity is high (I2 ≥ 75%).

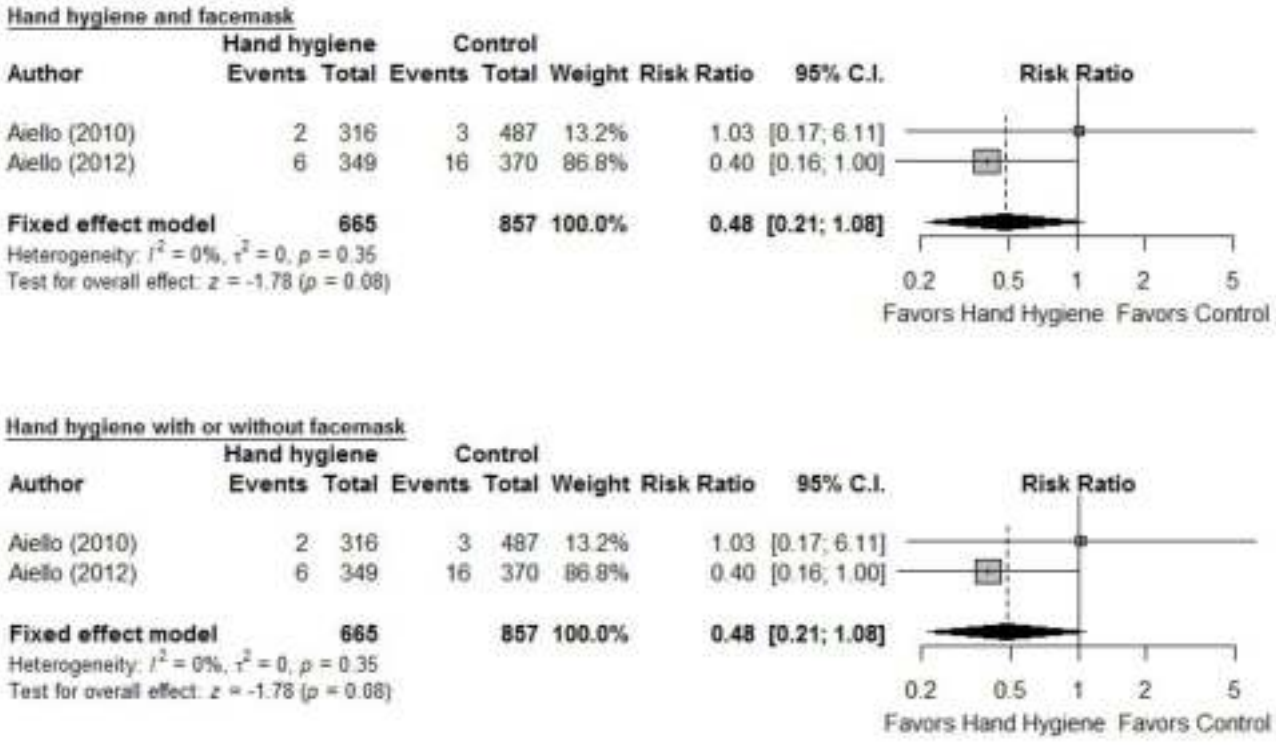

Fig. 6. Risk ratios for the effect of hand hygiene interventions with or without face mask on laboratory-confirmed influenza in university residential hall setting

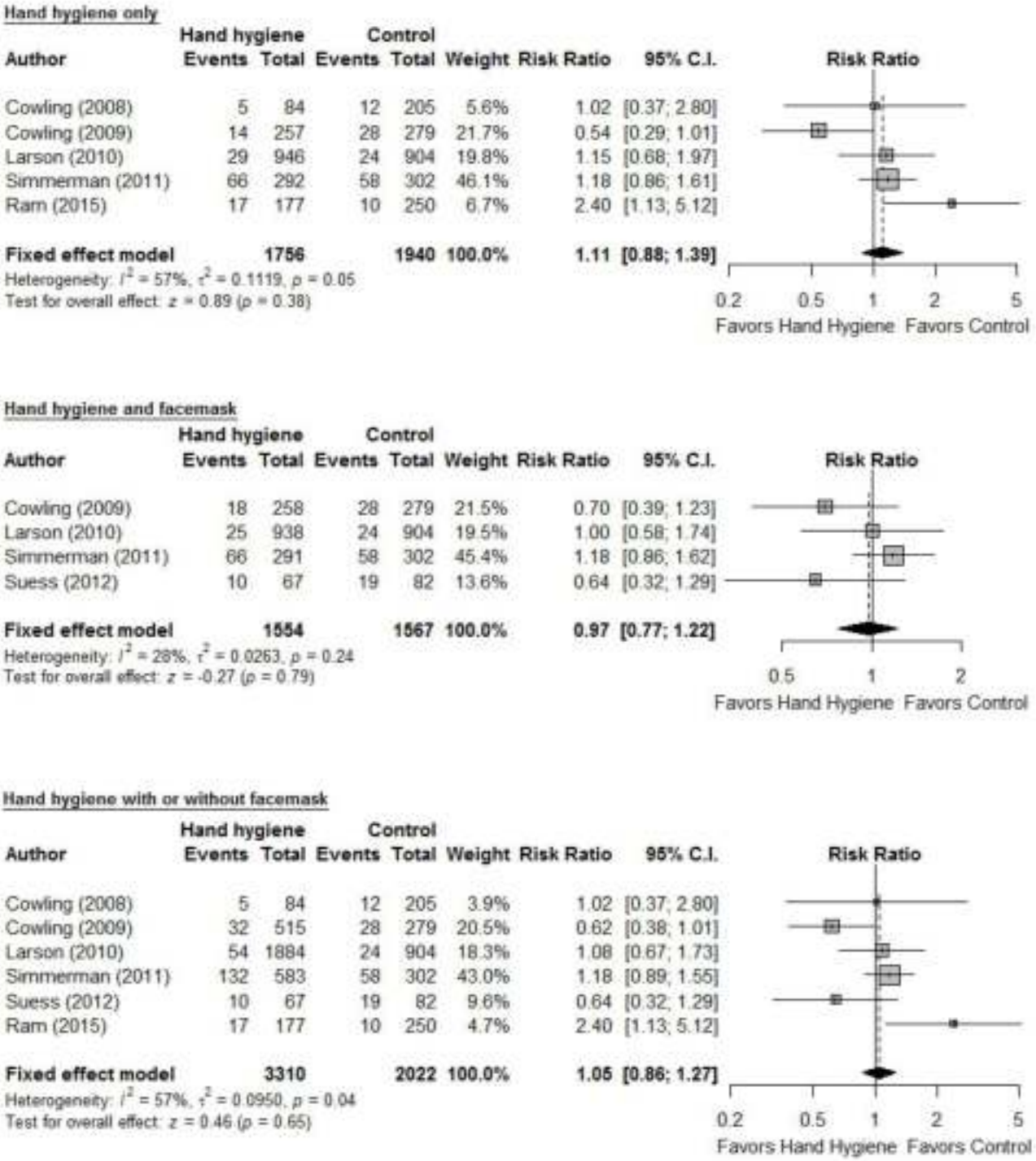

Fig. 7. Risk ratios for the effect of hand hygiene interventions with or without face mask on laboratory-confirmed influenza in household setting

1.2. Respiratory etiquette

Terminology
Definitions of respiratory etiquette are shown in Table 5.

Table 5. Definitions of respiratory etiquette terms

TERM	DEFINITION
Respiratory etiquette	Respiratory etiquette is also known as 'cough etiquette' (*38*). It is a simple hygiene practice to prevent person-to-person transmission of respiratory infections. Measures include (*39*): 1) Cover the mouth and nose with a tissue when coughing or sneezing 2) Find the nearest waste basket to dispose the used tissue immediately 3) Wash hands after touching respiratory secretions and/or contaminated objects

Methods
On 6 November 2018, we conducted a literature search in four databases: Medline (January 1946 to October 2018), PubMed (January 1950 to October 2018), EMBASE (1980 to October 2018), and CENTRAL (The Cochrane Library, 2018, Issue 5). Reference lists of retrieved articles were also reviewed for additional potential articles for this review. Articles of all languages were reviewed. Studies were selected if they investigated specifically the use of respiratory/ cough etiquette as the intervention along with the study outcome of laboratory-confirmed influenza virus infection. Studies that reported use of face mask as part of the respiratory etiquette were excluded because they will be covered in Section 1.3. Two independent reviewers (ES and SG) reviewed retrieved titles and subsequent relevant abstracts independently.

Results
A total of 80 articles were retrieved from four electronic databases after removing duplicate publications. Titles, abstract content and full text were subsequently reviewed for inclusion; 35 abstracts were selected for screening and then 18 full-text articles were assessed for eligibility. No studies were identified for this review to quantify the efficacy of respiratory etiquette with the outcome of laboratory-confirmed influenza. The flow chart is shown Fig. 8.

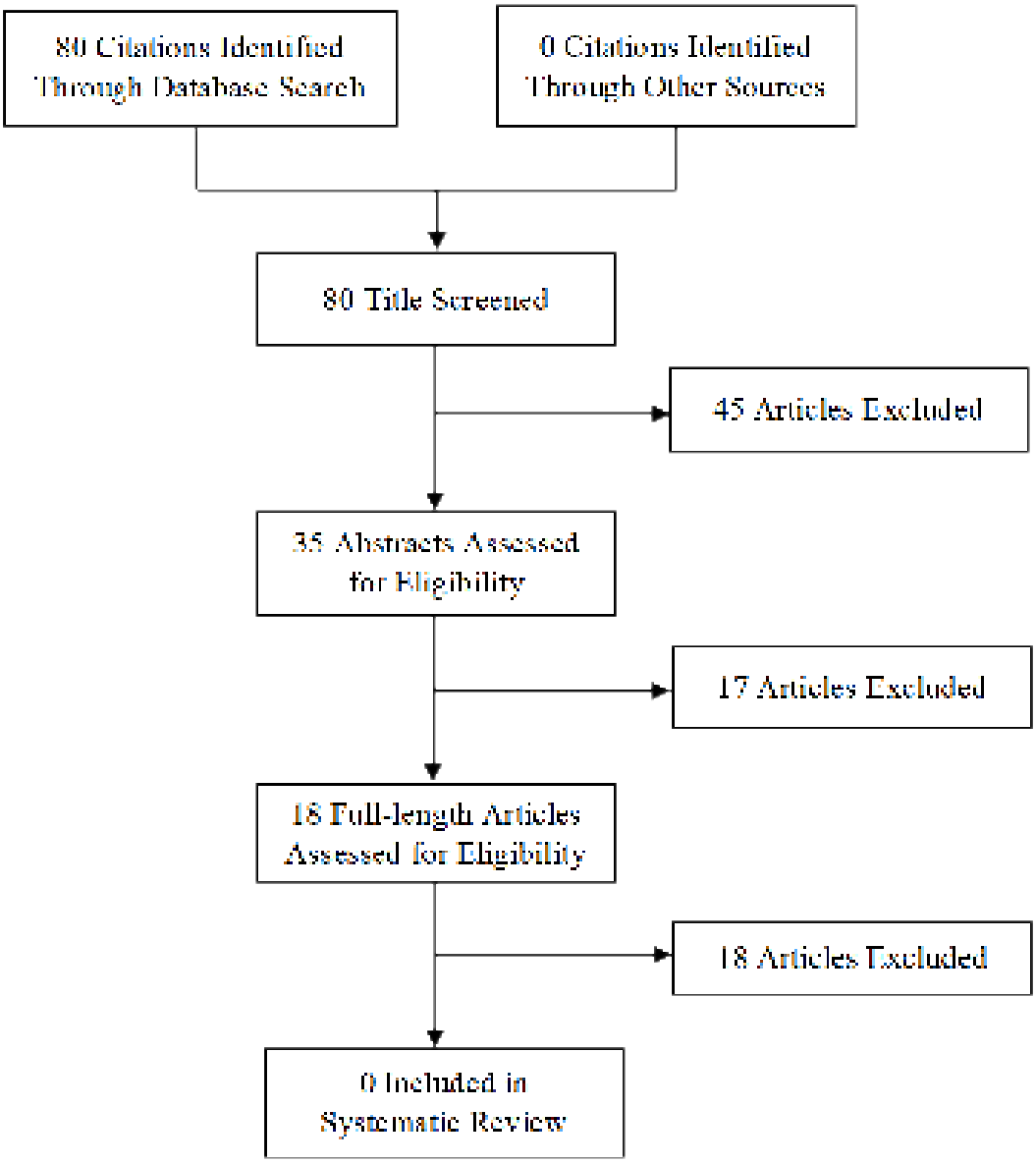

Fig. 8. Flow chart of the process and results of study selection

Balaban et al. reported a 2% reduction of self-reported respiratory illnesses, defined by one or more symptoms in cough, congestion, sore throat, sneezing or breathing problems, with the practice of cough etiquette among US pilgrims in the 2009 Hajj (*40*). Zayas et al. conducted an observational study to determine the effectiveness of respiratory etiquette manoeuvres in blocking the release of droplets or aerosols during coughing (*38*). They concluded the common respiratory etiquette (using surgical mask and hand, arm or sleeve, tissue) is not effective in blocking different diameter droplets to the surrounding environment and the majority of droplets dispersed to the environment when practicing the manoeuvre were < 1 µm.

Ethical considerations

No major ethical considerations. Cultural contexts may need to be considered when recommending specific actions such as covering coughs with hands or tissues.

Knowledge gaps

There is a need for further research in the best measures of respiratory etiquette for reducing influenza transmission (38).

1.3. Face masks

Terminology
Relevant terminology relating to face masks is shown in Table 6.

Table 6. Definitions of masks terms

TYPES OF MASKS	TERMINOLOGY
Clothing, scarf or rags tied over the nose and mouth	These are referred as alternative barriers to medical masks, but there is insufficient information available on their effectiveness *(41)*.
Cloth mask Face mask	Cloth masks can be referred to 'reusable masks made of cloth or any other fabric, including cotton, silk or muslin'*(42)* . Fitness of fabric and number of layers of a cloth mask determine its filtration capacity *(42)*. Cloth masks should be cleaned thoroughly between each use *(43)*. Washing with household detergent at normal temperature will be sufficient *(43)*.
Respirator	A face mask, also known as surgical, isolation, dental or medical procedure masks, is a loose-fitting, disposable device that covers the mouth and nose of the user, and helps block large-particle droplets, splashes, sprays or splatter that may contain infectious agents *(44)*. Face masks may also help reduce exposure of user's saliva and respiratory secretions to others *(44)*. They may come with or without a face shield and are not designed to be shared *(44)*. They are not designed to protect against breathing in small-particle aerosols that may contain viruses. Face masks should be used once and then disposed in the trash *(45)*. Respirator, also known as filtering facepiece respirator, is a personal protective device that covers the nose and mouth of the user, and helps reduce the risk of inhaling hazardous airborne particles (including dust particles and infectious agents), gases, or vapours on the user *(46)*. NIOSH in the USA certifies N, R and P series particulate filtering respirator types 95, 99 and 100 with minimum filtration efficiencies of 95, 99 and 99.97%, respectively. This certification is recognized by countries like Canada, Mexico and Chile. Several countries including Canada, Mexico and Chile. In Europe, respirators marked with 'Conformité Européen' (CE) such as FFP1 (class P1), FFP2 (class P2) and FFP3 (class P3) types meet minimum filtration efficiencies of 80, 94 and 99%, respectively *(47)*. A label 'NIOSH' is required to be printed on the NIOSH-approved products with other information including part, lot number and company name; A label 'CE' on the product indicates EC conformity *(47)*.

EC: European Community; NIOSH: National Institute for Occupational Safety and Health; USA: United States of America.

Methods

On 28 July 2018, we conducted a literature search in four databases: Medline (January 1946 to June 2018), PubMed (January 1950 to July 2018), EMBASE (1980 to June 2018), and CENTRAL (The Cochrane Library, 2018, Issue 5). Reference lists of retrieved articles were also reviewed for additional potential articles for this review. Articles of all languages were reviewed. Studies were selected if they were conducted in RCT in community settings such as households and schools, evaluated the use of face masks with or without the combination of other intervention as one intervention, and included the incidence of laboratory-confirmed influenza case as study outcome. Two independent reviewers (ES and ZX) reviewed retrieved titles and subsequent relevant abstracts independently.

Qualities of studies were assessed by GRADE with an aim to evaluate the efficacy of community-based face mask use in the prevention of laboratory-confirmed influenza virus infections.

Results

A total of 1100 articles were retrieved from four electronic databases after removing duplicate records. Titles, abstract content and full text were subsequently reviewed for inclusion; 10 relevant studies were identified for this review and meta-analysis to quantify the efficacy of community based use of face masks after excluding 89 articles by full-text assessment. The flow chart is shown in Fig. 9. Of 10 studies, seven were conducted in household settings (*19, 21, 22, 24, 26, 48, 49*), with two studies conducted in university residence halls (*20, 23*), and one study conducted in Hajj pilgrims (*50*). Nearly half of the studies evaluated the effect of face mask use with the practice of handwashing, therefore results were analysed in two groups: comparison of control group with intervention group of face mask use only; and comparison of control group with intervention group of face mask use with or without handwashing.

Among the 10 selected studies, two studies by MacIntyre et al. had a slightly different study design. One study enrolled families in which one person had laboratory-confirmed influenza, and only required the household contacts to wear face masks or P2 masks (equivalent to a N95 respirator) (48), whereas the other study required only the ill members to wear face mask to evaluate the protective effect of face mask if worn by the ill individual (i.e. source control) (*49*). In the remaining eight studies, every participant in the face mask intervention group was supposed to wear a face mask.

MacIntyre et al. compared the protective effect of face mask and P2 mask but found no significant difference in influenza-like illness (ILI) and laboratory-confirmed respiratory infections (influenza A and B virus, respiratory syncytial virus [RSV], human metapneumovirus [hMPV], adenovirus, human parainfluenza virus [PIV], coronavirus, rhinovirus, enterovirus or picornovirus); however, they reported a significant reduction in ILI if the mask was worn with good compliance in a secondary analysis (*48*).

Two studies by Aiello et al. were conducted in residence hall settings (*20, 23*). They randomized university residents by cluster (each residential hall forming a cluster unit) to face masks, enhanced hand hygiene, or both. They then measured the incidence of laboratory-confirmed influenza in students in each hall. The authors reported no significant difference in ILI and laboratory-confirmed influenza in these three randomized groups; however, they observed a significant reduction in ILI in the combined face mask and hand hygiene intervention group during the latter half of the study period in a secondary analysis.

Seven studies were conducted in household settings where a person with laboratory-confirmed influenza was recruited as a household index case, and the rate of secondary infections in the education group (control), mask group and/or hand hygiene group was monitored for illnesses and infections. All studies found no significant differences in the rate of laboratory-confirmed

influenza virus infections in contacts in the face mask arms, and some studies reported that low compliance of the use of NPIs could affect the results (*21*). One study reported a significant reduction in laboratory-confirmed influenza virus infections in contacts in the face mask and hand hygiene group in the subset of households where the intervention was applied within 36 hours of symptom onset in the index case (*24*).

Ten studies were pooled to conduct a meta-analysis to quantify the efficacy of community based use of face masks in the reduction of laboratory-confirmed influenza virus infection (Table 7). In the pooled analysis, there was a non-significant relative risk reduction of 22% (RR = 0.78, 95% CI: 0.51–1.20, I2 = 30%, p = 0.25) in the face mask group and 8% in the face mask group regardless of the addition of practice of hand hygiene (RR = 0.92, 95% CI: 0.75–1.12, I2 = 30%, p = 0.40). The evidence profile for face masks outcome is summarized in Table 8.

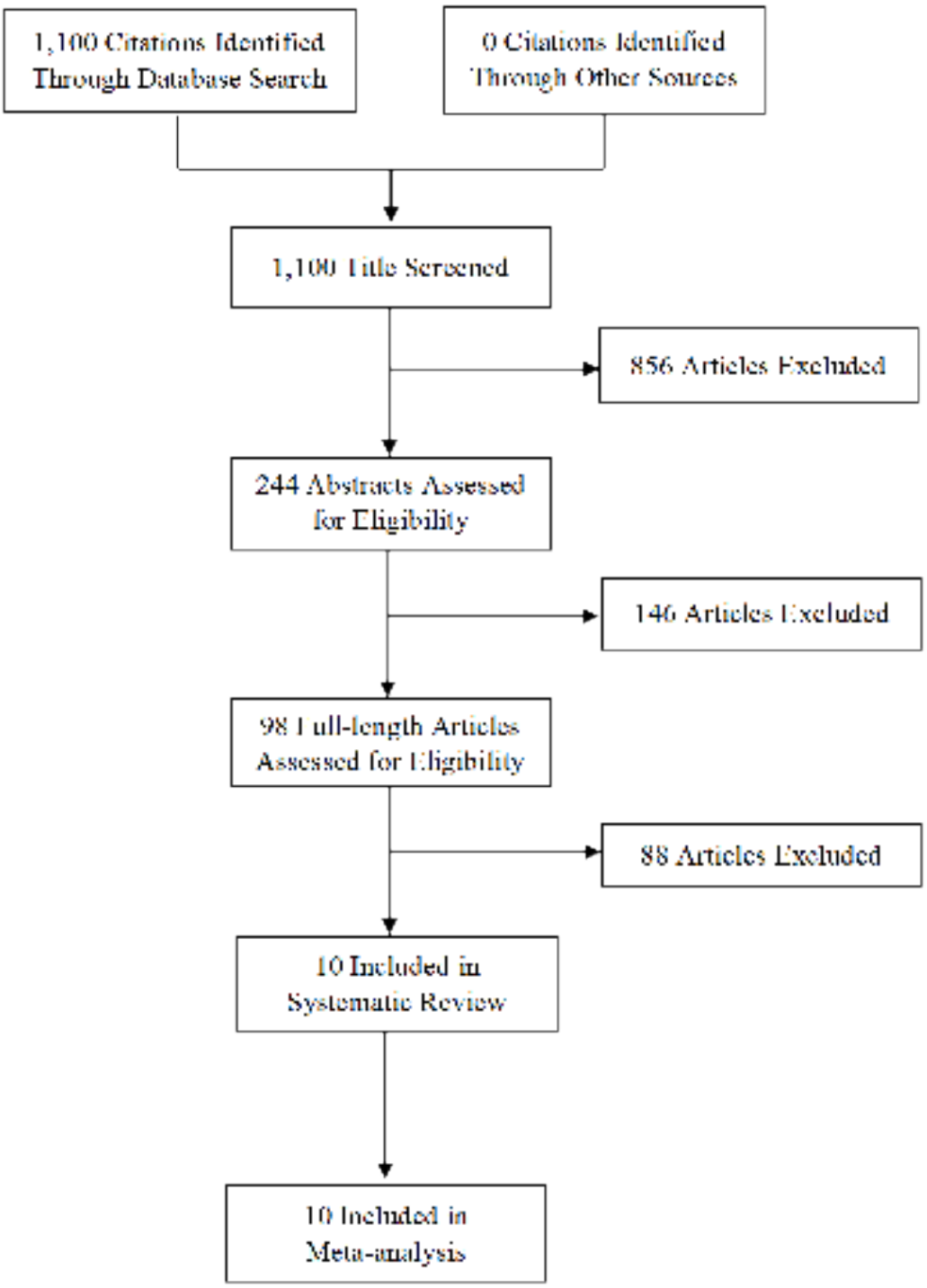

Fig. 9. The flow chart of the process and results of study selection

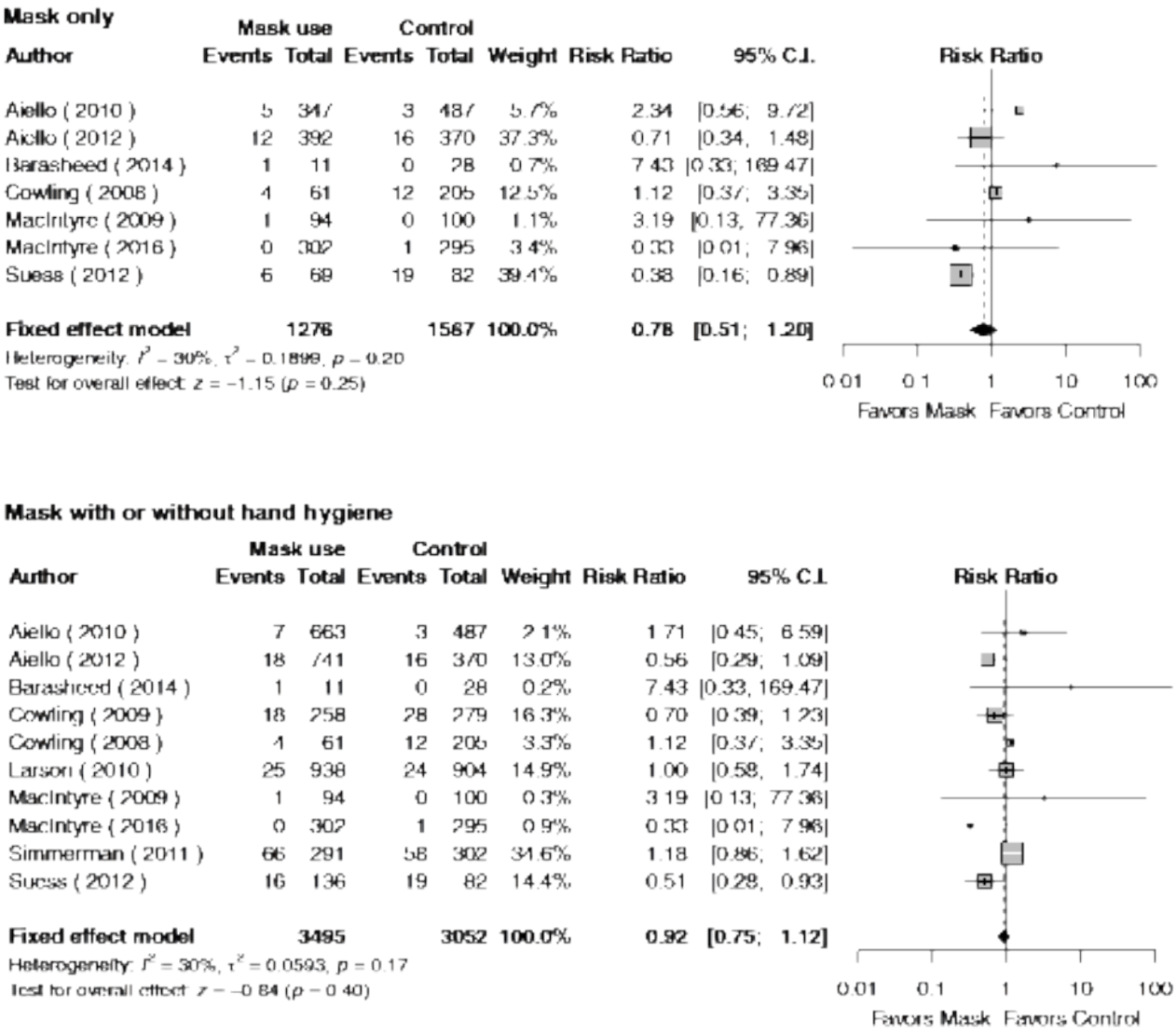

Fig. 10. Effects of face mask use interventions with or without enhanced hand hygiene on laboratory-confirmed influenza in 10 studies

Ethical considerations

No major ethical considerations. Masks may be more culturally acceptable in some locations than others, and a variety of factors may affect compliance.

Knowledge gaps

In the studies of face mask use with or without hand hygiene, the pooled estimate of the risk reduction against laboratory-confirmed influenza was 0.90 (95% CI: 0.75–1.12), which suggests that additional randomized trials would be less likely to identify a substantial protective efficacy of face masks. However, the majority of these studies were conducted in households in which at least one person was infected, and exposure levels might be relatively higher. Additional studies of face mask use in the general community would be valuable. While respirators should provide better protection against respiratory infections compared to face masks because of their higher filtration efficiency, a household randomized controlled study showed no difference in their effect on ILIs and laboratory-confirmed influenza virus infection (*48*). One issue is that respirators require fit testing for optimal performance, but fit testing facilities are not widely available in the community.

Table 7. Description of studies included in the review of face masks

STUDY	STUDY DESIGN	STUDY PERIOD	POPULATION & SETTING	INTERVENTION	OUTCOME & FINDING	QUALITY OF EVIDENCE
Aiello AE, 2010 (20)	Cluster-randomized intervention trial	Nov 2006 – Mar 2007	1437 university hall residents (USA)	Mask; Mask + Hand hygiene; control	Significant reduction in ILI during weeks 4–6 in mask and hand hygiene group compared to control; No significant reduction in ILI in mask and hand group or mask-only group or control	Moderate
Aiello AE, 2012(*23*)	Cluster-randomized interventional trial	Nov 2007 – Mar 2008	1178 university hall residents (USA)	Mask; Mask + Hand hygiene; control	No significant reduction in rates of laboratory-confirmed influenza in mask and hand group or mask-only group or control group	Moderate
Barasheed O, 2014 (*50*)	Non-blinded cluster-randomized trial	Nov 2011 – Nov 2011	164 Australian pilgrims (Saudi Arabia)	Mask; control	No significant difference in laboratory-confirmed influenza in two arms; protective effect against syndromic ILI compared to controls (31% versus 53%, p = 0.04)	Moderate
Cowling BJ, 2008 (*26*)	Cluster-randomized intervention trial	Feb 2007 – Sep 2007	198 laboratory-confirmed influenza case and their household contacts	Mask; Hand hygiene; control	No significant reduction in the secondary influenza attack rate in control, mask or hand group	Moderate
Cowling BJ, 2009 (*19*)	Cluster-randomized intervention trial	Jan 2008 – Sep 2008	407 laboratory-confirmed influenza case and 794 household members	Mask; Mask + Hand hygiene; control	No significant difference in rates of laboratory-confirmed influenza in hand-only or mask and hand group	Moderate
Larson EL, 2010 (*21*)	Cluster-randomized intervention trial	Nov 2006 – Jul 2008	617 households	Mask + Hand hygiene; Hand hygiene; control	No significant reduction in rates of laboratory-confirmed influenza in control, hand, mask or hand group	Moderate
MacIntyre CR, 2009 (*48*)	Cluster-randomized intervention trial	Aug 2006 – Oct 2006 & Jun 2007 – Oct 2007	145 laboratory-confirmed influenza case and their adult household contacts	Surgical mask; P2 mask; control	No significant difference in rate of laboratory-confirmed influenza in control, face mask or P2 mask group	Moderate
MacIntyre CR, 2016 (*49*)	Cluster-randomized intervention trial	Nov 2013 – Jan 2014	245 ILI index case and 597 household contacts	Mask; control	Clinical respiratory illness, ILI and laboratory-confirmed viral infections were lower in the mask arm compared to control, but results were not statistically significant	Moderate
Simmerman JM, 2011) (*22*)	Cluster-randomized intervention trial	Apr 2008 – Aug 2009	465 laboratory-confirmed influenza case and their household contacts	Mask + Hand hygiene; hand hygiene; control	No significant reduction in rate of secondary influenza infection in control, hand, mask or hand group	Moderate
Suess (2012) (*24*)	Cluster-randomized intervention trial	Nov 2009 – Jan 2010 & Jan 2011 – Apr 2011	84 laboratory-confirmed influenza case and 218 household contacts	Mask; Mask + Hand; control	No significant difference in rate of laboratory-confirmed influenza in control, mask, mask or hand group	Moderate

ILI: influenza-like illness; USA: United States of America.

Table 8. Grade evidence profile for face masks

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mask	Control	Risk ratio	Quality	Importance
10	RCT [1,2]	No serious risk of bias [3,4]	No serious inconsistency [5]	No serious indirectness	Serious [6]	None	156/3495	161/3052	0.92 (0.75,1.12)	Moderate	Important

RCT: randomized controlled trial.

1 All studies were randomized trials.
2 All studies were cluster-RCTs at household and university residence level.
3 Eight studies reported blinding of study staffs including clinical staff, laboratory staff or recruiting physicians. Subjects of all studies were not blinded.
4 Three studies used block randomization; six studies used computer program to generate the randomization order and one study used ticket-picking for selection.
5 Moderate heterogeneity was observed in the pooled analysis.
6 Six studies did not have sufficient sample size in each intervention group; 3 studies reported insufficient statistical power; one study reported insufficient detection of influenza case.

2. ENVIRONMENTAL MEASURES

2.1. Surface and object cleaning

Methods

We conducted a systematic review on the effect of surface and object cleaning in preventing influenza virus infections in non-health care settings. PubMed, Medline, EMBASE and CENTRAL were searched for articles on 15 October 2018.

Study selection criteria were studies reporting the effect of surface and object cleaning intervention with no intervention in preventing influenza virus infections in community settings. RCTs and other types of epidemiological studies were included if they aimed to study the effect of surface and object cleaning on laboratory-confirmed influenza, ILI or respiratory illness. Simulation studies, recommendations, and commentaries or editorials were excluded. A community setting was defined as an open setting without confinement and special care for the patients. Articles describing any surface and object cleaning related interventions were included. No language limits were applied.

Two independent reviewers (ZX and ES) reviewed titles, abstracts and full texts. After confirmed included studies, data extraction and evidence quality assessment were performed by the reviewers. The GRADE framework was used to evaluate the effect of surface and object cleaning on influenza.

Results

There were 484 articles retrieved through database search. 462 articles were excluded through title and abstract screening. In the full-text assessment, 19 articles were screened out due to no surface and object cleaning intervention or no specific respiratory infection outcome. Finally, three articles were included in the systematic review to study the effectiveness of surface and object cleaning to prevent influenza infection. The article selection flow is shown in Fig. 11.

A cross-sectional study showed that bleach use in households was significantly associated with an increased in the rate of self-reported influenza (influenza data were obtained from self-administered questionnaires and the paper did not specify whether it was laboratory-confirmed influenza or ILI), and the authors hypothesized that this might due to the immunosuppressive properties of bleach (*51*). An RCT with disinfection of toys and linen in day care nurseries found a reduction in the detections of viruses in the environment, but no significant effect on influenza virus specifically and no significant reduction in acute respiratory illnesses among children *(52)*. Another RCT conducted in elementary schools demonstrated that hand hygiene with alcohol-based hand sanitizer and surface disinfection with quaternary ammonium wipes intervention could reduce gastrointestinal illness absenteeism, but not respiratory illness absenteeism (*53*). Detailed data extraction is shown in Table 9 below.

Experimental studies found that laboratory-grown influenza virus could survive on common surfaces and objects (e.g. stainless steel, wood, plastic, cloth and banknotes) from community settings for a few hours and up to 1 week (*28, 30, 54-56*). Influenza virus RNA could be detected by polymerase chain reaction (PCR) on surfaces and objects in household, school and airport settings in the field studies (*31, 52, 57-60*). Killingley et al. found viable influenza virus in the environment with laboratory-confirmed influenza individuals (*59*). These results suggested the biological plausibility that influenza virus could transmit via the fomite route. And the results from some experimental studies showed that disinfection process with different disinfection products (e.g. ethanol and 1-propanol) was effective to inactivate or reduce infectious influenza virus on surfaces (*61-63*), which suggested the importance of surface and object cleaning in influenza transmission prevention.

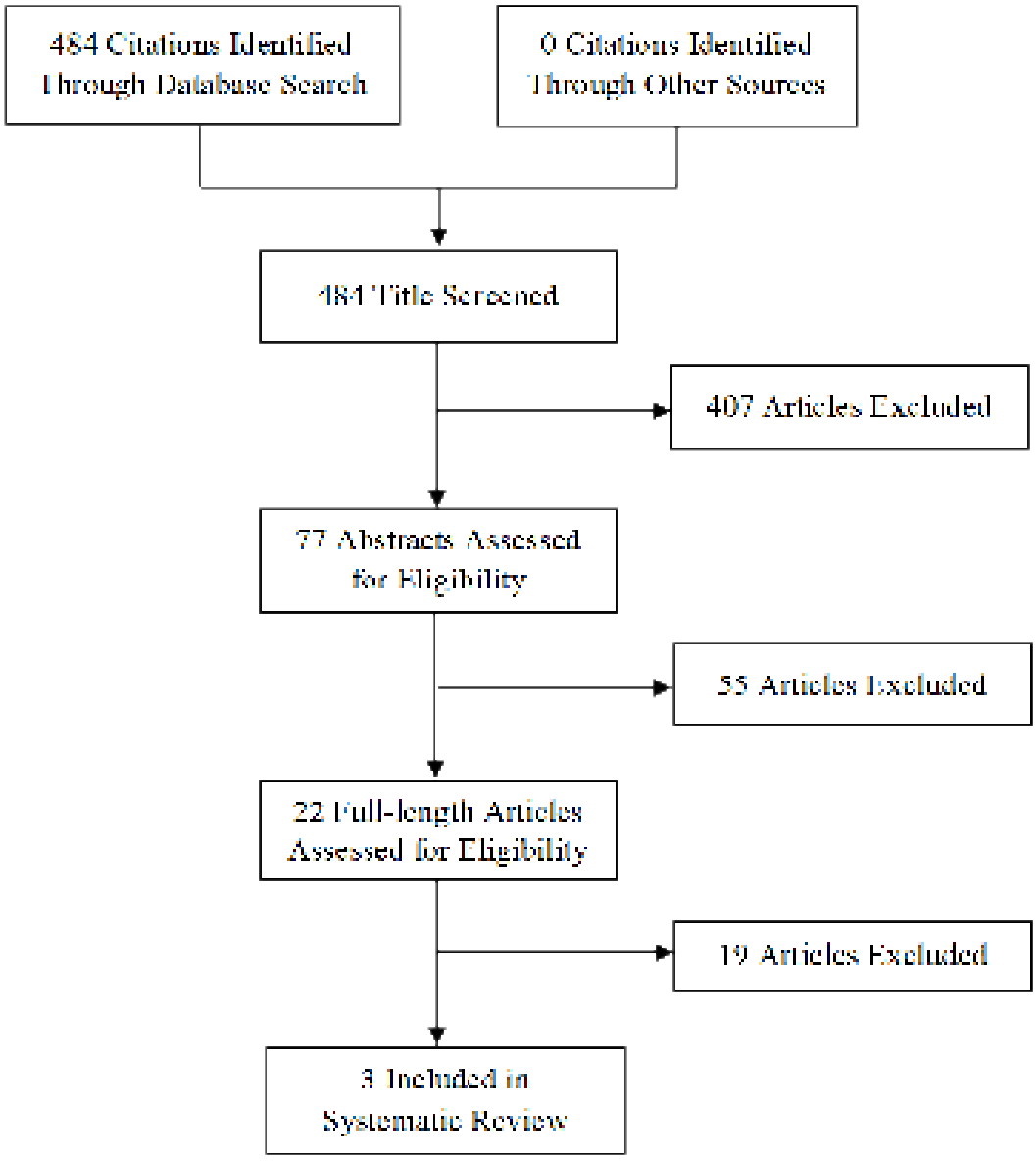

Fig. 11. The flow chart of surface and object cleaning articles selection

Ethical considerations

Disinfection product selection is a major issue, especially in public settings. Some disinfectants are irritants and may lead to adverse effect in sensitive population (*51*), and some disinfectants with alcohol may not be applicable in some countries or regions due to religious objections (*35*). In addition, the safety of cleaning personnel should also be considered. Proper training should be provided for the cleaning personnel, including proper use of the disinfectant (usage, dosage and time) and precautions before cleaning, such as wearing protective clothing.

Knowledge gaps

Only three studies were included in our systematic review and only two of them were RCTs. More trials are needed to study the effect of surface and object cleaning on influenza prevention. The best evidence for pandemic preparedness would be provided by studies in which the outcome is laboratory-confirmed influenza, rather than acute respiratory infections. Studies in various settings (e.g. household, school, workplace and public place) are also needed. The effect of different disinfection products to prevent influenza virus infection in terms of disinfection frequency, disinfection dosage, disinfection time point, and disinfection targeted surface and object material remained unknown.

Table 9. Description of studies included in the review of surface and object cleaning

STUDY	STUDY DESIGN	STUDY PERIOD	POPULATION & SETTING	INTERVENTION	OUTCOME MEASURE	MAIN FINDING	QUALITY OF EVIDENCE
Casas L, 2015 (*51*)	Cross-sectional study	2008–2010	9102 students from schools in Spain, Netherlands and Finland	Environment cleaning with bleach	Self-reported influenza	Passive contact with cleaning bleach in the household may increase the risk of respiratory and other infections in children, which may adversely affect the health of school-age children	Very low
Ibfelt T, 2015 (*52*)	Cluster-RCT	Autumn 2012 – April 2013	Twelve day-care nurseries (caring for 587 children) in Copenhagen, Denmark	Disinfection of toys	Respiratory infections and surface sample influenza virus detection	Frequently disinfection of toys could reduce environmental microbial presence, but not significantly reduce respiratory sickness of nursery children	Low
Sandora TJ, 2008 (*53*)	Cluster-RCT	March-May 2006	285 students from elementary schools in Avon, Ohio, USA	Hand hygiene and surface cleaning	Respiratory illness	Surface disinfection reduced gastrointestinal related absenteeism among school-age children, but not respiratory illness-related ones	Low

RCT: randomized controlled trial; USA: United States of America.

2.2. (*1*) Other environmental measures (UV light)

Terminology

The definition of ultraviolet (UV) light is shown in Table 10.

Table 10. Definition of UV light terms

TERM	DEFINITION
Ultraviolet light (UV light)	UV light is electromagnetic radiation that can be categorized into three groups by wavelength bands *(64)*: 1) UV-A (400–315 nm): It can be used for various purposes like pest control or identifying counterfeit banknotes. 2) UV-B (315–280 nm): It is known for the development of skin cancer. 3) UV-C (280–100 nm): It is used for disinfection of drinking water and sterilization of apparatus.
Ultraviolet germicidal irradiation (UVGI)	It is a mean of disinfection which breaks down microorganisms and can be used to prevent the spread of certain infectious diseases (*65*)

Methods

On 25 September 2018, we conducted a literature search in four databases: Medline (January 1946 to September 2018), PubMed (January 1950 to September 2018), EMBASE (1980 to September 2018), and CENTRAL (The Cochrane Library, 2018, Issue 5). Articles of all languages were included. Reference lists of retrieved articles were also reviewed for additional potential articles for this review. Studies were selected if they mentioned the use of UV light in community setting and reported laboratory-confirmed influenza virus infections as a study outcome. Two independent reviewers (ES and ZX) reviewed retrieved titles and subsequent relevant abstracts independently.

Results

A total of 1155 articles were retrieved from four electronic databases after removing duplicate publications. Titles, abstract content and full text were subsequently reviewed for inclusion; 67 abstracts were selected for subsequently screening and eventually 39 full texts were assessed for eligibility. No studies were identified in this review to quantify the efficacy of UV light with the laboratory-confirmed influenza outcome. The flow chart is shown in Fig. 12.

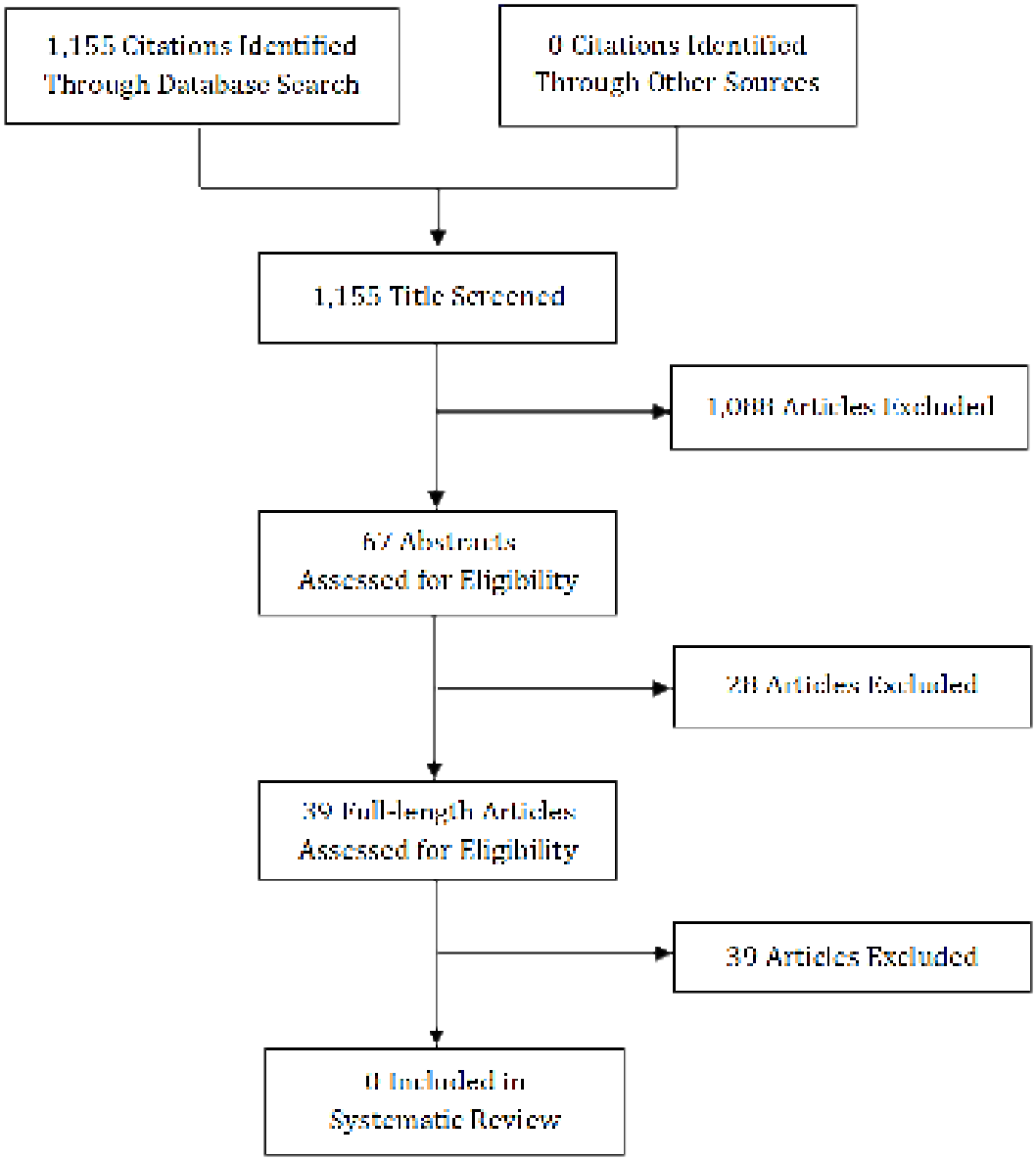

Fig. 12. The flow chart of the process and results of study selection

Ethical considerations

Exposure to UV light at certain wavelengths can increase the risk of skin cancer and cataracts; one study estimated that up to 20% of cataracts were due to UV overexposure (*64*). The use of UV light in occupied areas would need to be implemented carefully to control risks.

Knowledge gaps

The effectiveness of UV light in reducing the incidence of influenza virus infections still requires more evidence. Potential safety issues are also an important issue. Welch et al. reported that a low dose of far-UV-C light could inactivate aerosolized influenza H1N1 virus in a test chamber, and they reported an harmless effect on exposed mammalian skin (*66*), but more evidence is needed to confirm the impact of far-UV-C light in natural settings.

2.2. (*2*) Other environmental measures (ventilation)

Terminology
Definitions of ventilation are shown in Table 11 (*67*).

Table 11. Definition of ventilation terms

TERM	DEFINITION
Ventilation	Ventilation moves outdoor air into a building or a room, and distributes the air within the building.
Natural ventilation	Natural forces such as winds exchange the air in the building through windows, doors, solar chimneys, wind towers or trickle ventilators.
Mechanical ventilation	Mechanical ventilation uses mechanical fans to drive the outdoor air into the building at a designed flow rate.
	Mechanical ventilation can be integrated with air-conditioning system to control the indoor air temperature and humidity.
Hybrid (mixed-mode) ventilation	Combination of both mechanical and natural ventilation.
Air changes per hour (ACH)	The volume of air supplied to a room, in m3/hour, divided by the room volume, in m^3.

Methods
On 25 September 2018, we conducted a literature search in four databases: Medline (January 1946 to September 2018), PubMed (January 1950 to September 2018), EMBASE (1980 to September 2018), and CENTRAL (The Cochrane Library, 2018, Issue 5). Articles of all languages were included. Reference lists of retrieved articles were also reviewed for additional potential articles for this review. Studies that used modelling or simulation to describe the impact of ventilation on the rate of influenza virus infection in community settings were included. Two independent reviewers (ES and ZX) reviewed retrieved titles and subsequent relevant abstracts independently.

Results
A total of 630 articles were retrieved from four electronic databases after removing duplicate publications. Titles, abstract content and full text were subsequently reviewed for inclusion; 35 abstracts were selected for screening and then 18 full texts were assessed for eligibility. Three studies were identified for this review to evaluate the contribution of ventilation in influenza infection in community settings, both from the same author. The flow chart is shown in Fig. 13. and the description for each study is shown in Table 12.

A stimulation study modelled the transmission potential levels in an elementary school and predicted a reduction of R0 (from 11.38 to 3.97) with an increase in air changes per hour (ACH) from 0.5 to 2 (*68*).

Another stimulation study on an influenza outbreak, with consideration of possible airborne transmission in a community predicted a 40% reduction of peak daily-infected ratio by increasing the ventilation from 1 ACH to 9 ACH, and the peak would delay from Day 30 to Day 240 by increasing the ventilation from 1 ACH to 7 ACH (*69*). The authors further predicted that the overall attack rate during an epidemic would reduce from 100% to 3.3% if the ACH increased

from 1 to 7. They further studied the effectiveness of ventilation in another study, and predicted that doubling or tripling the ventilation rate could reduce the peak infection rate by over 60% under the assumption of equal contribution of airborne and close contact transmission; the authors concluded that an overall 30% reduction of peak infections was possible, even if airborne transmission only contributed to 20% of total infections (*70*).

Ethical considerations

No major ethical considerations.

Knowledge gaps

Mathematical models can only provide an indication of the potential spread of respiratory infections, and results can vary depending on the model assumptions. Experimental studies such as RCTs would provide more compelling evidence on the efficacy of increasing ventilation in reducing influenza transmission.

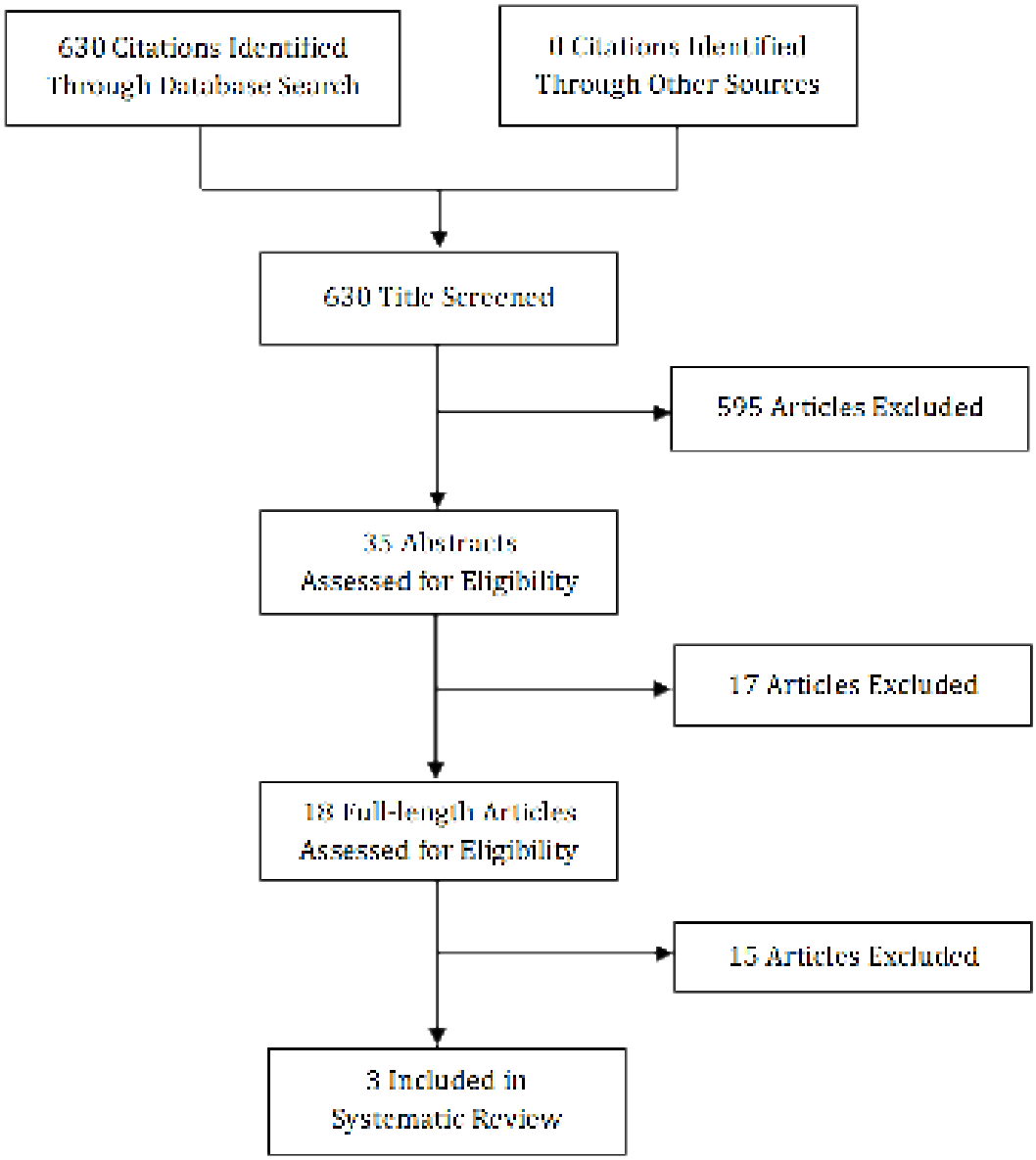

Fig. 13. The flow chart of the process and results of study selection

Table 12. Description of simulation studies included in the review of ventilation

STUDY	STUDY POPULATION	STUDY DESIGN	INTERVENTION	OUTCOME
Chen S, 2007 (*68*)	494 students (60 kindergarten and 434 elementary students) in an elementary school in Taipei City, Taiwan	Mathematical modelling	ACH, ACH + mask, 80% vaccination rate + 80% mask + 1.5 ACH	R0 is estimated to reduce from 11.38 to 3.97 for enhanced 0.5 and 2 ACH
Gao XL, 2009 (*69*)	Hong Kong SAR data in 2007	Mathematical modelling at community level	ACH, ACH + mask, ACH + UVGI, ACH + HEPA filter	Peak daily-infected ratio was reduced from 43% at 1 ACH to 21% at 3 ACH, 10% at 5 ACH, 3% at 7 ACH and 0.2% at 9 ACH; when ACH were increased from 1 to 5 ACH and 7 ACH, the disease attack rate was reduced from 100% to 69.8% and 3.3% respectively
Gao X, 2016 (*70*)	8 population groups (home stayers, office workers, classroom attendees, food service workers, shop workers, drivers, public space workers and other)	Mathematical modelling at 7 locations in communities	Ventilation, Ventilation + mask	Increasing ACH by doubling or tripling could reduce the peak infection rate by 65% and 83%; peak infection rate could reduce by about 34%, and outbreak could be delayed by over 50 days if applying a higher ventilation rate and masks for ill person

ACH: air changes per hour; HEPA: high-efficiency particulate air; R0: basic reproductive number; SAR: Special Administrative Region; UVGI: ultraviolet germicidal irradiation.

2.2. (*3*) Other environmental measures (humidity)

Terminology

Definitions of humidity are shown in Table 13.

Table 13. The definition of humidity terms

TERMS	TERMINOLOGY
Absolute humidity	A measure of actual amount of water vapour in the air, regardless of the air's temperature (expressed as grams of water per cubic metre volume of air) (*71*)
Relative humidity	A measure of amount of water vapour but relative to the temperature of air (expressed as a percentage) (*71*)

Methods
On 25 September 2018, we conducted a literature search in four databases: Medline (January 1946 to September 2018), PubMed (January 1950 to September 2018), EMBASE (1980 to September 2018), and Cochrane Library databases and the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2018, Issue 5). Articles of all languages were included. Reference lists of retrieved articles were also reviewed for additional potential articles for this review. Studies that evaluated the impact of humidification in respect to the reduction of number of infected individuals in community settings were included.

Results
A total of 631 articles were retrieved from four electronic databases after removing duplicated publications. Titles, abstract content and full text were subsequently reviewed for inclusion; 16 abstracts were selected for subsequent screening, and eventually three full texts were assessed for eligibility. No studies were identified in Fig. 14.

Reiman et al. studied the effect of elevated humidification on influenza virus survival in preschool classrooms with the outcome measure being the detection of influenza virus in air and fomites *(72)*. They reported a significant reduction of influenza A virus in air and on fomite (markers and wooden toys) in humidified preschool classrooms compared to control rooms. Detection rate of influenza A virus in air and fomites were 20% at humidified rooms (humidification maintained at 9.89 millibar) compared to 14.5% at control rooms (at 6.33millibar); the differences in influenza detection were statistically significant in both air and fomites. Myatt et al. simulated the airborne survival of influenza virus with the impacts of home humidification with the CONTAM a multi-zone indoor air quality model, and described a 17.5% to 31.6% reduction of influenza virus survival in rooms with a humidifier operating (*73*). Noti et al. used a manikin to stimulate coughs containing influenza virus and assessed the viral infectivity under various levels of relative humidity in the examination room (*74*), and found that total virus during a 1-hour collection remained at about 70% infectivity at RH ≤ 23% but only about18% at RH ≥ 43% .

Ethical considerations
No major ethical considerations.

Knowledge gaps
The exact mechanism of how humidity affects the survival of the influenza virus is not clear (*72, 75*). Many studies have studied the effect under laboratory conditions, but very few have tested in natural settings.

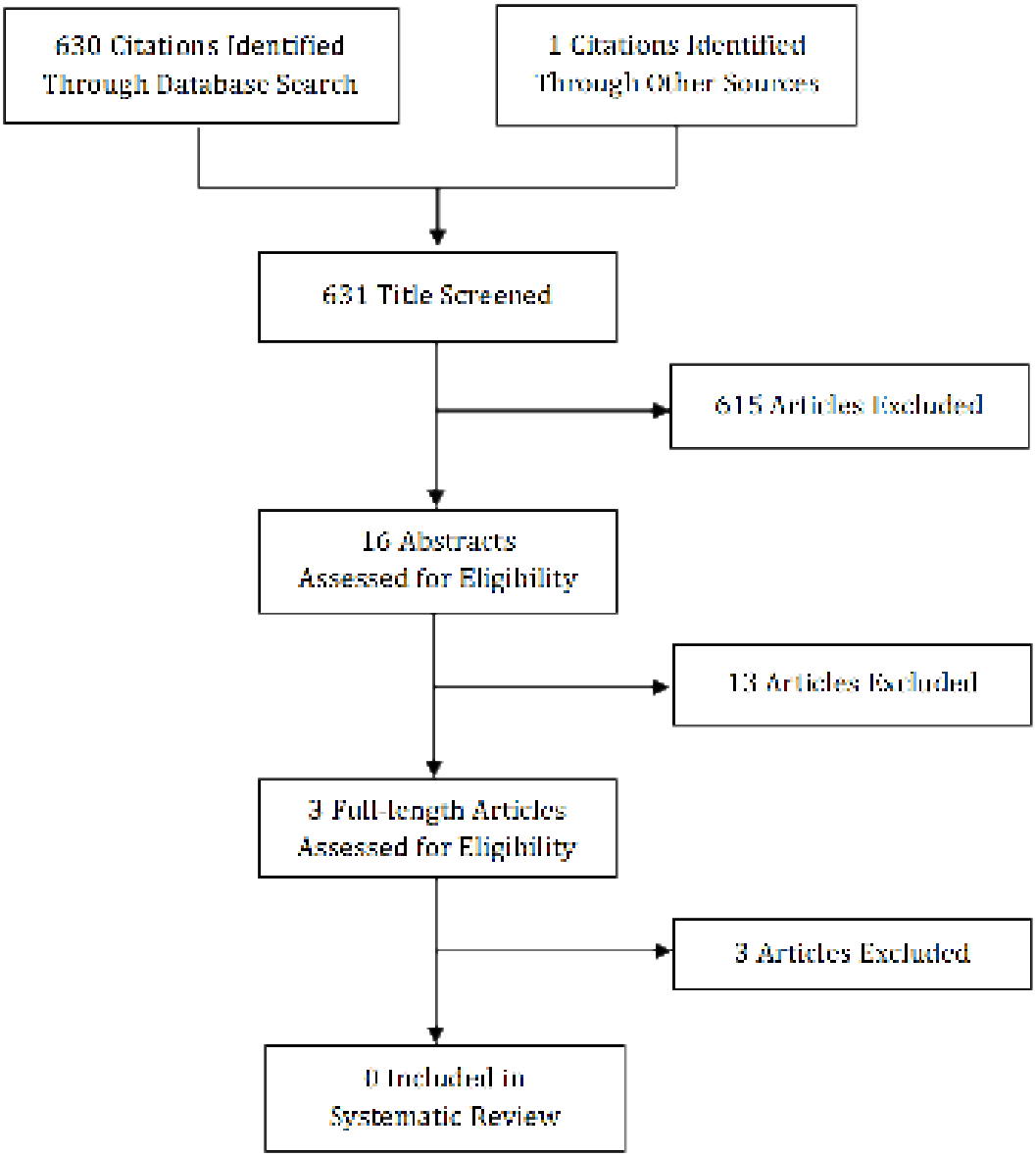

Fig. 14. The flow chart of the process and results of study selection

3. SOCIAL DISTANCING MEASURES

3.1. Contact tracing

Terminology

Contact tracing is the identification and follow-up of persons who may have come into contact with an infected person (76). Although contact tracing is often coupled with quarantine or provision of antiviral prophylaxis to exposed contacts, the term "contact tracing" does not involve these processes.

Methods

A literature search was conducted using PubMed, MEDLINE, EMBASE and CENTRAL (search date 12 November 2018). No language limit was applied for the literature search; however, literatures in languages other than English were excluded during full-text screening. The inclusion criteria were studies reporting the effectiveness of contact tracing on the control of influenza in non-health care settings. No limitation on study design was applied for study inclusion because preliminary works have identified no RCTs for this topic. Systematic reviews and meta-analyses, as well as studies involving clinical settings were excluded. Two reviewers independently (MF and SG) screened the titles, abstracts and full texts to identify articles for inclusion. Quality assessment of evidence was not conducted because no epidemiological study was included in this systematic review.

Results

The initial database search yielded 1188 articles, of which 75 were selected for full-text screening based on their title and abstract contents. Of these, 71 articles were excluded; the main reasons for exclusion of these articles include absence of discussion on effectiveness of contact tracing and irrelevance. The study selection process is detailed in Fig.15.

All four studies were simulation studies (*77-80*). None studied contact tracing as a single intervention; instead, this measure was studied in combination with other interventions, such as quarantine, isolation and provision of antiviral drugs (Table 14). Such combinations of interventions have been suggested to reduce transmission and delay the epidemic peak (*77, 79, 80*).

Reduction of impact

Wu et al. suggested in their simulation model of an influenza pandemic with a reproductive number (R_0) of 1.8 that the combination of contact tracing, quarantine, isolation and antivirals reduced the infection attack rate to 34% from the baseline of 74% (*77*). However, the addition of contact tracing on top of quarantine and isolation measures was suggested to provide only modest benefit, while at the same time greatly increasing the proportion of quarantined individuals. On the other hand, Fraser et al. found that it would be difficult to control influenza even with 90% contact tracing and quarantine, due to the presumed high level of presymptomatic or asymptomatic transmission in influenza (*79*).

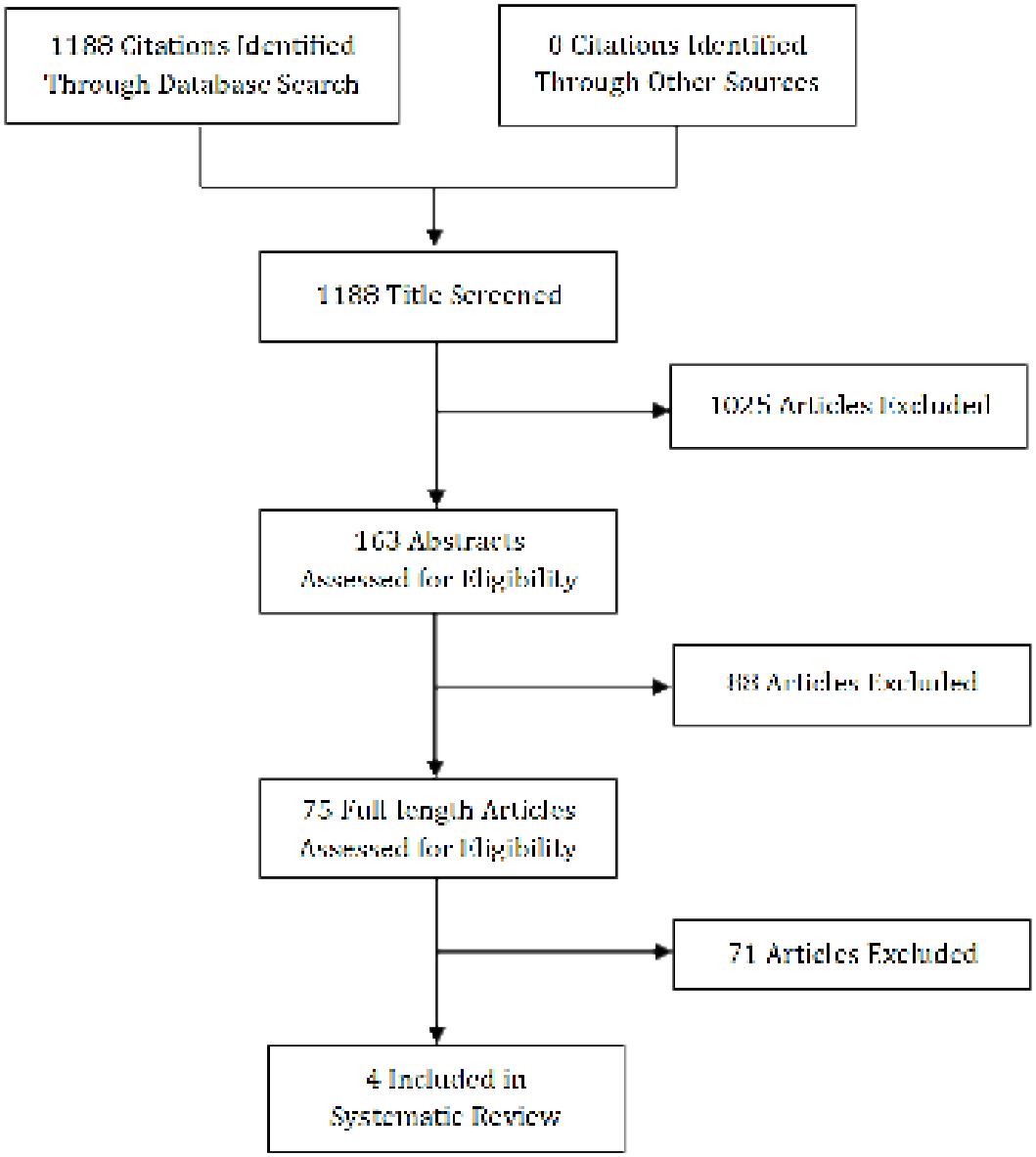

Fig. 15. The flow chart of contact tracing

Delay of epidemic peak

A combination of isolation, treatment of cases, contact tracing, quarantine and post-exposure prophylaxis for both community and household contacts, in addition to some household-focused measures, have been suggested to bring about delay in epidemic peak for up to 6 weeks, assuming a case detection rate of 10–30% (*80*). The study was set in the population structure of Germany in an epidemic with an R0 of 1.58. The authors assumed that the above combination of measures would be 75% effective in reducing secondary cases, while household-focused measures would be 50% effective.

Table 14. Summary of included studies

AUTHOR, YEAR PUBLISHED	TRANSMISSIBILITY OF THE INFLUENZA STRAIN (R_0)	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS
Wu JT, 2006 (*77*)	1.80	(1) Model based on distribution of household sizes and average numbers of children in household of different sizes in Hong Kong SAR (2) Constant introduction of 1.5 infected individuals per day per 100 000 people for 365 days (3) 70% of transmission occur outside home (in schools and workplaces)	Combination of contact tracing with other interventions such as quarantine, isolation and antivirals. When contact tracing was in effect, each compliant adult member of a household named on average five members of their peer group. Contacts were traced with a mean delay of 1 day. Contacts were asked to take precautionary measures. Interventions were active before arrival of infected individuals in the city	Combination of quarantine, isolation and antivirals reduce the baseline infection attack rate of 74% to 40%. Addition of contact tracing further reduce infection attack rate to 34%, but increase proportion of population in quarantine considerably
Peak CM, 2017 (*78*)	1.54	Initial infected population of 1000 individuals in early epidemic phase, assuming no substantial depletion of susceptible within first few generations of transmission	Symptomatic contacts were isolated immediately, contacts who were asymptomatic when identified were placed under either quarantine or symptom monitoring (at high performance, delay in contact tracing was 0.5 ± 0.5 days, 90% of contacts were traced, 50% were truly infected among traced contacts)	Combination of contact tracing with quarantine is more effective in reducing reproduction number than combination of contact tracing with symptom monitoring
Fraser C, 2004 (*79*)	Upper bound of R0 was 21	(1) Disease outbreak in its early stages in a community of homogenous mixing (2) Proportion of presymptomatic transmission is 30–50%	Isolation of symptomatic individuals, contact tracing and quarantine of a proportion of contacts that are infected prior to isolation of symptomatic individual. Isolation and quarantine were implemented without delay. Efficacy of isolation of symptomatic individuals considered were 75%, 90%, and 100%; contact tracing and isolation of infected contacts were 100% effective	Control of influenza is very difficult even at 90% quarantine and contact tracing, due to the high level of presymptomatic transmission
an der Heiden M, 2009 (*80*)	1.34, 1.58, 2.04	(1) Model based on the age distribution and size of the population of Germany: 71 000 000 adult population and 11 000 000 children (< 15 years old), entire population is fully susceptible at onset of the epidemic (2) Children are 2.06 times as susceptible as adults, 86% of infected individuals become symptomatic	(1) Intensive case-based measures (CCM1; consisting of isolation and therapy of cases, contact tracing, quarantine and post-exposure prophylaxis of selected contacts in- and outside of the household) (2) Less-intensive measures (CCM2; isolation and therapy of cases, quarantine and post-exposure prophylaxis of household contacts); CCM1 and CCM2 were set to be 75% and 50% effective in reducing secondary cases	(1) When the first 500 cases are managed with CCM1 followed by 10 000 cases managed by CCM2, the peak of epidemic is delayed for up to 6 weeks (R0 1.58, 5 imported cases per day, case detection rate 10–30%). If only CCM1 was adopted without CCM2, delay was estimated to be 6–20 days (case detection rate 10–30%). (2) Effectiveness of these combination of interventions is affected by the R0 of the influenza strain and case detection rate, i.e. higher R0 causes interventions to be ineffective at an earlier time point

CCM: combination of case-based methods; R0: basic reproductive number; SAR: Special Administrative Region.

Reduction in transmissibility

Peak et al. compared the combination of contact tracing with quarantine or symptom monitoring in the early phase of an epidemic with an R0 of 1.54 (*78*). The study suggested that contact tracing combined with quarantine was more effective than a combination with symptom monitoring in reducing transmission.

Ethical considerations

There are no major ethical issues. Identification of contacts of infected individuals does bring about privacy concerns; however, this may be justified because contact tracing does allow identification of persons at-risk and timely provision of treatment and care (81, 82). There may be more ethical concerns when contact tracing is coupled with measures such as household quarantine, discussed further in Section 3.3. As discussed in the results section above, contact tracing is able to increase substantially the proportion of people quarantined, but may not offer much additional benefit to existing interventions (*77*). A considerable amount of resources is also needed for contact tracing is these circumstances. Wu et al. suggested addition of contact tracing to existing interventions is only justified when the R0 can be reduced below 1 (*77*).

Methods

A literature search was conducted using PubMed, MEDLINE, EMBASE and CENTRAL (search on 5 August 2018). No language limit was applied for the literature search; however, literatures in languages other than English were excluded during full-text screening. The inclusion criterion is studies reporting the effectiveness of isolation on control of influenza in non-health care settings. No limitation on study design was applied for study inclusion as preliminary works have identified no RCT for this topic. Systematic review and meta-analyses, as well as studies involving clinical settings were excluded. Two reviewers independently (MF and SG) screened the titles, abstracts and full texts to identify articles for inclusion. Quality assessment of evidence was conducted for epidemiological studies for effectiveness of isolation on mitigation of influenza.

Results

The initial database search yielded 588 articles, of which 70 were selected for full-text screening based on their title and abstract contents. Of these, 56 articles were excluded; the main reasons for exclusion of relevant articles included absence of discussion on effectiveness of isolation and focus on health care setting. One other study for inclusion was identified through snowball searches. The study selection process is detailed in Fig.16.

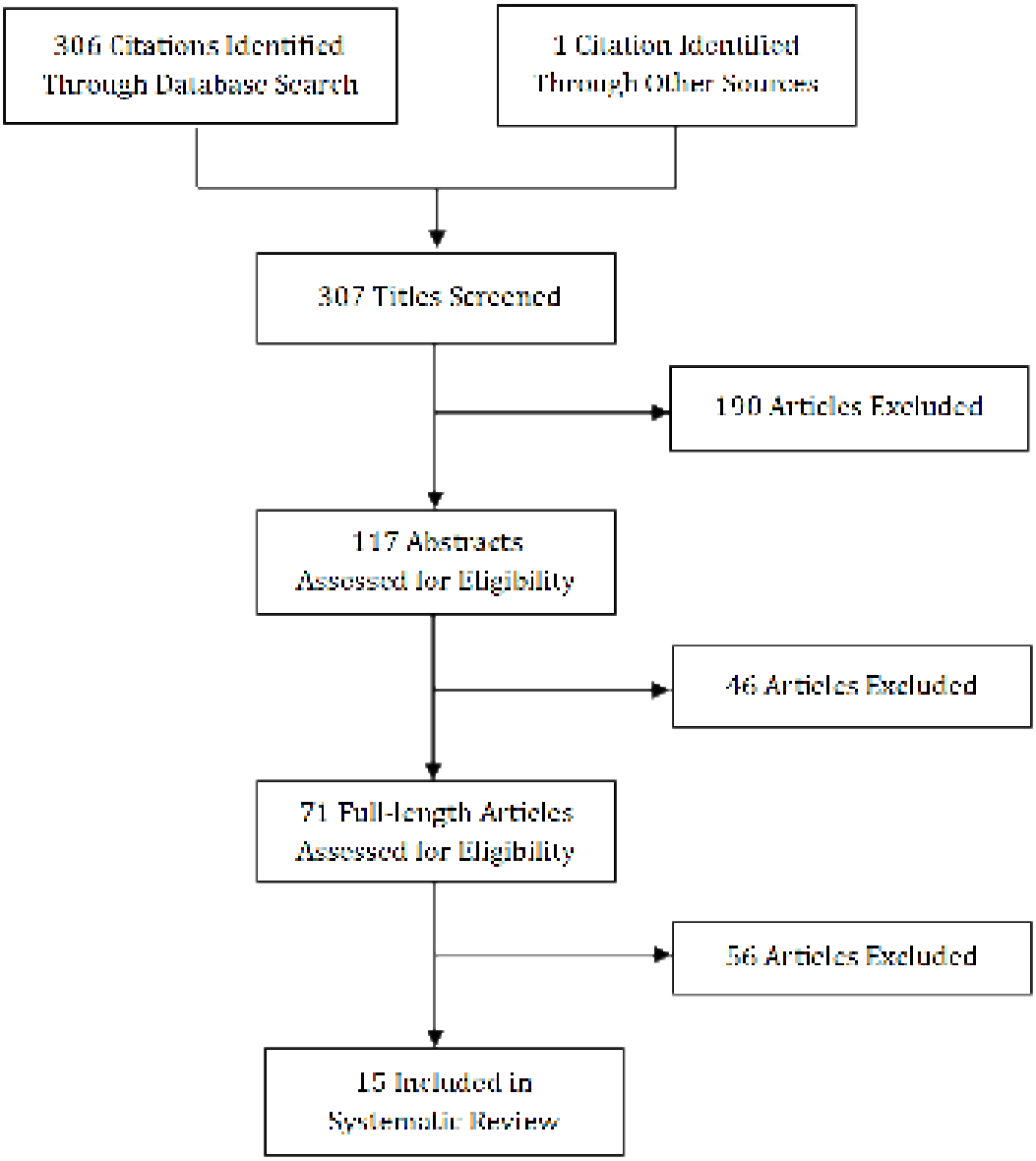

Fig. 16. The flow chart of isolation

Of the 15 included studies, four were epidemiological studies, of which one was an analysis of historical data from the 1918–1919 pandemic in 43 cities in the USA and three were outbreak investigations that occurred in a home for the elderly in France, a training camp in China and a Peruvian navy ship, respectively (Table 15) (*83-86)*. The remaining 11 were simulation studies (Table 16) (*77, 79, 87-94*). Case isolation was implemented in the outbreaks as a combination with various other interventions, such as antiviral prophylaxis and use of face mask. Case isolation was also studied as a single intervention or combined with other interventions in the 11 simulation studies. It is of note that the simulation studies were conducted based on a wide range of assumptions; for example, asymptomatic fraction and contact rate reduction brought forth by isolation, hence providing wide-ranging insights on effectiveness of isolation in different scenarios. These included studies focused mostly on reduction of attack rate, epidemic size, transmissibility and delay in epidemic peak as outcomes of interest. All but one study suggested a favourable impact of isolation, or combination of isolation with other interventions in epidemics with R0 1.5–2.0.

Reduction of impact

Eight studies suggested a decrease in attack rate brought about by implementation of case isolation (*77, 83, 86-91*). An individual-based simulation model for the United Kingdom and the USA suggested rapid case isolation could reduce the cumulative clinical attack rate from 34% to 27% for a pandemic with R_0 2.0, assuming uniform reductions in contact rates in schools, workplaces and households (*87*). Kelso and colleagues reported similar findings, in which case isolation alone was able to prevent an epidemic (<10% infected) in a community of 30 000 persons with R_0 1.5, when 90% of cases are isolated and such a measure is implemented within 3 weeks from the introduction of an initial case (*90*). While isolation alone has been suggested to be more impactful than other interventions, combination with other interventions further improved the effectiveness (*77, 89-91*). In addition, the increase in isolation rate is quasi-linearly correlated with the decrease in attack rate of influenza (*88*).

A reduction in the cumulative incidence of infections due to an isolation policy was also recorded during an influenza A(H1N1)pdm09 outbreak on a navy ship (86). A combination of isolating ILI cases, and use of masks and hand sanitizers was implemented. The clinical attack rate of the outbreak was 23.9%, a significant reduction from the 97% projected in the absence of any intervention. This also corresponded to a reduction in the effective reproduction number (R) from 1.55 to 0.7 with the intervention. Chu et al. reported similar findings in an outbreak in a physical training camp, in which the final attack rate recorded was about one quarter of the projected attack rate of 81% in absence of previous exposure, immunity and any interventions (*83*). In the 1918–1919 pandemic, excess death rates due to pneumonia and influenza decreased in New York City and Denver after isolation and quarantine were implemented (*85*).

On the contrary, Fraser et al. discussed the difficulty in controlling influenza even with high level of case isolation combined with contact tracing and quarantine, due to high proportion of asymptomatic transmission of influenza (*79*). The probability of isolation without increased public health effort by individuals in the community have also been suggested to be high, at 50% and 90% for adult and children respectively (*90*).

Delay of epidemic peak

The study by Flauhault et al. suggested that case isolation would have the strongest impact on global spread of a pandemic involving 52 cities, as compared to air-travel restrictions and antiviral treatment, such that isolation of 40% of cases would delay the epidemic by 83 days as compared to absence of any intervention (*88*). A combination of isolation of 10% of symptomatic cases with 60% reduction in air traffic, on the other hand, would delay the start of epidemics in each city by an average of 19 days, with considerable case reduction (88). The study by Wang et al. showed a similar effect, albeit focusing on arrival time of influenza pandemic, in which isolation of a moderate proportion of cases delayed the arrival of the pandemic in a subpopulation for about a month, in the circumstance of high compliance and early implementation (*92*). Delay in response will reduce significantly the effectiveness. Combined intervention with quarantine, school closure (SC), community-contact reduction, and personal protective measures further augmented the effect (*91*).

Table 15. Summary of epidemiological studies

AUTHOR, YEAR PUBLISHED	INFLUENZA STRAIN OR TRANSMISSIBILITY (R_0)	TYPE OF STUDY	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS	GRADE EVIDENCE
Chu C, 2012 (*83*)	A(H1N1)pdm09	Outbreak investigation	Outbreak in a physical training camp in China with 3256 persons	Combination of isolation with other interventions including oseltamivir treatment and prophylaxis, cancellation of training and group activities, face mask usage, ventilation and disinfection (implemented within a few days of surge in ILI)	(1) 72.7% clinical cases were reported before intervention, 27.3% after intervention. (2) The clinical attack rate recorded for the outbreak was 18.2%, while the projected attack rate in absence of previous exposure, immunity and any interventions was 80.9%	Very low
Gaillat J, 2008 (*84*)	Seasonal	Outbreak investigation	Outbreak in elderly home with 81 residents in summer (recorded attack rate of 39.5%)	Sick residents were immediately isolated and used face masks, oseltamivir treatment and post-exposure prophylaxis were given to residents and staffs	No new case was reported among residents and staffs within 2 days of implementation of intervention	Very low
Markel H, 2007 (*85*)	1918 pandemic H1N1	Analysis of historical data	43 large cities in the USA; utilized historical mortality data from the US Census Bureau and other historical archival documents	Combination of SC, public gathering bans, and isolation and quarantine (enforced and mandated respectively)	(1) All 43 cities implemented at least one intervention, and 15 cities implemented all three interventions. Cities that started implementation earlier had lower peak mortality and total mortality. (2) Excess death rate in New York decreased to baseline when isolation and quarantine were implemented, similarly in Denver when SC, isolation and quarantine were implemented	Very low
Vera DM, 2014 (*86*)	A(H1N1)pdm09	Outbreak investigation, stochastic model	Outbreak on a navy ship with 355 crews	Suspected ILI cases were placed in isolation, active case finding, face mask usage and hand hygiene, and antiviral provision	(1) Significant reduction in reproduction number during implementation of interventions (54.4%, from 1.55 to 0.7). The projected reproduction number without isolation was 4.5. (2) Clinical attack rate recorded was 23.9%, while the projected rate was 97%.	Very low

GRADE: Grading of Recommendations Assessment, Development and Evaluation; ILI: influenza-like illness; R0: basic reproductive number; SC: school closure; USA: United States of America.

Table 16. Summary of simulation studies

AUTHOR, YEAR PUBLISHED	TRANSMISSIBILITY OF THE INFLUENZA STRAIN (R_0)	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS
Flahault A, 2006 (*88*)	Constant (3.1) in tropical zone, 0.3–3.24 elsewhere with seasonal differences	(1) Spread of influenza pandemic to 52 cities globally from Hong Kong SAR via air transport (2) 25% of the population has pre-existing immunity, 60% of cases are symptomatic	(1) Combination of isolation (exclusion of 10% of symptomatic individuals from simulation) and 60% air traffic reduction (implemented since day 1) (2) Combination of (1) with antiviral treatment and vaccination	(1) Isolation reduced case number by 9% (2) Combination of isolation and air traffic reduction delayed time to reach epidemic status (1/100 000) in each city by an average of 19 days (3) Increasing isolation proportion to 40% delayed epidemic by an average of 83 days; combination of isolation, air traffic reduction, antiviral, vaccination reduced case number by 65%
Fraser C, 2004 (*79*)	Upper bound of R_0 was 21	(1) Disease outbreak in its early stages in a community of homogenous mixing (2) Proportion of presymptomatic transmission is 30–50%	Isolation of symptomatic individuals, contact tracing and quarantine of a proportion of contacts that are infected prior to isolation of symptomatic individual. Isolation and quarantine were implemented without delay. Efficacy of isolation of symptomatic individuals considered were 75%, 90%, and 100%; contact tracing and isolation of infected contacts were 100% effective.	Control of influenza is very difficult even at 90% quarantine and contact tracing, due to the high level of presymptomatic transmission.
Halloran ME, 2008 (89)	1.9–2.1, 2.4 and 3.0	(1) Model based on population of Chicago (8.6 million people) (2) 67% of influenza infections are symptomatic, case ascertainment levels are 60–80%	Combination of home isolation of ascertained cases (compliance 60% or 90%; isolated in but not from household members) with quarantine and other social distancing measures, implemented at intervention threshold of 1, 0.1, and 0.01%	At R_0 of 1.9–2.1, 60% ascertainment and 90% compliance, intervention threshold of 0.1%, attack rate was 0.17–1.2%, as compared to baseline scenario of 42.4–46.8%
Kelso JK, 2009 (*90*)	1.5, 2.5, and 3.5	(1) Population of 30 000, grouped into hubs of schools, workplaces and other facilities. Other contacts were biased towards meetings between neighbouring individuals (2) Asymptomatic fraction matched seasonal influenza	(1) Isolation (assumed isolated individuals only made household contacts, 90% and 100% chance respectively for adults and children to be compliant) (2) Combination of isolation with SC, workplace non-attendance and community-contact reduction	(1) At R_0 of 1.5, case isolation implemented within 3 weeks was the only single intervention capable of preventing an epidemic (≥10% attack rate), daily attack rate reduced from 90/10,000 to < 35 if introduced within a month (2) Combination of all four measures reduced attack rate from baseline of 33% to 9%, influenza control is more difficult at higher R_0

AUTHOR, YEAR PUBLISHED	TRANSMISSIBILITY OF THE INFLUENZA STRAIN (R_0)	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS
Saunders-Hastings P, 2017 (*91*)	1.5–2.5	(1) Model based on population of Ottawa–Gatineau census metropolitan area in 2011	Combination of isolation with other interventions including vaccination, antiviral treatment, prophylaxis, SC, community-contact reduction, personal protective measures and quarantine; best guess for adherence for voluntary isolation is 30%	(1) Combination of isolation and quarantine resulted in reduction of attack rate to 33.9%, from the baseline of 53.4%, lowest among all interventions studied. (2) Combination of isolation, quarantine, SC, community-contact reduction and personal protective measures reduced attack rate to 15.2% and delayed pandemic peak to more than 100 days
Zhang Q, 2015 (*94*)	2.5	(1) A community of households with distribution of household sizes based on Australian census data in 2001 (2) Chances of infection from community contacts is negligible as compared to infection from household member	Self-isolation or combination with antiviral prophylaxis (self-isolation assumed to have no impact on household contacts)	Self-isolation is able to overcome negative effect of delay in antiviral drug provision of 1 and 2 days by reducing household reproduction number, albeit compliance for self-isolation have to be significantly higher for 2-days delay
Zhang Q, 2014 (*93*)	1.5	(1) Stable population with homogenous mixing (2) Asymptomatic fraction is 0.5, and symptomatic cases are twice as infectious	Isolation or combination with antiviral prophylaxis	(1) Case isolation reduced reproduction number to below one (2) Combination of isolation and antiviral prophylaxis reduced substantially the cumulative number of infected individuals
Ferguson NM, 2006 (*87*)	1.4–2.0	(1) Model based on population density data and data on travel patterns of the USA and United Kingdom (2) 30% of transmission occurred in household, the rest in general community, workplaces and schools; asymptomatic fraction was 0.5	Rapid case isolation (assumed uniform reduction of contact including household contacts)	Rapid case isolation reduced cumulative attack rates from 34% to 27% for R0 2.0 if 90% of cases were isolated
Wu JT, 2006 (*77*)	1.80	(1) Model based on distribution of household sizes and average numbers of children in household of different sizes in Hong Kong SAR (2) Constant introduction of 1.5 infected individuals per day per 100 000 people for 365 days (3) 70% of transmission occur outside home (e.g. in schools and workplaces)	Combination of isolation and voluntary quarantine. Interventions were active before arrival of infected individuals in the city.	Combination of isolation and voluntary quarantine reduced the baseline attack rate of 74% to 43%.

AUTHOR, YEAR PUBLISHED	TRANSMISSIBILITY OF THE INFLUENZA STRAIN (R_0)	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS
Wang L, 2012 (*92*)	1.75	International spread of influenza to cities at early stage of a pandemic outbreak	Isolation (implemented by removing some infectious individuals from the simulation model)	Isolation of a moderate proportion of cases delayed the arrival of the pandemic for about a month, in the circumstance where cases were fully compliant and intervention was started at the first instance of the pandemic
Yasuda H, 2009 (*95*)	A(H1N1)pdm09	Community of 8800 individuals, with family structures based on Japanese census data	Home isolation of one in three adults and 70–90% of school-aged children	Total number of infections reduced by 33% when one in three adults and all children were isolated at home compared to baseline situation

R_0: basic reproductive number; SC: school closure; United Kingdom: United Kingdom of Great Britain and Northern Ireland; USA: United States of America.

Reduction in transmissibility

Zhang et al. showed in their simulation studies that isolation of cases can reduce the household reproduction number to below one, and compensate for a delay in antiviral drug distribution by 1 to 2 days. Compliance for self-isolation has to be significantly higher to offset longer delays (*93, 94*). An outbreak in a home for the elderly in France reported an abrupt cessation of outbreak after case isolation, antiviral treatment and prophylaxis were implemented (*84*). Reduction in eproduction number was also recorded in the navy ship outbreak previously described, by 54% from 1.55 to 0.7 with a combination of interventions (*86*). The projected reproduction number without implementation of isolation was 4.5.

Ethical considerations

Home isolation is commonly done voluntarily by ill individuals who do not feel well enough to work or engage in other daily activities (*88, 90*). Some ethical concerns may arise when isolation interventions are mandated, of which the main concern is freedom of movement (*96*). Studies on acceptability of isolation as an intervention to control influenza have also suggested the potential of social stigma as a concern for some individuals (97). Home isolation may also bring about increased risks of infection among household members, in the circumstances in which the contact rate between the infected individual with household members increase due to home isolation. Such risks can be reduced by adopting good precautionary measures such as wearing a face mask or employing hand hygiene. Such concern is more significant when concurrent quarantine of household members is mandated.

Knowledge gaps

Most currently available studies on effectiveness of isolation are simulation studies, which have a low strength of evidence. Available epidemiological studies studied isolation together with other interventions, or did not use laboratory confirmation as the outcome of interest. Although it is difficult to study isolation in an RCT, robust findings from such studies would be very valuable. In addition, in some of the relevant simulation studies, assumptions have been used to predict the effect of isolation on social contact rate, which in turn affect the transmission dynamics and control of influenza. Limited information exists at present for this aspect, as well as other commonly used assumptions including asymptomatic fraction, and dynamicity due to the nature of compliance behaviour, resource planning and distribution capacity (*77*).

3.2. Quarantine of exposed individuals

Terminology

Terms relevant to quarantine are defined in Table 17.

Table 17. Definition of terms relevant to quarantine

TERM	DEFINITION
Quarantine	Imposed separation or restriction of movement of persons who are exposed, who may or may not be infected but are not ill, and may become infectious to others (*98*).
Household quarantine	Confinement (commonly at home) of non-ill household contacts of a person with proven or suspected influenza (*2, 98*).
Home quarantine	Home confinement of non-ill contacts of a person with proven or suspected influenza.
Self-quarantine	Voluntary confinement of non-ill contacts of a person with proven or suspected influenza.

TERM	DEFINITION
Work quarantine	1) Measures taken by workers who have been exposed and who work in a setting where the disease is especially liable to transmit (or where there are people at higher risk from infection), e.g. people working in elderly homes and nurses in high risk units (*98*). 2) Measures taken by health care workers who chose to stay away from their families when off-duty so as not to carry the infection home (*98*).
Maritime quarantine	Monitoring of all passengers and crew for a defined period before disembarking from a ship is permitted in a jurisdiction (*99*).
Onboard quarantine	Monitoring of all passengers and crew for a defined period before disembarking from a flight is permitted (100). Also known as 'airport quarantine' (*100*).

Methods

Literature search was conducted using PubMed, MEDLINE, EMBASE and CENTRAL (search date 24 July 2018). No language limit was applied for the literature search; however, literatures in languages other than English were excluded during full-text screening. Studies reporting the effectiveness of quarantine on the control of influenza in non-health care settings were included. No limitation on study design was applied for study inclusion as preliminary works identified no RCT for this topic. Systematic review and meta-analyses, as well as studies involving clinical settings, were excluded. Two reviewers (MF and SG) independently screened the titles, abstracts and full texts to identify articles for inclusion. Quality assessment of evidence was conducted for epidemiological studies for effectiveness of quarantine on mitigation of influenza.

Results

The initial database search yielded 1873 articles, of which 120 were selected for full-text screening based on their title and abstract contents. Of these, 104 articles were excluded; the main reasons for exclusion of relevant articles include absence of discussion on effectiveness of quarantine and focus on health care setting. The study selection process is detailed in Fig.17.

The included studies were comprised of 10 simulation studies (Table 19) (*77, 80, 87, 89, 91, 101-105*). The epidemiological studies included one modelling study based on pandemic influenza A(H1N1)pdm09 transmission in Beijing (106), two analyses of historical data (1918–19 influenza pandemic in the USA and South Pacific, respectively) (*85, 99*), two observational studies and one a quasi-cluster-RCT in Japan (Table 18) (*100, 107, 108*). Quarantine measures studied include home quarantine, household quarantine, border quarantine as well as maritime quarantine. Quarantine were studied as a single intervention or as combination with other interventions, commonly with isolation and antiviral prophylaxis. These included studies focused mostly on reduction of attack rate, transmissibility and delay in epidemic peak as outcomes of interest.

Reduction of impact

Five studies suggested reduction in attack rate with implementation of household quarantine measures (77, 87, 89, 91, 107). Miyaki and colleagues conducted a quasi-cluster RCT in Japan in 2009–2010, which involved two clusters of company workers; the intervention was voluntary waiting at home on full pay if a family member was experiencing ILI. The intervention reduced risk and number of infections for members of the cluster and in the workplace involved (107).

Ferguson et al. reported in their simulation study that household quarantine were effective in reducing attack rate at R0 1–4.2, especially at low values (87). Combination of quarantine with other interventions such as household isolation with prophylaxis, SC and workplace distancing were suggested to further reduce the cumulative incidence of infections (77, 87, 89).

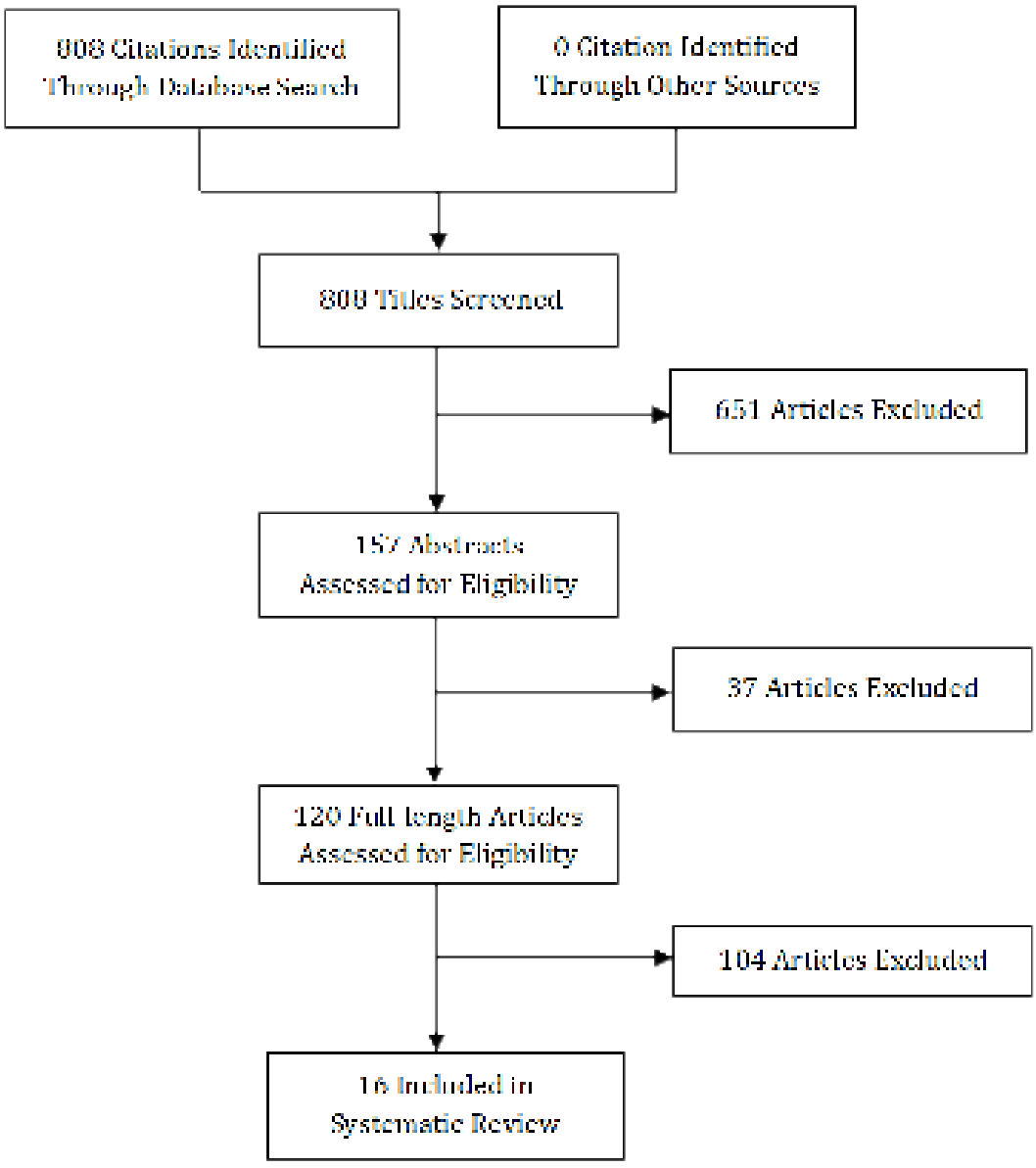

Fig. 17. The flow chart of quarantine

Household quarantine has also been suggested to be highly effective in reducing peak and total number of cases in a pandemic, provided that compliance is high (*105*). Longini et al. reported similar findings; that is, the effectiveness of household quarantine in reducing number of cases is conditioned by high compliance at 70% and relatively low R0, in addition to early implementation *(101)*. On the other hand, border quarantine has been suggested to cause minimal impact on reduction of number of cases (*104*).

Both analyses of historical data of the 1918–19 pandemic studied the effectiveness of interventions on mortality (*85, 99*). When a combination of isolation and quarantine was implemented, excess death rates due to pneumonia and influenza were shown to decrease in New York City and Denver (*85*). Maritime quarantine in the pacific islands have also delayed or prevented arrival of the epidemic, indirectly reducing mortality in the region (*99*).

Transmissibility

Both household quarantine and border quarantine have been suggested to reduce transmissibility, albeit with moderate effectiveness (*100, 102, 103*). Fujita et al. reported in their assessment of onboard quarantine inspection in Japan during the 2009 H1N1 pandemic, minimal impact in detecting and preventing entry of cases; however, following up with passengers thereafter was found to be effective in preventing secondary infection in the community from travellers (*100*). Nishiura and colleagues also suggested that border quarantine of 9 days would prevent 99% of entry of infectious travellers into small island nations (*102*).

Increased risk to household contacts

While reducing risk and number of infections in the intervention cluster, the quasi-cluster RCT of Miyaki et al. also reported that more individuals fell ill in the intervention group when there was an ill family member (*107*). The likelihood of a household contact (concurrently quarantined with an isolated individual) becoming a secondary case has been estimated to increase with each day of quarantine (*108*).

Table 18. Summary of epidemiological studies

AUTHOR, YEAR PUBLISHED	INFLUENZA STRAIN OR TRANSMISSIBILITY (R_0)	TYPE OF STUDY	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS	GRADE EVIDENCE
Markel H, 2007 (*85*)	1918 pandemic H1N1	Analysis of historical data	43 large cities in the USA; utilized historical mortality data from the US Census Bureau and other historical archival documents	Combination of SC, public gathering bans, and isolation and quarantine (enforced and mandated respectively)	(1) All 43 cities implemented at least one intervention, and 15 cities implemented all 3 together. Cities that started implementation earlier have lower peak mortality and total mortality; (2) Excess death rate in New York decreased to baseline when isolation and quarantine were implemented, similarly in Denver when SC, isolation and quarantine were implemented	Very low
Fujita M, 2011 (*100*)	A(H1N1)pdm09	Observational	Japan (passengers at Narita International Airport for onboard quarantine and Japan at-large for the outbreak)	Onboard quarantine was conducted for 500 flights carrying 120 069 passengers in Narita International Airport over 25 days. Patients identified by positive rapid test, and persons seated around them were isolated. If patient was subsequently confirmed of their infection by PCR, patient was isolated while persons seated around them were quarantined	Onboard quarantine detected few cases and was not effective in preventing virus entry into the country, however onboard quarantine improved traceability of travellers. Upon monitoring after travellers are in town, onward transmission/ secondary infection is prevented	Very low
Li X, 2013 (*106*)	A(H1N1)pdm09	Model based on epidemiologic dynamics of influenza A(H1N1)pdm09	Beijing (N = 20 million); utilized data of daily confirmed cases reported by Beijing Municipal Bureau of Health (May-July 2009)	Mandatory quarantine for all close contacts	Reduced number of cases at peak of epidemic to 5 times less than the projected scenario in which mandatory quarantine was not conducted, and delayed epidemic peak. Pandemic size remained the same and authors discussed on high economic and social costs of quarantine	Very Low

CI: confidence interval; GRADE: Grading of Recommendations Assessment, Development and Evaluation; ILI: influenza-like illness; PCR: polymerase chain reaction; R0: basic reproductive number; RCT: randomized controlled trial; SC: school closure; USA: United States of America.

Table 18. Summary of epidemiological studies

AUTHOR, YEAR PUBLISHED	INFLUENZA STRAIN OR TRANSMISSIBILITY (R_0)	TYPE OF STUDY	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS	GRADE EVIDENCE
McLeod MA, 2008 (*99*)	1918 pandemic H1N1	Analysis of historical data	South Pacific islands (including Australia); utilized archival data from national archives of relevant countries, government departments and international organizations	Maritime quarantine (monitoring all passengers and crew for on average 5–7 days before allowing disembarkation)	Strict maritime quarantine have delayed or prevented arrival of the pandemic in said jurisdictions, and associated with reduced mortality rate. Partial quarantine (routine release, without quarantine of asymptomatic passengers) in Fiji and Tahiti was unsuccessful, as in other jurisdictions that did not adopt any border control interventions	Very low
Miyaki K, 2011 (*107*)	A(H1N1)pdm09	Quasi-cluster-RCT	15 134 general employees (aged 19–72 years) of two sibling companies in Japan	Employees in intervention group were asked to stay home voluntarily if any co-habiting family members showed signs of ILI, until 5 days had passed since the resolution of ILI symptoms or 2 days after alleviation of fever, while on full pay. Employees in the control group reported to work as usual even if a household member developed ILI	Infection in workplace is significantly reduced among intervention group, however participants in this group are at higher risks of getting infected when there is an infected household member	Low
van Gemert C, 2011 (*108*)	A(H1N1)pdm09	Retrospective cross-sectional	Confirmed cases reported to the Victorian Department of Health, Australia from May-June 2009 (n = 36 index case-patients, 131 household contacts)	Antiviral drug usage (treatment and prophylaxis) and household quarantine	Odds of a household contact who was concurrently quarantined with the index case-patient becoming a secondary case-patient increased for each additional day (adjusted odds ratio 1.25, 95% CI 1.06–1.47)	Very low

CI: confidence interval; GRADE: Grading of Recommendations Assessment, Development and Evaluation; ILI: influenza-like illness; PCR: polymerase chain reaction; R0: basic reproductive number; RCT: randomized controlled trial; SC: school closure; USA: United States of America.

Table 19. Summary of simulation studies

AUTHOR, YEAR PUBLISHED	TRANSMISSIBILITY OF THE INFLUENZA STRAIN (R_0)	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS
an der Heiden M, 2009 (*80*)	1.34, 1.58, 2.04	(1) Model based on the age distribution and size of the population of Germany: 71 000 000 adult population and 11 000 000 children (< 15 years old), entire population is fully susceptible at onset of the epidemic; (2) Children are 2.06 times as susceptible as adults, 86% of infected individuals become symptomatic	(1) Intensive case-based measures (CCM1; consisting of isolation and therapy of cases, contact tracing, quarantine and post-exposure prophylaxis of selected contacts in- and outside of the household); (2) Less-intensive measures (CCM2; isolation and therapy of cases, quarantine and post-exposure prophylaxis of household contacts); CCM1 and CCM2 were set to be 75% and 50% effective in reducing secondary cases	(1) When the first 500 cases are managed with CCM1 followed by 10 000 cases managed by CCM2, the peak of epidemic is delayed for up to 6 weeks (R0 1.58, 5 imported cases per day, case detection rate 10–30%). If only CCM1 was adopted without CCM2, delay was estimated to be 6–20 days (case detection rate 10–30%); (2) Effectiveness of these combination of interventions is affected by the R0 of the influenza strain and case detection rate (i.e. higher R0 causes interventions to be ineffective at an earlier time point).
Saunders-Hastings P, 2017 (*91*)	1.5–2.5	(1) Model based on population of Ottawa–Gatineau census metropolitan area in 2011	Combination of quarantine with other interventions including vaccination, antiviral treatment, prophylaxis, SC, community-contact reduction, personal protective measures and isolation; best guess for adherence for quarantine is 15%	(1) Combination of quarantine and isolation resulted in reduction of attack rate to 33.9%, from the baseline of 53.4%, lowest among all interventions studied. (2) Combination of quarantine, isolation SC, community-contact reduction and personal protective measures reduced attack rate to 15.2% and delayed pandemic peak to more than 100 days
Ferguson NM, 2006(*87*)	1.4–2.0	(1) Model based on population density data and data on travel patterns of the USA and United Kingdom; (2) 30% of transmission occurred in household, the rest in general community, workplaces and schools; asymptomatic fraction was 0.5	Voluntary household quarantine for 14 days (assumed 50% compliance, external contact rates reduced by 75% and intra-household contact rate increased by 100%)	Voluntary household quarantine was effective in reducing attack rates in the community and delaying epidemic peak, in the circumstance where compliance is high. A combination of household quarantine and antiviral prophylaxis provision will further strengthen the effect, at the same time alleviate the ethical dilemma of household quarantine

AUTHOR, YEAR PUBLISHED	TRANSMISSIBILITY OF THE INFLUENZA STRAIN (R_0)	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS
Wu JT, 2006 (*77*)	1.80	(1) Model based on distribution of household sizes and average numbers of children in household of different sizes in Hong Kong SAR; (2) Constant introduction of 1.5 infected individuals per day per 100 000 people for 365 days; (3) 70% of transmission occur outside home (in schools and workplaces)	Combination isolation and voluntary quarantine (household quarantine of on average 7.5–8.2 days). Interventions were active before arrival of infected individuals in the city	Combination of isolation and voluntary quarantine reduced the baseline infection attack rate of 74% to 43%
Halloran ME, 2008 (89)	1.9–2.1, 2.4 and 3.0	(1) Model based on population of Chicago (8.6 million people); (2) 67% of influenza infections are symptomatic, case ascertainment levels are 60–80%	Combination of household quarantine (for 10 days with compliance of 30%, 60% or 90%) with isolation, and other social distancing measures, implemented at intervention threshold of 1, 0.1, and 0.01%	At R_0 1.9–2.1, 60% ascertainment and 90% compliance, intervention threshold of 0.1%, attack rate was 0.17–1.2%, as compared to baseline scenario of 42.4–44.7%
Sato H, 2010 (104)	2.3	(1) Population of 100 000 individuals (2) Transmission caused by cases undetected by onboard quarantine	Onboard quarantine combined with SC and home quarantine (with compliance of 10%, 30% and 50%; quarantined individuals were assumed to have no contact with infectious individuals for 3, 7 or 14 days)	The interventions were effective in reducing maximum number of daily asymptomatic cases and delaying the epidemic peak. Such effectiveness depends heavily on compliance; low compliance result in minimal impact. Home quarantine for 14 days with compliance of 50%, starting on day 6 was the most effective, which reduced number of cases by 44% and delayed the epidemic peak by 17 days
Longini IM Jr, 2005 (101)	1.4	Population of 500 000 individuals, with age and household sizes based on the Thai 2000 census (rural Thailand)	Household quarantine (contact probabilities within households and household clusters were doubled for quarantined individuals)	Household quarantine alone was effective in reducing number of cases. Early implementation and high compliance are needed for successful intervention

AUTHOR, YEAR PUBLISHED	TRANSMISSIBILITY OF THE INFLUENZA STRAIN (R_0)	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS
Nishiura H, 2009 (*102*)	1.67	Disease-free small island nation, which permitted arrival of 20 aircraft with a total of 8000 incoming individuals before closing all airports	Border quarantine – all incoming individuals were placed into routine quarantine on arrival, and were monitored for onset of symptoms. All infected individuals who develop influenza symptoms were successfully detected. Quarantine security was assumed to be fully effective and that no secondary transmission would occur in the quarantine facility	Reduction of 99% of risks of introducing infectious individuals into small island nations with quarantine period of 9 days. Combination with rapid diagnostic testing can reduce the quarantine period to 6 days
Roberts MG, 2007 (*103*)	2.0	(1) Population of one million persons (2) Proportion of symptomatic infective 67%, asymptomatic individuals have 50% infectivity as compared to symptomatic individuals	(1) Home quarantine (70% compliance) for 6 days, hence 56% of all transmission from those infected within their household is prevented. (2) Home quarantine (50% compliance), hence 40% of transmission from household contacts is prevented (3) Combination of home quarantine with SC, and targeted antiviral prophylaxis	Home quarantine alone was successful in reducing the reproduction number, as well as proportion of population infected. At higher transmissibility, R0 3.0, only the combination of home quarantine with SC and targeted antiviral prophylaxis is effective in preventing an epidemic
Yang Y, 2011 (*105*)	1.79	(1) Population of 8382 persons, with population and social structure based on the city of Eemnes	(1) Household quarantine (stay at home at all times with compliance 25%, 50%, 75%, and 100%). (2) Combination of household quarantine with SC and refrain from social activities; Delay between interventions and out-break threshold was less than one day	At 50% compliance, household quarantine reduced 22.4% and 20.8% total number of cases and peak cases respectively, as well as delayed epidemic peak. A combination of all 3 interventions did not add much benefit in reducing the total number of cases, however reduced the peak cases by 56%, and delayed the epidemic peak

CCM: combination of case-based methods; R0: basic reproductive number; SAR: Special Administrative Region; SC: school closure; United Kingdom: United Kingdom of Great Britain and Northern Ireland; USA: United States of America.

Delay of epidemic peak

Five studies reported the effectiveness of household quarantine, border quarantine and maritime quarantine in delaying peak of epidemic (*80, 91, 99, 104, 106*). As previously described, analysis of historical data suggested maritime quarantine effectively delayed or prevented arrival of the 1918–1919 pandemic in the pacific islands. Similarly, a model based on the 2009 H1N1 pandemic in Beijing reported delay in epidemic peak as compared to a projected scenario without mandatory quarantine (*106*). Combination with other interventions may improve effectiveness of quarantine (80). Saunders-Hastings et al. reported in their simulation study that a combination of quarantine with seven other interventions including voluntary isolation, SC, and personal protective measures can delay peak of pandemic for more than 100 days (*91*). On the other hand, as for reduction of impact, Sato et al. suggested minimal impact of border quarantine in delaying epidemic peak, mainly due to the low detection rate of cases (*104*).

Ethical considerations

As with isolation, the main concern of quarantine is freedom of movement of individuals (*106*). However, such concern is more significant for quarantine, because currently available evidence on effectiveness of quarantine varies and it involves restriction of movement of some healthy or non-ill individuals. Mandatory quarantine considerably increases such ethical concern as compared to voluntary quarantine (*96*). In addition, household quarantine can increase the risks of household members becoming infected, and such risk increases with the duration of quarantine (*87, 107, 108*). A combined policy of household quarantine with household prophylaxis has been suggested to be able to alleviate such concerns (*87*). Maritime quarantine and border quarantine are subject to similar concerns. On the other hand, onboard quarantine involves a shorter duration of restriction of movement, but currently available evidence has suggested the intervention to have low cost–effectiveness and minimal impact on influenza control.

Knowledge gaps

Most of the currently available evidence on effectiveness of quarantine on influenza control was drawn from simulation studies, which have very low strength of evidence. Available epidemiological studies did not rely fully on laboratory-confirmed influenza as the outcome of interest. While acknowledging the difficulties of studying quarantine in an RCT, robust data from experimental studies would be valuable. In addition, as part of simulation studies, assumptions have been used in various aspects of model construction, of which many still require more robust evidence, such as the asymptomatic fraction among all infections, as well as the possibility of superspreaders and the nature of compliance behaviour (*77, 102*).

3.3. School closures

Terminology

Closure of schools include scenarios either when virus transmission is observed in the school, or an early planned closure of schools before influenza transmission initiates. Types of closure are shown in Table 20 (*109*).

Table 20. The definition of SC terms

TERM	DEFINITION
School closure	School is closed to all children and staff.
Class dismissal	School campus remains open with administrative staff, but most children stay home.
Reactive Closure/ Dismissal	School is closed after a substantial incidence of ILI is reported among children and/or staff in that school.
Proactive Closure/ Dismissal	School is closed before a substantial transmission among children and staff is reported.

ILI: influenza-like illness.

Methods

The latest systematic review to review the effects of SCs on influenza outbreaks was published in 2013 by Jackson et al. (*110*). We conducted an additional search to update the systematic in PubMed, Medline, EMBASE and CENTRAL from 1 January 2011 to 4 September 2018. Inclusion criteria included study designs of RCTs, epidemiological studies and modelling studies reporting the effectiveness of SC in non-health care settings. Studies that described one or more influenza outbreaks, as well as the combination of SC and other NPIs, were also included. Modelling studies were included only if they used influenza surveillance data to evaluate the effectiveness of SC. Modelling studies based on stimulated data and/or on avian influenza virus, studies without school-specific data and studies published other than full report were excluded. Articles published other than English were also excluded after full-text screening. Two reviewers (SG and MF) independently screened titles, abstracts and full texts to identify the eligible articles. The quality of evidence was evaluated based on GRADE to assess the overall effectiveness of SC in mitigating influenza pandemics or epidemics, with seven specific metrics: reducing the epidemic peak, reducing overall attack rate, reducing incidence, reducing duration of the epidemic, reducing transmission, delaying the epidemic peak and reducing school absenteeism.

Results

The most recent systematic review was published in 2013, Jackson et al. identified 79 epidemiological studies on SCs and summarized the evidence as demonstrating that this intervention could reduce the transmission of pandemic and seasonal influenza among schoolchildren, but owing to the heterogeneity in the available data, the optimum strategy (e.g. the length of closure, reactive or proactive closure) remained unclear (*110*). The flow chart of study selection is shown in Fig. 19.

In the additional search to update the systematic review that was published by Jackson et al. in 2013, 287 papers were identified from the four databases and 12 citations were found from other sources, resulting in total of 299 citations for screening. Of these, 101 full-length articles were assessed for eligibility and 22 additional articles were identified. In total, 101 articles were included in our systematic review. The flow chart of study selection is shown in Fig. 18. The quality of evidence was assessed to be very low according to the GRADE criteria.

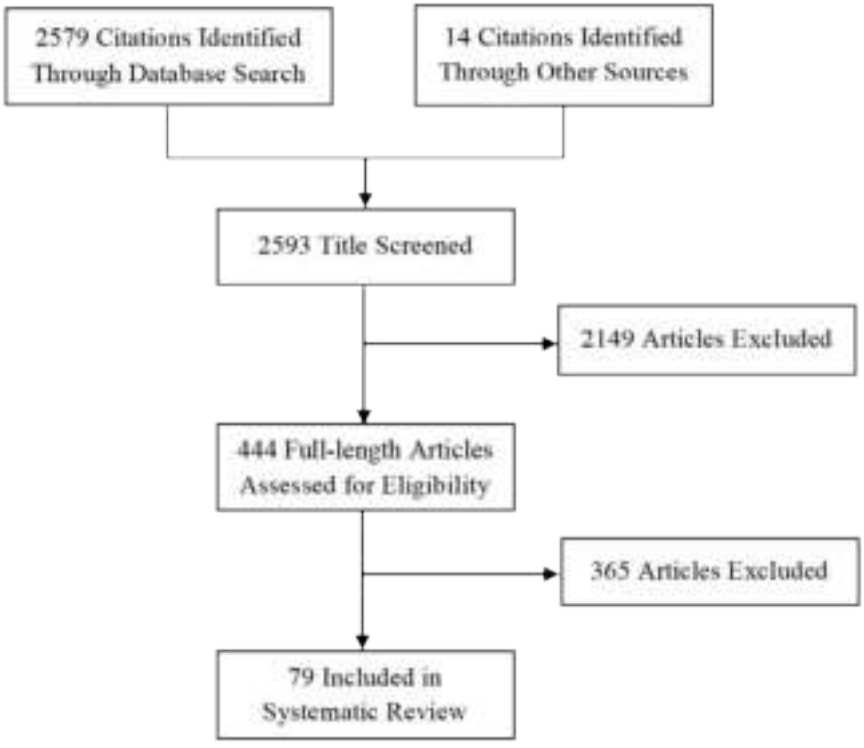

Fig. 18. The flow chart of systematic review by Jackson

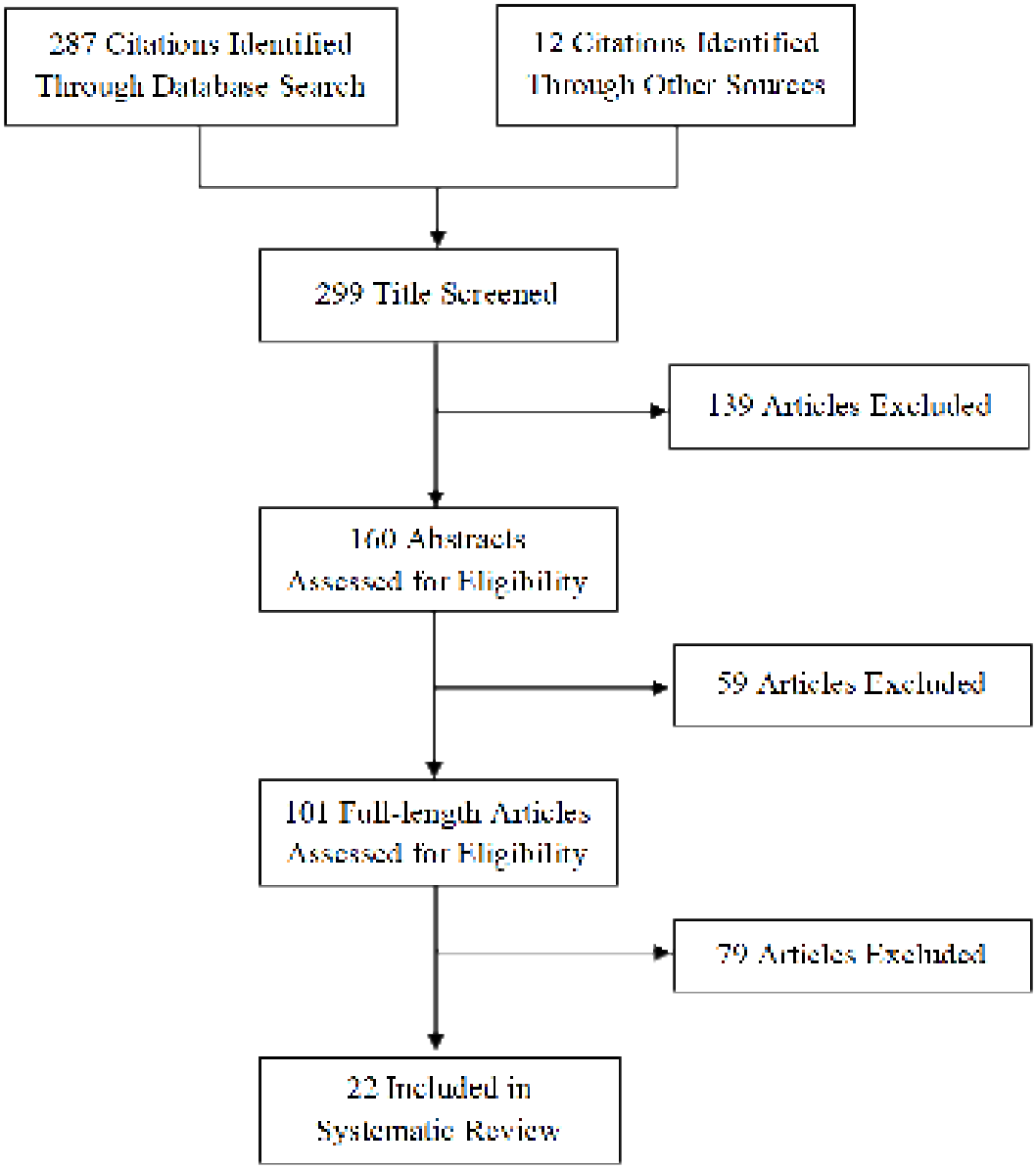

Fig. 19. The flow chart of updated studies in school closures

Among the included 101 articles, 16 articles presented data on reactive SCs (111-126), 13 articles examining proactive SCs (*85, 127-138*), 28 articles examined the impact of regular school holidays on transmission (*123, 125, 136, 139-163*), and 47 articles were related to outbreak reports or teachers' strike (*164-210*). The basic characteristic of the studies is shown in Table 21.

Table 21. Basic characteristic of the studies

	Number of studies (n=101)
Type of influenza strain	
Seasonal	30
1918 pandemic	7
1968 pandemic	1
2009 pandemic	62
Seasonal and 2009 pandemic	1
Study setting	
Asia	30
Europe	26
America	38
Africa	1
Australia	6
Nature of closure[a]	
Outbreak report or teachers' strike	47
Planned holiday	28
Reactive closure	16
Proactive closure	13
Duration of closure[b]	
7–13 days	40
14–20 days	24
≥ 21 days	22
< 7 days	13
Varied	8
Not clear	5

[a] A single article can contain different types of closure.

[b] Each study may present more than one dataset for which the durations of closure differed.

A total of 16 studies demonstrated that reactive SC could be a useful control measure during influenza epidemics or pandemics, with impacts that included reducing the incidence and reducing the peak size (Table 22). Several studies reported a reduction in number of confirmed or ILI cases (*114, 115, 117, 119, 123, 125, 126*). One study also showed a reduction in total infected cases by 32.7% (total reduced number of cases from 127.1 to 85.5) (*122*). Another observational study suggested a reduction in the peak of influenza epidemic curve by 24% during the 4-day closure, and also a reduction of the total number of infected students by 8% (*118*). However, two observational studies in China did not identify a significant difference on total attack rate between the control (SC not implemented) and intervention group (school closed) (*112, 113*). Two studies in the USA showed that absenteeism was lower after school reopening compared to before SC (*120, 121*).

Effectiveness of SCs can also be assessed by evaluating the transmission rate; that is, reproduction number. Hens el at. showed a reduction of the reproduction number from 1.33 (95% CI: 1.11–1.56) to 0.43 (95% CI: 0.35–0.52) after SC (116). An observational study from Japan reported that SC was more effective than class closure (dismissal of that particular class with substantial increase in influenza incidence) (126). In another study from Japan, a 2-day SC in the outbreak situation

(after a 10% of absentee occurrence in a school) was also shown to associate with the interruption of an outbreak within a week (124). One detailed study of transmission in a school in Pennsylvania identified no effect of the reactive closure that was implemented when 27% of students already had symptoms (*111*).

Effectiveness of proactive SC was studied in 13 articles (Table 23). A study showed that proactive SC had an advantage in delaying the epidemic peak for more than a week, affecting the modelled mean peak, and reducing the overall attack rate from 9.7% to 8.6% (*127*). Bootsma et al. estimated that early and sustained interventions, including SCs, reduced overall mortality by up to 25% in some cities (128). Hatchett et al. and Markel et al. also examined NPIs in the 1918–1919 pandemic, reporting that the combined use of NPIs including SCs were able to delay the time to peak mortality, and to reduce peak mortality and overall mortality (*85, 135*).

One study estimated a 29–37% reduction in influenza transmission by the 18-day period of mandatory SCs and other social distancing measures including closure of restaurants and theatres, and cancellation events (130). A study in Mexico City estimated that effective reproduction ratio declined from 1.6 before closure to less than 1 during closure (134). Wu et al. estimated that the reproduction number was reduced from 1.7 to 1.5 during the proactive closures and to 1.1 during the rest of the summer holiday (*138*). One study in Mexico showed a 80% reduction of contact rate during closure period and a subsequent planned holiday (*136*). However, closing kindergartens and primary schools for 2 weeks in Hong Kong SAR did not show any significant effect on community transmission, although the incidence remained low after the peak during proactive closure (133).

A total of 28 studies monitored the change of influenza incidence across planned school holidays (e.g. the scheduled winter holiday each year), to estimate the impact of SC on influenza transmission (Table 24). Eight of these studies illustrated that planned holidays could reduce influenza transmission (*136, 139, 141, 147, 148, 150, 159, 163*). One study demonstrated that school holidays reduced the R0 of influenza A(H1N1)pdm09 by 14–27% in different regions of India compared with non-holiday period (139). One study also reported an association of school holiday with a reduction of 63% to 100% in transmission in Canada (148). Another study reported a reduction of R0 from 1.25 to 0.79 during the 8 days-national holidays in China, but reported that the 8-week summer school holiday had a limited effect on incidence of ILI (*163*). Two studies in the United Kingdom and Mexico showed that SCs could reduce contact rate by around 48–80% (*136, 141*). Two studies in Belgium and the Netherlands suggested that holidays delayed the epidemic peak by more than 1 week, and reduced the peak incidence by 4–27% (*155, 160*). A study from the USA showed that absenteeism in Adrian reduced by approximately 6% (*157*), whereas Rodriguez et al. reported no difference between closed schools and those that did not close (*158*).

Observational studies also reported a reduction in incidence of influenza associated with planned school holidays (*123, 125, 140, 142-146, 149, 150, 152-154, 156, 159, 161, 162*). Studies showed that summer or winter holidays were associated with the reduction of ILI incidences by showing significant changes of ILI incidence rate ratios of schoolchildren to adults during the breaks (*143, 145, 153*). A study based on national surveillance data in France showed that routine school holidays prevented 18% of seasonal influenza cases (18–21% in children) (*142*). Another study in Japan estimated a 38% reduction in number of medically attended clinical ILI cases (*152*). Wheeler et al. suggested that planned holidays could prevent or delay potential influenza cases among school-age children by around 42% (*161*). In comparison, a systematic of simulation studies that reviewed the effects of SCs on influenza outbreaks found that this intervention can be a useful control measure during an influenza pandemic (*211*).

A study conducted a review on social distancing interventions in schools other than SC (212). A total of 16 articles met the inclusion criteria, and 16 states in the USA mentioned school practices to promote social distancing in the published guideline documents. The most frequent categories of school measures included cancelling or postponing after-school activities, increasing space among students, cancelling classes or activities, and reducing mixing during transport.

A simulation study showed that classroom restrictions (the children must remain seated while in their classroom) were the best single intervention at lower infection probabilities. At higher transmission rates, staggered shifts (each classroom follows one of three different schedules put forth by the school: the current schedule, a shift of 45 minutes, and a shift of 90 minutes) is the best single intervention (*213*). A study by Cooley et al. reported that a 3-day weekend for schools could be effective at reducing peak attack rate, and would be less detrimental than sustained SC (*214*). Closing the playground and other common areas could significantly reduce the total number of infected students (*215*). However, the evidence is limited on the effectiveness of school measures.

Ethical considerations

Apart from a potential health impact, SCs can have a substantial social impact by requiring parents to make other arrangements for care or supervision of their children, which can be particularly challenging for some families and for prolonged closures. In addition there may be social equity concerns; for example, because of access to subsidized or free food at school for lower income families (*121*).

Knowledge gaps

More research is needed on the best trigger factors, timing and duration of SCs in order to maximize the impact of this disruptive intervention.

Table 22. Summary table of reactive closure

AUTHOR, YEAR	REDUCE PEAK	REDUCE OVERALL ATTACK RATE	REDUCE INCIDENCE	REDUCE DURATION	REDUCE TRANSMISSION	REDUCE ABSENTEEISM
Cauchemez S, 2011 (*111*)	–	–	–	–	Reproduction number remained unchanged during SC and after the reopening of school (R = 0.3)	–
Chen T, 2017 (*112*)	–	Total attack rate of 1–3 week of SC were close to that for no intervention	–	Duration of outbreak was prolonged	–	–
Chen T, 2018 (*113*)	–	Total attack rate of 1–3 week of SC were close to that for no intervention	–	Duration of outbreak was prolonged	–	–
Davis BM, 2015 (114) [a]	–	–	ILI rate ratio changed from 3.13 (3 weeks before peak), to 2.75 (at peak) and 1.79 (3 weeks after the peak)	–	–	–
Egger JR, 2012 (115)	–	–	7.1% reduction in ILI case over the outbreak period	–	–	–
Hens N, 2012 (116)	–	–	–	– –	Influenza case reproduction number decreased from 1.33 (during outbreak before SC) to 0.43 (after SC)	–
Janjua NZ, 2010 (117)	–	–	Daily number of ILI cases declined during SC	–	–	–

ILI: influenza-like illness (fever plus cough and/or sore throat); SC: school closure.

AUTHOR, YEAR	REDUCE PEAK	REDUCE OVERALL ATTACK RATE	REDUCE INCIDENCE	REDUCE DURATION	REDUCE TRANSMISSION	REDUCE ABSENTEEISM
Kawano S, 2015 (*118*)[b]	Number of infected students in a SC decreased by 24% at its peak	Cumulative number of infected students decreased by 8.0%	–	–	–	–
Loustalot F, 2011 (*119*)	–	–	Incidence remained low during closure	–	–	–
Miller JC, 2010 (*120*)	–	–	–	–	–	Absenteeism was lower after reopening compared to before closure
Russell ES, 2016 (*121*)	–	–	–	–	Closing schools after a widespread ILI activity did not reduce ILI transmission	Absenteeism changed from 1% (baseline), to 3.62% (during SC), and 0.68% (after school reopening)
Sato T, 2013 (*122*)	–	Total number of infected persons decreased from 127.1 to 85.5; the maximum number of infected cases decreased from 63.7 to 53.1	–	–	–	–
Sonoguchi T, 1985 (*123*)	–	–	Number of cases declined from 16 on the day before closure to almost 13, 5 and 0 on the three days of closure in high school	–	–	–
Sugisaki K, 2013 (*124*)	–	–	–	Outbreak duration decreased by 4.98 days if the class is closed for 2 days upon the observed 10% ILI-related absentee rate	–	–
Uchida M, 2011 (*125*)	–	–	Incidence declined during closure period	–	–	–
Uchida M, 2012 (*126*)[c]	–	–	At elementary school, subsequent peak of H1N1 case showed up despite school or class closure (Fig. 1); at junior high school, SC significant reduced the number of H1N1 case but not in class closure (Fig. 2)	–	–	–

ILI: influenza-like illness (fever plus cough and/or sore throat); SC: school closure.
[a] ILI rate ratio is compared at school district level, with 51–100% of schools being closed, compared with district level, with 1–50% of schools being closed.
[b] Author mentioned the recommended period of SC is > 4 days.
[c] Closure duration is significantly related with the number of cases within the 7-day of school opening.

Table 23. Summary table of proactive closure

AUTHOR, YEAR	REDUCE PEAK	REDUCE OVERALL ATTACK RATE	DELAY TIME TO PEAK	REDUCE INCIDENCE	REDUCE TRANSMISSION
Bolton, 2012 (*127*)	–	Overall attack rate decreased from 9.7% to 8.6%[a]	Epidemic peak would be delayed by over a week	–	–
Bootsma MC, 2007 (*128*)[b]	Earlier intervention may reduce peak mortality	Earlier intervention may reduce total mortality	–	–	–
Caley P, 2008 (*129*)[b]	–	–	–	–	Transmission reduced by 38% during period of social distancing
Chowell G, 2011 (*130*)[b]	–	–	–	–	Reproduction number decreased from 2.2 (before SC) to 1.0 (during SC); transmission rate is estimated to reduce by 29.6% during the intervention period
Copeland DL, 2013 (*131*)	–	–	–	Incidence rate of ARI increased from 0.6% (before closure), to 1.2% (during SC) and dropped to 0.4% (after school reopening)	–
Cowling BJ, 2008 (*133*)[c]	–	–	–	–	Not found a substantial effect on community transmission
Cowling BJ, 2010 (*216*)[c]	–	–	–	–	The estimated reproduction number changed from 1.5 (initial peak) to below 1 (during proactive closure), and fluctuated between 0.8 and 1.3 through the school vacations
Cruz-Pacheco G, 2009 (*134*)[b]	–	–	–	Incidence increased to peak then decreased gradually during closure period	Effective reproductive ratio R(t) declined from 1.6 before to < 1 during closure

ARI: acute respiratory infection (presence of at least 2 of the following symptoms: fever, cough, sore throat and runny nose);
ILI: influenza-like illness (fever plus cough and/or sore throat); SC: school closure.
[a] Assuming schools were closed for 4 weeks and the attack rate in children was threefold higher than in adults.
[b] SC combined with other interventions.
[c] Proactive closure followed by planned holidays.

AUTHOR, YEAR	REDUCE PEAK	REDUCE OVERALL ATTACK RATE	DELAY TIME TO PEAK	REDUCE INCIDENCE	REDUCE TRANSMISSION
Hatchett RJ, 2007 (135)[b]	Earlier intervention reduced peak weekly excess pneumonia and influenza death rate	–	–	–	–
Herrera-Valdez MA, 2011 (*136*) [b]	–	–	–	–	Reduced contact rates by around 80% during closure period
Markel H, 2007 (85) [b]	Earlier intervention reduced peak excess death rate	Earlier and increased duration of intervention reduced total excess death	Earlier interventions increased time to epidemic peak	–	–
Tinoco Y, 2009 (*137*)	–	–	–	Number of ILI cases decreased throughout closure period	–
Wu JT, 2010 (*138*) [c]					The reproduction number was reduced from 1.7 to 1.5 during the proactive closures and to 1.1 during the rest of the summer holiday

[a] Assuming schools were closed for 4 weeks and the attack rate in children was threefold higher than in adults.

[b] SC combined with other interventions.

[c] Proactive closure followed by planned holidays.

Table 24. Summary table of planned holidays

AUTHOR, YEAR	REDUCE PEAK	DELAY PEAK	REDUCE OVERALL ATTACK RATE	REDUCE INCIDENCE	REDUCE TRANSMISSION	REDUCE ABSENTEEISM
Ali ST, 2013 (*139*)	–	–	–	–	Reproduction number reduced by 14–27% in different regions of India	–
Baguelin M, 2010 (*140*)	–	–	–	Incidence declined throughout the closure period	–	–
Birrell PJ, 2011 (*141*)	–	–	–	–	Reduce contact rate among 5–14 years old by 72% (summer holiday) and 48% (half term holiday)	–
Cauchemez S, 2008 (*142*)	–	–	–	Routine school holidays prevented 18% of seasonal influenza cases (18–21% in children)	–	–
Chowell G, 2011 (*144*)	–	–	–	Number of confirmed cases declined throughout closure period	–	–
Chowell,G, 2014 (*143*)[a]	–	–	–	Schoolchildren-to-adult ratios decreased by 40–68% during the 2-week period immediately preceding the winter break	–	–
Chu Y, 2017 (*145*)	–	–	–	ILI incidence rate ratio of age 5–14 (schoolchildren) to adult (aged above 60) declined by 13.3% during summer break	–	–
Davies JR, 1988 (*146*)	–	–	–	Clinical influenza cases increased during closure period	–	–
Eames KT, 2012 (*147*)	–	–	–	–	The initial growth rate of the epidemic during holidays would be 35% lower than during term time (from 1.57 to 1.07)	–

AUTHOR, YEAR	REDUCE PEAK	DELAY PEAK	REDUCE OVERALL ATTACK RATE	REDUCE INCIDENCE	REDUCE TRANSMISSION	REDUCE ABSENTEEISM
Earn DJ, 2012 (*148*)	_	_	_	_	Reduction in transmission rate in school-age children was 63%, 100% and 86% as a result of schools closing for the summer in Calgary, Edmonton and the province of Alberta as a whole respectively	_
Evans B, 2011 (*149*)	_	_	_	Estimated number of ILI cases declined during school holiday	_	_
Ewing A, 2017 (*150*)[b]	_	Fig. 5A suggested a peak delay	_	Fig. 5B illustrated a reduction of influenza incidence	Influenza transmission decreased by approximately 15% (from 1.1 to 0.9) in most seasons and decreased to < 1 immediately following Christmas	_
Flasche S, 2011 (*151*)	_	_	_	_	No evidence found of a relationship between the effective reproduction number and the start of school holidays	_
Fujii H, 2002 (*152*)	_	_	_	Number of ILI cases declined by 38% during the first week of closure (from 191 to 118 cases), then increased to 173 cases during the second week of closure	_	_
Garza RC, 2013 (*153*)	_	_	_	ILI incidence rate ratio reduced by 37% among children 5–14 years of age during the week after the winter school break	_	_
Herrera-Valdez MA, 2011 (*136*)[c]	_	_	_	_	Reduced contact rates by around 80% during closure period	_

AUTHOR, YEAR	REDUCE PEAK	DELAY PEAK	REDUCE OVERALL ATTACK RATE	REDUCE INCIDENCE	REDUCE TRANSMISSION	REDUCE ABSENTEEISM
Louie JK, 2007 (*154*)	_	_	_	ILI incidence declined throughout closure; laboratory-confirmed declined slightly first, then increased	_	_
Luca G, 2018 (*155*)[d]	Peak incidence reduced by 4%	All holidays delay the peak time of 1.7 weeks	Epidemic size reduced by approximately 2%	_	_	_
Merler S, 2011 (*156*)[e]	_	_	_	Incidence declined during closure	_	_
Monto AS, 1970 (*157*)	_	_	_	_	_	Absenteeism reduced by approximately 6% in Adrin
Rodriguez CV, 2009 (*158*)	_	_	_	_	_	No difference in post-break absenteeism in schools on holidays compared with schools that remained open at the same times (relative rate = 1.07, 95% CI = 0.96–1.20)
Smith S, 2011 (*159*)	_	_	_	Consultation rates decreased in school-aged children	Transmission of influenza may be interrupted in that school-age group	_
Sonoguchi T, 1985 (*123*)	_	_	_	Case number remained low during closure period in middle school	_	_
Te Beest DE, 2015 (*160*)	Epidemic peak is lowered by 27%	Peak is delayed for approximately 1 week	_	_	_	_

AUTHOR, YEAR	REDUCE PEAK	DELAY PEAK	REDUCE OVERALL ATTACK RATE	REDUCE INCIDENCE	REDUCE TRANSMISSION	REDUCE ABSENTEEISM
Uchida M, 2011 (*125*)	–	–	–	Incidence declined during closure period	–	–
Wheeler CC, 2010 (*161*)	–	–	Daily number of ILI cases declined during SC	Prevent or delay around 42% of potential influenza cases among school-age children	–	–
Wu J, 2010 (*162*)	–	–	–	Cumulative incidence of confirmed cases increased during SC	–	–
Yu H, 2012 (*163*)	–	–	–	–	Reproduction number changed from 1.25 (before National Day holiday), to < 1 (during that holiday), and 1.23 (after that holiday); National day holiday reduced the reproduced number by 37%	–

CI: confidence interval; ILI: influenza-like illness; SC: school closure.

[a] Decline in ratio is caused by a decrease in ILI rates among schoolchildren and the average reduction in ILI incidence among schoolchildren in the 2 weeks during the winter break compared with the 2 weeks before.

[b] The holiday model combined the changes associated with both the SC and travel models.

[c] All holidays included Fall holiday, Christmas holiday, Winter holiday and Easter holiday.

[d] Mainly planned holidays, some reactive closures.

[e] SC combined with other interventions.

Table 25. Summary of outbreak reports and teachers' strike

AUTHOR,YEAR	OUTCOME
Armstrong C, 1921 (*164*)	Number of cases peaked on the day following closure and declined thereafter
Baker MG, 2009 (*165*)	Start of the school holidays in New Zealand reduced influenza transmission and that the return to school slightly accelerated the epidemic
Briscoe JH, 1977 (*166*)	Number of clinical cases declined during closure
Calatayud L, 2010 (*167*)	Cases decline after the half way of SC
Carrillo-Santisteve P, 2010 (*168*)	Number of confirmed and probable cases declined during closure
Cashman P, 2007 (*169*)	A planned SC may have contributed to controlling the outbreak without quantitative information
Chieochansin T, 2009 (*170*)	Laboratory-confirmed cases declined throughout period of closure
Cohen NJ, 2011 (*171*)	Number of respiratory illness cases were lower on the first day of closure compared to previous days, increased during closure and then declined
Danis K, 2004 (*172*)	Number of ILI cases declined during closure period
Echevarria-Zuno S, 2009 (*173*)	Epidemic continued while schools were closed and peaked around 1 week after closure
Effler PV, 2010 (*174*)	Number of confirmed cases declined during closure period
Engelhard D, 2011 (*175*)	ILI rate peaked and declined during closure
Farley TA, 1992 (*176*)	Absenteeism remained low after school reopening
Glass RI, 1978 (*177*)	School absenteeism was lower after the holiday than before
Gomez J, 2009 (*178*)	Number of pneumonia cases decreased from 130 cases at peak to around 40 during closure
Grilli EA, 1989 (*179*)	During the mid-term break there were a further 15 ILI cases (daily cases not provided)
Guinard A, 2009 (*180*)	No further cases during SC period, but epidemic appear to be over before the school was closed

AUTHOR, YEAR	OUTCOME
Health Protection Agency West Midlands H1N1v Investigation Team, 2009 (*181*)	Confirmed number of cases declined during closure period
Heymann A, 2004 (*182*)[a]	Significant decreases in the rate of diagnoses of respiratory infections (42%), visits to physician (28%) and emergency departments (28%) and medication purchases (35%)
Heymann AD, 2009 (*183*)[a]	Decease in ratio of 14.7% for 6–12 years old associated with teachers' strike
Hsueh PR, 2010 (*184*)	Number of class suspensions or SC generally associated with the number of hospitalizations
Huai Y, 2010 (*185*)	Number of confirmed cases peak at 30 cases on the first day of closure, then declined during closure period
Janusz KB, 2011 (*186*)	Absenteeism changed from 8% (baseline), to 15% (2-days before school outbreak), and 13% (post-school outbreak)
Johnson AJ, 2008 (*187*)	Number of parentally-reported ILI cases decline because of SC
Jordan EO, 1919 (*188*)	Incidence declined from 19 cases to 15 cases the following week in elementary school, and declined from 16 to 5 cases in high school
Kawaguchi R, 2009 (*189*)	Number of confirmed cases declined throughout closure period
Lajous M, 2010 (*190*)	Planned holiday was followed by a slight decrease in ILI case numbers
Leonida DDJ, 1970 (*191*)	Absenteeism continued decline during second SC
Lessler J, 2009 (*192*)	Both confirmed H1N1 influenza and self-reported ILI declined through closure period
Leung YH, 2011 (*193*)	Number of laboratory-confirmed cases increased during first two days of closure and then declined
Lo JY, 2003 (*204*)	Change in proportion of positive specimens were 50–100% lower in April-June than the average because of community control measures
Marchbanks TL, 2011 (*194*)	Number of ILI cases increased during first two days of closure and then declined
Miller DL, 1969 (*195*)	In children aged 5–14 years, rates of influenza declined during the Christmas holidays

[a] Articles related to teachers' strike.

AUTHOR,YEAR	OUTCOME
Nishiura H, 2009 (*196*)	Number of laboratory-confirmed cases declined throughout the closure
Olson JG, 1980 (*197*)	School absenteeism (all-cause) declined in Girls Teachers' Colleges Primary School; absenteeism very similar before and after closure in Taipei American School
Paine S, 2010 (*198*)	Case numbers peaked and declined during holiday, effective reproduction number declined before holiday and continued to decrease during the holiday
Petrovic V, 2011 (*199*)	Weekly incidence rate of ILI and the number of hospitalized cases decreased after the SC
Poggensee G, 2010 (*200*)	Practice index was associated with vacation density
Rajatonirina S, 2011 (*201*)	Only few cases continued to occur during closure period
Shaw C, 2006 (*202*)	Absenteeism was lower after closure than before closure in both reactive closure and planned holiday
Shimada T, 2009 (*203*)	Number of new confirmed cases decreased after SCs
Smith A, 2009 (*206*)	Number of ILI cases declined during closure period
Strong M, 2010 (*207*)	Number of self-reported ILI cases declined during closure period
van Gageldonk-Lafeber AB, 2011 (*208*)	Possible reduced incidence, or slowed epidemic growth
Wallensten A, 2009 (*209*)	Absenteeism almost not changed before and after closure
WHO, 2009 (*205*)	School absenteeism in the following weeks did not increase after school reopening
Winslow CEA, 1920 (*210*)	Cities with SCs had higher deaths rates; timing and duration of closure were not stated

ILI: influenza-like illness; SC: school closure.

3.4. Workplace closures

Methods

PubMed, Medline, EMBASE and CENTRAL were searched until 18 September 2018. No language limits were applied but papers in languages other than English were excluded in screening. The inclusion criteria included RCTs, epidemiological studies and simulation studies reporting the effectiveness of workplace closure (WC) in non-health care settings, as well as the combination of WC and other NPIs. The exclusion criteria included the following: studies in health care settings; studies do not have specific data related to WC; review, letter, news or summary articles; studies related to avian influenza; and the language of articles not in English. Two reviewers (SG and ES) independently screened titles, abstracts and full texts to identify eligible articles.

Results

A total of 475 citations were identified through database search and other sources, of which 18 full-length articles assessed for eligibility and six articles were selected for this systematic review. The flow chart of study selection is shown in Fig. 20.

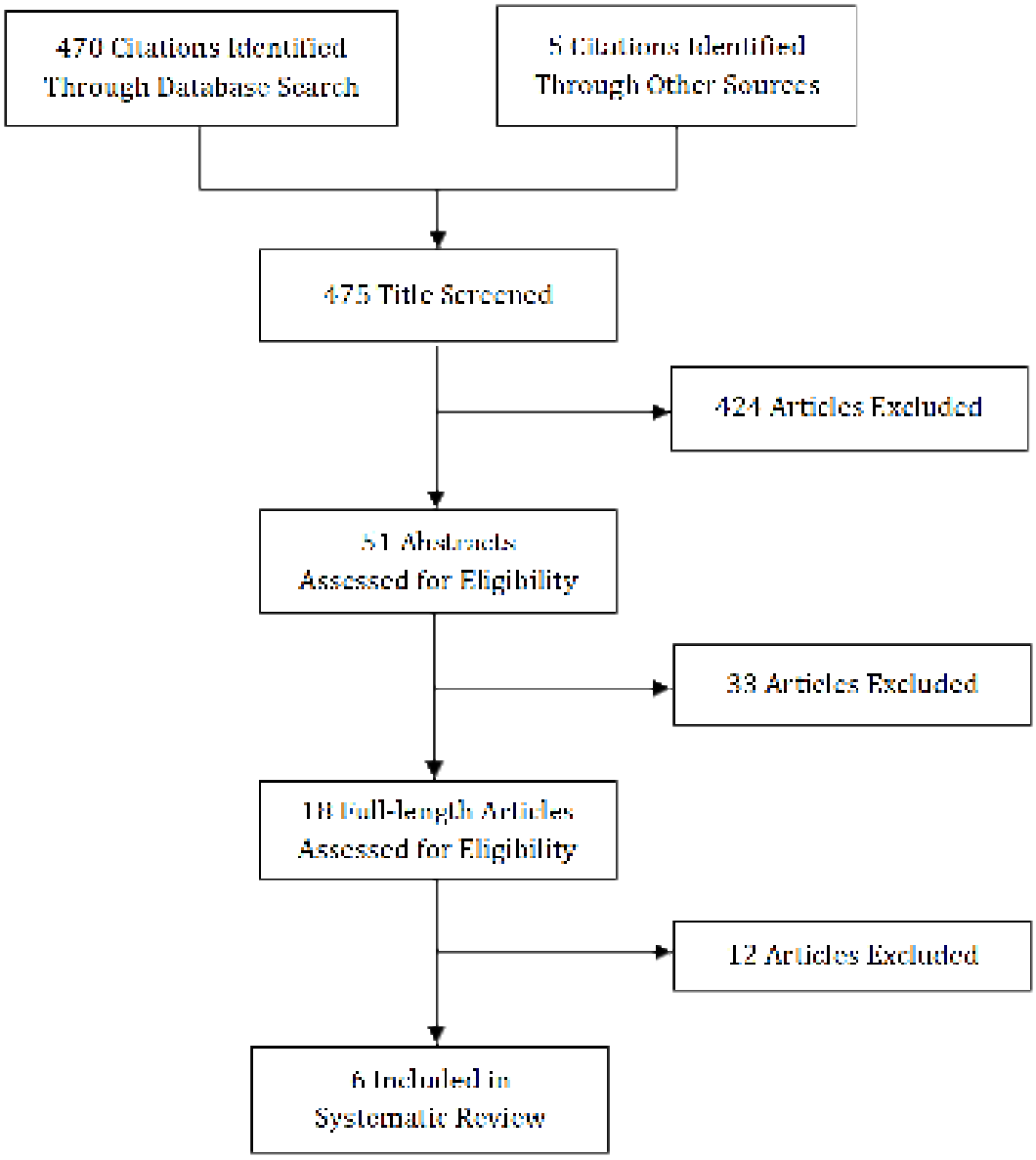

Fig. 20. The flow chart of workplace closure

Among these six studies, four were measured with SC, one targeted different single and multiple strategies, and another evaluated the effectiveness of WC alone (Table 26). All six studies represented simulation studies that met the inclusion criteria and the main outcome include the reduction of attack rate, peak number and delay of epidemic peak.

Predicted effects reduction

Five studies suggested the reduction in attack rate, infected duration or peak number. In the studies by Ferguson et al. (*87*) and Xia et al. (*217*), WC resulted in a small reduction in cumulative attack rate, while Carrat et al. (218) and Mao et al. (*219*) suggested an obvious decrease when assessing the effect of combining intervention. The study by Carrat et al. simulated individual and community level model in France, which suggested a decline of the cumulative attack rate from 46.8% to 1.1%, assuming the R0 of 2.07 (*218*). Mao et al. used an agent-based stochastic simulation model with R0 = 1.3–1.4 in the USA, and predicted a decline of overall attack rates from 18.6% to 11.9% with 100% SC and 10% WC, and from 18.6% to 4.9% with 100% SC and 33% WC (*219*).

A heuristic model using R0 of 1.7 and 2.0 suggested a small reduction in cumulative attack rate but a more substantial reduction in peak attack rates (up to 40%) when 100% SC and 10% WC was implemented. It also suggested that effectiveness could increase if 50% of workplaces were closed, but this would have a higher economic cost (*87*). A simulation model for the control of influenza in an isolated geographical region by Roberts et al. suggested the single WC strategy could not prevent the epidemic (with R0 = 2.0).

Delay the time of peak occurrence

Delaying the epidemic peak is another factor to consider the effectiveness of this intervention. A simulation study using individual-based model suggested that nationwide closure of schools and workplaces for weeks would delay the time of peak occurrence by 5–8 days, depending on the R0 = 1.4, 1.7 and 2.0 (*220*). However, the study by Mao et al. suggested that 100% SC and 33% WC could advance the peak by approximately 1 week (*219*).

Ethical considerations

Apart from a potential health impact, WC can have a substantial impact on the economy and productivity of the society (*221*).

Knowledge gaps

As with SCs, more research is needed on the best trigger factors, timing and duration of WCs in order to maximize the impact of this disruptive intervention.

Table 26. Description of studies included in the review of WCs

STUDY	INFLUENZA STRAIN & TRANSMISSIBILITY (R_0)	STUDY SETTING AND POPULATION	STUDY DESIGN	CLOSURE DURATION	CLOSURE PROPORTION	CLOSURE THRESHOLD	INTERVENTION	OUTCOME
Carrat F, 2006 (*218*)	Future pandemic strain; R_0 = 2.07	General population in France (n = 10 000)	Simulation both individual and community level	N/A	N/A	5 infections per 1000 subjects	SC + WC	Mean accumulation infection rate reduced from 46.8% (42.3–50.5%) to 1.1% (0.6–2.1%)
Ciofi degli Atti ML, 2008 (*220*)	Future pandemic strain; R_0 = 1.4, 1.7, 2	General population in Italy (n = 56 995 744)	Global SEIR model for importation of cases with an individual-based model	4 weeks	N/A	N/A	SC + WC	Nationwide closure could delay the time of peak occurrence by 5–8 days, based on various scenarios
Ferguson NM, 2006 (*87*)	Future pandemic strain; R_0 = 1.7, 2.0	300 million in USA, 58.1 million in United Kingdom	Heuristic model	N/A	Varied: 10%, 50%	N/A	100% SC + varied WC (10%, 50%)	100% SC + 10% WC could slightly reduce the cumulative attack rate, and might reduce the peak attack rate of up to 40%; 50% of WC could further improve the effectiveness with a higher economic cost
Mao L, 2011 (*219*)	Future pandemic strain; R_0 = 1.3–1.4	Urbanized area of Buffalo, NY, USA (n = 985 001)	Agent-based stochastic simulations	N/A	Varied: 10%, 33%	N/A	1) 100% SC + varied (10%, 33%) WC; 2) 100% SC + varied (10%, 33%) WC + preventive behaviour	1) Overall attack rates declined from 18.6% to 11.9% (10% WC) and 4.9% (33% WC), respectively 2); overall attack rate reduced to 3.99% (10% WC) and 1.83% (33% WC), respectively
Roberts MG, 2007 (*103*)	Future pandemic strain; R_0 = 1.1, 2.0 and 3.0	Isolated geographical region (n = 1 000 000)	A model based on published parameters	N/A	70%	N/A	1) WC; 2) WC + SC; 3) WC + SC + antiviral treat + 70% home quarantine	The single strategy of WC is not successful, the combination of four strategies would prevent the epidemic
Xia H, 2015 (*217*)	Simulate H1N1; R_0 = 1.35, 1.40, 1.45, 1.60 (all similar to R_0 = 1.35)	Delhi, India (over 13 million)	Realistic individual-based social contact network and agent-based modelling	3 weeks	60%	Over 0.1% population are infected	Single: WC	Intervention could reduce the attack rate and peak number, and delay the time of peak occurrence; single WC is the most ineffective method among vaccination, antiviral drugs, SC and WC

N/A: not applicable; NY: New York; R0: basic reproductive number; SC: school closure; SD: standard deviation; SEIR: susceptible–exposed–infectious–recovered; United Kingdom: United Kingdom of Great Britain and Northern Ireland; USA: United States of America; WC: workplace closure.

3.5. Workplace measures

Methods

The latest systematic review to review the effects of workplace measures in reducing influenza virus transmission was published by Ahmed et al. in 2018 (*222*). We conducted an additional search in PubMed, Medline, EMBASE and CENTRAL from 1 January 2017 to 28 September 2018. Workplace measures includes teleworking, flexible leave policies, working from home, weekend extension, segregation into smaller groups and social distancing at workplaces. All RCTs, epidemiological studies or simulation studies in non-health care workplaces were included in this review. Review, commentary, editorial articles, studies on WC and studies on generic social distancing not in workplace were excluded from our review. The following outcomes were extracted from the studies: cumulative attack rate, peak attack rate, occurrence of peak and other effects. Two reviewers (SG and ZX) worked independently. The GRADE method was used to evaluate the quality of evidence for the effectiveness of workplace measures in reducing influenza transmission.

Results

The most recent systematic review was published in 2018; Ahmed et al. identified 15 epidemiological or simulation studies (from 14 articles) on workplace measures. In the additional search to update the systematic review that was published by Ahmed et al., 81 articles were identified from the databases and one paper from other sources, resulting in total of 82 for title screening. Ten full-length articles were assessed for eligibility and four additional articles were identified. In total, 19 studies (18 articles) were included in our systematic review. The flow charts of study selection are shown in Fig. 21 and Fig. 22.

Among the included 19 studies, there were six epidemiological studies (Table 27) (*107, 223-227*). A cross-sectional study that randomly selected US adults from the Knowledge Networks online research panel showed that those who could not work from home from 7 to 10 days were more likely to have ILI symptoms compared to those who could (*223*). Another cohort study suggested that respondents who could work from home had a 30% lower rate of attending work with severe ILI symptoms compared to employees without such ability, which may be able to reduce employee-to-employee transmission (*225*). A cohort study in Singapore estimated that the intervention of enhanced surveillance and segregation of units into smaller working subgroups had significant lower serologically confirmed infections compared to those with standard pandemic plan (17% versus 44%) (*224*). A RCT study evaluated the effectiveness of voluntary waiting at home on full pay measure against influenza A(H1N1)pdm09 transmission in workplaces showed an overall risk reduction by 20% (*107*). Piper et al. (*227*) and Asfaw et al. (*226*) used the resources data from nationally representative survey in the USA, and illustrated that adults with paid sick days had a higher probability of staying at home and hence reduced the face-to-face transmission in workplace.

The remaining 13 studies were simulation studies (*89-91, 228-236*). The 12 simulation studies from the review by Ahmed et al. suggested that the workplace measure alone reduced the cumulative attack rate by 23%, as well as delaying and reducing the peak influenza attack rate (*89, 90, 228-236*). A study in Ottawa suggested that working from home measure combined with other interventions could reduce the illness attack rate from 55% to 8% (*91*).

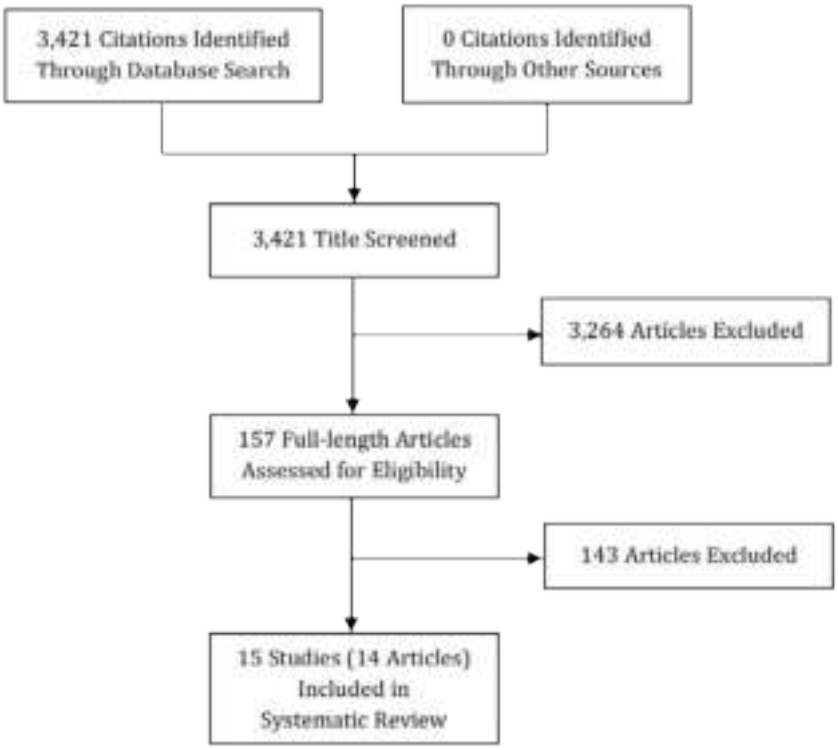

Fig. 21. The flow chart of systematic review by Ahmed

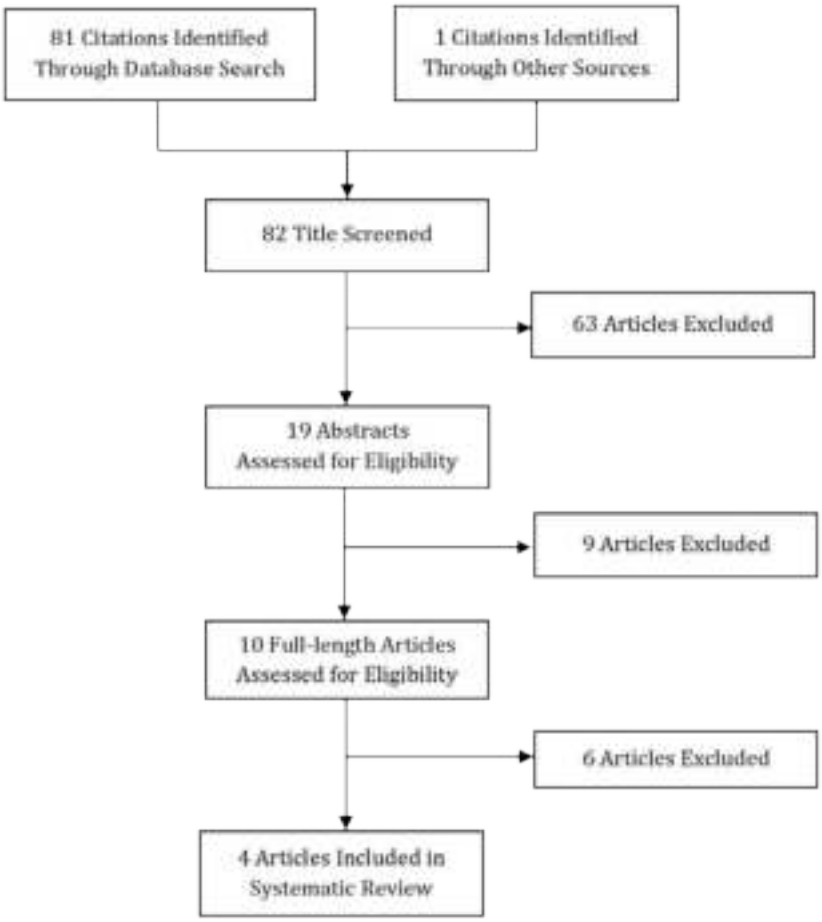

Fig. 22. The flow chart of updated studies in workplace measures

Ethical considerations
Similar to WC, workplace measures could affect the economy and productivity of the society.

Knowledge gaps
A comprehensive review of the ethical issues of workplace measures is lacking, as is a comparison of the benefits and costs of implementing the measures. Other workplace measures have not been studied in depth, such as providing separate studios for people with ILI. In addition, the studies on feasibility and scope of implementation of workplace measures, and the potential impact on families and society transmission are limited.

Table 27. Description of epidemiological studies included in the review of workplace measures

STUDY	STUDY DESIGN	INFLUENZA STRAIN	POPULATION AND SETTING	INTERVENTION	OUTCOME	QUALITY OF EVIDENCE
Asfaw A, 2017 (*226*)	National representative survey	Influenza A(H1N1)pdm09	71 200 people in the USA	Single: paid sick leave	Employees with paid sick leave have a 32% higher probability of staying at home than workers without paid sick leave, which might reduce the transmission of influenza	Very low
Kumar S, 2012 (*223*)	Cross-sectional study	Influenza A(H1N1)pdm09	Nationally representative sample (n = 2079) of USA	Single: can work from home	The people who unable to work at home were more likely to have had ILI (P< 0.05)	Very low
Lee V, 2010 (*224*)	Cohort study	Influenza A(H1N1)pdm09	Singapore military personnel (n = 437 in control group and n = 470 in intervention group)	Multiple: enhanced surveillance and segregation of units into smaller working subgroups	Confirmed infections were significantly (p< 0.001) lower in intervention group (17%) than in the control group (44%)	Very low
Miyaki K, 2011 (*107*)	Quasi-cluster-RCT	Influenza A(H1N1)pdm09	Two sibling companies (Cohort 1 n = 6634, Cohort 2 n = 8500) in Kanagawa Prefecture, Japan	Single: Voluntary waiting at home on full pay if the family became ILI	The intervention reduced around 20% of overall infection risk in the workplace	Low
Rousculp M, 2010 (*225*)	Cohort study	2007–2008 seasonal influenza	793 employees with ILI in three large US companies	Single: can work from home	Employees who could telework had a 29.7% lower rate of attending work with severe ILI symptoms, which indicated that implement teleworking policies may be able to reduce employee-to-employee transmission	Very low
Piper K, 2017 (*227*)	National representative survey (3 rounds interviews in 2009)	Influenza A(H1N1)pdm09	12 044 employees over 16 years old in the USA	Single: paid sick days	Individuals with paid sick leave are more likely to stay at home in order to reduce the influenza transmission in workplace	Very low

ILI: influenza-like illness; RCT: randomized controlled trial; USA: United States of America.

3.6. Avoiding crowding

Methods

The citations were identified from PubMed, Medline, EMBASE and CENTRAL until 18 October 2018. Two reviewers (SG and ES) screened each title, abstract and article that met the criteria in full. Both epidemiological and simulation studies relative to the effectiveness of avoiding crowding (e.g. cancellation or postpone of events and limitation of attendance) in public area are included. Studies that only report an outbreak event in a crowded area or perceptions on mass gathering but without specific data related to the effectiveness of avoid crowding and studies published in review, letter, news or summary articles were excluded. The effectiveness of cancelling, postponing or limiting attendance in reducing influenza transmission was used when examined the quality of evidence by GRADE.

Results

We identified three studies for the systematic review after reviewing 815 titles and 121 abstracts identified from databases and other sources. The flow chart is shown as Fig. 23. Among these three articles, two of them were based on the 1918 influenza pandemic and one focused on World Youth Day gathering in 2008 (details shown in Table 28).

Hachett et al. and Markel et al. reported a strong association between the early implementation of interventions and the mitigation of pandemic influenza. The study by Markel et al. showed three major categories for NPI: SC, cancellation of public gatherings, and isolation or quarantine in 43 cities in the USA. SC combined with a ban on public gatherings was the most common intervention with a median duration of 4 weeks, which can significantly reduce weekly excess death rate (EDR). Also, early implementation led to greater delays in reaching peak mortality (Spearman $\rho = -0.74$, $P < 0.001$), lower peak mortality rates (Spearman $\rho = 0.31$, $P = 0.02$) and lower total mortality (Spearman $\rho = 0.37$, $P = 0.008$) (*85*). There was a statistically significant association between increased duration of interventions and a reduction in total mortality burden (Spearman $\rho = -0.39$, $P = 0.005$) (*85*). Another study by Hatchett et al. also emphasized the early bans on public gathering, closure public places implementation in reducing the EDR (135). In addition, the basic group accommodation for 1 week during World Youth Day was described by Staff el at. (*237*). People accommodated in a single large place (17.2%) had a significantly higher attack rate compared with people who lived in small classrooms (9.2%) in the context of mass gatherings ($p < 0.01$) (*237*).

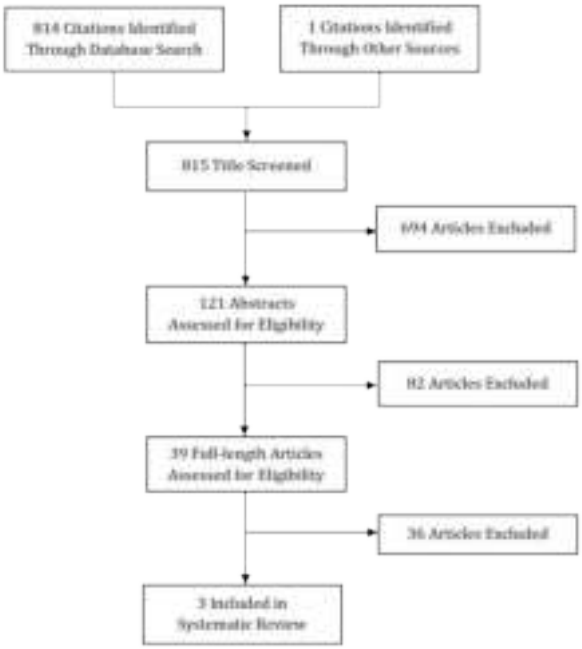

Fig. 23. The flow chart of avoiding crowding

Table 28. Description of studies included in the review of avoiding crowding

STUDY	INFLUENZA	INTERVENTION	OUTCOME	QUALITY OF EVIDENCE
Hatchett RJ, 2007 (*135*)	1918 Pandemic	Early church closure, theatre closure and bans on public gathering	Associated with lower peak excess death rates (Spearman $\rho = 0.56$, $\rho = 0.56$, $\rho = 0.46$ separately)	Very low
Markel H, 2007 (*85*)	1918 Pandemic	Multiple: SC + cancellation of public gatherings + isolation and quarantine.	Implemented earlier and longer duration are significantly associated with the reduction of influenza transmission	Very low
Staff M, 2011 (*237*)	World Youth Day 2008 pilgrims	1 group of pilgrims was accommodated as a large group in a gymnasium and another group was sub-divided into smaller groups and accommodated in classrooms for 1 week.	The attack rate was significantly ($p< 0.01$) higher among pilgrims accommodated in the gymnasium (17.2%) than those staying in the classrooms (9.2%)	Very low

SC: school closure.

Ethical considerations

In urban locations it can be difficult to avoid crowding without considerable social costs. Modification, postponement or cancellation of mass gatherings may have cultural or religious considerations, in addition to public health aspects.

Knowledge gaps

There are still major gaps in our understanding of person-to-person transmission dynamics. Reducing mass gatherings is likely to reduce transmission in the community, but the potential effects are difficult to predict with accuracy. Large-scale RCTs are unlikely to be feasible.

4. TRAVEL-RELATED MEASURES

4.1. Travel advice

Terminology
Travel advice refers to advice from official government to help members of the public to make informed decisions when they are planning to travel, and offer them an objective assessment of risk (*238*). Travel bans are more extreme, and discussed separately. Travel advice can increase travellers' awareness of the travel risk in pandemic countries or areas and may affect decisions to travel.

Methods
The databases including PubMed, Medline, EMBASE and Cochrane Library were searched until September 2018. Inclusion criteria were primary research evaluating travel advice for influenza in the community setting. Studies had to demonstrate any effectiveness following travel advice to the public. We excluded studies conducting at the health care settings, animal-related studies, systematic reviews and/or meta-analysis without updated evidences, not measuring effectiveness of travel advice to the community, and article type of letter, commentary or news. Two reviewers (SR and SG) contributed to the title, abstract and full-text screening.

Results
A total of 168 records were identified and included in the title and abstract screening, and 146 of the records were excluded. Twelve full-text records were evaluated for eligibility and all were excluded. No full-length articles were included in this systematic review. The flow chart of study selection is shown in Fig. 24.

Ethical considerations
Policy decisions and justification should be open to the public, so that the public awareness of influenza can be increased, and public trust to follow travel advice can be maintained (239).

Regarding the impact for the global economy through the public avoidance of travel or trade, travel advice may develop financial loss of the public (*239*).

Knowledge gaps
There is still no evidence measuring the quantitative effect of travel advice on influenza pandemic, which may hamper the development of policy in this area. Because the outcomes of effectiveness may vary by reproduction number, study of the level of infectivity and travel restriction, influenza strain-specific travel advice can be considered.

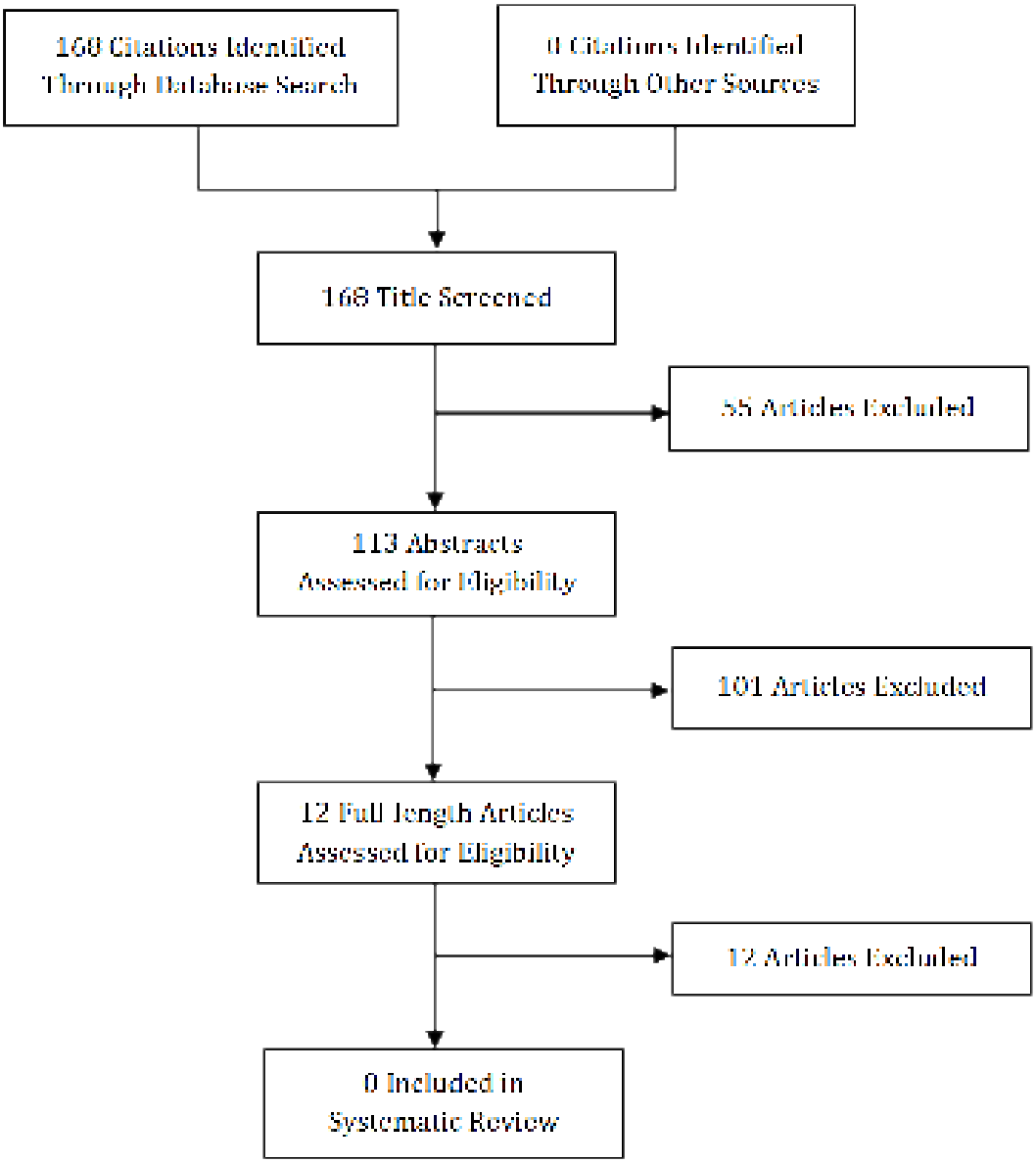

Fig. 24. The flow chart of travel advice

4.2. Entry and exit screening

Terminology

The aim of screening travellers for influenza is to reduce the number of infectious individuals entering or leaving a country. Screening measures include health declarations, visual inspection, and thermography to detect individuals with influenza-related symptoms (*240*). These measures can be conducted at arrival terminal (entry screening) or at departure terminal departure (exit screening) (*241*).

Methods

The databases PubMed, Medline, EMBASE and Cochrane Library were searched until September 2018. Inclusion criteria were primary research evaluating entry and/or exit screening for influenza in the community setting. Studies had to demonstrate any effectiveness following entry and/or exit screening in the community. We excluded studies conducting at health care settings, animal-related studies, systematic reviews and/or meta-analysis without updated evidence, not

measuring effectiveness of travel advice to the community, and article type of letter, commentary or news. Two reviewers (SR and SG) contributed to the title, abstract and full-text screening. The quality of evidence was measured using the GRADE approach. The rating was made for the overall effectiveness of entry and exit screening by two independent reviewers.

Results

A total of 297 records were identified and included in the title and abstract screening, and 230 were excluded; 31 full texts were evaluated for eligibility and 19 full texts were excluded. Ten full-length articles were included in this systematic review. A flow chart of study selection shown in Fig. 25. Study details are shown in Table 29, Table 30, Table 31 and Table 32.

A simulation study in the USA estimated that entry screening can detect 50% of infected travellers and is likely to lower the predicted pandemic influenza attack rate by less than 1% (*242*). Furthermore, several simulation studies showed that screening international travellers may help to delay the epidemic by a few days (0–12 days) (*163, 242-244*). However, several observational studies that were conducted at international airports demonstrated that the sensitivity of entry screening was low (5.8% at New Zealand, 6.6% at Japan and 1.1% at USA) (*245-247*), and half of international travel-related case-patients were identified more than a day after arrival by passive case finding and contact tracing in the community, although 37% of international travel-related cases of influenza were screened at the border entry site (*163*). Simulation studies predicted that screening of travellers may not prevent case import and local epidemics (*243*, *244*).

Fig. 25. The flow chart of entry and exit screening

Sensitivity of screening can affect the effectiveness of travellers' screening. One of the major criteria for screening influenza infected travellers is fever, because it is a relatively specific sign of influenza compared with other signs or symptoms. Infrared thermometers have been used for border screening in many locations due to the instantaneous and non-invasive nature. One study showed that the sensitivity and specificity of infrared thermometer were 50.8–70.4% and 63.6–81.7% respectively during influenza A(H1N1)pdm09 in Japan (*248*). An infrared thermal image scanner (ITIS) is another screening tool for the massive number of travellers. A study conducted in New Zealand demonstrated that the sensitivity and specificity of ITIS ranged from 84–86% and 31–71%, respectively (*249*).

Molecular diagnostics can be used, but will be expensive and resource intensive if used in a large population (*250*). Point-of-care antigen detection tests might be more feasible but would still be costly (*250*).

Considering the incubation period of influenza virus infection of 1–2 days (*163*), the variation of symptom presentation and imperfect screening methods (*251*), screening travellers to prevent the introduction of influenza still has limitations. Furthermore, the public health resources including trained staff, screening devices and laboratory resources are limited (247); thus, screening targeted travellers from and to high risk area should be carefully considered.

Although exit screening has been recommended in the past, we did not identify any reports of the actual implementation of exit screening in the literature.

Ethical considerations

Screening should be conducted voluntarily as much as possible, and compulsory screening should be considered very carefully (*239*). Informed consent from the traveller for the screening of specimen-collection including nasal swabs should be obtained in accordance with the International Health Regulations (*252*).

Knowledge gaps

There were no high-quality studies on the effectiveness of entry and exit screening. Quantitative study for the implementation of screening programmes at different times, different combinations, and different pathogens are required to understand the potential advantage of screening (*251*).

Table 29. Summary of epidemiological studies included in the review

STUDY	INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	NO. OF TRAVELLERS HAD MEDICAL ASSESSMENT	CASE DEFINITION FOR SCREENING AND NO. OF TRAVELLERS MET	LABORATORY TEST FOR THE CASE AND NO. OF SPECIMENS ANALYSED	OUTCOME	COMMENTS AND LIMITATIONS	QUALITY OF EVIDENCE
Hale MJ, et al. 2012 (*245*)	• Influenza A(H1N1)pdm09 • R_0 = N/A	• Cross-sectional study • Auckland international airport, New Zealand. • 456 518 international travellers including flight passenger and crew member arriving between 27 April and 22 June 2009	• Entry screening - In-flight announcement - Locator card completion - Travel advisory information - Self presentation	• 409 (0.09%)	• ILI • 109 (27% of medical assessment)	• RT-PCR from 109 respiratory swab	• 4 were positive. • 69 travellers were confirmed as cases passed through airport. • Sensitivity of screening: 5.8% (95% CI: 2.3–14.0%)	• Low sensitivity of entry screening • Mild illness might not see a doctor or did not diagnosed. • The number of cases who passed through the airport was based on estimated fraction of data from the first 100 cases	Very low
Priest PC, et al. 2013 (*247*)	Seasonal influenza	• Cross-sectional study • Christchurch airport, New Zealand. • 23 513 international travellers including flight passenger and crew member arriving between 23 June and 12 September 2008	• Entry screening - In-flight questionnaire (symptoms)	• 1358 (17%)	• Traveller who reported 1 or more of: cough, sore throat, sneezing, fever or chill, runny or blocked nose, muscle aches or pains, feeling generally unwell, chest discomfort or breathing difficulties	• Commercial EasyPlex multiplexed tandem PCR kit from respiratory swab No. of Case and non-case:1331 and 2438	• 60 were positive (51, type B; 8, type A; 1 type A&B) • Estimated prevalence: 1.13% (95% CI: 0.77–1.48)	• Either resource intensive or ineffective • Symptom based screening • Not report symptom	Very low
Sakaguchi H, et al. 2009 (*246*)	• Influenza A(H1N1) pdm09; • R_0 = N/A	• Cross-sectional study • Narita airport, Japan • 471 933 international travellers including flight passenger and crew member visited affected countries arriving between 28 April and 18 June 2008	• Entry screening – Screening surface body temperature using infrared thermal scanners	N/A	• Traveller who visited influenza affected countries with 2 symptoms or more of 4 symptoms (1. Nasal discharge or nasal obstruction; 2. Sore throat; 3. Cough; 4. Fever or feeling feverish and chills) or travellers with body temperature > 38°c	• Rapid influenza diagnostic test and RT-PCR from 805 respiratory specimens	• 9 were positive. • 141 travellers were found during the community containment measures. • Sensitivity of screening: 6.6%	• Require large amount of human resources • Mild illness travellers were not examined • Not report symptom	Very low
Yu H, et al. 2012 (*163*)	• Influenza A(H1N1)pdm09; • R_0 = N/A	• Retrospective cohort study • China (193 sentinel hospital, 30 provinces) • 7 1 665 persons with confirmed A (H1N1) pdm09 virus between 7 May and 30 November 2009.	• Entry screening – active surveillance at the border and medical monitoring	N/A	• Confirmed case: ARI with laboratory evidence of influenza A(H1N1) pdm09 • ARI: fever (≥ 37.3), and/or recent onset of 1 or more of the following: rhinorrhea, nasal congestion, sore throat or cough	• RT-PCR	• 932 were related to international travel. • 37% of int'l travel-related cases identified at the border. • Half (468/932) were identified 1 or more days after their arrival. • Detection rate of case identified at the entry screening: fever + before arrival: 76%, fever- before arrival 63%	• Epidemic likely delayed by 4 days (100% of screening sensitivity) • Mild illness or subclinical infection might not be examined • Case-based surveillance	Very low

ARI: acute respiratory infection; CI: confidence interval; ILI: influenza-like illness; N/A: not applicable; PCR: polymerase chain reaction; R0: basic reproductive number; RT: reverse transcription.

Table 30. Summary of simulation studies included in the review

STUDY	INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	NO. OF TRAVELLERS HAD MEDICAL ASSESSMENT	SCENARIO	OUTCOME	COMMENTS AND LIMITATIONS	QUALITY OF EVIDENCE
Malone JD, 2009 (*242*)	• Pandemic influenza • R0 = 2.4 (Europe), 2.1 (Latin America), and 2.0 (Canada and USA)	• Stochastic discrete event simulation model • 18 US international airport	• Entry screening	• 409 (0.09%)	• 50% of passengers predicted to be infected and high detection rate of 80% for symptomatic travellers for the screening • 100% of passengers infected and 80% of detection rate from screening • 50% of passengers infected and < 50% of detection rate from the screening	• Lowest number of arriving infected passengers (peak day 45–980); attack rate of without and with screening: 30.7% and 30.4% • Peak days 24 and 45 arrive; attack rate of without and with screening: 30.8% and 30.5% • Highest number of arriving Peak day 45–1600 arrive; attack rate of without and with screening: 30.9% and 30.6%	• Entry screening lower the attack rate by less than 1% • Possible variation by airline patterns, screening effectiveness and test accuracy of RT-PCR.	Very low
Cowling BJ, 2010 (*244*)	•R0 = influenza H1N1 N/A	• Bootstrapping • 35 countries had reported to WHO by 6 July 2009 • 100 confirmed cases	• Entry screening - Temperature check prior to disembarkation - Health declaration forms - Observation of symptoms by staffs - Body temperature scan by thermal scanners	N/A	• No screening • a) Medical check before disembarkation • b) Health declaration forms • c) Symptom screening • d) Thermal scanning • e) b) OR c) OR d) • f) b) AND c) AND d)	• Median interval with inter quartile range between first imported case and first local case: 22 days (0, 22days) • a) 21 days (14, 28) • b) 22 days (13, 34) • c) 33 days (7, 41) • d) 22 days (7, 33) • e) 22 days (7, 35) • f) 23 days (9, 35)	• Entry screening did not delay significantly in local transmission • Mild illness or self-limiting nature may affect the result • Did not consider the size of local epidemics.	Very low
Caley P, 2007 (*243*)	• New pandemic influenza •R0 = 1.5, 2.5, and 3.5	• Simulation study • 100% sensitivity for detecting symptomatic infection, • 12 hours of travel	• Exit screening • Entry screening – Screening surface body temperature using infrared thermal scanners	N/A	• Traveller who visited influenza affected countries with 2 symptoms or more of 4 symptoms (1. Nasal discharge or nasal obstruction; 2. Sore throat; 3. Cough; 4. Fever or feeling feverish and chills) or travellers with body temperature > 38°c	• Rate of evading screening: 0.26 (R0 = 1.5), 0.45(R0 = 2.5), 0.59 (R0 = 3.5) • Median delay from 57 to 60 days by screening (R0 = 1.5, 400 travellers / day); natural median delay 57 days * Time delay: the start of an influenza pandemic and its subsequent initiation in other countries	• Delay effect by implementing screening is small compare with natural delay • In-flight transmission not fully considered.	Very low

N/A: not applicable; PCR: polymerase chain reaction; R0: basic reproductive number; RT: reverse transcription; USA: United States of America; WHO: World Health Organization.

Table 29. Summary of epidemiological studies included in the review

STUDY	INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	NO. OF TRAVELLERS HAD MEDICAL ASSESSMENT	CASE DEFINITION FOR SCREENING AND NO. OF TRAVELLERS MET	LABORATORY TEST FOR THE CASE AND NO. OF SPECIMENS ANALYSED	OUTCOME	COMMENTS AND LIMITATIONS	QUALITY OF EVIDENCE
Nishiura H, 2011 (*248*)	• Influenza including A(H1N1)pdm09 and other • R_0 = N/A	• Observational study • A) 471 733 travellers including flight passengers and crew members from 28 April 2009 to 18 June 2009 • B) 9 140 435 flight passengers from 1 September 2009 to 31 January 2010	• Entry screening	• a) 805 • b) 1049	• a) (1) contract in Canada, Mexico or USA, or (2) fever ≥ 38°C or 2≥ acute upper respiratory symptoms • b) (a) self-reported symptoms, (2) relatives or friends of (1) or identified by an infrared thermal scanner	• a) RT-PCR from 805 respiratory swab	• a) sensitivity of entry screening: 22% (18/805) • b) sensitivity and specificity of infrared thermal scanners in detecting hyperthermia: 50.8–70.4% and 63.6–81.7%. PPV: 37.3–68.0%	• Fever screening as a sole measure of entry screening is insufficient • Used non-randomized dataset • Confounding factors including age and outdoor temperature should be considered for the performance of infrared thermal scanners	Very low
Priest PC, 2011 (*249*)	Seasonal influenza	• Observational study • Christchurch airport, New Zealand. • 8020 travellers including flight passengers and crew members from 2008	• Entry screening - In-flight questionnaire (symptoms)	• 5274 questionnaires returned • 823 were symptomatic • 1281 were measured temperature using tympanic and ITIS.	• Traveller who reported 1 or more of: cough, sore throat, sneezing, fever or chill, runny or blocked nose, muscle aches or pains, feeling generally unwell, chest discomfort or breathing difficulties.	• MT-PCR	• Sensitivity and specificity of ITIS (84–86% and 42–72%)	• Fever screening using ITIS is insufficient to detect influenza infection • Majority of travellers in this population was afebrile. • Some of infected travellers had anti-pyretic before arrival	Very low

ITIS: infrared thermal image scanner; MT: multiplexed tandem; N/A: not applicable; PCR: polymerase chain reaction; PPV: positive predictive value; R0: basic reproductive number; RT: reverse transcription; USA: United States of America.

Table 32. Summary of studies of PCR assay included in the review

STUDY	INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	NO. OF TRAVELLERS HAD MEDICAL ASSESSMENT	CASE DEFINITION FOR SCREENING AND NO. OF TRAVELLERS MET	LABORATORY TEST FOR THE CASE AND NO. OF SPECIMENS ANALYSED	OUTCOME	COMMENTS AND LIMITATIONS	QUALITY OF EVIDENCE
Chen J, 2018 (*250*)	• Seasonal influenza • R_0 = N/A	• Observational study • Xiamen international airport China • 1 540 076 incoming travellers between May 2015 and May 2016	• Entry screening	• 1224	• ILI (fever≥ 37.5°C, either cough, rhinorrhea, sore throat and/or gastrointestinal discomfort)	• Flu Dot-ELISA • Viral culture	• Sensitivity of Flu Dot-ELISA: 96.6% (95% CI: 92.7–98.7)	• suitable to use rapid influenza test (Flu Dot-ELSIA) • Missed detection of asymptomatic travellers • Sensitivity of viral culture is less than 100%	Very low

ILI: influenza-like illness; PCR: polymerase chain reaction; R0: basic reproductive number.

4.3. Internal travel restrictions

Terminology

Because airports and land transportation are associated with long-distance spread of influenza (*253*), travel restrictions are considered as a measure to reduce regional and international spread (*254*). Although a previous quantitative expert survey study suggests that this travel restriction is likely to be ineffective due to its limited evidence (1), internal travel restriction to prevent domestic travel of persons to influenza is still considered as an NPI.

Methods

The most recent systematic review of travel restriction was published in 2014 by Mateus et al. (*255*). They identified eight studies, which found that internal travel restriction has limited effectiveness and remained unclear. This review included few simulation studies and several reviews of simulation studies, and was intended to measure the overall travel restriction including internal and international restriction. Instead of using this previous review, we conducted a new search in the databases PubMed, Medline, EMBASE and Cochrane Library, until September 2018. Inclusion criteria were primary research evaluating internal travel restriction for influenza pandemic in the community setting. Studies had to demonstrate any effectiveness following internal travel restriction to the public. We excluded studies conducting at the health care settings, animal-related studies, systematic reviews and/or meta-analysis without updated evidence, not measuring effectiveness of travel advice to the community, and article type of letter, commentary or news. Two reviewers (SR and SG) contributed to the title, abstract and full-text screening. The quality of evidence was measured using the GRADE approach. The rating was made for the overall effectiveness of internal travel restrictions by two independent reviewers. The flow chart of study selection is shown in Fig. 26.

Results

At total of 67 records were identified and included in the title and abstract screening, and 56 were excluded; 11 full-text articles were evaluated for eligibility and six of these were excluded; thus, five full-length articles were included in this systematic review. The summary is shown in Table 33.

A time series analysis study conducted in the USA showed that frequency of domestic airline travel is temporally associated with the rate of influenza spread and following September 11 2001, had markedly delayed the epidemic peak 13 days later than the average for other years (*256*). A simulation study predicted that implementation of strict travel restriction (95% travel restriction and enforced for 4 weeks) could reduce the ILI peak by 12% and moderate restriction (50% travel restriction and enforced for 2–4 weeks) could delay the pandemic peak between 1 and 1.5 weeks (127). Another simulation study predicted that more than 80% of internal travel restriction is beneficial (R0 = 1.5; 80% and 99% restriction delayed median days of 22–32 and 52, respectively, until 20 infectious persons arrivals in the designated city) (254). One simulation study estimated that strict internal travel restrictions (90%) could have some impact in delaying the epidemic peak by 2 weeks in the United Kingdom and by less than 1 week in the USA; however, 75% travel restriction would be ineffective (*87*).

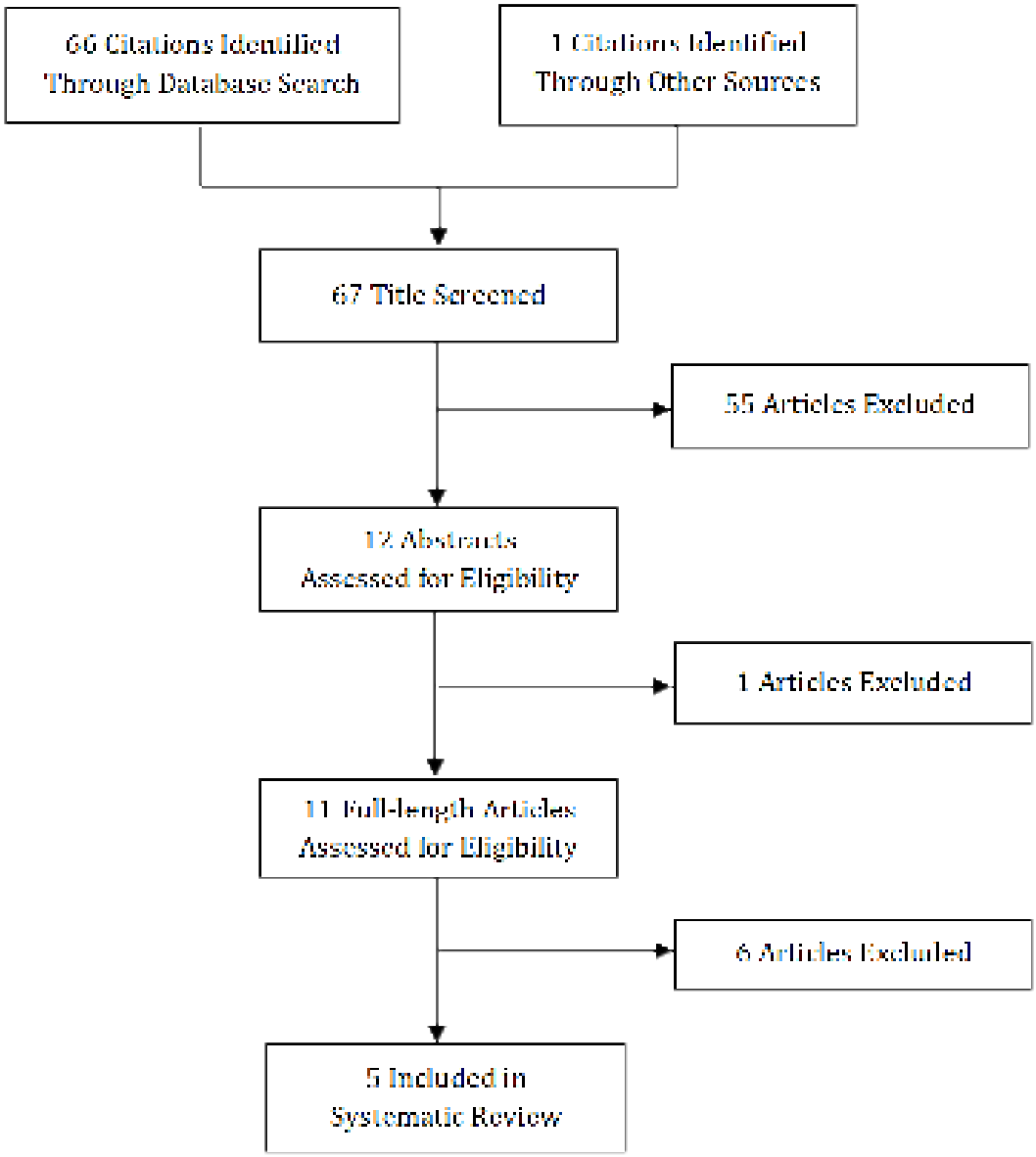

Fig. 26. The flow chart of internal travel restriction

Ethical considerations

Travel restriction should be voluntarily applied as much as possible, and compulsory intervention should be involved as a last resort (*239*). Furthermore, governments should pay close attention to adverse economic consequences, particularly on vulnerable populations including workers who have frequent travel and individuals who need to have immediate medical treatment (*239*).

Knowledge gaps

Although most of the literature on this topic results from simulation studies and natural experiments, it is unlikely that large trials will ever be done. Improved understanding of transmission dynamics of influenza would be advantageous; for example, on how environmental or other factors can affect influenza transmission and seasonality (*256*).

Table 33. Summary of studies included in the review

STUDY	STUDY DESIGN INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	OUTCOME	COMMENTS AND IMITATIONS	EVIDENCE QUALITY RATING
Brownstein JS, 2006 (*256*)	• Seasonal influenza • R_0 = N/A	• Time series analysis • USA • Weekly mortality from pneumonia and influenza for 9 influenza seasons (from 1996–1997 to 2004–2005)	• N/A	• Following September 11 2001, had markedly delayed peak 13 day later than average	• Domestic air travel affects the influenza spread in USA • Study used the data from voluntarily reporting system • Study used influenza mortality time series data which may not correspond to influenza activity	Very low
Bolton KJ, 2012 (*127*)	• Seasonal influenza • R_0 = around 2	• Stochastic, compartmental patch model of SEIR • Mongolia	• Travel restriction - 50% reduction in mean travel volume in early epidemic	• Delayed the pandemic peak by about 1.5 weeks if maintained for 4 weeks of restriction and by about 1 week if maintained for 2 weeks of restriction • Reduced the attack rates by less than 0.1% when travel volume was reduced by 95%	• Benefit of travel restriction may be limited • Not considered the transmission at the level of household	Very low
Wood JG, 2007 (*254*)	• Seasonal influenza • R_0 = 1.5–3.5	• Stochastic SIR model • Australia • Average daily volumes of domestic air travel between Sydney, Melbourne and Darwin	• 80%, 90% and 99% of travel restriction • Median time between the day when the no. infected person first reached 20	• Scenario (Sydney to Melbourne) Beginning of epidemic was delayed in 22–32 days (80% restriction), and 52 days (99% restriction)	• Strict travel restriction required to delay the time • Seasonal variation and further importation of influenza was not considered	Very low
Ferguson NM, 2006 (87)	• Seasonal influenza • R_0 = 1.4–2.0	• Stochastic mathematical individual-based model • United Kingdom and USA	• Reactive movement restrictions in a 20 km exclusion zone around every case – 75 and 90% restriction • Peak time delay	• Delaying the peak of the epidemic by less than 1 week in USA (without int'l travel restriction) – 90% restriction have some effect on the delaying the peak, but 75% restriction have almost none effect	• Internal travel restriction must be highly strict to have impact • Not considered the effect of personal protective measures on transmission	Very low
Germann TC, 2006 (*257*)	• Seasonal influenza H5N1 • R_0 = 1.6, 1.9, 2.1, and 2.4	• Stochastic agent-based discrete-time simulation model • USA	• 90% of travel restriction	• Epidemic peak delayed few days • 0.2% of increase of cumulative incidence (R_0 = 1.6) • 0.5% of increase of cumulative incidence (R_0 = 1.9)	• The combination of intervention such as social distancing and vaccination may increase the effectiveness of travel restriction	Very low

N/A: not applicable; R0: basic reproductive number; SEIR: susceptible–exposed–infectious–recovered; SIR: susceptible–infectious–recovered; United Kingdom: United Kingdom of Great Britain and Northern Ireland; USA: United States of America.

4.4. Border closures

Terminology
International travel can cause infectious disease cross-border transmission; thus, border closure, one of the measures that can be rapidly implemented, may reduce the epidemic spread of influenza. The transportation of international travel includes ship, bus, train and aeroplane.

Methods
The databases (PubMed, Medline, EMBASE and Cochrane Library) were searched until September 2018. Inclusion criteria were primary research evaluating border closure for influenza pandemics in the community setting. Studies had to demonstrate any effectiveness following border closure in the community. We excluded studies conducted in health care settings, animal-related studies, systematic reviews and/or meta-analysis without updated evidence, not measuring effectiveness of travel advice to the community, and article type of letter, commentary or news. Two reviewers (SR and SG) contributed to the title, abstract and full-text screening. The quality of evidence was measured using the GRADE approach. The rating is made for the overall effectiveness of border closure by two independent reviewers.

Results
A total of 327 records were identified and included in the title and abstract screening, and 314 were excluded; 13 full texts were assessed for eligibility and 11 full-length articles were identified for inclusion in the systematic review. The flow chart of study selection is shown in Fig. 27.
The description of the studies shown in Table 34.

An epidemiological study demonstrated that international airline travel could significantly reduce the mortality impact of a pandemic (*256*). Another simulation study estimated that a 99% restriction of border travel between Hong Kong SAR and mainland China may delay the epidemic peak compare with non-travel restriction (sole air restriction, 2 week–delay; both air and land, 3.5 week–delay; all air, land and sea, 12 weeks) (*258*). However, international travel restrictions of other modes of transportation such as land and sea would have less impact (2–3 day delay of the epidemic peak) (*258*). Implementing border crossing travel restrictions within three months of identification of first global case could reduce the seven–month cumulative attack rate by around 2% (*258*). However, implementing travel restrictions after the 5 months of arrival of the first global case would not be expected to be effective (*258*).

Another simulation study reported that international air-travel restriction could delay the peak of epidemic by about 1–3 weeks depending on the transmission rate (1.4, 1.7, or 2) and the level of restriction (90% or 99%), although the attack rate was not significantly affected (*220*). Furthermore, global-scale simulation study reported that travel restrictions could delay the epidemics by about 2 to 3 weeks (*259*) and significantly delay global spread by 5–133 days (*260*).

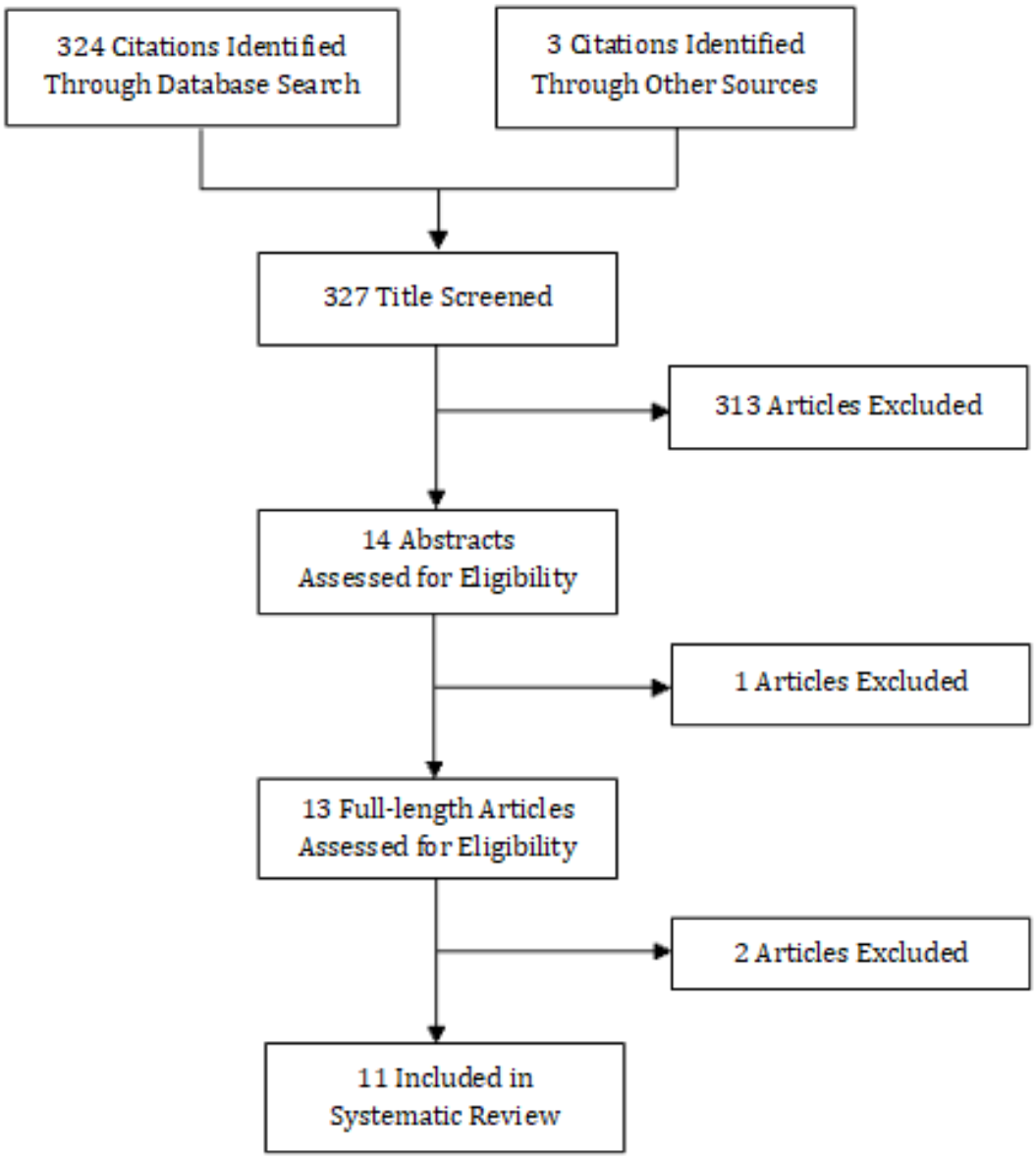

Fig. 27. The flow chart of border closures

A simulation study predicted that 99.9% border control could delay the epidemic peak by 6 weeks (90% and 99% of border control would delay 1.5 and 3 weeks, respectively) (87). Another study estimated that international travel restrictions would slow the importation of cases, and an 80–99% travel restriction would delay of the exportation of cases range 6.6–133 days; however, it did not reduce the magnitude of spread (*261*). Another simulation study predicted that children-selective restriction could be helpful to delay epidemic for a few weeks (*262*).

A simulation study based on travel data from Pacific Island Countries and Territories (PICTs), only six PICTs would be likely to prevent importation of influenza pandemic by 99% of travel restriction through border control. In PICTs, critical necessity such as food and medical supplies are largely dependent on importation, so that strict border closure was carefully considered in PICTs (*263*). Although 99% of travel restriction of all mode of transportation has delayed the epidemic peak, the magnitude of the epidemic was reduced less than 10% in this study. Another observational study in South Pacific Island jurisdictions, during the influenza pandemic which began in 1918,

reported that strict maritime quarantine reduced attributable mortality rate from pandemic influenza between 0 and 840 (crude mortality rate per 1000 population) (*99*).

Border closure such as travel restriction is a measure that can be rapidly implemented and it may decelerate the epidemic growth; however, this may not be effective at limiting the magnitude of influenza epidemics (*258*).

Ethical considerations

The human rights of mobility should be considered (*239*). Therefore, as with internal travel restriction, border controls should be voluntarily applied as much as possible, and compulsory intervention should be involved as a last resort (*239*). Furthermore, the stigmatization and discrimination of individuals from influenza affected areas, and economic consequences by implementing border closures should also be considered (*239*, *264*).

Knowledge gaps

Although most of the literature on this topic results from simulation studies and natural experiments, it is unlikely that large trials will ever be done. Improved understanding of transmission dynamics of influenza would be advantageous; for example, on how environmental or other factors can affect influenza transmission and seasonality (*256*).

Table 33. Summary of studies included in the review

STUDY	STUDY DESIGN INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	OUTCOME	COMMENTS AND IMITATIONS	EVIDENCE QUALITY RATING
Brownstein JS, 2006 (*256*)	• Seasonal influenza • R_0 = N/A	• Time series analysis • USA • Weekly mortality from pneumonia and influenza for 9 influenza seasons (from 1996–1997 to 2004–2005)	• N/A	• September 11 2001 affected international flight volume decreased by 27%, and the peak of influenza mortality was delayed by 2 weeks	• Decrease in travel volume was associated with a delayed and prolonged influenza season. • Study used the data from voluntarily reporting system • Study used influenza mortality time series data which may not correspond to influenza activity	Very Low
Chong KC, 2012 (*258*)	• Influenza H1N1 pandemic • R_0 = 1.4	• Stochastic SEIR model • Hong Kong SAR and mainland China	• Travel restriction – 90%, and 99% travel restriction on different mode transportation (air, land, sea) • Measure the first passage time (first global case onset ~ first local case report)	• 99% of international air-travel restriction delayed the interval between the first imported case and one hundred infected case passed the border by a week and the epidemic peak delayed by two weeks • 99% of restriction of both air and land travel delayed the interval (passage time) by an additional one to two weeks and the epidemic peak delayed about 3.5 weeks • 99% restriction of all mode of transportation delayed the interval by additional 2 months, and delayed the epidemic peak time for about 12 weeks • Travel restriction 3 month after the arrival of first global case reduce the 7-months cumulative attack rate around 2%	• Travel restriction may not be effective • Not considered the infection risk for the out bound susceptible travellers • No adjustment of multi-step journey	Very Low
Ciofi degli Atti ML, 2008 (*220*)	• Pandemic influenza • R_0 = 1.4, 1.7, 2.0	• Global deterministic SEIR model • Italy	• Incoming international flight restriction (90% or 99%)	• Int'l air-travel restriction delayed the interval between first global case report and the importation of the first cases by 7–37 days. Furthermore, the pandemic peak delayed by 6–39 days. The attack rate was reduced less than 0.1%	• Air-travel restrictions can delay 1 to 3 weeks in delaying the epidemic.	Very Low

Table 34. Summary table of studies included in the review

STUDY	STUDY DESIGN INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	OUTCOME	COMMENTS AND IMITATIONS	EVIDENCE QUALITY RATING
Epstein JM, 2007 (*259*)	• Pandemic influenza • R_0 = 1.4, 1.7, 2.0	• Global influenza transmission model • Global (Hong Kong SAR, London and Sydney)	• Travel restriction (90%, 95%, and 99%) • The interval between the outbreaks occurred in Hong Kong SAR or London and the case-passage time to USA	• First passage time is delayed from 18 days to 31 days (outbreak originated from Hong Kong SAR), and from 7 days to 27 days (from London) with R_0 = 1.7 The delays are larger for smaller R_0	• Air-travel restrictions can delay 2 to 3 weeks in delaying the epidemic. • Model is based on the largest metropolitan areas	Very Low
Cooper BS, 2006 (*260*)	• Pandemic influenza • R_0 = 1.8–5	• Metapopulation model • Global (Hong Kong SAR, London, Sydney)	• Air-travel restriction from affected cities (50, 90, 99 and 99.9%) • Susceptibility (10%, 60%, and 100%)	• Median epidemic peak delay can be ranged between 7–102 days	• Banning flight from affected region would be effective delaying global spread	Very Low
Ferguson NM, 2006 (*87*)	• Seasonal influenza • R_0 = 1.4–2.0	• Stochastic spatially structured mathematical model • USA	• 90, 99% or 99.9% border control in USA	• Imported infections might delay the epidemic peak of USA by 1.5 weeks (90% border control), 3 weeks (99%), and 6 weeks (99.9%)	• Combing travel restriction measure including internal and international have more impact delaying epidemic peak	Very Low
Hollingsworth TD, 2006 (*261*)	• Pandemic influenza • R_0 = N/A • Pandemic influenza	• Simple mathematical SEIR model of an epidemic in a source country with cases exported to other countries	• 80, 99, or 99% of travel restriction • Peak time delay	• The mean time delay exporting the infected case is 5.3 days (80% of restriction), 11.7 days (90%), and 131.7 days (99%)	• Restriction on travel may have limited benefit of global spread of pandemic influenza	Very Low

Table 34. Summary table of studies included in the review

STUDY	STUDY DESIGN INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	OUTCOME	COMMENTS AND IMITATIONS	EVIDENCE QUALITY RATING
Eichner M, 2009 (*263*)	• R_0 = 1.5, 2.25, and 3.0	• Probalistic model • PICTs	• 79% or 99% of travel restriction • Assess the probability that an island either occur epidemics or escape the pandemic	• Among 17 PICTs, with 99% travel restriction, six countries (with R_0 = 1.5) and four to five countries (with $R_0 \geq$ 2.25) would be likely escaped the pandemic influenza with more than 50% probability. However, with 79% of travel restriction, only one country (with R_0 = 1.5) and no country (with R0≥ 2.25) was likely escaped the pandemic	• Border control can benefit only a few PICTs for avoiding pandemic influenza • Some of data used in this analysis was missing and suboptimal	Very Low
McLeod MA, 2008 (*99*)	• Pandemic influenza • R_0 = N/A	• Epidemiological study • 11 South Pacific Island jurisdictions	• 5–7 days' maritime quarantine • Death rate	• Arrival of pandemic and death rates attributed to influenza per 1000 population was significantly delayed and reduced compare with the other Pacific Island Jurisdiction - American Samoa (1920, no death reported) - Australia (early January 1919, death rate = 2.4) - Tasmania (August 1919, death rate = 0.81) - New Caledonia (1921, death rate less than 11)	• Strict border control in the island can be advantage to delay the pandemic and reduce the mortality • Confounding factors including pre-existing immunity may affect this result	Very Low
Lam ET, 2011 (*262*)	• Pandemic influenza • R_0 = 1.2, 1.6, 2.0	• Simple stochastic model • Hong Kong SAR	• 100% border crossing travel restriction among children	• Children-selective travel restriction delayed the epidemic for a 19–35 days (R_0 = 1.2), and less than 15 days (R_0 = 1.6 and 2.0)	• The intervention was assumed to implemented after pandemic declared	Very low
Bajardi P, 2011 (*265*)	• Pandemic influenza • R_0 = 1.7 with generation interval 3.6 days	• SEIR-like Global Epidemic and Mobility model	• 40% and 90% of int'l travel restriction to and from Mexico	• Mean delay of the arrival of infection from other countries was less than 3 days (40% of restriction), and about 2 weeks (90% of restriction)	• The intervention was assumed to implemented at the early stage of the outbreak (by 3 months)	Very low

N/A: not applicable; PICTs: Pacific Island Countries and Territories; R0: basic reproductive number; SAR: Special Administrative Region; SEIR: susceptible–exposed–infectious–recovered; USA: United States of America.

SUMMARY OF EVIDENCE

Personal protective measures

Personal hygiene measures such as hand hygiene, respiratory etiquette and face masks are widely used as non-pharmaceutical intervention measures to reduce the risk of acquiring or spreading respiratory infections, and for mitigating pandemic influenza. However, our review identified a lack of compelling evidence for the effectiveness of hand hygiene, respiratory etiquette and face masks against influenza transmission in the community. There are still gaps in the evidence base which further research would help to fill.

Environmental measures

Environmental measures including surface and object cleaning are generally conducted to limit the risk of acquiring or spreading respiratory infections within an area. The evidence for the effect of surface and object cleaning on influenza prevention is limited, and no significant reductions in influenza infections were observed by surface and object cleaning intervention; studies provided very low to low quality evidence. Other environmental measures including UV light as air disinfection, ventilation as increasing air change and humidity as amount of water vapour in the air were limited. Therefore, additional research is required to confirm whether these measures could be of value in mitigating pandemic influenza.

Social distancing measures

Social distancing measures including contact tracing, isolation and quarantine of influenza affected individuals, closures of school and workplace, and avoiding crowding reduce the risk of influenza transmission in community settings. Evidence for the overall effectiveness of contact tracing is very limited. Only one study discussed the benefit of adding contact tracing to isolation and quarantine. The addition of contact tracing is estimated to provide at most modest benefit; however, it will increase considerably the proportion of individuals in quarantine. For isolation, currently available evidence showed that even as a single intervention isolation is effective. Compliance of individuals and timeliness of intervention do affect the effectiveness of isolation in mitigation of influenza. Quality of evidence based on GRADE assessment is, however, very low. More robust evidence drawn from epidemiological studies is needed. The effectiveness of quarantine in mitigation of influenza varies. Household quarantine is suggested to be effective in reducing the impact and transmissibility, and in delaying the epidemic peak; the combination of quarantine with other interventions such as case isolation and SC will further strengthen the effectiveness. There is also an increased risk of infection in individuals quarantined concurrently with an isolated individual. Hence, ethical concerns arise for mandated quarantine. Onboard quarantine, on the other hand, has a minimal impact, based on a very low quality of evidence. More robust evidence drawn from epidemiological studies is needed.

SC can reduce the spread of the influenza; however, the threshold for closing time and duration are uncertain. The combination of SC with other interventions is more effective in reducing the spread of infection. Unlike the evidence of effectiveness of SC, evidence on WCs is limited and all six studies for this effectiveness measure were simulation models (i.e. the quality of evidence is very low). Five of these studies suggested that reductions in attack rate, duration of infection or peak numbers occurred because of the WC. The combination with other interventions may enhance the effectiveness of the individual measures. Workplace measures are effective and feasible during a pandemic. Avoiding crowding, which includes separating people into small groups or cancellation of public gatherings, is effective as an intervention in preventing transmission of influenza as well. However, the quality of evidence is very low based on the GRADE approach.

Travel-related measures

Travel-related measures including travel advice, traveller screening, travel restriction and border closures have been used in previous pandemics to limit international spread. The evidence of travel advice against influenza transmission is still uncertain. The effectiveness of screening incoming and/or outbound travellers against influenza spread is also controversial. However, travel restriction and border closure may slow the spread of influenza at the community level, although all the evidence available was of very low quality.

Table 35. Quality of evidence and summary of results for each NPI

MEASURES	QUALITY OF EVIDENCE		RESULTS
1. Hand hygiene	Moderate (lack of effectiveness in reducing influenza transmission)		Eleven RCTs were included in this review. While hand hygiene was not effective against laboratory-confirmed influenza in meta-analysis in community settings and university halls, it was effective in one of two trials conducted in schools.
2. Respiratory etiquette	**None**		No scientific studies were identified for inclusion in this review.
3. Face masks	Moderate (lack of effectiveness in reducing influenza transmission)		Ten RCTs were included in meta-analysis, and there was no evidence that face masks are effective in reducing transmission of laboratory-confirmed influenza.
4. Surface and object cleaning	Low (lack of effectiveness in reducing influenza transmission)		Two RCTs and one cross-sectional study were included in the systematic review. There was evidence that surface and object cleaning could reduce detections of virus in the environment, but there was no evidence of effectiveness against laboratory-confirmed influenza virus infection.
5. Other environmental measures	**UV light**	**None**	No scientific studies were identified for inclusion in this review.
	Ventilation	Very low (effective)	In simulation studies, increasing the ventilation rate reduced influenza transmission.
	Humidity	**None**	No scientific studies were identified for inclusion in this review.
6. Contact tracing	Very low (unknown)		Evidence for overall effectiveness of contact tracing was limited. All included studies were simulation models. Only one study suggested the benefit of adding contact tracing on top of isolation and quarantine. Such addition was estimated to provide at most modest benefit, at the same time this would considerably increase the number of quarantined individuals.

MEASURES	QUALITY OF EVIDENCE	RESULTS
7. Isolation of sick individuals	Very low (effective)	Simulation studies suggested that isolation of sick individuals can reduce transmission in epidemics and pandemics. The overall effectiveness of the measure is moderate and combination with other interventions may improve the effectiveness.
8. Quarantine of exposed individuals	Very low (variable effectiveness)	We identified 6 epidemiological studies and 10 simulation studies eligible for inclusion in our review. Quarantine is generally effective in reducing burden of disease, transmissibility and delaying epidemic peak.
9. SCs	Very low (variable effectiveness)	The effect of reactive SC in reducing influenza transmission varied but was generally limited. Proactive closures and planned school holidays had a moderate impact on transmission. While SCs alone might have an impact, combination with other interventions further improved the effectiveness.
10. WCs	Very low (effective)	The strength of evidence on WC is very low since the identified studies are all simulation studies. Large-scale WCs could delay the epidemic peak for more than one week, and small-scale closures may have a modest impact on attack rate or peak number.
11. Workplace measures	Very low (effective)	The included studies indicated that workplace measures could reduce overall and the peak number of influenza cases, as well as delaying the peak occurrence. While the overall effectiveness and feasibility of workplace measures is modest, combination with other interventions can further improve its effectiveness.
12. Avoiding crowding	Very low (unknown)	Avoiding crowding including separating people into small groups or cancelling public gatherings is an effective intervention to prevent the spread of influenza. However, the effects of measures to avoid crowding in reducing transmission is uncertain.

Table 35. Quality of evidence and summary of results for each NPI

MEASURES	QUALITY OF EVIDENCE	RESULTS
13. Travel advice	**None**	No scientific studies were identified for inclusion in this review.
14. Entry and exit screening	Very low (lack of effectiveness in reducing influenza transmission)	Ten studies were included in this review. Considering the asymptomatic period of infected patients and the sensitivity of screening devices, the effectiveness of screening travellers is likely to be very limited.
15. Internal travel restrictions	Very low (effective)	The effectiveness of internal travel restriction is dependent on the level of restriction, and only very strict restrictions would be expected to have an impact on influenza transmission.
16. Border closures	Very low (variable effectiveness)	Eleven studies were included in this review. Generally, only strict border closures are expected to be effective within small island nations. For island nations, border closure should be carefully considered because it may affect the supply of essential items to the population.

NPI: non-pharmaceutical intervention; RCT: randomized controlled trial; SC: school closure; UV: ultraviolet; WC: workplace closure.

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Nonpharmaceutical Measures for Pandemic Influenza in Nonhealthcare Settings—Social Distancing Measures

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Influenza virus infections are believed to spread mostly by close contact in the community. Social distancing measures are essential components of the public health response to influenza pandemics. The objective of these mitigation measures is to reduce transmission, thereby delaying the epidemic peak, reducing the size of the epidemic peak, and spreading cases over a longer time to relieve pressure on the healthcare system. We conducted systematic reviews of the evidence base for effectiveness of multiple mitigation measures: isolating ill persons, contact tracing, quarantining exposed persons, school closures, workplace measures/closures, and avoiding crowding. Evidence supporting the effectiveness of these measures was obtained largely from observational studies and simulation studies. Voluntary isolation at home might be a more feasible social distancing measure, and pandemic plans should consider how to facilitate this measure. More drastic social distancing measures might be reserved for severe pandemics.

Experiences from previous influenza pandemics, in particular the 2009–10 pandemic, have demonstrated that we cannot expect to contain geographically the next influenza pandemic in the location it emerges, nor can we expect to prevent international spread of infection for more than a short period. Vaccines are not expected to be available during the early stage of the next pandemic (*1*), and stockpiles of antiviral drugs will be limited, mostly reserved for treating more severe illnesses and for patients at higher risk for influenza complications. Therefore, nonpharmaceutical interventions (NPIs), such as social distancing (*2*), will be heavily relied on by health authorities to slow influenza transmission in the community, with 3 desired outcomes (Figure). The first outcome would be to delay the timing of the peak of infections to buy time for preparations in the healthcare system, the second to reduce the size of the epidemic peak so that the healthcare system is not overwhelmed, and the third to spread infections over a longer time period, enabling better management of those cases and the potential for vaccines to be used at least later in the epidemic to reduce impact.

Influenza virus infections are believed to spread mainly through close contact in the community (e.g., homes, workplaces, preschool and day care centers, schools, public places), and more frequent and intense contact among children has a particularly major role in transmission (*5*). Social distancing measures aim to reduce the frequency of contact and increase physical distance between persons, thereby reducing the risks of person-to-person transmission. These measures have played a role in mitigating previous pandemics, including the 1918–19 pandemic (*6*,*7*), and are a key part of current pandemic preparedness plans (*3*,*4*). Although a clear biological and epidemiologic rationale supports the potential effectiveness of social distancing measures, there are few opportunities for rigorous controlled trials of community interventions against influenza. Our objective was to review the evidence base for social distancing measures, focusing on the evidence supporting the effectiveness of these measures in reducing influenza transmission in the community.

Methods and Results

We conducted separate systematic reviews to gather available evidence on the effectiveness of 6 measures in reducing influenza transmission in the community: isolating ill persons; contact tracing; quarantining exposed persons; school dismissals or closures; workplace measures, including workplace closures; and

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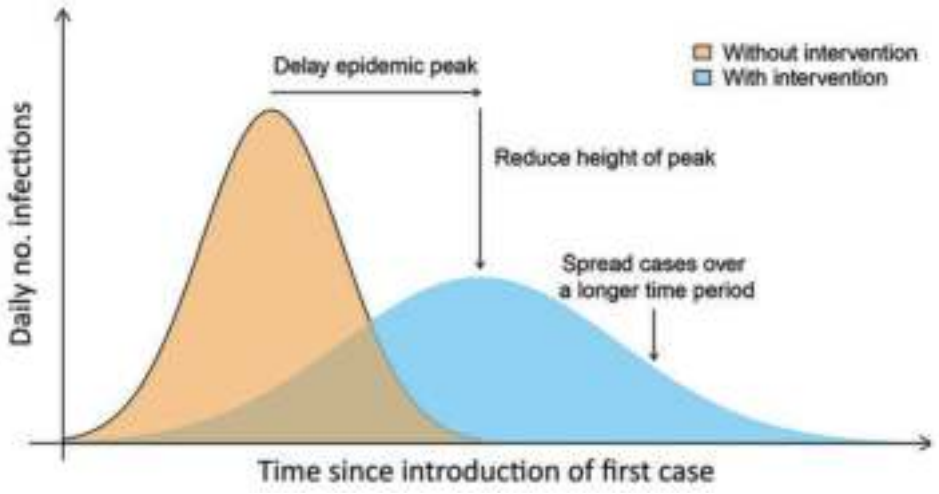

Figure. Intended impact of social distancing measures as nonpharmaceutical interventions for an influenza pandemic. Adapted from similar diagrams in the European Centre for Disease Prevention and Control Technical Report (*3*) and the Centers for Disease Control and Prevention Guidance Report (*4*).

avoiding crowding (Table 1). We retrieved literature from the Cochrane Library, Embase, Medline, and PubMed. Two authors (M.W.F. and H.G.) reviewed the retrieved literature independently for inclusion and synthesis of evidence, and a third author (J.Y.W.) resolved any discrepancies. We were unable to identify randomized controlled trials for the listed social distancing measures. Therefore, we included observational studies (contemporary as well as analysis of archival data from the 1918 pandemic) and simulation studies. We gave greater weight to observational studies than to simulation studies when we inferred the effectiveness of each measure, because assumptions and parameters in simulation studies are more difficult to assess and validate.

Isolating Ill Persons

We focused on the measure of isolating ill persons at home, but not in medical facilities, because it is unlikely that medical facilities would have the capacity for isolating persons with mild symptoms beyond the early stages of the next pandemic. We reviewed 4 observational studies (*6*,*8*–*10*) and 11 simulation studies (Appendix Tables 3, 4, https://wwwnc.cdc.gov/EID/article/26/5/19-0995-App1.pdf). Outbreaks of influenza A(H1N1)pdm09 during 2009 in various settings, including a navy ship from Peru and a physical training camp in China, have provided evidence that isolating case-patients, together with other personal protective, social distancing, and environmental measures, had substantial effect on reducing attack rates of outbreaks (*8*,*10*). During the 1918–19 pandemic, excess death rates caused by pneumonia and influenza decreased in some cities in the United States after a mixture of interventions were implemented, including isolation or quarantine, school closure, banning of public gatherings, and staggered business hours (*6*).

Although simulation studies were conducted on the basis of a wide range of assumptions, most of these studies suggested that isolation would reduce transmission, including reducing the epidemic size and delaying the epidemic peak. However, Fraser et al. (*11*) discussed the difficulty in controlling influenza transmission, even with high level of isolation combined with contact tracing and quarantine, because of the potentially high proportion of influenza transmission that occurs from mild or asymptomatic infections.

Given that influenza is believed to spread from person to person mostly through close contact, there is a clear rationale for preventing contact between infectious and susceptible persons. However, we found limited scientific evidence to support the effectiveness of this intervention in the community. The observational studies included in this review were conducted in atypical settings, and the effectiveness of isolation in these settings might not be generalizable to the community-at-large. Nonetheless, with the rationale discussed, and assuming that a high level of compliance with home isolation is possible for symptomatic persons, voluntary home isolation could be a preferable strategy to prevent onward transmission compared with other personal protective measures, which have not shown effectiveness in multiple randomized controlled trials.

One area in which there is a lack of evidence is the duration of infectivity, which has implications for the period of voluntary isolation. Current recommendations include voluntary isolation until cessation of fever or until 5–7 days after illness onset (*4*,*12*). The second recommendation would be a better trigger for uncomplicated cases without concurrent conditions, benchmarking the duration of viral shedding (*13*). Another area of uncertainty is the

Table 1. Summary of results for systematic review of literature on nonpharmaceutical interventions for pandemic influenza*

Type of NPI	No. studies identified	Study designs included	Main findings
Isolation	15	Observational, simulation	Isolation has moderate impact in reducing influenza transmission and impact.
Quarantine	16	Intervention study, observational, simulation	Quarantine has in general moderate impact in reducing influenza transmission and impact.
Contact tracing	4	Simulation	Combination of contact tracing with other measures (e.g., isolation and quarantine) can reduce influenza transmission and impact; the addition of contact tracing to existing measures might provide only modest benefit but will need substantial resources.
School closure			
Planned holiday	28	Observational	The transmission of influenza decreases during routine school holidays but might increase after schools reopen.
Reactive closures	16	Observational	The effectiveness of reactive school closure varies.
Preemptive closures	13	Observational	Preemptive school closure has moderate impact in reducing influenza transmission.
Workplace measures	18	Intervention study, observational, simulation	Workplace measures are effective; combination with other interventions will further strengthen the effect.
Workplace closures	10	Simulation	Workplace closures might have modest impact in reducing influenza transmission.
Avoiding crowding	3	Observational	Timely and sustained application of measures to avoid crowding might reduce influenza transmission.

*Details of literature review are described in the Appendix (https://wwwnc.cdc.gov/EID/article/26/5/19-0995-App1.pdf)

degree to which transmission occurs before illness onset (presymptomatic transmission) and the degree to which mild or asymptomatic cases are infectious. If there is a substantial fraction of asymptomatic transmission (*14*), this fraction would reduce the impact of isolation.

Contact Tracing

We reviewed 4 simulation studies, all of which found contact tracing to be effective when used in combination with other interventions, including isolation, quarantine, and prophylactic treatment with antiviral drugs (*11*,*15*–*17*). However, Wu et al. (*15*) estimated that the addition of contact tracing to an existing combination of quarantine, isolation, and antiviral prophylaxis measures would only provide modest benefit, while increasing considerably the proportion of population in quarantine and the consequent costs.

Contact tracing requires substantial resources to sustain after the early phases of a pandemic because the number of case-patients and contacts grows exponentially within a short generation time. Therefore, there is no obvious rationale for the routine use of contact tracing in the general population for control of pandemic influenza. However, contact tracing might be implemented for other purposes, such as identification of case-patients in high-risk groups to enable early treatment. There are some specific circumstances in which contact tracing might be more feasible and justified, such as to enable short delay of widespread transmission in small, isolated communities, or within aircraft settings to prevent importation of cases.

Quarantine of Exposed Persons

We reviewed 1 intervention study (*18*), 5 observational studies (*6*,*19*–*22*), and 10 simulation studies (Appendix Tables 9, 10). Miyaki et al. (*18*) conducted an intervention study in Japan during 2009–2010 involving 2 companies. One company was used as a control; in the other company, a change was introduced in which employees could voluntarily stay at home on receiving full pay when a household member showed development of influenza-like illness (ILI) until days after the symptoms subside. The authors reported a significant reduced rate of infections among members of the intervention cluster (*18*). However, when comparing persons who had an ill household member in the 2 clusters, significantly more infections were reported in the intervention group, suggesting that quarantine might increase risk for infection among quarantined persons (*18*).

Among the observational studies, Li et al. (*20*) estimated that the mandatory quarantine policy in Beijing during the influenza A(H1N1)pdm09 pandemic reduced the number of cases at the peak of the epidemic by a factor of 5 compared with a projected scenario without the intervention, and also delayed the epidemic peak, albeit at high economic and social costs (*20*). Similar to the intervention study in Japan, van Gemert et al. (*21*) reported an increased risk for infection among household contacts who were concurrently quarantined with an isolated person and estimated that the risk for infection increased with a longer duration of quarantine. The evidence base from simulation studies supplemented these

findings, and in general, quarantine is suggested to be able to reduce transmission.

In addition, we found some observational evidence for maritime and onboard quarantine. McLeod et al. (*22*) analyzed archival data for the 1918–19 pandemic from the South Pacific jurisdictions and found that strict maritime quarantine delayed or prevented arrival of the pandemic, indirectly reducing the mortality rate compared with that for islands that practiced partial or no maritime quarantine. However, the applicability of these findings is uncertain because maritime travel is uncommon in the 21st century. Conversely, Fujita et al. (*19*) reviewed the onboard quarantine experience at Narita International Airport in Tokyo, Japan, during the influenza A(H1N1) pdm09 pandemic, and reported that the intervention detected few cases and was ineffective in preventing virus entry into the country (*19*).

Overall, we found that the evidence base was weak for home quarantine. In general, the intervention is estimated to be effective. However, being able to identify case-patients and their close contacts in a timely manner can be challenging during the early phase of a pandemic, and impossible for health authorities after the early phase. Quarantine also raises major ethical concerns regarding freedom of movement because the evidence on the effectiveness is limited, providing no solid rationale for the intervention, in addition to restricting movement of some uninfected and noninfectious persons. The increased risks of infection among quarantined persons (*18*,*21*,*23*) further exacerbate the ethical concerns. Therefore, voluntary/self-quarantine is likely to be preferred over mandatory quarantine in most scenarios (*24*). No evidence-based insights or discussions have addressed the optimal duration of quarantine or deactivating trigger. Theoretically, a quarantine duration of 4 days might be sufficient, covering 2 incubation periods of influenza (*25*). If necessary, the duration could be adjusted once the incubation period distribution of the pandemic virus strain is established. Prolonged quarantine can cause substantial burden to social services and working persons (*26*). Some measures can be taken to minimize the possible harms, such as pairing quarantine with antiviral prophylaxis provision for the household (*23*).

School Dismissals or Closures

School dismissal refers to the situation where a school campus remains open with administrative staff and teachers present but most children stay at home. Schools can then continue to provide meals for children from low-income families or look after children of essential workers. School closure is a stricter intervention in which a school campus is closed to all children and all staff. Although most of the currently available studies on the impact of school dismissals or closures on influenza transmission are presented as studies of school closures, we found that the interventions applied were in some instances school dismissals. Because it was not always possible to identify whether a scenario involved closure or dismissal, and because we expected the effects of closure and dismissal on transmission to be roughly similar, we did not distinguish between the 2 scenarios in our systematic review.

Jackson et al. (*27*) published a systematic review in 2013 that included 79 epidemiologic studies on school closures and found compelling evidence that school closures could reduce influenza transmission, especially among school-age children. However, the duration and the optimal timing of closure were not clear because of the heterogeneity in the available data, and transmission tended to increase when schools reopened (*27*). To update the evidence base presented by Jackson et al., we identified 22 additional studies published since 2013 and included 101 epidemiologic studies in total (Appendix Tables 14–17). Most of these studies were conducted in primary and secondary schools; only a few studies were conducted in universities. Overall, findings from the updated systematic review supported the conclusions by Jackson et al.

Thirteen studies investigated preemptive school closures, in which schools are closed with the aim of slowing transmission in the community (*28*). A correlation analysis between weekly mortality rates and interventions (which included school closure) during the 1918–19 pandemic in cities in the United States estimated that early and sustained interventions reduced mortality rates by ≤25% (*29*). Two studies conducted in Hong Kong as a public health response to influenza A(H1N1)pdm09 estimated that school closures, followed by planned school holidays, reduced influenza transmission (*30*,*31*).

We found 16 studies reporting the effectiveness of reactive school closures, in which individual schools or groups of schools were closed after substantial ILI outbreaks in those schools (*28*). Two studies conducted in Japan estimated that the peak number of cases and the cumulative number of cases were reduced by ≈24% (*32*) and 20% (*33*). However, some studies estimated that reactive school closures had no effect in reducing the total attack rate and duration of school outbreaks, and the spread of influenza (*34*–*36*).

The effect of routine school holidays in reducing influenza transmission was investigated in 28 studies. Planned school holidays were estimated to reduce influenza transmission and delay the time to epidemic peak occurrence for >1 week (*37*,*38*). In some instances, transmission resurged after schools reopened (*39*).

It is well established that school children play a major role in spreading influenza virus because of higher person-to-person contact rates, higher susceptibility to infection, and greater infectiousness than adults (*40*,*41*). Therefore, school closures or dismissals are a common-sense intervention to suppress transmission in the community, and several observational studies have confirmed that overall transmission of influenza in the community is reduced when schools are closed. However, major caveats are noted in the literature, primarily that transmission will only be reduced when schools are closed. In some past epidemics, closing of schools after the epidemic peak showed little impact on the overall attack rate and none on the timing of the peak or the size of the epidemic peak because it has already passed (*27*). In other past epidemics, transmission resurges after schools reopen, so that the closures delayed the epidemic peak but might not necessarily have reduced the size of the epidemic peak or the overall attack rate (*27*). Although these points seem obvious, the appropriate timing and duration of school closures can be difficult to discern in the heat of an epidemic with delays in information and difficulties in interpreting surveillance data.

School closures can also have adverse impacts on ethical and social equity, particularly among vulnerable groups (e.g., low-income families), which could be ameliorated by dismissing classes, but allowing some children to attend school for free school meals or to enable parents to go to work. Extended school closures might increase domestic travel and contact rates in households and other social gatherings (e.g., malls, theaters), with the potential to increase transmission in the community. The optimum combination of timing, geographic scale, and duration of school closure might differ for the control of different epidemic/pandemic scenarios (*42*). A useful area for further research would be providing validated tools to enable real-time estimation of not only how an epidemic or pandemic is progressing (*43*), but also what the public health impact of an intervention, such as school closure, would be with alternative choices of timing and duration.

Workplace Measures and Closures

Workplace measures and closures aim to reduce influenza transmission in workplaces or during the commute to and from work. Teleworking at home, staggered shifts, and extended holidays are some common workplace measures considered for mitigating influenza pandemics. A systematic review of workplace measures by Ahmed et al. (*2*) concluded that there was evidence, albeit weak, to indicate that these measures could slow transmission, reduce overall attack rates or peak attack rates, and delay the epidemic peak. We updated the evidence base with 3 additional recently published studies and obtained similar results (Appendix Table 20). Paid sick leave could improve compliance with a recommendation to stay away from work while ill (*44*,*45*).

We conducted a separate search for evidence on the effectiveness of workplace closures in influenza pandemics and identified 10 studies, all of which were simulation studies (Appendix Table 21). In general, the simulation studies predicted that workplace closures would be able to reduce transmission somewhat in the community, but probably would have a smaller effect on transmission than school closures.

We found limited evidence that workplace measures and closures would be effective in reducing influenza transmission. Two recent studies not included in our systematic review have contrasting findings on the effect of having paid sick leave and taking a day off from work because of ILI (*46*,*47*). As with school closures, the timing and duration of workplace interventions would be a critical issue affecting their impact in mitigating a pandemic. This scenario is an area with rich potential for intervention studies to contribute higher quality evidence (e.g., teleworking policies or staggered shifts). However, workplace measures and closures could have considerable economic consequences, and inclusion in pandemic plans would need careful deliberations over which workplaces might be suitable for application of interventions, whether to compensate employees or companies for any loss in income or productivity, and how to avoid social inequities in lower income workers, including persons working on an ad hoc basis.

Avoiding Crowding

We reviewed 3 observational studies (*6*,*48*,*49*). Timely bans on public gatherings and closure of public places, including theaters and churches, were suggested to have had a positive effect on reducing the excess death rate during the 1918 pandemic in the United States (*6*,*48*). During an influenza outbreak that occurred during World Youth Day 2008, a higher attack rate was reported among a group of pilgrims accommodated in 1 large hall than in pilgrims sleeping in smaller groups (*49*).

The evidence for avoiding crowding is limited. The implementation of measures to avoid crowding

might require a large amount of resources (e.g., financial and trained personnel), which might be less feasible in low-income and middle-income countries. Measures to avoid crowding might also be difficult to implement in some settings because of cultural and religious reasons (e.g., Hajj).

Discussion

Overall, our systematic reviews suggested that social distancing measures could be effective interventions to reduce transmission and mitigate the impact of an influenza pandemic. However, the evidence base for these measures was derived largely from observational studies and simulation studies; thus, the overall quality of evidence is relatively low. Natural experiments or controlled studies of single or combined interventions are needed to clarify the use of social distancing measures; improve knowledge on basic transmission dynamics of influenza, including the role of presymptomatic contagiousness and the fraction of infections that are asymptomatic (*50*); determine the optimal timing and duration for implementation of these measures, and school closures in particular; and provide cost-benefit assessment for implementation of these measures (Table 2).

Table 2. Knowledge gaps on social distancing measures as nonpharmaceutical interventions for pandemic influenza and suggested areas for future study

Intervention	Knowledge gaps	Suggested studies
Isolation of sick persons	Few observational studies use laboratory-confirmed influenza as outcome and study isolation as a single intervention; most observational studies were in atypical settings; transmission dynamics of influenza: role of presymptomatic contagiousness, fraction of infections that are asymptomatic, duration of infectivity; optimal strategy for symptomatic persons, trigger to stop isolation	Randomized trials in community settings to evaluate the effectiveness of voluntary isolation against transmission of laboratory-confirmed influenza; epidemiologic studies to understand transmission dynamics of influenza, including symptomatic profiles and duration of infectiousness; compliance of the public with voluntary isolation at home
Contact tracing	Value of adding contact tracing on top of other existing interventions remain unclear; strategy for feasible implementation	Might not be a research priority for pandemic preparedness because of the lack of feasibility of this intervention
Quarantine of exposed persons	Few observational studies use laboratory-confirmed influenza as outcome and provide evidence on the effect of quarantine as a single intervention or the value quarantine adds to existing interventions; transmission dynamics of influenza: fraction of infections that are asymptomatic, possibility of superspreaders; optimal duration of quarantine	Randomized trials in community settings to evaluate the effectiveness of quarantine against transmission of laboratory-confirmed influenza; epidemiologic studies to understand transmission dynamics of influenza including the incubation period and the asymptomatic fraction
School closures	Triggers to close and reopen schools; optimal timing and duration of school closures, taking into account the possible disruptions to the public; compliance of persons of different socioeconomic status; alternative school-based measures, such as staggering lunch breaks and increasing spacing between desks: feasibility and effectiveness	Observational studies on optimal closure triggers and duration, taking into account the possible disruptions brought by school closures; comprehensive review of the acceptance and compliance of the interventions by different subgroups of the population; develop tools to enable real-time estimation of epidemic or pandemic growth, and the effect of implementing closures at different time points of the epidemic/pandemic; while school-based measures were not specifically covered in our systematic review, it would be useful to examine randomized trials of measures to prevent influenza transmission in schools, such as increasing spacing between desks during influenza seasons
Workplace measures and closures	Triggers to close and reopen workplaces; optimal timing and duration of workplace closure, taking into account the possible disruption to the public; alternative workplace measures (e.g., improving teleworking infrastructure, or providing segregated working areas for persons with mild symptoms): feasibility and effectiveness, cost-benefit	Randomized control trials to evaluate the effectiveness of workplace measures (e.g., telework from home, staggered shifts, weekend extension and paid-leave policies) against laboratory-confirmed influenza transmission; studies on optimal triggers, timing and duration for workplace measures and closures, taking into account the possible disruptions caused by workplace measures; cost-benefit analyses of alternative workplace measures
Avoiding crowding	Methods to reduce population density in different settings (e.g., transport hub, mass events, and public places): feasibility and effectiveness	More observational or simulation studies on the alternative methods to avoid crowding in different settings.
Combined interventions	Limited evidence on synergy of alternative interventions or the best combinations of interventions	Policy studies to identify feasible interventions that would complement each other when combined

Although we reviewed the evidence for each NPI individually, it is common for social distancing measures to be implemented in combination. For example, during the 1918 pandemic, multiple NPIs were implemented simultaneously in some cities in the United States, including school closures and public gathering bans (*6*). Although simulation studies have estimated progressively increasing effectiveness as more NPIs are added, we believe that some thought should be given to identifying interventions that would complement each other when combined. Social distancing measures such as school closures and mall closures could be implemented simultaneously to prevent an increase in social contact rates outside schools. School closures could also be paired with teleworking policies to provide opportunities for parents to take care of school-age children at home.

Despite the limitations and uncertainties, social distancing measures will be useful components of the public health response to the next pandemic. Careful consideration of these measures is required when composing pandemic plans, particularly in terms of public compliance and resource planning and distribution. Recommending that ill persons stay at home is probably the most straightforward social distancing measure, and pandemic plans should consider how to enable ill children and employees to stay at home from school or work. For example, health authorities might recommend suspending the usual requirement for doctors' notes to support absence from school or work. Finally, although our review focused on nonpharmaceutical measures to be taken during influenza pandemics, the findings could also apply to severe seasonal influenza epidemics.

In conclusion, our review found some evidence from observational and simulation studies to support the effectiveness of social distancing measures during influenza pandemics. Timely implementation and high compliance in the community would be useful factors for the success of these interventions. Additional research on transmission dynamics, and research on the optimal timing and duration of school and workplace closures would be useful.

This study was conducted in preparation for the development of guidelines by the World Health Organization on the use of nonpharmaceutical interventions for pandemic influenza in nonmedical settings.

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Public health interventions and epidemic intensity during the 1918 influenza pandemic

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Nonpharmaceutical interventions (NPIs) intended to reduce infectious contacts between persons form an integral part of plans to mitigate the impact of the next influenza pandemic. Although the potential benefits of NPIs are supported by mathematical models, the historical evidence for the impact of such interventions in past pandemics has not been systematically examined. We obtained data on the timing of 19 classes of NPI in 17 U.S. cities during the 1918 pandemic and tested the hypothesis that early implementation of multiple interventions was associated with reduced disease transmission. Consistent with this hypothesis, cities in which multiple interventions were implemented at an early phase of the epidemic had peak death rates ≈50% lower than those that did not and had less-steep epidemic curves. Cities in which multiple interventions were implemented at an early phase of the epidemic also showed a trend toward lower cumulative excess mortality, but the difference was smaller (≈20%) and less statistically significant than that for peak death rates. This finding was not unexpected, given that few cities maintained NPIs longer than 6 weeks in 1918. Early implementation of certain interventions, including closure of schools, churches, and theaters, was associated with lower peak death rates, but no single intervention showed an association with improved aggregate outcomes for the 1918 phase of the pandemic. These findings support the hypothesis that rapid implementation of multiple NPIs can significantly reduce influenza transmission, but that viral spread will be renewed upon relaxation of such measures.

mitigation | nonpharmaceutical interventions | closures

Influenza pandemics have occurred periodically in human populations, with three pandemics in the 20th century. The 1918 influenza pandemic resulted in unprecedented mortality, with an estimated 500,000–675,000 deaths in the U.S. and 50–100 million deaths worldwide (1–3). The spread of H5N1 avian influenza has provoked public concern (4) and accelerated efforts to plan for the next pandemic. Because antiviral medications and effective vaccines may not be widely available at the beginning of a pandemic, many authorities have suggested using nonpharmaceutical interventions (NPIs; i.e., voluntary quarantine of infected households, closure of schools, bans on public gatherings, and other measures) to decrease disease transmission. This approach is supported by mathematical models, which suggest that multiple simultaneous NPIs applied early in an epidemic may significantly reduce disease transmission (5). A recent review, however, concluded that the evidence base for recommending such interventions is limited, consisting primarily of historical and contemporary observations, rather than controlled studies (6).

The intensity of the 1918 pandemic, whether assessed as total excess deaths, the rate of increase in the epidemic curve, or peak death rates, varied widely among U.S. cities. Cities also varied widely in their choice and timing of implementation of NPIs designed to reduce disease spread. Many cities closed schools, churches, theaters, dance halls, or other public accommodations; made influenza a notifiable disease; banned funerals or other public gatherings; or introduced isolation of sick persons. In some cases, these NPIs were put in place in the first days of epidemic spread in a city, whereas in other cases, they were introduced late or not at all (Table 1).

We noted that, in some cases, outcomes appear to have correlated with the quality and timing of the public health response. The contrast of mortality outcomes between Philadelphia and St. Louis is particularly striking (Fig. 1). The first cases of disease among civilians in Philadelphia were reported on September 17, 1918, but authorities downplayed their significance and allowed large public gatherings, notably a city-wide parade on September 28, 1918, to continue. School closures, bans on public gatherings, and other social distancing interventions were not implemented until October 3, when disease spread had already begun to overwhelm local medical and public health resources. In contrast, the first cases of disease among civilians in St. Louis were reported on October 5, and authorities moved rapidly to introduce a broad series of measures designed to promote social distancing, implementing these on October 7. The difference in response times between the two cities (≈14 days, when measured from the first reported cases) represents approximately three to five doubling times for an influenza epidemic. The costs of this delay appear to have been significant; by the time Philadelphia responded, it faced an epidemic considerably larger than the epidemic St. Louis faced. Philadelphia ultimately experienced a peak weekly excess pneumonia and influenza (P&I) death rate of 257/100,000 and a cumulative excess P&I death rate (CEPID) during the period September 8–December 28, 1918 (the study period) of 719/100,000. St. Louis, on the other hand, experienced a peak P&I death rate, while NPIs were in place, of 31/100,000 and had a CEPID during the study period of 347/100,000. Consistent with the predictions of modeling, the effect of the NPIs in St. Louis appear to have had a less-pronounced effect on CEPID than on peak death rates, and death rates were observed to climb after the NPIs were lifted in mid-November (7–9).

To investigate whether early implementation of individual interventions or of multiple measures reduces disease transmission during influenza pandemics, we analyzed the NPIs used in a collection of U.S. cities during the fall wave of the 1918 pandemic, identifying the NPIs used in each city as well as the timing of their implementation [details of individual city outcomes and interven-

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Abbreviations: P&I, pneumonia and influenza; CEPID, cumulative excess P&I deaths; NPI, nonpharmaceutical intervention; CFP, case-fatality proportion.

See Commentary on page 7313.

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Table 1. Summary of interventions and their timing across 17 cities

Intervention	Number of 17 cities implementing	Median (interquartile range) epidemic stage (CEPID) at time of implementation*
Making influenza a notifiable disease	15	5.6 (3.1, 25.9)
Emergency declarations	4	—
Isolation policies	14	15.7 (7.6, 30.8)
Quarantine of households where infection identified	5	—
School closures	14	30.8 (15.1, 96.3)
Church closures	15	29.9 (12.4, 130.6)
Theater closures	15	29.9 (10.3, 66.9)
Dance hall closures	11	44.7 (12.4, –)
Other closures	13	84.7 (29.9, 322.0)
Staggered business hours to reduce congestion in stores and on transit systems	8	—
Mask ordinances	2	—
Rules forbidding crowding on streetcars	6	—
Private funerals	11	92.1 (30.8, –)
Bans on door-to-door sales	1	—
Interventions designed to reduce transmission in the workplace	0	—
Protective sequestration of children	3	—
Bans on public gatherings	15	30.8 (12.4, 118.1)
No-crowding rules in locations other than transit systems	3	—
Community-wide business closures	1	—

*Shown only for interventions implemented in at least nine cities (>50%); 75th percentile not shown for interventions implemented in <13 cities.

tions are included in supporting information (SI) *Appendix*]. We then related this information to the observed outcomes of the peak weekly death rate and CEPID during the period September–December, 1918. Excess death rates were used as a proxy for case incidence because of the more accurate reporting of deaths than cases. We hypothesized that early implementation of multiple NPIs in an immunologically naïve population would slow the progression of the epidemic, resulting in a flatter epidemic curve, but that over time aggregate outcomes would approach those observed in cities not implementing such measures, until roughly comparable levels of herd immunity were achieved.

Results

Effect of Early Interventions on Epidemic Spread. We assessed the relationship between the timing of NPIs and three measures of epidemic outcome: (*i*) the peak weekly rate of excess P&I deaths per 100,000 population (peak death rate) during the study period; (*ii*) the "normalized" peak weekly excess P&I death rate (peak weekly death rate during the study period divided by the median weekly rate during the period); and (*iii*) the CEPID per 100,000 population during the study period. The stage of the epidemic at the time of each intervention was defined as the CEPID from the start of the study period until

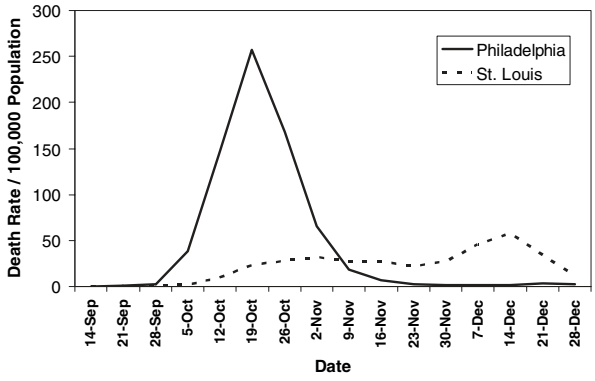

Fig. 1. Excess P&I mortality over 1913–1917 baseline in Philadelphia and St. Louis, September 8–December 28, 1918. Data are derived from ref. 10.

the date on which the intervention was announced. Thus, early interventions in a given city were those that were implemented when relatively few individuals had died, whereas later ones

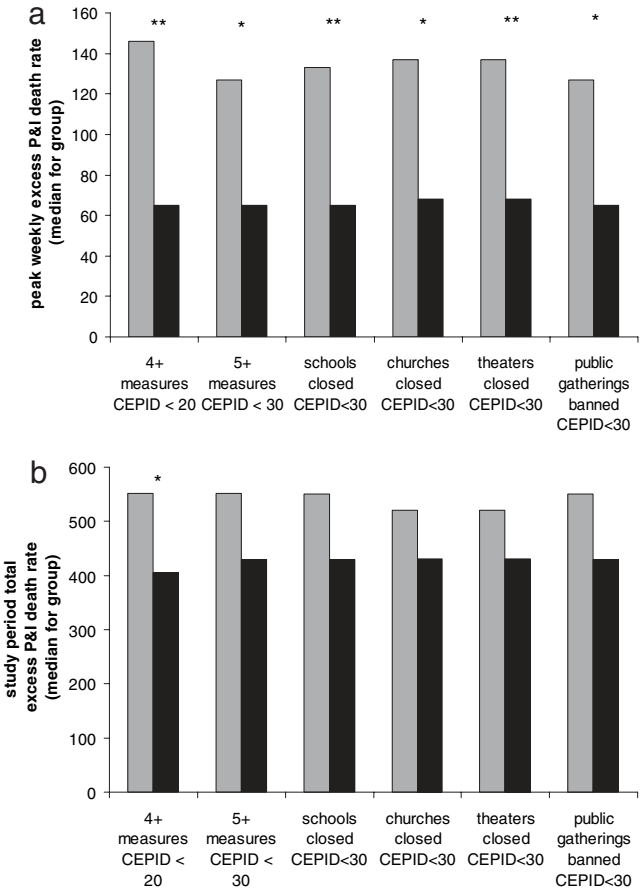

Fig. 2. Relationship of (*a*) peak weekly excess P&I death rate and (*b*) total excess P&I death rate during the study period to the timing of various NPIs. Cities were divided evenly into those intervening early (black bars) vs. late or not at all (gray bars), and the median outcome for the early and late groups was plotted. The first two groups of bars assess overall timing of intervention, comparing those cities that announced four or more NPIs before experiencing 20/100,000 CEPID with those with three or fewer and those that announced five or more NPIs before experiencing 30/100,000 CEPID with those with four or fewer. The remaining groups compare those cities that announced particular measures before experiencing 30/100,000 CEPID with those that did not. Significance by Mann–Whitney *U* test: *, $P < 0.05$; **, $P < 0.01$.

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Table 2. Correlation between influenza epidemic outcomes and timing of interventions in 17 U.S. cities in 1918

Measure of interventions	Outcome: Excess weekly P&I deaths		
	Peak	Normalized peak	1918 total
Number of interventions before:			
10/100,000 CEPID	**−0.53, $P = 0.03$**	**−0.53, $P = 0.03$**	−0.31, $P = 0.22$
20/100,000 CEPID	**−0.68, $P = 0.002$**	**−0.64, $P = 0.005$**	**−0.52, $P = 0.03$**
30/100,000 CEPID	**−0.51, $P = 0.04$**	**−0.55, $P = 0.02$**	−0.29, $P = 0.27$
40/100,000 CEPID	−0.32, $P = 0.21$	−0.40, $P = 0.11$	−0.07, $P = 0.80$
CEPID at time of intervention:			
First	0.08, $P = 0.76$	0.004, $P = 0.87$	0.07, $P = 0.79$
Second	**0.54, $P = 0.02$**	0.47, $P = 0.06$	0.39, $P = 0.12$
Third	**0.54, $P = 0.02$**	**0.52, $P = 0.03$**	0.31, $P = 0.22$
Fourth	**0.66, $P = 0.004$**	**0.70, $P = 0.002$**	0.38, $P = 0.13$
Fifth	**0.55, $P = 0.02$**	**0.67, $P = 0.003$**	0.27, $P = 0.30$
Sixth	0.26, $P = 0.31$	0.44, $P = 0.08$	0.05, $P = 0.84$
CEPID at time of:			
Closing schools	**0.54, $P = 0.02$**	**0.63, $P = 0.007$**	0.25, $P = 0.34$
Closing theaters	**0.56, $P = 0.02$**	**0.72, $P = 0.001$**	0.17, $P = 0.52$
Closing churches	**0.56, $P = 0.02$**	**0.70, $P = 0.002$**	0.17, $P = 0.53$
Closing dance halls	0.03, $P = 0.90$	0.04, $P = 0.87$	0.15, $P = 0.57$
Other closures	0.33, $P = 0.19$	0.34, $P = 0.18$	0.24, $P = 0.35$
Making influenza notifiable	0.01, $P = 0.97$	−0.07, $P = 0.79$	0.11, $P = 0.67$
Bans on public gatherings	0.46, $P = 0.06$	**0.56, $P = 0.02$**	0.27, $P = 0.30$
Imposing case isolation	0.16, $P = 0.53$	0.14, $P = 0.59$	0.13, $P = 0.62$
Bans on public funerals	−0.09, $P = 0.75$	0.09, $P = 0.72$	−0.41, $P = 0.10$

Three measures of epidemic intensity. Peak weekly excess P&I death rate, normalized peak weekly excess P&I death rate (peak divided by median weekly rate during the study period), and 1918 study period total excess P&I death rate are related to number of interventions before reaching a specified CEPID, CEPID at time when specified numbers of interventions had been imposed, and CEPID at time when specific interventions had been imposed. Spearman rank correlations and associated P values are shown, with bold type for $P < 0.05$.

were those implemented after more excess P&I deaths had occurred.

In comparisons across cities (Fig. 2*a*, Table 2), we found that aggressive early intervention was significantly associated with a lower peak of excess mortality (Spearman $\rho = -0.49$ to -0.68, $P = 0.002$–0.047; see Table 2, *Number of interventions before*, for the number of NPIs before a given CEPID cutoff vs. peak mortality). Cities that implemented three or fewer NPIs before 20/100,000 CEPID had a median peak weekly death rate of 146/100,000, compared with 65/100,000 in those implementing four or more NPIs by that time (Fig. 2*a*, $P = 0.005$). The relationship was similar for normalized peak death rates and for a range of possible cutoffs (see Table 2, *CEPID at time of intervention*), although the relationship became weaker as later interventions were included. Cities with more early NPIs also had fewer total excess deaths during the study period (Fig. 2*b*, Table 2, *1918 total*), but this association was weaker: cities with three or fewer NPIs before CEPID = 20/100,000 experienced a median total excess death rate of 551/100,000, compared with a median rate of 405/100,000 in cities with four or more NPIs ($P = 0.03$).

The association of early intervention and lower peak death rates was also observed when cities were ranked according to the CEPID in each city at the time of the second, third, fourth, or fifth intervention (Table 2, *CEPID at time of intervention*). Similar relationships were again detected for the normalized peak death rate [Table 2, *CEPID at time of intervention/Normalized peak*]. Again, the relationship with total death rate was weaker and in this case not statistically significant.

Effects of Individual Interventions. To assess whether particular NPIs were associated with better outcomes, we calculated a Spearman rank correlation coefficient between outcome measures and the stage at which individual NPIs were implemented in each city (cities that never implemented a given intervention were ranked last in each analysis). Results are shown in Table 2, *CEPID at time of*. Early school, church, or theater closure was associated with lower peak excess death rates (Spearman $\rho = 0.54$–0.56, $P = 0.02$). Cities that made each of these interventions before they reached 30/100,000 CEPID had a median peak death rate of 65–68/100,000, compared with median peaks of 127–146/100,000 for cities that made these interventions later or not at all (Fig. 2*a*, $P = 0.005$–0.01). Announcements of school, church, and theater closures were linked in most cities, occurring within a span of ≤6 days in the majority, and this near simultaneity of implementation precludes multivariate analysis or strong inference about the relative importance of the individual NPIs. Early bans on public gatherings were also associated with lower peak excess death rates, but the statistical significance of this result depended on the test used [Table 2, *CEPID at time of*, and Fig. 2*a*]. Of the other NPIs considered (closure of dance halls, other closures, isolation of cases, bans on public funerals, and making influenza notifiable), none showed a statistically significant association between the stage of implementation and the peak or cumulative excess death rates (Table 2, *CEPID at time of*, and Fig. 2).

Other Predictors of Epidemic Severity. We assessed the correlation between peak mortality rate and each of the following variables: latitude, longitude, 1910 population density, 1920 population density, 1918 population size, and epidemic start week, defined as the first week in which excess P&I mortality exceeded 10/100,000. Of these variables, only longitude (Spearman $\rho = -0.61$, $P = 0.009$) and epidemic start week (Spearman $\rho = -0.55$, $P = 0.02$) were significantly associated with the peak weekly excess P&I mortality rate, and these two variables were strongly associated with one another (Spearman $\rho = 0.66$, $P = 0.004$), indicating that eastern U.S. cities were hit earlier in our data set. In addition, cities whose epidemics began later tended to intervene at an earlier stage of their

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epidemics (Spearman $\rho = 0.77$, $P = 0.0003$), presumably because local officials in these cities observed the effects of the epidemic along the Eastern seaboard and resolved to act quickly.

In linear regressions of peak death rates vs. stage of the epidemic at the time of interventions (number of NPIs before CEPID = 20/100,000) and timing of epidemic onset, the association of peak with intervention stage was statistically significant and stronger than that with epidemic onset in univariate models (SI Table 3). If both predictors are used in a bivariate regression, the point estimate for interventions remains unchanged while the p value increases to 0.13; no independent effect of week of onset is seen in this bivariate model. Similar results are found for longitude (data not shown). Subject to the caveats of performing a linear regression on only 17 cities with such highly correlated explanatory variables, this finding suggests that the relationship between early intervention and lower peak death rates is explained by factors of geography or timing of epidemic onset only to the extent that these factors influenced the quality of the public health response.

Sensitivity Analyses. Similar results were obtained when the intervention date was defined as the date public health orders were promulgated (Table 2) or the last date a particular type of gathering was permitted (e.g., Sunday church service; SI Table 4). Results were identical or improved when 7- and 10-day lags in assessing CEPID were introduced to account for the lag between infection and death (SI Tables 5 and 6).

Relationship Between Interventions and Subsequent Waves. Although it was not the primary intent of this paper to analyze pandemic wave dynamics, it is possible to formulate descriptive observations from the data at hand (SI Table 7). In offering these observations, it is important to underscore that in some cities, information about the dates of relaxation of the interventions used was incomplete.

All cities showed some fluctuation in mortality rates after the main wave of the 1918 pandemic subsided. The peak weekly mortality rates observed in "second waves" in the cities we studied ranged from 13.60 to 79.69/100,000, as compared with 31.29–256.96/100,000 during the first wave. There was a statistically significant inverse correlation of the height of the first and second peaks (Spearman $\rho = -0.53$, $P = 0.03$), so that cities that had low peaks during the first wave were at greater risk of a large second wave. Cities that had lower peak mortality rates during the first wave also tended to experience their second waves after a shorter interval of time, ≈6–8 weeks after the first peak vs. 10–14 weeks for cities with higher peak mortality rates (Spearman $\rho = -0.84$, $P < 0.0001$). These patterns were also observed in cities that implemented NPIs sooner [as assessed by ranking the cities according to their CEPID at school closure (Spearman $\rho = 0.63$, $P = 0.006$) or CEPID at time of the fourth intervention (Spearman $\rho = 0.52$, $P = 0.03$)]. Finally, and this is perhaps the most important observation, no city in our analysis experienced a second wave while its main battery of NPIs was in place. Second waves occurred only after the relaxation of interventions.

Discussion

Comparisons across 17 U.S. cities show that the first peak in excess P&I death rates during the fall wave of the 1918 influenza pandemic was ≈50% lower in cities that implemented multiple NPIs to control disease spread early in their epidemics than in cities that made such interventions late or not at all. This finding suggests that such interventions may be capable of significantly reducing the rate of disease transmission so long as they remain in effect.

If NPIs were maintained indefinitely once they were put in place, one would expect that early interventions would be associated with a reduction in both the peak incidence (and therefore peak death rate) and also in the cumulative incidence or cumulative excess death rate. However, NPIs used in 1918 did not last indefinitely; rather, most of the NPIs in the study cities appear to have been relaxed within 2–8 weeks, whereas opportunities for reintroduction and transmission of the pandemic virus extended for many months. If highly effective NPIs are put in place early in the epidemic, and these result in a smaller epidemic, then a large proportion of the population will remain susceptible to the renewed spread of the virus once interventions are relaxed. In the absence of an effective method of otherwise inducing immunity in the uninfected population (i.e., a well matched vaccine), such an epidemic is likely to have two phases, with the first phase mitigated by NPIs and the second commencing after NPIs are relaxed. In our review of 17 cities, we observed that cities that implemented NPIs sooner had lower peak mortality rates during the first wave and were at greater risk of a large second wave. These cities also tended to experience their second waves after a shorter interval of time. As described above, no city in our analysis experienced a second wave while its main battery of NPIs was in place, and second waves occurred only after the relaxation of NPIs.

A mitigated two-phase epidemic may result in a cumulative burden of morbidity and mortality less than that observed in a single unchecked epidemic because of reduced epidemic overshoot (7–9). However, the relationship between the timing of transiently maintained NPIs and final outcomes will be complicated and not necessarily monotonic (10). Because our goal was to assess the evidence for an effect of NPIs on transmission, rather than to assess whether the particular NPIs in 1918 were sustained long enough to prevent epidemic spread altogether, we defined peak death rates *a priori* as the main outcome measure. Consistent with these expectations, the relationship between intervention timing and peak death rates was stronger and statistically more convincing than that with total death rates in 1918.

The most important limitation of our study is that we used observed weekly excess fatality rates as a proxy for weekly community morbidity rates, which are not available for the study period. We believe that untransformed excess mortality rates are the most reliable (and least assumption-laden) record of the effects of the pandemic, but it is important to note that case fatality proportions (CFP) in 1918 appear to have varied between populations [being higher, for example, among the Inuit than in the general United States population (1)], likely as a result of differing levels of general public health, and it is possible that they varied between cities in the United States for similar reasons. Varying patterns of bacterial colonization or other, unidentified factors could also have contributed to variation in CFP. Differences in CFP between the cities could introduce a systematic error into our results (because they would lead to higher total deaths at a given stage of the epidemic, and higher peaks, in the same subset of cities). Our use of a normalized peak death rate was designed to avoid this error. If our results were artifacts of city-to-city variation in CFP, then the associations found should become weaker after this normalization; in fact, each of the strongest associations was at least comparably strong after the normalization (Table 2, *Normalized peak*), suggesting that variation in CFP did not create the associations we found.

More generally, a possible explanation for our findings is that inherently small epidemics (i.e., epidemics with flatter and smaller overall mortality curves, because of variation in CFP or in other factors not considered in our analysis) could appear to be associated with earlier interventions as an artifact of how we defined "early." If this were the case, however, even ineffectual NPIs, considered individually, should correlate with lower peak mortality rates. In fact, NPIs that seem less likely to block transmission directly (e.g., making influenza a notifiable disease, closing dance halls, and bans on public funerals) had no such association. That several individual interventions were found not to be associated with lower peaks suggests this statistical artifact is not present.

Previous authors have noted that epidemics that started later tended to be milder and have speculated that this might be due to

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attenuation of the causative virus (3). Although viral attenuation may explain changes in the CFP over the course of the pandemic period (which extended to approximately March 1920), this mechanism seems an unlikely explanation for the striking variability of outcomes during the 1918 fall wave, given the marked transmissibility of the lethal virus and the short intervals between the onset of epidemics in different cities. A potentially more plausible explanation is that public health and political authorities in cities that were struck later responded more quickly and aggressively because they had several weeks' notice of the severity of the pandemic. Subject to the caveats attendant on a linear regression in such a small data set, we found that the stage of the epidemic at the time of interventions predicted peak mortality better than timing of epidemic onset. This finding suggests that the association between early intervention and lower peak mortality may be explained in large part by the fact that later-hit cities responded more promptly. Similar results were obtained when longitude was included in the analysis along with or in place of time of epidemic onset. Although we do not know of any mechanistic hypothesis connecting longitude directly to epidemic severity, our analysis similarly suggests that longitude is not an important confounder of our results.

In a related vein, the analysis of second peaks adds credence to the inference that NPIs were responsible for the observed lower first peaks in cities that implemented NPIs promptly. If lower first peaks were attributable to some other mechanism (e.g., a less virulent virus, seasonal changes in transmission, etc.), it is difficult to explain why, upon relaxation of NPIs, these low-peak cities tended to have larger second peaks. On the other hand, if NPIs curtailed the first wave, leaving more susceptibles in the early-intervention cities, then one would expect a more severe second wave in these cities, as was observed. Altogether, we take these findings as evidence that NPIs were capable of reducing influenza transmission in 1918, but that their benefits (as one would expect) were limited to the time they remained in effect.

In sensitivity analyses, we found that associations between early intervention and better outcomes were strengthened when we timed interventions based on the cumulative excess deaths up to 7 or 10 days after the intervention, an effort to account for the delay expected from case incidence (which is affected by interventions) to mortality. In part, this strengthening likely is due to the fact that delayed death figures better reflect the true stage of the epidemic at time of intervention. However, use of a delay time in this fashion raises concerns about reverse causality. If a delay longer than the shortest time from infection to death is used (e.g., the median, rather than the minimum, time to death), then the number of deaths before intervention, the independent variable in our analysis, is affected by the intervention itself. To avoid such difficulties, we took as our primary analysis the simpler, more conservative approach of defining the stage of the epidemic based on the date of intervention, with no delay. This choice has the additional benefit that in future pandemics, the cumulative excess death rate at the time of an intervention is in principle knowable in nearly real time, whereas the delayed death rate cannot by definition be known at the time of an intervention.

The implications of our analysis should be interpreted with care. Our univariate analyses of the relationship between individual NPIs and outcomes are consistent with the hypothesis that social distancing through closure of particular institutions (schools, churches, and theaters) led to reduced transmission, but the similarities in timing of various NPIs within a given city make it very difficult to discriminate the relative contributions of individual interventions (Fig. 2). Similarly, it was not possible to evaluate the effects of NPIs that were undertaken only in a small number of cities, or that were generally implemented only late in the epidemic, if at all, such as mass transit interventions (rules forbidding crowding and introduction of staggered business hours to reduce crowding on mass transit) or mask ordinances. Whether these NPIs might have made a difference in particular cities where they were implemented early, such early implementation was not common enough to evaluate whether it was associated with better outcomes. A third consideration is that the historical record is not seamless, and it is possible that our source material did not capture the full range of interventions used or reflect the true timing of implementation of those it identifies. Finally, we note that causality may be complicated; the interventions used may themselves have produced the observed effects, or they could have worked by shaping perceptions about the epidemic and causing changes in unmeasured private behaviors. Despite these caveats about the details of interpretation, the relationships detected in our analyses strongly suggest that the aggressive implementation of NPIs resulted in flatter epidemic curves and a trend toward better overall outcomes in the fall of 1918.

To the extent that these results provide evidence that multiple NPIs can reduce influenza transmission and mitigate the impact of a pandemic, they should inform current efforts related to pandemic preparedness. In particular, our results underscore the need for prompt action by public health authorities. The strongest relationship between peak death rates and timing of NPIs was observed for the number of interventions in place before the CEPID exceeded 20/100,000. If we assume a 2% CFP, this approximately corresponds to interventions undertaken before the deaths caused by infections in 1% of the population in a given city had occurred. Given the rate of growth of the pandemic and the lag between infection and death, perhaps 3–6% of the population would have been infected at this time. This finding emphasizes the need for very rapid interventions to stem the spread of the disease. Communities that prepare to implement layered NPIs aggressively are likely to achieve better outcomes than communities that introduce such interventions reactively, and they may be better positioned to manage the disruption caused by the more stringent interventions, such as school closure.

Finally, an important practical issue that requires further study is the question of when such interventions can be relaxed. The implication of patterns observed in the timing and severity of second waves in 1918 seems clear, however. In the absence of an effective vaccine, cities that use NPIs to mitigate the impact of a pandemic remain vulnerable. In practice, and until emergency vaccine production capacity increases, this means that in the event of a severe pandemic, cities will likely need to maintain NPIs for longer than the 2–8 weeks that was the norm in 1918.

Methods

Historical Data. We defined our study period as September 8–December 28, 1918, encompassing the first 16 weeks for which excess P&I death rates were reported by ref. 11. Of the 45 cities reported in ref. 11, we eliminated those cities for which >4 weeks during the study period had missing or partial data (partial data included excess pneumonia deaths only or excess influenza deaths only). Of the remaining cities, we included in the final analysis those 17 cities for which we were able to obtain a complete account of public health responses during the study period from our research in period newspapers, public health reports, or municipal records; from consultations with current public health officials in the study cities; or from well documented secondary sources. We defined 19 categories of public health responses (NPIs, interventions, or measures) and scored the date on which a city implemented each of these interventions. Citations for the scoring of individual NPIs in each city are provided in *SI Appendix*.

Interventions. Cities were scored as implementing an intervention if available evidence suggested that a measure was implemented on a community-wide basis through policy actions. Cities attempting to influence public behavior through exhortation alone (e.g., a recommendation to "avoid crowds" without an explicit ban on their formation) were not scored as implementing an intervention.

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Where possible, dates of implementation of NPIs were cross-checked against multiple sources.

Timing of NPIs was assessed relative to the epidemic in each city by defining the "stage" of an epidemic for a given intervention as the estimated CEPID from September 8, 1918, through the calendar date on which the intervention was announced. Linear interpolation was used for cumulative deaths when this date was between weekly reporting dates in ref. 11. In sensitivity analyses performed to account for the interval between infection (the true measure of transmission) and death (an outcome of infection), we also considered lags of 7 or 10 days in calculating the CEPID, that is, defining the stage of the epidemic at which an intervention was implemented as the CEPID 7 or 10 days after the date of intervention (the median time from infection to death in autopsy reports tabulated in ref. 12 was ≈10 days). In a separate sensitivity analysis, we defined the date of the intervention as the last day that a particular activity was possible, rather than the date on which it was banned. Thus, for example, if a ban on church services was announced on a day other than Sunday, the last activity date was defined as the preceding Sunday; likewise, if school closure was announced during a weekend, the last activity date was the preceding Friday.

The timing of a city's overall response was scored in two closely related ways. First, the number of NPIs (of a possible 19) announced by a city before the CEPID reached a particular threshold (e.g., 20/100,000) was quantified as "number of interventions before CEPID = 20/100,000." This threshold was varied from 10 to 40/100,000 to encompass the range in which there was substantial intercity variation. Second, the CEPID at the time of the first intervention imposed in a city, the second intervention, and so on up to the sixth intervention was calculated.

Outcomes. Epidemic outcomes were measured as (*i*) the first weekly peak excess death rate during the fall wave of the pandemic; (*ii*) normalized peak death rate: the ratio of *i* to the median weekly death rate for a given city during the study period; and (*iii*) cumulative excess deaths during the study period. Outcome *ii* was selected as a measure of the "peakedness" of the epidemic curve that would be insensitive to intercity differences in the CFP.

Data in SI Tables 8–11. Outcomes and CEPID at the time of each intervention are provided in SI Table 8. Dates of intervention intent used in the primary analysis are provided in SI Table 9, whereas last activity dates used in sensitivity analyses are provided in SI Table 10. Weekly excess P&I death rate data transcribed from ref. 10 are provided in SI Table 11. SI Tables 7–11 are in Excel format.

Analysis. To avoid issues of reverse causality and reduce some forms of confounding, the data were analyzed in a fashion similar to an "intention to treat" analysis: that is, NPIs were scored on the date they were announced, and the duration, effectiveness, or other features of the intervention were not considered in the analysis.

Associations between overall intervention timing and outcomes were assessed by Spearman rank correlation coefficients and associated *P* values calculated between the measures of overall response (number of interventions before CEPID = *x* or CEPID at the time of the *x*th intervention) and the three outcome measures. Univariate associations between the timing of particular NPIs and the outcomes were also assessed by Spearman rank correlation coefficients and associated *P* values. In these cases, multivariate analyses were not performed because of the small sample size and strong collinearity of many intervention timings.

Because of specific concerns that later-hit cities might have had milder epidemics for reasons other than interventions, we did perform linear regression of peak death rate on longitude and epidemic onset week, along with intervention timing (number of interventions before CEPID = 20/100,000) and eliminated model variables by backward selection.

For NPIs that showed significant or nearly significant overall correlations with outcomes, we divided cities as evenly as possible into early and late-intervening cities (eight in the early group and nine in the late or vice versa) and plotted the median outcome for each group. The round-numbered cutoff that created this division is shown in Fig. 2. Mann–Whitney *U* tests were used to assess statistical significance of differences in the distributions.

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Nonpharmaceutical Interventions Implemented by US Cities During the 1918-1919 Influenza Pandemic

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Context A critical question in pandemic influenza planning is the role nonpharmaceutical interventions might play in delaying the temporal effects of a pandemic, reducing the overall and peak attack rate, and reducing the number of cumulative deaths. Such measures could potentially provide valuable time for pandemic-strain vaccine and antiviral medication production and distribution. Optimally, appropriate implementation of nonpharmaceutical interventions would decrease the burden on health care services and critical infrastructure.

Objectives To examine the implementation of nonpharmaceutical interventions for epidemic mitigation in 43 cities in the continental United States from September 8, 1918, through February 22, 1919, and to determine whether city-to-city variation in mortality was associated with the timing, duration, and combination of nonpharmaceutical interventions; altered population susceptibility associated with prior pandemic waves; age and sex distribution; and population size and density.

Design and Setting Historical archival research, and statistical and epidemiological analyses. Nonpharmaceutical interventions were grouped into 3 major categories: school closure; cancellation of public gatherings; and isolation and quarantine.

Main Outcome Measures Weekly excess death rate (EDR); time from the activation of nonpharmaceutical interventions to the first peak EDR; the first peak weekly EDR; and cumulative EDR during the entire 24-week study period.

Results There were 115 340 excess pneumonia and influenza deaths (EDR, 500/100 000 population) in the 43 cities during the 24 weeks analyzed. Every city adopted at least 1 of the 3 major categories of nonpharmaceutical interventions. School closure and public gathering bans activated concurrently represented the most common combination implemented in 34 cities (79%); this combination had a median duration of 4 weeks (range, 1-10 weeks) and was significantly associated with reductions in weekly EDR. The cities that implemented nonpharmaceutical interventions earlier had greater delays in reaching peak mortality (Spearman $r=-0.74$, $P<.001$), lower peak mortality rates (Spearman $r=0.31$, $P=.02$), and lower total mortality (Spearman $r=0.37$, $P=.008$). There was a statistically significant association between increased duration of nonpharmaceutical interventions and a reduced total mortality burden (Spearman $r=-0.39$, $P=.005$).

Conclusions These findings demonstrate a strong association between early, sustained, and layered application of nonpharmaceutical interventions and mitigating the consequences of the 1918-1919 influenza pandemic in the United States. In planning for future severe influenza pandemics, nonpharmaceutical interventions should be considered for inclusion as companion measures to developing effective vaccines and medications for prophylaxis and treatment.

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THE INFLUENZA PANDEMIC OF 1918-1919 was the most deadly contagious calamity in human history. Approximately 40 million individuals died worldwide, including 550 000 individuals in the United States.[1-4] The historical record demonstrates that when faced with a devastating pandemic, many nations, communities, and individuals adopt what they perceive to be effective social distancing measures or nonpharmaceutical interventions including isolation of those who are ill, quarantine of those suspected of having contact with those who are ill, school and selected business closure, and public gathering cancellations.[5,6] One compelling question emerges: can lessons from the 1918-1919 pandemic be applied to contemporary pandemic planning efforts to maximize public health benefit while minimizing the disruptive social consequences of the pandemic as well as those accompanying public health response measures?[7-10]

Most pandemic influenza policy makers agree that even the most rigorous nonpharmaceutical interventions are unlikely either to prevent a pandemic or change a population's underlying biological susceptibility to the pandemic virus. However, a growing

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body of theoretical modeling research suggests that nonpharmaceutical interventions might play a salubrious role in delaying the temporal effect of a pandemic; reducing the overall and peak attack rate; and reducing the number of cumulative deaths.[11-15] Such measures could potentially provide valuable time for production and distribution of pandemic-strain vaccine and antiviral medication. Optimally, appropriate implementation of nonpharmaceutical interventions would decrease the burden on health care services and critical infrastructure.

The historical record of the 1918-1919 influenza pandemic in the United States constitutes one of the largest recorded experiences with the use of nonpharmaceutical interventions to mitigate an easily spread, high mortality and morbidity influenza virus strain (ie, a category 4-5 pandemic using the Centers for Disease Control and Prevention February 2007 *Interim Pre-Pandemic Planning Guidance*).[16] Our study focused on this data set by assessing the nonpharmaceutical interventions implemented in 43 cities in the continental United States from September 8, 1918, through February 22, 1919, a period that encompasses all of the second pandemic wave (September-December 1918) and the first 2 months of the third wave (January-April 1919) and represents the principal time span of activation and deactivation of nonpharmaceutical interventions. The purpose was to determine whether city-to-city variation in mortality was associated with the timing, duration, and combination (or layering) of nonpharmaceutical interventions; altered population susceptibility associated with prior pandemic waves; age and sex distribution; and population size and density.

METHODS

Data Collection

We combined systematic historical data collection and contemporary epidemiological and statistical analytic tools. Mortality data were obtained from the US Census Bureau's *Weekly Health Index*[17] for 1918-1919, a series of reports listing total deaths and death rates for 43 large US cities. These 43 cities were among the 66 most populous urban centers according to the 1920 census, and all had a population greater than 100 000. Of the 66 most populous cities, the remaining 23 had incomplete archival and mortality records. No city with a comprehensive archival record of nonpharmaceutical interventions was excluded. The *Weekly Health Index* is the most complete extant compilation of weekly pneumonia and influenza mortality data in US urban areas during the 1918-1919 pandemic.

In addition, we captured all of the available public health documents on nonpharmaceutical interventions implemented by these 43 cities during the 1918-1919 pandemic, including municipal public health department annual and monthly reports and weekly bulletins; every state and federal report on the 1918-1919 influenza pandemic published between 1917 and 1922; US Census pneumonia and influenza mortality data from 1910-1920; the corpus of published historical, medical, and public health literature on the 1918-1919 pandemic; 86 different newspapers from the 43 different cities; records of US military installations between 1917-1920; and additional holdings housed in several major libraries and archival repositories (the complete bibliography of the 1144 primary and secondary sources is available as an online supplement at http://www.cdc.gov/ncidod/dq/index.htm).[17-23]

Data Analysis

From the census reports, we extracted the weekly pneumonia and influenza mortality data covering the 24 weeks from September 8, 1918, through February 22, 1919, for the 43 US cities. In 1920, these 43 cities had a combined population of approximately 23 million (22% of the total US population). A small number of missing values (846 [0.6%] of 136 563 deaths) was imputed. Using estimated weekly baseline pneumonia and influenza death rates generated from the 1910-1916 median monthly values found by Collins et al,[18] weekly excess death rates (EDR) were computed. Based on available mortality data and epidemiological reports from that era, as well as a recent retrospective statistical analysis, we estimated that those who succumbed to influenza contracted it 10 days earlier.[3,24-27]

The onset of the epidemic in a particular city was estimated as either the day of the first reported pneumonia and influenza case, or the calendar day of the first recorded pneumonia and influenza death minus 10 days, whichever was earlier. Information on nonpharmaceutical interventions was captured by reviewing at least 2 daily, high-circulation newspapers for each city and available municipal or state health reports. Nonpharmaceutical interventions were grouped into 3 major categories: school closure; public gathering bans; and isolation and quarantine. We also considered an additional general category of ancillary nonpharmaceutical interventions (eg, altering work schedules, limited closure or regulations of businesses, transportation restrictions, public risk communications, face mask ordinances).

Nonpharmaceutical interventions were considered either activated ("on") or deactivated ("off"), according to data culled from the historical record and daily newspaper accounts. Specifically, these nonpharmaceutical interventions were legally enforced and affected large segments of the city's population. Isolation of ill persons and quarantine of those suspected of having contact with ill persons refers only to mandatory orders as opposed to voluntary quarantines being discussed in our present era. School closure was considered activated when the city officials closed public schools (grade school through high school); in most, but not all cases, private and parochial schools followed suit. Public gathering bans typically meant the closure of saloons, public entertainment venues, sporting events, and indoor gatherings were banned or moved outdoors; outdoor gatherings were not always canceled during this period (eg, Liberty bond parades); there were no recorded bans on shopping in grocery and drug stores. Based on an estimated 10-day time frame between disease onset and death,

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we estimated that the association of nonpharmaceutical interventions with reductions in EDR occurred 10 days after their actual date of implementation.[3,24-27]

To test the association of the layering and timing of nonpharmaceutical interventions with mortality, an analysis of variance (ANOVA) model was constructed with weekly EDR as the dependent variable and epidemiological week, city, and the status (on/off) of every combination of nonpharmaceutical interventions as the independent variables. In the ANOVA model, each possible combination of nonpharmaceutical interventions was treated as an independent variable to test for layering effects. Any factor with a *P* value of less than .10 was included in the model. Because there is ambiguity over the rigor with which the category of ancillary nonpharmaceutical interventions was applied, enforced, and deactivated, we focused primarily on the 3 major categories of nonpharmaceutical interventions discussed above and we included the ancillary nonpharmaceutical interventions in the multivariate model for purposes of completeness.

We defined additional outcome (dependent) variables: (1) the time to first peak as the time in days from the activation of the first major category of nonpharmaceutical interventions to the date of the first peak EDR; (2) the magnitude of the first peak as the first peak weekly EDR; and (3) the mortality burden as the cumulative EDR during the entire 24-week study period.

We also defined the following independent variables. The first was the public health response time (PHRT) as the time in days (either positive or negative) between the date when weekly EDR first exceeds twice the baseline pneumonia and influenza death rate (2 × baseline; ie, when the mortality rate begins to accelerate) and the activation of the first major nonpharmaceutical interventions. Interventions that occurred prior to this reference point are recorded as negative PHRT values, indicating that public health officials responded to events prior to the acceleration of weekly death rates. However, most cities had positive PHRT in that they reacted after the 2 × baseline mortality threshold, indicating that the epidemic had already entered its acceleration phase. The second independent variable was total days of nonpharmaceutical interventions, which was defined as the total cumulative number of days that nonpharmaceutical interventions from the 3 major categories were activated during the entire 24-week study period.

The ANOVA models were based on the study design of a 43 (city) × 24 (week) factorial design without replication. Because there is no replication, the city × week interaction term was treated as the error term in the multivariate analysis. We considered 4 different nonpharmaceutical interventions. Hence, there are 15 different combinations of these interventions (excluding the no intervention combination). Each of these 15 combinations was either implemented (on) or not implemented (off) in each city for each week. Thus, the effects of each of these combinations of nonpharmaceutical interventions are included in the city × week interaction term. Each of these terms (along with their × city and × week interaction terms) were extracted from the original city × week interaction term. The remaining unexplained variation was used as the error term in the ANOVA model. The remaining error term is likely to be larger than a true error term generated through replication so the analysis of any effects using this error term can be expected to be conservative. Such a factorial model without replication can be used to test hypotheses but the lack of natural error in the model makes estimates or predictions from the model such as effect size measures and confidence intervals nonestimable.

We also generated scatterplots and Spearman rank correlation coefficients to explore the associations between PHRT and each of the 2 additional dependent variables and associations between total days of nonpharmaceutical interventions and mortality burden. We further investigated these associations by using box plots and Wilcoxon rank sum tests to compare the outcomes for the cities above and below the median of each independent variable.

We also generated scatterplots and Spearman rank correlation coefficients to explore other potential or confounding associations (as independent determinants): (1) EDR in the 4 successive waves of the pandemic; (2) city-specific population size vs EDR; (3) city-specific population density vs EDR; (4) city-specific population age distribution vs EDR; and (5) city-specific sex distribution vs EDR. Analyses were performed using SAS statistical software version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

There were 115 340 excess pneumonia and influenza deaths (EDR, 500/100 000 population) in the 43 cities during the 24 weeks analyzed. TABLE 1 shows considerable city-to-city variation in mortality profiles and intervention characteristics; lists the earliest reported dates of the first pneumonia and influenza cases by city, mortality acceleration (2 × baseline EDR), first implementation of nonpharmaceutical interventions, and first peak EDR; and lists the values for each of the independent and outcome variables described above.

TABLE 2 shows the categories of nonpharmaceutical intervention combinations, the number of cities implementing those combinations, and the median and range of duration of implementation by each of the 43 cities during the study period. Every city adopted at least 1 of the 3 major categories of nonpharmaceutical interventions; 15 applied all 3 categories of nonpharmaceutical interventions concurrently. School closure concurrently combined with public gathering bans represented the most common combination, implemented in 34 cities (79%) for a median duration of 4 weeks (range, 1-10 weeks). School closure was ultimately used in some combination with the other categories of nonpharmaceutical interventions by 40 cities (93%). Three cities never officially closed their schools (New York City, New York, New Haven, Connecticut, and Chicago, Illinois, although the latter reported a student absenteeism

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rate of ≥45% at the peak of its epidemic); 25 cities closed their schools once, 14 closed them twice, and 1 (Kansas City, Missouri) closed its schools 3 times. Schools were officially closed a median of 6 weeks (range, 0-15 weeks).

The ANOVA multivariate model had an r^2 of 86.7% ($P < .001$). Nonpharmaceutical interventions were a significant

Table 1. Characteristics of Influenza Pandemic for 43 US Cities Between September 8, 1918, and February 22, 1919

City	First Case Date	Mortality Acceleration Date[a]	Date of First Nonpharmaceutical Intervention	Public Health Response Time, d[b]	Total No. of Days of Nonpharmaceutical Interventions	Date of Peak Excess Death Rate	Time to Peak, d	Magnitude of First Peak, Excess Deaths/ 100 000 Population[c]	Excess Pneumonia and Influenza Mortality, Deaths/ 100 000 Population[d]
Albany, NY	9/27	10/6	10/9	3	47	10/24	15	161.8	553.2
Baltimore, MD	9/18	9/29	10/9	10	43	10/18	9	182.1	559.3
Birmingham, AL	9/24	9/30	10/9	9	48	10/22	13	70.9	591.8
Boston, MA	9/4	9/12	9/25	13	50	10/3	8	159.9	710.0
Buffalo, NY	9/24	9/28	10/10	12	49	10/22	12	140.9	529.5
Cambridge, MA	9/4	9/11	9/25	14	49	10/3	8	125.5	541.0
Chicago, IL	9/17	9/28	9/26	–2	68	10/21	25	84.8	373.2
Cincinnati, OH	9/24	10/4	10/6	2	123	10/24	18	67.6	451.2
Cleveland, OH	9/20	10/7	10/5	–2	99	10/31	26	83.6	474.0
Columbus, OH	9/20	10/6	10/11	5	147	10/24	13	47.3	311.7
Dayton, OH	9/20	10/5	9/30	–5	156	10/20	20	87.8	410.0
Denver, CO	9/17	9/27	10/6	9	151	10/20	14	55.0	630.9
Fall River, MA	9/9	9/16	9/26	10	60	10/12	16	165.2	621.3
Grand Rapids, MI	9/23	10/2	10/19	17	62	10/25	6	15.0	210.5
Indianapolis, IN	9/22	9/30	10/7	7	82	10/18	11	38.8	290.0
Kansas City, MO	9/20	9/26	9/26	0	170	10/27	31	58.1	579.8
Los Angeles, CA	9/27	10/6	10/11	5	154	10/30	19	64.2	493.8
Louisville, KY	9/13	10/1	10/7	6	145	10/20	13	74.8	406.4
Lowell, MA	9/9	9/16	9/27	11	59	10/10	13	123.1	522.9
Milwaukee, WI	9/14	10/6	10/11	5	132	10/23	12	36.4	291.5
Minneapolis, MN	9/21	10/6	10/12	6	116	10/24	18	37.6	267.1
Nashville, TN	9/21	10/6	10/7	1	55	10/16	9	160.1	610.4
New Haven, CT	9/14	9/23	10/15	22	39	10/24	9	109.5	586.5
New Orleans, LA	9/10	10/1	10/8	7	78	10/20	12	172.9	734.0
New York City, NY	9/5	9/29	9/18	–11	73	10/23	35	90.1	452.3
Newark, NJ	9/6	9/30	10/10	10	33	10/22	12	101.5	533.0
Oakland, CA	10/1	10/8	10/12	4	127	10/30	18	107.0	506.2
Omaha, NE	9/18	10/4	10/5	1	140	10/18	13	81.7	554.0
Philadelphia, PA	8/27	9/25	10/3	8	51	10/16	13	249.7	748.4
Pittsburgh, PA	9/4	9/27	10/4	7	53	11/5	32	130.7	806.8
Portland, OR	10/2	10/7	10/11	4	162	11/2	22	59.4	505.2
Providence, RI	9/8	9/17	10/6	19	42	10/17	11	105.2	574.2
Richmond, VA	9/21	9/29	10/6	7	60	10/16	10	112.2	508.3
Rochester, NY	9/22	10/6	10/9	3	54	10/26	17	70.2	359.1
St Louis, MO	9/23	10/7	10/8	1	143	10/29	21	30.0	358.0
St Paul, MN	9/21	10/2	11/6	35	28	11/12	6	55.6	413.2
San Francisco, CA	9/24	10/7	10/18	11	67	10/29	11	143.0	672.7
Seattle, WA	9/24	10/1	10/6	5	168	10/23	17	49.5	414.1
Spokane, WA	9/28	10/9	10/10	1	164	11/5	26	66.0	481.8
Syracuse, NY	9/12	9/18	10/7	19	39	10/14	7	145.4	541.4
Toledo, OH	9/21	10/13	10/15	2	102	10/25	10	54.8	294.5
Washington, DC	9/11	9/23	10/3	10	64	10/15	12	140.1	607.6
Worcester, MA	9/9	9/12	9/27	15	44	10/7	10	126.1	654.7

[a] Defined as 2 × baseline death rate.
[b] Defined as days between 2 × baseline death rate and first nonpharmaceutical intervention.
[c] Weekly excess death rate.
[d] Total excess death rate through 24 weeks.

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Table 2. Nonpharmaceutical Interventions Implemented in 43 US Cities Between September 8, 1918, and February 22, 1919

Type of Nonpharmaceutical Intervention	No. (%) of Cities Implementing Nonpharmaceutical Intervention for ≥1 wk (N = 43)[a]	Median (Range) Duration of Nonpharmaceutical Intervention, wk
Isolation or quarantine only	15 (35)	1 (1-10)
School closure only	22 (51)	1 (1-7)
Public gathering ban only	6 (14)	1.5 (1-5)
Isolation and quarantine and school closure	2 (5)	5.5 (4-7)
Isolation and quarantine and public gathering ban	4 (9)	4 (2-5)
School closure and public gathering ban	34 (79)	4 (1-10)
Isolation and quarantine, school closure, and public gathering ban	15 (35)	4 (2-6)

[a] Cities often implemented more than 1 nonpharmaceutical intervention combination during the outbreak period, so the total adds to more than 100%. The number of categories of nonpharmaceutical interventions implemented during some part of the outbreak was 1 in 1 city, 2 in 23 cities, and 3 in 19 cities. The total number of weeks that at least 1 nonpharmaceutical intervention was implemented was 4 in 6 cities, 5 in 6 cities, 6 in 8 cities, 7 in 3 cities, 8 in 6 cities, 10 in 5 cities, 11 in 4 cities, 13 in 1 city, 14 in 2 cities, 15 in 1 city, and 16 in 1 city. No cities had at least 1 nonpharmaceutical intervention implemented for durations of 9 and 12 weeks.

source of the variation in the weekly EDRs within and between the cities. The ANOVA results are shown in TABLE 3. The multivariate model demonstrates that layered nonpharmaceutical interventions generally had a more significant association with weekly EDR than individual nonpharmaceutical interventions. Specifically, combinations of nonpharmaceutical interventions including school closure and public gathering bans appeared to have the most significant association with weekly EDR (ie, the lowest P values, most were $P<.001$). The large number of significant nonpharmaceutical interventions × week interactions in the model confirms that the timing of the implementation of a given combination of nonpharmaceutical interventions was a significant factor in reducing mortality. One caveat is persistent nonpharmaceutical interventions × city interactions, meaning that the success of a strategy of nonpharmaceutical interventions in a particular city does not uniformly translate to all other cities. The 2 outlier cities in our study, Grand Rapids, Michigan, and St Paul, Minnesota, exemplify this point.

The scatterplots in FIGURE 1A, Figure 1B, and Figure 1C display the associations between the PHRT and each of the 3 dependent variables. Figure 1A displays the association between PHRT in days and time to first peak EDR; cities that implemented nonpharmaceutical interventions earlier had greater delays in reaching peak mortality (Spearman $r=-0.74$, $P<.001$). Figure 1B shows the association between PHRT and the magnitude of the first peak EDR; cities that implemented nonpharmaceutical interventions earlier had lower peak mortality rates (Spearman $r=0.31$, $P=.02$). Figure 1C depicts the association between PHRT and total mortality burden; cities that implemented nonpharmaceutical interventions earlier experienced a lower total mortality (Spearman $r=0.37$, $P=.008$). In summary, when comparing the 21 cities with earlier (less than the median) PHRT with the 21 cities with the later (greater than the median) PHRT, there are statistically significant differences for each of the outcome measures ($P\leq.001$; TABLE 4).

Figures 1C and 1D show the association between early, sustained, and layered application of nonpharmaceutical interventions and total excess pneumonia and influenza mortality burden in 43 cities. Figure 1C shows the statistically significant association between PHRT and total mortality burden. Figure 1D shows a statistically significant association between increased duration of nonpharmaceutical interventions and a reduced total mortality burden (Spearman $r=-0.39$, $P=.005$). In summary, the 21 cities that had earlier PHRT (ie, less than the median) and the most sustained and most days of nonpharmaceutical interventions had a statistically significant reduction in excess pneumonia and influenza mortality rates compared with the 21 cities that had later PHRT and fewer days of nonpharmaceutical interventions (Table 4).

FIGURE 2 shows the aggregate city mortality curves by region (East, Midwest and South, and West). FIGURE 3 displays 4 city-specific mortality curves, including weekly EDR and the nonpharmaceutical interventions implemented as well as their activation and deactivation dates for St Louis, Missouri, New York City, Denver, Colorado, and Pittsburgh, Pennsylvania. These 4 cities were chosen because they indicate the broad spectrum of outcomes seen in the 43 cities studied as well as for their geographical and social diversity. (The mortality curves for all 43 cities are available at http://www.cdc.gov/ncidod/dq/index.htm.) Overall, cities that implemented nonpharmaceutical interventions earlier experienced associated delays in the time to peak mortality, reductions in the magnitude of the peak mortality, and decreases in the total mortality burden.

In exploring alternative and potentially confounding explanations for variation in city-specific EDR, we used a scatterplot to compare the cumulative EDR of the 43 cities during pandemic waves 1 (February-May 1918), 2 (September-December 1918), 3 (January-April 1919), and 4 (January-April 1920).[2,3] We found no statistically significant association of the EDR across the 43 cities when comparing successive waves. Specifically, the severity or occurrence of wave 1 is not associated, either positively or negatively, with the severity of wave 2; the severity of wave 2 is not associated with the severity of wave 3; and the severity of wave 3 is not associated with the severity of wave 4 (figures appear in the online supplement at http://www.cdc.gov/ncidod/dq/index.htm).[28,29]

Published virological evidence for strain variation during wave 2 is limited to a single genotypic variant without evidence for significant phenotypic change in virulence.[30-33] While plausible, no virologi-

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cal evidence yet exists to explain the perplexing mortality difference between the spring 1918 wave, which was reportedly milder, and the subsequent fall and winter waves. Additional studies may clarify the understanding of the 1918 pandemic's wave phenomena.

Similarly, scatterplots comparing the cumulative EDR to the city-specific population size and density; sex distribution; and proportion of ages of younger than 1 month to 5 years, 15 to 40 years, and older than 65 years, which corresponded to high reported specific mortality rates in 1918 demonstrated no association. Among the 43 cities we investigated, neither the city's population size, density, sex distribution, nor age distribution accounted for the differences in mortality (figures appear in supplement at http://www.cdc.gov/ncidod/dq/index.htm).

Table 3. Multivariate Model Showing Effect of Combinations of Nonpharmaceutical Interventions on Weekly Excess Death Rates for 43 US Cities Between September 8, 1918, and February 22, 1919[a]

Source of Variation	*df*	Sum of Squares	Mean Square	*F* Score	*P* Value
Type of confounders					
Week	29	75 677.0	2609.6	16.24	<.001
City	42	65 557.9	1560.9	9.72	<.001
1 Nonpharmaceutical intervention					
School closure	1	1288.7	1288.7	8.02	.005
× Week	8	4551.8	569.0	3.54	<.001
Banning public gatherings	1	1342.0	1342.0	8.35	.004
Isolation and quarantine	1	911.1	911.1	5.67	.02
× City	10	3976.5	397.7	2.48	.006
Ancillary nonpharmaceutical interventions	1	897.3	897.3	5.59	.02
× Week	13	6122.4	471.0	2.93	<.001
× City	12	10 257.6	854.8	5.32	<.001
2 Nonpharmaceutical interventions					
School closure and banning public gatherings	1	681.3	681.3	4.24	.04
× Week	9	6497.0	721.9	4.49	<.001
× City	13	6229.9	479.2	2.98	<.001
School closure and isolation and quarantine	1	2335.3	2335.3	14.54	<.001
× Week	4	2434.2	608.6	3.79	.005
Banning public gatherings and isolation and quarantine	1	292.3	292.3	1.82	.18
× Week	1	563.9	563.9	3.51	.06
Banning public gatherings and ancillary nonpharmaceutical interventions	1	272.6	272.6	1.70	.19
× Week	4	7444.6	1861.1	11.59	<.001
× City	4	5547.6	1386.9	8.63	<.001
Isolation and quarantine and ancillary nonpharmaceutical interventions	1	48.1	48.1	0.30	.58
× Week	2	1507.6	753.8	4.69	.009
× City	2	824.7	412.4	2.57	.08
3 Nonpharmaceutical interventions					
School closure, banning public gatherings, and isolation and quarantine	1	762.4	762.4	4.75	.03
× Week	2	2239.3	1119.7	6.97	.001
School closure, banning public gatherings, and ancillary nonpharmaceutical interventions	1	691.6	691.6	4.41	.04
× Week	10	12 260.5	1226.0	7.63	<.001
× City	26	51 423.8	1977.8	12.31	<.001
School closure, isolation and quarantine, and ancillary nonpharmaceutical interventions	1	3451.1	3451.1	21.48	<.001
× Week	4	2493.5	623.4	3.88	.004
Banning public gatherings, isolation and quarantine, and ancillary nonpharmaceutical interventions	1	51.9	51.9	0.32	.57
× Week	8	4535.2	566.9	3.53	<.001
4 Nonpharmaceutical interventions					
School closure, banning public gatherings, isolation and quarantine, and ancillary nonpharmaceutical interventions	1	503.7	503.7	3.14	.08
× Week	9	6068.3	674.3	4.20	<.001
× City	13	23 509.7	1808.4	11.26	<.001
Error	770	123 691.2	160.6		

[a] r^2 = 86.7%

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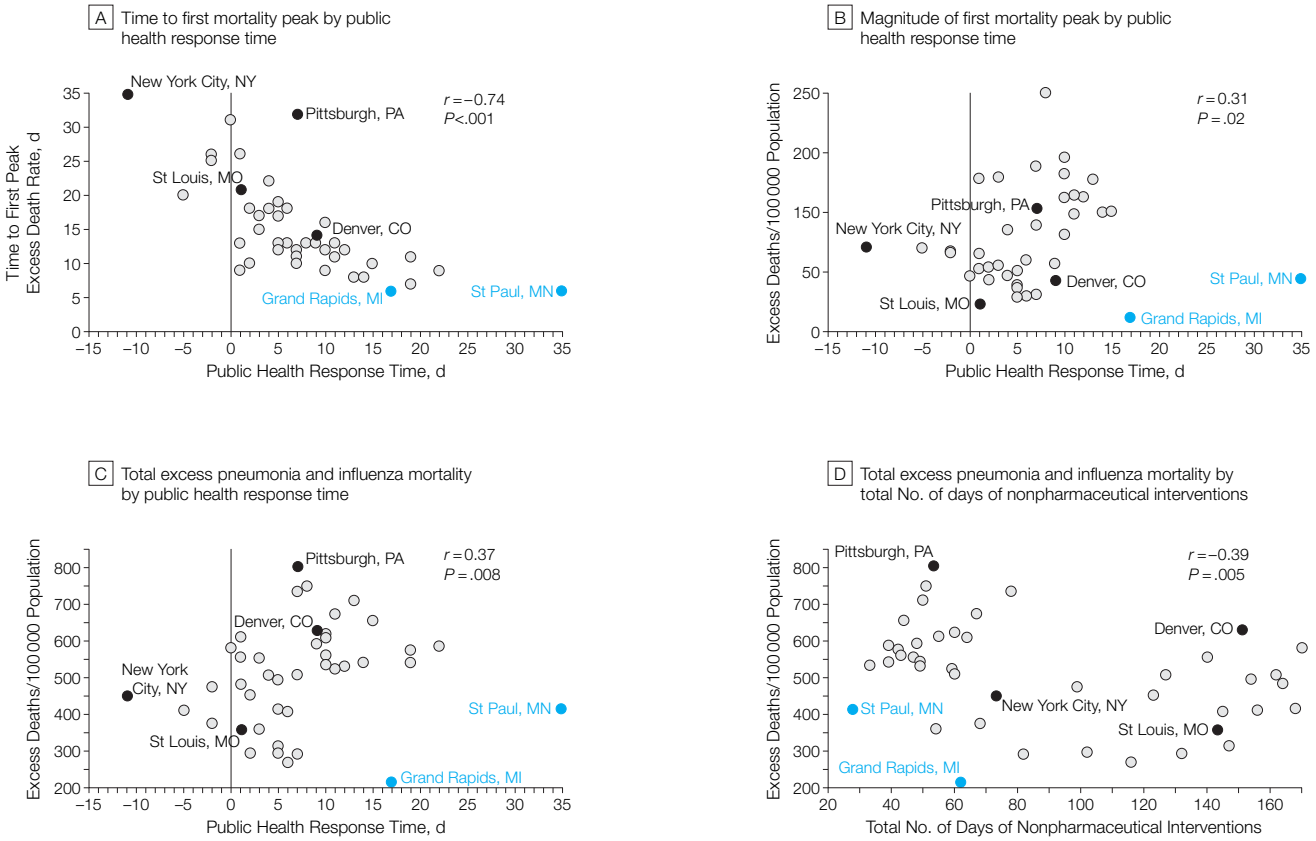
COMMENT

During the 1918-1919 influenza pandemic, all 43 cities eventually implemented nonpharmaceutical interventions but the time of activation, duration, and choice or combination of these nonpharmaceutical interventions appear to have been key factors in their success or failure. In 1918, decisions to activate nonpharmaceutical interventions were typically triggered by excess morbidity, mortality, or both, as well as situational awareness of other communities near and far. Because discerning precisely the first arrival of pandemic virus in a community was difficult, we chose to measure public health response time in reference to excess pneumonia and influenza mortality (ie, when weekly EDR first crossed the threshold of 2 × the baseline and the mortality rates entered an acceleration phase).

Figure 1. Scatterplot of Public Health Response Time for 43 US Cities From September 8, 1918, Through February 22, 1919



The 4 cities represented by black circles are discussed further in the text. The 2 cities represented by blue circles are outliers chosen to demonstrate that the associations shown are not perfect. The Spearman rank correlation coefficient was used.

Table 4. Implementation Strategy of Nonpharmaceutical Interventions for 21 Cities Between September 8, 1918, and February 22, 1919

	Public Health Response Time, d						
	Early (<7 d)			Late (≥7 d)			
Outcome Variable	25th Percentile	50th Percentile	75th Percentile	25th Percentile	50th Percentile	75th Percentile	*P* Value
Time to peak, d	13	18	22	9	11	13	<.001
Magnitude of first peak (weekly EDR)	54.7	67.6	84.8	101.5	125.8	145.4	.001
Excess pneumonia and influenza mortality rate (total EDR)	359.1	451.2	505.2	529.5	580.3	654.7	<.001
	Total Days of Nonpharmaceutical Interventions						
	Most (≥65 d)			Least (<65 d)			
Excess pneumonia and influenza mortality rate (total EDR)	358.0	451.2	505.2	529.5	559.3	610.4	<.001

Abbreviation: EDR, excess death rate.

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Hence, the difference in time between the first nonpharmaceutical interventions and this excess mortality threshold may be a positive or negative value. For example, in Philadelphia, Pennsylvania, which was affected early and was unprepared to respond, the PHRT was 8 and the EDR was approximately 37/100 000 population at the point of implementing nonpharmaceutical interventions; in contrast, New York City's PHRT was –11 days and the EDR was 0/100 000 population at the point of implementing nonpharmaceutical interventions. New York City responded to its first influenza cases and the perceived severity of the epidemic in nearby cities without waiting for excess deaths to accumulate.

The US Centers for Disease Control and Prevention's newly released interim community mitigation guidance recommends activating nonpharmaceutical interventions when outbreaks due to a pandemic virus strain first are confirmed in a state or metropolitan service region.[16] Several theoretical models suggest that the effect of targeted, layered strategies for nonpharmaceutical interventions may be optimized when community influenza attack rates are 1% or lower.[11-15] Given the exponential growth of an unmitigated influenza pandemic, it is reasonable to expect that the timing of interventions will be among the most critical factors. Such expectations and biological realities are consistent with our observations of the 1918 pandemic, when rapid public health response time was a critical factor in the successful application of nonpharmaceutical interventions.

Late interventions, regardless of their duration or permutation of use, almost always were associated with worse outcomes. However, timing alone was not consistently associated with success. The combination and choice of nonpharmaceutical interventions also appeared to be critical as confirmed by the multivariate model.

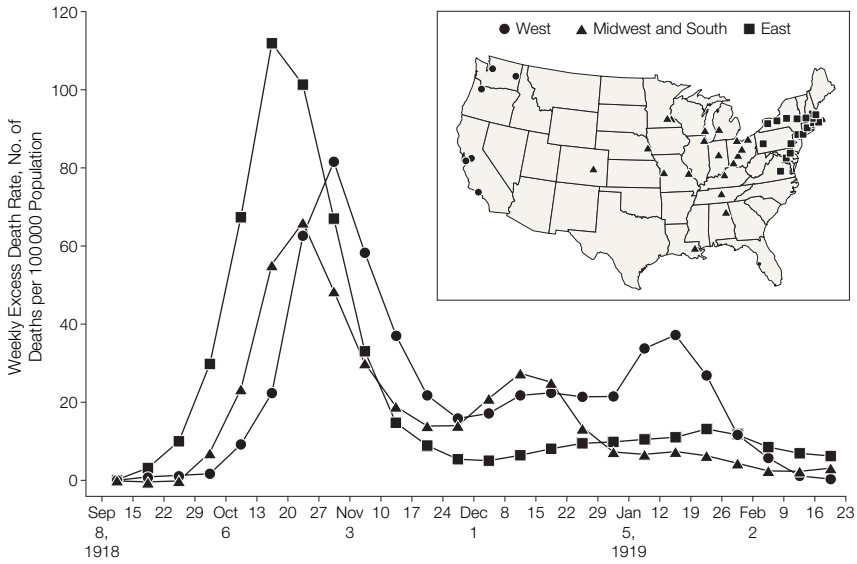
For example, New York City reacted earliest to the gathering influenza crisis, primarily with the sustained (>10 weeks beginning September 19, 1918) and rigidly enforced application of compulsory isolation and quarantine procedures, along with an enforced staggered business hour ordinance from October 5 through November 3, 1918.[34] During this era, New York City's health department was renowned internationally for its innovative policies of mandatory case reporting and rigidly enforced isolation and quarantine procedures.[35] Typically, individuals diagnosed with influenza were isolated in hospitals or makeshift facilities, while those suspected to have contact with an ill person (but who were not yet ill themselves) were quarantined in their homes with an official placard declaring that location to be under quarantine. New York City mounted an early and sustained response to the epidemic and experienced the lowest death rate on the Eastern seaboard but it did not layer its response. New York City's cumulative mortality burden, 452/100 000, ranked 15 out of the 43 cities studied.

In contrast, Pittsburgh, under orders from the Pennsylvania health department, executed a public gathering ban on October 4, 1918, but city officials delayed until October 24 before implementing school closure. A week later, on November 2, the state rescinded public gathering bans. The city applied its nonpharmaceutical interventions late and individually rather than combined. Pittsburgh's cumulative excess mortality burden (EDR=807/100 000) ranked 43 out of 43 cities during the study period.

However, the benefits of these interventions were not equally distributed. Those cities acting in a timely and comprehensive manner appear to have benefited most in terms of reductions in total EDR. For example, St Louis, which implemented a relatively early, layered strategy (school closure and cancellation of public gatherings), and sustained these nonpharmaceutical interventions for about 10 weeks each, did not experience nearly as deleterious an outbreak as 36 other communities in the study (cumulative EDR=358/100 000 population).

The 1918 experience suggests that sustained nonpharmaceutical interventions are beneficial and need to be "on" throughout the particular peak of a local experience. Many of the 43 cities in the study, particularly in the Midwest and South and West, experienced 2 peaks of excess pneumonia and influenza mortality (eg, Birmingham, Alabama, Cincinnati, Ohio, Columbus, Ohio, Denver, Indianapolis, Indiana, Kansas City,

Figure 2. Aggregate Weekly Excess Death Rates for 43 US Cities by Region From September 8, 1918, Through February 22, 1919



The total excess death rate is 555 for the East region; 413 for the Midwest and South region; and 529 for the West region.

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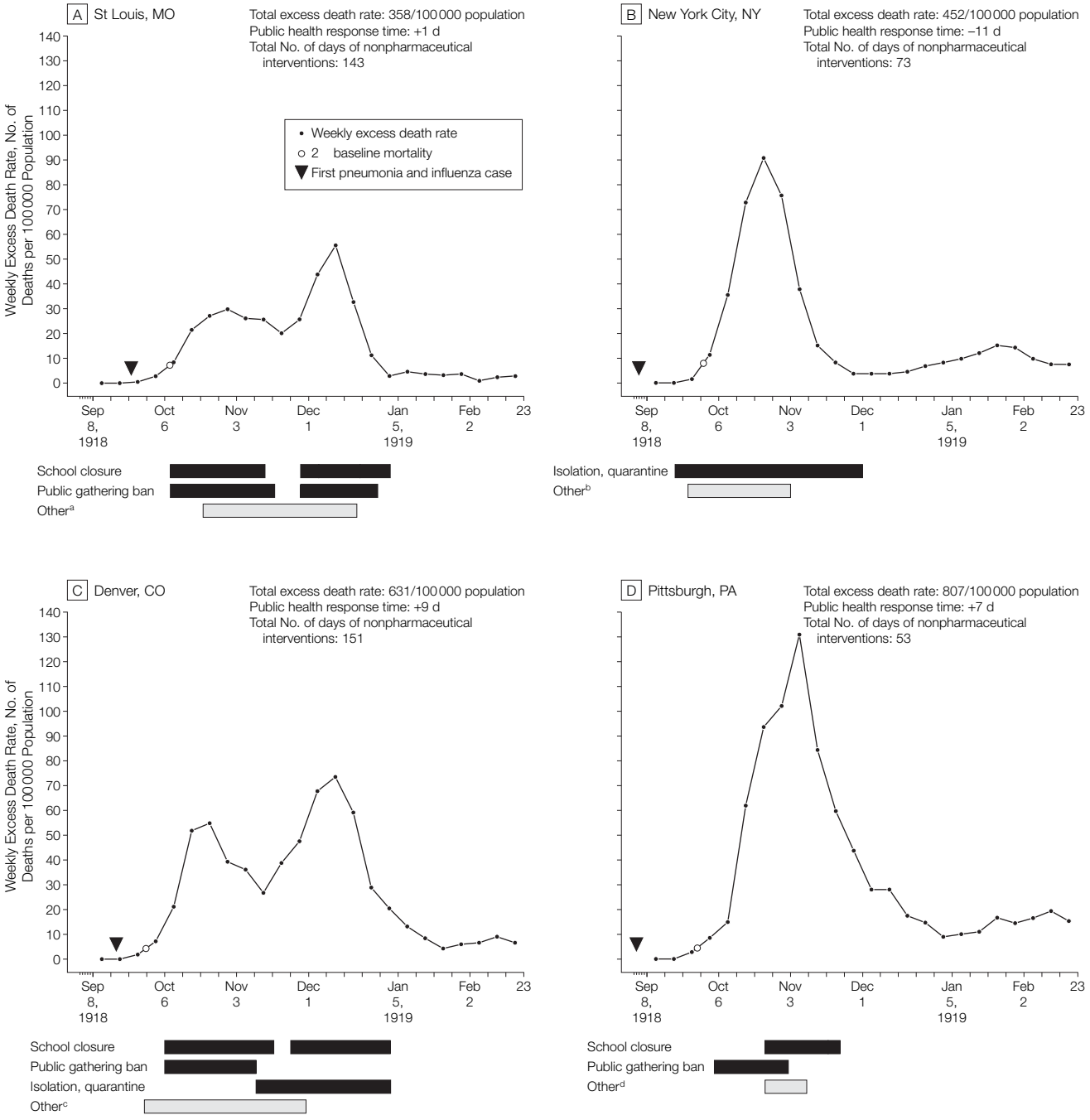
Louisville, Kentucky, Milwaukee, Wisconsin, Minneapolis, Minnesota, Oakland, California, Omaha, Nebraska, Portland, Oregon, Rochester, New York, St Louis, San Francisco, California, Seattle, Washington, Spokane, Washington, Toledo, Ohio; see figures in online supplement at http://www.cdc.gov/ncidod/dq/index.htm). These second

Figure 3. Weekly Excess Death Rates From September 8, 1918, Through February 22, 1919



Type and duration of nonpharmaceutical interventions are indicated under each plot. For the specific nonpharmaceutical interventions, black bars indicate activation.
[a] Business hours restricted, streetcars' capacity limited.
[b] Staggered business hours, signs with "cover coughs."
[c] Staggered business hours, warning signs posted in theaters.
[d] Schoolchildren given information to take home, warned not to gather in groups.

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peaks frequently followed the sequential activation, deactivation, and reactivation of nonpharmaceutical interventions, highlighting the transient protective nature of nonpharmaceutical interventions and the need for a sustained response. For example, Denver (cumulative EDR=631/100 000 population) responded twice with an extensive menu of nonpharmaceutical interventions that included public gathering bans, school closure, isolation and quarantine, and several ancillary nonpharmaceutical interventions and these actions are reflected temporally in its 2-peak mortality curve.

Such dual-peaked cities are of particular interest because of the specificity and temporal associations between excess mortality and the triggers of activation and deactivation of nonpharmaceutical interventions and the implications for a causal relationship. Among the 43 cities, we found no example of a city that had a second peak of influenza while the first set of nonpharmaceutical interventions were still in effect, suggesting that each city with a bimodal pattern served as its own control. In dual-peaked cities, activation of nonpharmaceutical interventions was followed by a diminution of deaths and, typically, when nonpharmaceutical interventions were deactivated, death rates increased.

History is not a predictive science. There exist numerous well-documented and vast differences between US society and public health during the 1918 pandemic compared with the present. We acknowledge the inherent difficulties of interpreting data recorded nearly 90 years ago and contending with the gaps, omissions, and errors that may be included in the extant historical record. The associations observed are not perfect; for example, 2 outlier cities (Grand Rapids and St Paul) experienced better outcomes with less than perfect public health responses. Future work by our research team will explore social, political, and ecological determinants, which may further help to explain some of this variation.

The United States of 1918 had many similar features to the present era: rapid transportation in the form of trains and automobiles; rapid means of communication in the form of the telegraph and telephone; large, heterogeneous populations with substantial urban concentrations (although a much higher percentage of the US population lived in rural areas compared with the present); a news system that was able to circulate information widely during the epidemic, including many daily newspapers and broadsheets distributed in communities; and a wide spectrum of public health agencies at various levels of government.

When examining the 1918 pandemic, however, it is important to recognize the numerous social, cultural, and scientific differences that do exist between that period and the present. For example, the legal understanding of privacy, civil, and constitutional rights as they relate to public health and governmentally directed measures (such as mass vaccination programs) has changed markedly over the past 9 decades. In addition, public support of and trust in these measures, along with trust in the medical profession as a whole, has shifted over time. Finally, other features of the modern era that need to be considered when applying lessons from history to the present era include the increased speed and mode of travel, above all high-volume commercial aviation; instantaneous access to information via the Internet and personal computers; a baseline understanding among the general population that the etiologic agents of infectious diseases are microbial; and advances in medical technology and therapeutics that have expanded considerably the options available for dealing with a pandemic.

Historical contextual issues and statistical limitations aside, the US urban experience with nonpharmaceutical interventions during the 1918-1919 pandemic constitutes one of the largest data sets of its kind ever assembled in the modern, postgerm theory era.

Our findings conform to 8 of A. Bradford Hill's 9 tenets on causal associations in the consideration of disease and the environment.[36] Specifically, during the 1918-1919 pandemic, the relation of early, sustained, and layered nonpharmaceutical interventions to EDR in 43 US cities demonstrate satisfaction of the criteria of *strength* (the magnitude and statistical significance of our findings, which also argue against an association by chance alone), *consistency* (early and combined nonpharmaceutical interventions were consistently associated with reductions in mortality, and our analysis is consistent with 2 recent smaller, preliminary historical epidemiological reports, although these studies look at only 16 US urban centers, do not include actual activation and deactivation time points, duration, or layering of nonpharmaceutical interventions, and rely extensively on secondary historical sources.[37,38]

Further, our retrospective study is consistent with the results from recent theoretical models of the spread of a contemporary pandemic, which highlight the value of early, combined, and sustained nonpharmaceutical interventions to mitigate a pandemic[11-15]), *specificity* (best demonstrated in cities with bimodal mortality peaks when the triggers were activated, deactivated, and reactivated), *temporality* (interventions always preceded the reduction of EDR), *dose response* (layering and increased duration of the nonpharmaceutical interventions were associated with better outcomes), *biological plausibility* (these interventions reduce person-to-person interactions and biologically would be expected to reduce the spread of a communicable agent such as influenza), *coherence* (our data align with the established body of knowledge on the epidemiology of influenza), and *analogy* (isolation and social distancing have been demonstrated as effective means of preventing person-to-person spread of other respiratory tract diseases, such as rhinovirus, severe acute respiratory syndrome, respiratory syncytial virus, varicella, and seasonal influenza).

The ninth tenet, *experiment*, could not be demonstrated directly because of the paucity of influenza pandemics in the past century, the trend away from such traditional public health mea-

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sures for disease control during the past 50 years, and ethical limitations of using population-wide nonpharmaceutical interventions in the absence of a serious threat.

These findings contrast with the conventional wisdom that the 1918 pandemic rapidly spread through each community killing everyone in its path. Although these urban communities had neither effective vaccines nor antivirals, cities that were able to organize and execute a suite of classic public health interventions before the pandemic swept fully through the city appeared to have an associated mitigated epidemic experience. Our study suggests that nonpharmaceutical interventions can play a critical role in mitigating the consequences of future severe influenza pandemics (category 4 and 5) and should be considered for inclusion in contemporary planning efforts as companion measures to developing effective vaccines and medications for prophylaxis and treatment. The history of US epidemics also cautions that the public's acceptance of these health measures is enhanced when guided by ethical and humane principles.[39-41]

Author Contributions: Drs Markel and Cetron had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Markel, Lipman, Navarro, Stern, Cetron.
Acquisition of data: Markel, Navarro, Sloan, Michalsen, Stern.
Analysis and interpretation of data: Markel, Lipman, Navarro, Sloan, Michalsen, Stern, Cetron.
Drafting of the manuscript: Markel, Lipman, Navarro, Sloan, Michalsen, Stern, Cetron.
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Statistical analysis: Markel, Lipman, Cetron.
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Saturated fatty acids increase levels of low-density lipoprotein cholesterol (LDL-C) and HDL-C,[2] whereas *trans*-fatty acids increase LDL-C level but decrease HDL-C level.[2,3] This distinction is important, because *trans*-fatty acids are more strongly associated with the risk of cardiovascular disease than saturated fatty acids due to their undesirable effects on LDL-C and HDL-C levels, endothelial cell function, adipocytes, and inflammatory response.[3,4]

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In Reply: Dr Kim distinguishes the effects of saturated fatty acids and *trans*-fatty acids on lipoproteins. However, reports of the effect of *trans*-fatty acids on HDL-C have been variable, with a large meta-analysis finding a statistically nonsignificant effect on HDL-C.[1] In addition to increasing levels of LDL-C, *trans*-fatty acids promote vascular inflammation and endothelial dysfunction and reduce paraoxonase activity.[2] These lipid and biochemical effects act synergistically to increase cardiovascular disease risk.[2]

The issue is more complex than indicated by HDL-C. Saturated fat rapidly promotes proinflammatory changes in HDL without changing HDL-C level.[3] Thus, as mentioned in our review, dietary intake of both saturated fatty acids and *trans*-fatty acids should be avoided and substituted with intake of monounsaturated and polyunsaturated fatty acids.

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CORRECTIONS

Data Error: In the Review article entitled "Data Extraction Errors in Meta-analyses That Use Standardized Mean Differences" published in the July 25, 2007, issue of *JAMA* (2007;298:430-437), Figure 4 included incorrect data. The reported point estimate and its 95% confidence interval for the meta-analysis standardized mean differences "–0.74 (–0.98 to –0.49)" for the Edmonds et al article should have read "–0.77 (–1.26 to –0.28)." The error was caused by a wrong label in the Cochrane Library at the time of the study. A meta-analysis was stated to have been done with a random-effects model; however, it was done with a fixed-effect model. The Cochrane Library no longer contains this error.

Typographical Errors in Tables: In the Research Letter entitled "Patterns of Prevalent Major Chronic Disease Among Older Adults in the United States" published in the September 12, 2007, issue of *JAMA* (2007;298[10]:1160-1162), both tables contained typographical errors. In both tables, the column headings of "Estimated Frequency (×1000)" and "CVA" were erroneously transposed and the brace under the column head "Disease Pattern, No. of Diseases" should have extended to include the CVA column. Online versions of this article on the *JAMA* Web site were corrected on October 4, 2007.

Unreported Financial Disclosures: In the Original Contribution entitled "Nonpharmaceutical Interventions Implemented by US Cities During the 1918-1919 Influenza Pandemic" published in the August 8, 2007, issue of *JAMA* (2007; 298[6]:644-654), financial disclosures were inadvertently not reported. On page 654, under "Financial Disclosures," the following should appear: "Dr Markel reported having received honoraria for delivering lectures on the social and cultural history of the 1918-1919 influenza pandemic at academic conferences or colloquia presented by Yale University, the US Department of Defense, the RAND Corporation, Columbia University, the US Department of Health and Human Services, the Michigan Society for Infection Control and Prevention, University of Michigan, and Emory University. None of the other authors reported financial disclosures."

Incorrect Affiliation: In the Research Letter entitled "Cardiovascular Response to a Modern Roller Coaster Ride" published in the August 15, 2007, issue of *JAMA* (2007;298[7]:739-741), the affiliations were reversed for 2 authors and 1 author's name was listed out of order. Joachim Brade, MSc, is affiliated with the Department of Medical Statistics and Dariusch Haghi, MD, is affiliated with the 1st Department of Medicine-Cardiology, University Hospital of Mannheim, Mannheim, Germany. The name for Christian Wolpert, MD, should have been placed last among the list of author names.

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Peer-reviewed articles

An influenza outbreak among pilgrims sleeping at a school without purpose built overnight accommodation facilities

Michael Staff, Maria I Torres

Abstract

This report describes a respiratory illness outbreak amongst a group of over 700 World Youth Day 2008 pilgrims staying at a basic accommodation venue for 1 week in July 2008. At this venue, 1 group of pilgrims was accommodated as a large group in a gymnasium and another group was sub-divided into smaller groups and accommodated in classrooms. Following confirmation of an influenza B outbreak by influenza point of care testing, control measures were promptly implemented. Isolation of cases, improved hand, respiratory and general hygiene, establishment of a mobile tent health facility at the accommodation venue, and the use of oseltamivir for the treatment of cases and prophylaxis of high risk contacts were implemented and the outbreak was brought under control within the week. Overall, 20% of pilgrims met the case definition for an influenza-like illness and 36% had an onset prior to arrival at the venue. The attack rate for those with onset while at the venue was significantly higher amongst pilgrims accommodated in the gymnasium than those staying in the classrooms. Findings from this study highlight the importance of early detection, the rapid implementation of control measures and appropriate prescribing of antivirals to manage influenza outbreaks. The findings also highlight the benefits of accommodating individuals in smaller groups within basic accommodation venues in the context of mass gatherings. *Commun Dis Intell* 2011;35(1):10–15.

Keywords: influenza, outbreak management, mass gathering, basic group accommodation

Introduction

In July 2008 Sydney was host to the World Youth Day (WYD), a large Catholic youth festival, which has been held every 2 to 3 years since 1986, each time in a different country. Of the 223,000 people who registered as pilgrims for WYD 2008, 110,000 were international pilgrims who came from 170 countries.[1] The majority of WYD 2008 activities occurred between 15 and 20 July. However, pilgrims started congregating in locations all over Australia from the second week in July. During this period, known as Days in the Dioceses, many of the international pilgrims were received by parishes and billeted in the homes of local pilgrims. All pilgrims then travelled to Sydney for the week of WYD 2008 activities. Approximately 100,000 pilgrims stayed at basic accommodation venues such as parish halls or schools.[2]

During the Days in the Dioceses there were unconfirmed reports of several cases of respiratory tract infections occurring among some groups of pilgrims prior to them arriving at their mass accommodation venues in Sydney. This paper aims to describe an outbreak of influenza among pilgrims at a WYD accommodation venue; describe and assess the management of the outbreak; and to determine whether sleeping in small groups in classrooms within the venue reduced the risk of contracting influenza during an established outbreak, in comparison with sleeping in a large hall.

Methods

Description of the facility and the study population

Seven hundred and five Solomon Islander and Australian pilgrims were provided with simple accommodation at a school, which did not have any purpose built facilities for overnight accommodation, from Sunday 13 July to Sunday 20 July 2008. There were 4 accommodation areas; 1 large school gymnasium with toilets and showering facilities and 3 groups of standard classrooms with each classroom housing approximately 8 pilgrims. The pilgrims in the classrooms shared a toilet/shower block that was separate to that accessed by the pilgrims sleeping in the gymnasium. The ratio of toilet/shower facilities to pilgrims met the recommendations that had been provided to the event organisers. Australian pilgrims were assigned to one of the 3 classroom groups based upon their parish of residence, and pilgrims from the Solomon Islands were accommodated in the gymnasium. Breakfast was provided in a communal area at the school while lunch and the evening meal were provided off site at other venues arranged for WYD activities. Pilgrims had been advised to be

vaccinated for influenza prior to attending WYD 2008 but it is not known what level of compliance with this recommendation was achieved.

Outbreak management

On Tuesday 15 July health authorities were notified of a probable respiratory illness outbreak at the venue. Initially, no designated health or medical facilities were available at the school and the 8 pilgrims who presented with a respiratory illness were isolated from the group and accommodated in separate classrooms where they were cared for by school staff. Cases were assessed by public health and ambulance staff with the more seriously ill transported to a local hospital emergency department for further treatment. Five cases with a clinically compatible influenza illness had point of care tests (QuickVue Influenza A+B Test, Quidel Corporation, San Diego, CA, USA) performed on nasal swabs with samples subsequently sent for laboratory immunofluorescence (IF) and polymerase chain reaction (PCR) testing. On Wednesday 16 July an additional 21 cases had nose and throat swabs collected.

When it became apparent that an outbreak was well established among the group, a decision was made to establish a designated mobile tent health facility at the school. This was a 30 bed tent hospital staffed by nurses and medical practitioners from the local Area Health Service and was operational from 16 to 21 July 2008. It had primary care treatment capacity with more serious cases requiring transport to local emergency departments for more complex assessments such as chest x-ray. Treatment guidelines consistent with national guidelines were provided to the clinicians at the facility.[3] The guidelines recommended oseltamivir treatment (75 mg bi-daily for 5 days) for all cases meeting the case definition and whose illness onset was within 48 hours of being seen and oseltamivir prophylaxis (75 mg daily for 10 days) for well pilgrims with predisposing conditions that may have increased their risk of influenza complications.

Individuals diagnosed with suspected influenza were isolated at the mobile health facility or in other suitable rooms at the school whilst infectious (infectious period = 5 days since onset of symptoms or 48 hours after commencing treatment with oseltamivir) or allowed to return home if this was their preference. Information on simple control measures such as hand washing and cough etiquette was distributed among pilgrims, increased hand washing facilities and facial tissues were made available and professional cleaners were engaged to maximise the venue's general cleanliness. Oseltamivir was used at the mobile health facility for influenza treatment and prophylaxis. Public health practitioners also assessed contacts and provided oseltamivir prophylaxis.

Epidemiological investigation

The following case definition, modified from the National case definition for influenza, was used to identify cases:

- self reported or measured (> 38°C) fever, plus
- cough or shortness of breath or coryza or sore throat, plus
- fatigue or myalgia or rigors or headache.

On Wednesday 16 July, a written questionnaire was administered to all pilgrims at the school. For the Solomon Islander group the questionnaire was administered in a single group setting with the assistance of a leader from the group who spoke English and was able to provide translation. The questionnaire asked about the presence and time of onset of influenza-like illness symptoms. For each symptom, respondents were asked to circle the day of onset in the previous 5 days. Age, gender, church group and accommodation site at the school were also recorded.

In the week prior to the WYD the pilgrims from Solomon Islander church groups had been billeted at several of the parishes of the Australian pilgrims who were also at the school during WYD. Church groupings allowed identification of potential exposures between the two nationalities prior to arrival at the school.

The clinical medical records and facility logs from the onsite health facility were used to verify and supplement the information obtained from the self completed questionnaires. Data obtained included medical history, clinical examination findings, medication prescribed, and referral for further treatment. Information was also obtained from public health records of assessments of contacts and antiviral prophylaxis prescription logs.

Data analysis

Data were entered into Epi Info with data analysis conducted using STATA 9.2 (StataCorp, College Station, Texas 77845 USA). Chi-square and Fisher's exact tests of significance were used to test for association between attack rates and accommodation arrangements.

Results

Initial cases and laboratory confirmation of outbreak

Of the 5 initial cases swabbed on 15 July, 2 tested positive for influenza B on point of care testing. Subsequent laboratory influenza B antigen detection by IF was positive for four of this group with

3 cases also PCR positive for influenza B. Of the 21 cases tested on Wednesday 16 July, five tested positive for influenza B on point of care tests, eight were confirmed as influenza B positive by PCR, and an additional three, who had positive influenza B results on IF, returned negative PCR results.

Questionnaire results

Six hundred and ninety-three pilgrims (433 Solomon Islanders and 260 Australians) provided responses to the questionnaire (98% response rate). Of the 693 responses, 653 provided sufficient information to allow a comparison with the case definition. Of these, 132 (20%) reported a recent fever and 233 (36%) complained of having had a cough. Seventeen per cent of pilgrims reported fevers commencing five or more days prior to the date of the questionnaire and 24% reported coughs.

Mobile health facility data

The mobile health facility attended to a total of 119 pilgrims (62 Solomon Islanders and 57 Australians); 5 pilgrims were seen on two occasions. There was sufficient information available to allow a comparison with the case definition for 101 of the pilgrims seen at the mobile health facility. Fifty-six (55%) met the case definition for influenza with 37 having had symptoms commencing in the last 48 hours. Six cases were referred from the mobile health facility to hospital for further assessment and management of their influenza-like illness. Twenty-three of the presentations to the mobile health facility who met the case definition and were identified within 48 hours of onset of symptoms, were treated with oseltamivir (Table 1). A total of 43 pilgrims received prophylactic courses of oseltamivir (13 from public health practitioners and 30 from the mobile health facility). Of those who received prophylactic antivirals, 15 were eligible for prophylaxis, 10 should have received treatment doses and 18 had no indication for receiving antivirals.

Cases meeting case definition

After combining the questionnaire and mobile health facility data 131 or 20% of pilgrims met the case definition for influenza (Table 2). Thirty-six per cent of cases commenced before arrival at the school on Sunday 13 July, with the first case reported to have started on 9 July. The attack rate for the period including both the time prior and following arrival at the school was significantly higher among the Solomon Islanders at 26%, compared with that for the Australians of 11% ($P < 0.01$).

Illness among Solomon Islanders when billeted prior to the World Youth Day

There were 13 church groups from the Solomon Islands who were billeted with parishes in Australia in the week prior to staying at the school. Based upon self-reported questionnaire responses all but two of these groups (both with 6 or less members) had one or more members being unwell with a cough

Table 1: Oseltamivir treatment of presentations to mobile health facility

Received treatment	Eligible to receive treatment		Total
	Yes	No	
Yes	23	5	28
No	14	13	27
Total	37	18	55

Table 2: Attack rates, by period and by accommodation group

Nationality	Number of pilgrims	Pilgrims became unwell over whole period*		Accommodation	Number of pilgrims†	Pilgrims unwell prior to arriving at the school		Pilgrims became unwell whilst at the school‡	
		n	%			n	%	n	%
Solomon Islanders	398	104	26.1	Gymnasium	398	43	10.8	61	17.2
Australians	255	27	10.7	Classrooms A	107	3	2.8	7	6.7
				Classrooms B	54	1	1.9	3	5.7
				Classrooms C	92	0	0	13	14.1
				Classrooms total	253	4	1.6	23	9.2§
Total	653	131	20.1		651	47	7.2	84	13.9

* Whole period i.e. from 9 July to 21 July 2008.

† Accommodation data were not available for 2 pilgrims.

‡ Denominator is well pilgrims as of Sunday 13 July (i.e. 355, 104, 53 and 92 for each accommodation group).

§ *P* value <0.05, comparison of Solomon Islanders and Australians' attack rates whilst at the school.

and/or fever before arrival at the school. Each of the 3 Australian classroom accommodation groups had some members from a parish that had billeted a Solomon Islander church group with an ill member.

Attack rates by accommodation

Table 2 shows the number of cases in each accommodation area broken down by time of onset of symptoms. There were cases of influenza among pilgrims prior to arriving at the school in three of the 4 accommodation groups with the greatest number from the Solomon Islander groups. After arriving at the school, the attack rates among the pilgrims in the Australian groups were 6.7%, 5.7% and 14.1% with no significant statistical difference between groups ($P = 0.1$). Among Solomon Islanders, the attack rate after arriving at the school was 17.2%; this was significantly higher than the attack rate of 9.2% among the Australian pilgrims considered as a single group ($P < 0.01$). The Figure describes the epidemiological curve for the outbreak broken down by nationality of pilgrim, commencing from 13 July, (the commencement of their accommodation in groups at the school).

Discussion

This study describes an influenza outbreak within a group of pilgrims brought together during a week long mass gathering. It highlights the usefulness of point of care tests in confirming the outbreak, the difficulty in administering antivirals despite deploying an onsite health facility and the potential impact of different accommodation arrangements.

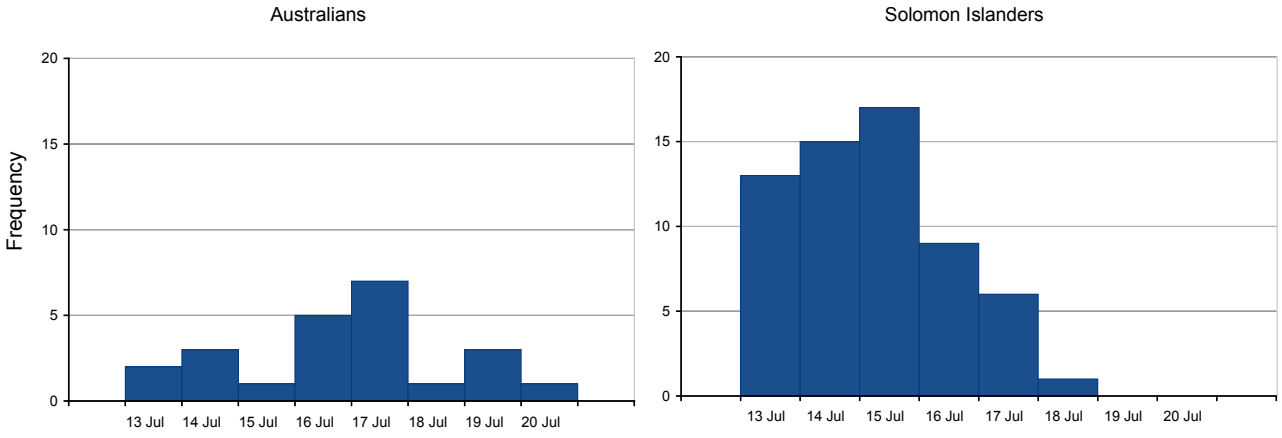
The overall attack rate of 20% observed in this study was within the range of rates reported by outbreak studies conducted during other, somewhat comparable, mass gatherings.[4,5] The setting of this outbreak differs from other group accommodation venues such as military and naval settings or residential aged care facilities, which have been the subject of previous influenza outbreak studies. WYD 2008 pilgrims accommodated at the school were grouped only shortly before or on arrival to the accommodation venue, and while they spent a significant amount of time with their group they also mixed with other pilgrims at and outside the accommodation venue. This was not comparable to military and other confined settings where members remain as part of their groups for extended periods, and where movement in and out of the setting and interaction with the outside environment is controlled.[6,7,8]

It is generally agreed that no single strategy used alone is effective in controlling infectious respiratory outbreaks.[9] As per national and state protocols, in addition to the use of antivirals for treatment and prophylaxis, several other measures including isolation of cases, promotion of sneeze and cough etiquette and hand hygiene were implemented to control the influenza outbreak. It is unknown how compliant sick pilgrims were with these voluntary control measures, but they appear to have had an effect in this population as the data suggest that the outbreak was under control by the end of the surveillance period on Monday 21 July 2008.

Given the anticipated high specificity and positive predictive value of point of care tests, a positive influenza point of care test result is very suggestive of influenza and may be sufficient to trigger an outbreak response.[10–12] The finding of 2 positive influenza B tests on the first day of this investigation gave health authorities grounds to implement control measures at the school very early in the response. Unfortunately, it is likely that their effectiveness to control the outbreak was undermined by the circulation of the virus amongst pilgrims for some time before they arrived at the school.

Establishing a mobile health facility was an exceptional measure implemented to deal with a special

Figure: Epidemiological curve, World Youth Day 2008 pilgrims, by nationality



situation. The implementation of such a measure has its own challenges such as sourcing and deploying appropriate clinical staff, maintaining appropriate documentation and medical records and establishing clear coordination and role definitions for clinicians and public health practitioners participating in the response. These issues need to be considered by all parties involved in an outbreak response to determine if and in what circumstances would such a strategy be used and how to best plan for this eventuality.

The use of oseltamivir for treatment and prophylaxis was one of the strategies considered appropriate to manage influenza outbreaks in the context of the special event that was WYD 2008, and the relevant protocols were available to clinicians and public health practitioners. The finding that only 62% of the cases eligible to be treated with oseltamivir actually received treatment is of some concern. This could be explained by the failure to identify cases, for example as a result of poor history taking by clinicians or poor symptom recall by patients, or by prescribing errors. These could also explain the mismatch between eligibility for prophylaxis and actual prescribing of prophylaxis. Strategies such as just-in-time training should be considered to ensure better clinician compliance with management protocols.

An important aspect of the WYD 2008 outbreak described here is the significantly higher attack rate observed amongst Solomon Islanders than Australian pilgrims, both prior to and after arrival at the school. It is likely that the influenza virus first started to spread amongst Solomon Islanders when they congregated in the Solomon Islands prior to arrival in Australia and continued to spread amongst the group while en-route hence explaining the higher prior to arrival attack rate.

The difference in attack rates observed between the Solomon Islander and the Australian groups whilst at the school, could be attributed to the differences in accommodation used whilst at the school. The Solomon Islander pilgrims, who were accommodated in a single large open plan area, had a significantly higher attack rate. The Australians, who were accommodated in smaller groups in classrooms, had, as a group, a significantly lower attack rate than the Solomon Islanders. The differences in attacks rates observed between the three classroom groups accommodating Australian pilgrims, although not statistically significant, suggest that the spread of illness was contained within discrete accommodation areas to some extent. This finding may have implications for planning future mass gatherings where non-purpose built facilities are used to accommodate participants.

An alternate explanation for the higher attack rate among the Solomon Islanders is that the outbreak was halted prematurely among the Australian pilgrims with the end of WYD 2008 activities. However, if this had been the case, the number of influenza cases among the Australian pilgrims would probably have continued to increase during the period at the school; this was not observed, on the contrary the outbreak appeared to peak among the Australian groups, as well as among the Solomon Islanders, before the end of their stay at the school.

One of the major limitations of this study is the lack of information that was available about symptoms prior to pilgrims arriving at the school. Although it is clear that a respiratory illness was circulating among the Solomon Island pilgrims prior to arrival at the school and that there was a potential for Australian pilgrims from each classroom group to have been exposed to the illness, it is likely that estimates of illness prior to arrival at the school are inaccurate. Furthermore, when looking at attack rates among accommodation groups it was not possible to adjust for the mixing that occurred during the various daytime and evening activities in which pilgrims participated.

This study has highlighted the potential of influenza to cause large outbreaks in a mass gathering setting and the need to consider the physical layout of accommodation facilities to help control the spread of illness. Early detection, rapid implementation of control measures, appropriate prescribing of antivirals and accommodating individuals in smaller groups within an accommodation venue, are all measures that need to be considered in managing and preventing these outbreaks.

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This study was conducted as part of the public health response to the outbreak and did not require approval by an ethics committee.

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[Intervention Review]

Physical interventions to interrupt or reduce the spread of respiratory viruses

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ABSTRACT

Background

Viral epidemics or pandemics of acute respiratory infections (ARIs) pose a global threat. Examples are influenza (H1N1) caused by the H1N1pdm09 virus in 2009, severe acute respiratory syndrome (SARS) in 2003, and coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in 2019. Antiviral drugs and vaccines may be insufficient to prevent their spread. This is an update of a Cochrane Review published in 2007, 2009, 2010, and 2011. The evidence summarised in this review does not include results from studies from the current COVID-19 pandemic.

Objectives

To assess the effectiveness of physical interventions to interrupt or reduce the spread of acute respiratory viruses.

Search methods

We searched CENTRAL, PubMed, Embase, CINAHL on 1 April 2020. We searched ClinicalTrials.gov, and the WHO ICTRP on 16 March 2020. We conducted a backwards and forwards citation analysis on the newly included studies.

Selection criteria

We included randomised controlled trials (RCTs) and cluster-RCTs of trials investigating physical interventions (screening at entry ports, isolation, quarantine, physical distancing, personal protection, hand hygiene, face masks, and gargling) to prevent respiratory virus transmission. In previous versions of this review we also included observational studies. However, for this update, there were sufficient RCTs to address our study aims.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. We used GRADE to assess the certainty of the evidence. Three pairs of review authors independently extracted data using a standard template applied in previous versions of this review, but which was revised

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to reflect our focus on RCTs and cluster-RCTs for this update. We did not contact trialists for missing data due to the urgency in completing the review. We extracted data on adverse events (harms) associated with the interventions.

Main results

We included 44 new RCTs and cluster-RCTs in this update, bringing the total number of randomised trials to 67. There were no included studies conducted during the COVID-19 pandemic. Six ongoing studies were identified, of which three evaluating masks are being conducted concurrent with the COVID pandemic, and one is completed.

Many studies were conducted during non-epidemic influenza periods, but several studies were conducted during the global H1N1 influenza pandemic in 2009, and others in epidemic influenza seasons up to 2016. Thus, studies were conducted in the context of lower respiratory viral circulation and transmission compared to COVID-19. The included studies were conducted in heterogeneous settings, ranging from suburban schools to hospital wards in high-income countries; crowded inner city settings in low-income countries; and an immigrant neighbourhood in a high-income country. Compliance with interventions was low in many studies.

The risk of bias for the RCTs and cluster-RCTs was mostly high or unclear.

Medical/surgical masks compared to no masks

We included nine trials (of which eight were cluster-RCTs) comparing medical/surgical masks versus no masks to prevent the spread of viral respiratory illness (two trials with healthcare workers and seven in the community). There is low certainty evidence from nine trials (3507 participants) that wearing a mask may make little or no difference to the outcome of influenza-like illness (ILI) compared to not wearing a mask (risk ratio (RR) 0.99, 95% confidence interval (CI) 0.82 to 1.18. There is moderate certainty evidence that wearing a mask probably makes little or no difference to the outcome of laboratory-confirmed influenza compared to not wearing a mask (RR 0.91, 95% CI 0.66 to 1.26; 6 trials; 3005 participants). Harms were rarely measured and poorly reported. Two studies during COVID-19 plan to recruit a total of 72,000 people. One evaluates medical/surgical masks (N = 6000) (published *Annals of Internal Medicine*, 18 Nov 2020), and one evaluates cloth masks (N = 66,000).

N95/P2 respirators compared to medical/surgical masks

We pooled trials comparing N95/P2 respirators with medical/surgical masks (four in healthcare settings and one in a household setting). There is uncertainty over the effects of N95/P2 respirators when compared with medical/surgical masks on the outcomes of clinical respiratory illness (RR 0.70, 95% CI 0.45 to 1.10; very low-certainty evidence; 3 trials; 7779 participants) and ILI (RR 0.82, 95% CI 0.66 to 1.03; low-certainty evidence; 5 trials; 8407 participants). The evidence is limited by imprecision and heterogeneity for these subjective outcomes. The use of a N95/P2 respirator compared to a medical/surgical mask probably makes little or no difference for the objective and more precise outcome of laboratory-confirmed influenza infection (RR 1.10, 95% CI 0.90 to 1.34; moderate-certainty evidence; 5 trials; 8407 participants). Restricting the pooling to healthcare workers made no difference to the overall findings. Harms were poorly measured and reported, but discomfort wearing medical/surgical masks or N95/P2 respirators was mentioned in several studies. One ongoing study recruiting 576 people compares N95/P2 respirators with medical surgical masks for healthcare workers during COVID-19.

Hand hygiene compared to control

Settings included schools, childcare centres, homes, and offices. In a comparison of hand hygiene interventions with control (no intervention), there was a 16% relative reduction in the number of people with ARIs in the hand hygiene group (RR 0.84, 95% CI 0.82 to 0.86; 7 trials; 44,129 participants; moderate-certainty evidence), suggesting a probable benefit. When considering the more strictly defined outcomes of ILI and laboratory-confirmed influenza, the estimates of effect for ILI (RR 0.98, 95% CI 0.85 to 1.13; 10 trials; 32,641 participants; low-certainty evidence) and laboratory-confirmed influenza (RR 0.91, 95% CI 0.63 to 1.30; 8 trials; 8332 participants; low-certainty evidence) suggest the intervention made little or no difference. We pooled all 16 trials (61,372 participants) for the composite outcome of ARI or ILI or influenza, with each study only contributing once and the most comprehensive outcome reported. The pooled data showed that hand hygiene may offer a benefit with an 11% relative reduction of respiratory illness (RR 0.89, 95% CI 0.84 to 0.95; low-certainty evidence), but with high heterogeneity. Few trials measured and reported harms.

There are two ongoing studies of handwashing interventions in 395 children outside of COVID-19.

We identified one RCT on quarantine/physical distancing. Company employees in Japan were asked to stay at home if household members had ILI symptoms. Overall fewer people in the intervention group contracted influenza compared with workers in the control group (2.75% versus 3.18%; hazard ratio 0.80, 95% CI 0.66 to 0.97). However, those who stayed at home with their infected family members were 2.17 times more likely to be infected.

We found no RCTs on eye protection, gowns and gloves, or screening at entry ports.

Authors' conclusions

The high risk of bias in the trials, variation in outcome measurement, and relatively low compliance with the interventions during the studies hamper drawing firm conclusions and generalising the findings to the current COVID-19 pandemic.

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There is uncertainty about the effects of face masks. The low-moderate certainty of the evidence means our confidence in the effect estimate is limited, and that the true effect may be different from the observed estimate of the effect. The pooled results of randomised trials did not show a clear reduction in respiratory viral infection with the use of medical/surgical masks during seasonal influenza. There were no clear differences between the use of medical/surgical masks compared with N95/P2 respirators in healthcare workers when used in routine care to reduce respiratory viral infection. Hand hygiene is likely to modestly reduce the burden of respiratory illness. Harms associated with physical interventions were under-investigated.

There is a need for large, well-designed RCTs addressing the effectiveness of many of these interventions in multiple settings and populations, especially in those most at risk of ARIs.

PLAIN LANGUAGE SUMMARY

Do physical measures such as hand-washing or wearing masks stop or slow down the spread of respiratory viruses?

What are respiratory viruses?

Respiratory viruses are viruses that infect the cells in your airways: nose, throat, and lungs. These infections can cause serious problems and affect normal breathing. They can cause flu (influenza), severe acute respiratory syndrome (SARS), and COVID-19.

How do respiratory viruses spread?

People infected with a respiratory virus spread virus particles into the air when they cough or sneeze. Other people become infected if they come into contact with these virus particles in the air or on surfaces on which they have landed. Respiratory viruses can spread quickly through a community, through populations and countries (causing epidemics), and around the world (causing pandemics).

How can we stop the spread of respiratory viruses?

Physical measures to try to stop respiratory viruses spreading between people include:

· washing hands often;

· not touching your eyes, nose, or mouth;

· sneezing or coughing into your elbow;

· wiping surfaces with disinfectant;

· wearing masks, eye protection, gloves, and protective gowns;

· avoiding contact with other people (isolation or quarantine);

· keeping a certain distance away from other people (distancing); and

· examining people entering a country for signs of infection (screening).

Why we did this Cochrane Review

We wanted to find out whether physical measures stop or slow the spread of respiratory viruses.

What did we do?

We searched for studies that looked at physical measures to stop people catching a respiratory virus infection.

We were interested in how many people in the studies caught a respiratory virus infection, and whether the physical measures had any unwanted effects.

Search date: This is an update of a review first published in 2007. We included evidence published up to 1 April 2020.

What we found

We identified 67 relevant studies. They took place in low-, middle-, and high-income countries worldwide: in hospitals, schools, homes, offices, childcare centres, and communities during non-epidemic influenza periods, the global H1N1 influenza pandemic in 2009, and epidemic influenza seasons up to 2016. No studies were conducted during the COVID-19 pandemic. We identified six ongoing, unpublished studies; three of them evaluate masks in COVID-19.

One study looked at quarantine, and none eye protection, gowns and gloves, or screening people when they entered a country.

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We assessed the effects of:

· medical or surgical masks;

· N95/P2 respirators (close-fitting masks that filter the air breathed in, more commonly used by healthcare workers than the general public); and

· hand hygiene (hand-washing and using hand sanitiser).

What are the results of the review?

Medical or surgical masks

Seven studies took place in the community, and two studies in healthcare workers. Compared with wearing no mask, wearing a mask may make little to no difference in how many people caught a flu-like illness (9 studies; 3507 people); and probably makes no difference in how many people have flu confirmed by a laboratory test (6 studies; 3005 people). Unwanted effects were rarely reported, but included discomfort.

N95/P2 respirators

Four studies were in healthcare workers, and one small study was in the community. Compared with wearing medical or surgical masks, wearing N95/P2 respirators probably makes little to no difference in how many people have confirmed flu (5 studies; 8407 people); and may make little to no difference in how many people catch a flu-like illness (5 studies; 8407 people) or respiratory illness (3 studies; 7799 people). Unwanted effects were not well reported; discomfort was mentioned.

Hand hygiene

Following a hand hygiene programme may reduce the number of people who catch a respiratory or flu-like illness, or have confirmed flu, compared with people not following such a programme (16 studies; 61,372 people). Few studies measured unwanted effects; skin irritation in people using hand sanitiser was mentioned.

How reliable are these results?

Our confidence in these results is generally low for the subjective outcomes related to respiratory illness, but moderate for the more precisely defined laboratory-confirmed respiratory virus infection, related to masks and N95/P2 respirators. The results might change when further evidence becomes available. Relatively low numbers of people followed the guidance about wearing masks or about hand hygiene, which may have affected the results of the studies.

Key messages

We are uncertain whether wearing masks or N95/P2 respirators helps to slow the spread of respiratory viruses.

Hand hygiene programmes may help to slow the spread of respiratory viruses.

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Summary of findings 1. Medical/surgical masks compared to no masks for preventing the spread of viral respiratory illness

Randomised studies: medical/surgical masks compared to no masks for preventing the spread of viral respiratory illness

Patient or population: general population and healthcare workers
Setting: community and hospitals
Intervention: medical/surgical masks
Comparison: no masks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no masks	Risk with randomised studies: masks				
Viral illness - influenza-like illness	Study population		RR 0.99 (0.82 to 1.18)	3507 (9 RCTs)	⊕⊕⊖⊖ LOW[a,b]	
	160 per 1000	158 per 1000 (131 to 189)				
Viral illness - laboratory-confirmed influenza	Study population		RR 0.91 (0.66 to 1.26)	3005 (6 RCTs)	⊕⊕⊕⊖ MODERATE[b]	
	40 per 1000	36 per 1000 (26 to 50)				
Influenza-like illness in healthcare workers	Study population		RR 0.37 (0.05 to 2.50)	1070 (2 RCTs)	⊕⊕⊖⊖ LOW[a,b]	Studies in healthcare workers only
	40 per 1000	15 per 1000 (2 to 100)				
Adverse events	-		-	(3 RCTs)	⊕⊖⊖⊖ VERY LOW[a,c]	Adverse events were not reported consistently and could not be meta-analysed. Adverse events reported for masks included warmth, discomfort, respiratory difficulties, humidity, pain, and shortness of breath, in up to 45% of participants.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the median observed risk in the comparison group of included studies and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

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High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Study limitations (lack of blinding).
[b]Imprecision (wide confidence intervals).
[c]Imprecision: 2 steps (only 3 studies enumerated adverse events; another study mentioned no adverse events).

Summary of findings 2. N95 respirators compared to medical/surgical masks for preventing the spread of viral respiratory illness

Randomised studies: N95 respirators compared to medical/surgical masks for preventing the spread of viral respiratory illness

Patient or population: healthcare workers and general population
Setting: hospitals and households
Intervention: N95 masks
Comparison: medical/surgical masks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with medical masks	Risk with randomised studies: N95				
Viral illness - clinical respiratory illness	Study population		RR 0.70 (0.45 to 1.10)	7799 (3 RCTs)	⊕⊖⊖⊖ VERY LOW[a,b,c]	All studies were conducted in hospital settings with healthcare workers.
	120 per 1000	84 per 1000 (54 to 132)				
Viral illness - influenza-like illness	Study population		RR 0.82 (0.66 to 1.03)	8407 (5 RCTs)	⊕⊕⊖⊖ LOW[a,b]	1 study was conducted in households (MacIntyre 2009).
	50 per 1000	41 per 1000 (33 to 52)				
Viral illness - laboratory-confirmed influenza	Study population		RR 1.10 (0.90 to 1.34)	8407 (5 RCTs)	⊕⊕⊕⊖ MODERATE[b]	1 study was conducted in households (MacIntyre 2009).
	70 per 1000	77 per 1000 (63 to 94)				

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Adverse events	-	-	(5 RCTs)	⊕⊖⊖⊖ VERY LOW[a,b,c]	There was insufficient consistent reporting of adverse events to enable meta-analysis. Only 1 study reported detailed adverse events: discomfort was reported in 41.9% of N95 wearers versus 9.8% of medical mask wearers (P < 0.001); headaches were more common with N95 (13.4% versus 3.9%; P < 0.001); difficulty breathing was reported more often in the N95 group (19.4% versus 12.5%; P = 0.01); and N95 caused more problems with pressure on the nose (52.2% versus 11.0%; P < 0.001). 4 RCTs either reported no adverse events or only reported on comfort wearing masks.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the median risk in the comparison group and the observed __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Study limitations (lack of blinding).
[b]Imprecision (wide confidence interval or no meta-analysis conducted).
[c]Inconsistency of results (heterogeneity).

Summary of findings 3. Hand hygiene compared to control for preventing the spread of viral respiratory illness

Hand hygiene compared to control for preventing the spread of viral respiratory illness

Patient or population: prevention of spread of viral respiratory illness
Setting: schools, childcare centres, homes, offices
Intervention: hand hygiene
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with hand hygiene				
Acute respiratory illness	Study population		RR 0.84 (0.82 to 0.86)	44,129 (7 RCTs)	⊕⊕⊕⊖ MODERATE[a]	
	380 per 1000	319 per 1000 (312 to 327)				

Physical interventions to interrupt or reduce the spread of respiratory viruses (Review)
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Influenza-like illness	Study population		RR 0.98 (0.85 to 1.13)	32,641 (10 RCTs)	⊕⊕⊖⊖ LOW[a,b]	
	90 per 1000	88 per 1000 (77 to 102)				
Laboratory-confirmed influenza	Study population		RR 0.91 (0.63 to 1.30)	8332 (8 RCTs)	⊕⊕⊖⊖ LOW[b,c]	
	80 per 1000	73 per 1000 (50 to 104)				
Composite of acute respiratory illness, influenza-like illness, influenza	Study population		RR 0.89 (0.84 to 0.95)	61,372 (16 RCTs)	⊕⊕⊖⊖ LOW[a,b]	
	200 per 1000	178 per 1000 (168 to 190)				
Adverse events	-		-	(2 RCTs)	⊕⊖⊖⊖ VERY LOW[a,b,c]	Data were insufficient to conduct meta-analysis. 1 study reported that no adverse events were observed, and another study reported that skin reaction was recorded for 10.4% of participants in the hand sanitiser group versus 10.3% in the control group.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the median observed risk in the comparison groups of included studies and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Study limitation (majority of studies were unblinded, with participant-assessed outcome).
[b]Inconsistent results across studies.
[c]Imprecision (wide confidence interval or no meta-analysis conducted).

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BACKGROUND

Description of the condition

Epidemic and pandemic viral infections pose a serious threat to people worldwide. Epidemics of note include severe acute respiratory syndrome (SARS) in 2003 and the Middle East respiratory syndrome (MERS), which began in 2012. Major pandemics include the H1N1 influenza caused by the H1N1pdm09 virus in 2009 and the coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2.

Even non-epidemic acute respiratory infections (ARIs) place a huge burden on healthcare systems around the world, and are a prominent cause of morbidity (WHO 2017). Furthermore, ARIs are often antecedents to lower respiratory tract infections caused by bacterial pathogens (i.e. pneumonia), which cause millions of deaths worldwide, mostly in low-income countries (Schwartz 2018).

High viral load, high levels of transmissibility, susceptible populations, and symptomatic patients are considered to be the drivers of such epidemics and pandemics (Jefferson 2006a). Preventing the spread of respiratory viruses from person to person may be effective at reducing the spread of outbreaks. Physical interventions, such as the use of masks and physical distancing measures, might prevent the spread of respiratory viruses which are transmitted by large droplets from infected to susceptible people. This review assumes that physical interventions used to prevent transmission of respiratory viruses are similar for most viral ARIs.

Description of the intervention

Single measures of intervention (Demicheli 2018a; Demicheli 2018b; Jefferson 2014; Jefferson 2018; Thomas 2010), such as the use of vaccines or antivirals, may be insufficient to contain the spread of influenza, but combinations of interventions may reduce the reproduction number to below 1. For some respiratory viruses there are no licensed interventions, and a combination of social and physical interventions may be the only option to reduce the spread of outbreaks, particularly those that may be capable of becoming epidemic or pandemic in nature (Luby 2005). Such interventions were emphasised in the World Health Organization's latest Global Influenza Strategy 2019 to 2030, and have several possible advantages over other methods of suppressing ARI outbreaks since they may be instituted rapidly and may be independent of any specific type of infective agent, including novel viruses. In addition, the possible effectiveness of public health measures during the Spanish flu pandemic of 1918 to 1919 in US cities supports the impetus to investigate the existing evidence on the effectiveness of such interventions (Bootsma 2007), including quarantine (such as isolation, physical distancing) and the use of disinfectants. We also considered the major societal implications for any community adopting these measures (CDC 2005a; CDC 2005b; WHO 2006b; WHO 2020a; WHO 2020b).

How the intervention might work

Epidemics and pandemics are more likely during antigenic change (changes in the viral composition) in the virus or transmission from animals (domestic or wild) when there is no natural human immunity (Bonn 1997). High viral load, high levels of transmissibility, and symptomatic patients are considered to be the drivers of such epidemics and pandemics (Jefferson 2006b).

Physical interventions, such as the use of masks, physical distancing measures, school closures, and limitations of mass gatherings, might prevent the spread of the virus transmitted by large droplets or aerosols from infected to susceptible individuals. The use of hand hygiene, gloves, and protective gowns can also prevent the spread by limiting the transfer of viral particles onto and from fomites (inanimate objects such as flat surfaces, tabletops, utensils, porous surfaces, or nowadays cell phones, which can transmit the agent if contaminated). Such public health measures were widely adopted during the Spanish flu pandemic and have been the source of considerable debate (Bootsma 2007).

Why it is important to do this review

Although the benefits of physical interventions seem self-evident, given the global importance of interrupting viral transmission, having up-to-date estimates of their effectiveness is necessary to inform planning, decision-making, and policy. The outbreak of COVID-19 has prompted this update. Physical methods have several possible advantages over other methods of suppressing ARI outbreaks, including their rapid deployment and ability to be independent of the infective agent, including novel viruses.

The last update of this review in 2011, Jefferson 2011, identified 23 trials on physical interventions that might interrupt or reduce the spread of respiratory viruses. Because of poor reporting and heterogeneity, and the relatively small number of included trials, it was not possible to perform a meta-analysis. Case-control studies were sufficiently homogenous to permit meta-analysis, which provided evidence that hand-washing for a minimum of 11 times daily prevented cases of SARS during the 2003 epidemic (odds ratio 0.54, 95% confidence interval 0.44 to 0.67). Many randomised trials have been published in the past decade, prompting us to focus only on these for the current update.

This is the fourth update of a Cochrane Review first published in 2007 (Jefferson 2007; Jefferson 2009; Jefferson 2010; Jefferson 2011).

OBJECTIVES

To assess the effectiveness of physical interventions to interrupt or reduce the spread of acute respiratory viruses.

METHODS

Criteria for considering studies for this review

Types of studies

For this 2020 update we only considered individual-level RCTs, or cluster-RCTs, or quasi-RCTs for inclusion.

In previous versions of the review we also included observational studies (cohorts, case-controls, before-after, and time series studies). However, for this update there were sufficient randomised studies to address our study aims, so we excluded observational studies (which are known to be at a higher risk of bias).

Types of participants

People of all ages.

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Types of interventions

We included randomised controlled trials (RCTs) and cluster-RCTs of trials investigating physical interventions (screening at entry ports, isolation, quarantine, physical distancing, personal protection, hand hygiene, face masks, and gargling) to prevent respiratory virus transmission compared with doing nothing or with another intervention.

Types of outcome measures

For this 2020 update we added one outcome: adverse events related to the intervention, and we split the outcomes into primary and secondary outcomes.

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, influenza-like illness (ILI), and laboratory-confirmed influenza, or other viral pathogens).
2. Adverse events related to the intervention.

Secondary outcomes

1. Deaths.
2. Severity of viral illness as reported in the studies.
3. Absenteeism.
4. Hospital admissions.
5. Complications related to the illness, e.g. pneumonia.

Search methods for identification of studies

Electronic searches

For this 2020 update, we refined the original search strategy using a combination of previously included studies and automation tools (Clark 2020). We converted this search using the Polyglot Search Translator (Clark 2020), and ran the searches in the following databases:

1. the Cochrane Central Register of Controlled Trials (CENTRAL) (2020, Issue 3), which includes the Acute Respiratory Infections Group's Specialised Register (searched 1 April 2020) (Appendix 1);
2. PubMed (2010 to 1 April 2020) (Appendix 2);
3. Embase (2010 to 1 April 2020) (Appendix 3);
4. CINAHL (Cumulative Index to Nursing and Allied Health Literature) (2010 to 1 April 2020) (Appendix 4);
5. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (January 2010 to 16 March 2020); and
6. World Health Organization International Clinical Trials Registry Platform (January 2010 to 16 March 2020).

We combined the database searches with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2011). Details of previous searches are available in Appendix 5.

Searching other resources

We conducted a backwards-and-forwards citation analysis in Scopus on all newly included studies to identify other potentially relevant studies.

Data collection and analysis

Selection of studies

The search and citation analysis results were initially screened via the RobotSearch tool (Marshall 2018) to exclude all studies that were obviously not RCTs. We scanned the titles and abstracts of studies identified by the searches. We obtained the full-text articles of studies that either appeared to meet our eligibility criteria or for which there was insufficient information to exclude it. We then used a standardised form to assess the eligibility of each study based on the full article.

Data extraction and management

Three pairs of review authors (MJ/EF, LA/GB, EB/TOJ) independently applied the inclusion criteria to all identified and retrieved articles, and extracted data using a standard template that had been developed for and applied to previous versions of the review, but was revised to reflect our focus on RCTs and cluster-RCTs for this update. Any disagreements were resolved through discussion. We extracted and reported descriptions of interventions using the Template for Intervention Description and Replication (TIDieR) template (Table 1).

Assessment of risk of bias in included studies

Three pairs of review authors (TOJ/EB, LA/GB, MJ/EF) independently assessed risk of bias for the method of random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), outcome reporting (attrition bias), and selective reporting (reporting bias). We used the Cochrane 'Risk of bias' tool to assess risk of bias, classifying each 'Risk of bias' domain as 'low', 'high', or 'unclear'. The following were indications for low risk of bias:

1. method of random sequence generation: the method was well-described and is likely to produce balanced and truly random groups;
2. allocation concealment: the next treatment allocation was not known to participant/cluster or treating staff until after consent to join the study;
3. blinding of participants and personnel: the method is likely to maintain blinding throughout the study;
4. blinding of outcome assessors: all outcome assessors were unaware of treatment allocation;
5. outcome reporting: participant attrition throughout the study is reported, and reasons for loss are appropriately described; and
6. selective reporting: all likely planned and collected outcomes have been reported.

Measures of treatment effect

When possible, we performed meta-analysis and summarised effectiveness as risk ratio (RR) using 95% confidence intervals (CIs). For studies that could not be pooled, we used the effect measures reported by the trial authors (such as RR or incidence rate ratio (IRR) with 95% CI or, when these were not available, relevant P values).

Unit of analysis issues

Many of the included studies were cluster-RCTs. To avoid any unit of analysis issues, we only included treatment effect estimates that were based on methods that were appropriate for the analysis of

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cluster trials, such as mixed models and generalised estimating equations. Given this restriction, we used the generalised inverse-variance method of meta-analysis. Some cluster-RCTs that did not report cluster-adjusted treatment effects provided sufficient data (number of events and participants by treatment group and intraclass correlations) for us to calculate appropriate treatment effect estimates and standard errors. For studies with multiple treatment groups but only one control group, where appropriate, we adjusted standard errors upwards to avoid unit of analysis errors in the meta-analyses.

Dealing with missing data

Given the urgency of this update, we did not contact authors of studies with significant missing data. Previously, whenever details of studies were unclear, or studies were only known to us by abstracts or communications at meetings, we corresponded with first or corresponding authors.

Assessment of heterogeneity

Aggregation of data was dependent on types of comparisons, sensitivity and homogeneity of definitions of exposure, populations and outcomes used. We calculated the I^2 statistic and Chi^2 test for each pooled estimate to assess the presence of statistical heterogeneity (Higgins 2002; Higgins 2003).

Assessment of reporting biases

Given the widely disparate nature of our evidence base, we limited our assessment of possible reporting biases to funnel plot visual inspection if we had > 10 included studies.

Data synthesis

If possible and appropriate, we combined studies in a meta-analysis. We used the generalised inverse-variance random-effects model. We chose the random-effects model because we expected clinical heterogeneity due to differences in pooled interventions and outcome definitions, and methodological heterogeneity due to pooling of RCTs and cluster-RCTs.

Subgroup analysis and investigation of heterogeneity

We conducted two post hoc subgroup analyses:

1. healthcare workers for the comparison of masks versus control; and
2. children for the comparison of hand hygiene versus control.

We did not conduct further investigation of heterogeneity due to insufficient numbers of studies included in the comparisons.

Sensitivity analysis

We conducted a sensitivity analysis for hand hygiene versus control where we included the most precise and unequivocal measure of viral illness reported for each included study.

Summary of findings and assessment of the certainty of the evidence

We created three 'Summary of findings' tables using the following outcomes: numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza) and adverse events related to the intervention (Summary of findings 1; Summary of findings 2; Summary of findings 3). We planned to include the secondary outcomes of deaths; severity of viral illness as reported in the studies; absenteeism; hospital admissions; and complications related to the illness (e.g. pneumonia). However, this data were poorly reported in the included studies. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of evidence as it related to the studies which contributed data to the meta-analyses for the prespecified outcomes (Atkins 2004). We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro GDT software (GRADEpro GDT 2015). We justified all decisions to down- or upgrade the certainty of the evidence in footnotes, and made comments to aid the reader's understanding of the review where necessary.

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies tables.

Results of the search

We identified a total of 3180 titles in this 2020 update. We excluded 3092 titles and retrieved the full papers of 88 studies, to include 44 new studies. See Figure 1.

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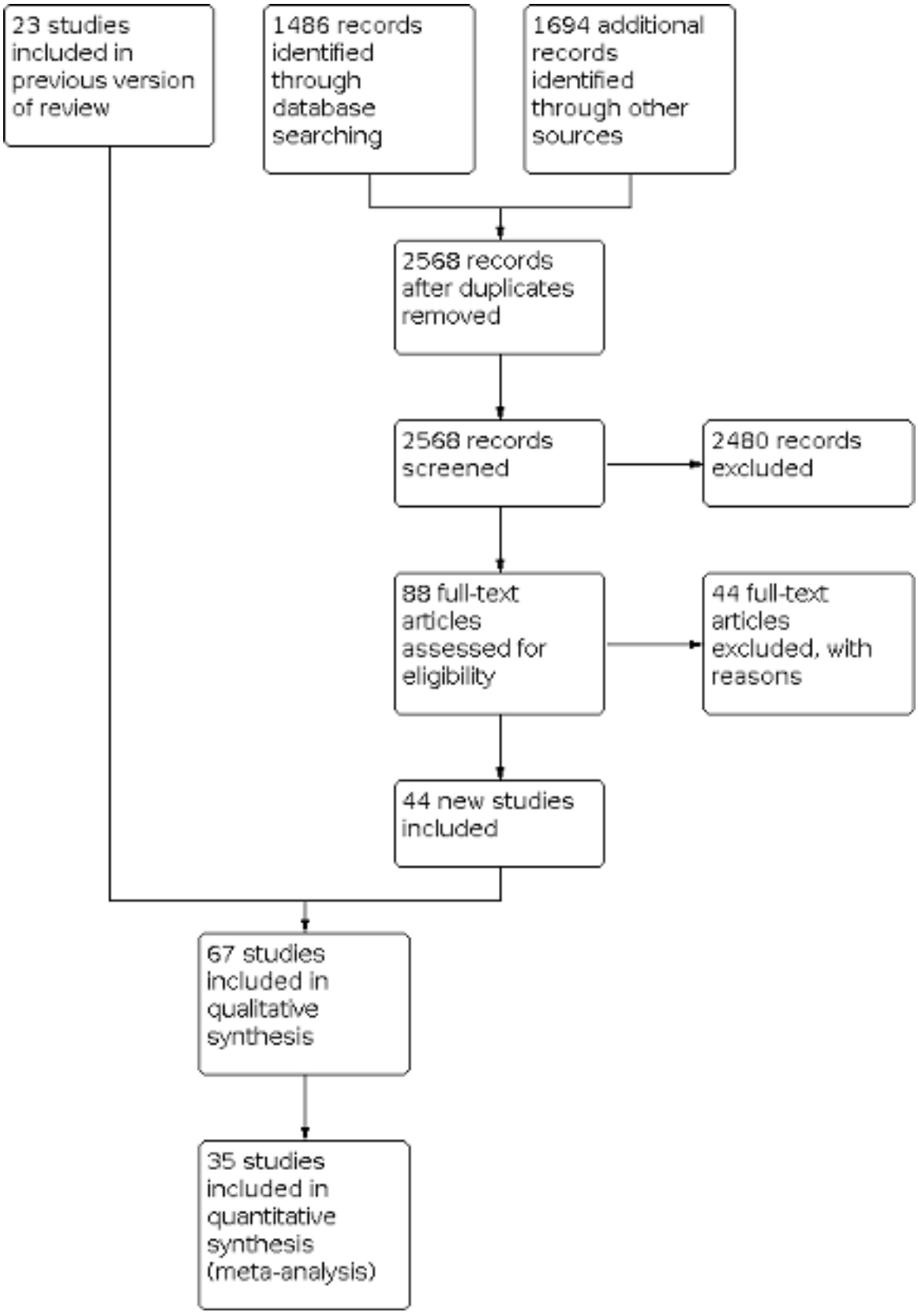
Figure 1. Study flow diagram.



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Included studies

The 44 newly included studies were all RCTs (n = 11) or cluster-RCTs (n = 33) published between 2010 and 2019. We included 23 RCTs in the 2011 version of the review. For detailed descriptions of the interventions of the included studies, see Table 1.

Fifteen trials focused on using masks (Aiello 2010; Aiello 2012; Barasheed 2014; Canini 2010; Cowling 2008; Ide 2016; Jacobs 2009; Loeb 2009; MacIntyre 2009; MacIntyre 2011; MacIntyre 2013; MacIntyre 2015; MacIntyre 2016; Radonovich 2019; Suess 2012). Ten of the 15 trials compared medical/surgical masks to no mask (control) (Aiello 2010; Aiello 2012; Barasheed 2014; Canini 2010; Cowling 2008; Jacobs 2009; MacIntyre 2009; MacIntyre 2015; MacIntyre 2016; Suess 2012). One study compared catechin-treated masks to no mask (Ide 2016), and one study included cloth masks versus control (third arm in MacIntyre 2015). Three of the 15 trials were in healthcare workers (Ide 2016; Jacobs 2009; MacIntyre 2015), whilst the remaining trials were in non-healthcare workers (students, households, families, or pilgrims). Only one trial was conducted during H1N1 pandemic season (Suess 2012).

Five of the 15 trials compared N95 masks or P2 masks to medical/surgical masks (Loeb 2009; MacIntyre 2009; MacIntyre 2011; MacIntyre 2013; Radonovich 2019). All of these trials, except for one study that was conducted on household individuals (MacIntyre 2009), included healthcare workers either in a hospital setting, Loeb 2009; MacIntyre 2011; MacIntyre 2013, or an outpatient setting (MacIntyre 2009; Radonovich 2019).

One trial evaluated the effectiveness of quarantining workers of one of two sibling companies in Japan whose family members had developed an ILI during the 2009 to 2010 H1N1 influenza pandemic (Miyaki 2011).

Fifteen trials compared hand hygiene interventions with no hand hygiene (control) and provided data suitable for meta-analysis. The populations in these trials included adults, children, and families, in settings such as schools (Biswas 2019; Stebbins 2011), childcare centres (Azor-Martinez 2018; Correa 2012; Roberts 2000; Zomer 2015), homes/households (Cowling 2009; Larson 2010; Little 2015; Nicholson 2014; Ram 2015; Sandora 2005; Simmerman 2011), offices (Hubner 2010), and military trainees (Millar 2016). None of the trials was conducted during a pandemic, although some of the studies were conducted during peak influenza seasons.

A further 10 trials that compared a variety of hand hygiene modalities to control provided insufficient information to include in meta-analyses. Three trials were in children: one was conducted in daycare centres in Denmark examining a multimodal hygiene programme (Ladegaard 1999), and two trials compared a hand hygiene campaign or workshop in an elementary school environment in Saudi Arabia, Alzaher 2018, and Egypt, Talaat 2011. Three trials tested virucidal hand treatment in an experimental setting, Gwaltney 1980; Turner 2004a, and in a community, Turner 2012, in the USA. Feldman 2016 compared hand-washing with chlorhexidine gluconate amongst Israeli sailors. One trial compared hand sanitiser packaged in a multimodal hygiene programme amongst office employees in the USA (Arbogast 2016). Two trials were conducted in a long-term facility setting: one trial examined the effect of a bundle hand hygiene programme on infectious risk in nursing home residents in France (Temime 2018), and the other trial compared the effect of using hand sanitisers in healthcare workers on the rate of infections (including respiratory infections) in nursing home residents in Hong Kong (Yeung 2011).

Five trials compared different hand hygiene interventions in a variety of settings such as schools (Morton 2004 in kindergartens and elementary schools in the USA; Priest 2014 in primary schools in New Zealand; and Pandejpong 2012 in kindergartens in Thailand). One study was conducted in low-income neighbourhoods in Karachi, Pakistan (Luby 2005), and one was conducted in a workplace environment in Finland (Savolainen-Kopra 2012). A variety of interventions were used across these trials such as soap and water (Luby 2005; Savolainen-Kopra 2012), hand sanitiser (Morton 2004; Pandejpong 2012; Priest 2014; Savolainen-Kopra 2012), body wash (Luby 2005), and alcohol-based hand wipes (Morton 2004), with or without additional hygiene education. There was considerable variation in interventions, and the information in the trial reports was insufficient to permit meta-analysis.

Seven trials compared a combined intervention of hand hygiene and face masks with control. Four of these trials were carried out in households in Germany (Suess 2012), Thailand (Simmerman 2011), Hispanic immigrant communities in the USA (Larson 2010), and households in Hong Kong (Cowling 2009). Two trials were conducted amongst university student residences (Aiello 2010; Aiello 2012), and one trial in a group of pilgrims at the annual Hajj (Aelami 2015). Moreover, six trials evaluated the incremental benefit of combining surgical mask in addition to hand hygiene with soap, Simmerman 2011, hand sanitiser, Aiello 2010; Aiello 2012; Larson 2010; Suess 2012, or both, Cowling 2009, versus mask or hand hygiene alone on the outcomes of ILI and influenza. Aelami 2015 investigated a hygienic package (alcohol-based handrub (gel or spray), surgical masks, soap, and paper handkerchiefs) with a control group.

Seven trials compared a multimodal combination of hand hygiene and disinfection of surfaces, toys, linen, or other components of the environment with a control (Ban 2015; Carabin 1999; Ibfelt 2015; Kotch 1994; McConeghy 2017; Sandora 2008; White 2001). Variation in scope and type of interventions and insufficient data in trial reports precluded meta-analysis. All studies except for one were in children (McConeghy 2017 was in nursing population).

Three trials included in two papers investigated the role of virucidal tissues in interrupting transmission of naturally occurring respiratory infections in households (Farr 1988a; Farr 1988b; Longini 1988). Four cluster-RCTs implemented complex, multimodal sanitation, education, cooking, and hygiene interventions (Chard 2019; Hartinger 2016; Huda 2012; Najnin 2019). All four of these trials were conducted in low-income countries in settings with minimal to no access to basic sanitation.

Three trials assessed the effect of gargling on the incidence of upper respiratory tract infections (URTIs) or influenza: gargling with povidone-iodine (Satomura 2005), green tea (Ide 2014), and tap water (Goodall 2014).

Ongoing studies

We identified six ongoing studies. Two assess hand hygiene measures (NCT03454009; NCT04267952), and four assess face masks (NCT04471766; NCT04296643; NCT04337541; Wang 2015) one of which – NCT04337541 - published as this review update was going to press.

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Excluded studies

We excluded a total of 160 studies. We identified 12 new studies for exclusion at the data extraction stage of this 2020 update, all of which appeared to be eligible at screening. Six of the 12 studies were ineligible due to only reporting composite outcomes that included other infections besides those caused by respiratory viruses (Azor-Martinez 2014; Bowen 2007; Chami 2012; Denbak 2018; Stedman-Smith 2015; Vessey 2007); two trials measured absenteeism due to non-specific infection (Lennell 2008; Rosen 2006); one trial only had two clusters (Nandrup-Bus 2009); one study was not an RCT (Patel 2012); one study evaluated a hand hygiene intervention that was antibacterial rather than antiviral (Slayton 2016); and one study had no respiratory illness data for extraction (Uhari 1999).

Risk of bias in included studies

The overall risk of bias is presented graphically in Figure 2 and summarised in Figure 3. Details on risk of bias for the included studies are provided below.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.

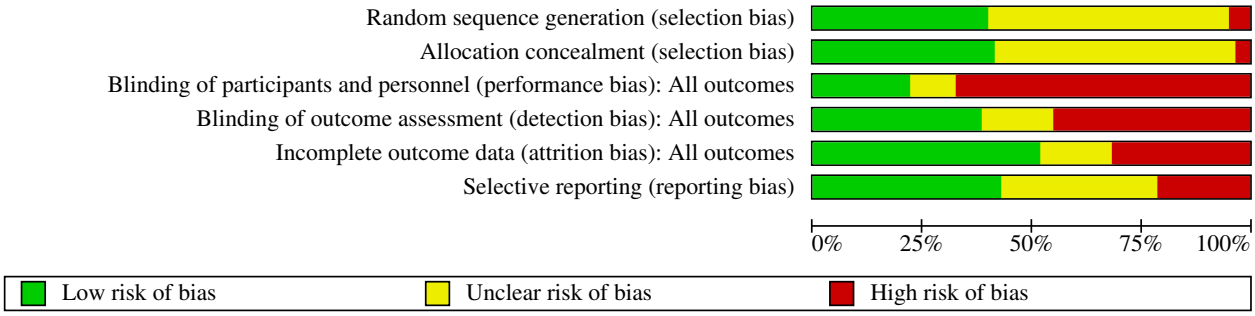

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Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included trial.

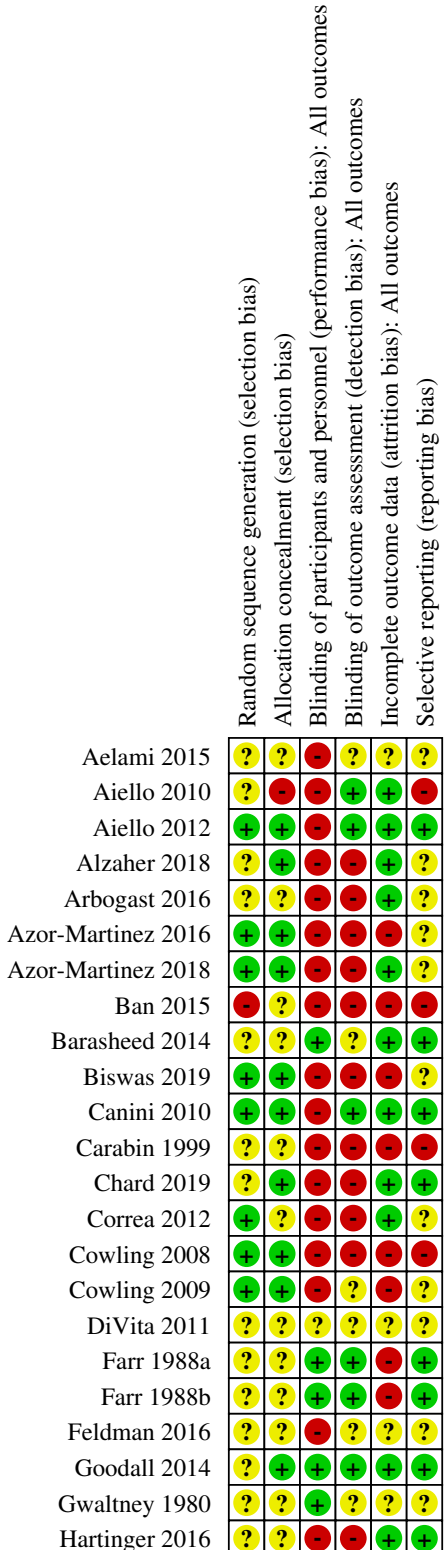

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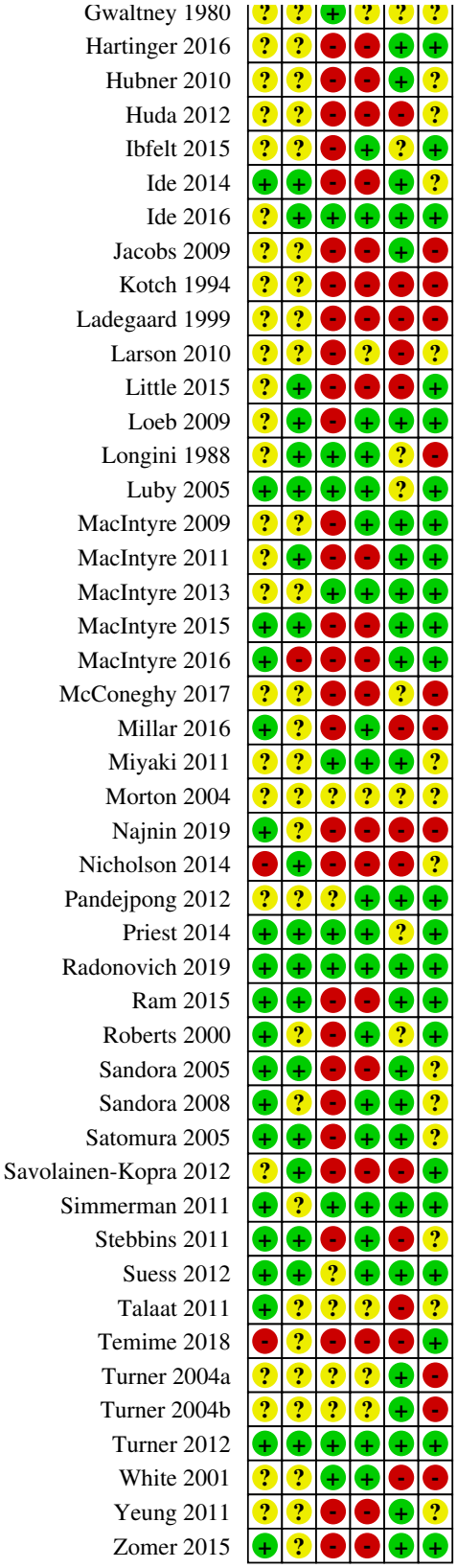
Figure 3. (Continued)



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Allocation

For this 2020 review, information on sequence generation was overall poorly reported in most of the newly included studies. Twenty-one newly included studies provided adequate information on randomisation scheme and were judged as at low risk of bias (Aiello 2012; Azor-Martinez 2016; Azor-Martinez 2018; Biswas 2019; Canini 2010; Correa 2012; Goodall 2014; Ide 2014; MacIntyre 2015; MacIntyre 2016; Millar 2016; Najnin 2019; Priest 2014; Radonovich 2019; Ram 2015; Simmerman 2011; Stebbins 2011; Suess 2012; Talaat 2011; Turner 2012; Zomer 2015). Nine studies described the use of computerised sequence generation program/software (Aiello 2012; Azor-Martinez 2018; Biswas 2019; Canini 2010; Millar 2016; Najnin 2019; Radonovich 2019; Talaat 2011; Turner 2012). One study used random number tables for sequence generation (Azor-Martinez 2016). Three studies described using the random function in Microsoft Excel (Correa 2012; MacIntyre 2016; Suess 2012). Two studies used statistical software to generate a randomisation allocation (MacIntyre 2015; Priest 2014). Two studies reported using block randomisation: Ram 2015 used block randomisation, and an independent investigator generated the list of random assignments, whilst Simmerman 2011 performed block randomisation. Stebbins 2011 used constrained randomisation, and Zomer 2015 reported using stratified randomisation by means of computer generation with a 1:1 ratio in each of the strata.

Fourteen studies reported insufficient information to permit a judgement on the adequacy of the process to minimise selection bias (Aelami 2015; Alzaher 2018; Arbogast 2016; Barasheed 2014; Chard 2019; DiVita 2011; Feldman 2016; Hubner 2010; Ibfelt 2015; McConeghy 2017; Miyaki 2011; Pandejpong 2012; Savolainen-Kopra 2012; Yeung 2011). Six studies provided some description about sequence generation, but it was still unclear (Hartinger 2016; Huda 2012; Ide 2016; Little 2015; MacIntyre 2011; MacIntyre 2013). Huda 2012 mentioned random number tables, but it was unclear if this was for random selection or randomisation. Ide 2016 used computer-generated randomisation, but the method was not stated. Hartinger 2016 used covariate-constrained randomisation, but the method was not described. In Little 2015, participants were automatically randomly assigned by the intervention software, but the sequence generation was not described. Two studies used a secure computerised randomisation program (MacIntyre 2011; MacIntyre 2013), but the sequence generation was not described.

Three of the newly included studies were poorly randomised (Ban 2015; Nicholson 2014; Temime 2018). Ban 2015 included only two clusters, and the randomisation scheme was not reported. Nicholson 2014 used coin tossing, which can lead to a large imbalance. Temime 2018 used “simple randomisation” with no further description.

For the RCTs included in previous versions of the review, three were poorly reported with no description of randomisation sequence or concealment of allocation (Gwaltney 1980; Turner 2004a; Turner 2004b). The quality of the cluster-RCTs varied, with four studies not providing a description of the randomisation procedure (Carabin 1999; Kotch 1994; Morton 2004; White 2001). We rated seven studies as at low risk of bias for sequence generation (Cowling 2008; Cowling 2009; Luby 2005; Roberts 2000; Sandora 2005; Sandora 2008; Satomura 2005), and a further six studies as at unclear risk of bias (Farr 1988a; Farr 1988b; Ladegaard 1999; Loeb 2009; Longini 1988; MacIntyre 2009).

Many of the newly included cluster-RCTs did not report adequately on allocation concealment. Twenty-one of these studies reported adequate allocation and were judged as at low risk of bias (Aiello 2012; Alzaher 2018; Azor-Martinez 2016; Azor-Martinez 2018; Biswas 2019; Canini 2010; Chard 2019; Goodall 2014; Ide 2014; Ide 2016; Little 2015; MacIntyre 2011; MacIntyre 2015; Nicholson 2014; Priest 2014; Radonovich 2019; Ram 2015; Savolainen-Kopra 2012; Stebbins 2011; Suess 2012; Turner 2012). Aiello 2012 randomised all residence houses in each of the residence halls prior to the intervention implementation. Alzaher 2018 allocated schools prior to all schoolgirls attending selected schools being invited to participate. Azor-Martinez 2016 allocated schools/classes prior to children's recruitment. Azor-Martinez 2018 assigned clusters prior to recruitment. Biswas 2019 completed the allocation prior to individuals being recruited. Chard 2019 allocated schools prior to individuals being recruited. Goodall 2014 used opaque, sealed, serially numbered envelopes that were only accessed when two study personnel were present. Ide 2014 also reported using individual drawing of sealed, opaque envelopes to randomly assign participants to the study groups. MacIntyre 2011 randomised hospitals prior to inclusion of participants. In MacIntyre 2015, hospital wards were randomised prior to recruitment of individuals. Nicholson 2014 used coin tossing to assign communities to intervention or control arms. Radonovich 2019 used constrained randomisation to resolve any potential imbalance between covariates between the trial arms. Four studies reported the use of central randomisation: Canini 2010 used central randomisation employing an interactive voice response system; Ide 2016 used central randomisation services; in Little 2015 participants were automatically randomly assigned by the intervention software; and Ram 2015 described a central allocation through data collectors notifying the field research officer, who consulted the block randomisation list to make the assignment of the household compound to intervention or control. Savolainen-Kopra 2012 randomised clusters by matching prior to the onset of the interventions. Four studies reported that allocation was assigned by personnel (investigator, physician, or statistician) unaware of the randomisation sequence (Priest 2014; Stebbins 2011; Suess 2012; Turner 2012). Twenty-two studies reported insufficient information to permit a judgement on the adequacy of the process to minimise selection bias (Aelami 2015; Arbogast 2016; Ban 2015; Barasheed 2014; Correa 2012; DiVita 2011; Feldman 2016; Hartinger 2016; Hubner 2010; Huda 2012; Ibfelt 2015; MacIntyre 2013; McConeghy 2017; Millar 2016; Miyaki 2011; Najnin 2019; Pandejpong 2012; Simmerman 2011; Talaat 2011; Temime 2018; Yeung 2011; Zomer 2015). Two studies provided some information about allocation, but it was not enough to permit a judgement on risk of bias (Barasheed 2014; Simmerman 2011). Barasheed 2014 randomised pilgrim tents using an independent study co-ordinator who was not an investigator, but did not describe how this was done. Simmerman 2011 described using a study co-ordinator to assign households to study arm (after consent was obtained). Only one of the newly added studies was judged as at high risk of bias, where random assignment was allocated by doctors enrolling the participants (MacIntyre 2016). Of the previously included RCTs, 14 provided no or an insufficient description of concealment of allocation (Carabin 1999; Farr 1988a; Farr 1988b; Gwaltney 1980; Kotch 1994; Ladegaard 1999; Larson 2010; MacIntyre 2009; Morton 2004; Roberts 2000; Sandora 2008; Turner 2004a; Turner 2004b; White 2001). We assessed all of the remaining studies as at low risk of bias (Canini 2010; Cowling 2008; Cowling 2009; Loeb 2009; Longini 1988; Luby 2005; Sandora

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2005; Satomura 2005). Aiello 2010 used the drawing of a uniform ticket with the name of each hall out of a container and was rated as at high risk of bias.

Blinding

Although blinding is less of a concern in cluster-RCTs, the risk of bias is substantial when the outcomes are subjective and the outcome assessor is not blinded. We judged 26 studies to have a high risk of bias (Aiello 2012; Alzaher 2018; Arbogast 2016; Azor-Martinez 2016; Azor-Martinez 2018; Ban 2015; Biswas 2019; Carabin 1999; Chard 2019; Correa 2012; Cowling 2008; Ide 2014; Kotch 1994; Ladegaard 1999; Little 2015; MacIntyre 2011; MacIntyre 2015; MacIntyre 2016; McConeghy 2017; Najnin 2019; Nicholson 2014; Ram 2015; Sandora 2008; Savolainen-Kopra 2012; Temime 2018; Zomer 2015). We assessed five cluster-RCTs as at low risk of bias. Farr 1988a and Farr 1988b were double-blinded studies and were judged as at low risk of bias. MacIntyre 2013 and Simmerman 2011 reported laboratory-confirmed influenza, and blinding would not have affected the result. In Miyaki 2011 the self-reported respiratory symptoms were confirmed by a physician. We judged three cluster-RCTs to have a low risk of detection bias because the outcome was laboratory-confirmed influenza, Barasheed 2014; Suess 2012, or physician-confirmed ILI, Pandejpong 2012. Two cluster-RCTs provided insufficient data to judge the effect of non-blinding. Talaat 2011 included outcomes that were both self-reported ILI and laboratory-confirmed influenza. In Yeung 2011 the detection of cases was based on record for hospitalisation related to infection (including pneumonia). Eleven cluster-RCTs were not blinded, but we judged the primary outcome to be unaffected by non-blinding. Seven trials reported laboratory-confirmed influenza (Aiello 2012; Cowling 2009; Larson 2010; Loeb 2009; MacIntyre 2009; Millar 2016; Stebbins 2011). Four studies reported self-reported outcome (Canini 2010; Priest 2014; Roberts 2000; Sandora 2008), but outcome assessors were not aware of the intervention assignment. Five RCTs were double-blinded and were judged as at low risk of bias (Goodall 2014; Ide 2016; Longini 1988; Luby 2005; White 2001), whilst two studies were single-blinded where investigators, Radonovich 2019, or laboratory personnel, Turner 2012, were blinded. Four RCTs were not blinded and were judged as at high risk of bias given the subjective nature of the outcome assessed (Hubner 2010; Ibfelt 2015; Jacobs 2009; Satomura 2005). Turner 2004a and Turner 2004b were double-blind studies, but insufficient information was provided to assess risk of bias.

Incomplete outcome data

In this 2020 review, we assessed 26 newly included trials as having a low risk of attrition bias, with sufficient evidence from the participant flow chart, and explanation of loss to follow-up (which was minimal) similar between groups (Aiello 2012; Alzaher 2018; Arbogast 2016; Azor-Martinez 2018; Barasheed 2014; Canini 2010; Chard 2019; Correa 2012; Goodall 2014; Hartinger 2016; Hubner 2010; Ide 2014; Ide 2016; MacIntyre 2011; MacIntyre 2013; MacIntyre 2015; MacIntyre 2016; Miyaki 2011; Pandejpong 2012; Radonovich 2019; Ram 2015; Simmerman 2011; Suess 2012; Turner 2012; Yeung 2011; Zomer 2015). Seven studies did not report sufficient information on incomplete data (attrition bias) (Aelami 2015; DiVita 2011; Feldman 2016; Hartinger 2016; Ibfelt 2015; McConeghy 2017; Priest 2014). Twelve studies had a high risk of attrition bias (Azor-Martinez 2016; Ban 2015; Biswas 2019; Huda 2012; Little 2015; Millar 2016; Najnin 2019; Nicholson 2014; Savolainen-Kopra 2012; Stebbins 2011; Talaat 2011; Temime 2018). In Azor-Martinez 2016, attrition levels were high and differed between the two groups. Ban 2015 did not report on reasons for loss to follow-up. Biswas 2019 did not provide information on missing participants (28 children in the control schools and two children in the intervention schools). Huda 2012 did not provide a flow diagram of study participants. Little 2015 had high attrition that differed between the two groups. Attrition in Millar 2016 differed amongst the three groups. In addition, ARI cases were captured utilising clinic-based medical records for those participants who sought hospital care only. In Najnin 2019, there was high migration movement during the study, which could have distorted the baseline characteristics even more. There was no description of how such migration and changes in the intervention group were dealt with. In Nicholson 2014, households were removed from the study if they provided no data for five consecutive weeks. Although attrition was reported in Savolainen-Kopra 2012, and 76% of volunteers who were recruited at the beginning of the reporting period completed the study, new recruits were added during the study to replace volunteers lost in most clusters. The total number of reporting participants at the end of the trial was 626 (91.7%) compared to the beginning, meaning that 15.7% of participants were replaced during the study. In Stebbins 2011 reasons for episodes of absence in 66% of the study participants were not reported. Talaat 2011 did not provide a flow chart of clusters flow during the study period and provided no information on withdrawal. Temime 2018 was greatly biased due to underreporting of outcomes in the control groups. Furthermore, no study flow chart was provided, and there was no reporting on any exclusions.

Selective reporting

In this 2020 review, 22 newly included studies reported all specified outcomes and were judged as at low risk of reporting bias (Aiello 2012; Barasheed 2014; Canini 2010; Chard 2019; Goodall 2014; Hartinger 2016; Ibfelt 2015; Ide 2016; Little 2015; MacIntyre 2011; MacIntyre 2013; MacIntyre 2015; MacIntyre 2016; Pandejpong 2012; Priest 2014; Radonovich 2019; Savolainen-Kopra 2012; Simmerman 2011; Suess 2012; Temime 2018; Turner 2012; Zomer 2015). For 18 studies, it is unlikely that other outcomes were measured and not reported, although no protocol was available to assess reporting bias (Aelami 2015; Alzaher 2018; Arbogast 2016; Azor-Martinez 2016; Azor-Martinez 2018; Ban 2015; Biswas 2019; Correa 2012; DiVita 2011; Feldman 2016; Hubner 2010; Huda 2012; Ide 2014; Miyaki 2011; Nicholson 2014; Stebbins 2011; Talaat 2011; Yeung 2011). Three studies were at high risk of reporting bias (McConeghy 2017; Millar 2016; Najnin 2019). In McConeghy 2017, URTI was mentioned in the methods (the intervention presumably would have targeted these), but only lower respiratory tract infection (LRTI) and overall infection were reported. Millar 2016 was originally conducted for another purpose; we could not find the respiratory outcomes reported in the study as part of the original study protocol. In Najnin 2019, the published study protocol did not include respiratory illness as an outcome.

Other potential sources of bias

An additional consideration for cluster-RCTs is identification/recruitment bias, where individuals are recruited in the trial after clusters are randomised. Such bias can introduce an imbalance amongst groups. Of the cluster-RCTs included in our 2020 review, we judged 13 to have a low risk of identification/recruitment bias (Arbogast 2016; Biswas 2019; Canini 2010; Cowling 2008; Longini

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1988; Luby 2005; MacIntyre 2015; MacIntyre 2016; Roberts 2000; Sandora 2005; Suess 2012; Temime 2018; White 2001). In Arbogast 2016, all identified individuals (office workers) were included in the assigned cluster. Schools were identified and then randomised to the clusters; students were then randomly selected from each classroom and school. Nine studies described identification of participants, consenting/enrolling, and then randomising to the clusters (Canini 2010; Cowling 2008; Longini 1988; Luby 2005; MacIntyre 2015; MacIntyre 2016; Roberts 2000; Sandora 2005; White 2001). Suess 2012 identified and consented patients, then recruitment was performed by physicians unaware of cluster assignment. In Temime 2018, directors of the included nursing homes agreed to participate in the study before randomisation, and written consent was not required from the residents. We judged 11 cluster-RCTs as at high risk of identification/recruitment bias (Aiello 2010; Aiello 2012; Azor-Martinez 2018; Chard 2019; Correa 2012; Cowling 2009; Larson 2010; McConeghy 2017; Nicholson 2014; Priest 2014; Savolainen-Kopra 2012). In Aiello 2010 and Aiello 2012, recruitment continued for two weeks after start of the study, which could have introduced bias. Six trials identified and recruited participants after cluster randomisation (Azor-Martinez 2018; Chard 2019; Cowling 2009; Larson 2010; McConeghy 2017; Nicholson 2014). Three trials recruited new participants after the start of the study to replace those lost to follow-up (Correa 2012; Priest 2014; Savolainen-Kopra 2012). We judged five cluster-RCTs to have probable identification/recruitment bias (Alzaher 2018; Barasheed 2014; MacIntyre 2011; Najnin 2019; Radonovich 2019), whereas in 19 studies there were insufficient details to permit a judgement of risk of bias (Carabin 1999; DiVita 2011; Feldman 2016; Hartinger 2016; Huda 2012; Ibfelt 2015; Kotch 1994; Ladegaard 1999; MacIntyre 2009; MacIntyre 2013; Millar 2016; Miyaki 2011; Pandejpong 2012; Radonovich 2019; Sandora 2008; Stebbins 2011; Talaat 2011; Yeung 2011; Zomer 2015).

Twenty-six cluster-RCTs reported intracluster correlation coefficient (ICC) to adjust sample size, taking into consideration clustering effects, and described adjusting outcomes for clustering effect using different statistical methods, or provided justification for not performing adjusted analysis for clustering (Aiello 2010; Aiello 2012; Arbogast 2016; Canini 2010; Carabin 1999; Correa 2012; Cowling 2008; Cowling 2009; Hartinger 2016; Huda 2012; Little 2015; Luby 2005; MacIntyre 2009; MacIntyre 2011; MacIntyre 2013; MacIntyre 2015; MacIntyre 2016; McConeghy 2017; Priest 2014; Radonovich 2019; Ram 2015; Roberts 2000; Stebbins 2011; Suess 2012; Talaat 2011; Temime 2018). Five cluster-RCTs did not report the ICC but described adjusting outcomes for clustering effect using different statistical methods, or explained why adjusted analysis for clustering was not performed (Biswas 2019; Chard 2019; McConeghy 2017; Simmerman 2011; Zomer 2015). Thirteen cluster-RCTs provided insufficient details on ICC and/or did not perform adjusted analysis or justified the absence of it (Alzaher 2018; Azor-Martinez 2016; Azor-Martinez 2018; Barasheed 2014; Feldman 2016; Larson 2010; Millar 2016; Miyaki 2011; Najnin 2019; Nicholson 2014; Pandejpong 2012; Savolainen-Kopra 2012; Yeung 2011). Two cluster-RCTs reported the ICC but did not perform adjusted analysis or justified the absence of it (Sandora 2005; Sandora 2008).

Effects of interventions

See: **Summary of findings 1** Medical/surgical masks compared to no masks for preventing the spread of viral respiratory illness; **Summary of findings 2** N95 respirators compared to medical/surgical masks for preventing the spread of viral respiratory illness; **Summary of findings 3** Hand hygiene compared to control for preventing the spread of viral respiratory illness

Comparison 1: Medical/surgical masks compared to no masks

We included nine trials (eight of which were cluster-RCTs) comparing medical/surgical masks versus no masks (Aiello 2012; Barasheed 2014; Canini 2010; Cowling 2008; Jacobs 2009; MacIntyre 2009; MacIntyre 2015; MacIntyre 2016; Suess 2012). Two trials were conducted with healthcare workers (HCWs) (Jacobs 2009; MacIntyre 2015), whilst the other seven studies included people living in the community. All trials were conducted in non-pandemic settings.

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

Pooling of all nine trials found an estimate of effect for the outcomes of ILI cases (risk ratio (RR) 0.99, 95% confidence interval (CI) 0.82 to 1.18; low-certainty evidence; Analysis 1.1) suggesting that wearing a medical/surgical mask may make little or no difference for this outcome. Similarly, the estimate of effect for laboratory-confirmed influenza cases (RR 0.91, 95% CI 0.66 to 1.26; 6 trials; moderate-certainty evidence; Analysis 1.1) suggests that wearing a medical/surgical mask probably makes little or no difference compared to not wearing a mask for this outcome. We downgraded the certainty of the evidence two levels for ILI due to inconsistency of the effect across studies and wide CI of the pooled effect. Sixty-five per cent of the weight of the ILI analysis was carried by one study (Aiello 2012).

A separate analysis of the two trials in healthcare workers for the outcome ILI (RR 0.37, 95% CI 0.05 to 2.50; low-certainty evidence; Analysis 1.2) suggests that there is considerable uncertainty as to whether there is any benefit (Jacobs 2009; MacIntyre 2015). The effect estimate was downgraded due to very wide CI interval of the pooled effect.

The design of most trials assessed whether masks protected the wearer. Four trials were cluster-RCTs, with all participants in the intervention clusters required to wear masks, thus assessing both source control and personal protection. In two trials the clusters were households with a member with new influenza; neither of these studies found any protective effect (RR 1.03 in 105 households (Canini 2010); RR 1.21 in 145 households (MacIntyre 2009)). In two trials the clusters were college dormitories during the influenza season; neither study found any reduction (RR 1.10 in 37 dormitories (Aiello 2012); RR 0.90 in three dormitories (Aiello 2010)). We excluded Aiello 2010 from the meta-analysis since we did not consider 'randomisation' of three clusters to three arms to be a proper randomised trial.

2. Adverse events related to the intervention

Canini 2010 reported that 38 (75%) of participants in the intervention arm experienced discomfort with the mask use due to warmth (45%), respiratory difficulties (33%), and humidity (33%). Children reported feeling pain more frequently (3/12) than other participants wearing adult face masks (1/39; P = 0.04). In MacIntyre 2015, adverse events associated with face mask use were reported in 40.4% (227/562) of HCWs in the medical-mask arm. General discomfort (35.1%; 397/1130) and breathing problems (18.3%;

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207/1130) were the most frequently reported adverse events. Suess 2012 reported that the majority of participants (107/172; 62%) did not report any problems with mask-wearing. More adults reported no problems (71%) compared to children (36/72; 50%; P = 0.005). The main issues when wearing a face mask for adults as well as for children were "heat/humidity" (18/34; 53% of children; 10/29; 35% of adults; P = 0.1), followed by "pain" and "shortness of breath". Cowling 2008 mentioned that no adverse events were reported. The other trials did not report measuring adverse outcomes.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Jacobs 2009 reported that participants in the mask group were significantly more likely to experience more days with headache and feeling bad. They found no significant differences between the two groups for symptom severity scores. None of the other trials reported this outcome.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 2: N95/P2 respirators compared to medical/surgical masks

We included five trials comparing medical/surgical masks with N95/P2 respirators (Loeb 2009; MacIntyre 2009; MacIntyre 2011; MacIntyre 2013; Radonovich 2019). All of these trials except MacIntyre 2009 included HCWs. MacIntyre 2009 included carers and household members of children with a respiratory illness recruited from a paediatric outpatient department and a paediatric primary care practice in Sydney, Australia.

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

Pooling of three trials found an estimate of effect suggesting considerable uncertainty as to whether an N95/P2 respirator provides any benefit compared to medical/surgical masks for the outcome of clinical respiratory illness (RR 0.70, 95% CI 0.45 to 1.10; very low-certainty evidence; Analysis 2.1) (MacIntyre 2011; MacIntyre 2013 (2 arms); Radonovich 2019). Based on five trials conducted in four healthcare settings and one household (Loeb 2009; MacIntyre 2009; MacIntyre 2011; MacIntyre 2013; Radonovich 2019), the estimates of effect for the outcome of ILI (RR 0.82, 95% CI 0.66 to 1.03; low-certainty evidence; Analysis 2.1) suggest that N95/P2 respirators may make little or no difference for this outcome. The estimate of the effect for the outcome of laboratory-confirmed influenza infection (RR 1.10, 95% CI 0.90 to 1.34; moderate-certainty evidence; Analysis 2.1) suggests that the use of a N95/P2 respirator compared to a medical/surgical mask probably makes little or no difference for this more precise and objective outcome. The outcomes clinical respiratory illness and ILI were reported separately. Considering how these outcomes were defined, it is highly likely that there was considerable overlap between the two, therefore these outcomes were not combined into a single clinical outcome (Analysis 2.1). The laboratory-confirmed viral respiratory infection outcome included influenza primarily but multiple other common viral respiratory pathogens were also included in several studies. The laboratory-confirmed viral infection outcome was considered more precise and objective in comparison to the clinical outcomes, which were more subjective and considered to be less precise. The findings did not change when we restricted the evidence to HCWs (Analysis 2.2).

2. Adverse events related to the intervention

Harms were poorly reported, but generally discomfort wearing medical/surgical masks and N95/P32 respirators was mentioned in several studies. Radonovich 2019 mentioned that participants wearing the N95 respirator reported skin irritation and worsening of acne. MacIntyre 2011 reported that adverse events were more common with N95 respirators; in particular, discomfort was reported in 41.9% of N95 wearers versus 9.8% of medical-mask wearers (P < 0.01); headaches were more common with N95 (13.4% versus 3.9%; P < 0.01); difficulty breathing was reported more often in the N95 group (19.4% versus 12.5%; P = 0.01); and N95 caused more problems with pressure on the nose (52.2% versus 11.0%; P < 0.01). In MacIntyre 2013, fewer participants using the N95 respirator reported problems (38% (195/512) versus 48% (274/571) of participants in the medical-mask arm; P = 0.001). Loeb 2009 mentioned that no adverse events were reported.

The one trial conducted in the community mentioned that more than 50% of participants reported concerns with both types of masks, mainly that wearing them was uncomfortable, but there were no significant differences between the P2 (N95) and surgical-mask groups (MacIntyre 2009).

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Not reported.

3. Absenteeism

Loeb 2009 reported that 42 participants (19.8%) in the surgical-mask group reported an episode of work-related absenteeism compared with 39 (18.6%) of participants in the N95 respiratory group (absolute risk difference −1.24%, 95% CI −8.75% to 6.27%; P = 0.75).

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Loeb 2009 reported that there were no episodes of LRTIs.

Comparison 3: Hand hygiene compared to control

Sixteen trials compared hand hygiene interventions with control and provided sufficient data to include in meta-analyses (Azor-Martinez 2018; Biswas 2019; Correa 2012; Cowling 2008; Cowling

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2009; Hubner 2010; Larson 2010; Little 2015; Millar 2016; Nicholson 2014; Ram 2015; Roberts 2000; Sandora 2005; Simmerman 2011; Stebbins 2011; Zomer 2015). The populations of these studies included adults, children, and families, in settings such as schools, childcare centres, homes, and offices. None of the studies was conducted during a pandemic, although a few studies were conducted during peak influenza seasons. A further 16 trials comparing hand hygiene to a control had other outcomes or insufficient information to include in meta-analyses (Alzaher 2018; Arbogast 2016; Azor-Martinez 2016; DiVita 2011; Feldman 2016; Gwaltney 1980; Ladegaard 1999; Luby 2005; Morton 2004; Priest 2014; Savolainen-Kopra 2012; Talaat 2011; Temime 2018; Turner 2012; White 2001; Yeung 2011). The results of these trials were consistent with the findings of our meta-analyses. The results for all outcomes from the 16 trials that were meta-analysed and the 16 trials that were not meta-analysed are shown in Table 2.

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

Pooling of seven trials for the broad outcome of ARI showed a 16% relative reduction in the numbers of participants with ARI (RR 0.84, 95% CI 0.82 to 0.86; moderate-certainty evidence; Analysis 3.1.1) in the hand hygiene group (Analysis 3.1), suggesting a probable benefit (Azor-Martinez 2018; Correa 2012; Larson 2010; Little 2015; Millar 2016; Nicholson 2014; Sandora 2005). When considering the more strictly defined outcomes of ILI, Biswas 2019; Cowling 2008; Cowling 2009; Hubner 2010; Larson 2010; Little 2015; Ram 2015; Roberts 2000; Simmerman 2011; Zomer 2015, and laboratory-confirmed influenza, Biswas 2019; Cowling 2008; Cowling 2009; Hubner 2010; Larson 2010; Ram 2015; Simmerman 2011; Stebbins 2011, the estimates of the effect were heterogeneous, suggesting that hand hygiene made little or no difference (RR 0.98, 95% CI 0.85 to 1.13 for ILI; low-certainty evidence; Analysis 3.1.2) (RR 0.91, 95% CI 0.63 to 1.30 for laboratory-confirmed influenza; low-certainty evidence; Analysis 3.1.3) (Analysis 3.1). All 16 trials could be pooled for analysis of the composite outcome 'ARI or ILI or influenza', with each study only contributing once with the most comprehensive outcome (in terms of number of events) reported showing an 11% relative reduction in participants with a respiratory illness, suggesting that hand hygiene may offer a benefit (RR 0.89, 95% CI 0.84 to 0.95; low-certainty evidence; Analysis 3.2), but with high heterogeneity. In a sensitivity analysis we used only the most precise and unequivocal (with laboratory confirmed considered the most precise and an undefined ARI considered the least precise) outcome reported in each of 11 studies identified by JMC, an infectious disease physician, and found an estimate of effect in favour of hand hygiene, but with wider CIs (RR 0.92, 95% CI 0.80 to 1.05; Analysis 3.3).

We considered that studies in children might have a different effect than studies in adults, so we conducted subgroup analysis by age group. We found no evidence of a difference in treatment effect by age group (P = 0.21; Analysis 3.4).

2. Adverse events related to the intervention

Correa 2012 reported that no adverse events were observed; in the study by Priest 2014, skin reaction was recorded for 10.4% of participants in the hand sanitiser group versus 10.3% in the control group (RR 1.01, 95% CI 0.78 to 1.30).

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Not reported.

3. Absenteeism

Three trials measured absenteeism from school or work and demonstrated a 36% relative reduction in the numbers of participants with absence in the hand hygiene group (RR 0.64, 95% CI 0.58 to 0.71; Analysis 3.5) (Azor-Martinez 2016; Hubner 2010; Nicholson 2014).

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 4: Hand hygiene + medical/surgical masks compared to control

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

Six trials (Aelami 2015; Aiello 2012; Cowling 2009; Larson 2010; Simmerman 2011; Suess 2012) were able to be pooled to compare the use of the combination of hand hygiene and medical/surgical masks with control. Four of these trials were in households, two in university student residences, and one at the annual Hajj pilgrimage. For both outcomes (ILI and influenza), pooling demonstrated an estimate of effect suggesting little or no difference between the hand hygiene and medical/surgical mask combination and control. The number of trials and events was lower than for comparisons of hand hygiene alone, or medical/surgical masks alone, and the confidence interval was wide. For ILI, the RR for intervention compared to control was 1.03 (95% CI 0.77 to 1.37; Analysis 4.1.1), and for influenza it was 0.97 (95% CI 0.69 to 1.36; Analysis 4.1.2) (Analysis 4.1). Full results of these trials are shown in Table 3

2. Adverse events related to the intervention

Adverse events related to mask wearing in the study by Suess 2012 are reported under Comparison 1 (medical/surgical masks). There was no mention of adverse events related to hand hygiene.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Not reported.

3. Absenteeism

Not reported.

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4. Hospital admissions

Not reported.

5. Complications related to the illness, e.g. pneumonia

Not reported.

Comparison 5: Hand hygiene + medical/surgical masks compared to hand hygiene

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI and laboratory-confirmed influenza)

Three trials studied the addition of medical/surgical masks to hand hygiene (Cowling 2009; Larson 2010; Simmerman 2011). All three trials had three arms, and are also included in the comparison of hand hygiene plus medical/surgical mask versus control (Comparison 4). All three studies showed no difference between hand hygiene plus medical/surgical mask groups and hand hygiene alone, for all outcomes. The estimates of effect suggested little or no difference when adding masks to hand hygiene compared to hand hygiene alone: for the outcome ILI (RR 1.03, 95% CI 0.69 to 1.53; 3 trials) and the outcome laboratory-confirmed influenza (RR 0.99, 95% CI 0.69 to 1.44), the estimates of effect were not different and the CIs were relatively wide, suggesting little or no difference (Analysis 5.1). However, the CIs around the estimates were wide and do not rule out an important benefit.

2. Adverse events related to the intervention

Not reported.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Not reported.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 6: Medical/surgical masks compared to other (non-N95) masks

One trial compared medical/surgical masks with cloth masks in hospital healthcare workers (MacIntyre 2015), and another trial compared catechin-treated masks versus control masks in healthcare workers and staff of hospitals, rehabilitation centres, and nursing homes in Japan (Ide 2016).

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

MacIntyre 2015 found that the rate of ILI was higher in the cloth mask arm compared to the medical/surgical masks arm (RR 13.25, 95% CI 1.74 to 100.97).

Ide 2016 did not find a benefit from the catechin-treated masks over untreated masks on influenza infection rates (adjusted odds ratio (OR) 2.35, 95% CI 0.40 to 13.72; P = 0.34).

2. Adverse events related to the intervention

In MacIntyre 2015 adverse events associated with face mask use were reported in 40.4% (227/562) of HCWs in the medical/surgical mask arm and 42.6% (242/568) in the cloth mask arm (P = 0.45). The most frequently reported adverse events were general discomfort (35.1%; 397/1130) and breathing problems (18.3%; 207/1130). Laboratory tests showed the penetration of particles through the cloth masks to be very high (97%) compared with medical/surgical masks (44%). Ide 2016 reported that there were no serious adverse events associated with the intervention.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Not reported.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 7: Soap + water compared to sanitiser, and comparisons of different types of sanitiser

Two trials compared soap and water with sanitiser (Azor-Martinez 2018; Savolainen-Kopra 2012). Another trial compared different types of hand sanitiser in a virus challenge study (Turner 2004a; Turner 2004b), and one trial studied the frequency of use of hand sanitiser (Pandejpong 2012). The full results of these four trials are shown in Table 4.

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

In the trial by Azor-Martinez 2018, ARI incidence was significantly higher in the soap-and-water group compared with the hand sanitiser group (rate ratio 1.21, 95% CI 1.06 to 1.39). In contrast, there was no significant difference between interventions in Savolainen-Kopra 2012. In the rhinovirus challenge study (Turner 2004a; Turner 2004b), all hand sanitisers tested led to a significant lowering of infection rates, but no differences between sanitisers were observed. The study sample size was small.

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2. Adverse events related to the intervention

Two trials stated that no adverse events were observed (Pandejpong 2012; Savolainen-Kopra 2012).

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Not reported.

3. Absenteeism

The authors of Azor-Martinez 2018 also observed a significant benefit for hand sanitiser in reduction in days absent, whereas there was no difference between intervention groups in the Savolainen-Kopra 2012 trial. The study on frequency of use of sanitiser found that use of sanitiser every hour significantly reduced days absent compared with use every two hours or with use only before the lunch break (Pandejpong 2012).

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 8: Surface/object disinfection (with or without hand hygiene) compared to control

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

Six trials contributed data to this comparison (Ban 2015; Carabin 1999; Ibfelt 2015; Kotch 1994; McConeghy 2017; Sandora 2008). Full results of these trials are shown in Table 5. Five of the six trials combined disinfection with other interventions such as hand hygiene education, provision of hand hygiene products, and audits. Ban 2015 utilised a combination of provision of hand hygiene products, and cleaning and disinfection of surfaces, and demonstrated a significant reduction in ARI in the intervention group (OR 0.47, 95% CI 0.48 to 0.65). A similar result was seen in Carabin 1999, with a significant reduction in episodes of ARI. Two studies tested multicomponent interventions and observed no significant difference in ARI outcomes (Kotch 1994; McConeghy 2017).

One trial compared disinfection alone to usual care (Ibfelt 2015). This study demonstrated a significant reduction in some viruses detected on surfaces in the childcare centres (adenovirus, rhinovirus, respiratory syncytial virus (RSV), and metapneumovirus), but not in other viruses, including coronavirus.

2. Adverse events related to the intervention

Not reported.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Not reported.

3. Absenteeism

Only one study measured this outcome (Sandora 2008), observing no significant difference between groups for the outcome of absence due to respiratory illness (rate ratio for intervention to control 1.10, 95% CI 0.97 to 1.24).

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 9: Complex interventions compared to control

Complex interventions are either multifaceted environmental programmes (such as those in low-income countries) or combined interventions including hygiene measures and gloves, gowns, and masks.

Four trials studied complex hygiene and sanitation interventions in low-income country settings (Chard 2019; Hartinger 2016; Huda 2012; Najnin 2019). Full results from these studies are given in Table 6.

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

All four trials of complex interventions observed no significant differences between groups in rates of viral respiratory illness.

2. Adverse events related to the intervention

Not reported

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Not reported.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 10: Physical distancing/quarantine compared to control

We found one quasi-cluster-RCT assessing the effectiveness of quarantining workers of one of two sibling companies in Japan whose family members developed an ILI during the 2009 to 2010 H1N1 influenza pandemic (Miyaki 2011). Workers in the intervention group were asked to stay home on full pay until

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five days after the household member(s) showed resolution of symptoms or two days after alleviation of fever.

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

Compliance with the intervention was 100%. In the intervention group 2.75% of workers contracted influenza, compared with 3.18% in the control group (Cox hazard ratio 0.799, 95% CI 0.66 to 0.97; P = 0.02), indicating that the rate of infection was reduced by 20% in the intervention group. However, the risk of a worker being infected was 2.17-fold higher in the intervention group where workers stayed at home with their infected family members. The authors concluded that quarantining workers who have infected household members could be a useful additional measure to control the spread of respiratory viruses in an epidemic setting.

2. Adverse events related to the intervention

Not reported.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Not reported.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 11: Eye protection compared to control

We did not find any randomised studies investigating the effect of eye protection compared to control.

Comparison 12: Gargling compared to control

Three trials investigated the effect of gargling. Satomura 2005 compared throat gargling with povidone-iodine versus tap water in healthy adults. Ide 2014 compared gargling with green tea versus tap water in high school students, and Goodall 2014 compared gargling with tap water with no gargling in university students.

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

Satomura 2005 reported that gargling with tap water reduced the incidence of URTIs compared to the control group (usual care) (hazard ratio (HR) 0.60, 95% CI 0.39 to 0.95). Gargling with povidone-iodine did not reduce the incidence of URTIs compared to the control group (HR 0.88, 95% CI 0.58 to 1.34).

Goodall 2014 found no difference in laboratory-confirmed URTIs between the gargling (tap water) and no-gargling groups (RR for gargling versus no gargling 0.82, 95% CI 0.53 to 1.26; P = 0.36).

In a meta-analysis of gargling versus control based on two trials (Goodall 2014; Satomura 2005), the pooled estimate of effect suggested little or no difference for the outcome of clinical URTI due to gargling (RR 0.91, 95% CI 0.63 to 1.31; Analysis 6.1).

There was no difference in the incidence of laboratory-confirmed influenza between high school students gargling with green tea compared with those using tap water (adjusted OR 0.69, 95% CI 0.37 to 1.28; P = 0.24) (Ide 2014). There was also no difference in the incidence of clinically defined influenza (adjusted OR 0.75, 95% CI 0.50 to 1.13; P = 0.17). However, the authors reported that adherence to the interventions amongst students was low.

2. Adverse events related to the intervention

Satomura 2005 reported no adverse events during the 60-day intervention period. Ide 2014 also did not observe any adverse events during the study. Goodall 2014 did not report on adverse effects.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Satomura 2005 reported that the mean peak score in bronchial symptoms was lower in the water gargling group (0.97) than in the povidone-iodine gargling group (1.41) and the control group (1.40), P = 0.055. Other symptoms were not significantly different between groups. Goodall 2014 reported that symptom severity was greater in the gargling group for clinical and laboratory-confirmed URTI, but this was not statistically significant (225.3 versus 191.8, and 210.5 versus 191.8, respectively). Ide 2014 did not report symptom or illness severity.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 13: Virucidal tissues compared to control

Two reports (three trials) conducted in the USA studied the effect of virucidal tissues (Farr 1988a; Farr 1988b; Longini 1988). Full results from these studies are given in Table 7.

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

The three trials of virucidal tissues reported no differences in infection rates between tissues and placebo, and between tissues and no tissues (Farr 1988a; Farr 1988b; Longini 1988).

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2. Adverse events related to the intervention

Farr 1988b reported cough in 4% of participants using virucidal tissues versus 57% in the placebo group, but 24% reported nasal burning in the virucidal tissue group versus 8% in the placebo group. Longini 1988 did not report on adverse effects.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Not reported.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

DISCUSSION

Summary of main results

See Table 8.

1. Medical/surgical masks compared to no masks

The pooled estimates of effect from RCTs and cluster-RCTs for wearing medical/surgical masks compared to no masks suggests little or no difference in interrupting the spread of ILI (RR 0.99, 95% CI 0.82 to 1.18; low-certainty evidence) or laboratory-confirmed influenza (RR 0.91, 95% CI 0.66 to 1.26; moderate-certainty evidence) in the combined analysis of all populations from the included trials. We found similar results for ILI in HCWs (RR 0.37, 95% CI 0.05 to 2.50; very low-certainty evidence). Four trials were cluster-RCTs, with all participants in the intervention clusters required to wear masks, thus assessing both source control and personal protection. In two trials the clusters were households with a member with new influenza; neither trial found any protective effect (RR 1.03 in 105 households (Canini 2010); RR 1.21 in 145 households (MacIntyre 2009)). In two trials the clusters were college dormitories during the influenza season; neither trial found any reduction (RR 1.10 in 37 dormitories (Aiello 2012); RR 0.90 in three dormitories (Aiello 2010)). We excluded Aiello 2010 from meta-analysis since we did not consider 'randomisation' of three clusters to three arms was a proper randomised trial.

Less than half of the trials comparing masks with no masks addressed harms of mask wearing (Canini 2010; Cowling 2008; MacIntyre 2015; Suess 2012). Warmth, respiratory difficulties, humidity, and general discomfort were the most frequently reported adverse events. More adults reported no harms compared to children.

In one trial (MacIntyre 2015), cloth masks were associated with a significantly higher risk of both ILI and laboratory-confirmed respiratory virus infection in HCWs. In addition, filtration capacity of the two-ply cotton cloth masks was found to be only 3% and markedly less than with surgical masks based on standardised particle testing. The authors suggested moisture retention, poor filtration, and penetration of the virus through the mask as plausible explanations for the increased risk of infection.

We did not find any randomised trials assessing the effectiveness of barrier interventions using a combination of masks, gloves, and gowns.

2. N95 respirators compared to medical/surgical masks

Comparisons between N95 respirators and surgical masks for the outcomes of clinical respiratory illness and the outcome of laboratory-confirmed influenza showed estimates of effect suggesting considerable uncertainty for any benefit for the former outcome and probably little or no difference for the latter outcome. Five trials (four in healthcare settings and one in a household setting) compared N95/P2 respirators with surgical masks. Pooling of three of these trials showed an estimate of effect suggesting considerable uncertainty as to whether there was any benefit comparing N95 respirators and medical/surgical face masks for the outcome of clinical respiratory illness (RR 0.70, 95% CI 0.45 to 1.10; very low-certainty evidence), and that N95 respirators may make little or no difference for the outcome ILI (RR 0.82, 95% CI 0.66 to 1.03; low-certainty evidence) and probably little or no difference for the outcome laboratory-confirmed influenza (RR 1.10, 95% CI 0.90 to 1.34; moderate-certainty evidence). The presence of imprecision (wide confidence intervals) and heterogeneity, particularly for the more subjective and less precise outcomes of clinical respiratory illness and ILI compared to laboratory-confirmed influenza infection, makes it difficult to assess whether there may be a benefit of either medical/surgical masks or N95/P2 respirators. Restricting the pooling to HCWs made no difference to the overall findings. The two trials with the largest event rates were quite consistent in their findings of no significant differences between N95 and surgical masks for the outcomes laboratory-confirmed influenza and all laboratory-confirmed viral infections (Loeb 2009; Radonovich 2019). Three of the trials contributing to this analysis were carried out by members of the same group (MacIntyre 2009; MacIntyre 2011; MacIntyre 2013).

In general, harms were poorly reported or not reported at all in trials comparing N95 respirators with surgical masks. General discomfort resulting in reduced wear compliance was the most frequently reported harm.

3. Hand hygiene compared to control

We found that the estimate of effect may offer a benefit for hand hygiene for the composite outcome 'ARI or ILI or influenza' (RR 0.89, 95% CI 0.84 to 0.95; low-certainty evidence), and probably offers a benefit for the outcomes ARI alone (RR 0.84, 95% CI 0.82 to 0.86; moderate-certainty evidence) and absenteeism (RR 0.64, 95% CI 0.58 to 0.71). An observed estimate of effect in favour of hand hygiene for laboratory-confirmed influenza but with wider CIs may be a consequence of smaller sample sizes in conjunction with a more rigorous outcome measure.

4. Hand hygiene + medical/surgical masks compared to control

The estimate of effect of combined hand hygiene and mask interventions compared to control in six (mostly small) trials suggested that the intervention may make little or no difference for the outcomes ILI (RR 1.03, 95% CI 0.77 to 1.37) and laboratory-confirmed influenza (four trials) (RR 0.97, 95% CI 0.69 to 1.36).

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5. Hand hygiene + medical/surgical masks compared to hand hygiene

We also found an estimate of effect suggesting that adding masks to hand hygiene compared to hand hygiene alone may make little or no difference for the outcomes ILI (RR 1.03, 95% CI 0.69 to 1.53; 3 trials) and laboratory-confirmed influenza (RR 0.99, 95% CI 0.69 to 1.44).

6. Medical/surgical masks compared to other (non-N95) masks

One trial found that medical/surgical masks were more effective than cloth masks at reducing the rate of ILI (RR 13.25, 95% CI 1.74 to 100.97) (MacIntyre 2015), but the extremely wide CIs make this finding difficult to interpret. One trial did not find a benefit from catechin-treated masks over untreated masks on influenza infection rates (adjusted OR 2.35, 95% CI 0.40 to 13.72; P = 0.34) (Ide 2016).

Harms of wearing masks were reported in 40.4% of HCWs using medical/surgical masks, and in 42.6% of those wearing cloth masks (P = 0.45) (MacIntyre 2015). The penetration of particles was higher in cloth masks (97%) compared to medical/surgical masks (44%).

7. Soap + water compared to sanitiser, and comparisons of different types of sanitiser

There were too few trials comparing different types of hand hygiene interventions to be certain of any true differences between soap and water, alcohol-based hand sanitisers, or other types of interventions. Also, it is uncertain whether the incremental effect of adding virucidals or antiseptics to hand-washing actually decreased the respiratory disease burden outside the confines of the rather atypical studies. The extra benefit may have been, at least in part, accrued by confounding additional routines.

8. Surface/object disinfection (with or without hand hygiene) compared to control

We identified six trials on surface/object disinfection (with or without hand hygiene), and although they were heterogeneous (and therefore could not be pooled), three of them showed a clear benefit compared to controls (Ban 2015; Carabin 1999; Ibfelt 2015).

We found no RCTs with nose disinfection, or disinfection of living quarters as described in observational studies reported in Jefferson 2011.

9. Complex interventions compared to control

Four trials studied complex hygiene and sanitation interventions, all in low-income country settings (Chard 2019; Hartinger 2016; Huda 2012; Najnin 2019). These trials could not be pooled due to the heterogeneity of the interventions and settings. All four trials found no significant differences between groups in the rates of viral respiratory illness.

10. Physical distancing/quarantine compared to control

A disappointing finding was the lack of proper evaluation of global and highly resource-intensive measures such as screening at entry ports and physical distancing. We identified only one trial that evaluated the effect of quarantine (Miyaki 2011), and found a reduction in influenza transmission to co-workers when those with infected household members stayed home from work. However, staying home increased their risk of being infected two-fold.

11. Eye protection compared to control

We did not find any trials assessing the effectiveness and safety of eye protection.

12. Gargling compared to control

Three trials addressed the use of gargling in preventing respiratory infections (Goodall 2014; Ide 2014; Satomura 2005). Although the trials used a variety of liquids and different outcomes, pooling the results of the two trials that compared gargling with tap water versus control did not show a favourable effect in reducing URTIs (RR 0.91, 95% CI 0.63 to 1.31) (Goodall 2014; Satomura 2005).

13. Virucidal tissues compared to control

Two reports (three trials) identified in Jefferson 2011 studied the effect of virucidal tissues compared to placebo or no tissues (Farr 1988a; Farr 1988b; Longini 1988). These trials found no differences in infection rates and could not be pooled.

Overall completeness and applicability of evidence

Several features need consideration before making generalisations based on the included studies.

The settings of the included studies, which were conducted over four decades, were heterogeneous and ranged from suburban schools, Carabin 1999, to emergency departments, intensive care units, and paediatric wards, Loeb 2009, in high-income countries; slums in low-income countries (Luby 2005); and an upper Manhattan immigrant Latino neighbourhood (Larson 2010). Few attempts were made to obtain socio-economic diversity by (for example) involving more schools in the evaluations of the same programme. We identified only a few studies from low-income countries, where the vast majority of the burden of ARIs lies and where inexpensive interventions are so critical. Additionally, limited availability of over-the-counter medications and national universal comprehensive health insurance provided with consequent physician prescription of symptomatic treatment may further limit the generalisability of findings.

The included trials generally reported few events and were conducted mostly during non-epidemic periods. The large study by Radonovich 2019 is an exception as it crossed over two of the highest reporting years for influenza in the USA between 2010 and 2017 (Elflein 2019). None of the trials were conducted during a pandemic such as SARS-CoV-1, SARS-CoV-2, or Middle East respiratory syndrome (MERS).

Of the trials assessing the effect of masks, six were carried out in those at greater exposure (i.e. HCWs) (Jacobs 2009; Loeb 2009; MacIntyre 2011; MacIntyre 2013; MacIntyre 2015; Radonovich 2019). None of these studies included HCWs undertaking aerosol-generating procedures, for which the World Health Organization (WHO) currently recommends the N95 or equivalent mask. Three trials on hand hygiene interventions were carried out in nursing homes, and included HCWs (McConeghy 2017; Temime 2018; Yeung 2011). The scarcity of RCTs on HCWs limits the generalisability of such results.

The variable quality of the methods of some studies is striking. Incomplete or no reporting of randomisation (Turner 2004a), blinding (Farr 1988a; Farr 1988b), numerators and denominators (Carabin 1999; Kotch 1994), interventions, and cluster coefficients

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in the relevant trials (Carabin 1999), led to a considerable loss of information. Potential biases were often not discussed.

Inappropriate placebos caused design problems. In some studies the placebo probably carried sufficient effect to dilute the intervention effects (Longini 1988). Two valiant attempts with virucidal tissues probably failed because placebo handkerchiefs were impregnated with a dummy compound that stung the users' nostrils (Farr 1988a; Farr 1988b).

Some studies used impractical interventions. Volunteers subjected to the intervention hand cleaner (organic acids) were not allowed to use their hands between cleaning and virus challenge, so the effect of normal use of the hands on the intervention remains unknown (Turner 2004a; Turner 2004b). Two per cent aqueous iodine painted on the hands, although a successful antiviral intervention, causes unacceptable cosmetic staining, which is impractical for all but those at the highest risk of epidemic contagion (Gwaltney 1980).

Compliance with interventions, especially educational programmes, was a problem for many studies despite the importance of many such low-cost interventions. Compliance with mask wearing varied; it was generally around 60% to 80%, but was reported to be as low as 40% (see Table 1). Overall, the logistics of carrying out trials that involve sustained behaviour change are demanding, particularly in challenging settings such as immigrant neighbourhoods or students' halls of residence.

The identified trials provided sparse and unsystematic data on adverse effects of the intervention, and few of the RCTs measured or reported compliance with the intervention, which is especially important for the use of medical/surgical masks or N95 respirators. No studies investigated how the level of adherence may have influenced the effect size.

We did not identify any studies assessing the effects of eye protection, and we identified only one study on physical distancing, during the 2009 H1N1 influenza pandemic. The dearth of evidence and predominant setting of seasonal viral circulation limits generalisability of our findings to other contexts such as the COVID-19 pandemic and any future epidemics due to other respiratory viruses.

Quality of the evidence

We found the available evidence base identified through our search processes to be of variable quality. Reporting of sequence generation and allocation concealment were poor in 30% to 50% of studies across the categories of intervention comparisons. Given the nature of the intervention comparison, blinding of treatment allocation after randomisation was rarely achieved. Although blinding of outcome assessment is highly feasible and desirable, most outcomes were assessed by self-reports. Outcomes in some studies were poorly defined, with a lack of clarity as to the possible aetiologic agents (bacterial versus viral). Some studies used laboratory-confirmed outcomes, both adding precision and lowering the risk of bias (see Table 9 for heterogeneity of trial outcome definitions). We found no evidence of selective reporting of outcomes within the included studies. We believe publication bias is unlikely, as the included studies demonstrated a range of effects, both positive and negative, over all study sizes. The variable quality of the studies hampers drawing any firm conclusions.

Potential biases in the review process

The non-drug (and often locally manufactured) nature of most of the interventions in this review, the lack of effective regulation in some settings, and the possible endless number of manufacturers make it difficult to gauge the existence of unpublished data. Non-drug interventions typically have no or very poor regulation.

In this 2020 update, we focused on RCTs and cluster-RCTs, providing a higher level of evidence compared with the previous version of the review, which also meta-analysed observational studies when appropriate (Jefferson 2011). However, many of the trials were small and hence underpowered, and at high or unclear risk of bias due to poor reporting of methods and lack of blinding. The populations, outcomes, comparators, and interventions tested were heterogeneous.

Due to the urgency of this update in the context of the COVID-19 pandemic, we did not contact trial authors to request missing data. This means that we have not considered studies that included other non-respiratory infections and did not provide stratified data by type of infection.

Agreements and disagreements with other studies or reviews

Several reviews of RCTs have found broadly similar results to this review for face masks. In a meta-analysis comparing surgical masks with N95 respirators, Smith 2016 pooled three trials (Loeb 2009; MacIntyre 2011; MacIntyre 2013), and found an estimate of effect suggesting no difference for laboratory-confirmed respiratory infections (OR 0.89, 95% CI 0.64 to 1.24) or ILI (OR 0.51, 95% CI 0.19 to 1.41). A similar meta-analysis, Offeddu 2017, based on two trials, MacIntyre 2011; MacIntyre 2015, concluded that masks (either N95/P2 respirators or medical/surgical masks) were effective against clinical respiratory infections (RR 0.59, 95% CI 0.46 to 0.77) and ILI (RR 0.34, 95% CI 0.14 to 0.82). Pooling of two studies, MacIntyre 2011; MacIntyre 2013, also found an estimate of effect that favoured N95 respirators to medical/surgical masks for clinical respiratory infections (RR 0.47, 95% CI 0.36 to 0.62), but not for ILI based on three studies, Loeb 2009: MacIntyre 2011; MacIntyre 2013 (RR 0.59, 95% CI 0.27 to 1.28) (Offeddu 2017). The outcome of clinical respiratory infection is considered to be the most subjective and least precise outcome.

A recent meta-analysis included five trials comparing N95/P2 respirators with medical/surgical masks and found no difference between groups for either influenza (RR 1.09, 95% CI 0.92 to 1.28) or respiratory viral infections (RR 0.89, 95% CI 0.70 to 1.11) (Long 2020). By excluding Loeb 2009 (an open, non-inferiority RCT that compared surgical masks with N95 respirators in protecting HCWs against influenza), the authors reported a significant protective effect against viral infections (RR 0.61, 95% CI 0.39 to 0.98). The authors do not report a rationale for the exclusion in the sensitivity analysis and do not report on exclusion of the studies with low weighting, which arguably would be more relevant in a sensitivity analysis. The two trials that make up 96% of the weighting, Loeb 2009; Radonovich 2019, demonstrated no significant differences in the outcome events. A recent meta-analysis of four RCTs (Bartoszko 2020), adjusting for clustering, which compared N95 respirators with the use of medical masks, found pooled estimates of effect that did not demonstrate any difference in any laboratory-confirmed viral respiratory infection

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(OR 1.06, 95% CI 0.90 to 1.25), laboratory-confirmed influenza (OR 0.94, 95% CI 0.73 to 1.20), or clinical respiratory illness (OR 1.49, 95% CI 0.98 to 2.28), with the evidence profile suggesting that there was greater imprecision and inconsistency in the outcome of clinical respiratory illness. Moreover, in another recent systematic review that assessed the effectiveness of personal protective and environmental measures in non-healthcare settings (funded by the WHO), 10 RCTs reporting estimates of the effectiveness of face masks in reducing laboratory-confirmed influenza virus infections in the community were identified (Xiao 2020). The evidence from these RCTs suggested that the use of face masks either by infected persons or by uninfected persons does not have a substantial effect on influenza transmission.

The findings from several systematic reviews and meta-analyses over the last decade have not demonstrated any difference in the clinical effectiveness of N95 respirators or equivalent compared to the use of surgical masks when used by HCWs in multiple healthcare settings for the prevention of respiratory virus infections, including influenza.

Reviews based on observational studies have usually found a stronger protective effect for face masks, but have important biases. The review by Chu 2020 did not consider RCTs of influenza transmission, but only the observational studies examining impact on SARS, MERS, or SARS-CoV-2. For N95 masks versus no mask in HCWs, there was a large protective effective with an OR of 0.04 (95% CI 0.004 to 0.30); for surgical masks versus no masks, there was an OR of 0.33 (0.17 to 0.61) overall, but four of these studies were in healthcare settings. Chu 2020 has been criticised for several reasons: use of an outdated 'Risk of bias' tool; inaccuracy of distance measures; and not adequately addressing multiple sources of bias, including recall and classification bias and in particular confounding. Confounding is very likely, as preventive behaviours such as mask use, social distancing, and hand hygiene are correlated behaviours, and hence any effect estimates are likely to be overly optimistic.

Also based on observational studies, Jefferson 2011 found a protective effect of wearing surgical masks with hygienic measures compared to not wearing masks in the SARS 2003 outbreak (OR 0.32, 95% CI 0.26 to 0.39). However, the evidence was based on case-control studies carried out during the outbreak. There was some additional but very limited supportive evidence from the cohort studies in Jefferson 2011.

Although the use of eye protection and physical distancing measures are widely believed to be effective in reducing transmission of respiratory viruses and mitigating the impact of an influenza pandemic, we found only one trial investigating the role of self-quarantine in reducing the incidence of H1N1 influenza events in the workplace, and no trials examining the effect of eye protection. The evidence for these measures was derived largely from observational studies and simulation studies, and the overall quality of supporting evidence is relatively low. The finding of limited evidence evaluating these interventions was also consistent with a recent review funded by the WHO for the preparation of its guidelines on the use of non-pharmaceutical interventions for pandemic influenza in non-medical settings (Fong 2020).

There are several previous systematic reviews on hand hygiene and respiratory infections. Five of them reviewed the evidence in a community setting (Moncion 2019; Rabie 2006; Saunders-Hastings 2017; Warren-Gash 2013: Wong 2014), and three focused on children (Mbakaya 2017; Willmott 2016; Zivich 2018). The earliest review in 2006 included eight studies (Rabie 2006), three of which were RCTs. The pooled estimate of seven studies was described as “indicative” of the effect of hand hygiene, but the studies were of poor quality. The Warren-Gash 2013 review included 16 studies (10 of which were RCTs) and reported mixed and inconclusive results. A 2014 review identified 10 RCTs and reported that the combination of hand hygiene with face masks in high-income countries (five trials) significantly reduced the incidence of laboratory-confirmed influenza and ILI, whilst hand hygiene alone did not (Wong 2014). This significant reduction in laboratory-confirmed influenza and ILI for hand hygiene and face masks may have been based on the raw numbers without adjusting for any clustering effects in the included cluster trials, which produced inappropriately narrow CIs, and possibly biased treatment effect estimates. Moreover, trials from the low-income countries were not included in the review, and this significant effect was not demonstrated when all the trials identified in the review were combined. The Saunders-Hastings 2017 review of studies evaluating the effectiveness of personal protective measures in interrupting pandemic influenza transmission only identified two RCTs (Azor-Martinez 2014; Suess 2012), which reported a significant effect of hand hygiene. The Moncion 2019 review identified seven RCTs of hand hygiene compared to control, with mixed results for preventing the transmission of laboratory-confirmed or possible influenza. Systematic reviews of RCTs of hand hygiene interventions amongst children, Mbakaya 2017; Willmott 2016, or at a non-clinical workplace, Zivich 2018, identified heterogeneous trials with quality problems including small numbers of clusters and participants, inadequate randomisation, and self-reported outcomes. Evidence of impact on respiratory infections was equivocal.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence summarised in this review on the use of masks is largely based on studies conducted during traditional peak respiratory virus infection seasons up until 2016. We will incorporate relevant published studies in COVID-19 when their results are available. The observed lack of effect of mask wearing in interrupting the spread of ILI or influenza in our review has many potential reasons, including: poor study design; insufficiently powered studies arising from low viral circulation in some studies; lower compliance with mask wearing, especially among children; quality of the masks used; self-contamination of the mask by hands; lack of protection from eye exposure from respiratory droplets (allowing a route of entry of respiratory viruses into the nose via the lacrimal duct); saturation of masks with saliva from extended use (promoting virus survival in proteinaceous material); and risk compensation behaviour leading to an exaggerated sense of security (Brosseau 2020; Canini 2010; Cassell 2006; MacIntyre 2015; Rengasamy 2010; Zamora 2006).

Our findings show that hand hygiene has a modest effect as a physical intervention to interrupt the spread of respiratory viruses, but several questions remain. First, the high heterogeneity between studies may suggest that there are differences in the effect of different interventions. The poor reporting limited our ability to extract the information needed to assess any 'dose response'

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relationship, and there are few head-to-head trials comparing hand hygiene materials (such as alcohol-based sanitiser or soap and water). Second, the sustainability of hand hygiene is unclear where participants in some studies achieved 5 to 10 hand-washings per day, but compliance may have diminished with time as motivation decreased, or due to adverse effects from frequent hand-washing. Third, there is little evidence about the effectiveness of combinations of hand hygiene with other interventions, and how those are best introduced and sustained. Finally, some interventions were intensively implemented within small organisations, and involved education or training as a component, and the ability to scale these up to broader interventions is unclear.

Our findings with respect to hand hygiene should be considered generally relevant to all viral respiratory infections, given the diverse populations where transmission of viral respiratory infections occurs. The participants were adults, children and families, and multiple congregation settings including schools, childcare centres, homes, and offices. Most respiratory viruses, including the pandemic SARS-CoV-2, are considered to be predominantly spread via respiratory droplets or contact routes, or both (WHO 2020c). Data from studies of SARS-CoV-2 contamination of the environment based on the presence of viral ribonucleic acid (RNA) suggest significant fomite contamination from the virus (Ong 2020; Wu 2020). Hand hygiene would be expected to be beneficial in reducing the spread of SARS-CoV-2 similar to other beta coronaviruses (SARS-CoV-1, Middle East respiratory syndrome (MERS), and human coronaviruses), which are very susceptible to the concentrations of alcohol commonly found in most hand sanitiser preparations (Rabenau 2005; WHO 2020c). Support for this effect is the finding that poor hand hygiene, despite the use of full PPE, was independently associated with an increased risk of SARS-CoV-2 transmission to healthcare workers in a retrospective cohort study in Wuhan, China in both a high-risk and low-risk clinical unit for patients infected with COVID-19 (Ran 2020). The practice of hand hygiene appears to have a consistent effect in all settings, and should be an essential component of other interventions.

The highest-quality cluster-RCTs indicate that the most effect on preventing respiratory virus spread from hygienic measures occurs in younger children. This may be because younger children are least capable of hygienic behaviour themselves (Roberts 2000), and have longer-lived infections and greater social contact, thereby acting as portals of infection into the household (Monto 1969). Additional benefit from reduced transmission from them to other members of the household is broadly supported by the results of other study designs where the potential for confounding is greater.

Routine long-term implementation of some of the interventions covered in this review may be problematic, particularly maintaining strict hygiene and barrier routines for long periods of time. This would probably only be feasible in highly motivated environments, such as hospitals. Many of the trial authors commented on the major logistical burdens that barrier routines imposed at the community level. However, the threat of a looming epidemic may provide stimulus for their inception.

Implications for research

Public health measures and physical interventions can be highly effective to interrupt the spread of respiratory viral infections, especially when they are part of a structured and co-ordinated programme that includes instruction and education, and when they are delivered together. Our review has provided important insights into research gaps that need to be addressed with respect to these physical interventions and their implementation. The 2014 WHO document 'Infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care' identified several research gaps as part of their GRADE assessment of their infection prevention and control recommendations, which remain very relevant (WHO 2014). Research gaps identified during the course of our review and the WHO 2014 document may be considered from the perspective of both general and specific themes.

A general theme identified was the need to provide outcomes with explicitly defined clinical criteria for acute respiratory infections (ARIs) and discrete laboratory-confirmed outcomes of viral ARIs using molecular diagnostic tools which are now widely available. Our review found large disparities between studies with respect to the clinical outcome events, which were imprecisely defined in several studies, and there were differences in the extent to which laboratory-confirmed viruses were included in the studies that assessed them. Another general theme identified was the lack of consideration of sociocultural factors that might affect compliance with the interventions, especially those employed in the community setting. In addition, the cost and resource implications of the physical interventions employed in different settings would have important relevance for low- to middle-income countries. Resources have been a major issue with the COVID-19 pandemic, with global shortages of several components of PPE. Several specific research gaps related to physical interventions were identified within the WHO 2014 document and are congruent with many of the findings of our current update, including the following: transmission dynamics of respiratory viruses from patients to healthcare workers during aerosol-generating procedures; a lack of precision with regards to defining aerosol-generating procedures; the safety of cohorting of patients with the same suspected but unconfirmed diagnosis in a common unit or ward with patients infected with the same known pathogen in healthcare settings; the optimal duration of the use of physical interruptions to prevent spread of ARI viruses; use of spatial separation or physical distancing (in healthcare and community settings, respectively) alone versus spatial separation or physical distancing with the use of other added physical interventions coupled with examining discrete distance parameters (e.g. 1 metre, 2 metres, or > 2 metres); the effectiveness of respiratory etiquette (i.e. coughing/sneezing into tissues or a sleeved bent elbow); the effectiveness of triage and early identification of infected individuals with an ARI in both hospital and community settings; use of frequent disinfection techniques appropriate to the setting (high-touch surfaces in the environment, gargling with oral disinfectants, and virucidal tissues or clothing) alone or in combination with facial masks and hand hygiene; the use of ultraviolet light germicidal irradiation for disinfection of air in healthcare and selected community settings; and the use of widespread compliance with effective vaccination strategies.

There is a clear requirement to conduct large, pragmatic trials to evaluate the best combinations in the community and in healthcare settings with multiple respiratory viruses and in different sociocultural settings. RCTs with a pragmatic design, similar to the Luby 2005 trial, should be conducted whenever possible. Alternately, large population-based cohort studies may

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also be considered if individual RCTs prove to be too expensive or less practical, depending on the issue that is being addressed.

Several specific research gaps deserve expedited attention and may be highlighted within the context of the COVID-19 pandemic. The use of facial masks in the community setting represents one of the most pressing needs to address, given the polarised opinions around the world. Both broad-based ecological studies, adjusting for confounding and high-quality randomised trials, may be necessary to determine if there is an independent contribution to their use as a physical intervention, and how they may best be deployed to optimise their contribution. The type of fabric and weave used in the face mask is an equally pressing concern, given that surgical masks with their cotton-polypropylene fabric appear to be effective in the healthcare setting, but there are questions about the effectiveness of simple cotton masks. In addition, these masking intervention studies should focus on measuring not only benefits but also compliance, harms, and risk compensation if the latter may lead to a lower protective effect. In addition, although the use of surgical masks versus N95 respirators demonstrates no differences in clinical effectiveness to date, their use needs to be studied in the setting of a new pandemic such as COVID-19, and with concomitant measurement of harms, which to date have been poorly studied. Physical distancing represents another major research gap which needs to be addressed expediently, especially within the context of the COVID-19 pandemic setting as well as in future epidemic settings. The use of quarantine and screening at entry ports needs to be investigated in well-designed, high-quality studies. We found only one RCT of quarantine, and no trials of screening at entry ports or physical distancing. Given that this is one of the primary strategies applied globally in the face of the COVID-19 pandemic, future trials should be conducted within the context of this pandemic, as well as in future epidemics with other respiratory viruses of less virulence.

The variable quality and small scale of some studies is known from descriptive studies (Aiello 2002; Fung 2006; WHO 2006b), and systematic reviews of selected interventions (Meadows 2004). In summary, more high-quality studies are needed to evaluate the most effective strategies to implement successful physical interventions in practice, both on a small scale and at a population level. Finally, we emphasise that more attention should be paid to describing and quantifying the harms of the interventions assessed in this review and their relationship with compliance.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aelami 2015

Study characteristics	
Methods	A prospective cross-sectional study conducted during the Hajj season 2012. Pilgrims were randomised into 2 groups. The intervention group received education on personal hygiene including a hygienic package containing alcohol-based hand rub (gel or spray), surgical masks, soap, paper handkerchiefs, and user instructions; the control group did not receive any intervention. ILI was defined as the presence of at least 2 of the following during their stay: fever, cough, and sore throat. Questionnaires including demographic and clinical information were distributed amongst trained physicians before departure from Iran.
Participants	Total enrolled: 664 Iranian pilgrims (306 in the intervention group and 358 in the control group) Inclusion criteria: not reported Exclusion criteria: not reported

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Aelami 2015 *(Continued)*

Interventions	Hygiene education and package. See Table 1 for details.
Outcomes	ILI defined as the presence of at least 2 of the following during their stay: fever, cough, and sore throat. No safety outcomes were reported.
Notes	This is an abstract, therefore few details were reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details provided
Allocation concealment (selection bias)	Unclear risk	Insufficient details provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details provided
Selective reporting (reporting bias)	Unclear risk	Insufficient details provided

Aiello 2010

Study characteristics

Methods	Cluster-RCT assessing the effects of hand sanitiser and masks versus masks or no intervention on ILI symptoms. The trial was conducted in university halls of residence with more than 100 student residents in a US university during the 2006 to 2007 influenza "season". The study lasted 6 weeks. The units of randomisation were 7 of the 15 halls. 1 hall was very large (1240 residents), and the 6 remaining ones, which had between 110 and 830 residents, were combined into 2 clusters roughly equivalent in size. The 3 clusters were then randomised by random extraction of the clustered halls' names out of a container. The largest hall (single-cluster) was randomised to the mask and hand sanitiser arm; the 4-halls cluster received masks; and the remaining 2 halls were assigned as controls.
Participants	A total of 1297 with completed baseline survey and at least 1 weekly survey result were analysed (face mask and hand hygiene group = 367; face mask–only group = 378; control group = 552). Inclusion criteria: aged 18 or more, willing to wear mask and use alcohol-based hand sanitiser, have a throat swab specimen collected when ill, and complete the baseline and weekly surveys over the 6-week study period Exclusion criteria: individuals reporting a skin allergy to alcohol were excluded

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Aiello 2010 *(Continued)*

	Recruitment of students began in 26 November, but the trial did not go "live" with distribution of intervention materials until 22 January 2007 when the first case of influenza was confirmed on campus by laboratory tests. Enrolment continued until 16 February 2007, and the study was completed on 16 March 2007. During the study period there was a 1-week break when the majority of residents left campus. There were 1327 eligible participants, 1297 of which had a complete baseline survey and at least 1-weekly survey result. It is unclear what the ineligibility criteria were for the 30 missing (1327 minus 1297), but the explanation may be in the appendix.
Interventions	Alcohol-based hand sanitiser (62% ethyl alcohol in a gel base) in a squeeze bottle and TECNOL procedure masks with ear loops (KC Ltd) and educational material or masks and educational material or no intervention. Compliance was encouraged within halls and outside. Sleep wearing was optional. All participants received basic video-linked instruction on cough etiquette and hand sanitation. At baseline and weekly during the study, participants were asked to fill in a web-based survey collecting demographic and ILI symptom data. This was supplemented by direct observation of compliance by staff. Compliance with "optimal handwashing" (at least 20 seconds 5 or more times a day) was significantly higher in the sanitiser-and-mask arm.
Outcomes	Laboratory details are described in appendix. Effectiveness: ILI, defined as cough and at least 1 constitutional symptom (fever/feverishness, chills, headache, myalgia). ILI cases were given contact nurses' phone numbers to record the illness and paid USD 25 to provide a throat swab. 368 participants had ILI, and 94 of these had a throat swab analysed by PCR. 10 of these were positive for influenza (7 for A and 3 for B). Safety: N/A
Notes	The authors conclude that "These findings suggest that face masks and hand hygiene may reduce respiratory illnesses in shared living settings and mitigate the impact of the influenza A (H1N1) pandemic". This conclusion is based on a significantly lower level of ILI incidence in the mask and hand sanitiser arm compared to the other 2 arms after adjustment for covariates (30% to 50% less in arm 1 compared to controls in the last 2 weeks of the study). Comparison with the ILI rate of the control arm may not be a reflection of the underlying rate of ILI because the intervention arm received instruction on hand sanitation and hand etiquette. The play of adjustments is unclear. The intracluster correlation coefficient is reported in the footer of Table 4. Its very small size suggests lack of clustering within halls. The role of spring break is mentioned in the Discussion, as are the results of this study compared to other studies included in our review (Cowling 2008 and MacIntyre 2009). The authors report that 147 of 1297 participants (11.3%) had ILI symptoms "at baseline" and were excluded from analysis. During the 6 weeks of the study, 368 of 1150 participants (32%) had ILI. This averages out at about 5% per week. It is unclear what the term "at baseline" means; presumably this means during the 2 to 3 weeks of participant enrolment. If this is so, the reason for the triggering of the interventions (tied to influenza isolation) are obscure, as the trial is supposedly about ILI, and an ILI outbreak was already under way "at baseline".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but sequence generation not reported
Allocation concealment (selection bias)	High risk	The residence hall units were randomised by blindly selecting a uniform ticket with the name of each hall out of a container (A.S.M. and A.A.) for randomisation assignment to each study arm.

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Aiello 2010 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition is reported as follows: 9, 11, and 19 ineligible and 26, 52, and 21 lost to follow-up (respectively by arm), for a total of 39 and 99 for each reason for attrition. In total, 1297 (97%) of 1331 participants completed a baseline and at least 1-weekly survey. The text reports an ITT analysis with only 1 ILI episode included by participant. No reasons for the attrition of participants and swab volunteers are reported (were the swabs taken from a random sample or not?).
Selective reporting (reporting bias)	High risk	There is no information on the causes of ILI other than the reporting on the 10 influenza PCR-positive swabs of 94 out of 368 students with ILI. This is a very low rate (and the Discussion confirms that the influenza season was mild), but investigation of the other known causes of ILI is not even mentioned in the text. This is especially important because stress, alcohol intake levels, and influenza vaccination were a significant predictor of ILI symptoms (Table 1). The reason for selective testing and/or reporting of influenza viruses tests over the other causes of ILI are unclear, especially as the study objective was focused on ILI. The text is also difficult to follow, weaving the reporting of ILI and influenza without a clear rationale.

Aiello 2012

Study characteristics	
Methods	During the 2007 to 2008 influenza season, 1111 students residing in university residence halls were cluster-randomised by residence house (N = 37) to either face mask and hand hygiene, face mask only, or control arms. Discrete time survival analysis using generalised models estimated rate ratios according to study arm, each week and cumulatively over the 6-week intervention period, for clinically verified ILI and laboratory-confirmed influenza A or B.
Participants	A total of 1187 young adults living in 37 residence halls, randomly assigned to 1 of 3 groups for 6 weeks: face mask use (n = 392), face masks with hand hygiene (n = 349), control (n = 370) Inclusion criteria: aged 18 or more, willing to wear mask and use alcohol-based hand sanitiser, have a throat swab specimen collected when ill, and complete the baseline and weekly surveys over the 6-week study period Exclusion criteria: individuals reporting a skin allergy to alcohol were excluded
Interventions	Participants were assigned to face mask and hand hygiene, face mask only, or control group during the study. See Table 1 for details.
Outcomes	Clinically verified ILI: case definition (presence of cough and at least 1 or more of fever/feverishness, chills, or body aches) Laboratory-confirmed influenza A or B. Throat swab specimens were tested for influenza A or B using RT-PCR.

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Aiello 2012 *(Continued)*

	No safety outcomes reported.
Notes	This study has the same trial registration number as the Aiello 2010 study; the study was funded by government and pharmaceutical industry.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generation of sequence described.
Allocation concealment (selection bias)	Low risk	All residence houses in each of the residence halls were randomised prior to the intervention implementation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding for study participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition low and similar in each group
Selective reporting (reporting bias)	Low risk	2 outcomes specified and reported.

Aiello 2010

Study characteristics

Methods	Cluster-RCT assessing the effects of hand sanitiser and masks versus masks or no intervention on ILI symptoms. The trial was conducted in university halls of residence with more than 100 student residents in a US university during the 2006 to 2007 influenza "season". The study lasted 6 weeks. The units of randomisation were 7 of the 15 halls. 1 hall was very large (1240 residents), and the 6 remaining ones, which had between 110 and 830 residents, were combined into 2 clusters roughly equivalent in size. The 3 clusters were then randomised by random extraction of the clustered halls' names out of a container. The largest hall (single-cluster) was randomised to the mask and hand sanitiser arm; the 4-halls cluster received masks; and the remaining 2 halls were assigned as controls.
Participants	A total of 1297 with completed baseline survey and at least 1 weekly survey result were analysed (face mask and hand hygiene group = 367; face mask–only group = 378; control group = 552). Inclusion criteria: aged 18 or more, willing to wear mask and use alcohol-based hand sanitiser, have a throat swab specimen collected when ill, and complete the baseline and weekly surveys over the 6-week study period Exclusion criteria: individuals reporting a skin allergy to alcohol were excluded Recruitment of students began in 26 November, but the trial did not go "live" with distribution of intervention materials until 22 January 2007 when the first case of influenza was confirmed on campus by laboratory tests. Enrolment continued until 16 February 2007, and the study was completed on 16 March 2007. During the study period there was a 1-week break when the majority of residents left cam-

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Aiello 2010 *(Continued)*

	pus. There were 1327 eligible participants, 1297 of which had a complete baseline survey and at least 1-weekly survey result. It is unclear what the ineligibility criteria were for the 30 missing (1327 minus 1297), but the explanation may be in the appendix.
Interventions	Alcohol-based hand sanitiser (62% ethyl alcohol in a gel base) in a squeeze bottle and TECNOL procedure masks with ear loops (KC Ltd) and educational material or masks and educational material or no intervention. Compliance was encouraged within halls and outside. Sleep wearing was optional. All participants received basic video-linked instruction on cough etiquette and hand sanitation. At baseline and weekly during the study, participants were asked to fill in a web-based survey collecting demographic and ILI symptom data. This was supplemented by direct observation of compliance by staff. Compliance with "optimal handwashing" (at least 20 seconds 5 or more times a day) was significantly higher in the sanitiser-and-mask arm.
Outcomes	Laboratory details are described in appendix. Effectiveness: ILI, defined as cough and at least 1 constitutional symptom (fever/feverishness, chills, headache, myalgia). ILI cases were given contact nurses' phone numbers to record the illness and paid USD 25 to provide a throat swab. 368 participants had ILI, and 94 of these had a throat swab analysed by PCR. 10 of these were positive for influenza (7 for A and 3 for B). Safety: N/A
Notes	The authors conclude that "These findings suggest that face masks and hand hygiene may reduce respiratory illnesses in shared living settings and mitigate the impact of the influenza A (H1N1) pandemic". This conclusion is based on a significantly lower level of ILI incidence in the mask and hand sanitiser arm compared to the other 2 arms after adjustment for covariates (30% to 50% less in arm 1 compared to controls in the last 2 weeks of the study). Comparison with the ILI rate of the control arm may not be a reflection of the underlying rate of ILI because the intervention arm received instruction on hand sanitation and hand etiquette. The play of adjustments is unclear. The intracluster correlation coefficient is reported in the footer of Table 4. Its very small size suggests lack of clustering within halls. The role of spring break is mentioned in the Discussion, as are the results of this study compared to other studies included in our review (Cowling 2008 and MacIntyre 2009). The authors report that 147 of 1297 participants (11.3%) had ILI symptoms "at baseline" and were excluded from analysis. During the 6 weeks of the study, 368 of 1150 participants (32%) had ILI. This averages out at about 5% per week. It is unclear what the term "at baseline" means; presumably this means during the 2 to 3 weeks of participant enrolment. If this is so, the reason for the triggering of the interventions (tied to influenza isolation) are obscure, as the trial is supposedly about ILI, and an ILI outbreak was already under way "at baseline".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but sequence generation not reported
Allocation concealment (selection bias)	High risk	The residence hall units were randomised by blindly selecting a uniform ticket with the name of each hall out of a container (A.S.M. and A.A.) for randomisation assignment to each study arm.
Blinding of participants and personnel (performance bias)	High risk	Unblinded study

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Aiello 2010 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition is reported as follows: 9, 11, and 19 ineligible and 26, 52, and 21 lost to follow-up (respectively by arm), for a total of 39 and 99 for each reason for attrition. In total, 1297 (97%) of 1331 participants completed a baseline and at least 1-weekly survey. The text reports an ITT analysis with only 1 ILI episode included by participant. No reasons for the attrition of participants and swab volunteers are reported (were the swabs taken from a random sample or not?).
Selective reporting (reporting bias)	High risk	There is no information on the causes of ILI other than the reporting on the 10 influenza PCR-positive swabs of 94 out of 368 students with ILI. This is a very low rate (and the Discussion confirms that the influenza season was mild), but investigation of the other known causes of ILI is not even mentioned in the text. This is especially important because stress, alcohol intake levels, and influenza vaccination were a significant predictor of ILI symptoms (Table 1). The reason for selective testing and/or reporting of influenza viruses tests over the other causes of ILI are unclear, especially as the study objective was focused on ILI. The text is also difficult to follow, weaving the reporting of ILI and influenza without a clear rationale.

Aiello 2012

Study characteristics	
Methods	During the 2007 to 2008 influenza season, 1111 students residing in university residence halls were cluster-randomised by residence house (N = 37) to either face mask and hand hygiene, face mask only, or control arms. Discrete time survival analysis using generalised models estimated rate ratios according to study arm, each week and cumulatively over the 6-week intervention period, for clinically verified ILI and laboratory-confirmed influenza A or B.
Participants	A total of 1187 young adults living in 37 residence halls, randomly assigned to 1 of 3 groups for 6 weeks: face mask use (n = 392), face masks with hand hygiene (n = 349), control (n = 370) Inclusion criteria: aged 18 or more, willing to wear mask and use alcohol-based hand sanitiser, have a throat swab specimen collected when ill, and complete the baseline and weekly surveys over the 6-week study period Exclusion criteria: individuals reporting a skin allergy to alcohol were excluded
Interventions	Participants were assigned to face mask and hand hygiene, face mask only, or control group during the study. See Table 1 for details.
Outcomes	Clinically verified ILI: case definition (presence of cough and at least 1 or more of fever/feverishness, chills, or body aches) Laboratory-confirmed influenza A or B. Throat swab specimens were tested for influenza A or B using RT-PCR. No safety outcomes reported.

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Aiello 2012 *(Continued)*

Notes	This study has the same trial registration number as the Aiello 2010 study; the study was funded by government and pharmaceutical industry.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generation of sequence described.
Allocation concealment (selection bias)	Low risk	All residence houses in each of the residence halls were randomised prior to the intervention implementation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding for study participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition low and similar in each group
Selective reporting (reporting bias)	Low risk	2 outcomes specified and reported.

Alzaher 2018

Study characteristics

Methods	A cluster-RCT conducted amongst girls attending 4 primary schools between January and March 2018. The participants attended a hand hygiene workshop. The schoolgirls' absences were followed up for 5 weeks. Incidence rate, percentage of absence days, and absence rate were calculated for total and upper respiratory infections absences.
Participants	A total of 496 schoolgirls aged of 6 to 12 years, attending 4 public primary girls' schools in the city of Riyadh, Saudi Arabia between January and March 2018. Students were randomised to education group (n = 234) or control group (n = 262). Exclusion criteria: not reported
Interventions	Hand hygiene workshop. See Table 1 for details.
Outcomes	Incidence rate, percentage of absence days, and absence rate were calculated for total and upper respiratory infections absences. The episode of URIs was defined as having 2 of the following symptoms for a day or 1 of the symptoms for 2 or more consecutive days: 1) a runny nose, 2) a stuffy or blocked nose or noisy breathing, 3) sneezing, 4) a cough, 5) a sore throat, and 6) feeling hot, having a fever or a chill. No safety outcomes reported.
Notes	Source of funding unclear

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Alzaher 2018 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail provided.
Allocation concealment (selection bias)	Low risk	Schools allocated prior to all schoolgirls attending selected schools were invited to participate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available

Arbogast 2016

Study characteristics	
Methods	A 13.5-month prospective cluster-RCT executed with alcohol-based hand sanitiser in strategic workplace locations and personal use (intervention group) and brief hand hygiene education (both groups). 4 years of retrospective data were collected for all participants.
Participants	Data for a total of 1183 participants were analysed (intervention group = 525, control group = 607). Inclusion criteria: all employees at 3 facilities who were 18 years of age or older, were enrolled in the company health insurance coverage, did not transfer between sites, and worked onsite full time (≥ 32 hours) were eligible for the study Exclusion criteria: not reported
Interventions	Alcohol-based hand sanitiser in strategic workplace locations and personal use (intervention group) and brief hand hygiene education (both groups). See Table 1 for details.
Outcomes	(1) The number of healthcare insurance claims, for a defined set of preventable illnesses, per participant per year, and (2) absenteeism, defined as the number of sick episodes per participant per year Claims based on ICD-9 codes No safety outcomes reported.
Notes	Industry funded; only 2 clusters (1 per group) included, hence study data not included in meta-analysis.
Risk of bias	

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Arbogast 2016 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition minimal and similar in 2 groups
Selective reporting (reporting bias)	Unclear risk	No protocol available

Arbogast 2016

Study characteristics	
Methods	A 13.5-month prospective cluster-RCT executed with alcohol-based hand sanitiser in strategic workplace locations and personal use (intervention group) and brief hand hygiene education (both groups). 4 years of retrospective data were collected for all participants.
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Notes	Industry funded; only 2 clusters (1 per group) included, hence study data not included in meta-analysis.
Risk of bias	

Bias	Authors' judgement	Support for judgement

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Arbogast 2016 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition minimal and similar in 2 groups
Selective reporting (reporting bias)	Unclear risk	No protocol available

Azor-Martinez 2016

Study characteristics	
Methods	Randomised, controlled, and open study with an 8-month follow-up. The experimental group washed their hands with soap and water, together with using hand sanitiser, and the control group followed their usual handwashing procedures. Absenteeism rates due to URIs were compared between the 2 groups through a multivariate Poisson regression analysis. The per cent of days missed in both groups were compared with a z test.
Participants	A sample of 1341 (intervention group = 621, control group = 720) Inclusion criteria: children 4 to 12 years old, attending 5 state schools in Almeria (Spain) whose parents/guardians had signed an informed consent document Exclusion criteria: children who had any of the following chronic illnesses that predisposed them to infection: neoplasia, primary and secondary immunodeficiencies, cystic fibrosis, chronic treatment with high doses of steroids or immunosuppressants
Interventions	Hand-washing workshops of 2-hour duration. The experimental group washed their hands with soap and water together with using hand sanitiser, whilst the control group followed usual hand-washing procedures. See Table 1 for details.
Outcomes	Absenteeism rates due to URIs Per cent of days missed Respiratory illness was defined by 2 of the following symptoms during 1 day, or 1 of the symptoms for 2 consecutive days: (1) runny nose; (2) stuffy or blocked nose or noisy breathing; (3) cough; (4) feeling hot or feverish or having chills; (5) sore throat; or (6) sneezing. A school absenteeism case (episode) was defined as when a child failed to attend school due to an URI. Common infectious illnesses, such as conjunctivitis, and skin infections were not included. Other causes for absenteeism, such as doctors' appointments, family vacations, and accident injuries, were also excluded.

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Azor-Martinez 2016 *(Continued)*

	No safety outcomes reported.
Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random number table was used.
Allocation concealment (selection bias)	Low risk	Schools/classes allocated prior to children recruited.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition levels high and different in the 2 groups
Selective reporting (reporting bias)	Unclear risk	No protocol available

Azor-Martinez 2016

Study characteristics

Methods	Randomised, controlled, and open study with an 8-month follow-up. The experimental group washed their hands with soap and water, together with using hand sanitiser, and the control group followed their usual handwashing procedures. Absenteeism rates due to URIs were compared between the 2 groups through a multivariate Poisson regression analysis. The per cent of days missed in both groups were compared with a z test.
Participants	A sample of 1341 (intervention group = 621, control group = 720) Inclusion criteria: children 4 to 12 years old, attending 5 state schools in Almeria (Spain) whose parents/guardians had signed an informed consent document Exclusion criteria: children who had any of the following chronic illnesses that predisposed them to infection: neoplasia, primary and secondary immunodeficiencies, cystic fibrosis, chronic treatment with high doses of steroids or immunosuppressants
Interventions	Hand-washing workshops of 2-hour duration. The experimental group washed their hands with soap and water together with using hand sanitiser, whilst the control group followed usual hand-washing procedures. See Table 1 for details.
Outcomes	Absenteeism rates due to URIs Per cent of days missed

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Azor-Martinez 2016 *(Continued)*

	Respiratory illness was defined by 2 of the following symptoms during 1 day, or 1 of the symptoms for 2 consecutive days: (1) runny nose; (2) stuffy or blocked nose or noisy breathing; (3) cough; (4) feeling hot or feverish or having chills; (5) sore throat; or (6) sneezing. A school absenteeism case (episode) was defined as when a child failed to attend school due to an URI. Common infectious illnesses, such as conjunctivitis, and skin infections were not included. Other causes for absenteeism, such as doctors' appointments, family vacations, and accident injuries, were also excluded. No safety outcomes reported.
Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random number table was used.
Allocation concealment (selection bias)	Low risk	Schools/classes allocated prior to children recruited.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition levels high and different in the 2 groups
Selective reporting (reporting bias)	Unclear risk	No protocol available

Azor-Martinez 2018

Study characteristics

Methods	A cluster-RCT, controlled, and open study of 911 children aged 0 to 3 years attending 24 DCCs in Almería, Spain, with an 8-month follow-up. 2 intervention groups of DCC families performed educational and hand hygiene measures, 1 with soap and water (n = 274), another with hand sanitiser (n = 339), and the control group followed usual hand-washing procedures (n = 298). Respiratory infection (RI) episode rates were compared through multilevel Poisson regression models. The percentage of days missed were compared with Poisson exact tests.
Participants	A total of 911 children attending 24 DCCs in Almería (Spain). Inclusion criteria: children between 0 and 3 years old enrolled in DCCs and attending for at least 15 hours per week whose parents or guardians had signed an informed consent Exclusion criteria: children with chronic illness or medication that could affect their likelihood of contracting an infection

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Azor-Martinez 2018 *(Continued)*

	Data were analysed for 911 participants: hand sanitiser group (n = 339), soap and water group (n = 274), and control group (n = 298).
Interventions	2 intervention groups. 1 group used soap and water, another used hand sanitiser, whilst the control group followed usual hand-washing procedures. Groups received 1-hour hand hygiene workshop. See Table 1 for details.
Outcomes	Primary: RI incidence rate Secondary: (1) the presence or absence of at least 1 antibiotic prescription for each new RI episode during the study period (topical antibiotics were excluded), and (2) the percentage of RI absenteeism days in the 3 groups calculated as the ratio of RI absenteeism days to all possible days of attendance DCC absenteeism episode was defined as when a child failed to attend a DCC because of an RI. Respiratory illness was defined as the presence of 2 of the following symptoms during 1 day or the presence of 1 of the symptoms for 2 consecutive days: (1) runny nose, (2) stuffy or blocked nose or noisy breathing, (3) cough, (4) feeling hot or feverish or having chills, (5) sore throat, or (6) sneezing. No safety outcomes reported.
Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomisation using statistical software for the sequence
Allocation concealment (selection bias)	Low risk	Clusters assigned prior to recruitment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition minimal and similar in 3 groups
Selective reporting (reporting bias)	Unclear risk	No protocol available

Azor-Martinez 2018

Study characteristics

Methods	A cluster-RCT, controlled, and open study of 911 children aged 0 to 3 years attending 24 DCCs in Almería, Spain, with an 8-month follow-up. 2 intervention groups of DCC families performed educational and hand hygiene measures, 1 with soap and water (n = 274), another with hand sanitiser (n = 339), and the control group followed usual hand-washing procedures (n = 298). Respiratory infection (RI)

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Azor-Martinez 2018 *(Continued)*

	episode rates were compared through multilevel Poisson regression models. The percentage of days missed were compared with Poisson exact tests.
Participants	A total of 911 children attending 24 DCCs in Almería (Spain). Inclusion criteria: children between 0 and 3 years old enrolled in DCCs and attending for at least 15 hours per week whose parents or guardians had signed an informed consent Exclusion criteria: children with chronic illness or medication that could affect their likelihood of contracting an infection Data were analysed for 911 participants: hand sanitiser group (n = 339), soap and water group (n = 274), and control group (n = 298).
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Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomisation using statistical software for the sequence
Allocation concealment (selection bias)	Low risk	Clusters assigned prior to recruitment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition minimal and similar in 3 groups
Selective reporting (reporting bias)	Unclear risk	No protocol available

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Ban 2015

Study characteristics	
Methods	"Group randomised" trial. Only 2 clusters, which were 2 kindergartens in Xiantao City, Hubei Province, China
Participants	Data for a total of 393 participants were analysed (intervention group = 194, control group = 199). 5 classes (221 children) randomly selected from 1 kindergarten in the intervention group and 6 classes (244 children) randomly selected from another kindergarten in the control group. Children were aged 5 or under. There were 72 exclusions from the analysis.
Interventions	Intervention group: hand hygiene and surface-cleaning education and provision of products for kindergarten and home use. Control group: usual practice. See Table 1 for details.
Outcomes	Respiratory illness, defined as: 2 or more of the following: fever, cough and expectoration, runny nose and nasal congestion, collected by parental questionnaire. Axillary temperature higher than 37.3 °C or the range of temperature fluctuation is more than 1 °C. 'Cough and expectoration' were defined as 3 or more coughs in a single hour and lasting for 4 or more hours in a single day, with or without expectoration. 'Runny nose and nasal congestion' were defined as a runny nose lasting for 4 or more hours in 1 day, with or without nasal congestion.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Method not described, and only 2 clusters.
Allocation concealment (selection bias)	Unclear risk	Method not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	Parental report, and parents were aware of treatment allocation
Selective reporting (reporting bias)	High risk	Attrition reported and balanced between groups, but high rate of attrition in a trial with small numbers of participants.

Ban 2015

Study characteristics

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Ban 2015 *(Continued)*

Methods	"Group randomised" trial. Only 2 clusters, which were 2 kindergartens in Xiantao City, Hubei Province, China
Participants	Data for a total of 393 participants were analysed (intervention group = 194, control group = 199). 5 classes (221 children) randomly selected from 1 kindergarten in the intervention group and 6 classes (244 children) randomly selected from another kindergarten in the control group. Children were aged 5 or under. There were 72 exclusions from the analysis.
Interventions	Intervention group: hand hygiene and surface-cleaning education and provision of products for kindergarten and home use. Control group: usual practice. See Table 1 for details.
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Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method not described, and only 2 clusters.
Allocation concealment (selection bias)	Unclear risk	Method not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	Parental report, and parents were aware of treatment allocation
Selective reporting (reporting bias)	High risk	Attrition reported and balanced between groups, but high rate of attrition in a trial with small numbers of participants.

Barasheed 2014

Study characteristics

Methods	Pilot, non-blinded, parallel, cluster-RCT
Participants	22 tents were randomly selected from the Australian pilgrims camped in Mina, during Hajj in 2011; 12 tents were allocated to the mask group and 10 tents to the control group. A total of 164 Australian pil-

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Barasheed 2014 *(Continued)*

	grims were recruited: 75 in the mask group (39 'cases' and 36 'contacts') and 89 in the control group (36 'cases' and 53 'contacts'). Inclusion criteria for index case: 1) Australian pilgrims of any gender aged > 15 years who attend the Hajj 2011, and 2) have symptoms of respiratory infection for 3 days. For close tent contact: 1) Australian pilgrims of any gender aged 15 years or more who attend the Hajj 2011, and 2) pilgrims who share the same tent and sleep "immediately close" to the index case. Exclusion criteria: for index case: 1) pilgrims who do not suffer from symptoms of respiratory infection, 2) pilgrims who present with symptoms of respiratory infection for > 3 days, and 3) children aged less than 15 years. For close tent contact: 1) pilgrims who are symptomatic at presentation, 2) pilgrims who are not close tent contacts of an index case, and 3) children aged less than 15 years. Only 10% to 15% of potential participants took part in the study.
Interventions	"supervised mask use" versus "no supervised mask use". See Table 1 for details.
Outcomes	Laboratory: 2 nasal swabs from all ILI cases and contacts, 1 for influenza POCT using the QuickVue Influenza (A+B) assay (Quidel Corporation, San Diego, USA) and 1 for later nucleic acid testing for influenza and other respiratory viruses. However, there was a problem with getting POCT on time during Hajj. Effectiveness: to assess the effectiveness of face masks in the prevention of transmission of ILI. ILI was defined as subjective (or proven) fever plus 1 respiratory symptom (e.g. dry or productive cough, runny nose, sore throat, shortness of breath). Safety: none planned or reported
Notes	The study was conducted from 4 November 2011 to 10 November 2011. Funding: government (Qatar National Research Fund (QNRF)) Compliance with face mask use by pilgrims was 56 of 75 (76%) in the mask group and 11 of 89 (12%) in the control group (P < 0.001). The proportion of face mask user in the 'mask' tents was 76% for both males (19/25) and females (38/50). The most often reported reason for not wearing face masks was discomfort (15%).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided.
Allocation concealment (selection bias)	Unclear risk	"tents were randomised to either intervention group (supervised mask tent) or control group (no supervised mask tent) by an independent study coordinator who was not an investigator", but did not mention how
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Because advice from the Saudi Ministry of Hajj to all pilgrims included recommending the wearing of masks, all pilgrims, both cases and controls, were asked about mask-wearing"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes (nasal swab was performed for those who reported ILI symptoms and was not intended as systematic detection). ILI was defined as subjective (or proven) fever plus 1 respiratory symptom.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up, all numbers were reported from enrolment to analysis

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Barasheed 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.

Barasheed 2014

Study characteristics	
Methods	Pilot, non-blinded, parallel, cluster-RCT
Participants	22 tents were randomly selected from the Australian pilgrims camped in Mina, during Hajj in 2011; 12 tents were allocated to the mask group and 10 tents to the control group. A total of 164 Australian pilgrims were recruited: 75 in the mask group (39 'cases' and 36 'contacts') and 89 in the control group (36 'cases' and 53 'contacts'). Inclusion criteria for index case: 1) Australian pilgrims of any gender aged > 15 years who attend the Hajj 2011, and 2) have symptoms of respiratory infection for 3 days. For close tent contact: 1) Australian pilgrims of any gender aged 15 years or more who attend the Hajj 2011, and 2) pilgrims who share the same tent and sleep "immediately close" to the index case. Exclusion criteria: for index case: 1) pilgrims who do not suffer from symptoms of respiratory infection, 2) pilgrims who present with symptoms of respiratory infection for > 3 days, and 3) children aged less than 15 years. For close tent contact: 1) pilgrims who are symptomatic at presentation, 2) pilgrims who are not close tent contacts of an index case, and 3) children aged less than 15 years. Only 10% to 15% of potential participants took part in the study.
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Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided.
Allocation concealment (selection bias)	Unclear risk	"tents were randomised to either intervention group (supervised mask tent) or control group (no supervised mask tent) by an independent study coordinator who was not an investigator", but did not mention how

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Barasheed 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Because advice from the Saudi Ministry of Hajj to all pilgrims included recommending the wearing of masks, all pilgrims, both cases and controls, were asked about mask-wearing"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes (nasal swab was performed for those who reported ILI symptoms and was not intended as systematic detection). ILI was defined as subjective (or proven) fever plus 1 respiratory symptom.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up, all numbers were reported from enrolment to analysis
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.

Biswas 2019

Study characteristics	
Methods	Cluster-RCT in 24 primary schools in Dhaka to assess the effectiveness of hand sanitiser and a respiratory hygiene education intervention in reducing ILI and laboratory-confirmed influenza during June to September 2015. 12 schools were randomly selected to receive hand sanitiser and respiratory hygiene education, and 12 schools received no intervention. Field staff actively followed children daily to monitor for new ILI episodes (cough with fever) through school visits and by phone if a child was absent. When an illness episode was identified, medical technologists collected nasal swabs to test for influenza viruses.
Participants	A total of 10,855 students were enrolled in the study (intervention schools = 5077 children; control schools = 5778 children). Children aged 5 to 10 years educated in 24 randomly selected primary schools in Dhaka, Bangladesh Exclusion: schools that offered education above grade 5 because of differences in student populations, as well as schools that had previously received a hand or respiratory hygiene intervention
Interventions	Hand sanitiser and respiratory hygiene education versus no intervention. See Table 1 for details.
Outcomes	Incidence of ILI Incidence of laboratory-confirmed influenza (RT-PCR) An ILI episode was defined as measured fever ≥ 38 °C or subjective fever and cough. If a child was absent, the field staff followed up by phone to identify the reason for absenteeism and to determine if the child met the ILI case definition. If a child in a participating school had an ILI episode, a trained medical technologist visited the child's household to obtain consent from the child's parent/guardian and collect a nasal swab from the child within 48 hours of symptom onset. If it was outside the 48-hour window, the sample was not collected. No safety outcomes reported.
Notes	Government funded
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

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Biswas 2019 *(Continued)*

Random sequence generation (selection bias)	Low risk	Sequence generated using a computer-based random number generator.
Allocation concealment (selection bias)	Low risk	Allocation completed prior to individuals being recruited.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	Information missing for 30 children (28 children in the control schools and 2 children in the intervention schools)
Selective reporting (reporting bias)	Unclear risk	No protocol available

Biswas 2019

Study characteristics	
Methods	Cluster-RCT in 24 primary schools in Dhaka to assess the effectiveness of hand sanitiser and a respiratory hygiene education intervention in reducing ILI and laboratory-confirmed influenza during June to September 2015. 12 schools were randomly selected to receive hand sanitiser and respiratory hygiene education, and 12 schools received no intervention. Field staff actively followed children daily to monitor for new ILI episodes (cough with fever) through school visits and by phone if a child was absent. When an illness episode was identified, medical technologists collected nasal swabs to test for influenza viruses.
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Biswas 2019 *(Continued)*

Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generated using a computer-based random number generator.
Allocation concealment (selection bias)	Low risk	Allocation completed prior to individuals being recruited.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	Information missing for 30 children (28 children in the control schools and 2 children in the intervention schools)
Selective reporting (reporting bias)	Unclear risk	No protocol available

Canini 2010

Study characteristics

Methods	A cluster-RCT conducted in France during the 2008 to 2009 influenza season. Households were recruited during a medical visit of a household member with a positive rapid influenza A test and symptoms lasting less than 48 hours. Households were randomised either to the mask or control group for 7 days. In the intervention arm, the index case had to wear a surgical mask from the medical visit and for a period of 5 days. The trial was initially intended to include 372 households, but was prematurely interrupted after the inclusion of 105 households (306 contacts) following the advice of an independent steering committee. Generalised estimating equations were used to test the association between the intervention and the proportion of household contacts who developed an ILI during the 7 days following the inclusion.
Participants	A total of 105 households were randomised, which represented 148 contacts in the intervention arm and 158 in the control arm. The study was conducted in 3 French regions (Ile de France, Aquitaine, and Franche-Comté) and included households of size 3 to 8. Exclusion criteria: if index patient was treated for asthma or chronic obstructive pulmonary disease or was hospitalised
Interventions	Surgical mask versus no mask. See Table 1 for details.
Outcomes	The primary endpoint was the proportion of household contacts who developed an ILI during the 7 days following inclusion. Exploratory cluster-level efficacy outcome, the proportion of households with 1 or more secondary illness in household contacts.

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Canini 2010 *(Continued)*

	A temperature over 37.8 °C with cough or sore throat was used as primary clinical case definition. Adverse reactions due to mask-wearing
Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation lists were generated by a computerised program.
Allocation concealment (selection bias)	Low risk	Randomisation was performed centrally by the GP after written consent on an interactive voice response system dedicated to the study.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All households included in analysis.
Selective reporting (reporting bias)	Low risk	All specified outcomes reported.

Canini 2010

Study characteristics

Methods	A cluster-RCT conducted in France during the 2008 to 2009 influenza season. Households were recruited during a medical visit of a household member with a positive rapid influenza A test and symptoms lasting less than 48 hours. Households were randomised either to the mask or control group for 7 days. In the intervention arm, the index case had to wear a surgical mask from the medical visit and for a period of 5 days. The trial was initially intended to include 372 households, but was prematurely interrupted after the inclusion of 105 households (306 contacts) following the advice of an independent steering committee. Generalised estimating equations were used to test the association between the intervention and the proportion of household contacts who developed an ILI during the 7 days following the inclusion.
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Interventions	Surgical mask versus no mask. See Table 1 for details.

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Canini 2010 *(Continued)*

Outcomes	The primary endpoint was the proportion of household contacts who developed an ILI during the 7 days following inclusion. Exploratory cluster-level efficacy outcome, the proportion of households with 1 or more secondary illness in household contacts. A temperature over 37.8 °C with cough or sore throat was used as primary clinical case definition. Adverse reactions due to mask-wearing
Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation lists were generated by a computerised program.
Allocation concealment (selection bias)	Low risk	Randomisation was performed centrally by the GP after written consent on an interactive voice response system dedicated to the study.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All households included in analysis.
Selective reporting (reporting bias)	Low risk	All specified outcomes reported.

Carabin 1999

Study characteristics

Methods	Cluster-RCT carried out in DCCs in the Canadian province of Quebec between 1 September 1996 and 30 November 1997 (15 months). The aim was to test the effects of a hygiene programme on the incidence of diarrhoea and fecal contamination (data not extracted) and on colds and URTIs. The design included before and after periods analysed to assess the Hawthorne effect of study participation on control DCCs. The unit of randomisation was DCC, but analysis was also carried out at classroom and single-child level. This is a common mistake in cluster-RCT analysis. DCCs were stratified by URTI incidence preceding the trial and randomised by location. Cluster coefficients are not reported.
Participants	A total of 1729 children aged 18 to 36 months in 47 DCCs (83 toddler classrooms) Inclusion criteria: presence of at least 1 sandbox and 1 play area and of at least 12 available toddler places For the autumn of 1997 intervention group (24 DCCs, 43 classrooms, and 414 children), control group (23 DCCs, 23 classrooms, and 374 children). It is not clear what is the distribution and data for the autumn of 1996.

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Carabin 1999 *(Continued)*

Interventions	Training session (1 day) with washing of hands, toy cleaning, window opening, sand pit cleaning, and repeated exhortations to hand wash
Outcomes	Laboratory: N/A Effectiveness: diarrhoea and coliform contamination (data not extracted) Colds (nasal discharge with at least 1 of the following: fever, sneezing, cough, sore throat, earache, malaise, irritability) URTI (cold of at least 2 days' duration) Surveillance was carried out by educators, annotating absences or illness on calendars. Researchers also filled in a phone questionnaire with answers by DCC directors. Safety: N/A
Notes	Risk of bias: high (no description of randomisation; partial reporting of outcomes, numerators, and denominators) Notes: the authors conclude that the intervention reduced the incidence of colds (IRR 0.80, 95% CI 0.68 to 0.93). This was a confusingly written study with unclear interweaving of 2 study designs. For unclear reasons analysis was only carried out for the first autumn. Unclear why colds are not reported in the results. Cluster-coefficients and randomisation process were not described.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Block randomisation of DCC according to region, but sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not possible (hygiene session plus educational material versus none)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Originally 52 eligible DCCs with 89 classrooms agreed to take part, but 5 dropped out (2 closed, 1 was sold, 2 either did not provide data or the data were "unreliable", and 6 classrooms had insufficient data). 43 children failing to attend DCC for at least 5 days in the autumn were also excluded. ITT analysis was carried out including an additional DCC whose director refused to let staff attend the training session. No correction made for clustering.
Selective reporting (reporting bias)	High risk	Denominators unclear and not explained

Chard 2019

Study characteristics

Methods	Cluster-RCT conducted amongst 100 randomly selected primary schools lacking functional WASH facilities in Saravane Province, Lao People's Democratic Republic. Schools were randomly assigned to either

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Chard 2019 *(Continued)*

	the intervention (n = 50) or comparison (n = 50) arm. Intervention schools received a school water supply, sanitation facilities, hand-washing facilities, drinking water filters, and behaviour change education and promotion. Comparison schools received the intervention after research activities had ended. At unannounced visits every 6 to 8 weeks, enumerators recorded pupils' roll-call absence, enrolment, attrition, progression to the next grade, and reported illness (diarrhoea, respiratory infection, conjunctivitis), and conducted structured observations to measure intervention fidelity and adherence. Stool samples were collected annually prior to de-worming and analysed for soil-transmitted helminth (STH) infection. In addition to our primary ITT analysis, we conducted secondary analyses to quantify the role of intervention fidelity and adherence on project impacts.
Participants	100 primary schools (50 intervention, 50 comparison) with a total of 3993 pupils were enrolled throughout the study period (intervention schools = 2021 pupils, control schools = 1972 pupils). Up to 40 pupils selected from grades 3 to 5 in each school using systematic stratified sampling, with grade and sex as the stratification variables. Pupils selected at baseline were followed throughout the entire study period; pupils who left the school due to abandonment or transfer were replaced at the beginning of the following academic year, maintaining equal grade and sex ratios when possible. Pupils who progressed from fifth to the sixth grade were replaced with pupils from grade 3 the following academic year.
Interventions	Water supply, sanitation facilities, hand-washing facilities, drinking water filters, and behaviour change education and promotion versus control. See Table 1 for details.
Outcomes	Primary impact of interest was pupil absence, measured by school-wide roll-call at each visit. Secondary health impacts included diarrhoea, symptoms of respiratory infection, and conjunctivitis/non-vision-related eye illness collected through pupil interviews. Pupils were considered to have symptoms of respiratory infection if they reported cough, runny nose, stuffy nose, or sore throat. No safety outcomes reported.
Notes	Funded by government and pharmaceutical industry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details provided.
Allocation concealment (selection bias)	Low risk	Schools allocated prior to recruitment of individuals.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions were due to participants leaving school, hence unlikely to cause bias.
Selective reporting (reporting bias)	Low risk	All specified outcomes reported.

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Carabin 1999

Study characteristics	
Methods	Cluster-RCT carried out in DCCs in the Canadian province of Quebec between 1 September 1996 and 30 November 1997 (15 months). The aim was to test the effects of a hygiene programme on the incidence of diarrhoea and fecal contamination (data not extracted) and on colds and URTIs. The design included before and after periods analysed to assess the Hawthorne effect of study participation on control DCCs. The unit of randomisation was DCC, but analysis was also carried out at classroom and single-child level. This is a common mistake in cluster-RCT analysis. DCCs were stratified by URTI incidence preceding the trial and randomised by location. Cluster coefficients are not reported.
Participants	A total of 1729 children aged 18 to 36 months in 47 DCCs (83 toddler classrooms) Inclusion criteria: presence of at least 1 sandbox and 1 play area and of at least 12 available toddler places For the autumn of 1997 intervention group (24 DCCs, 43 classrooms, and 414 children), control group (23 DCCs, 23 classrooms, and 374 children). It is not clear what is the distribution and data for the autumn of 1996.
Interventions	Training session (1 day) with washing of hands, toy cleaning, window opening, sand pit cleaning, and repeated exhortations to hand wash
Outcomes	Laboratory: N/A Effectiveness: diarrhoea and coliform contamination (data not extracted) Colds (nasal discharge with at least 1 of the following: fever, sneezing, cough, sore throat, earache, malaise, irritability) URTI (cold of at least 2 days' duration) Surveillance was carried out by educators, annotating absences or illness on calendars. Researchers also filled in a phone questionnaire with answers by DCC directors. Safety: N/A
Notes	Risk of bias: high (no description of randomisation; partial reporting of outcomes, numerators, and denominators) Notes: the authors conclude that the intervention reduced the incidence of colds (IRR 0.80, 95% CI 0.68 to 0.93). This was a confusingly written study with unclear interweaving of 2 study designs. For unclear reasons analysis was only carried out for the first autumn. Unclear why colds are not reported in the results. Cluster-coefficients and randomisation process were not described.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Block randomisation of DCC according to region, but sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not possible (hygiene session plus educational material versus none)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded

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Carabin 1999 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Originally 52 eligible DCCs with 89 classrooms agreed to take part, but 5 dropped out (2 closed, 1 was sold, 2 either did not provide data or the data were "unreliable", and 6 classrooms had insufficient data). 43 children failing to attend DCC for at least 5 days in the autumn were also excluded. ITT analysis was carried out including an additional DCC whose director refused to let staff attend the training session. No correction made for clustering.
Selective reporting (reporting bias)	High risk	Denominators unclear and not explained

Chard 2019

Study characteristics	
Methods	Cluster-RCT conducted amongst 100 randomly selected primary schools lacking functional WASH facilities in Saravane Province, Lao People's Democratic Republic. Schools were randomly assigned to either the intervention (n = 50) or comparison (n = 50) arm. Intervention schools received a school water supply, sanitation facilities, hand-washing facilities, drinking water filters, and behaviour change education and promotion. Comparison schools received the intervention after research activities had ended. At unannounced visits every 6 to 8 weeks, enumerators recorded pupils' roll-call absence, enrolment, attrition, progression to the next grade, and reported illness (diarrhoea, respiratory infection, conjunctivitis), and conducted structured observations to measure intervention fidelity and adherence. Stool samples were collected annually prior to de-worming and analysed for soil-transmitted helminth (STH) infection. In addition to our primary ITT analysis, we conducted secondary analyses to quantify the role of intervention fidelity and adherence on project impacts.
Participants	100 primary schools (50 intervention, 50 comparison) with a total of 3993 pupils were enrolled throughout the study period (intervention schools = 2021 pupils, control schools = 1972 pupils). Up to 40 pupils selected from grades 3 to 5 in each school using systematic stratified sampling, with grade and sex as the stratification variables. Pupils selected at baseline were followed throughout the entire study period; pupils who left the school due to abandonment or transfer were replaced at the beginning of the following academic year, maintaining equal grade and sex ratios when possible. Pupils who progressed from fifth to the sixth grade were replaced with pupils from grade 3 the following academic year.
Interventions	Water supply, sanitation facilities, hand-washing facilities, drinking water filters, and behaviour change education and promotion versus control. See Table 1 for details.
Outcomes	Primary impact of interest was pupil absence, measured by school-wide roll-call at each visit. Secondary health impacts included diarrhoea, symptoms of respiratory infection, and conjunctivitis/non-vision-related eye illness collected through pupil interviews. Pupils were considered to have symptoms of respiratory infection if they reported cough, runny nose, stuffy nose, or sore throat. No safety outcomes reported.
Notes	Funded by government and pharmaceutical industry
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details provided.

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Chard 2019 *(Continued)*

Allocation concealment (selection bias)	Low risk	Schools allocated prior to recruitment of individuals.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions were due to participants leaving school, hence unlikely to cause bias.
Selective reporting (reporting bias)	Low risk	All specified outcomes reported.

Correa 2012

Study characteristics	
Methods	Cluster-RCT in childcare facilities in Colombia from 16 April to 18 December 2008 (3 school terms) testing the effects of hand hygiene using an alcohol-based hand rub versus standard practice
Participants	42 childcare facilities in 6 towns in Colombia. A total of 1727 were enrolled (intervention group = 794 from 21 centres, control group = 933 from 21 centres). Inclusion criteria: licensed to care for 12 or more children aged 1 to 5 years for 8 hours a day, 5 times per week, and where availability of tap water was limited
Interventions	Intervention: alcohol-based hand wash as an addition to hand-washing Control: usual hand-washing practice See Table 1 for details.
Outcomes	ARI defined as: 2 or more of the following symptoms for at least 24 hours, lasting at least 2 days: runny, stuffy, or blocked nose or noisy breathing; cough; fever, hot sensation, or chills; and/or sore throat. Ear pain alone was considered an ARI.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...using the random function in Microsoft Excel™ (Microsoft Corp., Redmond, Washington, United States), random numbers (1 or 2) were generated and allotted 1:1 within each group. Finally, a researcher flipped a coin to decide which number would correspond to either arm (heads = 1, intervention; tails = 2, control)."
Allocation concealment (selection bias)	Unclear risk	Method not described

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Correa 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up similar in each group and not substantial
Selective reporting (reporting bias)	Unclear risk	No protocol available

Cowling 2008

Study characteristics	
Methods	Cluster-RCT carried out in Hong Kong SARS between February and September 2007. The study assessed the effects of non-pharmaceutical interventions on the household transmission of influenza over a 9-day period. ILI cases whose family contacts had been symptom-free for at least 2 weeks rapid-tested for influenza A and B were used and randomised to 3 interventions. Randomisation was carried out in 2 different schedules (2:1:1 for the first 100 households, and subsequently 8:1:1), but it is unclear why and how this was done.
Participants	A total of 350 of 944 originally enrolled participants representing 122 households were analysed (control group = 71 households with 205 household contacts, face mask = 21 households with 61 household contacts, HH = 30 households with 84 household contacts). Inclusion criteria: residents of Hong Kong aged at least 2 years, reporting at least 2 symptoms of ILI ((such as fever ≥ 38 degrees, cough, headache, coryza, sore throat, muscle aches and pains) and positive influenza A+B rapid test and living in a household with at least 2 other individuals, none of whom had ILI in the preceding 14 days Households were excluded because subsequent laboratory testing (culture) was negative. Attrition was not explained.
Interventions	Households were randomised to either wearing face masks with education (as the control group plus education about face mask use) or hand-washing with special medicated soap (with alcohol sanitiser) with education (as the control group plus education about hand-washing) or education about general healthy lifestyle and diet (control group). The soap was distributed in special containers that were weighed at the start and end of the study. Interventions visits to the households were done on average 1 day after randomisation of index case household.
Outcomes	Laboratory: QuickVue RTI MDCK culture Samples were harvested using NTS, but the text refers to a second procedure from June 2007 onwards testing for non-influenza viruses, with no data reported. Effectiveness: secondary attack ratios (SAR): SAR is the proportion of household contacts of an index case who were subsequently ill with influenza (symptomatic contact individuals with at least 1 NTS positive for influenza by viral culture or PCR)

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Cowling 2008 *(Continued)*

	3 clinical definitions were used for secondary analysis: 1. Fever ≥ 38 degrees, or at least 2 of following symptoms: headache, coryza, sore throat, muscle aches and pains 2. At least 2 of the following S/S: fever ≥ 37.8 degrees, cough, headache, sore throat, muscle aches and pains 3. Fever ≥ 37.8 degrees plus cough or sore throat Safety: no harms were reported in any of the arms
Notes	The trial authors conclude that "The secondary attack ratios were lower than anticipated, and lower than reported in other countries, perhaps due to differing patterns of susceptibility, lack of significant antigenic drift in circulating influenza virus strains recently, and/or issues related to the symptomatic recruitment design. Lessons learnt from this pilot have informed changes for the main study in 2008". Although billed as a pilot study, the text is highly confusing and at times contradictory. The intervention was delivered at a home visit up to 36 hours after the index case was seen in the outpatients. This is a long time and perhaps the reason for failure of the intervention. Practically, the intervention will have to be organised before even seeking medical care, i.e. people know to do it when the child gets sick at home.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer generated by a biostatistician. "A pre-specified table of random numbers will be used to assign one of the three interventions to the household of the index case."
Allocation concealment (selection bias)	Low risk	The households of eligible study index patients were allocated to 3 groups in a 1:1:1 ratio under a block randomisation structure with randomly permuted block sizes of 18, 24, and 30 using a random-number generator. Allocation was concealed from treating physicians and clinics and implemented by study nurses at the time of the initial household visit.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and people who administered the interventions were not blinded to the interventions, but participants were not informed of the specific nature of the interventions applied to other participating households.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was accounted for. Dropout from the randomised population was high: 32% in control group, 37.5% in hand hygiene group, and 39.4% in face mask and hand hygiene group. Reasons for dropout were distributed evenly across the 3 groups. Authors report follow-up as proportion of patients remaining in the study after initial dropout.
Selective reporting (reporting bias)	High risk	The choice of season, change in randomisation schedules, and unexplained dropouts amongst contacts; the use of QuickVue, which proved unreliable, reporting bias on non-influenza isolates resulted in a judgement of high risk of bias.

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Cowling 2009

Study characteristics	
Methods	Cluster-RCT
Participants	A total of 407 index cases and 794 household contacts were analysed. Of 407 enrolled households, 322 received the allocated interventions as follows: 1. control group = 112 households with 346 contacts (only 91 households analysed with 279 contacts); 2. hand hygiene = 106 households with 329 contacts (only 85 households analysed with 257 contacts); 3. face mask + hand hygiene = 104 households with 340 contacts (only 83 households analysed with 258 contacts). Inclusion criteria: households in Hong Kong. Index cases from 45 outpatient clinics in both the private and public sectors across Hong Kong. They enrolled individuals who reported at least 2 symptoms of ARI (temperature 37.8 °C, cough, headache, sore throat, or myalgia); had symptom onset within 48 hours; and lived in a household with at least 2 other people, none of whom had reported ARI in the preceding 14 days. After giving informed consent, participants provided nasal and throat swab specimens. 2750 patients were eligible and tested between 2 January and 30 September 2008.
Interventions	Participants with a positive rapid-test result and their household contacts were randomly assigned to 1 of 3 study groups: control (lifestyle measures - 134 households), control plus enhanced hand hygiene only (136 households), and control plus face masks and enhanced hand hygiene (137 households) for all household members. No detailed description of the instructions was given to participants.
Outcomes	Influenza virus infection in household contacts, as confirmed by RT-PCR or diagnosed clinically after 7 days "The primary outcome measure was the secondary attack ratio at the individual level: that is, the proportion of household contacts infected with influenza virus. We evaluated the secondary attack ratio using a laboratory definition (a household contact with a nose and throat swab specimen positive for influenza by RT-PCR) as the primary analysis and 2 secondary clinical definitions of influenza based on self-reported data from the symptom diaries as secondary analyses." Statistical analysis: adjusted for clustering Results: no statistically significant difference in secondary attack ratio between groups in total population. Statistically significant reduction in RT-PCR confirmed influenza virus infections in the household contacts in 154 households in which the intervention was applied within 36 hours of symptom onset in the index patient. Adherence to hand hygiene was between 44% and 62%. Adherence of index patient to wearing a face mask between 15% and 49%.
Notes	"In an unintentional deviation from that protocol, 49 of the 407 randomly allocated persons had a household contact with influenza symptoms at recruitment (a potential co-index patient). We also randomly assigned 6 of 407 persons who had symptoms for slightly more than 48 hours." The trial authors conclude that "Hand hygiene and face masks seemed to prevent household transmission of influenza virus when implemented within 36 hours of index patient symptom onset. These findings suggest that non-pharmaceutical interventions are important for mitigation of pandemic and interpandemic influenza".

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was computer generated by a biostatistician. "A pre-specified table of random numbers will be used to assign one of the three interventions to the household of the index case."

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Cowling 2009 *(Continued)*

Allocation concealment (selection bias)	Low risk	The households of eligible study index patients were allocated to 3 groups in a 1:1:1 ratio under a block randomisation structure with randomly permuted block sizes of 18, 24, and 30 using a random-number generator. Allocation was concealed from treating physicians and clinics and implemented by study nurses at the time of the initial household visit.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Participants and personnel administering the interventions were not blinded to group assignment."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not stated if the outcome assessor was blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was accounted for. Dropout from the randomised population was high: 32% in control group, 37.5% in hand hygiene group, and 39.4% in face mask and hand hygiene group. Reasons for dropout were distributed evenly across the 3 groups. Trial authors report follow-up as proportion of patients remaining in the study after initial dropout.
Selective reporting (reporting bias)	Unclear risk	In general good reporting

DiVita 2011

Study characteristics	
Methods	The impact of hand-washing promotion on the risk of household transmission of influenza, ILI, and fever was tested in rural Bangladesh. ILI was defined as fever in children < 5 years old and fever with cough or sore throat in individuals > 5 years old. Households were randomised to intervention or control. The intervention group received hand-washing stations with soap and daily hand-washing motivation at critical times for pathogen transmission, such as after coughing or sneezing. Daily surveillance was conducted, and household members with fever were tested for influenza viruses by PCR. Secondary attack ratios (SAR) were calculated for influenza, ILI, and fever in each arm. Logistic regression with generalised estimating equations was used to estimate the significance of the SAR comparison whilst controlling for clustering by household.
Participants	The study included 233 patient index cases (intervention group = 100, control group 133) with 2540 household contacts (intervention group = 134, control group = 1226). Inclusion criteria: index case patients (individuals who developed ILI within the previous 2 days and were the only symptomatic person in their household) as well as their household contacts
Interventions	Hand-washing stations with soap and daily hand-washing motivation versus control. See Table 1 for details.
Outcomes	SAR were calculated for influenza, ILI, and fever. ILI was defined as fever in children < 5 years old and fever with cough or sore throat in individuals > 5 years old. No safety outcomes reported.
Notes	Funding source unknown

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DiVita 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details provided
Allocation concealment (selection bias)	Unclear risk	Insufficient details provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details provided
Selective reporting (reporting bias)	Unclear risk	Insufficient details provided

Cowling 2008

Study characteristics	
Methods	Cluster-RCT carried out in Hong Kong SARS between February and September 2007. The study assessed the effects of non-pharmaceutical interventions on the household transmission of influenza over a 9-day period. ILI cases whose family contacts had been symptom-free for at least 2 weeks rapid-tested for influenza A and B were used and randomised to 3 interventions. Randomisation was carried out in 2 different schedules (2:1:1 for the first 100 households, and subsequently 8:1:1), but it is unclear why and how this was done.
Participants	A total of 350 of 944 originally enrolled participants representing 122 households were analysed (control group = 71 households with 205 household contacts, face mask = 21 households with 61 household contacts, HH = 30 households with 84 household contacts). Inclusion criteria: residents of Hong Kong aged at least 2 years, reporting at least 2 symptoms of ILI ((such as fever ≥ 38 degrees, cough, headache, coryza, sore throat, muscle aches and pains) and positive influenza A+B rapid test and living in a household with at least 2 other individuals, none of whom had ILI in the preceding 14 days Households were excluded because subsequent laboratory testing (culture) was negative. Attrition was not explained.
Interventions	Households were randomised to either wearing face masks with education (as the control group plus education about face mask use) or hand-washing with special medicated soap (with alcohol sanitiser) with education (as the control group plus education about hand-washing) or education about general healthy lifestyle and diet (control group). The soap was distributed in special containers that were

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Cowling 2008 *(Continued)*

	weighed at the start and end of the study. Interventions visits to the households were done on average 1 day after randomisation of index case household.
Outcomes	Laboratory: QuickVue RTI MDCK culture Samples were harvested using NTS, but the text refers to a second procedure from June 2007 onwards testing for non-influenza viruses, with no data reported. Effectiveness: secondary attack ratios (SAR): SAR is the proportion of household contacts of an index case who were subsequently ill with influenza (symptomatic contact individuals with at least 1 NTS positive for influenza by viral culture or PCR) 3 clinical definitions were used for secondary analysis: 1. Fever ≥ 38 degrees, or at least 2 of following symptoms: headache, coryza, sore throat, muscle aches and pains 2. At least 2 of the following S/S: fever ≥ 37.8 degrees, cough, headache, sore throat, muscle aches and pains 3. Fever ≥ 37.8 degrees plus cough or sore throat Safety: no harms were reported in any of the arms
Notes	The trial authors conclude that “The secondary attack ratios were lower than anticipated, and lower than reported in other countries, perhaps due to differing patterns of susceptibility, lack of significant antigenic drift in circulating influenza virus strains recently, and/or issues related to the symptomatic recruitment design. Lessons learnt from this pilot have informed changes for the main study in 2008”. Although billed as a pilot study, the text is highly confusing and at times contradictory. The intervention was delivered at a home visit up to 36 hours after the index case was seen in the outpatients. This is a long time and perhaps the reason for failure of the intervention. Practically, the intervention will have to be organised before even seeking medical care, i.e. people know to do it when the child gets sick at home.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer generated by a biostatistician. "A pre-specified table of random numbers will be used to assign one of the three interventions to the household of the index case."
Allocation concealment (selection bias)	Low risk	The households of eligible study index patients were allocated to 3 groups in a 1:1:1 ratio under a block randomisation structure with randomly permuted block sizes of 18, 24, and 30 using a random-number generator. Allocation was concealed from treating physicians and clinics and implemented by study nurses at the time of the initial household visit.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and people who administered the interventions were not blinded to the interventions, but participants were not informed of the specific nature of the interventions applied to other participating households.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was accounted for. Dropout from the randomised population was high: 32% in control group, 37.5% in hand hygiene group, and 39.4% in face

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Cowling 2008 *(Continued)*

		mask and hand hygiene group. Reasons for dropout were distributed evenly across the 3 groups. Authors report follow-up as proportion of patients remaining in the study after initial dropout.
Selective reporting (reporting bias)	High risk	The choice of season, change in randomisation schedules, and unexplained dropouts amongst contacts; the use of QuickVue, which proved unreliable, reporting bias on non-influenza isolates resulted in a judgement of high risk of bias.

Cowling 2009

Study characteristics	
Methods	Cluster-RCT
Participants	A total of 407 index cases and 794 household contacts were analysed. Of 407 enrolled households, 322 received the allocated interventions as follows: 1. control group = 112 households with 346 contacts (only 91 households analysed with 279 contacts); 2. hand hygiene = 106 households with 329 contacts (only 85 households analysed with 257 contacts); 3. face mask + hand hygiene = 104 households with 340 contacts (only 83 households analysed with 258 contacts). Inclusion criteria: households in Hong Kong. Index cases from 45 outpatient clinics in both the private and public sectors across Hong Kong. They enrolled individuals who reported at least 2 symptoms of ARI (temperature 37.8 °C, cough, headache, sore throat, or myalgia); had symptom onset within 48 hours; and lived in a household with at least 2 other people, none of whom had reported ARI in the preceding 14 days. After giving informed consent, participants provided nasal and throat swab specimens. 2750 patients were eligible and tested between 2 January and 30 September 2008.
Interventions	Participants with a positive rapid-test result and their household contacts were randomly assigned to 1 of 3 study groups: control (lifestyle measures - 134 households), control plus enhanced hand hygiene only (136 households), and control plus face masks and enhanced hand hygiene (137 households) for all household members. No detailed description of the instructions was given to participants.
Outcomes	Influenza virus infection in household contacts, as confirmed by RT-PCR or diagnosed clinically after 7 days "The primary outcome measure was the secondary attack ratio at the individual level: that is, the proportion of household contacts infected with influenza virus. We evaluated the secondary attack ratio using a laboratory definition (a household contact with a nose and throat swab specimen positive for influenza by RT-PCR) as the primary analysis and 2 secondary clinical definitions of influenza based on self-reported data from the symptom diaries as secondary analyses." Statistical analysis: adjusted for clustering Results: no statistically significant difference in secondary attack ratio between groups in total population. Statistically significant reduction in RT-PCR confirmed influenza virus infections in the household contacts in 154 households in which the intervention was applied within 36 hours of symptom onset in the index patient. Adherence to hand hygiene was between 44% and 62%. Adherence of index patient to wearing a face mask between 15% and 49%.
Notes	"In an unintentional deviation from that protocol, 49 of the 407 randomly allocated persons had a household contact with influenza symptoms at recruitment (a potential co-index patient). We also randomly assigned 6 of 407 persons who had symptoms for slightly more than 48 hours."

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Cowling 2009 *(Continued)*

The trial authors conclude that "Hand hygiene and face masks seemed to prevent household transmission of influenza virus when implemented within 36 hours of index patient symptom onset. These findings suggest that non-pharmaceutical interventions are important for mitigation of pandemic and interpandemic influenza".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer generated by a biostatistician. "A pre-specified table of random numbers will be used to assign one of the three interventions to the household of the index case."
Allocation concealment (selection bias)	Low risk	The households of eligible study index patients were allocated to 3 groups in a 1:1:1 ratio under a block randomisation structure with randomly permuted block sizes of 18, 24, and 30 using a random-number generator. Allocation was concealed from treating physicians and clinics and implemented by study nurses at the time of the initial household visit.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Participants and personnel administering the interventions were not blinded to group assignment."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not stated if the outcome assessor was blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was accounted for. Dropout from the randomised population was high: 32% in control group, 37.5% in hand hygiene group, and 39.4% in face mask and hand hygiene group. Reasons for dropout were distributed evenly across the 3 groups. Trial authors report follow-up as proportion of patients remaining in the study after initial dropout.
Selective reporting (reporting bias)	Unclear risk	In general good reporting

DiVita 2011

Study characteristics

Methods	The impact of hand-washing promotion on the risk of household transmission of influenza, ILI, and fever was tested in rural Bangladesh. ILI was defined as fever in children < 5 years old and fever with cough or sore throat in individuals > 5 years old. Households were randomised to intervention or control. The intervention group received hand-washing stations with soap and daily hand-washing motivation at critical times for pathogen transmission, such as after coughing or sneezing. Daily surveillance was conducted, and household members with fever were tested for influenza viruses by PCR. Secondary attack ratios (SAR) were calculated for influenza, ILI, and fever in each arm. Logistic regression with generalised estimating equations was used to estimate the significance of the SAR comparison whilst controlling for clustering by household.
Participants	The study included 233 patient index cases (intervention group = 100, control group 133) with 2540 household contacts (intervention group = 134, control group = 1226).

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DiVita 2011 *(Continued)*

	Inclusion criteria: index case patients (individuals who developed ILI within the previous 2 days and were the only symptomatic person in their household) as well as their household contacts
Interventions	Hand-washing stations with soap and daily hand-washing motivation versus control. See Table 1 for details.
Outcomes	SAR were calculated for influenza, ILI, and fever. ILI was defined as fever in children < 5 years old and fever with cough or sore throat in individuals > 5 years old. No safety outcomes reported.
Notes	Funding source unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details provided
Allocation concealment (selection bias)	Unclear risk	Insufficient details provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details provided
Selective reporting (reporting bias)	Unclear risk	Insufficient details provided

Farr 1988a

Study characteristics

Methods	6-month cluster-RCT, controlled, double-blind of the efficacy of virucidal nasal tissues in the prevention of natural cold, conducted in Charlottesville, Virginia, USA. Many of the families were enrolled because 1 or more family members worked at the State Farm Insurance Company; the remaining families were recruited from the Charlottesville community by advertisement in a local newspaper. Families were randomly assigned by the sponsoring company to receive boxes of treated tissues, placebo tissues, or no tissues. The randomisation was performed by computer. Study participants and investigators were unaware of the type of tissues each family was randomised to receive. Blinding efficacy was tested using a questionnaire: the mothers in each family were asked twice if she believed her family was using virucidal or placebo tissues. Participants in the treated and placebo groups were instructed to use only tissues received through the study, whilst families in the additional control group without tissues were allowed to continue their

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Farr 1988a *(Continued)*

	usual practice of personal hygiene. Each family member kept a daily listing of respiratory symptoms on a record card. A nurse epidemiologist visited each family monthly to encourage recording.
Participants	186 families, 58 in the active group, 59 in the placebo group, and 69 in the no-tissues group. A total of 302 families were originally recruited; 116 families who did not comply with the study protocol, lost their surveillance cards, could not complete the protocol were excluded from the analysis.
Interventions	Use of virucidal tissues versus placebo tissues versus no tissues. The treated tissues were impregnated with malic and citric acids and sodium lauryl sulphate, whilst placebo tissues contained saccharin.
Outcomes	Laboratory: serological evidence: no Effectiveness: respiratory illness Safety: N/A
Notes	The authors concluded that virucidal tissues have only a small impact on the overall rate of natural acute respiratory illnesses. The total illness rate was lower in families using virucidal tissues than in both of the other study groups, but only the difference between active and placebo groups was statistically significant (3.4 illness per person versus 3.9 for placebo group, P = 0.04, and 3.6 for the no-tissue control group, P = 0.2, and overall 14% to 5% reduction). The questionnaire results suggest that some bias may have been present since a majority of mothers in the virucide group believed they were receiving the 'active' tissues. Another possible explanation of the low effectiveness of virucidal tissues is poor compliance by children in use of the virucidal tissues. A well-designed and honestly reported study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The randomisation was performed by computer in each trial." However, method of sequence generation is not stated.
Allocation concealment (selection bias)	Unclear risk	"In trial I, families were randomly assigned by the sponsoring company to receive boxes of treated tissues, placebo tissues or no tissues." "Families with one or two children were randomised in one stratum, and families with three or more children were randomised in a second stratum in trial I." Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Study participants and investigators were unaware of the type of tissues which each family was randomised to receive in both trials. In trial I, the mother in each family was asked twice if she believed her family was using active or placebo tissues, first after three months and then at the end of the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Study participants and investigators were unaware of the type of tissues which each family was randomised to receive in both trials. In trial I, the mother in each family was asked twice if she believed her family was using active or placebo tissues, first after three months and then at the end of the study."
Incomplete outcome data (attrition bias) All outcomes	High risk	"A total of 116 of the 302 families were excluded from the analysis. Families were excluded if they lost their surveillance cards or did not conscientiously record data, did not comply with the study protocol, or simply could not complete the protocol for family reasons. It was discovered that families with five or more members had so many colds that it was not possible to distinguish primary and secondary illnesses. These large families were therefore excluded from the analysis in trial I and were excluded from enrolment in trial II."

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Farr 1988a *(Continued)*

Selective reporting (reporting bias)	Low risk	All indicated outcomes are reported.

Farr 1988b

Study characteristics	
Methods	6-month randomised, controlled, double-blind trial of the efficacy of virucidal nasal tissues in the prevention of natural cold, conducted in Charlottesville, Virginia, USA. Families were recruited from the Charlottesville community by advertisement in a local newspaper. Families were randomly assigned by the sponsoring company to receive either virucidal tissues or placebo-treated tissues. Stratified randomisation was performed by computer, and the strata were defined by total number in the family. Study participants and investigators were unaware of the type of tissues each family was randomised to receive. Each family member kept a daily listing of respiratory symptoms on a record card. A nurse epidemiologist visited each family monthly to encourage recording. In addition, a study monitor visited each family bimonthly to further encourage compliance and reporting of symptoms.
Participants	98 families, 58 in the active group and 40 in the placebo group. 231 families were initially recruited, 222 completed the trial, data of 98 families were analysed. The other families were excluded from the analysis because they complained of side effects (sneezing, etc.) or reported not using the tissues regularly.
Interventions	Use of virucidal tissues versus placebo tissues. The treated tissues were impregnated with malic and citric acids and sodium lauryl sulphate, whilst the placebo tissues contained succinic acid. Participants in the treated and placebo groups were instructed to only use tissues received through the study.
Outcomes	Laboratory: serological evidence: no Effectiveness: respiratory illness Safety: N/A
Notes	The study suggests that virucidal tissues have only a small impact on the overall rate of natural acute respiratory illnesses. The total illness rate was lower in families using virucidal tissues than in the other study group, but the difference between active and placebo groups was not statistically significant. There was a small, non-significant drop in illness rates across families (5%). The tissues appeared to be ineffective as the drop was confined to primary illness unaffected by tissue use. The placebo (succinic acid) was not inert, and was associated with cough and nasal burning. This impacted on allocation concealment. A well-designed and honestly reported study marred by transparent allocation

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The randomisation was performed by computer in each trial." However, method of sequence generation is not stated.
Allocation concealment (selection bias)	Unclear risk	"In trial II, families were randomly assigned by the sponsor to receive either virucidal tissues or placebo treated tissues." "In trial II, stratified randomisation was again used, but this time the strata were defined by total number in the family (i.e., one stratum for two-member families, another stratum for three-member families, and a final one for four-member families)." Concealment of allocation not described

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Farr 1988b *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Study participants and investigators were unaware of the type of tissues which each family was randomised to receive in both trials."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Study participants and investigators were unaware of the type of tissues which each family was randomised to receive in both trials."
Incomplete outcome data (attrition bias) All outcomes	High risk	"A total of 222 (of 231) families completed trial II; 9 families were terminated early (table 1). In 124 families, one or more family members reported not using the tissues regularly and/or reported having significant side effects. The data from these families were not analysed, leaving 58 families (177 persons) and 40 families (114 persons) for analysis in the virucide and placebo groups, respectively."
Selective reporting (reporting bias)	Low risk	All indicated outcomes are reported.

Feldman 2016

Study characteristics	
Methods	Prospective cluster-RCT. Ships from a single, central naval base. Ships were stratified by vessel classes (corvette, fast missile boat, and patrol boat).
Participants	All people participating in security operations, routine exercises, and patrol at a single, central naval base were eligible. The actual number of participants in the groups is not reported.
Interventions	Chlorhexidine gluconate (CHG) dispensers in addition to soap-and-water hand-washing versus soap-and-water hand-washing. See Table 1 for details.
Outcomes	Laboratory: bacterial palm cultures from 30 sailors from each group using a modified bag broth technique with sterile brain-heart broth, at 0 and 4 months (sample participants) Effectiveness: Primary outcome: incidence of infectious diseases reported by the computerised patient records system using ICD-9 diagnoses and grouped into diarrhoeal, respiratory, and skin infections; the number of sick call visits; and the number of sick leave and light-duty days incurred by the sailors Secondary outcome: subclinical morbidity (i.e. symptoms of self-reported infectious diseases) Safety: not reported
Notes	No report on adherence Funding: governmental (Israeli Defense Force Medical Corps) Study was conducted between May and September 2014 (4 months follow-up). CHG availability onboard the ships did not reduce the transmission of infectious diseases or colonisation.
Risk of bias	

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Feldman 2016 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of randomisation
Allocation concealment (selection bias)	Unclear risk	No description of allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded. Self-reported outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information if personnel collecting data for ICD-9 diagnosis were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No participants flow chart, no attrition data
Selective reporting (reporting bias)	Unclear risk	No protocol to compare

Goodall 2014

Study characteristics	
Methods	A 2X2 factorial RCT with 4 treatment arms: 1. Vitamin D_3 and gargling 2. Placebo and gargling 3. Vitamin D_3 and no gargling 4. Placebo and no gargling
Participants	600 students from McMaster University, Hamilton, Ontario, Canada, randomised to the following: 1. Vitamin D and gargling (N = 150, analysed 135) 2. Vitamin D and no gargling (N = 150, 123 outcomes included in analysis) 3. Placebo and gargling (N = 150, 121 known outcomes included in analysis) 4. Placebo and no gargling (N = 150, 113 known outcomes included in analysis) Inclusion criteria: aged ≥ 17 years and lived with at least 1 student housemate. Exclusion criteria: students with contraindicated medical conditions (hypercalcaemia, parathyroid disorder, chronic kidney disease, use of anticonvulsants, malabsorption syndromes, sarcoidosis), who were currently or planning to become pregnant, who were taking ≥ 1000 international units (IU)/day vitamin D, or who were unable to swallow capsules
Interventions	See TIDieR Table (Table 9).
Outcomes	Laboratory (influenza assessed via weekly self-collected nasal swabs; only swabs for symptomatic participants were assessed). Lab-confirmed influenza was determined by testing the Day 1 nasal swabs using an in-house enterovirus/rhinovirus PCR and, if negative, a commercial multiplex PCR able to detect 16 respiratory viruses and viral subtypes (xTAG RVP FAST, Luminex, Austin TX).

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Goodall 2014 *(Continued)*

	Clinical URTI assessed via weekly online surveys. Clinical URTI is defined as the participant's perception of cold in conjunction with 1 or more symptoms (runny/stuffy nose, congestion, cough, sneezing, sore throat, muscle aches, or fever). When participants reported symptoms but were uncertain if they were ill, adjudication was applied by 2 clinicians. Safety: None assessed/reported by the investigators.
Notes	Study was conducted during 2 periods: September to October in 2010 and 2011. Partial governmental funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description on how the randomisation sequence was generated
Allocation concealment (selection bias)	Low risk	Study used opaque, sealed, serially numbered envelopes. Envelopes were only accessed when both personnel were present.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Due to the nature of gargling with tap water, this intervention was not blinded. However, all other aspects of the study were blinded. Self-reported symptoms were adjudicated by 2 clinicians.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Except for gargling, all other participants and study personnel were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study flow chart and reasons for lost to follow-up are provided, imputation used for missing outcomes.
Selective reporting (reporting bias)	Low risk	All planned study outcomes were reported and match the published study protocol.

Gwaltney 1980

Study characteristics

Methods	Study assessed the effectiveness of aqueous iodine applied to the fingers in blocking hand transmission of experimental infection with rhinovirus from 1 volunteer to another. Healthy, young adult volunteers were recruited from the general population at the University of Virginia, Charlottesville. Volunteers were not informed about the contents of the hand preparation until after the study. 2 experiments were conducted to evaluate the virucidal activity of aqueous iodine applied to the fingers immediately before viral contamination. Another 2 experiments were conducted to determine whether there was sufficient residual activity of aqueous iodine after 2 hours to interrupt viral spread by the hand route. Volunteers who were donors of virus for the hand exposures were challenged intranasally on 3 consecutive days with the rhinovirus strain HH. Recipients were randomly assigned to receive iodine or placebo. The donors contaminated their hands with nasal secretions by finger to nose contact before the exposure. Hand contact was made between a donor and a recipient by stroking of the fingers for 10 seconds. Donors and recipients wore masks during the exposure period.

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Gwaltney 1980 *(Continued)*

Participants	15 and 20 volunteers in 2 experiments
Interventions	Treatment of fingers with iodine versus placebo. The virucidal preparation used was aqueous iodine (2% iodine and 4% potassium iodide). The placebo was an aqueous solution of food colours.
Outcomes	Experimental rhinovirus infection reduced (P = 0.06) Laboratory: serological evidence Effectiveness: rhinovirus infection (based on serology, isolation, and clinical symptoms) with high-score clinical illness. Score was published elsewhere. Safety: N/A
Notes	Risk of bias: high (poor description of randomisation process, concealment, or allocation) Notes: the study suggests that aqueous iodine applied to the fingers was effective in blocking transmission by hand contact of experimental infection with rhinovirus for up to 2 hours after application (1 out 10 volunteers were infected compared to 6 out of 10 in the placebo preparation arm, P = 0.06 with Fisher's exact test). The effectiveness of iodine treatment of the fingers in interrupting viral transmission in volunteers recommends its use for attempting to block transmission of rhinovirus under natural conditions. Although the cosmetic properties of 2% aqueous iodine make it impractical for routine use, it can be used as an epidemiologic tool to study the importance of the hand transmission route and to develop an effective cosmetically acceptable hand preparation. A summarily reported study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The viricidal preparation used was aqueous iodine... . The placebo was an aqueous solution of food colors... mixed to resemble the color of iodine. An odor of iodine was given to the placebo... . Volunteers were not informed about the contents of the hand preparation until after the study."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not stated whether the outcome assessor was blinded or not.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information

Hartinger 2016

Study characteristics

Methods	Communities were randomised to a comprehensive intervention was an improved solid-fuel stove, installation of a kitchen sink with running water, solar drinking water disinfection, education on handwashing, and separating animals from the kitchen environment.

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Hartinger 2016 *(Continued)*

Participants	534 children (267 in each group) in 51 communities (25 in intervention, 26 in control group). 250 children/households in the intervention group and 253 children/households in the control group were available for follow-up. Conducted in a rural farming area
Interventions	Environmental home-based intervention package consisting of improved solid-fuel stoves, kitchen sinks, solar disinfection of drinking water, and hygiene promotion. See Table 1 for details.
Outcomes	Laboratory: *Escherichia coli* (not relevant to this review) Effectiveness: weekly collection of daily diary data on illness. ARI was defined as child presenting cough or difficulty breathing, or both. ALRI was defined as child presenting cough or difficulty breathing, with a raised respiratory rate (> 50 per min in children aged 6 to 11 months and > 40 per min in children aged 12 months) on 2 consecutive measurements. Safety: none described in methods and none reported
Notes	The authors conclude that "combined home-based environmental interventions slightly reduced childhood diarrhoea, but the confidence interval included unity. Effects on growth and respiratory outcomes were not observed, despite high user compliance of the interventions. The absent effect on respiratory health might be due to insufficient household air quality improvements of the improved stoves and additional time needed to achieve attitudinal and behaviour change when providing composite interventions". Well-reported trial. Age of children not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Covariate-constrained randomisation is mentioned, but method not described.
Allocation concealment (selection bias)	Unclear risk	Method not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Data collected by field worker and recorded by parent. All would be aware of allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition rate, reasons stated, balanced between groups.
Selective reporting (reporting bias)	Low risk	It is unlikely that other outcomes were measured but not reported.

Gwaltney 1980

Study characteristics

Methods	Study assessed the effectiveness of aqueous iodine applied to the fingers in blocking hand transmission of experimental infection with rhinovirus from 1 volunteer to another. Healthy, young adult vol-

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Gwaltney 1980 *(Continued)*

	unteers were recruited from the general population at the University of Virginia, Charlottesville. Volunteers were not informed about the contents of the hand preparation until after the study. 2 experiments were conducted to evaluate the virucidal activity of aqueous iodine applied to the fingers immediately before viral contamination. Another 2 experiments were conducted to determine whether there was sufficient residual activity of aqueous iodine after 2 hours to interrupt viral spread by the hand route. Volunteers who were donors of virus for the hand exposures were challenged intranasally on 3 consecutive days with the rhinovirus strain HH. Recipients were randomly assigned to receive iodine or placebo. The donors contaminated their hands with nasal secretions by finger to nose contact before the exposure. Hand contact was made between a donor and a recipient by stroking of the fingers for 10 seconds. Donors and recipients wore masks during the exposure period.
Participants	15 and 20 volunteers in 2 experiments
Interventions	Treatment of fingers with iodine versus placebo. The virucidal preparation used was aqueous iodine (2% iodine and 4% potassium iodide). The placebo was an aqueous solution of food colours.
Outcomes	Experimental rhinovirus infection reduced (P = 0.06) Laboratory: serological evidence Effectiveness: rhinovirus infection (based on serology, isolation, and clinical symptoms) with high-score clinical illness. Score was published elsewhere. Safety: N/A
Notes	Risk of bias: high (poor description of randomisation process, concealment, or allocation) Notes: the study suggests that aqueous iodine applied to the fingers was effective in blocking transmission by hand contact of experimental infection with rhinovirus for up to 2 hours after application (1 out 10 volunteers were infected compared to 6 out of 10 in the placebo preparation arm, P = 0.06 with Fisher's exact test). The effectiveness of iodine treatment of the fingers in interrupting viral transmission in volunteers recommends its use for attempting to block transmission of rhinovirus under natural conditions. Although the cosmetic properties of 2% aqueous iodine make it impractical for routine use, it can be used as an epidemiologic tool to study the importance of the hand transmission route and to develop an effective cosmetically acceptable hand preparation. A summarily reported study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The viricidal preparation used was aqueous iodine... . The placebo was an aqueous solution of food colors... mixed to resemble the color of iodine. An odor of iodine was given to the placebo... . Volunteers were not informed about the contents of the hand preparation until after the study."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not stated whether the outcome assessor was blinded or not.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information

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Hartinger 2016

Study characteristics	
Methods	Communities were randomised to a comprehensive intervention was an improved solid-fuel stove, installation of a kitchen sink with running water, solar drinking water disinfection, education on handwashing, and separating animals from the kitchen environment.
Participants	534 children (267 in each group) in 51 communities (25 in intervention, 26 in control group). 250 children/households in the intervention group and 253 children/households in the control group were available for follow-up. Conducted in a rural farming area
Interventions	Environmental home-based intervention package consisting of improved solid-fuel stoves, kitchen sinks, solar disinfection of drinking water, and hygiene promotion. See Table 1 for details.
Outcomes	Laboratory: *Escherichia coli* (not relevant to this review) Effectiveness: weekly collection of daily diary data on illness. ARI was defined as child presenting cough or difficulty breathing, or both. ALRI was defined as child presenting cough or difficulty breathing, with a raised respiratory rate (> 50 per min in children aged 6 to 11 months and > 40 per min in children aged 12 months) on 2 consecutive measurements. Safety: none described in methods and none reported
Notes	The authors conclude that "combined home-based environmental interventions slightly reduced childhood diarrhoea, but the confidence interval included unity. Effects on growth and respiratory outcomes were not observed, despite high user compliance of the interventions. The absent effect on respiratory health might be due to insufficient household air quality improvements of the improved stoves and additional time needed to achieve attitudinal and behaviour change when providing composite interventions". Well-reported trial. Age of children not reported.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Covariate-constrained randomisation is mentioned, but method not described.
Allocation concealment (selection bias)	Unclear risk	Method not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Data collected by field worker and recorded by parent. All would be aware of allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition rate, reasons stated, balanced between groups.
Selective reporting (reporting bias)	Low risk	It is unlikely that other outcomes were measured but not reported.

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Hubner 2010

Study characteristics	
Methods	A prospective, controlled, intervention-control group design to assess the epidemiological and economical impact of alcohol-based hand disinfectants use at workplace. Volunteers in public administrations in the municipality of the city of Greifswald were randomised into 2 groups. Participants in the intervention group were provided with alcoholic hand disinfection, the control group was unchanged. In all, 1230 person-months were evaluated.
Participants	Employees (n = 134) from the administration of the Ernst-Moritz-Arndt University Greifswald, the municipality of Greifswald and the state of Mecklenburg-Pomerania, were recruited for the study and randomised to intervention (N = 67) or control (N = 67). Final analysis was performed on 64 from the intervention and 65 from the control group. Inclusion criteria: all administrative officers, who did not already apply hand disinfection at work, were considered for participation and were invited by email or mail (n = 850). The 134 participants declared their written consent to participate and completed a pre-study survey with demographic, social, health, and work-related questions to provide data for randomisation. Exclusion criteria: employees that were already using hand disinfectants at work
Interventions	Alcohol-based hand disinfectants use at workplace versus usual hygiene. See Table 1 for details.
Outcomes	Respiratory and gastrointestinal symptoms and days of work were recorded based on a monthly questionnaire over 1 year.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up minimal and similar in 2 groups
Selective reporting (reporting bias)	Unclear risk	No protocol available

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Huda 2012

Study characteristics	
Methods	Poorly described cluster-RCT. Partial report of the SHEWA-B trial focused on changing 11 targeted behaviours in villages to measure the impact on diarrhoea and respiratory illness amongst children. Unit of randomisation is not clear, but was probably a village. A group of 10 to 17 households within a village were the participants, based on the household having at least 1 child under the age of 5.
Participants	A total of 1692 participants (intervention = 848, control = 844) at baseline and 1699 participants at 18 months (intervention = 849, control = 850) Households were eligible if they have a child < 5 years of age and a guardian agreed to participate.
Interventions	SHEWA-B programme targeting improved latrine coverage and usage, access to and use of arsenic-free water, and improved hygiene practices using soaps. See Table 1 for details.
Outcomes	Laboratory: none described in methods and none reported Effectiveness: ARI and diarrhoea. ARI defined as cough and fever or difficulty breathing and fever within 48 h prior to interview. Safety: none described in methods and none reported
Notes	The authors conclude that "The prevalence of childhood diarrhea and respiratory illness was similar in the intervention and control communities". Poorly reported trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Mentions random-number tables, but not clear if this was for random selection or randomisation
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Data on illness were collected by a resident of the village, who was likely to know treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported. No flow diagram
Selective reporting (reporting bias)	Unclear risk	Unlikely that other outcomes were measured and not reported

Huda 2012

Study characteristics

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Huda 2012 *(Continued)*

Methods	Poorly described cluster-RCT. Partial report of the SHEWA-B trial focused on changing 11 targeted behaviours in villages to measure the impact on diarrhoea and respiratory illness amongst children. Unit of randomisation is not clear, but was probably a village. A group of 10 to 17 households within a village were the participants, based on the household having at least 1 child under the age of 5.
Participants	A total of 1692 participants (intervention = 848, control = 844) at baseline and 1699 participants at 18 months (intervention = 849, control = 850) Households were eligible if they have a child < 5 years of age and a guardian agreed to participate.
Interventions	SHEWA-B programme targeting improved latrine coverage and usage, access to and use of arsenic-free water, and improved hygiene practices using soaps. See Table 1 for details.
Outcomes	Laboratory: none described in methods and none reported Effectiveness: ARI and diarrhoea. ARI defined as cough and fever or difficulty breathing and fever within 48 h prior to interview. Safety: none described in methods and none reported
Notes	The authors conclude that "The prevalence of childhood diarrhea and respiratory illness was similar in the intervention and control communities". Poorly reported trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Mentions random-number tables, but not clear if this was for random selection or randomisation
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Data on illness were collected by a resident of the village, who was likely to know treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported. No flow diagram
Selective reporting (reporting bias)	Unclear risk	Unlikely that other outcomes were measured and not reported

Ibfelt 2015

Study characteristics

Methods	Cluster-RCT in 12 daycare nurseries in Denmark. Centres in the intervention group had their linen and children's toys commercially cleaned and disinfected every 2 weeks. Control group centres had usual

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Ibfelt 2015 *(Continued)*

	practice. Swabbing for bacteria and respiratory viruses was conducted at baseline and the end of the intervention period.
Participants	12 nurseries in Copenhagen (intervention = 6, control = 6) with a total of 587 children aged 6 months to 3 years Not clear how many children were in each group. Data on illness collected at the individual level, and on presence of bacteria and viruses at the cluster level.
Interventions	Washing and disinfection of toys and linen every 2 weeks for 3 months. See Table 1 for details.
Outcomes	Laboratory: counts of bacteria (not relevant to this review) and 11 respiratory viruses at baseline and end of intervention period, taken from swabs of 10 predefined locations in playroom (7 locations) and toilet area (3 locations). Viruses were influenza A and B; coronavirus NL63229E, OC43, and HKU1; parainfluenza virus 1, 2, 3, and 4; rhinovirus; RSV A/B; adenovirus; enterovirus; parechovirus; metapneumovirus; and bocavirus. Testing by PCR Effectiveness: illness counts in the children. Absence due to sickness recorded daily with reason categorised, but no definitions of illness provided. Safety: none mentioned in methods and none reported
Notes	The authors conclude that "Although cleaning and disinfection of toys every two weeks can decrease the microbial load in nurseries, it does not appear to reduce sickness absence among nursery children". The results of the disinfection are reported as follows: "The most prevalent virus was coronavirus (97% positive samples), followed by bocavirus (96%), adenovirus (73%) and rhinovirus (46%). The intervention reduced the presence of adenovirus, rhinovirus and RSV approximately two- to five-fold [odds ratio (OR) 2.4, 95% confidence interval (CI) 1.1-5.0 for adenovirus; OR 5.3, 95% CI 2.3-12.4 for rhinovirus; OR 4.1, 95% CI 1.5-11.2 for RSV] compared with the control group. On the other hand, metapneumovirus was found significantly less often in the control group than in the intervention group. The intervention had no effect on the detection of other viruses. The fomites with the highest presence of respiratory virus were pillows and sofas, followed by toys and playroom tables. When looking at the samples from the toys alone, there was a significant decrease following the intervention in the intervention group compared with the control group for rhinovirus (OR 3.8, 95% CI 1.3-10.5; P = 0.01) and RSV (OR 5.2, 95% CI 1.1-23.8; P = 0.04), but not adenovirus". This a poorly reported cluster-RCT. Its importance lies in the surface viral prevalence data (which could have been overestimated by PCR) and the finding that even in the presence of high viral prevalence, sickness was lower in the control (no surface disinfection) arm. This suggests the absence of other factors that could activate surface respiratory viruses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not mentioned
Allocation concealment (selection bias)	Unclear risk	Method not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias)	Low risk	Objective measure of bacterial and viral counts. However, illness reporting is unclear.

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Ibfelt 2015 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No attrition or denominators given for results.
Selective reporting (reporting bias)	Low risk	Unlikely that other outcomes were measured but not reported

Ibfelt 2015

Study characteristics	
Methods	Cluster-RCT in 12 daycare nurseries in Denmark. Centres in the intervention group had their linen and children's toys commercially cleaned and disinfected every 2 weeks. Control group centres had usual practice. Swabbing for bacteria and respiratory viruses was conducted at baseline and the end of the intervention period.
Participants	12 nurseries in Copenhagen (intervention = 6, control = 6) with a total of 587 children aged 6 months to 3 years Not clear how many children were in each group. Data on illness collected at the individual level, and on presence of bacteria and viruses at the cluster level.
Interventions	Washing and disinfection of toys and linen every 2 weeks for 3 months. See Table 1 for details.
Outcomes	Laboratory: counts of bacteria (not relevant to this review) and 11 respiratory viruses at baseline and end of intervention period, taken from swabs of 10 predefined locations in playroom (7 locations) and toilet area (3 locations). Viruses were influenza A and B; coronavirus NL63229E, OC43, and HKU1; parainfluenza virus 1, 2, 3, and 4; rhinovirus; RSV A/B; adenovirus; enterovirus; parechovirus; metapneumovirus; and bocavirus. Testing by PCR Effectiveness: illness counts in the children. Absence due to sickness recorded daily with reason categorised, but no definitions of illness provided. Safety: none mentioned in methods and none reported
Notes	The authors conclude that "Although cleaning and disinfection of toys every two weeks can decrease the microbial load in nurseries, it does not appear to reduce sickness absence among nursery children". The results of the disinfection are reported as follows: "The most prevalent virus was coronavirus (97% positive samples), followed by bocavirus (96%), adenovirus (73%) and rhinovirus (46%). The intervention reduced the presence of adenovirus, rhinovirus and RSV approximately two- to five-fold [odds ratio (OR) 2.4, 95% confidence interval (CI) 1.1-5.0 for adenovirus; OR 5.3, 95% CI 2.3-12.4 for rhinovirus; OR 4.1, 95% CI 1.5-11.2 for RSV] compared with the control group. On the other hand, metapneumovirus was found significantly less often in the control group than in the intervention group. The intervention had no effect on the detection of other viruses. The fomites with the highest presence of respiratory virus were pillows and sofas, followed by toys and playroom tables. When looking at the samples from the toys alone, there was a significant decrease following the intervention in the intervention group compared with the control group for rhinovirus (OR 3.8, 95% CI 1.3-10.5; P = 0.01) and RSV (OR 5.2, 95% CI 1.1-23.8; P = 0.04), but not adenovirus". This a poorly reported cluster-RCT. Its importance lies in the surface viral prevalence data (which could have been overestimated by PCR) and the finding that even in the presence of high viral prevalence, sickness was lower in the control (no surface disinfection) arm. This suggests the absence of other factors that could activate surface respiratory viruses.

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Ibfelt 2015 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not mentioned
Allocation concealment (selection bias)	Unclear risk	Method not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective measure of bacterial and viral counts. However, illness reporting is unclear.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No attrition or denominators given for results.
Selective reporting (reporting bias)	Low risk	Unlikely that other outcomes were measured but not reported

Ide 2014

Study characteristics	
Methods	Randomised, open-label, 2-group parallel study of 757 high school students (15 to 17 years of age) conducted for 90 days during the influenza epidemic season from 1 December 2011 to 28 February 2012, in 6 high schools in Shizuoka Prefecture, Japan. The green tea gargling group gargled 3 times a day with bottled green tea, and the water gargling group did the same with tap water. The water group was restricted from gargling with green tea.
Participants	A total of 747 students were enrolled (green tea gargling group = 384, water gargling group = 363) High school students (15 to 17 years of age) who attended 6 high schools in the Kakegawa and Ogasa districts of Shizuoka Prefecture, Japan
Interventions	See TIDieR Table (Table 1).
Outcomes	Incidence of laboratory-confirmed influenza Incidence of clinically defined influenza infection Time for which the participant was free from clinically defined influenza infection Clinically defined influenza infection, specified as fever (≥ 37.8 °C) plus any 2 of the following additional symptoms: cough, sore throat, headache, or myalgia. Influenza infection with viral antigen was detected by immunochromatographic assay. No safety data reported.
Notes	

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Ide 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated permuted block randomised schema
Allocation concealment (selection bias)	Low risk	Randomised at the Data Management Center of Shizuoka General Hospital in Japan
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal attrition
Selective reporting (reporting bias)	Unclear risk	Protocol not available

Ide 2014

Study characteristics	
Methods	Randomised, open-label, 2-group parallel study of 757 high school students (15 to 17 years of age) conducted for 90 days during the influenza epidemic season from 1 December 2011 to 28 February 2012, in 6 high schools in Shizuoka Prefecture, Japan. The green tea gargling group gargled 3 times a day with bottled green tea, and the water gargling group did the same with tap water. The water group was restricted from gargling with green tea.
Participants	A total of 747 students were enrolled (green tea gargling group = 384, water gargling group = 363) High school students (15 to 17 years of age) who attended 6 high schools in the Kakegawa and Ogasa districts of Shizuoka Prefecture, Japan
Interventions	See TIDieR Table (Table 1).
Outcomes	Incidence of laboratory-confirmed influenza Incidence of clinically defined influenza infection Time for which the participant was free from clinically defined influenza infection Clinically defined influenza infection, specified as fever (≥ 37.8 °C) plus any 2 of the following additional symptoms: cough, sore throat, headache, or myalgia. Influenza infection with viral antigen was detected by immunochromatographic assay. No safety data reported.
Notes	

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Ide 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated permuted block randomised schema
Allocation concealment (selection bias)	Low risk	Randomised at the Data Management Center of Shizuoka General Hospital in Japan
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal attrition
Selective reporting (reporting bias)	Unclear risk	Protocol not available

Ide 2016

Study characteristics	
Methods	Randomised controlled study in Japan. Participants were randomly allocated into the catechin-treated (epigallocatechin gallate-treated) or non-treated face mask groups for 60 days from January to March 2016. Incidence of laboratory-confirmed influenza infection was measured and compared between groups using Fisher's exact test. Multivariate analysis was performed to calculate adjusted ORs and associated 95% CIs.
Participants	Participants included workers in a nursing home, a rehabilitation facility, and a hospital. A total of 234 participants were eligible for the study (catechin group, n = 118; control group, n = 116).
Interventions	Catechin-treated mask versus non-treated face mask. See Table 1 for details.
Outcomes	Incidence of laboratory-confirmed influenza infection Laboratory-confirmed influenza infection with viral antigen detected by immunochromatographic assay performed when participants reported ILI. No safety outcomes reported.
Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement

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Ide 2016 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Computer-generated randomisation, but method not stated
Allocation concealment (selection bias)	Low risk	Central randomisation service at Data Management Centre of Shizouka General Hospital
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Attrition minimal
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition minimal
Selective reporting (reporting bias)	Low risk	Specified outcomes reported.

Ide 2016

Study characteristics	
Methods	Randomised controlled study in Japan. Participants were randomly allocated into the catechin-treated (epigallocatechin gallate-treated) or non-treated face mask groups for 60 days from January to March 2016. Incidence of laboratory-confirmed influenza infection was measured and compared between groups using Fisher's exact test. Multivariate analysis was performed to calculate adjusted ORs and associated 95% CIs.
Participants	Participants included workers in a nursing home, a rehabilitation facility, and a hospital. A total of 234 participants were eligible for the study (catechin group, n = 118; control group, n = 116).
Interventions	Catechin-treated mask versus non-treated face mask. See Table 1 for details.
Outcomes	Incidence of laboratory-confirmed influenza infection Laboratory-confirmed influenza infection with viral antigen detected by immunochromatographic assay performed when participants reported ILI. No safety outcomes reported.
Notes	Government funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Computer-generated randomisation, but method not stated
Allocation concealment (selection bias)	Low risk	Central randomisation service at Data Management Centre of Shizouka General Hospital

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Ide 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Attrition minimal
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition minimal
Selective reporting (reporting bias)	Low risk	Specified outcomes reported.

Jacobs 2009

Study characteristics	
Methods	Open RCT lasting 77 days from January 2008 to test “superiority” of face masks in preventing "URTI". This term appears as an acronym in the introduction and is not explained. It is assumed that it stands for 'upper respiratory infections', but it is preceded in the text by the term 'common cold', which is also lacking a definition. Randomisation was carried out in blocks within each of 3 professional figures (physicians, nurses, and “co-medical” personnel).
Participants	33 HCWs mainly females aged around 34 to 37 in a tertiary healthcare hospital in Tokyo, Japan. HCW with “predisposing conditions” (undefined) to “URTI” and those taking antibiotics were excluded. A baseline descriptive survey was carried out including “quality of life”. 1 participant dropped out at end of week 1, but no reason is reported nor the allocation arm. Analysis was performed on 32 participants (mask = 17, no mask = 15).
Interventions	Surgical mask MA-3 (Osu Sangyo, Japan) during all phases of hospital work (n = 17) or no mask (n = 15) (except when specifically required by hospital SOPs)
Outcomes	Laboratory: N/A Effectiveness: URTI is defined on the basis of a symptoms score, with a score > 14 being a URTI according to Jackson’s 1958 criteria (“Jackson score”). These are not explained in text, although the symptoms are listed in Table 3 (any, sore throat, runny nose, stuffy nose, sneeze, cough, headache, ear ache, feel bad) together with their mean and scores SD by intervention arm. Safety: the text does not mention or report harms. These appear to be indistinguishable from URTI symptoms (e.g. headache which is reported as of significantly longer duration in the intervention arm). Compliance is self-reported as high (84.3% of participants).
Notes	The authors conclude that “Face mask use in healthcare workers has not been demonstrated to provide benefit in terms of cold symptoms or getting colds. A larger study is needed to definitively establish non-inferiority of no mask use”. This is a small, badly reported trial. The purpose of trials is to test hypotheses not to prove or disprove 'superiority' of interventions. There is no power calculation, and CIs are not reported (although there is a mention in Discussion). No accurate definitions of a series of important variables (e.g. URTI, runny nose, etc.) are reported, and the Jackson scores are not explained, nor their use in Japanese personnel or language validated.

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Jacobs 2009 *(Continued)*

	Intervention arm data not extracted due to the uncertainty of its meaning.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Open RCT, but sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	"Mask and no mask groups were formed using block randomisation of subjects within their respective job categories: nurses, doctors, and co-medical personnel." Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study. Blinding not possible, as 1 group wore face masks
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 dropout in each group accounted for. "Analyses were performed following the principles of intention-to-treat."
Selective reporting (reporting bias)	High risk	NB: influenza vaccine coverage was 100% in mask group and only 81% in the non-mask-wearing group.

Kotch 1994

Study characteristics

Methods	Pair-matched, cluster-RCT conducted from 19 October 1988 to 23 May 1989 in 24 childcare centres in North Carolina, USA The trial tested the effects of a hand-washing and environment sterilising programme on diarrhoea (data not extracted) and ARIs. Child daycare centres had to care for 30 children or less, at least 5 of whom had to be in nappies, and intending to stay open for at least another 2 years. Randomisation is not described, nor are cluster coefficients reported.
Participants	389 children aged 3 years or less in daycare for at least 20 hours a week. There were some withdrawals, but attrition of participants is not stated, only that in the end data for 31 intervention classrooms and 36 control classrooms were available. 291 children aged up to 24 months and 80 over 24 months took part. The text is very confusing, as 371 seems to be the total of the number of families that took part. No denominator breakdown by arm is reported, and numerators are only reported as new episodes per child-year.
Interventions	Structured hand-washing and environment (including surfaces, sinks, toilets, and toys) disinfecting programme with waterless disinfectant scrub
Outcomes	Laboratory: N/A Effectiveness: ARI (coughing, runny nose, wheezing, sore throat, or earache) Safety: N/A
Notes	Risk of bias: high (poor reporting of randomisation, outcomes, numerators and denominators)

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Kotch 1994 *(Continued)*

	Note: the authors conclude that the fully adjusted RR for prevention of ARIs was 0.94 (−2.43 to 0.66). A poorly reported study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Pair-matched cluster-randomised, controlled trial", but sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Centres were matched in pairs and then randomly allocated to either intervention or control programmes. Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible (intervention was training session)
Blinding of outcome assessment (detection bias) All outcomes	High risk	"The same staff who conducted the training unobtrusively recorded observations at 5-week intervals"
Incomplete outcome data (attrition bias) All outcomes	High risk	18 families were dropped, denominator not clear.
Selective reporting (reporting bias)	High risk	Denominators not clearly reported

Ladegaard 1999

Study characteristics	
Methods	RCT with cluster-randomisation to intervention or control. Of 10 institutions, 2 were excluded because they wanted institutions to be comparable in uptake area (i.e. housing and income). Interventions were administered to children, parents, and teachers at the institutions.
Participants	Children 0 to 6 years old
Interventions	Multifaceted: information, t-shirts to the children with: "Clean hands - yes, thank you", performance of a fairytale "The princess who did not want to wash her hands", exercise in hand-washing, importance of clean and fresh air. The aims of the intervention were to: 1. increase the hygiene education of the daycare teachers; 2. motivate the children by practical learning to have better hand hygiene; and 3. inform the parents about better hand hygiene.
Outcomes	34% decrease in "sickness" (probably mostly gastroenteritis)
Notes	Risk of bias: only limited data available Note: the authors conclude that there was a 34% decrease in sickness in the intervention arm; this is probably overall sickness, as gastroenteritis is part of the outcomes (data not extracted). Only limited data available from translation by Jørgen Lous.
Risk of bias	

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Ladegaard 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Randomisation by "lottery", the same as "flip the coin". Concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not possible
Incomplete outcome data (attrition bias) All outcomes	High risk	Total numbers of children included in each arm not reported.
Selective reporting (reporting bias)	High risk	Limited data reported, in particular denominators missing.

Larson 2010

Study characteristics	
Methods	Cluster block-randomised, controlled trial carried out between 20 November 2006 and 20 June 2008 in an upper Manhattan immigrant Latino neighbourhood ("19 month data collection period"). The study aimed at assessing the effects of education versus education and hand sanitiser use versus education and hand sanitiser use and common mask use against upper respiratory infections over a period of under 2 years. Follow-up was through an automated telephone system with a small financial incentive (USD 20) for those with 75% or more compliance. Those reporting an ILI received a visit within 48 hours for swabbing. An index case was someone who at the "onset day of illness nobody else in the household had been symptomatic within the previous five days". A secondary case for each episode "was any member of the household who developed symptoms within five days following the index case"; "The secondary attack rate was defined as the number of secondary cases recorded within 5 days of the onset of symptoms in the index case divided by the number of household members minus one". The text implies that the unit of observation was the episode ("study subjects contributed more than one episode in which they were considered to be the index case").
Participants	617 households were randomised to the education group (n = 211), the hand sanitiser group (n = 205), and the hand sanitiser and mask group (n = 201). There were 2708 participants, mostly adult Latino immigrants to the USA. Recruitment and allocation were carried out by household. There had to be at least 3 people living in the household, with at least 1 being a preschool or elementary school child, speaking English or Spanish, having a telephone, willingness to complete symptom assessments and have bimonthly home visits, and not using alcohol-based hand sanitiser routinely. Intracluster correlation coefficients are reported on page 179 of the manuscript.

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Larson 2010 *(Continued)*

Interventions	Written Spanish or English language educational materials regarding the prevention and treatment of URTIs and influenza or the same educational materials and hand sanitiser (Purell, J&J), in large (8- and 4-ounce) and small (1-ounce) containers to be carried by individual household members to work or school, or the same interventions as well as regular surgical face masks (Procedure Face Masks for adults and children, Kimberly-Clark) with instructions for both the caretaker and the ill person to wear them when an ILI occurred in any household member. Replenishment of intervention stocks was done at the bimonthly home visit. Caretakers had to wear a mask for 7 days when within 3 feet of a symptomatic case. They were also encouraged to wear masks within 3 feet of any household member. Reinforcing phone calls were made 3 times in 6 days. The text clearly reports active influenza vaccine promotion during the bimonthly visits. (“The home visit to each household was made every 2 months to minimise study dropout, reinforce adherence to the assigned intervention, replenish product supplies and record use of supplies, answer questions, and correct ongoing misconceptions. At each visit, new educational materials regarding URTI prevention and treatment and influenza vaccination were distributed.” (PDF page 3). Also just before the Discussion as follows: “Influenza vaccination rates: There was an increase between the baseline and exit interview in all three groups that reported 50% of more of members receiving influenza vaccine (pre- versus post-intervention for each group: 21.1% and 40.8% in the Education group, 19.0% and 57.1% in the hand sanitiser group, and 22.4% and 43.5% in the hand sanitiser and face mask group (P = 0.001). Additionally, those in the hand sanitiser group reported a significantly greater increase than the other 2 groups, controlling for baseline rates (P = 0.002)”) Coverage was unequal across groups, no information on the progressive impact of the vaccine, or indeed the nature of the vaccine(s) is reported. Apparently the first season was mild and the vaccine mismatched, compliance with the trial interventions was low in Arm 3, and a local epidemic of *Staphylococcus aureus* meant that the control group started washing hands. The trial authors report no effect on reporting rates of vaccine coverage by arms, but with so many confounders who knows?
Outcomes	Laboratory: PCR carried out on samples from deep nasal swabs for influenza and the most common other pathogens (RSV, rhinovirus, enterovirus, parainfluenza viruses, etc.). The text describing the results of the swabbing is confusing, but in general appears to be non-random “Households reported 669 episodes of ILI (0 to 5 per individual)". Of the 234 deep nasal swabs obtained, 33.3% (n = 78) tested positive for influenza: 43.6% (n = 34) were influenza A and 56.4% (n = 44) were influenza B. Amongst the 66.7% who tested negative for influenza, 30.8% (48/156) tested positive for other viruses: 7 for respiratory syncytial virus, 9 for parainfluenza, 11 for enterovirus, 10 for rhinovirus, 6 for adenovirus, and 5 for metapneumovirus. Swabs were not obtained from the remaining 435 reported ILI episodes for the following reasons: 72.0% (n = 313) did not meet the CDC definition of an ILI and were therefore included in the URTI symptom count; 21.4% of episodes (n = 93) were reported after 48 hours of ILI onset or the participant refused to be swabbed; and the research staff were unable to reach the participant in 6.7% of episodes (n = 29). As no definition of URTI is given, it is unclear what kind of biases were introduced by the non-swabbing of the 313/435 “not meeting CDC definition”. Effectiveness: ILI (CDC definition): “temperature of 37.8°C or more and cough and/or sore throat in the absence of a known cause other than influenza” URTI only referred to as “Viral upper respiratory infections (URTIs)”. Safety: N/A
Notes	The authors conclude that “the Hand Sanitizer group was significantly more likely to report that no household member had symptoms (P,0.01), but there were no significant differences in rates of infection by intervention group in multivariate analyses. Knowledge improved significantly more in the Hand Sanitizer group (P,0.0001). The proportion of households that reported >50% of members receiving influenza vaccine increased during the study (P,0.001). Despite the fact that compliance with mask wearing was poor, mask wearing as well as increased crowding, lower education levels of caretakers, and index cases 0–5 years of age (compared with adults) were associated with significantly lower sec-

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Larson 2010 *(Continued)*

ondary transmission rates (all P,0.02). In this population, there was no detectable additional benefit of hand sanitiser or face masks over targeted education on overall rates of URTIs, but mask wearing was associated with reduced secondary transmission and should be encouraged during outbreak situations. During the study period, community concern about methicillin-resistant *Staphylococcus aureus* was occurring, perhaps contributing to the use of hand sanitiser in the Education control group, and diluting the intervention's measurable impact".

The study is at high risk of bias. Randomisation and reasons for dropout are not described. Differentials in cluster characteristics across arms point to randomisation not having worked, and the confounding effects of a postrandomisation staphylococcal scare are difficult to judge. Symptom-driven follow-up gives no idea of the effects on asymptomatic ILI/influenza. Poor definitions (URTI?). There are unexplained dropouts, and the analysis plan is unclear. Finally, the very small number of cases of influenza and an unclear swabbing attrition may introduce further elements of confounding.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Cluster block randomised, controlled trial", but sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	"Households were block randomised into one of three groups" Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel was not possible.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment is not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	In control group households (n = 211), 26 dropped out and 37 did not consent. In hand sanitiser group households (n = 205), 21 dropped out and 36 did not consent. In hand sanitiser and face mask group households (n = 201), 19 dropped out and 35 did not consent. Reasons for dropout were not described.
Selective reporting (reporting bias)	Unclear risk	617 of 772 eligible households were randomised.

Little 2015

Study characteristics

Methods	Individuals sharing a household by mailed invitation through general practices in England were recruited. After consent, participants were randomised online by an automated computer-generated random-number program to receive either no access or access to a bespoke automated web-based intervention that maximised hand-washing intention, monitored hand-washing behaviour, provided tailored feedback, reinforced helpful attitudes and norms, and addressed negative beliefs. Participants were enrolled into an additional cohort (randomised to receive intervention or no intervention) to assess whether the baseline questionnaire on hand-washing would affect hand-washing behav-

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Little 2015 *(Continued)*

	iour. Participants were not masked to intervention allocation, but statistical analysis commands were constructed masked to group. The primary outcome was number of episodes of RTIs in index participants in a modified intention-to-treat population of randomly assigned participants who completed follow-up at 16 weeks.
Participants	344 physician offices were recruited over a wide area of England, and 20,066 participants were enrolled and randomised to intervention (N = 16,086) and control (N = 10,026). Modified ITT was performed on 16,908 participants who completed the follow-up questionnaire at 16 weeks (intervention = 8241 and control = 8667). Inclusion criteria: adult patients (aged 18 years or older) identified from computerised lists in general practitioner (GP) practices in England, for whom there was at least 1 other individual living in the household who was willing to report illness to the index person Exclusion criteria: patients with severe mental problems (e.g. major uncontrolled depression or schizophrenia, dementia, or severe mental impairment) or who were terminally ill, and those reporting a skin complaint that would restrict hand-washing
Interventions	Automated web-based intervention that maximised hand-washing intention, monitored hand-washing behaviour, provided tailored feedback, reinforced helpful attitudes and norms, and addressed negative beliefs. Control no access to intervention web pages. See Table 1 for details.
Outcomes	The primary outcome was the number of index individuals that reported 1 or more RTIs (including ILI) at 16 weeks. Secondary: duration of symptoms, transmission of respiratory infections, gastrointestinal infections, attendance at the practice, and use of health service resources Infections self-reported by participants. RTI defined as 2 symptoms of an RTI for at least 1 day or 1 symptom for 2 consecutive days. Definition of ILI was a high temperature (feeling very hot or very cold; or measured temperature > 37.5 °C), a respiratory symptom (sore throat, cough, or runny nose), and a systemic symptom (headache, severe fatigue, severe muscle aches, or severe malaise). No safety outcomes reported.
Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were automatically randomly assigned by the intervention software, but sequence generation not described.
Allocation concealment (selection bias)	Low risk	Participants were automatically randomly assigned by the intervention software.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition that was different in the 2 groups

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Little 2015 *(Continued)*

Selective reporting (reporting bias)	Low risk	Specified outcomes reported.

Jacobs 2009

Study characteristics	
Methods	Open RCT lasting 77 days from January 2008 to test “superiority” of face masks in preventing "URTI". This term appears as an acronym in the introduction and is not explained. It is assumed that it stands for 'upper respiratory infections', but it is preceded in the text by the term 'common cold', which is also lacking a definition. Randomisation was carried out in blocks within each of 3 professional figures (physicians, nurses, and “co-medical” personnel).
Participants	33 HCWs mainly females aged around 34 to 37 in a tertiary healthcare hospital in Tokyo, Japan. HCW with “predisposing conditions” (undefined) to “URTI” and those taking antibiotics were excluded. A baseline descriptive survey was carried out including “quality of life”. 1 participant dropped out at end of week 1, but no reason is reported nor the allocation arm. Analysis was performed on 32 participants (mask = 17, no mask = 15).
Interventions	Surgical mask MA-3 (Osu Sangyo, Japan) during all phases of hospital work (n = 17) or no mask (n = 15) (except when specifically required by hospital SOPs)
Outcomes	Laboratory: N/A Effectiveness: URTI is defined on the basis of a symptoms score, with a score > 14 being a URTI according to Jackson’s 1958 criteria (“Jackson score”). These are not explained in text, although the symptoms are listed in Table 3 (any, sore throat, runny nose, stuffy nose, sneeze, cough, headache, ear ache, feel bad) together with their mean and scores SD by intervention arm. Safety: the text does not mention or report harms. These appear to be indistinguishable from URTI symptoms (e.g. headache which is reported as of significantly longer duration in the intervention arm). Compliance is self-reported as high (84.3% of participants).
Notes	The authors conclude that “Face mask use in healthcare workers has not been demonstrated to provide benefit in terms of cold symptoms or getting colds. A larger study is needed to definitively establish non-inferiority of no mask use”. This is a small, badly reported trial. The purpose of trials is to test hypotheses not to prove or disprove 'superiority' of interventions. There is no power calculation, and CIs are not reported (although there is a mention in Discussion). No accurate definitions of a series of important variables (e.g. URTI, runny nose, etc.) are reported, and the Jackson scores are not explained, nor their use in Japanese personnel or language validated. Intervention arm data not extracted due to the uncertainty of its meaning.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Open RCT, but sequence generation not reported

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Jacobs 2009 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	"Mask and no mask groups were formed using block randomisation of subjects within their respective job categories: nurses, doctors, and co-medical personnel." Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study. Blinding not possible, as 1 group wore face masks
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 dropout in each group accounted for. "Analyses were performed following the principles of intention-to-treat."
Selective reporting (reporting bias)	High risk	NB: influenza vaccine coverage was 100% in mask group and only 81% in the non-mask-wearing group.

Kotch 1994

Study characteristics	
Methods	Pair-matched, cluster-RCT conducted from 19 October 1988 to 23 May 1989 in 24 childcare centres in North Carolina, USA The trial tested the effects of a hand-washing and environment sterilising programme on diarrhoea (data not extracted) and ARIs. Child daycare centres had to care for 30 children or less, at least 5 of whom had to be in nappies, and intending to stay open for at least another 2 years. Randomisation is not described, nor are cluster coefficients reported.
Participants	389 children aged 3 years or less in daycare for at least 20 hours a week. There were some withdrawals, but attrition of participants is not stated, only that in the end data for 31 intervention classrooms and 36 control classrooms were available. 291 children aged up to 24 months and 80 over 24 months took part. The text is very confusing, as 371 seems to be the total of the number of families that took part. No denominator breakdown by arm is reported, and numerators are only reported as new episodes per child-year.
Interventions	Structured hand-washing and environment (including surfaces, sinks, toilets, and toys) disinfecting programme with waterless disinfectant scrub
Outcomes	Laboratory: N/A Effectiveness: ARI (coughing, runny nose, wheezing, sore throat, or earache) Safety: N/A
Notes	Risk of bias: high (poor reporting of randomisation, outcomes, numerators and denominators) Note: the authors conclude that the fully adjusted RR for prevention of ARIs was 0.94 (−2.43 to 0.66). A poorly reported study

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Pair-matched cluster-randomised, controlled trial", but sequence generation not reported

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Kotch 1994 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Centres were matched in pairs and then randomly allocated to either intervention or control programmes. Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible (intervention was training session)
Blinding of outcome assessment (detection bias) All outcomes	High risk	"The same staff who conducted the training unobtrusively recorded observations at 5-week intervals"
Incomplete outcome data (attrition bias) All outcomes	High risk	18 families were dropped, denominator not clear.
Selective reporting (reporting bias)	High risk	Denominators not clearly reported

Ladegaard 1999

Study characteristics	
Methods	RCT with cluster-randomisation to intervention or control. Of 10 institutions, 2 were excluded because they wanted institutions to be comparable in uptake area (i.e. housing and income). Interventions were administered to children, parents, and teachers at the institutions.
Participants	Children 0 to 6 years old
Interventions	Multifaceted: information, t-shirts to the children with: "Clean hands - yes, thank you", performance of a fairytale "The princess who did not want to wash her hands", exercise in hand-washing, importance of clean and fresh air. The aims of the intervention were to: 1. increase the hygiene education of the daycare teachers; 2. motivate the children by practical learning to have better hand hygiene; and 3. inform the parents about better hand hygiene.
Outcomes	34% decrease in "sickness" (probably mostly gastroenteritis)
Notes	Risk of bias: only limited data available Note: the authors conclude that there was a 34% decrease in sickness in the intervention arm; this is probably overall sickness, as gastroenteritis is part of the outcomes (data not extracted). Only limited data available from translation by Jørgen Lous.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Randomisation by "lottery", the same as "flip the coin". Concealment not reported

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Ladegaard 1999 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not possible
Incomplete outcome data (attrition bias) All outcomes	High risk	Total numbers of children included in each arm not reported.
Selective reporting (reporting bias)	High risk	Limited data reported, in particular denominators missing.

Larson 2010

Study characteristics	
Methods	Cluster block-randomised, controlled trial carried out between 20 November 2006 and 20 June 2008 in an upper Manhattan immigrant Latino neighbourhood ("19 month data collection period"). The study aimed at assessing the effects of education versus education and hand sanitiser use versus education and hand sanitiser use and common mask use against upper respiratory infections over a period of under 2 years. Follow-up was through an automated telephone system with a small financial incentive (USD 20) for those with 75% or more compliance. Those reporting an ILI received a visit within 48 hours for swabbing. An index case was someone who at the "onset day of illness nobody else in the household had been symptomatic within the previous five days". A secondary case for each episode "was any member of the household who developed symptoms within five days following the index case"; "The secondary attack rate was defined as the number of secondary cases recorded within 5 days of the onset of symptoms in the index case divided by the number of household members minus one". The text implies that the unit of observation was the episode ("study subjects contributed more than one episode in which they were considered to be the index case").
Participants	617 households were randomised to the education group (n = 211), the hand sanitiser group (n = 205), and the hand sanitiser and mask group (n = 201). There were 2708 participants, mostly adult Latino immigrants to the USA. Recruitment and allocation were carried out by household. There had to be at least 3 people living in the household, with at least 1 being a preschool or elementary school child, speaking English or Spanish, having a telephone, willingness to complete symptom assessments and have bimonthly home visits, and not using alcohol-based hand sanitiser routinely. Intracluster correlation coefficients are reported on page 179 of the manuscript.
Interventions	Written Spanish or English language educational materials regarding the prevention and treatment of URTIs and influenza or the same educational materials and hand sanitiser (Purell, J&J), in large (8- and 4-ounce) and small (1-ounce) containers to be carried by individual household members to work or school, or the same interventions as well as regular surgical face masks (Procedure Face Masks for adults and children, Kimberly-Clark) with instructions for both the caretaker and the ill person to wear them when an ILI occurred in any household member. Replenishment of intervention stocks was done at the bimonthly home visit.

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Larson 2010 *(Continued)*

	Caretakers had to wear a mask for 7 days when within 3 feet of a symptomatic case. They were also encouraged to wear masks within 3 feet of any household member. Reinforcing phone calls were made 3 times in 6 days. The text clearly reports active influenza vaccine promotion during the bimonthly visits. ("The home visit to each household was made every 2 months to minimise study dropout, reinforce adherence to the assigned intervention, replenish product supplies and record use of supplies, answer questions, and correct ongoing misconceptions. At each visit, new educational materials regarding URTI prevention and treatment and influenza vaccination were distributed." (PDF page 3). Also just before the Discussion as follows: "Influenza vaccination rates: There was an increase between the baseline and exit interview in all three groups that reported 50% of more of members receiving influenza vaccine (pre- versus post-intervention for each group: 21.1% and 40.8% in the Education group, 19.0% and 57.1% in the hand sanitiser group, and 22.4% and 43.5% in the hand sanitiser and face mask group (P = 0.001). Additionally, those in the hand sanitiser group reported a significantly greater increase than the other 2 groups, controlling for baseline rates (P = 0.002)") Coverage was unequal across groups, no information on the progressive impact of the vaccine, or indeed the nature of the vaccine(s) is reported. Apparently the first season was mild and the vaccine mismatched, compliance with the trial interventions was low in Arm 3, and a local epidemic of *Staphylococcus aureus* meant that the control group started washing hands. The trial authors report no effect on reporting rates of vaccine coverage by arms, but with so many confounders who knows?
Outcomes	Laboratory: PCR carried out on samples from deep nasal swabs for influenza and the most common other pathogens (RSV, rhinovirus, enterovirus, parainfluenza viruses, etc.). The text describing the results of the swabbing is confusing, but in general appears to be non-random "Households reported 669 episodes of ILI (0 to 5 per individual)". Of the 234 deep nasal swabs obtained, 33.3% (n = 78) tested positive for influenza: 43.6% (n = 34) were influenza A and 56.4% (n = 44) were influenza B. Amongst the 66.7% who tested negative for influenza, 30.8% (48/156) tested positive for other viruses: 7 for respiratory syncytial virus, 9 for parainfluenza, 11 for enterovirus, 10 for rhinovirus, 6 for adenovirus, and 5 for metapneumovirus. Swabs were not obtained from the remaining 435 reported ILI episodes for the following reasons: 72.0% (n = 313) did not meet the CDC definition of an ILI and were therefore included in the URTI symptom count; 21.4% of episodes (n = 93) were reported after 48 hours of ILI onset or the participant refused to be swabbed; and the research staff were unable to reach the participant in 6.7% of episodes (n = 29). As no definition of URTI is given, it is unclear what kind of biases were introduced by the non-swabbing of the 313/435 "not meeting CDC definition". Effectiveness: ILI (CDC definition): "temperature of 37.8°C or more and cough and/or sore throat in the absence of a known cause other than influenza" URTI only referred to as "Viral upper respiratory infections (URTIs)". Safety: N/A
Notes	The authors conclude that "the Hand Sanitizer group was significantly more likely to report that no household member had symptoms (P,0.01), but there were no significant differences in rates of infection by intervention group in multivariate analyses. Knowledge improved significantly more in the Hand Sanitizer group (P,0.0001). The proportion of households that reported >50% of members receiving influenza vaccine increased during the study (P,0.001). Despite the fact that compliance with mask wearing was poor, mask wearing as well as increased crowding, lower education levels of caretakers, and index cases 0–5 years of age (compared with adults) were associated with significantly lower secondary transmission rates (all P,0.02). In this population, there was no detectable additional benefit of hand sanitiser or face masks over targeted education on overall rates of URTIs, but mask wearing was associated with reduced secondary transmission and should be encouraged during outbreak situations. During the study period, community concern about methicillin-resistant *Staphylococcus aureus* was occurring, perhaps contributing to the use of hand sanitiser in the Education control group, and diluting the intervention's measurable impact". The study is at high risk of bias. Randomisation and reasons for dropout are not described. Differentials in cluster characteristics across arms point to randomisation not having worked, and the confounding

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Larson 2010 *(Continued)*

effects of a postrandomisation staphylococcal scare are difficult to judge. Symptom-driven follow-up gives no idea of the effects on asymptomatic ILI/influenza. Poor definitions (URTI?). There are unexplained dropouts, and the analysis plan is unclear. Finally, the very small number of cases of influenza and an unclear swabbing attrition may introduce further elements of confounding.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Cluster block randomised, controlled trial", but sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	"Households were block randomised into one of three groups" Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel was not possible.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment is not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	In control group households (n = 211), 26 dropped out and 37 did not consent. In hand sanitiser group households (n = 205), 21 dropped out and 36 did not consent. In hand sanitiser and face mask group households (n = 201), 19 dropped out and 35 did not consent. Reasons for dropout were not described.
Selective reporting (reporting bias)	Unclear risk	617 of 772 eligible households were randomised.

Little 2015

Study characteristics

Methods	Individuals sharing a household by mailed invitation through general practices in England were recruited. After consent, participants were randomised online by an automated computer-generated random-number program to receive either no access or access to a bespoke automated web-based intervention that maximised hand-washing intention, monitored hand-washing behaviour, provided tailored feedback, reinforced helpful attitudes and norms, and addressed negative beliefs. Participants were enrolled into an additional cohort (randomised to receive intervention or no intervention) to assess whether the baseline questionnaire on hand-washing would affect hand-washing behaviour. Participants were not masked to intervention allocation, but statistical analysis commands were constructed masked to group. The primary outcome was number of episodes of RTIs in index participants in a modified intention-to-treat population of randomly assigned participants who completed follow-up at 16 weeks.
Participants	344 physician offices were recruited over a wide area of England, and 20,066 participants were enrolled and randomised to intervention (N = 16,086) and control (N = 10,026).

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Little 2015 *(Continued)*

	Modified ITT was performed on 16,908 participants who completed the follow-up questionnaire at 16 weeks (intervention = 8241 and control = 8667). Inclusion criteria: adult patients (aged 18 years or older) identified from computerised lists in general practitioner (GP) practices in England, for whom there was at least 1 other individual living in the household who was willing to report illness to the index person Exclusion criteria: patients with severe mental problems (e.g. major uncontrolled depression or schizophrenia, dementia, or severe mental impairment) or who were terminally ill, and those reporting a skin complaint that would restrict hand-washing
Interventions	Automated web-based intervention that maximised hand-washing intention, monitored hand-washing behaviour, provided tailored feedback, reinforced helpful attitudes and norms, and addressed negative beliefs. Control no access to intervention web pages. See Table 1 for details.
Outcomes	The primary outcome was the number of index individuals that reported 1 or more RTIs (including ILI) at 16 weeks. Secondary: duration of symptoms, transmission of respiratory infections, gastrointestinal infections, attendance at the practice, and use of health service resources Infections self-reported by participants. RTI defined as 2 symptoms of an RTI for at least 1 day or 1 symptom for 2 consecutive days. Definition of ILI was a high temperature (feeling very hot or very cold; or measured temperature > 37.5 °C), a respiratory symptom (sore throat, cough, or runny nose), and a systemic symptom (headache, severe fatigue, severe muscle aches, or severe malaise). No safety outcomes reported.
Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were automatically randomly assigned by the intervention software, but sequence generation not described.
Allocation concealment (selection bias)	Low risk	Participants were automatically randomly assigned by the intervention software.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition that was different in the 2 groups
Selective reporting (reporting bias)	Low risk	Specified outcomes reported.

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Loeb 2009

Study characteristics	
Methods	Open non-inferiority RCT carried out to compare the surgical mask with the N95 respirator in protecting healthcare workers against influenza. The trial was carried out between 2008 (enrolment started in September and follow-up on 12 January 2009) and 23 April 2009 (when all HCWs caring for febrile patients were told to wear an N95 respirator) because of the appearance of novel A/H1N1). The trial trigger was the beginning of the influenza season, defined as isolation of 2 or more viruses in a district in the same week. Following the 2003 SARS outbreak, all Ontario nurses caring for febrile patients (38 °C or more and new onset cough or SOB) had to wear surgical masks. The randomisation (carried out in blocks of 4 by centre) then consisted of either confirmation to same-maker surgical mask wear or N95 respirator wear. Investigators and laboratory staff were blind to allocation status, but for obvious reasons (the visible difference in interventions), participants were unblinded. "The criterion for non-inferiority was met if the lower limit of the 95% confidence interval (CI) for the reduction in incidence (N95 respirator minus surgical group) was greater than -9%". So this is the non-inferiority margin. It is assumed that the "minus surgical group" means minus surgical mask group.
Participants	Consenting nurses (n = 446 randomised) aged a mean of 36.2 years working full time (≥ 37 hours/week) in 23 acute units (a mix of paediatric, A&E, and acute medical units) in 8 hospitals in Ontario, Canada. 225 were randomised to the surgical mask and 221 to the N95 respirator. There were 13 and 11 dropouts, respectively from each arm (all accounted for), plus 21 and 19 lost to follow-up; 11 in each arm gave no reason, the others are accounted for. There were no deaths. The final total of 212 and 210 was included in the analysis. Table 1 reports the demographic data of participants by arm, which appear comparable.
Interventions	Surgical masks (as standard wear by the standard distributor) or fit–tested N95 respirator. All nurses wore gloves or gowns in the presence of a febrile patient.
Outcomes	Laboratory RT-PCR paired sera with 4-fold antibody rise from baseline (only for unvaccinated) nurses Effectiveness: follow-up (lasting a mean of around 97 days for both arms) was carried out twice-weekly on a web-based instrument. Nurses with new symptoms were asked to swab a nostril if any of the following signs or symptoms had developed: fever (temperature ≥ 38 °C), cough, nasal congestion, sore throat, headache, sinus problems, muscle aches, fatigue, earache, ear infection, or chills. The text defines influenza with laboratory confirmation, and separately reports criteria for swab triggering and a definition of ILI ("Influenza-like illness was defined as the presence of cough and fever: a temperature ≥ 38°C"). But this is not formally linked to influenza in the text, as it appears that primary focus was the detection of laboratory-confirmed influenza (either by RT-PCR or serology). Additional outcome data sought were work-related absenteeism and physician visits for respiratory illness. Secondary outcomes included detection of the following non-influenza viruses by PCR: parainfluenza virus types 1, 2, 3, and 4; respiratory syncytial virus types A and B; adenovirus; metapneumovirus; rhinovirus-enterovirus; and coronaviruses OC43, 229E, SARS, NL63, and HKU1. Audits to assess nurse compliance with the interventions were carried out in the room of each patient cared for. The text reports that 50 and 48 nurses in the surgical mask and N95 groups, respectively, had laboratory confirmation of influenza infection, indicating non-inferiority. Interestingly, non-inferiority seemed to be applicable both to seasonal viruses and nH1N1 viruses (as 8% and 11.9% were serologically positive to nH1N1). This finding is explained either by seeding or cross reaction with seasonal H1N1. Equivalent conclusions could be drawn for nurses with complete follow-up. Non-inferiority was applicable also to other ILI agents identified. None of the 52 individuals with positive isolates met the criteria for ILI. All cases of ILI were confirmed as having influenza (9 and 2 respectively). This means that all the 11 cases of ILI had influenza, but that most of those with a laboratory diagnosis of influenza did not have cough and fever. For example, the text reports that "Of the 44 nurses in each group who had influenza diagnosed by serology, 29 (65.9%) in the surgical mask group and 31 (70.5%) in the N95 respirator group had no symptoms". By implication, of the 88 nurses with antibody rises, 28 had symptoms of some kind, i.e. two-thirds were asymptomatic. Absenteeism was 1 versus 39 episodes in the mask ver-

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Loeb 2009 *(Continued)*

	sus respirator arms. No episodes of LRTI were recorded. The number of family contacts with ILI were the same for each arm (45 versus 47). Physician visits were similar in both groups. Safety: no AEs are reported
Notes	The authors conclude that "Among nurses in Ontario tertiary care hospitals, use of a surgical mask compared with a N95 respirator resulted in non-inferior rates of laboratory-confirmed influenza". This a well-designed and conducted trial with credible conclusions. The only comment is that the focus in the analysis on influenza (symptomatic and asymptomatic) is not well-described, although the rationale is clear (interruption of transmission).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomisation was performed centrally ....", but method of sequence generation not described.
Allocation concealment (selection bias)	Low risk	"...by an independent clinical trials coordinating group such that investigators were blind to the randomisation procedure and group assignment and was stratified by centre in permuted blocks of 4 participants."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"It was not possible to conceal the identity of the N95 respirator or the surgical mask since manipulating these devices would interfere with their function"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment blinded: "Laboratory personnel conducting hemagglutinin inhibition assays, polymerase chain reaction (PCR), and viral culture for influenza were blinded to allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	21 of 225 randomised to mask group and 19 of 221 randomised to N95 group were lost to follow-up, reasons reported. Study stopped early: "We had planned to stop the study at the end of influenza season. However, because of the 2009 influenza A(H1N1) pandemic, the study was stopped on April 23, 2009, when the Ontario Ministry of Health and Long-Term Care recommended N95 respirators for all healthcare workers taking care of patients with febrile respiratory illness."
Selective reporting (reporting bias)	Low risk	All outcomes reported.

Longini 1988

Study characteristics

Methods	Cluster-controlled, double-blind, randomised trial to assess the efficacy of virucidal tissues in interrupting family transmission of rhinovirus and influenza virus. The study was carried out in the community of Tecumseh, Michigan, USA during the period of 25 November 1984 to 28 April 1985. However, the authors only report results for the period of 13 January to 23 March 1985, when a high circulation of influenza A H3N2 and rhinovirus was detected.
Participants	296 households were enrolled, but 5 households were eliminated from the analysis for "technical reasons". The analysis was carried out in households with 3 to 5 members. The authors report data on 143 households randomised to virucidal tissues and 148 to placebo tissue. The average age in households

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Longini 1988 *(Continued)*

	was around 22, and the difference between arms was not significant. Randomisation was carried out by the sponsor, and tissues were pre-packed in coded boxes with no other identifying features and delivered to households at the beginning of the study period.
Interventions	Disposable 3-layered virucidal tissues (citric and malic acids with sodium lauryl sulphate in the middle layer) or placebo (succinic acid in the middle layer) tissues. They were used to blow the nose and for coughing or sneezing into. Households were also stratified by level of tissue use. Tissue use was significantly higher in the intervention arm (82% versus 71%).
Outcomes	Laboratory: yes - viral culture from nasal and throat swabs from symptomatic participants Effectiveness: ARI (with a proportion of laboratory-confirmed diagnosis in non-randomly chosen participants with symptoms lasting 2 days or more) Follow-up and surveillance was carried out using a telephone questionnaire. Safety: N/A
Notes	Risk of bias: high (inappropriate choice of placebo) Note: the authors conclude that virucidal tissues were up to 36.9% effective in preventing transmission of ARIs as measured by secondary attack rates (18.7% versus 11.8%). This finding was not statistically significant, but may well have been affected by the lack of do-nothing community controls. This a well-designed, well-written study despite the unexplained attrition of 5 families, the lack of reporting of cluster coefficients, and the differential in tissue use between the 2 arms, which raises questions about the robustness of double-blinding. Particularly notable is the discussion on the low generalisability of results from the study from the placebo arm given that even the inert barrier of the tissues is likely to have limited spread. Also, the lengths to which the authors went to obtain allocation concealment and maintenance of double-blind conditions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Treated and placebo tissues were randomly assigned ..." Sequence generation not reported
Allocation concealment (selection bias)	Low risk	"Treated and placebo tissues were randomly assigned by the sponsor to 296 participating households stratified by household size, such that roughly half the households would receive treated tissues. Thus, the investigators were unaware of the assignment of treated tissues."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Treated and placebo tissues were randomly assigned by the sponsor to the randomly assigned 296 households stratified by household size... The type of tissue was identified by code, and the boxes in which tissues were contained were not marked with any specific identifiers. Therefore, the study was double-blinded."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The investigators were unaware of the assignment of the treated tissues"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	296 households eligible. "The final sample used for analysis consisted of 143 households in the treatment group and 148 households in the placebo group."
Selective reporting (reporting bias)	High risk	"The analysis of secondary spread was restricted to households of three to five members for technical reasons, which eliminated five households." "The two groups were almost identical in composition."

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Luby 2005

Study characteristics	
Methods	Partly double-blind, cluster-RCT carried out during 15 April 2002 to 5 April 2003 in Karachi, Pakistan. The trial assessed the effects of mother and child hand-washing on the incidence of respiratory infections, impetigo (data not extracted), and diarrhoea (data not extracted). Randomisation took place by computer-generated random numbers in 3 phases. 1. 25 neighbourhoods were assigned to hand-washing and 11 to standard practice. 2. 300 households were assigned to using antiseptic soap. 3. 300 households were assigned to using plain soap. 4. 306 households were assigned to standard practice. 5. 1523 children younger than 15 years were assigned to using antiseptic soap. 6. 1640 children younger than 15 years were assigned to using plain soap. 7. 1528 children younger than 15 years were assigned to standard practice. Soaps were of identical weight, colour, and smell and were packed centrally with a coded packing case matched to households containing 96 bars. Neither fieldworkers nor participants were aware of the content. Control arm households were visited with the same frequency as intervention household but were given books and pens. Codes were held centrally by the manufacturer and broken after the end of the trial to allow analysis.
Participants	Householders of slums in Karachi. Of the 1523 children younger then 15 years assigned to using antiseptic soap, 117 dropped out (1 died, 51 were born in, and 65 aged out) = 1406; 504 were aged less than 5. Of 1640 children younger then 15 years assigned to using plain soap, 117 dropped out (3 died, 44 were born in, and 70 aged out) = 1523; 517 were aged less than 5. Of 1528 children younger then 15 years assigned to standard practice, 125 dropped out (3 died, 40 were born in, and 82 aged out) = 1403; 489 were aged less than 5.
Interventions	Instruction programme and antibacterial soap containing 1.2% triclocarban, or ordinary soap to be used throughout the day by householders, or standard procedure
Outcomes	Laboratory: N/A Effectiveness: 1. Number of new respiratory illness per person per week 2. Pneumonia (cough or difficulty in breathing with a respiratory rate of > 60 min in children less than 60 days old, > 50 min in those less than 1 year old, and > 40 min for those aged 1 to 5 years) Follow-up was weekly with household interview and direct observation. Children aged less than 5 were weighed, and the report presents stratification of results by child weight. Safety: N/A
Notes	Risk of bias: low (cluster coefficients and analysis by unit of randomisation provided) Note: the authors conclude that "handwashing" neighbourhoods has significantly fewer episodes of respiratory disease than controls (e.g. 50% less cough). "Handwashing" children aged less than 5 had 50% fewer episodes of pneumonia than controls (−65% to −35%). However, there was no difference in respiratory illness between types of soap. The report is confusing, with a shifting focus between children age groups. The impression reading is of an often rewritten manuscript. There is some loss of data (e.g. in the results by weight, i.e. risk group) because of lack of clarity on denominators. Despite this, the trial is a landmark.
Risk of bias	

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Luby 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation took place by computer-generated random numbers in 3 phases.
Allocation concealment (selection bias)	Low risk	"One of the investigators (SL) who did not participate in recruiting neighbourhoods or households programmed a spreadsheet to randomly generate the integers of a 1 or a 2. He applied the random numbers sequentially to the list of neighbourhoods. Neighbourhoods with a 1 were assigned to control, and those with a 2 were assigned to handwashing promotion. Random assignment continued until neighbourhoods consisted of at least 600 handwashing promotion households and 300 control households were assigned."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The antibacterial soap ... contained 1-2% triclocarban as an antibacterial substance. The plain soap was identical to the antibacterial soap except that it did not contain triclocarban... . Neither the fieldworkers nor the families knew whether soaps were antibacterial or plain."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Neither the fieldworkers nor the families knew whether soaps were antibacterial or plain."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	89% of the study population followed up, but no data on the clusters.
Selective reporting (reporting bias)	Low risk	"At baseline, households in the three intervention groups were similar."

MacIntyre 2009

Study characteristics	
Methods	Prospective cluster-RCT carried out in Sydney, Australia, to assess the use of surgical masks, P2 masks, and no masks in preventing ILI in households. The study was carried out during the 2 winter seasons of 2006 and 2007 (August to the end of October 2006 and June to the end of October 2007). “Gaussian random effects were incorporated in the model to account for the natural clustering of persons in households"
Participants	290 adults from 145 families. 47 households (94 enrolled adults and 180 children) were randomised to the surgical mask group, 46 (92 enrolled adults and 172 children) to the P2 mask group, and 52 (104 enrolled adults and 192 children) to the no-mask (control) group.
Interventions	Use of surgical masks and P2 mask versus no mask. The P2 mask is described as very cumbersome.
Outcomes	Laboratory: serological evidence Effectiveness: ILI (described as fever, history of fever or feeling feverish in the past week, myalgia, arthralgia, sore throat, cough, sneezing, runny nose, nasal congestion, headache) However, a positive laboratory finding for influenza converts the ILI definition into one of influenza. Safety: N/A
Notes	The study authors conclude that adherence to mask use significantly reduced the risk for ILI-associated infection, but < 50% of participants wore masks most of the time. They concluded that household use of face masks is associated with low adherence and is ineffective for controlling seasonal respiratory disease. Compliance was by self-report, therefore likely to be an underestimate.

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MacIntyre 2009 *(Continued)*

The primary outcome was ILI or lab-positive illness. This showed no effect.
Sensitivity analysis by adherence showed that under the assumption that the incubation period is equal to 1 day (the most probable value for the 2 most common viruses isolated, influenza (21) and rhinovirus (26)), adherent use of P2 or surgical masks significantly reduces the risk for ILI infection, with a hazard ratio = 0.26 (95% CI 0.09 to 0.77; P = 0.015). No other covariate was significant. Under the less likely assumption that the incubation period is equal to 2 days, the quantified effect of complying with P2 or surgical mask use remains strong, although borderline significant; hazard ratio was 0.32 (95% CI 0.11 to 0.98; P = 0.046). The study was underpowered to determine if there was a difference in efficacy between P2 and surgical masks (Table 5). The study conclusion appears to be a post hoc data exploration. Regardless of this, the study message is that respirator use in a family setting is unlikely to be effective as compliance is difficult unless there is a situation of real impending risk.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Participating households were randomised to 1 of 3 arms by a secure computerised randomisation process", but sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Study participants and trial staff were not blinded, as it is not technically possible to blind the mask type to which participants were randomised."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"However, laboratory staff were blinded to the arm of randomisation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	143 of 145 randomised families were analysed; 2 families in the control group were lost to follow-up during the study, for which no reasons were given.
Selective reporting (reporting bias)	Low risk	No differences between groups at baseline

MacIntyre 2011

Study characteristics

Methods	A cluster-RCT of 1441 HCWs in 15 Beijing hospitals was performed during the 2008 to 2009 winter. Participants wore masks or respirators during the entire work shift for 4 weeks. Outcomes included CRI, ILI, laboratory-confirmed respiratory virus infection, and influenza. A convenience no-mask/respirator group of 481 health workers from 9 hospitals was compared.
Participants	Participants (N = 1441) were hospital HCWs aged > 18 years from the emergency departments and respiratory wards of 15 hospitals. These wards were selected as high-risk settings in which repeated and multiple exposures to respiratory infections are expected. Participants were randomised to medical mask (N = 492 staff from 5 hospitals), N95 fit-tested masks (N = 461 staff from 5 hospitals), and N95 non-fit-tested mask (N = 488 staff from 5 hospitals).
Interventions	Fit-tested N95 respirators versus non-fit-tested N95 respirators versus medical masks. See Table 1 for details.

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MacIntyre 2011 *(Continued)*

Outcomes	Clinical respiratory illness, defined as 2 or more respiratory symptoms or 1 respiratory symptom and a systemic symptom Influenza-like illness, defined as fever ≥ 38 °C plus 1 respiratory symptom (i.e. cough, runny nose, etc.) Laboratory-confirmed viral respiratory infection (detection of adenoviruses, human metapneumovirus, coronavirus 229E/NL63, parainfluenza viruses 1, 2, and 3, influenza viruses A and B, respiratory syncytial virus A and B, rhinovirus A or B, and coronavirus OC43/HKU1 by multiplex PCR) Laboratory-confirmed influenza A or B Adherence with mask or respirator use. Reported problems associated with using the masks or respirators
Notes	Funding source unknown; control arm not randomised so has been ignored

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process (using a secure computerised randomisation program), but sequence generation not described
Allocation concealment (selection bias)	Low risk	Hospitals randomised prior to inclusion of participants.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Specified outcomes reported.

MacIntyre 2013

Study characteristics

Methods	A cluster-RCT
Participants	A total of 1669 nurses and doctors from 68 emergency departments and respiratory wards of 19 Beijing hospitals were included. Inclusion criteria: any nurse or doctor aged 18 years or older who worked full time in the emergency or respiratory wards was eligible. Exclusion: HCWs if they (1) were unable or refused to consent; (2) had beards, long moustaches, or long facial hair stubble; (3) had a current respiratory illness, rhinitis, and/or allergy; or (4) worked part time or did not work in the aforementioned wards or departments Final analysis was performed on 572 staff and 24 wards in medical mask group, 516 staff and 20 wards in the targeted N95 mask group, and 581 staff and 24 wards in the N95 mask group.

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MacIntyre 2013 *(Continued)*

Interventions	Quote: "Masks used in the study were the 3M Standard Tie-On Surgical Mask (catalog number mask 1817; 3M, St. Paul, MN) and the 3M Health Care N95 Particulate Respirator (catalog number 1860; 3M)... . Participants wore the mask or respirator on every shift after being shown how to fit and wear it. Participants were supplied daily with either three masks for the medical mask arm or two N95 respirators. Participants using N95 respirators underwent a fit testing procedure using a 3M FT-30 Bitrex Fit Test Kit according to the manufacturer's instructions (3M)." See Table 1 for details.
Outcomes	Laboratory: 1. Laboratory-confirmed viral respiratory infection in symptomatic participants, defined as detection of adenoviruses; human metapneumovirus; coronaviruses 229E/NL63 and OC43/HKU1; parainfluenza viruses 1, 2, and 3; influenza viruses A and B; respiratory syncytial viruses A and B; or rhinoviruses A/B by nucleic acid testing (NAT) using a commercial multiplex polymerase chain reaction (Seegen, Inc., Seoul, Korea). 2. Laboratory-confirmed influenza A or B in symptomatic participants. 3. Laboratory-confirmed bacterial colonisation in symptomatic participants, defined as detection of *Streptococcus pneumoniae*, *Legionella*, *Bordetella pertussis*, chlamydia, *Mycoplasma pneumoniae*, or *Haemophilus influenzae* type B by multiplex polymerase chain reaction (Seegen, Inc.). Effectiveness: CRI, defined as 2 or more respiratory symptoms or 1 respiratory symptom and a systemic symptom. ILI, defined as fever (38 °C) plus 1 respiratory symptom Safety: adverse effects measured using a semi-structured questionnaire. Investigators stated that there was higher reported adverse effects and discomfort of N95 respirators compared with the other 2 arms. In terms of comfort, 52% (297 of 571) of the medical mask arm reported no problems, compared with 62% (317 of 512) of the targeted arm and 38% (217 of 574) of the N95 arm (P < 0.001).
Notes	Compliance with the product was highest in the targeted N95 arm (82%; 422 of 516), then the medical mask arm (66%; 380 of 572), and the N95 arm (57%; 333 of 581); these differences were statistically significant (P < 0.001). The period study conducted: 28 December 2009 to 7 February 2010 Funding: unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"using a secure computerized randomization program", but sequence generation not described
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Outcome was objectively assessed with lab confirmation in addition to clinical illness.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Laboratory outcomes are reported for all subjects (with at least one respiratory symptom or fever) tested, and then for the subset meeting the CRI definition"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. Flow chart and text match, investigators conducted ITT and PP analysis. All the outcomes were accounted for amongst all participants.

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MacIntyre 2013 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes were reported as planned.

MacIntyre 2015

Study characteristics	
Methods	A cluster-RCT of cloth masks compared with medical masks in healthcare workers in 14 secondary-/tertiary-level hospitals in Hanoi, Vietnam. Hospital wards were randomised to: medical masks, cloth masks, or a control group (usual practice, which included mask wearing). Participants used the mask on every shift for 4 consecutive weeks.
Participants	1607 hospital HCWs aged ≥ 18 years working full time in selected high-risk wards. Medical mask group (n = 580 HCWs), cloth mask group (n = 569 HCWs), control group (n = 458 HCWs)
Interventions	Medical masks, cloth masks, or a control group. See Table 1 for details.
Outcomes	Clinical respiratory illness, influenza-like illness, and laboratory-confirmed respiratory virus infection 1. Clinical respiratory illness, defined as 2 or more respiratory symptoms or 1 respiratory symptom and a systemic symptom 2. Influenza-like illness, defined as fever ≥ 38 °C plus 1 respiratory symptom 3. Laboratory-confirmed viral respiratory infection. Laboratory confirmation was by nucleic acid detection using multiplex reverse transcriptase PCR (RT-PCR) for 17 respiratory viruses. Adverse events associated with mask use
Notes	Government funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Epi info V.6 was used to generate a randomisation allocation.
Allocation concealment (selection bias)	Low risk	74 wards randomised prior to recruitment of individuals.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Specified endpoints reported.

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MacIntyre 2015

Study characteristics	
Methods	A cluster-RCT of cloth masks compared with medical masks in healthcare workers in 14 secondary-/tertiary-level hospitals in Hanoi, Vietnam. Hospital wards were randomised to: medical masks, cloth masks, or a control group (usual practice, which included mask wearing). Participants used the mask on every shift for 4 consecutive weeks.
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Risk of bias		
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Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Specified endpoints reported.

MacIntyre 2016

Study characteristics

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MacIntyre 2016 *(Continued)*

Methods	Cluster-RCT to examine medical mask use as source control for people with respiratory illness in 6 major hospitals in 2 districts of Beijing, China. Index cases with ILI were randomly allocated to medical mask (n = 123) and control arms (n = 122). Since 43 index cases in the control arm also used a mask during the study period, an as-treated post hoc analysis was performed by comparing outcomes amongst household members of index cases who used a mask (mask group) with household members of index cases who did not use a mask (no mask group).
Participants	245 index cases with ILI (medical mask = 123, control group = 122) and 597 household contacts (medical mask = 302, control group = 295)
Interventions	Medical mask versus no mask (control). See Table 1 for details.
Outcomes	Clinical respiratory illness, ILI, and laboratory-confirmed viral respiratory infection 1. Clinical respiratory illness, defined as 2 or more respiratory symptoms (cough, nasal congestion, runny nose, sore throat, or sneezes) or 1 respiratory symptom and a systemic symptom (chill, lethargy, loss of appetite, abdominal pain, muscle or joint aches). 2. ILI, defined as fever ≥ 38 °C plus 1 respiratory symptom. 3. Laboratory-confirmed viral respiratory infection, defined as detection of adenoviruses, human metapneumovirus, coronaviruses 229E/NL63 and OC43/HKU1, parainfluenza viruses 1, 2, and 3, influenza viruses A and B, respiratory syncytial virus A and B, or rhinovirus A/B by nucleic acid testing using a commercial multiplex PCR. No safety outcomes reported.
Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation sequence using Microsoft Excel
Allocation concealment (selection bias)	High risk	Doctors enrolled the participants randomly to intervention and control arms.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Clinical endpoints assessed unblinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Specified outcomes reported.

MacIntyre 2016

Study characteristics

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MacIntyre 2016 *(Continued)*

Methods	Cluster-RCT to examine medical mask use as source control for people with respiratory illness in 6 major hospitals in 2 districts of Beijing, China. Index cases with ILI were randomly allocated to medical mask (n = 123) and control arms (n = 122). Since 43 index cases in the control arm also used a mask during the study period, an as-treated post hoc analysis was performed by comparing outcomes amongst household members of index cases who used a mask (mask group) with household members of index cases who did not use a mask (no mask group).
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Outcomes	Clinical respiratory illness, ILI, and laboratory-confirmed viral respiratory infection 1. Clinical respiratory illness, defined as 2 or more respiratory symptoms (cough, nasal congestion, runny nose, sore throat, or sneezes) or 1 respiratory symptom and a systemic symptom (chill, lethargy, loss of appetite, abdominal pain, muscle or joint aches). 2. ILI, defined as fever ≥ 38 °C plus 1 respiratory symptom. 3. Laboratory-confirmed viral respiratory infection, defined as detection of adenoviruses, human metapneumovirus, coronaviruses 229E/NL63 and OC43/HKU1, parainfluenza viruses 1, 2, and 3, influenza viruses A and B, respiratory syncytial virus A and B, or rhinovirus A/B by nucleic acid testing using a commercial multiplex PCR. No safety outcomes reported.
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Blinding of outcome assessment (detection bias) All outcomes	High risk	Clinical endpoints assessed unblinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Specified outcomes reported.

McConeghy 2017

Study characteristics

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McConeghy 2017 *(Continued)*

Methods	Pilot study of comprehensive intervention (education, cleaning of surfaces, audit and feedback) to staff of nursing homes versus usual care. Pair-matched cluster-randomised design with only 5 clusters (nursing homes) in each group
Participants	10 nursing homes in Colorado, USA Intervention group = 481 long-stay residents and control group = 380 'Long-stay' defined as resident at least 90 days prior to baseline, or recently readmitted after previous long stay.
Interventions	A multifaceted hand-washing/surface-cleaning intervention comprised of 1) 1-hour online educational module focused on how to prevent infections; 2) provided with an "essential bundle" of 7 products, ranging from hand sanitiser gel and foam to antiviral facial tissues, disinfecting spray, and hand and face wipe and recommendation to use 4 skin cream and wipe products; 3) audit and feedback system. See Table 1 for details.
Outcomes	Laboratory: surface cultures mentioned in Methods, but no results given Effectiveness: LRTI, all infections, hospitalisation, use of antibiotics (not relevant to this review) Safety: none mentioned in Methods and no results given
Notes	The authors conclude that "This multifaceted hand-washing and surface cleaning intervention was designed to reduce infection rates among nursing homes residents. In our 10-facility randomized, matched pair pilot study, we observed program compliance and satisfaction along with reductions in surface bacterial counts, but did not observe a statistically significant reduction in infection rates, antimicrobial use, or hospitalizations". Very poorly reported study with results not explained, summarised in Table 3 as RDs. Denominators and attrition are unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Illness and absenteeism reported by treating staff.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No attrition given. Data were collected from e-medical record at baseline, but not clear whether illness data during the study were collected by the same method.
Selective reporting (reporting bias)	High risk	Upper respiratory tract infection was mentioned in the Methods (intervention presumably would target these), but only LRTI and overall infection reported.

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McConeghy 2017

Study characteristics	
Methods	Pilot study of comprehensive intervention (education, cleaning of surfaces, audit and feedback) to staff of nursing homes versus usual care. Pair-matched cluster-randomised design with only 5 clusters (nursing homes) in each group
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McConeghy 2017 *(Continued)*

Selective reporting (reporting bias)	High risk	Upper respiratory tract infection was mentioned in the Methods (intervention presumably would target these), but only LRTI and overall infection reported.

Millar 2016

Study characteristics	
Methods	Cluster-RCT, open-label study, factorial design
Participants	Around 30,000 healthy, male army trainees aged 18 to 42 years at Fort Benning, Georgia were included. Inclusion criteria: trainees assigned to 1 of the 6 selected training battalions, trainees who present with an SSTI at the clinic or the hospital, provide informed consent. Exclusion criteria: fails to meet inclusion criteria. No denominator breakdown by arm is reported.
Interventions	Promotion of hand-washing in addition to a once-weekly application of chlorhexidine-based body wash. See Table 1 for details.
Outcomes	This study was nested in a large field-based RCT and utilised clinic-based medical records. Laboratory: none Effectiveness: incidence of ARI at 20 months. The case definition was any occurrence of the following ICD-9 symptom or disease-specific codes: 460 to 466, 480 to 488, and specifically 465.9, 482.9, 486, and 487.1. Safety: adverse effects neither planned nor reported by the investigators
Notes	The period study conducted: May 2010 to January 2012 Funding: government

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated random numbers to 1 of the 3 study groups"
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was open-label and self-reporting of ARI. It is planned as secondary objective of an original trial. Data abstractors were blinded to group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data abstractors were blinded to group assignment.
Incomplete outcome data (attrition bias) All outcomes	High risk	There is a statistically significant difference between attrition rates in the 3 groups. The reasons for attrition are briefly reported in Table 1 of the original study (Ellis and colleagues 2014), but are unlikely to be related to the outcomes of this study. ARI cases were captured utilising clinic-based medical records, but this outcome is not prespecified in the protocol.

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Millar 2016 *(Continued)*

Selective reporting (reporting bias)	High risk	The study was conducted for another purpose. According to the study protocol, the outcomes of interest in the current report were not mentioned as outcomes when the study was planned. ARI is not prespecified as an outcome in the protocol published on ClinicalTrials.gov.

Millar 2016

Study characteristics	
Methods	Cluster-RCT, open-label study, factorial design
Participants	Around 30,000 healthy, male army trainees aged 18 to 42 years at Fort Benning, Georgia were included. Inclusion criteria: trainees assigned to 1 of the 6 selected training battalions, trainees who present with an SSTI at the clinic or the hospital, provide informed consent. Exclusion criteria: fails to meet inclusion criteria. No denominator breakdown by arm is reported.
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Millar 2016 *(Continued)*

		comes of this study. ARI cases were captured utilising clinic-based medical records, but this outcome is not prespecified in the protocol.
Selective reporting (reporting bias)	High risk	The study was conducted for another purpose. According to the study protocol, the outcomes of interest in the current report were not mentioned as outcomes when the study was planned. ARI is not prespecified as an outcome in the protocol published on ClinicalTrials.gov.

Miyaki 2011

Study characteristics	
Methods	A quasi-cluster-RCT
Participants	A total of 15,134 assigned to intervention (N = 6634 workers) and control (N = 8500 workers) Inclusion criteria: all general employees (aged 19 to 72 years in 2009) of 2 sibling companies of a major car industry in Kanagawa Prefecture, Japan. All workers who regularly reported to the workplace were included, regardless of treatment for chronic diseases. All employees have the same health insurance plan and were followed up in the same way.
Interventions	"The intervention involved asking workers whose family members developed an influenza-like illness (ILI) to stay at home. If any co-habiting family members showed signs of influenza-like illness (ILI), employees ... were asked to stay at home voluntarily until 5 days has passed since the resolution of the ILS symptoms or 2 days after alleviation of fever." See Table 1 for details.
Outcomes	Workroom: influenza A test kit (rapid test) Effectiveness: assess the effectiveness of household quarantine in reducing the incidence of influenza A H1N1. ILI was defined as a body temperature greater than 38 °C or more than 1 °C above the normal temperature accompanied with more than 2 of these symptoms: nasal mucus, pharyngeal pain, cough, chills or heat sensation Safety: the incidence of influenza A H1N1 amongst workers who were told to stay home if a family member developed ILI was higher (relative risk of 2.17; P < 0.001) compared to control group. No other safety measures/harms reported. Compliance: quote: "our intervention was not compulsory; we only asked the employees to leave the workplace for a while on full pay, and we succeeded in getting all workers' agreement. In our case, explaining that the home waiting policy might be beneficial to the whole workers and help to avoid stopping the manufacturing lines (explaining it is for the benefit of the public) and guaranteeing payment during the leave (financial support) helped them to obey our request."
Notes	Period study conducted: 1 July 2009 to 19 February 2010 Unfunded

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information given.
Allocation concealment (selection bias)	Unclear risk	No information given.

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Miyaki 2011 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	The nature of the intervention (stay at home) was confirmed in the intervention group, where all workers agree as they were financially supported during absences due to ILI.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Company doctors diagnosed the disease through a positive result of an influenza A test or clinical symptoms", but not clear if they were blinded to assignment; however, the diagnostic process is meticulous and objectively confirmed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All cases are included in the analysis, and none were lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Although all outcomes of interest are clearly specified, described, and followed up, and text and numbers checked out well and based on the outcome stated for the study, there is no published protocol to match the planned vs the reported outcomes.

Miyaki 2011

Study characteristics	
Methods	A quasi-cluster-RCT
Participants	A total of 15,134 assigned to intervention (N = 6634 workers) and control (N = 8500 workers) Inclusion criteria: all general employees (aged 19 to 72 years in 2009) of 2 sibling companies of a major car industry in Kanagawa Prefecture, Japan. All workers who regularly reported to the workplace were included, regardless of treatment for chronic diseases. All employees have the same health insurance plan and were followed up in the same way.
Interventions	"The intervention involved asking workers whose family members developed an influenza-like illness (ILI) to stay at home. If any co-habiting family members showed signs of influenza-like illness (ILI), employees ... were asked to stay at home voluntarily until 5 days has passed since the resolution of the ILS symptoms or 2 days after alleviation of fever." See Table 1 for details.
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Notes	Period study conducted: 1 July 2009 to 19 February 2010

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Miyaki 2011 *(Continued)*

	Unfunded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given.
Allocation concealment (selection bias)	Unclear risk	No information given.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The nature of the intervention (stay at home) was confirmed in the intervention group, where all workers agree as they were financially supported during absences due to ILI.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Company doctors diagnosed the disease through a positive result of an influenza A test or clinical symptoms", but not clear if they were blinded to assignment; however, the diagnostic process is meticulous and objectively confirmed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All cases are included in the analysis, and none were lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Although all outcomes of interest are clearly specified, described, and followed up, and text and numbers checked out well and based on the outcome stated for the study, there is no published protocol to match the planned vs the reported outcomes.

Morton 2004

Study characteristics

Methods	Cross-over study to evaluate the effectiveness of an alcohol gel as an adjunct to regular hand-washing for decreasing absenteeism amongst elementary children by reducing specific communicable diseases such cold, flu, and conjunctivitis. The study was conducted in an elementary school in New England, USA. In the cross-over design, classrooms in each grade level were randomised to begin as the experimental group (alcohol gel) or the control group (regular hand-washing). A study protocol for hand hygiene was introduced following the germ unit education. The hand-washing product was a soap-and-water alternative that is approximately 60% ethyl alcohol. In phase 1 (46 days) children in 9 classrooms were in the experimental group, and children in 8 classrooms were in the control group. After a 1-week washout period when no children had access to the alcohol gel, phase 2 (47 days) started, and the classroom that had participated before as experimental group passed into the control group and vice versa. Data were collected by the parents, who informed the secretary or the school nurse of the reasons for a child's absence, including symptoms of any illness. Respiratory illnesses were defined by symptoms of URTI.
Participants	253 children, 120 girls and 133 boys, from kindergarten to 3rd grade. Of the eligible 285 students, 32 children dropped out (10 due to skin irritation and 22 because of lack of parental consent). No denominator breakdown by arm is reported because the study used a cross-over design.
Interventions	Use of an alcohol gel as an adjunct to regular hand-washing and educational programme versus regular hand-washing and educational programme
Outcomes	Laboratory: no

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Morton 2004 *(Continued)*

	Effectiveness: days of absences from school for respiratory illness Safety: N/A
Notes	Risk of bias: high (no description of randomisation; partial reporting of outcomes, numerators and denominators) Note: the authors conclude that significantly fewer children became ill whilst using the alcohol gel as an adjunct to regular hand-washing than when using regular hand-washing only (decreased school absenteeism of 43% with the use of alcohol gel on top of hand-washing). The authors also described, as a limitation of the study, the fact that the school nurse served as the data collector, which could be perceived as bias in measurement of the outcome variable. Randomisation and allocation are not described; no cluster coefficients were reported; and attrition was not taken into consideration during the analysis. Unit of randomisation and analysis are different. No reporting by arm. No ORs, no CIs reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"A cross-over design was used. In the crossover design, classrooms in each grade level were randomized to begin as the experimental group (regular hand washing)."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The school nurse served as the data collector for the duration of the study. This could be perceived as bias in the measurement of the outcome variable, absenteeism related to infectious illness."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information

Najnin 2019

Study characteristics

Methods	Cluster-RCT, parallel assignment
Participants	Residents of the high-risk, cholera-prone study areas. Low-income communities in Mirpur area of urban Dhaka defined by low per capita income, poor sanitation, unsafe water use, sharing of water source, and poor living conditions. 90 geographic clusters were included, with 30-metre buffer zones. A total of 7842 households, with 52,237 individuals analysed Vaccine-only area: data were analysed for 1965 households consisting of 13,148 individuals Vaccine-plus-behaviour-change area: data were analysed for 3886 households consisting of 25,566 individuals Control area: data were analysed for 1991 households consisting of 13,523 individuals

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Najnin 2019 *(Continued)*

	Study criteria from published protocol: Inclusion criteria: apparently healthy residents of selected vaccination sites, aged 1 year and above, non-pregnant women, written informed consent Exclusion criteria: age less than 1 year and pregnant women
Interventions	Hand-washing and water treatment promotion. See Table 1 for details.
Outcomes	Laboratory: none used Effectiveness: prevalence of respiratory illness. People were classified as having respiratory illness if they reported having fever plus either cough or nasal congestion or fever plus breathing difficulty in the past 2 days of unannounced home visits: in each intervention group and amongst those who had soap/soapy water with water present in the hand-washing station (35% of all groups combined) versus those without this (regardless of the intervention group). Planned secondary outcome: prevalence of reported respiratory illness during 2-year intervention period Safety: no adverse effects planned or reported
Notes	The period study conducted: 2011 to 2013 Funding: government and private Bill & Melinda Gates Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence was used to allocate 90 geographical clusters to 1 of 3 groups. Before randomisation, clusters were stratified blocked into 2 categories according to the distance to the hospital. (parent article: Lancet. 2015 Oct 3;386(10001):1362-1371)
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	All trial participants and investigators were aware of group assignment. Several in and out migrations across all groups before, after, and during outcome monitoring, and large number of changes in intervention areas
Blinding of outcome assessment (detection bias) All outcomes	High risk	Several in and out migrations across all groups before, after, and during outcome monitoring, and large number of changes in intervention areas
Incomplete outcome data (attrition bias) All outcomes	High risk	High migration movement. This could have distorted the baseline characteristics even more. Very hard to assess because the numbers in the index paper are different from the parent paper (Qadri 2015). In addition to that, for each intervention, data were analysed for 15% to 30% of those allocated on start date. Each group started with approximately 80,000 people; the number analysed is much lower (237,216 people were in the study area on start date of outcome monitoring, the total number analysed across all groups was 52,237). No info about data on migrated individuals or on those who changed intervention areas was dealt with? Also data for prevalence of ARI adjusted for age and wealth were not shown. The outcome is addressed in the 2 days preceding an unannounced visit. This means that if there was a respiratory illness in the past week it would not have been reported. Moreover, these monthly unannounced visits were done to a different set of participants in each group!

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Najnin 2019 *(Continued)*

Selective reporting (reporting bias)	High risk	Published protocol does not include respiratory illness as an outcome.

Morton 2004

Study characteristics

Methods	Cross-over study to evaluate the effectiveness of an alcohol gel as an adjunct to regular hand-washing for decreasing absenteeism amongst elementary children by reducing specific communicable diseases such cold, flu, and conjunctivitis. The study was conducted in an elementary school in New England, USA. In the cross-over design, classrooms in each grade level were randomised to begin as the experimental group (alcohol gel) or the control group (regular hand-washing). A study protocol for hand hygiene was introduced following the germ unit education. The hand-washing product was a soap-and-water alternative that is approximately 60% ethyl alcohol. In phase 1 (46 days) children in 9 classrooms were in the experimental group, and children in 8 classrooms were in the control group. After a 1-week washout period when no children had access to the alcohol gel, phase 2 (47 days) started, and the classroom that had participated before as experimental group passed into the control group and vice versa. Data were collected by the parents, who informed the secretary or the school nurse of the reasons for a child's absence, including symptoms of any illness. Respiratory illnesses were defined by symptoms of URTI.
Participants	253 children, 120 girls and 133 boys, from kindergarten to 3rd grade. Of the eligible 285 students, 32 children dropped out (10 due to skin irritation and 22 because of lack of parental consent). No denominator breakdown by arm is reported because the study used a cross-over design.
Interventions	Use of an alcohol gel as an adjunct to regular hand-washing and educational programme versus regular hand-washing and educational programme
Outcomes	Laboratory: no Effectiveness: days of absences from school for respiratory illness Safety: N/A
Notes	Risk of bias: high (no description of randomisation; partial reporting of outcomes, numerators and denominators) Note: the authors conclude that significantly fewer children became ill whilst using the alcohol gel as an adjunct to regular hand-washing than when using regular hand-washing only (decreased school absenteeism of 43% with the use of alcohol gel on top of hand-washing). The authors also described, as a limitation of the study, the fact that the school nurse served as the data collector, which could be perceived as bias in measurement of the outcome variable. Randomisation and allocation are not described; no cluster coefficients were reported; and attrition was not taken into consideration during the analysis. Unit of randomisation and analysis are different. No reporting by arm. No ORs, no CIs reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Unclear risk	"A cross-over design was used. In the crossover design, classrooms in each grade level were randomized to begin as the experimental group (regular hand washing)."

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Morton 2004 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The school nurse served as the data collector for the duration of the study. This could be perceived as bias in the measurement of the outcome variable, absenteeism related to infectious illness."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information

Najnin 2019

Study characteristics	
Methods	Cluster-RCT, parallel assignment
Participants	Residents of the high-risk, cholera-prone study areas. Low-income communities in Mirpur area of urban Dhaka defined by low per capita income, poor sanitation, unsafe water use, sharing of water source, and poor living conditions. 90 geographic clusters were included, with 30-metre buffer zones. A total of 7842 households, with 52,237 individuals analysed Vaccine-only area: data were analysed for 1965 households consisting of 13,148 individuals Vaccine-plus-behaviour-change area: data were analysed for 3886 households consisting of 25,566 individuals Control area: data were analysed for 1991 households consisting of 13,523 individuals Study criteria from published protocol: Inclusion criteria: apparently healthy residents of selected vaccination sites, aged 1 year and above, non-pregnant women, written informed consent Exclusion criteria: age less than 1 year and pregnant women
Interventions	Hand-washing and water treatment promotion. See Table 1 for details.
Outcomes	Laboratory: none used Effectiveness: prevalence of respiratory illness. People were classified as having respiratory illness if they reported having fever plus either cough or nasal congestion or fever plus breathing difficulty in the past 2 days of unannounced home visits: in each intervention group and amongst those who had soap/soapy water with water present in the hand-washing station (35% of all groups combined) versus those without this (regardless of the intervention group). Planned secondary outcome: prevalence of reported respiratory illness during 2-year intervention period Safety: no adverse effects planned or reported
Notes	The period study conducted: 2011 to 2013 Funding: government and private Bill & Melinda Gates Foundation
Risk of bias	

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Najnin 2019 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence was used to allocate 90 geographical clusters to 1 of 3 groups. Before randomisation, clusters were stratified blocked into 2 categories according to the distance to the hospital. (parent article: Lancet. 2015 Oct 3;386(10001):1362-1371)
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	All trial participants and investigators were aware of group assignment. Several in and out migrations across all groups before, after, and during outcome monitoring, and large number of changes in intervention areas
Blinding of outcome assessment (detection bias) All outcomes	High risk	Several in and out migrations across all groups before, after, and during outcome monitoring, and large number of changes in intervention areas
Incomplete outcome data (attrition bias) All outcomes	High risk	High migration movement. This could have distorted the baseline characteristics even more. Very hard to assess because the numbers in the index paper are different from the parent paper (Qadri 2015). In addition to that, for each intervention, data were analysed for 15% to 30% of those allocated on start date. Each group started with approximately 80,000 people; the number analysed is much lower (237,216 people were in the study area on start date of outcome monitoring, the total number analysed across all groups was 52,237). No info about data on migrated individuals or on those who changed intervention areas was dealt with? Also data for prevalence of ARI adjusted for age and wealth were not shown. The outcome is addressed in the 2 days preceding an unannounced visit. This means that if there was a respiratory illness in the past week it would not have been reported. Moreover, these monthly unannounced visits were done to a different set of participants in each group!
Selective reporting (reporting bias)	High risk	Published protocol does not include respiratory illness as an outcome.

Nicholson 2014

Study characteristics	
Methods	Cluster-RCT
Participants	70 low-income communities in Mumbai, India (35 communities per arm) were randomised to intervention arm (N = 1025) and control arm (N = 1026). Households located in low-income urban communities in west and south Mumbai, India. Each household contains 1 target child in the first year of a municipal school (typically aged 5 years).
Interventions	Combination of hand-washing promotion with provision of free soap aimed at 5-year-olds with provision of free soap. See Table 1 for details.
Outcomes	Laboratory: none reported Effectiveness: Primary outcomes: episodes of diarrhoea, ARIs, and school absences amongst target children, and episodes of diarrhoea and ARIs among their families

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Nicholson 2014 *(Continued)*

	Secondary outcomes: episodes of eye infections, vomiting, abscesses or boils, headaches, and earache Operational definitions for all the illnesses were taken from *Black's Medical Dictionary* (MacPherson 1999). ARIs as "pneumonia, cough, fever, chest pain and shortness of breath, cold, inflammation of any or all of the airways, that is, nose, sinuses, throat, larynx, trachea and bronchi" Safety: no safety measures planned or reported by the investigators
Notes	The period study conducted: 22 October 2007 to 2 August 2008 Funding: multinational corporate company (Unilever plc.)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Coin tossing used, which could have led to a large imbalance.
Allocation concealment (selection bias)	Low risk	"a coin toss was used to assign one community in each pair to intervention and one to control"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants knew to which arm they had been recruited. Households were removed from the study if they provided no data for 5 consecutive weeks.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Data collectors were independent of the behaviour change intervention. Each was assigned exclusively to either households in the intervention group or to control households. However, communities, where very low literacy levels exist, were replaced after randomisation.
Incomplete outcome data (attrition bias) All outcomes	High risk	Data for non-completers were available and similar across groups. ITT and PP were performed. However, households were removed from the study if they provided no data for 5 consecutive weeks.
Selective reporting (reporting bias)	Unclear risk	No information to judge

Pandejpong 2012

Study characteristics

Methods	Cluster-RCT, single study centre
Participants	Children (total number = 1437) were randomised to alcohol hand gel every 60 minutes (N = 452 children), every 120 minutes (N = 447 children), and once before lunch (N = 540 children). Inclusion criteria: all children in a large private school in suburban Bangkok, Thailand, all ages, both genders with parental consent to participate. Exclusion criteria: an allergy to alcohol hand gel
Interventions	3 disinfection interventions: Alcohol hand gel applied every 60 minutes vs every 120 minutes vs once before lunch (3 groups). The current school standard for hand hygiene (q lunch group). See Table 1 for details.
Outcomes	Laboratory: none

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Pandejpong 2012 *(Continued)*

	Effectiveness: Primary: rates of absenteeism from physician-confirmed ILI Secondary: rate of absenteeism caused by total reported ILI (with and without a doctor's confirmation) In case the child was sick but did not see a doctor, the parents were asked to report any of the following symptoms: runny nose or cough, fever or chills, sore throat, headache, diarrhoea, and presence of hand, foot, or mouth ulcers. If 2 or more of these symptoms were reported, then the child's illness was documented as an ILI. Safety: investigators reported that no adverse reaction to the alcohol hand gel was reported in any participants
Notes	The period study conducted: December 2009 to February 2010 Funding: Royal College of Physicians of Thailand

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Parents and teachers are aware of the assignment. Teachers were responsible for recording the absenteeism case record forms. Parents would report child sickness. No diagnostic tests, even in the case of physician-confirmed ILI
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome is physician-confirmed ILI.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"No students were lost to follow-up or discontinued the intervention during the study period."
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Pandejpong 2012

Study characteristics

Methods	Cluster-RCT, single study centre
Participants	Children (total number = 1437) were randomised to alcohol hand gel every 60 minutes (N = 452 children), every 120 minutes (N = 447 children), and once before lunch (N = 540 children). Inclusion criteria: all children in a large private school in suburban Bangkok, Thailand, all ages, both genders with parental consent to participate. Exclusion criteria: an allergy to alcohol hand gel

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Pandejpong 2012 *(Continued)*

Interventions	3 disinfection interventions: Alcohol hand gel applied every 60 minutes vs every 120 minutes vs once before lunch (3 groups). The current school standard for hand hygiene (q lunch group). See Table 1 for details.
Outcomes	Laboratory: none Effectiveness: Primary: rates of absenteeism from physician-confirmed ILI Secondary: rate of absenteeism caused by total reported ILI (with and without a doctor's confirmation) In case the child was sick but did not see a doctor, the parents were asked to report any of the following symptoms: runny nose or cough, fever or chills, sore throat, headache, diarrhoea, and presence of hand, foot, or mouth ulcers. If 2 or more of these symptoms were reported, then the child's illness was documented as an ILI. Safety: investigators reported that no adverse reaction to the alcohol hand gel was reported in any participants
Notes	The period study conducted: December 2009 to February 2010 Funding: Royal College of Physicians of Thailand

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Parents and teachers are aware of the assignment. Teachers were responsible for recording the absenteeism case record forms. Parents would report child sickness. No diagnostic tests, even in the case of physician-confirmed ILI
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome is physician-confirmed ILI.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"No students were lost to follow-up or discontinued the intervention during the study period."
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Priest 2014

Study characteristics	
Methods	A cluster-RCT

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Priest 2014 *(Continued)*

Participants	Study included children aged 5 to 11 years at 68 primary schools in New Zealand. Schools were randomised to hand sanitiser + education session arm (34 schools and 8859 children) and education session arm (34 schools and 7386 children). Inclusion criteria: School-level inclusion: at least 100 children of primary school age (school years 1 to 6; children will generally range in age from 5 years to 11 years) at November 2008. Schools that are not currently using hand sanitiser products or are willing to not use them for the period of the trial. Schools are within the City boundaries of Christchurch, Dunedin, or Invercargill in New Zealand. The principal of the school consents to the school being included in the trial. Not ''special schools'' (e.g. schools for children with deafness or disability) and either not currently using hand sanitiser products or willing to not use them for the period of the trial if they were randomised to the control group were eligible to participate in the trial. Student-level inclusion (follow-up children): children were eligible to participate in the follow-up group, for whom more detailed information on absences was collected, if they attended a school year 1 to 6 class in 1 of the included schools at the beginning of the second school term in 2009 (the end of April), and their caregivers completed the consent form indicating that they were willing to be telephoned following their child's absences and that they were able to take part in telephone interviews in English Exclusion criteria: School-level exclusion: special needs schools Student-level exclusion (follow-up children): children of the principal investigators and study personnel of the trial. Or, children of families that the principal of the primary school directs us not to approach
Interventions	Hand sanitiser provision (in addition to hand hygiene education session also provided to control group) in schoolchildren. See Table 1 for details.
Outcomes	Laboratory: none Effectiveness: Primary outcome: the incidence rate of absence episodes from school (reported by the parents during telephone calls) due to any illness during the study period (winter term) Secondary outcomes: assessing whether hand sanitiser was effective in reducing the: 1. incidence rate of respiratory illness absence episodes, 2. incidence rate of gastrointestinal illness absence episodes, 3. incidence rate of absence for any reason, 4. length of illness episode, 5. length of illness absence episode, and 6. incidence rate of subsequent illness amongst other children or adults in the household. Definition of respiratory illness: at least 2 of the following caregiver-reported symptoms for 1 day, or 1 of the following symptoms for 2 days (but not fever alone): runny nose, stuffy or blocked nose or noisy breathing, cough, fever, sore throat, or sneezing Safety: examined whether the use of hand sanitiser was associated with an increased risk of any skin reactions during the intervention period. Skin reactions: dryness, redness, flakiness, itchiness, eczema, and any other skin reactions
Notes	The period study conducted: 27 April to 25 September 2009 Funding: government (Health Research Council of New Zealand)

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Priest 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Stata/MP 10.1 for Windows was used to generate the random numbers"
Allocation concealment (selection bias)	Low risk	Done by trial statistician provided with school codes and district and randomised the schools to either "A" or "B"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Outcome assessors were blinded to the group allocation until the analysis was completed.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to the group allocation until the analysis was completed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The flow diagram gives a clear account on follow-up, with numbers of those lost to follow-up and those who discontinued the intervention along with the reasons for doing so. No child was excluded from the analysis. Only PP analysis was reported.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the published protocol were reported in the study. The exception was "1 planned secondary outcome (that is irrelevant to our study) that was not collected and 2 collected secondary outcomes that were not planned in the original protocol".

Priest 2014

Study characteristics

Methods	A cluster-RCT
Participants	Study included children aged 5 to 11 years at 68 primary schools in New Zealand. Schools were randomised to hand sanitiser + education session arm (34 schools and 8859 children) and education session arm (34 schools and 7386 children). Inclusion criteria: School-level inclusion: at least 100 children of primary school age (school years 1 to 6; children will generally range in age from 5 years to 11 years) at November 2008. Schools that are not currently using hand sanitiser products or are willing to not use them for the period of the trial. Schools are within the City boundaries of Christchurch, Dunedin, or Invercargill in New Zealand. The principal of the school consents to the school being included in the trial. Not ‘‘special schools’’ (e.g. schools for children with deafness or disability) and either not currently using hand sanitiser products or willing to not use them for the period of the trial if they were randomised to the control group were eligible to participate in the trial. Student-level inclusion (follow-up children): children were eligible to participate in the follow-up group, for whom more detailed information on absences was collected, if they attended a school year 1 to 6 class in 1 of the included schools at the beginning of the second school term in 2009 (the end of April), and their caregivers completed the consent form indicating that they were willing to be telephoned following their child’s absences and that they were able to take part in telephone interviews in English

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Priest 2014 *(Continued)*

	Exclusion criteria: School-level exclusion: special needs schools Student-level exclusion (follow-up children): children of the principal investigators and study personnel of the trial. Or, children of families that the principal of the primary school directs us not to approach
Interventions	Hand sanitiser provision (in addition to hand hygiene education session also provided to control group) in schoolchildren. See Table 1 for details.
Outcomes	Laboratory: none Effectiveness: Primary outcome: the incidence rate of absence episodes from school (reported by the parents during telephone calls) due to any illness during the study period (winter term) Secondary outcomes: assessing whether hand sanitiser was effective in reducing the: 1. incidence rate of respiratory illness absence episodes, 2. incidence rate of gastrointestinal illness absence episodes, 3. incidence rate of absence for any reason, 4. length of illness episode, 5. length of illness absence episode, and 6. incidence rate of subsequent illness amongst other children or adults in the household. Definition of respiratory illness: at least 2 of the following caregiver-reported symptoms for 1 day, or 1 of the following symptoms for 2 days (but not fever alone): runny nose, stuffy or blocked nose or noisy breathing, cough, fever, sore throat, or sneezing Safety: examined whether the use of hand sanitiser was associated with an increased risk of any skin reactions during the intervention period. Skin reactions: dryness, redness, flakiness, itchiness, eczema, and any other skin reactions
Notes	The period study conducted: 27 April to 25 September 2009 Funding: government (Health Research Council of New Zealand)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Stata/MP 10.1 for Windows was used to generate the random numbers"
Allocation concealment (selection bias)	Low risk	Done by trial statistician provided with school codes and district and randomised the schools to either "A" or "B"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Outcome assessors were blinded to the group allocation until the analysis was completed.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to the group allocation until the analysis was completed.
Incomplete outcome data (attrition bias)	Unclear risk	The flow diagram gives a clear account on follow-up, with numbers of those lost to follow-up and those who discontinued the intervention along with the

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Priest 2014 *(Continued)*

All outcomes		reasons for doing so. No child was excluded from the analysis. Only PP analysis was reported.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the published protocol were reported in the study. The exception was "1 planned secondary outcome (that is irrelevant to our study) that was not collected and 2 collected secondary outcomes that were not planned in the original protocol".

Radonovich 2019

Study characteristics	
Methods	Cluster-RCT, multicentre, pragmatic effectiveness trial
Participants	Study included 280 clusters randomly assigned to N95 respirators (189 clusters and 1993 HCPs) and medical masks (191 clusters and 2058 HCPs). All participants in a cluster worked in the same outpatient clinic or outpatient setting. All participants were permitted to participate for 1 or more years and gave written consent for each year of participation. Inclusion criteria: healthcare workers in outpatient settings serving adult and paediatric patients with a high prevalence of acute respiratory illness. Participants were aged at least 18 years and employed at 1 of the 7 participating health systems, and self-identified as routinely positioned within 6 feet (1.83 m) of patients. Participants were full-time employees (defined as direct patient care for approximately ≥ 24 hours weekly) and worked primarily at the study site (defined as ≥ 75% of working hours). Exclusion criteria: medical conditions precluding safe participation or anatomic features that could interfere with respirator fit, such as facial hair or third-trimester pregnancy. Participants self-identified race and sex using fixed categories; these variables were collected because facial anthropometrics related to race and sex may influence N95 respirator fit.
Interventions	Fit-tested N95 respirators versus medical masks when near patients with respiratory illness. See Table 1 for details.
Outcomes	Laboratory. Primary outcome: the incidence of laboratory-confirmed influenza, defined as: 1. detection of influenza A or B virus by RT-PCR in an upper respiratory specimen collected within 7 days of symptom onset; 2. detection of influenza from a randomly obtained swab from an asymptomatic participant; and 3. influenza seroconversion (symptomatic or asymptomatic), defined as at least a 4-fold rise in haemagglutination inhibition antibody titres to influenza A or B virus between pre-season and postseason serological samples deemed not attributable to vaccination. Effectiveness. Secondary outcomes: the incidence of 4 measures of viral respiratory illness or infection as follows: 1. acute respiratory illness with or without laboratory confirmation; 2. laboratory-detected respiratory infection, defined as detection of a respiratory pathogen by PCR or serological evidence of infection with a respiratory pathogen during the study surveillance period(s), which was added to the protocol prior to data analysis; 3. laboratory-confirmed respiratory illness, identified as previously described (defined as self-reported acute respiratory illness plus the presence of at least PCR–confirmed viral pathogen in a specimen collected from the upper respiratory tract within 7 days of the reported symptoms and/or at least a 4-fold rise from pre-intervention to postintervention serum antibody titres to influenza A or B virus; and 4. influenza-like illness, defined as temperature of at least 100 °F (37.8 °C) plus cough and/or a sore throat, with or without laboratory confirmation.

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Radonovich 2019 *(Continued)*

	Safety: no serious study-related adverse events were reported. 19 participants reported skin irritation or worsening acne during years 3 and 4 at 1 site in the N95 respirator group.
Notes	The study was conducted from September 2011 to May 2015, with final follow-up on 28 June 2016. Funding: government Compliance: adherence was reported on daily surveys 22,330 times in the N95 respirator group and 23,315 times in the medical mask group. “Always” was reported 14,566 (65.2%) times in the N95 respirator group and 15,186 (65.1%) times in the medical mask group; “sometimes” 5407 (24.2%) times in the N95 respirator group and 5853 (25.1%) times in the medical mask group; “never” 2272 (10.2%) times in the N95 respirator group and 2207 (9.5%) times in the medical mask group; and “did not recall” 85 (0.4%) times in the N95 respirator group and 69 (0.3%) times in the medical mask group. Participant-reported adherence could not be assessed in 784 participants (31.2%) in the N95 respirator group and 822 (30.8%) in the medical mask group (P = 0.84) because of lack of response to surveys or lack of adherence opportunities (i.e. participants did not encounter an individual with respiratory signs or symptoms). Analysed post hoc, participant adherence was reported as always or sometimes 89.4% of the time in the N95 respirator group and 90.2% of the time in the medical mask group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequences by an individual not involved in the study implementation and data analyses. Used stratified randomisation
Allocation concealment (selection bias)	Low risk	Used constrained randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants cannot be blinded, but it seems that all the measures otherwise were the same with meticulous follow-up. Besides, the primary outcome was lab based (an objective outcome), which is unlikely to be affected by of lack of blinding. Investigators were blinded to the randomisation until completion of the study and analysis.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome is laboratory-confirmed diagnosis.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Missing outcomes were imputed using standard multiple imputation techniques, creating multiple imputed data sets with no missing values for each analysis"
Selective reporting (reporting bias)	Low risk	Reported study outcomes matched the published protocol. Every outcome was accounted for.

Radonovich 2019

Study characteristics

Methods	Cluster-RCT, multicentre, pragmatic effectiveness trial
Participants	Study included 280 clusters randomly assigned to N95 respirators (189 clusters and 1993 HCPs) and medical masks (191 clusters and 2058 HCPs).

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Radonovich 2019 *(Continued)*

	All participants in a cluster worked in the same outpatient clinic or outpatient setting. All participants were permitted to participate for 1 or more years and gave written consent for each year of participation. Inclusion criteria: healthcare workers in outpatient settings serving adult and paediatric patients with a high prevalence of acute respiratory illness. Participants were aged at least 18 years and employed at 1 of the 7 participating health systems, and self-identified as routinely positioned within 6 feet (1.83 m) of patients. Participants were full-time employees (defined as direct patient care for approximately ≥ 24 hours weekly) and worked primarily at the study site (defined as ≥ 75% of working hours). Exclusion criteria: medical conditions precluding safe participation or anatomic features that could interfere with respirator fit, such as facial hair or third-trimester pregnancy. Participants self-identified race and sex using fixed categories; these variables were collected because facial anthropometrics related to race and sex may influence N95 respirator fit.
Interventions	Fit-tested N95 respirators versus medical masks when near patients with respiratory illness. See Table 1 for details.
Outcomes	Laboratory. Primary outcome: the incidence of laboratory-confirmed influenza, defined as: 1. detection of influenza A or B virus by RT-PCR in an upper respiratory specimen collected within 7 days of symptom onset; 2. detection of influenza from a randomly obtained swab from an asymptomatic participant; and 3. influenza seroconversion (symptomatic or asymptomatic), defined as at least a 4-fold rise in haemagglutination inhibition antibody titres to influenza A or B virus between pre-season and postseason serological samples deemed not attributable to vaccination. Effectiveness. Secondary outcomes: the incidence of 4 measures of viral respiratory illness or infection as follows: 1. acute respiratory illness with or without laboratory confirmation; 2. laboratory-detected respiratory infection, defined as detection of a respiratory pathogen by PCR or serological evidence of infection with a respiratory pathogen during the study surveillance period(s), which was added to the protocol prior to data analysis; 3. laboratory-confirmed respiratory illness, identified as previously described (defined as self-reported acute respiratory illness plus the presence of at least PCR–confirmed viral pathogen in a specimen collected from the upper respiratory tract within 7 days of the reported symptoms and/or at least a 4-fold rise from pre-intervention to postintervention serum antibody titres to influenza A or B virus; and 4. influenza-like illness, defined as temperature of at least 100 °F (37.8 °C) plus cough and/or a sore throat, with or without laboratory confirmation. Safety: no serious study-related adverse events were reported. 19 participants reported skin irritation or worsening acne during years 3 and 4 at 1 site in the N95 respirator group.
Notes	The study was conducted from September 2011 to May 2015, with final follow-up on 28 June 2016. Funding: government Compliance: adherence was reported on daily surveys 22,330 times in the N95 respirator group and 23,315 times in the medical mask group. “Always” was reported 14,566 (65.2%) times in the N95 respirator group and 15,186 (65.1%) times in the medical mask group; “sometimes” 5407 (24.2%) times in the N95 respirator group and 5853 (25.1%) times in the medical mask group; “never” 2272 (10.2%) times in the N95 respirator group and 2207 (9.5%) times in the medical mask group; and “did not recall” 85 (0.4%) times in the N95 respirator group and 69 (0.3%) times in the medical mask group. Participant-reported adherence could not be assessed in 784 participants (31.2%) in the N95 respirator group and 822 (30.8%) in the medical mask group (P = 0.84) because of lack of response to surveys or lack of adherence opportunities (i.e. participants did not encounter an individual with respiratory signs or symptoms). Analysed post hoc, participant adherence was reported as always or sometimes 89.4% of the time in the N95 respirator group and 90.2% of the time in the medical mask group.
Risk of bias	

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Radonovich 2019 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequences by an individual not involved in the study implementation and data analyses. Used stratified randomisation
Allocation concealment (selection bias)	Low risk	Used constrained randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants cannot be blinded, but it seems that all the measures otherwise were the same with meticulous follow-up. Besides, the primary outcome was lab based (an objective outcome), which is unlikely to be affected by of lack of blinding. Investigators were blinded to the randomisation until completion of the study and analysis.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome is laboratory-confirmed diagnosis.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Missing outcomes were imputed using standard multiple imputation techniques, creating multiple imputed data sets with no missing values for each analysis"
Selective reporting (reporting bias)	Low risk	Reported study outcomes matched the published protocol. Every outcome was accounted for.

Ram 2015

Study characteristics	
Methods	RCT
Participants	377 household compounds (index cases) completed the study. Control arm has 184 compounds with 1607 contacts, and intervention group has 193 compounds with 1814 contacts. Final analysis was performed on 193 index cases and 1661 contacts in the intervention group and 184 index cases and 1498 contacts in the control group. In 2009, index case-patients with symptom onset within 7 days preceding enrolment were eligible. Eligibility criteria changed in 2010 to include index case-patient with symptom onset within 48 hours preceding enrolment. Inclusion criteria: 1. Individuals ≥ 5 years old: ILI, defined as history of fever and either cough or sore throat with fever onset within the previous 24 hours. 2. Individuals < 5 years old: any child with acute fever with onset within the previous 24 hours. 3. Return to home within 24 hours of presentation to Upazilla Health Complex, Jahurul Islam Medical College Hospital or the local pharmacies, i.e. the index case cannot be admitted for treatment. If admitted, the patient would not be eligible. 4. No fever in any bari resident during the 7 days preceding the patient's presentation to hospital (see definition below). 5. At least 2 individuals (in addition to the index case-patient) who intend to reside in the bari during the subsequent 20 days. 6. Residence within 30 minutes travel time (1-way) from the Upazilla Health Complex or Jahurul Islam Medical College Hospital or the local pharmacy. Exclusion criteria: compounds were excluded if any compound member(s) was reported to have fever within 3 days before index case-patient enrolment. At another time point, compounds were excluded

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Ram 2015 *(Continued)*

	if any primary household member was reported to have fever (fever occurring within 48 hours prior to enrolment recorded).
Interventions	Promoting intensive hand-washing in households to prevent transmission of ILI. See Table 1 for details.
Outcomes	Laboratory: PCR for influenza A and B, with further subtyping of influenza A isolates for all ILI amongst contacts Effectiveness: incidence of ILI. An age-based definition of ILI was used as follows. 1. For individuals > 5 years old, ILI was defined as history of fever with cough or sore throat. 2. For children < 5 years old, ILI was defined as fever (the authors used this relatively liberal case definition in order to include influenza cases with atypical presentations in children). Safety: no safety data planned or reported by investigators
Notes	Inclusion/exclusion criteria changed 3 times during the study conduct. The period study conducted: June 2009 to December 2010 Funding: government

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation, with a block size of 4, in order to promote random and even allocation of household compounds to the 2 treatment arms. The list of random assignments was generated by an investigator with no contact with the participants.
Allocation concealment (selection bias)	Low risk	Once baseline data collection was complete, the data collector notified the field research officer, who consulted the block randomisation list to make the assignment of the household compound to intervention or control.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Relied on symptom reporting from the head of family. Inclusion/exclusion criteria changed 3 times during the study conduct. Given the provision of a hand-washing station as part of the intervention, it was not possible to ensure blinding of participants, intervention staff, or data collectors.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Relied on symptom reporting from the head of family. Inclusion/exclusion criteria changed 3 times during the conduct of the study. Given the provision of a hand-washing station as part of the intervention, it was not possible to ensure blinding of participants, intervention staff, or data collectors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow chart followed all households an individuals from recruitment to analysis.
Selective reporting (reporting bias)	Low risk	The specified outcomes are clearly accounted for. Investigators report all outcomes for each modified enrolment.

Ram 2015

Study characteristics

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Ram 2015 *(Continued)*

Methods	RCT
Participants	377 household compounds (index cases) completed the study. Control arm has 184 compounds with 1607 contacts, and intervention group has 193 compounds with 1814 contacts. Final analysis was performed on 193 index cases and 1661 contacts in the intervention group and 184 index cases and 1498 contacts in the control group. In 2009, index case-patients with symptom onset within 7 days preceding enrolment were eligible. Eligibility criteria changed in 2010 to include index case-patient with symptom onset within 48 hours preceding enrolment. Inclusion criteria: 1. Individuals ≥ 5 years old: ILI, defined as history of fever and either cough or sore throat with fever onset within the previous 24 hours. 2. Individuals < 5 years old: any child with acute fever with onset within the previous 24 hours. 3. Return to home within 24 hours of presentation to Upazilla Health Complex, Jahurul Islam Medical College Hospital or the local pharmacies, i.e. the index case cannot be admitted for treatment. If admitted, the patient would not be eligible. 4. No fever in any bari resident during the 7 days preceding the patient's presentation to hospital (see definition below). 5. At least 2 individuals (in addition to the index case-patient) who intend to reside in the bari during the subsequent 20 days. 6. Residence within 30 minutes travel time (1-way) from the Upazilla Health Complex or Jahurul Islam Medical College Hospital or the local pharmacy. Exclusion criteria: compounds were excluded if any compound member(s) was reported to have fever within 3 days before index case-patient enrolment. At another time point, compounds were excluded if any primary household member was reported to have fever (fever occurring within 48 hours prior to enrolment recorded).
Interventions	Promoting intensive hand-washing in households to prevent transmission of ILI. See Table 1 for details.
Outcomes	Laboratory: PCR for influenza A and B, with further subtyping of influenza A isolates for all ILI amongst contacts Effectiveness: incidence of ILI. An age-based definition of ILI was used as follows. 1. For individuals > 5 years old, ILI was defined as history of fever with cough or sore throat. 2. For children < 5 years old, ILI was defined as fever (the authors used this relatively liberal case definition in order to include influenza cases with atypical presentations in children). Safety: no safety data planned or reported by investigators
Notes	Inclusion/exclusion criteria changed 3 times during the study conduct. The period study conducted: June 2009 to December 2010 Funding: government

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation, with a block size of 4, in order to promote random and even allocation of household compounds to the 2 treatment arms. The list of random assignments was generated by an investigator with no contact with the participants.

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Ram 2015 *(Continued)*

Allocation concealment (selection bias)	Low risk	Once baseline data collection was complete, the data collector notified the field research officer, who consulted the block randomisation list to make the assignment of the household compound to intervention or control.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Relied on symptom reporting from the head of family. Inclusion/exclusion criteria changed 3 times during the study conduct. Given the provision of a hand-washing station as part of the intervention, it was not possible to ensure blinding of participants, intervention staff, or data collectors.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Relied on symptom reporting from the head of family. Inclusion/exclusion criteria changed 3 times during the conduct of the study. Given the provision of a hand-washing station as part of the intervention, it was not possible to ensure blinding of participants, intervention staff, or data collectors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow chart followed all households an individuals from recruitment to analysis.
Selective reporting (reporting bias)	Low risk	The specified outcomes are clearly accounted for. Investigators report all outcomes for each modified enrolment.

Roberts 2000

Study characteristics	
Methods	Open cluster-RCT carried out between March and November 1996 (the Southern Hemisphere winter season) in 23 childcare centres caring for a minimum of 50 children 10 hours a day, 5 days a week in Australia. The study assessed the effects of an Australian national hand-washing programme compared to standard procedure. Randomisation was according to a random-number table, and cluster coefficients are reported.
Participants	Children (299 in the intervention arm and 259 in the control arm) aged 3 or younger attending the centres at least 3 days a week. Attrition was 51 children in the intervention arm and 72 children in the control arm due mainly to staff leaving the centres.
Interventions	Hand-washing programme with training for staff and children. It is unclear whether any extra hand-cleansing agents were used, as GloGerm (?) is mentioned when it was used in a preliminary study.
Outcomes	Laboratory: N/A Effectiveness: ARI (runny nose, cough, and blocked nose) Follow-up was via a parental phone interview every 2 weeks. Safety: N/A
Notes	Risk of bias: low (cluster coefficients and analysis by unit of randomisation) Note: the authors conclude that although there was no overall decrease in respiratory illness (RR 0.95, 95% CI 0.89 to 1.01), in children up to 24 months the decrease was statistically significant (RR 0.90, 95% CI 0.83 to 0.97). The authors speculated that this was because maximum benefits are likely from this age group due to their limited ability to wipe their nose and hands without a structured programme. Analyses by 3 compliance levels are also reported. A so-so reported and well-conducted trial
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

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Roberts 2000 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomisation was according to a random-number table.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was not possible to blind the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The observer was not informed of the content of the training sessions or the intervention status of the centres."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Recruitment rate 88% (23 of 26 CCCs); loss to follow-up not clear, as no denominator given
Selective reporting (reporting bias)	Low risk	Centres were comparable at baseline.

Sandora 2005

Study characteristics	
Methods	Single-blind, cluster-RCT carried around the Boston area, USA, in the period of November 2002 to April 2003. The trial tested the effects of using a hand sanitiser and a programme of instruction on the transmissions of GI infections (data not extracted) and ARIs in families. Units of randomisation were child-care centres and were carried out on enrolment by an investigator using random block size generated by computer. Assignment was single-blind (i.e. investigator blinded to the status of the centre). Cluster correlation was 0.01.
Participants	292 families with 1 or more children aged 6 months to 5 years who were in child care for 10 or more hours a week 155 children in 14 centres were allocated to the intervention arm and 137 children in 12 centres to the control arm**.** The mean age was 3 to 2.7 years. Attrition was respectively 15 (3 lost to follow-up and 12 who discontinued the intervention) and 19 (8 lost to follow-up and 11 who discontinued the intervention). ITT analysis was carried out.
Interventions	Alcohol-based hand sanitiser with biweekly hand hygiene educational materials over 5 months versus biweekly educational material on healthy diet
Outcomes	Effectiveness: ARI (2 of the following symptoms for 1 day or 1 of the following symptoms for 2 days: runny nose, cough, sneezing, stuffy or blocked nose, fever, sore throat). An illness episode had to be separated by 2 symptom-free days from a previous episode. A secondary illness was when it followed a similar illness in another family member by 2 to 7 days. Follow-up was by means of biweekly phone calls to caregivers. Safety: dry skin (71 reports), stinging (11 reports), bad smell (7 reports), dislike (2 reports), allergic reaction (2 reports), slippery feel (1 report), and irritation (20 reports)
Notes	Risk of bias: low Note: the authors conclude that although the rate of GI illnesses was significantly lower in the intervention group, the IRR was not significantly different for ARIs (0.97, 95% CI 0.72 to 1.30). Compliance and droplet route spread may account for this apparent lack of effect. A well-reported trial

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Sandora 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random assignments were generated by computer using a permuted-blocks design with random block sizes."
Allocation concealment (selection bias)	Low risk	"Assignments were concealed in opaque envelopes, and centers were assigned to control or intervention groups by a study investigator as they were enrolled."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Teachers in the intervention classrooms were responsible for encouraging the use of the disinfecting wipes and hand sanitizer according to the study protocol ... Given that no placebo was provided and sanitizer use was recorded, neither families nor data collectors could be blinded as to the group assignment of the family."
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Given that no placebo was provided and sanitizer use was recorded, neither families nor data collectors could be blinded as to the group assignment of the family."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 15 in intervention arm (3 lost to follow-up and 12 who discontinued the intervention) and 19 in the control arm (8 lost to follow-up and 11 who discontinued the intervention). ITT analysis was carried out.
Selective reporting (reporting bias)	Unclear risk	Well-reported

Sandora 2008

Study characteristics

Methods	Cluster-RCT carried out in a single elementary school system located in Avon, Ohio, USA to assess the effectiveness of a multifactorial infection-control intervention, including alcohol-based hand sanitiser and surface disinfection, in reducing absenteeism caused by gastrointestinal and respiratory illnesses amongst elementary school students. The study also aimed to describe the viral and bacterial contamination of common surfaces in the school classroom and to assess the impact of an environmental disinfectant on the presence of selected viruses and bacteria on these surfaces. Clustering was described as "teams of 3-4 classes depending on the class year".
Participants	A total of 363 students in 15 different classrooms were eligible to participate and received letters about the study. A sample of 285 of these students provided written informed consent and were randomly assigned to the intervention group (146) or to the control group (139) and contributed to final analysis. No students were lost to follow-up or discontinued the intervention during the study period. Baseline demographic characteristics were similar in the intervention and control groups. Most families were white and non-Hispanic and in excellent or very good health at baseline.
Interventions	Alcohol-based hand sanitiser to use at school and quaternary ammonium wipes to disinfect classroom surfaces daily for 8 weeks versus usual hand-washing and cleaning practices
Outcomes	Laboratory: Serological evidence: no Swabs for bacteria and viruses from 3 types of classroom surfaces were taken.

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Sandora 2008 *(Continued)*

	Effectiveness: Respiratory illness defined as days absent as measured by a (blinded) school worker who routinely recorded reason for absenteeism either for gastrointestinal or respiratory causes. Safety: N/A
Notes	The authors conclude that the multifaceted intervention that included alcohol-based hand sanitiser use and disinfection of common classroom surfaces reduced absenteeism from gastrointestinal illness amongst elementary school students. The intervention did not impact on absenteeism from respiratory illness. In addition, norovirus was detected less frequently on classroom surfaces in the group receiving the intervention. The study is of good quality with low risk of bias. The authors checked compliance by counting discarded wipes. Reasons given for the apparent lack of effect against ARIs but good effect on GI illness are that disinfecting the classroom surfaces (daily at lunchtime with alkali) was important, as were the alcohol wipes. The authors measured the norovirus concentration on surfaces and found this to be reduced. Other reasons may be that droplets are not affected by this method, or that contamination of hands by respiratory infections is likely to be continuous (in orofaecal transmission is mostly at the time of defecation).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The allocation sequence was generated by computer ..."
Allocation concealment (selection bias)	Unclear risk	"...and teams were assigned to study groups by a study investigator (Dr Shih)." Blinding of allocation cannot be guaranteed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All of the students absences were recorded in the usual fashion by the school employee who normally answers this dedicated telephone line. This employee was blinded to the group assignment of the child."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No students were lost to follow-up or discontinued the intervention during the study period.
Selective reporting (reporting bias)	Unclear risk	Well-reported

Satomura 2005

Study characteristics

Methods	RCT. Randomisation was achieved by simple computer-generated random digit. Allocation was concealed using sealed, opaque envelopes. Not clear if there was a central randomisation centre. Post hoc exchange of envelopes was prevented by writing both the name of each participant and the number on the envelope he/she drew before breaking the seal. Participants were not blinded to the intervention; however, disease incidence was determined by 1 study physician who was not informed of the results of assignment. Analysis was done based on the intention-to-treat principle. The study targeted community healthcare all over Japan and was conducted between December 2002 and March 2003 for a follow-up period of 60 days.

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Satomura 2005 *(Continued)*

Participants	387 participants at 18 sites were recruited, 384 were included in the analysis: water gargling (N = 122), povidone-iodine gargling (N = 132), and control (N = 130). Follow-up was completed on 338 participants. Attrition was fully explained for URTI analysis; however, 2 participants were not accounted for in the ILI analysis. 46 participants did not complete the follow-up due to either discontinuation of diary use (n = 9) or contracting ILI (n = 37). Of the 37 participants with ILI, 11 were in the povidone-iodine group, 12 in the water group, and 14 in the control group. Analysis was performed on 35 participants (Kitamura 2007).
Interventions	Participants were randomised to 1 of the following: water gargling, n = 122 (20 mL of water for about 15 seconds 3 times consecutively, at least 3 times a day); povidone-iodine gargling, n = 133 (20 mL of 15 to 30 times diluted 7% povidone-iodine (as indicated by the manufacturer) in the same way as water gargling); and control, n = 132 (retain their previous gargling habits). All groups were asked to fill a daily gargling diary (standardised form to record: gargling habits, hand-washing, and influenza complaints). The frequency of gargling in the water group was higher (3.6); the frequency of hand-washing was similar amongst the 3 groups. URTI symptom was classified according to Jackson methods. Diary recording was continued throughout the follow-up period and for 1 week after the onset of URTI. ILI was reported separately.
Outcomes	Laboratory: none Effectiveness: Primary outcome: incidence of first URTI. Index cases were defined as all of the following conditions: 1. both nasal and pharyngeal symptoms, 2. severity of at least 1 symptom increased by 2 grades or more, and 3. worsening of a symptom of 1 increment or more for > 3 days. Secondary outcome: severity of URTI of the incident cases was assessed by grading each symptom during the initial 7 days after the onset of URTI in numeric scores: none = 0, mild = 1, moderate = 2, and severe = 3 ILI was defined as both developing a fever of 38 °C or higher and worsening arthralgia in addition to some respiratory symptoms (Kitamura 2007). Safety: no harm was reported. However, 2 participants in the povidone-iodine group switched to water gargling (analysed in their assignment group).
Notes	The authors concluded that simple water gargling is effective in preventing URTIs amongst healthy people. However, no statistically significant difference was observed against ILIs. The study was well-conducted; blinding would have added to the validity of the results. In addition, the study was not powered enough to detect a statistically significant preventative effect against ILI. The study demonstrates that in addition to hand-washing, simple gargling even with water can reduce URTI, but not ILI. However, during periods of endemic influenza, multiple inexpensive and simple modalities (hand-washing, masks, gargling) can be utilised together to reduce infection and transmission. Overall, the reporting of the 2 combined studies together is highly confusing. In the first study (Satomura 2005), the main outcome is URTI defined as fever and arthralgia. The second study (which is a presentation of further data from the 2005 publication in the guise of a short report) introduces the outcome ILI with a definition similar to that of URTI in the first study but referring to the earlier outcome as common cold. Also of note is reporting of significance without confidence intervals. Overall, this potentially important study should be repeated with a larger denominator. Unclear risk of bias because of confused reporting and absence of double-blinding

Risk of bias

Bias	Authors' judgement	Support for judgement

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Satomura 2005 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Group assignment was based on simple computer-generated random digits..."
Allocation concealment (selection bias)	Low risk	"By an individual drawing of sealed opaque envelopes, subjects were randomly assigned to the following three groups" "allocation was completely concealed from study administrators"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"To prevent post hoc exchange of the envelopes, local administrators wrote down both the name of each subject and the number on the envelope he/she drew before breaking the seal."
Incomplete outcome data (attrition bias) All outcomes	Low risk	338 of 385 randomised followed up; reasons reported.
Selective reporting (reporting bias)	Unclear risk	Confusing reporting

Savolainen-Kopra 2012

Study characteristics	
Methods	Open cluster-RCT, 3-arm intervention trial
Participants	A total of 21 clusters (683 individuals) were randomised to implement hand hygiene with soap and water (257 individuals), alcohol-based hand rub (202 individuals), or control (224 individuals). The study was conducted in distinct office work units in 6 corporations in the Helsinki Region that together employed some 10,000 staff. All employees (age ≥ 18 years, both genders) were contacted by email survey. Inclusion criteria: "Volunteers working in defined units" Exclusion criteria: "Persons with open wounds or chronic eczema in hands" The designated 21 study clusters were identified as operationally distinct working units, each containing at least 50 people.
Interventions	Hand hygiene with soap and water and standardised instructions on how to limit the transmission of infections. Usual hand hygiene (control). See Table 1 for details.
Outcomes	Laboratory: "Between November 2008 and May 2010, the seven occupational health clinics serving the six participating corporations were advised to collect, using standard techniques, two to three respiratory samples per week from typical RTI patients and also faecal samples from a few representative patients with gastrointestinal symptoms when a GIT outbreak was suspected. The samples could originate from the study participants and also from work units not included in the study. In the laboratory, viral nucleic acids were extracted with well-characterized commercial kits and tested by validated real-time PCR methods to detect influenza A and B viruses, respiratory syncytial virus, parainfluenza virus types 1, 2, and 3, adenoviruses, human rhinoviruses and human enteroviruses from respiratory specimens, and norovirus from faecal specimens (detailed descriptions of the test procedures are available from the authors)."

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Savolainen-Kopra 2012 *(Continued)*

	Effectiveness: Predefined primary endpoints: 1. Number of reported infection episodes in a cluster per total reported weeks. 2. Number of reported sick leave episodes in a cluster per total reported weeks. Secondary endpoints and outcome measures: 1. Number of days with reported symptoms of RTI and/or GTI in a cluster within a time frame of 100 reporting weeks. 2. Number of days-off due to own RTI or GTI in a cluster within a time frame of 100 reporting weeks. Safety: reported 0 adverse events
Notes	The period study conducted: January 2009 to May 2010 Funding: government

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Low risk	"clusters were matched and randomized prior to onset of the interventions"
Blinding of participants and personnel (performance bias) All outcomes	High risk	The interventions were not blinded to any party involved (i.e. the study group, participants, or the occupational health services). Subjective reporting of disease episodes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Subjective reporting of disease episodes
Incomplete outcome data (attrition bias) All outcomes	High risk	24% loss to follow-up. However, new recruiting in most clusters; the total number of reporting participants at the end of the trial was 91.7% compared to that at the beginning. Attrition was reported, and 76% of volunteers who started reporting continued to do so until the end of the study. Because of new recruiting in most clusters, the total number of reporting participants at the end of the trial was 626, or 91.7%, compared to that at the beginning. This means that 15.7% of the participants were replaced during the study!!! Raw data on the effects of the interventions on the occurrence of respiratory infections and vomiting/diarrhoea diseases were not reported. Zero adverse effects were reported.
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.

Roberts 2000

Study characteristics

Methods	Open cluster-RCT carried out between March and November 1996 (the Southern Hemisphere winter season) in 23 childcare centres caring for a minimum of 50 children 10 hours a day, 5 days a week in

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Roberts 2000 *(Continued)*

	Australia. The study assessed the effects of an Australian national hand-washing programme compared to standard procedure. Randomisation was according to a random-number table, and cluster coefficients are reported.
Participants	Children (299 in the intervention arm and 259 in the control arm) aged 3 or younger attending the centres at least 3 days a week. Attrition was 51 children in the intervention arm and 72 children in the control arm due mainly to staff leaving the centres.
Interventions	Hand-washing programme with training for staff and children. It is unclear whether any extra hand-cleansing agents were used, as GloGerm (?) is mentioned when it was used in a preliminary study.
Outcomes	Laboratory: N/A Effectiveness: ARI (runny nose, cough, and blocked nose) Follow-up was via a parental phone interview every 2 weeks. Safety: N/A
Notes	Risk of bias: low (cluster coefficients and analysis by unit of randomisation) Note: the authors conclude that although there was no overall decrease in respiratory illness (RR 0.95, 95% CI 0.89 to 1.01), in children up to 24 months the decrease was statistically significant (RR 0.90, 95% CI 0.83 to 0.97). The authors speculated that this was because maximum benefits are likely from this age group due to their limited ability to wipe their nose and hands without a structured programme. Analyses by 3 compliance levels are also reported. A so-so reported and well-conducted trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was according to a random-number table.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was not possible to blind the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The observer was not informed of the content of the training sessions or the intervention status of the centres."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Recruitment rate 88% (23 of 26 CCCs); loss to follow-up not clear, as no denominator given
Selective reporting (reporting bias)	Low risk	Centres were comparable at baseline.

Sandora 2005

Study characteristics

Methods	Single-blind, cluster-RCT carried around the Boston area, USA, in the period of November 2002 to April 2003. The trial tested the effects of using a hand sanitiser and a programme of instruction on the transmissions of GI infections (data not extracted) and ARIs in families. Units of randomisation were child-care centres and were carried out on enrolment by an investigator using random block size generated

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Sandora 2005 *(Continued)*

	by computer. Assignment was single-blind (i.e. investigator blinded to the status of the centre). Cluster correlation was 0.01.
Participants	292 families with 1 or more children aged 6 months to 5 years who were in child care for 10 or more hours a week 155 children in 14 centres were allocated to the intervention arm and 137 children in 12 centres to the control arm**.** The mean age was 3 to 2.7 years. Attrition was respectively 15 (3 lost to follow-up and 12 who discontinued the intervention) and 19 (8 lost to follow-up and 11 who discontinued the intervention). ITT analysis was carried out.
Interventions	Alcohol-based hand sanitiser with biweekly hand hygiene educational materials over 5 months versus biweekly educational material on healthy diet
Outcomes	Effectiveness: ARI (2 of the following symptoms for 1 day or 1 of the following symptoms for 2 days: runny nose, cough, sneezing, stuffy or blocked nose, fever, sore throat). An illness episode had to be separated by 2 symptom-free days from a previous episode. A secondary illness was when it followed a similar illness in another family member by 2 to 7 days. Follow-up was by means of biweekly phone calls to caregivers. Safety: dry skin (71 reports), stinging (11 reports), bad smell (7 reports), dislike (2 reports), allergic reaction (2 reports), slippery feel (1 report), and irritation (20 reports)
Notes	Risk of bias: low Note: the authors conclude that although the rate of GI illnesses was significantly lower in the intervention group, the IRR was not significantly different for ARIs (0.97, 95% CI 0.72 to 1.30). Compliance and droplet route spread may account for this apparent lack of effect. A well-reported trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random assignments were generated by computer using a permuted-blocks design with random block sizes."
Allocation concealment (selection bias)	Low risk	"Assignments were concealed in opaque envelopes, and centers were assigned to control or intervention groups by a study investigator as they were enrolled."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Teachers in the intervention classrooms were responsible for encouraging the use of the disinfecting wipes and hand sanitizer according to the study protocol ... Given that no placebo was provided and sanitizer use was recorded, neither families nor data collectors could be blinded as to the group assignment of the family."
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Given that no placebo was provided and sanitizer use was recorded, neither families nor data collectors could be blinded as to the group assignment of the family."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 15 in intervention arm (3 lost to follow-up and 12 who discontinued the intervention) and 19 in the control arm (8 lost to follow-up and 11 who discontinued the intervention). ITT analysis was carried out.
Selective reporting (reporting bias)	Unclear risk	Well-reported

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Sandora 2008

Study characteristics	
Methods	Cluster-RCT carried out in a single elementary school system located in Avon, Ohio, USA to assess the effectiveness of a multifactorial infection-control intervention, including alcohol-based hand sanitiser and surface disinfection, in reducing absenteeism caused by gastrointestinal and respiratory illnesses amongst elementary school students. The study also aimed to describe the viral and bacterial contamination of common surfaces in the school classroom and to assess the impact of an environmental disinfectant on the presence of selected viruses and bacteria on these surfaces. Clustering was described as "teams of 3-4 classes depending on the class year".
Participants	A total of 363 students in 15 different classrooms were eligible to participate and received letters about the study. A sample of 285 of these students provided written informed consent and were randomly assigned to the intervention group (146) or to the control group (139) and contributed to final analysis. No students were lost to follow-up or discontinued the intervention during the study period. Baseline demographic characteristics were similar in the intervention and control groups. Most families were white and non-Hispanic and in excellent or very good health at baseline.
Interventions	Alcohol-based hand sanitiser to use at school and quaternary ammonium wipes to disinfect classroom surfaces daily for 8 weeks versus usual hand-washing and cleaning practices
Outcomes	Laboratory: Serological evidence: no Swabs for bacteria and viruses from 3 types of classroom surfaces were taken. Effectiveness: Respiratory illness defined as days absent as measured by a (blinded) school worker who routinely recorded reason for absenteeism either for gastrointestinal or respiratory causes. Safety: N/A
Notes	The authors conclude that the multifaceted intervention that included alcohol-based hand sanitiser use and disinfection of common classroom surfaces reduced absenteeism from gastrointestinal illness amongst elementary school students. The intervention did not impact on absenteeism from respiratory illness. In addition, norovirus was detected less frequently on classroom surfaces in the group receiving the intervention. The study is of good quality with low risk of bias. The authors checked compliance by counting discarded wipes. Reasons given for the apparent lack of effect against ARIs but good effect on GI illness are that disinfecting the classroom surfaces (daily at lunchtime with alkali) was important, as were the alcohol wipes. The authors measured the norovirus concentration on surfaces and found this to be reduced. Other reasons may be that droplets are not affected by this method, or that contamination of hands by respiratory infections is likely to be continuous (in orofaecal transmission is mostly at the time of defecation).

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The allocation sequence was generated by computer ..."
Allocation concealment (selection bias)	Unclear risk	"...and teams were assigned to study groups by a study investigator (Dr Shih)." Blinding of allocation cannot be guaranteed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible

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Sandora 2008 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All of the students absences were recorded in the usual fashion by the school employee who normally answers this dedicated telephone line. This employee was blinded to the group assignment of the child."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No students were lost to follow-up or discontinued the intervention during the study period.
Selective reporting (reporting bias)	Unclear risk	Well-reported

Satomura 2005

Study characteristics	
Methods	RCT. Randomisation was achieved by simple computer-generated random digit. Allocation was concealed using sealed, opaque envelopes. Not clear if there was a central randomisation centre. Post hoc exchange of envelopes was prevented by writing both the name of each participant and the number on the envelope he/she drew before breaking the seal. Participants were not blinded to the intervention; however, disease incidence was determined by 1 study physician who was not informed of the results of assignment. Analysis was done based on the intention-to-treat principle. The study targeted community healthcare all over Japan and was conducted between December 2002 and March 2003 for a follow-up period of 60 days.
Participants	387 participants at 18 sites were recruited, 384 were included in the analysis: water gargling (N = 122), povidone-iodine gargling (N = 132), and control (N = 130). Follow-up was completed on 338 participants. Attrition was fully explained for URTI analysis; however, 2 participants were not accounted for in the ILI analysis. 46 participants did not complete the follow-up due to either discontinuation of diary use (n = 9) or contracting ILI (n = 37). Of the 37 participants with ILI, 11 were in the povidone-iodine group, 12 in the water group, and 14 in the control group. Analysis was performed on 35 participants (Kitamura 2007).
Interventions	Participants were randomised to 1 of the following: water gargling, n = 122 (20 mL of water for about 15 seconds 3 times consecutively, at least 3 times a day); povidone-iodine gargling, n = 133 (20 mL of 15 to 30 times diluted 7% povidone-iodine (as indicated by the manufacturer) in the same way as water gargling); and control, n = 132 (retain their previous gargling habits). All groups were asked to fill a daily gargling diary (standardised form to record: gargling habits, hand-washing, and influenza complaints). The frequency of gargling in the water group was higher (3.6); the frequency of hand-washing was similar amongst the 3 groups. URTI symptom was classified according to Jackson methods. Diary recording was continued throughout the follow-up period and for 1 week after the onset of URTI. ILI was reported separately.
Outcomes	Laboratory: none Effectiveness: Primary outcome: incidence of first URTI. Index cases were defined as all of the following conditions: 1. both nasal and pharyngeal symptoms, 2. severity of at least 1 symptom increased by 2 grades or more, and 3. worsening of a symptom of 1 increment or more for > 3 days. Secondary outcome: severity of URTI of the incident cases was assessed by grading each symptom during the initial 7 days after the onset of URTI in numeric scores: none = 0, mild = 1, moderate = 2, and severe = 3

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Satomura 2005 *(Continued)*

	ILI was defined as both developing a fever of 38 °C or higher and worsening arthralgia in addition to some respiratory symptoms (Kitamura 2007). Safety: no harm was reported. However, 2 participants in the povidone-iodine group switched to water gargling (analysed in their assignment group).
Notes	The authors concluded that simple water gargling is effective in preventing URTIs amongst healthy people. However, no statistically significant difference was observed against ILIs. The study was well-conducted; blinding would have added to the validity of the results. In addition, the study was not powered enough to detect a statistically significant preventative effect against ILI. The study demonstrates that in addition to hand-washing, simple gargling even with water can reduce URTI, but not ILI. However, during periods of endemic influenza, multiple inexpensive and simple modalities (hand-washing, masks, gargling) can be utilised together to reduce infection and transmission. Overall, the reporting of the 2 combined studies together is highly confusing. In the first study (Satomura 2005), the main outcome is URTI defined as fever and arthralgia. The second study (which is a presentation of further data from the 2005 publication in the guise of a short report) introduces the outcome ILI with a definition similar to that of URTI in the first study but referring to the earlier outcome as common cold. Also of note is reporting of significance without confidence intervals. Overall, this potentially important study should be repeated with a larger denominator. Unclear risk of bias because of confused reporting and absence of double-blinding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Group assignment was based on simple computer-generated random digits..."
Allocation concealment (selection bias)	Low risk	"By an individual drawing of sealed opaque envelopes, subjects were randomly assigned to the following three groups" "allocation was completely concealed from study administrators"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"To prevent post hoc exchange of the envelopes, local administrators wrote down both the name of each subject and the number on the envelope he/she drew before breaking the seal."
Incomplete outcome data (attrition bias) All outcomes	Low risk	338 of 385 randomised followed up; reasons reported.
Selective reporting (reporting bias)	Unclear risk	Confusing reporting

Savolainen-Kopra 2012

Study characteristics

Methods	Open cluster-RCT, 3-arm intervention trial
Participants	A total of 21 clusters (683 individuals) were randomised to implement hand hygiene with soap and water (257 individuals), alcohol-based hand rub (202 individuals), or control (224 individuals).

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Savolainen-Kopra 2012 *(Continued)*

	The study was conducted in distinct office work units in 6 corporations in the Helsinki Region that together employed some 10,000 staff. All employees (age ≥ 18 years, both genders) were contacted by email survey. Inclusion criteria: "Volunteers working in defined units" Exclusion criteria: "Persons with open wounds or chronic eczema in hands" The designated 21 study clusters were identified as operationally distinct working units, each containing at least 50 people.
Interventions	Hand hygiene with soap and water and standardised instructions on how to limit the transmission of infections. Usual hand hygiene (control). See Table 1 for details.
Outcomes	Laboratory: "Between November 2008 and May 2010, the seven occupational health clinics serving the six participating corporations were advised to collect, using standard techniques, two to three respiratory samples per week from typical RTI patients and also faecal samples from a few representative patients with gastrointestinal symptoms when a GIT outbreak was suspected. The samples could originate from the study participants and also from work units not included in the study. In the laboratory, viral nucleic acids were extracted with well-characterized commercial kits and tested by validated real-time PCR methods to detect influenza A and B viruses, respiratory syncytial virus, parainfluenza virus types 1, 2, and 3, adenoviruses, human rhinoviruses and human enteroviruses from respiratory specimens, and norovirus from faecal specimens (detailed descriptions of the test procedures are available from the authors)." Effectiveness: Predefined primary endpoints: 1. Number of reported infection episodes in a cluster per total reported weeks. 2. Number of reported sick leave episodes in a cluster per total reported weeks. Secondary endpoints and outcome measures: 1. Number of days with reported symptoms of RTI and/or GTI in a cluster within a time frame of 100 reporting weeks. 2. Number of days-off due to own RTI or GTI in a cluster within a time frame of 100 reporting weeks. Safety: reported 0 adverse events
Notes	The period study conducted: January 2009 to May 2010 Funding: government

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Low risk	"clusters were matched and randomized prior to onset of the interventions"
Blinding of participants and personnel (performance bias) All outcomes	High risk	The interventions were not blinded to any party involved (i.e. the study group, participants, or the occupational health services). Subjective reporting of disease episodes
Blinding of outcome assessment (detection bias)	High risk	Subjective reporting of disease episodes

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Savolainen-Kopra 2012 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	24% loss to follow-up. However, new recruiting in most clusters; the total number of reporting participants at the end of the trial was 91.7% compared to that at the beginning. Attrition was reported, and 76% of volunteers who started reporting continued to do so until the end of the study. Because of new recruiting in most clusters, the total number of reporting participants at the end of the trial was 626, or 91.7%, compared to that at the beginning. This means that 15.7% of the participants were replaced during the study!!! Raw data on the effects of the interventions on the occurrence of respiratory infections and vomiting/diarrhoea diseases were not reported. Zero adverse effects were reported.
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.

Simmerman 2011

Study characteristics	
Methods	Randomised controlled study
Participants	Study recruited 348 households and 885 members and randomised them as follows: 1. Control (index household = 119, with 302 family members) 2. Hand-washing (index household = 119, with 292 family members) 3. Hand-washing and face mask (index household = 110, with 291 family members) The household members of children (index cases) presenting with ILI at the outpatient department of the Queen Sirikit National Institute of Child Health (QSNICH) in Bangkok, the largest public paediatric hospital in Thailand Inclusion criteria: For index cases: children aged 1 month through 15 years, residents of the Bangkok metropolitan area, and had an onset of illness < 48 hours before respiratory specimens tested positive for influenza by an RIDT that was later confirmed by qualitative real-time RT-PCR (rRT-PCR) Eligible index cases' households must have had at least 2 other members aged ≥ 1 month who planned to sleep inside the house for a period of at least 21 days from the time of enrolment. Exclusion criteria: For index cases: children at high risk for severe influenza complications (e.g. chronic lung disease, renal disease, and long-term aspirin therapy) and those treated with influenza antiviral medications Excluded households: those with any member reporting an ILI that preceded the index case by 7 days or less and households where any member had received influenza vaccination during the preceding 12 months
Interventions	Hand-washing, or hand-washing plus paper surgical face mask, or control. See Table 1 for details.
Outcomes	Laboratory: To identify index cases: QuickVue Influenza A+B rapid diagnostic kit (Quidel Co., San Diego, CA, USA), followed by rRT-PCR for influenza viral RNA Index cases and contacts tested with nasal swab and throat swab both processed for rRT-PCR.

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Simmerman 2011 *(Continued)*

	2 blood samples for antibody seroconversion collected on Days 1 and 21 (seroconversion defined as a fourfold rise in HI titre between paired sera for any of the antigens assayed). Effectiveness: Laboratory-confirmed secondary influenza virus infections amongst household members described as the secondary attack rate (SAR). A secondary influenza virus infection was defined as a positive rRT-PCR result on Days 3 or 7 or a fourfold rise in influenza HI antibody titres with the virus type and sub-type matching the index case. SAR for ILI defined by the WHO as fever plus cough or sore throat, based on self-reported symptoms. Safety: no safety measures planned or reported by the investigators Adherence: participants in the control arm reported an average of 3.9 hand-washing episodes/day (on Day 7), whilst participants in the hand-washing arm reported an average of 4.7 hand-washing episodes/day (95% CI 4.3 to 5.0; P = 0.002 compared to controls), and participants in the hand-washing plus face mask arm reported 4.9 episodes/day (95% CI 4.5 to 5.3; P < 0.001 compared to controls). In the intervention arms, parents had the highest reported daily hand-washing frequency (5.7, 95% CI 5.3 to 6.0) followed by others (4.8, 95% CI 4.3 to 5.3), siblings (4.3, 95% CI 3.7 to 4.8), and the index cases (4.1, 95% CI 3.8 to 4.4). There was no difference in the average amount of soap used in a week in the hand-washing arm (54 mL per person) and the hand-washing plus face mask arm (58.1 mL per person) (P = 0.15). 289 participants in the hand-washing plus face mask arm used an average of 12 masks per person per week (median 11, IQR 7 to 16) and reported wearing a face mask a mean of 211 minutes/day (IQR 17 to 317 minutes/day). Parents wore their masks for a median of 153 (IQR 40 to 411) minutes per day, far more than other relations (median 59; IQR 9 to 266), the index patients themselves (median 35; IQR 4 to 197), or their siblings (median 17; IQR 6 to 107). The study authors note that differences in average usage may be an attenuated measure of appropriate use in relation to the actual unmeasured exposure risk such as proximity to the index case.
Notes	The period study conducted: April 2008 and August 2009 Funding: government

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was achieved using a block randomization method using a list of blocks each with 12 household IDs, four of which were assigned to each of the three study arms."
Allocation concealment (selection bias)	Unclear risk	"A study coordinator assigned each household to one study arm after consent was obtained"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Recruiting clinicians were blinded to the allocation of the specific intervention. The participants were not blinded, but it is unlikely that the outcome would have been affected by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The primary outcome is a laboratory-confirmed influenza.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Household flow chart provided with reasons for exclusions, all numbers provided. Analysis was done by ITT and PP.
Selective reporting (reporting bias)	Low risk	All outcomes are accounted for in the ITT analysis of the results.

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Stebbins 2011

Study characteristics	
Methods	Cluster-RCT, open-label
Participants	Study included 3360 students from 10 Pittsburgh elementary schools. Intervention arm (5 schools, 1695 people) and control arm (5 schools, 1665 people) No inclusion or exclusion criteria were provided.
Interventions	Training in hand and respiratory (cough) hygiene. Hand sanitiser was provided and encouraged to be used regularly. See Table 1 for details.
Outcomes	Laboratory: Primary outcome: laboratory-confirmed influenza (RT-PCR) amongst children presenting with ILIs leading to their absence from school 2 nasal swabs were obtained using test manufacturer-approved sterile Dacron swabs. 1 swab was employed for influenza testing using the QuickVue Influenza A+B test (Quidel Corp, San Diego, CA). The second nasal swab was delivered on cold pack to the University of Pittsburgh Medical Center Clinical Virology Laboratory, Pittsburgh, PA for RT-PCR testing (performed within 48 hours). The RT-PCR used viral nucleic acid extract (EasyMag; bioMerieux, Durham, NC) and primer/probe sequences for influenza A, influenza B, and influenza A H1 and H3 subtypes (CDC, Atlanta GA). Effectiveness: Secondary outcome: absence episodes and cumulative days of absence due to ILI, any illness, and all causes Safety: none mentioned
Notes	The period study conducted: 1 November 2007 through 24 April 2008 Funding: unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"constrained randomization algorithm"
Allocation concealment (selection bias)	Low risk	"Random allocation of schools to two arms was created by Dr. Cummings and concealed until intervention assignment". "At the beginning of the school year parents and guardians were given the opportunity to decline participation"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	In 76% and 78% of illness in intervention and control group were laboratory confirmed. ILI is objectively defined.

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Stebbins 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Only episodes of identified causes were analysed. Causes of absence episodes in 66% of the study participants were not identified (2092 in the intervention group and 2232 in the control group). The parents could be contacted in only 34% cases of absence. About half of them had an illness, and in one-third of these cases the illness met the criteria of ILI (361 cases (33%)). Of these, 279 (77%) were tested for influenza.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to judge

Stebbins 2011

Study characteristics	
Methods	Cluster-RCT, open-label
Participants	Study included 3360 students from 10 Pittsburgh elementary schools. Intervention arm (5 schools, 1695 people) and control arm (5 schools, 1665 people) No inclusion or exclusion criteria were provided.
Interventions	Training in hand and respiratory (cough) hygiene. Hand sanitiser was provided and encouraged to be used regularly. See Table 1 for details.
Outcomes	Laboratory: Primary outcome: laboratory-confirmed influenza (RT-PCR) amongst children presenting with ILIs leading to their absence from school 2 nasal swabs were obtained using test manufacturer-approved sterile Dacron swabs. 1 swab was employed for influenza testing using the QuickVue Influenza A+B test (Quidel Corp, San Diego, CA). The second nasal swab was delivered on cold pack to the University of Pittsburgh Medical Center Clinical Virology Laboratory, Pittsburgh, PA for RT-PCR testing (performed within 48 hours). The RT-PCR used viral nucleic acid extract (EasyMag; bioMerieux, Durham, NC) and primer/probe sequences for influenza A, influenza B, and influenza A H1 and H3 subtypes (CDC, Atlanta GA). Effectiveness: Secondary outcome: absence episodes and cumulative days of absence due to ILI, any illness, and all causes Safety: none mentioned
Notes	The period study conducted: 1 November 2007 through 24 April 2008 Funding: unclear

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"constrained randomization algorithm"

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Stebbins 2011 *(Continued)*

Allocation concealment (selection bias)	Low risk	"Random allocation of schools to two arms was created by Dr. Cummings and concealed until intervention assignment". "At the beginning of the school year parents and guardians were given the opportunity to decline participation"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	In 76% and 78% of illness in intervention and control group were laboratory confirmed. ILI is objectively defined.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only episodes of identified causes were analysed. Causes of absence episodes in 66% of the study participants were not identified (2092 in the intervention group and 2232 in the control group). The parents could be contacted in only 34% cases of absence. About half of them had an illness, and in one-third of these cases the illness met the criteria of ILI (361 cases (33%)). Of these, 279 (77%) were tested for influenza.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to judge

Suess 2012

Study characteristics	
Methods	Cluster-RCT, open-label, parallel design
Participants	Study sample included 84 households randomised as follows: 1. 30 control (index cases = 30, household contact = 82) 2. 26 mask group (index cases = 26, household contact = 69) 3. 28 mask and hand hygiene group (index cases = 28, household contact = 67) Inclusion criteria: patients presenting to general practitioners or family physicians at the study sites within 2 days of symptom onset; had a positive rapid antigen test for influenza (later to be confirmed by quantitative RT-PCR (qRT-PCR); and was at least 2 years old. Index cases also had to be the only household member suffering from respiratory disease within 14 days prior to symptom onset. Exclusion criteria were pregnancy, severely reduced health status, and HIV infection. 1-person households were also not eligible or inclusion.
Interventions	Quote: "facemask and practising intensified hand hygiene (MH group), wearing facemask only (M group) and none of the 2 (control group)". See Table 1 for details.
Outcomes	Primary outcomes: SAR of laboratory-confirmed (qRT-PCR) influenza infection amongst household members (secondary infection cases) presenting with ILI within the observation period (8 days from the date of onset). ILI was defined as fever (> 38.0 °C) + cough or sore throat. Nasal wash specimens (or if these were not possible, nasal swabs) from all participating household members Effectiveness: Secondary outcomes: laboratory-confirmed influenza infection in a household contact (secondary infection cases). The study authors defined a symptomatic secondary influenza virus infection as a laboratory-confirmed influenza infection in a household member who developed fever (> 38.0 °C), cough, or sore throat during the observation period. They termed all other secondary cases as subclinical. A

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Suess 2012 *(Continued)*

	secondary outcome measure was the occurrence of ILI as defined by WHO as fever plus cough or sore throat. Safety: study reported that the majority of participants (107/172, 62%) did not report any problems with mask-wearing. This proportion was significantly higher in the group of adults (71/100, 71%) compared to the group of children (36/72, 50%) (P = 0.005). The main problem reported by participants (adults as well as children) was "heat/humidity" (18/34, 53% of children; 10/29, 35% of adults) (P = 0.1), followed by "pain" and "shortness of breath" when wearing a face mask.
Notes	Period study conducted: November 2009 to April 2011 Funding: governmental Adherence: in general, daily adherence was good, reaching a plateau of over 50% in nearly all groups (M and MH groups; 2009/10 and 2010/11) from the third day on (by then the intervention had been implemented in all households). A gradual decline towards lower adherence began around the sixth day of the index patient's illness.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"prepared lists of random numbers with Microsoft Excel 2003 (Mircosoft™ Cooperation, Seattle, USA) which were divided between the three intervention groups. Each participating physician received a list of random numbers with the interventions represented in a 1:1:1 ratio"
Allocation concealment (selection bias)	Low risk	"the participating physician received a list of random numbers with the interventions represented in a 1:1:1 ratio. Eligible index patients were randomly assigned a number, which was then communicated to the study center. The resulting intervention was only communicated to the households with the physicians. Intervention material was given to the study sites in closed boxes marked only with the randomisation number. Recruiting physicians were not aware of the allocation of the numbers to the interventions and the boxes for the three intervention arms looked identical. After randomisation, participants were given their box by the physician's assistants"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Outcomes are very objective and therefore unlikely to be influenced by lack of blinding. In addition, “physicians (as well as laboratory personnel) blinded from the randomisation results”.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	“physicians (as well as laboratory personnel) blinded from the randomisation results”. Outcomes are very objective and therefore unlikely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. Daily follow-up home visits over the short period of data collection (8 days)
Selective reporting (reporting bias)	Low risk	The follow-up period is very short (8 days) with very good coverage, and the criteria for defining the outcome are highly objective. All planned outcomes were reported.

Suess 2012

Study characteristics

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Suess 2012 *(Continued)*

Methods	Cluster-RCT, open-label, parallel design
Participants	Study sample included 84 households randomised as follows: 1. 30 control (index cases = 30, household contact = 82) 2. 26 mask group (index cases = 26, household contact = 69) 3. 28 mask and hand hygiene group (index cases = 28, household contact = 67) Inclusion criteria: patients presenting to general practitioners or family physicians at the study sites within 2 days of symptom onset; had a positive rapid antigen test for influenza (later to be confirmed by quantitative RT-PCR (qRT-PCR); and was at least 2 years old. Index cases also had to be the only household member suffering from respiratory disease within 14 days prior to symptom onset. Exclusion criteria were pregnancy, severely reduced health status, and HIV infection. 1-person households were also not eligible or inclusion.
Interventions	Quote: "facemask and practising intensified hand hygiene (MH group), wearing facemask only (M group) and none of the 2 (control group)". See Table 1 for details.
Outcomes	Primary outcomes: SAR of laboratory-confirmed (qRT-PCR) influenza infection amongst household members (secondary infection cases) presenting with ILI within the observation period (8 days from the date of onset). ILI was defined as fever (> 38.0 °C) + cough or sore throat. Nasal wash specimens (or if these were not possible, nasal swabs) from all participating household members Effectiveness: Secondary outcomes: laboratory-confirmed influenza infection in a household contact (secondary infection cases). The study authors defined a symptomatic secondary influenza virus infection as a laboratory-confirmed influenza infection in a household member who developed fever (> 38.0 °C), cough, or sore throat during the observation period. They termed all other secondary cases as subclinical. A secondary outcome measure was the occurrence of ILI as defined by WHO as fever plus cough or sore throat. Safety: study reported that the majority of participants (107/172, 62%) did not report any problems with mask-wearing. This proportion was significantly higher in the group of adults (71/100, 71%) compared to the group of children (36/72, 50%) (P = 0.005). The main problem reported by participants (adults as well as children) was "heat/humidity" (18/34, 53% of children; 10/29, 35% of adults) (P = 0.1), followed by "pain" and "shortness of breath" when wearing a face mask.
Notes	Period study conducted: November 2009 to April 2011 Funding: governmental Adherence: in general, daily adherence was good, reaching a plateau of over 50% in nearly all groups (M and MH groups; 2009/10 and 2010/11) from the third day on (by then the intervention had been implemented in all households). A gradual decline towards lower adherence began around the sixth day of the index patient's illness.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"prepared lists of random numbers with Microsoft Excel 2003 (Mircosoft™ Cooperation, Seattle, USA) which were divided between the three intervention groups. Each participating physician received a list of random numbers with the interventions represented in a 1:1:1 ratio"
Allocation concealment (selection bias)	Low risk	"the participating physician received a list of random numbers with the interventions represented in a 1:1:1 ratio. Eligible index patients were randomly assigned a number, which was then communicated to the study center. The resulting intervention was only communicated to the households with the

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Suess 2012 *(Continued)*

		physicians. Intervention material was given to the study sites in closed boxes marked only with the randomisation number. Recruiting physicians were not aware of the allocation of the numbers to the interventions and the boxes for the three intervention arms looked identical. After randomisation, participants were given their box by the physician's assistants"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Outcomes are very objective and therefore unlikely to be influenced by lack of blinding. In addition, "physicians (as well as laboratory personnel) blinded from the randomisation results".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"physicians (as well as laboratory personnel) blinded from the randomisation results". Outcomes are very objective and therefore unlikely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. Daily follow-up home visits over the short period of data collection (8 days)
Selective reporting (reporting bias)	Low risk	The follow-up period is very short (8 days) with very good coverage, and the criteria for defining the outcome are highly objective. All planned outcomes were reported.

Talaat 2011

Study characteristics	
Methods	Cluster-RCT
Participants	Children (N = 44,451) in the first 3 primary grades from 60 governmental elementary schools in Cairo, Egypt were included and randomised to 30 schools in the intervention arm (N = 20,882 students) and 30 control schools (N = 23,569 students). No exclusion criteria provided.
Interventions	Students were required to wash their hands at least twice during the school days for about 45 seconds, followed by proper rinsing and drying on a clean towel. Campaign material was developed, and posters were placed near sinks in the classroom and playground to encourage hand-washing with soap and water upon arriving at school, before and after meals, using the bathroom, and after coughing and sneezing. See Table 1 for details.
Outcomes	Laboratory: point-of-care influenza A and B viruses using QuickVue (QuickVue; Quidel Corp., San Diego, CA, USA). School nurses collected nasal swabs from children who visited the school clinic with ILI, and only for students who had prior written approval of a parent. Effectiveness: rates of absenteeism caused by ILI and laboratory-confirmed influenza. ILI defined as fever > 38 °C and either cough or sore throat. Safety: none planned or reported by the investigators
Notes	The period study conducted: 16 February to 12 May 2008 Funding: unclear

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

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Talaat 2011 *(Continued)*

Random sequence generation (selection bias)	Low risk	"computer-generated random number table"
Allocation concealment (selection bias)	Unclear risk	No information given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The participants and study personnel were not blinded, although lack of blinding is unlikely to have influenced the outcome. Laboratory-confirmed influenza was only conducted only for students who had prior written approval of a parent.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	“Differential interest of study teams may have contributed to the low rate of testing in students who were absent because of ILI in the control schools compared to the intervention schools (12% vs 22%)”
Incomplete outcome data (attrition bias) All outcomes	High risk	No flow chart of clusters flow during the study period. No information on withdrawal. Differential interest of study teams may have contributed to the low rate of testing in students who were absent because of ILI in the control schools compared to the intervention schools (12% vs 22%) incomplete or loss of data. The total number ILI episodes could be an underestimate, as there is no proactive method to look for symptoms of ILI amongst the students; it depends on the student being absent or in class with symptoms that are picked up by the teachers at school.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to judge

Talaat 2011

Study characteristics	
Methods	Cluster-RCT
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Talaat 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
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Allocation concealment (selection bias)	Unclear risk	No information given.
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Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	“Differential interest of study teams may have contributed to the low rate of testing in students who were absent because of ILI in the control schools compared to the intervention schools (12% vs 22%)”
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Selective reporting (reporting bias)	Unclear risk	Insufficient information to judge

Temime 2018

Study characteristics	
Methods	2-arm cluster-RCT
Participants	All residents and staff of 27 privately held chains of nursing homes owned by Korian. 26 nursing homes (13 per arm), with an average of 80 residents per nursing home, were included in the study.
Interventions	"The intervention was based on a bundle of HH-related measures aimed at NH staff, residents, visitors, and outside care providers. These measures included facilitated access to handrub solution using pocket-sized containers and new dispensers, a campaign to promote HH with posters and event organization, the formation of local work groups in each NH to work on HH guidelines, and staff education using e-learning on infection control and HH training performed by the same nurse for all NHs." See Table 1 for details.
Outcomes	Laboratory: none used Effectiveness: Primary outcomes: incidence rate of ARIs and AGE reported in the context of episodes of clustered cases, defined as at least 5 cases within 4 days amongst nursing home residents or staff. ARIs were defined as the combination of at least 1 respiratory symptom with 1 symptom of systemic infection. AGE was defined as the sudden onset of diarrhoea or vomiting in the absence of a non-infectious aetiology.

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Temime 2018 *(Continued)*

	Secondary endpoints were mortality rate, hospitalisation rate, and antibiotic prescription rate (measured in defined daily doses (DDDs) per 100 resident days). Safety: no adverse event surveillance planned or reported by the investigators
Notes	The period study conducted: 1 April 2014 to 1 April 2015 Funding: private (Institute of Ageing Well Korian (Institut du bien vieillir Korian), which runs the nursing homes included in the study)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"simple" randomisation is used
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"we suspected that underreporting occurred. The data were verified qualitatively after the end of the intervention through individual phone interviews with each participating NH. Based on these interviews, ARI clustered cases episodes had actually occurred in 12 out of 13 control NHs; however, only 1 had been notified to health authorities. No unreported clustered cases episodes were identified in the intervention NHs"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Data were collected at NH level and reported to centralised by the NH group headquarters in Paris through computerised databases. There was underreporting of ARI and AGE in the control groups. The trial authors suspected that underreporting occurred. Primary outcome: high risk. Secondary outcomes: low risk
Incomplete outcome data (attrition bias) All outcomes	High risk	For the primary outcome, there was underreporting of ARI and AGE in the control groups; no study flow chart was provided; and no reporting on any exclusions. Surveillance is based on voluntary and standardised notifications to health authorities of any AGE or ARI clustered case episode.
Selective reporting (reporting bias)	Low risk	Reported outcomes match planned outcomes published in the protocol.

Temime 2018

Study characteristics

Methods	2-arm cluster-RCT
Participants	All residents and staff of 27 privately held chains of nursing homes owned by Korian. 26 nursing homes (13 per arm), with an average of 80 residents per nursing home, were included in the study.
Interventions	"The intervention was based on a bundle of HH-related measures aimed at NH staff, residents, visitors, and outside care providers. These measures included facilitated access to handrub solution using pocket-sized containers and new dispensers, a campaign to promote HH with posters and event organization, the formation of local work groups in each NH to work on HH guidelines, and staff education using e-learning on infection control and HH training performed by the same nurse for all NHs."

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Temime 2018 *(Continued)*

	See Table 1 for details.
Outcomes	Laboratory: none used Effectiveness: Primary outcomes: incidence rate of ARIs and AGE reported in the context of episodes of clustered cases, defined as at least 5 cases within 4 days amongst nursing home residents or staff. ARIs were defined as the combination of at least 1 respiratory symptom with 1 symptom of systemic infection. AGE was defined as the sudden onset of diarrhoea or vomiting in the absence of a non-infectious aetiology. Secondary endpoints were mortality rate, hospitalisation rate, and antibiotic prescription rate (measured in defined daily doses (DDDs) per 100 resident days). Safety: no adverse event surveillance planned or reported by the investigators
Notes	The period study conducted: 1 April 2014 to 1 April 2015 Funding: private (Institute of Ageing Well Korian (Institut du bien vieillir Korian), which runs the nursing homes included in the study)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"simple" randomisation is used
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"we suspected that underreporting occurred. The data were verified qualitatively after the end of the intervention through individual phone interviews with each participating NH. Based on these interviews, ARI clustered cases episodes had actually occurred in 12 out of 13 control NHs; however, only 1 had been notified to health authorities. No unreported clustered cases episodes were identified in the intervention NHs"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Data were collected at NH level and reported to centralised by the NH group headquarters in Paris through computerised databases. There was underreporting of ARI and AGE in the control groups. The trial authors suspected that underreporting occurred. Primary outcome: high risk. Secondary outcomes: low risk
Incomplete outcome data (attrition bias) All outcomes	High risk	For the primary outcome, there was underreporting of ARI and AGE in the control groups; no study flow chart was provided; and no reporting on any exclusions. Surveillance is based on voluntary and standardised notifications to health authorities of any AGE or ARI clustered case episode.
Selective reporting (reporting bias)	Low risk	Reported outcomes match planned outcomes published in the protocol.

Turner 2004a

Study characteristics

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Turner 2004a *(Continued)*

Methods	Double-blind RCT conducted by Hill Top Research, Inc., Winnipeg, Canada, to assess the efficacy of acids with virucidal activity for the inactivation of virus and prevention of experimental rhinovirus colds. Participants in good health, aged 18 to 60, were recruited from Winnipeg and surrounding communities for participation. Qualified participants were randomised to treatment with vehicle (62% ethanol, 1% ammonium lauryl sulphate, and 1% Klucel), vehicle containing 3.5% salicylic acid, or vehicle containing 1% salicylic acid and 3.5% pyroglutamic acid. The volunteers' hands were disinfected, and then test product was applied to both hands of participant. 15 minutes after application, the fingerprints of each hand were contaminated with rhinovirus type 39. The volunteers touched conjunctiva and the nasal mucosa only with the right hand. Viral contamination of the fingers was assessed in the left hands of the volunteers, and viral infection was assessed by culture of nasal lavage specimens and blood samples.
Participants	85 volunteers; 31 control group, 27 used vehicle with 3.5% salicylic acid, 27 used vehicle with 1% salicylic acid and 3.5% pyroglutamic acid
Interventions	Use of salicylic acid versus salicylic acid and pyroglutamic acid versus "placebo" substance
Outcomes	Laboratory: yes Effectiveness: rhinovirus type 39 infection Safety: N/A
Notes	Risk of bias: unclear (no description of randomisation process, concealment or allocation) Note: the authors concluded that organic acids commonly used in over-the-counter skin care and cosmetic products have substantial virucidal activity against rhinovirus. These preparations provided effective residual antiviral activity on the hands. The virucidal effect of these hand treatments resulted in a reduction in the incidence of rhinovirus infection in the treated volunteers (P = 0.025). The utility of this observation in the natural setting remains to be determined. The volunteers were not allowed to use their hands in the interval between the hand treatment and the virus challenge, so the effect of normal use of the hands on the virucidal activity of these organic acids is not known. Similarly, the virus challenge method used in these experiments may not simulate the natural setting in all aspects. The effect of nasal secretions that would be transferred with the virus in the natural setting on the activity of the acids or on the transmission of virus was not tested in the model. We are unsure as to the practical significance of this study and the generalisability of its results to the real world. Poorly reported study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised" Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double blind", but no description
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double blind", but no description
Incomplete outcome data (attrition bias) All outcomes	Low risk	All accounted for (short study).

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Turner 2004a *(Continued)*

Selective reporting (reporting bias)	High risk	Poorly reported

Turner 2004b

Study characteristics

Methods	Double-blind RCT conducted by Hill Top Research, Inc., Winnipeg, Canada, to assess the residual virucidal activity of a skin cleanser wipe and its effectiveness in preventing experimental rhinovirus colds. Participants in good health, aged 18 to 60 years, were recruited from Winnipeg and surrounding communities for participation. The residual activity of a skin cleanser wipe containing 4% pyroglutamic acid formulated with 0.1% benzalkonium chloride was tested. The negative control treatment was 62% ethanol. Benzalkonium chloride had been previously tested and was found to have no virucidal activity. Volunteers were randomly assigned to use the control preparation or the active preparation. The study material was applied to hands with a towelette. 15 minutes later, when the fingers were completely dry, the fingertips of each hand of the control participants and the volunteers in the active treatment group were contaminated with rhinovirus type 39. An additional volunteer in the active group was challenged with virus 1 hour after application, and the final group of volunteers was challenged 3 hours after application. Viral infection was assessed by culture of nasal lavage specimens and blood samples.
Participants	122 volunteers; 30 in control group, 92 in active group (30 tested after 15 minutes, 30 after 1 hour, 32 after 2 hours)
Interventions	Use of a skin cleanser wipe containing 4% pyroglutamic acid formulated with 0.1% benzalkonium chloride versus skin cleanser wipe containing ethanol
Outcomes	Laboratory: yes Effectiveness: rhinovirus type 39 infection Safety: N/A
Notes	Risk of bias: unclear (no description of randomisation process, concealment or allocation)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised" Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double blind", but no description given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double blind", but no description given
Incomplete outcome data (attrition bias) All outcomes	Low risk	All accounted for (short study).

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Turner 2004b *(Continued)*

Selective reporting (reporting bias)	High risk	Poorly reported

Turner 2012

Study characteristics

Methods	Randomised controlled clinical trial
Participants	A total of 212 participants were enrolled (116 in the treatment group, 96 in the control group). Healthy adult volunteers aged > 18 years from the University of Virginia community Written informed consent was obtained, and volunteers were compensated for participation. Exclusion: individuals with skin conditions that would interfere with safety evaluations or medical conditions that could impact the person's well-being or affect study results, and those whose occupations required frequent hand-washing
Interventions	Antiviral hand treatment containing 2% citric acid, 2% malic acid, and 62% ethanol (n = 116) or to a no-treatment control group (n = 96). The hand treatment was applied every 3 hours and after hand-washing whilst the participants were awake. See Table 1 for details.
Outcomes	Laboratory: PCR using AmpliTaq Gold DNA Polymerase from Applied Biosystems Effectiveness: reduction of rhinovirus-induced common colds; comparison of the number of RV-associated illnesses per 100 participants in the control group with that in the treatment group over 9 weeks. Definitions: a common cold illness was defined as the presence of any of the symptoms of nasal obstruction, rhinorrhoea, sore throat, or cough on at least 3 consecutive days. Illnesses separated by at least 3 symptom-free days were considered to be separate illnesses. Rhinovirus infection was defined as the detection of RV in nasal lavage. All volunteers were seen weekly for nasal lavage, and specimens were assayed by PCR for the presence of RV. PCR–positive specimens separated by at least 8 days and at least 1 negative PCR specimen were considered to be separate infections. RV-associated illnesses were based on detection of RV either at the time of the illness or at the first weekly visit after the illness. Safety: hand irritation occurred in 11 of the 116 volunteers (9%) in the treatment group, which met protocol criteria for removal from the study. An additional 8 participants who did not meet these protocol criteria voluntarily withdrew due to hand irritation. There was no hand irritation in the control group. No other adverse effects of the study treatment were noted.
Notes	The period study conducted: August 2009 to November 2009 Funding: The Dial Corporation - a Henkel Company, Scottsdale, Arizona, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A randomization code generated using commercially available software was provided by the sponsor"
Allocation concealment (selection bias)	Low risk	"staff at the study site assigned sequential subject numbers as they enrolled volunteers into the study, and treatment assignment was determined by the subject number."
Blinding of participants and personnel (performance bias)	Low risk	The outcomes are unlikely to be influenced by lack of blinding.

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Turner 2012 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Personnel who conducted the laboratory assays were blinded to study groups and to whether the specimen was from a routine or illness related visit"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition (and reasons for it) was reported. Study outcomes reported as ITT and PP.
Selective reporting (reporting bias)	Low risk	All planned outcomes in study protocol were reported on.

Turner 2004a

Study characteristics	
Methods	Double-blind RCT conducted by Hill Top Research, Inc., Winnipeg, Canada, to assess the efficacy of acids with virucidal activity for the inactivation of virus and prevention of experimental rhinovirus colds. Participants in good health, aged 18 to 60, were recruited from Winnipeg and surrounding communities for participation. Qualified participants were randomised to treatment with vehicle (62% ethanol, 1% ammonium lauryl sulphate, and 1% Klucel), vehicle containing 3.5% salicylic acid, or vehicle containing 1% salicylic acid and 3.5% pyroglutamic acid. The volunteers' hands were disinfected, and then test product was applied to both hands of participant. 15 minutes after application, the fingerprints of each hand were contaminated with rhinovirus type 39. The volunteers touched conjunctiva and the nasal mucosa only with the right hand. Viral contamination of the fingers was assessed in the left hands of the volunteers, and viral infection was assessed by culture of nasal lavage specimens and blood samples.
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Risk of bias

Bias	Authors' judgement	Support for judgement

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Turner 2004a *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"randomised" Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double blind", but no description
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double blind", but no description
Incomplete outcome data (attrition bias) All outcomes	Low risk	All accounted for (short study).
Selective reporting (reporting bias)	High risk	Poorly reported

Turner 2004b

Study characteristics	
Methods	Double-blind RCT conducted by Hill Top Research, Inc., Winnipeg, Canada, to assess the residual virucidal activity of a skin cleanser wipe and its effectiveness in preventing experimental rhinovirus colds. Participants in good health, aged 18 to 60 years, were recruited from Winnipeg and surrounding communities for participation. The residual activity of a skin cleanser wipe containing 4% pyroglutamic acid formulated with 0.1% benzalkonium chloride was tested. The negative control treatment was 62% ethanol. Benzalkonium chloride had been previously tested and was found to have no virucidal activity. Volunteers were randomly assigned to use the control preparation or the active preparation. The study material was applied to hands with a towelette. 15 minutes later, when the fingers were completely dry, the fingertips of each hand of the control participants and the volunteers in the active treatment group were contaminated with rhinovirus type 39. An additional volunteer in the active group was challenged with virus 1 hour after application, and the final group of volunteers was challenged 3 hours after application. Viral infection was assessed by culture of nasal lavage specimens and blood samples.
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Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

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Turner 2004b *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"randomised" Sequence generation not described.
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Turner 2012

Study characteristics	
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Turner 2012 *(Continued)*

	criteria voluntarily withdrew due to hand irritation. There was no hand irritation in the control group. No other adverse effects of the study treatment were noted.
Notes	The period study conducted: August 2009 to November 2009 Funding: The Dial Corporation - a Henkel Company, Scottsdale, Arizona, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A randomization code generated using commercially available software was provided by the sponsor"
Allocation concealment (selection bias)	Low risk	"staff at the study site assigned sequential subject numbers as they enrolled volunteers into the study, and treatment assignment was determined by the subject number."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The outcomes are unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Personnel who conducted the laboratory assays were blinded to study groups and to whether the specimen was from a routine or illness related visit"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition (and reasons for it) was reported. Study outcomes reported as ITT and PP.
Selective reporting (reporting bias)	Low risk	All planned outcomes in study protocol were reported on.

White 2001

Study characteristics

Methods	Double-blind, placebo-controlled, cluster-RCT that took place in 3 schools in California during March to April 1999. The study assessed the incremental value of using an alcohol hand rub together with water-and-soap hand-washing. Both arms were administered an educational programme beginning 2 weeks prior to start of the trial. Randomisation was by classroom, and the placebo hand rub was indistinguishable from the active ingredient. Details of randomisation are not given.
Participants	Of the 72 classes originally recruited, lack of compliance (use of supplementary product at least 3 times a day) reduced the classes to 32 (16 in both arms) and a total of 769 participants aged 5 to 12 (381 students who received the sanitiser, and 388 who received the placebo).
Interventions	Pump-activated antiseptic hand rub with benzalkonium chloride (SAB) (Woodward Laboratories) or inert placebo that "virtually" looked the same in batches of 4 colour-coded bottles. School staff, parents, and participants were blinded.
Outcomes	Laboratory: testing of virucidal and bactericidal activity of the active compound Effectiveness: ARI (cough, sneezing, sinus trouble, bronchitis, fever, red eye, headache, mononucleosis, acute exacerbations of asthma) Gastrointestinal and other illnesses (data not extracted) Follow-up and observation was carried out by classroom staff, and illnesses were described by parents.

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White 2001 *(Continued)*

	Safety: 7 students dropped out because of mild sensitivity to the rub
Notes	Risk of bias: high (no description of randomisation; partial reporting of outcomes, numerators and denominators) Note: the authors conclude that addition of the rub led to a 30% to 38% decrease of illness and absenteeism (RR for illness absence incidence 0.69, RR for absence duration 0.71). Very high attrition, unclear randomisation procedure, educational programme and use of placebo hand rub make generalisability of the results debatable. No confidence intervals reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised trial", but sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"To distinguish content, both the active and placebo formulations were distributed in four color-coded groups of 1oz spritz bottles. The content were and distribution patters were only know to the researchers and were indecipherable by the school staff or students."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Teachers were responsible for recording attendance for each day during the study"
Incomplete outcome data (attrition bias) All outcomes	High risk	Partial reporting of outcomes, numerators and denominators
Selective reporting (reporting bias)	High risk	Poor reporting

Yeung 2011

Study characteristics

Methods	Clustered-RCT of a hand hygiene intervention involving pocket-sized containers of alcohol-based hand rub for the control of infections in long-term care facilities. Staff hand hygiene adherence was directly observed, and residents' infections necessitating hospitalisation were recorded. After a 3-month preintervention period, long-term care facilities (LTCFs) were randomised to receive pocket-sized containers of alcohol-based gel, reminder materials, and education for all HCWs (treatment group) or to receive basic life support education and workshops for all HCWs (control group). A 2-week intervention period (1 to 15 April 2007) was followed by 7 months of postintervention observations.
Participants	6 out of 7 community-based, private or semiprivate, residential LTCFs in Hong Kong agreed to participate and were randomised to: 1. hand hygiene group (3 LTCFs, 73 nursing staff and 244 residents analysed); or 2. control group (3 LTCFs, 115 nursing staff and 379 residents analysed). All were nursing homes serving an elderly population. All LTCFs were situated in different regions of Hong Kong, including urban and rural areas. The targets of the intervention were all full- and part-time HCWs at these LTCFs.

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Yeung 2011 *(Continued)*

	The LTCFs employed 3 types of HCWs: nurses, nursing assistants, and physiotherapists.
Interventions	Pocket-sized containers of alcohol-based gel, reminder materials, and education (intervention group) or basic life-support education and workshop (control group). See Table 1 for details.
Outcomes	Rates of infection (requiring hospitalisation) Outbreaks Death due to infection Diagnoses of infection coded into 6 categories, all of which were common endemic infections in LTCFs: 1. pneumonia, 2. urinary tract infection, 3. septicaemia, 4. skin or soft-tissue infection (including cellulitis or pressure sores), 5. gastroenteritis, and 6. fever. Infections recorded in death certificates were also included, regardless of whether the resident had been hospitalised. The causes of death were categorised as due to infection, not due to infection, or unknown. If the primary or the secondary diagnosis on the death certificate belonged to 1 of the 6 endemic infection categories, the death was coded as due to infection. No safety outcomes reported.
Notes	University and industry funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available

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Zomer 2015

Study characteristics	
Methods	Cluster-RCT
Participants	71 daycare centres (36 intervention DCCs, and 35 control) in Rotterdam-Rijnmond, Gouda and Leiden in the Netherlands Study enrolled 545 children (intervention = 278, control = 267). Inclusion/exclusion criteria: children who attended the DCC at least 2 days a week; were aged between 6 months and 3.5 years at start of the trial; intended to attend the DCC throughout the study period; and if their parents consented, were Dutch-speaking, and had access to email or regular post. Children were excluded if they had a chronic illness or medication that predisposed them to infection, a sibling taking part in the trial (i.e. 1 child per family could be included), or if they started attending CCC after the beginning of the trial).
Interventions	4 components: 1. HH products, paper towel dispensers, soap, alcohol-based hand sanitiser, and hand cream were provided for 6 months. 2. Training and a booklet outlining the training. 3. 2 team training sessions aimed at specific HH improvement activities. 4. Posters and stickers for caregivers and children as reminders. See Table 1 for details.
Outcomes	Laboratory: none Effectiveness: incidence of respiratory infections in children monitored by parents. The common cold was defined as a blocked or runny nose with at least 1 of the following symptoms: coughing, sneezing, fever, sore throat, or earache. Safety: none planned or reported by the investigators
Notes	The period study conducted: September 2011 to April 2012 Funding: mixed. The Netherlands Organisation for Health Research and Development (ZonMw). Dispensers and refills were sponsored by SCA Hygiene Products, Sweden.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Stratified randomization is performed by assigning each DCC to one of six strata based on size (i.e. small < 46 children per day versus large ≥ 46 children per day) and geographic location (i.e. highly urban versus urban versus slightly/non-urban). DCCs are assigned to either intervention or control group by means of computer generation with a 1:1 ratio in each of the strata"
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Outcome is subjective.
Blinding of outcome assessment (detection bias)	High risk	Symptoms were reported by parents, no validation.

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Zomer 2015 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Very few children were excluded or lost to follow-up (reasons for exclusions provided).
Selective reporting (reporting bias)	Low risk	All planned outcomes are reported. However, between published protocol and the paper, secondary outcomes became the primary outcome in the published paper!

AEs: adverse events
AFH: Armed Forces Hospital
AGE: acute gastroenteritis
ALRI: acute lower respiratory infection
ARI: acute respiratory infection
ASR: adverse skin reactions
A&E: accident and emergency
BIPAP: bilevel positive airway pressure
CCC: childcare centre
CDC: Centers for Disease Control and Prevention
CG: control group
CHG: chlorhexidine gluconate
CI: confidence interval
CMF: citric acid: malic acid: sodium lauryl sulphate (a virucidal mixture added to tissue paper)
CoV: coronavirus
cluster-RCT: cluster-randomised controlled trial
CRI: clinical respiratory illness
CXR: chest X-ray
DCC: daycare centre
EG: experimental group
FRI: febrile respiratory illness
GI: gastrointestinal
GTI: gastrointestinal infection
GP: general practitioner
HCW: healthcare worker
HFH: Hanoi French Hospital
HH: hand hygiene
HR: high risk
HSG: hand sanitiser group
ICD-9: International Classification of Disease, 9th Revision, Clinical Modification
ICU: intensive care unit
ILI: influenza-like illness
IQR: interquartile range
IRR: incident rate ratio
ITT: intention-to-treat
LRTI: lower respiratory tract infection
LTCF: long-term care facility
MCU: medical convalescent unit
MDCK: Madin Darby canine kidney cell line
M group: face mask group
MH group: face mask and hand hygiene group
MS: monkey-derived cell line
N/A: not applicable
NAT: nucleic acid testing
NH: nursing home
NICU: neonatal intensive care unit
NOS: Newcastle-Ottawa Scales
NTS: nasal and throat swab
OR: odds ratio
PCR: polymerase chain reaction

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PCU: physical conditioning unit
POCT: point-of-care testing
PP: per protocol
PPE: personal protective equipment
QNAF: Qatar National Research Fund
RCT: randomised controlled trial
RDS: respiratory distress syndrome
RI: respiratory infection
RIDT: rapid influenza diagnostic test
RNA: ribonucleic acid
RR: risk ratio
rRT-PCR: real-time reverse transcription-polymerase chain reaction
RTI: respiratory tract infection
RT-PCR: reverse-transcriptase polymerase chain reaction
RSV: respiratory syncytial virus
RV: rhinovirus
SAB: surfactant, allantoin, and benzalkonium chloride
SAR: secondary attack rate
SARS: severe acute respiratory syndrome
SCBU: special care baby unit
SD: standard deviation
SHEWA-B: Sanitation, Hygiene Education and Water Supply in Bangladesh
SOB: shortness of breath
SOPs: standard operating procedures
S/S: signs/symptoms
SSTI: skin and soft-tissue infection
STH: soil-transmitted helminth
SWG: soap and water group
TIDieR: Template for Intervention Description and Replication
UHR-I: ultra high-risk infection
UHR-S: ultra high-risk SARS
URI: upper respiratory infection
URTI: upper respiratory tract infection
WBC: white blood cell
WHO: World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abou El Hassan 2004	Topic completely extraneous
Amirav 2005	Randomised controlled trial of aerosol treatment
Anderson 2004	Mathematical model with interesting discussion of interaction between public health measures
Anonymous 2002	News item
Anonymous 2004	News item
Anonymous 2005a	News item
Anonymous 2005b	News item
Anonymous 2005c	News item
Apisarnthanarak 2009	Intervention bundle not broken down.
Apisarnthanarak 2010	Participants took antivirals.

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Study	Reason for exclusion
Aragon 2005	Descriptive paper (non-comparative). Has no viral outcomes
Azor-Martinez 2014	Results reported as respiratory and gastrointestinal infections. No extractable respiratory data
Barros 1999	Correlational study between incidence of URTI and factors such as overcrowding
Bauer 2009	Historical comparison with RSV gammaglobulin amongst interventions
Bell 2004	Has unpublished entry exit screening data and extensive references but no comparative data
Bellissimo-Rodrigues 2009	Intervention is chlorhexidine.
Ben-Abraham 2002	Exclude - bacterial illness only
Black 1981	Diarrhoea only outcome
Borkow 2010	No human beings involved.
Bouadma 2010	Hospital-based ventilator routine
Bowen 2007	Outcomes of composite infections. Respiratory infections are not reported separately.
Breugelmans 2004	Description of risk factors in aircraft
Cai 2009	Compliance study
Cantagalli 2010	Outcome outside inclusion criteria
Carbonell-Estrany 2008	Immunoglobulin intervention and descriptive review
Carter 2002	News item
Castillo-Chavez 2003	Editorial
Cava 2005a	Survey of quarantinees' views
Cava 2005b	Personal experiences of quarantine
CDC 2003a	Case reports
CDC 2003b	No data presented.
Chai 2005	Letter - about MRSA
Chami 2012	Outcomes of composite infections. Respiratory infections are not reported separately.
Chaovavanich 2004	Case report
Chau 2003	No original retrievable data. Mathematical model fitting expected to observed cases with quarantine in the SARS of Hong Kong
Chau 2008	Audit of infection control procedures and compliance with guidelines
Chen 2007	An assessment of the impact of different hand-washing teaching methods. No clinical outcomes

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Study	Reason for exclusion
Cheng 2010	Confounded by antiviral use for postexposure prophylaxis
Chia 2005	Knowledge survey
Clynes 2010	Letters
Cowling 2007	Epidemiology, non-comparative, non-interventions study
Daniels 2010	Commentary
Daugherty 2008	No free data presented.
Davies 1994	Antibody titres as outcomes with so many biases that interpretation of study is problematic
Day 1993	No acute respiratory infection outcome data
Day 2006	Mathematical model; no new data
Dell'Omodarme 2005	Probabilistic and Bayesian mathematical model of screening at entry
Denbak 2018	Outcomes of composite infections. Respiratory infections are not reported separately.
Desenclos 2004	Description of transmission
DiGiovanni 2004	Qualitative study of compliance factors in quarantine
Doebbeling 1992	RCT respiratory data not present. Only 3 viruses isolated in total with no viral typing available.
Dwosh 2003	Case series
Edmonds 2010	Lab study
Fendler 2002	Cohort study badly biased with differential health profiles and healthcare workers dependency in intervention and control semi-cohorts. No attempt to adjust for confounders was made. No de-nominators available.
Flint 2003	Description of spread in aircraft and non-comparative data
Fung 2004	Non-comparative
Garcia 2010	Commentary
Gaydos 2001	Editorial linked to Ryan 2001. (Ryan 2001 was an included trial in the previous version of this review (2011). Non-RCTs were removed in this 2020 update).
Gensini 2004	Interesting historical review
Girou 2002	Non-clinical outcomes
Glass 2006	Mathematical model - no original data presented
Goel 2007	Non-comparative study
Gomersall 2006	Non-comparative study

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Study	Reason for exclusion
Gore 2001	Summary of Dyer 2000. (Dyer 2000 was a prospective, cluster open-label cross-over cohort study included in the previous version of this review (2011). Non-RCTs were removed in this 2020 update).
Gostin 2003	Not an analytical study
Gralton 2010	Review
Guinan 2002	It would appear that 9 classes took part and "acted as their own controls", but it is not clear if there was cross-over of classes or not. In addition, the outcome is combined gastrointestinal/respiratory. The clue lies in the presence of a nested economic analysis which shows considerable savings in time for staff and pupils if the soap is used: in other words this is a (covert) publicity study.
Gupta 2005	Economic model - no new data
Gwaltney 1982	No breakdown of cases given by arm.
Han 2003	Non-comparative
Hayden 1985	This is an RCT with laboratory-induced colds, small numbers, and uncertain numerators, but almost certainly because of the unique laboratory conditions (placebo tissues not being a placebo at all) of impossible generalisation. It was a pilot to the far bigger trial by Farr 1988a; Farr 1988b.
Hendley 1988	Inappropriate intervention
Hens 2009	Model
Heymann 2009	Already included in review as Heymann 2004. (Heymann 2004 was a controlled before and after study included in the previous version of this review (2011). Non-RCTs were removed in this 2020 update).
Hilburn 2003	No ARI/viral outcomes (e.g. URTIs)
Hilmarsson 2007	Animal study
Hirsch 2006	Study tested pharmacological interventions.
Ho 2003	Descriptive review
Hsieh 2007	Mathematical model
Hugonnet 2007	Letter without any data
Jiang 2003	2 papers that are probably different versions of the same paper: Jiang SP, Huang LW, Wang JF, Wu W, Yin SM, Chen WX, et al. A study of the architectural factors and the infection rates of healthcare workers in isolation units for severe acute respiratory syndrome. Chung-Hua Chieh Ho Ho Hu Hsi Tsa Chih [Chinese Journal of Tuberculosis & Respiratory Diseases]. 26(10):594-7, 2003 Oct
Johnson 2009	Outcomes are non-clinical.
Jones 2005	Historical account
Kaydos-Daniels 2004	Not an analytical study
Kelso 2009	Model

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Study	Reason for exclusion
Khaw 2008	Assessing the efficacy of O_2 delivery
Kilabuko 2007	Aetiological study
Kosugi 2004	Non-comparative study
Lam 2004	Outcomes were generic (infection rates). No laboratory data available for viral diagnosis.
Lange 2004	No data presented.
Larson 2004a	Inappropriate outcomes
Larson 2004b	Inappropriate outcomes
Larson 2005	Cluster-RCT comparing the effects of 2 hand hygiene regimens on infection rates and skin condition and microbial counts of nurses' hands in neonatal intensive care units. Outcomes were generic (e.g. pneumonia and microbial counts of participants' skin). No laboratory data available for viral diagnosis.
Lau 2004	Attitude survey
Lau 2005	Herbal remedy effectiveness assessment
Lee 2005	Descriptive study of risk and protective factors of transmission in households. No assignment took place.
Lee 2010	Cohort study; unclear numbers were vaccinated against influenza
Lennell 2008	Measured absenteeism due to non-specific infection
Lipsitch 2003	Mathematical model fit to evidence
Luckingham 1984	Historical report on Tucson experience during Spanish flu pandemic
Ma 2004	Case-control study of risk factors for SARS
MacIntyre 2010	Commentary on Cowling 2009
Malone 2009	Model
Marin 1991	Viral resistance study
McSweeny 2007	Historical description
Mielke 2009	Review
Mikolajczyk 2008	No intervention
Monsma 1992	Non-comparative study
Nandrup-Bus 2009	The trial had only 2 clusters.
Nishiura 2009	Model

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Study	Reason for exclusion
O'Callaghan 1993	Letter linked to Isaacs 1991. (Isaacs 1991 was a retrospective and prospective cohort study included in the previous version of this review (2011). Non-RCTs were removed in this 2020 update).
Olsen 2003	Description of transmission
Ooi 2005	Descriptive study, but with interesting organisational chart
Orellano 2010	Confounded by antiviral use
Panchabhai 2009	Pharma intervention
Pang 2004	Descriptive study of Beijing outbreak. Some duplicate data in common with Pang 2003. (Pang 2003 was an eclogical study included in the previous version of this review (2011). Non-RCTs were removed in this 2020 update).
Patel 2012	Although within each district the participating schools and households were randomly selected, the allocation of districts to the intervention and comparison arms was not randomly assigned.
Pittet 2000	Analysis of relationship between hand-washing compliance campaign and nosocomial bacterial infections (e.g. MRSA)
Prasad 2004	Letter about retrospective cohort - behavioural
Rabenau 2005	In vitro test of several disinfectants
Reynolds 2008	Describes the psychological effects of quarantine
Richardson 2010	Non-clinical study
Riley 2003	Mathematical model fit to evidence
Rodriguez 2009	A “reasonable attempt at minimizing bias” (see inclusion criteria) does not include absenteeism
Rosen 2006	Non-specific outcome. Measured absenteeism
Rosenthal 2005	Outcomes were generic (e.g. pneumonia, URTIs). No laboratory data available for viral diagnosis.
Safiulin 1972	Non-comparative set of studies with no clinical outcomes
Sandrock 2008	Review
Sattar 2000	Experiment assessing virucidal activity of fingertip surface - no clinical outcome data
Schull 2007	Describes the impact of SARS in a Toronto study
Seal 2010	Lab study
Seale 2009	Study looking at whether using respirators in A&E department is feasible
Sizun 1996	This is a review; no original data presented.
Slayton 2016	Compares hand-washing plus (antibacterial) towel versus hand-washing without towel
Stebbins 2009	Attitude survey

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Study	Reason for exclusion
Stedman-Smith 2015	Composite outcome. No data on separate respiratory illnesses reported.
Stoner 2007	No study data available.
Stukel 2008	Impact of the SARS disruption on care/mortality for other pathologies (e.g. acute myocardial infarction). There are no interventions, and outcomes are unrelated to acute respiratory infections.
Svoboda 2004	Descriptive study with before-and-after data but shifting denominators
Tracht 2010	Model
Ueno 1990	Experimental study. No clinical intervention
Uhari 1999	No respiratory illness data to be extracted
van der Sande 2008	Laboratory study without any clinical outcomes
Vessey 2007	Composite outcome. No data on separate respiratory illnesses reported.
Viscusi 2009a	Lab study
Viscusi 2009b	Lab study
Wang 2003	Descriptive study
Wang 2005	Case-control study of susceptibility factors
Weber 2004	Editorial linked to Larson 2004a
Wen 2010	Lab study
White 2005	Redundant publication of White 2003. (White 2003 was a prospective, open, cohort study included in the previous version of this review (2011). Non-RCTs were removed in this 2020 update).
Wilczynski 1997	Clinical trial of the effects of breastfeeding
Wilder-Smith 2003	Description of risk factors in aircraft
Wilder-Smith 2005	Descriptive review
Wong 2005	Attitude survey
Yen 2010	Model
Yu 2004	Description of transmission
Zamora 2006	Head-to-head comparison of 2 sets of PPEs with no controls and no clinical outcomes
Zhai 2007	Non-comparative study
Zhao 2003	CCT of SARS treatment

A&E: accident and emergency
ARI: acute respiratory infection
CCT: controlled clinical trial

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MRSA: methicillin-resistant *Staphylococcus aureus*
RCT: randomised controlled trial
RSV: respiratory syncytial virus
PPE: personal protective equipment
SARS: severe acute respiratory syndrome
URTI: upper respiratory tract infection

Characteristics of ongoing studies *[ordered by study ID]*

NCT03454009

Study name	Appropriate time-interval application of alcohol hand gel on reducing influenza-like illness among preschool children: a randomized, controlled trial
Methods	This is a comprehensive randomised cluster hand-hygiene improvement intervention to reduce self-reported ARI/ILI and GI illness, absenteeism, presenteeism and related behavioural and attitudinal change over a 90-day trial. The intervention group will receive hand hygiene supplies and a variety of educational materials, including environmental posters in common areas. The control group will perform their usual hygiene activities and will not receive an intervention. Identical weekly surveys will be administered to the intervention and control groups to measure self-reported illness, absenteeism, presenteeism, along with behaviour and attitudes measured at specified intervals during the study. The intervention and control groups were randomised by work floors before the onset of the enrolment period. It is hypothesised that employees in the intervention group will experience reduced self-reported illness, absenteeism, and presenteeism along with improved protective hygiene behaviours and related attitudes, relative to those in the control group over the 90-day trial.
Participants	Inclusion criteria: 1. At least 18 years of age or older 2. No known allergies to alcohol or surface disinfecting wipes 3. Works at least 30% of office hours at the study host site 4. Consent to receiving emails from Kent State University Exclusion criteria: 1. Under 18 years of age 2. Known allergies to alcohol or surface disinfecting wipes 3. Works less than 30% of office hours at the study host site 4. Does not consent to receiving emails from Kent State University
Interventions	The intervention group will receive hand hygiene supplies and a variety of educational materials, including environmental posters in common areas. The control group will perform their usual hygiene activities and will not receive an intervention.
Outcomes	Self-reported ARI/ILI and GI illness, absenteeism, presenteeism and related behavioural and attitudinal change over a 90-day trial
Starting date	5 February 2018
Contact information	Maggie Stedman-Smith, PhD, Kent State University College of Public Health
Notes	Recruitment completed. Last update in ClinicalTrials.gov was 1 May 2019. NCT03454009

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NCT04267952

Study name	Hand hygiene intervention program on primary school students' health outcomes and absenteeism in school
Methods	Study Type: interventional (clinical trial) Estimated enrolment: 200 participants Allocation: randomised Intervention model: parallel assignment Masking: single (participant) Masking description: participation will not know whether they are in the experimental or control group
Participants	Inclusion criteria: primary school student (especially third- and fourth-class student) Exclusion criteria: people with chronic disease
Interventions	Experimental: first group Hand hygiene intervention programme prepared by using planned behaviour theory will be applied to the students in this group. Active comparator: second group Students in this group will be given classic hand hygiene training.
Outcomes	Primary outcome measure: children with symptoms of infection will be referred to the family physician to have a rapid antigen test and to report the result to the researcher. 10 identified upper respiratory tract symptoms (fever, sore throat, runny nose, etc.) will be recorded weekly by family of children. The researcher will receive symptom information from the family via weekly SMS. The number of days the child does not attend school due to illness and the percentage of absenteeism 1. Group A streptococcal infections in rapid antigen test (time frame: total 20 weeks) 2. Incidence of symptoms of acute upper respiratory tract infection (time frame: total 20 weeks) 3. School absenteeism (time frame: total 20 weeks) Secondary outcome measures: Glogerm gel applied hands will shine areas containing micro-organisms. Contamination rate will be calculated by taking a photo of the hands and performing brightness analysis in Adobe Photoshop program. 1. Pollution rate of hands (time frame: from date of randomisation until the date of first documented progression assessed up to 7 months)
Starting date	9 September 2019
Contact information	Contact: Uyanık +905068949969; gulcinyelten@hotmail.com
Notes	Recruitment is ongoing. Last update in ClinicalTrials.gov was 13 February 2020. NCT04267952

NCT04296643

Study name	Medical masks vs N95 respirators for COVID-19

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NCT04296643 *(Continued)*

Methods	A RCT in which nurses will be randomised to either medical masks or N95 respirators when providing medical care to patients with COVID-19. This Canadian multicentre RCT will assess whether medical masks are non-inferior to N95 respirators when nurses provide care involving non-aerosol generating procedures. Nurses will be randomised to either use of a medical mask or to a fit-tested N95 respirator when providing care for patients with febrile respiratory illness. The primary outcome is laboratory confirmed COVID-19 amongst nurse participants.
Participants	Inclusion criteria: 1. Nurses who work > 37 hours per week in medical, emergency, paediatric units Exclusion criteria: 1. Nurses with 1 or more comorbidities 2. Nurses who cannot pass an N95 respirator fit-test
Interventions	Experimental: medical mask Medical mask worn when providing care to patient with febrile respiratory illness Active comparator: N95 respirator N95 respirator worn when providing care to patient with febrile respiratory illness
Outcomes	Primary outcome measures: 1. Number of participants with RT-PCR confirmed COVID-19 infection 2. RT-PCR confirmed COVID-19 infection (time frame: 6 months) Secondary outcome measures: 1. Number of participants with acute respiratory illness 2. Number of participants with absenteeism 3. Number of participants with lower respiratory infection 4. Number of participants with pneumonia 5. Number of participants with ICU admission 6. Number of participants needing mechanical ventilation 7. Number of participants that died
Starting date	Started 2 April 2020
Contact information	Contact: Mark Loeb, MD, 9053340010; loebm@mcmaster.ca
Notes	NCT04296643

NCT04337541

Study name	Reduction in COVID-19 infection using surgical facial masks outside the healthcare system
Methods	Parallel RCT
Participants	18 years of age and older. The participants recruited are people working outside of their home, who have not previously been infected with COVID-19 and who do not wear facial masks (e.g. healthcare personnel) when working. They will be randomised for: 1. normal behaviour according to the authority's recommendations; or

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NCT04337541 *(Continued)*

	2. normal behaviour according to the authority's recommendations and use of facial masks.
Interventions	All participants will follow authority recommendations and be randomised to either wear facial masks or not. They will perform swab-test if they experience symptoms during the study as well as at the end of study. Participants will be instructed in using the facial mask consistently when outside their home (and at home when receiving visits from others). The instruction is given in writing and via an instruction video. The participants will be contacted once weekly to optimise compliance. It will be registered if the participants are diagnosed with COVID-19. Participants will perform antibody screening at study start and end. Participants who do not test positive for COVID-19 during the study period will perform a swab self-test if experiencing symptoms or when the study ends (instruction video).
Outcomes	Primary outcome: reduction in COVID-19 infection frequency Secondary outcome: number of participants testing positive in antibody screening at study start and study end, respectively
Starting date	2 April 2020
Contact information	Prof Henning Bundgaard, DMSc +4526112290; henning.bundgaard@regionh.dk
Notes	NCT04337541. Published *Annals of Internal Medicine*, https://www.acpjournals.org/doi/10.7326/M20-6817, 18 Nov 2020).

NCT04471766

Study name	Evaluation of locally produced cloth face mask on COVID-19 and respiratory illnesses prevention at the community level - a cluster-RCT
Methods	Study type: interventional (clinical trial) Estimated enrolment: 66,000 participants Allocation: randomised Intervention model: parallel assignment Masking: single (outcomes assessor) Primary purpose: prevention
Participants	Ages eligible for study: 10 years and older (child, adult, older adult) Sexes eligible for study: all Accepts healthy volunteers: no Criteria Inclusion criteria: 1. Household resident 2. Age 10 years and older Exclusion criteria: 1. Refusal to participate
Interventions	Experimental: certified cloth face mask plus preventive information

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NCT04471766 *(Continued)*

	Active comparator: information on COVID-19 prevention
Outcomes	Self-reported main symptoms of COVID-19 (3 or more of fever, cough, fatigue, shortness of breath, loss of smell/taste) Consultation for COVID-19 like illness or reported positive test, or both Self reported COVID-19 like illness plus hospitalisation or death Any death during the follow-up period: 1. Reported COVID-19 like illness (time frame: 4 months' follow-up) 2. Consultation (time frame: 4 months' follow-up) 3. Severe illness (time frame: 4 months' follow-up) 4. Mortality (time frame: 4 months' follow-up)
Starting date	Estimated study start date: July 2020
Contact information	Amabelia Rodrigues, PhD, 00245966078659; a.rodrigues@bandim.org
Notes	The number of cases of COVID-19 is still increasing, and transmission of SARS-CoV-2 seems to occur mainly through person-to-person transmission through respiratory droplets, indirect contact with infected people and surfaces. The use of face masks is recommended as a public health measure, but in many settings only domestic cloth made masks are available to the majority of the people. However, masks can be of different quality, and very little is known about the utility of cloth face masks at the community level. In Bandim Health Project's Health and Demographic Surveillance System we will evaluate the effect of providing locally produced cloth face masks on the severity of COVID-19 like illness and mortality in an urban population. The locally produced cloth mask is made according to a laboratory-certified model and will be provided to the intervention group alongside information of how the risk of transmission can be reduced. The control group will receive information alone. Follow-up will be implemented through telephone calls and postepidemic home visits.

Wang 2015

Study name	A cluster-RCT to test the efficacy of face masks in preventing respiratory viral infection among Hajj pilgrims
Methods	Cluster-randomised trial, randomising worshippers' accommodation tents during several seasons of the Hajj pilgrimage in Saudi Arabia. In the intervention tents, free face masks will be distributed to be worn for 7 days.
Participants	Pilgrims to the Hajj
Interventions	Standard surgical masks distributed free of charge to pilgrims in the intervention accommodation tents. Control group receives no intervention.
Outcomes	Flu-like illness, recorded in diaries, with laboratory confirmation where possible
Starting date	
Contact information	
Notes	Australian New Zealand Clinical Trials Registry (ANZCTR), ACTRN12613001018707

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ARI: acute respiratory tract infections
ICU: intensive care unit
ILI: influenza-like illness
GI: gastrointestinal
RCT: randomised controlled trial
RT-PCR: reverse-transcriptase polymerase chain reaction

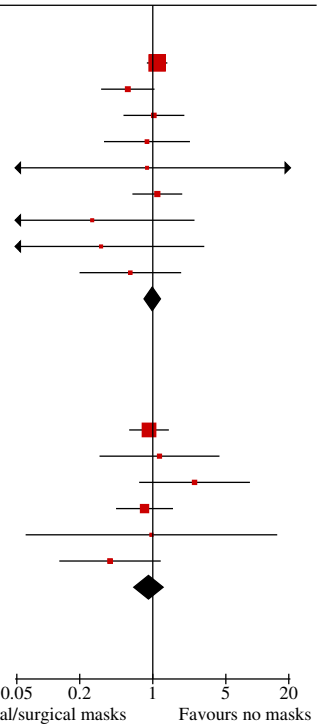
DATA AND ANALYSES

Comparison 1. Randomised trials: medical/surgical masks versus no masks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Viral illness	9		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1.1 Influenza-like illness	9	3507	Risk Ratio (IV, Random, 95% CI)	0.99 [0.82, 1.18]
1.1.2 Laboratory-confirmed influenza	6	3005	Risk Ratio (IV, Random, 95% CI)	0.91 [0.66, 1.26]
1.2 Influenza-like illness in healthcare workers	2	1070	Risk Ratio (IV, Random, 95% CI)	0.37 [0.05, 2.50]

Analysis 1.1. Comparison 1: Randomised trials: medical/surgical masks versus no masks, Outcome 1: Viral illness

Study or Subgroup	log[RR]	SE	Medical/surgical masks Total	No masks Total	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 Influenza-like illness						
Aiello 2012	0.095	0.115	392	370	64.5%	1.10 [0.88 , 1.38]
Barasheed 2014	-0.55	0.3	75	89	9.5%	0.58 [0.32 , 1.04]
Canini 2010	0.025	0.342	148	158	7.3%	1.03 [0.52 , 2.00]
Cowling 2008	-0.128	0.483	61	205	3.7%	0.88 [0.34 , 2.27]
Jacobs 2009	-0.126	1.83	17	15	0.3%	0.88 [0.02 , 31.84]
MacIntyre 2009	0.1	0.28	186	100	10.9%	1.11 [0.64 , 1.91]
MacIntyre 2015	-1.335	1.15	580	458	0.6%	0.26 [0.03 , 2.51]
MacIntyre 2016	-1.139	1.16	302	295	0.6%	0.32 [0.03 , 3.11]
Suess 2012	-0.494	0.571	26	30	2.6%	0.61 [0.20 , 1.87]
Subtotal (95% CI)			**1787**	**1720**	**100.0%**	**0.99 [0.82 , 1.18]**
Heterogeneity: Tau² = 0.00; Chi² = 7.29, df = 8 (P = 0.51); I² = 0%						
Test for overall effect: Z = 0.13 (P = 0.90)						
1.1.2 Laboratory-confirmed influenza						
Aiello 2012	-0.083	0.223	392	370	51.6%	0.92 [0.59 , 1.42]
Cowling 2008	0.148	0.674	61	205	6.0%	1.16 [0.31 , 4.34]
MacIntyre 2009	0.92	0.6225	186	100	7.0%	2.51 [0.74 , 8.50]
MacIntyre 2015	-0.182	0.32	580	458	25.8%	0.83 [0.45 , 1.56]
MacIntyre 2016 (1)	-0.03	1.414	302	295	1.4%	0.97 [0.06 , 15.51]
Suess 2012	-0.942	0.57	26	30	8.3%	0.39 [0.13 , 1.19]
Subtotal (95% CI)			**1547**	**1458**	**100.0%**	**0.91 [0.66 , 1.26]**
Heterogeneity: Tau² = 0.00; Chi² = 5.08, df = 5 (P = 0.41); I² = 1%						
Test for overall effect: Z = 0.58 (P = 0.56)						



Footnotes
(1) Both MacIntyre studies reported on laboratory confirmed respiratory virus infection

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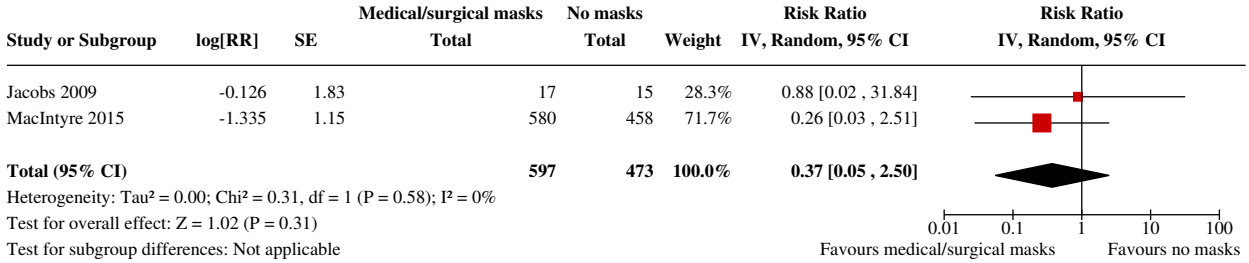
Analysis 1.2. Comparison 1: Randomised trials: medical/surgical masks versus no masks, Outcome 2: Influenza-like illness in healthcare workers



Comparison 2. Randomised trials: N95 respirators compared to medical/surgical masks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Viral illness	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.1.1 Clinical respiratory illness	3	7799	Risk Ratio (IV, Random, 95% CI)	0.70 [0.45, 1.10]
2.1.2 Influenza-like illness	5	8407	Risk Ratio (IV, Random, 95% CI)	0.82 [0.66, 1.03]
2.1.3 Laboratory-confirmed influenza	5	8407	Risk Ratio (IV, Random, 95% CI)	1.10 [0.90, 1.34]
2.2 Viral illness in healthcare workers	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.2.1 Clinical respiratory illness	3	7799	Risk Ratio (IV, Random, 95% CI)	0.70 [0.45, 1.10]
2.2.2 Influenza-like illness	4	8221	Risk Ratio (IV, Random, 95% CI)	0.81 [0.59, 1.11]
2.2.3 Laboratory-confirmed influenza	4	8221	Risk Ratio (IV, Random, 95% CI)	1.05 [0.79, 1.40]

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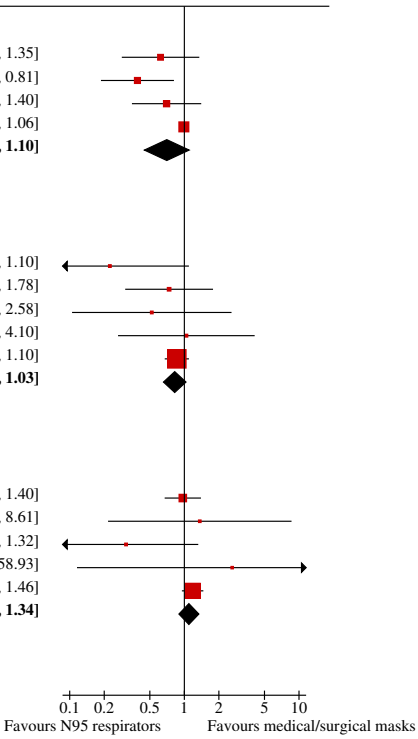
Analysis 2.1. Comparison 2: Randomised trials: N95 respirators compared to medical/surgical masks, Outcome 1: Viral illness

Study or Subgroup	log[RR]	SE	N95 respirators Total	Medical/surgical masks Total	Weight	Risk Ratio IV, Random, 95% CI
2.1.1 Clinical respiratory illness						
MacIntyre 2011	-0.478	0.397	949	492	18.5%	0.62 [0.28 , 1.35]
MacIntyre 2013	-0.942	0.374	581	286	19.7%	0.39 [0.19 , 0.81]
MacIntyre 2013 (1)	-0.357	0.355	516	286	20.8%	0.70 [0.35 , 1.40]
Radonovich 2019	-0.01	0.035	2243	2446	41.0%	0.99 [0.92 , 1.06]
Subtotal (95% CI)			**4289**	**3510**	**100.0%**	**0.70 [0.45 , 1.10]**
Heterogeneity: Tau² = 0.13; Chi² = 8.37, df = 3 (P = 0.04); I² = 64%						
Test for overall effect: Z = 1.54 (P = 0.12)						
2.1.2 Influenza-like illness						
Loeb 2009	-1.496	0.81	210	212	2.0%	0.22 [0.05 , 1.10]
MacIntyre 2009	-0.306	0.45	92	94	6.6%	0.74 [0.30 , 1.78]
MacIntyre 2011	-0.654	0.817	949	492	2.0%	0.52 [0.10 , 2.58]
MacIntyre 2013	0.04	0.7	1097	572	2.7%	1.04 [0.26 , 4.10]
Radonovich 2019	-0.151	0.124	2243	2446	86.7%	0.86 [0.67 , 1.10]
Subtotal (95% CI)			**4591**	**3816**	**100.0%**	**0.82 [0.66 , 1.03]**
Heterogeneity: Tau² = 0.00; Chi² = 3.19, df = 4 (P = 0.53); I² = 0%						
Test for overall effect: Z = 1.68 (P = 0.09)						
2.1.3 Laboratory-confirmed influenza						
Loeb 2009	-0.031	0.186	210	212	27.7%	0.97 [0.67 , 1.40]
MacIntyre 2009 (2)	0.31	0.94	92	94	1.2%	1.36 [0.22 , 8.61]
MacIntyre 2011	-1.171	0.74	949	492	1.9%	0.31 [0.07 , 1.32]
MacIntyre 2013	0.96	1.59	1097	572	0.4%	2.61 [0.12 , 58.93]
Radonovich 2019	0.166	0.11	2243	2446	68.8%	1.18 [0.95 , 1.46]
Subtotal (95% CI)			**4591**	**3816**	**100.0%**	**1.10 [0.90 , 1.34]**
Heterogeneity: Tau² = 0.00; Chi² = 4.15, df = 4 (P = 0.39); I² = 4%						
Test for overall effect: Z = 0.89 (P = 0.37)						



Footnotes

(1) MacIntyre 2013 includes 2 comparisons: N95 vs surgical masks and targeted N95 vs surgical masks

(2) MacIntyre 2009 reported on outcome laboratory confirmed infections

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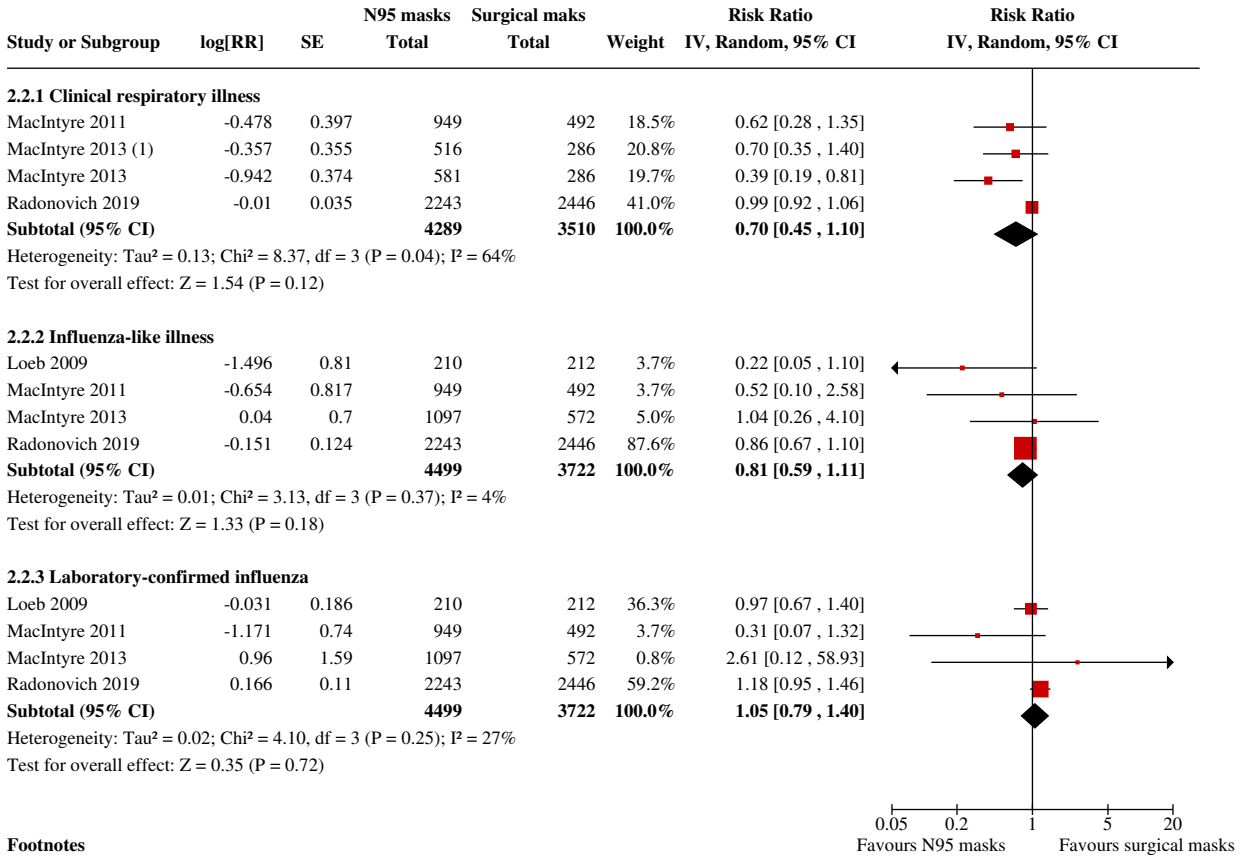
Analysis 2.2. Comparison 2: Randomised trials: N95 respirators compared to medical/surgical masks, Outcome 2: Viral illness in healthcare workers



Footnotes

(1) MacIntyre 2013 includes 2 comparisons: N95 vs surgical masks and targeted N95 vs surgical masks

Comparison 3. Randomised trials: hand hygiene compared to control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Viral illness	16		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.1.1 Acute respiratory illness	7	44129	Risk Ratio (IV, Random, 95% CI)	0.84 [0.82, 0.86]
3.1.2 Influenza-like illness	10	32641	Risk Ratio (IV, Random, 95% CI)	0.98 [0.85, 1.13]
3.1.3 Laboratory-confirmed influenza	8	8332	Risk Ratio (IV, Random, 95% CI)	0.91 [0.63, 1.30]
3.2 ARI or ILI or influenza (including outcome with most events from each study)	16	61372	Risk Ratio (IV, Random, 95% CI)	0.89 [0.84, 0.95]
3.3 Influenza or ILI: sensitivity analysis including outcomes with the most precise and unequivocal definitions	11	26343	Risk Ratio (IV, Random, 95% CI)	0.92 [0.80, 1.05]
3.4 ARI or ILI or influenza: subgroup analysis	16	61372	Risk Ratio (IV, Random, 95% CI)	0.89 [0.84, 0.95]

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Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.4.1 Children	9	21283	Risk Ratio (IV, Random, 95% CI)	0.92 [0.84, 1.01]
3.4.2 Adults	7	40089	Risk Ratio (IV, Random, 95% CI)	0.85 [0.79, 0.92]
3.5 Absenteeism	3	3150	Risk Ratio (IV, Random, 95% CI)	0.64 [0.58, 0.71]

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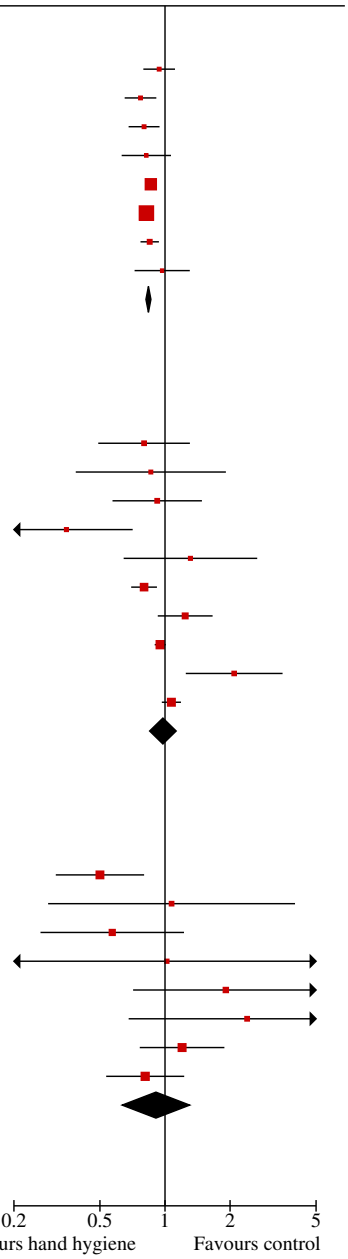
Analysis 3.1. Comparison 3: Randomised trials: hand hygiene compared to control, Outcome 1: Viral illness

Study or Subgroup	log[RR]	SE	Hand hygiene Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
3.1.1 Acute respiratory illness						
Azor-Martinez 2018	-0.062	0.086	274	149	2.4%	0.94 [0.79 , 1.11]
Azor-Martinez 2018 (1)	-0.261	0.086	339	149	2.4%	0.77 [0.65 , 0.91]
Correa 2012	-0.223	0.084	794	933	2.5%	0.80 [0.68 , 0.94]
Larson 2010	-0.199	0.134	946	904	1.0%	0.82 [0.63 , 1.07]
Little 2015	-0.151	0.02	8241	8667	35.2%	0.86 [0.83 , 0.89]
Millar 2016	-0.198	0.016	10000	10000	48.7%	0.82 [0.80 , 0.85]
Nicholson 2014	-0.163	0.05	847	833	6.9%	0.85 [0.77 , 0.94]
Sandora 2005	-0.03	0.15	602	451	0.8%	0.97 [0.72 , 1.30]
Subtotal (95% CI)			**22043**	**22086**	**100.0%**	**0.84 [0.82 , 0.86]**
Heterogeneity: Tau² = 0.00; Chi² = 7.51, df = 7 (P = 0.38); I² = 7%						
Test for overall effect: Z = 13.09 (P < 0.00001)						
3.1.2 Influenza-like illness						
Biswas 2019	-0.223	0.249	5077	5778	6.1%	0.80 [0.49 , 1.30]
Cowling 2008	-0.151	0.408	84	205	2.7%	0.86 [0.39 , 1.91]
Cowling 2009	-0.083	0.243	257	279	6.3%	0.92 [0.57 , 1.48]
Hubner 2010	-1.05	0.36	64	65	3.4%	0.35 [0.17 , 0.71]
Larson 2010	0.271	0.363	946	904	3.4%	1.31 [0.64 , 2.67]
Little 2015	-0.223	0.07	8241	8667	18.7%	0.80 [0.70 , 0.92]
Ram 2015	0.215	0.149	193	184	11.5%	1.24 [0.93 , 1.66]
Roberts 2000	-0.051	0.03	299	259	21.8%	0.95 [0.90 , 1.01]
Simmerman 2011	0.737	0.263	292	302	5.6%	2.09 [1.25 , 3.50]
Zomer 2015	0.068	0.052	278	267	20.3%	1.07 [0.97 , 1.19]
Subtotal (95% CI)			**15731**	**16910**	**100.0%**	**0.98 [0.85 , 1.13]**
Heterogeneity: Tau² = 0.02; Chi² = 32.18, df = 9 (P = 0.0002); I² = 72%						
Test for overall effect: Z = 0.31 (P = 0.76)						
3.1.3 Laboratory-confirmed influenza						
Biswas 2019	-0.693	0.24	508	689	19.8%	0.50 [0.31 , 0.80]
Cowling 2008	0.07	0.671	84	205	6.0%	1.07 [0.29 , 4.00]
Cowling 2009	-0.562	0.39	257	279	12.7%	0.57 [0.27 , 1.22]
Hubner 2010	0.02	0.834	64	65	4.2%	1.02 [0.20 , 5.23]
Larson 2010	0.648	0.504	946	904	9.2%	1.91 [0.71 , 5.13]
Ram 2015	0.875	0.644	193	184	6.4%	2.40 [0.68 , 8.48]
Simmerman 2011	0.182	0.23	292	302	20.4%	1.20 [0.76 , 1.88]
Stebbins 2011	-0.211	0.212	1695	1665	21.4%	0.81 [0.53 , 1.23]
Subtotal (95% CI)			**4039**	**4293**	**100.0%**	**0.91 [0.63 , 1.30]**
Heterogeneity: Tau² = 0.11; Chi² = 13.58, df = 7 (P = 0.06); I² = 48%						
Test for overall effect: Z = 0.53 (P = 0.60)						



Footnotes

(1) Azor 2018 included 2 hand-washing groups: one using soap and water (RR 0.94) and the other using hand sanitizer (RR 0.77)

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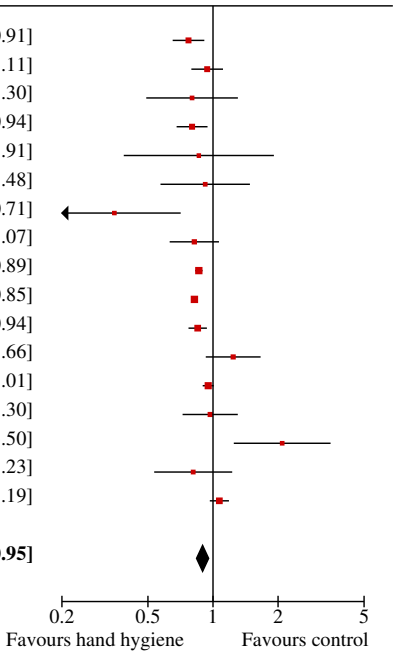
Analysis 3.2. Comparison 3: Randomised trials: hand hygiene compared to control, Outcome 2: ARI or ILI or influenza (including outcome with most events from each study)

Study or Subgroup	log[RR]	SE	Hand hygiene Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Azor-Martinez 2018	-0.261	0.086	339	149	7.1%	0.77 [0.65 , 0.91]
Azor-Martinez 2018 (1)	-0.062	0.086	274	149	7.1%	0.94 [0.79 , 1.11]
Biswas 2019	-0.223	0.249	5077	5778	1.5%	0.80 [0.49 , 1.30]
Correa 2012	-0.223	0.084	794	933	7.2%	0.80 [0.68 , 0.94]
Cowling 2008	-0.151	0.408	84	205	0.6%	0.86 [0.39 , 1.91]
Cowling 2009	-0.083	0.243	257	279	1.6%	0.92 [0.57 , 1.48]
Hubner 2010	-1.05	0.36	64	65	0.8%	0.35 [0.17 , 0.71]
Larson 2010	-0.199	0.134	946	904	4.2%	0.82 [0.63 , 1.07]
Little 2015	-0.151	0.02	8241	8667	13.1%	0.86 [0.83 , 0.89]
Millar 2016	-0.198	0.016	10000	10000	13.3%	0.82 [0.80 , 0.85]
Nicholson 2014	-0.163	0.05	847	833	10.4%	0.85 [0.77 , 0.94]
Ram 2015	0.215	0.149	193	184	3.6%	1.24 [0.93 , 1.66]
Roberts 2000	-0.051	0.03	299	259	12.3%	0.95 [0.90 , 1.01]
Sandora 2005	-0.03	0.15	602	451	3.5%	0.97 [0.72 , 1.30]
Simmerman 2011	0.737	0.263	292	302	1.4%	2.09 [1.25 , 3.50]
Stebbins 2011	-0.211	0.212	1695	1665	2.0%	0.81 [0.53 , 1.23]
Zomer 2015	0.068	0.052	278	267	10.2%	1.07 [0.97 , 1.19]
Total (95% CI)			**30282**	**31090**	**100.0%**	**0.89 [0.84 , 0.95]**

Heterogeneity: Tau² = 0.01; Chi² = 65.64, df = 16 (P < 0.00001); I² = 76%
Test for overall effect: Z = 3.38 (P = 0.0007)
Test for subgroup differences: Not applicable

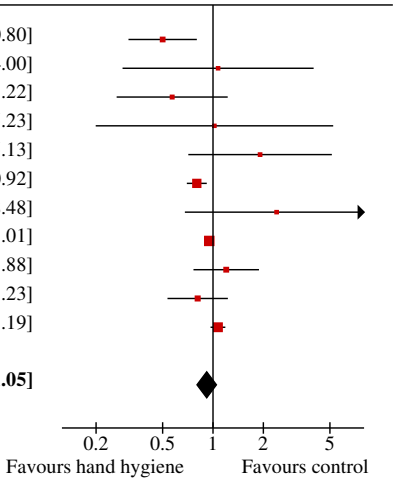


Footnotes
(1) Azor 2018 included 2 treatment groups: soap and water (RR 0.94); and hand sanitizer (RR 0.77)

Analysis 3.3. Comparison 3: Randomised trials: hand hygiene compared to control, Outcome 3: Influenza or ILI: sensitivity analysis including outcomes with the most precise and unequivocal definitions

Study or Subgroup	log[RR]	SE	Hand hygiene Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Biswas 2019	-0.693	0.24	508	689	6.2%	0.50 [0.31 , 0.80]
Cowling 2008	0.07	0.671	84	205	1.0%	1.07 [0.29 , 4.00]
Cowling 2009	-0.562	0.39	257	279	2.7%	0.57 [0.27 , 1.22]
Hubner 2010	0.02	0.834	64	65	0.7%	1.02 [0.20 , 5.23]
Larson 2010	0.648	0.504	946	904	1.7%	1.91 [0.71 , 5.13]
Little 2015	-0.223	0.07	8241	8667	21.6%	0.80 [0.70 , 0.92]
Ram 2015	0.875	0.644	193	184	1.1%	2.40 [0.68 , 8.48]
Roberts 2000	-0.051	0.03	299	259	26.6%	0.95 [0.90 , 1.01]
Simmerman 2011	0.182	0.23	292	302	6.7%	1.20 [0.76 , 1.88]
Stebbins 2011	-0.211	0.212	1695	1665	7.5%	0.81 [0.53 , 1.23]
Zomer 2015	0.068	0.052	278	267	24.1%	1.07 [0.97 , 1.19]
Total (95% CI)			**12857**	**13486**	**100.0%**	**0.92 [0.80 , 1.05]**

Heterogeneity: Tau² = 0.02; Chi² = 25.77, df = 10 (P = 0.004); I² = 61%
Test for overall effect: Z = 1.27 (P = 0.20)
Test for subgroup differences: Not applicable



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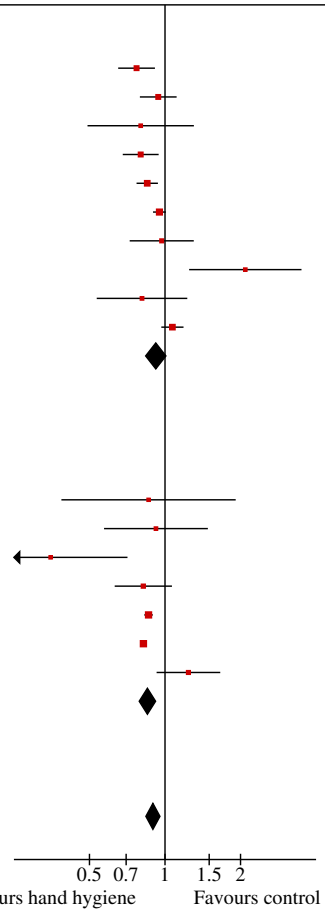
Analysis 3.4. Comparison 3: Randomised trials: hand hygiene compared to control, Outcome 4: ARI or ILI or influenza: subgroup analysis

Study or Subgroup	log[RR]	SE	Hand hygiene Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
3.4.1 Children						
Azor-Martinez 2018 (1)	-0.261	0.086	339	149	7.1%	0.77 [0.65 , 0.91]
Azor-Martinez 2018	-0.062	0.086	274	149	7.1%	0.94 [0.79 , 1.11]
Biswas 2019	-0.223	0.249	5077	5778	1.5%	0.80 [0.49 , 1.30]
Correa 2012	-0.223	0.084	794	933	7.2%	0.80 [0.68 , 0.94]
Nicholson 2014	-0.163	0.05	847	833	10.4%	0.85 [0.77 , 0.94]
Roberts 2000	-0.051	0.03	299	259	12.3%	0.95 [0.90 , 1.01]
Sandora 2005	-0.03	0.15	602	451	3.5%	0.97 [0.72 , 1.30]
Simmerman 2011	0.737	0.263	292	302	1.4%	2.09 [1.25 , 3.50]
Stebbins 2011	-0.211	0.212	1695	1665	2.0%	0.81 [0.53 , 1.23]
Zomer 2015	0.068	0.052	278	267	10.2%	1.07 [0.97 , 1.19]
Subtotal (95% CI)			**10497**	**10786**	**62.8%**	**0.92 [0.84 , 1.01]**
Heterogeneity: Tau² = 0.01; Chi² = 29.46, df = 9 (P = 0.0005); I² = 69%						
Test for overall effect: Z = 1.79 (P = 0.07)						
3.4.2 Adults						
Cowling 2008	-0.151	0.408	84	205	0.6%	0.86 [0.39 , 1.91]
Cowling 2009	-0.083	0.243	257	279	1.6%	0.92 [0.57 , 1.48]
Hubner 2010	-1.05	0.36	64	65	0.8%	0.35 [0.17 , 0.71]
Larson 2010	-0.199	0.134	946	904	4.2%	0.82 [0.63 , 1.07]
Little 2015	-0.151	0.02	8241	8667	13.1%	0.86 [0.83 , 0.89]
Millar 2016	-0.198	0.016	10000	10000	13.3%	0.82 [0.80 , 0.85]
Ram 2015	0.215	0.149	193	184	3.6%	1.24 [0.93 , 1.66]
Subtotal (95% CI)			**19785**	**20304**	**37.2%**	**0.85 [0.79 , 0.92]**
Heterogeneity: Tau² = 0.00; Chi² = 16.39, df = 6 (P = 0.01); I² = 63%						
Test for overall effect: Z = 4.22 (P < 0.0001)						
Total (95% CI)			**30282**	**31090**	**100.0%**	**0.89 [0.84 , 0.95]**
Heterogeneity: Tau² = 0.01; Chi² = 65.64, df = 16 (P < 0.00001); I² = 76%						
Test for overall effect: Z = 3.38 (P = 0.0007)						
Test for subgroup differences: Chi² = 1.59, df = 1 (P = 0.21), I² = 37.2%						

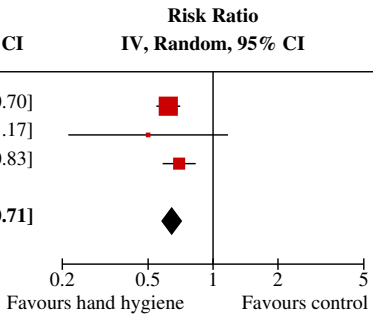


Footnotes

(1) Azor 2018 includes 2 intervnetion groups: soap and water (RR 0.94) and hand sanitizer (RR 0.77)

Analysis 3.5. Comparison 3: Randomised trials: hand hygiene compared to control, Outcome 5: Absenteeism

Study or Subgroup	log[RR]	SE	Hand Hygiene Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Azor-Martinez 2016	-0.478	0.065	621	720	64.8%	0.62 [0.55 , 0.70]
Hubner 2010	-0.693	0.435	64	65	1.4%	0.50 [0.21 , 1.17]
Nicholson 2014	-0.362	0.09	847	833	33.8%	0.70 [0.58 , 0.83]
Total (95% CI)			**1532**	**1618**	**100.0%**	**0.64 [0.58 , 0.71]**
Heterogeneity: Tau² = 0.00; Chi² = 1.43, df = 2 (P = 0.49); I² = 0%						
Test for overall effect: Z = 8.45 (P < 0.00001)						
Test for subgroup differences: Not applicable						



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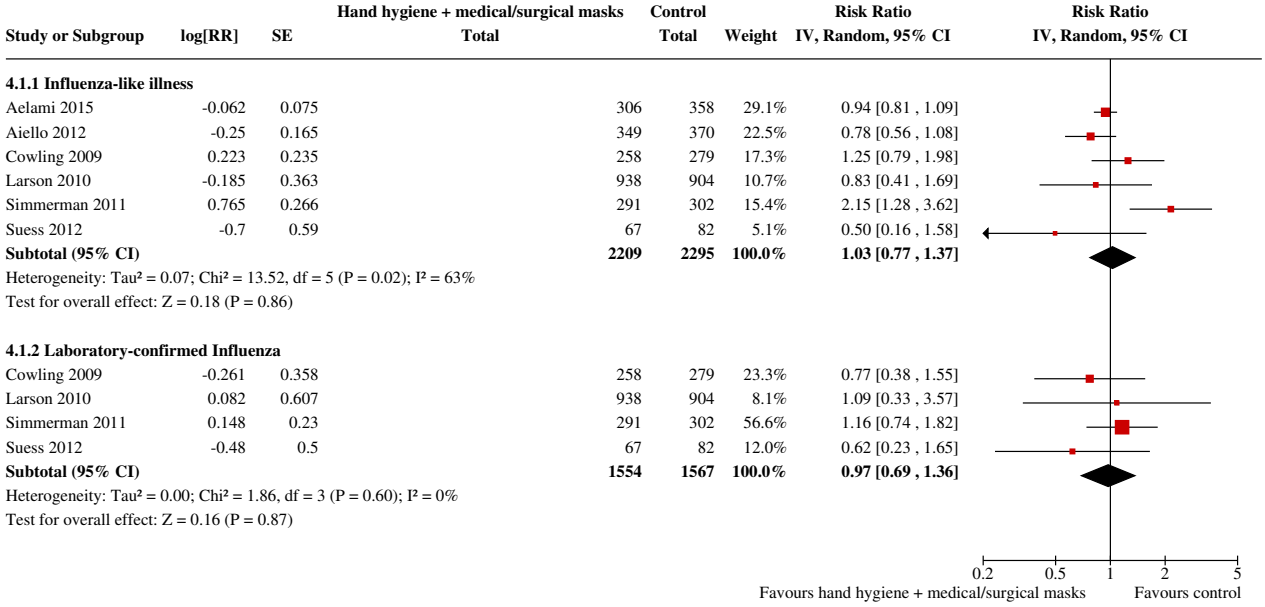
Comparison 4. Randomised trials: hand hygiene + medical/surgical masks compared to control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Viral illness	6		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.1.1 Influenza-like illness	6	4504	Risk Ratio (IV, Random, 95% CI)	1.03 [0.77, 1.37]
4.1.2 Laboratory-confirmed Influenza	4	3121	Risk Ratio (IV, Random, 95% CI)	0.97 [0.69, 1.36]

Analysis 4.1. Comparison 4: Randomised trials: hand hygiene + medical/surgical masks compared to control, Outcome 1: Viral illness



Comparison 5. Randomised trials: hand hygiene + medical/surgical masks compared to hand hygiene

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Viral illness	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.1.1 Influenza-like illness	3	2982	Risk Ratio (IV, Random, 95% CI)	1.03 [0.69, 1.53]
5.1.2 Laboratory-confirmed influenza	3	2982	Risk Ratio (IV, Random, 95% CI)	0.99 [0.69, 1.44]

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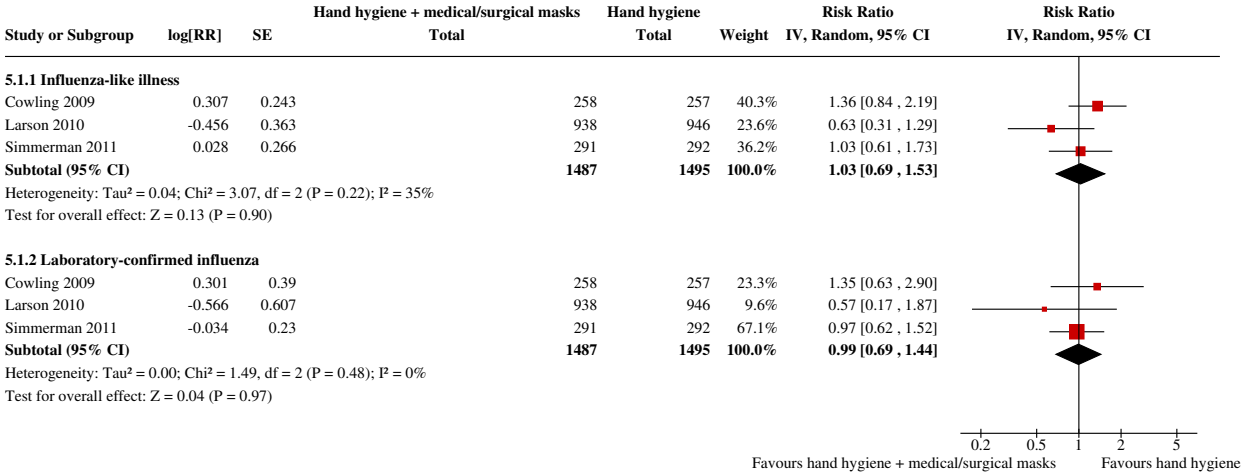
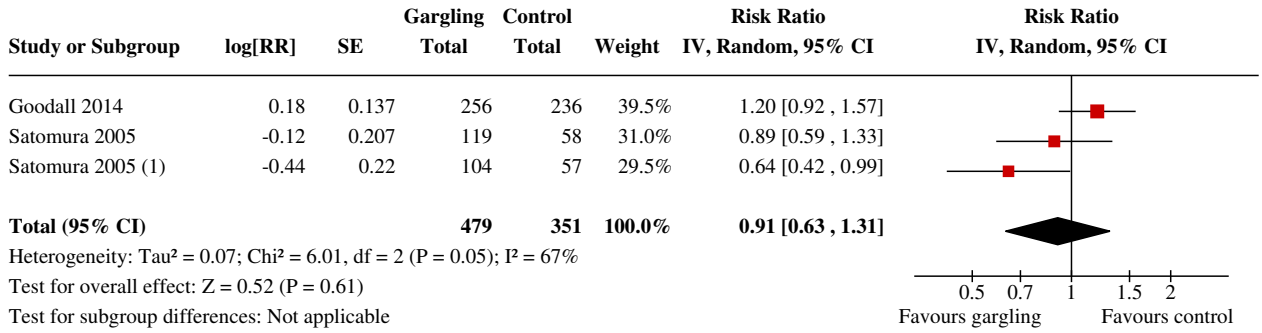
Analysis 5.1. Comparison 5: Randomised trials: hand hygiene + medical/surgical masks compared to hand hygiene, Outcome 1: Viral illness



Comparison 6. Randomised trials: gargling compared to control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Viral illness	2	830	Risk Ratio (IV, Random, 95% CI)	0.91 [0.63, 1.31]

Analysis 6.1. Comparison 6: Randomised trials: gargling compared to control, Outcome 1: Viral illness



Footnotes

(1) Satomura 2005 included 2 intervention groups

ADDITIONAL TABLES

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist

Author, year	Brief name	Recipient	Why	What (materials)	What (procedures)	Who provided	How	Where	When and how much	Tailoring	Modification of intervention throughout trial	Strategies to improve or maintain intervention fidelity	Extent of intervention fidelity
Masks compared to either no masks or different mask types													
Barasheed 2014	Supervised mask use	Religious pilgrims ≥ 15 years	Prevent respiratory virus infections at mass gatherings through mask use	Plain surgical face masks (3M Standard Tie-On Surgical Mask, Cat No: 1816) manufactured by 3M company, USA; 5 masks per day Written instructions on face mask use Special polythene bags for disposal	Masks provided to index case and their contacts with advice on mask use (before prayers, in seminars, and after meals). Written instructions provided on face mask use, need to change them, and disposal.	Not described, presumably the medical researchers	Face-to-face provision of masks, instructions, and reminders	Tents of pilgrimage site (Mina Valley, Saudi Arabia)	Advice on mask use given throughout pilgrimage stay (5 days)	None reported.	None reported.	The medical researchers followed pilgrims each day to remind participants about recording their mask usage in health diary.	Face mask use: mask group: 56/75 (76%), control group: 11/89 (12%) (P < 0.001) 76% of intervention tents wore masks. 10 of 75 (13%) pilgrims in 'mask' tents wore face masks during sleep.
Canini 2010	Surgical face masks	Householders (over 5 years)	Limit transmission of influenza transmission by large	Initial supply of 30 masks: for adults and children > 10: surgery masks with earloops, 3 plys, anti fog (AEROKYN, LCH medical products, Paris, France)	Masks given immediately on home visit by attending general practitioner with demonstration of proper use	General practitioners	Face-to-face individually	Households in France	One-off provision of masks worn for 5 days	None described.	None described.	Not described, but reported mask usage was measured	34/51 (66%) wore masks > 80% of the duration.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

			droplets produced during coughing in households	Children 5 to 10: face mask KC47127, (Kimberly-Clark, Dallas, TX, USA) Closed plastic bags for disposal	and instruction to be worn for 5 days in presence of another household member or in confined space (e.g. car) and to change every 3 hours or if damaged.								Reported mask-wearing: 11 ± 7.2 masks during 4.0 ± 1.6 days with an average use of 2.5 ± 1.3 masks per day and duration of use of 3.7 ± 2.7 hours/day
Jacobs 2009	Face masks	Hospital healthcare providers (nurses, doctors, and co-medical personnel)	Decrease risk of infection through limiting droplet spread through masks	Hospital-standard disposable surgical Mask MA-3 (Ozu Sangyo, Tokyo, Japan); quantity not specified	Provision of masks and instructions for use	Not described, presumably research team	Face-to-face	Tertiary care hospital in Tokyo, Japan Face masks worn whilst on hospital property.	77 days	None described.	None described.	Self-reported compliance	Self-reported compliance for both groups reported as good, with full compliance by 84.3% and remainder complying 79.2% to 98.7%.
Loeb 2009	2 active interventions A. sur-	Healthcare workers (nurses)	Reduce transmission of influenza in healthcare settings through coughing	A. Surgical masks B. N95 respirators	Provision of masks or N95 respirators Instruction in use and proper placement of devices	Provided by research team (not further	In-person face-to-face	Tertiary hospitals in Ontario,	1 influenza season (12 weeks) Use of mask as required[2] when pro-	Fit-testing of nurses not already	Ceased before end of season	Compliance audits during peak of season by trained auditor who stood	18 episodes: N95: 6/7 participants (85.7%) wearing assigned

Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	gical masks B. N95 respirators		or sneezing with protective masks		Fit-testing and demonstration of positioning of N95 using standard protocol and procedure (details provided) Qualitative fit-testing using saccharin or Bitrex protocol[1]	described) Fit-testing by technician for N95		Canada	viding care to or within 1 m of patient with febrile respiratory illness, ≥ 38 °C, and new or worsening cough or shortness of breath Nurses to wear N95 when caring for patients with "febrile respiratory illness"	fit-tested		short distance from patient isolation room	device versus 100% for masks
MacIntyre 2009	2 active interventions in addition to infection control guidelines A. Surgical masks (SM)	Householders with a child with fever and respiratory symptoms	Prevent or reduce respiratory virus transmission in the community through non-pharmaceutical interventions	A. 3M surgical mask, catalogue no. 1820; St Paul, MN, USA for adults B. P2 masks (3M flat-fold P2 mask, catalogue no. 9320; Bracknell, Berkshire, UK) A and B: health guidelines and pamphlets about infection control	Provision of masks and pamphlets and education about infection prevention and mask use Telephone calls and exit interviews to record adherence to mask use All groups: health guidelines, pamphlets about infection control were provided	Not described, presumably research team	Face-to-face and by telephone	Households in Sydney, Australia	2 winter seasons (3 months and 6 months) 2 weeks of follow-up Masks to be worn at all times when in same room as index child, regardless of distance from child	None described.	None described.	Daily telephone calls to record mask use throughout day Exit interviews about adherence	Reported mask use: Day 1 SM: 36/94 (38%) P2: 42/92 (46%) stated wearing "most or all" of the time. Other participants were wearing face masks rarely or never. Day 5:

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	B. P2 masks (P2)												SM: 29/94 (31%) P2: 23/92 (25%)
MacIntyre 2011	3 active interventions A. Medical masks B. N95 respirators fit-tested C. N95 respirators non-fit-tested	Healthcare workers	Protect HCWs by preventing transmission of influenza and other respiratory viruses from patients through mask wearing	Daily supply of A. 3 medical masks (3M medical mask, catalogue number 1820, St Paul, MN, USA) 2 respirators: B. N95 fit-tested mask (3M flat-fold N95 respirator, catalogue number 9132) fit-tested with 3M FT-30 Bitrex Fit Test kit according to manufacturer's instructions (3M, St Paul, MN, USA) C. N95 non-fit-tested mask (3M flat-fold N95 respirator, catalogue number 9132) Diary cards for usage recording	Supply of masks or respirators. Instruction in when to wear it, correct fitting, and storage (in paper bag in personal locker) Instruction in importance of hand hygiene before and after removal For fit-tested group: fit-testing procedure	Masks provided to hospitals. Training of staff provided by 1 member of research team.	Masks and training provided face-to-face, not described if training was individually or in groups.	Emergency departments and respiratory wards in hospitals in Beijing, China	Entire work shift for 4 weeks	Taken off for toilet and meal breaks and at end of shift	None described.	Mask/respirator use monitored by: (i) observed compliance by head ward nurse recorded daily; (ii) self-report diary cards carried during day recording; (i) no. hours; (ii) usage. Exit interviews	Adherence for usage was high for all and not significantly different amongst arms. Medical mask: 76%, 5 hours N95 fit-tested: 74%, 5.2 hours N95 non-fit-tested: 68%, 4.9 hours
MacIntyre 2013	3 active interventions A. N95 respirators at all times	Healthcare workers (nurses and doctors)	Protect HCWs from respiratory infections from patients through mask use	Daily supply of: A. and B. 2 respirators (3M Health Care N95 Particulate Respirator; catalogue number 1860) 3M FT-30 Bitrex Fit Test Kit C. 3 masks 3 masks	Supply of respirators Instructions in use including times and fit Fit-testing procedure according to the manufacturer's instructions (3M) For targeted N95:	3M supplied respirators and masks. Provider of instructions	Masks and training provided face-to-face, not described	Emergency departments and respiratory wards of ter-	For 4 weeks, A and B worn at all times on shift; B. targeted (intermittent) use of N95 respirators only whilst	None described.	None described.	Self-reported daily record of number of hours worked, mask or respirator use, number of high-	Compliance highest for targeted N95 (82%; 422/516) versus N95 (57%; 333/581) versus medical mask

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	B. N95 respirators targeted use C. Medical masks			(3M Standard Tie-On Surgical Mask catalogue number mask 1817; 3M, St Paul, MN, USA) Pocket-sized diary card with tick boxes for mask use	checklist of defined high-risk procedures, including common aerosol-generating procedures	not specified.	if training was individually or in groups.	tiary hospitals in Beijing, China	performing high-risk procedures or barrier.			risk procedures undertaken collected by study staff.	(66%; 380/572).
MacIntyre 2015	2 active interventions A. Cloth masks B. Medical masks	Hospital healthcare workers	Prevent respiratory infections in HCWs from patients through mask-wearing	A. 5 cloth masks for study duration (2- layer, cotton) B. 2 medical masks daily for each 8-hour shift for study duration (3 layers, non-woven material) All masks locally manufactured. Written instructions on cleaning cloth masks	Cloth or medical masks to be worn at all times on shift. Cloth masks to be washed with soap and water daily after shifts, and the process of cleaning to be documented. Provision of written instructions for cloth mask cleaning	Researchers arranged supply of masks and instructions and any training of staff assisting the delivery.	Masks and written instructions provided face-to-face.	Hospital wards in Vietnam	4 weeks (25 days) of face mask use	Masks not worn while in the toilet or during tea or lunch breaks.	None described.	Monitored compliance with mask use by self-report diary card and exit survey and interviews with a sub-sample (ACTRN12610000823757)	Mask-wearing compliance: cloth mask: 56.8%; medical mask: 56.6%; Reported cloth mask washing: 23/25 days (92%)
MacIntyre 2016	Medical mask use	Sick householders with ILI (index	Protect well people in the community from transmission of res-	21 medical masks (3M 1817 surgical mask) Diary cards for mask use	Supply of masks Instructions for mask wearing and hand-washing protocol Provision of diary cards	Study staff member provided masks and	Masks and instructions provided face-	Fever clinics of major hospitals in	3 masks/day for 21 days Mask wearing: whenever in the same	Allowed to remove their masks during	None reported.	Self-reported daily record of mask use using diary card	Mask use: mask group: 4.4 hours; control group: 1.4 hours

Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

		cases) and their well contacts of the same household	piratory pathogens by contacts with ILI through mask use			in-structions in use.	to-face and indi-vidu-ally.	Bei-jing, Chi-na	room as a household member or a visi-tor to the household Hand-washing: before putting on and after taking off	meal-times and whilst asleep and to cease wear-ing once symp-toms re-solved		
Radonovich 2019	2 ac-tive inter-ven-tions A. N95 res-pira-tors (N95) B. Med-ical masks (MM)	Health-care per-son-nel of out-pa-tient sites with-in med-ical cen-tres	Prevent HCP from acquiring workplace viral respi-ratory in-fections and trans-mitting them to others by effective respira-tory pro-tection by N95 respira-tors which reduce aerosol exposure and in-halation of small airborne particles, meet fil-tration	A. N95 respirators: 3M Corporation 1860, 1860S, and 1870 (St Paul, MN, USA) or Kim-berly Clark Technol Flu-idshield PFR95-270, PFR95-274 (Dallas, TX, USA) B. Medical mask Precept 15320 (Arden, NC, USA) or Kimberly Clark Technol Fluidshield 47107 (Dal-las, TX, USA). Reminder signs posted at each site A portable comput-er equipped with da-ta recording software (HandyAudit; Toronto, Canada) to document	Participants in-structed to wear assigned pro-tective devices whenever they were positioned within 6 feet (1.83 m) of patients with sus-pected or con-firmed respiratory ill-ness and to don a new N95/MM with each patient in-teraction. Hand hygiene recommended to all participants in accordance with Centers for Disease Control	Cen-tres pro-vided de-vice sup-plied by study to HCP. Study per-son-nel post-ed re-minder signs and emails and con-duct-ed ad-	Face-to-face indi-vid-ual pro-vi-sion of de-vices and ad-her-ence ob-ser-va-tions On-site post-ing of signs Oth-er re-minders	Out-pa-tient sites with-in med-ical cen-tres in USA	As in-structed, for each new pa-tient in-teraction during 12-week peri-od of peak viral respi-ratory ill-ness each year for 4 years (to-tal of 48 weeks)	Fit-ting of N95 masks	None de-scribed.	Reminder signage posted at study sites, and emails sent by study per-son-nel. Self-re-ported daily de-vice wear-ing of “al-ways”, “some-times”, “never”, or “did not recall" Observa-tion of de-vice-wear-ing behav-iours as parti-cipants en-tered and	Device wearing: N95: 89.4% re-ported “al-ways” or “some-times” versus MM: 90.2% “Never” N95: 10.2% MM: 9.5%

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

			require-ments, and fit tightly	adherence (Radonovich 2016)	and Prevention guidelines. Infection preven-tion policies were followed at each study site. Reminder signs posted at sites and emails sent. Annual fit-testing conducted for all participants. Filtration testing performed on the device models in the study. Further details in proto-col (Radonovich 2016).	her-ence ob-ser-va-tions.	by email				exited care rooms conduct-ed dur-ing unan-nounced, inconspic-uous vis-its to ran-domly selected sites docu-mented on portable computer	
Hand hygiene													
Alza-her 2018	Hand hy-giene work-shop	Pri-mary school girls	Target-ed school children to improve hand hy-giene to reduce school ab-sences due to up-per res-pirato-ry infec-tion and spread of infection in schools	6-minute video-clip of 2 siblings that attended school-based health ed-ucation about hand hy-giene Short interactive lecture about: common infections in schools, methods of transmis-sion, hand-washing pro-cedure using soap and water including when to wash hands	Delivery of work-shop and distri-bution of sup-porting materi-als (games and posters) to school and students	Study in-vesti-gator deliv-ered work-shop.	De-liv-ered face-to-face in group for-mat for the work-shop	2 pri-mary girls' schools in Sau-di Ara-bia	1-hour once-off workshop; posters and games provided to school	Not de-scribed	Not de-scribed	Posters in restrooms as re-minders of hand-washing hygiene during 5-week fol-low-up pe-riod after workshop	Not re-ported

Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

			and to families	Puzzle games related to hand hygiene Posters with cartoon princesses' picture promoting hand-washing										
Arbogast 2016	Multimodal hand hygiene intervention programme in addition to control of brief video	Office buildings and the employees of health insurance company	Reduce hand-to-mouth germ transmission from shared workspaces and workplace facilities and thereby healthcare claims and absenteeism through improved workplace hand hygiene	Alcohol-based hand sanitiser (PURELL Advanced, GOJO Industries Inc, Akron, OH, USA) installed as wall-mounted dispensers, stands, or free-standing bottles One 8-ounce bottle of hand sanitiser (PURELL Advanced) per cubicle One 100-count canister of hand wipes (PURELL Wipes) per cubicle Replenishment products stored in supply room (in addition to existing foam hand wash (GOJO Green Certified Foam Handwash) and an alcohol-based hand sanitiser foam wall-mounted dispenser (PURELL, GOJO Industries) already provided near the restroom exits prior to intervention) Identical soap in all restrooms Intervention and control group: brief (< 1-minute educational video) about	Hand hygiene supplies installed in offices. Replenishment product was made easily available to individual employees upon request via a simple process. Monitoring of product shipments into sites Physical collection and full replacement of soap, sanitiser, and wipes Intervention and control group: educational video embedded at end of baseline online knowledge survey	Not described, presumably study investigators arranged installations	Hand hygiene supplies provided in office environments and individually at staff cubicles/offices. Video provided individually via email.	High-traffic common areas of 2 US health insurance company offices (e.g. near elevators, at entrances) and appropriate public spaces (e.g. coffee area, break rooms,	13.5 months overall One-off email video 11 days before study hand hygiene supplies installed. 13 months of provision of supplies 2 times evening collection and full replacement of products	Sanitiser installed in high-use areas of the offices.	Not described	Employee survey at 4 months included questions about hand hygiene practice compliance. Monitoring of product shipments into the sites and physical collection of the soap, sanitiser, and wipes products 2 times in the study; collected samples were measured and usage rates were estimated	Intervention group employees: reported 40% more cleaning of work area regularly; significantly more likely to keep the hand sanitiser with them and use it throughout the day; significant increases in hand sanitiser use for at-risk activities[3] Estimated use by average employee from sample collection:

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

				proper hand hygiene technique, for both washing and sanitising hands ''Wash Your Hands'', signage promoting hand hygiene compliance, was already posted next to restroom exits at both the control and intervention sites.				con-ference rooms, train-ing rooms, lob-bies, re-cep-tion ar-eas); indi-vid-ual staff cubi-cles of most-ly open plan of-fices (av-erage 309 square feet). Of-fice re-strooms				sanitiser 1.8 to 3.0 times/day, soap 2.1 to 4.4 times/day, wipes at their desk 1.4 to 1.5 times/ week
Azor-Mar-tinez 2016	Hand-wash-ing pro-gramme	Pri-mary school chil-dren and their	Prevent transmis-sion of up-per respi-ratory in-fections in schools	Brochure about hand-washing awareness and habits Workshop content mate-rials	Brochure sent to parents by mail with study infor-mation sheet.	Brochure sent by school ad-min-	Brochure sent by mail to in-di-vid-	Pri-mary school class-es in Spain (de-	8 months overall One-off brochure and instal-lation of	Su-per-vi-sion and ad-min-	Not de-scribed	Daily re-inforce-ment by teachers of hand hygiene	Self-re-ported correct hand-washing included in analy-

Physical interventions to interrupt or reduce the spread of respiratory viruses (Review)
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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	parents and teachers	and to families through non-pharmaceutical intervention of handwashing programme in schools	Stories, songs, and classroom posters about hand hygiene and infection transmission Hand sanitiser (ALCO ALOE GEL hand sanitiser by Americo Govantes Burguete, S.L. Madrid, Spain containing 0.2% chlorhexidine digluconate, 1% phenoxyethanol, 0.1% benzalkonium chloride, 5% aloe barbadensis, 70% denat ethyl alcohol, excipients quantity sufficient for 100 mL alcohol 70%, pH 7.0 to 7.5) Informational poster about when and how to wash hands Written and verbal guidance to teachers, parents, and students on properties, possible side effects, and precautionary measures for gel use and storage	Workshop provided for pupils and teachers: frequent infections in schools, transmission and prevention, instructions on correct handwashing (water and soap, soaping > 20 s, drying hands), use of hand sanitisers and possible side effects Classroom activities linked to hand hygiene and infection transmission Reinforcement of hand hygiene by teachers Hand sanitiser dispensers fixed to walls with an informational poster about hand-washing Supervision of younger children when using hand sanitiser and administration of sanitiser if needed Instruction of children in handwashing procedure	istration. Workshop and verbal and written information presumably provided by the study research assistant. Classroom activities provided by research assistant and teachers. Supervision	ual parents. Workshops and classroom activities delivered in groups face-to-face. Teacher reinforcement of hand hygiene provided to class face-to-face. Hand sanitiser use supervision was	tails not provided)	hand sanitiser dispensers 2-hour workshop held 1 month before study commencement Fortnightly classroom activities As required, teacher supervision and administration of hand sanitiser Daily reinforcement of hand hygiene by teachers	istration of hand sanitiser as needed by teachers, especially for younger children	Fortnightly support by research assistant promoting handwashing Self-reported correct handwashing procedure (water and soap, soaping > than 20 s, drying hands)	sis but not separately reported.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					dures after toilet and when dirty and correct hand sanitiser use[4]	and administration of hand sanitiser for younger children by teachers	provided individually and face-to-face.						
Azor-Martinez 2018	Educational and hand hygiene programme 2 active interventions: A. soap and water B. hand sanitiser	Day care centres and their attending children, their parents, and DCC staff	Prevent transmission of respiratory infections by improved hand hygiene of children, parents, and staff through handwashing practices and use of hand sanitiser due to its bactericide and virucide properties	A. Liquid soap (no specific antibacterial components (pH = 5.5)) OR B. Hand sanitiser (70% ethyl alcohol (pH = 7.0 to 7.5)) for home use and in dispensers for school classroom Workshop content handout Stories, songs, and posters about hand hygiene and infection transmission	Installation of liquid soap or hand sanitiser dispensers in classrooms Supervision and administration of hand sanitiser if required 3 hand hygiene workshops for parents and DCC staff: 1. Hand-washing practices, hand sanitiser use, possible side effects and precautionary measures (HSG only) 2. RIs and their treatments	Workshop delivered by researchers Research assistant provided hand hygiene materials to DCCs and parents. Parents and staff	Workshops delivered face-to-face in groups to parents and staff. Workshop content emailed to attendees individually.	Classroom of DCCs (in Spain) for child interventions Workshops provided at DCCs.	8 months overall Initial 1-hour workshop 1 month before study commencement 3 further identical sessions/DCC provided again 1 month apart Fortnightly classrooms and DCC activities	Administration of hand sanitiser in the case of young children DCC staff could attend training at other DCC if unable to attend	Not described	Not described Reported that no monitoring of compliance through continuous observation of hand hygiene behaviours was done, but amount of hand sanitiser was measured	Families or DCC staff, or both, used 1660 L of hand sanitiser, estimated use by each child of dose 6 to 8 times/day.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					3. Fever Instructions to children, parents, and DCC staff on usual hand-washing practices and protocol [5] Classroom activities (stories and songs) about hand hygiene and infection transmission	supervised and administered sanitiser where indicated.	Individual face-to-face supervision of hand sanitiser use, as indicated	One-off installation of dispensers As-needed supervision of hand sanitiser use Dose of sanitiser: 1 to 2 mL/ disinfection	at own DCC.			
Biswas 2019	Hand sanitiser and respiratory hygiene education	Primary schools and their students and staff	Reduce community-wide influenza virus transmission by improving handwashing and respiratory hygiene and use of sanitiser in schoolchildren as contributors to community-wide virus transmission	Hand sanitiser (63% ethyl alcohol) in colourless, transparent 1.5-litre local plastic bottles (manufactured by a local pharmaceutical company and was available commercially in Bangladesh (price: USD 5.75/L)) Video clip on respiratory hygiene practices Behavioural change materials – 3 colour posters (see Appendix of paper) Curriculum materials for hygiene classes	Installation of hand sanitiser in wall dispensers in all classrooms and outside all toilets, refilled by field staff as needed Encouragement of use of sanitiser at 5 key times during the day[6] Hand and respiratory hygiene education provided.[7] Integration of hygiene messages into school's hygiene curriculum Delivery of video clip on respirato-	Selected teachers responsible for dissemination of intervention messages throughout were trained over 2 days	Hand sanitiser and education materials provided to schools. Education provided in classrooms in groups and	Primary schools (in Bangladesh) Sanitiser in each classroom and outside toilets Education in classroom	10 weeks Intervention messages conveyed in classrooms 3 times/ week.	Refills provided as needed.	Not described	Structured field observation by 2 field staff of 5 hours/ school observing handwashing and respiratory hygiene behaviours of children at 2 different locations in a classroom or outside Every other day, field staff measured the level	Handwashing observed opportunities: IG 604/921 (66%) vs CG 171/802 (21%) Hand sanitiser used in 91% of observed handwashing events in intervention schools. Average

Physical interventions to interrupt or reduce the spread of respiratory viruses (Review)
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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

						ry hygiene practice Behaviour change materials distributed and placed around schools. Use of sanitiser by classroom teachers after training Training of selected teachers in consultation with head of school and management committee in key messages Communication of key messages by the selected teachers to other teachers	in these messages, behaviour change communication, sanitiser use, and practices for preventing spread of respiratory secretions. Classroom teachers conveyed intervention messages during regular	face-to-face.			
									of hand sanitiser in the morning and in the afternoon to calculate amount of hand sanitiser used/day/school and enrolled children.	consumption of hand sanitiser/child/day: 4.3 mL Observation of proper cough or sneeze etiquette: IG: 33% vs CG: 2%

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

						hygiene classes. Field staff replaced supplies as needed.							
Correa 2012	Alcohol-based hand rubs	Childcare centres and their staff and children	Reduce incidence and transmission of infection in children by improved hand hygiene where water is scarce including provision of ABH and training in hand hygiene teaching techniques	Dispensers of alcohol-based hand rubs with ethanol 62.0% (PURELL, GOJO Industries, Akron, OH, USA) Workshop materials[8] Visual reminders on ABH techniques in bathrooms and next to dispensers	ABH and training on proper use to staff and children Pre-trial ABH use workshop to teachers that followed recommended HH teaching techniques and instructed teachers to add ABH to routine HH and give preference to hand-washing with soap and water if hands visibly soiled Continuous refilling of ABH ABH technique refresher workshops (8/centre) Monitoring of safety, proper use	Local representative of GOJO Industries Inc. provided dispensers and dispenser installations free of charge.	Face-to-face training and provision of materials; group training	Childcare centres in Colombia (centres or community homes) ABH in centres, classrooms, and common areas depending on size	8 months overall 1 ABH dispenser per centre with < 14 children; 1 per classroom in larger centres; 1 per classroom + 1 for common areas in centres with > 28 children 1 workshop pretrial to staff Monthly 30-minute ABH technique re-	Refilled ABH as needed	Not described	Visual reminders and monthly refresher training Monitoring of safety, proper use of ABH, amount of ABH used Semi-structured survey on completion of teachers' perceptions about changes in HH practices and use of	Teachers at 7 intervention centres reported almost complete substitution of HSW with ABH, and HSW decreased from 3 times per day to 1 per day, and ABH rose to 6 per day. Teachers at remaining 14 centres reported partial substi-

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					of ABH, amount of ABH used	Field-work team deliv-ered other com-po-nents.	Visu-al re-minders in bath-rooms and next to dis-pensers Work-shops and train-ing pre-sum-ably pro-vid-ed in cen-tres.	fresher training (8 per cen-tre) Biweekly monitor-ing			HSW and ABH. Measure-ment of consump-tion of re-sources and costs related to ABH use and HSW	tution of HSW with ABH. Controls report-ed HSW 3 times per day. Median number of ABH ap-plications per child rose from 3.5 to 4.5 in preschools and 3.5 to 5.5 in commun-ity centres.
Di-Vita 2011	House-hold hand-wash-ing pro-mo-tion	House-hold-ers with index pa-tient with ILI	Prevent influen-za trans-mission in house-holds in re-source-poor settings through provision of hand-washing facilities and use of them at critical	Hand-washing stations with soap	Provision of hand-washing stations Hand-washing motivation to wash at criti-cal times for pathogen trans-mission (e.g. af-ter coughing or sneezing)	Not specif-ical-ly de-scribed, pre-sum-ably the re-searchers	Face-to-face pro-vi-sion of fa-cili-ties in house-holds "Mo-tiva-tion" not	House-hold in Bangladesh	Over 2 in-fluenza seasons One-off provision of hand-washing facilities Frequen-cy of "mo-tivation" not de-scribed	Not de-scribed	Not de-scribed	Not de-scribed	Not de-scribed

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

			times for pathogen transmission				de-scribed						
Feldman 2016	2 active interventions A. Hand disinfection with chlorhexidine gluconate + hygiene education B. Hygiene education	Naval ships and their sailors	Reduced infection transmission and improved hand hygiene in sailors who are at increased risk due to closed environments, contact with shared surfaces, and poor HH culture	Septadine solution (Floris, Misgav, Israel) 70% alcohol and 0.5% CHG; inactive materials: purified water, glycerin, propylene glycol, and methylene blue	Installation of CHG disinfection devices on ships alongside regular soap and water Supply and replenishment of CHG (sent to ships regardless of replenishment demands) Hygiene instruction by a naval physician (to both intervention groups and study control group)	Provision of CHG presumably by study team and funds Hygiene instruction by naval physician	CHG sent to ships directly. Mode of hygiene instruction not described.	Navy fast missile boats and patrol boats of naval base in Israel Dispensers installed in key locations onboard (adjacent to heads (toilets), mess decks (dining rooms), common	4 months Unlimited supply of CHG replenished on demand for 4 to 5 months. Automatic amount dispensed: 3 mL	CHG replenished on demand.	Not described	Total amount of CHG dispensed was tallied.	Mean volume CHG: 8.2 mL per sailor per day (projected yearly cost USD 45 per sailor)

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

								areas).					
Gwaltney 1980	A. Virucidal hand preparation B. Placebo (no control)	Healthy young adults	Reduce infection rates by interrupting viral spread by hand or self-inoculation route	A. Virucidal hand preparation: aqueous iodine (2% iodine and 4% potassium iodide) B. Placebo: aqueous solution of food colours (Kroger; Kroger Co., Cincinnati, OH, USA) mixed to resemble the colour of iodine with 0.01% iodine and 0.02% potassium iodide to give an odour of iodine Masks	Immersion of each finger and thumb of both hands to proximal interphalangeal joint (interphalangeal joint of thumb) into designated preparation for 5 seconds then air-dried for 5 to 6 min Exposure of recipients to donors either immediately after treatment or after 2-hour delay by hand contact with donor stroking fingers for 10 s Masks worn by donors and recipients during procedure. Recipients placed in single isolation rooms after second exposure till end of experiment.	Researchers	Face-to-face and individually	US university	Exposure to donors on 3 consecutive days (days 2, 3, and 4) after initial exposure	Not described	Not described	Reported knowledge of hand preparation use as active, placebo, or don't know	Active (n = 24): 6 active 2 placebo 16 don't know Placebo (n = 22): 6 active 7 placebo 9 don't know
Hubner 2010	Alcoholic hand disin-	Employees (admin-	Reduce absenteeism and spread of	2 alcohol-based hand rubs (500 mL bottles) for desktop use to ensure minimal effort for use:	Provision of hand rub and instruction on use as needed at work only and in ac-	Presumably provid-	In person to staff	Administration of-	12 months overall Hand rub used as	Hand rub use especially	Not described	Self-reported compliance with hand hy-	Reported mean hand disinfection frequency

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	fection	istrative officers)	infection in administration employees with frequent customer contact and work with paper documents through improved hand hygiene	1. Amphisept E (Bode Chemie, Hamburg, Germany) ethanol (80% w/w) based formula with antibacterial, antifungal, and limited virus inactivating activity. 2. For participants with skin problems: Sterillium (Bode Chemie, Hamburg, Germany) 2-propanol (45% w/w), 1-propanol (30% w/w), and mecetronium etilsulfate (0.2% w/w), with a refatting effect and has activity against bacteria, fungi and enveloped viruses. Hand cream: Baktolan balm, water-in-oil emulsion with no non-antibacterial properties (Bode Chemie, Hamburg, Germany)	cordance with prevailing standard[7]: at least 5 times per day, especially after toileting, blowing nose, before eating, and after contact with ill colleagues, customers, and archive material	ed or arranged by study team	fices in Germany Hand rubs used at desk or work (not outside of work).	much needed for complete wetting of the hands (at least 3 mL or a palmful)[8] at least 5 times per day.	after toileting, blowing nose, before eating, and after contact with ill colleagues, customers, and archive material		giene measures	times per day: > 5: 19% 3 to 5: 59.8% 1 to 2: 20.5% < 1: 0.7%
Ladegaard 1999 (translated from Danish)	Hand hygiene programme	Daycare centres and their staff, children, and parents of children	Reduce risk of infection in child care through increased hygienic education of daycare professionals, motivation of daycare facilities for regular	Personnel guide on recommendations for: hygiene, ventilation, out-of-stay care, stricter hygienic regulations in cases with selected diseases Fairy tale and poster "The Princess Who Won't Wash Hands" Colouring in drawings "Wash hands" song and rhymes	Staff meeting in each DCC and training in microbiological cause of infection spread guided by National Board of Health and Hygiene Education of children in handwashing (about bacteria and why and when to wash hands)	Research team presumably provided training.	Face-to-face with training and activities by group with staff and children	On-site in DCCs	2-month intervention period 1-hour training of children	None described.	None described.	None described.	None reported.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

			hand hygiene, and informing parents about hand hygiene	T-shirt for children with the inscription "Clean hands - yes thank you" Diploma for children and book "The Princess Who Won't Wash Hands" to also be used by parents with their child Informational leaflet for parents in envelope	Practical handwashing classes with 4 to 5 children at a time Provision of t-shirt, book, and diploma to children Provision of leaflet for parents		Information sent home to parents via children.					
Little 2015	Web-based handwashing intervention	Householders (over 18) who were general practice patients	Prevent transmission of respiratory tract infections through improved hand hygiene to reduce spread via close contact (via droplets) and hand-to-face contact	Website-based programme: provided information about the importance of influenza and role of hand-washing; developed a plan to maximise intention formation for hand-washing; reinforced helpful attitudes and norms; addressed negative beliefs (URL provided for demonstration version no longer active; see www.lifeguideonline.org)	Provision of link to website for direct log in Automated emails prompted participants to use sessions and complete monthly questionnaires and maintain hand-washing.	Researchers delivered web-based programme and emails.	Online individually	Households in England	4 months overall 4 weekly web-based sessions Monthly email questions to maintain handwashing over 4 months	Tailored feedback provided within web programme	None described.	Emailed questions monthly to maintain handwashing	None reported.
Luby 2005	Handwashing promotion at neighbourhood	Neighbourhoods and their households	Improve handwashing and bathing with soap in settings where communicable dis-	Slide shows, videotapes, and pamphlets illustrating health problems from contaminated hands and specific hand-washing instructions Soaps: 90-gram white bars without brand	Hand-washing promotion to neighbourhoods: Neighbourhood meetings of 10 to 15 householders (mothers) from nearby homes	Research team in collaboration with Health	Face-to-face in small groups and individually	Neighbourhoods and homes in Karachi, Pakistan	1-year weekly household visits 30- to 45-minute neighbourhood meet-	Soap replaced regularly.	None described.	None described, though soap use measured.	Households' mean use of study soap per week: 3.3 bars Average use per

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	level with 2 interventions at household level A. Antibacterial soap B. Plain soap	eases are leading causes of childhood morbidity and mortality	names or symbols, same smell with identical generic white wrappers with serial numbers matched to households A. Households: 2 to 4 white bars of 90-gram antibacterial soap containing 1.2% triclocarban (Safeguard Bar Soap: Procter & Gamble Company (Cincinnati, OH, USA) B. Households: plain soap (no triclocarban) Soap packets	and monthly meetings for men Soap to households Fieldworker home visits: discussed importance of and correct hand-washing (wet hands, lather them completely with soap, rub them together for 45 seconds, and rinse off completely) technique and promote regular hand-washing habits[11] Encouragement of daily bathing with soap and water	Oriented Preventive Education (HOPE)[12] Fieldworkers were trained in interviewing and handwashing promotion.		ings 2 to 3 times/week first 2 months then weekly for months 2 to 9, then monthly Monthly men's meetings first 3 months Weekly household visits			resident per day: 4.4 g
Millar 2016 additional details from Ellis 2010	Skin and soft-tissue infection prevention intervention in addition to	Military trainees	Improve personal hygiene practices to prevent infection, especially acute respiratory infection in military trainees who are at increased risk	A. Enhanced standard: supplemental materials (a pocket card and posters in the barracks) B. CHG: CHG-based body wash (Hibiclens, Mölnlycke Heath Care, Norcross, GA, USA)	Provision of education and hygiene-based measures in addition to standard SSTI prevention brief upon entry: Enhanced standard: supplemental materials CHG: as for enhanced standard	Not described, presumably the researchers	Face-to-face and individually for body wash and pocket card Mode of	US military training base	One-off education on entry to training CHG: use of wash 1 per week for entire training period (14 weeks)	None described.	None described.	None described.	None described.

Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	SSTI brief on entry also provided to control A. Enhanced standard B. Chlorhexidine				group, plus a CHG-based body wash and instructions for use				ed-uca-tion not de-scribed.				
Mor-ton 2004	Healthy hands (alco-hol gel as hand-wash-ing ad-junct)	Ele-men-tary schools and their chil-dren and staff	Prevent infections in ele-mentary school-age children who are particu-larly vul-nerable through adjunct use of al-cohol gel and ed-ucation based on Health Be-lief Mod-el (HBM) (Kirscht 1974)	Alcohol gel and dis-pensers: AlcoSCRUB (60% eth-yl alcohol) supplied by Erie Scientific Company, Portsmouth, NH, USA ''Healthy Hands Rules'' protocol[13] (Figure 3 in paper) Healthy Hand Resource Manual for school nurse, available for parents Monthly newsletters to parents ''Healthy Hands'' refrig-erator magnet for fam-ilies (see Figure 2 in pa-per) Informational letter to local primary care	Healthy hands protocol in-troduced after "Germ unit" edu-cation in classes Daily reminders to children on public address system (in first week) then week-ly reminders Review of proto-col in each class-room after vaca-tion by school nurse 2 classroom vis-its from school nurse "Healthy Hands" magnet provid-	Gel pro-vid-ed by sup-pli-ers. Re-search team pro-vided ed-uca-tion-al as-pects. Class-room teach-ers re-spon-sible	Face-to-face train-ing in class-es and indi-vid-ual infor-ma-tion giv-ing and mon-itor-ing	Ele-men-tary schools in USA Wall-mount-ed near door en-trance of each class-room at age-ap-pro-pri-ate height	46 days 0.5 mL dis-pensed per appli-cation. Use of "special soap" ac-cording to "Healthy Hands Proto-col" (Fig-ure 3 in paper)	Rein-force-ment teach-ing pro-vided if gel us-age indi-cated that it was need-ed. Germ unit ed-uca-tion tai-lored for	1 stu-dent was con-cerned gel was mak-ing her sick, so school nurse pro-vided addi-tion-al class-room vis-it to allay con-cerns.	Usage of gel calcu-lated.	5 gel ap-plications per day 1 dis-penser lasted 1 month.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

				providers, paediatricians, family practitioners, and advanced practice nurses "Germ Unit" curriculum and materials including Germ models and Glo Germ	ed to parents and guardians. "Hand Checks on Wednesdays" to identify adverse effects of gel	for encouraging use of gel and reinforcing protocol School nurse assisted in monitoring and hand checks for adverse effects.				each grade level.			
Nicholson 2014	Handwashing with soap	Households with 5-year-olds and their mothers	Targeted 5-year-old children and their mothers as change agents to reduce incidence of respiratory infections (and diarrhoeal disease) through	Initial supply of 5 bars of free soap (90-gram Lifebuoy bars) replenished on submission of empty wrappers. Environmental cue reminders (wall hangers, danglers) Rewards (e.g. stickers, coins, toy animals)	Provision of soap and social marketing programme (Sidibe 2009) (Lifebuoy branding) to educate, motivate, and reward children for HWWS at key times Weeks 1 to 17: hand-washing occasions, germ education, soap's	Dedicated team of "promoters" delivered education and home	Face-to-face in groups Individually by mother to child	"Classrooms" held in community buildings Home visits of households	41 weeks Weekly "classrooms" after school and home visits HWWS encouraged 5 key occasions: after defecation, be-	Mothers were asked to provide and share handwashing tips with other	Technical difficulties with "soap acceleration sensors" to measure	Registers for "classrooms" and home visits where 3-week gaps in attendance triggered supervisors to ask participants to resume	Soap consumption: IG vs CG: 235 g vs 45 g

Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	hand-washing using behaviour change principles (Claessen 2008), including social norms for child and mother (Perkins 2003), using fear of contamination and disgust (Curtis 2001), peer pressure (Sidibe 2003), morale boosting, and networking support	importance in germ removal Week 18 onward: encouragement of HWWS on 5 key occasions supported by environmental cues "Classrooms" for children Home visits for mothers Parents' evenings to boost morale, build networks, and run competition for compliance, assignment completion, and folder decoration Establishment of a "Good Mums" club for sharing HWWS tips Rewards provided by mothers. Children encouraged to advocate HWWS within families before meals. Establishment of social norms for child and mother with pledges in front of peers	visits. Mothers provided supplied rewards.	in Mumbai, India	fore each of 3 meals, and during bathing. Week 18 onward: hand-washing on 5 occasions for 10 consecutive days 6 weekly parents' meetings	mothers, competitions held for mothers.	HWWS behaviours prevented successful use.	or be withdrawn Monitoring of soap resale on open market by use of unique identifiers on soap wrappers and twice weekly checks in local shops Collection of used soap wrappers as soap consumption measure

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

Pandejpong 2012	3 active interventions (no control) different time-interval applications of alcohol hand gel A. Every 60 min B. Every 120 min C. Once before lunch	Preschool classes (students and teachers) and their parents	Targeted preschool children who can have high infection rates in ILI; have close interaction so at risk of airborne, droplet, and contact transmission; and are of increasingly younger ages through hand gel as a single strategy of convenient and effective disinfection	1 container of alcohol hand gel per classroom (active ingredients: ethyl alcohol, 70%; chlorhexidine gluconate,1%; Irgasan (triclosan), 0.3%) Cost of hand gel every 60 minutes was USD 6.39 per child per 12-week period Leaflet describing risk factors for ILI for each family	Teachers instructed to: assist each child with dispensing hand gel at required time interval, store hand gel properly, and refill gel as needed. Monitoring of hand gel use at specified times	Teachers supervised, stored, and refilled hand gel. Instructions to teachers presumably provided by researchers. Leaflets distributed through school. Monitoring of use by 2 research assistants	Face-to-face to schools, teachers and children Individual assistance to children with hand gel Leaflets given to each family.	Kindergarten school in Bangkok, Thailand	12 weeks overall 1 pump of gel per child per disinfection round at 1 of 3 time intervals of school day: A. every 60 min B. every 120 min C. once only before lunch, the school standard for hand hygiene	None described.	Students whose families declined to participate were not asked to use alcohol hand gel. These students remained in their classrooms and continued to follow the school standard for hand	2 research assistants monitored hand gel use every 60 or 120 minutes for the duration of study. Classroom teachers were required to co-sign after each disinfection round.	Reported that compliance was ensured for each intervention group Cost of hand gel every 60 minutes was USD 6.39 per child per 12-week period.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

											hy-giene.		
Priest 2014	Hand sanitiser provision (in addition to hand hygiene education session also provided to control group)	Primary schools and their students, teachers, and administrative staff	Reduce person-to-person community transmission of infectious disease by targeting improved and additional hand hygiene of school children through supervised hand sanitiser provision as an alternative to improving and maintaining bathroom facilities	‘‘No touch’’ dispensers (> 60% ethanol) for each classroom that dispensed dose when hands were placed under an infrared sensor Supply of top-up sanitiser as needed	Dispensers installed into each classroom. Teachers asked to ensure that the children used sanitiser at particular times and to oversee general use (McKenzie 2010). Weekly classroom visits to top-up of sanitiser and measure quantity used 30-minute in-class hand hygiene education session provided (also to control group) plus instruction in hand sanitiser use.	School liaison research assistants topped-up sanitiser. Teachers	Installation of dispensers to classrooms Supervision of children by teachers delivered face-to-face individually and as a class.	City schools in New Zealand	20 weeks (2 school terms) Sanitiser to be used by students at least after coughing/sneezing, blowing their nose, and as they leave for morning break and for lunch break. Approximately 0.45 mL of sanitiser dispensed per wash. Weekly top-up of sanitiser	Children were able to use the sanitiser at any time they wished as well as at key times (McKenzie 2010).	Change of sanitiser after week 10 to flavourless type of the same % ethanol in 41 of 396 classrooms (10%) (in 9 of 34 schools) due to children tasting it when eating, affecting use.	Weekly classroom visits by school liaison research assistants who recorded quantity of sanitiser used Total amount of sanitiser per classroom was measured. Compliance defined as dispensing a volume equivalent to at least 45 mL per child of hand sanitiser solution over the trial period.	100% dispensing 45 mL per child Average hand sanitiser dispensed/child for 34 schools: 94 mL Median classroom difference in sanitiser usage between first 10 weeks and second 10 weeks amongst classes that switched products was 220 mL.

Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

Ram 2015	Soap and intensive hand-washing promotion	Household compounds and its householders (adults and children) that had a householder with ILI	Reduce household transmission of ILI and influenza by promoting hand-washing in households with householder with ILI as other householders who are well are at highest risk of exposure due to crowded and poorly ventilated homes. Followed constructs of Social Cognitive Theory and the Health Belief Model (Glanz 2008) and behaviour change communication using social	Hand-washing station in central location of each compound using: large water container with a tap; plastic case for soap; bar of soap. Cue cards depicting critical times for hand-washing: after coughing or sneezing; after cleaning one's nose or child's nose, after defecation; after clearing a child who has defecated; before food preparation or serving; before eating.	Hand-washing station in each compound Didactic and interactive group-level education and skills training describing influenza symptoms, transmission, and prevention, promoting health and non-health benefits of hand-washing with soap and identification of barriers and proposed solutions to hand-washing with soap Daily surveillance including weighing of soap and replacing if ≥ 20 g and resupply of water in container if needed Posting of cue cards Asking householders to demonstrate hand-washing with soap technique	Intervention staff arranged provision of hand-washing station and presumably provided education. Intervention staff conducted daily surveillance and reinforcement visits.	All elements delivered face-to-face but at compound (facilities), group (education), and individual levels (reinforcement).	Household compounds in a rural area of Bangladesh consisting of several households with common courtyard, shared latrine, water source, and cooking facilities	Initiation of intervention within 18 hours of study enrolment, then daily visits until 10 days following resolution of index case patient's symptoms Day 1 set up of hand-washing station	Daily surveillance included observation of individual hand-washing reinforcement and modelling as needed.	None described.	Daily surveillance of facilities and reinforcement and modelling of hand-washing behaviours including observed hand-washing Cue cards in common areas of courtyard Presence or absence of soap during each of first 10 days of surveillance from 180 household compounds Patterns and amount of soap use measured.[14]	Soap present for at least 7 days in all compounds and on all 10 days in 133 compounds (74%). Soap and water together were present 7 or more of first 10 days in 99% of compounds, with water and soap observed together on all 10 days in 99 compounds (55%) Soap consumption per capita: median: 2.3 g maximal: 5 g (on Day 7)

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

			marketing concepts										
Roberts 2000	Education about infection control measures, handwashing, and aseptic nose wiping	Childcare centres and their staff and children	Reduce transmission of respiratory infections in childcare centres through improved infection control procedures	GloGerm (GloGerm, Moab, UT, USA) Newsletters to staff Songs and rhymes on hand-washing Plastic bags (sandwich bags available at supermarkets) to cover hand for nose wiping	Staff training in good health (developed by Kendrick 1994) and practical exercise of handwashing with GloGerm Fortnightly visits and newsletter to reinforce training and to communicate techniques Recommended hand-washing technique as per guidelines of the time[15] and after toileting, before eating, after changing diaper (staff and child), and after wiping nose unless barrier used Teaching of technique to children and wash hands for infants	Training and reinforcement activities provided by 1 of the researchers Teachers delivered training to children based on their training.	Face-to-face in groups for training and classes and individually as needed to children or staff	Childcare centres in Canberra, Australia	8 months overall 3-hour training in evening or 1-hour during lunch for new staff after study start Duration of handwashing: "count to 10" to wash and "count to 10" to rinse	Training for new staff provided as needed.	None described.	6-weekly compliance measured by recorded observation of recommended practice for 3 hours in morning in each centre, graded by quantiles of frequency of recommended handwashing by children.	Compliance was reported only in relation to analysis of outcomes. High compliance reported for nose wiping and child handwashing.
Sandora 2005	Healthy Hands Healthy Families	Families with an index child in out-of-	Reduce illness transmission in the home through multifactorial campaign centred on	Alcohol-based hand sanitiser: active ingredient: 62% ethyl alcohol (PURELL Instant Hand Sanitizer; GOJO Industries, Inc, Akron, OH, USA)	Supply of hand sanitiser and hand hygiene materials Biweekly telephone calls	Study investigator	Not stated whether materials mailed or	Homes in USA Sanitiser use in home	5 months overall Biweekly educational materials	None described.	None described.	Recorded amount of hand sanitiser used (as reported by the primary caregiver)	Median frequency of reported times of hand sanitiser use: 5.2 per day

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

		home child-care	hand hygiene education and hand sanitiser	Hand hygiene educational materials at home (fact sheets, toys, games)	Biweekly educational materials		delivered in person	Sanitiser dispensed 1 mL each pump.				38% used > 2 ounces of hand sanitiser per fortnight = 4 to 5 uses per day
Savolainen-Kopra 2012 further details from Savolainen-Kopra 2010	STOPFLU Enhanced hygiene 2 active interventions IR1. Soap and water wash IR2. Alcohol-based hand rub	Office workers of office work units	Prevent transmission of respiratory infections in workplaces through enhanced hand hygiene with behavioural recommendations to reduce transmission by droplets during coughing or sneezing	IR1: Liquid hand soap ("Erisan Nonsid" by Farmos Inc., Turku, Finland) IR2: in addition: Alcohol-based hand rub, 80% ethanol ("LV" by Berner Inc., Helsinki, Finland) Bottles of hand hygiene product (free of charge) to be used at home and in the office (IR2). Written instructions on hygiene for further reference	Toilets equipped with liquid hand soap (all groups) or alcohol-based hand rub (IR2). Guidance on other ways to limit transmission of infections, e.g. frequent handwashing in office and at home, coughing, sneezing into disposable handkerchief or sleeve, avoiding handshaking Visits to work clusters and monitoring of materials availability Monthly electronic "information spot" about viral diseases for motivation to maintain hygiene habits Adherence activities	In collaboration with occupational health clinics servicing the corporation Specially trained research nurse provided guidance and visited worker	In-person provision of soap or hand rub Guidance and written instructions given personally. Face-to-face visits by study nurse	Office work units in corporations in Helsinki, Finland	15 to 16 months overall Monthly visits by nurse throughout	Nurses assisted with any practical problems with intervention as they arose. New employees received guidance on hand hygiene and habits.	None described.	Adherence assessed by an electronic self-report survey of transmission-limiting habits 3 times (more details in protocol). Use of soap (IR1) and alcohol-based disinfectant (IR2) for personal use was recorded. Study nurse checked availability of soap and alcohol rub.	Avoiding handshaking became more common and remained high in both groups. Recorded use for personal use smaller than predicted use based on hand hygiene instructions. Soap or disinfectant usage per participant: IR1: 6.1 IR2: 6.9

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					clusters throughout intervention period.								
Stebbins 2011	"WHACK the Flu" (hand sanitiser and training in hand and respiratory hygiene)	Elementary schools and their students and homeroom teachers	Targeted school-aged children as important sources of influenza transmission through improved cough etiquette and hand hygiene in schools including sanitiser as potential inexpensive non-pharmaceutical interventions	Hand sanitiser dispensers with 62% alcohol-based hand sanitiser from PURELL (GOJO Industries, Inc, Akron, OH, USA) automatically dispensing 1 dose	Delivery of grade-specific presentations on "WHACK the Flu" concepts and proper handwashing technique and sanitiser use: (W)ash or sanitise your hands often; (H)ome is where you stay when you are sick; (A)void touching your eyes, nose and mouth; (C)over your coughs and sneezes; and (K)eep your distance from sick people (provided URL no longer active) Desired frequency of hand wash use taught to student (see When and how much)	Project staff provided education. Homeroom teachers reinforced message and monitored proper use of sanitiser.	Face-to-face at schools, presumably as a group in classes	Elementary schools (Pittsburgh, USA) Dispensers installed in each classroom and all major common areas.	Whole intervention over 1 influenza season One-off installation of hand sanitiser dispensers One-off 45-minute education presentation and one-off refresher training at onset of influenza season Goal of use of 1 dose (0.6 mL) of sanitiser 4 times per day[16]	Encouraged to wash hands or use additional doses of hand sanitiser, or both, as needed	None reported.	Monthly teacher surveys of observed NPI-related behaviour in their students before, during, and after influenza season Measurement of hand sanitiser use at 2-week intervals throughout the intervention period	Teacher surveys of observed classroom NPI behaviour indicated successful adoption and maintenance of behaviours throughout influenza season. Average sanitiser use: 2.4 times per day

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					Installation of hand sanitiser dispensers Refresher training at each school Reinforcement of message and monitoring of sanitiser								
Talaat 2011	Intensive hand hygiene campaign	Schools and their students, teachers, and parents	Reduce or prevent transmission of influenza viruses amongst children through intensive hand hygiene intervention campaign	Soap supplied as needed. Grade-specific student booklets each including a set of 12 games and fun activities that promoted hand-washing Hand hygiene activities materials including: games (e.g. how to escape from the germs); puzzles; soap activities (e.g. soap drawing); song specially developed to promote hand hygiene Teachers' guidebook including detailed description of the students' activities and methods to encourage students to practice these activities. Posters with messages to wash hands with soap and water upon arriv-	Establishment of a hand hygiene team in each school Provision of hand hygiene activities: weekly exercises (e.g. games, aerobics, songs, experiments); school activities, (e.g. obligatory hand-washing under supervision, morning broadcast, parent meetings, students-parents information transfer); specific school initiatives: (e.g. competitions and awards, hand-washing committee, school trips to soap factory	Hand hygiene team (3 teachers from social studies, arts, and sports and the school nurse) ensured that all pre-designed activities for the hand hy-	Delivered face-to-face in groups and individually	Elementary schools (grades 1 to 3) in Cairo, Egypt In school environment and classrooms Poster near sinks in classrooms and on playground	12 weeks overall Weekly hand hygiene campaign activities Weekly visits by social workers Twice-daily obligatory supervised hand-washing required by students for about 45 seconds, followed by proper rinsing and drying with a clean	Soap and hand-drying material provided by school administration if children did not bring their own as was the custom or families could	None described.	Observation by social workers of hand hygiene activities, availability of soap and drying material, and students' hand-washing during the day Schools created own activities to improve compliance.	About 93% of the students had soap and drying material available. All but 2 intervention schools "had a rigorous system of ensuring that school-children were washing their hands at least twice daily".

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	ing at school, before and after meals, after using the bathroom, and after coughing or sneezing. Informational flyers for parents reinforcing the messages delivered at the schools.	and water purification plant) More details in Table 1 of paper Song played regularly. Social worker weekly visits Distribution of flyers to parents	giene campaign were implemented. 6 independent social workers visited the schools.	cloth towel.	not afford it. Schools could create own motivating activities such as selecting a weekly hand hygiene champion, developing theatre plays, and launching school contests for drawings and songs.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

Temime 2018	Multifaceted hand hygiene programme (including alcohol-based hand rub)	Nursing home staff, residents, visitors, and outside care providers	Nursing homes and their residents, staff, and visitors and external providers have an increased risk of person-to-person transmission of pathogens, and HH is a simple and cost-effective tool for infection control; however, compliance with HH is poor in nursing homes.	Dispensers and pocket-sized containers of hand rub solution Posters promoting hand hygiene Developed local HH guidelines eLearning module on infection control and HH training with online quizzes requiring sufficient performance	Facilitated access to hand rub solution Campaign to promote HH with posters and event organisation Formation of local work groups in each NH Development of local HH guidelines Staff education using eLearning Monitoring of quantity of hand rub solution used	Same nurse provided HH training for all NHs. Provision of hand rub by NH Local work group developed guideline. eLearning module and posters presumably developed by research team.	Provision of materials face-to-face Education and quizzes via eLearning	Nursing homes in France	1 year overall One-off provision of hand rub One-off eLearning repeated if unsatisfactory performance.	If staff did not score sufficiently on online quiz, they were invited to repeat the eLearning.	None described.	Estimated mean amount of hand rub solution used per resident per day assessed as proxy for HH frequency, based on quantity of hand rub solution bought by NH (which was routinely monitored in all the NHs).	Hand rub solution used: baseline quantity of consumed hand rub solution was 4.5 mL per resident per day. Over the 1 year, mean quantity consumed was significantly higher in intervention NH (7.9 mL per resident per day) than control (5.7 per resident per day).

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

Turner 2004a Clinical trial 1	3 active interventions (no control) Product: A. Ethanol B. Salicylic acid C. Salicylic acid with pyroglutamic acid	Healthy volunteers	Assess the residual virucidal activity of organic acids used in currently available over-the-counter skin products for the prevention of experimental rhinovirus colds	1.7 mL of hand products: A. 62% ethanol, 1% ammonium lauryl sulphate, and 1% Klucel) B. 3.5% salicylic acid, or vehicle containing C. 1% salicylic acid and 3.5% pyroglutamic acid	Disinfection of hands then application of test product then allowed to dry. 15 min later, fingertips of each hand contaminated with 155 $TCID_{50}$ of rhinovirus type 39 in a volume of 100 µL. Hands air-dried for 10 min. Intentional attempted inoculation with virus by contact with fingers, conjunctiva, and nasal mucosa with fingers of right hand. Left hand eluted in 2 mL of virus-collecting broth.	Researchers	Face-to-face individually	Communities in Manitoba, Canada	1.7 mL of product applied. See What for timing	Not described	Not described	Not described	Not described
Turner 2004b Clinical trial 2	2 active interventions (no control) Skin cleaner wipe	Healthy volunteers	Assess the residual virucidal activity of organic acids used in currently available over-the-counter skin products for	Skin cleanser wipe containing: A. 4% pyroglutamic acid formulated with 0.1% benzalkonium chloride B. 62% ethanol	Application of product to hands with towelette then allowed to dry. 15 min later, fingertips of each hand contaminated with 106 $TCID_{50}$	Researchers	Face-to-face individually	Communities in Manitoba, Canada	Dose not reported; see What for timing Additional group challenged 1 h after application; final group chal-	Not described	Not described	Not described	Not described

Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	product: A. Pyroglutamic acid B. Ethanol	the prevention of experimental rhinovirus colds		of rhinovirus type 39 in a volume of 100 µL. Intentional attempted inoculation with virus by contact with fingers, conjunctiva, and nasal mucosa with fingers of right hand. Left hand eluted in 2 mL of virus-collecting broth.				lenged 3 h after application (remained at study site and not allowed to use or wash hands between).				
Turner 2012	Antiviral hand lotion	Healthy adults	Reduce rhinovirus infection and illness through hand disinfection with ethanol and organic acid sanitiser	Lotion containing 62% ethanol, 2% citric acid, and 2% malic acid Daily diary	Provision of lotion and instructions for use Meetings with participants to check compliance	Staff of study site presumably supplied lotion. Study site staff met with participants.	Face-to-face and presumably individually, but not specified	Study site at university community in the USA	9 weeks Every 3 hours whilst awake and after handwashing for 9 weeks Compliance meetings twice weekly for first 5 weeks then weekly meetings with participants	None reported.	None reported.	Self-reported daily diary of time of each product application Twice weekly for 5 weeks then weekly meetings with participants to reinforce compliance with treatment	"All subjects … applied at least 90% of the expected amount of hand treatment" (p.1424)

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

Yeung 2011	Multifaceted hand hygiene programme (including alcohol-based hand rub)	Long-term care facilities and their healthcare workers	Promote use of alcohol-based hand rub by staff in LTCFs as an effective, timely, and low-irritant method of hand hygiene in a high-risk environment	Free supply of pocket-sized containers of alcohol-based antiseptic hand rub (either WHO formulation I (80% ethanol) or II (80% propanol) carried by each HCW (supplier: Vickmans Laboratories) Replacement hand rub as required Hand hygiene seminar content Reminder materials (3 to 5 posters and specially designed ballpoint pens)	Provision of materials Provision of hand hygiene seminars to HCWs covering: indications, proper method, and importance of antiseptic hand rubbing and washing according to WHO 2006a) guidelines Provision of feedback session Direct, unobtrusive observation of hand hygiene adherence Training of observation staff	Study team delivered the materials, seminars, and observer training. Administrative staff of LTCF provided replacement hand rub and communicated with HCWs. 6 registered nurses	Delivered face-to-face and individually for hand rub and pens; not described if education was individually or by group, but seminar implies as a group	LTCFs in Hong Kong Posters posted in common areas. Adherence observations occurred in common rooms and resident rooms but not bathing or toilet areas.	7 months overall Initial 2-week intervention period, then 7 months of hand rub provision and reminders 3 identical seminars at start of intervention; each staff member to attend once Feedback session 3 months after start of intervention 2-hour training of observers Adherence observations either 9 am to 12 pm or 3 pm to 6 pm, 1 LTCF at a time	Replacement of hand rub as required	As adherence dropped off in the middle months, the feedback session was delivered.	Direct observation of HCW adherence to handwashing and antiseptic hand rubbing (recorded separately and anonymously) during bedside procedures or physical contact with residents 3300 hand hygiene opportunities during 248.5 hours of observation on 92 days	90% attendance of seminars Hand rubbing with gel increased significantly from 1.5% to 15.9%. Handwashing decreased significantly from 24.3% to 17.4%. Control: 30% Overall handwashing adherence increased from 25.8% to 33.3%.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

						conducted direct observation of adherence after 2-hour training (100% inter-rater reliability).							
Zomer 2015	Hand hygiene products and training	Day-care centres and their caregivers (staff)	Reduce infections in children attending DCCs through improved access to HH materials (Zomer 2013a) and compliance of their DCC caregivers to hand hygiene guidelines based on	HH products: dispensers for paper towels, soap, alcohol-based hand sanitiser, and hand cream, with refills for 6 months Reminder posters and stickers for children and DCC caregivers Training materials including booklet	Provision of free HH products sponsored by SCA Hygiene Products, Sweden. Provision of posters and stickers for children and staff Provision of training about RIVM 2011 for mandatory HH[18] Distribution of training booklet	Study team arranged supply of HH products and presumably provided training.	Products provided to DCCs in person for staff use. Mode of training not specified.	DCCs in regions of the Netherlands	6 months overall Initial one-off supply of products 3 training sessions with 1-month interval 2 team training sessions	Replacement hand hygiene provided as required.	None described.	6-month follow-up observation of whether intervention dispensers and posters/ stickers in use Survey of DCC caregivers HH guidelines compliance observed	2 DCCs did not use any HH products. Sanitiser products used in at least 1 of 2 groups in 94%, 89%, 86%, and 45% of intervention DCCs. Posters used in 86%, stickers in 74%.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

				socio-cognitive and environmental determinants of caregivers' HH behaviour[17] (Zomer 2013b)	Team training sessions aimed at goal-setting and formulating HH improvement activities (Erasmus 2011; Huis 2013)						at 1, 3, and 6 months' follow-up: no. of HH actions/no. of opportunities	DCC survey results: 79% attended at least 1 training session; 77% received HH guidelines booklet. HH compliance at 6 months: IG: 59% vs CG: 44% (Zomer TP, et al, unpublished data) All intervention DCCs received guidelines training; all but 2 received at least 1 team training.
Hang hygiene and masks													
Aelami 2015	Hygienic education and	Religious pilgrims	Prevent influenza-like illness by reduced infection	Hygiene package of: alcohol-based hand rub (gel or spray) surgical masks	Not clearly described, but it appears that packages may have been distributed by trained physi-	Not specifically described	Not described, but it appears	Not described if before de-	One-off during Hajj season	Not described	Not described	Not described	None described

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	package		transmission through personal hygiene measures	soap paper handkerchiefs user instructions	cians before departure to or on site of country of pilgrimage		that packages were distributed face-to-face and individually	parture (from Iran) or on site (in Saudi Arabia)					
Aiello 2010	2 active interventions: A. Face mask (FM) B. Face mask and hand hygiene (FM + HH)	Students living in university residences	Reduce the incidence of and mitigate ILI by use of non-pharmaceutical interventions of personal protection measures	7 face masks (standard medical procedure masks with ear loops TECNOL procedure masks; Kimberly-Clark) 7 resealable plastic bags for mask storage when not in use (e.g. eating) and for disposal Alcohol-based hand sanitiser (62% ethyl alcohol in a gel base, portable 2-ounce squeeze bottle, 8-ounce pump) Hand hygiene education (proper hand hygiene practices and cough etiquette) via emailed video, study website, written materials detailing appropriate hand sanitiser and mask use	Weekly supply of masks through student mailboxes Provision of basic hand hygiene education through an email video link, the study website, and written materials; instruction to wear mask as much as possible; education in correct mask use, change of masks daily, use of provided resealable bags for mask storage and disposal Provision of replacement supplies which students signed for upon receipt	Not described, except education provided via study website (URL not provided) "Trained staff" for compliance monitoring	Education via email and study website; provision of masks and sanitiser in person to residences	University residence halls in the USA	One-off education, 6 weeks (excluding spring break) of face mask and/or hand hygiene measures which commenced at "the beginning of the influenza season just after identification of the first case of influenza on campus" (p.496). Replacement supplies pro-	Mask wearing during sleep optional and encouraged outside of residence.	University spring break occurred during weeks 4 and 5 of the study, with most students leaving campus and travelling; they were not	Weekly web-based student survey included: self-reported average number of times hands washed/day and average duration of hand-washing to obtain composite "optimal hand-washing" score (at least 20 s ≥ 5/day); average no. of mask hours/	Average mask use hours/day: FM + HH 2.99 vs FM 3.92 Average hand-washing times/day: FM + HH 6.11 vs FM 8.18 vs control group 8.75 Daily washing seconds/day: FM + HH 20.65 vs FM 23.15 vs control 22.35

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

						Study-affiliated residence hall staff provided replacement supplies.			vided as needed.		re-quired to continue protective measures at that time.	day/week; average hand sanitiser use/day/week and amount used. Trained staff in residence hall common areas observed silently and anonymously improper mask use, instances of hand sanitiser use.	Hand sanitiser use times/day: FM + HH: 5.2 vs FM 2.31 vs control 2.02 No. of proper mask wearing participants/hour of observation: FM + HH 2.26 vs FM 1.94
Aiello 2012	2 interventions: A. Face mask (FM) B. Face mask and hand sanitiser (FM + HH)	Students living in university residences	Prevent ILI and laboratory-confirmed influenza by use of non-pharmaceutical interventions of personal protection measures (e.g. face masks and hand hygiene)	Packets of 7 standard medical procedure masks with ear loops (TECNOL procedure masks, Kimberly-Clark, Roswell, GA, USA) and plastic bags for storage during interruptions in mask use (e.g. whilst eating, sleeping) and for daily disposal Hand sanitiser (2-ounce squeeze bottle, 8-ounce pump bottle with 62% ethyl alcohol in a gel base)	Intervention materials and educational video provided. Supply of masks and instructions on wearing Provision of replacement masks or sanitisers as needed on site	Trained study staff available at tables in each residence hall for surplus masks and sanitiser	Hygiene packs delivered to student mailboxes; face-to-face supply also available	University residence halls in the USA	One-off educational video at start Weekly supply of hygiene packs Masks to be worn at least 6 hours/day Study staff available onsite with re-	Students encouraged but not obliged to wear masks outside of residence hall.	1-week university spring break during the study when majority of students left	Weekly student survey including compliance (e.g. masks hours/day, frequency and amount of sanitiser use, number of hand washes/day, duration of hand-	Self-reported mask wearing: no significant difference Sanitiser use: significantly more in FM + HH than FM or control groups

Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

				Replacement face masks and hand sanitiser Educational video: proper hand hygiene and use of standard medical procedure face masks		and for observing compliance		placement supplies as needed for duration of intervention (6 weeks, excluding spring break)	campus	washing (seconds) Observed compliance completed by trained study staff who daily and anonymously observed mask wearing in public areas of residences.	More results in S1 of paper. Staff observed an average of 0.0007 participants properly wearing a mask for each hour of observation.
Cowling 2009	2 active interventions in addition to control of lifestyle education: A. Enhanced hand hygiene (HH)	Householders with index patient with influenza	Reduce transmission of influenza in households through personal protective measures	A. and B. Liquid soap for each kitchen and bathroom: 221 mL Ivory liquid hand soap (Proctor & Gamble, Cincinnati, OH, USA) Alcohol hand rub in individual small bottles (100 mL) WHO recommended formulation I, 80% ethanol, 1.45% glycerol, and 0.125% hydrogen peroxide (Vickmans Laboratories, Hong Kong, China) B. Adults: box of 50 surgical face masks (Tecnol–The Lite One (Kimberly-Clark, Roswell, GA, USA) to each household member or C. Children 3	Home visits Provision of soap, hand rub, and masks as applicable and when to use them HH: education about efficacy of hand hygiene Demonstration of proper handwashing and antisepsis techniques + FM: education about efficacy of surgical face masks in reducing disease spread to household contacts if	Trained study nurse provided interventions.	Face-to-face to householders	Households in Hong Kong	Initial home visit scheduled within 2 days (ideally 12 h) of index case identification. Further home visits day 3 and 6, 7-day follow-up HH: use of liquid soap after every washroom visit, sneezing or	Not described	Not described	Monitoring of adherence during home visits Evaluation of adherence on final visit by interview or self-reported practices and counting of amount of soap and rub left in bottles and remaining masks for FM group	Most initial visits completed within 12 h. Intervention groups "reported higher adherence … than the control group. Self-reported data were consistent with measurements of amount of soap,

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	B. Face masks and enhanced hygiene (FM + HH)			to 7: box of 75 paediatric masks	all parties wear masks Demonstration of proper wearing and hygienic disposal All groups: provision of education about the importance of a healthy diet and lifestyle, both in terms of illness prevention (for household contacts) and symptom alleviation (for the index case)				coughing, when their hands were soiled. Use rub when first returning home and immediately after touching any potentially contaminated surfaces FM: masks worn as often as possible at home (except eating or sleeping) and when the index patient was with the household members outside of the household				alcohol hand rub, and face masks used" (p.443) (see Table 6 in paper). "Adherence to the hand hygiene intervention was slightly higher in the hand hygiene group than the face mask plus hand hygiene group." Median masks used: Index: 9 Contact: 4 More details in paper and Appendices
Larson 2010	2 active interventions	Hispanic households	Reduce incidence and sec-	A. and B.	Provision of materials and instructions for	4 trained bilin-	Face-to-face	Households in	19-month follow-up	Change masks be-	None described.	RA home visits for adherence	Sanitiser use (mean

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

ventions in addition to control of URI education: A. Alcohol-based hand sanitiser (HS) B. Face masks and hand sanitiser (FM + HS)	holders with at least 1 preschool or elementary school child	ondary transmission of URIs and influenza through non-pharmaceutical household level interventions	2-month supply of hand sanitiser in 8-, 4-, and 1-ounce containers: PURELL (Johnson & Johnson, Morris Plains, NJ, USA) B. 2-month supply of masks: Procedure Face Masks for adults and children (Kimberly-Clark, Roswell, GA, USA) Replacement supplies at least once every 2 months Disposable thermometers Educational materials about URI prevention, treatment, and vaccination (written in Spanish or English language)	when to use including demonstration of use and observation of return demonstration by householder A. Mask worn when householder had: "temperature of ≥37.8°C and cough and/or sore throat in the absence of a known cause other than influenza" (CDC definition of influenza-like illness at the time). Home visits to reinforce adherence, replenish supplies and record use, answer questions B. Telephone calls to reinforce mask use All groups received URI educational materials.	gual research assistants (RAs) with minimum baccalaureate degree and experience in community-based research; procedures were practised with each other until demonstrated proficiency	to householders	New York, USA	Initial home visit, then at least every 2 months Sanitiser for use at home, work, and school B. Telephone calls days 1, 3, 6 Masks worn for 7 days when within 3 feet of person with ILL or no symptoms.	tween interactions with person with ILL Householders' questions and misconceptions addressed on home visits.	with random accompaniment by project manager, who also made random calls to householders Telephone calls to reinforce mask use Used bottles or face masks, or both, monitored for usage.	ounces/month) HH: 12.1 FM + HH: 11.6 Mask compliance was "poor": 22/44 (50%) used within 48 hours of onset. Mask users reported mean mask use of 2.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

Simmerman 2011	2 active interventions: A. Handwashing education and handwashing kit (HW) B. Handwashing education, handwashing kit, and face masks (HW + FM)	Households with a febrile, influenza-positive child	Decrease influenza virus transmission in household with a febrile influenza-positive child through promoted use of handwashing or handwashing with face mask use	A. and B. Hand-washing kit per household including graduated dispenser with standard unscented liquid hand soap (Teepol brand. Active ingredients: linear alkyl benzene sulfonate, potassium salt, and sodium lauryl ether sulphate) Replacement soap as needed Written materials from education including pamphlets and posters attached near sinks in household. B. Box of 50 standard paper surgical face masks and 20 paediatric face masks (Med-con company, Thailand #14IN-20AMB-30IN)	A. and B. Provision of intensive handwashing education on initial home visit to household members with 5 approaches: discussion, individual hand-washing training, self-monitoring diary, provision of soap, and provision of written materials (Kaewchana 2012) Individual handwashing training ("why to wash", "when to wash", and "how to wash" in 7 handwashing steps described in Thailand Ministry of Public Health guidelines) B. Provision of education of benefits of and appropriate face mask wearing Soap replaced as needed. More details (Kaewchana 2012)	Study nurse conducted home visits, provided education and monitoring activities.	Education provided face-to-face as a group to household member and individually for handwashing training.	In homes (in Bangkok, Thailand)	One-off provision of kits at initial home visit conducted within 24 hours of enrolment Subsequent home visits on days 3, 7, and 21 90-day supply of handwashing supplies 30-minute education provided at initial home visit	B. No face masks whilst eating or sleeping as impractical and could hinder breathing in ill child Impromptu education and training provided by nurses as questions arose.	None described.	Self-monitoring diary recording handwashing frequency > 20 s and face mask use for that group Reinforcement of messages by nurses on subsequent home visits Amount of household liquid soap and number of face masks used	Reported average handwashing episodes/day: HW: 4.7 HW + FM: 4.9 Parents had highest frequency (5.7), others (4.8), siblings (4.3), index cases (4.1). Average soap used/week: HW: 54 mL/person HW + FM: 58.1 mL/person B. Mask use: 12/person/week Mask wearing median min-

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

													utes/day: 211 Parents 153, other relations 59, index patients 35, siblings 17
Suess 2012	2 active interventions in addition to written information: A. Mask/hygiene (MH) B. Mask (M)	Households with an influenza-positive index case in the absence of further respiratory illness within the preceding 14 days	Prevent influenza transmission in households through easily applicable and accessible non-pharmaceutical interventions such as face masks or hand hygiene measures	A. Alcohol-based hand rub (Sterilium, Bode Chemie, Germany) A. and B. Surgical face masks in 2 different sizes: children < 14 years (Child's Face Mask, Kimberly-Clark, USA) and adults (Aérokyn Masques, LCH Medical Products, France) Written information provided on correct use of intervention and on infection prevention (Seuss 2011) (Tips and information on the new flu A/H1N1) (URL provided is no longer active) Digital tympanic thermometer General written information on infection prevention	A. Provision of hand rub and masks A. and B. Provision of masks only Provision of thermometer and how to use it Mask fit assessed (at first household visit) Information provided by telephone and written instructions at home visit on proper use of interventions and recommendations to sleep in a different room than the index patient, not to take meals with the index patient, etc. (Seuss 2011)	Study personnel arranged provision of materials, rang the participants, visited the homes, demonstrated and assessed fit of masks.	Provision of materials in person to households Initial telephone delivery of information Face-to-face home visits	Households in Berlin, Germany	Over 2 consecutive flu seasons Day 1 households received all necessary material instructions. Household visits no later than 2 days after symptom onset of the index case, then days 2, 3, 4, 6, 8 (5 times) or on days 3, 4, 6, 8 (4 times) depending on the day	Adult masks worn if masks for under 14-year-olds did not fit properly. If other household members developed fever (> 38.0 °C),	In the season 2010/11 participants also recorded number of masks used per day.	Self-reported daily adherence with face masks, i.e. if they wore masks "always", "mostly", "sometimes", or "never" as instructed. Participants of the MH households additionally noted the number of hand disinfections per day. Exit questionnaire about	Face mask use (median/individual): MH: 12.6 M: 12.9 Daily adherence was good, reaching a plateau of over 50% in nearly all groups from the third day on. MH hand rub use (median): 87 mL (Seuss 2011) MH mean frequency of daily

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

		In-person demonstration of interventions at first home visit All participating households received general written information on infection prevention.		of recruitment Hand rub use: after direct contact with the index patient (or other symptomatic household members), after at-risk activities or contact[19] Mask use: at all times when index patient and/or any other household member with respiratory symptoms were together in 1 room Regular change of face masks, not worn during the night or	cough, or sore throat, they were asked to adopt the same preventive behaviour as the index patient.	(preventive) behaviour during the past 8 days, general attitudes towards NPI, the actual amount of used intervention materials, and, if applicable, problems with wearing face masks. Used intervention material per household member was calculated by dividing the amount used per household by the number of household members. See paper and Suess 2011 for	hand disinfection: 7.6 (SD 6.4) times per day See paper and Suess 2011 for more results.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

									outside the household			more details.	
Hand hygiene and surface/object disinfection													
Ban 2015	Hand hygiene and surface cleaning or disinfection	Kindergartens and the families of their students	Reduce transmission of infection in young children from contaminated surfaces or hands through hand hygiene and surface cleaning or disinfection	Antibacterial products for hand hygiene and surface cleaning or disinfection: liquid antimicrobial soap for hand-washing (0.2% to 0.3% parachlorometaxylenol). Instant hand sanitiser for hand disinfecting (72% to 75% ethanol), antiseptic germicide (4.5% to 5.5% parachlorometaxylenol, diluting before use). Bleach (4.5% to 5.0% sodium hypochlorite, diluting before use) for surface disinfecting. Produced by Whealthfields Lohmann (Guangzhou) Company Ltd.	Provision of products to kindergartens and families Instruction of parents or guardians and teachers in hand hygiene techniques and use of antibacterial products Daily cleaning of kindergartens with products At least twice/week cleaning of homes and weekly cleaning or disinfecting of items such as children's toys, house furnishings, frequently touched objects (doorknobs, tables or desks), kitchen surfaces (utensils, cutlery, countertops, chopping boards, sinks, floors, etc.), bathroom surfaces (toilet, sink, floor, etc.)	Research team provided products and instructions and monitoring.	Materials provided to kindergartens and families in person and presumably instructions in person to families and staff.	In kindergartens (hard surfaces) and families' homes (Xiantao, China)	1 year overall Daily handwashing with soap before eating, after using bathroom, nose blowing, and outdoor activities Hand sanitiser carried daily. Kindergarten cleaning daily Home cleaning at least twice/week	Families and teachers could contact study management at any time as needed. Exchange of empty bottles for new ones at any time	Not described	Close contact with teachers and families for monitoring, e.g. unscheduled parents' meetings, quarterly home visits, phone interviews, and monthly cell phone messages Monthly survey of consumption of products by volume, total usage, person usage	Consumption of products by person (mL/person/day). Liquid soap: 7.7 Sanitiser: 1.4 Bleach: 25.0 Antiseptic-germicide: 12.5

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					Monitoring activities								
Carabin 1999	Hygiene programme	Daycare centres and their staff and children	Reduce infections in at-risk children (under 3 years old) in DCCs with inexpensive, easily implementable and practical interventions	Hygiene materials and documents, e.g. colouring books, hand-washing posters, hygiene videotapes Materials for training Reimbursement of equivalent of 1 full-time educator's salary Bleach (diluted 1:10) for toy and play area cleaning	Provision of comprehensive hygiene training session to entire DCC staff, especially the educators of participating classrooms Training in recommendations for hygiene practices: i. toy cleaning ii. hand-washing technique and schedule iii. use of creative reminder cues for hand-washing iv. open window for daily period v. sandbox and play area cleaning Payment of salary of educator for the day to encourage participation DCC meetings to discuss training session with all staff	Training appears to have been provided by study team.	Appears staff trained as a group, i.e. "entire DCC staff"	Daycare centres in Canada Location of training not described, except may have been offsite from DCCs since 1 DCC did not "send" staff to training.	15-month trial One-off 1-day training Toy cleaning at least every 2 days Hand-washing at least after DCC arrival, after outside play, after bathroom, before lunch Open windows at least 30 min/day Biweekly cleaning of sandbox/play area	Teachers to use creative reminder cues for hand-washing with children	Not described	Follow-up telephone questionnaire for DCC directors about following training recommendations	Use of materials: colouring book: 22/24 poster: 23/24 videotapes: 18/24 staff meetings: 19/24 Increased frequency of toy cleaning: 6/24 Use of rake and shovel for sandpit: 17/24 Frequency of cleaning sandbox: 14/24

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

Kotch 1994	Hygiene	Caregivers at child day-care centres (CDCCs)	Develop feasible, multicomponent hygienic intervention to reduce infections in children at CDCCs who are at increased risk	Hygiene curriculum for caregivers Availability of soap, running water, and disposable towels Waterless disinfectant scrub (Cal Stat) used only if alternative was not washing at all. Handouts posted in CDCC.	Delivery of hygiene curriculum to caregivers through initial training session which required demonstration of participants' hand-washing and diapering skills Local procedures: Hand-washing of children and staff Disinfection of toilet and diapering areas Physical separation of diapering areas from food preparation and serving areas Hygienic diaper disposal Daily washing and disinfection of toys, sinks, kitchen and bathroom floors Daily laundering of blankets, sheets, dress-up clothes Hygienic preparation, serving, and clean up of food	Research team delivered training. Scrub donated by Calgon Vetal Laboratories.	Face-to-face training and follow-up group and individually	Classrooms of child day-care centres in the USA	8 months overall 3-hour initial training session Cleaning schedules as described in column What (procedures) Onsite follow-up training 1 week and 5 weeks later	Follow-up sessions addressed questions and local adaptations to procedures. As required induction training	During intervention, research team encouraged directors to address physical barrier to hygiene practice, such as distance between sink and diapering areas and sink access in rooms.	Follow-up sessions reinforced training. Meeting with directors 5 weekly unobtrusive recorded observation by training staff	Rate of compliance to barrier modification was better in younger centres, which were more likely to have written guidelines.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					Separate training of food handlers As-required induction training for new staff Onsite follow-up training reinforcing adaptations, demonstrations and discussion of hygiene techniques, responding to questions, and review of handouts Monthly meeting with centre directors to encourage leadership and support								
McConeghy 2017	Multifaceted handwashing and surface-cleaning intervention	Nursing homes and their staff	Reduce exposure to pathogens and person-person transmission in high-risk facility of close environment and potentially contaminated surfaces through multifaceted inter-	Education and launch materials Online module for certified nursing assistants about: infection prevention, product, and monitoring "Essential bundle" of hygiene products supplied at no cost: - hand sanitiser gel and foam - antiviral facial tissues - disinfecting spray - hand and face wipes Plus additional:	Pre-intervention: NH administrators required to: - identify a "Heroes In Prevention" champion and team - allow all staff participation in education - iPad use for staff in each floor or community - ask staff to incorporate intervention into workflow	Study personnel equipped staff with knowledge and tools and support. NH staff (e.g. champion, hy-	Face-to-face interaction with staff for planning and some aspects and delivery of products	Nursing homes in the USA On-site and at unit/team levels On-line training	6 months overall: training period: 3 months 1-hour launch event 1 or 2 hygiene monitors/site 1 champion/site 1-hour online module for selected	Sites could use existing comparable products from another vendor and fill in any gaps with study	2 sites retrained due to low training participation rate.	Cloud-based audit and feedback system via secure login to web browsers on NHs' existing computers or via iPads included weekly product consumption to get measure:	Online training participation rates: > 90% for 3/5 sites, 13% and 23% for 2/5 Administrators demonstrated high fidelity in reporting measures of

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	vention equipping staff to protect residents from infection within the "culture" of care	- 4 skin cream and wipe products iPads for compliance audits Newsletters for support during intervention	Delivery of 3 components: - education - cleaning products - compliance audit and feedback Education: Launch event for all staff to publicise programme and explain roles Intensive training of "hygiene monitors" for data collection and compliance audit and feedback tool Training of site champion Training of select group of certified nursing assistants (online module) Audit and feedback activities Ongoing support during intervention: - newsletter with best practices - teleconferences with each NH	giene monitors, nursing assistants) delivered aspects of interventions after specific training.	Some aspects delivered online (e.g. nursing modules, compliance auditing)	nursing assistants iPads for each community or floor Weekly teleconferences initially decreased in frequency over time. Weekly measurement of product consumption	products. New staff provided with education, as needed and came onboard. Retraining of sites with low training participation rates	weekly count of product units consumed x no. of hand hygiene occasions	handwashing (> 80% of time). Handwashing rates in Figure 1B in paper reported as "relatively constant" and "not ideal in the first few months", but improved significantly over time.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					- "onboarding" education of new staff								
Sandora 2008	Multifactorial intervention, including alcohol-based hand sanitiser and surface disinfection	Elementary school and its students	Reduce transmission of infections in schoolchildren through improved hand hygiene and environmental disinfection	1 container of disinfecting wipes (Clorox Disinfecting Wipes (The Clorox Company, Oakland, CA, USA); active ingredient, 0.29% quaternary ammonium chloride compound) Pre-labeled 1.7-ounce containers of alcohol-based hand sanitiser (AeroFirst non-aerosol alcohol-based foaming hand sanitiser (DEB SBS Inc, Stanley, NC, USA, for The Clorox Company); active ingredient, 70% ethyl alcohol) Receptacle in classrooms for empty containers	Sanitiser and wipes provided to classroom/teacher with instructions for use. Teachers disinfected desks once daily. Hand sanitiser to be used: before and after lunch, after use of the restroom (on return to the classroom; hand hygiene with soap and water occurred in the restroom, because sanitisers were not placed there), after any contact with potentially infectious secretions (e.g. after exposure to other ill children or shared toys that had been mouthed)	Research team arranged supply of materials and instructed teachers on use. Teachers instructed in use of materials and in collecting empty containers and distrib-	Products provided to schools. Instruction provided face-to-face to teachers and children.	Elementary schools and their classrooms in the USA	8-week period Desks disinfected once a day.	Products replenished as needed.	None described.	Individually labelled containers collected every 3 weeks from the classroom to assess adherence.	Product usage: average wipes used/week: 897 (128 wipes/classroom/week) Average bottles of hand sanitiser used per week: 8.75 (1.25 bottles/classroom/week)

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

						uting new product.							
Quarantine													
Miyaki 2011	Quarantine from work (stay-at-home order)	Employees	Prevent spread of influenza in workplaces by quarantining workers who had a cohabitating family member with an ILI	Full wages to employee	Non-compulsory asking of workers whose family members developed an ILI to stay at home voluntarily on full wages. Daily measuring of temperature before leaving work. Where symptoms were doubtful, industrial physician made judgement. Company doctors provided input on cancelling of stay-at-home orders as required.	Health management department oversaw the procedures and decisions.	Mode of advice to employees not described.	Car industries in Japan	Stay-at-home order for 5 days after resolution of ILI symptoms or 2 days after alleviation of fever over 7.5 months	Strict standard for cancelling of stay-at-home orders described.	None described.	Recording of compliance with stay-at-home request	100% compliance to stay at home reported.
Other (miscellaneous) interventions													
Farr 1988a trial 1	2 active interventions in addition to control	Families	Reduce transmission of viruses from hand contamination via hand-to-hand contact or large-	3-ply tissues with: A. 5.1 mg/inch^2 (2.54 cm^2) of the virucidal mixture (58.8% citric acid, 29.4% malic acid, 11.8% sodium lauryl sulphate) B. 3 mg/inch^2 (2.54 cm^2) of saccharin	Family visits to distribute tissues Weekly contact of mother Families instructed to only use supplied tissues.	Nurse epidemiologist visited families.	Face-to-face visits to families and individuals in	Communities in the USA	6 months overall Monthly family visits Weekly contact with mother	Not described	Not described	Family visits and weekly contact with mother to encourage compliance	Not described

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	of no tissues: A. Virucidal nasal tissues B. Placebo tissues		particle aerosol through tissues for nose blowing and coughs and sneezes	applied uniformly to all 3 plies of the tissue Tissues prepared by Kimberly-Clark Corporation, Neenah, WI, USA.				families (especially mothers)					
Farr 1988b trial 2	2 active interventions (no control): A. Virucidal nasal tissues B. Placebo tissues	Families	Reduce transmission of viruses from hand contamination via hand-to-hand contact or large-particle aerosol through tissues for nose blowing and coughs and sneezes	2-ply tissues containing: A. 4.0 mg/inch^2 (2.54 cm^2) of antiviral mixture (53.3% citric acid, 26.7% malic acid, 20% sodium lauryl sulphate) B. 3 mg/inch^2 (2.54 cm^2) of succinic acid, malic acid, sodium hydroxide, and polyethylene glycol Tissues prepared by Kimberly-Clark Corporation, Neenah, WI, USA.	Family visits to distribute tissues and encourage compliance Weekly contact of mother Families instructed to only use supplied tissues.	Nurse epidemiologist visited families monthly. Study monitor visited bimonthly.	Face-to-face visits to families and individuals in families (especially mothers)	Communities in the USA	6 months overall Monthly family visits Weekly contact with mother Bimonthly study monitor visit	None described.	None described.	Bimonthly study monitor visits to encourage compliance as well as monthly and weekly contact by nurse	In 124/222 families, 1 or more family members reported not using the tissues regularly and/or reported having side effects from the tissues.
Longini 1988	2 active interventions (no	Households and their families	Prevent intrafamilial transmission of viral agents in a	Treated tissues of 3-ply material identified with no specific identifiers (Kimberly-Clark Corporation)	Tissues delivered to households with specific instructions on use (all purposes, when blowing	Tissues assigned by study	Supply of tissues throughout	Households in the USA	5 months' overall supply	Resupply of tissues	None described.	Reported use of tissues "not at all, some of the time,	Reported use "all of the time": A. vs B.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	control): A. Virucidal nasal tissues B. Placebo tissues	community setting	with inside layer containing: A. citric and malic acid plus sodium lauryl sulphate; B. succinic acid.	nose, coughing or sneezing) and to discard after use and to help young children use tissues if develop a cold.	sponsor (Kimberly-Clark Corporation).	5-month trial period			as required	most of the time, or all of the time"	82% vs 71%
Chard 2019 (additional details from Chard 2018)	Water, Sanitation, and Hygiene for Health and Education in Laotian Primary Schools (WASH HELPS)	Primary schools and their students	Prevent the spread of pathogens within schools through improved water supply and hygiene facilities and improved WASH habits in children at home and throughout the life course	For each school: Water supply for school compound: (borehole, protected dug well with pump, or gravity-fed system) Water tank to supply toilet and hand-washing station School sanitation facilities (3 toilet compartments) Hand-washing facilities: 2 sinks with tapped water and supply of soap available (1 bar of soap/pupil) 3 group hand-washing tables with soap and water At least 1 drinking water filter per classroom	Provision of school: Water supply, sanitation facilities, hand-washing facilities (individual and group), drinking water filters Behaviour change education and promotion including daily group hygiene activities Daily hand-washing and cleaning schedules	UNICEF paid for materials. School and teachers conducted daily hand-washing activities with children. Students participat-	Facilities provided within schools. Children participated in group hand-washing and cleaning.	Primary schools and their classrooms (in Laos)	One-off provision of water and hygiene facilities Daily hand-washing activities and cleaning for 1 school year Cleaning schedules posted in at least 1 classroom near toilet.	Water supply tailored to the school requirements/environment. Sanitation facilities provided as needed and desig-	Rain water tank provision affected by rain water supply, so changed to tanks with motorised hand pumps or gravity-fed wa-	Unannounced visits every 6 to 8 weeks for structured observations to measure fidelity and adherence Fidelity Index score (0 to 20): for hardware provided see Table 1 in paper and protocol Adherence index: student report of behavioural out-	Fidelity: 30.9% across all schools and visits Adherence: 29.4% Hardware provision: 87.8% of schools School-level adherence: 61.4% Group compound cleaning: 94.8%, toilet use: 75.5%, group toilet cleaning: 68.3%,

Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

				Schedules of daily group hand-washing, compound and toilet cleaning Cost per school: USD 13,000 to 17,500		ed in daily group cleaning activities.				nated for boys, girls, and students with disabilities.	ter supply systems. Theft and animal consumption of supplied soap reduced supply.	comes index score (0 to 4)	group hand-washing: 48.7%, individual hand-washing with soap after toilet use: 23.9%. Further details (Chard 2018)
Hartinger 2016	Integrated environmental home-based intervention package (IHIP)	Households and their householders including children	Reduce infections and improve child growth in households in rural communities with limited facilities through a multicomponent, low-cost environmental intervention to improve drinking water,	Per household: "OPTIMA-improved stove": improved ventilated solid-fuel stove Kitchen sink with in-kitchen water connection providing piped water Point-of-use water quality intervention applying solar disinfection to drinking water	Community engagement with local and regional stakeholders in design and development Provision of stoves, kitchen sinks, and plastic bottles for solar water treatment, and hygiene education Training of mothers/caretakers in: - solar drinking-water disinfection (SODIS)[20] ac-	Health promoters hired local elementary school teachers and implemented and promoted the inter-	Face-to-face and to individual households; mode of delivery of training as individual or group not	Households in rural communities in Peru	Stoves and sinks installed over initial 3 months. Monthly reinforcement over 12 months of SODIS, child and kitchen hygiene Weekly spot checks of compliance	Tailored to particular household facilities and environments as needed and to local beliefs and	Not described	Weekly spot-check observations of household hygiene and environmental health conditions (e.g. presence of SODIS bottles on the roof or kitchen) using a checklist Monthly self-report by	SODIS use: 60% initially and 10% at end of study Self-reported use by mothers: 90% with slight decrease at end Self-reported stove use: 90% daily Sink use: 66% daily

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

				sanitation, personal hygiene, and household air quality developed in pilot (Hartinger 2011; Hartinger 2012) using a participatory approach that addressed local beliefs and cultural views		cording to standard procedures - hand hygiene (washing own and children's hands with soap at critical times[21]) - advice to separate animals and their excreta from the kitchen environment Project-initiated repairs	ventions. 4 teams of field staff conducted spot-check observations.	described	Repairs after 9 months Environmental samples test middle and end of 12-month surveillance.	cultural customs Repairs to stoves as needed and checked at 9 months		mothers of stove and sink use	35% of stoves needed minor repairs, 1% needed major repairs. Best-functioning stoves achieved mean 45% and 27% reduction of $PM_{2.5}$ and CO, respectively, in mothers' personal exposure.
Huda 2012	Sanitation Hygiene Education and Water Supply in Bangladesh (SHEWA-B)	Villages and their households with a child < 5 years old	Reduce illness in children < 5 years by improving hygiene practices, sanitation and water supply and treatment in their household	Materials for training of community hygiene promoters and promotion activities including flip charts and flash cards with messages alerting participants to presence of unobservable "germs" and practices to minimise germs See Box 1 in paper for 11 key messages.[22]	Engaging local residents under guidance of local NGOs to develop community action plans addressing: Latrine coverage and usage Access to and use of arsenic-free water Improved hygiene practices, especially handwashing with soap	Community hygiene promoters (local residents with at least 10 years' schooling trained for 10	Face-to-face delivery to groups (villages and households) and individuals	Villages and households in districts of Bangladesh Community activities held in villages.	18 months overall Expected household visit and courtyard meeting every 2 months Handwashing opportunities: after own or child's defecation,	Community action plans developed for and by local residents.	Not described	Structured observation of handwashing and child faeces disposal behaviour in households and spot checks of type of household water and sanitation facilities	HW: Food-related: No significant difference from baseline to 18 months; IG versus CG After anus cleaning: 36% versus 27%

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					Recruitment and appointment of community hygiene promoters Household visits, courtyard meetings, and social mobilisation activities (e.g. water, sanitation and hygiene fairs, village theatre, group discussions in tea stalls (the social meeting point for village men)) by community promoters Structured observation in households	days on behaviour change communication in water, sanitation, and hygiene)	Meetings held in courtyards of groups of households. Household visits	prior to preparing and serving food, prior to eating and feeding a child				Defecation: 30% versus 23% No access to latrine decreased from 10.3% to 6.8%. No significant improvement in access to improved latrines, solid waste disposal, drainage systems, and covered containers for water storage
Ibfelt 2015	Disinfection of toys	Daycare nurseries	Reduce transmission of pathogens via shared toys in daycare environment through regular disinfection treatment	Disinfectants: Turbo Oxysan (Ecolab, Valby, Denmark) for washing machines Sirafan M, Ecolab (1% to 3% benzalkonium chloride, 1% to 3% didecyldimethylammonium chloride, and 5% to 7% alcohol ethoxylates) for immersion or wiping	Collection and commercial cleaning of toys from nurseries: - linen and toys suitable for washing machines were washed at 46 °C and subsequently disinfected - toys not suitable for washing machines immersed	Commercial cleaning company: Berendsen A/S, Søborg, Denmark	Cleaning companies collected the toys and linen and cleaned them	Daycare nurseries in Denmark Commercial industrial clean-	2 to 3 months overall Cleaning every 2 weeks	Staggered cleaning to ensure children had toys to play with whilst oth-	None described.	None described.	None described.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					in disinfectant or wiped with microfibre cloth		off-site, then returned them.	ing facility		ers were being cleaned		
Najnin 2019 (see also Qadri 2015 for further details)	2 active interventions: A. Combined cholera vaccine and 'behaviour change communication' intervention B. Cholera vaccine-alone group	Low-income households and compounds	Prevent or reduce transmission of respiratory illness based on the Integrated Behavioural Model for Water Sanitation and Hygiene (IBM-WASH) theoretical framework (Dreibelbis 2013; Hulland 2013)	A. and B. Cholera vaccine ShanChol™ (Shantha Biotechnics-Sanofi, India) A. Following hardware per compound: a. Hand-washing hardware: (i) Bucket with a tap (provided free of charge) (ii) Soapy water bottle (mixture of a commercially available sachet of powdered detergent (~USD 0.03) with 1.5 L of water in a plastic bottle with a hole punched in the cap) supplied by participating compounds (iii) Bowl to collect rinse water after washing hands (see photo in text or in Najnin 2017 doi.org/10.1093/ije/dyx187) b. Water treatment hardware:	A. and B. Provision of cholera vaccine (2 doses at least 14 days apart) Provision of hand-washing hardware and behaviour change communication activities Encouragement of hand-washing after defecation, after cleaning child's anus, and before preparing food Encouragement to add chlorine to own water vessels Benefits were again explained. Follow-up visits by health promoters	Dushtha Shasthya Kendra (DSK), an NGO, delivered the hardware and behavioural intervention (through community health promoters). Separate data collectors observed soap avail-	Handwashing and water treatment hardware mostly delivered at the compound level in person. Behaviour change communication messages were delivered both at	Households and compounds (where several households share a common water source, kitchen, and toilets) in Bangladesh	Behaviour change communication messages delivered first (within 3 months of cholera vaccination). Point-of-use water hardware provided 3 months later. Follow-up health promoter visits 3 times in 2 months after hardware installation, then 2 times/month (over nearly 2 years).	Hardware-related problems (breakage/leakage) were addressed on health promoter follow-up visits.	None described.	Unannounced home visits by data collectors who observed presence of soap/soapy water and water in most convenient place for handwashing (either reserved in a container or available at the tap) Residual chlorine was measured indicating uptake of chlorine dispenser.	Presence of soap / soapy water and water: A. Handwashing group compounds: 45% (1,729 / 3,886); B. Vaccine-only group compound: 22% (438 / 1,965); C. Control: 28% (556 / 1991) Residual chlorine present in stored drinking water of 4% (160/3886) of households in the vac-

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

				Dispenser containing liquid sodium hypochlorite See Figure 2 in Najnin 2017 for photos of both doi.org/10.1093/ije/dyx187 and more details. Participants own water vessels for water treatment Print materials for behaviour change to compounds and households		abili-ty.	com-pound and house-hold lev-els.					cine-plus-behaviour-change com-pound and none in the oth-er 2 com-pounds.
Gargling													
Goodall 2014	2 ac-tive inter-ven-tions: A. Vi-ta-min D_3 sup-ple-men-ta-tion B. Gar-gling wa-ter	Uni-ver-sity stu-dents	Decrease the in-cidence of URTI through increased vitamin D levels (associ-ated with greater frequen-cy and severity of URTI) and gargling (as pre-ventative measure against URTI)	A. Vitamin D_3: container of 8 capsules of 10,000 IU (purchased from Eu-ro-Pharm International Canada Inc.) Weekly email reminder B. Gargling: 30 mL of tap water 2/day	A. Vitamin D: in-structed to take 1 pill weekly B. Gargling: in-structed to gargle twice daily for 30 seconds All participants received general lifestyle and health advice on sleep, nutrition, hand hygiene, and exercise.	Not spec-ified, pre-sum-ably the re-searchers in-clud-ing a study phar-ma-cist	Vita-min D_3 sup-plied indi-vidu-ally, but no fur-ther de-tails. Method of lifestyle and health ad-vice pro-vi-sion	In uni-ver-sity stu-dent hous-ing (in resi-dences or off-cam-pus) in Cana-da	2 months overall Vitamin D_3: week-ly supple-mentation and email reminder Gargling: 30 mL of water for 30 sec-onds twice daily	None de-scribed.	None de-scribed.	None de-scribed.	None de-scribed.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

							also not described.						
Ide 2014	2 active interventions (no control): A. Green tea gargling B. Water gargling	High school students	Prevent influenza spread and infection in high school students who are at increased risk from close interaction through gargling as a non-pharmaceutical intervention, specifically green tea containing highly bioactive catechin (-)-epigallocatechin gallate, with possible anti-influenza virus properties	A. Bottled green tea (500 mL) containing a catechin concentration of 37 ± 0.2 mg/dL, including approximately 18% (-)-epigallocatechin gallate (manufactured by the Kakegawa Tea Merchants Association). Concentration measured by high-performance liquid chromatography based on the average concentration in 10 bottles from the same production lot (September 2011) used for gargling in the study. B. Tap water	A. Provision of green tea B. Advice to gargle with tap water and not to gargle green tea during study A. and B. Advice to gargle at least 3 times/day (after arriving at school, after lunch, and after school) Consumption of green tea and other tea was not restricted for either group. Safety monitoring carried out throughout the study (not further described).	Materials supplied by researchers. High schools' vice principals and head teachers assisted with safety monitoring.	Green tea supplied individually to students. Mode of gargling advice not described.	High schools in Japan	Gargling 3 times/day for 90 days	None described.	None described.	Daily questionnaire included questions about daily adherence to gargling regimen. Adherence rate of gargling at or above 75%, and absence of green tea gargling when in the water gargling group.	Gargling adherence rate: green tea group: 73.7%; water group: 67.2%
Satomura 2005	2 active inter-	Healthy adults	Prevent URTIs through	A. Water B. 15 to 30 times diluted 7% povidone-iodine (as	Local administrators instructed participants to:	Local project ad-	Not specified,	18 healthcare	60 days overall	If diluted povi-	3 partici-	Completion of gargling	9 participants did not com-

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

ventions: A. Water gargling B. Povidone-iodine gargling	gargling water alone, which may wash out pathogens from the pharynx and oral cavity through whirling water or through chlorine, or povidone-iodine for its perceived virucidal properties	indicated by manufacturer)	- gargle dose of water or povidone-iodine 3 times/day; - maintain hand-washing routine; - not change other hygiene habits; - not take any cold remedies; - complete gargling diary. Weekly monitoring of hygienic actions and encouragement to keep up assigned intervention every week	ministrators (18 healthcare professionals) provided instructions and monitoring and encouragement.	but likely to have been face-to-face and individually, at least initially for instructions	sites in Japan (4 in northern region, 9 in central region, 5 in western region)	1. Water gargling: 20 mL for 15 s at least 3 times/day 2. Povidone-iodine gargling: 20 mL of dilution 3 times/day	done-iodine caused serious discomfort or was not available, participants were allowed to gargle with water instead.	pants assigned to povidone-iodine gargled with water instead as the povidone-iodine "did not agree with them".	diary: frequency of gargling and hand-washing Weekly monitoring and encouragement by local administrators	plete diary. Average frequency of gargling / person / day: With water: A: 3.6 B: 0.8 Control: 0.9 With povidone-iodine: A.: <0.1 B: 2.9 Control: 0.2

ABH: alcohol-based rub
ARI: acute respiratory infection
CDC: Centers for Disease Control and Prevention
CG: control group
CHG: chlorhexidine gluconate
CO: carbon monoxide
DCCs: daycare centres
FM: face masks
HCP: healthcare personnel
HCW: healthcare worker
HH: hand hygiene
HSG: hand sanitiser group
HSW: hand-washing with soap and water
HWWS: hand-washing with soap
IG: intervention group
IHIP: integrated environmental home-based intervention package

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ILI: influenza-like illness
IU: international units
LTCFs: long-term care facilities
NGOs: non-governmental organisations
NH: nursing home
no.: number
NPIs: non-pharmaceutical interventions
PM2.5: particulate matter of less than 2.5 microns
RAs: research assistants
RIs: respiratory infections
RTIs: respiratory tract infections
SD: standard deviation
SSTI: skin and soft-tissue infection
SWG: soap-and-water group
TCID: tissue-culture infectious dose
URTI: upper respiratory tract infection
WHO: World Health Organization
wk: week
w/w: weight for weight

[1]: Occupational Safety and Health Administration (OSHA). OSHA technical manual: section VIII: chapter 2: respiratory protection. US Department of Labor. www.osha.gov/dts/osta/otm/otm_viii/otm_viii_2.html (accessed 21 April 2020).

[2]: Ministry of Health and Long-Term Care, Public Health Division, Provincial Infectious Diseases Advisory Committee. Preventing respiratory illnesses: protecting patient and staff: infection control and surveillance standards for febrile respiratory illness (FRI) in non-outbreak conditions in acute care hospitals [September 2005] http://www.health.gov.on.ca/english/providers/program/infectious/diseases/best_prac/bp_fri_080406.pdf (accessed September 11 2009). [URL inactive]

[3]: Before eating, after sneezing, coughing, handling money, using restroom, returning to desk and interacting with others who may be sick

[4]: after coming into classroom, before and after lunch, after break, after physical education, when they went home and after coughing, sneezing or blowing their noses

[5]: after toileting and when visibly dirty plus a protocol for particular circumstances: after coming into the classroom; before and after lunch; after playing outside; when they went home; after coughing, sneezing, or blowing their noses; and after diapering

[6]: 1) when entering into the classroom; 2) after sneezing, coughing, or blowing their nose; 3) after using the toilet/washroom; 4) before eating any food; and 5) when leaving the school at the end of the day

[7]: what to do if hands were dirty, why students should wash their hands, benefits of washing hands and using hand sanitizer, procedure for washing hands using hand sanitizer, to cover mouth and nose with upper part of sleeve while coughing and/or sneezing

[8]: Boyce JM, Pittet D, Healthcare Infection Control Practices Advisory Committee, HICPAC/ SHEA/APIC/IDSA Hand Hygiene Task Force. Guideline for hand hygiene in healthcare settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/ IDSA Hand Hygiene Task Force. MMWR Recommendations and Reports 2002;51(RR-16):1–45. www.cdc.gov/mmwr/preview/mmwrhtml/rr5116a1.htm (accessed 21 April 2020). International Bank for Reconstruction and Development/ World Bank, Bank-Netherlands Water Partnership, Water and Sanitation Program. Hand washing manual: a guide for developing a hygiene promotion program to increase handwashing with soap. http://go.worldbank.org/PJTS4A53C0 (Accessed 16 May 2007). *[URL inactive]* California State Department of Education. *Techniques for Preventing the Spread of Infectious Diseases*. Sacramento (CA): California State Department of Education, 1983. Geiger BF, Artz L, Petri CJ, Winnail SD, Mason JW. *Fun with Handwashing Education*. Birmingham (AL): University of Alabama, 2000. Roberts A, Pareja R, Shaw W, Boyd B, Booth E, Mata JI. A tool box for building health communication capacity. www.globalhealthcommunication.org/tools/29 (Accessed 10 October 2007). *[URL inactive]* Stark P. *Handwashing Technique. Instructor's Packet. Learning Activity Package*. Sacramento (CA): California State Department of Education, 1982.

[9]: DIN EN 1500: Chemische Desinfektionsmittel und Antiseptika, Hygienische Händedesinfektion, Prüfverfahren und Anforderungen (Phase 2/Stufe 2). Brüssel (Belgium): CEN, European Comittee for Standardization 1997;1-20.

[10]: DIN EN 12791: Chemische Desinfektionsmittel und Antiseptika, Chirugische Händedesinfektionsmittel - Prüfverfahren und Anforderungen (Phase 2/Stufe 2). Brüssel (Belgium): CEN, European Comittee for Standardization 2005;1-31.

[11]: after defaecation, after cleaning an infant who had defaecated, before preparing food, before eating, and before feeding infants

[12]: non-governmental organisation that supports community-based health and development initiatives

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[13]: “Healthy Hands” Rules (from Figure 3 in paper): Do use “special soap” when arrive to school, before lunch, after go to bathroom (only if soap and water not available), if rub nose or eyes or if fingers in mouth, if teacher asks. Do not: use “special soap” if hand dirt on them, put “special soap” on another student, play with ‘special soap”, put hands near eyes after using “special soap”.
[14]: Calculated by subtracting each day’s soap weight from the previous day’s weight. Maximum number of grams of soap consumed for each compound was identified and the day on which the maximum soap consumption was recorded. A per capita estimate of daily soap consumption was calculated
[15]: National Health and Medical Research Council. Staying Healthy in Child Care. Canberra (Australia): Australian Government Publishing Service, 1994
[16]: upon arrival, before and after lunch, and prior to departure
[17]: knowledge and awareness of HH guidelines, perceived importance of performing HH, perceived behavioural control (i.e. perceived ease or difficulty of performing the behaviour), and habit
[18]: “According to the Dutch national guidelines, HH is mandatory for caregivers before touching/preparing food, before caregivers themselves ate or assisted children with eating, and before wound care; and after diapering, after toilet use/wiping buttocks, after caregivers themselves coughed/sneezed/wiped their own nose, after contact with body fluids (e.g. saliva, vomit, urine, blood, or mucus when wiping children’s noses), after wound care, and after hands were visibly soiled.” (p. 2495)
[19]: having touched household items being used by the index patients and/or other symptomatic household contacts, and after coughing/sneezing, before meals, before preparing meals and when returning home
[20]: SODIS: www.sodis.ch/index_EN.html
[21]: after defecation, after changing diapers, before food preparation and before eating
[22]: 1. Wash both hands with water and soap before eating/ handling food 2. Wash both hands with water and soap/ash after defecation 3. Wash both hands with water and soap/ash after cleaning baby’s bottom 4. Use hygienic latrine by all family members including Children 5. Dispose of children’s faeces into hygienic latrines 6. Clean and maintain latrine 7. Construct a new latrine if the existing one is full and fill the pit with soil/ash. 8. Safe collection and storage of drinking water 9. Draw drinking water from arsenic safe water point 10. Wash raw fruits and vegetables with safe water before eating and cover food properly 11. Manage menstruation period safely (p.605)

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Table 2. Results from trials of hand hygiene compared to control

Study	Comparison (see Table 1 for details of interventions)	Reported outcomes	Results
Alzaher 2018 cluster-RCT Saudi Arabia	Hand-washing workshop and posters vs usual practice	% absence days due to URI	0.39% and 0.72% in intervention group schools; 0.86% and 1.39% in control schools
Arbogast 2016 cluster-RCT USA	Hand sanitiser + wipes + hand foam vs none Both groups received education + signage about hand-washing	1. Health insurance claims for preventable illnesses per employee 2. Absences per employee	1. 0.30 claims in intervention; 0.37 in control (27% relative reduction; P = 0.03) 2. 1.45 in intervention; 1.53 in control (5.0% relative reduction in intervention; P = 0.30)
Azor-Martinez 2016 RCT Spain	Hand-washing with soap and water plus hand sanitiser vs usual hand-washing practices	% absence days due to URI	1.15% in intervention; 1.68% in control. Significantly lower in intervention (P < 0.001)
Azor-Martinez 2018 cluster-RCT Spain	Education and hand hygiene with soap and water vs hand hygiene with sanitiser vs usual hand-washing procedures	1. URI incidence rate ratio (primary) 2. Percentage difference in absenteeism days	1. HH soap vs control 0.94 (95% CI 0.82 to 1.08); HH sanitiser vs control 0.77 (95% CI 0.68 to 0.88); HH soap vs HH sanitiser 1.21 (95% CI 1.06 to 1.39) 2. HH soap 3.9% vs control 4.2% (P < 0.001); HH sanitiser 3.25% vs control 4.2% (P = 0.026); HH soap 3.9% vs HH sanitiser 3.25% (P < 0.001)
Biswas 2019 cluster-RCT Bangladesh	Hand sanitiser and respiratory hygiene education and cough/sneeze hygiene vs no intervention	1. ILI incidence rate (at least 1 episode) 2. Laboratory-confirmed influenza	1. 22 per 1000 student-weeks in intervention; 27 per 1000 student-weeks in control, not statistically significantly different 2. 3 per 1000 student-weeks in intervention; 6 per 1000 student-weeks in control, P = 0.01
Correa 2012 cluster-RCT Colombia	Alcohol-based hand sanitiser in addition to hand-washing vs usual hand-washing practice	ARIs in 3rd trimester of follow-up	Hazard ratio for intervention to control 0.69 (95% CI 0.57 to 0.83)
Cowling 2008 cluster-RCT Hong Kong	Hand hygiene (36 households) vs face mask (mask) vs education (control)	Secondary attack rate for: 1. laboratory-confirmed influenza; 2. ILI definition 1; 3. ILI definition 2; 4. ILI definition 3.	1. HH 0.06; mask 0.07; control 0.06 2. HH 0.18; mask 0.18; control 0.18 3. HH 0.11; mask 0.10; control 0.11 4. HH 0.04; mask 0.08; control 0.04
Cowling 2009 cluster-RCT Hong Kong	Hand hygiene (HH) vs face mask + hand hygiene (HH + mask) vs education (control)	Secondary attack rate for: 1. laboratory-confirmed influenza;	1. HH 5; HH + mask 7; control 10 2. HH 16; HH + mask 21; control 19 3. HH 4; HH + mask 7; control 5

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Table 2. Results from trials of hand hygiene compared to control *(Continued)*

		2. ILI definition 1; 3. ILI definition 2.	
DiVita 2011 (conference abstract) RCT Bangladesh	Hand-washing stations with soap and motivation vs none	1. SAR for laboratory-confirmed influenza 2. SAR for ILI	1. SAR higher in intervention group (11.0% vs 7.5%) 2. SAR higher in intervention group (14.2% vs 11.9%)
Feldman 2016 cluster-RCT Israel	Hand disinfection + soap and water installed vs none	1. Number of respiratory infections 2. Number of off-duty days	1. 11 in each group 2. 112 in intervention; 104 in control
Gwaltney 1980 RCT USA	Virucidal hand wash vs placebo	1. Number with illness after immediate exposure 2. Number with illness after 2-hour delay in exposure	1. 0 of 8 in intervention; 7 of 7 in control 2. 1 of 10 in intervention; 6 of 10 in control
Hubner 2010 RCT Germany	Hand disinfection provided vs none	Odds ratios (95% CI) (intervention:control) 1. Influenza 2. Common cold 3. Sinusitis 4. Sore throat 5. Fever 6. Cough	1. 1.02 (0.20 to 5.23) 2. 0.35 (0.17 to 0.71) 3. 1.87 (0.52 to 6.74) 4. 0.62 (0.31 to 1.25) 5. 0.38 (0.14 to 0.99) 6. 0.45 (0.22 to 0.91)
Ladegaard 1999 RCT Denmark	Hand hygiene and education vs none	Sick days during the "effect period"	22 days/child in the intervention group vs 36 days/child in the control group
Larson 2010 cluster-RCT USA	Education vs education with alcohol-based hand sanitiser vs education with hand sanitiser and face masks	Incidence rate ratios (episodes per 1000 person-weeks) for: 1. URI; 2. ILI; 3. influenza; Secondary attack rates for: 4. URI/ILI/influenza; 5. ILI/influenza.	1. HS 29; HS + masks 39; control 35 2. HS 1.9; HS + masks 1.6; control 2.3 3. HS 0.6; HS + masks 0.5; control 2.3 4. HS 0.14; HS + masks 0.12; control 0.14 5. HS 0.02; HS + masks 0.02; control 0.02
Little 2015 RCT England	Bespoke automated web-based hand hygiene motivational intervention with tailored feedback vs none	Number of participants with 1 or more episodes of URI	Risk ratio for intervention to control 0.86 (95% CI 0.83 to 0.89; P < 0.001)

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Table 2. Results from trials of hand hygiene compared to control *(Continued)*

Luby 2005 RCT Pakistan	Antibacterial soap and education about hand-washing vs plain soap and education vs none	1. Cough or difficulty breathing in children < 15 yrs (episodes/100 person-weeks) 2. Congestion or coryza in children < 15 yrs (episodes/100 person-weeks) 3. Pneumonia in children < 5 yrs (episodes/100 person-weeks)	All outcomes significantly lower than control 1. 4.21 in antibacterial soap group; 4.16 in plain soap group; 8.50 in control group 2. 7.32 in antibacterial soap group; 6.87 in plain soap group; 14.78 in control group 3. 2.42 in antibacterial soap group; 2.20 in plain soap group; 4.40 in control group
Millar 2016 cluster-RCT USA	Standard educational promotion of hand-washing vs enhanced promotion vs promotion plus a once-weekly application of chlorhexidine-based body wash	Incidence rates of ARI over 20 months	37.7 enhanced + body wash; 29.3 enhanced; 35.3 standard; RR for enhanced + body wash to standard 1.07 (95% CI 1.03 to 1.11); RR for enhanced to enhanced + body wash 0.78 (95% CI 0.75 to 0.81)
Morton 2004 cluster-RCT Cross-over study USA	Alcohol gel plus education vs regular hand-washing	Absence due to infectious illness	Results not stated numerically
Nicholson 2014 cluster-RCT India	Combination hand-washing promotion with provision of free soap vs none	Target children: 1. Episodes of ARI (per 100 person-weeks) 2. School absence episodes (per 100 person-days) Families: 3. Episodes of ARI	1. 16 in intervention; 19 in control 2. 1.2 in intervention; 1.7 in control 3. 10 in intervention; 11 in control
Priest 2014 cluster-RCT New Zealand	Hand hygiene education and hand sanitiser vs education alone	1. % absence days due to respiratory illness 2. % absence days due to any illness	1. 0.84% in intervention group; 0.80% in control (P = 0.44) 2. 1.21% in intervention group; 1.16% in control (P = 0.35)
Ram 2015 RCT Bangladesh	Education to promote intensive hand-washing in households plus soap provision vs none	1. Secondary attack ratio for intervention to control for ILI 2. Laboratory-confirmed influenza	1. 1.24 (95% CI 0.93 to 1.65) 2. 2.40 (95% CI 0.68 to 8.47)
Roberts 2000 cluster-RCT Australia	Hand-washing programme with training for staff and children vs none	Incidence rate ratio for ARI	IRR 0.92 for intervention to control (95% CI 0.86 to 0.99)
Sandora 2008 cluster-RCT USA	Hand sanitiser and education vs none	Incidence rates for ARI (episodes per person-month)	0.43 in intervention; 0.42 in control

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Table 2. Results from trials of hand hygiene compared to control *(Continued)*

Savolainen-Kopra 2012 cluster-RCT Finland	Hand hygiene with soap and water (IR1 group) vs with alcohol-based hand rub (IR2 group) vs control (none); intervention groups also received education	1. Number of respiratory infection episodes/week 2. Number of reported infection episodes/week 3. Number of reported sick leave episodes/week	1. 0.076 in IR1; 0.085 in IR2; 0.080 in control, NS 2. 0.097 in IR1; 0.107 in IR2; 0.104 in control, NS 3. 0.042 in IR1; 0.035 in IR2; 0.035 in control. Significantly higher in IR1 compared with control
Simmerman 2011 cluster-RCT Thailand	Hand-washing (HW) vs hand-washing plus paper surgical face masks (HW + FM) vs control (none)	Odds ratios for secondary attack rates for influenza	OR for HW: control 1.20 (95% CI 0.76 to 1.88) OR for HW + masks: control 1.16 (95% CI 0.74 to 1.82) OR for HW + masks: HW 0.72 (95% CI 0.21 to 2.48)
Stebbins 2011 cluster-RCT USA	Training in hand and respiratory (cough) hygiene + hand sanitiser vs none	Incidence rate ratios for intervention to control for: 1. laboratory-confirmed influenza (RT-PCR); 2. influenza-A; 3. absence.	1. IRR 0.81 (95% CI 0.54 to 1.23) 2. IRR 0.48 (95% CI 0.26 to 0.87) 3. IRR 0.74 (95% CI 0.56 to 0.97)
Talaat 2011 cluster-RCT Egypt	Mandatory hand-washing intervention + education vs none	1. Number of absence days due to ILI 2. Number of absence days	1. 917 in intervention; 1671 in control (P < 0.001) 2. 13,247 in intervention; 19,094 in control (P < 0.001)
Temime 2018 cluster-RCT France	Hand hygiene with alcohol-based hand rub, promotion, staff education, and local work groups vs none	Incidence rate of ARI clusters (5 or more people in same nursing home)	2 ARI clusters in intervention; 1 in control
Turner 2012 RCT USA	Antiviral hand treatment vs no treatment	1. Number of rhinovirus infections 2. Common cold infections 3. Rhinovirus-associated illnesses	1. 49 in intervention; 49 in control, NS 2. 56 in intervention; 72 in control, NS 3. 26 in intervention; 24 in control, NS
White 2001 DB-RCT USA	Hand rub with benzalkonium chloride (hand sanitiser) vs placebo	ARI symptoms Laboratory: testing of virucidal and bactericidal activity of the product	30% to 38% decrease of illness and absenteeism (RR for illness absence incidence 0.69; RR for absence duration 0.71)
Yeung 2011 cluster-RCT Hong Kong	Alcohol-based hand gel + materials + education vs control (basic life support workshop)	Difference between pre-study period and poststudy in pneumonia infections recorded in residents	0.63/1000 reduction in intervention group; 0.16/1000 increase in control
Zomer 2015 cluster-RCT Netherlands	4 components: 1. Hand hygiene products, paper towel dispensers, soap, alcohol-based hand sanitiser,	Incidence rate ratio for intervention to control for common cold	IRR 1.07 (95% CI 0.97 to 1.19) 8.2 episodes per child-year in intervention; 7.4 episodes per child-year in control

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Table 2. Results from trials of hand hygiene compared to control *(Continued)*

	and hand cream provided for 6 months 2. Training and booklet 3. 2 team training sessions aimed at hand hygiene improvement 4. Posters and stickers for caregivers and children as reminders Combination vs usual practice		

ARI: acute respiratory infection
CI: confidence interval
cluster-RCT: cluster-randomised controlled trial
DB-RCT: double-blind randomised controlled trial
HH: hand hygiene
HS: hand sanitiser
HW: hand-washing
ILI: influenza-like illness
IRR: incidence rate ratio
NS: non-significant
OR: odds ratio
RCT: randomised controlled trial
RR: risk ratio
RT-PCR: reverse-transcriptase polymerase chain reaction
SAR: secondary attack rate
URI: upper respiratory infection
yrs: years

Table 3. Results from trials of hand hygiene + medical/surgical masks compared to control

Study	Comparison (see Table 1 for details of interventions)	Reported outcomes	Results
Aelami 2015 (conference abstract) RCT Saudi Arabia	Hand hygiene education + alcohol-based hand rub + soap + surgical masks vs none	Proportion with ILI (defined as presence of ≥ 2 of the following during their stay: fever, cough, and sore throat)	52% in intervention; 55.3% in control (P < 0.001)
Aiello 2010 cluster-RCT USA	Face mask use (FM) vs face masks + hand hygiene (FM + HH) vs control Note that this study is not included in meta-analysis as each treatment group included only 1 cluster.	1. ILI 2. Laboratory-confirmed influenza A or B	Significant reduction in ILI cases in both intervention groups compared with control over weeks 3 to 6 No significant differences between FM and FM + HH
Aiello 2012 cluster-RCT USA	Face mask use (FM) vs face masks + hand hygiene (FM + HH) vs control	1. Clinical ILI 2. Laboratory-confirmed influenza A or B	1. Non-significant reductions in FM group compared with control over all weeks. Significant reduction in FM + HH group compared with control in weeks 3 to 6

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Table 3. Results from trials of hand hygiene + medical/surgical masks compared to control *(Continued)*

			2. Non-significant reductions in both intervention groups compared with control
Cowling 2009 cluster-RCT Hong Kong	Hand hygiene (HH) vs hand hygiene plus face masks (HH + mask) vs control	Secondary attack ratio for: 1. laboratory-confirmed influenza; 2. ILI definition 1; 3. ILI definition 2.	1. HH 5; HH + mask 7; control 10 2. HH 16; HH + mask 21; control 19 3. HH 4; HH + mask 7; control 5
Larson 2010 cluster-RCT USA	Education (control) vs education with alcohol-based hand sanitiser (HS) vs education + HS + face masks (HS + mask)	Incidence rate ratios (episodes per 1000 person-weeks) for: 1. URI; 2. ILI; 3. influenza. Secondary attack rates for: 4. URI/ILI/influenza; 5. ILI/influenza.	1. HS 29; HS + mask 39; control 35 2. HS 1.9; HS + mask 1.6; control 2.3 3. HS 0.6; HS + mask 0.5; control 2.3 4. HS 0.14; HS + mask 0.12; control 0.14 5. HS 0.02; HS + mask 0.02; control 0.02
Simmerman 2011 cluster-RCT Thailand	Control vs hand-washing (HW) vs hand-washing + paper surgical face masks (HW + mask)	Odds ratio for secondary attack rates for influenza	OR for HW: control 1.20 (95% CI 0.76 to 1.88) OR for HW + mask: control 1.16 (95% CI 0.74 to 1.82) OR for HW + mask: HW 0.72 (95% CI 0.21 to 2.48)
Suess 2012 cluster-RCT Germany	Face mask + hand hygiene (mask + HH) vs face masks only (mask) vs none (control)	Secondary attack rates in household contacts: 1. Laboratory-confirmed influenza 2. ILI	1. Mask 9; mask + HH 15; control 23 2. Mask 9; mask + HH 9; control 17

CI: confidence interval
cluster-RCT: cluster-randomised controlled trial
FM: face mask
HH: hand hygiene
HS: hand sanitiser
HW: hand-washing
ILI: influenza-like illness
OR: odds ratio
RCT: randomised controlled trial
URI: upper respiratory infection

Table 4. Results from trials of soap + water compared to hand sanitisers

Study	**Comparison** (see Table 1 for details of interventions)	**Reported outcomes**	**Results**
Azor-Martinez 2018 cluster-RCT Spain	Education and hand hygiene with soap and water (HH soap) vs hand hygiene with sanitiser (HH sanitiser) vs usual hand-washing procedures	1. URI incidence rate ratio (primary) 2. Percentage difference in absenteeism days	1: HH soap vs control 0.94 (95% CI 0.82 to 1.08); HH sanitiser vs control 0.77 (95% CI 0.68 to 0.88); HH soap vs HH sanitiser 1.21 (95% CI 1.06 to 1.39) 2: HH soap 3.9% vs control 4.2% (P < 0.001); HH sanitiser 3.25% vs control 4.2% (P = 0.026); HH soap 3.9% vs HH sanitiser 3.25% (P < 0.001)
Pandejpong 2012	Alcohol hand gel applied every 60 minutes vs every 120 minutes vs once before lunch (3 groups).	Absent days due to confirmed ILI/present days	0.017 in every hour group; 0.025 in every 2 hours group; 0.026 in before lunch group. Statistically significant difference between every hour group and

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Table 4. Results from trials of soap + water compared to hand sanitisers *(Continued)*

cluster-RCT Thailand			before lunch group, and between every hour and every 2 hours groups
Savolainen-Kopra 2012 cluster-RCT Finland	Hand hygiene with soap and water (IR1 group) vs with alcohol-based hand rub (IR2 group) vs control (none); intervention groups also received education	1. Number of respiratory infection episodes/week 2. Number of reported infection episodes/week 3. Number of reported sick leave episodes/week	1. 0.076 in IR1; 0.085 in IR2; 0.080 in control, NS 2: 0.097 in IR1; 0.107 in IR2; 0.104 in control, NS 3: 0.042 in IR1; 0.035 in IR2; 0.035 in control. Significantly higher in IR1 compared with control
Turner 2004a and-Turner 2004b RCT Canada	Study 1. Ethanol vs salicylic acid 3.5% vs salicylic acid 1% and pyroglutamic acid 3.5% Study 2. Skin cleanser wipe vs ethanol (control)	% of volunteers infected with rhinovirus	7% in each intervention group; 32% in control (study 1) 22% in intervention, 30% in control (study 2)

CI: confidence interval
cluster-RCT: cluster-randomised controlled trial
HH: hand hygiene
ILI: influenza-like illness
NS: non-significant
RCT: randomised controlled trial
URI: upper respiratory infection

Table 5. Results from trials of surface/object disinfection (with or without hand hygiene) compared to control

Study	**Comparison** (see Table 1 for details of interventions)	**Reported outcomes**	**Results**
Ban 2015 cluster-RCT China	Hand hygiene products, surface cleaning and disinfection provided to families and kindergartens vs none	1. Respiratory illness 2. Cough and expectoration	1. OR 0.47 for intervention to control (95% CI 0.38 to 0.59) 2. OR 0.56 (95% CI 0.48 to 0.65)
Carabin 1999 cluster-RCT Canada	One-off hygiene education and disinfection of toys with bleach vs none	Difference in incidence rate for URTI (cluster-level result)	0.28 episodes per 100 child-days lower in intervention group (95% CI 1.65 lower to 1.08 higher); URTI incidence rate IRR 0.80 (95% CI 0.68 to 0.93)
Ibfelt 2015 cluster-RCT Denmark	Disinfectant washing of linen and toys by commercial company every 2 weeks vs usual care	Presence of respiratory viruses on surfaces	Statistically significant reduction in intervention group in adenovirus, rhinovirus, RSV, metapneumovirus, but not other viruses including coronavirus
Kotch 1994 RCT USA	Training in hand-washing and diapering and disinfection of surfaces vs none	Respiratory illness incidence rate in: 1. children < 24 months; 2. children >= 24 months.	1. 14.78 episodes per child-year in intervention; 15.66 in control 2. 12.87 in intervention; 11.77 in control

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Table 5. Results from trials of surface/object disinfection (with or without hand hygiene) compared to control *(Continued)*

McConeghy 2017 RCT USA	Staff education, cleaning products, and audit of compliance and feedback vs none	Infection rates	Upper respiratory infections not reliably recorded or reported.
Sandora 2008 cluster-RCT USA	Hand sanitiser and disinfection of classroom surfaces vs materials about good nutrition (control)	Absence due to respiratory illness (multivariable analysis)	Rate ratio 1.10 for intervention to control (95% CI 0.97 to 1.24)

CI: confidence interval
cluster-RCT: cluster-randomised controlled trial
IRR: incident rate ratio
OR: odds ratio
RCT: randomised controlled trial
RSV: respiratory syncytial virus
URTI: upper respiratory tract infection

Table 6. Results from trials of complex interventions compared to control

Study	**Comparison** (see Table 1 for details of interventions)	**Reported outcomes**	**Results**
Complex hygiene and sanitation interventions compared to control			
Chard 2019 cluster-RCT Laos	Complex sanitation intervention and education vs none	Pupil-reported symptoms of respiratory infection over 1 week	NS difference between groups. 29% of intervention group; 32% control group; adjusted risk ratio 1.08 (95% CI 0.95 to 1.23)
Hartinger 2016 cluster-RCT Peru	Cooking and sanitation provision and education vs none	Number of ARI episodes per child-year	NS difference between groups. Risk ratio for intervention to control 0.95 (95% CI 0.82 to 1.10)
Huda 2012 cluster-RCT Bangladesh	Sanitation provision and education vs none	Respiratory illness	12.6% in intervention group; 13.0% in control group. Not adjusted for multiple outcome measurements. No CIs reported.
Najnin 2019 cluster-RCT Bangladesh	Sanitation and behaviour change intervention (plus cholera vaccine) vs none	Respiratory illness in past 2 days	2.8% in intervention group; 2.9% in control group

ARI: acute respiratory infection
CI: confidence interval
cluster-RCT: cluster-randomised controlled trial
NS: non-significant
RCT: randomised controlled trial

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Table 7. Results from trials of virucidal tissues compared to control

Study	Comparison	Reported outcomes	Results
Virucidal tissues compared with placebo or no tissues			
Farr 1988a and Farr 1988b cluster-RCT USA Trial 1 and Trial 2	Trial 1. Virucidal nasal tissues vs placebo vs none Trial 2. Virucidal nasal tissues vs placebo	Respiratory illnesses per person over 24 weeks Trial 1 Trial 2	Trial 1: 3.4 in tissues group; 3.9 in placebo group; 3.6 in no-tissues group Trial 2: 3.4 in tissues group; 3.6 in placebo group NS
Longini 1988 DB-PC RCT USA	Virucidal nasal tissues vs placebo	Secondary attack rate of viral infections (number of infections in household members of index case)	10.0 in intervention; 14.3 in placebo; NS

cluster-RCT: cluster-randomised controlled trial
DB-PC: double-blind, placebo-controlled
NS: non-significant
RCT: randomised controlled trial
vs: versus

Table 8. Summary of main results of the review for the primary outcomes

Interventions	RCT/cluster-RCT (N = 67)
Medical/surgical masks	**Masks (medical/surgical) compared to no masks** 9 trials no effect on ILI (RR 0.99, 0.82 to 1.18) (Aiello 2010; Barasheed 2014; Canini 2010; Cowling 2008; Jacobs 2009; MacIntyre 2009; MacIntyre 2015; MacIntyre 2016; Suess 2012); 6 trials no effect on laboratory-confirmed influenza 95% CI RR 0.84 (0.61 to 1.17) (Aiello 2012; Cowling 2008; MacIntyre 2009; MacIntyre 2015; MacIntyre 2016; Suess 2012); 2 trials in HCWs no effect on ILI (RR 0.37, 0.05 to 2.50) (Jacobs 2009; MacIntyre 2015). **Medical/surgical masks vs other (non-N95) masks:** 1 trial more ILI with cloth mask (RR 13.25, 1.74 to 100.97) (MacIntyre 2015); 1 trial no effect of catechin-treated masks on influenza (adjusted OR 2.35, 0.40 to 13.72) (Ide 2016).
N95 respirator	**N95 respirators compared to medical/surgical masks** 3 trials no difference for clinical respiratory illness (RR 0.70, 0.45 to 1.10) (MacIntyre 2011; MacIntyre 2013; Radonovich 2019); 4 trials no difference for ILI (95% CI RR 0.81, 0.62 to 1.05) (Loeb 2009; MacIntyre 2009; MacIntyre 2011; Radonovich 2019); 4 trials no difference for laboratory-confirmed influenza (95% CI RR 1.06, 0.81 to 1.38) (Loeb 2009; MacIntyre 2009; MacIntyre 2011; Radonovich 2019). 4 studies conducted in HCWs, 3 trials no difference for clinical respiratory illness (RR 0.70, 0.45 to 1.10) (MacIntyre 2011; MacIntyre 2013; Radonovich 2019); 3 trials no difference for ILI (RR 0.64, 0.32 to 1.31) (Loeb 2009; MacIntyre 2011; Radonovich 2019); 3 trials no difference for laboratory-confirmed ILI (RR 1.02, 0.73 to 1.43) (Loeb 2009; MacIntyre 2011; Radonovich 2019).
Hand hygiene	**Hand hygiene compared to control** 16 trials found effect on combined outcome (ARI or ILI or influenza) (RR 0.89, 0.84 to 0.95) (Azor-Martinez 2018; Biswas 2019; Correa 2012; Cowling 2008; Cowling 2009; Hubner 2010; Larson 2010; Little 2015; Millar 2016; Nicholson 2014; Ram 2015; Roberts 2000; Sandora 2005; Simmerman 2011; Stebbins 2011; Zomer 2015); 7 trials effect on ARI (RR 0.84, 0.82 to 0.86) (Azor-Martinez 2018; Correa 2012; Larson 2010; Little 2015; Millar 2016; Nicholson 2014; Sandora 2005); 10 trials no effect on ILI

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Table 8. Summary of main results of the review for the primary outcomes *(Continued)*

	(RR 0.98, 0.85 to 1.13) (Biswas 2019; Cowling 2008; Cowling 2009; Hubner 2010; Larson 2010; Little 2015; Ram 2015; Roberts 2000; Simmerman 2011; Zomer 2015); 8 trials no effect on laboratory-confirmed influenza (RR 0.91, 95% CI 0.63 to 1.30) (Biswas 2019; Cowling 2008; Cowling 2009; Hubner 2010; Larson 2010; Ram 2015; Simmerman 2011; Stebbins 2011)
Hand hygiene + medical/surgical masks	**Hand hygiene + medical/surgical masks compared to control** 7 trials no effect on ILI (95% CI RR 0.97, 0.80 to 1.19) (Aelami 2015; Aiello 2010; Aiello 2012; Cowling 2009; Larson 2010; Simmerman 2011; Suess 2012); 4 trials no effect on laboratory-confirmed influenza (RR 0.97, 0.69 to 1.36) (Cowling 2009; Larson 2010; Simmerman 2011; Suess 2012). **Hand hygiene + medical/surgical masks compared to hand hygiene** 3 trials no effect on ILI (RR 1.03, 0.69 to 1.53) or laboratory-confirmed influenza (RR 0.99, 0.69 to 1.44) (Cowling 2009; Larson 2010; Simmerman 2011).
Soap + water compared to sanitiser, and comparisons of different types of sanitiser	**Soap + water compared to sanitiser, and comparisons of different types of sanitiser** 1 trial hand sanitiser was more effective than soap and water (Azor-Martinez 2018); 1 trial there was no difference (Savolainen-Kopra 2012). 2 trials in children antiseptic was more effective (Morton 2004; White 2001); 1 trial in children antiseptic = soap (Luby 2005). 1 trial hand sanitisers were better than placebo, but no difference between sanitisers (Turner 2004a); 1 trial no difference between different wipes (Turner 2004b).
Surface/object disinfection (with or without hand hygiene) compared to control	**Surface/object disinfection compared to control** 2 trials were effective on ARI (Ban 2015; Carabin 1999); 1 trial was effective for viruses detected on surface (Ibfelt 2015); 2 trials showed no difference in ARIs (Kotch 1994; McConeghy 2017).
Disinfection of living quarters	-
Complex interventions	**Complex interventions compared to control** 4 trials in low-income countries found no effect on respiratory viral illness (Chard 2019; Hartinger 2016; Huda 2012; Najnin 2019).
Physical interventions (masks, gloves, gowns combined)	-
Gloves	-
Gowns	-
Physical distancing	-
Quarantine in the community	**Quarantine compared to control** 1 trial effective for influenza (Cox hazard ratio 0.799, 95% CI 0.66 to 0.97) (Miyaki 2011).
Eye protection	-
Gargling	**Gargling compared to control** 1 trial gargling with tap water was effective, povidone-iodine was not effective (Satomura 2005); 1 trial gargling with green tea was not more effective than tap water (Ide 2014); 1 trial gargling with water was not effective (Goodall 2014); pooling of 2 trials no effect of gargling (RR 0.91, 95% CI 0.63 to 1.31) (Goodall 2014; Satomura 2005).
Virucidal tissues	**Virucidal tissues compared to control**

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Table 8. Summary of main results of the review for the primary outcomes *(Continued)*

	1 trial had a small effect (Farr 1988a) ("The study authors conclude that virucidal tissues have only a small impact upon the overall rate of natural acute respiratory illnesses"); 2 trials non-significant difference (Farr 1988b; Longini 1988).
Nose wash	-

ARI: acute respiratory infection
CI: confidence interval
HCW: healthcare worker
ILI: influenza-like illness
OR: odds ratio
RCT: randomised controlled trial
RR: risk ratio

Table 9. Trial authors' outcome definitions

	Study	Outcomes definitions
Masks (n = 13)		
1.	Cowling 2008 cluster-RCT Hong Kong	Laboratory: QuickVue Influenza A+B rapid test Viral culture on MDCK (Madin-Darby canine kidney cells) Samples were harvested using NTS, but the text refers to a second procedure from June 2007 onwards with testing for influenza viruses on index participants with a negative QuickVue result but a fever ≥ 38 °C who were also randomised and further followed up. Data on clinical signs and symptoms were collected for all participants, and an additional NTS was collected for later confirmation of influenza infection by viral culture. It is noteworthy that dropout was higher in households of index participants who had a negative result on the rapid influenza test (25/44, 57%) compared to those who had a positive result (45/154, 29%). Effectiveness: secondary attack ratios (SAR): SAR is the proportion of household contacts of an index case who subsequently were ill with influenza (symptomatic contact individuals with at least 1 NTS positive for influenza by viral culture or PCR) 3 clinical definitions were used for secondary analysis: 1. fever ≥ 38 °C or at least 2 of the following symptoms: headache, coryza, sore throat, muscle aches and pains; 2. at least 2 of the following S/S: fever ≥ 37.8 °C, cough, headache, sore throat and muscle aches and pains; and 3. fever of ≥ 37.8 °C plus cough or sore throat. Safety: harms were not mentioned as an outcome in the methods, but it was reported in the results that there were no adverse events.
2.	Jacobs 2009 RCT Japan	Laboratory-confirmation not reported. Effectiveness: URTI is defined on the basis of a symptom score with a score > 14 being a URTI according to Jackson's 1958 criteria ("Jackson score"). These are not explained in text, although the symptoms are listed in Table 3 (any, sore throat, runny nose, stuffy nose, sneeze, cough, headache, earache, feel bad) together with their mean and scores (SD) by intervention arm. Safety: the text does not mention or report harms. These appear to be indistinguishable from URTI symptoms (e.g. headache, which is reported as of significantly longer duration in the intervention arm). Compliance is self-reported as high (84.3% of participants).

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Table 9. Trial authors' outcome definitions *(Continued)*

3.	Loeb 2009 cluster-RCT HCW Canada	Clinical respiratory illness, influenza-like illness, and laboratory-confirmed respiratory virus infection. 1. Clinical respiratory illness, defined as 2 or more respiratory symptoms or 1 respiratory symptom and a systemic symptom. 2. Influenza-like illness, defined as fever ≥ 38 °C plus 1 respiratory symptom. 3. Laboratory-confirmed viral respiratory infection. Laboratory confirmation was by nucleic acid detection using multiplex RT-PCR for 17 respiratory viruses. Safety: harms were not mentioned as an outcome in the methods, but it is stated in the results that no adverse events were reported by participants.
4.	MacIntyre 2009 cluster-RCT Australia	Eligibility criteria were stipulated as follows: 1. the household contained > 2 adults > 16 years of age and 1 child 0 to 15 years of age; 2. the index child had fever (temperature > 37.8 °C) and either a cough or sore throat; 3. the child was the first and only person to become ill in the family in the previous 2 weeks; 4. adult caregivers consented to participate in the study; and 5. the index child was not admitted to the hospital. Definitions used for outcomes: 1. ILI defined by the presence of fever (temperature > 37.8 °C), feeling feverish or a history of fever, > 2 symptoms (sore throat, cough, sneezing, runny nose, nasal congestion, headache), or 1 of the symptoms listed plus laboratory confirmation of respiratory viral infection. 2. Laboratory confirmation: multiplex RT-PCR tests to detect influenza A and B and RSV, PIV types 1–3, picornaviruses (enteroviruses or rhinoviruses), adenoviruses, coronaviruses 229E and OC43, and hMPV plus ≥ 1 sym Effectiveness: presence of ILI or a laboratory diagnosis of respiratory virus infection within 1 week of enrolment. Safety: harms not mentioned as an outcome in the methods, but it is reported in the results that more than 50% of participants reported concerns with mask wearing, mainly that wearing a face mask was uncomfortable, but there were no significant differences between the P2 (N95) and surgical mask groups. Other concerns were that the child did not want the parent wearing a mask.
5.	Aiello 2010 cluster-RCT USA	Laboratory details are described in appendix. Effectiveness: ILI, defined as cough and at least 1 constitutional symptom (fever/feverishness, chills, headache, myalgia). ILI cases were given contact nurses phone numbers to record the illness and paid USD 25 to provide a throat swab. 368 participants had ILI, 94 of which had a throat swab analysed by PCR. 10 of these were positive for influenza (7 for A and 3 for B), respectively by arm 2, 5 and 3 using PCR, 7 using cell culture. Safety: no outcomes on harms planned or reported.
6.	Canini 2010 cluster-RCT USA	The primary endpoint was the proportion of household contacts who developed an ILI during the 7 days following inclusion. Exploratory cluster-level efficacy outcome, the proportion of households with 1 or more secondary illness in household contacts. A temperature over 37.8 °C with cough or sore throat was used as primary clinical case definition. The authors also used a more sensitive case definition based on a temperature over 37.8 °C or at least 2 of the following: sore throat, cough, runny nose, or fatigue.

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Table 9. Trial authors' outcome definitions *(Continued)*

		Safety: adverse reactions due to mask wearing were reported, with 38 (75%) participants in the intervention arm experiencing discomfort with mask use due to warmth (45%), respiratory difficulties (33%), and humidity (33%). Children wearing children face masks reported feeling pain more frequently than other participants wearing adult face masks (P = 0.036).
7.	Aiello 2012 cluster-RCT in halls of residence in the USA	Clinically verified ILI - case definition (presence of cough and at least 1 or more of fever/feverishness, chills, or body aches) Laboratory-confirmed influenza A or B. Throat swab specimens were tested for influenza A or B using real-time PCR. Safety: no outcomes on harms planned or reported.
8.	Barasheed 2014 cluster-RCT Saudi Arabia	Laboratory: 2 nasal swabs from all ILI cases and contacts. 1 for influenza POCT using the QuickVue Influenza (A+B) assay (Quidel Corporation, San Diego, USA) and 1 for later NAT for influenza and other respiratory viruses. However, there was a problem with getting POCT on time during Hajj. Effectiveness: to assess the effectiveness of face masks in the prevention of transmission of ILI. ILI was defined as subjective (or proven) fever plus 1 respiratory symptom (e.g. dry or productive cough, runny nose, sore throat, shortness of breath). Safety: no outcomes on harms planned or reported.
9.	MacIntyre 2011 cluster-RCT China	Clinical respiratory illness Influenza-like illness Laboratory-confirmed viral respiratory infection Laboratory-confirmed influenza A or B 1. Clinical respiratory illness, defined as 2 or more respiratory or 1 respiratory symptom and a systemic symptom. 2. Influenza-like illness, defined as fever ≥ 38 °C plus 1 respiratory symptom (i.e. cough, runny nose, etc.). 3. Laboratory-confirmed viral respiratory infection (detection of adenoviruses, human metapneumovirus, coronavirus 229E/NL63, parainfluenza viruses 1, 2, and 3, influenza viruses A and B, respiratory syncytial virus A and B, rhinovirus A/B and coronavirus OC43/HKU1 by multiplex PCR). 4. Laboratory-confirmed influenza A or B. 5. Adherence with mask/respirator use. Safety: adherence and adverse effects of mask wearing were collected at exit interviews 4 weeks' poststudy. Significantly higher adverse events with N95 respirator compared to medical mask for discomfort, headache, difficulty breathing, nose pressure, trouble communicating, not wearing, and unspecified "other" side effects. Over 50% of those wearing N95 respirators reported adverse events. Of those wearing medical masks versus N95 respirators, 85.5% (420/491) versus 47.4% (447/943) reported no adverse events (P < 0.001), respectively.
10.	MacIntyre 2013 cluster-RCT China	Laboratory: 1. Laboratory-confirmed viral respiratory infection in symptomatic participants, defined as detection of adenoviruses; human metapneumovirus; coronaviruses 229E/NL63 and OC43/HKU1; parainfluenza viruses 1, 2, and 3; influenza viruses A and B; respiratory syncytial viruses A and B; or rhinoviruses A/B by NAT using a commercial multiplex PCR (Seegen, Inc., Seoul, Korea). 2. Laboratory-confirmed influenza A or B in symptomatic participants.

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Table 9. Trial authors' outcome definitions *(Continued)*

		3. Laboratory-confirmed bacterial colonisation in symptomatic participants, defined as detection of *Streptococcus pneumoniae*, *Legionella*, *Bordetella pertussis*, *Chlamydia*, *Mycoplasma pneumoniae*, *or Haemophilus influenzae* type B by multiplex PCR (Seegen, Inc.). Effectiveness: clinical respiratory illness defined as 2 or more respiratory symptoms or 1 respiratory symptom and a systemic symptom. ILI defined as fever (38 °C) plus 1 respiratory symptom. Safety: adverse effects measured using a semi-structured questionnaire. Investigators stated that there was higher reported adverse effects and discomfort of N95 respirators compared with the other 2 arms. In terms of comfort, 52% (297 of 571) of the medical mask arm reported no problems, compared with 62% (317 of 512) of the targeted arm and 38% (217 of 574) of the N95 arm (P < 0.001).
11.	MacIntyre 2015 cluster-RCT Vietnam	Clinical respiratory illness, influenza-like illness, and laboratory-confirmed respiratory virus infection. 1. Clinical respiratory illness, defined as 2 or more respiratory symptoms or 1 respiratory symptom and a systemic symptom. 2. Influenza-like illness, defined as fever ≥ 38 °C plus 1 respiratory symptom. 3. Laboratory-confirmed viral respiratory infection. Laboratory confirmation was by nucleic acid detection using multiplex RT-PCR for 17 respiratory viruses. Safety: adverse events associated with face mask use were reported in 40.4% (227/562) of HCWs in the medical/surgical mask arm and 42.6% (242/568) in the cloth mask arm (P = 0.45). The most frequently reported adverse events were: general discomfort (35.1%; 397/1130) and breathing problems (18.3%; 207/1130). The rate of ILI was higher in the cloth mask arm compared to medical/surgical masks (RR 13.25, 95% CI 1.74 to 100.97).
12.	MacIntyre 2016 cluster-RCT China	Clinical respiratory illness, influenza-like illness, and laboratory-confirmed viral respiratory infection. 1. Clinical respiratory illness, defined as 2 or more respiratory symptoms (cough, nasal congestion, runny nose, sore throat, or sneezes) or 1 respiratory symptom and a systemic symptom (chill, lethargy, loss of appetite, abdominal pain, muscle or joint aches). 2. Influenza-like illness, defined as fever ≥ 38 °C plus 1 respiratory symptom. 3. Laboratory-confirmed viral respiratory infection, defined as detection of adenoviruses, human metapneumovirus, coronaviruses 229E/NL63 and OC43/HKU1, parainfluenza viruses 1, 2, and 3, influenza viruses A and B, respiratory syncytial virus A and B, or rhinovirus A/B by NAT using a commercial multiplex PCR. Safety: no outcomes on harms planned or reported.
13.	Radonovich 2019 cluster-RCT USA	Laboratory. Primary outcome: incidence of laboratory-confirmed influenza, defined as: 1. detection of influenza A or B virus by RT-PCR in an upper respiratory specimen collected within 7 days of symptom onset; 2. detection of influenza from a randomly obtained swab from an asymptomatic participant; and 3. influenza seroconversion (symptomatic or asymptomatic), defined as at least a 4-fold rise in haemagglutination inhibition antibody titres to influenza A or B virus between pre-season and postseason serological samples deemed not attributable to vaccination. Effectiveness. Secondary outcomes: incidence of 4 measures of viral respiratory illness or infection as follows:

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Table 9. Trial authors' outcome definitions *(Continued)*

		1. acute respiratory illness with or without laboratory confirmation; 2. laboratory-detected respiratory infection, defined as detection of a respiratory pathogen by PCR or serological evidence of infection with a respiratory pathogen during the study surveillance period(s), which was added to the protocol prior to data analysis; and 3. laboratory-confirmed respiratory illness, identified as previously described (defined as self-reported acute respiratory illness plus the presence of at least PCR–confirmed viral pathogen in a specimen collected from the upper respiratory tract within 7 days of the reported symptoms and/or at least a 4-fold rise from pre-intervention to postintervention serum antibody titres to influenza A or B virus). Influenza-like illness, defined as temperature of at least 100 °F (37.8 °C) plus cough and/or a sore throat, with or without laboratory confirmation. Safety: 19 participants reported skin irritation or worsening acne during years 3 and 4 at 1 site in the N95 respirator group.
Hand and hygiene (n = 32)		
14.	Alzaher 2018 cluster-RCT Saudi Arabia	Episode of URI was defined as having 2 of the following symptoms for a day or 1 of the symptoms for 2 or more consecutive days: 1) a runny nose, 2) a stuffy or blocked nose or noisy breathing, 3) sneezing, 4) a cough, 5) a sore throat, and 6) feeling hot, having a fever or a chill.
15.	Arbogast 2016 cluster-RCT USA	ICD-9 used: 46611: acute bronchiolitis due to respiratory syncytial virus, 46619: acute bronchiolitis due to other infectious organisms, 4800: pneumonia due to adenovirus, 4809: viral pneumonia, unspecified, 4870: influenza with pneumonia, 07999: unspecified viral infection, 4658: acute upper respiratory infections of other multiple sites, 4659: acute upper respiratory infections of unspecified site, 4871: influenza with other respiratory manifestations.
16.	Azor-Martinez 2016 RCT Spain	Upper respiratory illness was defined as 2 of the following symptoms during 1 day, or 1 of the symptoms for 2 consecutive days: (1) runny nose; (2) stuffy or blocked nose or noisy breathing; (3) cough; (4) feeling hot or feverish or having chills; (5) sore throat; or (6) sneezing.
17.	Azor-Martinez 2018 RCT Spain	Respiratory illness (RI) was defined as the presence of 2 of the following symptoms during 1 day or the presence of 1 of the symptoms for 2 consecutive days: (1) runny nose, (2) stuffy or blocked nose or noisy breathing, (3) cough, (4) feeling hot or feverish or having chills, (5) sore throat, or (6) sneezing. ICD-10 and ICD-9 diagnosis codes used: nonspecific upper respiratory tract infection (465.9), otitis media (382.9), pharyngotonsillitis (463), lower respiratory tract infections (485 and 486), acute bronchitis (490), and bronchiolitis (466.19). Study authors combined the bronchopneumonia code (485) and pneumonia code (486) under the label "lower respiratory tract infections." If > 1 antibiotic was prescribed during an episode, they used the first prescription for analysis. The final diagnosis was done by the medical researchers on the basis of the symptoms described above and a review of the medical history of children with RIs.
18.	Biswas 2019 cluster-RCT Bangladesh	Influenza-like illness: an ILI episode was defined as measured fever > 38 °C or subjective fever and cough. Laboratory-confirmed influenza Nasal swabs for real-time RT-PCR.
19.	Correa 2012	Acute respiratory infection was defined as 2 or more of the following symptoms for at least 24 hours, lasting at least 2 days: runny, stuffy, or blocked nose or noisy

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Table 9. Trial authors' outcome definitions *(Continued)*

	cluster-RCT Colombia	breathing; cough; fever, hot sensation, or chills; and/or sore throat. Ear pain alone was considered ARI alternately.
20.	Cowling 2009 cluster-RCT Hong Kong	Laboratory-confirmed of influenza virus infection by RT-PCR for influenza A and B virus. Clinical influenza-like illness: used 2 clinical definitions of influenza based on self-reported data from the symptom diaries as secondary analyses. The first definition of clinical influenza was at least 2 of the following signs and symptoms: temperature 37.8 °C or greater, cough, headache, sore throat, and myalgia; the second definition was temperature 37.8 °C or greater plus cough or sore throat.
21.	DiVita 2011 (conference abstract) RCT Bangladesh	Influenza-like illness was defined as fever in children < 5 years old and fever with cough or sore throat in individuals > 5 years old.
22.	Feldman 2016 cluster-RCT Israel	Infectious diseases grouped into diarrhoeal, respiratory, and skin infection. Based on ICD-9, but no supplementary material was accessible for further definition (Supplementary Material C lists all ICD-9 diagnoses tallied in this "outcome").
23.	Gwaltney 1980 RCT USA	Viral cultures and serology if rhinovirus in laboratory-inoculation
24.	Hubner 2010 RCT Germany	Assessing illness rates due to common cold and diarrhoea. Collecting data on illness symptoms (common cold, sinusitis, sore throat, fever, cough, bronchitis, pneumonia, influenza, diarrhoea) and associated absenteeism at the end of every month. Definitions of symptoms were given to the participants as part of the individual information at the beginning of the study. Whilst most symptoms are quite self-explanatory, "influenza" and "pneumonia" are specific diagnoses that were confirmed by professional diagnosis only. Similarly, (self-) diagnosis of "fever" required objective measurement with a thermometer.
25.	Ladegaard 1999 RCT Denmark	Laboratory: serological evidence Effectiveness: influenza-like illness (described as fever, history of fever or feeling feverish in the past week, myalgia, arthralgia, sore throat, cough, sneezing, runny nose, nasal congestion, headache). However, a positive laboratory finding for influenza converts the ILI definition into one of influenza.
26.	Larson 2010 cluster-RCT USA	Study goals: rates of symptoms and secondary transmission of URIs, incidence of virologically confirmed influenza, knowledge of prevention and treatment strategies for influenza and URIs, and rates of influenza vaccination. 1. Laboratory-confirmed influenza: nasal swabs to test for influenza types A and B as well as other common respiratory viruses by rapid culture (R-Mix, Diagnostic Hybrids, Inc., Athens, OH, USA). PCR and subtyping of the samples was done during the second half of the second year of the study. 2. Influenza-like illness: CDC definition of ILI from the Sentinel Physicians' Network was used to determine when masks should be worn: "temperature of ≥37.8°C and cough and/or sore throat in the absence of a known cause other than influenza".

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Table 9. Trial authors' outcome definitions *(Continued)*

		3. Episodes of URI = upper respiratory infection: not clear, no explicitly stated definition, reported that the most commonly reported URI symptoms are cough or rhinorrhoea.
27.	Little 2015 RCT England	Respiratory tract infections defined as 2 symptoms of an RTI for at least 1 day or 1 symptom for 2 consecutive days. For reported ILI, study authors did not use WHO or CDC definitions because these definitions require measured temperature, and thus were not appropriate (participants were not included after a clinical examination), and they did not use the European Centre for Disease Prevention and Control definition (1 systemic and 1 respiratory symptom) because, according to the international influenza collaboration, this definition does not necessarily differentiate ILI from a common cold. Influenzanet suggests making high temperature a separate element. Their pragmatic definition of ILI therefore required a high temperature (feeling very hot or very cold; or measured temperature > 37.5 °C), a respiratory symptom (sore throat, cough, or runny nose), and a systemic symptom (headache, severe fatigue, severe muscle aches, or severe malaise).
28.	Luby 2005 RCT Pakistan	Defined pneumonia in children according to the WHO clinical case definition: cough or difficulty breathing with a raised respiratory rate (> 60 per minute in individuals younger than 60 days old, > 50 per minute for those aged 60 to 364 days, and > 40 per minute for those aged 1 to 5 years)
29.	Millar 2016 cluster-RCT USA	Medically attended, outpatient cases of acute respiratory infection in the study population. The case definition was any occurrence of the following International Classification of Disease, 9 Revision, Clinical Modification (ICD-9) symptom or disease-specific codes: 460-466, 480-488, and specifically 465.9, 482.9, 486, and 487.1. **Acute respiratory infections (460 to 466)** 460 Acute nasopharyngitis (common cold) 461 Acute sinusitis 462 Acute pharyngitis 463 Acute tonsillitis 464 Acute laryngitis and tracheitis 465 Acute upper respiratory infections of multiple or unspecified sites 466 Acute bronchitis and bronchiolitis **Pneumonia and influenza (480 to 488)** 480 Viral pneumonia 481 Pneumococcal pneumonia (*Streptococcus pneumoniae* pneumonia) 482 Other bacterial pneumonia 483 Pneumonia due to other specified organism 484 Pneumonia in infectious diseases classified elsewhere 485 Bronchopneumonia, organism unspecified 486 Pneumonia, organism unspecified 487 Influenza 488 Influenza due to identified avian influenza virus 465.9 Acute upper respiratory infections of unspecified site

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Table 9. Trial authors' outcome definitions *(Continued)*

		482.9 Bacterial pneumonia NOS 487.1 Diagnosis of influenza with other respiratory manifestations
30.	Morton 2004 cluster-RCT Cross-over study USA	Respiratory illnesses defined by symptoms of upper respiratory infections such as nasal congestion, cough, or sore throat, in any combination, with or without fever
31.	Nicholson 2014 cluster-RCT India	Acute respiratory infections Operational definitions for all the illnesses were taken from Black's Medical Dictionary. ARIs defined as "Pneumonia, cough, fever, chest pain and shortness of breath, cold, inflammation of any or all of the airways, that is, nose, sinuses, throat, larynx, trachea and bronchi".
32.	Pandejpong 2012 cluster-RCT Thailand	Influenza-like illness defined if 2 or more symptoms of stuffy nose, cough, fever or chills, sore throat, headache, diarrhoea, presence of hand, foot, or mouth ulcers.
33.	Priest 2014 cluster-RCT New Zealand	Respiratory illness was defined as an episode of illness that included at least 2 of the following caregiver-reported symptoms for 1 day, or 1 of these symptoms for 2 days (but not fever alone): runny nose, stuffy or blocked nose or noisy breathing, cough, fever, sore throat, or sneezing.
34.	Ram 2015 RCT Bangladesh	Influenza-like illness Age-specific definitions of ILI. For individuals ≥ 5 years old, ILI was defined as history of fever with cough or sore throat. For children < 5 years old, ILI was defined as fever; study authors used this relatively liberal case definition in order to include influenza cases with atypical presentations in children. Laboratory-confirmed influenza infection Oropharyngeal swabs from index case patients for laboratory testing for influenza. All swabs were tested by PCR for influenza A and B, with further subtyping of influenza A isolates.
35.	Roberts 2000 cluster-RCT Australia	The symptoms of acute upper respiratory illness elicited from parents were: a runny nose, a blocked nose, and cough. Study authors used a definition of colds based on a community intervention trial of virucidal impregnated tissues. A cold was defined as either 2 symptoms for 1 day or 1 of the respiratory symptoms for at least 2 consecutive days, but not including 2 consecutive days of cough alone. Study authors defined a new episode of a cold as the occurrence of respiratory symptoms after a period of 3 symptom-free days.
36.	Sandora 2005 cluster-RCT USA	The overall rates of secondary respiratory and GI illness. Respiratory illness was defined as 2 of the following symptoms for 1 day or 1 of the symptoms for 2 consecutive days: (1) runny nose; (2) stuffy or blocked nose or noisy breathing; (3) cough; (4) fever, feels hot, or has chills; (5) sore throat; and (6) sneezing. An illness was considered new or separate when a period of at least 2 symptom-free days had elapsed since the previous illness. An illness was defined as a secondary case when it began 2 to 7 days after the onset of the same illness type (respiratory or GI) in another household member.

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Table 9. Trial authors' outcome definitions *(Continued)*

37.	Savolainen-Kopra 2012 cluster-RCT Finland	Nasal and pharyngeal stick samples from participants with respiratory symptoms
38.	Simmerman 2011 cluster-RCT Thailand	Influenza-like illness defined by WHO as fever plus cough or sore throat, based on self-reported symptoms. Laboratory-confirmed secondary influenza virus infections amongst household members described as the secondary attack rate. The secondary influenza virus infection was defined as a positive rRT-PCR result on days 3 or 7 or a four-fold rise in influenza HI antibody titres with the virus type and subtype matching the index case.
39.	Stebbins 2011 cluster-RCT USA	The primary outcome was an absence episode associated with an influenza-like illness that was subsequently laboratory confirmed as influenza A or B. The following CDC definition for ILI was used: fever ≥ 38 °C with sore throat or cough.
40.	Talaat 2011 cluster-RCT Egypt	Nasal swab for QuickVue test for influenza A and B viruses. Influenza-like illness (defined as fever > 38 °C and either cough or sore throat).
41.	Temime 2018 cluster-RCT France	ARIs were defined as the combination of at least 1 respiratory symptom and 1 symptom of systemic infection.
42.	Turner 2004b RCT Canada	Virologic assays
43.	Turner 2012 RCT USA	Laboratory-confirmed rhinovirus infection by PCR assay. Common cold illness was defined as the presence of any of the symptoms of nasal obstruction, rhinorrhoea, sore throat, or cough on at least 3 consecutive days. Illnesses separated by at least 3 symptom-free days were considered as separate illnesses.
44.	Yeung 2011 cluster-RCT Hong Kong	Pneumonia
45.	Zomer 2015 cluster-RCT Netherlands	Incidence of gastrointestinal and respiratory infections in children monitored by parents. The common cold was defined as a blocked or runny nose with at least 1 of the following symptoms: coughing, sneezing, fever, sore throat, or earache.
Hand hygiene and masks (n = 6)		
46.	Aelami 2015 (conference abstract)	Influenza-like illness was defined as the presence of at least 2 of the following during their stay: fever, cough, and sore throat.

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Table 9. Trial authors' outcome definitions *(Continued)*

	RCT Saudi Arabia	Safety: no outcomes on harms planned or reported.
47.	Aiello 2010 cluster-RCT USA	Influenza-like illness case definition (presence of cough and at least 1 constitutional symptom (fever/feverishness, chills, or body aches). Safety: no outcomes on harms planned or reported.
48.	Cowling 2009 cluster-RCT Hong Kong	2 clinical definitions of influenza. First definition was at least 2 of the following signs and symptoms: temperature 37.8 °C or greater, cough, headache, sore throat, and myalgia. The second was temperature 37.8 °C or greater plus cough or sore throat. Safety: no outcomes on harms planned or reported.
49.	Larson 2010 cluster-RCT USA	Study goals: rates of symptoms and secondary transmission of URIs, incidence of virologically confirmed influenza, knowledge of prevention and treatment strategies for influenza and URIs, and rates of influenza vaccination. 1. Laboratory-confirmed influenza: nasal swabs to test for influenza types A and B as well as other common respiratory viruses by rapid culture (R-Mix, Diagnostic Hybrids, Inc., Athens, OH, USA). PCR and subtyping of the samples was done during the second half of the second year of the study. 2. Influenza-like illness: CDC definition of ILI from the Sentinel Physicians' Network was used to determine when masks should be worn: "temperature of ≥37.8°C and cough and/or sore throat in the absence of a known cause other than influenza". 3. Episodes of URI = upper respiratory infection: not clear, no explicitly stated definition, reported that the most commonly reported URI symptoms are cough or rhinorrhoea. Safety: no outcomes on harms planned or reported.
50.	Simmerman 2011 cluster-RCT Thailand	Laboratory-confirmed secondary influenza virus infections amongst household members described as the secondary attack rate. The secondary influenza virus infection was defined as a positive rRT-PCR result on days 3 or 7 or a four-fold rise in influenza HI antibody titres with the virus type and subtype matching the index case. Influenza-like illness defined by WHO as fever plus cough or sore throat, based on self-reported symptoms. Safety: no outcomes on harms planned or reported.
51.	Suess 2012 cluster-RCT Germany	Quantitative RT-PCR for samples of nasal wash. Influenza virus infection as a laboratory-confirmed influenza infection in a household member who developed fever (> 38.0 °C), cough, or sore throat during the observation period. Also secondary outcome measure of the occurrence of ILI as defined by WHO as fever plus cough or sore throat. Safety: the study reported that the majority of participants (107/172, 62%) did not report any problems with mask wearing. This proportion was significantly higher in the group of adults (71/100, 71%) compared to the group of children (36/72, 50%) (P = 0.005). The main problem stated by participants (adults and children) was "heat/humidity" (18/34, 53% of children; 10/29, 35% of adults) (P = 0.1), followed by "pain" and "shortness of breath" when wearing a face mask.
Surface/object disinfection (with or without hand hygiene)(n = 8)		

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Table 9. Trial authors' outcome definitions *(Continued)*

52.	Ban 2015 cluster-RCT China	Acute respiratory illness classified as the appearance of 2 or more of the following symptoms: fever, cough and expectoration, runny nose and nasal congestion.
53.	Carabin 1999 cluster-RCT Canada	The presence of nasal discharge (runny nose) accompanied by 1 or several of the following symptoms: fever, sneezing, cough, sore throat, ear pain, malaise, irritability. A URTI was defined as a cold for 2 consecutive days.
54.	Chard 2019 cluster-RCT Laos	Pupils were considered to have symptoms of respiratory infection if they reported cough, runny nose, stuffy nose, or sore throat.
55.	Ibfelt 2015 cluster-RCT Denmark	Laboratory confirmation of 16 respiratory viruses: influenza A; influenza B; coronavirus NL63229E, OC43 and HKU1; parainfluenza virus 1, 2, 3, and 4; rhinovirus; RSV A/B; adenovirus; enterovirus; parechovirus; and bocavirus using quantitative PCR
56.	Kotch 1994 RCT USA	Respiratory symptoms include coughing, runny nose, wheezing or rattling in the chest, sore throat, or earache.
57.	McConeghy 2017 RCT USA	Classified infections as lower respiratory tract infections (i.e. pneumonia, bronchitis, or chronic obstructive pulmonary disease exacerbation) or other.
58.	Sandora 2008 cluster-RCT USA	RI was defined as an acute illness that included > 1 of the following symptoms: runny nose, stuffy or blocked nose, cough, fever or chills, sore throat, or sneezing.
59.	White 2001 DB-RCT USA	RI was defined as: cough, sneezing, sinus trouble, bronchitis, fever alone, pink-eye, headache, mononucleosis, and acute exacerbation of asthma.
Other (miscellaneous) interventions (n = 4)		
60.	Hartinger 2016 cluster-RCT Peru	ARI was defined as a child presenting cough or difficulty breathing, or both. ALRI was defined as a child presenting cough or difficulty breathing, with a raised respiratory rate > 50 per minute in children aged 6 to 11 months and > 40 per minute in children aged > 12 months on 2 consecutive measurements. An episode was defined as beginning on the first day of cough or difficulty breathing and ending with the last day of the same combination, followed by at least 7 days without those symptoms.
61.	Huda 2012 cluster-RCT Bangladesh	Study authors classified acute respiratory illness as having cough and fever or difficulty breathing and fever within 48 h prior to interview.

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Table 9. Trial authors' outcome definitions *(Continued)*

62.	Najnin 2019 cluster-RCT Bangladesh	Classified participants as having respiratory illness if they reported having fever plus either cough or nasal congestion or fever plus breathing difficult.
63.	Satomura 2005 RCT Japan	Upper respiratory tract infection defined as all of the following conditions: 1. both nasal and pharyngeal symptoms; 2. severity of at least 1 symptom increased by 2 grades or more; and 3. worsening of a symptom of 1 increment or more for > 3 days. Because of the difference in the mode of transmission, study authors excluded influenza-like diseases featured by moderate or severe fever; anti-influenza vaccination in the preseason and arthralgia, and treated them separately. The incidence was determined by 1 study physician who was blinded to group assignment.
Virucidal tissues (n = 2)		
64.	Farr 1988a cluster-RCT USA trial 1 and trial 2	RI defined as: occurrence of at least 2 respiratory symptoms on the same day or the occurrence of a single respiratory symptom on 2 consecutive days (except for sneezing). The respiratory symptoms were as follows: sneezing, nasal congestion, nasal discharge, sore throat, scratchy throat, hoarseness, coughing, malaise, headache, feverishness, chilliness and myalgia.
65.	Longini 1988 DB-PC RCT USA	Respiratory illness defined as 1 or more of the following symptoms occurring during the course of acute episode: coryza, sore throat or hoarseness, earache, cough, pain on respiration, wheezy breathing or phlegm from the chest.

ALRI: acute lower respiratory infection
ARIs: acute respiratory infections
CDC: Centers for Disease Control and Prevention
CI: confidence interval
cluster-RCT: cluster-randomised controlled trial
CRI: clinical respiratory illness
DB-PC: double-blind, placebo-controlled
DB-RCT: double-blind randomised controlled trial
GI: gastrointestinal
HCW: healthcare workers
HI: haemagglutinin
hMPV: human metapneumo virus
ICD-9: International Classification of Disease, 9th Revision, Clinical Modification
ICD-10: International Classification of Disease, 10th Revision, Clinical Modification
ILI: influenza-like illness
NAT: nucleic acid testing
NOS: not otherwise specified
NTS: nasal and throat swab
PCR: polymerase chain reaction
PIV: parainfluenza virus
POCT: point-of-care testing
RCT: randomised controlled trial
RI: respiratory infection
RR: risk ratio
rRT-PCR: real-time reverse transcriptase polymerase chain reaction
RSV: respiratory syncytial virus
RTI: respiratory tract infection
RT-PCR: reverse transcriptase polymerase chain reaction
SAR: secondary attack ratios

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SD: standard deviation
S/S: signs and symptoms
URI: upper respiratory infection
URTI: upper respiratory tract infection
WHO: World Health Organization

APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials (CENTRAL) search string

([mh "Influenza, Human"] OR [mh "Influenzavirus A"] OR [mh "Influenzavirus B"] OR [mh "Influenzavirus C"] OR Influenza:ti,ab OR [mh "Respiratory Tract Diseases"] OR Influenzas:ti,ab OR “Influenza-like”:ti,ab OR ILI:ti,ab OR Flu:ti,ab OR Flus:ti,ab OR [mh ^"Common Cold"] OR "common cold":ti,ab OR colds:ti,ab OR coryza:ti,ab OR [mh coronavirus] OR [mh "sars virus"] OR coronavirus:ti,ab OR Coronaviruses:ti,ab OR [mh "coronavirus infections"] OR [mh "severe acute respiratory syndrome"] OR "severe acute respiratory syndrome":ti,ab OR "severe acute respiratory syndromes":ti,ab OR sars:ti,ab OR [mh "respiratory syncytial viruses"] OR [mh "respiratory syncytial virus, human"] OR [mh "Respiratory Syncytial Virus Infections"] OR "respiratory syncytial virus":ti,ab OR "respiratory syncytial viruses":ti,ab OR rsv:ti,ab OR parainfluenza:ti,ab OR “Respiratory illness”:ti,ab OR ((Transmission) AND (Coughing OR Sneezing)) OR ((respiratory:ti,ab AND Tract) AND (infection:ti,ab OR Infections:ti,ab OR illness:ti,ab)))
AND
([mh "Hand Hygiene"] OR handwashing:ti,ab OR “hand-washing”:ti,ab OR ((Hand:ti,ab OR Alcohol:ti,ab) AND (wash:ti,ab OR Washing:ti,ab OR Cleansing:ti,ab OR Rinses:ti,ab OR hygiene:ti,ab OR rub:ti,ab OR Rubbing:ti,ab OR sanitizer:ti,ab OR sanitiser:ti,ab OR cleanser:ti,ab OR disinfected:ti,ab OR Disinfectant:ti,ab OR Disinfect:ti,ab OR antiseptic:ti,ab OR virucid:ti,ab)) OR [mh "gloves, protective"] OR Glove:ti,ab OR Gloves:ti,ab OR [mh Masks] OR [mh "respiratory protective devices"] OR facemask:ti,ab OR Facemasks:ti,ab OR mask:ti,ab OR Masks:ti,ab OR respirator:ti,ab OR respirators:ti,ab OR [mh ^"Protective Clothing"] OR [mh "Protective Devices"] OR "patient isolation":ti,ab OR ((school:ti,ab OR Schools:ti,ab) AND (Closure:ti,ab OR Closures:ti,ab OR Closed:ti,ab)) OR [mh Quarantine] OR quarantine:ti,ab OR "Hygiene intervention":ti,ab OR [mh Mouthwashes] OR gargling:ti,ab OR "nasal tissues":ti,ab OR [mh "Eye Protective Devices"] OR Glasses:ti,ab OR Goggle:ti,ab OR "Eye protection":ti,ab OR Faceshield:ti,ab OR Faceshields:ti,ab OR Goggles:ti,ab OR "Face shield":ti,ab OR "Face shields":ti,ab OR Visors:ti,ab)
AND
([mh "Communicable Disease Control"] OR [mh "Disease Outbreaks"] OR [mh "Disease Transmission, Infectious"] OR [mh "Infection Control"] OR "Communicable Disease Control":ti,ab OR "Secondary transmission":ti,ab OR ((Reduced:ti,ab OR Reduce:ti,ab OR Reduction:ti,ab OR Reducing:ti,ab OR Lower:ti,ab) AND (Incidence:ti,ab OR Occurrence:ti,ab OR Transmission:ti,ab OR Secondary:ti,ab))

Appendix 2. PubMed search string

("Influenza, Human"[Mesh] OR "Influenzavirus A"[Mesh] OR "Influenzavirus B"[Mesh] OR "Influenzavirus C"[Mesh] OR Influenza[tiab] OR "Respiratory Tract Diseases"[Mesh] OR "Bacterial Infections/transmission"[Mesh] OR Influenzas[tiab] OR “Influenza-like”[tiab] OR ILI[tiab] OR Flu[tiab] OR Flus[tiab] OR "Common Cold"[Mesh:NoExp] OR "common cold"[tiab] OR colds[tiab] OR coryza[tiab] OR coronavirus[Mesh] OR "sars virus"[Mesh] OR coronavirus[tiab] OR Coronaviruses[tiab] OR "coronavirus infections"[Mesh] OR "severe acute respiratory syndrome"[Mesh] OR "severe acute respiratory syndrome"[tiab] OR "severe acute respiratory syndromes"[tiab] OR sars[tiab] OR "respiratory syncytial viruses"[Mesh] OR "respiratory syncytial virus, human"[Mesh] OR "Respiratory Syncytial Virus Infections"[Mesh] OR "respiratory syncytial virus"[tiab] OR "respiratory syncytial viruses"[tiab] OR rsv[tiab] OR parainfluenza[tiab] OR “Respiratory illness”[tiab] OR ((Transmission[tiab]) AND (Coughing[tiab] OR Sneezing[tiab])) OR ((respiratory[tiab] AND Tract[tiab]) AND (infection[tiab] OR Infections[tiab] OR illness[tiab])))
AND
("Hand Hygiene"[Mesh] OR handwashing[tiab] OR hand-washing[tiab] OR ((Hand[tiab] OR Alcohol[tiab]) AND (wash[tiab] OR Washing[tiab] OR Cleansing[tiab] OR Rinses[tiab] OR hygiene[tiab] OR rub[tiab] OR Rubbing[tiab] OR sanitizer[tiab] OR sanitiser[tiab] OR cleanser[tiab] OR disinfected[tiab] OR Disinfectant[tiab] OR Disinfect[tiab] OR antiseptic[tiab] OR virucid[tiab])) OR "gloves, protective"[Mesh] OR Glove[tiab] OR Gloves[tiab] OR Masks[Mesh] OR "respiratory protective devices"[Mesh] OR facemask[tiab] OR Facemasks[tiab] OR mask[tiab] OR Masks[tiab] OR respirator[tiab] OR respirators[tiab] OR "Protective Clothing"[Mesh:NoExp] OR "Protective Devices"[Mesh] OR "patient isolation"[tiab] OR ((school[tiab] OR Schools[tiab]) AND (Closure[tiab] OR Closures[tiab] OR Closed[tiab])) OR Quarantine[Mesh] OR quarantine[tiab] OR “Hygiene intervention”[tiab] OR "Mouthwashes"[Mesh] OR gargling[tiab] OR “nasal tissues”[tiab] OR "Eye Protective Devices"[Mesh] OR Glasses[tiab] OR Goggle[tiab] OR “Eye protection”[tiab] OR Faceshield[tiab] OR Faceshields[tiab] OR Goggles[tiab] OR “Face shield”[tiab] OR “Face shields”[tiab] OR Visors[tiab])
AND
("Communicable Disease Control"[Mesh] OR "Disease Outbreaks"[Mesh] OR "Disease Transmission, Infectious"[Mesh] OR "Infection Control"[Mesh] OR Transmission[sh] OR “Prevention and control”[sh] OR "Communicable Disease Control"[tiab] OR “Secondary transmission”[tiab] OR ((Reduced[tiab] OR Reduce[tiab] OR Reduction[tiab] OR Reducing[tiab] OR Lower[tiab]) AND (Incidence[tiab] OR Occurrence[tiab] OR Transmission[tiab] OR Secondary[tiab])))
AND

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(Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab])
NOT
(Animals[Mesh] not (Animals[Mesh] and Humans[Mesh]))
NOT
("Case Reports"[pt] OR Editorial[pt] OR Letter[pt] OR Meta-Analysis[pt] OR "Observational Study"[pt] OR "Systematic Review"[pt] OR "Case Report"[ti] OR "Case series"[ti] OR Meta-Analysis[ti] OR "Meta Analysis"[ti] OR "Systematic Review"[ti])

Appendix 3. Embase (Elsevier) search string

('influenza'/exp OR Influenza:ti,ab OR 'Respiratory Tract Disease'/exp OR Influenzas:ti,ab OR Influenza-like:ti,ab OR ILI:ti,ab OR Flu:ti,ab OR Flus:ti,ab OR 'Common Cold'/de OR "common cold":ti,ab OR colds:ti,ab OR coryza:ti,ab OR 'coronavirus'/exp OR 'SARS coronavirus'/exp OR coronavirus:ti,ab OR Coronaviruses:ti,ab OR 'coronavirus infection'/exp OR 'severe acute respiratory syndrome'/exp OR "severe acute respiratory syndrome":ti,ab OR "severe acute respiratory syndromes":ti,ab OR sars:ti,ab OR 'Pneumovirus'/exp OR 'Human respiratory syncytial virus'/exp OR "respiratory syncytial virus":ti,ab OR "respiratory syncytial viruses":ti,ab OR rsv:ti,ab OR parainfluenza:ti,ab OR "Respiratory illness":ti,ab OR ((Transmission) AND (Coughing OR Sneezing)) OR ((respiratory:ti,ab AND Tract) AND (infection:ti,ab OR Infections:ti,ab OR illness:ti,ab)))
AND
('hand washing'/exp OR handwashing:ti,ab OR hand-washing:ti,ab OR ((Hand:ti,ab OR Alcohol:ti,ab) AND (wash:ti,ab OR Washing:ti,ab OR Cleansing:ti,ab OR Rinses:ti,ab OR hygiene:ti,ab OR rub:ti,ab OR Rubbing:ti,ab OR sanitizer:ti,ab OR sanitiser:ti,ab OR cleanser:ti,ab OR disinfected:ti,ab OR Disinfectant:ti,ab OR Disinfect:ti,ab OR antiseptic:ti,ab OR virucid:ti,ab)) OR 'protective glove'/exp OR Glove:ti,ab OR Gloves:ti,ab OR 'mask'/exp OR 'gas mask'/exp OR facemask:ti,ab OR Facemasks:ti,ab OR mask:ti,ab OR Masks:ti,ab OR respirator:ti,ab OR respirators:ti,ab OR 'protective clothing'/de OR 'protective equipment'/exp OR "patient isolation":ti,ab OR ((school:ti,ab OR Schools:ti,ab) AND (Closure:ti,ab OR Closures:ti,ab OR Closed:ti,ab)) OR 'Quarantine'/exp OR quarantine:ti,ab OR "Hygiene intervention":ti,ab OR 'mouthwash'/exp OR gargling:ti,ab OR "nasal tissues":ti,ab OR 'eye protective device'/exp OR Glasses:ti,ab OR Goggle:ti,ab OR "Eye protection":ti,ab OR Faceshield:ti,ab OR Faceshields:ti,ab OR Goggles:ti,ab OR "Face shield":ti,ab OR "Face shields":ti,ab OR Visors:ti,ab)
AND
('Communicable Disease Control'/exp OR 'epidemic'/exp OR 'disease transmission'/exp OR 'Infection Control'/exp OR "Communicable Disease Control":ti,ab OR "Secondary transmission":ti,ab OR ((Reduced:ti,ab OR Reduce:ti,ab OR Reduction:ti,ab OR Reducing:ti,ab OR Lower:ti,ab) AND (Incidence:ti,ab OR Occurrence:ti,ab OR Transmission:ti,ab OR Secondary:ti,ab)))
AND
(random* OR factorial OR crossover OR placebo OR blind OR blinded OR assign OR assigned OR allocate OR allocated OR 'crossover procedure'/exp OR 'double-blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single-blind procedure'/exp NOT ('animal'/exp NOT ('animal'/exp AND 'human'/exp)))

Appendix 4. CINAHL (EBSCO) search string

((MH "Influenza, Human+") OR (MH "Orthomyxoviridae+") OR TI Influenza OR AB Influenza OR (MH "Respiratory Tract Diseases+") OR TI Influenzas OR AB Influenzas OR TI Influenza-like OR AB Influenza-like OR TI ILI OR AB ILI OR TI Flu OR AB Flu OR TI Flus OR AB Flus OR (MH "Common Cold+") OR TI "common cold" OR AB "common cold" OR TI colds OR AB colds OR TI coryza OR AB coryza OR (MH "coronavirus+") OR (MH "sars virus+") OR TI coronavirus OR AB coronavirus OR TI Coronaviruses OR AB Coronaviruses OR (MH "coronavirus infections+") OR (MH "severe acute respiratory syndrome+") OR TI "severe acute respiratory syndrome" OR AB "severe acute respiratory syndrome" OR TI "severe acute respiratory syndromes" OR AB "severe acute respiratory syndromes" OR TI sars OR AB sars OR (MH "respiratory syncytial viruses+") OR TI "respiratory syncytial virus" OR AB "respiratory syncytial virus" OR TI "respiratory syncytial viruses" OR AB "respiratory syncytial viruses" OR TI rsv OR AB rsv OR TI parainfluenza OR AB parainfluenza OR TI "Respiratory illness" OR AB "Respiratory illness" OR ((Transmission) AND (Coughing OR Sneezing)) OR ((TI respiratory OR AB respiratory AND Tract) AND (TI infection OR AB infection OR TI Infections OR AB Infections OR TI illness OR AB illness)))
AND
((MH "Handwashing+") OR TI handwashing OR AB handwashing OR TI hand-washing OR AB hand-washing OR ((TI Hand OR AB Hand OR TI Alcohol OR AB Alcohol) AND (TI wash OR AB wash OR TI Washing OR AB Washing OR TI Cleansing OR AB Cleansing OR TI Rinses OR AB Rinses OR TI hygiene OR AB hygiene OR TI rub OR AB rub OR TI Rubbing OR AB Rubbing OR TI sanitizer OR AB sanitiser OR TI sanitizer OR AB sanitiser OR TI cleanser OR AB cleanser OR TI disinfected OR AB disinfected OR TI Disinfectant OR AB Disinfectant OR TI Disinfect OR AB Disinfect OR TI antiseptic OR AB antiseptic OR TI virucid OR AB virucid)) OR (MH "gloves+") OR TI Glove OR AB Glove OR Gloves OR (MH "Masks+") OR (MH "respiratory protective devices+") OR TI facemask OR AB facemask OR TI Facemasks OR AB Facemasks OR TI mask OR AB mask OR TI Masks OR AB Masks OR TI respirator OR AB respirator OR TI respirators OR AB respirators OR (MH "Protective Clothing") OR (MH "Protective Devices+") OR TI "patient isolation" OR AB "patient isolation" OR ((TI school OR AB school OR TI Schools OR AB Schools) AND (TI Closure OR AB Closure OR TI Closures OR AB Closures OR TI Closed OR AB Closed)) OR (MH "Quarantine+") OR TI quarantine OR AB quarantine OR TI "Hygiene intervention" OR AB "Hygiene intervention" OR (MH "Mouthwashes+") OR TI gargling OR AB gargling OR TI "nasal tissues" OR AB "nasal tissues" OR (MH "Eye Protective Devices+") OR TI Glasses OR AB Glasses OR TI Goggle OR AB Goggle OR TI "Eye protection" OR AB "Eye protection" OR TI Faceshield OR AB Faceshield OR TI Faceshields OR AB Faceshields OR TI Goggles OR AB Goggles OR TI "Face shield" OR AB "Face shield" OR TI "Face shields" OR AB "Face shields" OR TI Visors OR AB Visors)
AND

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((MH "Infection Control+") OR (MH "Disease Outbreaks+") OR (MH "Infection Control+") OR TI "Communicable Disease Control" OR AB "Communicable Disease Control" OR TI "Secondary transmission" OR AB "Secondary transmission" OR ((TI Reduced OR AB Reduced OR TI Reduce OR AB Reduce OR TI Reduction OR AB Reduction OR TI Reducing OR AB Reducing OR TI Lower OR AB Lower) AND (TI Incidence OR AB Incidence OR TI Occurrence OR AB Occurrence OR TI Transmission OR AB Transmission OR TI Secondary OR AB Secondary)))
AND
((MH "Clinical Trials+") OR (MH "Quantitative Studies") OR TI placebo* OR AB placebo* OR (MH "Placebos") OR (MH "Random Assignment") OR TI random* OR AB random* OR TI ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*)) OR AB ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*)) OR TI clinic* trial* OR AB clinic* trial* OR PT clinical trial)

Appendix 5. Previous search strategies (pre-2010)

Details of the 2010 update and the search strategy used in the original review and the 2009 search strategy updates for MEDLINE, CENTRAL, EMBASE and CINAHL

In the 2010 update we searched, as we have done previously, the Cochrane Central Register of Controlled Trials (CENTRAL) 2010, Issue 3, which includes the Acute Respiratory Infections Group's Specialised Register, MEDLINE (April 2009 to October week 2, 2010), EMBASE (April 2009 to October 2010) and CINAHL (January 2009 to October 2010). Details of previous searches are in Appendix 1. In addition, to include more of the literature of low-income countries in this update, we ran searches in LILACS (2008 to October 2010), Indian MEDLARS (2008 to October 2010) and IMSEAR (2008 to October 2010).

We used the following search strategy (updated to include new and emerging respiratory viruses) to search MEDLINE and CENTRAL. We combined the MEDLINE search strategy with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Ovid format) (Lefebvre 2011). We also included an additional search strategy based on the work of Fraser, Murray and Burr (Fraser 2006) to identify observational studies.

1 Influenza, Human/
2 exp Influenzavirus A/
3 exp Influenzavirus B/
4 Influenzavirus C/
5 (influenza* or flu).tw.
6 Common Cold/
7 common cold*.tw.
8 Rhinovirus/
9 rhinovir*.tw.
10 adenoviridae/ or mastadenovirus/ or adenoviruses, human/
11 adenoviridae infections/ or adenovirus infections, human/
12 adenovir*.tw.
13 coronavirus/ or coronavirus 229e, human/ or coronavirus oc43, human/ or infectious bronchitis virus/ or sars virus/
14 coronavir*.tw.
15 coronavirus infections/ or severe acute respiratory syndrome/
16 (severe acute respiratory syndrome* or sars).tw.
17 respiratory syncytial viruses/ or respiratory syncytial virus, human/
18 Respiratory Syncytial Virus Infections/
19 (respiratory syncytial virus* or rsv).tw.
20 Pneumovirus Infections/
21 parainfluenza virus 1, human/ or parainfluenza virus 3, human/
22 parainfluenza virus 2, human/ or parainfluenza virus 4, human/
23 (parainfluenza* or para-influenza* or para influenza).tw.
24 enterovirus a, human/ or exp enterovirus b, human/ or enterovirus c, human/ or enterovirus d, human/
25 Enterovirus Infections/
26 enterovir*.tw.
27 Human bocavirus/
28 bocavirus*.tw.
29 Metapneumovirus/
30 metapneumovir*.tw.
31 Parvovirus B19, Human/
32 parvoviridae infections/ or erythema infectiosum/
33 parvovirus*.tw.
34 Parechovirus/
35 parechovirus*.tw.
36 acute respiratory tract infection*.tw.
37 acute respiratory infection*.tw.
38 or/1-37

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39 Handwashing/
40 (handwashing or hand washing or hand-washing).tw.
41 hand hygiene.tw.
42 (sanitizer* or sanitiser*).tw.
43 (cleanser* or disinfectant*).tw.
44 gloves, protective/ or gloves, surgical/
45 glov*.tw.
46 masks/ or respiratory protective devices/
47 (mask or masks or respirator or respirators).tw.
48 Protective Clothing/
49 Protective Devices/
50 Patient Isolators/
51 Patient Isolation/
52 patient isolat*.tw.
53 (barrier* or curtain* or partition*).tw.
54 negative pressure room*.tw.
55 ((reverse barrier or reverse-barrier) adj3 (nurs* or unit or isolation)).tw.
56 Cross Infection/pc [Prevention & Control]
57 (cross infection* adj2 prevent*).tw.
58 Communicable Disease Control/
59 Infection Control/
60 (school* adj3 (clos* or dismissal*)).tw.
61 temporary closur*.tw.
62 mass gathering*.tw.
63 (public adj2 (gathering* or event*)).tw.
64 (bans or banning or banned or ban).tw.
65 (outbreak adj3 control*).tw.
66 distancing*.tw.
67 Quarantine/
68 quarantine*.tw.
69 (protective adj2 (cloth* or garment* or device* or equipment)).tw.
70 ((protective or preventive) adj2 (procedure* or behaviour* or behavior*)).tw.
71 personal protect*.tw.
72 (isolation room* or isolation strateg*).tw.
73 (distance adj2 patient*).tw.
74 ((spatial or patient) adj separation).tw.
75 cohorting.tw.
76 or/39-75
77 38 and 76
78 (animals not (animals and humans)).sh.
79 77 not 78

Ovid MEDLINE

1 Influenza, Human/
2 exp Influenzavirus A/
3 exp Influenzavirus B/
4 Influenzavirus C/
5 (influenza* or flu).tw.
6 Common Cold/
7 common cold*.tw.
8 Rhinovirus/
9 rhinovir*.tw.
10 adenoviridae/ or mastadenovirus/ or adenoviruses, human/
11 adenoviridae infections/ or adenovirus infections, human/
12 adenovir*.tw.
13 coronavirus/ or coronavirus 229e, human/ or coronavirus oc43, human/ or infectious bronchitis virus/ or sars virus/
14 coronavir*.tw.
15 coronavirus infections/ or severe acute respiratory syndrome/
16 (severe acute respiratory syndrome* or sars).tw.
17 respiratory syncytial viruses/ or respiratory syncytial virus, human/
18 Respiratory Syncytial Virus Infections/

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19 (respiratory syncytial virus* or rsv).tw.
20 Pneumovirus Infections/
21 parainfluenza virus 1, human/ or parainfluenza virus 3, human/
22 parainfluenza virus 2, human/ or parainfluenza virus 4, human/
23 (parainfluenza* or para-influenza* or para influenza).tw.
24 enterovirus a, human/ or exp enterovirus b, human/ or enterovirus c, human/ or enterovirus d, human/
25 Enterovirus Infections/
26 enterovir*.tw.
27 Human bocavirus/
28 bocavirus*.tw.
29 Metapneumovirus/
30 metapneumovir*.tw.
31 Parvovirus B19, Human/
32 parvoviridae infections/ or erythema infectiosum/
33 parvovirus*.tw.
34 Parechovirus/
35 parechovirus*.tw.
36 acute respiratory tract infection*.tw.
37 acute respiratory infection*.tw.
38 or/1-37
39 Handwashing/
40 (handwashing or hand washing or hand-washing).tw.
41 hand hygiene.tw.
42 (sanitizer* or sanitiser*).tw.
43 (cleanser* or disinfectant*).tw.
44 gloves, protective/ or gloves, surgical/
45 glov*.tw.
46 masks/ or respiratory protective devices/
47 (mask or masks or respirator or respirators).tw.
48 Protective Clothing/
49 Protective Devices/
50 Patient Isolators/
51 Patient Isolation/
52 patient isolat*.tw.
53 (barrier* or curtain* or partition*).tw.
54 negative pressure room*.tw.
55 ((reverse barrier or reverse-barrier) adj3 (nurs* or unit or isolation)).tw.
56 Cross Infection/pc [Prevention & Control]
57 (cross infection* adj2 prevent*).tw.
58 Communicable Disease Control/
59 Infection Control/
60 (school* adj3 (clos* or dismissal*)).tw.
61 temporary closur*.tw.
62 mass gathering*.tw.
63 (public adj2 (gathering* or event*)).tw.
64 (bans or banning or banned or ban).tw.
65 (outbreak adj3 control*).tw.
66 distancing*.tw.
67 Quarantine/
68 quarantine*.tw.
69 (protective adj2 (cloth* or garment* or device* or equipment)).tw.
70 ((protective or preventive) adj2 (procedure* or behaviour* or behavior*)).tw.
71 personal protect*.tw.
72 (isolation room* or isolation strateg*).tw.
73 (distance adj2 patient*).tw.
74 ((spatial or patient) adj separation).tw.
75 cohorting.tw.
76 or/39-75
77 38 and 76
78 (animals not (animals and humans)).sh.
79 77 not 78

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Embase.com search strategy, October 2010
The search strategy was broadened in 2010 to be more inclusive of new and emerging viruses.

#3 #1 AND #25899
#2 766172
#2.8 #2.3 NOT #2.7766172
#2.7 #2.4 NOT #2.6
#2.6 #2.4 AND #2.5
#2.5 'human'/de AND [embase]/lim
#2.4 'animal'/de OR 'nonhuman'/de OR 'animal experiment'/de AND [embase]/lim
#2.3 #2.1 OR #2.2
#2.2 random*:ab,ti OR placebo*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR allocat*:ab,ti OR trial:ti OR (doubl* NEXT/1 blind*):ab,ti AND [embase]/lim
#2.1 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp AND [embase]/lim

#1 74545
#1.65 #1.28 AND #1.6474545
#1.64 #1.29 OR #1.30 OR #1.31 OR #1.32 OR #1.33 OR #1.34 OR #1.35 OR
#1.36 OR #1.37 OR #1.38 OR #1.39 OR #1.40 OR #1.41 OR #1.42 OR #1.43
OR #1.44 OR #1.45 OR #1.46 OR #1.47 OR #1.48 OR #1.49 OR #1.50 OR
#1.51 OR #1.52 OR #1.53 OR #1.54 OR #1.55 OR #1.56 OR #1.57 OR #1.58
OR #1.59 OR #1.60 OR #1.61 OR #1.62 OR #1.63
#1.63 cohorting:ab,ti OR 'cohort isolation':ab,ti AND [embase]/lim
#1.62 ((spatial OR patient*) NEAR/2 separation):ab,ti AND [embase]/lim
#1.61 (distance NEAR/2 patient*):ab,ti AND [embase]/lim
#1.60 (isolation NEXT/1 (room* OR strateg*)):ab,ti AND [embase]/lim
#1.59 'personal protection':ab,ti AND [embase]/lim
#1.58 ((protective OR preventive) NEAR/2 (procedure* OR behaviour* OR behavior*)):ab,ti AND [embase]/lim
#1.57 (protective NEAR/2 (cloth* OR garment* OR device* OR equipment)):ab,ti AND [embase]/lim
#1.56 quarantin*:ab,ti AND [embase]/lim
#1.55 distancing:ab,ti AND [embase]/lim
#1.54 ((outbreak* OR transmission OR infection*) NEAR/2 control):ab,ti AND [embase]/lim
#1.53 bans:ab,ti OR banning:ab,ti OR banned:ab,ti OR ban:ab,ti AND [embase]/lim
#1.52 (public NEAR/2 (gathering* OR event*)):ab,ti AND [embase]/lim
#1.51 'mass gathering':ab,ti OR 'mass gatherings':ab,ti AND [embase]/lim
#1.50 (temporar* NEAR/2 closur*):ab,ti AND [embase]/lim
#1.49 (school* NEAR/3 (clos* OR dismissal*)):ab,ti AND [embase]/lim
#1.48 'infection control'/de AND [embase]/lim
#1.47 'epidemic'/dm_pc AND [embase]/lim
#1.46 (('cross infection' OR 'cross infections') NEAR/2 prevent*):ab,ti AND [embase]/lim
#1.45 'cross infection'/dm_pc AND [embase]/lim
#1.44 (('reverse barrier' OR 'reverse-barrier') NEAR/3 (nurs* OR unit OR isolat*)):ab,ti AND [embase]/lim
#1.43 'negative pressure room':ab,ti OR 'negative pressure rooms':ab,ti AND [embase]/lim
#1.42 barrier*:ab,ti OR curtain*:ab,ti OR partition*:ab,ti AND [embase]/lim
#1.41 (patient* NEAR/2 isolat*):ab,ti AND [embase]/lim
#1.40 'patient isolator'/de AND [embase]/lim
#1.39 'protective equipment'/de AND [embase]/lim
#1.38 'protective clothing'/de AND [embase]/lim
#1.37 facemask*:ab,ti OR mask:ab,ti OR masks:ab,ti OR goggles:ab,ti
OR respirator*:ab,ti OR respirators:ab,ti AND [embase]/lim
#1.36 'face mask'/exp OR 'mask'/de OR 'surgical mask'/de AND [embase]/lim
#1.35 glov*:ab,ti AND [embase]/lim
#1.34 'surgical glove'/de AND [embase]/lim
#1.33 cleanser*:ab,ti OR disinfect*:ab,ti OR antiseptic*:ab,ti OR virucid*:ab,ti AND [embase]/lim
#1.32 sanitizer*:ab,ti OR sanitiser*:ab,ti AND [embase]/lim
#1.31 (alcohol NEAR/2 rub*):ab,ti AND [embase]/lim
#1.30 handwash*:ab,ti OR (hand* NEAR/2 (wash* OR cleans* OR hygiene)):ab,ti AND [embase]/lim
#1.29 'hand washing'/de AND [embase]/lim
#1.28 #1.1 OR #1.2 OR #1.3 OR #1.4 OR #1.5 OR #1.6 OR #1.7 OR #1.8 OR #1.9 OR #1.10 OR #1.11 OR #1.12 OR #1.13 OR #1.14 OR #1.15 OR
#1.16 OR #1.17 OR #1.18 OR #1.19 OR #1.20 OR #1.21 OR #1.22 OR #1.23
OR #1.24 OR #1.25 OR #1.26 OR #1.27

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#1.27 (respiratory NEAR/2 (infect* OR illness* OR virus* OR pathogen* OR acute)):ab,ti AND [embase]/lim
#1.26 parechovirus*:ab,ti AND [embase]/lim
#1.25 'parechovirus'/de AND [embase]/lim
#1.24 parvovirus*:ab,ti AND [embase]/lim
#1.23 'parvovirus infection'/de OR 'erythema infectiosum'/exp AND [embase]/lim
#1.22 'parvovirus'/de OR 'human parvovirus b19'/de AND [embase]/lim
#1.21 'human metapneumovirus'/de OR 'human metapneumovirus infection'/de AND [embase]/lim
#1.20 'bocavirus'/de OR 'bocavirus infection'/de AND [embase]/lim
#1.19 enterovir*:ab,ti AND [embase]/lim
#1.18 'enterovirus infection'/de OR 'coxsackie virus infection'/de OR 'echovirus infection'/de AND [embase]/lim
#1.17 'enterovirus'/de OR 'coxsackie virus'/exp OR 'echo virus'/de AND [embase]/lim
#1.16 parainfluenza:ab,ti OR 'para influenza':ab,ti OR 'para-influenza':ab,ti AND [embase]/lim
#1.15 'parainfluenza virus'/exp AND [embase]/lim
#1.14 'pneumovirus infection'/de AND [embase]/lim
#1.13 'respiratory syncytial virus':ab,ti OR 'respiratory syncytial viruses':ab,ti OR rsv:ab,ti AND [embase]/lim
#1.12 'respiratory syncytial pneumovirus'/de OR 'respiratory syncytial virus infection'/exp AND [embase]/lim
#1.11 coronavir*:ab,ti OR sars:ab,ti OR 'severe acute respiratory syndrome':ab,ti AND [embase]/lim
#1.10 'coronavirus infection'/de OR 'severe acute respiratory syndrome'/de AND [embase]/lim
#1.9 'coronavirus'/de OR 'human coronavirus nl63'/de OR 'sars coronavirus'/de OR 'transmissible gastroenteritis virus'/de
#1.8 adenovir*:ab,ti AND [embase]/lim
#1.7 'adenovirus infection'/de OR 'human adenovirus infection'/de OR 'human adenovirus'/exp AND [embase]/lim
#1.6 rhinovir*:ab,ti AND [embase]/lim
#1.5 'rhinovirus infection'/de OR 'human rhinovirus'/de AND [embase]/lim
#1.4 'common cold':ab,ti OR 'common colds':ab,ti OR coryza:ab,ti OR colds:ab,ti AND [embase]/lim
#1.3 'common cold'/de OR 'common cold symptom'/de AND [embase]/lim
#1.2 influenza*:ab,ti OR flu:ab,ti AND [embase]/lim
#1.1 'influenza'/exp AND [embase]/lim

CINAHL (EBSCO) search strategy, October 2010
The search strategy was broadened in 2010 to be more inclusive of new and emerging viruses.

S54 S32 and S53
S53 S44 or S52
S52 S45 or S46 or S47 or S48 or S49 or S50 or S51
S51 TI observational stud* or AB observational stud*
S50 TI cohort stud* or AB cohort stud*
S49 (MH "Cross Sectional Studies")
S48 (MH "Nonconcurrent Prospective Studies")
S47 (MH "Correlational Studies")
S46 (MH "Case Control Studies+")
S45 (MH "Prospective Studies")
S44 S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43
S43 TI allocat* N1 random* or AB allocat* N1 random*
S42 (MH "Quantitative Studies")
S41 TI placebo* or AB placebo*
S40 (MH "Placebos")
S39 TI random* allocation* or AB random* allocation*
S38 (MH "Random Assignment")
S37 TI (randomised control* trial* or randomized control* trial*) or AB (randomised control* trial* or randomized control* trial)
S36 TI ((singl* W1 blind*) or (singl* W1 mask*) or (doubl* W1 blind*) or (doubl* W1 mask*) or (trebl* W1 blind*) or (trebl* W1 mask*) or (tripl* W1 blind*) or (tripl* W1 mask*)) or AB ((singl* W1 blind*) or (singl* W1 mask*) or (doubl* W1 blind*) or (doubl* W1 mask*) or (trebl* W1 blind*) or (trebl* W1 mask*) or (tripl* W1 blind*) or (tripl* W1 mask*))
S35 TI clinic* W1 trial* or AB clinic* W1 trial*
S34 PT clinical trial
S33 (MH "Clinical Trials+")
S32 S15 and S31
S31 S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30
S30 TI (bans or banning or banned or ban or "outbreak control" or "outbreak controls" or distancing* or quarantine* or "protective clothing" or "protective garment" or "protective garments" or "protective gown" or "protective gowns" or "protective device" or "protective devices" or "protective equipment" or "protective behaviour" or "protective behavior" or "protective behaviours" or "protective behaviors" or "protective procedure" or "protective procedures" or "preventive behaviours" or "preventive behaviour" or "preventive behavior" or "preventive behaviors" or "preventive procedure" or "preventive procedures" or "personal protective" or

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"isolation room" or "isolation rooms" or "isolation strategy" or "isolation strategies" or "patient distance" or "patient distancing" or "patient separation" or "spatial separation") or AB (handwashing or "hand washing" or hand-washing or "hand hygiene" or sanitizer or sanitiser or cleanser* or disinfectant* or glov* or mask or masks or respirator or respirators or "patient isolation" or "patient isolators" or barrier* or curtain* or partition* or "negative pressure room" or "negative pressure rooms" or "reverse barrier nursing" or "reverse barrier unit" or "reverse barrier isolation" or "cross infection" or "infection control" or "disease control" or "school closure" or "school closures" or "school dismissal" or "school dismissals" or "temporary closure" or "temporary closures" or "mass gathering" or "mass gatherings" or "public gathering" or "public gatherings" or "public event" or "public events")
S29 TI (handwashing or "hand washing" or hand-washing or "hand hygiene" or sanitizer or sanitiser or cleanser* or disinfectant* or glov* or mask or masks or respirator or respirators or "patient isolation" or "patient isolators" or barrier* or curtain* or partition* or "negative pressure room" or "negative pressure rooms" or "reverse barrier nursing" or "reverse barrier unit" or "reverse barrier isolation" or "cross infection" or "infection control" or "disease control" or "school closure" or "school closures" or "school dismissal" or "school dismissals" or "temporary closure" or "temporary closures" or "mass gathering" or "mass gatherings" or "public gathering" or "public gatherings" or "public event" or "public events") or AB (handwashing or "hand washing" or hand-washing or "hand hygiene" or sanitizer or sanitiser or cleanser* or disinfectant* or glov* or mask or masks or respirator or respirators or "patient isolation" or "patient isolators" or barrier* or curtain* or partition* or "negative pressure room" or "negative pressure rooms" or "reverse barrier nursing" or "reverse barrier unit" or "reverse barrier isolation" or "cross infection" or "infection control" or "disease control" or "school closure" or "school closures" or "school dismissal" or "school dismissals" or "temporary closure" or "temporary closures" or "mass gathering" or "mass gatherings" or "public gathering" or "public gatherings" or "public event" or "public events")
S28 (MH "Sterilization and Disinfection")
S27 (MH "Quarantine")
S26 (MH "Area Restriction (Iowa NIC)") OR (MH "Infection Protection (IowaNIC)")
S25 (MH "Infection Control")
S24 (MH "Cross Infection/PC")
S23 (MH "Isolation, Reverse")
S22 (MH "Patient Isolation")
S21 (MH "Protective Devices")
S20 (MH "Protective Clothing")
S19 (MH "Respiratory Protective Devices")
S18 (MH "Masks")
S17 (MH "Gloves")
S16 (MH "Handwashing+")
S15 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14
S14 TI ("acute respiratory tract infection" or "acute respiratory tract infections" or "acute respiratory infection" or "acute respiratory infections") or AB (influenza* or flu or "common cold" or "common colds" or rhinovir* or adenovir* or coronavir* or sars or "severe acute respiratory syndrome" or "respiratory syncytial virus" or "respiratory syncytial viruses" or rsv or pneumovir* or parainfluenza* or "para influenza" or para-influenza or enterovir* or bocavir* or metapneumovir* or parvovir* or parechovir*)
S13 TI (influenza* or flu or "common cold" or "common colds" or rhinovir* or adenovir* or coronavir* or sars or "severe acute respiratory syndrome" or "respiratory syncytial virus" or "respiratory syncytial viruses" or rsv or pneumovir* or parainfluenza* or "para influenza" or para-influenza or enterovir* or bocavir* or metapneumovir* or parvovir* or parechovir*) or AB (influenza* or flu or "common cold" or "common colds" or rhinovir* or adenovir* or coronavir* or sars or "severe acute respiratory syndrome" or "respiratory syncytial virus" or "respiratory syncytial viruses" or rsv or pneumovir* or parainfluenza* or "para influenza" or para-influenza or enterovir* or bocavir* or metapneumovir* or parvovir* or parechovir*)
S12 (MH "Respiratory Tract Infections+")
S11 (MH "Parvovirus Infections+")
S10 (MH "Enterovirus Infections+")
S9 (MH "Enteroviruses+")
S8 (MH "Respiratory Syncytial Virus Infections")
S7 (MH "Respiratory Syncytial Viruses")
S6 (MH "SARS Virus")
S5 (MH "Severe Acute Respiratory Syndrome")
S4 (MH "Coronavirus Infections+")
S3 (MH "Coronavirus+") OR (MH "Coronavirus Infections")
S2 (MH "Common Cold")
S1 (MH "Influenza+") OR (MH "Influenza A H5N1") OR (MH "Influenza A

LILACS (Latin America and Caribbean) search strategy
(mh:"Influenza, Human" OR "Gripe Humana" OR "Influenza Humana" OR influenza* OR flu OR grippe OR gripe OR mh:"Influenzavirus A" OR mh:b04.820.545.405* OR mh:b04.909.777.545.405* OR mh:"Influenzavirus B" OR mh:b04.820.545.407* OR mh:b04.909.777.545.407* OR "influenzavirus B" OR mh:"Influenzavirus C" OR "Influenzavirus C" OR mh:"Common Cold" OR "common cold" OR "common colds" OR "Resfriado Común" OR "Resfriado Comum" OR coryza OR "Coriza Aguda") AND (mh:handwashing OR "Lavado de Manos" OR "Lavagem de Mãos" OR "Desinfección de Manos" OR "Desinfecção de Mãos" OR "Higienização de Mãos Pré-Cirúrgica" OR handwash* OR "hand washing" OR "hand hygiene" OR "hand cleaning" OR "hand cleanse" OR "hand cleansing" OR higiene OR sanitizer* OR

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sanitiser* OR cleanser* OR disinfect* OR esteriliza* OR desinfectar* OR virucid* OR antiseptic* OR mh:"Gloves, Protective" OR "protective glove" OR "protective gloves" OR "Guantes Protectores" OR "Luvas Protetoras" OR mh:e07.700.600.400* OR mh:j01.637.215.600.400* OR mh:j01.637.708.600.400* OR glov* OR guantes OR luvas OR mh:masks OR mask* OR máscaras OR mascarillas OR facemask* OR goggles OR respirator* OR mh:"Respiratory Protective Devices" OR "Dispositivos de Protección Respiratoria" OR "Dispositivos de Proteção Respiratória" OR mh:"Protective Clothing" OR "Ropa de Protección" OR "Roupa de Proteção" OR mh:e07.700.600* OR mh:j01.637.215.600* OR mh:j01.637.708.600* OR mh:"Protective Devices" OR "Equipos de Seguridad" OR "Equipamentos de Proteção" OR mh:e07.700* OR mh:j01.637.708* OR mh:vs2.006.001.001* OR mh:vs4.002.001.001.007.002.002* OR mh:"Patient Isolation" OR "patient isolation" OR "Aislamiento de Pacientes" OR "Isolamento de Pacientes" OR mh:"Patient Isolators" OR "patient isolators" OR "Aisladores de Pacientes" OR "Isoladores de Pacientes" OR barrier* OR curtain* OR partition* OR barrera OR barreira OR cortina OR tabique OR mh:"Cross Infection" OR "cross infection" OR "Infección Hospitalaria" OR "Infecção Hospitalar" OR "Infecciones en Hospitales" OR "Infecciones Nosocomiales" OR "Infecções Nosocomiais" OR mh:"Infection Control" OR mh:n06.850.780.200.450* OR "Control de Infecciones" OR "Controle de Infecções" OR mh:"Communicable Disease Control" OR "Control de Enfermedades Transmisibles" OR "Controle de Doenças Transmissíveis" OR mh:n06.850.780.200* OR mh:sp8.946.819.811* OR mh:"Disease Outbreaks/prevention & control" OR mh:quarantine OR cuarentena OR quarentena OR "personal protection" OR "isolation room" OR "sala de aislamiento" OR "quarto de isolamento" OR "patient distance" OR "distancia del paciente" OR "spatial separation" OR cohort* OR ban OR bans OR banning OR banned OR prohibici* OR proibi* OR "outbreak control" OR distanc* OR "school closure" OR "school closures" OR "temporary closure" OR "temporary closures" OR "cierre de la escuela" OR "fechamento da escola" OR "public gathering" OR "public gatherings" OR "reunion publica" OR "reverse barrier nursing" OR "reverse barrier unit" OR "reverse barrier isolation" OR "negative pressure room" OR "negative pressure rooms" OR "patient separation") AND db:("LILACS") AND type_of_study:("clinical_trials" OR "cohort" OR "case_control")

Indian MEDLARS search strategy
(influenza$ or flu or common cold$ or rhinovir$ or coronavir$ or adenovir$ or severe acute respiratory syndrome$ or sars or respiratory syncytial virus$ or rsv or parainfluenza$ or enterovir$ or metapneumovir$ or parvovir$ or bocavir$ or parechovir$) and (handwashing or hand washing or mask$ or glov$ or protect$ or isolat$ or barrier$ or curtain$ or partition$ or cross infection$ or infection control$ or disease control$ or school$ or quarantine$ or ban$ or cohort$ or distanc$ or spatial separation$)
IMSEAR (Index Medicus for the South East Asia Region) search strategy
(influenza or flu or common cold or rhinovirus or coronavirus or adenovirus or severe acute respiratory syndrome or sars or respiratory syncytial virus or rsv or parainfluenza or enterovirus or bocavirus or metapneumovirus or parvovirus or parechovirus) and (handwashing or hand washing or hand hygiene or sanitizer or sanitiser or cleanser or disinfectant or gloves or masks or mask or protective clothing or protective devices or patient isolation or barrier or curtain or partition or cross infection or disease control or infection control or school or schools or bans or banning or banned or ban or distancing or quarantine or isolation or spatial separation or cohorting or cohort isolation)

In the first publication of this review we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2006, issue 4); MEDLINE (1966 to November 2006); OLDMEDLINE (1950 to 1965); EMBASE (1990 to November 2006) and CINAHL (1982 to November 2006). The MEDLINE search terms were modified for OLDMEDLINE, EMBASE and CINAHL.

In this 2009 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2009, issue 2); Ovid MEDLINE (2006 to May Week 1 2009); OLDMEDLINE (1950 to 1965); Ovid EMBASE (2006 to Week 18, 2009) and Ovid CINAHL (2006 to May Week 1 2009).

Ovid MEDLINE
1 exp Influenza/
2 influenza.tw.
3 flu.tw.
4 exp Common Cold/
5 common cold.tw.
6 exp Rhinovirus/
7 rhinovirus*.tw.
8 exp Adenoviridae/
9 adenovirus*.tw.
10 exp Coronavirus/
11 exp Coronavirus Infections/
12 coronavirus*.tw.
13 exp Respiratory Syncytial Viruses/
14 exp Respiratory Syncytial Virus Infections/
15 respiratory syncytial virus*.tw.
16 respiratory syncythial virus.tw.
17 exp Parainfluenza Virus 1, Human/
18 exp Parainfluenza Virus 2, Human/
19 exp Parainfluenza Virus 3, Human/
20 exp Parainfluenza Virus 4, Human/
21 (parainfluenza or para-influenza or para influenza).tw.
22 exp Severe Acute Respiratory Syndrome/

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23 (severe acute respiratory syndrome or SARS).tw.
24 acute respiratory infection*.tw.
25 acute respiratory tract infection*.tw.
26 or/1-25 (59810)
27 exp Hand Washing/
28 (handwashing or hand washing or hand-washing).tw.
29 hand hygiene.tw.
30 (sanitizer* or sanitiser*).tw.
31 (cleanser* or disinfectant*).tw.
32 exp Gloves, Protective/
33 exp Gloves, Surgical/
34 glov*.tw.
35 exp Masks/
36 mask*1.tw.
37 exp Patient Isolators/
38 exp Patient Isolation/
39 patient isolat*.tw.
40 (barrier* or curtain* or partition*).tw.
41 negative pressure room*.tw.
42 reverse barrier nursing.tw.
43 Cross Infection/pc [Prevention]
44 school closure*.tw.
45 (clos* adj3 school*).tw.
46 mass gathering*.tw.
47 public gathering*.tw.
48 (ban or bans or banned or banning).tw.
49 (outbreak* adj3 control*).tw.
50 distancing.tw.
51 exp Quarantine/
52 quarantine*.tw.
53 or/27-49
54 26 and 53
55 (animals not (humans and animals)).sh.
56 54 not 55

CENTRAL search strategy
#1 MeSH descriptor Influenza, Human explode all trees
#2 influenza:ti,ab,kw
#3 flu:ti,ab,kw
#4 MeSH descriptor Common Cold explode all trees
#5 "common cold":ti,ab,kw
#6 MeSH descriptor Rhinovirus explode all trees
#7 rhinovirus*:ti,ab,kw
#8 MeSH descriptor Adenoviridae explode all trees
#9 adenovirus*:ti,ab,kw
#10 MeSH descriptor Coronavirus explode all trees
#11 MeSH descriptor Coronavirus Infections explode all trees
#12 coronavirus*:ti,ab,kw
#13 MeSH descriptor Respiratory Syncytial Viruses explode all trees
#14 MeSH descriptor Respiratory Syncytial Virus Infections explode all trees
#15 respiratory syncytial virus*:ti,ab,kw
#16 respiratory syncythial virus*:ti,ab,kw
#17 MeSH descriptor Parainfluenza Virus 1, Human explode all trees
#18 MeSH descriptor Parainfluenza Virus 2, Human explode all trees
#19 MeSH descriptor Parainfluenza Virus 3, Human explode all trees
#20 MeSH descriptor Parainfluenza Virus 4, Human explode all trees
#21 (parainfluenza or para-influenza or para influenza):ti,ab,kw
#22 MeSH descriptor Severe Acute Respiratory Syndrome explode all trees
#23 (severe acute respiratory syndrome or SARS):ti,ab,kw
#24 acute respiratory infection*:ti,ab,kw
#25 acute respiratory tract infection*:ti,ab,kw

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#26 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25)
#27 MeSH descriptor Handwashing explode all trees
#28 (handwashing or hand washing or hand-washing):ti,ab,kw
#29 hand hygiene:ti,ab,kw
#30 (sanitizer* or sanitiser*):ti,ab,kw
#31 (cleanser* or disinfectant*):ti,ab,kw
#32 MeSH descriptor Gloves, Protective explode all trees
#33 MeSH descriptor Gloves, Surgical explode all trees
#34 glov*:ti,ab,kw
#35 MeSH descriptor Masks explode all trees
#36 mask*:ti,ab,kw
#37 MeSH descriptor Patient Isolators explode all trees
#38 MeSH descriptor Patient Isolation explode all trees
#39 (barrier* or curtain* or partition*):ti,ab,kw
#40 negative NEXT pressure NEXT room*:ti,ab,kw
#41 "reverse barrier nursing":ti,ab,kw
#42 MeSH descriptor Cross Infection explode all trees with qualifier: PC
#43 school NEXT closure*:ti,ab,kw
#44 (clos* NEAR/3 school*):ti,ab,kw
#45 mass NEXT gathering*:ti,ab,kw
#46 public NEXT gathering*:ti,ab,kw
#47 ("ban" or "bans" or banned or banning):ti,ab,kw
#48 (outbreak* NEAR/3 control*):ti,ab,kw
#49 distancing:ti,ab,kw
#50 MeSH descriptor Quarantine explode all trees
#51 quarantine*:ti,ab,kw
#52 (#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51)
#53 (#26 AND #52)

Ovid EMBASE search strategy
1 exp Influenza/
2 influenza.tw.
3 flu.tw.
4 exp Common Cold/
5 common cold.tw.
6 exp Human Rhinovirus/
7 rhinovirus*.tw.
8 exp Adenovirus/
9 adenovirus*.tw.
10 exp Coronavirus/
11 coronavirus*.tw.
12 exp Respiratory Syncytial Pneumovirus/
13 respiratory syncytial virus*.tw.
14 respiratory syncythial virus.tw.
15 (parainfluenza or para-influenza or para influenza).tw.
16 exp Severe Acute Respiratory Syndrome/
17 (severe acute respiratory syndrome or SARS).tw.
18 acute respiratory infection*.tw.
19 acute respiratory tract infection*.tw.
20 or/1-19
21 exp Hand Washing/
22 (handwashing or hand washing or hand-washing).tw.
23 hand hygiene.tw.
24 (sanitizer$ or sanitiser$).tw.
25 (cleanser$ or disinfectant$).tw.
26 exp Glove/
27 exp Surgical Glove/
28 glov*.tw.
29 exp Mask/
30 mask*1.tw.

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31 patient isolat*.tw.
32 (barrier* or curtain* or partition*).tw.
33 negative pressure room*.tw.
34 reverse barrier nursing.tw.
35 Cross Infection/pc [Prevention]
36 school closure*.tw.
37 (clos* adj3 school*).tw.
38 mass gathering*.tw.
39 public gathering*.tw. (5)
40 (ban or bans or banned or banning).tw.
41 (outbreak* adj3 control*).tw.
42 distancing.tw.
43 quarantine*.tw.
44 or/21-43
45 20 and 44

EBSCO CINAHL search strategy
S26 S10 and S24
S25 S10 and S24
S24 S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or 23 or S24
S23 TI outbreak* N3 control* or AB outbreak* N3 control*
S22 TI (school closure* or mass gathering* or public gathering* or ban or bans or banned or banning or distancing or quarantine*) or AB (school closure* or mass gathering* or public gathering* or ban or bans or banned or banning or distancing or quarantine*)
S21 TI (patient isolat* or barrier* or curtain* or partition* or negative pressure room* or reverse barrier nursing) or AB (patient isolat* or barrier* or curtain* or partition* or negative pressure room* or reverse barrier nursing)
S20 TI (glov* or mask*) or AB (glov* or mask*)
S19 TI (handwashing or hand washing or hand-washing or hand hygiene) or AB (handwashing or hand washing or hand-washing or hand hygiene)
S18 (MH "Quarantine")
S17 (MM "Cross Infection")
S16 (MH "Isolation, Reverse")
S15 (MH "Patient Isolation+")
S14 (MH "Respiratory Protective Devices")
S13 (MH "Masks")
S12 (MH "Gloves")
S11 (MH "Handwashing+")
S10 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9
S9 TI (influenza or flu or rhinovirus* or adenovirus* or coronavirus* or respiratory syncytial virus* or respiratory syncythial virus* or parainfluenza or para-influenza or para influenza or severe acute respiratory syndrome or SARS or respiratory viral infection* or viral respiratory infection*) or AB (influenza or flu or rhinovirus* or adenovirus* or coronavirus* or respiratory syncytial virus* or respiratory syncythial virus* or parainfluenza or para-influenza or para influenza or severe acute respiratory syndrome or SARS or respiratory viral infection* or viral respiratory
infection*)TI (influenza or flu or rhinovirus* or adenovirus* or coronavirus* or respiratory syncytial virus* or respiratory syncythial virus* or parainfluenza or para-influenza or para influenza or severe acute respiratory (syndrome or SARS or respiratory viral infection* or viral respiratory infection*) or AB (influenza or flu or rhinovirus* or adenovirus* or coronavirus* or respiratory syncytial virus* or respiratory syncythial virus* or parainfluenza or para-influenza or para influenza or severe acute respiratory syndrome or SARS or respiratory viral infection* or viral
respiratory infection*)
S8 (MH "SARS Virus")
S7 (MH "Severe Acute Respiratory Syndrome")
S6 (MH "Respiratory Syncytial Virus Infections")
S5 (MH "Respiratory Syncytial Viruses")
S4 (MH "Coronavirus+")
S3 (MH "Coronavirus Infections+")
S2 (MH "Common Cold")
S1 (MH "Influenza+")

WHAT'S NEW

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Date	Event	Description
1 April 2020	New citation required and conclusions have changed	There is now sufficient randomised controlled trial (RCT) evidence to show that hand hygiene is likely to provide a modest- benefit. Uncertainty remains for the other interventions. Further RCT evidence is needed.
1 April 2020	New search has been performed	Searches updated. In this 2020 update we only searched for RCTs and cluster-RCTs. We included 44 new trials (Aelami 2015; Aiello 2012; Alzaher 2018; Arbogast 2016; Azor-Martinez 2016; Azor-Martinez 2018; Ban 2015; Barasheed 2014; Biswas 2019; Canini 2010; Chard 2019; Correa 2012; DiVita 2011; Feldman 2016; Goodall 2014; Hartinger 2016; Hubner 2010; Huda 2012; Ibfelt 2015; Ide 2014; Ide 2016; Little 2015; MacIntyre 2011; MacIntyre 2013; MacIntyre 2015; MacIntyre 2016; McConeghy 2017; Millar 2016; Miyaki 2011; Najnin 2019; Nicholson 2014; Pandejpong 2012; Priest 2014; Radonovich 2019; Ram 2015; Savolainen-Kopra 2012; Simmerman 2011; Stebbins 2011; Suess 2012; Talaat 2011; Temime 2018; Turner 2012; Yeung 2011; Zomer 2015). We excluded 12 new trials (Azor-Martinez 2014; Bowen 2007; Chami 2012; Denbak 2018; Lennell 2008; Nandrup-Bus 2009; Patel 2012; Rosen 2006; Slayton 2016; Stedman-Smith 2015; Uhari 1999; Vessey 2007). We identified 5 new ongoing trials (NCT03454009; NCT04267952; NCT04296643; NCT04337541; Wang 2015) one of which – NCT04337541 - published as this review was going to press. We focused on RCTs and cluster-RCTs only and removed observational studies from this update.

HISTORY

Protocol first published: Issue 4, 2006
Review first published: Issue 4, 2007

Date	Event	Description
22 October 2010	New search has been performed	Searches conducted. We included 7 new trials: 4 randomised controlled trials and 3 non-randomised comparative studies. We excluded 36 new trials.
22 October 2010	New citation required but conclusions have not changed	We updated the review again at the behest of the World Health Organization (WHO). External sources of support amended. External support from the WHO. The WHO interim guidelines document on 'Infection Prevention and Control of Epidemic and Pandemic Prone Acute Respiratory Diseases in Health Care' was published in 2007 to provide infection control guidance to help prevent the transmission of acute respiratory diseases in health care. The update of these guidelines will be evidence-based, and an update of this review was requested to assist in informing the evidence base for the revision of the WHO guidelines. Dr John Conly, Dr Mark Jones, and Sarah Thorning joined the review team.
7 May 2009	New search has been performed	For the 2009 update, we included 3 cluster-randomised controlled trials, Cowling 2009; MacIntyre 2009; Sandora 2008, and 1

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Date	Event	Description
		individual randomised controlled trial (Satomura 2005, with its linked publication Kitamura 2007). We also included 1 retrospective cohort study (Foo 2006), 1 case-control study (Yu 2007), and 2 prospective cohort studies (Wang 2007; Broderick 2008). The content and conclusions of the 2007 review changed little, but the additional 8 studies add more information and certainty. Our meta-analysis remains unchanged as there were no new studies for pooling.
30 April 2009	New citation required but conclusions have not changed	New author joined the review team.
8 July 2008	Amended	Converted to new review format.
20 August 2007	Amended	Review first published Issue 4, 2007.

CONTRIBUTIONS OF AUTHORS

Tom Jefferson (TOJ), Chris Del Mar (CDM), and Liz Dooley (LD) were responsible for drafting the protocol.
TOJ, Eliana Ferroni (EF), Bill Hewak (BH), and Adi Prabhala (AP) extracted study data, and Sree Nair (SN) performed the analyses in the original review.

TOJ, EF, Lubna A Al-Ansary (LA), Ghada A Bawazeer (GB), and CDM adjudicated in data extraction in the 2009 update. Mieke van Driel (MvD) assisted in writing the review, updating with the most recent studies, and additional tables (apart from TiDIER). MvD constructed the summary of results table which was removed in the 2020 review update.

TOJ and John Conly (JMC) extracted data, and CDM checked extractions and arbitrated in the 2010 update. All three review authors checked the search strategy terms. Sarah Thorning (ST) designed and carried out the searches. All 2010 review authors contributed to the final report.

For the 2020 update:
Updated searches: ST
Co-ordinated the update: LD
Updated Background section: CDM
Designed Excel forms for extracting study characteristics and tested their usefulness/applicability: MJ
Screened titles and abstracts, excluded irrelevant citations: MJ
Excluded irrelevant citations based on title and text in the trial registry entry: ST
Excluded irrelevant citations based on titles/abstracts and the full-text articles: GB
Selection of studies: MvD, MJ, GB, JC
Data extraction and management: MJ, EF, LA, GB, TOJ, TH, EB
Assessment of risk of bias in the included studies: TOJ, EB, LA, GB, MJ, EF
Adjudicated data extraction: MJ
Data analysis: MJ, EB
Wrote the update: MJ, TOJ, LD, LA, JMC, EB, MVD, GB, TH, CDM, PG

DECLARATIONS OF INTEREST

Tom Jefferson: Tom Jefferson's full disclosure is available at restoringtrials.org/competing-interests-tom-jefferson/.
Chris B Del Mar: a grant from WHO paid to Bond University and a grant from UK National Institute for Health Research (NIHR) to be paid to Bond University on publication of the review in the Cochrane Library. Funding from National Health and Medical Research Council (NHMRC) for research on antibiotic resistance.
Liz Dooley: a grant from the World Health Organization (WHO) paid to Bond University and a grant from UK NIHR to be paid to Bond University on publication of the review in the Cochrane Library.
Eliana Ferroni: none known.
Lubna A Al-Ansary: none known.
Ghada A Bawazeer: none known.

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Mieke L van Driel: Dr van Driel has acted as a consultant for Therapeutic Guidelines Ltd and NPS Medicinewise, for which fees have been paid to her institution.
Mark A Jones: a grant from WHO paid to Bond University and a grant from UK NIHR to be paid to Bond University on publication of the review in the Cochrane Library.
Sarah Thorning: none known.
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Justin Clark: none known.
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Paul Glasziou: none known.
John M Conly: John Conly holds grants from the Canadian Institutes for Health Research on acute and primary care preparedness for COVID-19 in Alberta, Canada and was the primary local Investigator for a *Staphylococcus aureus* vaccine study funded by Pfizer for which all funding was provided only to the University of Calgary. He also received support from the Centers for Disease Control and Prevention (CDC) to attend an Infection Control Think Tank Meeting.

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- Sabbatical year (2010 to 2011) for John Conly while at the World Health Organization in Geneva, Switzerland was supported by the University of Calgary, Calgary, Canada

  2020/1011941
- World Health Organization, Geneva, Switzerland

  Requested and provided support to The Cochrane Collaboration for the 2011 update
- National Institute of Health Research (NIHR), UK

  This study/project is funded by the NIHR Incentive Scheme Award Reference 130721. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.
- World Health Organization, Geneva, Switzerland

  Provided financial support for the 2020 update of this review. Reference number 2020/1011941

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the title of the review in 2010 (see Published notes below).

For this 2020 update, we added one additional outcome: adverse events related to the intervention, and we split the outcomes into primary and secondary outcomes. We also focused only on RCTs and cluster-RCTs and removed observational studies.

NOTES

In Issue 1, 2010, the title of the review was changed from 'Interventions for the interruption or reduction of the spread of respiratory viruses' to 'Physical interventions to interrupt or reduce the spread of respiratory viruses'.

The original review was subsequently published as Jefferson T, Foxlee R, Del Mar C, Dooley L, Ferroni E, Hewak B, Prabhala A, Nair S, Rivetti A. Physical interventions to interrupt or reduce the spread of respiratory viruses: systematic review. BMJ 2008;336:77-80 and Jefferson T, Del Mar C, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, van Driel ML, Foxlee R, Rivetti A. Physical interventions to interrupt or reduce the spread of respiratory viruses: systematic review. BMJ 2009;339:b3675. DOI: 10.1136/bmj.b3675.

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INDEX TERMS

Medical Subject Headings (MeSH)

Case-Control Studies; Influenza, Human [transmission] [virology]; Randomized Controlled Trials as Topic; Respiratory Tract Infections [*prevention & control] [transmission] [virology]; Virus Diseases [*prevention & control] [transmission]; *Virus Shedding

MeSH check words

Humans

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CANADA COVID-19 WEEKLY EPIDEMIOLOGY REPORT

28 MARCH TO 03 APRIL 2021 (WEEK 13)

Published: 09 April 2021

39 639 (↑28%) New cases reported in the last 7 days[a]	**195 (↓8%)** New deaths reported in the last 7 days[a]
5 663 (↑28%) Average number of cases reported daily in the last 7 days[a]	**28 (↓8%)** Average number of deaths reported daily in the last 7 days[a]
115 653 (↑6%) Average number of tests performed daily in the last 7 days[b]	**5.1% (↑0.8)** Percentage of positive tests in the last 7 days[b]

[a]Source: Provincial and Territorial Ministry of Health (MOH) websites as of 03 April 2021

[b]Source: National Microbiology Laboratory (NML) data for laboratory analyses as of 03 April 2021

Note: The percentages are calculated based on the difference in the total number of cases, deaths, or tests in the past 7 days compared to the prior 7 days, divided by the number of cases, deaths, or tests in the prior 7 days. The change in the percentage of positive tests is based on the difference in percentage points compared to the previous week.

KEY MESSAGES

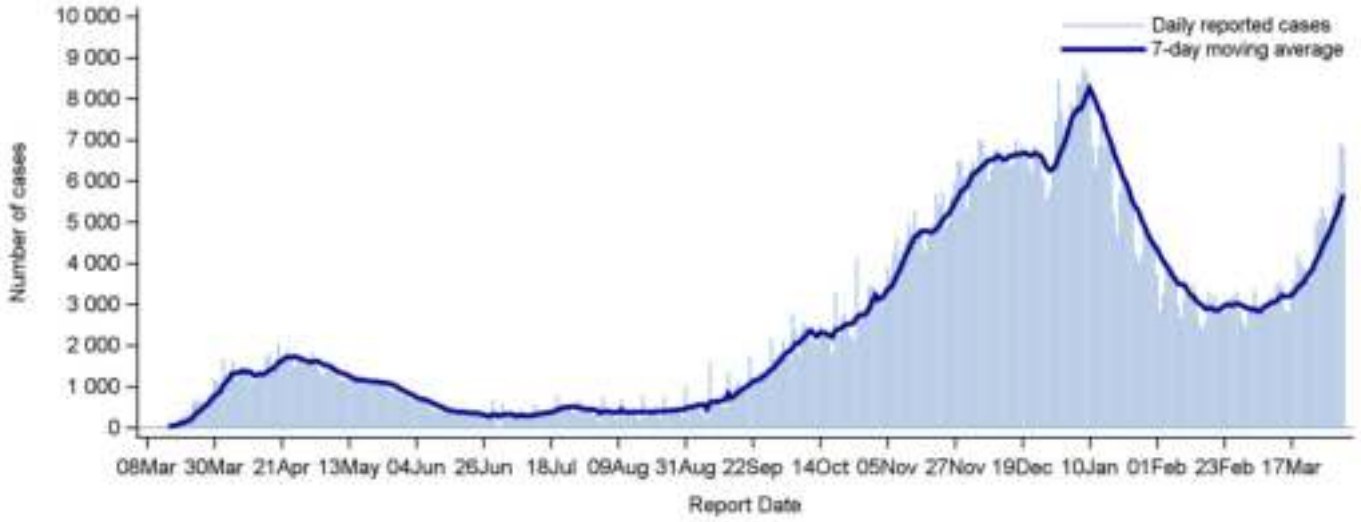
- In Canada, there was an average of **5 663 new cases reported daily** during the week of 28 March to 03 April (week 13), representing a **28% increase** compared to the previous week (week 12: 21 March to 27 March).
- British Columbia, Alberta, Saskatchewan, Ontario, Québec and Newfoundland and Labrador reported **increases in weekly numbers**, compared to the previous week.
- **Daily rates of cases per 100 000 population have increased among most age groups during the past week**. Among both males and females, case rates remain highest among individuals in the 20 to 39 year age group and lowest among individuals in the 80 years and older age group.
- **Long-term care facilities and retirement residences** continue to be the most commonly reported outbreak setting in Canada, and account for the greatest proportion of outbreak related cases and deaths.
- During week 13, **an average of 115 653 tests were performed daily** for COVID-19 across Canada. The weekly percentage of tests positive was **5.1%**, an increase from the previous week.
- There was an average of **28 new deaths reported daily** during week 13, representing an **8% decrease** compared to the previous week.
- **The number of hospitalizations and ICU admissions increased during week 13**. On 03 April 2021, there were 2 250 cases hospitalized and 801 cases in ICU, representing a 5% increase in the seven-day moving average of hospitalized cases and a 16% increase in the seven-day moving average of ICU admissions compared to one week prior.
- The overall cumulative hospitalization rate (including ICU admissions) is 139 cases per 100 000 population, with **the highest rates observed among those aged 80 years and older** (1 013 cases per 100 000 population).
- According to forecasting, between **1 093 510 to 1 150 910 cumulative reported cases** and **23 290 to 23 710 cumulative reported deaths** are expected by 18 April 2021.

NATIONAL DEMOGRAPHICS AND TRENDS

NATIONAL TRENDS IN CASES

- During week 13, a total of 39 639 cases of COVID-19 were reported in Canada, an average of 5 663 cases per day.
- The number of new cases represents a 28% increase compared to week 12.
- Since early March 2021, the number of new cases reported has consistently increased, with 6 822 new cases reported on 03 April 2021 (Figure 1).

Figure 1. Daily number of reported COVID-19 cases in Canada (and 7-day moving average), as of 03 April 2021 (N= 1 001 658)



Source: Provincial and Territorial MOH websites as of 03 April 2021

Note: The 7-day moving average is a trend indicator that captures the arithmetic mean of the daily reported cases over the previous seven days. The moving average helps smooth out day-to-day variability in reporting, filtering out the "noise" of short-term fluctuations. Fluctuations can be attributed to retrospective data, non-reporting on the weekends or provinces or territories reporting cases at a reduced frequency. Spikes in cases may be due to regular reporting variations (e.g. lower reporting on weekends or holidays), or periodic reporting of previous cases by provinces and territories.

Most provinces and territories, with the exception of Northwest Territories and Nunavut, reported new cases during week 13 (Table 1):

- The weekly number of new cases decreased in Manitoba, New Brunswick, Nova Scotia and Prince Edward Island, compared to the previous week. No change was observed in Yukon.
- The weekly number of new cases increased in British Columbia, Alberta, Saskatchewan, Ontario, Québec and Newfoundland and Labrador, compared to the previous week.
- Cases increased by 31% in Ontario and 33% in Québec, compared to the previous week. Together, these provinces accounted for about 64% of the cases reported during week 13.
- Cumulatively, Ontario reported the highest number of cases (n=358 558), while Québec has the highest incidence rate at 3 673.2 cases per 100 000 population.

Table 1. Trends of new cases in Canada and by province or territory, as of 03 April 2021

Province/Territory	Total number of cases (as of 03 April)[a]	Average number of cases reported daily (week 13)	Weekly number of cases reported		Percent change (%)[b]	Crude rate per 100 000 population (as of 03 April)
			21 March to 27 March (week 12)	28 March to 03 April (week 13)		
British Columbia	103 031	917	5 271	6 418	22%	2 001.5
Alberta	151 359	809	4 317	5 663	31%	3 423.0
Saskatchewan	34 323	220	1 324	1 540	16%	2 912.0
Manitoba	34 352	69	604	485	-20%	2 490.6
Ontario	358 558	2 552	13 609	17 866	31%	2 433.5
Québec	314 958	1 081	5 703	7 564	33%	3 673.2
Newfoundland and Labrador	1 020	1	1	5	400%	195.4
New Brunswick	1 641	10	82	70	-15%	210.0
Nova Scotia	1 732	3	27	23	-15%	176.9
Prince Edward Island	160	1	8	4	-50%	100.2
Yukon	74	0	1	1	0%	176.0
Northwest Territories	42	0	0	0	N/A	93.0
Nunavut	395	0	0	0	N/A	1 003.7
Canada[c]	**1 001 658**	**5 663**	**30 947**	**39 639**	**28%**	**2 635.5**

Source: Provincial and Territorial MOH websites as of 03 April 2021

[a] The number of cases includes the total confirmed and probable cases.

[b] The percentage is calculated based on the difference in the total number of cases in the past 7 days compared to the prior 7 days divided by the number of cases in the prior 7 days. Note that for provinces/territories with low case counts, an increase or decrease of only a few cases leads to a large percentage change. If the denominator is zero, the percent change cannot be calculated.

[c] Includes 13 cases identified in repatriated travelers (Grand Princess Cruise ship travelers) who were under quarantine in Trenton in March 2020.

Age-standardized rates take into account the differences in population size and age structure between provinces and territories to allow for more valid comparisons of COVID-19 spread in Canada.

Table 2 presents the age-standardized incidence rate by province or territory during week 13.

- Saskatchewan reported the highest age-standardized incidence rate (127.4 cases per 100 000 population).
- The second and third-highest age-standardized incidence rates were reported by Ontario (126.3 cases per 100 000 population) and British Columbia (125.2 cases per 100 000 population).

Table 2. Age-standardized incidence rates by province or territory for week 13

Province/Territory	Age-standardized incidence rate per 100 000 for week 13
British Columbia	125.2
Alberta	64.8
Saskatchewan	127.4
Manitoba	25.6
Ontario	126.3
Québec	75.1
Newfoundland and Labrador	N/A*
New Brunswick	N/A*
Nova Scotia	2.5
Prince Edward Island	3.8
Yukon	4.5
Northwest Territories	0.0
Nunavut	0.0
Canada	95.7**

Source: Detailed case information received by PHAC from provinces and territories, standardized to the July 1 2020 post-census population estimate.
*Age-standardized incidence could not be calculated as data was either not reported or partially reported to PHAC during week 13.
**The age-standardized incidence rate for Canada only includes provinces and territories for which data was available for week 13.
Note: Data are analyzed based on PHAC report date.

Table 3 outlines the total number of new cases, resolved cases, and deaths reported during week 13.

- Of the provinces and territories that reported new cases during week 13, all reported more new cases than new resolved cases.

Table 3. Summary of new COVID-19 cases, resolved cases, and deaths reported in Canada, and by province or territory, during week 13

Province/Territory	New cases	New resolved cases	New deaths
British Columbia	6 418	3 866	11
Alberta	5 663	2 210	14
Saskatchewan	1 540	1 208	6
Manitoba	485	418	5
Ontario	17 866	12 075	120
Québec	7 564	5 428	39
Newfoundland and Labrador	5	2	0
New Brunswick	70	27	0
Nova Scotia	23	16	0
Prince Edward Island	4	3	0
Yukon	1	0	0
Northwest Territories	0	0	0
Nunavut	0	0	0
Canada	**39 639**	**25 253**	**195**

Source: Provincial and Territorial MOH websites as of 03 April 2021

DEMOGRAPHIC DISTRIBUTION[a]

[a] Detailed case information received by PHAC from provinces and territories
Note: Data are analyzed based on PHAC report date.

- Cases for which PHAC received detailed individual case-level information during week 13 (n=34 754) ranged in age from less than one year to 102 years of age. The median age was 34 years, no change from what was observed during week 12.
- Table 4 presents a summary of the age and gender distribution of COVID-19 cases reported to PHAC during week 13:
    - Fifty-nine percent (59%) were individuals under 40 years of age.
    - The highest proportions of cases by age group were observed among those aged 0-19 years (22%) and 20-29 years (20%).
    - The highest age specific incidence rates were observed among those 20-29 and 30-39 years of age.

Table 4. Age, gender distribution, and rate of COVID-19 cases reported to PHAC, during week 13

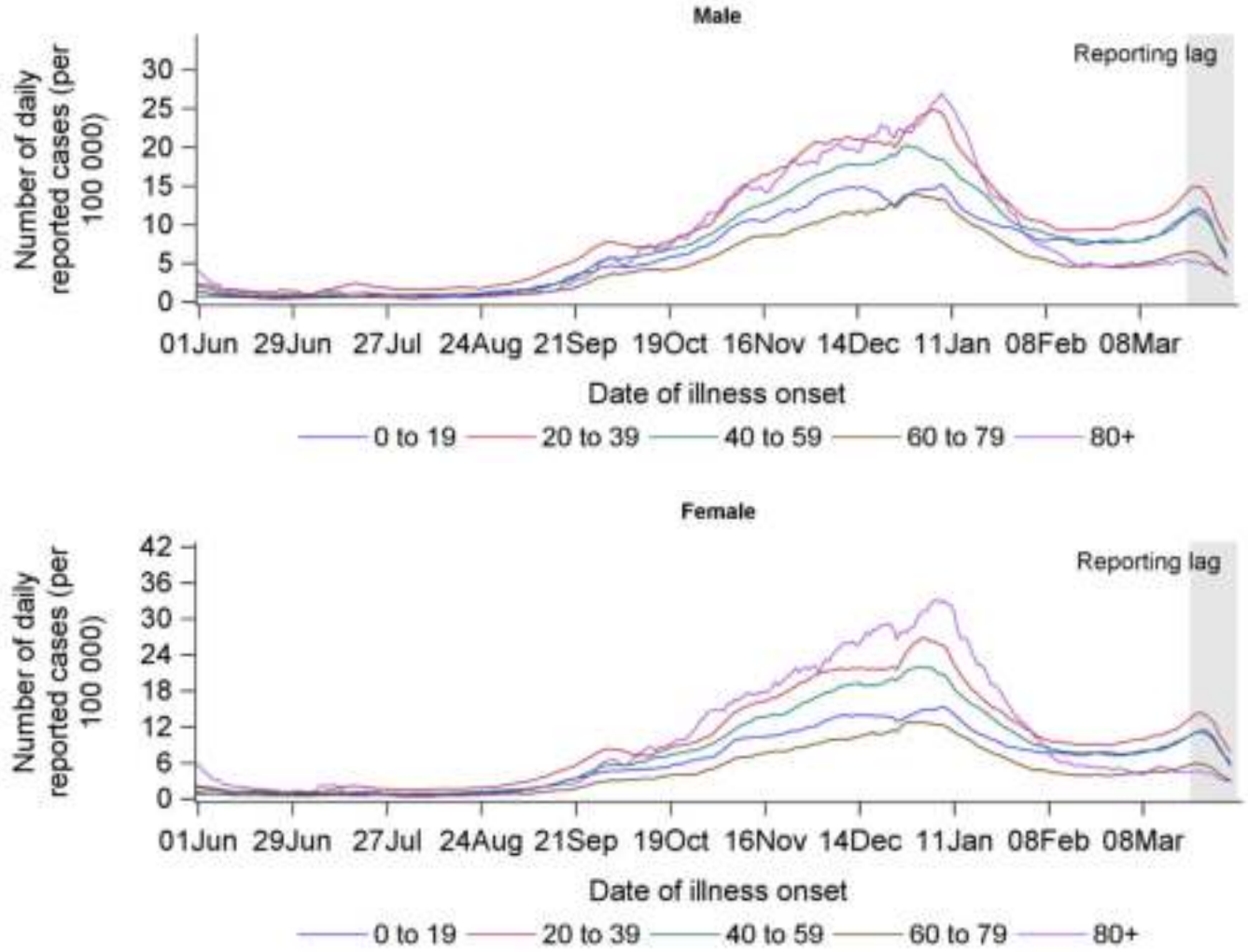
Age groups	Female			Male			Total[a]		
	n	%	Rate	n	%	Rate	n	%	Rate
≤ 19	3 945	22%	99.2	4 100	22%	98.5	8 045	22%	98.8
20-29	3 418	19%	138.6	3 644	20%	136.9	7 062	20%	137.7
30-39	2 893	16%	110.2	3 099	17%	116.2	5 992	17%	113.2
40-49	2 662	15%	108.7	2 659	14%	110.6	5 321	15%	109.6
50-59	2 289	13%	87.6	2 421	13%	93.7	4 710	13%	90.7
60-69	1 374	8%	56.9	1 538	8%	66.6	2 912	8%	61.6
70-79	679	4%	42.9	630	3%	44.2	1 309	4%	43.6
80+	396	2%	40.0	320	2%	47.5	716	2%	43.0
Total	17 656	100%	92.3	18 411	100%	97.5	36 067	100%	94.9

Source: Detailed case information received by PHAC from provinces and territories during week 13. Rates are presented per 100 000 individuals in the given age group based on the 1 July 2020 post-census population estimate.
[a] Cases not identified as male or female were removed from the total due to small numbers.
Note: Data are analyzed based on date reported to PHAC. Note that there is a period of time (lag time) where it is expected that cases have occurred but have not yet been reported nationally. Therefore, COVID-19 cases reported to PHAC during week 13 may include cases that occurred (based on date of illness onset, or lab related dates) in previous weeks.
Note: Cases with missing gender or age were excluded. Where available, gender data was used; when gender data was unavailable, sex data was used. Reliable data on gender diverse respondents are unavailable due to small counts.

Figure 2 presents cases by date of illness onset, stratified by gender and adjusted for population at the national level.

- Daily rates of cases have increased for most age groups in recent weeks; this follows the large decline observed since early January 2021.
- Daily rates of cases continue to remain highest among individuals in the 20 to 39 year age group for males and females. This age group has consistently been the highest since 20 January 2021 for males and 03 February 2021 for females.
- Daily rates of cases are lowest among individuals in the 80 years and older age group for both genders. The incidence rates for this age group are 1.9 times lower for males and 2.2 times lower for females compared to the 20 to 39 year age group.

Figure 2. Daily rate of cases per 100 000 population, by age and gender, from 1 June 2020 to 03 April 2021



Source: Detailed case information received by PHAC from provinces and territories. Rates are calculated based on the 1 July 2020 post-census population estimate.

Note: The shaded area represents a period of time (lag time) where it is expected that cases have occurred but have not yet been reported nationally. The earliest of the following dates were used as an estimate: Onset date, Specimen Collection Date, Laboratory Testing Date, Date Reported to Province or Territory, or Date Reported to PHAC.

Note: Where available, gender data was used; when gender data was unavailable, sex data was used. Reliable data on gender diverse respondents are unavailable due to small counts.

SYNDROMIC SURVEILLANCE

FLUWATCHERS

FluWatchers is an online health surveillance system that relies on volunteer reports to track the spread of Influenza-like illness (ILI) and symptoms compatible with COVID-19 across Canada. Some of the more commonly reported symptoms of COVID-19 include a new or worsening cough, fever or feeling feverish; therefore, reports of a minimum of cough or fever are being used to track COVID-19 within the FluWatchers system.

During week 13, 12 081 participants reported into the FluWatchers system. A total of 194 participants (1.6%) reported symptoms of cough or fever.

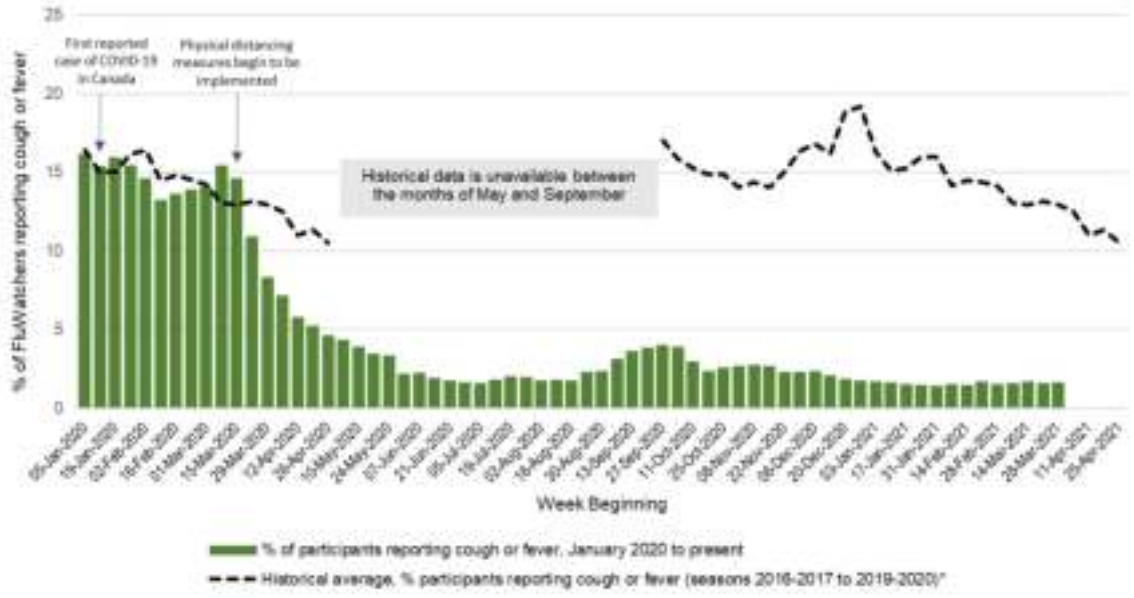
From mid-December 2020 to late-January 2021, FluWatchers activity was on a slow decline, despite increasing COVID-19 activity at the time. In recent weeks, activity due to seasonal respiratory viruses has been low and stable, COVID-19 activity has begun to increase and FluWatchers activity has slightly increased as well. Symptoms reports by FluWatchers participants remain below seasonal norms for this time of year.

Among the 194 participants reporting cough or fever:

- 88 (45%) sought medical attention;
- 76 (39%) were tested - 4 tests were positive for COVID-19 (8 tests had unknown results at the time of reporting)

Syndromic data captured by FluWatchers is sensitive to all circulating respiratory viruses, including COVID-19. The FluWatchers program is measuring total respiratory virus activity in the community. FluWatchers participants are a self-selected subset of the Canadian population that may not be representative of the Canadian population; thus, under representing the true measure of COVID activity in the population.

Figure 3. Percentage of FluWatchers Participants Reporting Cough or Fever (N=12 081 during week 13)



*Historical data is unavailable between the months of May and September. From January 2020 to May 2020, the historical epidemiological curve contains data from seasons 2016-2017 to 2018-2019. From October 2020 onwards, the historical epidemiological curve contains data from seasons 2016-2017 to 2019-2020; however, data from March 8, 2020 to May 2, 2020 are excluded from the historical epidemiological curve.

TRANSMISSION

TEMPORAL DISTRIBUTION BY EXPOSURE CATEGORY[a]

[a] Detailed case information received by PHAC from provinces and territories

During week 13, exposure and date of illness onset information was available for 20 329 cases. Of these:

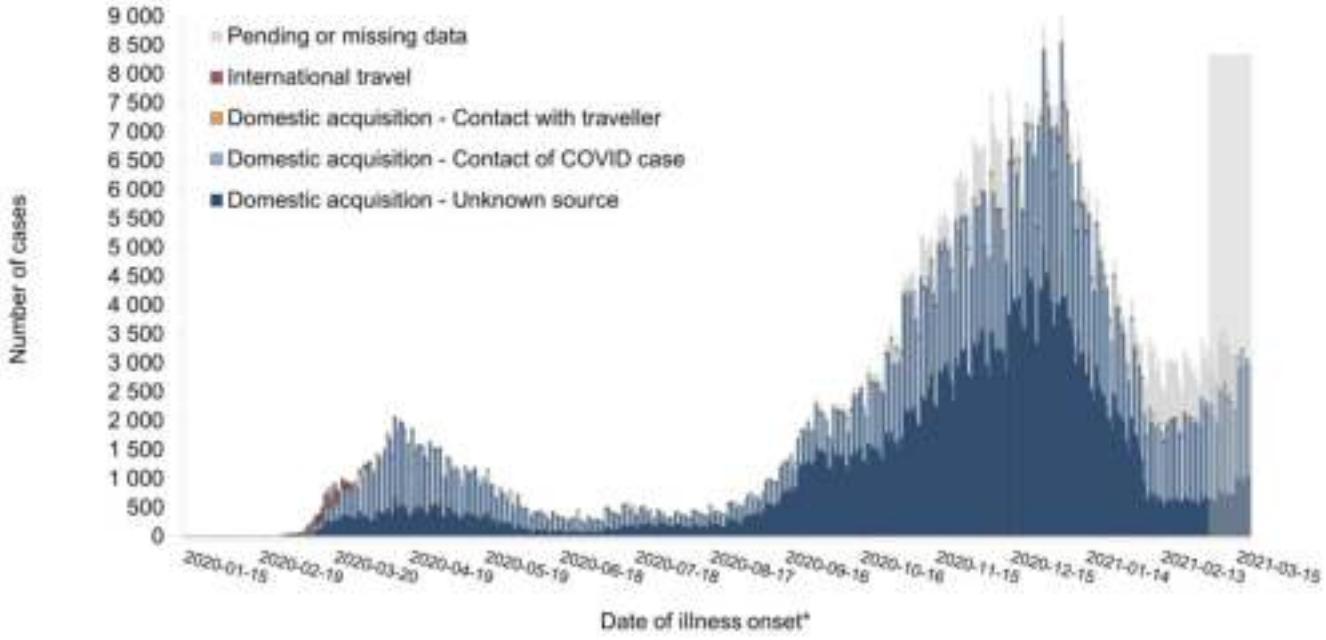
- 13 398 cases (66%) reported exposure in Canada to a known COVID-19 case;
- 6 820 cases (34%) reported exposure in Canada to an unknown source;
- 43 cases (<0.5%) reported exposure to a traveller; and
- 68 cases (<0.5%) reported having travelled outside of Canada during the exposure period.

Jurisdictions update exposure status on an ongoing basis as case investigations are completed and may result in changes to the percent distributions by exposure type for previous weeks (Figure 4).

Of the 883 392 cases submitted as of 03 April 2021 with information on the source of exposure and date of illness onset:

- 418 343 cases (47%) reported exposure in Canada to a known COVID-19 case;
- 449 898 cases (51%) reported exposure in Canada to an unknown source;
- 6 771 cases (1%) reported exposure to someone who had travelled; and
- 8 380 cases (1%) reported having travelled outside of Canada during the exposure period.

Figure 4. Number of reported COVID-19 cases in Canada, by date of illness onset and exposure category as of 03 April 2021 (n=991 533)



Source: Detailed case information received by PHAC from provinces and territories

* The earliest of the following dates were used as an estimate: Onset date, Specimen Collection Date, Laboratory Testing Date, Date Reported to Province or Territory, or Date Reported to PHAC.

Note: The shaded area represents a period of time (lag time) where it is expected that cases have occurred but have not yet been reported nationally. There is missing information for exposure variables from several provinces and territories.

INTERNATIONAL TRAVEL EXPOSURES[a]

[a] Detailed case information received by PHAC from provinces and territories

In Canada, the first cases of COVID-19 were attributed to international travel exposures. On 14 March 2020, the Government of Canada published a global Travel Health Notice advising Canadians against non-essential travel and advised Canadians abroad to return to Canada. By 21 March 2020, the Government of Canada prohibited all non-essential travel into Canada by foreign nationals. Since that time, the proportion of COVID-19 cases associated with international travel decreased from 22.3% (n=3 883) of all cases in March 2020 to 0.4% (n=127) in May 2020, and increased slightly over the summer months but has remained low since the fall (Table 5 and Figure 5). Since the spring of 2020, there have been significant efforts to enact border restrictions to reduce COVID-19 import to Canada.

As of 03 April 2021, 0.9% of cases with known exposure (n=8 380) have been associated with international travel. Since 01 July 2020, the United States, Mexico, and India are the top countries identified by cases that reported international travel during their exposure period.

Table 5. Number and percentage of COVID-19 cases associated with international travel by month of illness onset[a], as of 03 April 2021

Month	Number of COVID-19 cases associated with international travel	Percentage of COVID-19 cases associated with international travel[b]
January 2020	7	18.9%
February 2020	71	37.2%
March 2020	3 883	22.3%
April 2020	510	1.1%
May 2020	127	0.4%
June 2020	218	1.9%
July 2020	351	2.7%
August 2020	257	1.9%
September 2020	213	0.5%
October 2020	314	0.4%
November 2020	443	0.3%
December 2020	607	0.3%
January 2021	836	0.5%
February 2021	252	0.4%
March 2021	291	0.4%
Total	**8 380**	**0.9%**

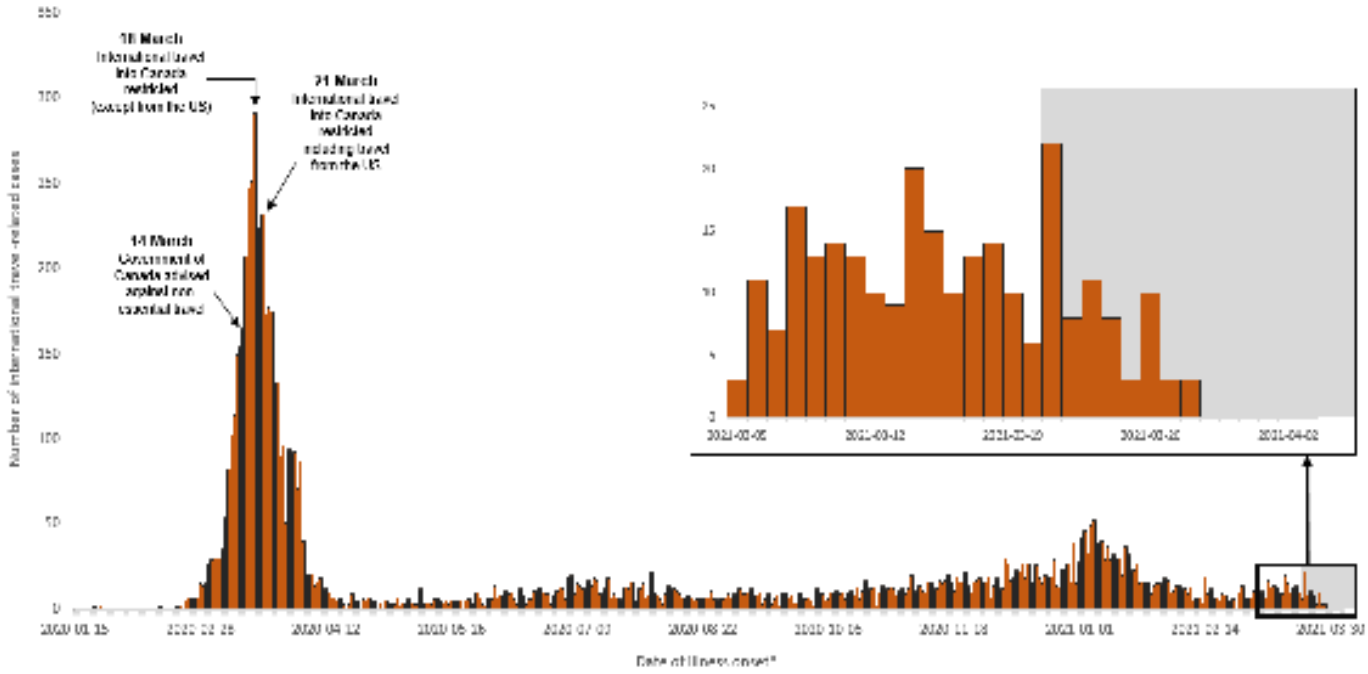
Source: Detailed case information received by PHAC from provinces and territories

Note: This is an underestimate of the total number of cases among returning travelers as exposure history are not available for all cases and not all jurisdictions have consistently reported exposure history to PHAC throughout the COVID-19 pandemic.

[a]The earliest of the following dates were used as an estimate: Onset Date, Specimen Collection Date, Laboratory Testing Date, Date Reported to Province or Territory, or Date Reported to PHAC.

[b]Only includes cases that have information on exposure.

Figure 5. Number of international travel-related COVID-19 cases in Canada, by date of illness onset[a] (n= 8 380) as of 03 April 2021



Source: Detailed case information received by PHAC from provinces and territories

* The earliest of the following dates were used as an estimate: Onset date, Specimen Collection Date, Laboratory Testing Date, Date Reported to Province or Territory, or Date Reported to PHAC.

Note: The shaded area represents a period of time (lag time) where it is expected that cases have occurred but have not yet been reported nationally.

Note: This is an underestimate of the total number of cases among returning travellers as exposure history are not available for all cases and not all jurisdictions have consistently reported exposure history to PHAC throughout the COVID-19 pandemic.

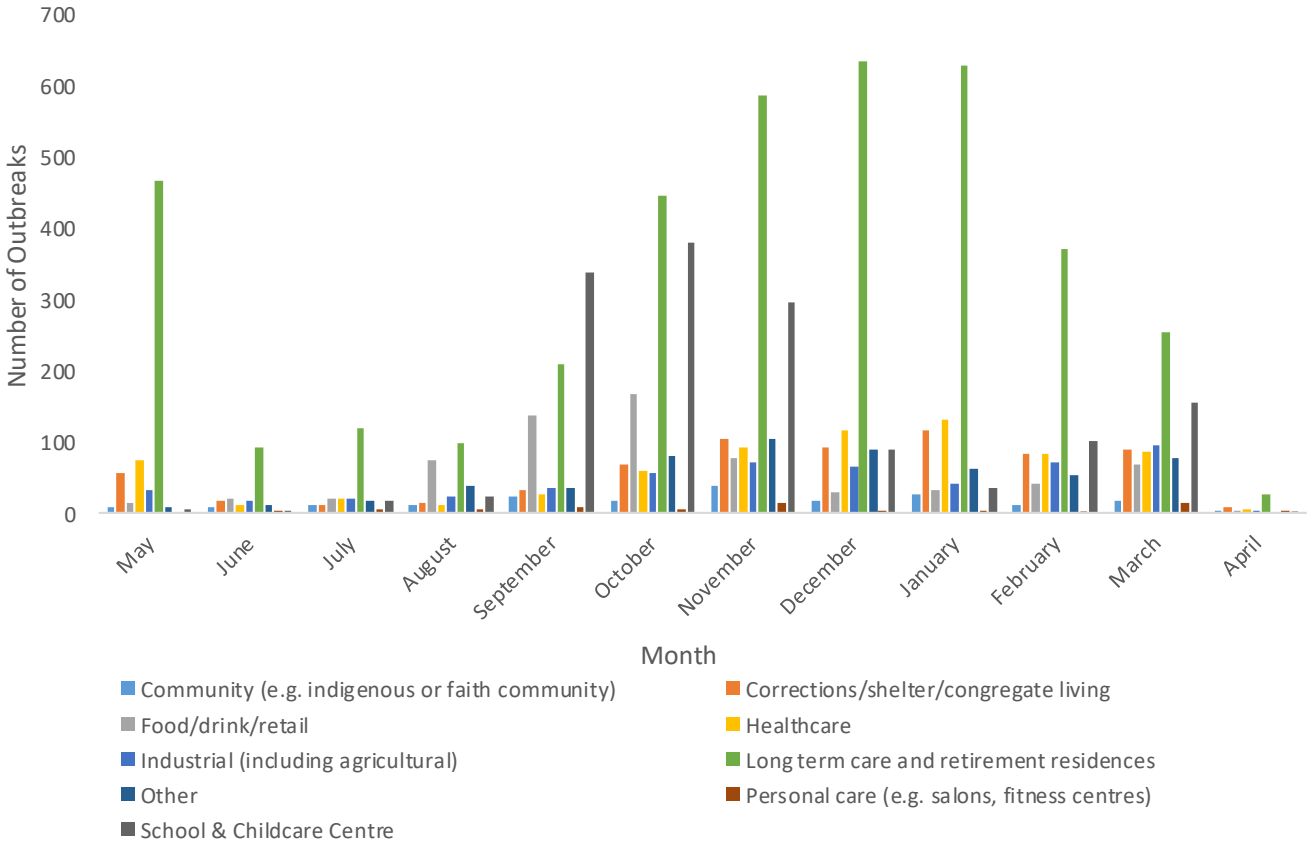
OUTBREAKS

Outbreaks have been a significant source of the spread of COVID-19 in Canada, and point to vulnerabilities in closed and crowded settings.

- Outbreaks have been detected in congregate living, workplace, and agricultural work settings, and namely in long-term care settings, meat processing plants, hospitals, small communities, and among farmworkers.
- Outbreaks continue to be observed in high-risk settings involving closed spaces, crowded places and close contact situations.
- Long-term care facilities and retirement residences continue to be the most commonly reported outbreak setting in Canada, and continue to account for the greatest proportion of outbreak related cases and deaths. This has been a consistent monthly trend with the exception of September, where reports of outbreaks in schools and childcare centres exceeded those in long-term care facilities and retirement residences.

Figure 6 and Table 6 identify common locations of outbreaks, as well as the number of cases and deaths associated with each.

Figure 6. Number of new outbreaks by setting as of 03 April 2021



Source: Publicly reported outbreak data, including Provincial and Territorial websites, as of 03 April 2021
Note: Schools with only one case, or those for which information on number of cases is unknown, have been excluded

Table 6. Total number of COVID-19 outbreaks, cases, and deaths by outbreak setting in Canada as of 03 April 2021[a]

Outbreak setting	Total number of outbreaks reported	Total number of cases reported	Total number of reported deaths	Outbreaks Reported in past 7 days
Community[b]	203	10 391	89	5
Corrections/shelter/congregate living	735	12 933	226	15
Food/drink/retail	685	2 489	3	20
Healthcare	765	10 648	812	18
Industrial (including agricultural)[c]	539	11 938	24	17
Long term care and retirement residences	4 430	66 863	12 473	61
Personal Care[d]	60	610	0	7
School & Childcare Centre[e]	1 438	8 199	1	31
Other[f]	585	5 331	6	17

Source: Publicly reported outbreak data, including Provincial and Territorial websites, as of 03 April 2021

[a]This is not an all-inclusive list and is subject to change based on current and active outbreak locations reported.

[b]Community includes population centres, Indigenous communities, Mennonite, Reserves, and small city outbreaks.

[c]The number of outbreaks in Windsor-Essex have been grouped into one cluster; industrial settings include: automotive manufacturing, distribution/processing facilities, worker camps, waste management/recycling, warehouse, etc.

[d]Personal care refers to personal care services, such as hair salons, nail salons, etc.

[e]Child and youth care include daycare centres and day camps; excludes any facilities that report only one case. Schools with only one case, or those for which information on number of cases is unknown, have been excluded

[f]Other groups together outbreaks in settings not listed in the categories above, for example social gatherings, office workplaces, recreational facilities, etc.

Note: These categories include both current and retrospective outbreak data.

LABORATORY-CONFIRMED COVID-19 DETECTION

During week 13, a total of 809 571 tests were performed, with an average of 115 653 tests performed daily for COVID-19 across Canada. The weekly percentage of tests positive during week 13 was 5.1%, an increase of 0.8% from the previous week (Table 7).

Table 7. Summary of COVID-19 tests performed in Canada, by province or territory, for week 13

Province/Territory	Cumulative number of tests performed as of 03 April 2021	Week 13 (28 March to 03 April, 2021)			
		Weekly number of tests performed	Average number of tests performed daily	Average # of tests performed daily per 1 000 population	Weekly percentage of tests positive[1]
British Columbia	2 222 958	61 093	8 728	1.7	10.4%
Alberta	3 746 782	80 346	11 478	2.6	7.5%
Saskatchewan	679 507	24 319	3 474	2.95	6.6%
Manitoba	598 266	12 269	1 753	1.27	4.7%
Ontario	12 630 159	353 513	50 502	3.43	5.3%
Québec	7 308 657	242 176	34 597	4.03	3.3%
Newfoundland and Labrador	223 240	3 977	568	1.09	0.2%
New Brunswick	269 376	7 763	1 109	1.42	1%
Nova Scotia	437 783	20 312	2 902	2.96	0.1%
Prince Edward Island	127 300	3 296	471	2.95	0.1%
Yukon	8 616	87	12	0.29	0%
Northwest Territories	16 195	308	44	0.97	0.6%
Nunavut	9 921	112	16	0.41	0%
Canada	**28 278 760**	**809 571**	**115 653**	**3.04**	**5.1%**

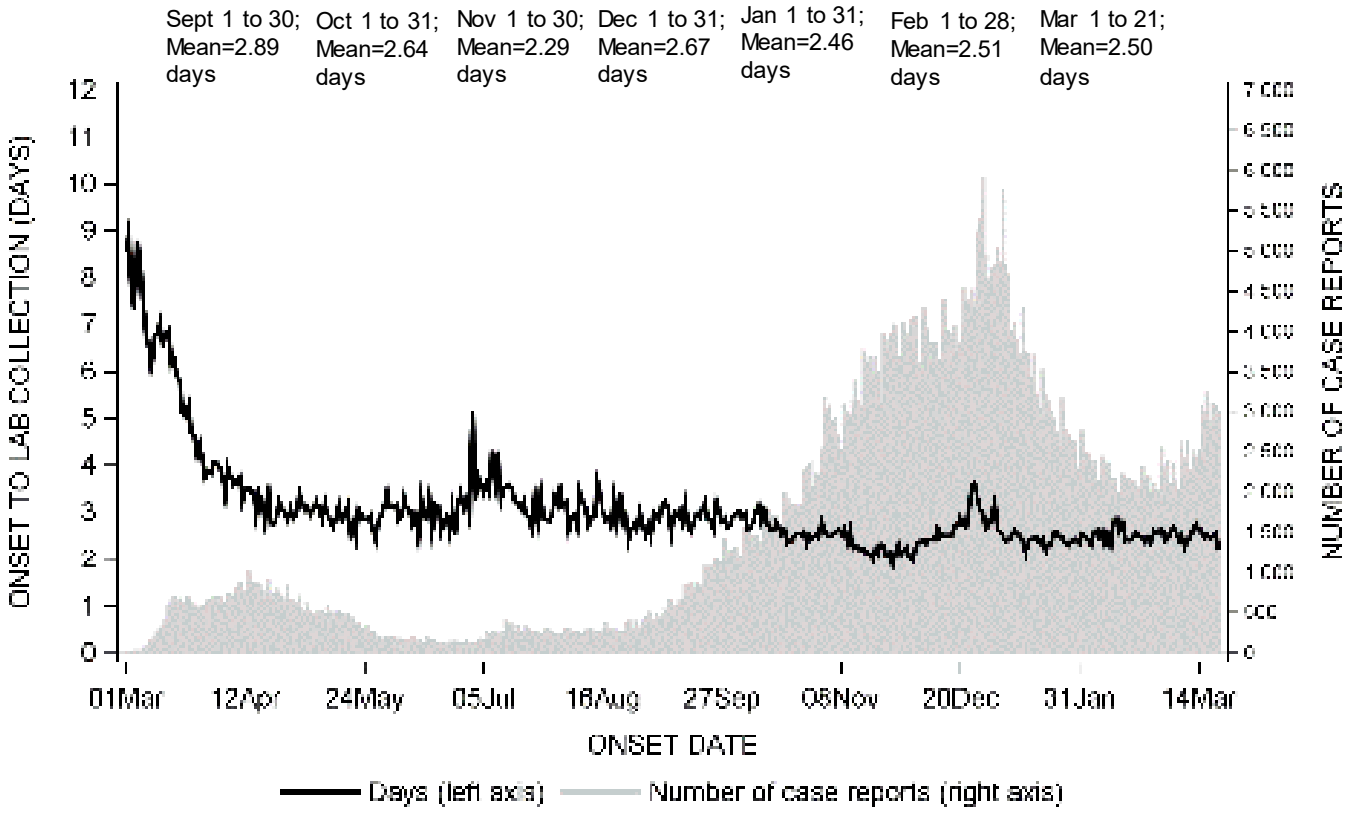
Source: NML Data for laboratory analyses as of 03 April 2021

[1] Weekly percentage of tests positive is calculated by dividing the total positive tests in the past 7 days by the total tests performed in the past 7 days

Note: Laboratory testing numbers may be an underestimate due to reporting delays and may not include additional sentinel surveillance or other testing conducted in the province or territory.

The mean time from symptom onset to lab specimen collection was 2.50 days in March 2021. This is similar to the mean of 2.51 days in February 2021 (Figure 7).

Figure 7. Onset date to laboratory collection date for cases reported to PHAC as of 03 April 2021



Source: Detailed case information received by PHAC from provinces and territories
Note: Date of symptom onset to date of specimen collection intervals of >15 days are deemed outliers, and not included in this figure.

SEVERITY INDICATORS

HOSPITALIZATIONS, INTENSIVE CARE, AND DEATHS

During week 13, detailed case information on hospitalization status was available for 18 578 cases. Among these cases:

- **700 (4%)** were hospitalized (including ICU admission), of whom:
  - **87 (12%)** were admitted to ICU.

Among the total number of hospitalizations reported during week 13 for which age information was available, 24% (n=166/695) were 40 to 59 years of age, 41% (n=287/695) were 60 to 79 years of age, and 21% (n=143/695) were 80 years and older (Table 8).

As of 03 April 2021, case information on hospitalization status was available for 694 621 cases, where:

- **52 835 (8%)** were hospitalized (including ICU admission), of whom:
  - **9 337 (18%)** were admitted to ICU.

Since the beginning of the pandemic, the 60 to 79 year age group has accounted for the highest proportion of cases hospitalized and admitted to ICU, followed closely by the 80 years and older age group (see table A5 in annex for cumulative counts).

Table 8. Number of COVID-19 cases hospitalized, and admitted to ICU, overall and by gender and age group, reported to PHAC during week 13[a]

Age groups	Hospitalized – non-ICU			Hospitalized – ICU		
	Female	Male	Total	Female	Male	Total
≤ 19	11	10	21	0	1	1
20-39	30	39	69	2	6	8
40-59	66	82	148	8	10	18
60-79	107	136	243	16	28	44
80+	61	66	127	9	7	16
Total	275	333	608	35	52	87

Source: Detailed case information received by PHAC from provinces and territories

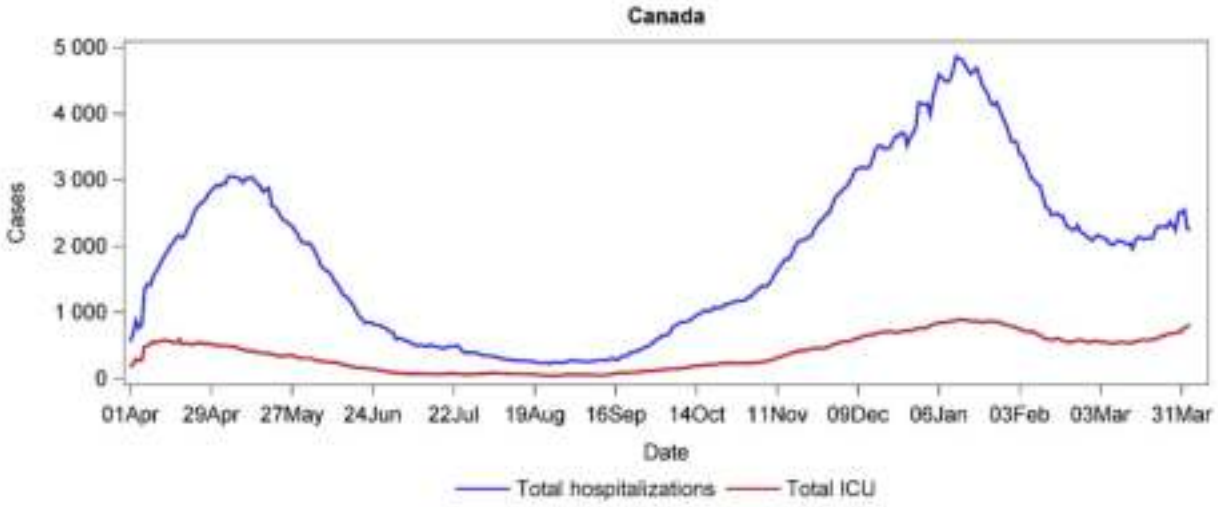
[a] Data are analyzed based on date reported to PHAC. Note that there is a period of time (lag time) where it is expected that cases have occurred but have not yet been reported nationally. Therefore, COVID-19 cases reported to PHAC during week 13 may include cases that occurred (based on date of illness onset, or lab related dates) in previous weeks.

Note: Non-ICU hospitalizations and ICU counts are mutually exclusive. Cases with missing gender, sex or age were excluded. Where available, gender data were used; when gender data were unavailable, sex data were used. Reliable data on gender diverse respondents are unavailable due to small counts.

Following a sharp decline in hospitalizations, and stabilized numbers of ICU admissions since early January 2021, the number of hospitalizations and ICU admissions have begun to increase (Figure 8). On 03 April 2021, there were 2 250 cases hospitalized and 801 cases in ICU, representing a 5% increase in the seven-day moving average of hospitalized cases and a 16% increase in the seven-day moving average of ICU admissions compared to one week prior.

Based on detailed case information received by PHAC from provinces and territories, the overall cumulative hospitalization rate (including ICU admissions) is 139 cases per 100 000 population, with the highest rates observed among those aged 80 years and older (1 013 cases per 100 000 population).

Figure 8. Number of COVID-19 cases in hospital and ICU daily in Canada, as of 03 April 2021



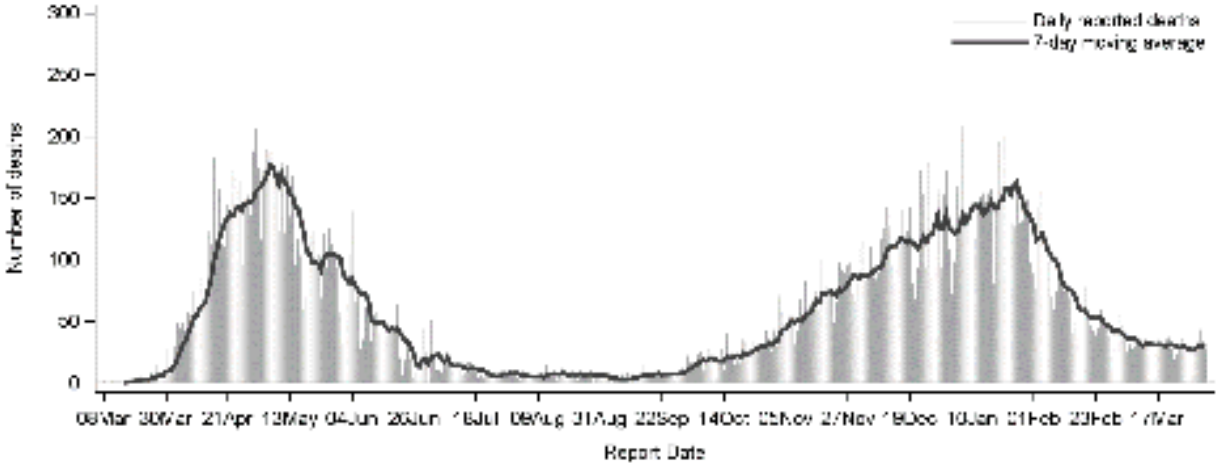
Source: Provincial and Territorial MOH websites as of 03 April 2021

During week 13, there were 195 COVID-19 related deaths reported in Canada.

- This represents an 8% decrease compared to the previous week.
- This amounts to an average of 28 deaths reported per day, compared to an average of 30 deaths per day during the previous week.
- There has been an overall decreasing trend in the number of deaths observed since late January 2021 (Figure 9).

Of the deaths reported during week 13, jurisdictions submitted case-level information to PHAC for 27 deaths, of which 18 (67%) were male and 96% were aged 60 years and older. To date, deaths are highest among those aged 80 years and older (Table A4 in the annex, cumulative counts).

Figure 9. Daily number of COVID-19 related deaths reported in Canada (and 7-day moving average), as of 03 April 2021 (N=23 050)



Source: Provincial and Territorial MOH websites as of 03 April 2021

Note: The 7-day moving average is a trend indicator that captures the arithmetic mean of the daily reported deaths over the previous seven days. The moving average helps smooth out day-to-day variability in reporting, filtering out the "noise" of short-term fluctuations. Fluctuations can be attributed to retrospective data or provinces or territories reporting cases at a reduced frequency.

CANADIAN ACUTE CARE HOSPITALS

Laboratory-confirmed COVID-19-associated hospitalizations in Canada are monitored through two sentinel hospital-based systems:

1. Canadian Nosocomial Infection Surveillance Program (CNISP) *
2. Serious Outcomes Surveillance Network of the Canadian Immunization Research Network (CIRN-SOS) **

NOTE: * denotes data from CNISP and ** data from CIRN-SOS

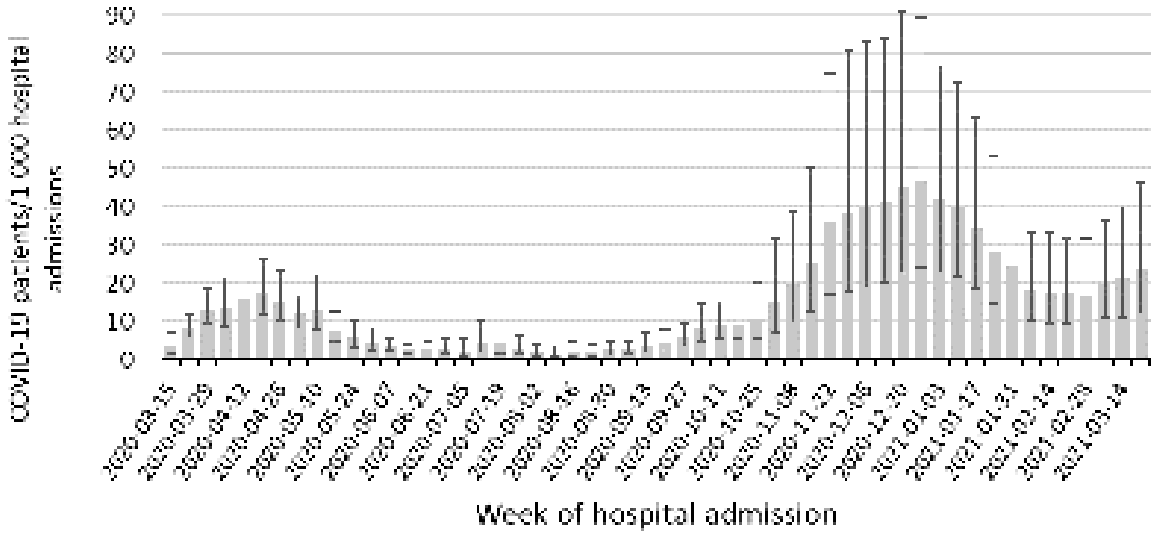
Key Findings*

- Among all patients hospitalized with COVID-19 since March 2020:
  - 20% have been admitted to the ICU (3 082/15 731)
  - 12% required mechanical ventilation (1 931/15 731)
  - <1% received extracorporeal membrane oxygenation (ECMO) (141/15 731)
  - 15% have died (all-cause mortality) (2 356/15 731)
- The median age of patients hospitalized with COVID-19 was 68 years (range 0-104 and 4% are pediatric (<18 years) (554/15 731)
- Males accounted for 54% of hospitalized patients (2 185/4 063)

Hospitalization Rates

- The weekly rate of new laboratory-confirmed COVID-19 patients per 1 000 hospital admissions was 23.8 for the most recent week of 21 March 2021 (Figure 10). The weekly incidence rate of hospitalizations has increased each week since the week of 28 February 2021 (Figure 10).

Figure 10. National rates of laboratory-confirmed COVID-19 patients per 1 000 admissions with 95% confidence intervals (n=15 731)*



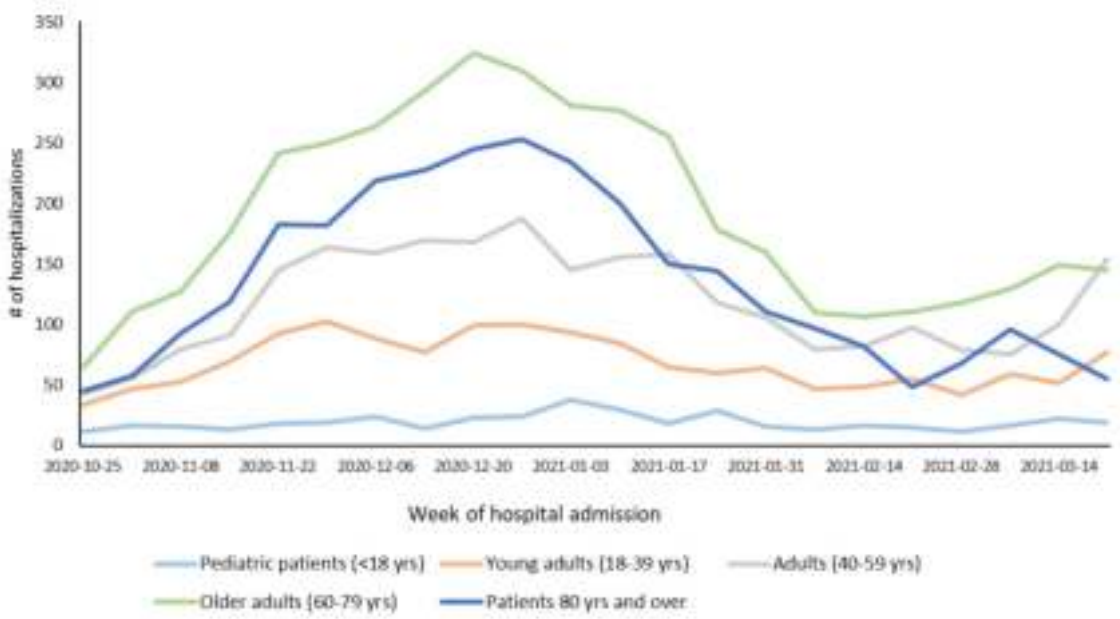
[a] Includes data from the 151 hospitals that have participated in all weeks of aggregate data collection. Denominator data are estimated using 2020 annual patient admissions.*

Hospitalization Trends

AGE *

- There was an increase observed in the number of hospitalizations among young adults (18-39 years) and adults (40-59 years) in the most recent week of 21 March 2021, with adults (40-59 years) accounting for the greatest number of hospitalizations for that week (Figure 11).
- Hospitalizations among patients 80 years and over have continued to decrease since the week of 07 March 2021 (Figure 11).
- Hospitalizations among pediatric patients (<18 years) have fluctuated, but consistently remained low (Figure 11).

Figure 11. Weekly number of new laboratory-confirmed COVID-19 patients by age group (n=11 728)*



CLINICAL PROGRESSION **

Time from symptom onset to hospital admission:

- Median length of time from symptom onset to hospital admission was shortest at 3 days among patients aged 80+ years (n=745), compared to 4 days among patients aged 16-39 years (n=162), 5 days among patients aged 60-79 years (n=852) and 6 days among patients aged 40-59 years (n=417).

Length of hospital stay:

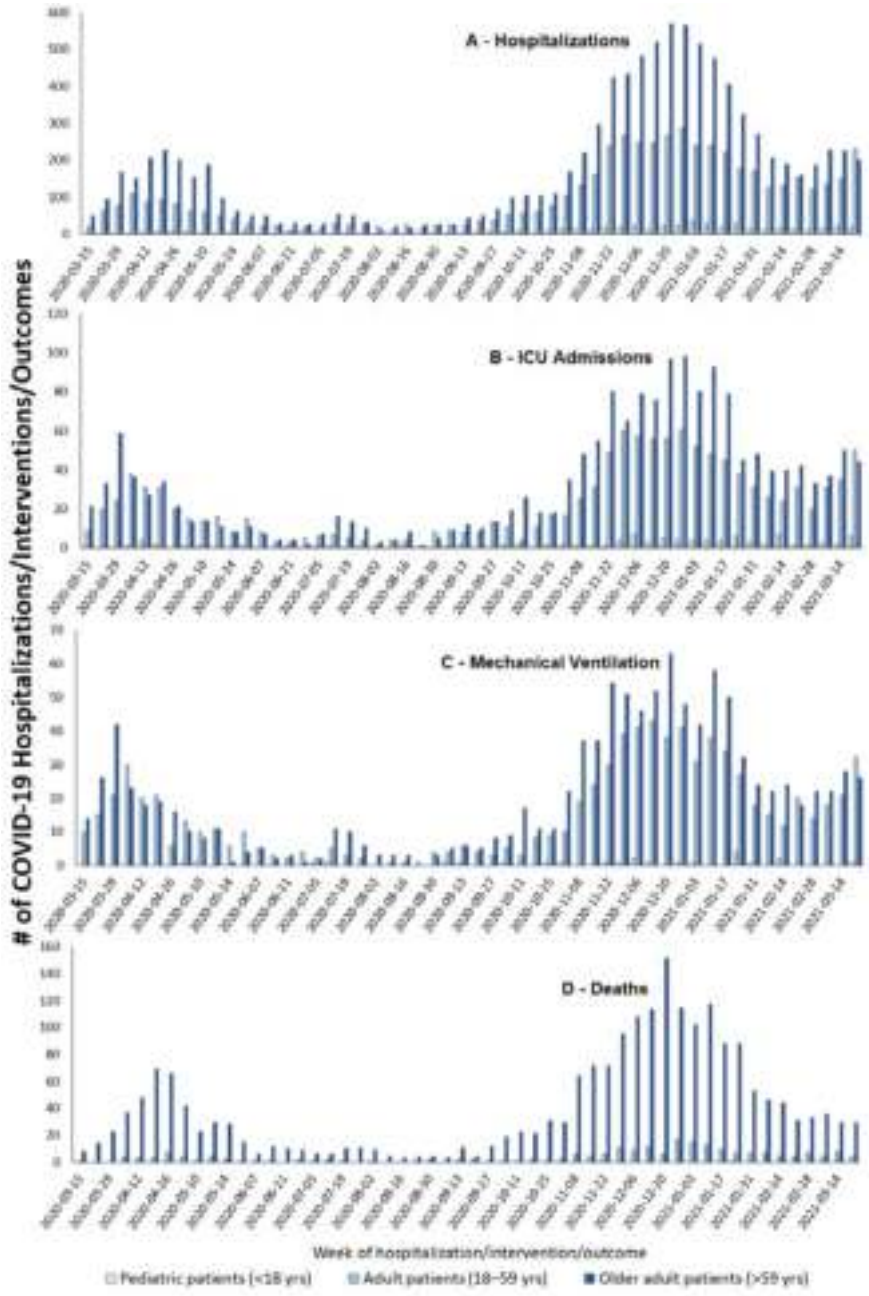
- Median length of hospital stay was longest among patients aged 80+ years (median=12 days, n=658) and patients aged 60-79 years (median=11 days, n=738). Values were comparatively lower for patients aged 40-59 years (median=6 days, n=352) and 16-39 years (median=4 days, n=134).

Note: Patients hospitalized before symptom onset were excluded from 'time from symptom onset to hospital admission' calculations. Length of stay is calculated as the time (in days) between date of hospital admission and date of outcome (including discharge, transfer, status change to alternate level of care, and death).

INTERVENTIONS/OUTCOMES *

- The number of new weekly hospitalizations, ICU admissions, and patients receiving mechanical ventilation have each increased since the week of 28 February 2021. Note that the increase observed in the most recent week of 21 March 2021 was largely driven by adult patients (18-59 years), as these measures all decreased among older adult patients (>59 years) (Figure 12).
- The number of deaths have remained relatively stable in recent weeks (Figure 12).

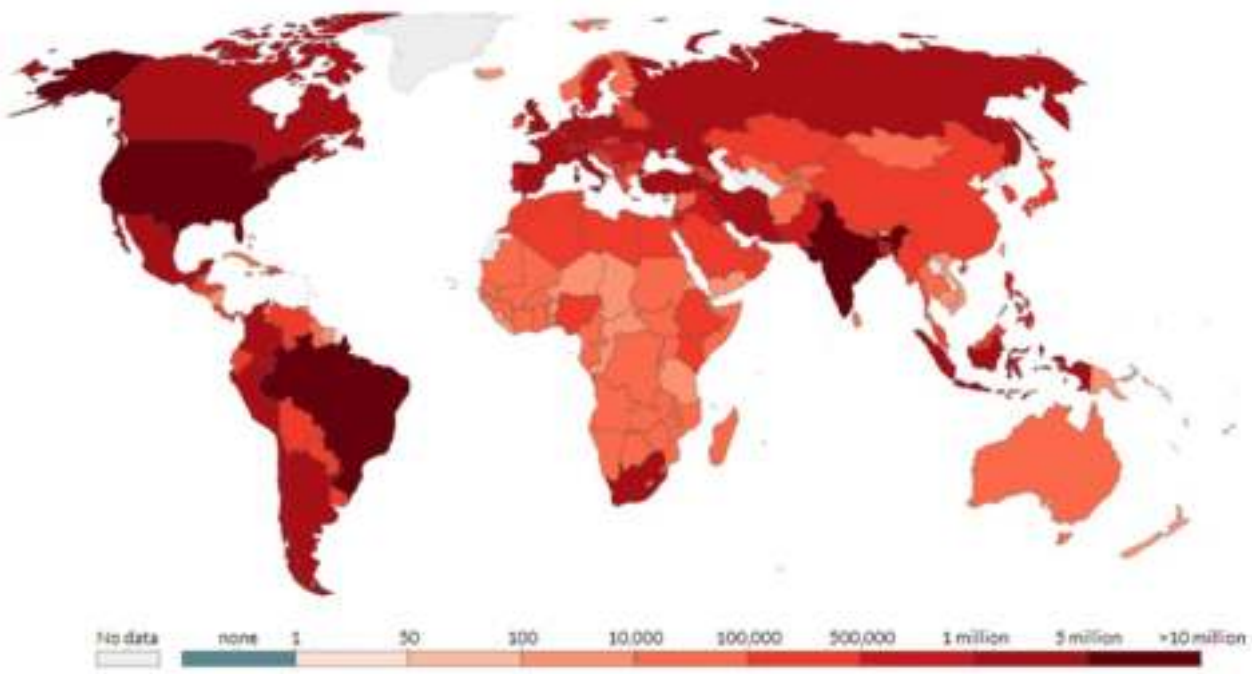
Figure 12. Weekly number of new laboratory-confirmed COVID-19 patients that were admitted to hospital (A; n=15 731), ICU (B; n=3 082), required mechanical ventilation (C; n=1 931), and deceased (D; n=2 356), by age group*



INTERNATIONAL

- As of 03 April 2021, there are over 129 million global cases of COVID-19 with over 2.8 million reported deaths (Figure 13).
- The region of Europe accounts for the highest number of cases reported.
- The following five countries account for the largest proportion of cases reported globally in the past 14 days:
    - Brazil (n=1 003 138)
    - India (n=886 379)
    - United States (n=885 934)
    - France (n=490 035)
    - Turkey (n=452 358)
- Canada's cases account for approximately 0.8% of all cases reported globally since the beginning of the pandemic.

Figure 13. International map of COVID-19 cases as of 03 April 2021 (n=129 943 007)

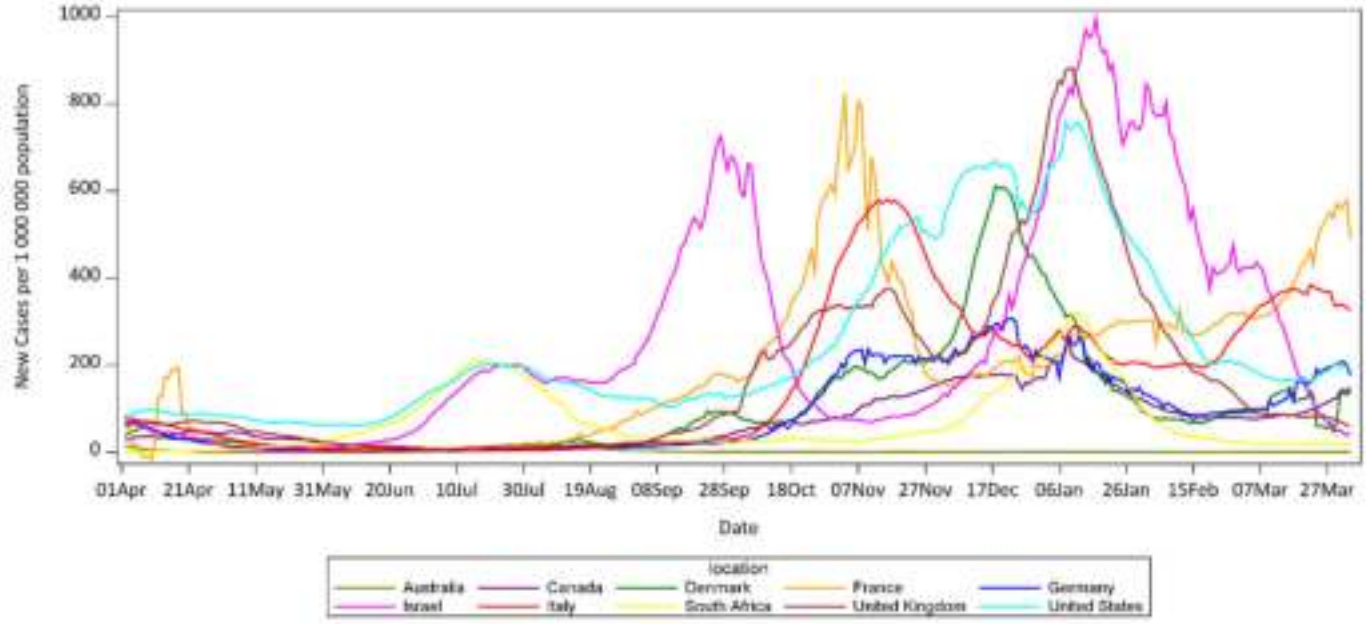


Source: Our World in Data – Coronavirus Pandemic (COVID-19) - https://ourworldindata.org/coronavirus

France continues to experience the highest rates of new cases compared to other countries, with 489.2 new cases per 100 000 population on 03 April 2021. Italy and the United States are second and third highest, with 325.6 and 195.2 new cases per 100 000 population, respectively.

Daily rates of cases in Canada are steadily increasing with 149.2 cases per 100 000 population on 03 April 2021. The rates of new cases in Canada are 3.3 times lower than France, 2.2 times lower than Italy, and 1.2 times lower than the United States.

Figure 14. Weekly new cases of COVID-19 in Canada compared to other countries as of 03 April 2021 (7-day moving average, population-adjusted)



Source: OurWorldInData, as of 03 April 2021

Up-to-date country-specific risk levels are found on travel health notices. For more information on COVID-19 internationally, please refer to the World Health Organization's COVID-19 Situation Report.

MODELLING

Estimates of transmission rates in Canada: Effective reproductive rate (*Rt*)

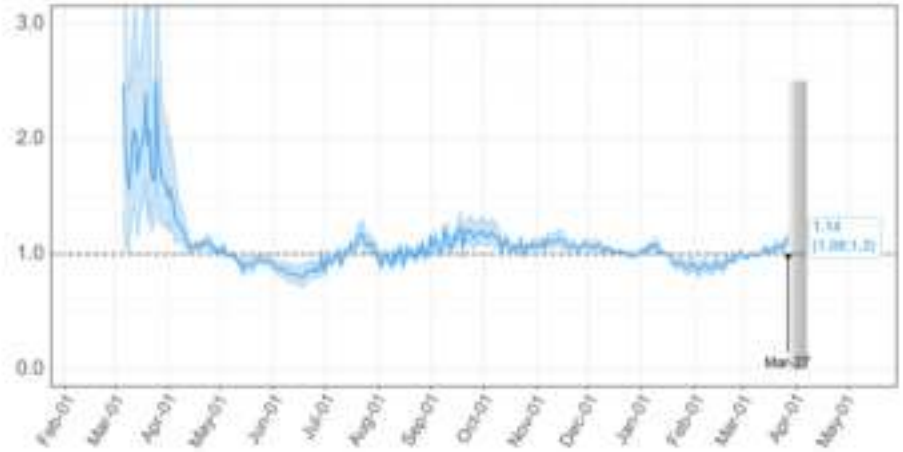
Rt is the time variable reproduction rate, representing the average number of newly infected people for each infected person. If Rt is less than 1 at a particular time (t), than the average number of people infected by one infected person is less than one, so the epidemic is being brought under control. If Rt is greater than 1, the average number of people infected by one infected person is greater than one, and the epidemic is growing. A value of Rt above 1 indicates that there is active community transmission, meaning that the disease will continue to spread in the population. The higher the Rt value, the faster the disease is spreading, which leads to an increase in the incidence of new cases.

However, there are some limitations to consider. As the epidemic continues, the Rt may not capture the current state of the epidemic with low case burden and the value must be interpreted based on the current landscape. The Rt can easily fluctuate when case numbers are low. It is also an average Rt for a population and does not point to local outbreaks driving case counts. Since the method used to calculate Rt is highly sensitive to the reported number of new cases, community outbreaks within specific provinces and territories will cause the estimated Rt value in that respective region to be higher, which may not always accurately depict overall transmission in the province or territory as a whole.

Figure 15 shows the Rt over time.

- In 2020, the reproductive rate was hovering under 1 in May and early June, followed by fluctuations in July. In early August, the Rt increased until the end of September when it decreased to just above 1. Between October 2020 and January 2021, the Rt fluctuated just above 1 with a slight increase in early November and early January. Starting in mid-January 2021, the Rt decreased to below 1, indicating that the epidemic was reducing nationally.
- Since early February 2021, the Rt has begun to slowly increase. The national Rt was 1.14 on 27 March 2021, an increase from 1.07 during the previous week.

Figure 15. Reproductive rate in Canada based on date of case report



Source: Calculated from detailed case information received by PHAC from provinces and territories
Note: Fluctuations are attributed to provincial and territorial reporting delays and non-reporting on the weekends

FORECASTING

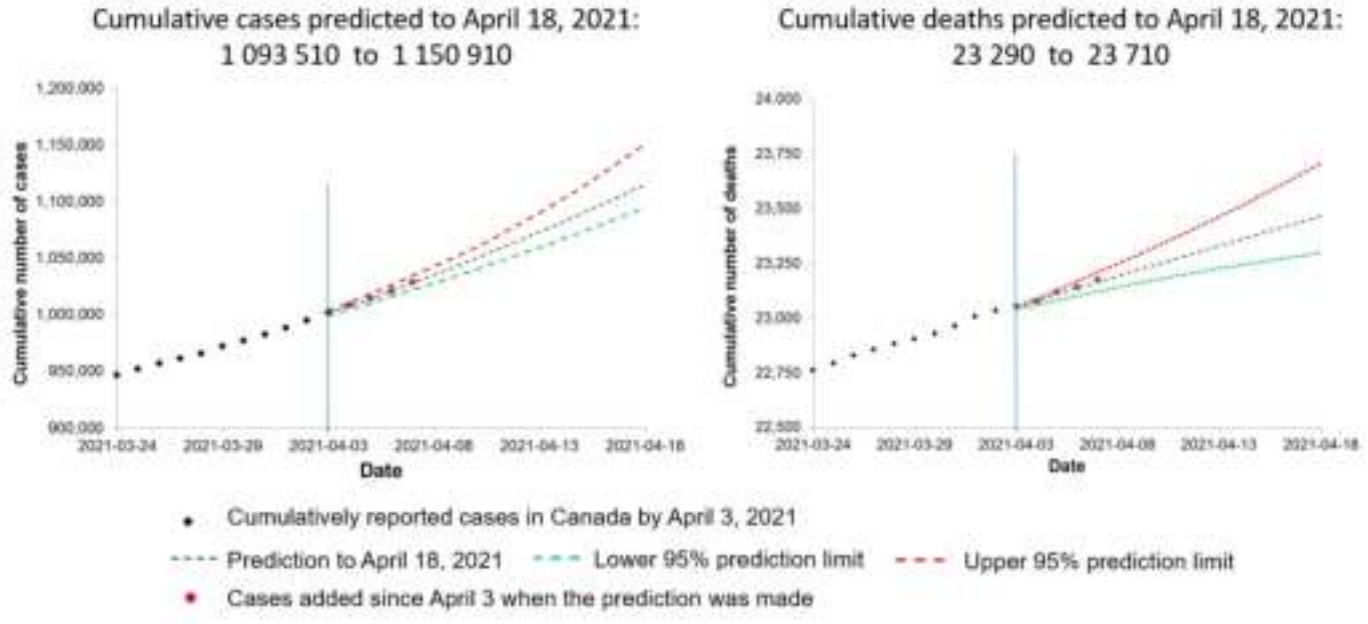
Canada's approach to modelling:

Models cannot predict the course of the COVID-19 pandemic, but can help us understand all possible scenarios, support decisions on public health measures and help the health care sector plan for these scenarios.

Forecasting models use data to estimate how many new cases can be expected in the coming weeks. Figure 16 below shows the projected number of cases and deaths in Canada, with a 95% prediction interval calculated to 18 April 2021, using available data as of 03 April 2021.

- According to forecasting, between 1 093 510 to 1 150 910 cumulative reported cases and 23 290 to 23 710 cumulative reported deaths are expected by 18 April 2021.
- The black dots represent actual data (cumulative cases and cumulative deaths) prior to 03 April 2021 and the dashed lines show the predicted trajectories after that date.
- It is important to communicate uncertainties in the predictions. The red and green lines represent the upper and lower limits with 95% confidence, respectively.
- If the added data points since 03 April 2021 stay between the red and green lines, it means both (i) the prediction model is performing as expected; (ii) data generated by the epidemic and reporting mechanisms are as expected.
- If the added data points since 03 April 2021 fall outside these limits, especially above the red line, the model detects unexpected signals that require further epidemiologic investigation.

Figure 16. Projected numbers to 18 April 2021 and 95% prediction intervals based on data reported as of 03 April 2021



For more information, please visit: https://www.canada.ca/en/public-health/services/diseases/coronavirus-disease-covid-19/epidemiological-economic-research-data/mathematical-modelling.html

TECHNICAL NOTES

The data in the report are based on information from various sources described below. The information presented for case-based analyses, trend analyses and laboratory analyses are available as of **03 April 2021 at 4 p.m. EDT.**

DATA SOURCES AND DATA CAVEATS

Epidemiological data received by PHAC

Some of the epidemiological data for this report are based on detailed case information received by PHAC from provinces/territories (P/Ts). This information is housed in the PHAC COVID-19 database. Case counts and level of detail in case information submitted to PHAC varies by P/T due to:

- Possible reporting delay between time of case notification to the P/T public health authority and when detailed information is sent/received by PHAC.
- Preliminary data may be limited and data are not complete for all variables.
- Data on cases are updated on an ongoing basis after being received by PHAC and are subject to change.
- Variation in approaches to testing and testing criteria over time within and between P/Ts.
- The lag time from illness onset to PHAC report date is approximately two weeks and data within this period is subject to change.

Note: Missing data for hospitalizations, ICU admissions, and deceased were not included in calculations. Unless calculations were broken down by age and gender, cases with missing values for age and gender were included. P/Ts may define gender differently and some may be referring to biological sex. Case severity is likely underestimated due to underreporting of related variables, as well as events th at may have occurred after the completion of public health reporting, and therefore is not captured in the case report forms. Transmission data should be interpreted with caution as information on exposure are missing from several provinces and territories.

Provincial and territorial case counts

P/T information on case counts, resolved cases, and deaths associated with COVID-19 are collected from publicly available P/T websites, generally from the P/T ministry of health. Case definitions may vary by P/T.

- National COVID-19 case definitions are provided by PHAC for the purpose of standardized case classification and reporting. PHAC's national case definitions can be found here: https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/health-professionals/national-case-definition.html
- Only cases and deaths meeting P/T's definition for case classification are reported. For details on case definitions, please consult each P/T ministry of health website.

Laboratory information

Data on the number of tests conducted in each P/T are received from the National Microbiology Laboratory.

- Laboratory testing numbers may be an underestimate due to reporting delays and may not include additional sentinel surveillance or other testing performed. They are subject to changes as updates are received.

Outbreak data

Reporting delays and gaps in information that are available at the federal level present difficulties in reporting on local outbreaks. To ensure timely information is available, PHAC utilizes web-scraping techniques to gather outbreak data from media and P/T public health agency websites. There are several important limitations to these data:

- A nationally standardized outbreak definition does not yet exist. Cluster definitions vary according to P/T. The methods for defining an outbreak are currently in development and may change over time.
- The data do not represent all outbreaks that have occurred in Canada over the course of the pandemic, but they do provide a summary of clusters reported via non-traditional data sources. Data collection on outbreaks began 12 March 2020.
- Case-level data are generally not available for outbreaks detected via non-traditional data sources. Information presented is at the aggregate level only.

Population data

- Canadian population data from Statistics Canada Population estimates on 1 July 2020 are used for age-standardized and age-specific rate calculations.

International data

International data are retrieved from the European Centre for Disease Prevention and Control (ECDC) Situation update and Our World in Data.

- Given that the pandemic is rapidly evolving and the reporting cycles from government sources are different, the case numbers may not necessarily match what is being reported publicly. Rather, this reflects what is publicly available from the sources listed above.
- International comparisons should be interpreted with caution. Number of tests conducted, indications for testing, and diagnostic capacity by country have a large influence on total number of reported cases. Therefore, the data displayed may not represent the true incidence of disease within each country.

Canadian Acute-Care Hospitalization Data

Canadian Nosocomial Infection Surveillance Program (CNISP) collects information on hospitalized patients across all age groups (pediatric and adult).

- As of 27 March 2021, CNISP has collected weekly aggregate data on 15 731 adult and pediatric patients hospitalized with COVID-19 from 151 hospitals across all 10 provinces and 1 territory.
- CNISP has conducted surveillance among 56 hospitals across 10 provinces and 1 territory and as of 12 March 2021 has collected case-level data on 4 063 adult and pediatric patients hospitalized with COVID-19

Serious Outcomes Surveillance Network of the Canadian Immunization Research Network (CIRN-SOS) collects information on hospitalized adult patients aged 16 years or older.

- As of 1 April 2021, CIRN-SOS has collected case-level data on 2 950 adult patients (≥16 years) hospitalized with COVID-19 across 9 hospital sites in Alberta, Ontario, Québec, and Nova Scotia.
- Denominators may be lower depending on variable completeness.

*** denotes data from CNISP and ** data from CIRN-SOS**

ANNEX

Table A1. Cumulative number of COVID-19 cases, resolved cases, and deaths reported in Canada by province or territory, as of 03 April 2021

Province/Territory	Total cases	Total resolved cases	Total deaths
British Columbia	103 031	91 732	1 463
Alberta	151 359	138 560	1 994
Saskatchewan	34 323	31 744	436
Manitoba	34 352	32 162	938
Ontario	358 558	327 940	7 428
Québec	314 958	294 560	10 684
Newfoundland and Labrador	1 020	1 006	6
New Brunswick	1 641	1 457	30
Nova Scotia	1 732	1 634	66
Prince Edward Island	160	147	0
Yukon	74	71	1
Northwest Territories	42	42	0
Nunavut	395	391	4
Canada [a]	**1 001 658**	**921 459**	**23 050**

Source: Provincial and Territorial MOH websites

[a] Includes 13 cases identified in repatriated travelers (Grand Princess Cruise ship travelers) who were under quarantine in Trenton in March 2020. Update on their status is not available.

Table A2. Age-standardized incidence rates of COVID-19 cases, by province or territory, as of 03 April 2021

Province/Territory	Cumulative age-standardized incidence rates (per 100 000 population)
British Columbia	1 944.0
Alberta	3 296.6
Saskatchewan	2 904.6
Manitoba	2 477.9
Ontario	2 440.2
Québec	3 632.5
Newfoundland and Labrador	201.0
New Brunswick	179.2
Nova Scotia	172.5
Prince Edward Island	98.9
Yukon	126.9
Northwest Territories	97.7
Nunavut	930.6
Canada	**2 611.1**

Source: Detailed case information received by PHAC from provinces and territories, standardized to the July 1 2020 post-census population estimate

Note: Data are analyzed based on date reported to PHAC.

Table A3. Cumulative age and gender distribution of COVID-19 cases reported to PHAC, as of 03 April 2021

Age group	Female			Male			Total[a]		
	n	%	Rate	n	%	Rate	n	%	Rate
≤ 19	84 158	17%	2 115.2	89 518	18%	2 151.5	173 676	18%	2 133.7
20-29	90 880	18%	3 684.0	94 289	19%	3 543.1	185 169	19%	3 610.9
30-39	80 405	16%	3 063.4	78 453	16%	2 940.8	158 858	16%	3 001.6
40-49	75 824	15%	3 095.9	68 928	14%	2 865.8	144 752	15%	2 981.9
50-59	67 167	13%	2 571.2	64 828	13%	2 510.2	131 995	13%	2 540.9
60-69	40 054	8%	1 657.4	43 254	9%	1 871.8	83 308	8%	1 762.2
70-79	23 850	5%	1 508.6	23 296	5%	1 636.0	47 146	5%	1 569.0
80+	41 849	8%	4 224.6	22 188	5%	3 296.6	64 037	6%	3 849.2
Total	**504 187**	**100%**	**2 637.0**	**484 754**	**100%**	**2 566.8**	**988 941**	**100%**	**2 602.1**

Source: Detailed case information received by PHAC from provinces and territories

[a] Cases not identified as male or female were removed from the total due to small numbers.

Note: Cases with missing gender, sex or age were excluded. Where available, gender data was used; when gender data was unavailable, sex data was used. Reliable data on gender diverse respondents are unavailable due to small counts.

Table A4. Cumulative age and gender distribution of COVID-19 deaths reported to PHAC as of 03 April 2021

Age group	Female	Male	Total[a]
≤ 19	2	4	6
20-39	44	75	119
40-59	327	506	833
60-79	2 475	3 799	6 274
80+	8 885	6 869	15 754
Total	**11 733**	**11 253**	**22 986**

Source: Detailed case information received by PHAC from provinces and territories

[a] Cases not identified as male or female were removed from the total due to small numbers.

Note: Cases with missing gender, sex or age were excluded. Where available, gender data was used; when gender data was unavailable, sex data was used. Reliable data on gender diverse respondents are unavailable due to small counts.

Table A5. Cumulative age and gender distribution of cases hospitalized, and admitted to ICU reported to PHAC as of 03 April 2021

Age groups	Hospitalized – non-ICU			Hospitalized – ICU		
	Female	Male	Total	Female	Male	Total
≤ 19	350	370	720	55	68	123
20-39	2 266	1 652	3 918	318	374	692
40-59	3 397	4 657	8 054	884	1 593	2 477
60-79	6 766	8 373	15 139	1 642	3 162	4 804
80+	8 660	6 948	15 608	542	688	1 230
Total	**21 439**	**22 000**	**43 439**	**3 441**	**5 885**	**9 326**

Source: Detailed case information received by PHAC from provinces and territories

[a] Cases not identified as male or female were removed from the total due to small numbers.

Note: Cases with missing gender, sex or age were excluded. Where available, gender data was used; when gender data was unavailable, sex data was used. Reliable data on gender diverse respondents are unavailable due to small counts.

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Clustering and superspreading potential of SARS-CoV-2 infections in Hong Kong

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Superspreading events (SSEs) have characterized previous epidemics of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) infections[1–6]. For SARS-CoV-2, the degree to which SSEs are involved in transmission remains unclear, but there is growing evidence that SSEs might be a typical feature of COVID-19[7,8]. Using contact tracing data from 1,038 SARS-CoV-2 cases confirmed between 23 January and 28 April 2020 in Hong Kong, we identified and characterized all local clusters of infection. We identified 4–7 SSEs across 51 clusters ($n = 309$ cases) and estimated that 19% (95% confidence interval, 15–24%) of cases seeded 80% of all local transmission. Transmission in social settings was associated with more secondary cases than households when controlling for age ($P = 0.002$). Decreasing the delay between symptom onset and case confirmation did not result in fewer secondary cases ($P = 0.98$), although the odds that an individual being quarantined as a contact interrupted transmission was 14.4 (95% CI, 1.9–107.2). Public health authorities should focus on rapidly tracing and quarantining contacts, along with implementing restrictions targeting social settings to reduce the risk of SSEs and suppress SARS-CoV-2 transmission.

As of 25 August 2020 there were a total of 4,711 laboratory-confirmed cases of SARS-CoV-2 infection in Hong Kong. Since the first case was detected on 23 January, few were confirmed in Hong Kong up to 1 March, after which a substantial increase in international importations of COVID-19 cases (Fig. 1) resulted in a total ban on non-resident entry, mandatory 14-day monitored home quarantine for all resident arrivals and the implementation of various physical distancing measures[9]. After the number of cases began to subside, distancing measures were progressively relaxed from 8 May onward until a local resurgence of cases from 5 July brought their subsequent reintroduction (and maintenance at the time of writing).

For this study we collected information on 1,038 cases identified in Hong Kong up to 28 April. The majority (51.3%, 533/1,038) of SARS-CoV-2 infections confirmed during the study period (23 January–28 April) were associated with at least 1 of 137 clusters. Cases were linked to clusters (≥2 confirmed cases) based on the reported contact histories between cases (Methods). The median cluster size was 2 and the largest involved 106 cases (Extended Data Fig. 1). Of the cluster cases, 220 (41.3%, 220/533) belonged to 22 (22/137,16.0%) clusters initiated by another local case, compared to 89 (89/533, 16.7%) cases that belonged to 29 local clusters initiated by an imported case (29/137, 21.0%). However, most clusters were characterized as solely overseas-acquired (63.0%, 86/137) clusters and involved 224 cluster cases (42.0%, 224/533) where no onward local transmission could be identified but infection and contact between them (as family, friends or co-workers) was established overseas. Among the 505 sporadic cases not linked to any other case, 90.9% were acquired overseas (459/505), while the remaining 46 (9.1%) were sporadic cases infected locally based on recent travel histories. Overall, 31.4% (326/1,038) of all SARS-CoV-2 infections confirmed in Hong Kong during the study period were acquired within Hong Kong either within clusters or as untraceable sporadic local cases occurring through limited community transmission. Complete cluster composition is detailed in Supplementary Table 1. Of all cases confirmed in Hong Kong, 195 (18.8%, 195/1,038) were asymptomatic at confirmation (Supplementary Table 2) and, of these, most (83.1%, 162/195) were PCR-confirmed from 27 March onward (Extended Data Fig. 2).

The largest cluster comprised 106 cases and was traced back to a collection of four bars across Hong Kong (Fig. 2a), but the original source could not be determined. The first cases associated with this 'bar and band' cluster were reported for two customers who reported exposure to a bar in Lan Kwai Fong on 7 March (onset 11 March) before two staff members from the same bar fell ill on 10 and 11 March (confirmed on 24 and 25 March, Extended Data Fig. 3). Transmission to the other three bars is suspected to have occurred via a number of musicians who performed at the four venues. The earliest onset among the musicians was on 17 March, with most subsequently infected bar cases reporting exposures between 17 and 20 March; this constitutes at least one or more probable SSE (SSE #1). Of the 73 primary bar cases, 39 customers, 20 staff and 14 musicians were infected; the remaining 33 infections were secondary, tertiary or quaternary family, work or social contacts traced to the primary cases. This single outbreak accounted for 10.2% (106/1,038) of all cases in Hong Kong during the study period, regardless of source, and 32.5% of all locally acquired SARS-CoV2 infections (106/326).

The second-largest cluster comprised a total of 22 cases and was linked to two SSEs at a wedding and a preceding social event (Fig. 2b). Ten cases (SSE #2) resulted directly (and two indirectly) from the preceding social exposure (in total 13 cases including the source case); four of these subsequently attended the wedding. Transmission between wedding attendees could not be determined, but at least seven additional infections were confirmed among other guests (SSE #3). Two additional cases were identified among family members of an infected wedding guest. The third-largest cluster

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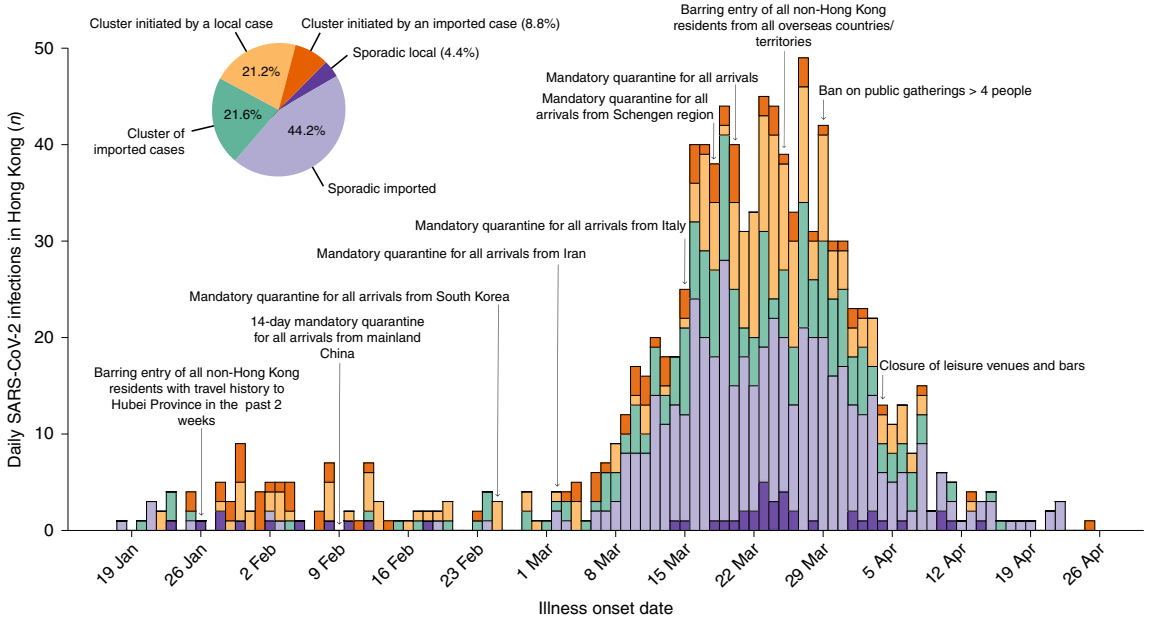

Fig. 1 | Epidemic curve of daily cases of laboratory-confirmed SARS-CoV-2 infection in Hong Kong by symptom onset date and colored by cluster category ($n=1,038$). The dates of major travel and community health interventions are indicated with arrows. Asymptomatic cases are included here by date of confirmation.

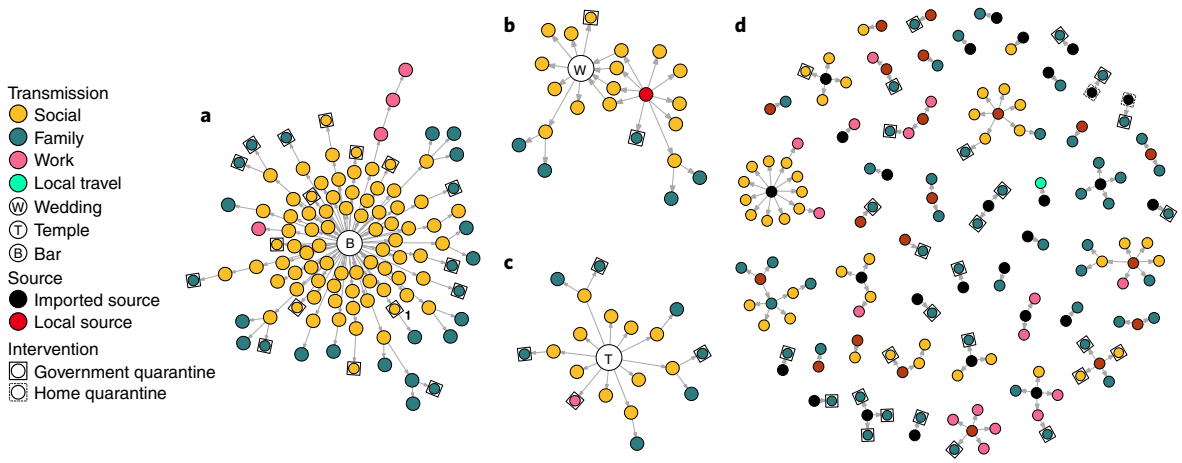

Fig. 2 | Chains of SARS-CoV-2 transmission in Hong Kong initiated by local or imported cases. a, Transmission network of the 'bar and band' cluster of undetermined source ($n=106$). **b**, Transmission network associated with a wedding without clear infector–infectee pairs but linked back to a preceding social gathering and local source ($n=22$). **c**, Transmission network associated with a temple cluster of undetermined source ($n=19$). **d**, All other clusters of SARS-CoV-2 infections where the source and transmission chain could be determined.

totaled 19 cases and was associated with attendance at a local temple, with 12 cases directly linked (SSE #4) to exposure at the temple (Fig. 2c). The seven remaining cases ($n=7/19$) were linked via secondary family exposures. The most recent case confirmed in this cluster was a monk who worked at the temple and reported no symptoms before confirmation. It is probable, but not definitive, that given the other 11 primary cases reported attending the temple over multiple days, the monk was the source of some or all of the other 11 temple cases[10]. All remaining local and imported SARS-CoV-2 clusters in Hong Kong, including three additional SSEs (SSE #5–7), are shown in Fig. 2d. In total we directly observed two to four SSEs (given a superspreading threshold of 6–8 secondary cases; Methods) where the sources were identified, or four to seven SSEs if including SSEs without a determined source.

Among the 533 cluster cases, all 224 solely overseas-acquired cluster cases were excluded from subsequent paired analyses due to uncertainties concerning the chain of transmission while overseas. For the remaining 309 cases within clusters initiated by a local or imported infection, 244 (244/309, 79.0%) were identified into 169 unique infector–infectee transmission pairs, with 91 unique infectors. The median serial interval (time between reported onset dates of all symptomatic infector–infectee pairs, $n=142$) was 4 days (interquartile range (IQR), 3–9 days), and the mean of the fitted normal distribution was 5.8 days (Fig. 3a, Supplementary Table 3 and Extended Data Fig. 4a). Seven instances of likely pre-symptomatic transmission were observed where onset of the infectee preceded that of the infector or occurred on the same day. The ages (two-sided t-test, $P=0.18$) and sex ($\chi^2=0.17$ $P=0.68$) of

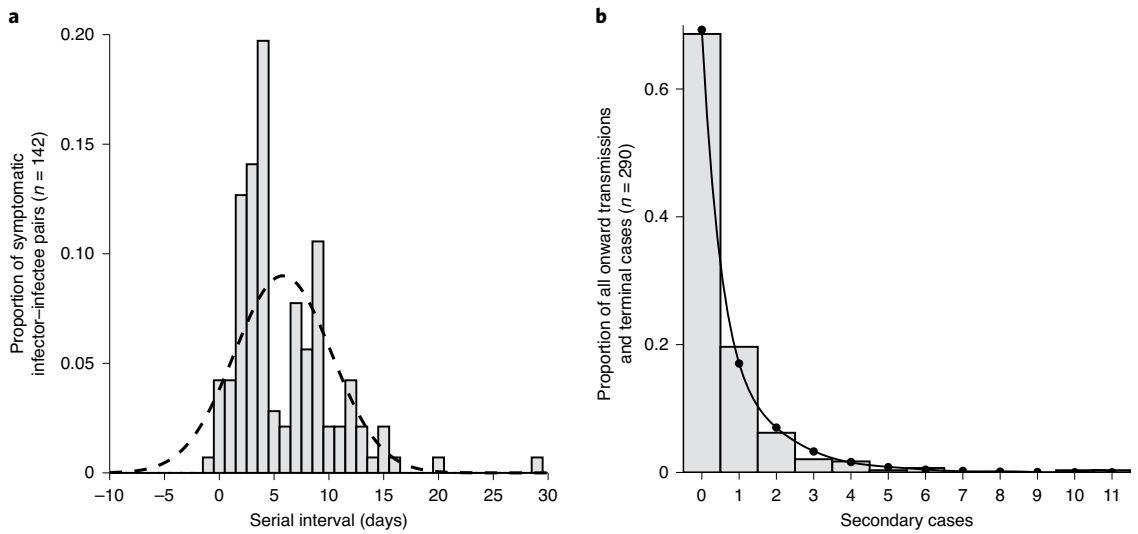

Fig. 3 | Characteristics of SARS-CoV-2 transmission in Hong Kong. a, Serial interval distribution of SARS-CoV-2 infections in Hong Kong among $n=142$ symptomatic infector–infectee pairs and the fitted normal distribution. This excludes 27 asymptomatic pairs (either as infector or infectee) due to a lack of symptom onset dates. **b**, Observed offspring distribution of $n=91$ SARS-CoV-2 infectors, $n=153$ terminal infectees and $n=46$ sporadic local cases in Hong Kong and corresponding fitted negative binomial distribution with parameters $R=0.58$ and $k=0.43$.

the infectors and infectees were not significantly different; however, a significantly higher risk of transmission was observed between cases of similar age ($P<0.001$, Extended Data Fig. 5).

From the observed offspring distribution and negative binomial distribution, we estimated an overall reproductive number, R, of 0.58 (95% confidence interval (CI), 0.45–0.72) and dispersion parameter, k, of 0.43 (95% CI, 0.29–0.67) during the study period (Fig. 3b, Supplementary Table 4 and Extended Data Fig. 4b). Because not all cases could be clearly linked into infector–infectee pairs using epidemiological data alone (35/309, 11.0%), a likelihood model based on the final size of all local clusters (cluster size model) was implemented to account for any potential bias. This increased the estimate of R to 0.74 (95% CI, 0.58–0.97) and decreased k to 0.33 (95% CI, 0.14–0.98). From these estimates we inferred that 17–19% (cluster size model and observed offspring distribution, respectively) of SARS-CoV-2 infections were responsible for 80% of all transmission events in Hong Kong, while 69% of cases did not infect anyone (Supplementary Table 5).

Additional sensitivity analyses slightly increased ($R=0.62$, 95% CI, 0.49–0.80) and decreased ($k=0.35$, 95% CI, 0.25–0.56) the estimates of R and k, respectively (relative to the observed offspring distribution) following the addition of likely but unconfirmed infector–infectee pairs from the wedding and temple clusters to the observed offspring distribution. Here, we assumed a single wedding guest infected seven other wedding guests and the temple monk infected all 11 other primary cases (Fig. 2b,c). These scenario estimates differed again ($R=0.72$, 95% CI, 0.53–0.94; $k=0.19$, 95% CI, 0.13–0.26) when assuming a single musician was the source of 67 unresolved bar and band cluster cases, excluding the earlier cases preceding the musician. Given these scenarios, the expected proportion of cases responsible for 80% of all SARS-CoV-2 transmission in Hong Kong was 18% (14–23%) in the first scenario and 13% (10–17%) in the second (Supplementary Table 5).

These results, however, should be interpreted in the context of constrained community transmission given the moderate levels of physical distancing practiced in Hong Kong, including school closures, some adults working at home, cancellation of mass gatherings, as well as improved hygiene and universal mask wearing, which exceeded 98% compliance from February onward[11,12]. In the absence of such policies it is possible that even greater levels of superspreading could be expected. For example, findings from Shenzhen (China)[13] estimated roughly comparable levels of SARS-CoV-2 overdispersion using contact tracing data ($k=0.58$, 95% CI, 0.35–1.18), but a study from Singapore[14] reported $k=0.11$ (95% CI, 0.05–0.25). Other studies utilizing global cluster size datasets have estimated similarly high potential for SARS-CoV-2 superspreading ($k=0.10$, 95% CI, 0.05–0.20), which together suggest that as few as 10% of cases could account for 80% of all SARS-CoV-2 transmission[15]. However, such extreme degrees of overdispersion can be advantageous to disease control efforts if interventions can effectively target the core high-risk groups or settings responsible for the majority of transmission[16,17].

We observed transmission within family households most frequently (92/169, 54.4%), followed by social (56/169, 33.1%) and work (20/169, 11.8%) settings. Social settings, however, were associated with both younger cases ($P=0.026$, Wilcoxon test) and more secondary cases compared to households with ($P<0.001$, negative binomial regression) and without ($P=0.002$) controlling for the age of individual infectors, although this was not the case for households versus work settings (Wilcoxon test, $P=0.64$; regression, $P=0.92$). Social venues such as bars, weddings, religious sites and restaurants, which have also been linked to an increased risk of SSE elsewhere[18], therefore appear at increased risk for large outbreaks and likely constitute the core behavioral risk factor for SARS-CoV-2 SSEs. This is certainly due to the greater numbers of contacts expected in such settings; however, owing to a lack of reported numbers on confirmed contacts who tested negative, we were unable to control for this in our study. We also cannot account for any potential selection bias in our results where small family clusters are more readily traceable than smaller social clusters, which might go unrecognized, thus biasing estimates of their frequency and size. Regardless, the potential for increased transmission or SSEs within social settings is apparent, and suppression measures should therefore focus on eliminating the risk of superspreading by reducing the numbers of contacts within such settings. This could be achieved either via venue closures, reduced capacity measures/physical distancing policies and mask usage[11].

Previous modeling has suggested that reduced delays between symptom onset and confirmation are important indicators in the control of SARS-CoV-2 outbreaks[16]. In our analysis, decreasing

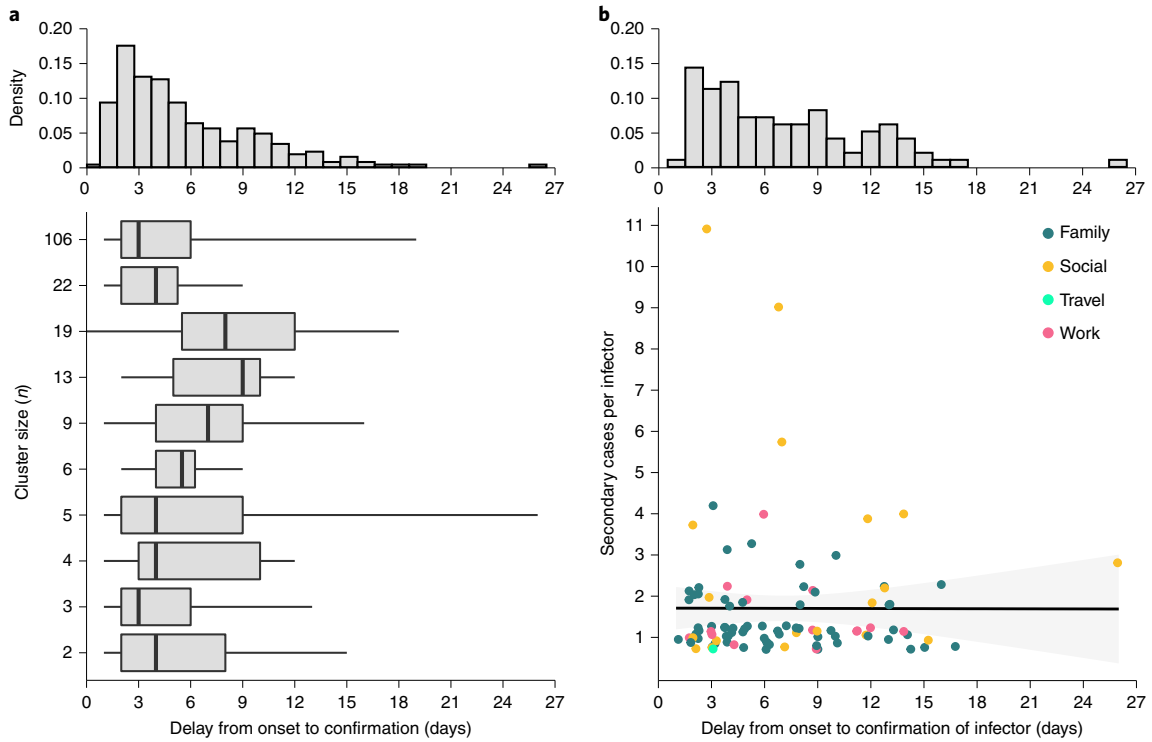

Fig. 4 | Delay from onset of symptoms to confirmation of SARS-CoV-2 infection in Hong Kong. a, Distribution and marginal density of delay in days from symptom onset to confirmation of $n=269$ local cluster cases by cluster size (excludes 40 asymptomatic cluster cases without reported onset dates). Whiskers identify the minima and maxima of the delays, bounds of boxes the 75th and 25th percentiles, and the center line the median. **b**, Delay from symptom onset to confirmation of $n=98$ symptomatic infectors (excludes two asymptomatic infectors) by the number of secondary infections and setting of contact. There is no linear relationship between an infector's delay to confirmation and the number of secondary infections (linear regression, $F<0.001$, d.f. $=96$, $R^2=-0.01$, two-sided $P=0.98$ without adjustment for multiple comparison). The center line of the regression indicates the conditional mean of the model and the shaded area the 95% CI. Note that both the number of secondary cases per infector and days from onset to confirmation are discrete integers (not continuous), but have been plotted here with a slight jitter to aid visualization.

delays from symptom onset to confirmation did not appear to correlate with smaller local cluster sizes (Fig. 4a) unless excluding the two largest clusters ($N<20$) (linear regression, $F=21.09$, d.f. $=6$, $R^2=-0.74$, two-sided $P=0.004$). However, among recognized transmission pairs, there was no linear relationship between increasing delay to confirmation of infectors and more secondary cases (Fig. 4b). By contrast, for SARS-CoV in 2003, delays in individual case confirmation had an adverse effect on disease control due to increased viral shedding during the late symptomatic period, which was highest approximately seven days after symptom onset[19–21]. For COVID-19, confirmation and isolation of cases will therefore have a limited effect on reducing transmission unless done very quickly, also noting the growing body of evidence of transmission during the pre- and early symptomatic periods[22–24]. In Hong Kong, the median time from symptom onset to confirmation was four days for local cluster cases and six days for infectors and, by this time, any onward transmission may have already occurred, although this does not take into account possible self-isolation prior to confirmation.

Sequestering confirmed contacts of cases to mandatory government quarantine was very effective at terminating chains of transmission. In total, 51 local cluster cases were placed in quarantine after identification as a close contact of a confirmed case but prior to their own confirmation. This total excludes two imported cases under travel-related home quarantine. Of the 189 cases terminal to the observable chain of transmission, 45 were first placed in government quarantine as contacts (23.8%, $n=45/189$). Only one quarantined contact, later confirmed as an asymptomatic case, was found to have passed on infection before sequestration (Fig. 2a,1). The odds, therefore, that a case was placed in government quarantine as a contact and terminated the chain of transmission (terminal case) was 14.4 (95% CI, 1.9–107.2, Supplementary Table 6). The most important public health measures are therefore likely to be early case identification followed by rapid and parallel (before contacts are confirmed as cases) contact tracing and quarantine (though we did not have data on the timing of contract tracing in relation to case confirmation, nor the timing of subsequent testing). Beyond such active suppression measures, intermittent physical distancing in high-risk social environments (together with mask wearing) may also be required to reduce transmission from unidentified infections and pre-symptomatic transmission, but must necessarily be balanced with the social, economic and educational costs associated with such policies. Notably, among infections acquired in Hong Kong, 14.1% (46/326) were sporadic local cases (that is, cases with neither traceable contact with another case/cluster nor a history of recent travel). This untraceable fraction could be interpreted as an upper bound on the proportion of transmission arising from anonymous interactions, fomites and/or aerosols. However, this finding may have to be restricted to the context of places similar to Hong Kong, where there is a widespread adoption of suppression measures[12].

Our study has some limitations. Primarily, because this study relies on contact tracing data, any degree of incompleteness in case and/or contact ascertainment could bias our results. Given that the source of 46 sporadic local cases could not be determined, as noted above, nor the source of 22 local index cluster cases, a degree of incompleteness and therefore bias is expected. In

Table 1 | Policy summary

Background	
Superspreading is a common feature of past betacoronavirus epidemics of SARS-CoV and MERS-CoV. We used contact tracing data to characterize SARS-CoV-2 clusters in Hong Kong and estimate the potential for superspreading while quantifying associated risks.	
Main findings and limitations	
Our findings indicate that there is substantial potential for SARS-CoV-2 superspreading. SARS-CoV-2 exhibits a high degree of individual transmission heterogeneity, and we estimate that 19% of SARS-CoV-2 infections in Hong Kong were responsible for 80% of all transmissions, while 69% of cases did not transmit to anyone. Gatherings in social settings such as bars, restaurants, weddings and religious sites appear to be at increased risk of superspreading events. Transmission in social settings was significantly associated with an increased number of secondary cases compared to transmission observed in family households. These findings take advantage of the quality of case ascertainment and contact tracing data in Hong Kong, although some incompleteness in links between cases could potentially bias our estimates of transmission heterogeneity.	
Policy implications	
These results suggest that reducing the occurrence of superspreading events by limiting gatherings in social settings can have a disproportionate effect on reducing SARS-CoV-2 transmission, which has important policy implications concerning the approach to COVID-19 suppression measures around the world.	

fact, the expected difference between R (biased downward) and k (biased upward) from our observed estimates and our cluster size model (Supplementary Table 5) indicates the presence of such bias. However, the inference of R and k in our cluster size model can also be affected by bias, where R may be underestimated due to imperfect case ascertainment or overestimated when larger clusters are more readily observed than smaller clusters[25]. In either case, however, k is more likely to be overestimated, as imperfect observation, regardless of the cause, tends to bias estimates toward greater transmission homogeneity[25]. This means that the potential for SARS-CoV-2 superspreading, as already suggested, and shown elsewhere[15], could be greater than our results suggest.

It is also possible that some cases may have been incorrectly attributed to clusters where the true source infection was elsewhere, such as an undetected or asymptomatic case, despite evidence of close contact. However, because there appears to be little evidence of widespread community transmission in Hong Kong during the study period (only 31.4% (326/1,038) of all confirmed cases acquired SARS-CoV-2 in Hong Kong), the risk of such an occurrence is low, albeit not zero. Interestingly, our dataset did not contain any instances of nosocomial transmission, which has been observed for SARS-CoV-2[26,27]. It should be noted, however, that hospital infection control in Hong Kong substantially strengthened following the 2002–2003 SARS epidemic. Seroprevalence studies among frontline healthcare workers in Hong Kong will be able to confirm the effectiveness of infection control and whether any unrecognized nosocomial transmission has occurred. Future studies could also incorporate SARS-CoV-2 genetic sequence data to assist in uncovering hidden chains of transmission within the city (including within hospitals) and to discretize clusters more accurately.

Overall, there is substantial heterogeneity in the transmissibility of SARS-CoV-2 infection and therefore potential for superspreading with COVID-19. SSEs pose considerable challenges for local SARS-CoV-2 control as they can quickly overwhelm contact tracing capacity, although most infected persons will generate few or no secondary infections but a small fraction can generate many. Indeed, we observed that 19% (15–24%) of cases were responsible for 80% of all SARS-CoV-2 transmission in Hong Kong (Supplementary Table 5), while 69% (65–71%) of cases did not transmit to anyone. Assuming that local elimination is not possible, disease control efforts should focus on the rapid tracing and quarantine of confirmed contacts, along with the implementation of physical distancing policies including either closures or reduced capacity measures targeting high-risk social settings such as bars, weddings, religious sites and restaurants to prevent the occurrence of SSEs; this would have considerable effect in reducing the overall reproductive number. In lieu of an effective and widely available vaccine, these results have important implications for the control of COVID-19 and the implementation and continuation of public health measures such as physical distancing policies and lockdowns around the world (Table 1).

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-020-1092-0.

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Methods

Characterization of clusters and chains of SARS-CoV-2 transmission. Using case line lists and contact tracing data collected in Microsoft Excel by the Centre for Health Protection (CHP) of the Department of Health in Hong Kong, we characterized clusters of SARS-CoV-2 infections and chains of transmission within clusters up to 7 May 2020. All cases of SARS-CoV-2 infection were laboratory-confirmed via nasopharyngeal swab and PCR with reverse transcription (RT-PCR). In Hong Kong, all contacts of a confirmed case are traced and sent to mandatory government quarantine facilities for 14 days if negative at identification, or admitted to hospital if testing positive, regardless of symptom presentation. A close contact was defined as someone with prolonged face-to-face interaction with a confirmed case (with or without prior symptoms) in excess of 2 h if both persons were wearing a mask or 15 min without mask usage. However, data on mask usage among cases and contacts was not provided. Quarantined contacts who test positive in quarantine are transferred and isolated in hospital, while those who test negative at the end of the quarantine period are released back into the community. For imported cases, self-isolation at home (home quarantine) was mandatory (for all returning residents) if arriving after 20 March 2020.

We defined clusters as two or more confirmed infections with reported close contact. Local clusters were characterized by the travel history of the index case as either initiated by an imported case (that is, index acquired SARS-CoV-2 infection overseas based on reported onset dates and a recent history of overseas travel given a maximum 14-day incubation period) or initiated by a local case. Clusters of solely imported cases were characterized as overseas-acquired clusters if all cases were determined to have acquired SARS-CoV-2 infection overseas as before. Cases not linked to any cluster were categorized as sporadic local cases or sporadic imported cases if infection was acquired locally or overseas, respectively.

For cases within local and imported clusters (excludes overseas clusters), probable infector–infectee transmission pairs and chains of transmission within clusters were determined from reported contact histories data provided by the CHP. Within clusters, the case with the earliest onset date was considered the source of subsequent cases where contact was confirmed within the primary cluster setting. Subsequent transmission generations and clusters settings (secondary, tertiary, quaternary and so on) were traced back to the primary cluster case based on the reported contact histories only and did not rely on symptom onset dates, meaning that instances of asymptomatic or pre-symptomatic transmission were possible from cases intermediate to the chain of transmission. In such cases, asymptomatic transmission was characterized among infector–infectee pairs where close contact was confirmed and the infector reported no symptoms before confirmation, while pre-symptomatic transmission was characterized when the difference in days between the reported symptom onset of infector–infectee pairs was a non-positive integer. Symptom presentation was screened only at detection/confirmation by a healthcare professional including retrospective self-report of onset dates. Cases within the largest clusters where the source and chain of transmission were highly uncertain were excluded from the paired analysis; however, subsequent generations of transmission where the source case could be linked to the primary setting were not excluded (for example results see Fig. 2a–c). The effect of quarantining contacts on eliminating onward transmission was determined by odds ratios given the terminal or intermediate position of the contact (later confirmed as a case) in the chain of transmission. Each transmission pair was characterized by the reported setting of contact as either family, social, work or local travel (such as on public transport).

Statistical analyses. The age and sex of unique infectors ($n=91$) versus infectees ($n=169$) were compared using a two-sided t-test and χ^2 test, respectively. The age relationship between paired infector and infectee was assessed by linear regression ($n=169$). We modeled the relationship between the number of secondary cases per infector by transmission setting using negative binomial regression with and without controlling for infector age. We used 'family' as the reference category while excluding 'travel' due to the small sample size ($n=99$ unique infectors with seven infectors included more than once because they were associated with onward transmission across two or more settings but excluding one pair with transmission related to travel). Differences in the age of infectors ($n=99$) by setting and all cases by setting (infectors $n=99$ and infectees $n=168$, excluding one infectee via travel) were assessed using non-parametric Kruskal–Wallis and Wilcoxon rank-sum tests, without adjustment for multiple comparisons. We modeled the relationship between the delay in days from symptom onset to confirmation and the number of secondary cases per infector by linear regression as a proxy for individual duration of potential infectiousness in the community ($n=98$ infectors, including one travel-related infector but excluding two asymptomatic infectors whose delay could not be calculated). The mean delay from symptom onset to confirmation of 269 symptomatic cases within local clusters was also assessed by linear regression by cluster size with (10 discrete cluster sizes) and without (eight discrete cluster sizes) excluding the largest two clusters.

Serial interval and observed offspring distribution. We calculated serial intervals as the difference between the symptom onset dates of each infector–infectee pair, excluding asymptomatic cases, and fitted normal, lognormal, gamma and Weibull distributions using the R package 'fitdistrplus' by maximum-likelihood, excluding seven non-positive intervals for the latter three distributions. We generated the observed offspring distribution by calculating the number of secondary cases and similarly fit negative binomial, geometric and Poisson distributions as before. Cases terminal to the inferred chain of transmission and sporadic local cases were considered to have zero secondary cases. We compared each fit distribution using Akaike information criterion (AIC) scores and calculated confidence intervals for parameters from 1,000 bootstrapped replicates.

Superspreading and individual variance of SARS-CoV-2 transmission. Following the approach described by Lloyd Smith et al., estimates of the effective reproductive number (R) were determined from the mean of the negative binomial distribution fit to the observed offspring distribution, and the degree of transmission heterogeneity from the corresponding dispersion parameter k (ref. [28]). This was performed for all resolved pairs within clusters, including later generation pairs where prior transmission chains could not be determined from epidemiological data alone, which were excluded from the primary analysis. Owing to potential biases affecting the observed offspring distributions resulting from these exclusions, we performed a sensitivity analysis by generated two additional offspring distributions based on presumed but unconfirmed transmission scenarios (described in the results) where evidence was indicative but insufficient to fully resolve all pairs within clusters in the primary analysis. Furthermore, we implemented a likelihood-based branching process model to jointly infer R and k based on the final size of all local clusters, where sporadic local cases were considered clusters of size one as per Kucharski and Althaus[29]. For a given range of values for R (0.10–3.00) and k (0.01–55), the probability that an index case generates n_j clusters of size j is given by[25,30]

$$r_j = \frac{\Gamma(kj+j-1)}{\Gamma(kj)\Gamma(j+1)} \frac{\left(\frac{R_0}{k}\right)^{j-1}}{\left(1+\frac{R_0}{k}\right)^{kj+j-1}}$$

and the likelihood, assuming that the branching chains are self-limited, is

$$L = \prod_{j=1}^{\infty} r_j^{n_j}$$

We repeated the above analyses after sub-setting the data into epochs (epoch one, January–February 2020; epoch two, March–May 2020) by illness onset date of the infector (observed offspring distribution) or the onset date of each cluster's index case (cluster size model). Following from ref. [15], given parameters R and k, the expected proportion of cases responsible for 80% of transmission in Hong Kong is given by

$$1 - P80\% = \int_0^X \mathrm{NB}\left(\lfloor x \rfloor; k, \frac{k}{R_0+k}\right) \mathrm{d}x$$

where X satisfies

$$1 - 0.8 = \frac{1}{R_0} \int_0^X \lfloor x \rfloor \mathrm{NB}\left(\lfloor x \rfloor; k, \frac{k}{R_0+k}\right) \mathrm{d}x$$

and

$$\frac{1}{R_0} \int_0^X \lfloor x \rfloor \mathrm{NB}\left(\lfloor x \rfloor; k, \frac{k}{R_0+k}\right) \mathrm{d}x = \int_0^{X-1} \mathrm{NB}\left(\lfloor x \rfloor; k+1, \frac{k}{R_0+k}\right) \mathrm{d}x$$

The proportion of cases responsible for 0% of transmission (that is, did not spread to anyone) was calculated from the negative binomial distributions given all calculated parameters R and k where the number of secondary cases was input as zero ($x=0$). Finally, when given R_0, the superspreading threshold can be calculated as the 99th percentile of the Poisson(R_0) distribution[28] where $\Pr\left(Z \leq Z^{(99)} | Z \sim \mathrm{Poisson}(R_0)\right) = 0.01$. Therefore, with the global consensus of R_0 in the range 2–3 (refs. [31,32]), we defined the superspreading threshold for SARS-CoV-2 here as 6 to 8 secondary cases. All statistical analyses were performed in R version 3.6.1 (R Foundation for Statistical Computing). Ethics approval for this study was obtained from the Institutional Review Board of the University of Hong Kong. Data collection and analysis were part of a continuing public health outbreak investigation. Accordingly, informed consent to be included in this study was not required.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

All anonymized data collected is publicly available at https://github.com/dcadam/covid-19-sse.

Code availability

The code used for analysis is publicly available at https://github.com/dcadam/covid-19-sse.

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Author contributions

The study was conceived by D.C.A. and B.J.C. Data were analyzed by D.C.A., J.Y.W., E.H.Y.L. and T.K.T. and interpreted by D.C.A., P.W., S.C., G.M.L. and B.J.C. D.C.A. wrote the first draft of the manuscript, which was revised by D.C.A., P.W., G.M.L. and B.J.C. All authors approved the final version of the manuscript.

Competing interests

B.J.C. consults for Roche and Sanofi Pasteur. The authors declare no other competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-020-1092-0.

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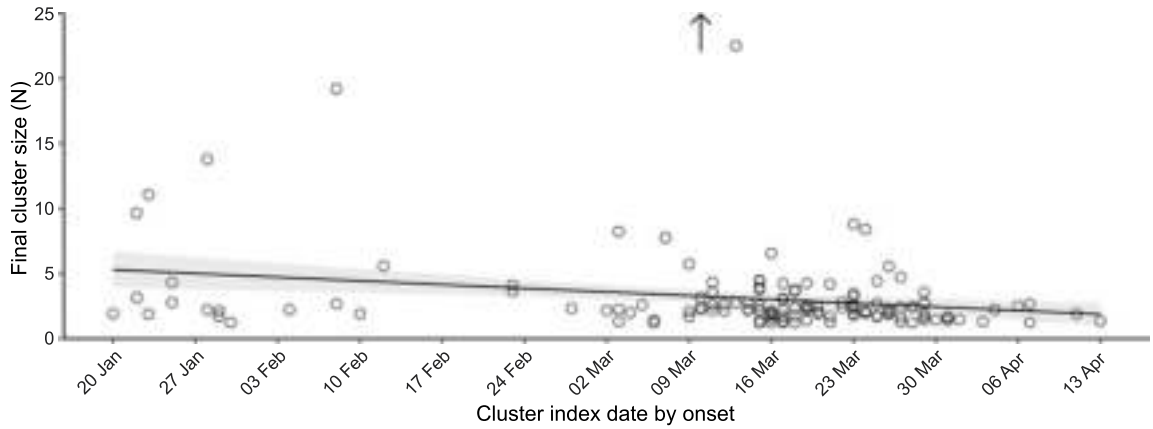
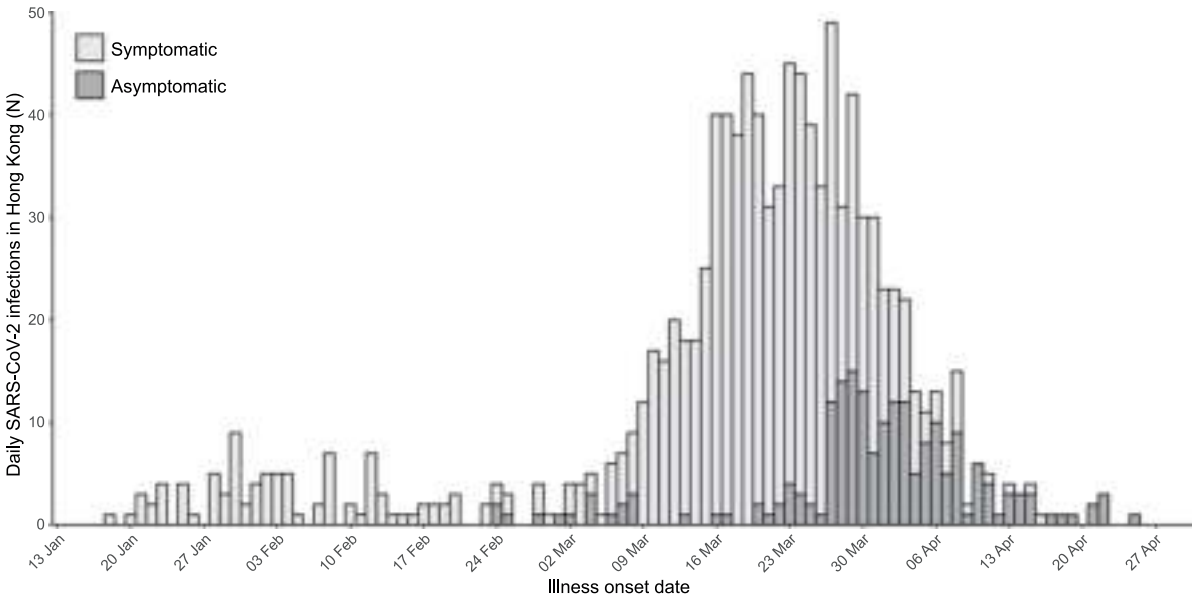
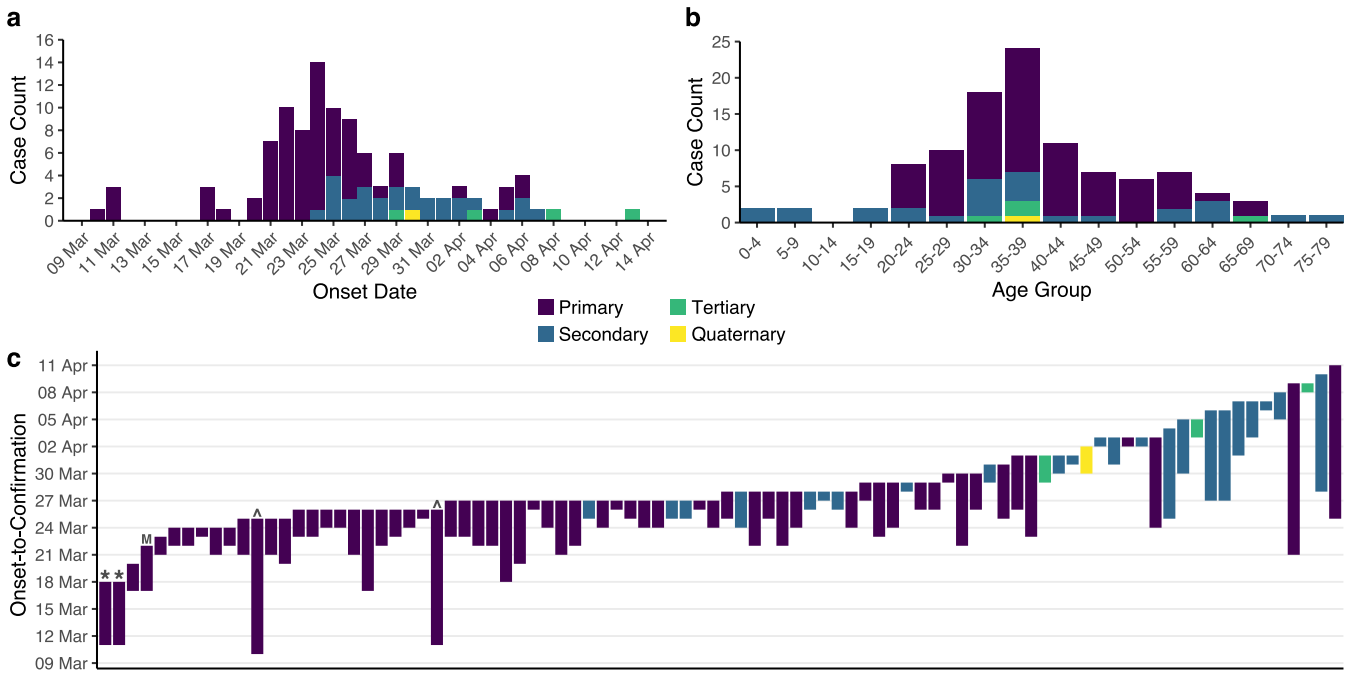


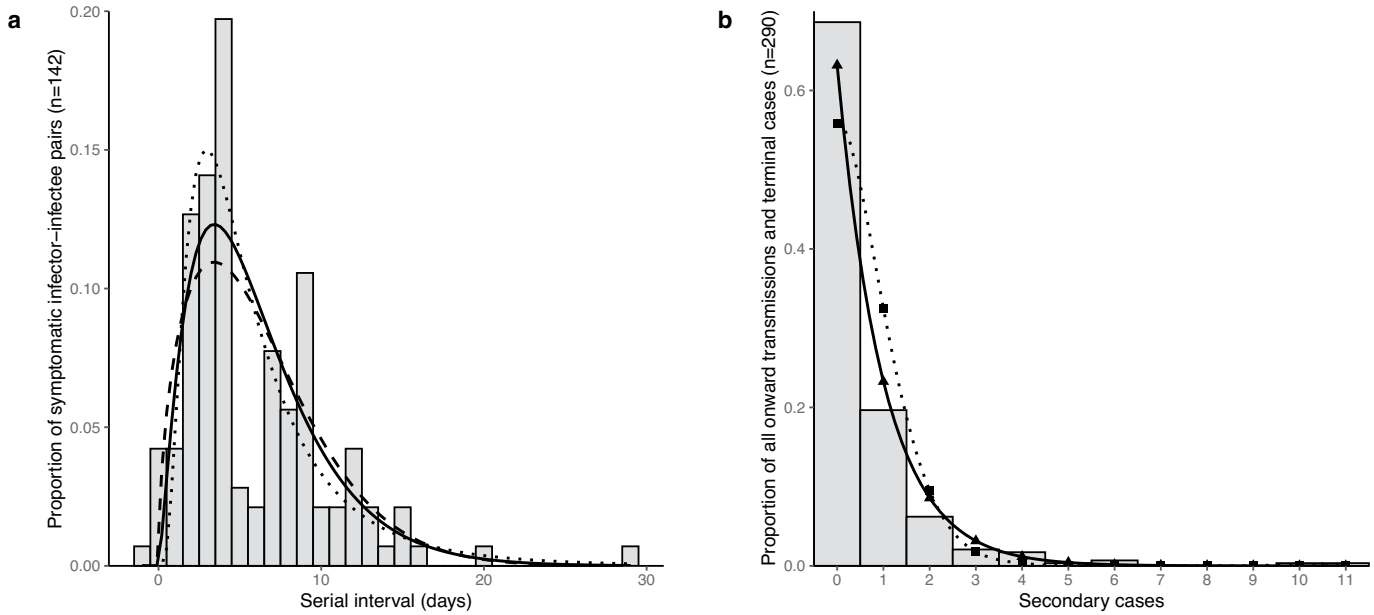
Extended Data Fig. 1 | SARS-CoV-2 cluster size in Hong Kong by onset date of the index case. SARS-CoV-2 cluster size in Hong Kong by onset date of the index case. Arrow indicates the earliest onset position (2020-03-10) of the largest local SARS-CoV-2 cluster (N = 106 cases) which is excluded here for visualization purposes only. The decreasing trend in clusters size was not significant (linear regression, F = 1.25, df = 135, R^2 = 0.001, p-value = 0.27). Shaded area indicates the 95% confidence interval of the regression. Final cluster sizes are plotted as integers however a slight vertical jitter is applied here also for visualization purposes.



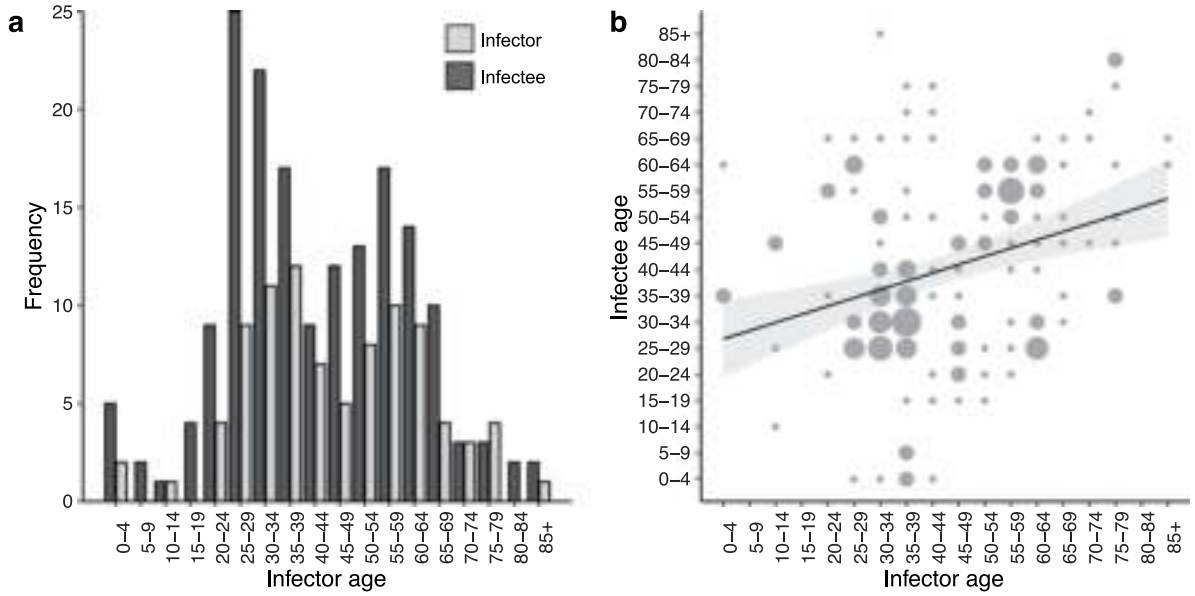
Extended Data Fig. 2 | Epidemic curve of daily SARS-CoV-2 infection in Hong Kong by symptom presentation. Epidemic curve of daily SARS-CoV-2 infection in Hong Kong by symptom presentation. Asymptomatic cases are indexed here by detection/confirmation date otherwise illness onset date is used. (Total = 1,038; Symptomatic = 843 [81.2%]; Asymptomatic = 195 [18.8%]).



Extended Data Fig. 3 | Characteristics of 106 'bar and band' SARS-CoV-2 cluster cases in Hong Kong. a, Epidemic curve of cases by onset date and transmission generation. Asymptomatic cases are included by date of confirmation. **b**, Age distribution of cases by generation. **c**, Period of symptom onset-to-confirmation and isolation of cases Asymptomatic cases are excluded due to a lack of reported onset date. *Two of the first customers described in the results with the earliest exposure dates linked to the cluster. ^Two staff at the first bar with the earliest onset and extended periods from onset to isolation. MThe first musician case who traveled between the other bars and is a potential but unconfirmed source of the remaining primary cases many of which reported exposure to the bar between the infectious period of the musician.



Extended Data Fig. 4 | Characteristics of SARS-CoV-2 transmission in Hong Kong with additional fitted distributions. a, Serial interval distribution among symptomatic SARS-CoV-2 infector-infectee pairs (n = 142) with fitted gamma (solid line), Weibull (dashed line) and lognormal (dotted) distributions. All distributions were fitted excluding observations ≤0. **b**, Empirical offspring distribution of n = 91 SARS-CoV-2 infectors, n = 153 terminal infectees and n = 46 sporadic local cases in Hong Kong with fitted geometric (solid – triangle) and Poisson distributions (dotted – square). Distribution parameters for a and b are shown in Supplementary Tables 3, 4.



Extended Data Fig. 5 | Age comparison among and between 169 SARS-CoV-2 transmission pairs. a, Age group distribution of infectors and infectees. The mean age difference between infectors (μ = 42.5) and infectees (μ = 46.1) was not significantly different (Two-sided t-test, t = −1.33 [−7.57, 1.49], df = 193.88, p-value = 0.18 without adjustment. Pairs were dependent only on the intermediate position in the transmission chain, so cases could be both an infector and infectee. **b**, Contact patterns among pairs by age group. The size of each point indicates the relative number of pairs in each combination. A significant positive trend by age group is shown (linear regression, F = 15.24, df = 156, R2 = 0.08, two=sided p-value = 0.000141 without adjustment). Shaded area indicates the 95% confidence interval of the regression. Age was missing for one case confirmed outside of Hong Kong and is excluded here.

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n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☒	☐	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Data was collected in MS Excel 365
Data analysis	All analyses were conducted with R version 3.6.1 (R Development Core Team, Vienna, Austria) and the 'fitdisterplus' package v1.0-14. Code for all analyses and figure production is available from https://github.com/dcadam/covid-19-sse

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

All anonymized data collected and used for analysis are publicly available at https://github.com/dcadam/covid-19-sse

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Analysis was based on all available data on 1,038 COVID-19 cases in Hong Kong as of 28 April 2020
Data exclusions	No exclusions
Replication	This was an observational study collecting all available data without experimental conditions so no replication was necessary
Randomization	This was an observational study collecting all available data without experimental conditions so no randomization was necessary
Blinding	This was an observational study collecting all available data without experimental conditions so no blinding was necessary

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	All COVID-19 patients in Hong Kong reported by the Centre for Health Protection of Hong Kong Special Administrative Region. Data collected included age, sex (M/F), symptom presentation (Y/N), date of symptom onset (if symptomatic), date of confirmation, contact setting with another confirmed case, quarantined as a contact of another case (Y/N) and travel-history.
Recruitment	No recruitment was necessary.
Ethics oversight	Ethics approval for this study was obtained from the Institutional Review Board of the University of Hong Kong. Data collection and analysis were part of a continuing public health outbreak investigation. Informed consent was not required.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Enhanced Epidemiologic Summary

COVID-19 Outbreaks and Cases in Ontario, by Setting: February 16, 2020 to December 26, 2020

This report includes the most current information available from the Ontario Ministry of Health (MOH) Case and Contact Management Solution (CCM) and other case management systems (CCM plus) as of **January 11, 2021.**

Please visit the interactive Ontario COVID-19 Data Tool to explore recent COVID-19 data by public health unit, age group, sex, and trends over time.[1] A Daily Epidemiological Summary, a Weekly Epidemiological Summary, as well as additional Enhanced Epidemiological Reports are available on the Public Health Ontario website.[2,3]

Purpose

This report provides an epidemiologic summary of cumulative confirmed COVID-19 outbreaks and outbreak-associated cases in Ontario by setting, with a focus on outbreaks and cases reported from other settings (i.e., outbreaks and associated cases outside of congregate care, congregate living and education settings). This report includes all COVID-19 cases linked to an outbreak.

Highlights

- In Ontario, from February 16, 2020 to December 26, 2020, there were 39,774 confirmed COVID-19 cases associated with 4,151 outbreaks reported across all settings. In comparison, there were 136,496 non-outbreak associated cases of COVID-19 reported in Ontario during the same period.
- Of the 4,151 outbreaks, 38.8% were in congregate care settings, 11.3% in congregate living settings, 17.7% in education settings, and 32.2% in other settings (Table 1).
    - Overall, long-term care homes (within congregate care settings) accounted for the largest proportion of all outbreaks (905/4,151, 21.8%).
    - Within other settings, workplaces accounted for the majority of outbreaks (872/1,335, 65.3%).
- Of the 39,774 outbreak-associated cases, 63.2% were in congregate care settings, 7.1% in congregate living settings, 6.2% in education settings, and 23.5% in other settings (Table 2).
    - Overall, long-term care homes accounted for the largest proportion of all reported outbreak-associated cases (18,475/39,774, 46.4%).

    - Within other settings, workplaces accounted for the majority of outbreak-associated cases (6,991/9,344, 74.8%).

    - Overall, across all setting types, a median of 2 cases (interquartile range [IQR]: 1-6) per outbreak was reported, with the highest median associated with farm workplace outbreaks (median of 14 cases per outbreak, maximum of 240 cases).

- Deaths were reported in 9.3% of all outbreak associated cases (Table 3).

    - Overall, long-term care homes accounted for the largest proportion of all outbreak-associated deaths (2,911/3,681, 79.1%).

- Compared to non-outbreak cases, a higher proportion of females and individuals 80 years and older were associated with outbreaks (Table 4).

- During the first wave of the pandemic, outbreaks were most commonly reported in congregate care settings. While fewer total outbreaks were reported during the first wave, these outbreaks were generally associated with more cases, peaking at 2,929 cases during week 16 (April 12, 2020 to April 18, 2020).

- In wave two, from August 30, 2020 (week 36) onward, the total number of outbreaks reported weekly increased. The number of outbreaks in congregate care continued to be significant, and outbreaks reported within congregate living, education, and other settings increased. Outbreak-associated cases have been steadily rising from week 36 onward.

Limitations

- The findings presented in this report include all cases and settings where local public health units declared an outbreak in a given setting. The outbreaks included in this report do not present the complete picture of settings where COVID-19 is being transmitted in Ontario, and may under-represent outbreaks in settings where contact tracing is more difficult.

- Outbreak-associated cases in this report do not include secondary cases acquired from outbreak-associated cases. As such, this report likely under-represents the true magnitude of cases impacted by a COVID-19 outbreak.

- Outbreak-associated cases in this report include all cases directly linked to an outbreak as determined by the local public health unit, but may not reflect where the case acquired the infection. Cases could represent employees, residents or members of the public.

- Definitions of outbreaks, including the number of cases, vary across settings. In addition, due to variations in data entry processes across public health units, some outbreaks included in this report may not have met the criteria included in an outbreak definition (i.e. size or duration of outbreak). Further there is no provincial outbreak definition for several setting types classified within the other settings category; as such, there may be variation in declaring outbreaks by public health unit.

- Trends in outbreaks reported across settings and within settings over time should be interpreted with caution, as provincial restrictions resulted in closures of several settings (e.g., school settings were subject to closure during wave one, and were permitted to open approximately

around week 36). The results in this report therefore do not represent a comprehensive assessment of risk in different settings.

Outbreak Characteristics

Table 1. Cumulative summary of confirmed COVID-19 outbreaks reported between February 16, 2020 and December 26, 2020, by setting type: Ontario

Setting Type	Number of outbreaks	Median number of cases per outbreak (IQR)	Maximum number of cases per outbreak	Median duration of closed outbreaks in days [1] (IQR)
Congregate care	**1,612**	**2 (1 - 9)**	**316**	**9 (0 - 21)**
Long-term care homes	905	2 (1 - 8)	316	9 (0 - 22)
Retirement homes	475	2 (1 - 7)	128	6 (0 - 18)
Hospitals	232	6 (3 - 12)	103	13 (6 - 21)
Congregate living	**470**	**2 (1 - 6)**	**215**	**6 (0 - 13)**
Correctional facility	16	2 (1 - 18)	114	3 (0 - 20)
Shelter	86	2 (1 - 5)	215	3 (0 - 13)
Group home/supportive housing	309	2 (1 - 6)	84	6 (0 - 13)
Short-term accommodations	7	1 (1 - 3)	5	4 (2 - 4)
Congregate other	52	4 (1 - 8)	75	7 (1 - 14)
Education	**734**	**2 (1 - 4)**	**50**	**6 (2 - 11)**
Child care	238	1 (1 - 2)	28	3 (0 - 9)
School – Elementary[2]	348	3 (2 - 4)	50	7 (4 - 12)
School – Elementary/secondary[2]	24	4 (2 - 6)	46	6 (2 - 14)
School – Secondary[2]	111	2 (2 - 5)	40	9 (5 - 16)
School – Post-secondary[2]	13	2 (2 - 3)	9	5 (5 - 6)

Setting Type	Number of outbreaks	Median number of cases per outbreak (IQR)	Maximum number of cases per outbreak	Median duration of closed outbreaks in days [1] (IQR)
Other settings[3]	**1,335**	**3 (1 - 6)**	**240**	**9 (5 - 16)**
Bar/restaurant/nightclub	122	3 (2 - 5)	40	7 (4 - 11)
Medical/health services	59	3 (1 - 5)	17	7 (4 - 13)
Medical/dental clinics	26	3 (1 - 4)	14	5 (4 - 10)
Other[4]	33	2 (1 - 5)	17	8 (5 - 18)
Personal service settings	11	2 (1 - 4)	16	15 (6 - 22)
Recreational fitness	49	5 (2 - 10)	54	5 (1 - 9)
Gym/fitness studios	14	2 (1 - 7)	54	5 (4 - 10)
Sporting teams/leagues	14	7 (3 - 9)	44	1 (0 - 7)
Other[5]	21	5 (2 - 10)	48	7 (2 - 13)
Retail	141	2 (1 - 4)	47	8 (4 - 12)
Grocery stores/pharmacies	34	2 (1 - 4)	36	12 (9 - 20)
Other[6]	107	2 (1 - 4)	47	6 (4 - 12)
Culture and other recreation	71	5 (2 - 12)	60	8 (4 - 13)
Places of worship	23	6 (3 - 15)	30	9 (7 - 12)
Private events	18	8 (2 - 15)	36	7 (5 - 13)
Other[7]	30	3 (1 - 6)	60	7 (4 - 14)
Workplace	872	3 (1 - 7)	240	11 (6 - 19)
Construction	83	2 (1 - 3)	8	8 (3 - 13)
Logistics	95	3 (1 - 10)	202	15 (8 - 23)
Farm	53	14 (4 - 42)	240	23 (14 - 45)
Food processing	115	5 (2 - 11)	168	17 (8 - 25)

Setting Type	Number of outbreaks	Median number of cases per outbreak (IQR)	Maximum number of cases per outbreak	Median duration of closed outbreaks in days [1] (IQR)
Manufacturing	298	3 (1 - 7)	57	12 (7 - 19)
Other[8]	228	3 (1 - 5)	56	7 (4 - 11)
Unknown	10	2 (0 - 15)	42	3 (0 - 22)
Total	**4,151**	**2 (1 - 6)**	**316**	**8 (2 - 16)**

Notes: Due to reporting delays and potential variations in data entry processes across public health units, there may be additional COVID-19 cases that have not yet been entered in CCM plus, or have not been entered as linked to an outbreak. As such, some outbreaks may have zero linked cases. This includes 121 outbreaks in congregate care, 46 outbreaks in congregate living, 61 outbreaks in education, and 204 outbreaks in other settings. Ongoing re-classification of settings for reported outbreaks can result in outbreak counts that may differ from counts previously reported in other reports. See Appendix A for full descriptions of outbreak categories.

[1]The median duration of outbreaks was only measured for outbreaks with a "Closed" Outbreak Classification status. Outbreak length was calculated using the 'Outbreak Date' as the start date and the 'Outbreak Date End' as the end date. The "Outbreak Date" is a calculated field used to determine the outbreak declared date using the following hierarchy of date fields (Onset date of the first case > Reported Date > Created Date). The "Outbreak Date End" is a calculated field used to determine the end date of the outbreak using the following hierarchy of date fields (Onset date of the last case > Date the outbreak was declared over). Due to variations in data entry practices and variability in case definitions, this can result in outbreaks having a duration length of 0 days (i.e. if only a single case is linked to an outbreak, the symptom onset date for the first and last case will be the same).

[2]Cumulative counts include COVID-19 school outbreaks reported starting week 36 (August 30 to September 5, 2020).

[3]Not all settings were open during the reporting period due to provincial public health measures.

[4]Captures outbreaks classified as having taken place in other medical/health-service related settings, including community health centres, home care services and wellness clinics.

[5]Captures outbreaks classified as having taken place in recreational settings including athletic facilities, recreational/community centres, golf courses, tennis courts and indoor playgrounds.

[6]Captures outbreaks classified as having taken place in auto dealerships and standalone retailers, as well as big box stores, among other retail settings.

[7]Captures outbreaks classified as having taken place in theatres, banquet halls (not including weddings), private transportation, private residences, and other community settings.

[8]Captures outbreaks classified as having taken place in locations such as: offices, banks, municipal services (e.g., fire station, police station), and veterinary clinics.

Data Source: CCM plus

Characteristics of outbreak-associated Cases

Table 2. Cumulative summary of confirmed COVID-19 cases associated with outbreaks reported between February 16, 2020 and December 26, 2020, by setting type: Ontario

Setting Type	Number of cases	Proportion male[1] (%)	Median age[2] (IQR)
Congregate care	**25,150**	**27.4**	**73 (49 - 87)**
Long-term care homes	18,475	26.7	74 (50 - 87)
Retirement homes	4,098	25.1	80 (49 - 89)
Hospitals	2,577	37.0	55 (36 - 78)
Congregate living	2,809	**54.3**	**41 (29 - 54)**
Correctional facility	286	89.5	35 (27 - 45)
Shelter	685	57.4	40 (31 - 52)
Group home/supportive housing	1,431	45.5	44 (30 - 56)
Short-term accommodations	14	50.0	40 (24 - 48)
Congregate other	393	55.2	38 (28 - 55)
Education	**2,471**	**46.4**	**13 (8 - 29)**
Child care	471	29.3	23 (3 - 41)
School – Elementary[3]	1,338	48.8	11 (8 - 13)
School – Elementary/secondary[3]	173	65.3	17 (13 - 36)
School – Secondary[3]	450	50.2	16 (14 - 19)
School – Post-secondary[3]	39	41.0	19 (17 - 27)
Other settings[4]	**9,344**	**67.3**	**38 (27 - 51)**
Bar/restaurant/nightclub	471	46.3	28 (23 - 43)
Medical/health services	221	28.1	42 (29 - 53)
Medical/dental clinics	95	26.3	39 (27 - 48)

Setting Type	Number of cases	Proportion male[1] (%)	Median age[2] (IQR)
Other[5]	126	29.4	46 (31 - 57)
Personal service settings	36	11.1	35 (25 - 42)
Recreational fitness	411	60.8	32 (21 - 54)
Gym/fitness studios	109	33.0	30 (27 - 37)
Sporting teams/leagues	127	84.3	40 (15 - 52)
Other[6]	175	61.1	40 (21 - 62)
Retail	508	60.0	35 (24 - 51)
Grocery stores/pharmacies	131	55.7	36 (23 - 53)
Other[7]	377	61.5	35 (24 - 51)
Culture and other recreation	620	51.8	33 (21 - 53)
Places of worship	221	52.9	40 (27 - 57)
Private events	193	54.9	30 (23 - 49)
Other[8]	206	47.6	28 (18 - 48)
Workplace	6,991	72.6	39 (29 - 51)
Construction	202	90.1	40 (28 - 51)
Logistics	1,211	58.8	36 (26 - 49)
Farm	1,779	86.6	35 (28 - 43)
Food processing	1,253	66.4	41 (30 - 52)
Manufacturing	1,681	75.1	47 (34 - 56)
Other[9]	865	63.1	41 (29 - 54)
Unknown	86	58.1	30 (21 - 47)
Total	**39,774**	**39.8**	**54 (34 - 81)**

Notes: See Appendix A for full descriptions of outbreak categories.
[1]Not all cases have a gender reported. The denominator for calculating male case percentages includes all cases.

[2]Includes all cases linked to an outbreak regardless of attendance/residence within the outbreak setting. Therefore, the range of ages of cases associated with an outbreak may not align with expected ages within that setting.
[3]Cumulative counts include COVID-19 school outbreaks reported starting week 36 (August 30 to September 5, 2020).
[4]Not all settings were open during the reporting period due to provincial public health measures.
[5]Captures outbreaks classified as having taken place in other medical/health-service related settings, including community health centres, home care services and wellness clinics.
[6]Captures outbreaks classified as having taken place in recreational settings including athletic facilities, recreational/community centres, golf courses, tennis courts and indoor playgrounds.
[7]Captures outbreaks classified as having taken place in auto dealerships and standalone retailers, including big box stores, among other retail settings.
[8]Captures outbreaks classified as having taken place in theatres, banquet halls (not including weddings), public and private transportation, private residences and other community settings.
[9]Captures outbreaks classified as having taken place in offices, banks, municipal services (e.g. fire station, police station), and veterinary clinics, among others.
Data Source: CCM plus

Severity

Table 3. Cumulative summary of hospitalizations and deaths among confirmed COVID-19 cases associated with outbreaks reported between February 16, 2020 and December 26, 2020, by setting type: Ontario

Setting Type	Number of hospitalized cases (% of outbreak-associated cases)	Number of deaths (% of outbreak-associated cases)	% of all outbreak-associated hospitalizations	% of all outbreak-associated deaths
Congregate care	**3,070 (12.2%)**	**3,626 (14.4%)**	**88.7%**	**98.5%**
Long-term care homes	1,517 (8.2%)	2,911 (15.8%)	43.8%	79.1%
Retirement homes	672 (16.4%)	418 (10.2%)	19.4%	11.4%
Hospitals	881 (34.2%)[1]	297 (11.5%)	25.5%	8.1%
Congregate living	**233 (8.3%)**	**33 (1.2%)**	**6.7%**	**0.9%**
Correctional facility	4 (1.4%)	0 (0.0%)	0.1%	0.0%
Shelter	94 (13.7%)	3 (0.4%)	2.7%	0.1%
Group home/supportive housing	110 (7.7%)	20 (1.4%)	3.2%	0.5%
Short-term accommodations	0 (0.0%)	0 (0.0%)	0.0%	0.0%
Congregate other	25 (6.4%)	10 (2.5%)	0.7%	0.3%
Education	**6 (0.2%)**	**0 (0.0%)**	**0.2%**	**0.0%**
Child care	1 (0.2%)	0 (0.0%)	<0.1%	0.0%
School – Elementary[2]	4 (0.3%)	0 (0.0%)	0.1%	0.0%
School – Elementary/secondary[2]	0 (0.0%)	0 (0.0%)	0.0%	0.0%
School – Secondary[2]	1 (0.2%)	0 (0.0%)	<0.1%	0.0%
School – Post-secondary[2]	0 (0.0%)	0 (0.0%)	0.0%	0.0%
Other settings[3]	**151 (1.6%)**	**22 (0.2%)**	**4.4%**	**0.6%**
Bar/restaurant/nightclub	6 (1.3%)	0 (0.0%)	0.2%	0%

Setting Type	Number of hospitalized cases (% of outbreak-associated cases)	Number of deaths (% of outbreak-associated cases)	% of all outbreak-associated hospitalizations	% of all outbreak-associated deaths
Medical/health services	15 (6.8%)	5 (2.3%)	0.4%	0.1%
Medical/dental clinics	0 (0.0%)	0 (0.0%)	0.0%	0.0%
Other[4]	15 (11.9%)	5 (4.0%)	0.4%	0.1%
Personal service settings	0 (0.0%)	0 (0.0%)	0.0%	0.0%
Recreational fitness	2 (0.5%)	0 (0.0%)	0.1%	0.0%
Gym/fitness studios	0 (0.0%)	0 (0.0%)	0.0%	0.0%
Sporting teams/leagues	1 (0.8%)	0 (0.0%)	<0.1%	0.0%
Other[5]	1 (0.6%)	0 (0.0%)	<0.1%	0.0%
Retail	8 (1.6%)	1 (0.2%)	0.2%	<0.1%
Grocery stores/pharmacies	2 (1.5%)	0 (0.0%)	0.1%	0.0%
Other[6]	6 (1.6%)	1 (0.3%)	0.2%	<0.1%
Culture and other recreation	20 (3.2%)	4 (0.6%)	0.6%	0.1%
Places of worship	5 (2.3%)	0 (0.0%)	0.1%	0.0%
Private events	4 (2.1%)	2 (1.0%)	0.1%	0.1%
Other[7]	11 (5.3%)	2 (1.0%)	0.3%	0.1%
Workplace	93 (1.3%)	12 (0.2%)	2.7%	0.3%
Construction	3 (1.5%)	1 (0.5%)	0.1%	<0.1%
Logistics	15 (1.2%)	0 (0.0%)	0.4%	0.0%
Farm	22 (1.2%)	3 (0.2%)	0.6%	0.1%
Food processing	24 (1.9%)	4 (0.3%)	0.7%	0.1%
Manufacturing	16 (1.0%)	2 (0.1%)	0.5%	0.1%

Setting Type	Number of hospitalized cases (% of outbreak-associated cases)	Number of deaths (% of outbreak-associated cases)	% of all outbreak-associated hospitalizations	% of all outbreak-associated deaths
Other[8]	13 (1.5%)	2 (0.2%)	0.4%	0.1%
Unknown	7 (8.1%)	0 (0.0%)	0.2%	0.0%
Total	**3,460 (8.7%)**	**3,681 (9.3%)**	100.0%	100.0%

Notes: See Appendix A for full descriptions of outbreak categories.
[1]Hospitalized cases associated with outbreaks classified within a hospital can include patients, staff or other hospital visitors. The number of hospitalized cases in hospital outbreak settings is lower than the total number of cases reported in hospital outbreak settings (Table 2), as the total number of cases includes healthcare workers in the facility who may not have been hospitalized.
[2]Includes COVID-19 school outbreaks reported starting week 36 (August 30 to September 5, 2020).
[3]Not all settings were opened during the reporting period due to provincial public health measures.
[4]Captures outbreaks classified as having taken place in other medical/health-service related settings, including community health centres, home care services and wellness clinics.
[5]Captures outbreaks classified as having taken place in recreational settings including athletic facilities, recreational/community centres, golf courses, tennis courts and indoor playgrounds.
[6]Captures outbreaks classified as having taken place in auto dealerships and standalone retailers, including big box stores, among other retail settings.
[7]Captures outbreaks classified as having taken place in theatres, banquet halls (not including weddings), public and private transportation, private residences and other community settings.
[8]Captures outbreaks classified as having taken place in offices, banks, municipal services (e.g. fire station, police station), and veterinary clinics, among others.
Data Source: CCM plus

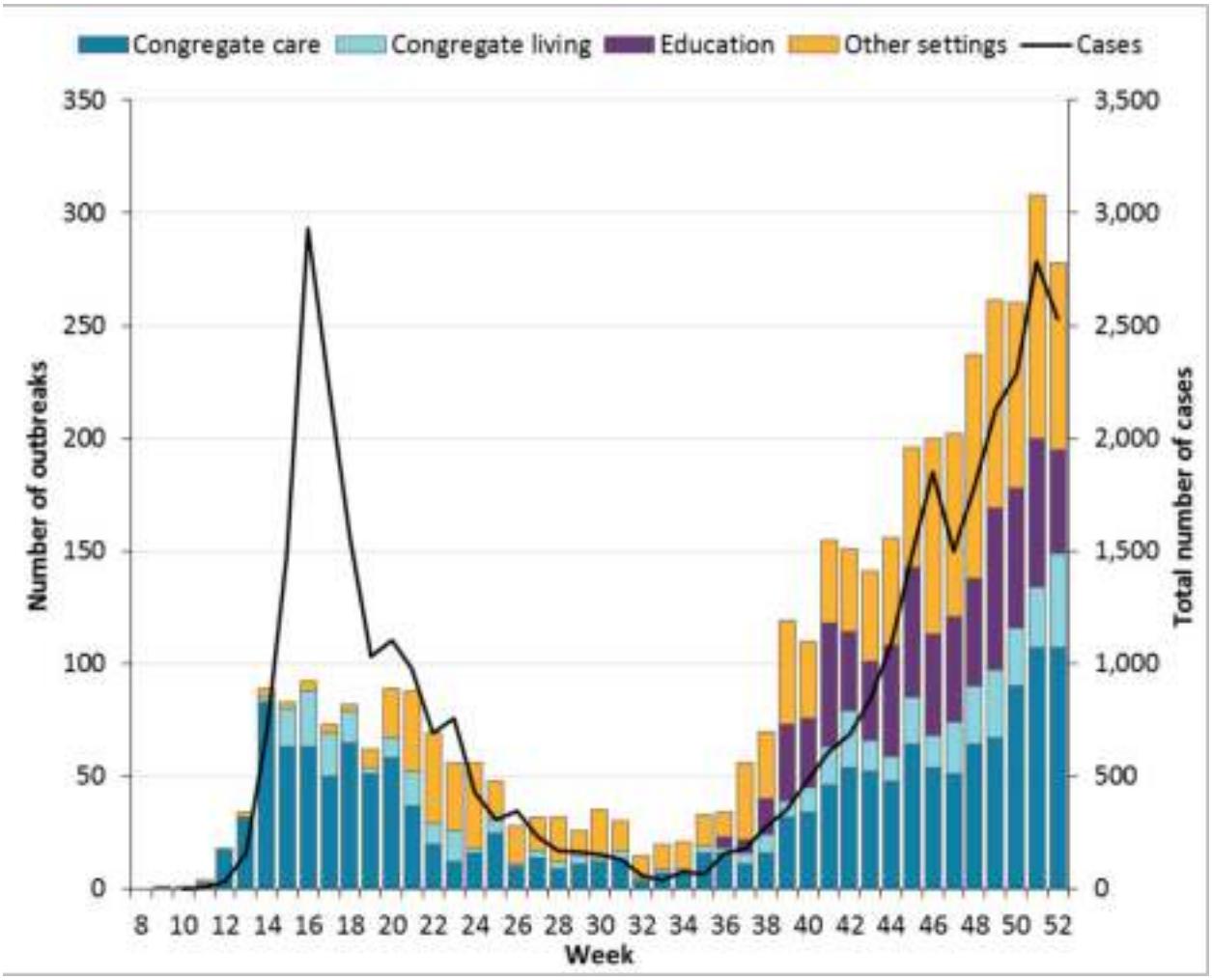
Table 4. Demographic characteristics of non-outbreak and outbreak-associated cases reported between February 16, 2020 and December 26, 2020

	Non-outbreak cases	Outbreak cases
Total number of cases	**136,496**	**39,774**
Gender: Female	65,801 (48.2%)	23,567 (59.3%)
Gender: Male	70,030 (51.3%)	15,840 (39.8%)
Age: 19 and under	19,856 (14.5%)	2,512 (6.3%)
Age: 20-39	54,023 (39.6%)	9,796 (24.6%)
Age: 40-59	40,039 (29.3%)	10,425 (26.2%)
Age: 60-79	19,086 (14.0%)	6,466 (16.3%)
Age: 80 and over	3,473 (2.5%)	10,565 (26.6%)

Note: Not all cases have an age or gender reported. The denominator for calculating percentages includes all cases.
Data Source: CCM plus

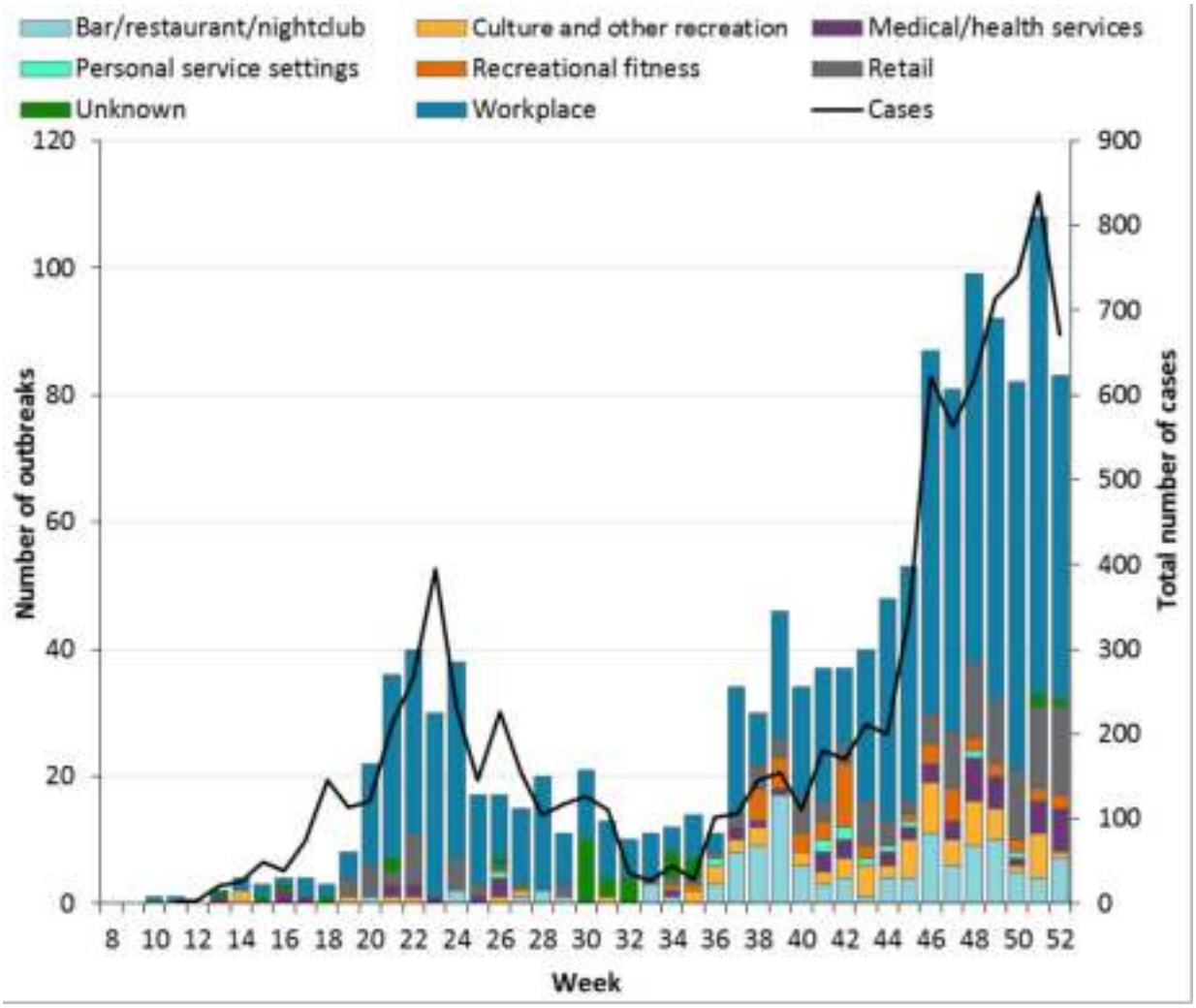
Time Trends

Figure 1a. Total number of public health unit declared COVID-19 outbreaks, and number of confirmed outbreak-associated cases, by setting type and week, reported between week 8 (February 16, 2020) and week 52 (December 26, 2020): Ontario



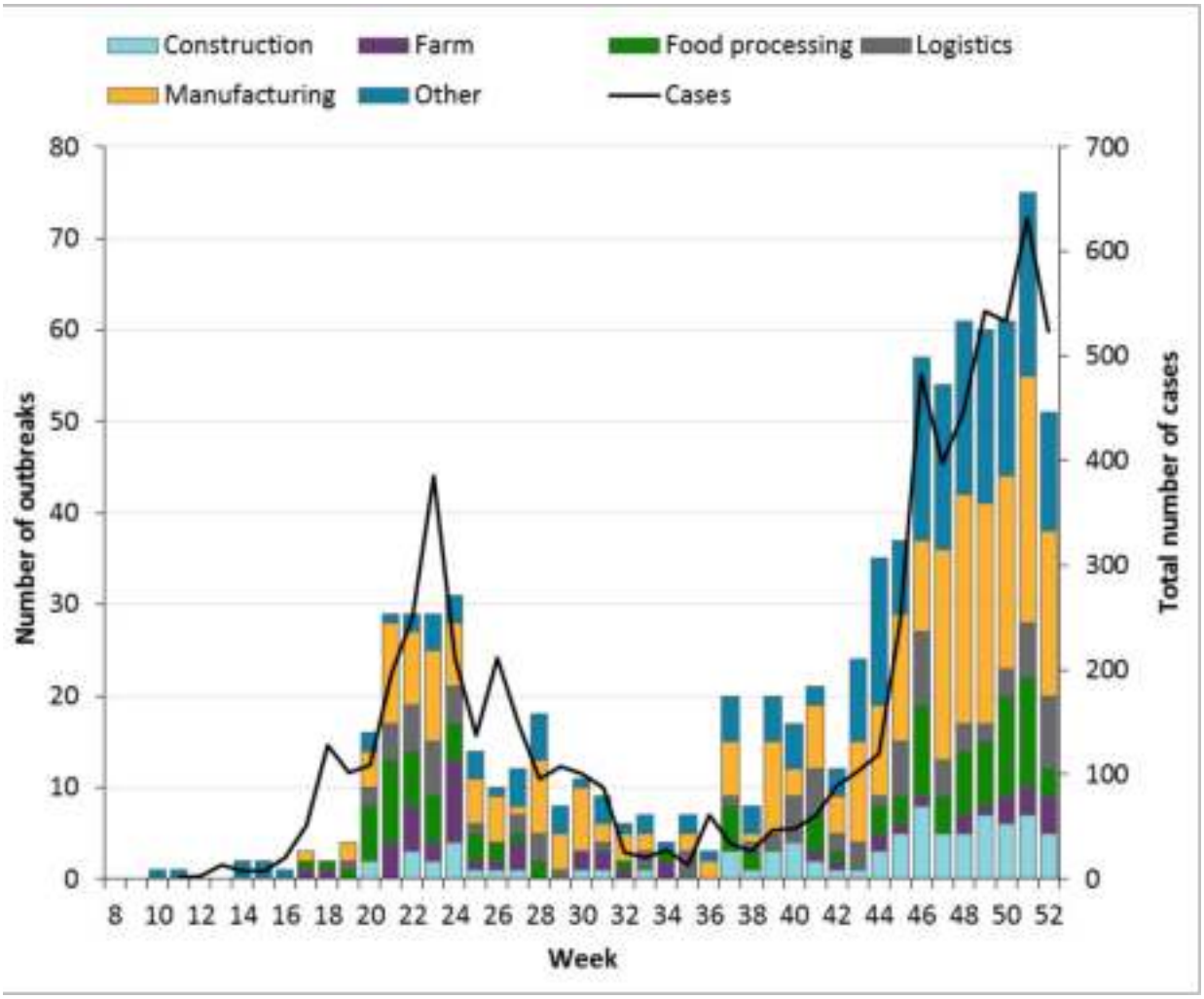
Notes: Number of outbreaks is based on week the outbreak was declared, while total number of cases is based on case reported week. Since many outbreaks are still ongoing, there were 3,261 cases with case reported dates that occurred outside of the week ranges of focus and were therefore not included in the figure. Includes outbreaks that are ongoing and outbreaks that are no longer active. Not all settings were open during the reporting period due to provincial public health measures. See Appendix A for full descriptions of outbreak categories.
Data Source: CCM plus

Figure 1b. Number of public health unit declared COVID-19 outbreaks in other settings, and number of confirmed other setting outbreak-associated cases, by setting type and week, reported between week 8 (February 16, 2020) and week 52 (December 26, 2020): Ontario



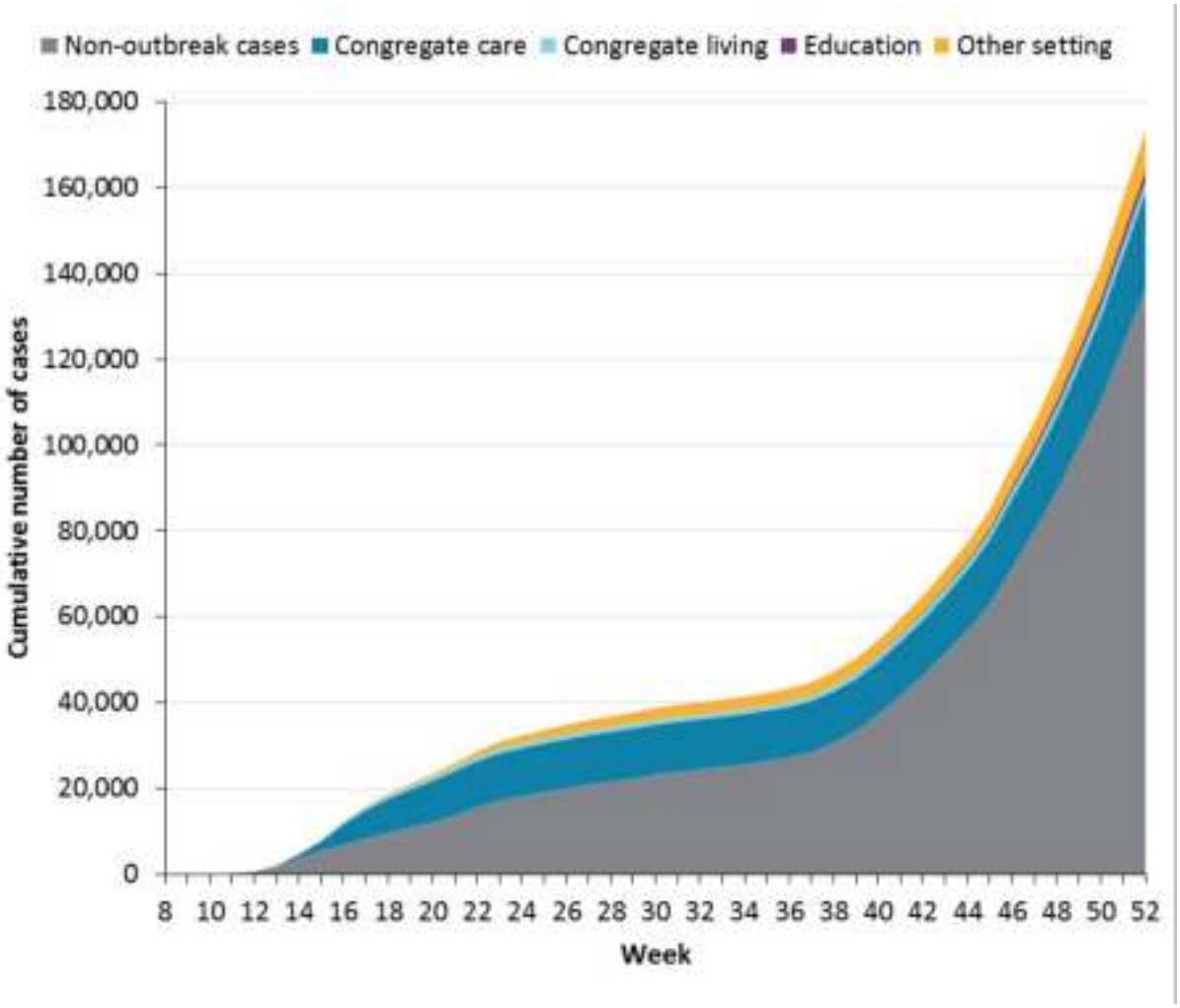
Notes: Number of outbreaks is based on week the outbreak was declared, while total number of cases is based on case reported week. Since many outbreaks are still ongoing, there were 399 cases with case reported dates that occurred outside of the week ranges of focus and were therefore not included in the figure. Includes outbreaks that are ongoing and outbreaks that are no longer active. Not all settings were open during the reporting period due to provincial public health measures. See Appendix A for full descriptions of outbreak categories.
Data Source: CCM plus

Figure 1c. Number of confirmed public health unit declared COVID-19 workplace[1] outbreaks, and number of confirmed workplace outbreak-associated cases, by setting type and week, reported between week 8 (February 16, 2020) and week 52 (December 26, 2020): Ontario



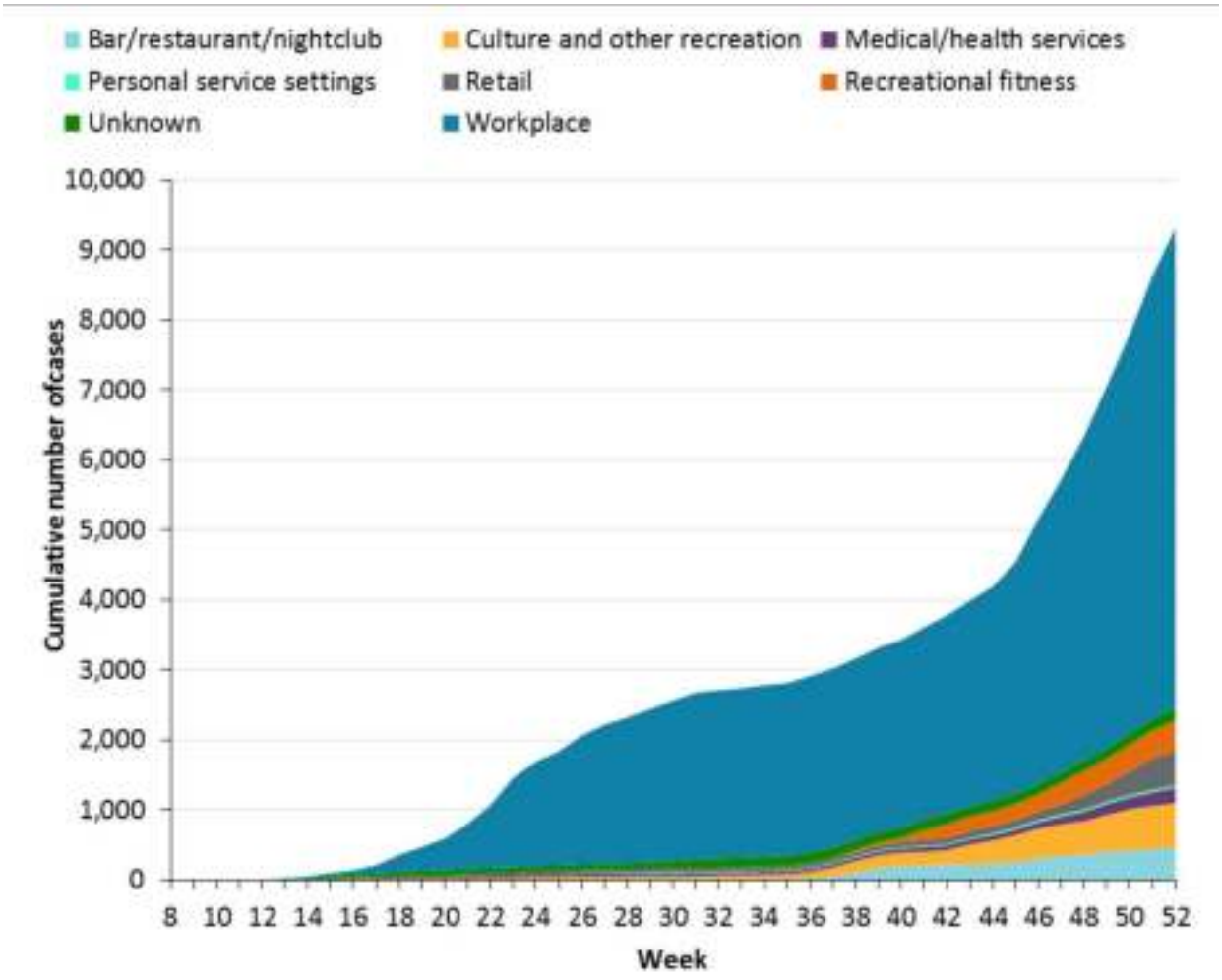
Notes: Number of outbreaks is based on week the outbreak was declared, while total number of cases is based on case reported week. Since many outbreaks are still ongoing, there were 347 cases with case reported dates that occurred outside of the week ranges of focus and were therefore not included in the figure. Includes outbreaks that are ongoing and outbreaks that are no longer active. Not all settings were open during the reporting period due to provincial public health measures. See Appendix A for full descriptions of outbreak categories.
[1]Workplaces do not include publically-accessible settings where people may also work (i.e., restaurants, gyms).
Data Source: CCM plus

Figure 2a. Cumulative number of outbreak and non-outbreak cases, by setting type and week, reported between week 8 (February 16, 2020) and week 52 (December 26, 2020): Ontario



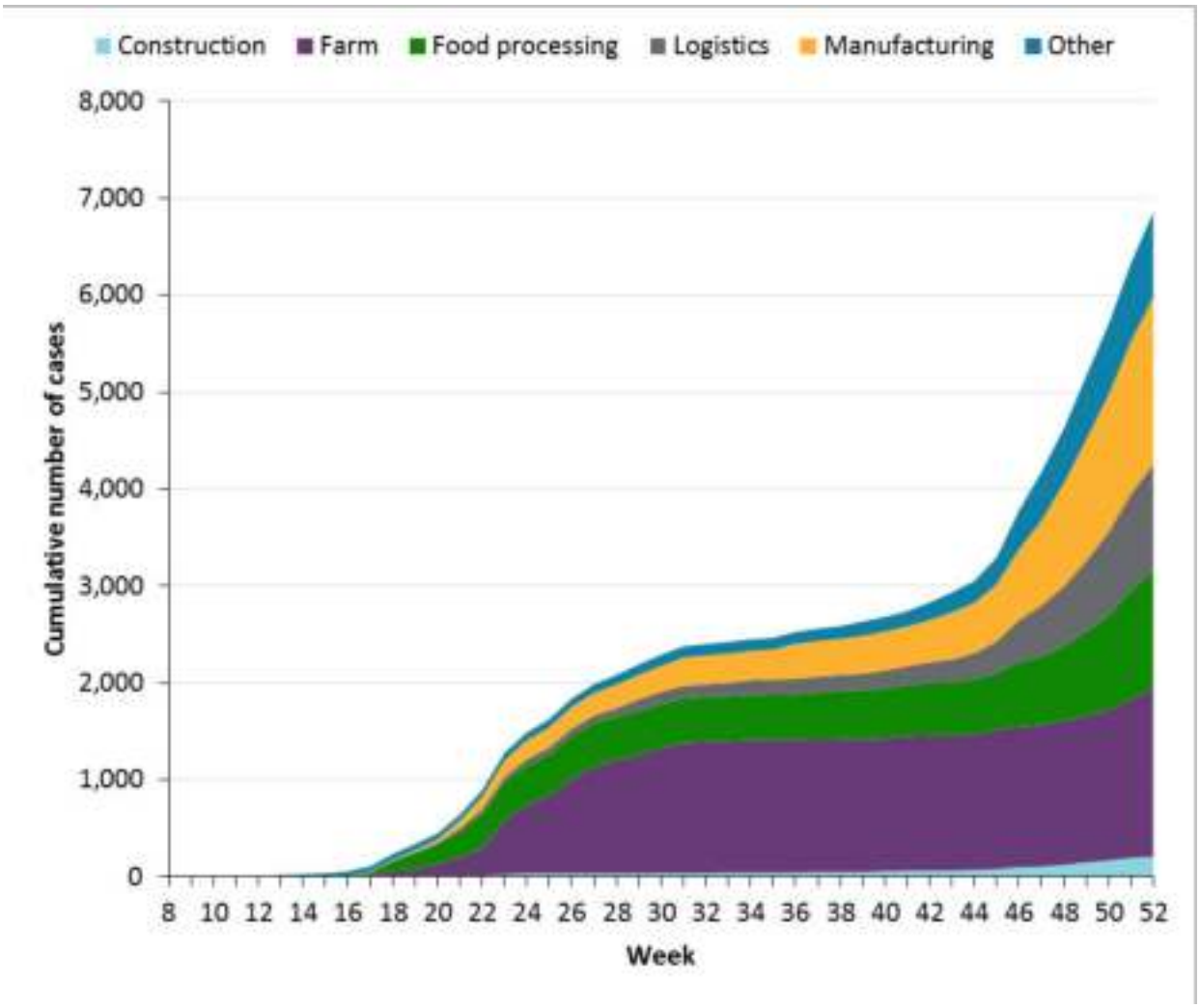
Notes: Based on case reported week. Non-outbreak cases refers to all COVID-19 cases not linked to a declared outbreak reported between weeks 8 and 52. Since many outbreaks are still ongoing, there were 3,267 outbreak-linked cases with case reported dates that occurred outside of the week ranges of focus and were therefore not included in the figure. Includes outbreaks that are ongoing and outbreaks that are no longer active. Not all settings were open during the reporting period due to provincial public health measures. See Appendix A for full descriptions of outbreak categories.
Data Source: CCM plus

Figure 2b. Cumulative number of confirmed cases from other setting outbreaks, by setting type and week, reported between week 8 (February 16, 2020) and week 52 (December 26, 2020): Ontario



Notes: Based on case reported week. Since many outbreaks are still ongoing, there were 399 cases with case reported dates that occurred outside of the week ranges of focus and were therefore not included in the figure. Includes outbreaks that are ongoing and outbreaks that are no longer active. Not all settings were open during the reporting period due to provincial public health measures. See Appendix A for full descriptions of outbreak categories.
Data Source: CCM plus

Figure 2c. Cumulative number of confirmed cases from workplace[1] outbreaks, by setting type and week, reported between week 8 (February 16, 2020) and week 52 (December 26, 2020): Ontario



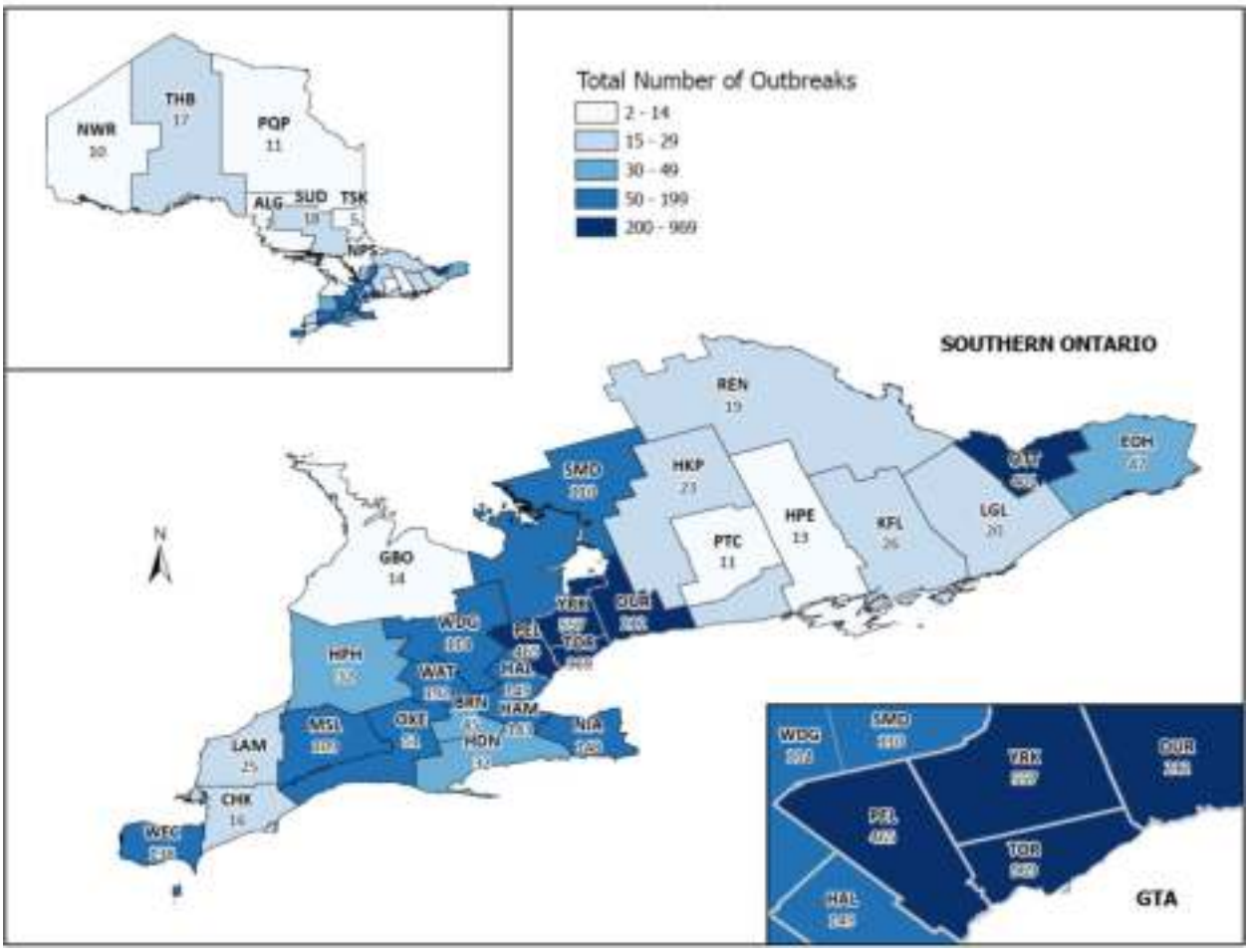
Notes: Based on case reported week. Since many outbreaks are still ongoing, there were 347 cases with case reported dates that occurred outside of the week ranges of focus and were therefore not included in the figure. Includes outbreaks that are ongoing and outbreaks that are no longer active. Not all settings were open during the reporting period due to provincial public health measures. See Appendix A for full descriptions of outbreak categories.

[1]Workplaces do not include publically-accessible settings where people may also work (i.e., restaurants, gyms).

Data Source: CCM plus

Geography

Figure 3. Number of confirmed COVID-19 outbreaks reported between February 16, 2020 and December 26, 2020 by public health unit: Ontario



Note: Includes outbreaks that are ongoing and outbreaks that are no longer active. Cut-offs for map categories were determined by natural breaks and adjusted for round numbers. Geography is based on public health unit where the outbreak was declared. Not all settings were open during the reporting period due to provincial public health measures. There was one outbreak that involved cases from Ontario and outside of Ontario and was not assigned to a public health unit. The data in this map are also available in Appendix B.
Data Source: CCM plus

Technical Notes

Data Sources

- The data for this report were based on:
    - Information extracted from the Ontario Ministry of Health (Ministry) integrated Public Health Information System (iPHIS) database for Toronto Public Health as of **January 11, 2021 at 1 p.m.**
    - Information successfully uploaded to the Ministry from Local Systems: Toronto Public Health (Coronavirus Rapid Entry System) CORES as of **January 11, 2021 at 2 p.m.**
    - Information successfully extracted from the Public Health Case and Contact Management Solution (CCM) for all other PHUs by PHO as of **January 11, 2021 at 1 p.m.**
- CCM and CCM plus (which includes CCM, iPHIS and CORES) are dynamic disease reporting systems, which allow ongoing updates to data previously entered. As a result, data extracted from CCM and the Local Systems represent a snapshot at the time of extraction and may differ from previous or subsequent reports. This applies to both case and outbreak data.

Data Caveats:

- The data included are for outbreaks reported in Ontario from February 16, 2020 to December 26, 2020 and cases linked to those outbreaks up until January 11th, 2021.
- Only confirmed outbreaks are included in this report.
- The outbreak data for these settings are restricted to those in which an outbreak was declared by the public health unit. The data also do not include cases linked to these settings as an exposure. Outbreaks are declared by the local medical officer of health or their designate in accordance to the Health Protection and Promotion Act and criteria outlined in Ministry guidance documents.[4]
- For outbreaks declared in certain settings such as long-term care, hospitals, educational settings, and workplaces, there are provincial outbreak definitions.[5-7] These definitions may have single case thresholds, and may also include changes in the case thresholds for declaring an outbreak over time (i.e.,., the threshold for declaring an outbreak in a child care setting increased from one to two cases as of November 9, 2020).[8] However, there is no provincial case definition for several other setting types reported as other settings. As such, a standard approach to declaring an outbreak across these settings may differ by public health unit.
    - All other setting outbreaks were manually classified based on the name, address, and additional relevant information available in CCM for the outbreak, as entered by the PHU. other setting outbreaks consisted of outbreaks outside of congregate care settings (i.e., hospitals, long-term care, retirement home), congregate living settings (i.e., correctional facilities, shelters, group homes, other congregate), and education settings (i.e., childcare settings and schools). All outbreak classifications are mutually exclusive. However, an outbreak declared in a restaurant may have been a workplace outbreak if cases were

identified among staff only. For the purposes of this report, a setting-based hierarchy was used.

    - Outbreaks reported in the workplace – arm category may include cases related to shared living amongst farm staff. As such, some of these outbreaks may be more similar to outbreaks in congregate living settings.

- For additional information regarding outbreak setting type classification definitions, please refer to Table 1 in the Appendix. Some outbreaks may be misclassified due to lack of information to assist with the manual classification process.

- All outbreaks reported as confirmed in CCM plus were included in these analyses regardless of whether the case data in CCM plus supported the outbreaks' classification.

- Due to reporting delays and potential variations in data entry processes across public health units, there may be additional COVID-19 cases that have not yet been entered in CCM plus, or have not been entered as linked to an outbreak. As such, some outbreaks may have zero linked cases as of the data extraction date. Results should be interpreted with caution due to potential under-detection of outbreak associated cases.

- The data only represent cases reported to public health units and recorded in CCM plus. As a result, all counts will be subject to varying degrees of underreporting due to a variety of factors, such as disease awareness and medical care seeking behaviours, which may depend on severity of illness, clinical practice, changes in laboratory testing, and reporting behaviours.

- Lags in CCM plus data entry due to weekend staffing may result in lower case counts than would otherwise be recorded.

- Outbreak-associated cases do not include secondary cases acquired from outbreak-associated cases.

- The data for these settings are restricted to those in which an outbreak was declared by the public health unit. They do not include cases linked to these settings as an exposure.

- Cases with unknown or missing ages were excluded from age-specific analyses.

- Only cases meeting the confirmed case classification as listed in the MOH COVID-19 case definition are included in the report counts from CCM plus.[4] This includes persons with a positive detection of serum/plasma immunoglobulin G (IgG) antibodies to SARS-CoV-2, which was added to the confirmed case definition on August 6, 2020.

- Cases of confirmed reinfection, i.e., where genome sequencing indicates the two episodes are caused by different viral lineages, added to the confirmed case definition on November 20, 2020, are counted as unique investigations.

- Case reported week uses the date the case was reported to the public health unit.

    - Outbreak reported week uses the date the public health unit reported the outbreak. If this date is unavailable, the date the public health unit created the outbreak is used.

    - Reported weeks were created to align with the Public Health Agency of Canada (PHAC) influenza surveillance weeks.

- ‘Cases associated with school outbreaks’ include cases that are linked to an outbreak, by school classification type (Elementary, Elementary/Secondary, Secondary, Post-Secondary), that met the definition of a school outbreak.

- School classification types are defined by the Ministry of Education. Some schools classified as secondary may also have an intermediate school in the same location that start in Grade 7.

    - Elementary/Secondary schools include public or private schools educating children in a combination of elementary and secondary grades (e.g., Kindergarten to Grade 8, Grades 9 to 12, and Kindergarten to Grade 12).

- School outbreaks include outbreaks declared on or after week 36 (August 30 to September 5, 2020).

- Hospitalization includes all cases for which a hospital admission date was reported at the time of data extraction. It includes cases that have been discharged from hospital as well as cases that are currently hospitalized. Emergency room visits are not included in the number of reported hospitalizations.

- Deaths are determined by using the outcome field in CCM. Any case marked ‘Fatal’ is included in the deaths data. The CCM field Type of Death is not used to further categorize the data.

- Ongoing outbreaks are those that are reported in CCM plus as ‘Open’ and without a ‘Declared Over Date’ recorded. Closed outbreaks are ‘Closed’ or have a ‘Declared Over Date’ recorded in CCM plus or where the outbreak start date (determined by the onset date of first case, or if missing the reported date, or if missing the created date) is more than 5 months from the current date, even for outbreaks where the outbreak status value selected in CCM/iPHIS is 'OPEN'.

- Orientation of case counts by geography is based on the diagnosing health unit (DHU). DHU refers to the case's public health unit of residence at the time of illness onset and not necessarily the location of exposure. Cases for which the DHU was reported as MOH (to signify a case that is not a resident of Ontario) have been excluded from the analyses.

- COVID-19 cases from CCM plus for which the Classification and/or Disposition was reported as ENTERED IN ERROR, DOES NOT MEET DEFINITION, IGNORE, DUPLICATE, or any variation on these values have been excluded. The provincial case count for COVID-19 includes cases that are counted once across all systems from which the case data are obtained. Duplicate records may exist if these records were not identified and resolved prior to data upload to the Ministry.

Appendix A: Definitions of outbreak settings

Table A1. Definitions for various setting types including congregate care, congregate living, education, and other settings.

Setting type	Definitions
Congregate care	
Long-term care homes	A facility that provides care and services for people who no longer are able to live independently or who require onsite nursing care, 24-hour supervision or personal support. LTC Homes are governed under the Long Term Care Homes Act (LTCHA) and Ontario Regulation 79/10.
Retirement homes	A residential complex or the part of a residential complex, that is occupied primarily by persons who are 65 years of age or older, that is occupied or intended to be occupied by at least the prescribed number of persons who are not related to the operator of the home, and where the operator of the home makes at least two care services available, directly or indirectly, to the residents. Retirement homes are governed under the Retirement Homes Act, 2010, S.O. 2010, c. 11.
Hospitals	Any institution, building or other premises or place that is established for the purposes of the treatment of patients and that is approved under the Public Hospitals Act, R.S.O. 1990, c. P.40.
Congregate living	
Correctional facility	An institution established or continued under section 14, whether it is operated or maintained by the Ministry or by a contractor, but does not include a place of open custody, a place of secure custody, a place of temporary detention or a lock-up established under section 16.1 of the *Police Services Act*; ("établissement correctional"). Ministry of Correctional Services Act, R.S.O. 1990, c. M.22.
Shelter	A facility set up to provide for the needs of homeless people; often including temporary residence, food, sanitation and other forms of support.
Group Home/Supportive Housing	A home providing staff-supported residential accommodation in a group setting for special populations that need a supervised living environment. Common examples include children and youth in care, individuals with developmental or physical disabilities, individuals recovering from substance abuse, teenaged mothers, or victims of domestic violence.

Setting type	Definitions
Short-term accommodations	A short-term rental is all or part of a dwelling unit that is offered for accommodations for less than 28 consecutive days with or without payment. This includes but is not limited to bed and breakfasts (B&Bs), hotels and motels.
Congregate other	Other setting in which persons live in a group setting with shared amenities.
Education	
Child care	Facility that provides temporary care for or supervision of children and is operated under the Child Care and Early Years Act, 2014, S.O. 2014, c. 11.
School – Elementary	Elementary schools include a public or private school educating children in elementary (Kindergarten to Grade 8) grades
School - Elementary/Secondary	Elementary/ Secondary schools include a public or private school educating children in a combination of elementary (Kindergarten to Grade 8) and secondary (Grade 9 to 12) grades (e.g., K-12 combined).
School – Secondary	Secondary schools include a public or private school educating children in secondary (Grade 9 to 12) grades
School - Post-secondary	Educational facility offering the highest level of educational attainment including apprenticeships or trades certificate or diploma; general or vocational college, or other non-university certificate or diploma; university certificate or diploma below bachelor level; or a university degree.
Other settings	
Bar/restaurant/nightclub	A facility for socialization/entertainment where food and/or drinks may be served.

Setting type	Definitions
Medical/Health Service	A facility or business that provides health or medical services in a community or non-institutional setting. This includes but is not limited to doctors offices or clinics, wellness clinics, dental offices, and at home care.
Personal service settings	A facility that provides personal services including invasive services that is operated under the O. Reg. 136/18. (e.g. tattoo parlours, hair salons, tanning studios).
Recreational fitness	A facility that provides activities where the primary purpose of the activity is participation, with the related goals of improved physical fitness, fun, and social involvement.
Retail	A setting in which goods and/or services are sold to individual consumers for their personal use. This includes but is not limited to grocery stores, pharmacies, and shopping malls.
Culture and other recreation	A setting in which social gatherings take place, including places of worship, indoor and outdoor private events (including weddings and funerals), and other community gathering spaces.
Workplace – Construction	A workplace comprised of employees working on developing, maintaining or repairing residential and non-residential buildings, or parts within. Outbreaks and cases captured in this setting include outbreaks associated with construction worksites and may include offices related to the construction industry.
Workplace – Logistics	A workplace comprised of employees working in warehouses, transportation, shipping or postal services.
Workplace – Farm	A workplace comprised of an area of land and its buildings used for growing crops and/or rearing animals, including greenhouses.
Workplace - Food Processing	A food service establishment that is a commercial operation that processes food for human consumption, and provides processed food for sale and distribution to other business entities such as restaurants and grocery stores.
Workplace – Manufacturing	A workplace comprised of employees working at a production line, where labour and machinery are used to produce goods from raw materials and smaller components.

Setting type	Definitions
Workplace – other	Other places of employment including offices, banks, municipal services (e.g. fire station), and veterinary clinics, among others.
Unknown	Setting that cannot be classified due to missing or inadequate data.

Appendix B: Outbreaks across public health units

Table A2. Number of confirmed COVID-19 outbreaks reported between February 16, 2020 and December 26, 2020 by public health unit: Ontario

Public Health Unit Name	Abbreviation	Number of outbreaks
Algoma Public Health	ALG	2
Brant County Health Unit	BRN	45
Chatham-Kent Public Health Services	CHK	16
City of Hamilton Public Health Services	HAM	143
Durham Region Health Department	DUR	212
Eastern Ontario Health Unit	EOH	47
Grey Bruce Health Unit	GBO	14
Haldimand-Norfolk Health Unit	HDN	32
Haliburton, Kawartha, Pine Ridge District Health Unit	HKP	23
Halton Region Public Health	HAL	149
Hastings & Prince Edward Public Health	HPE	13
Huron Perth Public Health	HPH	32
Kingston, Frontenac, Lennox & Addington Public Health	KPL	26
Lambton County Public Health	LAM	25
Leeds, Grenville and Lanark District Health Unit	LGL	20
Middlesex-London Health Unit	MSL	109
Niagara Region Public Health	NIA	148
North Bay Parry Sound District Health Unit	MPS	6
Northwestern Health Unit	NWR	10
Ottawa Public Health	OTT	401

Public Health Unit Name	Abbreviation	Number of outbreaks
Peel Public Health	PEL	465
Peterborough Public Health	PTC	11
Porcupine Health Unit	PQP	11
Public Health Sudbury & District	SUD	18
Region of Waterloo Public Health and Emergency Services	WAT	192
Renfrew County and District Health Unit	REN	19
Simcoe Muskoka District Health Unit	SMD	110
Southwestern Public Health	OXE	51
Thunder Bay District Health Unit	THB	17
Timiskaming Health Unit	TSK	5
Toronto Public Health	TOR	969
Wellington-Dufferin-Guelph Public Health	WDG	114
Windsor-Essex County Health Unit	WEC	138
York Region Public Health	YRK	557

Note: Includes outbreaks that are ongoing and outbreaks that are no longer active. Geography is based on public health unit where the outbreak was declared. Not all settings were open during the reporting period due to provincial public health measures. There was one outbreak that involved cases from Ontario and outside of Ontario and was not assigned to a public health unit.
Data Source: CCM plus

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For Further Information

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Ontario

Mask use in the context of COVID-19

Interim guidance

1 December 2020

World Health Organization

This document, which is an update of the guidance published on 5 June 2020, includes new scientific evidence relevant to the use of masks for reducing the spread of SARS-CoV-2, the virus that causes COVID-19, and practical considerations. It contains updated evidence and guidance on the following:

- mask management;
- SARS-CoV-2 transmission;
- masking in health facilities in areas with community, cluster and sporadic transmission;
- mask use by the public in areas with community and cluster transmission;
- alternatives to non-medical masks for the public;
- exhalation valves on respirators and non-medical masks;
- mask use during vigorous intensity physical activity;
- essential parameters to be considered when manufacturing non-medical masks (Annex).

Key points

- The World Health Organization (WHO) advises the use of masks as part of a comprehensive package of prevention and control measures to limit the spread of SARS-CoV-2, the virus that causes COVID-19. A mask alone, even when it is used correctly, is insufficient to provide adequate protection or source control. Other infection prevention and control (IPC) measures include hand hygiene, physical distancing of at least 1 metre, avoidance of touching one's face, respiratory etiquette, adequate ventilation in indoor settings, testing, contact tracing, quarantine and isolation. Together these measures are critical to prevent human-to-human transmission of SARS-CoV-2.
- Depending on the type, masks can be used either for protection of healthy persons or to prevent onward transmission (source control).
- WHO continues to advise that anyone suspected or confirmed of having COVID-19 or awaiting viral laboratory test results should wear a medical mask when in the presence of others (this does not apply to those awaiting a test prior to travel).
- For any mask type, appropriate use, storage and cleaning or disposal are essential to ensure that they are as effective as possible and to avoid an increased transmission risk.

<u>Mask use in health care settings</u>

- WHO continues to recommend that health workers (1) providing care to suspected or confirmed COVID-19 patients wear the following types of mask/respirator in addition to other personal protective equipment that are part of standard, droplet and contact precautions:
  - medical mask in the absence of aerosol generating procedures (AGPs)
  - respirator, N95 or FFP2 or FFP3 standards, or equivalent in care settings for COVID-19 patients where AGPs are performed; these may be used by health workers when providing care to COVID-19 patients in other settings if they are widely available and if costs is not an issue.
- In areas of known or suspected community or cluster SARS-CoV-2 transmission WHO advises the following:
  - universal masking for all persons (staff, patients, visitors, service providers and others) within the health facility (including primary, secondary and tertiary care levels; outpatient care; and long-term care facilities)
  - wearing of masks by inpatients when physical distancing of at least 1 metre cannot be maintained or when patients are outside of their care areas.
- In areas of known or suspected sporadic SARS-CoV-2 transmission, health workers working in clinical areas where patients are present should continuously wear a medical mask. This is known as targeted continuous medical masking for health workers in clinical areas;
- Exhalation valves on respirators are discouraged as they bypass the filtration function for exhaled air by the wearer.

<u>Mask use in community settings</u>

- Decision makers should apply a risk-based approach when considering the use of masks for the general public.
- In areas of known or suspected community or cluster SARS-CoV-2 transmission:
  - WHO advises that the general public should wear a non-medical mask in indoor (e.g. shops, shared workplaces, schools - see Table 2 for details) or outdoor settings where physical distancing of at least 1 metre cannot be maintained.
  - If indoors, unless ventilation has been be assessed to be adequate[1], WHO advises that the general public should wear a non-medical mask, regardless of whether physical distancing of at least 1 metre can be maintained.

[1] For adequate ventilation refer to regional or national institutions or heating, refrigerating and air-conditioning societies enacting ventilation requirements. If not available or applicable, a recommended ventilation rate of 10 l/s/person should be met (except healthcare facilities which have specific requirements). For more information consult "Coronavirus (COVID-19) response

- Individuals/people with higher risk of severe complications from COVID-19 (individuals ≥ 60 years old and those with underlying conditions such as cardiovascular disease or diabetes mellitus, chronic lung disease, cancer, cerebrovascular disease or immunosuppression) should wear medical masks when physical distancing of at least 1 metre cannot be maintained.

- In any transmission scenarios:
  - Caregivers or those sharing living space with people with suspected or confirmed COVID-19, regardless of symptoms, should wear a medical mask when in the same room.

Mask use in children (2)

- Children aged up to five years should not wear masks for source control.
- For children between six and 11 years of age, a risk-based approach should be applied to the decision to use a mask; factors to be considered in the risk-based approach include intensity of SARS-CoV-2 transmission, child's capacity to comply with the appropriate use of masks and availability of appropriate adult supervision, local social and cultural environment, and specific settings such as households with elderly relatives, or schools.
- Mask use in children and adolescents 12 years or older should follow the same principles as for adults.
- Special considerations are required for immunocompromised children or for paediatric patients with cystic fibrosis or certain other diseases (e.g., cancer), as well as for children of any age with developmental disorders, disabilities or other specific health conditions that might interfere with mask wearing.

Manufacturing of non-medical (fabric) masks (Annex)

- Homemade fabric masks of three-layer structure (based on the fabric used) are advised, with each layer providing a function: 1) an innermost layer of a hydrophilic material 2) an outermost layer made of hydrophobic material 3) a middle hydrophobic layer which has been shown to enhance filtration or retain droplets.
- Factory-made fabric masks should meet the minimum thresholds related to three essential parameters: filtration, breathability and fit.
- Exhalation valves are discouraged because they bypass the filtration function of the fabric mask rendering it unserviceable for source control.

Methodology for developing the guidance

Guidance and recommendations included in this document are based on published WHO guidelines (in particular the WHO Guidelines on infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care) (2) and ongoing evaluations of all available scientific evidence by the WHO ad hoc COVID-19 Infection Prevention and Control Guidance Development Group (COVID-19 IPC GDG) (see acknowledgement section for list of GDG members). During emergencies WHO publishes interim guidance, the development of which follows a transparent and robust process of evaluation of the available evidence on benefits and harms. This evidence is evaluated through expedited systematic reviews and expert consensus-building through weekly GDG consultations, facilitated by a methodologist and, when necessary, followed up by surveys. This process also considers, as much as possible, potential resource implications, values and preferences, feasibility, equity, and ethics. Draft guidance documents are reviewed by an external review panel of experts prior to publication.

Purpose of the guidance

This document provides guidance for decision makers, public health and IPC professionals, health care managers and health workers in health care settings (including long-term care and residential), for the public and for manufactures of non-medical masks (Annex). It will be revised as new evidence emerges.

WHO has also developed comprehensive guidance on IPC strategies for health care settings (3), long-term care facilities (LTCF) (4), and home care (5).

Background

The use of masks is part of a comprehensive package of prevention and control measures that can limit the spread of certain respiratory viral diseases, including COVID-19. Masks can be used for protection of healthy persons (worn to protect oneself when in contact with an infected individual) or for source control (worn by an infected individual to prevent onward transmission) or both.

However, the use of a mask alone, even when correctly used (see below), is insufficient to provide an adequate level of protection for an uninfected individual or prevent onward transmission from an infected individual (source control). Hand hygiene, physical distancing of at least 1 metre, respiratory etiquette, adequate ventilation in indoor settings, testing, contact tracing, quarantine, isolation and other infection prevention and control (IPC) measures are critical to prevent human-to-human transmission of SARS-CoV-2, whether or not masks are used (6).

Mask management

For any type of mask, appropriate use, storage and cleaning, or disposal are essential to ensure that they are as effective as possible and to avoid any increased risk of transmission. Adherence to correct mask management practices varies, reinforcing the need for appropriate messaging (7).

WHO provides the following guidance on the correct use of masks:

- Perform hand hygiene before putting on the mask.
- Inspect the mask for tears or holes, and do not use a damaged mask.
- Place the mask carefully, ensuring it covers the mouth and nose, adjust to the nose bridge and tie it securely to minimize any gaps between the face and the mask. If using ear loops, ensure these do not cross over as this widens the gap between the face and the mask.

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- Avoid touching the mask while wearing it. If the mask is accidently touched, perform hand hygiene.
- Remove the mask using the appropriate technique. Do not touch the front of the mask, but rather untie it from behind.
- Replace the mask as soon as it becomes damp with a new clean, dry mask.
- Either discard the mask or place it in a clean plastic resealable bag where it is kept until it can be washed and cleaned. Do not store the mask around the arm or wrist or pull it down to rest around the chin or neck.
- Perform hand hygiene immediately afterward discarding a mask.
- Do not re-use single-use mask.
- Discard single-use masks after each use and properly dispose of them immediately upon removal.
- Do not remove the mask to speak.
- Do not share your mask with others.
- Wash fabric masks in soap or detergent and preferably hot water (at least 60° Centigrade/140° Fahrenheit) at least once a day. If it is not possible to wash the masks in hot water, then wash the mask in soap/detergent and room temperature water, followed by boiling the mask for 1 minute.

Scientific evidence

Transmission of the SARS-CoV-2 virus

Knowledge about transmission of the SARS-CoV-2 virus is evolving continuously as new evidence accumulates. COVID-19 is primarily a respiratory disease, and the clinical spectrum can range from no symptoms to severe acute respiratory illness, sepsis with organ dysfunction and death.

According to available evidence, SARS-CoV-2 mainly spreads between people when an infected person is in close contact with another person. Transmissibility of the virus depends on the amount of viable virus being shed and expelled by a person, the type of contact they have with others, the setting and what IPC measures are in place. The virus can spread from an infected person's mouth or nose in small liquid particles when the person coughs, sneezes, sings, breathes heavily or talks. These liquid particles are different sizes, ranging from larger 'respiratory droplets' to smaller 'aerosols.' Close-range contact (typically within 1 metre) can result in inhalation of, or inoculation with, the virus through the mouth, nose or eyes (8-13).

There is limited evidence of transmission through fomites (objects or materials that may be contaminated with viable virus, such as utensils and furniture or in health care settings a stethoscope or thermometer) in the immediate environment around the infected person (14-17). Nonetheless, fomite transmission is considered a possible mode of transmission for SARS-CoV-2, given consistent finding of environmental contamination in the vicinity of people infected with SARS-CoV-2 and the fact that other coronaviruses and respiratory viruses can be transmitted this way (12).

Aerosol transmission can occur in specific situations in which procedures that generate aerosols are performed. The scientific community has been actively researching whether the SARS-CoV-2 virus might also spread through aerosol transmission in the absence of aerosol generating procedures (AGPs) (18, 19). Some studies that performed air sampling in clinical settings where AGPs were not performed found virus RNA, but others did not. The presence of viral RNA is not the same as replication- and infection-competent (viable) virus that could be transmissible and capable of sufficient inoculum to initiate invasive infection. A limited number of studies have isolated viable SARS-CoV-2 from air samples in the vicinity of COVID-19 patients (20, 21).

Outside of medical facilities, in addition to droplet and fomite transmission, aerosol transmission can occur in specific settings and circumstances, particularly in indoor, crowded and inadequately ventilated spaces, where infected persons spend long periods of time with others. Studies have suggested these can include restaurants, choir practices, fitness classes, nightclubs, offices and places of worship (12).

High quality research is required to address the knowledge gaps related to modes of transmission, infectious dose and settings in which transmission can be amplified. Currently, studies are underway to better understand the conditions in which aerosol transmission or superspreading events may occur.

Current evidence suggests that people infected with SARS-CoV-2 can transmit the virus whether they have symptoms or not. However, data from viral shedding studies suggest that infected individuals have highest viral loads just before or around the time they develop symptoms and during the first 5-7 days of illness (12). Among symptomatic patients, the duration of infectious virus shedding has been estimated at 8 days from the onset of symptoms (22-24) for patients with mild disease, and longer for severely ill patients (12). The period of infectiousness is shorter than the duration of detectable RNA shedding, which can last many weeks (17).

The incubation period for COVID-19, which is the time between exposure to the virus and symptom onset, is on average 5-6 days, but can be as long as 14 days (25, 26).

Pre-symptomatic transmission – from people who are infected and shedding virus but have not yet developed symptoms – can occur. Available data suggest that some people who have been exposed to the virus can test positive for SARS-CoV-2 via polymerase chain reaction (PCR) testing 1-3 days before they develop symptoms (27). People who develop symptoms appear to have high viral loads on or just prior to the day of symptom onset, relative to later on in their infection (28).

Asymptomatic transmission – transmission from people infected with SARS-CoV-2 who never develop symptoms – can occur. One systematic review of 79 studies found that 20% (17–25%) of people remained asymptomatic throughout the course of infection. (28). Another systematic review, which included 13 studies considered to be at low risk of bias, estimated that 17% of cases remain asymptomatic (14%–20%) (30). Viable virus has been isolated from specimens of pre-symptomatic and asymptomatic individuals, suggesting that people who do not have symptoms may be able to transmit the virus to others. (25, 29-37)

Studies suggest that asymptomatically infected individuals are less likely to transmit the virus than those who develop symptoms (29). A systematic review concluded that individuals who are asymptomatic are responsible for transmitting fewer infections than symptomatic and pre-symptomatic cases (38). One meta-analysis estimated that there is a 42% lower relative risk of asymptomatic transmission compared to symptomatic transmission (30).

Guidance on mask use in health care settings

Masks for use in health care settings

Medical masks are defined as surgical or procedure masks that are flat or pleated. They are affixed to the head with straps that go around the ears or head or both. Their performance characteristics are tested according to a set of standardized test methods (ASTM F2100, EN 14683, or equivalent) that aim to balance high filtration, adequate breathability and optionally, fluid penetration resistance (39, 40).

Filtering facepiece respirators (FFR), or respirators, offer a balance of filtration and breathability. However, whereas medical masks filter 3 micrometre droplets, respirators must filter more challenging 0.075 micrometre solid particles. European FFRs, according to standard EN 149, at FFP2 performance there is filtration of at least 94% solid NaCl particles and oil droplets. US N95 FFRs, according to NIOSH 42 CFR Part 84, filter at least 95% NaCl particles. Certified FFRs must also ensure unhindered breathing with maximum resistance during inhalation and exhalation. Another important difference between FFRs and other masks is the way filtration is tested. Medical mask filtration tests are performed on a cross-section of the masks, whereas FFRs are tested for filtration across the entire surface. Therefore, the layers of the filtration material and the FFR shape, which ensure the outer edges of the FFR seal around wearer's face, result in guaranteed filtration as claimed. Medical masks, by contrast, have an open shape and potentially leaking structure. Other FFR performance requirements include being within specified parameters for maximum CO_2 build up, total inward leakage and tensile strength of straps (41, 42).

A. Guidance on the use of medical masks and respirators to provide care to suspected or confirmed COVID-19 cases

Evidence on the use of mask in health care settings

Systematic reviews have reported that the use of N95/P2 respirators compared with the use of medical masks (see mask definitions, above) is not associated with statistically significant differences for the outcomes of health workers acquiring clinical respiratory illness, influenza-like illness (risk ratio 0.83, 95%CI 0.63-1.08) or laboratory-confirmed influenza (risk ratio 1.02, 95%CI 0.73-1.43); harms were poorly reported and limited to discomfort associated with lower compliance (43, 44). In many settings, preserving the supply of N95 respirators for high-risk, aerosol-generating procedures is an important consideration (45).

A systematic review of observational studies on the betacoronaviruses that cause severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and COVID-19 found that the use of face protection (including respirators and medical masks) is associated with reduced risk of infection among health workers. These studies suggested that N95 or similar respirators might be associated with greater reduction in risk than medical or 12–16-layer cotton masks. However, these studies had important limitations (recall bias, limited information about the situations when respirators were used and limited ability to measure exposures), and very few studies included in the review evaluated the transmission risk of COVID-19 (46). Most of the studies were conducted in settings in which AGPs were performed or other high-risk settings (e.g., intensive care units or where there was exposure to infected patients and health workers were not wearing adequate PPE).

WHO continues to evaluate the evidence on the effectiveness of the use of different masks and their potential harms, risks and disadvantages, as well as their combination with hand hygiene, physical distancing of at least 1 metre and other IPC measures.

Guidance

WHO's guidance on the type of respiratory protection to be worn by health workers providing care to COVID-19 patients is based on 1) WHO recommendations on IPC for epidemic- and pandemic-prone acute respiratory infections in health care (47); 2) updated systematic reviews of randomized controlled trials on the effectiveness of medical masks compared to that of respirators for reducing the risk of clinical respiratory illness, influenza-like illness (ILI) and laboratory-confirmed influenza or viral infections. WHO guidance in this area is aligned with guidelines of other professional organizations, including the European Society of Intensive Care Medicine and the Society of Critical Care Medicine, and the Infectious Diseases Society of America (48, 49).

The WHO COVID-19 IPC GDG considered all available evidence on the modes of transmission of SARS-CoV-2 and on the effectiveness of medical mask versus respirator use to protect health workers from infection and the potential for harms such as skin conditions or breathing difficulties.

Other considerations included availability of medical masks versus respirators, cost and procurement implications and equity of access by health workers across different settings.

The majority (71%) of the GDG members confirmed their support for previous recommendations issued by WHO on 5 June 2020:

1. In the absence of aerosol generating procedures (AGPs)[2], WHO recommends that health workers providing care to patients with suspected or confirmed COVID-19 should wear a medical mask (in addition to other PPE that are part of droplet and contact precautions).
2. In care settings for COVID-19 patients where AGPs are performed, WHO recommends that health workers should wear a respirator (N95 or FFP2 or FFP3 standard, or equivalent) in addition to other PPE that are part of airborne and contact precautions.

In general, health workers have strong preferences about having the highest perceived protection possible to prevent COVID-19 infection and therefore may place high value on the potential benefits of respirators in settings without AGPs. WHO recommends respirators primarily for settings where AGPs are performed; however, if health workers prefer them and they are sufficiently available and cost is not an issue, they could also be used during care for COVID-19 patients in other settings. For additional guidance on PPE, including PPE

[2] The WHO list of AGPs includes tracheal intubation, non-invasive ventilation, tracheotomy, cardiopulmonary resuscitation, manual ventilation before intubation, bronchoscopy, sputum induction using nebulized hypertonic saline, and dentistry and autopsy procedures.

beyond mask use by health workers, see WHO IPC guidance during health care when COVID-19 infection is suspected (3) and also WHO guidance on the rational use of PPE (45).

Exhalation valves on respirators are discouraged as they bypass the filtration function for exhaled air.

B. Guidance on the use of mask by health workers, caregivers and others based on transmission scenario

Definitions

Universal masking in health facilities is defined as the requirement for all persons (staff, patients, visitors, service providers and others) to wear a mask at all times except for when eating or drinking.

Targeted continuous medical mask use is defined as the practice of wearing a medical mask by all health workers and caregivers working in clinical areas during all routine activities throughout the entire shift.

Health workers are all people primarily engaged in actions with the primary intent of enhancing health. Examples are: nursing and midwifery professionals, doctors, cleaners, other staff who work in health facilities, social workers, and community health workers.

Evidence on universal masking in health care settings

In areas where there is community transmission or large-scale outbreaks of COVID-19, universal masking has been adopted in many hospitals to reduce the potential of transmission by health workers to patients, to other staff and anyone else entering the facility (50).

Two studies found that implementation of a universal masking policy in hospital systems was associated with decreased risk of healthcare-acquired SARS-CoV-2 infection. However, these studies had serious limitations: both were before-after studies describing a single example of a phenomenon before and after an event of interest, with no concurrent control group, and other infection control measures were not controlled for (51, 52). In addition, observed decreases in health worker infections occurred too quickly to be attributable to the universal masking policy.

Guidance

Although more research on universal masking in heath settings is needed, it is the expert opinion of the majority (79%) of WHO COVID-19 IPC GDG members that universal masking is advisable in geographic settings where there is known or suspected community or cluster transmission of the SARS-CoV-2 virus.

1. In areas of known or suspected community or cluster SARS-CoV-2 transmission, universal masking should be advised in all health facilities (see Table 1).

- All health workers, including community health workers and caregivers, should wear a medical mask at all times, for any activity (care of COVID-19 or non-COVID-19 patients) and in any common area (e.g., cafeteria, staff rooms).
- Other staff, visitors, outpatients and service providers should also wear a mask (medical or non-medical) at all times
- Inpatients are not required to wear a mask (medical or non-medical) unless physical distancing of at least 1 metre cannot be maintained (e.g., when being examined or visited at the bedside) or when outside of their care area (e.g., when being transported).
- Masks should be changed when they become soiled, wet or damaged or if the health worker/caregiver removes the mask (e.g., for eating or drinking or caring for a patient who requires droplet/contact precautions for reasons other than COVID-19).

2. In the context of known or suspected sporadic SARS-CoV-2 virus transmission, WHO provides the following guidance:

- Health workers, including community health workers and caregivers who work in clinical areas, should continuously wear a medical mask during routine activities throughout the entire shift, apart from when eating and drinking and changing their medical masks after caring for a patient who requires droplet/contact precautions for other reasons. In all cases, medical masks must be changed when wet, soiled, or damaged; used medical masks should be properly disposed of at the end of the shift; and new clean ones should be used for the next shift or when medical masks are changed.
- It is particularly important to adopt the continuous use of masks in potentially high transmission risk settings including triage, family physician/general practitioner offices; outpatient departments; emergency rooms; COVID-19 designated units; haematology, oncology and transplant units; and long-term health and residential facilities.
- Staff who do not work in clinical areas (e.g., administrative staff) do not need to wear a medical mask during routine activities if they have no exposure to patients.

Whether using masks for universal masking within health facilities or targeted continuous medical mask use throughout the entire shift, health workers should ensure the following:

- Medical mask use should be combined with other measures including frequent hand hygiene and physical distancing among health workers in shared and crowded places such as cafeterias, break rooms, and dressing rooms.
- The medical mask should be changed when wet, soiled, or damaged.
- The medical mask should not be touched to adjust it or if displaced from the face for any reason. If this happens, the mask should be safely removed and replaced, and hand hygiene performed.
- The medical mask (as well as other personal protective equipment) should be discarded and changed after caring for any patient who requires contact/droplet precautions for other pathogens, followed by hand hygiene.
- Under no circumstances should medical masks be shared between health workers or between others wearing them. Masks should be appropriately disposed of whenever removed and not reused.

- A particulate respirator at least as protective as a United States of America (US) National Institute for Occupational Safety and Health-certified N95, N99, US Food and Drug Administration surgical N95, European Union standard FFP2 or FFP3, or equivalent, should be worn in settings for COVID-19 patients where AGPs are performed (see WHO recommendations below). In these settings, this includes continuous use by health workers throughout the entire shift, when this policy is implemented.

Note: Decision makers may consider the transmission intensity in the catchment area of the health facility or community setting and the feasibility of implementing a universal masking policy compared to a policy based on assessed or presumed exposure risk. Decisions need to take into account procurement, sustainability and costs of the policy. When planning masks for all health workers, long-term availability of adequate medical masks (and when applicable, respirators) for all workers should be ensured, in particular for those providing care for patients with confirmed or suspected COVID-19. Proper use and adequate waste management should be ensured.

The potential harms and risks of mask and respirator use in the health facility setting include:

- contamination of the mask due to its manipulation by contaminated hands (53, 54);
- potential self-contamination that can occur if medical masks are not changed when wet, soiled or damaged; or by frequent touching/adjusting when worn for prolonged periods (55);
- possible development of facial skin lesions, irritant dermatitis or worsening acne, when used frequently for long hours (56-58);
- discomfort, facial temperature changes and headaches from mask wearing (44, 59, 60);
- false sense of security leading potentially to reduced adherence to well recognized preventive measures such as physical distancing and hand hygiene; and risk-taking behaviours (61-64);
- difficulty wearing a mask in hot and humid environments
- possible risk of stock depletion due to widespread use in the context of universal masking and targeted continuous mask use and consequent scarcity or unavailability for health workers caring for COVID 19 patients and during health care interactions with non-COVID-19 patients where medical masks or respirators might be required.

Alternatives to medical masks in health care settings

The WHO's disease commodity package (DCP) for COVID-19 recommends medical masks for health workers to be type II or higher (65). Type II medical masks provide a physical barrier to fluids and particulate materials and have bacterial filtration efficiency of ≥98% compared to Type I mask, which has bacterial filtration efficiency of ≥95% and lower fluid resistance (66) In case of stock outs of type II or higher medical masks, health workers should use a type I medical mask as an alternative. Other alternatives such as face shields or fabric masks should be carefully evaluated.

Face shields are designed to provide protection from splashes of biological fluid (particularly respiratory secretions), chemical agents and debris (67, 68) into the eyes. In the context of protection from SARS-CoV-2 transmission through respiratory droplets, face shields are used by health workers as personal protective equipment (PPE) for eye protection in combination with a medical mask or a respirator (69, 70) While a face shield may confer partial protection of the facial area against respiratory droplets, these and smaller droplets may come into contact with mucous membranes or with the eyes from the open gaps between the visor and the face (71,67).

Fabric masks are not regulated as protective masks or part of the PPE directive. They vary in quality and are not subject to mandatory testing or common standards and as such are not considered an appropriate alternative to medical masks for protection of health workers. One study that evaluated the use of cloth masks in a health care facility found that health care workers using 2 ply cotton cloth masks (a type of fabric mask) were at increased risk of influenza-like illness compared with those who wore medical masks (72).

In the context of severe medical mask shortage, face shields alone or in combination with fabric mask may be considered as a last resort (73). Ensure proper design of face shields to cover the sides of the face and below the chin.

As for other PPE items, if production of fabric masks for use in health care settings is proposed locally in situations of shortage or stock out, a local authority should assess the product according to specific minimum performance standards and required technical specifications (see Annex).

Additional considerations for community care settings

Like other health workers, community health workers should apply standard precautions for all patients at all times, with particular emphasis regarding hand and respiratory hygiene, surface and environmental cleaning and disinfection and the appropriate use of PPE. When a patient is suspected or confirmed of having COVID-19, community health workers should always apply contact and droplet precautions. These include the use of a medical mask, gown, gloves and eye protection (74).

IPC measures that are needed will depend on the local COVID-19 transmission dynamics and the type of contact required by the health care activity (see Table 1). The community health workforce should ensure that patients and workforce members apply precautionary measures such as respiratory hygiene and physical distancing of at least 1 metre (3.3 feet). They also may support set-up and maintenance of hand hygiene stations and community education (74). In the context of known or suspected community or cluster transmission, community health workers should wear a medical mask when providing essential routine services (see Table 1).

Table 1. Mask use in health care settings depending on transmission scenario, target population, setting, activity and type*

Transmission scenario	Target population (who)	Setting (where)	Activity (what)	Mask type (which one) *
Known or suspected community or cluster transmission of SARS-CoV-2	Health workers and caregivers	Health facility (including primary, secondary, tertiary care levels, outpatient care, and long-term care facilities)	For any activity in patient-care areas (COVID-19 or non-COVID-19 patients) or in any common areas (e.g., cafeteria, staff rooms)	Medical mask (or respirator if aerosol generating procedures performed)
	Other staff, patients, visitors, service suppliers		For any activity or in any common area	Medical or fabric mask
	Inpatients	In single or multiple-bed rooms	When physical distance of at least 1 metre cannot be maintained	
	Health workers and caregivers	Home visit (for example, for antenatal or postnatal care, or for a chronic condition)	When in direct contact with a patient or when a distance of at least 1 metre cannot be maintained.	Medical mask
		Community	Community outreach programmes/essential routine services	
Known or suspected sporadic transmission of SARS-CoV-2 cases	Health workers and caregivers	Health facility (including primary, secondary, tertiary care levels, outpatient care, and long-term care facilities)	In patient care area- irrespective of whether patients have suspected/confirmed COVID-19	Medical mask
	Other staff, patients, visitors, service suppliers and all others		No routine activities in patient areas	Medical mask not required. Medical mask should be worn if in contact or within 1 metre of patients, or according to local risk assessment
	Health workers and caregivers	Home visit (for example, for antenatal or postnatal care, or for a chronic condition)	When in direct contact or when a distance of at least 1metre cannot be maintained.	Medical mask
		Community	Community outreach programs (e.g., bed net distribution)	
No documented SARS-CoV-2 transmission	Health workers and caregivers	Health facility (including primary, secondary, tertiary care levels, outpatient care, and long-term care facilities)	Providing any patient care	Medical mask use according to standard and transmission-based precautions
		Community	Community outreach programs	
Any transmission scenario	Health workers	Health care facility (including primary, secondary, tertiary care levels, outpatient care, and long-term care facilities), in settings where aerosol generating procedures (AGP) are performed	Performing an AGP on a suspected or confirmed COVID-19 patient or providing care in a setting where AGPs are in place for COVID-19 patients	Respirator (N95 or N99 or FFP2 or FFP3)

**This table refers only to the use of medical masks and respirators. The use of medical masks and respirators may need to be combined with other personal protective equipment and other measures as appropriate, and always with hand hygiene.*

Guidance on mask use in community settings

Evidence on the protective effect of mask use in community settings

At present there is only limited and inconsistent scientific evidence to support the effectiveness of masking of healthy people in the community to prevent infection with respiratory viruses, including SARS-CoV-2 (75). A large randomized community-based trial in which 4862 healthy participants were divided into a group wearing medical/surgical masks and a control group found no difference in infection with SARS-CoV-2 (76). A recent systematic review found nine trials (of which eight were cluster-randomized controlled trials in which clusters of people, versus individuals, were randomized) comparing medical/surgical masks versus no masks to prevent the spread of viral respiratory illness. Two trials were with healthcare workers and seven in the community. The review concluded that wearing a mask may make little or no difference to the prevention of influenza-like illness (ILI) (RR 0.99, 95%CI 0.82 to 1.18) or laboratory confirmed illness (LCI) (RR 0.91, 95%CI 0.66-1.26) (44); the certainty of the evidence was low for ILI, moderate for LCI.

By contrast, a small retrospective cohort study from Beijing found that mask use by entire families before the first family member developed COVID-19 symptoms was 79% effective in reducing transmission (OR 0.21, 0.06-0.79) (77). A case-control study from Thailand found that wearing a medical or non-medical mask all the time during contact with a COVID-19 patient was associated with a 77% lower risk of infection (aOR 0.23; 95% CI 0.09–0.60) (78). Several small observational studies with epidemiological data have reported an association between mask use by an infected person and prevention of onward transmission of SARS-CoV-2 infection in public settings. (8, 79-81).

A number of studies, some peer reviewed (82-86) but most published as pre-prints (87-104), reported a decline in the COVID-19 cases associated with face mask usage by the public, using country- or region-level data. One study reported an association between community mask wearing policy adoption and increased movement (less time at home, increased visits to commercial locations) (105). These studies differed in setting, data sources and statistical methods and have important limitations to consider (106), notably the lack of information about actual exposure risk among individuals, adherence to mask wearing and the enforcement of other preventive measures (107, 108).

Studies of influenza, influenza-like illness and human coronaviruses (not including COVID-19) provide evidence that the use of a medical mask can prevent the spread of infectious droplets from a symptomatic infected person to someone else and potential contamination of the environment by these droplets (75). There is limited evidence that wearing a medical mask may be beneficial for preventing transmission between healthy individuals sharing households with a sick person or among attendees of mass gatherings (44, 109-114).

A meta-analysis of observational studies on infections due to betacoronaviruses, with the intrinsic biases of observational data, showed that the use of either disposable medical masks or reusable 12–16-layer cotton masks was associated with protection of healthy individuals within households and among contacts of cases (46). This could be considered to be indirect evidence for the use of masks (medical or other) by healthy individuals in the wider community; however, these studies suggest that such individuals would need to be in close proximity to an infected person in a household or at a mass gathering where physical distancing cannot be achieved to become infected with the virus. Results from cluster randomized controlled trials on the use of masks among young adults living in university residences in the United States of America indicate that face masks may reduce the rate of influenza-like illness but showed no impact on risk of laboratory-confirmed influenza (115, 116).

Guidance

The WHO COVID-19 IPC GDG considered all available evidence on the use of masks by the general public including effectiveness, level of certainty and other potential benefits and harms, with respect to transmission scenarios, indoor versus outdoor settings, physical distancing and ventilation. Despite the limited evidence of protective efficacy of mask wearing in community settings, in addition to all other recommended preventive measures, the GDG advised mask wearing in the following settings:

1. In areas with known or suspected community or cluster transmission of SARS-CoV-2, WHO advises mask use by the public in the following situations (see Table 2):

   Indoor settings:

- in public indoor settings where ventilation is known to be poor regardless of physical distancing: limited or no opening of windows and doors for natural ventilation; ventilation system is not properly functioning or maintained; or cannot be assessed;
- in public indoor settings that have adequate[3] ventilation if physical distancing of at least 1 metre cannot be maintained;
- in household indoor settings: when there is a visitor who is not a household member and ventilation is known to be poor, with limited opening of windows and doors for natural ventilation, or the ventilation system cannot be assessed or is not properly functioning, regardless of whether physical distancing of at least 1 metre can be maintained;
- in household indoor settings that have adequate ventilation if physical distancing of at least 1 metre cannot be maintained.

[3] For adequate ventilation refer to regional or national institutions or heating, refrigerating and air-conditioning societies enacting ventilation requirements. If not available or applicable, a recommended ventilation rate of 10 l/s/person should be met (except healthcare facilities which have specific requirements). For more information consult "Coronavirus (COVID-19) response resources from ASHRAE and others'' https://www.ashrae.org/technical-resources/resources

Table 2. Mask use in community settings depending on transmission scenario, setting, target population, purpose and type*

Transmission scenario	Situations/settings (where)	Target Population (who)	Purpose of mask use (why)	Mask type (which one)
Known or suspected community or cluster transmission of SARS-CoV-2	Indoor settings, where ventilation is known to be poor or cannot be assessed or the ventilation system is not properly maintained, regardless of whether physical distancing of at least 1 meter can be maintained	General population in public* settings such as shops, shared workplaces, schools, churches, restaurants, gyms, etc. or in enclosed settings such as public transportation. For households, in indoor settings, when there is a visitor who is not a member of the household	Potential benefit for source control	Fabric mask
	Indoor settings that have adequate [4] ventilation if physical distancing of at least 1 metre cannot be maintained			
	Outdoor settings where physical distancing cannot be maintained	General population in settings such as crowded open-air markets, lining up outside a building, during demonstrations, etc.		
	Settings where physical distancing cannot be maintained, and the individual is at increased risk of infection and/or negative outcomes	Individuals/people with higher risk of severe complications from COVID-19: • People aged ≥60 years • People with underlying comorbidities, such as cardiovascular disease or diabetes mellitus, chronic lung disease, cancer, cerebrovascular disease, immunosuppression, obesity, asthma	Protection	Medical mask
Known or suspected sporadic transmission, or no documented SARS-CoV-2 transmission	Risk-based approach	General population	Potential benefit for source control and/or protection	Depends on purpose (see details in the guidance content)
Any transmission scenario	Any setting in the community	Anyone suspected or confirmed of having COVID-19, regardless of whether they have symptoms or not, or anyone awaiting viral test results, when in the presence of others	Source control	Medical mask

**Public indoor setting includes any indoor setting outside of the household*

[4] For adequate ventilation refer to regional or national institutions or heating, refrigerating and air-conditioning societies enacting ventilation requirements. If not available or applicable, a recommended ventilation rate of 10l/s/person should be met (except healthcare facilities which have specific requirements).). For more information consult "Coronavirus (COVID-19) response resources from ASHRAE and others'' https://www.ashrae.org/technical-resources/resources

In outdoor settings:

- where physical distancing of at least 1 metre cannot be maintained;
- individuals/people with higher risk of severe complications from COVID-19 (individuals ≥ 60 years old and those with underlying conditions such as cardiovascular disease or diabetes mellitus, chronic lung disease, cancer, cerebrovascular disease or immunosuppression) should wear medical masks in any setting where physical distance cannot be maintained.

2. In areas with known or suspected sporadic transmission or no documented transmission, as in all transmission scenarios, WHO continues to advise that decision makers should apply a risk-based approach focusing on the following criteria when considering the use of masks for the public:

- **Purpose of mask use**. Is the intention source control (preventing an infected person from transmitting the virus to others) or protection (preventing a healthy wearer from the infection)?
- **Risk of exposure to SARS-CoV-2**. Based on the epidemiology and intensity of transmission in the population, is there transmission and limited or no capacity to implement other containment measures such as contact tracing, ability to carry out testing and isolate and care for suspected and confirmed cases? Is there risk to individuals working in close contact with the public (e.g., social workers, personal support workers, teachers, cashiers)?
- **Vulnerability of the mask wearer/population**. Is the mask wearer at risk of severe complications from COVID-19? Medical masks should be used by older people (≥ 60 years old), immunocompromised patients and people with comorbidities, such as cardiovascular disease or diabetes mellitus, chronic lung disease, cancer and cerebrovascular disease (117).
- **Setting in which the population lives**. Is there high population density (such as in refugee camps, camp-like settings, and among people living in cramped conditions) and settings where individuals are unable to keep a physical distance of at least 1 metre (for example, on public transportation)?
- **Feasibility**. Are masks available at an affordable cost? Do people have access to clean water to wash fabric masks, and can the targeted population tolerate possible adverse effects of wearing a mask?
- **Type of mask**. Does the use of medical masks in the community divert this critical resource from the health workers and others who need them the most? In settings where medical masks are in short supply, **stocks should be prioritized for health workers and at-risk individuals.**

The decision of governments and local jurisdictions whether to recommend or make mandatory the use of masks should be based on the above assessment as well as the local context, culture, availability of masks and resources required.

3. In any transmission scenario:

- Persons with any symptoms suggestive of COVID-19 should wear a medical mask and (5) additionally:
  - self-isolate and seek medical advice as soon as they start to feel unwell with potential symptoms of COVID-19, even if symptoms are mild);
  - follow instructions on how to put on, take off, and dispose of medical masks and perform hand hygiene (118);
  - follow all additional measures, in particular respiratory hygiene, frequent hand hygiene and maintaining physical distance of at least 1 metre from other persons (46). If a medical mask is not available for individuals with suspected or confirmed COVID-19, a fabric mask meeting the specifications in the Annex of this document should be worn by patients as a source control measure, pending access to a medical mask. The use of a non-medical mask can minimize the projection of respiratory droplets from the user (119, 120).
  - Asymptomatic persons who test positive for SARS-CoV-2, should wear a medical mask when with others for a period of 10 days after testing positive.

Potential benefits/harms

The potential advantages of mask use by healthy people in the general public include:

- reduced spread of respiratory droplets containing infectious viral particles, including from infected persons before they develop symptoms (121);
- reduced potential for stigmatization and greater of acceptance of mask wearing, whether to prevent infecting others or by people caring for COVID-19 patients in non-clinical settings (122);
- making people feel they can play a role in contributing to stopping spread of the virus;
- encouraging concurrent transmission prevention behaviours such as hand hygiene and not touching the eyes, nose and mouth (123-125);
- preventing transmission of other respiratory illnesses like tuberculosis and influenza and reducing the burden of those diseases during the pandemic (126).

The potential disadvantages of mask use by healthy people in the general public include:

- headache and/or breathing difficulties, depending on type of mask used (55);
- development of facial skin lesions, irritant dermatitis or worsening acne, when used frequently for long hours (58, 59, 127);
- difficulty with communicating clearly, especially for persons who are deaf or have poor hearing or use lip reading (128, 129);
- discomfort (44, 55, 59)
- a false sense of security leading to potentially lower adherence to other critical preventive measures such as physical distancing and hand hygiene (105);
- poor compliance with mask wearing, in particular by young children (111, 130-132);
- waste management issues; improper mask disposal leading to increased litter in public places and environmental hazards (133);
- disadvantages for or difficulty wearing masks, especially for children, developmentally challenged persons, those with mental illness, persons with cognitive impairment, those with asthma or chronic respiratory or breathing problems, those who have had facial trauma or recent oral maxillofacial surgery and those living in hot and humid environments (55, 130).

Considerations for implementation

When implementing mask policies for the public, decision-makers should:

- clearly communicate the purpose of wearing a mask, including when, where, how and what type of mask should be worn; explain what wearing a mask may achieve and what it will not achieve; and communicate clearly that this is one part of a package of measures along with hand hygiene, physical distancing, respiratory etiquette, adequate ventilation in indoor settings and other measures that are all necessary and all reinforce each other;
- inform/train people on when and how to use masks appropriately and safely (see mask management and maintenance sections);
- consider the feasibility of use, supply/access issues (cleaning, storage), waste management, sustainability, social and psychological acceptance (of both wearing and not wearing different types of masks in different contexts);
- continue gathering scientific data and evidence on the effectiveness of mask use (including different types of masks) in non-health care settings;
- evaluate the impact (positive, neutral or negative) of using masks in the general population (including behavioural and social sciences) through good quality research.

Mask use during physical activity

Evidence

There are limited studies on the benefits and harms of wearing medical masks, respirators and non-medical masks while exercising. Several studies have demonstrated statistically significant deleterious effects on various cardiopulmonary physiologic parameters during mild to moderate exercise in healthy subjects and in those with underlying respiratory diseases (134-140). The most significant impacts have been consistently associated with the use of respirators and in persons with underlying obstructive airway pulmonary diseases such as asthma and chronic obstructive pulmonary disease (COPD), especially when the condition is moderate to severe (136). Facial microclimate changes with increased temperature, humidity and perceptions of dyspnoea were also reported in some studies on the use of masks during exercise (134, 141). A recent review found negligeable evidence of negative effects of mask use during exercise but noted concern for individuals with severe cardiopulmonary disease (142).

Guidance

WHO advises that people should not wear masks during vigorous intensity physical activity (143) because masks may reduce the ability to breathe comfortably. The most important preventive measure is to maintain physical distancing of at least 1 meter and ensure good ventilation when exercising.

If the activity takes place indoors, adequate ventilation should be ensured at all times through natural ventilation or a properly functioning or maintained ventilation system (144). Particular attention should be paid to cleaning and disinfection of the environment, especially high-touch surfaces. If all the above measures cannot be ensured, consider temporary closure of public indoor exercise facilities (e.g., gyms).

Face shields for the general public

At present, face shields are considered to provide a level of eye protection only and should not be considered as an equivalent to masks with respect to respiratory droplet protection and/or source control. Current laboratory testing standards only assess face shields for their ability to provide eye protection from chemical splashes (145).

In the context of non-availability or difficulties wearing a non-medical mask (in persons with cognitive, respiratory or hearing impairments, for example), face shields may be considered as an alternative, noting that they are inferior to masks with respect to droplet transmission and prevention. If face shields are to be used, ensure proper design to cover the sides of the face and below the chin.

Medical masks for the care of COVID-19 patients at home

WHO provides guidance on how to care for patients with confirmed and suspected COVID-19 at home when care in a health facility or other residential setting is not possible (5).

- Persons with suspected COVID-19 or mild COVID-19 symptoms should wear a medical mask as much as possible, especially when there is no alternative to being in the same room with other people. The mask should be changed at least once daily. Persons who cannot tolerate a medical mask should rigorously apply respiratory hygiene (i.e., cover mouth and nose with a disposable paper tissue when coughing or sneezing and dispose of it immediately after use or use a bent elbow procedure and then perform hand hygiene).
- Caregivers of or those sharing living space with people with suspected COVID-19 or with mild COVID-19 symptoms should wear a medical mask when in the same room as the affected person.

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WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance document will expire 1 year after the date of publication.

Annex: Updated guidance on non-medical (fabric) masks

Background

A non-medical mask, also called fabric mask, community mask or face covering, is neither a medical device nor personal protective equipment. Non-medical masks are aimed at the general population, primarily for protecting others from exhaled virus-containing droplets emitted by the mask wearer. They are not regulated by local health authorities or occupational health associations, nor is it required for manufacturers to comply with guidelines established by standards organizations. Non-medical masks may be homemade or manufactured. The essential performance parameters include good breathability, filtration of droplets originating from the wearer, and a snug fit covering the nose and mouth. Exhalation valves on masks are discouraged as they bypass the filtration function of the mask.

Non-medical masks are made from a variety of woven and non-woven fabrics, such as woven cotton, cotton/synthetic blends, polyesters and breathable spunbond polypropylene, for example. They may be made of different combinations of fabrics, layering sequences and available in diverse shapes. Currently, more is known about common household fabrics and combinations to make non-medical masks with target filtration efficiency and breathability (119, 146-150). Few of these fabrics and combinations have been systematically evaluated and there is no single design, choice of material, layering or shape among available non-medical masks that are considered optimal. While studies have focussed on single fabrics and combinations, few have looked at the shape and universal fit to the wearer. The unlimited combination of available fabrics and materials results in variable filtration and breathability.

In the context of the global shortage of medical masks and PPE, encouraging the public to create their own fabric masks may promote individual enterprise and community integration. Moreover, the production of non-medical masks may offer a source of income for those able to manufacture masks within their communities. Fabric masks can also be a form of cultural expression, encouraging public acceptance of protection measures in general. The safe re-use of fabric masks will also reduce costs and waste and contribute to sustainability (151-156).

This Annex is destined intended for two types of readers: homemade mask makers and factory-made masks manufacturers. Decision makers and managers (national/sub-national level) advising on a type of non-medical mask are also the focus of this guidance and should take into consideration the following features of non-medical masks: breathability, filtration efficiency (FE), or filtration, number and combination of fabric layers material used, shape, coating and maintenance.

Evidence on the effectiveness of non-medical (fabric) masks

A number of reviews have been identified on the effectiveness of non-medical masks (151-156). One systematic review (155) identified 12 studies and evaluated study quality. Ten were laboratory studies (157-166), and two reports were from a single randomized trial (72, 167). The majority of studies were conducted before COVID-19 emerged or used laboratory generated particles to assess filtration efficacy. Overall, the reviews concluded that cloth face masks have limited efficacy in combating viral infection transmission.

Homemade non-medical masks

Homemade non-medical masks made of household fabrics (e.g., cotton, cotton blends and polyesters) should ideally have a three-layer structure, with each layer providing a function (see Figure 1) (168). It should include:

1. an innermost layer (that will be in contact with the face) of a hydrophilic material (e.g., cotton or cotton blends of terry cloth towel, quilting cotton and flannel) that is non-irritating against the skin and can contain droplets (148)
2. a middle hydrophobic layer of synthetic breathable non-woven material (spunbond polypropylene, polyester and polyaramid), which may enhance filtration, prevent permeation of droplets or retain droplets (148, 150)
3. an outermost layer made of hydrophobic material (e.g. spunbond polypropylene, polyester or their blends), which may limit external contamination from penetrating through the layers to the wearer's nose and mouth and maintains and prevents water accumulation from blocking the pores of the fabric (148).

Although a minimum of three layers is recommended for non-medical masks for the most common fabric used, single, double or other layer combinations of advanced materials may be used if they meet performance requirements. It is important to note that with more tightly woven materials, breathability may be reduced as the number of layers increases. A quick check may be performed by attempting to breathe, through the mouth, through the multiple layers.

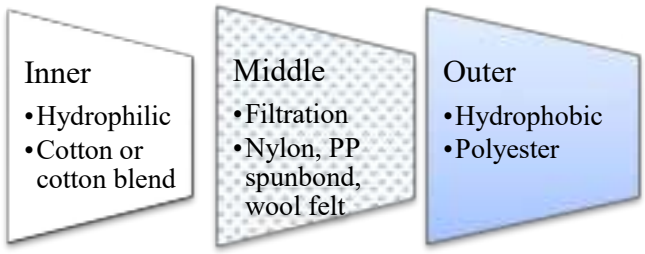

Figure 1. Non-medical mask construction using breathable fabrics such as cotton, cotton blends, polyesters, nylon and polypropylene spunbond that are breathable may impart adequate filtration performance when layered. Single- or double-layer combinations of advanced materials may be used if they meet performance requirements (72).

Assumptions regarding homemade masks are that individual makers only have access to common household fabrics and do not have access to test equipment to confirm target performance (filtration and breathability). Figure 1 illustrates a multi-layer mask construction with examples of fabric options. Very porous materials, such as gauze, even with multiple layers, may provide very low filtration efficiency (147). Higher thread count fabrics offer improved filtration performance (169). Coffee filters, vacuum bags and materials not meant for clothing should be avoided as they may contain injurious content when breathed in. Microporous films such as Gore-Tex are not recommended (170).

Factory-made non-medical masks: general considerations for manufacturers

The non-medical mask, including all components and packaging, must be non-hazardous, non-toxic and child-friendly (no exposed sharp edges, protruding hardware or rough materials). Factory-made non-medical masks must be made using a process that is certified to a quality management system (e.g., ISO 9001). Social accountability standards (e.g., SAI SA8000) for multiple aspects of fair labour practices, health and safety of the work force and adherence to UNICEF's Children's Rights and Business Principles are strongly encouraged.

Standards organizations' performance criteria

Manufacturers producing masks with consistent standardized performance can adhere to published, freely available guidance from several organizations including those from: the French Standardization Association (AFNOR Group), The European Committee for Standardization (CEN), Swiss National COVID-19 Task Force, the American Association of Textile Chemists and Colorists (AATCC), the South Korean Ministry of Food and Drug Safety (MFDS), the Italian Standardization Body (UNI) and the Government of Bangladesh.

Essential parameters

The essential parameters presented in this section are the synthesis of the abovementioned regional and national guidance. They include filtration, breathability and fit. Good performance is achieved when the three essential parameters are optimized at the preferred threshold (Figure 2).

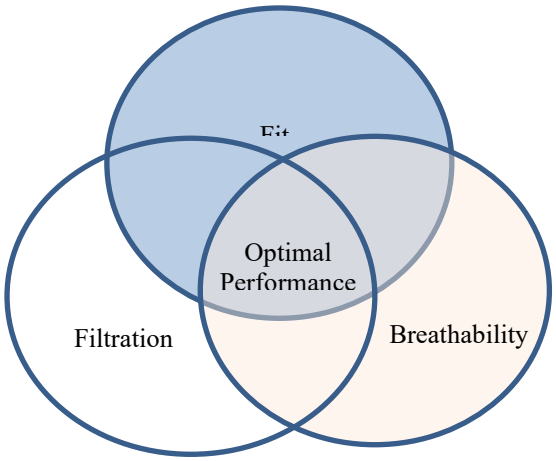

Figure 2. Illustration of the three essential parameters of filtration, breathability and fit.

The summary of the three essential parameters can be found in Table 1 and the additional performance considerations in Table 2. The minimum threshold is the minimum acceptable parameter, while the preferred threshold is the optimum.

Filtration and breathability

Filtration depends on the filtration efficiency (in %), the type of challenge particle (oils, solids, droplets containing bacteria) and the particle size (see Table 1). Depending on the fabrics used, filtration and breathability can complement or work against one another. The selection of material for droplet filtration (barrier) is as important as breathability. Filtration is dependent on the tightness of the weave, fibre or thread diameter. Non-woven materials used for disposable masks are manufactured using processes to create polymer fibres that are thinner than natural fibres such as cotton and that are held together by partial melting.

Breathability is the difference in pressure across the mask and is typically reported in millibars (mbar) or Pascals (Pa) or, normalized to the cm^2 in $mbar/cm^2$ or Pa/cm^2. Acceptable breathability of a medical mask should be below 49 Pa/cm^2. For non-medical masks, an acceptable pressure difference, over the whole mask, should be below 60 Pa/cm^2, with lower values indicating better breathability.

Non-medical fabric masks consisting of two layers of polypropylene spunbond and two layers of cotton have been shown to meet the minimum requirements for droplet filtration and breathability of the CEN CWA 17553 guidance. It is preferable not to select elastic material to make masks as the mask material may be stretched over the face, resulting in increased pore size and lower filtration through multiple usage. Additionally, elastic fabrics are sensitive to washing at high temperatures thus may degrade over time.

Coating the fabric with compounds like wax may increase the barrier and render the mask fluid resistant; however, such coatings may inadvertently completely block the pores and make the mask difficult to breathe through. In addition to decreased breathability unfiltered air may more likely escape the sides of the mask on exhalation. Coating is therefore not recommended.

Valves that let unfiltered air escape the mask are discouraged and are an inappropriate feature for masks used for the purpose of preventing transmission.

Table 1. Essential parameters (minimum and preferred thresholds) for manufactured non-medical mask

Essential Parameters	Minimum threshold	Preferred threshold
1. Filtration*		
1.1. filtration efficiency	70% @ 3 micron	> 70%, without compromising breathability
1.2. Challenge particle	Solid: sodium chloride (NaCl), Talcum powder, Holi powder, dolomite, Polystyrene Latex spheres Liquid: DEHS Di-Ethyl-Hexyl-Sebacat, paraffin oil	Based on availability
1.3. Particle size	Choose either sizes: 3 µm, 1 µm, or smaller	Range of particle sizes
2. Breathability		
2.1. Breathing resistance**	≤60 Pa/cm^2	Adult: ≤ 40 Pa/cm^2 Paediatric: ≤ 20 Pa/cm^2
2.2 Exhalation valves	Not recommended	N/A
3. Fit		
3.1. Coverage	Full coverage of nose and mouth, consistent, snug perimeter fit at the nose bridge, cheeks, chin and lateral sides of the face; adequate surface area to minimize breathing resistance and minimize side leakage	Same as current requirements
3.2 Face seal	Not currently required	Seal as good as FFR (respirator): Fit factor of 100 for N95 Maximum Total Inward Leakage of 25% (FFP1 requirement)
3.2. Sizing	Adult and child	Should cover from the bridge of the nose to below the chin and cheeks on either side of the mouth Sizing for adults and children (3-5, 6-9, 10-12, >12)
3.3Strap strength		> 44.5 N

* Smaller particle may result in lower filtration.
** High resistance can cause bypass of the mask. Unfiltered air will leak out the sides or around the nose if that is the easier path.

Fit: shape and sizing

Fit is the third essential parameter, and takes into consideration coverage, seal, sizing, and strap strength. Fit of masks currently is not defined by any standard except for the anthropometric considerations of facial dimensions (ISO/TS 16976-2) or simplified to height mask (South Korean standard for KF-AD). It is important to ensure that the mask can be held in place comfortably with as little adjustment of the elastic bands or ties as possible.

Mask shapes typically include flat-fold or duckbill and are designed to fit closely over the nose, cheeks and chin of the wearer. Snug fitting designs are suggested as they limit leaks of unfiltered air escaping from the mask (148). Ideally the mask should not have contact with the lips, unless hydrophobic fabrics are used in at least one layer of the mask (148). Leaks where unfiltered air moves in and out of the mask may be attributed to the size and shape of the mask (171).

Additional considerations

Optional parameters to consider in addition to the essential performance parameters include if reusable, biodegradability for disposal masks, antimicrobial performance where applicable and chemical safety (see Table 2).

Non-medical masks intended to be reusable should include instructions for washing and must be washed a minimum of five cycles, implying initial performance is maintained after each wash cycle.

Advanced fabrics may be biodegradable or compostable at the end of service life, according to a recognized standard process (e.g., UNI EN 13432, UNI EN 14995 and UNI / PdR 79).

Manufacturers sometimes claim their NM masks have antimicrobial performance. Antimicrobial performance may be due to coatings or additives to the fabric fibres. Treated fabrics must not come into direct contact with mucous membranes; the innermost fabric should not be treated with antimicrobial additives, only the outermost layer. In addition, antimicrobial fabric standards (e.g., ISO 18184, ISO 20743, AATCC TM100, AATCC 100) are generally slow acting. The inhibition on microbial growth may take full effect after 2- or 24-hour contact time depending on the standard. The standards have generally been used for athletic apparel and substantiate claims of odour control performance. These standards are not appropriate for non-medical cloth masks and may provide a false sense of protection from infectious agents. If claims are maid, manufacturers should specify which standard supports antimicrobial performance, the challenge organism and the contact time.

Volatile additives are discouraged as these may pose a health risk when inhaled repeatedly during wear. Certification according to organizations including OEKO-TEX (Europe) or SEK (Japan), and additives complying with REACH (Europe) or the Environmental Protection Agency (EPA, United States of America) indicate that textile additives are safe and added at safe levels.

Table 2. Additional parameters for manufactured non-medical masks

Additional parameters	Minimum thresholds
If reusable, number of wash cycles	5 cycles
Disposal	Reusable If biodegradable (CFC-BIO), according to UNI EN 13432, UNI EN 14995
Antimicrobial (bacteria, virus, fungus) performance	ISO 18184 (virus) ISO 20743 (bacteria) ISO 13629 (fungus) AATCC TM100 (bacteria)
Chemical safety	Comply with REACH regulation, including inhalation safety

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Annals of Internal Medicine ORIGINAL RESEARCH

Effectiveness of Adding a Mask Recommendation to Other Public Health Measures to Prevent SARS-CoV-2 Infection in Danish Mask Wearers

A Randomized Controlled Trial

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Background: Observational evidence suggests that mask wearing mitigates transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is uncertain if this observed association arises through protection of uninfected wearers (protective effect), via reduced transmission from infected mask wearers (source control), or both.

Objective: To assess whether recommending surgical mask use outside the home reduces wearers' risk for SARS-CoV-2 infection in a setting where masks were uncommon and not among recommended public health measures.

Design: Randomized controlled trial (DANMASK-19 [Danish Study to Assess Face Masks for the Protection Against COVID-19 Infection]). (ClinicalTrials.gov: NCT04337541)

Setting: Denmark, April and May 2020.

Participants: Adults spending more than 3 hours per day outside the home without occupational mask use.

Intervention: Encouragement to follow social distancing measures for coronavirus disease 2019, plus either no mask recommendation or a recommendation to wear a mask when outside the home among other persons together with a supply of 50 surgical masks and instructions for proper use.

Measurements: The primary outcome was SARS-CoV-2 infection in the mask wearer at 1 month by antibody testing, polymerase chain reaction (PCR), or hospital diagnosis. The secondary outcome was PCR positivity for other respiratory viruses.

Results: A total of 3030 participants were randomly assigned to the recommendation to wear masks, and 2994 were assigned to control; 4862 completed the study. Infection with SARS-CoV-2 occurred in 42 participants recommended masks (1.8%) and 53 control participants (2.1%). The between-group difference was −0.3 percentage point (95% CI, −1.2 to 0.4 percentage point; $P = 0.38$) (odds ratio, 0.82 [CI, 0.54 to 1.23]; $P = 0.33$). Multiple imputation accounting for loss to follow-up yielded similar results. Although the difference observed was not statistically significant, the 95% CIs are compatible with a 46% reduction to a 23% increase in infection.

Limitation: Inconclusive results, missing data, variable adherence, patient-reported findings on home tests, no blinding, and no assessment of whether masks could decrease disease transmission from mask wearers to others.

Conclusion: The recommendation to wear surgical masks to supplement other public health measures did not reduce the SARS-CoV-2 infection rate among wearers by more than 50% in a community with modest infection rates, some degree of social distancing, and uncommon general mask use. The data were compatible with lesser degrees of self-protection.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), has infected more than 54 million persons (1,2). Measures to impede transmission in health care and community settings are essential (3). The virus is transmitted person-to-person, primarily through the mouth, nose, or eyes via respiratory droplets, aerosols, or fomites (4,5). It can survive on surfaces for up to 72 hours (6), and touching a contaminated surface followed by face touching is another possible route of transmission (7). Face masks are a plausible means to reduce transmission of respiratory viruses by minimizing the risk that respiratory droplets will reach wearers' nasal or oral mucosa. Face masks are also hypothesized to reduce face touching (8,9), but frequent face and mask touching has been reported among health care personnel (10). Observational evidence supports the efficacy of face masks in health care settings (11,12) and as source control in patients infected with SARS-CoV-2 or other coronaviruses (13).

An increasing number of localities recommend masks in community settings on the basis of this observational evidence, but recommendations vary and controversy

See also:

Editorial comment
Web-Only
Supplement

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exists (14). The World Health Organization (WHO) and the U.S. Centers for Disease Control and Prevention (15) strongly recommend that persons with symptoms or known infection wear masks to prevent transmission of SARS-CoV-2 to others (source control) (16). However, WHO acknowledges that we lack evidence that wearing a mask protects healthy persons from SARS-CoV-2 (prevention) (17). A systematic review of observational studies reported that mask use reduced risk for SARS, Middle East respiratory syndrome, and COVID-19 by 66% overall, 70% in health care workers, and 44% in the community (12). However, surgical and cloth masks were grouped in preventive studies, and none of the 3 included non–health care studies related directly to COVID-19. Another systematic review (18) and American College of Physicians recommendations (19) concluded that evidence on mask effectiveness for respiratory infection prevention is stronger in health care than community settings.

Observational evidence suggests that mask wearing mitigates SARS-CoV-2 transmission, but whether this observed association arises because masks protect uninfected wearers (protective effect) or because transmission is reduced from infected mask wearers (source control) is uncertain. Here, we report a randomized controlled trial (20) that assessed whether a recommendation to wear a surgical mask when outside the home among others reduced wearers' risk for SARS-CoV-2 infection in a setting where public health measures were in effect but community mask wearing was uncommon and not recommended.

METHODS

Trial Design and Oversight

DANMASK-19 (Danish Study to Assess Face Masks for the Protection Against COVID-19 Infection) was an investigator-initiated, nationwide, unblinded, randomized controlled trial (ClinicalTrials.gov: NCT04337541). The trial protocol was registered with the Danish Data Protection Agency (P-2020-311) (Part 10 of the **Supplement**, available at Annals.org) and published (21). The researchers presented the protocol to the independent regional scientific ethics committee of the Capital Region of Denmark, which did not require ethics approval (H-20023709) in accordance with Danish legislation (Parts 11 and 12 of the **Supplement**). The trial was done in accordance with the principles of the Declaration of Helsinki.

Participants and Study Period

During the study period (3 April to 2 June 2020), Danish authorities did not recommend use of masks in the community and mask use was uncommon (<5%) outside hospitals (22). Recommended public health measures included quarantining persons with SARS-CoV-2 infection, social distancing (including in shops and public transportation, which remained open), limiting the number of persons seen, frequent hand hygiene and cleaning, and limiting visitors to hospitals and nursing homes (23,24). Cafés and restaurants were closed during the study until 18 May 2020.

Eligible persons were community-dwelling adults aged 18 years or older without current or prior symptoms or diagnosis of COVID-19 who reported being outside the home among others for at least 3 hours per day and who did not wear masks during their daily work. Recruitment involved media advertisements and contacting private companies and public organizations. Interested citizens had internet access to detailed study information and to research staff for questions (Part 3 of the **Supplement**). At baseline, participants completed a demographic survey and provided consent for researchers to access their national registry data (Parts 4 and 5 of the **Supplement**). Recruitment occurred from 3 through 24 April 2020. Half of participants were randomly assigned to a group on 12 April and half on 24 April.

Intervention

Participants were enrolled and data registered using Research Electronic Data Capture (REDCap) software (25). Eligible participants were randomly assigned 1:1 to the mask or control group using a computer algorithm and were stratified by the 5 regions of Denmark (**Supplement Table 1**, available at Annals.org). Participants were notified of allocation by e-mail, and study packages were sent by courier (Part 7 of the **Supplement**). Participants in the mask group were instructed to wear a mask when outside the home during the next month. They received 50 three-layer, disposable, surgical face masks with ear loops (TYPE II EN 14683 [Abena]; filtration rate, 98%; made in China). Participants in both groups received materials and instructions for antibody testing on receipt and at 1 month. They also received materials and instructions for collecting an oropharyngeal/nasal swab sample for polymerase chain reaction (PCR) testing at 1 month and whenever symptoms compatible with COVID-19 occurred during follow-up. If symptomatic, participants were strongly encouraged to seek medical care. They registered symptoms and results of the antibody test in the online REDCap system. Participants returned the test material by prepaid express courier.

Written instructions and instructional videos guided antibody testing, oropharyngeal/nasal swabbing, and proper use of masks (Part 8 of the **Supplement**), and a help line was available to participants. In accordance with WHO recommendations for health care settings at that time, participants were instructed to change the mask if outside the home for more than 8 hours. At baseline and in weekly follow-up e-mails, participants in both groups were encouraged to follow current COVID-19 recommendations from the Danish authorities.

Antibody and Viral PCR Testing

Participants tested for SARS-CoV-2 IgM and IgG antibodies in whole blood using a point-of-care test (Lateral Flow test [Zhuhai Livzon Diagnostics]) according to the manufacturer's recommendations and as previously described (26). After puncturing a fingertip with a lancet, they withdrew blood into a capillary tube and placed 1 drop of blood followed by 2 drops of saline in the test chamber in each of the 2 test plates (IgM and IgG). Participants reported IgM and IgG results separately as

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"1 line present" (negative), "2 lines present" (positive), or "I am not sure, or I could not perform the test" (treated as a negative result). Participants were categorized as seropositive if they had developed IgM, IgG, or both. The manufacturer reported that sensitivity was 90.2% and specificity 99.2%. A previously reported internal validation using 651 samples from blood donors before November 2019 and 155 patients with PCR-confirmed SARS-CoV-2 infection estimated a sensitivity of 82.5% (95% CI, 75.3% to 88.4%) and specificity of 99.5% (CI, 98.7% to 99.9%) (26). We (27) and others (28) have reported that oropharyngeal/nasal swab sampling for SARS-CoV-2 by participants, as opposed to health care workers, is clinically useful. Descriptions of RNA extraction, primer and probe used, reverse transcription, preamplification, and microfluidic quantitative PCR are detailed in Part 6 of the **Supplement**.

Data Collection

Participants received 4 follow-up surveys (Parts 4 and 5 of the **Supplement**) by e-mail to collect information on antibody test results, adherence to recommendations on time spent outside the home among others, development of symptoms, COVID-19 diagnosis based on PCR testing done in public hospitals, and known COVID-19 exposures.

Outcomes

The primary outcome was SARS-CoV-2 infection, defined as a positive result on an oropharyngeal/nasal swab test for SARS-CoV-2, development of a positive SARS-CoV-2 antibody test result (IgM or IgG) during the study period, or a hospital-based diagnosis of SARS-CoV-2 infection or COVID-19. Secondary end points included PCR evidence of infection with other respiratory viruses (**Supplement Table 2**, available at Annals.org).

Sample Size Calculations

The sample size was determined to provide adequate power for assessment of the combined composite primary outcome in the intention-to-treat analysis. Authorities estimated an incidence of SARS-CoV-2 infection of at least 2% during the study period. Assuming that wearing a face mask halves risk for infection, we estimated that a sample of 4636 participants would provide the trial with 80% power at a significance level of 5% (2-sided a level). Anticipating 20% loss to follow-up in this community-based study, we aimed to assign at least 6000 participants.

Statistical Analysis

Participants with a positive result on an antibody test at baseline were excluded from the analyses. We calculated CIs of proportions assuming binomial distribution (Clopper–Pearson).

The primary composite outcome (intention-to-treat) was compared between groups using the χ^2 test. Odds ratios and confidence limits were calculated using logistic regression. We did a per protocol analysis that included only participants reporting complete or predominant use of face masks as instructed. A conservative sensitivity analysis assumed that participants with a positive result on an antibody test at the end of the study who had not provided antibody test results at study entrance had had a positive result at entrance. To further examine the uncertainty of loss to follow-up, we did (post hoc) 200 imputations using the R package smcfcs, version 1.4.1 (29), to impute missing values of outcome. We included sex, age, type of work, time out of home, and outcome in this calculation.

Prespecified subgroups were compared by logistic regression analysis. In a post hoc analysis, we explored whether there was a subgroup defined by a constellation of participant characteristics for which a recommendation to wear masks seemed to be effective. We included sex, age, type of work, time out of home, and outcome in this calculation.

Two-sided *P* values less than 0.05 were considered statistically significant. Analyses were done using R, version 3.6.1 (R Foundation).

Role of the Funding Source

An unrestricted grant from the Salling Foundations supported the study, and the BESTSELLER Foundation donated the Livzon tests. The funders did not influence study design, conduct, or reporting.

Results

Participants

A total of 17 258 Danish citizens responded to recruitment, and 6024 completed the baseline survey and fulfilled eligibility criteria. The first participants (group 1; $n = 2995$) were randomly assigned on 12 April 2020 and were followed from 14 to 16 April through 15 May 2020. Remaining participants (group 2; $n = 3029$) were randomly assigned on 24 April 2020 and were followed from 2 to 4 May through 2 June 2020. A total of 3030 participants were randomly assigned to the recommendation to wear face masks, and 2994 were assigned not to wear face masks (**Figure**); 4862 participants (80.7%) completed the study. **Table 1** shows baseline characteristics, which were well balanced between groups. Participants reported having spent a median of 4.5 hours per day outside the home.

Adherence

Based on the lowest adherence reported in the mask group during follow-up, 46% of participants wore the mask as recommended, 47% predominantly as recommended, and 7% not as recommended.

Primary Outcome

The primary outcome occurred in 42 participants (1.8%) in the mask group and 53 (2.1%) in the control group. In an intention-to-treat analysis, the between-group difference was −0.3 percentage point (CI, −1.2 to 0.4 percentage point; $P = 0.38$) (odds ratio [OR], 0.82 [CI, 0.54 to 1.23]; $P = 0.33$) in favor of the mask group (**Supplement Figure 1**, available at Annals.org). When this analysis was repeated with multiple imputation for missing data due to loss to follow-up, it yielded similar results (OR, 0.81 [CI, 0.53 to 1.23]; $P = 0.32$). **Table 2**

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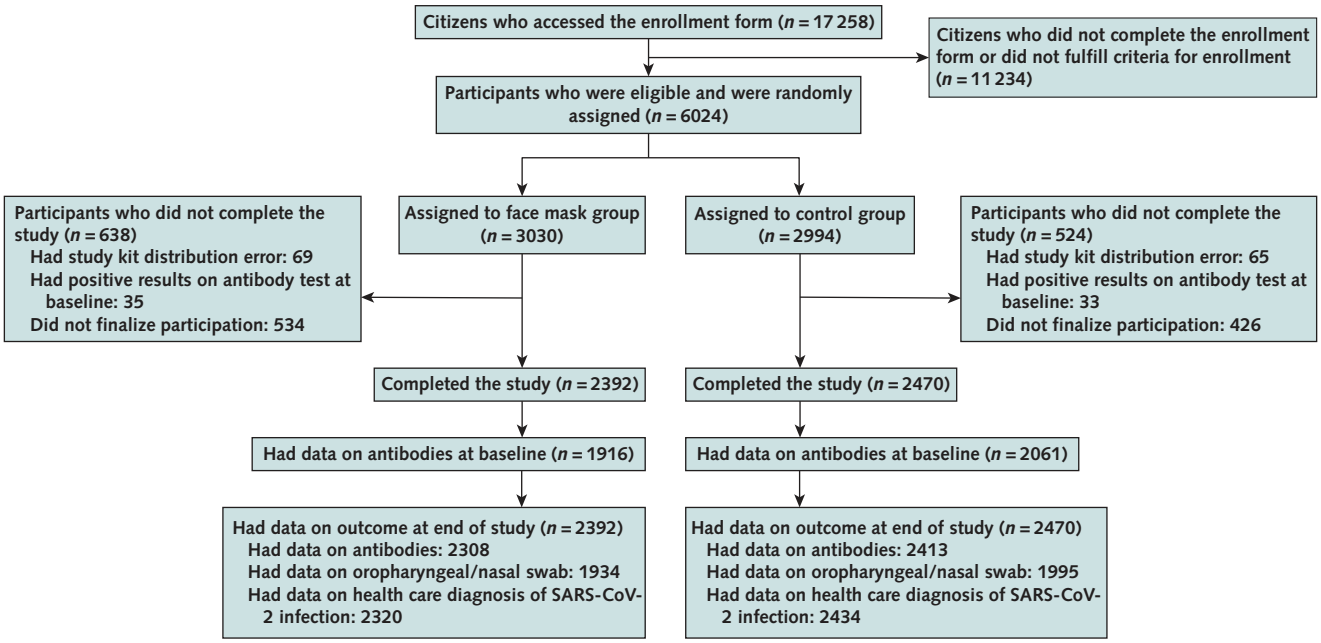
Figure 1. Study flow diagram.



Inclusion and exclusion criteria are described in the Methods section, and criteria for completion of the study are given in the Supplement (available at Annals.org). SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

provides data on the components of the primary end point, which were similar between groups.

In a per protocol analysis that excluded participants in the mask group who reported nonadherence (7%), SARS-CoV-2 infection occurred in 40 participants (1.8%) in the mask group and 53 (2.1%) in the control group (between-group difference, −0.4 percentage point [CI, −1.2 to 0.5 percentage point]; $P = 0.40$) (OR, 0.84 [CI, 0.55 to 1.26]; $P = 0.40$). **Supplement Figure 2** (available at Annals.org) provides results of the prespecified subgroup analyses of the primary composite end point. No statistically significant interactions were identified.

In the preplanned psensitivity analysis, those who had a positive result on an antibody test at 1 month but had not provided antibody results at baseline were considered to have had positive results at baseline ($n = 18$)—that is, they were excluded from the analysis. In this analysis, the primary outcome occurred in 33 participants (1.4%) in the face mask group and 44 (1.8%) in the control group (between-group difference, −0.4 percentage point [CI, −1.1 to 0.4 percentage point]; $P = 0.22$) (OR, 0.77 [CI, 0.49 to 1.22]; $P = 0.26$).

Three post hoc (not preplanned) analyses were done. In the first, which included only participants reporting wearing face masks "exactly as instructed," infection (the primary outcome) occurred in 22 participants (2.0%) in the face mask group and 53 (2.1%) in the control group (between-group difference, −0.2 percentage point [CI, −1.3 to 0.9 percentage point]; $P = 0.82$) (OR, 0.93 [CI, 0.56 to 1.54]; $P = 0.78$). The second post hoc analysis excluded participants who did not provide antibody test results at baseline; infection occurred in 33 participants (1.7%) in the face mask group and 44 (2.1%) in the control group (between-group difference, −0.4 percentage point [CI, −1.4 to 0.4 percentage point]; $P = 0.33$) (OR, 0.80 [CI, 0.51 to 1.27]; $P = 0.35$). In the third post hoc analysis, which investigated constellations of patient characteristics, we did not find a subgroup where face masks were effective at conventional levels of statistical significance (data not shown).

A total of 52 participants in the mask group and 39 control participants reported COVID-19 in their household. Of these, 2 participants in the face mask group and 1 in the control group developed SARS-CoV-2 infection, suggesting that the source of most observed infections was outside the home. Reported symptoms did not differ between groups during the study period (**Supplement Table 3**, available at Annals.org).

Secondary Outcomes

In the mask group, 9 participants (0.5%) were positive for 1 or more of the 11 respiratory viruses other than SARS-CoV-2, compared with 11 participants (0.6%) in the control group (between-group difference, −0.1

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percentage point [CI, −0.6 to 0.4 percentage point]; P = 0.87) (OR, 0.84 [CI, 0.35 to 2.04]; P = 0.71). Positivity for any virus, including SARS-CoV-2, occurred in 9 mask participants (0.5%) versus 16 control participants (0.8%) (between-group difference, −0.3 percentage point [CI, −0.9 to 0.2 percentage point]; P = 0.26) (OR, 0.58 [CI, 0.25 to 1.31]; P = 0.19).

Discussion

In this community-based, randomized controlled trial conducted in a setting where mask wearing was uncommon and was not among other recommended public health measures related to COVID-19, a recommendation to wear a surgical mask when outside the home among others did not reduce, at conventional levels of statistical significance, incident SARS-CoV-2 infection compared with no mask recommendation. We designed the study to detect a reduction in infection rate from 2% to 1%. Although no statistically significant difference in SARS-CoV-2 incidence was observed, the 95% CIs are compatible with a possible 46% reduction to 23% increase in infection among mask wearers. These findings do offer evidence about the degree of protection mask wearers can anticipate in a setting where others are not wearing masks and where other public health measures, including social distancing, are in effect. The findings, however, should not be used to conclude that a recommendation for everyone to wear masks in the community would not be effective in reducing SARS-CoV-2 infections, because the trial did not test the role of masks in source control of SARS-CoV-2 infection. During the study period, authorities did not recommend face mask use outside hospital settings and mask use was rare in community settings (22). This means that study participants' exposure was overwhelmingly to persons not wearing masks.

The observed infection rate was similar to that reported in other large Danish studies during the study period (26,30). Of note, the observed incidence of SARS-CoV-2 infection was higher than we had estimated when planning a sample size that would ensure more than 80% power to detect a 50% decrease in infection. The intervention lasted only 1 month and was carried out during a period when Danish authorities recommended quarantine of diagnosed patients, physical distancing, and hand hygiene as general protective means against SARS-CoV-2 transmission (23). Cafés and restaurants were closed through 18 May, but follow-up of the second randomized group continued through 2 June.

The first randomized group was followed while the Danish society was under lockdown. Reopening occurred (18 May 2020) during follow-up of the second group of participants, but it was not reflected in the outcome because infection rates were similar between groups (**Supplement Figure 2**). The relative infection rate between mask wearers and those not wearing masks would most likely be affected by changes in applied protective means or in the virulence of SARS-CoV-2, whereas the rate difference between the 2 groups would probably not be affected solely by a higher–or lower–number of infected citizens.

Although we saw no statistically significant difference in presence of other respiratory viruses, the study was not sufficiently powered to draw definite conclusions about the protective effect of masks for other viral infections. Likewise, the study had limited power for any of the subgroup analyses.

Table 1. Characteristics of Participants Completing the Study

Characteristic	Face Mask Group (n = 2392)	Control Group (n = 2470)
Mean age (SD), *y*	47.4 (14)	47.0 (13)
Female sex, *n (%)*	1545 (64.6)	1571 (63.6)
Smoker, *n (%)*	478 (20.0)	499 (20.2)
Wears eyeglasses daily, *n (%)*	956 (40.0)	929 (37.6)
Capital Region resident, *n (%)**	1220 (51.0)	1289 (52.2)
Provided antibody test results at baseline, *n (%)*	1916 (80.1)	2061 (83.4)
Occupation, *n (%)*		
Shop employee	108 (4.5)	85 (3.4)
Cashier	101 (4.2)	96 (3.9)
Craftsperson	110 (4.6)	103 (4.2)
Office employee	265 (11.1)	312 (12.6)
Manager	111 (4.6)	108 (4.4)
Transportation employee	617 (25.8)	625 (25.3)
Service employee	107 (4.5)	104 (4.2)
Home care/nursing home employee	197 (8.2)	229 (9.3)
Early childhood care staff	89 (3.7)	88 (3.6)
Salesperson	37 (1.5)	47 (1.9)
Other	650 (27.2)	673 (27.2)

* According to national authority data, the Capital Region had a higher frequency of coronavirus disease 2019 than other Danish regions; see subgroup analyses in **Supplement Figure 2** (available at Annals.org).

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Table 2. Distribution of the Components of the Composite Primary Outcome

Outcome Component	Face Mask Group (*n* = 2392), *n (%)*	Control Group (*n* = 2470), *n (%)*	Odds Ratio (95% CI)*
Primary composite end point	42 (1.8)	53 (2.1)	0.82 (0.54–1.23)
Positive antibody test result†			
IgM	31 (1.3)	37 (1.5)	0.87 (0.54–1.41)
IgG	33 (1.4)	32 (1.3)	1.07 (0.66–1.75)
Positive SARS-CoV-2 RT-PCR	0 (0)	5 (0.2)	–
Health care–diagnosed SARS-CoV-2 or COVID-19	5 (0.2)	10 (0.4)	0.52 (0.18–1.53)

COVID-19 = coronavirus disease 2019; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
* Calculated using logistic regression. The between-group differences in frequencies of positive SARS-CoV-2 RT-PCR were not statistically significant ($P = 0.079$).
† 124 participants in the mask group and 140 in the control group registered "not done" or unclear results of the antibody test–i.e., they were included in the analysis because they sent an oropharyngeal swab for PCR.

The primary outcome was mainly defined by antibodies against SARS-CoV-2. This definition was chosen because the viral load of infected patients may be only transiently detectable (31,32) and because approximately half of persons infected with SARS-CoV-2 are asymptomatic (33,26). Masks have been hypothesized to reduce inoculum size (34) and could increase the likelihood that infected mask users are asymptomatic, but this hypothesis has been challenged (35). For these reasons, we did not rely solely on identification of SARS-CoV-2 in oropharyngeal/nasal swab samples. As mentioned in the Methods section, an internal validation study estimated that the point-of-care test has 82.5% sensitivity and 99.5% specificity (26).

The observed rate of incident SARS-CoV-2 infection was similar to what was estimated during trial design. These rates were based on thorough screening of all participants using antibody measurements combined with PCR, whereas the observed official infection rates relied solely on PCR test–based estimates during the period. In addition, authorities tested only a small subset of primarily symptomatic citizens of the entire population, yielding low incidence rates. On this basis, the infection rates we report here are not comparable with the official SARS-CoV-2 infection rates in the Danish population. The eligibility requirement of at least 3 hours of exposure to other persons outside the home would add to this difference. Between 6 April and 9 May 2020, we found a similar seroprevalence of SARS-CoV-2 of 1.9% (CI, 0.8% to 2.3%) in Danish blood donors using the Livzon point-of-care test and assessed by laboratory technicians (36). Testing at the end of follow-up, however, may not have captured any infections contracted during the last part of the study period, but this would have been true in both the mask and control groups and was not expected to influence the overall findings.

The face masks provided to participants were high-quality surgical masks with a filtration rate of 98% (37). A published meta-analysis found no statistically significant difference in preventing influenza in health care workers between respirators (N95 [American standard] or FFP2 [European standard]) and surgical face masks (38). Adherence to mask use may be higher than observed in this study in settings where mask use is common. Some mask group participants (14%) reported adverse reactions from other citizens (**Supplement Table 4**, available at Annals.org). Although adherence may influence the protective effect of masks, sensitivity analyses had similar results across reported adherence.

How SARS-CoV-2 is transmitted–via respiratory droplets, aerosols, or (to a lesser extent) fomites–is not firmly established. Droplets are larger and rapidly fall to the ground, whereas aerosols are smaller ($\leq$5 μm) and may evaporate and remain in the air for hours (39). Transmission of SARS-CoV-2 may take place through multiple routes. It has been argued that for the primary route of SARS-CoV-2 spread–that is, via droplets–face masks would be considered effective, whereas masks would not be effective against spread via aerosols, which might penetrate or circumnavigate a face mask (37,39). Thus, spread of SARS-CoV-2 via aerosols would at least partially explain the present findings. Lack of eye protection may also have been of importance, and use of face shields also covering the eyes (rather than face masks only) has been advocated to halt the conjunctival route of transmission (40, 41). We observed no statistically significant interaction between wearers and nonwearers of eyeglasses (**Supplement Figure 2**). Recent reports indicate that transmission of SARS-CoV-2 via fomites is unusual (42), but masks may alter behavior and potentially affect fomite transmission.

The present findings are compatible with the findings of a review of randomized controlled trials of the efficacy of face masks for prevention (as personal protective equipment) against influenza virus (18). A recent meta-analysis that suggested a protective effect of face masks in the non–health care setting was based on 3 observational studies that included a total of 725 participants and focused on transmission of SARS-CoV-1 rather than SARS-CoV-2 (12). Of 725 participants, 138 (19%) were infected, so the transmission rate seems to be higher than for SARS-CoV-2. Further, these studies focused on prevention of infection in healthy mask wearers from patients with a known, diagnosed infection rather than prevention of transmission from persons in their surroundings in general. In addition, identified comparators (control participants) not wearing masks may also have missed other protective means. Recent observational studies that indicate a protective association between mandated mask use in the community and SARS-CoV-2 transmission are limited by study design

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and simultaneous introduction of other public health interventions (14, 43).

Several challenges regarding wearing disposable face masks in the community exist. These include practical aspects, such as potential incorrect wearing, reduced adherence, reduced durability of the mask depending on type of mask and occupation, and weather. Such circumstances may necessitate the use of multiple face masks during the day. In our study, participants used a mean of 1.7 masks per weekday and 1.3 per weekend day (**Supplement Table 4**). Wearing a face mask may be physically unpleasant, and psychological barriers and other side effects have been described (44). "Face mask policing" between citizens might reinforce use of masks but may be challenging. In addition, the wearer of a face mask may change to a less cautious behavior because of a false sense of security, as pointed out by WHO (17); accordingly, our face mask group seemed less worried (**Supplement Table 4**), which may explain their increased willingness to wear face masks in the future (**Supplement Table 5**, available at Annals.org). These challenges, including costs and availability, may reduce the efficacy of face masks to prevent SARS-CoV-2 infection.

The potential benefits of a community-wide recommendation to wear masks include combined prevention and source control for symptomatic and asymptomatic persons, improved attention, and reduced potential stigmatization of persons wearing masks to prevent infection of others (17). Although masks may also have served as source control in SARS-CoV-2–infected participants, the study was not designed to determine the effectiveness of source control.

The most important limitation is that the findings are inconclusive, with CIs compatible with a 46% decrease to a 23% increase in infection. Other limitations include the following. Participants may have been more cautious and focused on hygiene than the general population; however, the observed infection rate was similar to findings of other studies in Denmark (26,30). Loss to follow-up was 19%, but results of multiple imputation accounting for missing data were similar to the main results. In addition, we relied on patient-reported findings on home antibody tests, and blinding to the intervention was not possible. Finally, a randomized controlled trial provides high-level evidence for treatment effects but can be prone to reduced external validity.

Our results suggest that the recommendation to wear a surgical mask when outside the home among others did not reduce, at conventional levels of statistical significance, the incidence of SARS-CoV-2 infection in mask wearers in a setting where social distancing and other public health measures were in effect, mask recommendations were not among those measures, and community use of masks was uncommon. Yet, the findings were inconclusive and cannot definitively exclude a 46% reduction to a 23% increase in infection of mask wearers in such a setting. It is important to emphasize that this trial did not address the effects of masks as source control or as protection in settings where social distancing and other public health measures are not in effect.

Reduction in release of virus from infected persons into the environment may be the mechanism for mitigation of transmission in communities where mask use is common or mandated, as noted in observational studies. Thus, these findings do not provide data on the effectiveness of widespread mask wearing in the community in reducing SARS-CoV-2 infections. They do, however, offer evidence about the degree of protection mask wearers can anticipate in a setting where others are not wearing masks and where other public health measures, including social distancing, are in effect. The findings also suggest that persons should not abandon other COVID-19 safety measures regardless of the use of masks. While we await additional data to inform mask recommendations, communities must balance the seriousness of COVID-19, uncertainty about the degree of source control and protective effect, and the absence of data suggesting serious adverse effects of masks (45).

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[Intervention Review]

Physical interventions to interrupt or reduce the spread of respiratory viruses

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ABSTRACT

Background

Viral epidemics or pandemics of acute respiratory infections (ARIs) pose a global threat. Examples are influenza (H1N1) caused by the H1N1pdm09 virus in 2009, severe acute respiratory syndrome (SARS) in 2003, and coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in 2019. Antiviral drugs and vaccines may be insufficient to prevent their spread. This is an update of a Cochrane Review published in 2007, 2009, 2010, and 2011. The evidence summarised in this review does not include results from studies from the current COVID-19 pandemic.

Objectives

To assess the effectiveness of physical interventions to interrupt or reduce the spread of acute respiratory viruses.

Search methods

We searched CENTRAL, PubMed, Embase, CINAHL on 1 April 2020. We searched ClinicalTrials.gov, and the WHO ICTRP on 16 March 2020. We conducted a backwards and forwards citation analysis on the newly included studies.

Selection criteria

We included randomised controlled trials (RCTs) and cluster-RCTs of trials investigating physical interventions (screening at entry ports, isolation, quarantine, physical distancing, personal protection, hand hygiene, face masks, and gargling) to prevent respiratory virus transmission. In previous versions of this review we also included observational studies. However, for this update, there were sufficient RCTs to address our study aims.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. We used GRADE to assess the certainty of the evidence. Three pairs of review authors independently extracted data using a standard template applied in previous versions of this review, but which was revised

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to reflect our focus on RCTs and cluster-RCTs for this update. We did not contact trialists for missing data due to the urgency in completing the review. We extracted data on adverse events (harms) associated with the interventions.

Main results

We included 44 new RCTs and cluster-RCTs in this update, bringing the total number of randomised trials to 67. There were no included studies conducted during the COVID-19 pandemic. Six ongoing studies were identified, of which three evaluating masks are being conducted concurrent with the COVID pandemic, and one is completed.

Many studies were conducted during non-epidemic influenza periods, but several studies were conducted during the global H1N1 influenza pandemic in 2009, and others in epidemic influenza seasons up to 2016. Thus, studies were conducted in the context of lower respiratory viral circulation and transmission compared to COVID-19. The included studies were conducted in heterogeneous settings, ranging from suburban schools to hospital wards in high-income countries; crowded inner city settings in low-income countries; and an immigrant neighbourhood in a high-income country. Compliance with interventions was low in many studies.

The risk of bias for the RCTs and cluster-RCTs was mostly high or unclear.

Medical/surgical masks compared to no masks

We included nine trials (of which eight were cluster-RCTs) comparing medical/surgical masks versus no masks to prevent the spread of viral respiratory illness (two trials with healthcare workers and seven in the community). There is low certainty evidence from nine trials (3507 participants) that wearing a mask may make little or no difference to the outcome of influenza-like illness (ILI) compared to not wearing a mask (risk ratio (RR) 0.99, 95% confidence interval (CI) 0.82 to 1.18. There is moderate certainty evidence that wearing a mask probably makes little or no difference to the outcome of laboratory-confirmed influenza compared to not wearing a mask (RR 0.91, 95% CI 0.66 to 1.26; 6 trials; 3005 participants). Harms were rarely measured and poorly reported. Two studies during COVID-19 plan to recruit a total of 72,000 people. One evaluates medical/surgical masks (N = 6000) (published *Annals of Internal Medicine*, 18 Nov 2020), and one evaluates cloth masks (N = 66,000).

N95/P2 respirators compared to medical/surgical masks

We pooled trials comparing N95/P2 respirators with medical/surgical masks (four in healthcare settings and one in a household setting). There is uncertainty over the effects of N95/P2 respirators when compared with medical/surgical masks on the outcomes of clinical respiratory illness (RR 0.70, 95% CI 0.45 to 1.10; very low-certainty evidence; 3 trials; 7779 participants) and ILI (RR 0.82, 95% CI 0.66 to 1.03; low-certainty evidence; 5 trials; 8407 participants). The evidence is limited by imprecision and heterogeneity for these subjective outcomes. The use of a N95/P2 respirator compared to a medical/surgical mask probably makes little or no difference for the objective and more precise outcome of laboratory-confirmed influenza infection (RR 1.10, 95% CI 0.90 to 1.34; moderate-certainty evidence; 5 trials; 8407 participants). Restricting the pooling to healthcare workers made no difference to the overall findings. Harms were poorly measured and reported, but discomfort wearing medical/surgical masks or N95/P2 respirators was mentioned in several studies. One ongoing study recruiting 576 people compares N95/P2 respirators with medical surgical masks for healthcare workers during COVID-19.

Hand hygiene compared to control

Settings included schools, childcare centres, homes, and offices. In a comparison of hand hygiene interventions with control (no intervention), there was a 16% relative reduction in the number of people with ARIs in the hand hygiene group (RR 0.84, 95% CI 0.82 to 0.86; 7 trials; 44,129 participants; moderate-certainty evidence), suggesting a probable benefit. When considering the more strictly defined outcomes of ILI and laboratory-confirmed influenza, the estimates of effect for ILI (RR 0.98, 95% CI 0.85 to 1.13; 10 trials; 32,641 participants; low-certainty evidence) and laboratory-confirmed influenza (RR 0.91, 95% CI 0.63 to 1.30; 8 trials; 8332 participants; low-certainty evidence) suggest the intervention made little or no difference. We pooled all 16 trials (61,372 participants) for the composite outcome of ARI or ILI or influenza, with each study only contributing once and the most comprehensive outcome reported. The pooled data showed that hand hygiene may offer a benefit with an 11% relative reduction of respiratory illness (RR 0.89, 95% CI 0.84 to 0.95; low-certainty evidence), but with high heterogeneity. Few trials measured and reported harms.

There are two ongoing studies of handwashing interventions in 395 children outside of COVID-19.

We identified one RCT on quarantine/physical distancing. Company employees in Japan were asked to stay at home if household members had ILI symptoms. Overall fewer people in the intervention group contracted influenza compared with workers in the control group (2.75% versus 3.18%; hazard ratio 0.80, 95% CI 0.66 to 0.97). However, those who stayed at home with their infected family members were 2.17 times more likely to be infected.

We found no RCTs on eye protection, gowns and gloves, or screening at entry ports.

Authors' conclusions

The high risk of bias in the trials, variation in outcome measurement, and relatively low compliance with the interventions during the studies hamper drawing firm conclusions and generalising the findings to the current COVID-19 pandemic.

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There is uncertainty about the effects of face masks. The low-moderate certainty of the evidence means our confidence in the effect estimate is limited, and that the true effect may be different from the observed estimate of the effect. The pooled results of randomised trials did not show a clear reduction in respiratory viral infection with the use of medical/surgical masks during seasonal influenza. There were no clear differences between the use of medical/surgical masks compared with N95/P2 respirators in healthcare workers when used in routine care to reduce respiratory viral infection. Hand hygiene is likely to modestly reduce the burden of respiratory illness. Harms associated with physical interventions were under-investigated.

There is a need for large, well-designed RCTs addressing the effectiveness of many of these interventions in multiple settings and populations, especially in those most at risk of ARIs.

PLAIN LANGUAGE SUMMARY

Do physical measures such as hand-washing or wearing masks stop or slow down the spread of respiratory viruses?

What are respiratory viruses?

Respiratory viruses are viruses that infect the cells in your airways: nose, throat, and lungs. These infections can cause serious problems and affect normal breathing. They can cause flu (influenza), severe acute respiratory syndrome (SARS), and COVID-19.

How do respiratory viruses spread?

People infected with a respiratory virus spread virus particles into the air when they cough or sneeze. Other people become infected if they come into contact with these virus particles in the air or on surfaces on which they have landed. Respiratory viruses can spread quickly through a community, through populations and countries (causing epidemics), and around the world (causing pandemics).

How can we stop the spread of respiratory viruses?

Physical measures to try to stop respiratory viruses spreading between people include:

· washing hands often;

· not touching your eyes, nose, or mouth;

· sneezing or coughing into your elbow;

· wiping surfaces with disinfectant;

· wearing masks, eye protection, gloves, and protective gowns;

· avoiding contact with other people (isolation or quarantine);

· keeping a certain distance away from other people (distancing); and

· examining people entering a country for signs of infection (screening).

Why we did this Cochrane Review

We wanted to find out whether physical measures stop or slow the spread of respiratory viruses.

What did we do?

We searched for studies that looked at physical measures to stop people catching a respiratory virus infection.

We were interested in how many people in the studies caught a respiratory virus infection, and whether the physical measures had any unwanted effects.

Search date: This is an update of a review first published in 2007. We included evidence published up to 1 April 2020.

What we found

We identified 67 relevant studies. They took place in low-, middle-, and high-income countries worldwide: in hospitals, schools, homes, offices, childcare centres, and communities during non-epidemic influenza periods, the global H1N1 influenza pandemic in 2009, and epidemic influenza seasons up to 2016. No studies were conducted during the COVID-19 pandemic. We identified six ongoing, unpublished studies; three of them evaluate masks in COVID-19.

One study looked at quarantine, and none eye protection, gowns and gloves, or screening people when they entered a country.

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We assessed the effects of:

· medical or surgical masks;

· N95/P2 respirators (close-fitting masks that filter the air breathed in, more commonly used by healthcare workers than the general public); and

· hand hygiene (hand-washing and using hand sanitiser).

What are the results of the review?

Medical or surgical masks

Seven studies took place in the community, and two studies in healthcare workers. Compared with wearing no mask, wearing a mask may make little to no difference in how many people caught a flu-like illness (9 studies; 3507 people); and probably makes no difference in how many people have flu confirmed by a laboratory test (6 studies; 3005 people). Unwanted effects were rarely reported, but included discomfort.

N95/P2 respirators

Four studies were in healthcare workers, and one small study was in the community. Compared with wearing medical or surgical masks, wearing N95/P2 respirators probably makes little to no difference in how many people have confirmed flu (5 studies; 8407 people); and may make little to no difference in how many people catch a flu-like illness (5 studies; 8407 people) or respiratory illness (3 studies; 7799 people). Unwanted effects were not well reported; discomfort was mentioned.

Hand hygiene

Following a hand hygiene programme may reduce the number of people who catch a respiratory or flu-like illness, or have confirmed flu, compared with people not following such a programme (16 studies; 61,372 people). Few studies measured unwanted effects; skin irritation in people using hand sanitiser was mentioned.

How reliable are these results?

Our confidence in these results is generally low for the subjective outcomes related to respiratory illness, but moderate for the more precisely defined laboratory-confirmed respiratory virus infection, related to masks and N95/P2 respirators. The results might change when further evidence becomes available. Relatively low numbers of people followed the guidance about wearing masks or about hand hygiene, which may have affected the results of the studies.

Key messages

We are uncertain whether wearing masks or N95/P2 respirators helps to slow the spread of respiratory viruses.

Hand hygiene programmes may help to slow the spread of respiratory viruses.

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Summary of findings 1. Medical/surgical masks compared to no masks for preventing the spread of viral respiratory illness

Randomised studies: medical/surgical masks compared to no masks for preventing the spread of viral respiratory illness

Patient or population: general population and healthcare workers
Setting: community and hospitals
Intervention: medical/surgical masks
Comparison: no masks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no masks	Risk with randomised studies: masks				
Viral illness - influenza-like illness	Study population		RR 0.99 (0.82 to 1.18)	3507 (9 RCTs)	⊕⊕⊖⊖ LOW[a,b]	
	160 per 1000	158 per 1000 (131 to 189)				
Viral illness - laboratory-confirmed influenza	Study population		RR 0.91 (0.66 to 1.26)	3005 (6 RCTs)	⊕⊕⊕⊖ MODERATE[b]	
	40 per 1000	36 per 1000 (26 to 50)				
Influenza-like illness in healthcare workers	Study population		RR 0.37 (0.05 to 2.50)	1070 (2 RCTs)	⊕⊕⊖⊖ LOW[a,b]	Studies in healthcare workers only
	40 per 1000	15 per 1000 (2 to 100)				
Adverse events	-		-	(3 RCTs)	⊕⊖⊖⊖ VERY LOW[a,c]	Adverse events were not reported consistently and could not be meta-analysed. Adverse events reported for masks included warmth, discomfort, respiratory difficulties, humidity, pain, and shortness of breath, in up to 45% of participants.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the median observed risk in the comparison group of included studies and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

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High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Study limitations (lack of blinding).
[b]Imprecision (wide confidence intervals).
[c]Imprecision: 2 steps (only 3 studies enumerated adverse events; another study mentioned no adverse events).

Summary of findings 2. N95 respirators compared to medical/surgical masks for preventing the spread of viral respiratory illness

Randomised studies: N95 respirators compared to medical/surgical masks for preventing the spread of viral respiratory illness

Patient or population: healthcare workers and general population
Setting: hospitals and households
Intervention: N95 masks
Comparison: medical/surgical masks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with medical masks	Risk with randomised studies: N95				
Viral illness - clinical respiratory illness	Study population		RR 0.70 (0.45 to 1.10)	7799 (3 RCTs)	⊕⊖⊖⊖ VERY LOW[a,b,c]	All studies were conducted in hospital settings with healthcare workers.
	120 per 1000	84 per 1000 (54 to 132)				
Viral illness - influenza-like illness	Study population		RR 0.82 (0.66 to 1.03)	8407 (5 RCTs)	⊕⊕⊖⊖ LOW[a,b]	1 study was conducted in households (MacIntyre 2009).
	50 per 1000	41 per 1000 (33 to 52)				
Viral illness - laboratory-confirmed influenza	Study population		RR 1.10 (0.90 to 1.34)	8407 (5 RCTs)	⊕⊕⊕⊖ MODERATE[b]	1 study was conducted in households (MacIntyre 2009).
	70 per 1000	77 per 1000 (63 to 94)				

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Adverse events	-	-	(5 RCTs)	⊕⊖⊖⊖ VERY LOW[a,b,c]	There was insufficient consistent reporting of adverse events to enable meta-analysis. Only 1 study reported detailed adverse events: discomfort was reported in 41.9% of N95 wearers versus 9.8% of medical mask wearers (P < 0.001); headaches were more common with N95 (13.4% versus 3.9%; P < 0.001); difficulty breathing was reported more often in the N95 group (19.4% versus 12.5%; P = 0.01); and N95 caused more problems with pressure on the nose (52.2% versus 11.0%; P < 0.001). 4 RCTs either reported no adverse events or only reported on comfort wearing masks.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the median risk in the comparison group and the observed __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Study limitations (lack of blinding).
[b]Imprecision (wide confidence interval or no meta-analysis conducted).
[c]Inconsistency of results (heterogeneity).

Summary of findings 3. Hand hygiene compared to control for preventing the spread of viral respiratory illness

Hand hygiene compared to control for preventing the spread of viral respiratory illness

Patient or population: prevention of spread of viral respiratory illness
Setting: schools, childcare centres, homes, offices
Intervention: hand hygiene
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with hand hygiene				
Acute respiratory illness	Study population		RR 0.84 (0.82 to 0.86)	44,129 (7 RCTs)	⊕⊕⊕⊖ MODERATE[a]	
	380 per 1000	319 per 1000 (312 to 327)				

Influenza-like illness	Study population		RR 0.98 (0.85 to 1.13)	32,641 (10 RCTs)	⊕⊕⊖⊖ LOW[a,b]	
	90 per 1000	88 per 1000 (77 to 102)				
Laboratory-confirmed influenza	Study population		RR 0.91 (0.63 to 1.30)	8332 (8 RCTs)	⊕⊕⊖⊖ LOW[b,c]	
	80 per 1000	73 per 1000 (50 to 104)				
Composite of acute respiratory illness, influenza-like illness, influenza	Study population		RR 0.89 (0.84 to 0.95)	61,372 (16 RCTs)	⊕⊕⊖⊖ LOW[a,b]	
	200 per 1000	178 per 1000 (168 to 190)				
Adverse events	-		-	(2 RCTs)	⊕⊖⊖⊖ VERY LOW[a,b,c]	Data were insufficient to conduct meta-analysis. 1 study reported that no adverse events were observed, and another study reported that skin reaction was recorded for 10.4% of participants in the hand sanitiser group versus 10.3% in the control group.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the median observed risk in the comparison groups of included studies and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Study limitation (majority of studies were unblinded, with participant-assessed outcome).
[b]Inconsistent results across studies.
[c]Imprecision (wide confidence interval or no meta-analysis conducted).

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BACKGROUND

Description of the condition

Epidemic and pandemic viral infections pose a serious threat to people worldwide. Epidemics of note include severe acute respiratory syndrome (SARS) in 2003 and the Middle East respiratory syndrome (MERS), which began in 2012. Major pandemics include the H1N1 influenza caused by the H1N1pdm09 virus in 2009 and the coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2.

Even non-epidemic acute respiratory infections (ARIs) place a huge burden on healthcare systems around the world, and are a prominent cause of morbidity (WHO 2017). Furthermore, ARIs are often antecedents to lower respiratory tract infections caused by bacterial pathogens (i.e. pneumonia), which cause millions of deaths worldwide, mostly in low-income countries (Schwartz 2018).

High viral load, high levels of transmissibility, susceptible populations, and symptomatic patients are considered to be the drivers of such epidemics and pandemics (Jefferson 2006a). Preventing the spread of respiratory viruses from person to person may be effective at reducing the spread of outbreaks. Physical interventions, such as the use of masks and physical distancing measures, might prevent the spread of respiratory viruses which are transmitted by large droplets from infected to susceptible people. This review assumes that physical interventions used to prevent transmission of respiratory viruses are similar for most viral ARIs.

Description of the intervention

Single measures of intervention (Demicheli 2018a; Demicheli 2018b; Jefferson 2014; Jefferson 2018; Thomas 2010), such as the use of vaccines or antivirals, may be insufficient to contain the spread of influenza, but combinations of interventions may reduce the reproduction number to below 1. For some respiratory viruses there are no licensed interventions, and a combination of social and physical interventions may be the only option to reduce the spread of outbreaks, particularly those that may be capable of becoming epidemic or pandemic in nature (Luby 2005). Such interventions were emphasised in the World Health Organization's latest Global Influenza Strategy 2019 to 2030, and have several possible advantages over other methods of suppressing ARI outbreaks since they may be instituted rapidly and may be independent of any specific type of infective agent, including novel viruses. In addition, the possible effectiveness of public health measures during the Spanish flu pandemic of 1918 to 1919 in US cities supports the impetus to investigate the existing evidence on the effectiveness of such interventions (Bootsma 2007), including quarantine (such as isolation, physical distancing) and the use of disinfectants. We also considered the major societal implications for any community adopting these measures (CDC 2005a; CDC 2005b; WHO 2006b; WHO 2020a; WHO 2020b).

How the intervention might work

Epidemics and pandemics are more likely during antigenic change (changes in the viral composition) in the virus or transmission from animals (domestic or wild) when there is no natural human immunity (Bonn 1997). High viral load, high levels of transmissibility, and symptomatic patients are considered to be the drivers of such epidemics and pandemics (Jefferson 2006b).

Physical interventions, such as the use of masks, physical distancing measures, school closures, and limitations of mass gatherings, might prevent the spread of the virus transmitted by large droplets or aerosols from infected to susceptible individuals. The use of hand hygiene, gloves, and protective gowns can also prevent the spread by limiting the transfer of viral particles onto and from fomites (inanimate objects such as flat surfaces, tabletops, utensils, porous surfaces, or nowadays cell phones, which can transmit the agent if contaminated). Such public health measures were widely adopted during the Spanish flu pandemic and have been the source of considerable debate (Bootsma 2007).

Why it is important to do this review

Although the benefits of physical interventions seem self-evident, given the global importance of interrupting viral transmission, having up-to-date estimates of their effectiveness is necessary to inform planning, decision-making, and policy. The outbreak of COVID-19 has prompted this update. Physical methods have several possible advantages over other methods of suppressing ARI outbreaks, including their rapid deployment and ability to be independent of the infective agent, including novel viruses.

The last update of this review in 2011, Jefferson 2011, identified 23 trials on physical interventions that might interrupt or reduce the spread of respiratory viruses. Because of poor reporting and heterogeneity, and the relatively small number of included trials, it was not possible to perform a meta-analysis. Case-control studies were sufficiently homogenous to permit meta-analysis, which provided evidence that hand-washing for a minimum of 11 times daily prevented cases of SARS during the 2003 epidemic (odds ratio 0.54, 95% confidence interval 0.44 to 0.67). Many randomised trials have been published in the past decade, prompting us to focus only on these for the current update.

This is the fourth update of a Cochrane Review first published in 2007 (Jefferson 2007; Jefferson 2009; Jefferson 2010; Jefferson 2011).

OBJECTIVES

To assess the effectiveness of physical interventions to interrupt or reduce the spread of acute respiratory viruses.

METHODS

Criteria for considering studies for this review

Types of studies

For this 2020 update we only considered individual-level RCTs, or cluster-RCTs, or quasi-RCTs for inclusion.

In previous versions of the review we also included observational studies (cohorts, case-controls, before-after, and time series studies). However, for this update there were sufficient randomised studies to address our study aims, so we excluded observational studies (which are known to be at a higher risk of bias).

Types of participants

People of all ages.

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Types of interventions

We included randomised controlled trials (RCTs) and cluster-RCTs of trials investigating physical interventions (screening at entry ports, isolation, quarantine, physical distancing, personal protection, hand hygiene, face masks, and gargling) to prevent respiratory virus transmission compared with doing nothing or with another intervention.

Types of outcome measures

For this 2020 update we added one outcome: adverse events related to the intervention, and we split the outcomes into primary and secondary outcomes.

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, influenza-like illness (ILI), and laboratory-confirmed influenza, or other viral pathogens).
2. Adverse events related to the intervention.

Secondary outcomes

1. Deaths.
2. Severity of viral illness as reported in the studies.
3. Absenteeism.
4. Hospital admissions.
5. Complications related to the illness, e.g. pneumonia.

Search methods for identification of studies

Electronic searches

For this 2020 update, we refined the original search strategy using a combination of previously included studies and automation tools (Clark 2020). We converted this search using the Polyglot Search Translator (Clark 2020), and ran the searches in the following databases:

1. the Cochrane Central Register of Controlled Trials (CENTRAL) (2020, Issue 3), which includes the Acute Respiratory Infections Group's Specialised Register (searched 1 April 2020) (Appendix 1);
2. PubMed (2010 to 1 April 2020) (Appendix 2);
3. Embase (2010 to 1 April 2020) (Appendix 3);
4. CINAHL (Cumulative Index to Nursing and Allied Health Literature) (2010 to 1 April 2020) (Appendix 4);
5. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (January 2010 to 16 March 2020); and
6. World Health Organization International Clinical Trials Registry Platform (January 2010 to 16 March 2020).

We combined the database searches with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2011). Details of previous searches are available in Appendix 5.

Searching other resources

We conducted a backwards-and-forwards citation analysis in Scopus on all newly included studies to identify other potentially relevant studies.

Data collection and analysis

Selection of studies

The search and citation analysis results were initially screened via the RobotSearch tool (Marshall 2018) to exclude all studies that were obviously not RCTs. We scanned the titles and abstracts of studies identified by the searches. We obtained the full-text articles of studies that either appeared to meet our eligibility criteria or for which there was insufficient information to exclude it. We then used a standardised form to assess the eligibility of each study based on the full article.

Data extraction and management

Three pairs of review authors (MJ/EF, LA/GB, EB/TOJ) independently applied the inclusion criteria to all identified and retrieved articles, and extracted data using a standard template that had been developed for and applied to previous versions of the review, but was revised to reflect our focus on RCTs and cluster-RCTs for this update. Any disagreements were resolved through discussion. We extracted and reported descriptions of interventions using the Template for Intervention Description and Replication (TIDieR) template (Table 1).

Assessment of risk of bias in included studies

Three pairs of review authors (TOJ/EB, LA/GB, MJ/EF) independently assessed risk of bias for the method of random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), outcome reporting (attrition bias), and selective reporting (reporting bias). We used the Cochrane 'Risk of bias' tool to assess risk of bias, classifying each 'Risk of bias' domain as 'low', 'high', or 'unclear'. The following were indications for low risk of bias:

1. method of random sequence generation: the method was well-described and is likely to produce balanced and truly random groups;
2. allocation concealment: the next treatment allocation was not known to participant/cluster or treating staff until after consent to join the study;
3. blinding of participants and personnel: the method is likely to maintain blinding throughout the study;
4. blinding of outcome assessors: all outcome assessors were unaware of treatment allocation;
5. outcome reporting: participant attrition throughout the study is reported, and reasons for loss are appropriately described; and
6. selective reporting: all likely planned and collected outcomes have been reported.

Measures of treatment effect

When possible, we performed meta-analysis and summarised effectiveness as risk ratio (RR) using 95% confidence intervals (CIs). For studies that could not be pooled, we used the effect measures reported by the trial authors (such as RR or incidence rate ratio (IRR) with 95% CI or, when these were not available, relevant P values).

Unit of analysis issues

Many of the included studies were cluster-RCTs. To avoid any unit of analysis issues, we only included treatment effect estimates that were based on methods that were appropriate for the analysis of

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cluster trials, such as mixed models and generalised estimating equations. Given this restriction, we used the generalised inverse-variance method of meta-analysis. Some cluster-RCTs that did not report cluster-adjusted treatment effects provided sufficient data (number of events and participants by treatment group and intraclass correlations) for us to calculate appropriate treatment effect estimates and standard errors. For studies with multiple treatment groups but only one control group, where appropriate, we adjusted standard errors upwards to avoid unit of analysis errors in the meta-analyses.

Dealing with missing data

Given the urgency of this update, we did not contact authors of studies with significant missing data. Previously, whenever details of studies were unclear, or studies were only known to us by abstracts or communications at meetings, we corresponded with first or corresponding authors.

Assessment of heterogeneity

Aggregation of data was dependent on types of comparisons, sensitivity and homogeneity of definitions of exposure, populations and outcomes used. We calculated the I^2 statistic and Chi^2 test for each pooled estimate to assess the presence of statistical heterogeneity (Higgins 2002; Higgins 2003).

Assessment of reporting biases

Given the widely disparate nature of our evidence base, we limited our assessment of possible reporting biases to funnel plot visual inspection if we had > 10 included studies.

Data synthesis

If possible and appropriate, we combined studies in a meta-analysis. We used the generalised inverse-variance random-effects model. We chose the random-effects model because we expected clinical heterogeneity due to differences in pooled interventions and outcome definitions, and methodological heterogeneity due to pooling of RCTs and cluster-RCTs.

Subgroup analysis and investigation of heterogeneity

We conducted two post hoc subgroup analyses:

1. healthcare workers for the comparison of masks versus control; and
2. children for the comparison of hand hygiene versus control.

We did not conduct further investigation of heterogeneity due to insufficient numbers of studies included in the comparisons.

Sensitivity analysis

We conducted a sensitivity analysis for hand hygiene versus control where we included the most precise and unequivocal measure of viral illness reported for each included study.

Summary of findings and assessment of the certainty of the evidence

We created three 'Summary of findings' tables using the following outcomes: numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza) and adverse events related to the intervention (Summary of findings 1; Summary of findings 2; Summary of findings 3). We planned to include the secondary outcomes of deaths; severity of viral illness as reported in the studies; absenteeism; hospital admissions; and complications related to the illness (e.g. pneumonia). However, this data were poorly reported in the included studies. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of evidence as it related to the studies which contributed data to the meta-analyses for the prespecified outcomes (Atkins 2004). We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro GDT software (GRADEpro GDT 2015). We justified all decisions to down- or upgrade the certainty of the evidence in footnotes, and made comments to aid the reader's understanding of the review where necessary.

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies tables.

Results of the search

We identified a total of 3180 titles in this 2020 update. We excluded 3092 titles and retrieved the full papers of 88 studies, to include 44 new studies. See Figure 1.

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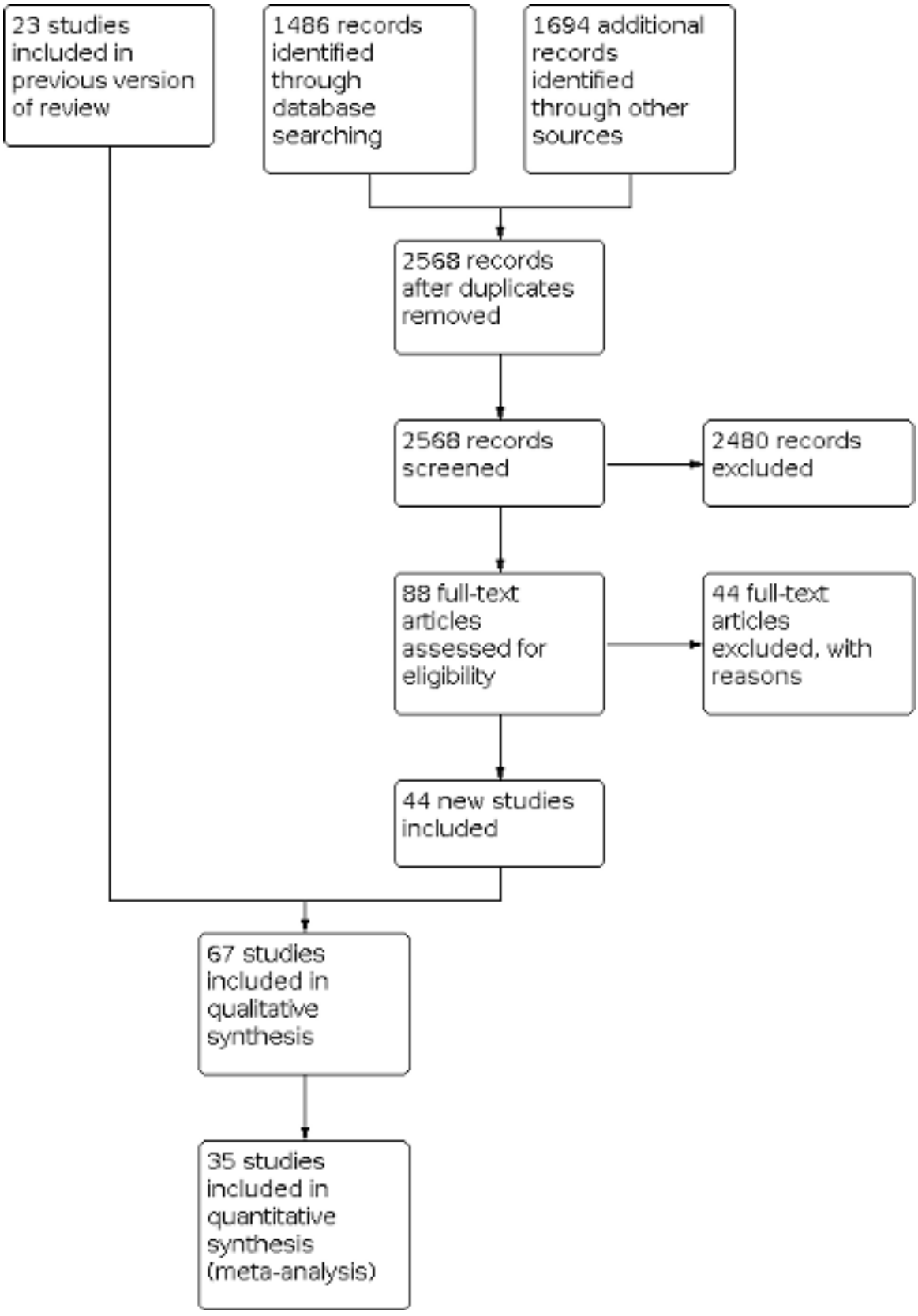
Figure 1. Study flow diagram.



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Included studies

The 44 newly included studies were all RCTs (n = 11) or cluster-RCTs (n = 33) published between 2010 and 2019. We included 23 RCTs in the 2011 version of the review. For detailed descriptions of the interventions of the included studies, see Table 1.

Fifteen trials focused on using masks (Aiello 2010; Aiello 2012; Barasheed 2014; Canini 2010; Cowling 2008; Ide 2016; Jacobs 2009; Loeb 2009; MacIntyre 2009; MacIntyre 2011; MacIntyre 2013; MacIntyre 2015; MacIntyre 2016; Radonovich 2019; Suess 2012). Ten of the 15 trials compared medical/surgical masks to no mask (control) (Aiello 2010; Aiello 2012; Barasheed 2014; Canini 2010; Cowling 2008; Jacobs 2009; MacIntyre 2009; MacIntyre 2015; MacIntyre 2016; Suess 2012). One study compared catechin-treated masks to no mask (Ide 2016), and one study included cloth masks versus control (third arm in MacIntyre 2015). Three of the 15 trials were in healthcare workers (Ide 2016; Jacobs 2009; MacIntyre 2015), whilst the remaining trials were in non-healthcare workers (students, households, families, or pilgrims). Only one trial was conducted during H1N1 pandemic season (Suess 2012).

Five of the 15 trials compared N95 masks or P2 masks to medical/surgical masks (Loeb 2009; MacIntyre 2009; MacIntyre 2011; MacIntyre 2013; Radonovich 2019). All of these trials, except for one study that was conducted on household individuals (MacIntyre 2009), included healthcare workers either in a hospital setting, Loeb 2009; MacIntyre 2011; MacIntyre 2013, or an outpatient setting (MacIntyre 2009; Radonovich 2019).

One trial evaluated the effectiveness of quarantining workers of one of two sibling companies in Japan whose family members had developed an ILI during the 2009 to 2010 H1N1 influenza pandemic (Miyaki 2011).

Fifteen trials compared hand hygiene interventions with no hand hygiene (control) and provided data suitable for meta-analysis. The populations in these trials included adults, children, and families, in settings such as schools (Biswas 2019; Stebbins 2011), childcare centres (Azor-Martinez 2018; Correa 2012; Roberts 2000; Zomer 2015), homes/households (Cowling 2009; Larson 2010; Little 2015; Nicholson 2014; Ram 2015; Sandora 2005; Simmerman 2011), offices (Hubner 2010), and military trainees (Millar 2016). None of the trials was conducted during a pandemic, although some of the studies were conducted during peak influenza seasons.

A further 10 trials that compared a variety of hand hygiene modalities to control provided insufficient information to include in meta-analyses. Three trials were in children: one was conducted in daycare centres in Denmark examining a multimodal hygiene programme (Ladegaard 1999), and two trials compared a hand hygiene campaign or workshop in an elementary school environment in Saudi Arabia, Alzaher 2018, and Egypt, Talaat 2011. Three trials tested virucidal hand treatment in an experimental setting, Gwaltney 1980; Turner 2004a, and in a community, Turner 2012, in the USA. Feldman 2016 compared hand-washing with chlorhexidine gluconate amongst Israeli sailors. One trial compared hand sanitiser packaged in a multimodal hygiene programme amongst office employees in the USA (Arbogast 2016). Two trials were conducted in a long-term facility setting: one trial examined the effect of a bundle hand hygiene programme on infectious risk in nursing home residents in France (Temime 2018), and the other trial compared the effect of using hand sanitisers in healthcare workers on the rate of infections (including respiratory infections) in nursing home residents in Hong Kong (Yeung 2011).

Five trials compared different hand hygiene interventions in a variety of settings such as schools (Morton 2004 in kindergartens and elementary schools in the USA; Priest 2014 in primary schools in New Zealand; and Pandejpong 2012 in kindergartens in Thailand). One study was conducted in low-income neighbourhoods in Karachi, Pakistan (Luby 2005), and one was conducted in a workplace environment in Finland (Savolainen-Kopra 2012). A variety of interventions were used across these trials such as soap and water (Luby 2005; Savolainen-Kopra 2012), hand sanitiser (Morton 2004; Pandejpong 2012; Priest 2014; Savolainen-Kopra 2012), body wash (Luby 2005), and alcohol-based hand wipes (Morton 2004), with or without additional hygiene education. There was considerable variation in interventions, and the information in the trial reports was insufficient to permit meta-analysis.

Seven trials compared a combined intervention of hand hygiene and face masks with control. Four of these trials were carried out in households in Germany (Suess 2012), Thailand (Simmerman 2011), Hispanic immigrant communities in the USA (Larson 2010), and households in Hong Kong (Cowling 2009). Two trials were conducted amongst university student residences (Aiello 2010; Aiello 2012), and one trial in a group of pilgrims at the annual Hajj (Aelami 2015). Moreover, six trials evaluated the incremental benefit of combining surgical mask in addition to hand hygiene with soap, Simmerman 2011, hand sanitiser, Aiello 2010; Aiello 2012; Larson 2010; Suess 2012, or both, Cowling 2009, versus mask or hand hygiene alone on the outcomes of ILI and influenza. Aelami 2015 investigated a hygienic package (alcohol-based handrub (gel or spray), surgical masks, soap, and paper handkerchiefs) with a control group.

Seven trials compared a multimodal combination of hand hygiene and disinfection of surfaces, toys, linen, or other components of the environment with a control (Ban 2015; Carabin 1999; Ibfelt 2015; Kotch 1994; McConeghy 2017; Sandora 2008; White 2001). Variation in scope and type of interventions and insufficient data in trial reports precluded meta-analysis. All studies except for one were in children (McConeghy 2017 was in nursing population).

Three trials included in two papers investigated the role of virucidal tissues in interrupting transmission of naturally occurring respiratory infections in households (Farr 1988a; Farr 1988b; Longini 1988). Four cluster-RCTs implemented complex, multimodal sanitation, education, cooking, and hygiene interventions (Chard 2019; Hartinger 2016; Huda 2012; Najnin 2019). All four of these trials were conducted in low-income countries in settings with minimal to no access to basic sanitation.

Three trials assessed the effect of gargling on the incidence of upper respiratory tract infections (URTIs) or influenza: gargling with povidone-iodine (Satomura 2005), green tea (Ide 2014), and tap water (Goodall 2014).

Ongoing studies

We identified six ongoing studies. Two assess hand hygiene measures (NCT03454009; NCT04267952), and four assess face masks (NCT04471766; NCT04296643; NCT04337541; Wang 2015) one of which – NCT04337541 - published as this review update was going to press.

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Excluded studies

We excluded a total of 160 studies. We identified 12 new studies for exclusion at the data extraction stage of this 2020 update, all of which appeared to be eligible at screening. Six of the 12 studies were ineligible due to only reporting composite outcomes that included other infections besides those caused by respiratory viruses (Azor-Martinez 2014; Bowen 2007; Chami 2012; Denbak 2018; Stedman-Smith 2015; Vessey 2007); two trials measured absenteeism due to non-specific infection (Lennell 2008; Rosen 2006); one trial only had two clusters (Nandrup-Bus 2009); one study was not an RCT (Patel 2012); one study evaluated a hand hygiene intervention that was antibacterial rather than antiviral (Slayton 2016); and one study had no respiratory illness data for extraction (Uhari 1999).

Risk of bias in included studies

The overall risk of bias is presented graphically in Figure 2 and summarised in Figure 3. Details on risk of bias for the included studies are provided below.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.

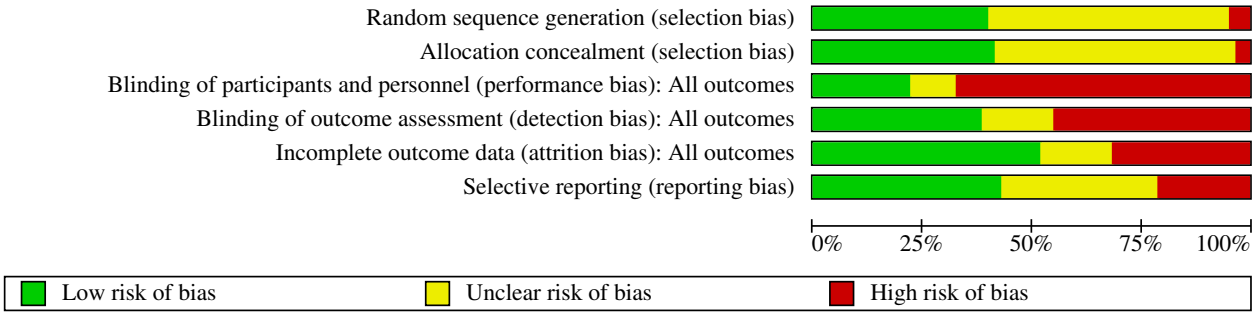

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Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included trial.

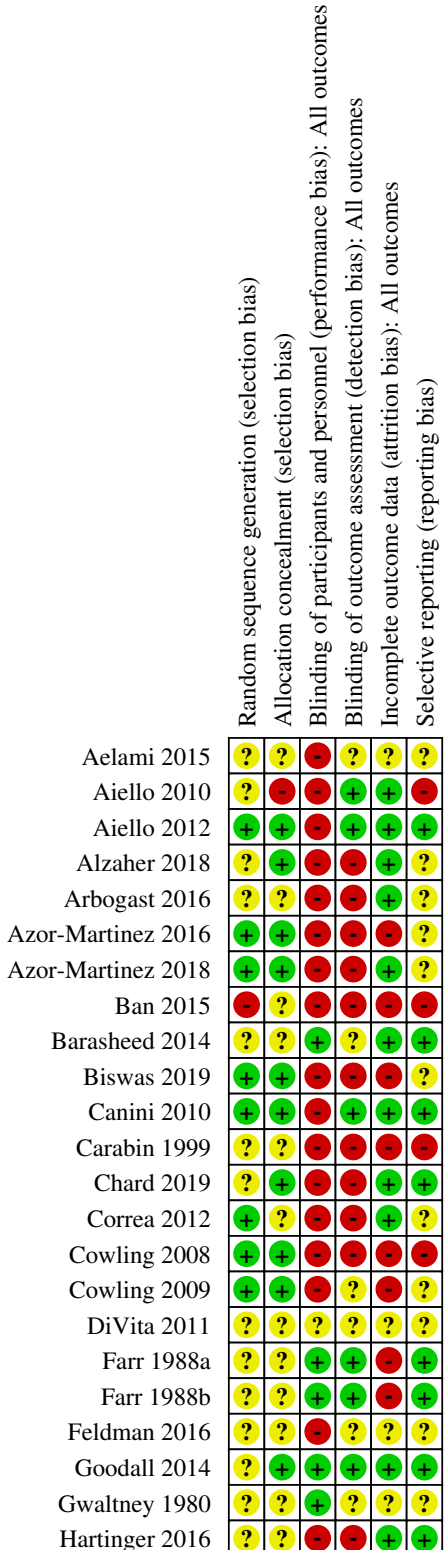

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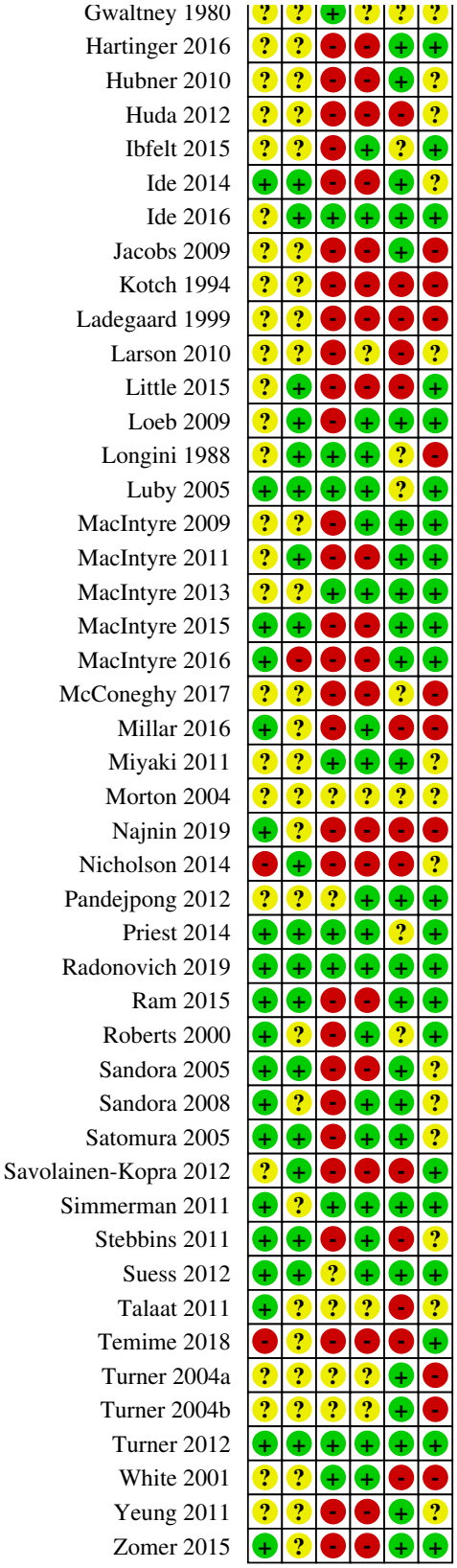
Figure 3. (Continued)



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Allocation

For this 2020 review, information on sequence generation was overall poorly reported in most of the newly included studies. Twenty-one newly included studies provided adequate information on randomisation scheme and were judged as at low risk of bias (Aiello 2012; Azor-Martinez 2016; Azor-Martinez 2018; Biswas 2019; Canini 2010; Correa 2012; Goodall 2014; Ide 2014; MacIntyre 2015; MacIntyre 2016; Millar 2016; Najnin 2019; Priest 2014; Radonovich 2019; Ram 2015; Simmerman 2011; Stebbins 2011; Suess 2012; Talaat 2011; Turner 2012; Zomer 2015). Nine studies described the use of computerised sequence generation program/software (Aiello 2012; Azor-Martinez 2018; Biswas 2019; Canini 2010; Millar 2016; Najnin 2019; Radonovich 2019; Talaat 2011; Turner 2012). One study used random number tables for sequence generation (Azor-Martinez 2016). Three studies described using the random function in Microsoft Excel (Correa 2012; MacIntyre 2016; Suess 2012). Two studies used statistical software to generate a randomisation allocation (MacIntyre 2015; Priest 2014). Two studies reported using block randomisation: Ram 2015 used block randomisation, and an independent investigator generated the list of random assignments, whilst Simmerman 2011 performed block randomisation. Stebbins 2011 used constrained randomisation, and Zomer 2015 reported using stratified randomisation by means of computer generation with a 1:1 ratio in each of the strata.

Fourteen studies reported insufficient information to permit a judgement on the adequacy of the process to minimise selection bias (Aelami 2015; Alzaher 2018; Arbogast 2016; Barasheed 2014; Chard 2019; DiVita 2011; Feldman 2016; Hubner 2010; Ibfelt 2015; McConeghy 2017; Miyaki 2011; Pandejpong 2012; Savolainen-Kopra 2012; Yeung 2011). Six studies provided some description about sequence generation, but it was still unclear (Hartinger 2016; Huda 2012; Ide 2016; Little 2015; MacIntyre 2011; MacIntyre 2013). Huda 2012 mentioned random number tables, but it was unclear if this was for random selection or randomisation. Ide 2016 used computer-generated randomisation, but the method was not stated. Hartinger 2016 used covariate-constrained randomisation, but the method was not described. In Little 2015, participants were automatically randomly assigned by the intervention software, but the sequence generation was not described. Two studies used a secure computerised randomisation program (MacIntyre 2011; MacIntyre 2013), but the sequence generation was not described.

Three of the newly included studies were poorly randomised (Ban 2015; Nicholson 2014; Temime 2018). Ban 2015 included only two clusters, and the randomisation scheme was not reported. Nicholson 2014 used coin tossing, which can lead to a large imbalance. Temime 2018 used “simple randomisation” with no further description.

For the RCTs included in previous versions of the review, three were poorly reported with no description of randomisation sequence or concealment of allocation (Gwaltney 1980; Turner 2004a; Turner 2004b). The quality of the cluster-RCTs varied, with four studies not providing a description of the randomisation procedure (Carabin 1999; Kotch 1994; Morton 2004; White 2001). We rated seven studies as at low risk of bias for sequence generation (Cowling 2008; Cowling 2009; Luby 2005; Roberts 2000; Sandora 2005; Sandora 2008; Satomura 2005), and a further six studies as at unclear risk of bias (Farr 1988a; Farr 1988b; Ladegaard 1999; Loeb 2009; Longini 1988; MacIntyre 2009).

Many of the newly included cluster-RCTs did not report adequately on allocation concealment. Twenty-one of these studies reported adequate allocation and were judged as at low risk of bias (Aiello 2012; Alzaher 2018; Azor-Martinez 2016; Azor-Martinez 2018; Biswas 2019; Canini 2010; Chard 2019; Goodall 2014; Ide 2014; Ide 2016; Little 2015; MacIntyre 2011; MacIntyre 2015; Nicholson 2014; Priest 2014; Radonovich 2019; Ram 2015; Savolainen-Kopra 2012; Stebbins 2011; Suess 2012; Turner 2012). Aiello 2012 randomised all residence houses in each of the residence halls prior to the intervention implementation. Alzaher 2018 allocated schools prior to all schoolgirls attending selected schools being invited to participate. Azor-Martinez 2016 allocated schools/classes prior to children's recruitment. Azor-Martinez 2018 assigned clusters prior to recruitment. Biswas 2019 completed the allocation prior to individuals being recruited. Chard 2019 allocated schools prior to individuals being recruited. Goodall 2014 used opaque, sealed, serially numbered envelopes that were only accessed when two study personnel were present. Ide 2014 also reported using individual drawing of sealed, opaque envelopes to randomly assign participants to the study groups. MacIntyre 2011 randomised hospitals prior to inclusion of participants. In MacIntyre 2015, hospital wards were randomised prior to recruitment of individuals. Nicholson 2014 used coin tossing to assign communities to intervention or control arms. Radonovich 2019 used constrained randomisation to resolve any potential imbalance between covariates between the trial arms. Four studies reported the use of central randomisation: Canini 2010 used central randomisation employing an interactive voice response system; Ide 2016 used central randomisation services; in Little 2015 participants were automatically randomly assigned by the intervention software; and Ram 2015 described a central allocation through data collectors notifying the field research officer, who consulted the block randomisation list to make the assignment of the household compound to intervention or control. Savolainen-Kopra 2012 randomised clusters by matching prior to the onset of the interventions. Four studies reported that allocation was assigned by personnel (investigator, physician, or statistician) unaware of the randomisation sequence (Priest 2014; Stebbins 2011; Suess 2012; Turner 2012). Twenty-two studies reported insufficient information to permit a judgement on the adequacy of the process to minimise selection bias (Aelami 2015; Arbogast 2016; Ban 2015; Barasheed 2014; Correa 2012; DiVita 2011; Feldman 2016; Hartinger 2016; Hubner 2010; Huda 2012; Ibfelt 2015; MacIntyre 2013; McConeghy 2017; Millar 2016; Miyaki 2011; Najnin 2019; Pandejpong 2012; Simmerman 2011; Talaat 2011; Temime 2018; Yeung 2011; Zomer 2015). Two studies provided some information about allocation, but it was not enough to permit a judgement on risk of bias (Barasheed 2014; Simmerman 2011). Barasheed 2014 randomised pilgrim tents using an independent study co-ordinator who was not an investigator, but did not describe how this was done. Simmerman 2011 described using a study co-ordinator to assign households to study arm (after consent was obtained). Only one of the newly added studies was judged as at high risk of bias, where random assignment was allocated by doctors enrolling the participants (MacIntyre 2016). Of the previously included RCTs, 14 provided no or an insufficient description of concealment of allocation (Carabin 1999; Farr 1988a; Farr 1988b; Gwaltney 1980; Kotch 1994; Ladegaard 1999; Larson 2010; MacIntyre 2009; Morton 2004; Roberts 2000; Sandora 2008; Turner 2004a; Turner 2004b; White 2001). We assessed all of the remaining studies as at low risk of bias (Canini 2010; Cowling 2008; Cowling 2009; Loeb 2009; Longini 1988; Luby 2005; Sandora

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2005; Satomura 2005). Aiello 2010 used the drawing of a uniform ticket with the name of each hall out of a container and was rated as at high risk of bias.

Blinding

Although blinding is less of a concern in cluster-RCTs, the risk of bias is substantial when the outcomes are subjective and the outcome assessor is not blinded. We judged 26 studies to have a high risk of bias (Aiello 2012; Alzaher 2018; Arbogast 2016; Azor-Martinez 2016; Azor-Martinez 2018; Ban 2015; Biswas 2019; Carabin 1999; Chard 2019; Correa 2012; Cowling 2008; Ide 2014; Kotch 1994; Ladegaard 1999; Little 2015; MacIntyre 2011; MacIntyre 2015; MacIntyre 2016; McConeghy 2017; Najnin 2019; Nicholson 2014; Ram 2015; Sandora 2008; Savolainen-Kopra 2012; Temime 2018; Zomer 2015). We assessed five cluster-RCTs as at low risk of bias. Farr 1988a and Farr 1988b were double-blinded studies and were judged as at low risk of bias. MacIntyre 2013 and Simmerman 2011 reported laboratory-confirmed influenza, and blinding would not have affected the result. In Miyaki 2011 the self-reported respiratory symptoms were confirmed by a physician. We judged three cluster-RCTs to have a low risk of detection bias because the outcome was laboratory-confirmed influenza, Barasheed 2014; Suess 2012, or physician-confirmed ILI, Pandejpong 2012. Two cluster-RCTs provided insufficient data to judge the effect of non-blinding. Talaat 2011 included outcomes that were both self-reported ILI and laboratory-confirmed influenza. In Yeung 2011 the detection of cases was based on record for hospitalisation related to infection (including pneumonia). Eleven cluster-RCTs were not blinded, but we judged the primary outcome to be unaffected by non-blinding. Seven trials reported laboratory-confirmed influenza (Aiello 2012; Cowling 2009; Larson 2010; Loeb 2009; MacIntyre 2009; Millar 2016; Stebbins 2011). Four studies reported self-reported outcome (Canini 2010; Priest 2014; Roberts 2000; Sandora 2008), but outcome assessors were not aware of the intervention assignment. Five RCTs were double-blinded and were judged as at low risk of bias (Goodall 2014; Ide 2016; Longini 1988; Luby 2005; White 2001), whilst two studies were single-blinded where investigators, Radonovich 2019, or laboratory personnel, Turner 2012, were blinded. Four RCTs were not blinded and were judged as at high risk of bias given the subjective nature of the outcome assessed (Hubner 2010; Ibfelt 2015; Jacobs 2009; Satomura 2005). Turner 2004a and Turner 2004b were double-blind studies, but insufficient information was provided to assess risk of bias.

Incomplete outcome data

In this 2020 review, we assessed 26 newly included trials as having a low risk of attrition bias, with sufficient evidence from the participant flow chart, and explanation of loss to follow-up (which was minimal) similar between groups (Aiello 2012; Alzaher 2018; Arbogast 2016; Azor-Martinez 2018; Barasheed 2014; Canini 2010; Chard 2019; Correa 2012; Goodall 2014; Hartinger 2016; Hubner 2010; Ide 2014; Ide 2016; MacIntyre 2011; MacIntyre 2013; MacIntyre 2015; MacIntyre 2016; Miyaki 2011; Pandejpong 2012; Radonovich 2019; Ram 2015; Simmerman 2011; Suess 2012; Turner 2012; Yeung 2011; Zomer 2015). Seven studies did not report sufficient information on incomplete data (attrition bias) (Aelami 2015; DiVita 2011; Feldman 2016; Hartinger 2016; Ibfelt 2015; McConeghy 2017; Priest 2014). Twelve studies had a high risk of attrition bias (Azor-Martinez 2016; Ban 2015; Biswas 2019; Huda 2012; Little 2015; Millar 2016; Najnin 2019; Nicholson 2014; Savolainen-Kopra 2012; Stebbins 2011; Talaat 2011; Temime 2018). In Azor-Martinez 2016, attrition levels were high and differed between the two groups. Ban 2015 did not report on reasons for loss to follow-up. Biswas 2019 did not provide information on missing participants (28 children in the control schools and two children in the intervention schools). Huda 2012 did not provide a flow diagram of study participants. Little 2015 had high attrition that differed between the two groups. Attrition in Millar 2016 differed amongst the three groups. In addition, ARI cases were captured utilising clinic-based medical records for those participants who sought hospital care only. In Najnin 2019, there was high migration movement during the study, which could have distorted the baseline characteristics even more. There was no description of how such migration and changes in the intervention group were dealt with. In Nicholson 2014, households were removed from the study if they provided no data for five consecutive weeks. Although attrition was reported in Savolainen-Kopra 2012, and 76% of volunteers who were recruited at the beginning of the reporting period completed the study, new recruits were added during the study to replace volunteers lost in most clusters. The total number of reporting participants at the end of the trial was 626 (91.7%) compared to the beginning, meaning that 15.7% of participants were replaced during the study. In Stebbins 2011 reasons for episodes of absence in 66% of the study participants were not reported. Talaat 2011 did not provide a flow chart of clusters flow during the study period and provided no information on withdrawal. Temime 2018 was greatly biased due to underreporting of outcomes in the control groups. Furthermore, no study flow chart was provided, and there was no reporting on any exclusions.

Selective reporting

In this 2020 review, 22 newly included studies reported all specified outcomes and were judged as at low risk of reporting bias (Aiello 2012; Barasheed 2014; Canini 2010; Chard 2019; Goodall 2014; Hartinger 2016; Ibfelt 2015; Ide 2016; Little 2015; MacIntyre 2011; MacIntyre 2013; MacIntyre 2015; MacIntyre 2016; Pandejpong 2012; Priest 2014; Radonovich 2019; Savolainen-Kopra 2012; Simmerman 2011; Suess 2012; Temime 2018; Turner 2012; Zomer 2015). For 18 studies, it is unlikely that other outcomes were measured and not reported, although no protocol was available to assess reporting bias (Aelami 2015; Alzaher 2018; Arbogast 2016; Azor-Martinez 2016; Azor-Martinez 2018; Ban 2015; Biswas 2019; Correa 2012; DiVita 2011; Feldman 2016; Hubner 2010; Huda 2012; Ide 2014; Miyaki 2011; Nicholson 2014; Stebbins 2011; Talaat 2011; Yeung 2011). Three studies were at high risk of reporting bias (McConeghy 2017; Millar 2016; Najnin 2019). In McConeghy 2017, URTI was mentioned in the methods (the intervention presumably would have targeted these), but only lower respiratory tract infection (LRTI) and overall infection were reported. Millar 2016 was originally conducted for another purpose; we could not find the respiratory outcomes reported in the study as part of the original study protocol. In Najnin 2019, the published study protocol did not include respiratory illness as an outcome.

Other potential sources of bias

An additional consideration for cluster-RCTs is identification/recruitment bias, where individuals are recruited in the trial after clusters are randomised. Such bias can introduce an imbalance amongst groups. Of the cluster-RCTs included in our 2020 review, we judged 13 to have a low risk of identification/recruitment bias (Arbogast 2016; Biswas 2019; Canini 2010; Cowling 2008; Longini

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1988; Luby 2005; MacIntyre 2015; MacIntyre 2016; Roberts 2000; Sandora 2005; Suess 2012; Temime 2018; White 2001). In Arbogast 2016, all identified individuals (office workers) were included in the assigned cluster. Schools were identified and then randomised to the clusters; students were then randomly selected from each classroom and school. Nine studies described identification of participants, consenting/enrolling, and then randomising to the clusters (Canini 2010; Cowling 2008; Longini 1988; Luby 2005; MacIntyre 2015; MacIntyre 2016; Roberts 2000; Sandora 2005; White 2001). Suess 2012 identified and consented patients, then recruitment was performed by physicians unaware of cluster assignment. In Temime 2018, directors of the included nursing homes agreed to participate in the study before randomisation, and written consent was not required from the residents. We judged 11 cluster-RCTs as at high risk of identification/recruitment bias (Aiello 2010; Aiello 2012; Azor-Martinez 2018; Chard 2019; Correa 2012; Cowling 2009; Larson 2010; McConeghy 2017; Nicholson 2014; Priest 2014; Savolainen-Kopra 2012). In Aiello 2010 and Aiello 2012, recruitment continued for two weeks after start of the study, which could have introduced bias. Six trials identified and recruited participants after cluster randomisation (Azor-Martinez 2018; Chard 2019; Cowling 2009; Larson 2010; McConeghy 2017; Nicholson 2014). Three trials recruited new participants after the start of the study to replace those lost to follow-up (Correa 2012; Priest 2014; Savolainen-Kopra 2012). We judged five cluster-RCTs to have probable identification/recruitment bias (Alzaher 2018; Barasheed 2014; MacIntyre 2011; Najnin 2019; Radonovich 2019), whereas in 19 studies there were insufficient details to permit a judgement of risk of bias (Carabin 1999; DiVita 2011; Feldman 2016; Hartinger 2016; Huda 2012; Ibfelt 2015; Kotch 1994; Ladegaard 1999; MacIntyre 2009; MacIntyre 2013; Millar 2016; Miyaki 2011; Pandejpong 2012; Radonovich 2019; Sandora 2008; Stebbins 2011; Talaat 2011; Yeung 2011; Zomer 2015).

Twenty-six cluster-RCTs reported intracluster correlation coefficient (ICC) to adjust sample size, taking into consideration clustering effects, and described adjusting outcomes for clustering effect using different statistical methods, or provided justification for not performing adjusted analysis for clustering (Aiello 2010; Aiello 2012; Arbogast 2016; Canini 2010; Carabin 1999; Correa 2012; Cowling 2008; Cowling 2009; Hartinger 2016; Huda 2012; Little 2015; Luby 2005; MacIntyre 2009; MacIntyre 2011; MacIntyre 2013; MacIntyre 2015; MacIntyre 2016; McConeghy 2017; Priest 2014; Radonovich 2019; Ram 2015; Roberts 2000; Stebbins 2011; Suess 2012; Talaat 2011; Temime 2018). Five cluster-RCTs did not report the ICC but described adjusting outcomes for clustering effect using different statistical methods, or explained why adjusted analysis for clustering was not performed (Biswas 2019; Chard 2019; McConeghy 2017; Simmerman 2011; Zomer 2015). Thirteen cluster-RCTs provided insufficient details on ICC and/or did not perform adjusted analysis or justified the absence of it (Alzaher 2018; Azor-Martinez 2016; Azor-Martinez 2018; Barasheed 2014; Feldman 2016; Larson 2010; Millar 2016; Miyaki 2011; Najnin 2019; Nicholson 2014; Pandejpong 2012; Savolainen-Kopra 2012; Yeung 2011). Two cluster-RCTs reported the ICC but did not perform adjusted analysis or justified the absence of it (Sandora 2005; Sandora 2008).

Effects of interventions

See: **Summary of findings 1** Medical/surgical masks compared to no masks for preventing the spread of viral respiratory illness; **Summary of findings 2** N95 respirators compared to medical/surgical masks for preventing the spread of viral respiratory illness; **Summary of findings 3** Hand hygiene compared to control for preventing the spread of viral respiratory illness

Comparison 1: Medical/surgical masks compared to no masks

We included nine trials (eight of which were cluster-RCTs) comparing medical/surgical masks versus no masks (Aiello 2012; Barasheed 2014; Canini 2010; Cowling 2008; Jacobs 2009; MacIntyre 2009; MacIntyre 2015; MacIntyre 2016; Suess 2012). Two trials were conducted with healthcare workers (HCWs) (Jacobs 2009; MacIntyre 2015), whilst the other seven studies included people living in the community. All trials were conducted in non-pandemic settings.

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

Pooling of all nine trials found an estimate of effect for the outcomes of ILI cases (risk ratio (RR) 0.99, 95% confidence interval (CI) 0.82 to 1.18; low-certainty evidence; Analysis 1.1) suggesting that wearing a medical/surgical mask may make little or no difference for this outcome. Similarly, the estimate of effect for laboratory-confirmed influenza cases (RR 0.91, 95% CI 0.66 to 1.26; 6 trials; moderate-certainty evidence; Analysis 1.1) suggests that wearing a medical/surgical mask probably makes little or no difference compared to not wearing a mask for this outcome. We downgraded the certainty of the evidence two levels for ILI due to inconsistency of the effect across studies and wide CI of the pooled effect. Sixty-five per cent of the weight of the ILI analysis was carried by one study (Aiello 2012).

A separate analysis of the two trials in healthcare workers for the outcome ILI (RR 0.37, 95% CI 0.05 to 2.50; low-certainty evidence; Analysis 1.2) suggests that there is considerable uncertainty as to whether there is any benefit (Jacobs 2009; MacIntyre 2015). The effect estimate was downgraded due to very wide CI interval of the pooled effect.

The design of most trials assessed whether masks protected the wearer. Four trials were cluster-RCTs, with all participants in the intervention clusters required to wear masks, thus assessing both source control and personal protection. In two trials the clusters were households with a member with new influenza; neither of these studies found any protective effect (RR 1.03 in 105 households (Canini 2010); RR 1.21 in 145 households (MacIntyre 2009)). In two trials the clusters were college dormitories during the influenza season; neither study found any reduction (RR 1.10 in 37 dormitories (Aiello 2012); RR 0.90 in three dormitories (Aiello 2010)). We excluded Aiello 2010 from the meta-analysis since we did not consider 'randomisation' of three clusters to three arms to be a proper randomised trial.

2. Adverse events related to the intervention

Canini 2010 reported that 38 (75%) of participants in the intervention arm experienced discomfort with the mask use due to warmth (45%), respiratory difficulties (33%), and humidity (33%). Children reported feeling pain more frequently (3/12) than other participants wearing adult face masks (1/39; P = 0.04). In MacIntyre 2015, adverse events associated with face mask use were reported in 40.4% (227/562) of HCWs in the medical-mask arm. General discomfort (35.1%; 397/1130) and breathing problems (18.3%;

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207/1130) were the most frequently reported adverse events. Suess 2012 reported that the majority of participants (107/172; 62%) did not report any problems with mask-wearing. More adults reported no problems (71%) compared to children (36/72; 50%; P = 0.005). The main issues when wearing a face mask for adults as well as for children were "heat/humidity" (18/34; 53% of children; 10/29; 35% of adults; P = 0.1), followed by "pain" and "shortness of breath". Cowling 2008 mentioned that no adverse events were reported. The other trials did not report measuring adverse outcomes.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Jacobs 2009 reported that participants in the mask group were significantly more likely to experience more days with headache and feeling bad. They found no significant differences between the two groups for symptom severity scores. None of the other trials reported this outcome.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 2: N95/P2 respirators compared to medical/surgical masks

We included five trials comparing medical/surgical masks with N95/P2 respirators (Loeb 2009; MacIntyre 2009; MacIntyre 2011; MacIntyre 2013; Radonovich 2019). All of these trials except MacIntyre 2009 included HCWs. MacIntyre 2009 included carers and household members of children with a respiratory illness recruited from a paediatric outpatient department and a paediatric primary care practice in Sydney, Australia.

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

Pooling of three trials found an estimate of effect suggesting considerable uncertainty as to whether an N95/P2 respirator provides any benefit compared to medical/surgical masks for the outcome of clinical respiratory illness (RR 0.70, 95% CI 0.45 to 1.10; very low-certainty evidence; Analysis 2.1) (MacIntyre 2011; MacIntyre 2013 (2 arms); Radonovich 2019). Based on five trials conducted in four healthcare settings and one household (Loeb 2009; MacIntyre 2009; MacIntyre 2011; MacIntyre 2013; Radonovich 2019), the estimates of effect for the outcome of ILI (RR 0.82, 95% CI 0.66 to 1.03; low-certainty evidence; Analysis 2.1) suggest that N95/P2 respirators may make little or no difference for this outcome. The estimate of the effect for the outcome of laboratory-confirmed influenza infection (RR 1.10, 95% CI 0.90 to 1.34; moderate-certainty evidence; Analysis 2.1) suggests that the use of a N95/P2 respirator compared to a medical/surgical mask probably makes little or no difference for this more precise and objective outcome. The outcomes clinical respiratory illness and ILI were reported separately. Considering how these outcomes were defined, it is highly likely that there was considerable overlap between the two, therefore these outcomes were not combined into a single clinical outcome (Analysis 2.1). The laboratory-confirmed viral respiratory infection outcome included influenza primarily but multiple other common viral respiratory pathogens were also included in several studies. The laboratory-confirmed viral infection outcome was considered more precise and objective in comparison to the clinical outcomes, which were more subjective and considered to be less precise. The findings did not change when we restricted the evidence to HCWs (Analysis 2.2).

2. Adverse events related to the intervention

Harms were poorly reported, but generally discomfort wearing medical/surgical masks and N95/P32 respirators was mentioned in several studies. Radonovich 2019 mentioned that participants wearing the N95 respirator reported skin irritation and worsening of acne. MacIntyre 2011 reported that adverse events were more common with N95 respirators; in particular, discomfort was reported in 41.9% of N95 wearers versus 9.8% of medical-mask wearers (P < 0.01); headaches were more common with N95 (13.4% versus 3.9%; P < 0.01); difficulty breathing was reported more often in the N95 group (19.4% versus 12.5%; P = 0.01); and N95 caused more problems with pressure on the nose (52.2% versus 11.0%; P < 0.01). In MacIntyre 2013, fewer participants using the N95 respirator reported problems (38% (195/512) versus 48% (274/571) of participants in the medical-mask arm; P = 0.001). Loeb 2009 mentioned that no adverse events were reported.

The one trial conducted in the community mentioned that more than 50% of participants reported concerns with both types of masks, mainly that wearing them was uncomfortable, but there were no significant differences between the P2 (N95) and surgical-mask groups (MacIntyre 2009).

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Not reported.

3. Absenteeism

Loeb 2009 reported that 42 participants (19.8%) in the surgical-mask group reported an episode of work-related absenteeism compared with 39 (18.6%) of participants in the N95 respiratory group (absolute risk difference −1.24%, 95% CI −8.75% to 6.27%; P = 0.75).

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Loeb 2009 reported that there were no episodes of LRTIs.

Comparison 3: Hand hygiene compared to control

Sixteen trials compared hand hygiene interventions with control and provided sufficient data to include in meta-analyses (Azor-Martinez 2018; Biswas 2019; Correa 2012; Cowling 2008; Cowling

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2009; Hubner 2010; Larson 2010; Little 2015; Millar 2016; Nicholson 2014; Ram 2015; Roberts 2000; Sandora 2005; Simmerman 2011; Stebbins 2011; Zomer 2015). The populations of these studies included adults, children, and families, in settings such as schools, childcare centres, homes, and offices. None of the studies was conducted during a pandemic, although a few studies were conducted during peak influenza seasons. A further 16 trials comparing hand hygiene to a control had other outcomes or insufficient information to include in meta-analyses (Alzaher 2018; Arbogast 2016; Azor-Martinez 2016; DiVita 2011; Feldman 2016; Gwaltney 1980; Ladegaard 1999; Luby 2005; Morton 2004; Priest 2014; Savolainen-Kopra 2012; Talaat 2011; Temime 2018; Turner 2012; White 2001; Yeung 2011). The results of these trials were consistent with the findings of our meta-analyses. The results for all outcomes from the 16 trials that were meta-analysed and the 16 trials that were not meta-analysed are shown in Table 2.

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

Pooling of seven trials for the broad outcome of ARI showed a 16% relative reduction in the numbers of participants with ARI (RR 0.84, 95% CI 0.82 to 0.86; moderate-certainty evidence; Analysis 3.1.1) in the hand hygiene group (Analysis 3.1), suggesting a probable benefit (Azor-Martinez 2018; Correa 2012; Larson 2010; Little 2015; Millar 2016; Nicholson 2014; Sandora 2005). When considering the more strictly defined outcomes of ILI, Biswas 2019; Cowling 2008; Cowling 2009; Hubner 2010; Larson 2010; Little 2015; Ram 2015; Roberts 2000; Simmerman 2011; Zomer 2015, and laboratory-confirmed influenza, Biswas 2019; Cowling 2008; Cowling 2009; Hubner 2010; Larson 2010; Ram 2015; Simmerman 2011; Stebbins 2011, the estimates of the effect were heterogeneous, suggesting that hand hygiene made little or no difference (RR 0.98, 95% CI 0.85 to 1.13 for ILI; low-certainty evidence; Analysis 3.1.2) (RR 0.91, 95% CI 0.63 to 1.30 for laboratory-confirmed influenza; low-certainty evidence; Analysis 3.1.3) (Analysis 3.1). All 16 trials could be pooled for analysis of the composite outcome 'ARI or ILI or influenza', with each study only contributing once with the most comprehensive outcome (in terms of number of events) reported showing an 11% relative reduction in participants with a respiratory illness, suggesting that hand hygiene may offer a benefit (RR 0.89, 95% CI 0.84 to 0.95; low-certainty evidence; Analysis 3.2), but with high heterogeneity. In a sensitivity analysis we used only the most precise and unequivocal (with laboratory confirmed considered the most precise and an undefined ARI considered the least precise) outcome reported in each of 11 studies identified by JMC, an infectious disease physician, and found an estimate of effect in favour of hand hygiene, but with wider CIs (RR 0.92, 95% CI 0.80 to 1.05; Analysis 3.3).

We considered that studies in children might have a different effect than studies in adults, so we conducted subgroup analysis by age group. We found no evidence of a difference in treatment effect by age group (P = 0.21; Analysis 3.4).

2. Adverse events related to the intervention

Correa 2012 reported that no adverse events were observed; in the study by Priest 2014, skin reaction was recorded for 10.4% of participants in the hand sanitiser group versus 10.3% in the control group (RR 1.01, 95% CI 0.78 to 1.30).

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Not reported.

3. Absenteeism

Three trials measured absenteeism from school or work and demonstrated a 36% relative reduction in the numbers of participants with absence in the hand hygiene group (RR 0.64, 95% CI 0.58 to 0.71; Analysis 3.5) (Azor-Martinez 2016; Hubner 2010; Nicholson 2014).

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 4: Hand hygiene + medical/surgical masks compared to control

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

Six trials (Aelami 2015; Aiello 2012; Cowling 2009; Larson 2010; Simmerman 2011; Suess 2012) were able to be pooled to compare the use of the combination of hand hygiene and medical/surgical masks with control. Four of these trials were in households, two in university student residences, and one at the annual Hajj pilgrimage. For both outcomes (ILI and influenza), pooling demonstrated an estimate of effect suggesting little or no difference between the hand hygiene and medical/surgical mask combination and control. The number of trials and events was lower than for comparisons of hand hygiene alone, or medical/surgical masks alone, and the confidence interval was wide. For ILI, the RR for intervention compared to control was 1.03 (95% CI 0.77 to 1.37; Analysis 4.1.1), and for influenza it was 0.97 (95% CI 0.69 to 1.36; Analysis 4.1.2) (Analysis 4.1). Full results of these trials are shown in Table 3

2. Adverse events related to the intervention

Adverse events related to mask wearing in the study by Suess 2012 are reported under Comparison 1 (medical/surgical masks). There was no mention of adverse events related to hand hygiene.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Not reported.

3. Absenteeism

Not reported.

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4. Hospital admissions

Not reported.

5. Complications related to the illness, e.g. pneumonia

Not reported.

Comparison 5: Hand hygiene + medical/surgical masks compared to hand hygiene

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI and laboratory-confirmed influenza)

Three trials studied the addition of medical/surgical masks to hand hygiene (Cowling 2009; Larson 2010; Simmerman 2011). All three trials had three arms, and are also included in the comparison of hand hygiene plus medical/surgical mask versus control (Comparison 4). All three studies showed no difference between hand hygiene plus medical/surgical mask groups and hand hygiene alone, for all outcomes. The estimates of effect suggested little or no difference when adding masks to hand hygiene compared to hand hygiene alone: for the outcome ILI (RR 1.03, 95% CI 0.69 to 1.53; 3 trials) and the outcome laboratory-confirmed influenza (RR 0.99, 95% CI 0.69 to 1.44), the estimates of effect were not different and the CIs were relatively wide, suggesting little or no difference (Analysis 5.1). However, the CIs around the estimates were wide and do not rule out an important benefit.

2. Adverse events related to the intervention

Not reported.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Not reported.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 6: Medical/surgical masks compared to other (non-N95) masks

One trial compared medical/surgical masks with cloth masks in hospital healthcare workers (MacIntyre 2015), and another trial compared catechin-treated masks versus control masks in healthcare workers and staff of hospitals, rehabilitation centres, and nursing homes in Japan (Ide 2016).

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

MacIntyre 2015 found that the rate of ILI was higher in the cloth mask arm compared to the medical/surgical masks arm (RR 13.25, 95% CI 1.74 to 100.97).

Ide 2016 did not find a benefit from the catechin-treated masks over untreated masks on influenza infection rates (adjusted odds ratio (OR) 2.35, 95% CI 0.40 to 13.72; P = 0.34).

2. Adverse events related to the intervention

In MacIntyre 2015 adverse events associated with face mask use were reported in 40.4% (227/562) of HCWs in the medical/surgical mask arm and 42.6% (242/568) in the cloth mask arm (P = 0.45). The most frequently reported adverse events were general discomfort (35.1%; 397/1130) and breathing problems (18.3%; 207/1130). Laboratory tests showed the penetration of particles through the cloth masks to be very high (97%) compared with medical/surgical masks (44%). Ide 2016 reported that there were no serious adverse events associated with the intervention.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Not reported.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 7: Soap + water compared to sanitiser, and comparisons of different types of sanitiser

Two trials compared soap and water with sanitiser (Azor-Martinez 2018; Savolainen-Kopra 2012). Another trial compared different types of hand sanitiser in a virus challenge study (Turner 2004a; Turner 2004b), and one trial studied the frequency of use of hand sanitiser (Pandejpong 2012). The full results of these four trials are shown in Table 4.

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

In the trial by Azor-Martinez 2018, ARI incidence was significantly higher in the soap-and-water group compared with the hand sanitiser group (rate ratio 1.21, 95% CI 1.06 to 1.39). In contrast, there was no significant difference between interventions in Savolainen-Kopra 2012. In the rhinovirus challenge study (Turner 2004a; Turner 2004b), all hand sanitisers tested led to a significant lowering of infection rates, but no differences between sanitisers were observed. The study sample size was small.

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2. Adverse events related to the intervention

Two trials stated that no adverse events were observed (Pandejpong 2012; Savolainen-Kopra 2012).

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Not reported.

3. Absenteeism

The authors of Azor-Martinez 2018 also observed a significant benefit for hand sanitiser in reduction in days absent, whereas there was no difference between intervention groups in the Savolainen-Kopra 2012 trial. The study on frequency of use of sanitiser found that use of sanitiser every hour significantly reduced days absent compared with use every two hours or with use only before the lunch break (Pandejpong 2012).

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 8: Surface/object disinfection (with or without hand hygiene) compared to control

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

Six trials contributed data to this comparison (Ban 2015; Carabin 1999; Ibfelt 2015; Kotch 1994; McConeghy 2017; Sandora 2008). Full results of these trials are shown in Table 5. Five of the six trials combined disinfection with other interventions such as hand hygiene education, provision of hand hygiene products, and audits. Ban 2015 utilised a combination of provision of hand hygiene products, and cleaning and disinfection of surfaces, and demonstrated a significant reduction in ARI in the intervention group (OR 0.47, 95% CI 0.48 to 0.65). A similar result was seen in Carabin 1999, with a significant reduction in episodes of ARI. Two studies tested multicomponent interventions and observed no significant difference in ARI outcomes (Kotch 1994; McConeghy 2017).

One trial compared disinfection alone to usual care (Ibfelt 2015). This study demonstrated a significant reduction in some viruses detected on surfaces in the childcare centres (adenovirus, rhinovirus, respiratory syncytial virus (RSV), and metapneumovirus), but not in other viruses, including coronavirus.

2. Adverse events related to the intervention

Not reported.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Not reported.

3. Absenteeism

Only one study measured this outcome (Sandora 2008), observing no significant difference between groups for the outcome of absence due to respiratory illness (rate ratio for intervention to control 1.10, 95% CI 0.97 to 1.24).

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 9: Complex interventions compared to control

Complex interventions are either multifaceted environmental programmes (such as those in low-income countries) or combined interventions including hygiene measures and gloves, gowns, and masks.

Four trials studied complex hygiene and sanitation interventions in low-income country settings (Chard 2019; Hartinger 2016; Huda 2012; Najnin 2019). Full results from these studies are given in Table 6.

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

All four trials of complex interventions observed no significant differences between groups in rates of viral respiratory illness.

2. Adverse events related to the intervention

Not reported

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Not reported.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 10: Physical distancing/quarantine compared to control

We found one quasi-cluster-RCT assessing the effectiveness of quarantining workers of one of two sibling companies in Japan whose family members developed an ILI during the 2009 to 2010 H1N1 influenza pandemic (Miyaki 2011). Workers in the intervention group were asked to stay home on full pay until

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five days after the household member(s) showed resolution of symptoms or two days after alleviation of fever.

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

Compliance with the intervention was 100%. In the intervention group 2.75% of workers contracted influenza, compared with 3.18% in the control group (Cox hazard ratio 0.799, 95% CI 0.66 to 0.97; P = 0.02), indicating that the rate of infection was reduced by 20% in the intervention group. However, the risk of a worker being infected was 2.17-fold higher in the intervention group where workers stayed at home with their infected family members. The authors concluded that quarantining workers who have infected household members could be a useful additional measure to control the spread of respiratory viruses in an epidemic setting.

2. Adverse events related to the intervention

Not reported.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Not reported.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 11: Eye protection compared to control

We did not find any randomised studies investigating the effect of eye protection compared to control.

Comparison 12: Gargling compared to control

Three trials investigated the effect of gargling. Satomura 2005 compared throat gargling with povidone-iodine versus tap water in healthy adults. Ide 2014 compared gargling with green tea versus tap water in high school students, and Goodall 2014 compared gargling with tap water with no gargling in university students.

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

Satomura 2005 reported that gargling with tap water reduced the incidence of URTIs compared to the control group (usual care) (hazard ratio (HR) 0.60, 95% CI 0.39 to 0.95). Gargling with povidone-iodine did not reduce the incidence of URTIs compared to the control group (HR 0.88, 95% CI 0.58 to 1.34).

Goodall 2014 found no difference in laboratory-confirmed URTIs between the gargling (tap water) and no-gargling groups (RR for gargling versus no gargling 0.82, 95% CI 0.53 to 1.26; P = 0.36).

In a meta-analysis of gargling versus control based on two trials (Goodall 2014; Satomura 2005), the pooled estimate of effect suggested little or no difference for the outcome of clinical URTI due to gargling (RR 0.91, 95% CI 0.63 to 1.31; Analysis 6.1).

There was no difference in the incidence of laboratory-confirmed influenza between high school students gargling with green tea compared with those using tap water (adjusted OR 0.69, 95% CI 0.37 to 1.28; P = 0.24) (Ide 2014). There was also no difference in the incidence of clinically defined influenza (adjusted OR 0.75, 95% CI 0.50 to 1.13; P = 0.17). However, the authors reported that adherence to the interventions amongst students was low.

2. Adverse events related to the intervention

Satomura 2005 reported no adverse events during the 60-day intervention period. Ide 2014 also did not observe any adverse events during the study. Goodall 2014 did not report on adverse effects.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Satomura 2005 reported that the mean peak score in bronchial symptoms was lower in the water gargling group (0.97) than in the povidone-iodine gargling group (1.41) and the control group (1.40), P = 0.055. Other symptoms were not significantly different between groups. Goodall 2014 reported that symptom severity was greater in the gargling group for clinical and laboratory-confirmed URTI, but this was not statistically significant (225.3 versus 191.8, and 210.5 versus 191.8, respectively). Ide 2014 did not report symptom or illness severity.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

Comparison 13: Virucidal tissues compared to control

Two reports (three trials) conducted in the USA studied the effect of virucidal tissues (Farr 1988a; Farr 1988b; Longini 1988). Full results from these studies are given in Table 7.

Primary outcomes

1. Numbers of cases of viral illness (including ARIs, ILI, and laboratory-confirmed influenza)

The three trials of virucidal tissues reported no differences in infection rates between tissues and placebo, and between tissues and no tissues (Farr 1988a; Farr 1988b; Longini 1988).

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2. Adverse events related to the intervention

Farr 1988b reported cough in 4% of participants using virucidal tissues versus 57% in the placebo group, but 24% reported nasal burning in the virucidal tissue group versus 8% in the placebo group. Longini 1988 did not report on adverse effects.

Secondary outcomes

1. Deaths

Not reported.

2. Severity of viral illness as reported in the studies

Not reported.

3. Absenteeism

Not reported.

4. Hospital admissions

Not reported.

5. Complications related to the illness (e.g. pneumonia)

Not reported.

DISCUSSION

Summary of main results

See Table 8.

1. Medical/surgical masks compared to no masks

The pooled estimates of effect from RCTs and cluster-RCTs for wearing medical/surgical masks compared to no masks suggests little or no difference in interrupting the spread of ILI (RR 0.99, 95% CI 0.82 to 1.18; low-certainty evidence) or laboratory-confirmed influenza (RR 0.91, 95% CI 0.66 to 1.26; moderate-certainty evidence) in the combined analysis of all populations from the included trials. We found similar results for ILI in HCWs (RR 0.37, 95% CI 0.05 to 2.50; very low-certainty evidence). Four trials were cluster-RCTs, with all participants in the intervention clusters required to wear masks, thus assessing both source control and personal protection. In two trials the clusters were households with a member with new influenza; neither trial found any protective effect (RR 1.03 in 105 households (Canini 2010); RR 1.21 in 145 households (MacIntyre 2009)). In two trials the clusters were college dormitories during the influenza season; neither trial found any reduction (RR 1.10 in 37 dormitories (Aiello 2012); RR 0.90 in three dormitories (Aiello 2010)). We excluded Aiello 2010 from meta-analysis since we did not consider 'randomisation' of three clusters to three arms was a proper randomised trial.

Less than half of the trials comparing masks with no masks addressed harms of mask wearing (Canini 2010; Cowling 2008; MacIntyre 2015; Suess 2012). Warmth, respiratory difficulties, humidity, and general discomfort were the most frequently reported adverse events. More adults reported no harms compared to children.

In one trial (MacIntyre 2015), cloth masks were associated with a significantly higher risk of both ILI and laboratory-confirmed respiratory virus infection in HCWs. In addition, filtration capacity of the two-ply cotton cloth masks was found to be only 3% and markedly less than with surgical masks based on standardised particle testing. The authors suggested moisture retention, poor filtration, and penetration of the virus through the mask as plausible explanations for the increased risk of infection.

We did not find any randomised trials assessing the effectiveness of barrier interventions using a combination of masks, gloves, and gowns.

2. N95 respirators compared to medical/surgical masks

Comparisons between N95 respirators and surgical masks for the outcomes of clinical respiratory illness and the outcome of laboratory-confirmed influenza showed estimates of effect suggesting considerable uncertainty for any benefit for the former outcome and probably little or no difference for the latter outcome. Five trials (four in healthcare settings and one in a household setting) compared N95/P2 respirators with surgical masks. Pooling of three of these trials showed an estimate of effect suggesting considerable uncertainty as to whether there was any benefit comparing N95 respirators and medical/surgical face masks for the outcome of clinical respiratory illness (RR 0.70, 95% CI 0.45 to 1.10; very low-certainty evidence), and that N95 respirators may make little or no difference for the outcome ILI (RR 0.82, 95% CI 0.66 to 1.03; low-certainty evidence) and probably little or no difference for the outcome laboratory-confirmed influenza (RR 1.10, 95% CI 0.90 to 1.34; moderate-certainty evidence). The presence of imprecision (wide confidence intervals) and heterogeneity, particularly for the more subjective and less precise outcomes of clinical respiratory illness and ILI compared to laboratory-confirmed influenza infection, makes it difficult to assess whether there may be a benefit of either medical/surgical masks or N95/P2 respirators. Restricting the pooling to HCWs made no difference to the overall findings. The two trials with the largest event rates were quite consistent in their findings of no significant differences between N95 and surgical masks for the outcomes laboratory-confirmed influenza and all laboratory-confirmed viral infections (Loeb 2009; Radonovich 2019). Three of the trials contributing to this analysis were carried out by members of the same group (MacIntyre 2009; MacIntyre 2011; MacIntyre 2013).

In general, harms were poorly reported or not reported at all in trials comparing N95 respirators with surgical masks. General discomfort resulting in reduced wear compliance was the most frequently reported harm.

3. Hand hygiene compared to control

We found that the estimate of effect may offer a benefit for hand hygiene for the composite outcome 'ARI or ILI or influenza' (RR 0.89, 95% CI 0.84 to 0.95; low-certainty evidence), and probably offers a benefit for the outcomes ARI alone (RR 0.84, 95% CI 0.82 to 0.86; moderate-certainty evidence) and absenteeism (RR 0.64, 95% CI 0.58 to 0.71). An observed estimate of effect in favour of hand hygiene for laboratory-confirmed influenza but with wider CIs may be a consequence of smaller sample sizes in conjunction with a more rigorous outcome measure.

4. Hand hygiene + medical/surgical masks compared to control

The estimate of effect of combined hand hygiene and mask interventions compared to control in six (mostly small) trials suggested that the intervention may make little or no difference for the outcomes ILI (RR 1.03, 95% CI 0.77 to 1.37) and laboratory-confirmed influenza (four trials) (RR 0.97, 95% CI 0.69 to 1.36).

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5. Hand hygiene + medical/surgical masks compared to hand hygiene

We also found an estimate of effect suggesting that adding masks to hand hygiene compared to hand hygiene alone may make little or no difference for the outcomes ILI (RR 1.03, 95% CI 0.69 to 1.53; 3 trials) and laboratory-confirmed influenza (RR 0.99, 95% CI 0.69 to 1.44).

6. Medical/surgical masks compared to other (non-N95) masks

One trial found that medical/surgical masks were more effective than cloth masks at reducing the rate of ILI (RR 13.25, 95% CI 1.74 to 100.97) (MacIntyre 2015), but the extremely wide CIs make this finding difficult to interpret. One trial did not find a benefit from catechin-treated masks over untreated masks on influenza infection rates (adjusted OR 2.35, 95% CI 0.40 to 13.72; P = 0.34) (Ide 2016).

Harms of wearing masks were reported in 40.4% of HCWs using medical/surgical masks, and in 42.6% of those wearing cloth masks (P = 0.45) (MacIntyre 2015). The penetration of particles was higher in cloth masks (97%) compared to medical/surgical masks (44%).

7. Soap + water compared to sanitiser, and comparisons of different types of sanitiser

There were too few trials comparing different types of hand hygiene interventions to be certain of any true differences between soap and water, alcohol-based hand sanitisers, or other types of interventions. Also, it is uncertain whether the incremental effect of adding virucidals or antiseptics to hand-washing actually decreased the respiratory disease burden outside the confines of the rather atypical studies. The extra benefit may have been, at least in part, accrued by confounding additional routines.

8. Surface/object disinfection (with or without hand hygiene) compared to control

We identified six trials on surface/object disinfection (with or without hand hygiene), and although they were heterogeneous (and therefore could not be pooled), three of them showed a clear benefit compared to controls (Ban 2015; Carabin 1999; Ibfelt 2015).

We found no RCTs with nose disinfection, or disinfection of living quarters as described in observational studies reported in Jefferson 2011.

9. Complex interventions compared to control

Four trials studied complex hygiene and sanitation interventions, all in low-income country settings (Chard 2019; Hartinger 2016; Huda 2012; Najnin 2019). These trials could not be pooled due to the heterogeneity of the interventions and settings. All four trials found no significant differences between groups in the rates of viral respiratory illness.

10. Physical distancing/quarantine compared to control

A disappointing finding was the lack of proper evaluation of global and highly resource-intensive measures such as screening at entry ports and physical distancing. We identified only one trial that evaluated the effect of quarantine (Miyaki 2011), and found a reduction in influenza transmission to co-workers when those with infected household members stayed home from work. However, staying home increased their risk of being infected two-fold.

11. Eye protection compared to control

We did not find any trials assessing the effectiveness and safety of eye protection.

12. Gargling compared to control

Three trials addressed the use of gargling in preventing respiratory infections (Goodall 2014; Ide 2014; Satomura 2005). Although the trials used a variety of liquids and different outcomes, pooling the results of the two trials that compared gargling with tap water versus control did not show a favourable effect in reducing URTIs (RR 0.91, 95% CI 0.63 to 1.31) (Goodall 2014; Satomura 2005).

13. Virucidal tissues compared to control

Two reports (three trials) identified in Jefferson 2011 studied the effect of virucidal tissues compared to placebo or no tissues (Farr 1988a; Farr 1988b; Longini 1988). These trials found no differences in infection rates and could not be pooled.

Overall completeness and applicability of evidence

Several features need consideration before making generalisations based on the included studies.

The settings of the included studies, which were conducted over four decades, were heterogeneous and ranged from suburban schools, Carabin 1999, to emergency departments, intensive care units, and paediatric wards, Loeb 2009, in high-income countries; slums in low-income countries (Luby 2005); and an upper Manhattan immigrant Latino neighbourhood (Larson 2010). Few attempts were made to obtain socio-economic diversity by (for example) involving more schools in the evaluations of the same programme. We identified only a few studies from low-income countries, where the vast majority of the burden of ARIs lies and where inexpensive interventions are so critical. Additionally, limited availability of over-the-counter medications and national universal comprehensive health insurance provided with consequent physician prescription of symptomatic treatment may further limit the generalisability of findings.

The included trials generally reported few events and were conducted mostly during non-epidemic periods. The large study by Radonovich 2019 is an exception as it crossed over two of the highest reporting years for influenza in the USA between 2010 and 2017 (Elflein 2019). None of the trials were conducted during a pandemic such as SARS-CoV-1, SARS-CoV-2, or Middle East respiratory syndrome (MERS).

Of the trials assessing the effect of masks, six were carried out in those at greater exposure (i.e. HCWs) (Jacobs 2009; Loeb 2009; MacIntyre 2011; MacIntyre 2013; MacIntyre 2015; Radonovich 2019). None of these studies included HCWs undertaking aerosol-generating procedures, for which the World Health Organization (WHO) currently recommends the N95 or equivalent mask. Three trials on hand hygiene interventions were carried out in nursing homes, and included HCWs (McConeghy 2017; Temime 2018; Yeung 2011). The scarcity of RCTs on HCWs limits the generalisability of such results.

The variable quality of the methods of some studies is striking. Incomplete or no reporting of randomisation (Turner 2004a), blinding (Farr 1988a; Farr 1988b), numerators and denominators (Carabin 1999; Kotch 1994), interventions, and cluster coefficients

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in the relevant trials (Carabin 1999), led to a considerable loss of information. Potential biases were often not discussed.

Inappropriate placebos caused design problems. In some studies the placebo probably carried sufficient effect to dilute the intervention effects (Longini 1988). Two valiant attempts with virucidal tissues probably failed because placebo handkerchiefs were impregnated with a dummy compound that stung the users' nostrils (Farr 1988a; Farr 1988b).

Some studies used impractical interventions. Volunteers subjected to the intervention hand cleaner (organic acids) were not allowed to use their hands between cleaning and virus challenge, so the effect of normal use of the hands on the intervention remains unknown (Turner 2004a; Turner 2004b). Two per cent aqueous iodine painted on the hands, although a successful antiviral intervention, causes unacceptable cosmetic staining, which is impractical for all but those at the highest risk of epidemic contagion (Gwaltney 1980).

Compliance with interventions, especially educational programmes, was a problem for many studies despite the importance of many such low-cost interventions. Compliance with mask wearing varied; it was generally around 60% to 80%, but was reported to be as low as 40% (see Table 1). Overall, the logistics of carrying out trials that involve sustained behaviour change are demanding, particularly in challenging settings such as immigrant neighbourhoods or students' halls of residence.

The identified trials provided sparse and unsystematic data on adverse effects of the intervention, and few of the RCTs measured or reported compliance with the intervention, which is especially important for the use of medical/surgical masks or N95 respirators. No studies investigated how the level of adherence may have influenced the effect size.

We did not identify any studies assessing the effects of eye protection, and we identified only one study on physical distancing, during the 2009 H1N1 influenza pandemic. The dearth of evidence and predominant setting of seasonal viral circulation limits generalisability of our findings to other contexts such as the COVID-19 pandemic and any future epidemics due to other respiratory viruses.

Quality of the evidence

We found the available evidence base identified through our search processes to be of variable quality. Reporting of sequence generation and allocation concealment were poor in 30% to 50% of studies across the categories of intervention comparisons. Given the nature of the intervention comparison, blinding of treatment allocation after randomisation was rarely achieved. Although blinding of outcome assessment is highly feasible and desirable, most outcomes were assessed by self-reports. Outcomes in some studies were poorly defined, with a lack of clarity as to the possible aetiologic agents (bacterial versus viral). Some studies used laboratory-confirmed outcomes, both adding precision and lowering the risk of bias (see Table 9 for heterogeneity of trial outcome definitions). We found no evidence of selective reporting of outcomes within the included studies. We believe publication bias is unlikely, as the included studies demonstrated a range of effects, both positive and negative, over all study sizes. The variable quality of the studies hampers drawing any firm conclusions.

Potential biases in the review process

The non-drug (and often locally manufactured) nature of most of the interventions in this review, the lack of effective regulation in some settings, and the possible endless number of manufacturers make it difficult to gauge the existence of unpublished data. Non-drug interventions typically have no or very poor regulation.

In this 2020 update, we focused on RCTs and cluster-RCTs, providing a higher level of evidence compared with the previous version of the review, which also meta-analysed observational studies when appropriate (Jefferson 2011). However, many of the trials were small and hence underpowered, and at high or unclear risk of bias due to poor reporting of methods and lack of blinding. The populations, outcomes, comparators, and interventions tested were heterogeneous.

Due to the urgency of this update in the context of the COVID-19 pandemic, we did not contact trial authors to request missing data. This means that we have not considered studies that included other non-respiratory infections and did not provide stratified data by type of infection.

Agreements and disagreements with other studies or reviews

Several reviews of RCTs have found broadly similar results to this review for face masks. In a meta-analysis comparing surgical masks with N95 respirators, Smith 2016 pooled three trials (Loeb 2009; MacIntyre 2011; MacIntyre 2013), and found an estimate of effect suggesting no difference for laboratory-confirmed respiratory infections (OR 0.89, 95% CI 0.64 to 1.24) or ILI (OR 0.51, 95% CI 0.19 to 1.41). A similar meta-analysis, Offeddu 2017, based on two trials, MacIntyre 2011; MacIntyre 2015, concluded that masks (either N95/P2 respirators or medical/surgical masks) were effective against clinical respiratory infections (RR 0.59, 95% CI 0.46 to 0.77) and ILI (RR 0.34, 95% CI 0.14 to 0.82). Pooling of two studies, MacIntyre 2011; MacIntyre 2013, also found an estimate of effect that favoured N95 respirators to medical/surgical masks for clinical respiratory infections (RR 0.47, 95% CI 0.36 to 0.62), but not for ILI based on three studies, Loeb 2009: MacIntyre 2011; MacIntyre 2013 (RR 0.59, 95% CI 0.27 to 1.28) (Offeddu 2017). The outcome of clinical respiratory infection is considered to be the most subjective and least precise outcome.

A recent meta-analysis included five trials comparing N95/P2 respirators with medical/surgical masks and found no difference between groups for either influenza (RR 1.09, 95% CI 0.92 to 1.28) or respiratory viral infections (RR 0.89, 95% CI 0.70 to 1.11) (Long 2020). By excluding Loeb 2009 (an open, non-inferiority RCT that compared surgical masks with N95 respirators in protecting HCWs against influenza), the authors reported a significant protective effect against viral infections (RR 0.61, 95% CI 0.39 to 0.98). The authors do not report a rationale for the exclusion in the sensitivity analysis and do not report on exclusion of the studies with low weighting, which arguably would be more relevant in a sensitivity analysis. The two trials that make up 96% of the weighting, Loeb 2009; Radonovich 2019, demonstrated no significant differences in the outcome events. A recent meta-analysis of four RCTs (Bartoszko 2020), adjusting for clustering, which compared N95 respirators with the use of medical masks, found pooled estimates of effect that did not demonstrate any difference in any laboratory-confirmed viral respiratory infection

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(OR 1.06, 95% CI 0.90 to 1.25), laboratory-confirmed influenza (OR 0.94, 95% CI 0.73 to 1.20), or clinical respiratory illness (OR 1.49, 95% CI 0.98 to 2.28), with the evidence profile suggesting that there was greater imprecision and inconsistency in the outcome of clinical respiratory illness. Moreover, in another recent systematic review that assessed the effectiveness of personal protective and environmental measures in non-healthcare settings (funded by the WHO), 10 RCTs reporting estimates of the effectiveness of face masks in reducing laboratory-confirmed influenza virus infections in the community were identified (Xiao 2020). The evidence from these RCTs suggested that the use of face masks either by infected persons or by uninfected persons does not have a substantial effect on influenza transmission.

The findings from several systematic reviews and meta-analyses over the last decade have not demonstrated any difference in the clinical effectiveness of N95 respirators or equivalent compared to the use of surgical masks when used by HCWs in multiple healthcare settings for the prevention of respiratory virus infections, including influenza.

Reviews based on observational studies have usually found a stronger protective effect for face masks, but have important biases. The review by Chu 2020 did not consider RCTs of influenza transmission, but only the observational studies examining impact on SARS, MERS, or SARS-CoV-2. For N95 masks versus no mask in HCWs, there was a large protective effective with an OR of 0.04 (95% CI 0.004 to 0.30); for surgical masks versus no masks, there was an OR of 0.33 (0.17 to 0.61) overall, but four of these studies were in healthcare settings. Chu 2020 has been criticised for several reasons: use of an outdated 'Risk of bias' tool; inaccuracy of distance measures; and not adequately addressing multiple sources of bias, including recall and classification bias and in particular confounding. Confounding is very likely, as preventive behaviours such as mask use, social distancing, and hand hygiene are correlated behaviours, and hence any effect estimates are likely to be overly optimistic.

Also based on observational studies, Jefferson 2011 found a protective effect of wearing surgical masks with hygienic measures compared to not wearing masks in the SARS 2003 outbreak (OR 0.32, 95% CI 0.26 to 0.39). However, the evidence was based on case-control studies carried out during the outbreak. There was some additional but very limited supportive evidence from the cohort studies in Jefferson 2011.

Although the use of eye protection and physical distancing measures are widely believed to be effective in reducing transmission of respiratory viruses and mitigating the impact of an influenza pandemic, we found only one trial investigating the role of self-quarantine in reducing the incidence of H1N1 influenza events in the workplace, and no trials examining the effect of eye protection. The evidence for these measures was derived largely from observational studies and simulation studies, and the overall quality of supporting evidence is relatively low. The finding of limited evidence evaluating these interventions was also consistent with a recent review funded by the WHO for the preparation of its guidelines on the use of non-pharmaceutical interventions for pandemic influenza in non-medical settings (Fong 2020).

There are several previous systematic reviews on hand hygiene and respiratory infections. Five of them reviewed the evidence in a community setting (Moncion 2019; Rabie 2006; Saunders-Hastings 2017; Warren-Gash 2013: Wong 2014), and three focused on children (Mbakaya 2017; Willmott 2016; Zivich 2018). The earliest review in 2006 included eight studies (Rabie 2006), three of which were RCTs. The pooled estimate of seven studies was described as “indicative” of the effect of hand hygiene, but the studies were of poor quality. The Warren-Gash 2013 review included 16 studies (10 of which were RCTs) and reported mixed and inconclusive results. A 2014 review identified 10 RCTs and reported that the combination of hand hygiene with face masks in high-income countries (five trials) significantly reduced the incidence of laboratory-confirmed influenza and ILI, whilst hand hygiene alone did not (Wong 2014). This significant reduction in laboratory-confirmed influenza and ILI for hand hygiene and face masks may have been based on the raw numbers without adjusting for any clustering effects in the included cluster trials, which produced inappropriately narrow CIs, and possibly biased treatment effect estimates. Moreover, trials from the low-income countries were not included in the review, and this significant effect was not demonstrated when all the trials identified in the review were combined. The Saunders-Hastings 2017 review of studies evaluating the effectiveness of personal protective measures in interrupting pandemic influenza transmission only identified two RCTs (Azor-Martinez 2014; Suess 2012), which reported a significant effect of hand hygiene. The Moncion 2019 review identified seven RCTs of hand hygiene compared to control, with mixed results for preventing the transmission of laboratory-confirmed or possible influenza. Systematic reviews of RCTs of hand hygiene interventions amongst children, Mbakaya 2017; Willmott 2016, or at a non-clinical workplace, Zivich 2018, identified heterogeneous trials with quality problems including small numbers of clusters and participants, inadequate randomisation, and self-reported outcomes. Evidence of impact on respiratory infections was equivocal.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence summarised in this review on the use of masks is largely based on studies conducted during traditional peak respiratory virus infection seasons up until 2016. We will incorporate relevant published studies in COVID-19 when their results are available. The observed lack of effect of mask wearing in interrupting the spread of ILI or influenza in our review has many potential reasons, including: poor study design; insufficiently powered studies arising from low viral circulation in some studies; lower compliance with mask wearing, especially among children; quality of the masks used; self-contamination of the mask by hands; lack of protection from eye exposure from respiratory droplets (allowing a route of entry of respiratory viruses into the nose via the lacrimal duct); saturation of masks with saliva from extended use (promoting virus survival in proteinaceous material); and risk compensation behaviour leading to an exaggerated sense of security (Brosseau 2020; Canini 2010; Cassell 2006; MacIntyre 2015; Rengasamy 2010; Zamora 2006).

Our findings show that hand hygiene has a modest effect as a physical intervention to interrupt the spread of respiratory viruses, but several questions remain. First, the high heterogeneity between studies may suggest that there are differences in the effect of different interventions. The poor reporting limited our ability to extract the information needed to assess any 'dose response'

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relationship, and there are few head-to-head trials comparing hand hygiene materials (such as alcohol-based sanitiser or soap and water). Second, the sustainability of hand hygiene is unclear where participants in some studies achieved 5 to 10 hand-washings per day, but compliance may have diminished with time as motivation decreased, or due to adverse effects from frequent hand-washing. Third, there is little evidence about the effectiveness of combinations of hand hygiene with other interventions, and how those are best introduced and sustained. Finally, some interventions were intensively implemented within small organisations, and involved education or training as a component, and the ability to scale these up to broader interventions is unclear.

Our findings with respect to hand hygiene should be considered generally relevant to all viral respiratory infections, given the diverse populations where transmission of viral respiratory infections occurs. The participants were adults, children and families, and multiple congregation settings including schools, childcare centres, homes, and offices. Most respiratory viruses, including the pandemic SARS-CoV-2, are considered to be predominantly spread via respiratory droplets or contact routes, or both (WHO 2020c). Data from studies of SARS-CoV-2 contamination of the environment based on the presence of viral ribonucleic acid (RNA) suggest significant fomite contamination from the virus (Ong 2020; Wu 2020). Hand hygiene would be expected to be beneficial in reducing the spread of SARS-CoV-2 similar to other beta coronaviruses (SARS-CoV-1, Middle East respiratory syndrome (MERS), and human coronaviruses), which are very susceptible to the concentrations of alcohol commonly found in most hand sanitiser preparations (Rabenau 2005; WHO 2020c). Support for this effect is the finding that poor hand hygiene, despite the use of full PPE, was independently associated with an increased risk of SARS-CoV-2 transmission to healthcare workers in a retrospective cohort study in Wuhan, China in both a high-risk and low-risk clinical unit for patients infected with COVID-19 (Ran 2020). The practice of hand hygiene appears to have a consistent effect in all settings, and should be an essential component of other interventions.

The highest-quality cluster-RCTs indicate that the most effect on preventing respiratory virus spread from hygienic measures occurs in younger children. This may be because younger children are least capable of hygienic behaviour themselves (Roberts 2000), and have longer-lived infections and greater social contact, thereby acting as portals of infection into the household (Monto 1969). Additional benefit from reduced transmission from them to other members of the household is broadly supported by the results of other study designs where the potential for confounding is greater.

Routine long-term implementation of some of the interventions covered in this review may be problematic, particularly maintaining strict hygiene and barrier routines for long periods of time. This would probably only be feasible in highly motivated environments, such as hospitals. Many of the trial authors commented on the major logistical burdens that barrier routines imposed at the community level. However, the threat of a looming epidemic may provide stimulus for their inception.

Implications for research

Public health measures and physical interventions can be highly effective to interrupt the spread of respiratory viral infections, especially when they are part of a structured and co-ordinated programme that includes instruction and education, and when they are delivered together. Our review has provided important insights into research gaps that need to be addressed with respect to these physical interventions and their implementation. The 2014 WHO document 'Infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care' identified several research gaps as part of their GRADE assessment of their infection prevention and control recommendations, which remain very relevant (WHO 2014). Research gaps identified during the course of our review and the WHO 2014 document may be considered from the perspective of both general and specific themes.

A general theme identified was the need to provide outcomes with explicitly defined clinical criteria for acute respiratory infections (ARIs) and discrete laboratory-confirmed outcomes of viral ARIs using molecular diagnostic tools which are now widely available. Our review found large disparities between studies with respect to the clinical outcome events, which were imprecisely defined in several studies, and there were differences in the extent to which laboratory-confirmed viruses were included in the studies that assessed them. Another general theme identified was the lack of consideration of sociocultural factors that might affect compliance with the interventions, especially those employed in the community setting. In addition, the cost and resource implications of the physical interventions employed in different settings would have important relevance for low- to middle-income countries. Resources have been a major issue with the COVID-19 pandemic, with global shortages of several components of PPE. Several specific research gaps related to physical interventions were identified within the WHO 2014 document and are congruent with many of the findings of our current update, including the following: transmission dynamics of respiratory viruses from patients to healthcare workers during aerosol-generating procedures; a lack of precision with regards to defining aerosol-generating procedures; the safety of cohorting of patients with the same suspected but unconfirmed diagnosis in a common unit or ward with patients infected with the same known pathogen in healthcare settings; the optimal duration of the use of physical interruptions to prevent spread of ARI viruses; use of spatial separation or physical distancing (in healthcare and community settings, respectively) alone versus spatial separation or physical distancing with the use of other added physical interventions coupled with examining discrete distance parameters (e.g. 1 metre, 2 metres, or > 2 metres); the effectiveness of respiratory etiquette (i.e. coughing/sneezing into tissues or a sleeved bent elbow); the effectiveness of triage and early identification of infected individuals with an ARI in both hospital and community settings; use of frequent disinfection techniques appropriate to the setting (high-touch surfaces in the environment, gargling with oral disinfectants, and virucidal tissues or clothing) alone or in combination with facial masks and hand hygiene; the use of ultraviolet light germicidal irradiation for disinfection of air in healthcare and selected community settings; and the use of widespread compliance with effective vaccination strategies.

There is a clear requirement to conduct large, pragmatic trials to evaluate the best combinations in the community and in healthcare settings with multiple respiratory viruses and in different sociocultural settings. RCTs with a pragmatic design, similar to the Luby 2005 trial, should be conducted whenever possible. Alternately, large population-based cohort studies may

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also be considered if individual RCTs prove to be too expensive or less practical, depending on the issue that is being addressed.

Several specific research gaps deserve expedited attention and may be highlighted within the context of the COVID-19 pandemic. The use of facial masks in the community setting represents one of the most pressing needs to address, given the polarised opinions around the world. Both broad-based ecological studies, adjusting for confounding and high-quality randomised trials, may be necessary to determine if there is an independent contribution to their use as a physical intervention, and how they may best be deployed to optimise their contribution. The type of fabric and weave used in the face mask is an equally pressing concern, given that surgical masks with their cotton-polypropylene fabric appear to be effective in the healthcare setting, but there are questions about the effectiveness of simple cotton masks. In addition, these masking intervention studies should focus on measuring not only benefits but also compliance, harms, and risk compensation if the latter may lead to a lower protective effect. In addition, although the use of surgical masks versus N95 respirators demonstrates no differences in clinical effectiveness to date, their use needs to be studied in the setting of a new pandemic such as COVID-19, and with concomitant measurement of harms, which to date have been poorly studied. Physical distancing represents another major research gap which needs to be addressed expediently, especially within the context of the COVID-19 pandemic setting as well as in future epidemic settings. The use of quarantine and screening at entry ports needs to be investigated in well-designed, high-quality studies. We found only one RCT of quarantine, and no trials of screening at entry ports or physical distancing. Given that this is one of the primary strategies applied globally in the face of the COVID-19 pandemic, future trials should be conducted within the context of this pandemic, as well as in future epidemics with other respiratory viruses of less virulence.

The variable quality and small scale of some studies is known from descriptive studies (Aiello 2002; Fung 2006; WHO 2006b), and systematic reviews of selected interventions (Meadows 2004). In summary, more high-quality studies are needed to evaluate the most effective strategies to implement successful physical interventions in practice, both on a small scale and at a population level. Finally, we emphasise that more attention should be paid to describing and quantifying the harms of the interventions assessed in this review and their relationship with compliance.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aelami 2015

Study characteristics	
Methods	A prospective cross-sectional study conducted during the Hajj season 2012. Pilgrims were randomised into 2 groups. The intervention group received education on personal hygiene including a hygienic package containing alcohol-based hand rub (gel or spray), surgical masks, soap, paper handkerchiefs, and user instructions; the control group did not receive any intervention. ILI was defined as the presence of at least 2 of the following during their stay: fever, cough, and sore throat. Questionnaires including demographic and clinical information were distributed amongst trained physicians before departure from Iran.
Participants	Total enrolled: 664 Iranian pilgrims (306 in the intervention group and 358 in the control group) Inclusion criteria: not reported Exclusion criteria: not reported

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Aelami 2015 *(Continued)*

Interventions	Hygiene education and package. See Table 1 for details.
Outcomes	ILI defined as the presence of at least 2 of the following during their stay: fever, cough, and sore throat. No safety outcomes were reported.
Notes	This is an abstract, therefore few details were reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details provided
Allocation concealment (selection bias)	Unclear risk	Insufficient details provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details provided
Selective reporting (reporting bias)	Unclear risk	Insufficient details provided

Aiello 2010

Study characteristics

Methods	Cluster-RCT assessing the effects of hand sanitiser and masks versus masks or no intervention on ILI symptoms. The trial was conducted in university halls of residence with more than 100 student residents in a US university during the 2006 to 2007 influenza "season". The study lasted 6 weeks. The units of randomisation were 7 of the 15 halls. 1 hall was very large (1240 residents), and the 6 remaining ones, which had between 110 and 830 residents, were combined into 2 clusters roughly equivalent in size. The 3 clusters were then randomised by random extraction of the clustered halls' names out of a container. The largest hall (single-cluster) was randomised to the mask and hand sanitiser arm; the 4-halls cluster received masks; and the remaining 2 halls were assigned as controls.
Participants	A total of 1297 with completed baseline survey and at least 1 weekly survey result were analysed (face mask and hand hygiene group = 367; face mask–only group = 378; control group = 552). Inclusion criteria: aged 18 or more, willing to wear mask and use alcohol-based hand sanitiser, have a throat swab specimen collected when ill, and complete the baseline and weekly surveys over the 6-week study period Exclusion criteria: individuals reporting a skin allergy to alcohol were excluded

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Aiello 2010 *(Continued)*

	Recruitment of students began in 26 November, but the trial did not go "live" with distribution of intervention materials until 22 January 2007 when the first case of influenza was confirmed on campus by laboratory tests. Enrolment continued until 16 February 2007, and the study was completed on 16 March 2007. During the study period there was a 1-week break when the majority of residents left campus. There were 1327 eligible participants, 1297 of which had a complete baseline survey and at least 1-weekly survey result. It is unclear what the ineligibility criteria were for the 30 missing (1327 minus 1297), but the explanation may be in the appendix.
Interventions	Alcohol-based hand sanitiser (62% ethyl alcohol in a gel base) in a squeeze bottle and TECNOL procedure masks with ear loops (KC Ltd) and educational material or masks and educational material or no intervention. Compliance was encouraged within halls and outside. Sleep wearing was optional. All participants received basic video-linked instruction on cough etiquette and hand sanitation. At baseline and weekly during the study, participants were asked to fill in a web-based survey collecting demographic and ILI symptom data. This was supplemented by direct observation of compliance by staff. Compliance with "optimal handwashing" (at least 20 seconds 5 or more times a day) was significantly higher in the sanitiser-and-mask arm.
Outcomes	Laboratory details are described in appendix. Effectiveness: ILI, defined as cough and at least 1 constitutional symptom (fever/feverishness, chills, headache, myalgia). ILI cases were given contact nurses' phone numbers to record the illness and paid USD 25 to provide a throat swab. 368 participants had ILI, and 94 of these had a throat swab analysed by PCR. 10 of these were positive for influenza (7 for A and 3 for B). Safety: N/A
Notes	The authors conclude that "These findings suggest that face masks and hand hygiene may reduce respiratory illnesses in shared living settings and mitigate the impact of the influenza A (H1N1) pandemic". This conclusion is based on a significantly lower level of ILI incidence in the mask and hand sanitiser arm compared to the other 2 arms after adjustment for covariates (30% to 50% less in arm 1 compared to controls in the last 2 weeks of the study). Comparison with the ILI rate of the control arm may not be a reflection of the underlying rate of ILI because the intervention arm received instruction on hand sanitation and hand etiquette. The play of adjustments is unclear. The intracluster correlation coefficient is reported in the footer of Table 4. Its very small size suggests lack of clustering within halls. The role of spring break is mentioned in the Discussion, as are the results of this study compared to other studies included in our review (Cowling 2008 and MacIntyre 2009). The authors report that 147 of 1297 participants (11.3%) had ILI symptoms "at baseline" and were excluded from analysis. During the 6 weeks of the study, 368 of 1150 participants (32%) had ILI. This averages out at about 5% per week. It is unclear what the term "at baseline" means; presumably this means during the 2 to 3 weeks of participant enrolment. If this is so, the reason for the triggering of the interventions (tied to influenza isolation) are obscure, as the trial is supposedly about ILI, and an ILI outbreak was already under way "at baseline".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but sequence generation not reported
Allocation concealment (selection bias)	High risk	The residence hall units were randomised by blindly selecting a uniform ticket with the name of each hall out of a container (A.S.M. and A.A.) for randomisation assignment to each study arm.

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Aiello 2010 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition is reported as follows: 9, 11, and 19 ineligible and 26, 52, and 21 lost to follow-up (respectively by arm), for a total of 39 and 99 for each reason for attrition. In total, 1297 (97%) of 1331 participants completed a baseline and at least 1-weekly survey. The text reports an ITT analysis with only 1 ILI episode included by participant. No reasons for the attrition of participants and swab volunteers are reported (were the swabs taken from a random sample or not?).
Selective reporting (reporting bias)	High risk	There is no information on the causes of ILI other than the reporting on the 10 influenza PCR-positive swabs of 94 out of 368 students with ILI. This is a very low rate (and the Discussion confirms that the influenza season was mild), but investigation of the other known causes of ILI is not even mentioned in the text. This is especially important because stress, alcohol intake levels, and influenza vaccination were a significant predictor of ILI symptoms (Table 1). The reason for selective testing and/or reporting of influenza viruses tests over the other causes of ILI are unclear, especially as the study objective was focused on ILI. The text is also difficult to follow, weaving the reporting of ILI and influenza without a clear rationale.

Aiello 2012

Study characteristics	
Methods	During the 2007 to 2008 influenza season, 1111 students residing in university residence halls were cluster-randomised by residence house (N = 37) to either face mask and hand hygiene, face mask only, or control arms. Discrete time survival analysis using generalised models estimated rate ratios according to study arm, each week and cumulatively over the 6-week intervention period, for clinically verified ILI and laboratory-confirmed influenza A or B.
Participants	A total of 1187 young adults living in 37 residence halls, randomly assigned to 1 of 3 groups for 6 weeks: face mask use (n = 392), face masks with hand hygiene (n = 349), control (n = 370) Inclusion criteria: aged 18 or more, willing to wear mask and use alcohol-based hand sanitiser, have a throat swab specimen collected when ill, and complete the baseline and weekly surveys over the 6-week study period Exclusion criteria: individuals reporting a skin allergy to alcohol were excluded
Interventions	Participants were assigned to face mask and hand hygiene, face mask only, or control group during the study. See Table 1 for details.
Outcomes	Clinically verified ILI: case definition (presence of cough and at least 1 or more of fever/feverishness, chills, or body aches) Laboratory-confirmed influenza A or B. Throat swab specimens were tested for influenza A or B using RT-PCR.

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Aiello 2012 *(Continued)*

	No safety outcomes reported.
Notes	This study has the same trial registration number as the Aiello 2010 study; the study was funded by government and pharmaceutical industry.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generation of sequence described.
Allocation concealment (selection bias)	Low risk	All residence houses in each of the residence halls were randomised prior to the intervention implementation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding for study participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition low and similar in each group
Selective reporting (reporting bias)	Low risk	2 outcomes specified and reported.

Aiello 2010

Study characteristics

Methods	Cluster-RCT assessing the effects of hand sanitiser and masks versus masks or no intervention on ILI symptoms. The trial was conducted in university halls of residence with more than 100 student residents in a US university during the 2006 to 2007 influenza "season". The study lasted 6 weeks. The units of randomisation were 7 of the 15 halls. 1 hall was very large (1240 residents), and the 6 remaining ones, which had between 110 and 830 residents, were combined into 2 clusters roughly equivalent in size. The 3 clusters were then randomised by random extraction of the clustered halls' names out of a container. The largest hall (single-cluster) was randomised to the mask and hand sanitiser arm; the 4-halls cluster received masks; and the remaining 2 halls were assigned as controls.
Participants	A total of 1297 with completed baseline survey and at least 1 weekly survey result were analysed (face mask and hand hygiene group = 367; face mask–only group = 378; control group = 552). Inclusion criteria: aged 18 or more, willing to wear mask and use alcohol-based hand sanitiser, have a throat swab specimen collected when ill, and complete the baseline and weekly surveys over the 6-week study period Exclusion criteria: individuals reporting a skin allergy to alcohol were excluded Recruitment of students began in 26 November, but the trial did not go "live" with distribution of intervention materials until 22 January 2007 when the first case of influenza was confirmed on campus by laboratory tests. Enrolment continued until 16 February 2007, and the study was completed on 16 March 2007. During the study period there was a 1-week break when the majority of residents left cam-

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Aiello 2010 *(Continued)*

	pus. There were 1327 eligible participants, 1297 of which had a complete baseline survey and at least 1-weekly survey result. It is unclear what the ineligibility criteria were for the 30 missing (1327 minus 1297), but the explanation may be in the appendix.
Interventions	Alcohol-based hand sanitiser (62% ethyl alcohol in a gel base) in a squeeze bottle and TECNOL procedure masks with ear loops (KC Ltd) and educational material or masks and educational material or no intervention. Compliance was encouraged within halls and outside. Sleep wearing was optional. All participants received basic video-linked instruction on cough etiquette and hand sanitation. At baseline and weekly during the study, participants were asked to fill in a web-based survey collecting demographic and ILI symptom data. This was supplemented by direct observation of compliance by staff. Compliance with "optimal handwashing" (at least 20 seconds 5 or more times a day) was significantly higher in the sanitiser-and-mask arm.
Outcomes	Laboratory details are described in appendix. Effectiveness: ILI, defined as cough and at least 1 constitutional symptom (fever/feverishness, chills, headache, myalgia). ILI cases were given contact nurses' phone numbers to record the illness and paid USD 25 to provide a throat swab. 368 participants had ILI, and 94 of these had a throat swab analysed by PCR. 10 of these were positive for influenza (7 for A and 3 for B). Safety: N/A
Notes	The authors conclude that "These findings suggest that face masks and hand hygiene may reduce respiratory illnesses in shared living settings and mitigate the impact of the influenza A (H1N1) pandemic". This conclusion is based on a significantly lower level of ILI incidence in the mask and hand sanitiser arm compared to the other 2 arms after adjustment for covariates (30% to 50% less in arm 1 compared to controls in the last 2 weeks of the study). Comparison with the ILI rate of the control arm may not be a reflection of the underlying rate of ILI because the intervention arm received instruction on hand sanitation and hand etiquette. The play of adjustments is unclear. The intracluster correlation coefficient is reported in the footer of Table 4. Its very small size suggests lack of clustering within halls. The role of spring break is mentioned in the Discussion, as are the results of this study compared to other studies included in our review (Cowling 2008 and MacIntyre 2009). The authors report that 147 of 1297 participants (11.3%) had ILI symptoms "at baseline" and were excluded from analysis. During the 6 weeks of the study, 368 of 1150 participants (32%) had ILI. This averages out at about 5% per week. It is unclear what the term "at baseline" means; presumably this means during the 2 to 3 weeks of participant enrolment. If this is so, the reason for the triggering of the interventions (tied to influenza isolation) are obscure, as the trial is supposedly about ILI, and an ILI outbreak was already under way "at baseline".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but sequence generation not reported
Allocation concealment (selection bias)	High risk	The residence hall units were randomised by blindly selecting a uniform ticket with the name of each hall out of a container (A.S.M. and A.A.) for randomisation assignment to each study arm.
Blinding of participants and personnel (performance bias)	High risk	Unblinded study

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Aiello 2010 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition is reported as follows: 9, 11, and 19 ineligible and 26, 52, and 21 lost to follow-up (respectively by arm), for a total of 39 and 99 for each reason for attrition. In total, 1297 (97%) of 1331 participants completed a baseline and at least 1-weekly survey. The text reports an ITT analysis with only 1 ILI episode included by participant. No reasons for the attrition of participants and swab volunteers are reported (were the swabs taken from a random sample or not?).
Selective reporting (reporting bias)	High risk	There is no information on the causes of ILI other than the reporting on the 10 influenza PCR-positive swabs of 94 out of 368 students with ILI. This is a very low rate (and the Discussion confirms that the influenza season was mild), but investigation of the other known causes of ILI is not even mentioned in the text. This is especially important because stress, alcohol intake levels, and influenza vaccination were a significant predictor of ILI symptoms (Table 1). The reason for selective testing and/or reporting of influenza viruses tests over the other causes of ILI are unclear, especially as the study objective was focused on ILI. The text is also difficult to follow, weaving the reporting of ILI and influenza without a clear rationale.

Aiello 2012

Study characteristics	
Methods	During the 2007 to 2008 influenza season, 1111 students residing in university residence halls were cluster-randomised by residence house (N = 37) to either face mask and hand hygiene, face mask only, or control arms. Discrete time survival analysis using generalised models estimated rate ratios according to study arm, each week and cumulatively over the 6-week intervention period, for clinically verified ILI and laboratory-confirmed influenza A or B.
Participants	A total of 1187 young adults living in 37 residence halls, randomly assigned to 1 of 3 groups for 6 weeks: face mask use (n = 392), face masks with hand hygiene (n = 349), control (n = 370) Inclusion criteria: aged 18 or more, willing to wear mask and use alcohol-based hand sanitiser, have a throat swab specimen collected when ill, and complete the baseline and weekly surveys over the 6-week study period Exclusion criteria: individuals reporting a skin allergy to alcohol were excluded
Interventions	Participants were assigned to face mask and hand hygiene, face mask only, or control group during the study. See Table 1 for details.
Outcomes	Clinically verified ILI: case definition (presence of cough and at least 1 or more of fever/feverishness, chills, or body aches) Laboratory-confirmed influenza A or B. Throat swab specimens were tested for influenza A or B using RT-PCR. No safety outcomes reported.

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Aiello 2012 *(Continued)*

Notes	This study has the same trial registration number as the Aiello 2010 study; the study was funded by government and pharmaceutical industry.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generation of sequence described.
Allocation concealment (selection bias)	Low risk	All residence houses in each of the residence halls were randomised prior to the intervention implementation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding for study participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition low and similar in each group
Selective reporting (reporting bias)	Low risk	2 outcomes specified and reported.

Alzaher 2018

Study characteristics

Methods	A cluster-RCT conducted amongst girls attending 4 primary schools between January and March 2018. The participants attended a hand hygiene workshop. The schoolgirls' absences were followed up for 5 weeks. Incidence rate, percentage of absence days, and absence rate were calculated for total and upper respiratory infections absences.
Participants	A total of 496 schoolgirls aged of 6 to 12 years, attending 4 public primary girls' schools in the city of Riyadh, Saudi Arabia between January and March 2018. Students were randomised to education group (n = 234) or control group (n = 262). Exclusion criteria: not reported
Interventions	Hand hygiene workshop. See Table 1 for details.
Outcomes	Incidence rate, percentage of absence days, and absence rate were calculated for total and upper respiratory infections absences. The episode of URIs was defined as having 2 of the following symptoms for a day or 1 of the symptoms for 2 or more consecutive days: 1) a runny nose, 2) a stuffy or blocked nose or noisy breathing, 3) sneezing, 4) a cough, 5) a sore throat, and 6) feeling hot, having a fever or a chill. No safety outcomes reported.
Notes	Source of funding unclear

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Alzaher 2018 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail provided.
Allocation concealment (selection bias)	Low risk	Schools allocated prior to all schoolgirls attending selected schools were invited to participate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available

Arbogast 2016

Study characteristics	
Methods	A 13.5-month prospective cluster-RCT executed with alcohol-based hand sanitiser in strategic workplace locations and personal use (intervention group) and brief hand hygiene education (both groups). 4 years of retrospective data were collected for all participants.
Participants	Data for a total of 1183 participants were analysed (intervention group = 525, control group = 607). Inclusion criteria: all employees at 3 facilities who were 18 years of age or older, were enrolled in the company health insurance coverage, did not transfer between sites, and worked onsite full time (≥ 32 hours) were eligible for the study Exclusion criteria: not reported
Interventions	Alcohol-based hand sanitiser in strategic workplace locations and personal use (intervention group) and brief hand hygiene education (both groups). See Table 1 for details.
Outcomes	(1) The number of healthcare insurance claims, for a defined set of preventable illnesses, per participant per year, and (2) absenteeism, defined as the number of sick episodes per participant per year Claims based on ICD-9 codes No safety outcomes reported.
Notes	Industry funded; only 2 clusters (1 per group) included, hence study data not included in meta-analysis.
Risk of bias	

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Arbogast 2016 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition minimal and similar in 2 groups
Selective reporting (reporting bias)	Unclear risk	No protocol available

Arbogast 2016

Study characteristics	
Methods	A 13.5-month prospective cluster-RCT executed with alcohol-based hand sanitiser in strategic workplace locations and personal use (intervention group) and brief hand hygiene education (both groups). 4 years of retrospective data were collected for all participants.
Participants	Data for a total of 1183 participants were analysed (intervention group = 525, control group = 607). Inclusion criteria: all employees at 3 facilities who were 18 years of age or older, were enrolled in the company health insurance coverage, did not transfer between sites, and worked onsite full time (≥ 32 hours) were eligible for the study Exclusion criteria: not reported
Interventions	Alcohol-based hand sanitiser in strategic workplace locations and personal use (intervention group) and brief hand hygiene education (both groups). See Table 1 for details.
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Notes	Industry funded; only 2 clusters (1 per group) included, hence study data not included in meta-analysis.
Risk of bias	

Bias	Authors' judgement	Support for judgement

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Arbogast 2016 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition minimal and similar in 2 groups
Selective reporting (reporting bias)	Unclear risk	No protocol available

Azor-Martinez 2016

Study characteristics	
Methods	Randomised, controlled, and open study with an 8-month follow-up. The experimental group washed their hands with soap and water, together with using hand sanitiser, and the control group followed their usual handwashing procedures. Absenteeism rates due to URIs were compared between the 2 groups through a multivariate Poisson regression analysis. The per cent of days missed in both groups were compared with a z test.
Participants	A sample of 1341 (intervention group = 621, control group = 720) Inclusion criteria: children 4 to 12 years old, attending 5 state schools in Almeria (Spain) whose parents/guardians had signed an informed consent document Exclusion criteria: children who had any of the following chronic illnesses that predisposed them to infection: neoplasia, primary and secondary immunodeficiencies, cystic fibrosis, chronic treatment with high doses of steroids or immunosuppressants
Interventions	Hand-washing workshops of 2-hour duration. The experimental group washed their hands with soap and water together with using hand sanitiser, whilst the control group followed usual hand-washing procedures. See Table 1 for details.
Outcomes	Absenteeism rates due to URIs Per cent of days missed Respiratory illness was defined by 2 of the following symptoms during 1 day, or 1 of the symptoms for 2 consecutive days: (1) runny nose; (2) stuffy or blocked nose or noisy breathing; (3) cough; (4) feeling hot or feverish or having chills; (5) sore throat; or (6) sneezing. A school absenteeism case (episode) was defined as when a child failed to attend school due to an URI. Common infectious illnesses, such as conjunctivitis, and skin infections were not included. Other causes for absenteeism, such as doctors' appointments, family vacations, and accident injuries, were also excluded.

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Azor-Martinez 2016 *(Continued)*

	No safety outcomes reported.
Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random number table was used.
Allocation concealment (selection bias)	Low risk	Schools/classes allocated prior to children recruited.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition levels high and different in the 2 groups
Selective reporting (reporting bias)	Unclear risk	No protocol available

Azor-Martinez 2016

Study characteristics

Methods	Randomised, controlled, and open study with an 8-month follow-up. The experimental group washed their hands with soap and water, together with using hand sanitiser, and the control group followed their usual handwashing procedures. Absenteeism rates due to URIs were compared between the 2 groups through a multivariate Poisson regression analysis. The per cent of days missed in both groups were compared with a z test.
Participants	A sample of 1341 (intervention group = 621, control group = 720) Inclusion criteria: children 4 to 12 years old, attending 5 state schools in Almeria (Spain) whose parents/guardians had signed an informed consent document Exclusion criteria: children who had any of the following chronic illnesses that predisposed them to infection: neoplasia, primary and secondary immunodeficiencies, cystic fibrosis, chronic treatment with high doses of steroids or immunosuppressants
Interventions	Hand-washing workshops of 2-hour duration. The experimental group washed their hands with soap and water together with using hand sanitiser, whilst the control group followed usual hand-washing procedures. See Table 1 for details.
Outcomes	Absenteeism rates due to URIs Per cent of days missed

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Azor-Martinez 2016 *(Continued)*

	Respiratory illness was defined by 2 of the following symptoms during 1 day, or 1 of the symptoms for 2 consecutive days: (1) runny nose; (2) stuffy or blocked nose or noisy breathing; (3) cough; (4) feeling hot or feverish or having chills; (5) sore throat; or (6) sneezing. A school absenteeism case (episode) was defined as when a child failed to attend school due to an URI. Common infectious illnesses, such as conjunctivitis, and skin infections were not included. Other causes for absenteeism, such as doctors' appointments, family vacations, and accident injuries, were also excluded. No safety outcomes reported.
Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random number table was used.
Allocation concealment (selection bias)	Low risk	Schools/classes allocated prior to children recruited.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition levels high and different in the 2 groups
Selective reporting (reporting bias)	Unclear risk	No protocol available

Azor-Martinez 2018

Study characteristics

Methods	A cluster-RCT, controlled, and open study of 911 children aged 0 to 3 years attending 24 DCCs in Almería, Spain, with an 8-month follow-up. 2 intervention groups of DCC families performed educational and hand hygiene measures, 1 with soap and water (n = 274), another with hand sanitiser (n = 339), and the control group followed usual hand-washing procedures (n = 298). Respiratory infection (RI) episode rates were compared through multilevel Poisson regression models. The percentage of days missed were compared with Poisson exact tests.
Participants	A total of 911 children attending 24 DCCs in Almería (Spain). Inclusion criteria: children between 0 and 3 years old enrolled in DCCs and attending for at least 15 hours per week whose parents or guardians had signed an informed consent Exclusion criteria: children with chronic illness or medication that could affect their likelihood of contracting an infection

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Azor-Martinez 2018 *(Continued)*

	Data were analysed for 911 participants: hand sanitiser group (n = 339), soap and water group (n = 274), and control group (n = 298).
Interventions	2 intervention groups. 1 group used soap and water, another used hand sanitiser, whilst the control group followed usual hand-washing procedures. Groups received 1-hour hand hygiene workshop. See Table 1 for details.
Outcomes	Primary: RI incidence rate Secondary: (1) the presence or absence of at least 1 antibiotic prescription for each new RI episode during the study period (topical antibiotics were excluded), and (2) the percentage of RI absenteeism days in the 3 groups calculated as the ratio of RI absenteeism days to all possible days of attendance DCC absenteeism episode was defined as when a child failed to attend a DCC because of an RI. Respiratory illness was defined as the presence of 2 of the following symptoms during 1 day or the presence of 1 of the symptoms for 2 consecutive days: (1) runny nose, (2) stuffy or blocked nose or noisy breathing, (3) cough, (4) feeling hot or feverish or having chills, (5) sore throat, or (6) sneezing. No safety outcomes reported.
Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomisation using statistical software for the sequence
Allocation concealment (selection bias)	Low risk	Clusters assigned prior to recruitment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition minimal and similar in 3 groups
Selective reporting (reporting bias)	Unclear risk	No protocol available

Azor-Martinez 2018

Study characteristics

Methods	A cluster-RCT, controlled, and open study of 911 children aged 0 to 3 years attending 24 DCCs in Almería, Spain, with an 8-month follow-up. 2 intervention groups of DCC families performed educational and hand hygiene measures, 1 with soap and water (n = 274), another with hand sanitiser (n = 339), and the control group followed usual hand-washing procedures (n = 298). Respiratory infection (RI)

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Azor-Martinez 2018 *(Continued)*

	episode rates were compared through multilevel Poisson regression models. The percentage of days missed were compared with Poisson exact tests.
Participants	A total of 911 children attending 24 DCCs in Almería (Spain). Inclusion criteria: children between 0 and 3 years old enrolled in DCCs and attending for at least 15 hours per week whose parents or guardians had signed an informed consent Exclusion criteria: children with chronic illness or medication that could affect their likelihood of contracting an infection Data were analysed for 911 participants: hand sanitiser group (n = 339), soap and water group (n = 274), and control group (n = 298).
Interventions	2 intervention groups. 1 group used soap and water, another used hand sanitiser, whilst the control group followed usual hand-washing procedures. Groups received 1-hour hand hygiene workshop. See Table 1 for details.
Outcomes	Primary: RI incidence rate Secondary: (1) the presence or absence of at least 1 antibiotic prescription for each new RI episode during the study period (topical antibiotics were excluded), and (2) the percentage of RI absenteeism days in the 3 groups calculated as the ratio of RI absenteeism days to all possible days of attendance DCC absenteeism episode was defined as when a child failed to attend a DCC because of an RI. Respiratory illness was defined as the presence of 2 of the following symptoms during 1 day or the presence of 1 of the symptoms for 2 consecutive days: (1) runny nose, (2) stuffy or blocked nose or noisy breathing, (3) cough, (4) feeling hot or feverish or having chills, (5) sore throat, or (6) sneezing. No safety outcomes reported.
Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomisation using statistical software for the sequence
Allocation concealment (selection bias)	Low risk	Clusters assigned prior to recruitment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition minimal and similar in 3 groups
Selective reporting (reporting bias)	Unclear risk	No protocol available

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Ban 2015

Study characteristics	
Methods	"Group randomised" trial. Only 2 clusters, which were 2 kindergartens in Xiantao City, Hubei Province, China
Participants	Data for a total of 393 participants were analysed (intervention group = 194, control group = 199). 5 classes (221 children) randomly selected from 1 kindergarten in the intervention group and 6 classes (244 children) randomly selected from another kindergarten in the control group. Children were aged 5 or under. There were 72 exclusions from the analysis.
Interventions	Intervention group: hand hygiene and surface-cleaning education and provision of products for kindergarten and home use. Control group: usual practice. See Table 1 for details.
Outcomes	Respiratory illness, defined as: 2 or more of the following: fever, cough and expectoration, runny nose and nasal congestion, collected by parental questionnaire. Axillary temperature higher than 37.3 °C or the range of temperature fluctuation is more than 1 °C. 'Cough and expectoration' were defined as 3 or more coughs in a single hour and lasting for 4 or more hours in a single day, with or without expectoration. 'Runny nose and nasal congestion' were defined as a runny nose lasting for 4 or more hours in 1 day, with or without nasal congestion.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Method not described, and only 2 clusters.
Allocation concealment (selection bias)	Unclear risk	Method not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	Parental report, and parents were aware of treatment allocation
Selective reporting (reporting bias)	High risk	Attrition reported and balanced between groups, but high rate of attrition in a trial with small numbers of participants.

Ban 2015

Study characteristics

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Ban 2015 *(Continued)*

Methods	"Group randomised" trial. Only 2 clusters, which were 2 kindergartens in Xiantao City, Hubei Province, China
Participants	Data for a total of 393 participants were analysed (intervention group = 194, control group = 199). 5 classes (221 children) randomly selected from 1 kindergarten in the intervention group and 6 classes (244 children) randomly selected from another kindergarten in the control group. Children were aged 5 or under. There were 72 exclusions from the analysis.
Interventions	Intervention group: hand hygiene and surface-cleaning education and provision of products for kindergarten and home use. Control group: usual practice. See Table 1 for details.
Outcomes	Respiratory illness, defined as: 2 or more of the following: fever, cough and expectoration, runny nose and nasal congestion, collected by parental questionnaire. Axillary temperature higher than 37.3 °C or the range of temperature fluctuation is more than 1 °C. 'Cough and expectoration' were defined as 3 or more coughs in a single hour and lasting for 4 or more hours in a single day, with or without expectoration. 'Runny nose and nasal congestion' were defined as a runny nose lasting for 4 or more hours in 1 day, with or without nasal congestion.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method not described, and only 2 clusters.
Allocation concealment (selection bias)	Unclear risk	Method not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	Parental report, and parents were aware of treatment allocation
Selective reporting (reporting bias)	High risk	Attrition reported and balanced between groups, but high rate of attrition in a trial with small numbers of participants.

Barasheed 2014

Study characteristics

Methods	Pilot, non-blinded, parallel, cluster-RCT
Participants	22 tents were randomly selected from the Australian pilgrims camped in Mina, during Hajj in 2011; 12 tents were allocated to the mask group and 10 tents to the control group. A total of 164 Australian pil-

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Barasheed 2014 *(Continued)*

	grims were recruited: 75 in the mask group (39 'cases' and 36 'contacts') and 89 in the control group (36 'cases' and 53 'contacts'). Inclusion criteria for index case: 1) Australian pilgrims of any gender aged > 15 years who attend the Hajj 2011, and 2) have symptoms of respiratory infection for 3 days. For close tent contact: 1) Australian pilgrims of any gender aged 15 years or more who attend the Hajj 2011, and 2) pilgrims who share the same tent and sleep "immediately close" to the index case. Exclusion criteria: for index case: 1) pilgrims who do not suffer from symptoms of respiratory infection, 2) pilgrims who present with symptoms of respiratory infection for > 3 days, and 3) children aged less than 15 years. For close tent contact: 1) pilgrims who are symptomatic at presentation, 2) pilgrims who are not close tent contacts of an index case, and 3) children aged less than 15 years. Only 10% to 15% of potential participants took part in the study.
Interventions	"supervised mask use" versus "no supervised mask use". See Table 1 for details.
Outcomes	Laboratory: 2 nasal swabs from all ILI cases and contacts, 1 for influenza POCT using the QuickVue Influenza (A+B) assay (Quidel Corporation, San Diego, USA) and 1 for later nucleic acid testing for influenza and other respiratory viruses. However, there was a problem with getting POCT on time during Hajj. Effectiveness: to assess the effectiveness of face masks in the prevention of transmission of ILI. ILI was defined as subjective (or proven) fever plus 1 respiratory symptom (e.g. dry or productive cough, runny nose, sore throat, shortness of breath). Safety: none planned or reported
Notes	The study was conducted from 4 November 2011 to 10 November 2011. Funding: government (Qatar National Research Fund (QNRF)) Compliance with face mask use by pilgrims was 56 of 75 (76%) in the mask group and 11 of 89 (12%) in the control group (P < 0.001). The proportion of face mask user in the 'mask' tents was 76% for both males (19/25) and females (38/50). The most often reported reason for not wearing face masks was discomfort (15%).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided.
Allocation concealment (selection bias)	Unclear risk	"tents were randomised to either intervention group (supervised mask tent) or control group (no supervised mask tent) by an independent study coordinator who was not an investigator", but did not mention how
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Because advice from the Saudi Ministry of Hajj to all pilgrims included recommending the wearing of masks, all pilgrims, both cases and controls, were asked about mask-wearing"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes (nasal swab was performed for those who reported ILI symptoms and was not intended as systematic detection). ILI was defined as subjective (or proven) fever plus 1 respiratory symptom.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up, all numbers were reported from enrolment to analysis

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Barasheed 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.

Barasheed 2014

Study characteristics	
Methods	Pilot, non-blinded, parallel, cluster-RCT
Participants	22 tents were randomly selected from the Australian pilgrims camped in Mina, during Hajj in 2011; 12 tents were allocated to the mask group and 10 tents to the control group. A total of 164 Australian pilgrims were recruited: 75 in the mask group (39 'cases' and 36 'contacts') and 89 in the control group (36 'cases' and 53 'contacts'). Inclusion criteria for index case: 1) Australian pilgrims of any gender aged > 15 years who attend the Hajj 2011, and 2) have symptoms of respiratory infection for 3 days. For close tent contact: 1) Australian pilgrims of any gender aged 15 years or more who attend the Hajj 2011, and 2) pilgrims who share the same tent and sleep "immediately close" to the index case. Exclusion criteria: for index case: 1) pilgrims who do not suffer from symptoms of respiratory infection, 2) pilgrims who present with symptoms of respiratory infection for > 3 days, and 3) children aged less than 15 years. For close tent contact: 1) pilgrims who are symptomatic at presentation, 2) pilgrims who are not close tent contacts of an index case, and 3) children aged less than 15 years. Only 10% to 15% of potential participants took part in the study.
Interventions	"supervised mask use" versus "no supervised mask use". See Table 1 for details.
Outcomes	Laboratory: 2 nasal swabs from all ILI cases and contacts, 1 for influenza POCT using the QuickVue Influenza (A+B) assay (Quidel Corporation, San Diego, USA) and 1 for later nucleic acid testing for influenza and other respiratory viruses. However, there was a problem with getting POCT on time during Hajj. Effectiveness: to assess the effectiveness of face masks in the prevention of transmission of ILI. ILI was defined as subjective (or proven) fever plus 1 respiratory symptom (e.g. dry or productive cough, runny nose, sore throat, shortness of breath). Safety: none planned or reported
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Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided.
Allocation concealment (selection bias)	Unclear risk	"tents were randomised to either intervention group (supervised mask tent) or control group (no supervised mask tent) by an independent study coordinator who was not an investigator", but did not mention how

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Barasheed 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Because advice from the Saudi Ministry of Hajj to all pilgrims included recommending the wearing of masks, all pilgrims, both cases and controls, were asked about mask-wearing"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Self-reported outcomes (nasal swab was performed for those who reported ILI symptoms and was not intended as systematic detection). ILI was defined as subjective (or proven) fever plus 1 respiratory symptom.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up, all numbers were reported from enrolment to analysis
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.

Biswas 2019

Study characteristics	
Methods	Cluster-RCT in 24 primary schools in Dhaka to assess the effectiveness of hand sanitiser and a respiratory hygiene education intervention in reducing ILI and laboratory-confirmed influenza during June to September 2015. 12 schools were randomly selected to receive hand sanitiser and respiratory hygiene education, and 12 schools received no intervention. Field staff actively followed children daily to monitor for new ILI episodes (cough with fever) through school visits and by phone if a child was absent. When an illness episode was identified, medical technologists collected nasal swabs to test for influenza viruses.
Participants	A total of 10,855 students were enrolled in the study (intervention schools = 5077 children; control schools = 5778 children). Children aged 5 to 10 years educated in 24 randomly selected primary schools in Dhaka, Bangladesh Exclusion: schools that offered education above grade 5 because of differences in student populations, as well as schools that had previously received a hand or respiratory hygiene intervention
Interventions	Hand sanitiser and respiratory hygiene education versus no intervention. See Table 1 for details.
Outcomes	Incidence of ILI Incidence of laboratory-confirmed influenza (RT-PCR) An ILI episode was defined as measured fever ≥ 38 °C or subjective fever and cough. If a child was absent, the field staff followed up by phone to identify the reason for absenteeism and to determine if the child met the ILI case definition. If a child in a participating school had an ILI episode, a trained medical technologist visited the child's household to obtain consent from the child's parent/guardian and collect a nasal swab from the child within 48 hours of symptom onset. If it was outside the 48-hour window, the sample was not collected. No safety outcomes reported.
Notes	Government funded
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

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Biswas 2019 *(Continued)*

Random sequence generation (selection bias)	Low risk	Sequence generated using a computer-based random number generator.
Allocation concealment (selection bias)	Low risk	Allocation completed prior to individuals being recruited.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	Information missing for 30 children (28 children in the control schools and 2 children in the intervention schools)
Selective reporting (reporting bias)	Unclear risk	No protocol available

Biswas 2019

Study characteristics	
Methods	Cluster-RCT in 24 primary schools in Dhaka to assess the effectiveness of hand sanitiser and a respiratory hygiene education intervention in reducing ILI and laboratory-confirmed influenza during June to September 2015. 12 schools were randomly selected to receive hand sanitiser and respiratory hygiene education, and 12 schools received no intervention. Field staff actively followed children daily to monitor for new ILI episodes (cough with fever) through school visits and by phone if a child was absent. When an illness episode was identified, medical technologists collected nasal swabs to test for influenza viruses.
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Biswas 2019 *(Continued)*

Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generated using a computer-based random number generator.
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Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
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Incomplete outcome data (attrition bias) All outcomes	High risk	Information missing for 30 children (28 children in the control schools and 2 children in the intervention schools)
Selective reporting (reporting bias)	Unclear risk	No protocol available

Canini 2010

Study characteristics

Methods	A cluster-RCT conducted in France during the 2008 to 2009 influenza season. Households were recruited during a medical visit of a household member with a positive rapid influenza A test and symptoms lasting less than 48 hours. Households were randomised either to the mask or control group for 7 days. In the intervention arm, the index case had to wear a surgical mask from the medical visit and for a period of 5 days. The trial was initially intended to include 372 households, but was prematurely interrupted after the inclusion of 105 households (306 contacts) following the advice of an independent steering committee. Generalised estimating equations were used to test the association between the intervention and the proportion of household contacts who developed an ILI during the 7 days following the inclusion.
Participants	A total of 105 households were randomised, which represented 148 contacts in the intervention arm and 158 in the control arm. The study was conducted in 3 French regions (Ile de France, Aquitaine, and Franche-Comté) and included households of size 3 to 8. Exclusion criteria: if index patient was treated for asthma or chronic obstructive pulmonary disease or was hospitalised
Interventions	Surgical mask versus no mask. See Table 1 for details.
Outcomes	The primary endpoint was the proportion of household contacts who developed an ILI during the 7 days following inclusion. Exploratory cluster-level efficacy outcome, the proportion of households with 1 or more secondary illness in household contacts.

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Canini 2010 *(Continued)*

	A temperature over 37.8 °C with cough or sore throat was used as primary clinical case definition. Adverse reactions due to mask-wearing
Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation lists were generated by a computerised program.
Allocation concealment (selection bias)	Low risk	Randomisation was performed centrally by the GP after written consent on an interactive voice response system dedicated to the study.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All households included in analysis.
Selective reporting (reporting bias)	Low risk	All specified outcomes reported.

Canini 2010

Study characteristics

Methods	A cluster-RCT conducted in France during the 2008 to 2009 influenza season. Households were recruited during a medical visit of a household member with a positive rapid influenza A test and symptoms lasting less than 48 hours. Households were randomised either to the mask or control group for 7 days. In the intervention arm, the index case had to wear a surgical mask from the medical visit and for a period of 5 days. The trial was initially intended to include 372 households, but was prematurely interrupted after the inclusion of 105 households (306 contacts) following the advice of an independent steering committee. Generalised estimating equations were used to test the association between the intervention and the proportion of household contacts who developed an ILI during the 7 days following the inclusion.
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Canini 2010 *(Continued)*

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Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
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Incomplete outcome data (attrition bias) All outcomes	Low risk	All households included in analysis.
Selective reporting (reporting bias)	Low risk	All specified outcomes reported.

Carabin 1999

Study characteristics

Methods	Cluster-RCT carried out in DCCs in the Canadian province of Quebec between 1 September 1996 and 30 November 1997 (15 months). The aim was to test the effects of a hygiene programme on the incidence of diarrhoea and fecal contamination (data not extracted) and on colds and URTIs. The design included before and after periods analysed to assess the Hawthorne effect of study participation on control DCCs. The unit of randomisation was DCC, but analysis was also carried out at classroom and single-child level. This is a common mistake in cluster-RCT analysis. DCCs were stratified by URTI incidence preceding the trial and randomised by location. Cluster coefficients are not reported.
Participants	A total of 1729 children aged 18 to 36 months in 47 DCCs (83 toddler classrooms) Inclusion criteria: presence of at least 1 sandbox and 1 play area and of at least 12 available toddler places For the autumn of 1997 intervention group (24 DCCs, 43 classrooms, and 414 children), control group (23 DCCs, 23 classrooms, and 374 children). It is not clear what is the distribution and data for the autumn of 1996.

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Carabin 1999 *(Continued)*

Interventions	Training session (1 day) with washing of hands, toy cleaning, window opening, sand pit cleaning, and repeated exhortations to hand wash
Outcomes	Laboratory: N/A Effectiveness: diarrhoea and coliform contamination (data not extracted) Colds (nasal discharge with at least 1 of the following: fever, sneezing, cough, sore throat, earache, malaise, irritability) URTI (cold of at least 2 days' duration) Surveillance was carried out by educators, annotating absences or illness on calendars. Researchers also filled in a phone questionnaire with answers by DCC directors. Safety: N/A
Notes	Risk of bias: high (no description of randomisation; partial reporting of outcomes, numerators, and denominators) Notes: the authors conclude that the intervention reduced the incidence of colds (IRR 0.80, 95% CI 0.68 to 0.93). This was a confusingly written study with unclear interweaving of 2 study designs. For unclear reasons analysis was only carried out for the first autumn. Unclear why colds are not reported in the results. Cluster-coefficients and randomisation process were not described.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Block randomisation of DCC according to region, but sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not possible (hygiene session plus educational material versus none)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Originally 52 eligible DCCs with 89 classrooms agreed to take part, but 5 dropped out (2 closed, 1 was sold, 2 either did not provide data or the data were "unreliable", and 6 classrooms had insufficient data). 43 children failing to attend DCC for at least 5 days in the autumn were also excluded. ITT analysis was carried out including an additional DCC whose director refused to let staff attend the training session. No correction made for clustering.
Selective reporting (reporting bias)	High risk	Denominators unclear and not explained

Chard 2019

Study characteristics

Methods	Cluster-RCT conducted amongst 100 randomly selected primary schools lacking functional WASH facilities in Saravane Province, Lao People's Democratic Republic. Schools were randomly assigned to either

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Chard 2019 *(Continued)*

	the intervention (n = 50) or comparison (n = 50) arm. Intervention schools received a school water supply, sanitation facilities, hand-washing facilities, drinking water filters, and behaviour change education and promotion. Comparison schools received the intervention after research activities had ended. At unannounced visits every 6 to 8 weeks, enumerators recorded pupils' roll-call absence, enrolment, attrition, progression to the next grade, and reported illness (diarrhoea, respiratory infection, conjunctivitis), and conducted structured observations to measure intervention fidelity and adherence. Stool samples were collected annually prior to de-worming and analysed for soil-transmitted helminth (STH) infection. In addition to our primary ITT analysis, we conducted secondary analyses to quantify the role of intervention fidelity and adherence on project impacts.
Participants	100 primary schools (50 intervention, 50 comparison) with a total of 3993 pupils were enrolled throughout the study period (intervention schools = 2021 pupils, control schools = 1972 pupils). Up to 40 pupils selected from grades 3 to 5 in each school using systematic stratified sampling, with grade and sex as the stratification variables. Pupils selected at baseline were followed throughout the entire study period; pupils who left the school due to abandonment or transfer were replaced at the beginning of the following academic year, maintaining equal grade and sex ratios when possible. Pupils who progressed from fifth to the sixth grade were replaced with pupils from grade 3 the following academic year.
Interventions	Water supply, sanitation facilities, hand-washing facilities, drinking water filters, and behaviour change education and promotion versus control. See Table 1 for details.
Outcomes	Primary impact of interest was pupil absence, measured by school-wide roll-call at each visit. Secondary health impacts included diarrhoea, symptoms of respiratory infection, and conjunctivitis/non-vision-related eye illness collected through pupil interviews. Pupils were considered to have symptoms of respiratory infection if they reported cough, runny nose, stuffy nose, or sore throat. No safety outcomes reported.
Notes	Funded by government and pharmaceutical industry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details provided.
Allocation concealment (selection bias)	Low risk	Schools allocated prior to recruitment of individuals.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions were due to participants leaving school, hence unlikely to cause bias.
Selective reporting (reporting bias)	Low risk	All specified outcomes reported.

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Carabin 1999

Study characteristics	
Methods	Cluster-RCT carried out in DCCs in the Canadian province of Quebec between 1 September 1996 and 30 November 1997 (15 months). The aim was to test the effects of a hygiene programme on the incidence of diarrhoea and fecal contamination (data not extracted) and on colds and URTIs. The design included before and after periods analysed to assess the Hawthorne effect of study participation on control DCCs. The unit of randomisation was DCC, but analysis was also carried out at classroom and single-child level. This is a common mistake in cluster-RCT analysis. DCCs were stratified by URTI incidence preceding the trial and randomised by location. Cluster coefficients are not reported.
Participants	A total of 1729 children aged 18 to 36 months in 47 DCCs (83 toddler classrooms) Inclusion criteria: presence of at least 1 sandbox and 1 play area and of at least 12 available toddler places For the autumn of 1997 intervention group (24 DCCs, 43 classrooms, and 414 children), control group (23 DCCs, 23 classrooms, and 374 children). It is not clear what is the distribution and data for the autumn of 1996.
Interventions	Training session (1 day) with washing of hands, toy cleaning, window opening, sand pit cleaning, and repeated exhortations to hand wash
Outcomes	Laboratory: N/A Effectiveness: diarrhoea and coliform contamination (data not extracted) Colds (nasal discharge with at least 1 of the following: fever, sneezing, cough, sore throat, earache, malaise, irritability) URTI (cold of at least 2 days' duration) Surveillance was carried out by educators, annotating absences or illness on calendars. Researchers also filled in a phone questionnaire with answers by DCC directors. Safety: N/A
Notes	Risk of bias: high (no description of randomisation; partial reporting of outcomes, numerators, and denominators) Notes: the authors conclude that the intervention reduced the incidence of colds (IRR 0.80, 95% CI 0.68 to 0.93). This was a confusingly written study with unclear interweaving of 2 study designs. For unclear reasons analysis was only carried out for the first autumn. Unclear why colds are not reported in the results. Cluster-coefficients and randomisation process were not described.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Block randomisation of DCC according to region, but sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not possible (hygiene session plus educational material versus none)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded

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Carabin 1999 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Originally 52 eligible DCCs with 89 classrooms agreed to take part, but 5 dropped out (2 closed, 1 was sold, 2 either did not provide data or the data were "unreliable", and 6 classrooms had insufficient data). 43 children failing to attend DCC for at least 5 days in the autumn were also excluded. ITT analysis was carried out including an additional DCC whose director refused to let staff attend the training session. No correction made for clustering.
Selective reporting (reporting bias)	High risk	Denominators unclear and not explained

Chard 2019

Study characteristics	
Methods	Cluster-RCT conducted amongst 100 randomly selected primary schools lacking functional WASH facilities in Saravane Province, Lao People's Democratic Republic. Schools were randomly assigned to either the intervention (n = 50) or comparison (n = 50) arm. Intervention schools received a school water supply, sanitation facilities, hand-washing facilities, drinking water filters, and behaviour change education and promotion. Comparison schools received the intervention after research activities had ended. At unannounced visits every 6 to 8 weeks, enumerators recorded pupils' roll-call absence, enrolment, attrition, progression to the next grade, and reported illness (diarrhoea, respiratory infection, conjunctivitis), and conducted structured observations to measure intervention fidelity and adherence. Stool samples were collected annually prior to de-worming and analysed for soil-transmitted helminth (STH) infection. In addition to our primary ITT analysis, we conducted secondary analyses to quantify the role of intervention fidelity and adherence on project impacts.
Participants	100 primary schools (50 intervention, 50 comparison) with a total of 3993 pupils were enrolled throughout the study period (intervention schools = 2021 pupils, control schools = 1972 pupils). Up to 40 pupils selected from grades 3 to 5 in each school using systematic stratified sampling, with grade and sex as the stratification variables. Pupils selected at baseline were followed throughout the entire study period; pupils who left the school due to abandonment or transfer were replaced at the beginning of the following academic year, maintaining equal grade and sex ratios when possible. Pupils who progressed from fifth to the sixth grade were replaced with pupils from grade 3 the following academic year.
Interventions	Water supply, sanitation facilities, hand-washing facilities, drinking water filters, and behaviour change education and promotion versus control. See Table 1 for details.
Outcomes	Primary impact of interest was pupil absence, measured by school-wide roll-call at each visit. Secondary health impacts included diarrhoea, symptoms of respiratory infection, and conjunctivitis/non-vision-related eye illness collected through pupil interviews. Pupils were considered to have symptoms of respiratory infection if they reported cough, runny nose, stuffy nose, or sore throat. No safety outcomes reported.
Notes	Funded by government and pharmaceutical industry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details provided.

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Chard 2019 *(Continued)*

Allocation concealment (selection bias)	Low risk	Schools allocated prior to recruitment of individuals.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions were due to participants leaving school, hence unlikely to cause bias.
Selective reporting (reporting bias)	Low risk	All specified outcomes reported.

Correa 2012

Study characteristics	
Methods	Cluster-RCT in childcare facilities in Colombia from 16 April to 18 December 2008 (3 school terms) testing the effects of hand hygiene using an alcohol-based hand rub versus standard practice
Participants	42 childcare facilities in 6 towns in Colombia. A total of 1727 were enrolled (intervention group = 794 from 21 centres, control group = 933 from 21 centres). Inclusion criteria: licensed to care for 12 or more children aged 1 to 5 years for 8 hours a day, 5 times per week, and where availability of tap water was limited
Interventions	Intervention: alcohol-based hand wash as an addition to hand-washing Control: usual hand-washing practice See Table 1 for details.
Outcomes	ARI defined as: 2 or more of the following symptoms for at least 24 hours, lasting at least 2 days: runny, stuffy, or blocked nose or noisy breathing; cough; fever, hot sensation, or chills; and/or sore throat. Ear pain alone was considered an ARI.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...using the random function in Microsoft Excel™ (Microsoft Corp., Redmond, Washington, United States), random numbers (1 or 2) were generated and allotted 1:1 within each group. Finally, a researcher flipped a coin to decide which number would correspond to either arm (heads = 1, intervention; tails = 2, control)."
Allocation concealment (selection bias)	Unclear risk	Method not described

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Correa 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up similar in each group and not substantial
Selective reporting (reporting bias)	Unclear risk	No protocol available

Cowling 2008

Study characteristics	
Methods	Cluster-RCT carried out in Hong Kong SARS between February and September 2007. The study assessed the effects of non-pharmaceutical interventions on the household transmission of influenza over a 9-day period. ILI cases whose family contacts had been symptom-free for at least 2 weeks rapid-tested for influenza A and B were used and randomised to 3 interventions. Randomisation was carried out in 2 different schedules (2:1:1 for the first 100 households, and subsequently 8:1:1), but it is unclear why and how this was done.
Participants	A total of 350 of 944 originally enrolled participants representing 122 households were analysed (control group = 71 households with 205 household contacts, face mask = 21 households with 61 household contacts, HH = 30 households with 84 household contacts). Inclusion criteria: residents of Hong Kong aged at least 2 years, reporting at least 2 symptoms of ILI ((such as fever ≥ 38 degrees, cough, headache, coryza, sore throat, muscle aches and pains) and positive influenza A+B rapid test and living in a household with at least 2 other individuals, none of whom had ILI in the preceding 14 days Households were excluded because subsequent laboratory testing (culture) was negative. Attrition was not explained.
Interventions	Households were randomised to either wearing face masks with education (as the control group plus education about face mask use) or hand-washing with special medicated soap (with alcohol sanitiser) with education (as the control group plus education about hand-washing) or education about general healthy lifestyle and diet (control group). The soap was distributed in special containers that were weighed at the start and end of the study. Interventions visits to the households were done on average 1 day after randomisation of index case household.
Outcomes	Laboratory: QuickVue RTI MDCK culture Samples were harvested using NTS, but the text refers to a second procedure from June 2007 onwards testing for non-influenza viruses, with no data reported. Effectiveness: secondary attack ratios (SAR): SAR is the proportion of household contacts of an index case who were subsequently ill with influenza (symptomatic contact individuals with at least 1 NTS positive for influenza by viral culture or PCR)

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Cowling 2008 *(Continued)*

	3 clinical definitions were used for secondary analysis: 1. Fever ≥ 38 degrees, or at least 2 of following symptoms: headache, coryza, sore throat, muscle aches and pains 2. At least 2 of the following S/S: fever ≥ 37.8 degrees, cough, headache, sore throat, muscle aches and pains 3. Fever ≥ 37.8 degrees plus cough or sore throat Safety: no harms were reported in any of the arms
Notes	The trial authors conclude that "The secondary attack ratios were lower than anticipated, and lower than reported in other countries, perhaps due to differing patterns of susceptibility, lack of significant antigenic drift in circulating influenza virus strains recently, and/or issues related to the symptomatic recruitment design. Lessons learnt from this pilot have informed changes for the main study in 2008". Although billed as a pilot study, the text is highly confusing and at times contradictory. The intervention was delivered at a home visit up to 36 hours after the index case was seen in the outpatients. This is a long time and perhaps the reason for failure of the intervention. Practically, the intervention will have to be organised before even seeking medical care, i.e. people know to do it when the child gets sick at home.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer generated by a biostatistician. "A pre-specified table of random numbers will be used to assign one of the three interventions to the household of the index case."
Allocation concealment (selection bias)	Low risk	The households of eligible study index patients were allocated to 3 groups in a 1:1:1 ratio under a block randomisation structure with randomly permuted block sizes of 18, 24, and 30 using a random-number generator. Allocation was concealed from treating physicians and clinics and implemented by study nurses at the time of the initial household visit.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and people who administered the interventions were not blinded to the interventions, but participants were not informed of the specific nature of the interventions applied to other participating households.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was accounted for. Dropout from the randomised population was high: 32% in control group, 37.5% in hand hygiene group, and 39.4% in face mask and hand hygiene group. Reasons for dropout were distributed evenly across the 3 groups. Authors report follow-up as proportion of patients remaining in the study after initial dropout.
Selective reporting (reporting bias)	High risk	The choice of season, change in randomisation schedules, and unexplained dropouts amongst contacts; the use of QuickVue, which proved unreliable, reporting bias on non-influenza isolates resulted in a judgement of high risk of bias.

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Cowling 2009

Study characteristics	
Methods	Cluster-RCT
Participants	A total of 407 index cases and 794 household contacts were analysed. Of 407 enrolled households, 322 received the allocated interventions as follows: 1. control group = 112 households with 346 contacts (only 91 households analysed with 279 contacts); 2. hand hygiene = 106 households with 329 contacts (only 85 households analysed with 257 contacts); 3. face mask + hand hygiene = 104 households with 340 contacts (only 83 households analysed with 258 contacts). Inclusion criteria: households in Hong Kong. Index cases from 45 outpatient clinics in both the private and public sectors across Hong Kong. They enrolled individuals who reported at least 2 symptoms of ARI (temperature 37.8 °C, cough, headache, sore throat, or myalgia); had symptom onset within 48 hours; and lived in a household with at least 2 other people, none of whom had reported ARI in the preceding 14 days. After giving informed consent, participants provided nasal and throat swab specimens. 2750 patients were eligible and tested between 2 January and 30 September 2008.
Interventions	Participants with a positive rapid-test result and their household contacts were randomly assigned to 1 of 3 study groups: control (lifestyle measures - 134 households), control plus enhanced hand hygiene only (136 households), and control plus face masks and enhanced hand hygiene (137 households) for all household members. No detailed description of the instructions was given to participants.
Outcomes	Influenza virus infection in household contacts, as confirmed by RT-PCR or diagnosed clinically after 7 days "The primary outcome measure was the secondary attack ratio at the individual level: that is, the proportion of household contacts infected with influenza virus. We evaluated the secondary attack ratio using a laboratory definition (a household contact with a nose and throat swab specimen positive for influenza by RT-PCR) as the primary analysis and 2 secondary clinical definitions of influenza based on self-reported data from the symptom diaries as secondary analyses." Statistical analysis: adjusted for clustering Results: no statistically significant difference in secondary attack ratio between groups in total population. Statistically significant reduction in RT-PCR confirmed influenza virus infections in the household contacts in 154 households in which the intervention was applied within 36 hours of symptom onset in the index patient. Adherence to hand hygiene was between 44% and 62%. Adherence of index patient to wearing a face mask between 15% and 49%.
Notes	"In an unintentional deviation from that protocol, 49 of the 407 randomly allocated persons had a household contact with influenza symptoms at recruitment (a potential co-index patient). We also randomly assigned 6 of 407 persons who had symptoms for slightly more than 48 hours." The trial authors conclude that "Hand hygiene and face masks seemed to prevent household transmission of influenza virus when implemented within 36 hours of index patient symptom onset. These findings suggest that non-pharmaceutical interventions are important for mitigation of pandemic and interpandemic influenza".

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was computer generated by a biostatistician. "A pre-specified table of random numbers will be used to assign one of the three interventions to the household of the index case."

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Cowling 2009 *(Continued)*

Allocation concealment (selection bias)	Low risk	The households of eligible study index patients were allocated to 3 groups in a 1:1:1 ratio under a block randomisation structure with randomly permuted block sizes of 18, 24, and 30 using a random-number generator. Allocation was concealed from treating physicians and clinics and implemented by study nurses at the time of the initial household visit.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Participants and personnel administering the interventions were not blinded to group assignment."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not stated if the outcome assessor was blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was accounted for. Dropout from the randomised population was high: 32% in control group, 37.5% in hand hygiene group, and 39.4% in face mask and hand hygiene group. Reasons for dropout were distributed evenly across the 3 groups. Trial authors report follow-up as proportion of patients remaining in the study after initial dropout.
Selective reporting (reporting bias)	Unclear risk	In general good reporting

DiVita 2011

Study characteristics	
Methods	The impact of hand-washing promotion on the risk of household transmission of influenza, ILI, and fever was tested in rural Bangladesh. ILI was defined as fever in children < 5 years old and fever with cough or sore throat in individuals > 5 years old. Households were randomised to intervention or control. The intervention group received hand-washing stations with soap and daily hand-washing motivation at critical times for pathogen transmission, such as after coughing or sneezing. Daily surveillance was conducted, and household members with fever were tested for influenza viruses by PCR. Secondary attack ratios (SAR) were calculated for influenza, ILI, and fever in each arm. Logistic regression with generalised estimating equations was used to estimate the significance of the SAR comparison whilst controlling for clustering by household.
Participants	The study included 233 patient index cases (intervention group = 100, control group 133) with 2540 household contacts (intervention group = 134, control group = 1226). Inclusion criteria: index case patients (individuals who developed ILI within the previous 2 days and were the only symptomatic person in their household) as well as their household contacts
Interventions	Hand-washing stations with soap and daily hand-washing motivation versus control. See Table 1 for details.
Outcomes	SAR were calculated for influenza, ILI, and fever. ILI was defined as fever in children < 5 years old and fever with cough or sore throat in individuals > 5 years old. No safety outcomes reported.
Notes	Funding source unknown

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DiVita 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details provided
Allocation concealment (selection bias)	Unclear risk	Insufficient details provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details provided
Selective reporting (reporting bias)	Unclear risk	Insufficient details provided

Cowling 2008

Study characteristics	
Methods	Cluster-RCT carried out in Hong Kong SARS between February and September 2007. The study assessed the effects of non-pharmaceutical interventions on the household transmission of influenza over a 9-day period. ILI cases whose family contacts had been symptom-free for at least 2 weeks rapid-tested for influenza A and B were used and randomised to 3 interventions. Randomisation was carried out in 2 different schedules (2:1:1 for the first 100 households, and subsequently 8:1:1), but it is unclear why and how this was done.
Participants	A total of 350 of 944 originally enrolled participants representing 122 households were analysed (control group = 71 households with 205 household contacts, face mask = 21 households with 61 household contacts, HH = 30 households with 84 household contacts). Inclusion criteria: residents of Hong Kong aged at least 2 years, reporting at least 2 symptoms of ILI ((such as fever ≥ 38 degrees, cough, headache, coryza, sore throat, muscle aches and pains) and positive influenza A+B rapid test and living in a household with at least 2 other individuals, none of whom had ILI in the preceding 14 days Households were excluded because subsequent laboratory testing (culture) was negative. Attrition was not explained.
Interventions	Households were randomised to either wearing face masks with education (as the control group plus education about face mask use) or hand-washing with special medicated soap (with alcohol sanitiser) with education (as the control group plus education about hand-washing) or education about general healthy lifestyle and diet (control group). The soap was distributed in special containers that were

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Cowling 2008 *(Continued)*

	weighed at the start and end of the study. Interventions visits to the households were done on average 1 day after randomisation of index case household.
Outcomes	Laboratory: QuickVue RTI MDCK culture Samples were harvested using NTS, but the text refers to a second procedure from June 2007 onwards testing for non-influenza viruses, with no data reported. Effectiveness: secondary attack ratios (SAR): SAR is the proportion of household contacts of an index case who were subsequently ill with influenza (symptomatic contact individuals with at least 1 NTS positive for influenza by viral culture or PCR) 3 clinical definitions were used for secondary analysis: 1. Fever ≥ 38 degrees, or at least 2 of following symptoms: headache, coryza, sore throat, muscle aches and pains 2. At least 2 of the following S/S: fever ≥ 37.8 degrees, cough, headache, sore throat, muscle aches and pains 3. Fever ≥ 37.8 degrees plus cough or sore throat Safety: no harms were reported in any of the arms
Notes	The trial authors conclude that “The secondary attack ratios were lower than anticipated, and lower than reported in other countries, perhaps due to differing patterns of susceptibility, lack of significant antigenic drift in circulating influenza virus strains recently, and/or issues related to the symptomatic recruitment design. Lessons learnt from this pilot have informed changes for the main study in 2008”. Although billed as a pilot study, the text is highly confusing and at times contradictory. The intervention was delivered at a home visit up to 36 hours after the index case was seen in the outpatients. This is a long time and perhaps the reason for failure of the intervention. Practically, the intervention will have to be organised before even seeking medical care, i.e. people know to do it when the child gets sick at home.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer generated by a biostatistician. "A pre-specified table of random numbers will be used to assign one of the three interventions to the household of the index case."
Allocation concealment (selection bias)	Low risk	The households of eligible study index patients were allocated to 3 groups in a 1:1:1 ratio under a block randomisation structure with randomly permuted block sizes of 18, 24, and 30 using a random-number generator. Allocation was concealed from treating physicians and clinics and implemented by study nurses at the time of the initial household visit.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and people who administered the interventions were not blinded to the interventions, but participants were not informed of the specific nature of the interventions applied to other participating households.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was accounted for. Dropout from the randomised population was high: 32% in control group, 37.5% in hand hygiene group, and 39.4% in face

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Cowling 2008 *(Continued)*

		mask and hand hygiene group. Reasons for dropout were distributed evenly across the 3 groups. Authors report follow-up as proportion of patients remaining in the study after initial dropout.
Selective reporting (reporting bias)	High risk	The choice of season, change in randomisation schedules, and unexplained dropouts amongst contacts; the use of QuickVue, which proved unreliable, reporting bias on non-influenza isolates resulted in a judgement of high risk of bias.

Cowling 2009

Study characteristics	
Methods	Cluster-RCT
Participants	A total of 407 index cases and 794 household contacts were analysed. Of 407 enrolled households, 322 received the allocated interventions as follows: 1. control group = 112 households with 346 contacts (only 91 households analysed with 279 contacts); 2. hand hygiene = 106 households with 329 contacts (only 85 households analysed with 257 contacts); 3. face mask + hand hygiene = 104 households with 340 contacts (only 83 households analysed with 258 contacts). Inclusion criteria: households in Hong Kong. Index cases from 45 outpatient clinics in both the private and public sectors across Hong Kong. They enrolled individuals who reported at least 2 symptoms of ARI (temperature 37.8 °C, cough, headache, sore throat, or myalgia); had symptom onset within 48 hours; and lived in a household with at least 2 other people, none of whom had reported ARI in the preceding 14 days. After giving informed consent, participants provided nasal and throat swab specimens. 2750 patients were eligible and tested between 2 January and 30 September 2008.
Interventions	Participants with a positive rapid-test result and their household contacts were randomly assigned to 1 of 3 study groups: control (lifestyle measures - 134 households), control plus enhanced hand hygiene only (136 households), and control plus face masks and enhanced hand hygiene (137 households) for all household members. No detailed description of the instructions was given to participants.
Outcomes	Influenza virus infection in household contacts, as confirmed by RT-PCR or diagnosed clinically after 7 days "The primary outcome measure was the secondary attack ratio at the individual level: that is, the proportion of household contacts infected with influenza virus. We evaluated the secondary attack ratio using a laboratory definition (a household contact with a nose and throat swab specimen positive for influenza by RT-PCR) as the primary analysis and 2 secondary clinical definitions of influenza based on self-reported data from the symptom diaries as secondary analyses." Statistical analysis: adjusted for clustering Results: no statistically significant difference in secondary attack ratio between groups in total population. Statistically significant reduction in RT-PCR confirmed influenza virus infections in the household contacts in 154 households in which the intervention was applied within 36 hours of symptom onset in the index patient. Adherence to hand hygiene was between 44% and 62%. Adherence of index patient to wearing a face mask between 15% and 49%.
Notes	"In an unintentional deviation from that protocol, 49 of the 407 randomly allocated persons had a household contact with influenza symptoms at recruitment (a potential co-index patient). We also randomly assigned 6 of 407 persons who had symptoms for slightly more than 48 hours."

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Cowling 2009 *(Continued)*

The trial authors conclude that "Hand hygiene and face masks seemed to prevent household transmission of influenza virus when implemented within 36 hours of index patient symptom onset. These findings suggest that non-pharmaceutical interventions are important for mitigation of pandemic and interpandemic influenza".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer generated by a biostatistician. "A pre-specified table of random numbers will be used to assign one of the three interventions to the household of the index case."
Allocation concealment (selection bias)	Low risk	The households of eligible study index patients were allocated to 3 groups in a 1:1:1 ratio under a block randomisation structure with randomly permuted block sizes of 18, 24, and 30 using a random-number generator. Allocation was concealed from treating physicians and clinics and implemented by study nurses at the time of the initial household visit.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Participants and personnel administering the interventions were not blinded to group assignment."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not stated if the outcome assessor was blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was accounted for. Dropout from the randomised population was high: 32% in control group, 37.5% in hand hygiene group, and 39.4% in face mask and hand hygiene group. Reasons for dropout were distributed evenly across the 3 groups. Trial authors report follow-up as proportion of patients remaining in the study after initial dropout.
Selective reporting (reporting bias)	Unclear risk	In general good reporting

DiVita 2011

Study characteristics

Methods	The impact of hand-washing promotion on the risk of household transmission of influenza, ILI, and fever was tested in rural Bangladesh. ILI was defined as fever in children < 5 years old and fever with cough or sore throat in individuals > 5 years old. Households were randomised to intervention or control. The intervention group received hand-washing stations with soap and daily hand-washing motivation at critical times for pathogen transmission, such as after coughing or sneezing. Daily surveillance was conducted, and household members with fever were tested for influenza viruses by PCR. Secondary attack ratios (SAR) were calculated for influenza, ILI, and fever in each arm. Logistic regression with generalised estimating equations was used to estimate the significance of the SAR comparison whilst controlling for clustering by household.
Participants	The study included 233 patient index cases (intervention group = 100, control group 133) with 2540 household contacts (intervention group = 134, control group = 1226).

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DiVita 2011 *(Continued)*

	Inclusion criteria: index case patients (individuals who developed ILI within the previous 2 days and were the only symptomatic person in their household) as well as their household contacts
Interventions	Hand-washing stations with soap and daily hand-washing motivation versus control. See Table 1 for details.
Outcomes	SAR were calculated for influenza, ILI, and fever. ILI was defined as fever in children < 5 years old and fever with cough or sore throat in individuals > 5 years old. No safety outcomes reported.
Notes	Funding source unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details provided
Allocation concealment (selection bias)	Unclear risk	Insufficient details provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details provided
Selective reporting (reporting bias)	Unclear risk	Insufficient details provided

Farr 1988a

Study characteristics

Methods	6-month cluster-RCT, controlled, double-blind of the efficacy of virucidal nasal tissues in the prevention of natural cold, conducted in Charlottesville, Virginia, USA. Many of the families were enrolled because 1 or more family members worked at the State Farm Insurance Company; the remaining families were recruited from the Charlottesville community by advertisement in a local newspaper. Families were randomly assigned by the sponsoring company to receive boxes of treated tissues, placebo tissues, or no tissues. The randomisation was performed by computer. Study participants and investigators were unaware of the type of tissues each family was randomised to receive. Blinding efficacy was tested using a questionnaire: the mothers in each family were asked twice if she believed her family was using virucidal or placebo tissues. Participants in the treated and placebo groups were instructed to use only tissues received through the study, whilst families in the additional control group without tissues were allowed to continue their

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Farr 1988a *(Continued)*

	usual practice of personal hygiene. Each family member kept a daily listing of respiratory symptoms on a record card. A nurse epidemiologist visited each family monthly to encourage recording.
Participants	186 families, 58 in the active group, 59 in the placebo group, and 69 in the no-tissues group. A total of 302 families were originally recruited; 116 families who did not comply with the study protocol, lost their surveillance cards, could not complete the protocol were excluded from the analysis.
Interventions	Use of virucidal tissues versus placebo tissues versus no tissues. The treated tissues were impregnated with malic and citric acids and sodium lauryl sulphate, whilst placebo tissues contained saccharin.
Outcomes	Laboratory: serological evidence: no Effectiveness: respiratory illness Safety: N/A
Notes	The authors concluded that virucidal tissues have only a small impact on the overall rate of natural acute respiratory illnesses. The total illness rate was lower in families using virucidal tissues than in both of the other study groups, but only the difference between active and placebo groups was statistically significant (3.4 illness per person versus 3.9 for placebo group, P = 0.04, and 3.6 for the no-tissue control group, P = 0.2, and overall 14% to 5% reduction). The questionnaire results suggest that some bias may have been present since a majority of mothers in the virucide group believed they were receiving the 'active' tissues. Another possible explanation of the low effectiveness of virucidal tissues is poor compliance by children in use of the virucidal tissues. A well-designed and honestly reported study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The randomisation was performed by computer in each trial." However, method of sequence generation is not stated.
Allocation concealment (selection bias)	Unclear risk	"In trial I, families were randomly assigned by the sponsoring company to receive boxes of treated tissues, placebo tissues or no tissues." "Families with one or two children were randomised in one stratum, and families with three or more children were randomised in a second stratum in trial I." Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Study participants and investigators were unaware of the type of tissues which each family was randomised to receive in both trials. In trial I, the mother in each family was asked twice if she believed her family was using active or placebo tissues, first after three months and then at the end of the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Study participants and investigators were unaware of the type of tissues which each family was randomised to receive in both trials. In trial I, the mother in each family was asked twice if she believed her family was using active or placebo tissues, first after three months and then at the end of the study."
Incomplete outcome data (attrition bias) All outcomes	High risk	"A total of 116 of the 302 families were excluded from the analysis. Families were excluded if they lost their surveillance cards or did not conscientiously record data, did not comply with the study protocol, or simply could not complete the protocol for family reasons. It was discovered that families with five or more members had so many colds that it was not possible to distinguish primary and secondary illnesses. These large families were therefore excluded from the analysis in trial I and were excluded from enrolment in trial II."

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Farr 1988a *(Continued)*

Selective reporting (reporting bias)	Low risk	All indicated outcomes are reported.

Farr 1988b

Study characteristics	
Methods	6-month randomised, controlled, double-blind trial of the efficacy of virucidal nasal tissues in the prevention of natural cold, conducted in Charlottesville, Virginia, USA. Families were recruited from the Charlottesville community by advertisement in a local newspaper. Families were randomly assigned by the sponsoring company to receive either virucidal tissues or placebo-treated tissues. Stratified randomisation was performed by computer, and the strata were defined by total number in the family. Study participants and investigators were unaware of the type of tissues each family was randomised to receive. Each family member kept a daily listing of respiratory symptoms on a record card. A nurse epidemiologist visited each family monthly to encourage recording. In addition, a study monitor visited each family bimonthly to further encourage compliance and reporting of symptoms.
Participants	98 families, 58 in the active group and 40 in the placebo group. 231 families were initially recruited, 222 completed the trial, data of 98 families were analysed. The other families were excluded from the analysis because they complained of side effects (sneezing, etc.) or reported not using the tissues regularly.
Interventions	Use of virucidal tissues versus placebo tissues. The treated tissues were impregnated with malic and citric acids and sodium lauryl sulphate, whilst the placebo tissues contained succinic acid. Participants in the treated and placebo groups were instructed to only use tissues received through the study.
Outcomes	Laboratory: serological evidence: no Effectiveness: respiratory illness Safety: N/A
Notes	The study suggests that virucidal tissues have only a small impact on the overall rate of natural acute respiratory illnesses. The total illness rate was lower in families using virucidal tissues than in the other study group, but the difference between active and placebo groups was not statistically significant. There was a small, non-significant drop in illness rates across families (5%). The tissues appeared to be ineffective as the drop was confined to primary illness unaffected by tissue use. The placebo (succinic acid) was not inert, and was associated with cough and nasal burning. This impacted on allocation concealment. A well-designed and honestly reported study marred by transparent allocation

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The randomisation was performed by computer in each trial." However, method of sequence generation is not stated.
Allocation concealment (selection bias)	Unclear risk	"In trial II, families were randomly assigned by the sponsor to receive either virucidal tissues or placebo treated tissues." "In trial II, stratified randomisation was again used, but this time the strata were defined by total number in the family (i.e., one stratum for two-member families, another stratum for three-member families, and a final one for four-member families)." Concealment of allocation not described

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Farr 1988b *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Study participants and investigators were unaware of the type of tissues which each family was randomised to receive in both trials."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Study participants and investigators were unaware of the type of tissues which each family was randomised to receive in both trials."
Incomplete outcome data (attrition bias) All outcomes	High risk	"A total of 222 (of 231) families completed trial II; 9 families were terminated early (table 1). In 124 families, one or more family members reported not using the tissues regularly and/or reported having significant side effects. The data from these families were not analysed, leaving 58 families (177 persons) and 40 families (114 persons) for analysis in the virucide and placebo groups, respectively."
Selective reporting (reporting bias)	Low risk	All indicated outcomes are reported.

Feldman 2016

Study characteristics	
Methods	Prospective cluster-RCT. Ships from a single, central naval base. Ships were stratified by vessel classes (corvette, fast missile boat, and patrol boat).
Participants	All people participating in security operations, routine exercises, and patrol at a single, central naval base were eligible. The actual number of participants in the groups is not reported.
Interventions	Chlorhexidine gluconate (CHG) dispensers in addition to soap-and-water hand-washing versus soap-and-water hand-washing. See Table 1 for details.
Outcomes	Laboratory: bacterial palm cultures from 30 sailors from each group using a modified bag broth technique with sterile brain-heart broth, at 0 and 4 months (sample participants) Effectiveness: Primary outcome: incidence of infectious diseases reported by the computerised patient records system using ICD-9 diagnoses and grouped into diarrhoeal, respiratory, and skin infections; the number of sick call visits; and the number of sick leave and light-duty days incurred by the sailors Secondary outcome: subclinical morbidity (i.e. symptoms of self-reported infectious diseases) Safety: not reported
Notes	No report on adherence Funding: governmental (Israeli Defense Force Medical Corps) Study was conducted between May and September 2014 (4 months follow-up). CHG availability onboard the ships did not reduce the transmission of infectious diseases or colonisation.
Risk of bias	

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Feldman 2016 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of randomisation
Allocation concealment (selection bias)	Unclear risk	No description of allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded. Self-reported outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information if personnel collecting data for ICD-9 diagnosis were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No participants flow chart, no attrition data
Selective reporting (reporting bias)	Unclear risk	No protocol to compare

Goodall 2014

Study characteristics	
Methods	A 2X2 factorial RCT with 4 treatment arms: 1. Vitamin D_3 and gargling 2. Placebo and gargling 3. Vitamin D_3 and no gargling 4. Placebo and no gargling
Participants	600 students from McMaster University, Hamilton, Ontario, Canada, randomised to the following: 1. Vitamin D and gargling (N = 150, analysed 135) 2. Vitamin D and no gargling (N = 150, 123 outcomes included in analysis) 3. Placebo and gargling (N = 150, 121 known outcomes included in analysis) 4. Placebo and no gargling (N = 150, 113 known outcomes included in analysis) Inclusion criteria: aged ≥ 17 years and lived with at least 1 student housemate. Exclusion criteria: students with contraindicated medical conditions (hypercalcaemia, parathyroid disorder, chronic kidney disease, use of anticonvulsants, malabsorption syndromes, sarcoidosis), who were currently or planning to become pregnant, who were taking ≥ 1000 international units (IU)/day vitamin D, or who were unable to swallow capsules
Interventions	See TIDieR Table (Table 9).
Outcomes	Laboratory (influenza assessed via weekly self-collected nasal swabs; only swabs for symptomatic participants were assessed). Lab-confirmed influenza was determined by testing the Day 1 nasal swabs using an in-house enterovirus/rhinovirus PCR and, if negative, a commercial multiplex PCR able to detect 16 respiratory viruses and viral subtypes (xTAG RVP FAST, Luminex, Austin TX).

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Goodall 2014 *(Continued)*

	Clinical URTI assessed via weekly online surveys. Clinical URTI is defined as the participant's perception of cold in conjunction with 1 or more symptoms (runny/stuffy nose, congestion, cough, sneezing, sore throat, muscle aches, or fever). When participants reported symptoms but were uncertain if they were ill, adjudication was applied by 2 clinicians. Safety: None assessed/reported by the investigators.
Notes	Study was conducted during 2 periods: September to October in 2010 and 2011. Partial governmental funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description on how the randomisation sequence was generated
Allocation concealment (selection bias)	Low risk	Study used opaque, sealed, serially numbered envelopes. Envelopes were only accessed when both personnel were present.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Due to the nature of gargling with tap water, this intervention was not blinded. However, all other aspects of the study were blinded. Self-reported symptoms were adjudicated by 2 clinicians.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Except for gargling, all other participants and study personnel were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study flow chart and reasons for lost to follow-up are provided, imputation used for missing outcomes.
Selective reporting (reporting bias)	Low risk	All planned study outcomes were reported and match the published study protocol.

Gwaltney 1980

Study characteristics

Methods	Study assessed the effectiveness of aqueous iodine applied to the fingers in blocking hand transmission of experimental infection with rhinovirus from 1 volunteer to another. Healthy, young adult volunteers were recruited from the general population at the University of Virginia, Charlottesville. Volunteers were not informed about the contents of the hand preparation until after the study. 2 experiments were conducted to evaluate the virucidal activity of aqueous iodine applied to the fingers immediately before viral contamination. Another 2 experiments were conducted to determine whether there was sufficient residual activity of aqueous iodine after 2 hours to interrupt viral spread by the hand route. Volunteers who were donors of virus for the hand exposures were challenged intranasally on 3 consecutive days with the rhinovirus strain HH. Recipients were randomly assigned to receive iodine or placebo. The donors contaminated their hands with nasal secretions by finger to nose contact before the exposure. Hand contact was made between a donor and a recipient by stroking of the fingers for 10 seconds. Donors and recipients wore masks during the exposure period.

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Gwaltney 1980 *(Continued)*

Participants	15 and 20 volunteers in 2 experiments
Interventions	Treatment of fingers with iodine versus placebo. The virucidal preparation used was aqueous iodine (2% iodine and 4% potassium iodide). The placebo was an aqueous solution of food colours.
Outcomes	Experimental rhinovirus infection reduced (P = 0.06) Laboratory: serological evidence Effectiveness: rhinovirus infection (based on serology, isolation, and clinical symptoms) with high-score clinical illness. Score was published elsewhere. Safety: N/A
Notes	Risk of bias: high (poor description of randomisation process, concealment, or allocation) Notes: the study suggests that aqueous iodine applied to the fingers was effective in blocking transmission by hand contact of experimental infection with rhinovirus for up to 2 hours after application (1 out 10 volunteers were infected compared to 6 out of 10 in the placebo preparation arm, P = 0.06 with Fisher's exact test). The effectiveness of iodine treatment of the fingers in interrupting viral transmission in volunteers recommends its use for attempting to block transmission of rhinovirus under natural conditions. Although the cosmetic properties of 2% aqueous iodine make it impractical for routine use, it can be used as an epidemiologic tool to study the importance of the hand transmission route and to develop an effective cosmetically acceptable hand preparation. A summarily reported study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The viricidal preparation used was aqueous iodine... . The placebo was an aqueous solution of food colors... mixed to resemble the color of iodine. An odor of iodine was given to the placebo... . Volunteers were not informed about the contents of the hand preparation until after the study."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not stated whether the outcome assessor was blinded or not.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information

Hartinger 2016

Study characteristics

Methods	Communities were randomised to a comprehensive intervention was an improved solid-fuel stove, installation of a kitchen sink with running water, solar drinking water disinfection, education on handwashing, and separating animals from the kitchen environment.

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Hartinger 2016 *(Continued)*

Participants	534 children (267 in each group) in 51 communities (25 in intervention, 26 in control group). 250 children/households in the intervention group and 253 children/households in the control group were available for follow-up. Conducted in a rural farming area
Interventions	Environmental home-based intervention package consisting of improved solid-fuel stoves, kitchen sinks, solar disinfection of drinking water, and hygiene promotion. See Table 1 for details.
Outcomes	Laboratory: *Escherichia coli* (not relevant to this review) Effectiveness: weekly collection of daily diary data on illness. ARI was defined as child presenting cough or difficulty breathing, or both. ALRI was defined as child presenting cough or difficulty breathing, with a raised respiratory rate (> 50 per min in children aged 6 to 11 months and > 40 per min in children aged 12 months) on 2 consecutive measurements. Safety: none described in methods and none reported
Notes	The authors conclude that "combined home-based environmental interventions slightly reduced childhood diarrhoea, but the confidence interval included unity. Effects on growth and respiratory outcomes were not observed, despite high user compliance of the interventions. The absent effect on respiratory health might be due to insufficient household air quality improvements of the improved stoves and additional time needed to achieve attitudinal and behaviour change when providing composite interventions". Well-reported trial. Age of children not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Covariate-constrained randomisation is mentioned, but method not described.
Allocation concealment (selection bias)	Unclear risk	Method not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Data collected by field worker and recorded by parent. All would be aware of allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition rate, reasons stated, balanced between groups.
Selective reporting (reporting bias)	Low risk	It is unlikely that other outcomes were measured but not reported.

Gwaltney 1980

Study characteristics

Methods	Study assessed the effectiveness of aqueous iodine applied to the fingers in blocking hand transmission of experimental infection with rhinovirus from 1 volunteer to another. Healthy, young adult vol-

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Gwaltney 1980 *(Continued)*

	unteers were recruited from the general population at the University of Virginia, Charlottesville. Volunteers were not informed about the contents of the hand preparation until after the study. 2 experiments were conducted to evaluate the virucidal activity of aqueous iodine applied to the fingers immediately before viral contamination. Another 2 experiments were conducted to determine whether there was sufficient residual activity of aqueous iodine after 2 hours to interrupt viral spread by the hand route. Volunteers who were donors of virus for the hand exposures were challenged intranasally on 3 consecutive days with the rhinovirus strain HH. Recipients were randomly assigned to receive iodine or placebo. The donors contaminated their hands with nasal secretions by finger to nose contact before the exposure. Hand contact was made between a donor and a recipient by stroking of the fingers for 10 seconds. Donors and recipients wore masks during the exposure period.
Participants	15 and 20 volunteers in 2 experiments
Interventions	Treatment of fingers with iodine versus placebo. The virucidal preparation used was aqueous iodine (2% iodine and 4% potassium iodide). The placebo was an aqueous solution of food colours.
Outcomes	Experimental rhinovirus infection reduced (P = 0.06) Laboratory: serological evidence Effectiveness: rhinovirus infection (based on serology, isolation, and clinical symptoms) with high-score clinical illness. Score was published elsewhere. Safety: N/A
Notes	Risk of bias: high (poor description of randomisation process, concealment, or allocation) Notes: the study suggests that aqueous iodine applied to the fingers was effective in blocking transmission by hand contact of experimental infection with rhinovirus for up to 2 hours after application (1 out 10 volunteers were infected compared to 6 out of 10 in the placebo preparation arm, P = 0.06 with Fisher's exact test). The effectiveness of iodine treatment of the fingers in interrupting viral transmission in volunteers recommends its use for attempting to block transmission of rhinovirus under natural conditions. Although the cosmetic properties of 2% aqueous iodine make it impractical for routine use, it can be used as an epidemiologic tool to study the importance of the hand transmission route and to develop an effective cosmetically acceptable hand preparation. A summarily reported study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The viricidal preparation used was aqueous iodine... . The placebo was an aqueous solution of food colors... mixed to resemble the color of iodine. An odor of iodine was given to the placebo... . Volunteers were not informed about the contents of the hand preparation until after the study."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not stated whether the outcome assessor was blinded or not.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information

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Hartinger 2016

Study characteristics	
Methods	Communities were randomised to a comprehensive intervention was an improved solid-fuel stove, installation of a kitchen sink with running water, solar drinking water disinfection, education on handwashing, and separating animals from the kitchen environment.
Participants	534 children (267 in each group) in 51 communities (25 in intervention, 26 in control group). 250 children/households in the intervention group and 253 children/households in the control group were available for follow-up. Conducted in a rural farming area
Interventions	Environmental home-based intervention package consisting of improved solid-fuel stoves, kitchen sinks, solar disinfection of drinking water, and hygiene promotion. See Table 1 for details.
Outcomes	Laboratory: *Escherichia coli* (not relevant to this review) Effectiveness: weekly collection of daily diary data on illness. ARI was defined as child presenting cough or difficulty breathing, or both. ALRI was defined as child presenting cough or difficulty breathing, with a raised respiratory rate (> 50 per min in children aged 6 to 11 months and > 40 per min in children aged 12 months) on 2 consecutive measurements. Safety: none described in methods and none reported
Notes	The authors conclude that "combined home-based environmental interventions slightly reduced childhood diarrhoea, but the confidence interval included unity. Effects on growth and respiratory outcomes were not observed, despite high user compliance of the interventions. The absent effect on respiratory health might be due to insufficient household air quality improvements of the improved stoves and additional time needed to achieve attitudinal and behaviour change when providing composite interventions". Well-reported trial. Age of children not reported.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Covariate-constrained randomisation is mentioned, but method not described.
Allocation concealment (selection bias)	Unclear risk	Method not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Data collected by field worker and recorded by parent. All would be aware of allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition rate, reasons stated, balanced between groups.
Selective reporting (reporting bias)	Low risk	It is unlikely that other outcomes were measured but not reported.

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Hubner 2010

Study characteristics	
Methods	A prospective, controlled, intervention-control group design to assess the epidemiological and economical impact of alcohol-based hand disinfectants use at workplace. Volunteers in public administrations in the municipality of the city of Greifswald were randomised into 2 groups. Participants in the intervention group were provided with alcoholic hand disinfection, the control group was unchanged. In all, 1230 person-months were evaluated.
Participants	Employees (n = 134) from the administration of the Ernst-Moritz-Arndt University Greifswald, the municipality of Greifswald and the state of Mecklenburg-Pomerania, were recruited for the study and randomised to intervention (N = 67) or control (N = 67). Final analysis was performed on 64 from the intervention and 65 from the control group. Inclusion criteria: all administrative officers, who did not already apply hand disinfection at work, were considered for participation and were invited by email or mail (n = 850). The 134 participants declared their written consent to participate and completed a pre-study survey with demographic, social, health, and work-related questions to provide data for randomisation. Exclusion criteria: employees that were already using hand disinfectants at work
Interventions	Alcohol-based hand disinfectants use at workplace versus usual hygiene. See Table 1 for details.
Outcomes	Respiratory and gastrointestinal symptoms and days of work were recorded based on a monthly questionnaire over 1 year.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up minimal and similar in 2 groups
Selective reporting (reporting bias)	Unclear risk	No protocol available

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Huda 2012

Study characteristics	
Methods	Poorly described cluster-RCT. Partial report of the SHEWA-B trial focused on changing 11 targeted behaviours in villages to measure the impact on diarrhoea and respiratory illness amongst children. Unit of randomisation is not clear, but was probably a village. A group of 10 to 17 households within a village were the participants, based on the household having at least 1 child under the age of 5.
Participants	A total of 1692 participants (intervention = 848, control = 844) at baseline and 1699 participants at 18 months (intervention = 849, control = 850) Households were eligible if they have a child < 5 years of age and a guardian agreed to participate.
Interventions	SHEWA-B programme targeting improved latrine coverage and usage, access to and use of arsenic-free water, and improved hygiene practices using soaps. See Table 1 for details.
Outcomes	Laboratory: none described in methods and none reported Effectiveness: ARI and diarrhoea. ARI defined as cough and fever or difficulty breathing and fever within 48 h prior to interview. Safety: none described in methods and none reported
Notes	The authors conclude that "The prevalence of childhood diarrhea and respiratory illness was similar in the intervention and control communities". Poorly reported trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Mentions random-number tables, but not clear if this was for random selection or randomisation
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Data on illness were collected by a resident of the village, who was likely to know treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported. No flow diagram
Selective reporting (reporting bias)	Unclear risk	Unlikely that other outcomes were measured and not reported

Huda 2012

Study characteristics

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Huda 2012 *(Continued)*

Methods	Poorly described cluster-RCT. Partial report of the SHEWA-B trial focused on changing 11 targeted behaviours in villages to measure the impact on diarrhoea and respiratory illness amongst children. Unit of randomisation is not clear, but was probably a village. A group of 10 to 17 households within a village were the participants, based on the household having at least 1 child under the age of 5.
Participants	A total of 1692 participants (intervention = 848, control = 844) at baseline and 1699 participants at 18 months (intervention = 849, control = 850) Households were eligible if they have a child < 5 years of age and a guardian agreed to participate.
Interventions	SHEWA-B programme targeting improved latrine coverage and usage, access to and use of arsenic-free water, and improved hygiene practices using soaps. See Table 1 for details.
Outcomes	Laboratory: none described in methods and none reported Effectiveness: ARI and diarrhoea. ARI defined as cough and fever or difficulty breathing and fever within 48 h prior to interview. Safety: none described in methods and none reported
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Mentions random-number tables, but not clear if this was for random selection or randomisation
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Data on illness were collected by a resident of the village, who was likely to know treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported. No flow diagram
Selective reporting (reporting bias)	Unclear risk	Unlikely that other outcomes were measured and not reported

Ibfelt 2015

Study characteristics

Methods	Cluster-RCT in 12 daycare nurseries in Denmark. Centres in the intervention group had their linen and children's toys commercially cleaned and disinfected every 2 weeks. Control group centres had usual

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Ibfelt 2015 *(Continued)*

	practice. Swabbing for bacteria and respiratory viruses was conducted at baseline and the end of the intervention period.
Participants	12 nurseries in Copenhagen (intervention = 6, control = 6) with a total of 587 children aged 6 months to 3 years Not clear how many children were in each group. Data on illness collected at the individual level, and on presence of bacteria and viruses at the cluster level.
Interventions	Washing and disinfection of toys and linen every 2 weeks for 3 months. See Table 1 for details.
Outcomes	Laboratory: counts of bacteria (not relevant to this review) and 11 respiratory viruses at baseline and end of intervention period, taken from swabs of 10 predefined locations in playroom (7 locations) and toilet area (3 locations). Viruses were influenza A and B; coronavirus NL63229E, OC43, and HKU1; parainfluenza virus 1, 2, 3, and 4; rhinovirus; RSV A/B; adenovirus; enterovirus; parechovirus; metapneumovirus; and bocavirus. Testing by PCR Effectiveness: illness counts in the children. Absence due to sickness recorded daily with reason categorised, but no definitions of illness provided. Safety: none mentioned in methods and none reported
Notes	The authors conclude that "Although cleaning and disinfection of toys every two weeks can decrease the microbial load in nurseries, it does not appear to reduce sickness absence among nursery children". The results of the disinfection are reported as follows: "The most prevalent virus was coronavirus (97% positive samples), followed by bocavirus (96%), adenovirus (73%) and rhinovirus (46%). The intervention reduced the presence of adenovirus, rhinovirus and RSV approximately two- to five-fold [odds ratio (OR) 2.4, 95% confidence interval (CI) 1.1-5.0 for adenovirus; OR 5.3, 95% CI 2.3-12.4 for rhinovirus; OR 4.1, 95% CI 1.5-11.2 for RSV] compared with the control group. On the other hand, metapneumovirus was found significantly less often in the control group than in the intervention group. The intervention had no effect on the detection of other viruses. The fomites with the highest presence of respiratory virus were pillows and sofas, followed by toys and playroom tables. When looking at the samples from the toys alone, there was a significant decrease following the intervention in the intervention group compared with the control group for rhinovirus (OR 3.8, 95% CI 1.3-10.5; P = 0.01) and RSV (OR 5.2, 95% CI 1.1-23.8; P = 0.04), but not adenovirus". This a poorly reported cluster-RCT. Its importance lies in the surface viral prevalence data (which could have been overestimated by PCR) and the finding that even in the presence of high viral prevalence, sickness was lower in the control (no surface disinfection) arm. This suggests the absence of other factors that could activate surface respiratory viruses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not mentioned
Allocation concealment (selection bias)	Unclear risk	Method not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias)	Low risk	Objective measure of bacterial and viral counts. However, illness reporting is unclear.

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Ibfelt 2015 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No attrition or denominators given for results.
Selective reporting (reporting bias)	Low risk	Unlikely that other outcomes were measured but not reported

Ibfelt 2015

Study characteristics	
Methods	Cluster-RCT in 12 daycare nurseries in Denmark. Centres in the intervention group had their linen and children's toys commercially cleaned and disinfected every 2 weeks. Control group centres had usual practice. Swabbing for bacteria and respiratory viruses was conducted at baseline and the end of the intervention period.
Participants	12 nurseries in Copenhagen (intervention = 6, control = 6) with a total of 587 children aged 6 months to 3 years Not clear how many children were in each group. Data on illness collected at the individual level, and on presence of bacteria and viruses at the cluster level.
Interventions	Washing and disinfection of toys and linen every 2 weeks for 3 months. See Table 1 for details.
Outcomes	Laboratory: counts of bacteria (not relevant to this review) and 11 respiratory viruses at baseline and end of intervention period, taken from swabs of 10 predefined locations in playroom (7 locations) and toilet area (3 locations). Viruses were influenza A and B; coronavirus NL63229E, OC43, and HKU1; parainfluenza virus 1, 2, 3, and 4; rhinovirus; RSV A/B; adenovirus; enterovirus; parechovirus; metapneumovirus; and bocavirus. Testing by PCR Effectiveness: illness counts in the children. Absence due to sickness recorded daily with reason categorised, but no definitions of illness provided. Safety: none mentioned in methods and none reported
Notes	The authors conclude that "Although cleaning and disinfection of toys every two weeks can decrease the microbial load in nurseries, it does not appear to reduce sickness absence among nursery children". The results of the disinfection are reported as follows: "The most prevalent virus was coronavirus (97% positive samples), followed by bocavirus (96%), adenovirus (73%) and rhinovirus (46%). The intervention reduced the presence of adenovirus, rhinovirus and RSV approximately two- to five-fold [odds ratio (OR) 2.4, 95% confidence interval (CI) 1.1-5.0 for adenovirus; OR 5.3, 95% CI 2.3-12.4 for rhinovirus; OR 4.1, 95% CI 1.5-11.2 for RSV] compared with the control group. On the other hand, metapneumovirus was found significantly less often in the control group than in the intervention group. The intervention had no effect on the detection of other viruses. The fomites with the highest presence of respiratory virus were pillows and sofas, followed by toys and playroom tables. When looking at the samples from the toys alone, there was a significant decrease following the intervention in the intervention group compared with the control group for rhinovirus (OR 3.8, 95% CI 1.3-10.5; P = 0.01) and RSV (OR 5.2, 95% CI 1.1-23.8; P = 0.04), but not adenovirus". This a poorly reported cluster-RCT. Its importance lies in the surface viral prevalence data (which could have been overestimated by PCR) and the finding that even in the presence of high viral prevalence, sickness was lower in the control (no surface disinfection) arm. This suggests the absence of other factors that could activate surface respiratory viruses.

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Ibfelt 2015 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not mentioned
Allocation concealment (selection bias)	Unclear risk	Method not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective measure of bacterial and viral counts. However, illness reporting is unclear.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No attrition or denominators given for results.
Selective reporting (reporting bias)	Low risk	Unlikely that other outcomes were measured but not reported

Ide 2014

Study characteristics	
Methods	Randomised, open-label, 2-group parallel study of 757 high school students (15 to 17 years of age) conducted for 90 days during the influenza epidemic season from 1 December 2011 to 28 February 2012, in 6 high schools in Shizuoka Prefecture, Japan. The green tea gargling group gargled 3 times a day with bottled green tea, and the water gargling group did the same with tap water. The water group was restricted from gargling with green tea.
Participants	A total of 747 students were enrolled (green tea gargling group = 384, water gargling group = 363) High school students (15 to 17 years of age) who attended 6 high schools in the Kakegawa and Ogasa districts of Shizuoka Prefecture, Japan
Interventions	See TIDieR Table (Table 1).
Outcomes	Incidence of laboratory-confirmed influenza Incidence of clinically defined influenza infection Time for which the participant was free from clinically defined influenza infection Clinically defined influenza infection, specified as fever (≥ 37.8 °C) plus any 2 of the following additional symptoms: cough, sore throat, headache, or myalgia. Influenza infection with viral antigen was detected by immunochromatographic assay. No safety data reported.
Notes	

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Ide 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated permuted block randomised schema
Allocation concealment (selection bias)	Low risk	Randomised at the Data Management Center of Shizuoka General Hospital in Japan
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal attrition
Selective reporting (reporting bias)	Unclear risk	Protocol not available

Ide 2014

Study characteristics	
Methods	Randomised, open-label, 2-group parallel study of 757 high school students (15 to 17 years of age) conducted for 90 days during the influenza epidemic season from 1 December 2011 to 28 February 2012, in 6 high schools in Shizuoka Prefecture, Japan. The green tea gargling group gargled 3 times a day with bottled green tea, and the water gargling group did the same with tap water. The water group was restricted from gargling with green tea.
Participants	A total of 747 students were enrolled (green tea gargling group = 384, water gargling group = 363) High school students (15 to 17 years of age) who attended 6 high schools in the Kakegawa and Ogasa districts of Shizuoka Prefecture, Japan
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Notes	

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Ide 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated permuted block randomised schema
Allocation concealment (selection bias)	Low risk	Randomised at the Data Management Center of Shizuoka General Hospital in Japan
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal attrition
Selective reporting (reporting bias)	Unclear risk	Protocol not available

Ide 2016

Study characteristics	
Methods	Randomised controlled study in Japan. Participants were randomly allocated into the catechin-treated (epigallocatechin gallate-treated) or non-treated face mask groups for 60 days from January to March 2016. Incidence of laboratory-confirmed influenza infection was measured and compared between groups using Fisher's exact test. Multivariate analysis was performed to calculate adjusted ORs and associated 95% CIs.
Participants	Participants included workers in a nursing home, a rehabilitation facility, and a hospital. A total of 234 participants were eligible for the study (catechin group, n = 118; control group, n = 116).
Interventions	Catechin-treated mask versus non-treated face mask. See Table 1 for details.
Outcomes	Incidence of laboratory-confirmed influenza infection Laboratory-confirmed influenza infection with viral antigen detected by immunochromatographic assay performed when participants reported ILI. No safety outcomes reported.
Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement

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Ide 2016 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Computer-generated randomisation, but method not stated
Allocation concealment (selection bias)	Low risk	Central randomisation service at Data Management Centre of Shizouka General Hospital
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Attrition minimal
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition minimal
Selective reporting (reporting bias)	Low risk	Specified outcomes reported.

Ide 2016

Study characteristics	
Methods	Randomised controlled study in Japan. Participants were randomly allocated into the catechin-treated (epigallocatechin gallate-treated) or non-treated face mask groups for 60 days from January to March 2016. Incidence of laboratory-confirmed influenza infection was measured and compared between groups using Fisher's exact test. Multivariate analysis was performed to calculate adjusted ORs and associated 95% CIs.
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Interventions	Catechin-treated mask versus non-treated face mask. See Table 1 for details.
Outcomes	Incidence of laboratory-confirmed influenza infection Laboratory-confirmed influenza infection with viral antigen detected by immunochromatographic assay performed when participants reported ILI. No safety outcomes reported.
Notes	Government funded
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Computer-generated randomisation, but method not stated
Allocation concealment (selection bias)	Low risk	Central randomisation service at Data Management Centre of Shizouka General Hospital

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Ide 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Attrition minimal
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition minimal
Selective reporting (reporting bias)	Low risk	Specified outcomes reported.

Jacobs 2009

Study characteristics	
Methods	Open RCT lasting 77 days from January 2008 to test “superiority” of face masks in preventing "URTI". This term appears as an acronym in the introduction and is not explained. It is assumed that it stands for 'upper respiratory infections', but it is preceded in the text by the term 'common cold', which is also lacking a definition. Randomisation was carried out in blocks within each of 3 professional figures (physicians, nurses, and “co-medical” personnel).
Participants	33 HCWs mainly females aged around 34 to 37 in a tertiary healthcare hospital in Tokyo, Japan. HCW with “predisposing conditions” (undefined) to “URTI” and those taking antibiotics were excluded. A baseline descriptive survey was carried out including “quality of life”. 1 participant dropped out at end of week 1, but no reason is reported nor the allocation arm. Analysis was performed on 32 participants (mask = 17, no mask = 15).
Interventions	Surgical mask MA-3 (Osu Sangyo, Japan) during all phases of hospital work (n = 17) or no mask (n = 15) (except when specifically required by hospital SOPs)
Outcomes	Laboratory: N/A Effectiveness: URTI is defined on the basis of a symptoms score, with a score > 14 being a URTI according to Jackson’s 1958 criteria (“Jackson score”). These are not explained in text, although the symptoms are listed in Table 3 (any, sore throat, runny nose, stuffy nose, sneeze, cough, headache, ear ache, feel bad) together with their mean and scores SD by intervention arm. Safety: the text does not mention or report harms. These appear to be indistinguishable from URTI symptoms (e.g. headache which is reported as of significantly longer duration in the intervention arm). Compliance is self-reported as high (84.3% of participants).
Notes	The authors conclude that “Face mask use in healthcare workers has not been demonstrated to provide benefit in terms of cold symptoms or getting colds. A larger study is needed to definitively establish non-inferiority of no mask use”. This is a small, badly reported trial. The purpose of trials is to test hypotheses not to prove or disprove 'superiority' of interventions. There is no power calculation, and CIs are not reported (although there is a mention in Discussion). No accurate definitions of a series of important variables (e.g. URTI, runny nose, etc.) are reported, and the Jackson scores are not explained, nor their use in Japanese personnel or language validated.

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Jacobs 2009 *(Continued)*

	Intervention arm data not extracted due to the uncertainty of its meaning.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Open RCT, but sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	"Mask and no mask groups were formed using block randomisation of subjects within their respective job categories: nurses, doctors, and co-medical personnel." Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study. Blinding not possible, as 1 group wore face masks
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 dropout in each group accounted for. "Analyses were performed following the principles of intention-to-treat."
Selective reporting (reporting bias)	High risk	NB: influenza vaccine coverage was 100% in mask group and only 81% in the non-mask-wearing group.

Kotch 1994

Study characteristics

Methods	Pair-matched, cluster-RCT conducted from 19 October 1988 to 23 May 1989 in 24 childcare centres in North Carolina, USA The trial tested the effects of a hand-washing and environment sterilising programme on diarrhoea (data not extracted) and ARIs. Child daycare centres had to care for 30 children or less, at least 5 of whom had to be in nappies, and intending to stay open for at least another 2 years. Randomisation is not described, nor are cluster coefficients reported.
Participants	389 children aged 3 years or less in daycare for at least 20 hours a week. There were some withdrawals, but attrition of participants is not stated, only that in the end data for 31 intervention classrooms and 36 control classrooms were available. 291 children aged up to 24 months and 80 over 24 months took part. The text is very confusing, as 371 seems to be the total of the number of families that took part. No denominator breakdown by arm is reported, and numerators are only reported as new episodes per child-year.
Interventions	Structured hand-washing and environment (including surfaces, sinks, toilets, and toys) disinfecting programme with waterless disinfectant scrub
Outcomes	Laboratory: N/A Effectiveness: ARI (coughing, runny nose, wheezing, sore throat, or earache) Safety: N/A
Notes	Risk of bias: high (poor reporting of randomisation, outcomes, numerators and denominators)

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Kotch 1994 *(Continued)*

	Note: the authors conclude that the fully adjusted RR for prevention of ARIs was 0.94 (−2.43 to 0.66). A poorly reported study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Pair-matched cluster-randomised, controlled trial", but sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Centres were matched in pairs and then randomly allocated to either intervention or control programmes. Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible (intervention was training session)
Blinding of outcome assessment (detection bias) All outcomes	High risk	"The same staff who conducted the training unobtrusively recorded observations at 5-week intervals"
Incomplete outcome data (attrition bias) All outcomes	High risk	18 families were dropped, denominator not clear.
Selective reporting (reporting bias)	High risk	Denominators not clearly reported

Ladegaard 1999

Study characteristics

Methods	RCT with cluster-randomisation to intervention or control. Of 10 institutions, 2 were excluded because they wanted institutions to be comparable in uptake area (i.e. housing and income). Interventions were administered to children, parents, and teachers at the institutions.
Participants	Children 0 to 6 years old
Interventions	Multifaceted: information, t-shirts to the children with: "Clean hands - yes, thank you", performance of a fairytale "The princess who did not want to wash her hands", exercise in hand-washing, importance of clean and fresh air. The aims of the intervention were to: 1. increase the hygiene education of the daycare teachers; 2. motivate the children by practical learning to have better hand hygiene; and 3. inform the parents about better hand hygiene.
Outcomes	34% decrease in "sickness" (probably mostly gastroenteritis)
Notes	Risk of bias: only limited data available Note: the authors conclude that there was a 34% decrease in sickness in the intervention arm; this is probably overall sickness, as gastroenteritis is part of the outcomes (data not extracted). Only limited data available from translation by Jørgen Lous.

Risk of bias

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Ladegaard 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Randomisation by "lottery", the same as "flip the coin". Concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not possible
Incomplete outcome data (attrition bias) All outcomes	High risk	Total numbers of children included in each arm not reported.
Selective reporting (reporting bias)	High risk	Limited data reported, in particular denominators missing.

Larson 2010

Study characteristics	
Methods	Cluster block-randomised, controlled trial carried out between 20 November 2006 and 20 June 2008 in an upper Manhattan immigrant Latino neighbourhood ("19 month data collection period"). The study aimed at assessing the effects of education versus education and hand sanitiser use versus education and hand sanitiser use and common mask use against upper respiratory infections over a period of under 2 years. Follow-up was through an automated telephone system with a small financial incentive (USD 20) for those with 75% or more compliance. Those reporting an ILI received a visit within 48 hours for swabbing. An index case was someone who at the "onset day of illness nobody else in the household had been symptomatic within the previous five days". A secondary case for each episode "was any member of the household who developed symptoms within five days following the index case"; "The secondary attack rate was defined as the number of secondary cases recorded within 5 days of the onset of symptoms in the index case divided by the number of household members minus one". The text implies that the unit of observation was the episode ("study subjects contributed more than one episode in which they were considered to be the index case").
Participants	617 households were randomised to the education group (n = 211), the hand sanitiser group (n = 205), and the hand sanitiser and mask group (n = 201). There were 2708 participants, mostly adult Latino immigrants to the USA. Recruitment and allocation were carried out by household. There had to be at least 3 people living in the household, with at least 1 being a preschool or elementary school child, speaking English or Spanish, having a telephone, willingness to complete symptom assessments and have bimonthly home visits, and not using alcohol-based hand sanitiser routinely. Intracluster correlation coefficients are reported on page 179 of the manuscript.

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Larson 2010 *(Continued)*

Interventions	Written Spanish or English language educational materials regarding the prevention and treatment of URTIs and influenza or the same educational materials and hand sanitiser (Purell, J&J), in large (8- and 4-ounce) and small (1-ounce) containers to be carried by individual household members to work or school, or the same interventions as well as regular surgical face masks (Procedure Face Masks for adults and children, Kimberly-Clark) with instructions for both the caretaker and the ill person to wear them when an ILI occurred in any household member. Replenishment of intervention stocks was done at the bimonthly home visit. Caretakers had to wear a mask for 7 days when within 3 feet of a symptomatic case. They were also encouraged to wear masks within 3 feet of any household member. Reinforcing phone calls were made 3 times in 6 days. The text clearly reports active influenza vaccine promotion during the bimonthly visits. (“The home visit to each household was made every 2 months to minimise study dropout, reinforce adherence to the assigned intervention, replenish product supplies and record use of supplies, answer questions, and correct ongoing misconceptions. At each visit, new educational materials regarding URTI prevention and treatment and influenza vaccination were distributed.” (PDF page 3). Also just before the Discussion as follows: “Influenza vaccination rates: There was an increase between the baseline and exit interview in all three groups that reported 50% of more of members receiving influenza vaccine (pre- versus post-intervention for each group: 21.1% and 40.8% in the Education group, 19.0% and 57.1% in the hand sanitiser group, and 22.4% and 43.5% in the hand sanitiser and face mask group (P = 0.001). Additionally, those in the hand sanitiser group reported a significantly greater increase than the other 2 groups, controlling for baseline rates (P = 0.002)”) Coverage was unequal across groups, no information on the progressive impact of the vaccine, or indeed the nature of the vaccine(s) is reported. Apparently the first season was mild and the vaccine mismatched, compliance with the trial interventions was low in Arm 3, and a local epidemic of *Staphylococcus aureus* meant that the control group started washing hands. The trial authors report no effect on reporting rates of vaccine coverage by arms, but with so many confounders who knows?
Outcomes	Laboratory: PCR carried out on samples from deep nasal swabs for influenza and the most common other pathogens (RSV, rhinovirus, enterovirus, parainfluenza viruses, etc.). The text describing the results of the swabbing is confusing, but in general appears to be non-random “Households reported 669 episodes of ILI (0 to 5 per individual)". Of the 234 deep nasal swabs obtained, 33.3% (n = 78) tested positive for influenza: 43.6% (n = 34) were influenza A and 56.4% (n = 44) were influenza B. Amongst the 66.7% who tested negative for influenza, 30.8% (48/156) tested positive for other viruses: 7 for respiratory syncytial virus, 9 for parainfluenza, 11 for enterovirus, 10 for rhinovirus, 6 for adenovirus, and 5 for metapneumovirus. Swabs were not obtained from the remaining 435 reported ILI episodes for the following reasons: 72.0% (n = 313) did not meet the CDC definition of an ILI and were therefore included in the URTI symptom count; 21.4% of episodes (n = 93) were reported after 48 hours of ILI onset or the participant refused to be swabbed; and the research staff were unable to reach the participant in 6.7% of episodes (n = 29). As no definition of URTI is given, it is unclear what kind of biases were introduced by the non-swabbing of the 313/435 “not meeting CDC definition”. Effectiveness: ILI (CDC definition): “temperature of 37.8°C or more and cough and/or sore throat in the absence of a known cause other than influenza” URTI only referred to as “Viral upper respiratory infections (URTIs)”. Safety: N/A
Notes	The authors conclude that “the Hand Sanitizer group was significantly more likely to report that no household member had symptoms (P,0.01), but there were no significant differences in rates of infection by intervention group in multivariate analyses. Knowledge improved significantly more in the Hand Sanitizer group (P,0.0001). The proportion of households that reported >50% of members receiving influenza vaccine increased during the study (P,0.001). Despite the fact that compliance with mask wearing was poor, mask wearing as well as increased crowding, lower education levels of caretakers, and index cases 0–5 years of age (compared with adults) were associated with significantly lower sec-

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Larson 2010 *(Continued)*

ondary transmission rates (all P,0.02). In this population, there was no detectable additional benefit of hand sanitiser or face masks over targeted education on overall rates of URTIs, but mask wearing was associated with reduced secondary transmission and should be encouraged during outbreak situations. During the study period, community concern about methicillin-resistant *Staphylococcus aureus* was occurring, perhaps contributing to the use of hand sanitiser in the Education control group, and diluting the intervention's measurable impact".

The study is at high risk of bias. Randomisation and reasons for dropout are not described. Differentials in cluster characteristics across arms point to randomisation not having worked, and the confounding effects of a postrandomisation staphylococcal scare are difficult to judge. Symptom-driven follow-up gives no idea of the effects on asymptomatic ILI/influenza. Poor definitions (URTI?). There are unexplained dropouts, and the analysis plan is unclear. Finally, the very small number of cases of influenza and an unclear swabbing attrition may introduce further elements of confounding.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Cluster block randomised, controlled trial", but sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	"Households were block randomised into one of three groups" Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel was not possible.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment is not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	In control group households (n = 211), 26 dropped out and 37 did not consent. In hand sanitiser group households (n = 205), 21 dropped out and 36 did not consent. In hand sanitiser and face mask group households (n = 201), 19 dropped out and 35 did not consent. Reasons for dropout were not described.
Selective reporting (reporting bias)	Unclear risk	617 of 772 eligible households were randomised.

Little 2015

Study characteristics

Methods	Individuals sharing a household by mailed invitation through general practices in England were recruited. After consent, participants were randomised online by an automated computer-generated random-number program to receive either no access or access to a bespoke automated web-based intervention that maximised hand-washing intention, monitored hand-washing behaviour, provided tailored feedback, reinforced helpful attitudes and norms, and addressed negative beliefs. Participants were enrolled into an additional cohort (randomised to receive intervention or no intervention) to assess whether the baseline questionnaire on hand-washing would affect hand-washing behav-

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Little 2015 *(Continued)*

	iour. Participants were not masked to intervention allocation, but statistical analysis commands were constructed masked to group. The primary outcome was number of episodes of RTIs in index participants in a modified intention-to-treat population of randomly assigned participants who completed follow-up at 16 weeks.
Participants	344 physician offices were recruited over a wide area of England, and 20,066 participants were enrolled and randomised to intervention (N = 16,086) and control (N = 10,026). Modified ITT was performed on 16,908 participants who completed the follow-up questionnaire at 16 weeks (intervention = 8241 and control = 8667). Inclusion criteria: adult patients (aged 18 years or older) identified from computerised lists in general practitioner (GP) practices in England, for whom there was at least 1 other individual living in the household who was willing to report illness to the index person Exclusion criteria: patients with severe mental problems (e.g. major uncontrolled depression or schizophrenia, dementia, or severe mental impairment) or who were terminally ill, and those reporting a skin complaint that would restrict hand-washing
Interventions	Automated web-based intervention that maximised hand-washing intention, monitored hand-washing behaviour, provided tailored feedback, reinforced helpful attitudes and norms, and addressed negative beliefs. Control no access to intervention web pages. See Table 1 for details.
Outcomes	The primary outcome was the number of index individuals that reported 1 or more RTIs (including ILI) at 16 weeks. Secondary: duration of symptoms, transmission of respiratory infections, gastrointestinal infections, attendance at the practice, and use of health service resources Infections self-reported by participants. RTI defined as 2 symptoms of an RTI for at least 1 day or 1 symptom for 2 consecutive days. Definition of ILI was a high temperature (feeling very hot or very cold; or measured temperature > 37.5 °C), a respiratory symptom (sore throat, cough, or runny nose), and a systemic symptom (headache, severe fatigue, severe muscle aches, or severe malaise). No safety outcomes reported.
Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were automatically randomly assigned by the intervention software, but sequence generation not described.
Allocation concealment (selection bias)	Low risk	Participants were automatically randomly assigned by the intervention software.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition that was different in the 2 groups

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Little 2015 *(Continued)*

Selective reporting (reporting bias)	Low risk	Specified outcomes reported.

Jacobs 2009

Study characteristics	
Methods	Open RCT lasting 77 days from January 2008 to test “superiority” of face masks in preventing "URTI". This term appears as an acronym in the introduction and is not explained. It is assumed that it stands for 'upper respiratory infections', but it is preceded in the text by the term 'common cold', which is also lacking a definition. Randomisation was carried out in blocks within each of 3 professional figures (physicians, nurses, and “co-medical” personnel).
Participants	33 HCWs mainly females aged around 34 to 37 in a tertiary healthcare hospital in Tokyo, Japan. HCW with “predisposing conditions” (undefined) to “URTI” and those taking antibiotics were excluded. A baseline descriptive survey was carried out including “quality of life”. 1 participant dropped out at end of week 1, but no reason is reported nor the allocation arm. Analysis was performed on 32 participants (mask = 17, no mask = 15).
Interventions	Surgical mask MA-3 (Osu Sangyo, Japan) during all phases of hospital work (n = 17) or no mask (n = 15) (except when specifically required by hospital SOPs)
Outcomes	Laboratory: N/A Effectiveness: URTI is defined on the basis of a symptoms score, with a score > 14 being a URTI according to Jackson’s 1958 criteria (“Jackson score”). These are not explained in text, although the symptoms are listed in Table 3 (any, sore throat, runny nose, stuffy nose, sneeze, cough, headache, ear ache, feel bad) together with their mean and scores SD by intervention arm. Safety: the text does not mention or report harms. These appear to be indistinguishable from URTI symptoms (e.g. headache which is reported as of significantly longer duration in the intervention arm). Compliance is self-reported as high (84.3% of participants).
Notes	The authors conclude that “Face mask use in healthcare workers has not been demonstrated to provide benefit in terms of cold symptoms or getting colds. A larger study is needed to definitively establish non-inferiority of no mask use”. This is a small, badly reported trial. The purpose of trials is to test hypotheses not to prove or disprove 'superiority' of interventions. There is no power calculation, and CIs are not reported (although there is a mention in Discussion). No accurate definitions of a series of important variables (e.g. URTI, runny nose, etc.) are reported, and the Jackson scores are not explained, nor their use in Japanese personnel or language validated. Intervention arm data not extracted due to the uncertainty of its meaning.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Open RCT, but sequence generation not reported

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Jacobs 2009 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	"Mask and no mask groups were formed using block randomisation of subjects within their respective job categories: nurses, doctors, and co-medical personnel." Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study. Blinding not possible, as 1 group wore face masks
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 dropout in each group accounted for. "Analyses were performed following the principles of intention-to-treat."
Selective reporting (reporting bias)	High risk	NB: influenza vaccine coverage was 100% in mask group and only 81% in the non-mask-wearing group.

Kotch 1994

Study characteristics	
Methods	Pair-matched, cluster-RCT conducted from 19 October 1988 to 23 May 1989 in 24 childcare centres in North Carolina, USA The trial tested the effects of a hand-washing and environment sterilising programme on diarrhoea (data not extracted) and ARIs. Child daycare centres had to care for 30 children or less, at least 5 of whom had to be in nappies, and intending to stay open for at least another 2 years. Randomisation is not described, nor are cluster coefficients reported.
Participants	389 children aged 3 years or less in daycare for at least 20 hours a week. There were some withdrawals, but attrition of participants is not stated, only that in the end data for 31 intervention classrooms and 36 control classrooms were available. 291 children aged up to 24 months and 80 over 24 months took part. The text is very confusing, as 371 seems to be the total of the number of families that took part. No denominator breakdown by arm is reported, and numerators are only reported as new episodes per child-year.
Interventions	Structured hand-washing and environment (including surfaces, sinks, toilets, and toys) disinfecting programme with waterless disinfectant scrub
Outcomes	Laboratory: N/A Effectiveness: ARI (coughing, runny nose, wheezing, sore throat, or earache) Safety: N/A
Notes	Risk of bias: high (poor reporting of randomisation, outcomes, numerators and denominators) Note: the authors conclude that the fully adjusted RR for prevention of ARIs was 0.94 (−2.43 to 0.66). A poorly reported study

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Pair-matched cluster-randomised, controlled trial", but sequence generation not reported

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Kotch 1994 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Centres were matched in pairs and then randomly allocated to either intervention or control programmes. Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible (intervention was training session)
Blinding of outcome assessment (detection bias) All outcomes	High risk	"The same staff who conducted the training unobtrusively recorded observations at 5-week intervals"
Incomplete outcome data (attrition bias) All outcomes	High risk	18 families were dropped, denominator not clear.
Selective reporting (reporting bias)	High risk	Denominators not clearly reported

Ladegaard 1999

Study characteristics	
Methods	RCT with cluster-randomisation to intervention or control. Of 10 institutions, 2 were excluded because they wanted institutions to be comparable in uptake area (i.e. housing and income). Interventions were administered to children, parents, and teachers at the institutions.
Participants	Children 0 to 6 years old
Interventions	Multifaceted: information, t-shirts to the children with: "Clean hands - yes, thank you", performance of a fairytale "The princess who did not want to wash her hands", exercise in hand-washing, importance of clean and fresh air. The aims of the intervention were to: 1. increase the hygiene education of the daycare teachers; 2. motivate the children by practical learning to have better hand hygiene; and 3. inform the parents about better hand hygiene.
Outcomes	34% decrease in "sickness" (probably mostly gastroenteritis)
Notes	Risk of bias: only limited data available Note: the authors conclude that there was a 34% decrease in sickness in the intervention arm; this is probably overall sickness, as gastroenteritis is part of the outcomes (data not extracted). Only limited data available from translation by Jørgen Lous.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Randomisation by "lottery", the same as "flip the coin". Concealment not reported

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Ladegaard 1999 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not possible
Incomplete outcome data (attrition bias) All outcomes	High risk	Total numbers of children included in each arm not reported.
Selective reporting (reporting bias)	High risk	Limited data reported, in particular denominators missing.

Larson 2010

Study characteristics	
Methods	Cluster block-randomised, controlled trial carried out between 20 November 2006 and 20 June 2008 in an upper Manhattan immigrant Latino neighbourhood ("19 month data collection period"). The study aimed at assessing the effects of education versus education and hand sanitiser use versus education and hand sanitiser use and common mask use against upper respiratory infections over a period of under 2 years. Follow-up was through an automated telephone system with a small financial incentive (USD 20) for those with 75% or more compliance. Those reporting an ILI received a visit within 48 hours for swabbing. An index case was someone who at the "onset day of illness nobody else in the household had been symptomatic within the previous five days". A secondary case for each episode "was any member of the household who developed symptoms within five days following the index case"; "The secondary attack rate was defined as the number of secondary cases recorded within 5 days of the onset of symptoms in the index case divided by the number of household members minus one". The text implies that the unit of observation was the episode ("study subjects contributed more than one episode in which they were considered to be the index case").
Participants	617 households were randomised to the education group (n = 211), the hand sanitiser group (n = 205), and the hand sanitiser and mask group (n = 201). There were 2708 participants, mostly adult Latino immigrants to the USA. Recruitment and allocation were carried out by household. There had to be at least 3 people living in the household, with at least 1 being a preschool or elementary school child, speaking English or Spanish, having a telephone, willingness to complete symptom assessments and have bimonthly home visits, and not using alcohol-based hand sanitiser routinely. Intracluster correlation coefficients are reported on page 179 of the manuscript.
Interventions	Written Spanish or English language educational materials regarding the prevention and treatment of URTIs and influenza or the same educational materials and hand sanitiser (Purell, J&J), in large (8- and 4-ounce) and small (1-ounce) containers to be carried by individual household members to work or school, or the same interventions as well as regular surgical face masks (Procedure Face Masks for adults and children, Kimberly-Clark) with instructions for both the caretaker and the ill person to wear them when an ILI occurred in any household member. Replenishment of intervention stocks was done at the bimonthly home visit.

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Larson 2010 *(Continued)*

	Caretakers had to wear a mask for 7 days when within 3 feet of a symptomatic case. They were also encouraged to wear masks within 3 feet of any household member. Reinforcing phone calls were made 3 times in 6 days. The text clearly reports active influenza vaccine promotion during the bimonthly visits. ("The home visit to each household was made every 2 months to minimise study dropout, reinforce adherence to the assigned intervention, replenish product supplies and record use of supplies, answer questions, and correct ongoing misconceptions. At each visit, new educational materials regarding URTI prevention and treatment and influenza vaccination were distributed." (PDF page 3). Also just before the Discussion as follows: "Influenza vaccination rates: There was an increase between the baseline and exit interview in all three groups that reported 50% of more of members receiving influenza vaccine (pre- versus post-intervention for each group: 21.1% and 40.8% in the Education group, 19.0% and 57.1% in the hand sanitiser group, and 22.4% and 43.5% in the hand sanitiser and face mask group (P = 0.001). Additionally, those in the hand sanitiser group reported a significantly greater increase than the other 2 groups, controlling for baseline rates (P = 0.002)") Coverage was unequal across groups, no information on the progressive impact of the vaccine, or indeed the nature of the vaccine(s) is reported. Apparently the first season was mild and the vaccine mismatched, compliance with the trial interventions was low in Arm 3, and a local epidemic of *Staphylococcus aureus* meant that the control group started washing hands. The trial authors report no effect on reporting rates of vaccine coverage by arms, but with so many confounders who knows?
Outcomes	Laboratory: PCR carried out on samples from deep nasal swabs for influenza and the most common other pathogens (RSV, rhinovirus, enterovirus, parainfluenza viruses, etc.). The text describing the results of the swabbing is confusing, but in general appears to be non-random "Households reported 669 episodes of ILI (0 to 5 per individual)". Of the 234 deep nasal swabs obtained, 33.3% (n = 78) tested positive for influenza: 43.6% (n = 34) were influenza A and 56.4% (n = 44) were influenza B. Amongst the 66.7% who tested negative for influenza, 30.8% (48/156) tested positive for other viruses: 7 for respiratory syncytial virus, 9 for parainfluenza, 11 for enterovirus, 10 for rhinovirus, 6 for adenovirus, and 5 for metapneumovirus. Swabs were not obtained from the remaining 435 reported ILI episodes for the following reasons: 72.0% (n = 313) did not meet the CDC definition of an ILI and were therefore included in the URTI symptom count; 21.4% of episodes (n = 93) were reported after 48 hours of ILI onset or the participant refused to be swabbed; and the research staff were unable to reach the participant in 6.7% of episodes (n = 29). As no definition of URTI is given, it is unclear what kind of biases were introduced by the non-swabbing of the 313/435 "not meeting CDC definition". Effectiveness: ILI (CDC definition): "temperature of 37.8°C or more and cough and/or sore throat in the absence of a known cause other than influenza" URTI only referred to as "Viral upper respiratory infections (URTIs)". Safety: N/A
Notes	The authors conclude that "the Hand Sanitizer group was significantly more likely to report that no household member had symptoms (P,0.01), but there were no significant differences in rates of infection by intervention group in multivariate analyses. Knowledge improved significantly more in the Hand Sanitizer group (P,0.0001). The proportion of households that reported >50% of members receiving influenza vaccine increased during the study (P,0.001). Despite the fact that compliance with mask wearing was poor, mask wearing as well as increased crowding, lower education levels of caretakers, and index cases 0–5 years of age (compared with adults) were associated with significantly lower secondary transmission rates (all P,0.02). In this population, there was no detectable additional benefit of hand sanitiser or face masks over targeted education on overall rates of URTIs, but mask wearing was associated with reduced secondary transmission and should be encouraged during outbreak situations. During the study period, community concern about methicillin-resistant *Staphylococcus aureus* was occurring, perhaps contributing to the use of hand sanitiser in the Education control group, and diluting the intervention's measurable impact". The study is at high risk of bias. Randomisation and reasons for dropout are not described. Differentials in cluster characteristics across arms point to randomisation not having worked, and the confounding

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Larson 2010 *(Continued)*

effects of a postrandomisation staphylococcal scare are difficult to judge. Symptom-driven follow-up gives no idea of the effects on asymptomatic ILI/influenza. Poor definitions (URTI?). There are unexplained dropouts, and the analysis plan is unclear. Finally, the very small number of cases of influenza and an unclear swabbing attrition may introduce further elements of confounding.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Cluster block randomised, controlled trial", but sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	"Households were block randomised into one of three groups" Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel was not possible.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment is not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	In control group households (n = 211), 26 dropped out and 37 did not consent. In hand sanitiser group households (n = 205), 21 dropped out and 36 did not consent. In hand sanitiser and face mask group households (n = 201), 19 dropped out and 35 did not consent. Reasons for dropout were not described.
Selective reporting (reporting bias)	Unclear risk	617 of 772 eligible households were randomised.

Little 2015

Study characteristics

Methods	Individuals sharing a household by mailed invitation through general practices in England were recruited. After consent, participants were randomised online by an automated computer-generated random-number program to receive either no access or access to a bespoke automated web-based intervention that maximised hand-washing intention, monitored hand-washing behaviour, provided tailored feedback, reinforced helpful attitudes and norms, and addressed negative beliefs. Participants were enrolled into an additional cohort (randomised to receive intervention or no intervention) to assess whether the baseline questionnaire on hand-washing would affect hand-washing behaviour. Participants were not masked to intervention allocation, but statistical analysis commands were constructed masked to group. The primary outcome was number of episodes of RTIs in index participants in a modified intention-to-treat population of randomly assigned participants who completed follow-up at 16 weeks.
Participants	344 physician offices were recruited over a wide area of England, and 20,066 participants were enrolled and randomised to intervention (N = 16,086) and control (N = 10,026).

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Little 2015 *(Continued)*

	Modified ITT was performed on 16,908 participants who completed the follow-up questionnaire at 16 weeks (intervention = 8241 and control = 8667). Inclusion criteria: adult patients (aged 18 years or older) identified from computerised lists in general practitioner (GP) practices in England, for whom there was at least 1 other individual living in the household who was willing to report illness to the index person Exclusion criteria: patients with severe mental problems (e.g. major uncontrolled depression or schizophrenia, dementia, or severe mental impairment) or who were terminally ill, and those reporting a skin complaint that would restrict hand-washing
Interventions	Automated web-based intervention that maximised hand-washing intention, monitored hand-washing behaviour, provided tailored feedback, reinforced helpful attitudes and norms, and addressed negative beliefs. Control no access to intervention web pages. See Table 1 for details.
Outcomes	The primary outcome was the number of index individuals that reported 1 or more RTIs (including ILI) at 16 weeks. Secondary: duration of symptoms, transmission of respiratory infections, gastrointestinal infections, attendance at the practice, and use of health service resources Infections self-reported by participants. RTI defined as 2 symptoms of an RTI for at least 1 day or 1 symptom for 2 consecutive days. Definition of ILI was a high temperature (feeling very hot or very cold; or measured temperature > 37.5 °C), a respiratory symptom (sore throat, cough, or runny nose), and a systemic symptom (headache, severe fatigue, severe muscle aches, or severe malaise). No safety outcomes reported.
Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were automatically randomly assigned by the intervention software, but sequence generation not described.
Allocation concealment (selection bias)	Low risk	Participants were automatically randomly assigned by the intervention software.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition that was different in the 2 groups
Selective reporting (reporting bias)	Low risk	Specified outcomes reported.

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Loeb 2009

Study characteristics	
Methods	Open non-inferiority RCT carried out to compare the surgical mask with the N95 respirator in protecting healthcare workers against influenza. The trial was carried out between 2008 (enrolment started in September and follow-up on 12 January 2009) and 23 April 2009 (when all HCWs caring for febrile patients were told to wear an N95 respirator) because of the appearance of novel A/H1N1). The trial trigger was the beginning of the influenza season, defined as isolation of 2 or more viruses in a district in the same week. Following the 2003 SARS outbreak, all Ontario nurses caring for febrile patients (38 °C or more and new onset cough or SOB) had to wear surgical masks. The randomisation (carried out in blocks of 4 by centre) then consisted of either confirmation to same-maker surgical mask wear or N95 respirator wear. Investigators and laboratory staff were blind to allocation status, but for obvious reasons (the visible difference in interventions), participants were unblinded. "The criterion for non-inferiority was met if the lower limit of the 95% confidence interval (CI) for the reduction in incidence (N95 respirator minus surgical group) was greater than -9%". So this is the non-inferiority margin. It is assumed that the "minus surgical group" means minus surgical mask group.
Participants	Consenting nurses (n = 446 randomised) aged a mean of 36.2 years working full time (≥ 37 hours/week) in 23 acute units (a mix of paediatric, A&E, and acute medical units) in 8 hospitals in Ontario, Canada. 225 were randomised to the surgical mask and 221 to the N95 respirator. There were 13 and 11 dropouts, respectively from each arm (all accounted for), plus 21 and 19 lost to follow-up; 11 in each arm gave no reason, the others are accounted for. There were no deaths. The final total of 212 and 210 was included in the analysis. Table 1 reports the demographic data of participants by arm, which appear comparable.
Interventions	Surgical masks (as standard wear by the standard distributor) or fit–tested N95 respirator. All nurses wore gloves or gowns in the presence of a febrile patient.
Outcomes	Laboratory RT-PCR paired sera with 4-fold antibody rise from baseline (only for unvaccinated) nurses Effectiveness: follow-up (lasting a mean of around 97 days for both arms) was carried out twice-weekly on a web-based instrument. Nurses with new symptoms were asked to swab a nostril if any of the following signs or symptoms had developed: fever (temperature ≥ 38 °C), cough, nasal congestion, sore throat, headache, sinus problems, muscle aches, fatigue, earache, ear infection, or chills. The text defines influenza with laboratory confirmation, and separately reports criteria for swab triggering and a definition of ILI ("Influenza-like illness was defined as the presence of cough and fever: a temperature ≥ 38°C"). But this is not formally linked to influenza in the text, as it appears that primary focus was the detection of laboratory-confirmed influenza (either by RT-PCR or serology). Additional outcome data sought were work-related absenteeism and physician visits for respiratory illness. Secondary outcomes included detection of the following non-influenza viruses by PCR: parainfluenza virus types 1, 2, 3, and 4; respiratory syncytial virus types A and B; adenovirus; metapneumovirus; rhinovirus-enterovirus; and coronaviruses OC43, 229E, SARS, NL63, and HKU1. Audits to assess nurse compliance with the interventions were carried out in the room of each patient cared for. The text reports that 50 and 48 nurses in the surgical mask and N95 groups, respectively, had laboratory confirmation of influenza infection, indicating non-inferiority. Interestingly, non-inferiority seemed to be applicable both to seasonal viruses and nH1N1 viruses (as 8% and 11.9% were serologically positive to nH1N1). This finding is explained either by seeding or cross reaction with seasonal H1N1. Equivalent conclusions could be drawn for nurses with complete follow-up. Non-inferiority was applicable also to other ILI agents identified. None of the 52 individuals with positive isolates met the criteria for ILI. All cases of ILI were confirmed as having influenza (9 and 2 respectively). This means that all the 11 cases of ILI had influenza, but that most of those with a laboratory diagnosis of influenza did not have cough and fever. For example, the text reports that "Of the 44 nurses in each group who had influenza diagnosed by serology, 29 (65.9%) in the surgical mask group and 31 (70.5%) in the N95 respirator group had no symptoms". By implication, of the 88 nurses with antibody rises, 28 had symptoms of some kind, i.e. two-thirds were asymptomatic. Absenteeism was 1 versus 39 episodes in the mask ver-

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Loeb 2009 *(Continued)*

	sus respirator arms. No episodes of LRTI were recorded. The number of family contacts with ILI were the same for each arm (45 versus 47). Physician visits were similar in both groups. Safety: no AEs are reported
Notes	The authors conclude that "Among nurses in Ontario tertiary care hospitals, use of a surgical mask compared with a N95 respirator resulted in non-inferior rates of laboratory-confirmed influenza". This a well-designed and conducted trial with credible conclusions. The only comment is that the focus in the analysis on influenza (symptomatic and asymptomatic) is not well-described, although the rationale is clear (interruption of transmission).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomisation was performed centrally ....", but method of sequence generation not described.
Allocation concealment (selection bias)	Low risk	"...by an independent clinical trials coordinating group such that investigators were blind to the randomisation procedure and group assignment and was stratified by centre in permuted blocks of 4 participants."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"It was not possible to conceal the identity of the N95 respirator or the surgical mask since manipulating these devices would interfere with their function"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment blinded: "Laboratory personnel conducting hemagglutinin inhibition assays, polymerase chain reaction (PCR), and viral culture for influenza were blinded to allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	21 of 225 randomised to mask group and 19 of 221 randomised to N95 group were lost to follow-up, reasons reported. Study stopped early: "We had planned to stop the study at the end of influenza season. However, because of the 2009 influenza A(H1N1) pandemic, the study was stopped on April 23, 2009, when the Ontario Ministry of Health and Long-Term Care recommended N95 respirators for all healthcare workers taking care of patients with febrile respiratory illness."
Selective reporting (reporting bias)	Low risk	All outcomes reported.

Longini 1988

Study characteristics

Methods	Cluster-controlled, double-blind, randomised trial to assess the efficacy of virucidal tissues in interrupting family transmission of rhinovirus and influenza virus. The study was carried out in the community of Tecumseh, Michigan, USA during the period of 25 November 1984 to 28 April 1985. However, the authors only report results for the period of 13 January to 23 March 1985, when a high circulation of influenza A H3N2 and rhinovirus was detected.
Participants	296 households were enrolled, but 5 households were eliminated from the analysis for "technical reasons". The analysis was carried out in households with 3 to 5 members. The authors report data on 143 households randomised to virucidal tissues and 148 to placebo tissue. The average age in households

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Longini 1988 *(Continued)*

	was around 22, and the difference between arms was not significant. Randomisation was carried out by the sponsor, and tissues were pre-packed in coded boxes with no other identifying features and delivered to households at the beginning of the study period.
Interventions	Disposable 3-layered virucidal tissues (citric and malic acids with sodium lauryl sulphate in the middle layer) or placebo (succinic acid in the middle layer) tissues. They were used to blow the nose and for coughing or sneezing into. Households were also stratified by level of tissue use. Tissue use was significantly higher in the intervention arm (82% versus 71%).
Outcomes	Laboratory: yes - viral culture from nasal and throat swabs from symptomatic participants Effectiveness: ARI (with a proportion of laboratory-confirmed diagnosis in non-randomly chosen participants with symptoms lasting 2 days or more) Follow-up and surveillance was carried out using a telephone questionnaire. Safety: N/A
Notes	Risk of bias: high (inappropriate choice of placebo) Note: the authors conclude that virucidal tissues were up to 36.9% effective in preventing transmission of ARIs as measured by secondary attack rates (18.7% versus 11.8%). This finding was not statistically significant, but may well have been affected by the lack of do-nothing community controls. This a well-designed, well-written study despite the unexplained attrition of 5 families, the lack of reporting of cluster coefficients, and the differential in tissue use between the 2 arms, which raises questions about the robustness of double-blinding. Particularly notable is the discussion on the low generalisability of results from the study from the placebo arm given that even the inert barrier of the tissues is likely to have limited spread. Also, the lengths to which the authors went to obtain allocation concealment and maintenance of double-blind conditions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Treated and placebo tissues were randomly assigned ..." Sequence generation not reported
Allocation concealment (selection bias)	Low risk	"Treated and placebo tissues were randomly assigned by the sponsor to 296 participating households stratified by household size, such that roughly half the households would receive treated tissues. Thus, the investigators were unaware of the assignment of treated tissues."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Treated and placebo tissues were randomly assigned by the sponsor to the randomly assigned 296 households stratified by household size... The type of tissue was identified by code, and the boxes in which tissues were contained were not marked with any specific identifiers. Therefore, the study was double-blinded."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The investigators were unaware of the assignment of the treated tissues"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	296 households eligible. "The final sample used for analysis consisted of 143 households in the treatment group and 148 households in the placebo group."
Selective reporting (reporting bias)	High risk	"The analysis of secondary spread was restricted to households of three to five members for technical reasons, which eliminated five households." "The two groups were almost identical in composition."

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Luby 2005

Study characteristics	
Methods	Partly double-blind, cluster-RCT carried out during 15 April 2002 to 5 April 2003 in Karachi, Pakistan. The trial assessed the effects of mother and child hand-washing on the incidence of respiratory infections, impetigo (data not extracted), and diarrhoea (data not extracted). Randomisation took place by computer-generated random numbers in 3 phases. 1. 25 neighbourhoods were assigned to hand-washing and 11 to standard practice. 2. 300 households were assigned to using antiseptic soap. 3. 300 households were assigned to using plain soap. 4. 306 households were assigned to standard practice. 5. 1523 children younger than 15 years were assigned to using antiseptic soap. 6. 1640 children younger than 15 years were assigned to using plain soap. 7. 1528 children younger than 15 years were assigned to standard practice. Soaps were of identical weight, colour, and smell and were packed centrally with a coded packing case matched to households containing 96 bars. Neither fieldworkers nor participants were aware of the content. Control arm households were visited with the same frequency as intervention household but were given books and pens. Codes were held centrally by the manufacturer and broken after the end of the trial to allow analysis.
Participants	Householders of slums in Karachi. Of the 1523 children younger then 15 years assigned to using antiseptic soap, 117 dropped out (1 died, 51 were born in, and 65 aged out) = 1406; 504 were aged less than 5. Of 1640 children younger then 15 years assigned to using plain soap, 117 dropped out (3 died, 44 were born in, and 70 aged out) = 1523; 517 were aged less than 5. Of 1528 children younger then 15 years assigned to standard practice, 125 dropped out (3 died, 40 were born in, and 82 aged out) = 1403; 489 were aged less than 5.
Interventions	Instruction programme and antibacterial soap containing 1.2% triclocarban, or ordinary soap to be used throughout the day by householders, or standard procedure
Outcomes	Laboratory: N/A Effectiveness: 1. Number of new respiratory illness per person per week 2. Pneumonia (cough or difficulty in breathing with a respiratory rate of > 60 min in children less than 60 days old, > 50 min in those less than 1 year old, and > 40 min for those aged 1 to 5 years) Follow-up was weekly with household interview and direct observation. Children aged less than 5 were weighed, and the report presents stratification of results by child weight. Safety: N/A
Notes	Risk of bias: low (cluster coefficients and analysis by unit of randomisation provided) Note: the authors conclude that "handwashing" neighbourhoods has significantly fewer episodes of respiratory disease than controls (e.g. 50% less cough). "Handwashing" children aged less than 5 had 50% fewer episodes of pneumonia than controls (−65% to −35%). However, there was no difference in respiratory illness between types of soap. The report is confusing, with a shifting focus between children age groups. The impression reading is of an often rewritten manuscript. There is some loss of data (e.g. in the results by weight, i.e. risk group) because of lack of clarity on denominators. Despite this, the trial is a landmark.
Risk of bias	

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Luby 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation took place by computer-generated random numbers in 3 phases.
Allocation concealment (selection bias)	Low risk	"One of the investigators (SL) who did not participate in recruiting neighbourhoods or households programmed a spreadsheet to randomly generate the integers of a 1 or a 2. He applied the random numbers sequentially to the list of neighbourhoods. Neighbourhoods with a 1 were assigned to control, and those with a 2 were assigned to handwashing promotion. Random assignment continued until neighbourhoods consisted of at least 600 handwashing promotion households and 300 control households were assigned."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The antibacterial soap ... contained 1-2% triclocarban as an antibacterial substance. The plain soap was identical to the antibacterial soap except that it did not contain triclocarban... . Neither the fieldworkers nor the families knew whether soaps were antibacterial or plain."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Neither the fieldworkers nor the families knew whether soaps were antibacterial or plain."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	89% of the study population followed up, but no data on the clusters.
Selective reporting (reporting bias)	Low risk	"At baseline, households in the three intervention groups were similar."

MacIntyre 2009

Study characteristics	
Methods	Prospective cluster-RCT carried out in Sydney, Australia, to assess the use of surgical masks, P2 masks, and no masks in preventing ILI in households. The study was carried out during the 2 winter seasons of 2006 and 2007 (August to the end of October 2006 and June to the end of October 2007). “Gaussian random effects were incorporated in the model to account for the natural clustering of persons in households"
Participants	290 adults from 145 families. 47 households (94 enrolled adults and 180 children) were randomised to the surgical mask group, 46 (92 enrolled adults and 172 children) to the P2 mask group, and 52 (104 enrolled adults and 192 children) to the no-mask (control) group.
Interventions	Use of surgical masks and P2 mask versus no mask. The P2 mask is described as very cumbersome.
Outcomes	Laboratory: serological evidence Effectiveness: ILI (described as fever, history of fever or feeling feverish in the past week, myalgia, arthralgia, sore throat, cough, sneezing, runny nose, nasal congestion, headache) However, a positive laboratory finding for influenza converts the ILI definition into one of influenza. Safety: N/A
Notes	The study authors conclude that adherence to mask use significantly reduced the risk for ILI-associated infection, but < 50% of participants wore masks most of the time. They concluded that household use of face masks is associated with low adherence and is ineffective for controlling seasonal respiratory disease. Compliance was by self-report, therefore likely to be an underestimate.

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MacIntyre 2009 *(Continued)*

The primary outcome was ILI or lab-positive illness. This showed no effect.
Sensitivity analysis by adherence showed that under the assumption that the incubation period is equal to 1 day (the most probable value for the 2 most common viruses isolated, influenza (21) and rhinovirus (26)), adherent use of P2 or surgical masks significantly reduces the risk for ILI infection, with a hazard ratio = 0.26 (95% CI 0.09 to 0.77; P = 0.015). No other covariate was significant. Under the less likely assumption that the incubation period is equal to 2 days, the quantified effect of complying with P2 or surgical mask use remains strong, although borderline significant; hazard ratio was 0.32 (95% CI 0.11 to 0.98; P = 0.046). The study was underpowered to determine if there was a difference in efficacy between P2 and surgical masks (Table 5). The study conclusion appears to be a post hoc data exploration. Regardless of this, the study message is that respirator use in a family setting is unlikely to be effective as compliance is difficult unless there is a situation of real impending risk.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Participating households were randomised to 1 of 3 arms by a secure computerised randomisation process", but sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Study participants and trial staff were not blinded, as it is not technically possible to blind the mask type to which participants were randomised."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"However, laboratory staff were blinded to the arm of randomisation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	143 of 145 randomised families were analysed; 2 families in the control group were lost to follow-up during the study, for which no reasons were given.
Selective reporting (reporting bias)	Low risk	No differences between groups at baseline

MacIntyre 2011

Study characteristics

Methods	A cluster-RCT of 1441 HCWs in 15 Beijing hospitals was performed during the 2008 to 2009 winter. Participants wore masks or respirators during the entire work shift for 4 weeks. Outcomes included CRI, ILI, laboratory-confirmed respiratory virus infection, and influenza. A convenience no-mask/respirator group of 481 health workers from 9 hospitals was compared.
Participants	Participants (N = 1441) were hospital HCWs aged > 18 years from the emergency departments and respiratory wards of 15 hospitals. These wards were selected as high-risk settings in which repeated and multiple exposures to respiratory infections are expected. Participants were randomised to medical mask (N = 492 staff from 5 hospitals), N95 fit-tested masks (N = 461 staff from 5 hospitals), and N95 non-fit-tested mask (N = 488 staff from 5 hospitals).
Interventions	Fit-tested N95 respirators versus non-fit-tested N95 respirators versus medical masks. See Table 1 for details.

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MacIntyre 2011 *(Continued)*

Outcomes	Clinical respiratory illness, defined as 2 or more respiratory symptoms or 1 respiratory symptom and a systemic symptom Influenza-like illness, defined as fever ≥ 38 °C plus 1 respiratory symptom (i.e. cough, runny nose, etc.) Laboratory-confirmed viral respiratory infection (detection of adenoviruses, human metapneumovirus, coronavirus 229E/NL63, parainfluenza viruses 1, 2, and 3, influenza viruses A and B, respiratory syncytial virus A and B, rhinovirus A or B, and coronavirus OC43/HKU1 by multiplex PCR) Laboratory-confirmed influenza A or B Adherence with mask or respirator use. Reported problems associated with using the masks or respirators
Notes	Funding source unknown; control arm not randomised so has been ignored

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process (using a secure computerised randomisation program), but sequence generation not described
Allocation concealment (selection bias)	Low risk	Hospitals randomised prior to inclusion of participants.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Specified outcomes reported.

MacIntyre 2013

Study characteristics

Methods	A cluster-RCT
Participants	A total of 1669 nurses and doctors from 68 emergency departments and respiratory wards of 19 Beijing hospitals were included. Inclusion criteria: any nurse or doctor aged 18 years or older who worked full time in the emergency or respiratory wards was eligible. Exclusion: HCWs if they (1) were unable or refused to consent; (2) had beards, long moustaches, or long facial hair stubble; (3) had a current respiratory illness, rhinitis, and/or allergy; or (4) worked part time or did not work in the aforementioned wards or departments Final analysis was performed on 572 staff and 24 wards in medical mask group, 516 staff and 20 wards in the targeted N95 mask group, and 581 staff and 24 wards in the N95 mask group.

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MacIntyre 2013 *(Continued)*

Interventions	Quote: "Masks used in the study were the 3M Standard Tie-On Surgical Mask (catalog number mask 1817; 3M, St. Paul, MN) and the 3M Health Care N95 Particulate Respirator (catalog number 1860; 3M)... . Participants wore the mask or respirator on every shift after being shown how to fit and wear it. Participants were supplied daily with either three masks for the medical mask arm or two N95 respirators. Participants using N95 respirators underwent a fit testing procedure using a 3M FT-30 Bitrex Fit Test Kit according to the manufacturer's instructions (3M)." See Table 1 for details.
Outcomes	Laboratory: 1. Laboratory-confirmed viral respiratory infection in symptomatic participants, defined as detection of adenoviruses; human metapneumovirus; coronaviruses 229E/NL63 and OC43/HKU1; parainfluenza viruses 1, 2, and 3; influenza viruses A and B; respiratory syncytial viruses A and B; or rhinoviruses A/B by nucleic acid testing (NAT) using a commercial multiplex polymerase chain reaction (Seegen, Inc., Seoul, Korea). 2. Laboratory-confirmed influenza A or B in symptomatic participants. 3. Laboratory-confirmed bacterial colonisation in symptomatic participants, defined as detection of *Streptococcus pneumoniae*, *Legionella*, *Bordetella pertussis*, chlamydia, *Mycoplasma pneumoniae*, or *Haemophilus influenzae* type B by multiplex polymerase chain reaction (Seegen, Inc.). Effectiveness: CRI, defined as 2 or more respiratory symptoms or 1 respiratory symptom and a systemic symptom. ILI, defined as fever (38 °C) plus 1 respiratory symptom Safety: adverse effects measured using a semi-structured questionnaire. Investigators stated that there was higher reported adverse effects and discomfort of N95 respirators compared with the other 2 arms. In terms of comfort, 52% (297 of 571) of the medical mask arm reported no problems, compared with 62% (317 of 512) of the targeted arm and 38% (217 of 574) of the N95 arm (P < 0.001).
Notes	Compliance with the product was highest in the targeted N95 arm (82%; 422 of 516), then the medical mask arm (66%; 380 of 572), and the N95 arm (57%; 333 of 581); these differences were statistically significant (P < 0.001). The period study conducted: 28 December 2009 to 7 February 2010 Funding: unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"using a secure computerized randomization program", but sequence generation not described
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Outcome was objectively assessed with lab confirmation in addition to clinical illness.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Laboratory outcomes are reported for all subjects (with at least one respiratory symptom or fever) tested, and then for the subset meeting the CRI definition"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. Flow chart and text match, investigators conducted ITT and PP analysis. All the outcomes were accounted for amongst all participants.

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MacIntyre 2013 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes were reported as planned.

MacIntyre 2015

Study characteristics	
Methods	A cluster-RCT of cloth masks compared with medical masks in healthcare workers in 14 secondary-/tertiary-level hospitals in Hanoi, Vietnam. Hospital wards were randomised to: medical masks, cloth masks, or a control group (usual practice, which included mask wearing). Participants used the mask on every shift for 4 consecutive weeks.
Participants	1607 hospital HCWs aged ≥ 18 years working full time in selected high-risk wards. Medical mask group (n = 580 HCWs), cloth mask group (n = 569 HCWs), control group (n = 458 HCWs)
Interventions	Medical masks, cloth masks, or a control group. See Table 1 for details.
Outcomes	Clinical respiratory illness, influenza-like illness, and laboratory-confirmed respiratory virus infection 1. Clinical respiratory illness, defined as 2 or more respiratory symptoms or 1 respiratory symptom and a systemic symptom 2. Influenza-like illness, defined as fever ≥ 38 °C plus 1 respiratory symptom 3. Laboratory-confirmed viral respiratory infection. Laboratory confirmation was by nucleic acid detection using multiplex reverse transcriptase PCR (RT-PCR) for 17 respiratory viruses. Adverse events associated with mask use
Notes	Government funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Epi info V.6 was used to generate a randomisation allocation.
Allocation concealment (selection bias)	Low risk	74 wards randomised prior to recruitment of individuals.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Specified endpoints reported.

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MacIntyre 2015

Study characteristics	
Methods	A cluster-RCT of cloth masks compared with medical masks in healthcare workers in 14 secondary-/tertiary-level hospitals in Hanoi, Vietnam. Hospital wards were randomised to: medical masks, cloth masks, or a control group (usual practice, which included mask wearing). Participants used the mask on every shift for 4 consecutive weeks.
Participants	1607 hospital HCWs aged ≥ 18 years working full time in selected high-risk wards. Medical mask group (n = 580 HCWs), cloth mask group (n = 569 HCWs), control group (n = 458 HCWs)
Interventions	Medical masks, cloth masks, or a control group. See Table 1 for details.
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Notes	Government funded

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Epi info V.6 was used to generate a randomisation allocation.
Allocation concealment (selection bias)	Low risk	74 wards randomised prior to recruitment of individuals.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Specified endpoints reported.

MacIntyre 2016

Study characteristics

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MacIntyre 2016 *(Continued)*

Methods	Cluster-RCT to examine medical mask use as source control for people with respiratory illness in 6 major hospitals in 2 districts of Beijing, China. Index cases with ILI were randomly allocated to medical mask (n = 123) and control arms (n = 122). Since 43 index cases in the control arm also used a mask during the study period, an as-treated post hoc analysis was performed by comparing outcomes amongst household members of index cases who used a mask (mask group) with household members of index cases who did not use a mask (no mask group).
Participants	245 index cases with ILI (medical mask = 123, control group = 122) and 597 household contacts (medical mask = 302, control group = 295)
Interventions	Medical mask versus no mask (control). See Table 1 for details.
Outcomes	Clinical respiratory illness, ILI, and laboratory-confirmed viral respiratory infection 1. Clinical respiratory illness, defined as 2 or more respiratory symptoms (cough, nasal congestion, runny nose, sore throat, or sneezes) or 1 respiratory symptom and a systemic symptom (chill, lethargy, loss of appetite, abdominal pain, muscle or joint aches). 2. ILI, defined as fever ≥ 38 °C plus 1 respiratory symptom. 3. Laboratory-confirmed viral respiratory infection, defined as detection of adenoviruses, human metapneumovirus, coronaviruses 229E/NL63 and OC43/HKU1, parainfluenza viruses 1, 2, and 3, influenza viruses A and B, respiratory syncytial virus A and B, or rhinovirus A/B by nucleic acid testing using a commercial multiplex PCR. No safety outcomes reported.
Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation sequence using Microsoft Excel
Allocation concealment (selection bias)	High risk	Doctors enrolled the participants randomly to intervention and control arms.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Clinical endpoints assessed unblinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Specified outcomes reported.

MacIntyre 2016

Study characteristics

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MacIntyre 2016 *(Continued)*

Methods	Cluster-RCT to examine medical mask use as source control for people with respiratory illness in 6 major hospitals in 2 districts of Beijing, China. Index cases with ILI were randomly allocated to medical mask (n = 123) and control arms (n = 122). Since 43 index cases in the control arm also used a mask during the study period, an as-treated post hoc analysis was performed by comparing outcomes amongst household members of index cases who used a mask (mask group) with household members of index cases who did not use a mask (no mask group).
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Outcomes	Clinical respiratory illness, ILI, and laboratory-confirmed viral respiratory infection 1. Clinical respiratory illness, defined as 2 or more respiratory symptoms (cough, nasal congestion, runny nose, sore throat, or sneezes) or 1 respiratory symptom and a systemic symptom (chill, lethargy, loss of appetite, abdominal pain, muscle or joint aches). 2. ILI, defined as fever ≥ 38 °C plus 1 respiratory symptom. 3. Laboratory-confirmed viral respiratory infection, defined as detection of adenoviruses, human metapneumovirus, coronaviruses 229E/NL63 and OC43/HKU1, parainfluenza viruses 1, 2, and 3, influenza viruses A and B, respiratory syncytial virus A and B, or rhinovirus A/B by nucleic acid testing using a commercial multiplex PCR. No safety outcomes reported.
Notes	Government funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation sequence using Microsoft Excel
Allocation concealment (selection bias)	High risk	Doctors enrolled the participants randomly to intervention and control arms.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Clinical endpoints assessed unblinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Specified outcomes reported.

McConeghy 2017

Study characteristics

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McConeghy 2017 *(Continued)*

Methods	Pilot study of comprehensive intervention (education, cleaning of surfaces, audit and feedback) to staff of nursing homes versus usual care. Pair-matched cluster-randomised design with only 5 clusters (nursing homes) in each group
Participants	10 nursing homes in Colorado, USA Intervention group = 481 long-stay residents and control group = 380 'Long-stay' defined as resident at least 90 days prior to baseline, or recently readmitted after previous long stay.
Interventions	A multifaceted hand-washing/surface-cleaning intervention comprised of 1) 1-hour online educational module focused on how to prevent infections; 2) provided with an "essential bundle" of 7 products, ranging from hand sanitiser gel and foam to antiviral facial tissues, disinfecting spray, and hand and face wipe and recommendation to use 4 skin cream and wipe products; 3) audit and feedback system. See Table 1 for details.
Outcomes	Laboratory: surface cultures mentioned in Methods, but no results given Effectiveness: LRTI, all infections, hospitalisation, use of antibiotics (not relevant to this review) Safety: none mentioned in Methods and no results given
Notes	The authors conclude that "This multifaceted hand-washing and surface cleaning intervention was designed to reduce infection rates among nursing homes residents. In our 10-facility randomized, matched pair pilot study, we observed program compliance and satisfaction along with reductions in surface bacterial counts, but did not observe a statistically significant reduction in infection rates, antimicrobial use, or hospitalizations". Very poorly reported study with results not explained, summarised in Table 3 as RDs. Denominators and attrition are unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Illness and absenteeism reported by treating staff.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No attrition given. Data were collected from e-medical record at baseline, but not clear whether illness data during the study were collected by the same method.
Selective reporting (reporting bias)	High risk	Upper respiratory tract infection was mentioned in the Methods (intervention presumably would target these), but only LRTI and overall infection reported.

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McConeghy 2017

Study characteristics	
Methods	Pilot study of comprehensive intervention (education, cleaning of surfaces, audit and feedback) to staff of nursing homes versus usual care. Pair-matched cluster-randomised design with only 5 clusters (nursing homes) in each group
Participants	10 nursing homes in Colorado, USA Intervention group = 481 long-stay residents and control group = 380 'Long-stay' defined as resident at least 90 days prior to baseline, or recently readmitted after previous long stay.
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McConeghy 2017 *(Continued)*

Selective reporting (reporting bias)	High risk	Upper respiratory tract infection was mentioned in the Methods (intervention presumably would target these), but only LRTI and overall infection reported.

Millar 2016

Study characteristics	
Methods	Cluster-RCT, open-label study, factorial design
Participants	Around 30,000 healthy, male army trainees aged 18 to 42 years at Fort Benning, Georgia were included. Inclusion criteria: trainees assigned to 1 of the 6 selected training battalions, trainees who present with an SSTI at the clinic or the hospital, provide informed consent. Exclusion criteria: fails to meet inclusion criteria. No denominator breakdown by arm is reported.
Interventions	Promotion of hand-washing in addition to a once-weekly application of chlorhexidine-based body wash. See Table 1 for details.
Outcomes	This study was nested in a large field-based RCT and utilised clinic-based medical records. Laboratory: none Effectiveness: incidence of ARI at 20 months. The case definition was any occurrence of the following ICD-9 symptom or disease-specific codes: 460 to 466, 480 to 488, and specifically 465.9, 482.9, 486, and 487.1. Safety: adverse effects neither planned nor reported by the investigators
Notes	The period study conducted: May 2010 to January 2012 Funding: government

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated random numbers to 1 of the 3 study groups"
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was open-label and self-reporting of ARI. It is planned as secondary objective of an original trial. Data abstractors were blinded to group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data abstractors were blinded to group assignment.
Incomplete outcome data (attrition bias) All outcomes	High risk	There is a statistically significant difference between attrition rates in the 3 groups. The reasons for attrition are briefly reported in Table 1 of the original study (Ellis and colleagues 2014), but are unlikely to be related to the outcomes of this study. ARI cases were captured utilising clinic-based medical records, but this outcome is not prespecified in the protocol.

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Millar 2016 *(Continued)*

Selective reporting (reporting bias)	High risk	The study was conducted for another purpose. According to the study protocol, the outcomes of interest in the current report were not mentioned as outcomes when the study was planned. ARI is not prespecified as an outcome in the protocol published on ClinicalTrials.gov.

Millar 2016

Study characteristics	
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Millar 2016 *(Continued)*

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Miyaki 2011

Study characteristics	
Methods	A quasi-cluster-RCT
Participants	A total of 15,134 assigned to intervention (N = 6634 workers) and control (N = 8500 workers) Inclusion criteria: all general employees (aged 19 to 72 years in 2009) of 2 sibling companies of a major car industry in Kanagawa Prefecture, Japan. All workers who regularly reported to the workplace were included, regardless of treatment for chronic diseases. All employees have the same health insurance plan and were followed up in the same way.
Interventions	"The intervention involved asking workers whose family members developed an influenza-like illness (ILI) to stay at home. If any co-habiting family members showed signs of influenza-like illness (ILI), employees ... were asked to stay at home voluntarily until 5 days has passed since the resolution of the ILS symptoms or 2 days after alleviation of fever." See Table 1 for details.
Outcomes	Workroom: influenza A test kit (rapid test) Effectiveness: assess the effectiveness of household quarantine in reducing the incidence of influenza A H1N1. ILI was defined as a body temperature greater than 38 °C or more than 1 °C above the normal temperature accompanied with more than 2 of these symptoms: nasal mucus, pharyngeal pain, cough, chills or heat sensation Safety: the incidence of influenza A H1N1 amongst workers who were told to stay home if a family member developed ILI was higher (relative risk of 2.17; P < 0.001) compared to control group. No other safety measures/harms reported. Compliance: quote: "our intervention was not compulsory; we only asked the employees to leave the workplace for a while on full pay, and we succeeded in getting all workers' agreement. In our case, explaining that the home waiting policy might be beneficial to the whole workers and help to avoid stopping the manufacturing lines (explaining it is for the benefit of the public) and guaranteeing payment during the leave (financial support) helped them to obey our request."
Notes	Period study conducted: 1 July 2009 to 19 February 2010 Unfunded

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information given.
Allocation concealment (selection bias)	Unclear risk	No information given.

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Miyaki 2011 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	The nature of the intervention (stay at home) was confirmed in the intervention group, where all workers agree as they were financially supported during absences due to ILI.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Company doctors diagnosed the disease through a positive result of an influenza A test or clinical symptoms", but not clear if they were blinded to assignment; however, the diagnostic process is meticulous and objectively confirmed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All cases are included in the analysis, and none were lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Although all outcomes of interest are clearly specified, described, and followed up, and text and numbers checked out well and based on the outcome stated for the study, there is no published protocol to match the planned vs the reported outcomes.

Miyaki 2011

Study characteristics	
Methods	A quasi-cluster-RCT
Participants	A total of 15,134 assigned to intervention (N = 6634 workers) and control (N = 8500 workers) Inclusion criteria: all general employees (aged 19 to 72 years in 2009) of 2 sibling companies of a major car industry in Kanagawa Prefecture, Japan. All workers who regularly reported to the workplace were included, regardless of treatment for chronic diseases. All employees have the same health insurance plan and were followed up in the same way.
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Miyaki 2011 *(Continued)*

	Unfunded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given.
Allocation concealment (selection bias)	Unclear risk	No information given.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The nature of the intervention (stay at home) was confirmed in the intervention group, where all workers agree as they were financially supported during absences due to ILI.
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Selective reporting (reporting bias)	Unclear risk	Although all outcomes of interest are clearly specified, described, and followed up, and text and numbers checked out well and based on the outcome stated for the study, there is no published protocol to match the planned vs the reported outcomes.

Morton 2004

Study characteristics

Methods	Cross-over study to evaluate the effectiveness of an alcohol gel as an adjunct to regular hand-washing for decreasing absenteeism amongst elementary children by reducing specific communicable diseases such cold, flu, and conjunctivitis. The study was conducted in an elementary school in New England, USA. In the cross-over design, classrooms in each grade level were randomised to begin as the experimental group (alcohol gel) or the control group (regular hand-washing). A study protocol for hand hygiene was introduced following the germ unit education. The hand-washing product was a soap-and-water alternative that is approximately 60% ethyl alcohol. In phase 1 (46 days) children in 9 classrooms were in the experimental group, and children in 8 classrooms were in the control group. After a 1-week washout period when no children had access to the alcohol gel, phase 2 (47 days) started, and the classroom that had participated before as experimental group passed into the control group and vice versa. Data were collected by the parents, who informed the secretary or the school nurse of the reasons for a child's absence, including symptoms of any illness. Respiratory illnesses were defined by symptoms of URTI.
Participants	253 children, 120 girls and 133 boys, from kindergarten to 3rd grade. Of the eligible 285 students, 32 children dropped out (10 due to skin irritation and 22 because of lack of parental consent). No denominator breakdown by arm is reported because the study used a cross-over design.
Interventions	Use of an alcohol gel as an adjunct to regular hand-washing and educational programme versus regular hand-washing and educational programme
Outcomes	Laboratory: no

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Morton 2004 *(Continued)*

	Effectiveness: days of absences from school for respiratory illness Safety: N/A
Notes	Risk of bias: high (no description of randomisation; partial reporting of outcomes, numerators and denominators) Note: the authors conclude that significantly fewer children became ill whilst using the alcohol gel as an adjunct to regular hand-washing than when using regular hand-washing only (decreased school absenteeism of 43% with the use of alcohol gel on top of hand-washing). The authors also described, as a limitation of the study, the fact that the school nurse served as the data collector, which could be perceived as bias in measurement of the outcome variable. Randomisation and allocation are not described; no cluster coefficients were reported; and attrition was not taken into consideration during the analysis. Unit of randomisation and analysis are different. No reporting by arm. No ORs, no CIs reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"A cross-over design was used. In the crossover design, classrooms in each grade level were randomized to begin as the experimental group (regular hand washing)."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The school nurse served as the data collector for the duration of the study. This could be perceived as bias in the measurement of the outcome variable, absenteeism related to infectious illness."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information

Najnin 2019

Study characteristics

Methods	Cluster-RCT, parallel assignment
Participants	Residents of the high-risk, cholera-prone study areas. Low-income communities in Mirpur area of urban Dhaka defined by low per capita income, poor sanitation, unsafe water use, sharing of water source, and poor living conditions. 90 geographic clusters were included, with 30-metre buffer zones. A total of 7842 households, with 52,237 individuals analysed Vaccine-only area: data were analysed for 1965 households consisting of 13,148 individuals Vaccine-plus-behaviour-change area: data were analysed for 3886 households consisting of 25,566 individuals Control area: data were analysed for 1991 households consisting of 13,523 individuals

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Najnin 2019 *(Continued)*

	Study criteria from published protocol: Inclusion criteria: apparently healthy residents of selected vaccination sites, aged 1 year and above, non-pregnant women, written informed consent Exclusion criteria: age less than 1 year and pregnant women
Interventions	Hand-washing and water treatment promotion. See Table 1 for details.
Outcomes	Laboratory: none used Effectiveness: prevalence of respiratory illness. People were classified as having respiratory illness if they reported having fever plus either cough or nasal congestion or fever plus breathing difficulty in the past 2 days of unannounced home visits: in each intervention group and amongst those who had soap/soapy water with water present in the hand-washing station (35% of all groups combined) versus those without this (regardless of the intervention group). Planned secondary outcome: prevalence of reported respiratory illness during 2-year intervention period Safety: no adverse effects planned or reported
Notes	The period study conducted: 2011 to 2013 Funding: government and private Bill & Melinda Gates Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence was used to allocate 90 geographical clusters to 1 of 3 groups. Before randomisation, clusters were stratified blocked into 2 categories according to the distance to the hospital. (parent article: Lancet. 2015 Oct 3;386(10001):1362-1371)
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	All trial participants and investigators were aware of group assignment. Several in and out migrations across all groups before, after, and during outcome monitoring, and large number of changes in intervention areas
Blinding of outcome assessment (detection bias) All outcomes	High risk	Several in and out migrations across all groups before, after, and during outcome monitoring, and large number of changes in intervention areas
Incomplete outcome data (attrition bias) All outcomes	High risk	High migration movement. This could have distorted the baseline characteristics even more. Very hard to assess because the numbers in the index paper are different from the parent paper (Qadri 2015). In addition to that, for each intervention, data were analysed for 15% to 30% of those allocated on start date. Each group started with approximately 80,000 people; the number analysed is much lower (237,216 people were in the study area on start date of outcome monitoring, the total number analysed across all groups was 52,237). No info about data on migrated individuals or on those who changed intervention areas was dealt with? Also data for prevalence of ARI adjusted for age and wealth were not shown. The outcome is addressed in the 2 days preceding an unannounced visit. This means that if there was a respiratory illness in the past week it would not have been reported. Moreover, these monthly unannounced visits were done to a different set of participants in each group!

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Najnin 2019 *(Continued)*

Selective reporting (reporting bias)	High risk	Published protocol does not include respiratory illness as an outcome.

Morton 2004

Study characteristics

Methods	Cross-over study to evaluate the effectiveness of an alcohol gel as an adjunct to regular hand-washing for decreasing absenteeism amongst elementary children by reducing specific communicable diseases such cold, flu, and conjunctivitis. The study was conducted in an elementary school in New England, USA. In the cross-over design, classrooms in each grade level were randomised to begin as the experimental group (alcohol gel) or the control group (regular hand-washing). A study protocol for hand hygiene was introduced following the germ unit education. The hand-washing product was a soap-and-water alternative that is approximately 60% ethyl alcohol. In phase 1 (46 days) children in 9 classrooms were in the experimental group, and children in 8 classrooms were in the control group. After a 1-week washout period when no children had access to the alcohol gel, phase 2 (47 days) started, and the classroom that had participated before as experimental group passed into the control group and vice versa. Data were collected by the parents, who informed the secretary or the school nurse of the reasons for a child's absence, including symptoms of any illness. Respiratory illnesses were defined by symptoms of URTI.
Participants	253 children, 120 girls and 133 boys, from kindergarten to 3rd grade. Of the eligible 285 students, 32 children dropped out (10 due to skin irritation and 22 because of lack of parental consent). No denominator breakdown by arm is reported because the study used a cross-over design.
Interventions	Use of an alcohol gel as an adjunct to regular hand-washing and educational programme versus regular hand-washing and educational programme
Outcomes	Laboratory: no Effectiveness: days of absences from school for respiratory illness Safety: N/A
Notes	Risk of bias: high (no description of randomisation; partial reporting of outcomes, numerators and denominators) Note: the authors conclude that significantly fewer children became ill whilst using the alcohol gel as an adjunct to regular hand-washing than when using regular hand-washing only (decreased school absenteeism of 43% with the use of alcohol gel on top of hand-washing). The authors also described, as a limitation of the study, the fact that the school nurse served as the data collector, which could be perceived as bias in measurement of the outcome variable. Randomisation and allocation are not described; no cluster coefficients were reported; and attrition was not taken into consideration during the analysis. Unit of randomisation and analysis are different. No reporting by arm. No ORs, no CIs reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Unclear risk	"A cross-over design was used. In the crossover design, classrooms in each grade level were randomized to begin as the experimental group (regular hand washing)."

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Morton 2004 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The school nurse served as the data collector for the duration of the study. This could be perceived as bias in the measurement of the outcome variable, absenteeism related to infectious illness."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information

Najnin 2019

Study characteristics	
Methods	Cluster-RCT, parallel assignment
Participants	Residents of the high-risk, cholera-prone study areas. Low-income communities in Mirpur area of urban Dhaka defined by low per capita income, poor sanitation, unsafe water use, sharing of water source, and poor living conditions. 90 geographic clusters were included, with 30-metre buffer zones. A total of 7842 households, with 52,237 individuals analysed Vaccine-only area: data were analysed for 1965 households consisting of 13,148 individuals Vaccine-plus-behaviour-change area: data were analysed for 3886 households consisting of 25,566 individuals Control area: data were analysed for 1991 households consisting of 13,523 individuals Study criteria from published protocol: Inclusion criteria: apparently healthy residents of selected vaccination sites, aged 1 year and above, non-pregnant women, written informed consent Exclusion criteria: age less than 1 year and pregnant women
Interventions	Hand-washing and water treatment promotion. See Table 1 for details.
Outcomes	Laboratory: none used Effectiveness: prevalence of respiratory illness. People were classified as having respiratory illness if they reported having fever plus either cough or nasal congestion or fever plus breathing difficulty in the past 2 days of unannounced home visits: in each intervention group and amongst those who had soap/soapy water with water present in the hand-washing station (35% of all groups combined) versus those without this (regardless of the intervention group). Planned secondary outcome: prevalence of reported respiratory illness during 2-year intervention period Safety: no adverse effects planned or reported
Notes	The period study conducted: 2011 to 2013 Funding: government and private Bill & Melinda Gates Foundation
Risk of bias	

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Najnin 2019 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence was used to allocate 90 geographical clusters to 1 of 3 groups. Before randomisation, clusters were stratified blocked into 2 categories according to the distance to the hospital. (parent article: Lancet. 2015 Oct 3;386(10001):1362-1371)
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	All trial participants and investigators were aware of group assignment. Several in and out migrations across all groups before, after, and during outcome monitoring, and large number of changes in intervention areas
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Incomplete outcome data (attrition bias) All outcomes	High risk	High migration movement. This could have distorted the baseline characteristics even more. Very hard to assess because the numbers in the index paper are different from the parent paper (Qadri 2015). In addition to that, for each intervention, data were analysed for 15% to 30% of those allocated on start date. Each group started with approximately 80,000 people; the number analysed is much lower (237,216 people were in the study area on start date of outcome monitoring, the total number analysed across all groups was 52,237). No info about data on migrated individuals or on those who changed intervention areas was dealt with? Also data for prevalence of ARI adjusted for age and wealth were not shown. The outcome is addressed in the 2 days preceding an unannounced visit. This means that if there was a respiratory illness in the past week it would not have been reported. Moreover, these monthly unannounced visits were done to a different set of participants in each group!
Selective reporting (reporting bias)	High risk	Published protocol does not include respiratory illness as an outcome.

Nicholson 2014

Study characteristics	
Methods	Cluster-RCT
Participants	70 low-income communities in Mumbai, India (35 communities per arm) were randomised to intervention arm (N = 1025) and control arm (N = 1026). Households located in low-income urban communities in west and south Mumbai, India. Each household contains 1 target child in the first year of a municipal school (typically aged 5 years).
Interventions	Combination of hand-washing promotion with provision of free soap aimed at 5-year-olds with provision of free soap. See Table 1 for details.
Outcomes	Laboratory: none reported Effectiveness: Primary outcomes: episodes of diarrhoea, ARIs, and school absences amongst target children, and episodes of diarrhoea and ARIs among their families

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Nicholson 2014 *(Continued)*

	Secondary outcomes: episodes of eye infections, vomiting, abscesses or boils, headaches, and earache Operational definitions for all the illnesses were taken from *Black's Medical Dictionary* (MacPherson 1999). ARIs as "pneumonia, cough, fever, chest pain and shortness of breath, cold, inflammation of any or all of the airways, that is, nose, sinuses, throat, larynx, trachea and bronchi" Safety: no safety measures planned or reported by the investigators
Notes	The period study conducted: 22 October 2007 to 2 August 2008 Funding: multinational corporate company (Unilever plc.)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Coin tossing used, which could have led to a large imbalance.
Allocation concealment (selection bias)	Low risk	"a coin toss was used to assign one community in each pair to intervention and one to control"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants knew to which arm they had been recruited. Households were removed from the study if they provided no data for 5 consecutive weeks.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Data collectors were independent of the behaviour change intervention. Each was assigned exclusively to either households in the intervention group or to control households. However, communities, where very low literacy levels exist, were replaced after randomisation.
Incomplete outcome data (attrition bias) All outcomes	High risk	Data for non-completers were available and similar across groups. ITT and PP were performed. However, households were removed from the study if they provided no data for 5 consecutive weeks.
Selective reporting (reporting bias)	Unclear risk	No information to judge

Pandejpong 2012

Study characteristics

Methods	Cluster-RCT, single study centre
Participants	Children (total number = 1437) were randomised to alcohol hand gel every 60 minutes (N = 452 children), every 120 minutes (N = 447 children), and once before lunch (N = 540 children). Inclusion criteria: all children in a large private school in suburban Bangkok, Thailand, all ages, both genders with parental consent to participate. Exclusion criteria: an allergy to alcohol hand gel
Interventions	3 disinfection interventions: Alcohol hand gel applied every 60 minutes vs every 120 minutes vs once before lunch (3 groups). The current school standard for hand hygiene (q lunch group). See Table 1 for details.
Outcomes	Laboratory: none

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Pandejpong 2012 *(Continued)*

	Effectiveness: Primary: rates of absenteeism from physician-confirmed ILI Secondary: rate of absenteeism caused by total reported ILI (with and without a doctor's confirmation) In case the child was sick but did not see a doctor, the parents were asked to report any of the following symptoms: runny nose or cough, fever or chills, sore throat, headache, diarrhoea, and presence of hand, foot, or mouth ulcers. If 2 or more of these symptoms were reported, then the child's illness was documented as an ILI. Safety: investigators reported that no adverse reaction to the alcohol hand gel was reported in any participants
Notes	The period study conducted: December 2009 to February 2010 Funding: Royal College of Physicians of Thailand

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Parents and teachers are aware of the assignment. Teachers were responsible for recording the absenteeism case record forms. Parents would report child sickness. No diagnostic tests, even in the case of physician-confirmed ILI
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome is physician-confirmed ILI.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"No students were lost to follow-up or discontinued the intervention during the study period."
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Pandejpong 2012

Study characteristics

Methods	Cluster-RCT, single study centre
Participants	Children (total number = 1437) were randomised to alcohol hand gel every 60 minutes (N = 452 children), every 120 minutes (N = 447 children), and once before lunch (N = 540 children). Inclusion criteria: all children in a large private school in suburban Bangkok, Thailand, all ages, both genders with parental consent to participate. Exclusion criteria: an allergy to alcohol hand gel

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Pandejpong 2012 *(Continued)*

Interventions	3 disinfection interventions: Alcohol hand gel applied every 60 minutes vs every 120 minutes vs once before lunch (3 groups). The current school standard for hand hygiene (q lunch group). See Table 1 for details.
Outcomes	Laboratory: none Effectiveness: Primary: rates of absenteeism from physician-confirmed ILI Secondary: rate of absenteeism caused by total reported ILI (with and without a doctor's confirmation) In case the child was sick but did not see a doctor, the parents were asked to report any of the following symptoms: runny nose or cough, fever or chills, sore throat, headache, diarrhoea, and presence of hand, foot, or mouth ulcers. If 2 or more of these symptoms were reported, then the child's illness was documented as an ILI. Safety: investigators reported that no adverse reaction to the alcohol hand gel was reported in any participants
Notes	The period study conducted: December 2009 to February 2010 Funding: Royal College of Physicians of Thailand

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Parents and teachers are aware of the assignment. Teachers were responsible for recording the absenteeism case record forms. Parents would report child sickness. No diagnostic tests, even in the case of physician-confirmed ILI
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome is physician-confirmed ILI.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"No students were lost to follow-up or discontinued the intervention during the study period."
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Priest 2014

Study characteristics	
Methods	A cluster-RCT

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Priest 2014 *(Continued)*

Participants	Study included children aged 5 to 11 years at 68 primary schools in New Zealand. Schools were randomised to hand sanitiser + education session arm (34 schools and 8859 children) and education session arm (34 schools and 7386 children). Inclusion criteria: School-level inclusion: at least 100 children of primary school age (school years 1 to 6; children will generally range in age from 5 years to 11 years) at November 2008. Schools that are not currently using hand sanitiser products or are willing to not use them for the period of the trial. Schools are within the City boundaries of Christchurch, Dunedin, or Invercargill in New Zealand. The principal of the school consents to the school being included in the trial. Not ''special schools'' (e.g. schools for children with deafness or disability) and either not currently using hand sanitiser products or willing to not use them for the period of the trial if they were randomised to the control group were eligible to participate in the trial. Student-level inclusion (follow-up children): children were eligible to participate in the follow-up group, for whom more detailed information on absences was collected, if they attended a school year 1 to 6 class in 1 of the included schools at the beginning of the second school term in 2009 (the end of April), and their caregivers completed the consent form indicating that they were willing to be telephoned following their child's absences and that they were able to take part in telephone interviews in English Exclusion criteria: School-level exclusion: special needs schools Student-level exclusion (follow-up children): children of the principal investigators and study personnel of the trial. Or, children of families that the principal of the primary school directs us not to approach
Interventions	Hand sanitiser provision (in addition to hand hygiene education session also provided to control group) in schoolchildren. See Table 1 for details.
Outcomes	Laboratory: none Effectiveness: Primary outcome: the incidence rate of absence episodes from school (reported by the parents during telephone calls) due to any illness during the study period (winter term) Secondary outcomes: assessing whether hand sanitiser was effective in reducing the: 1. incidence rate of respiratory illness absence episodes, 2. incidence rate of gastrointestinal illness absence episodes, 3. incidence rate of absence for any reason, 4. length of illness episode, 5. length of illness absence episode, and 6. incidence rate of subsequent illness amongst other children or adults in the household. Definition of respiratory illness: at least 2 of the following caregiver-reported symptoms for 1 day, or 1 of the following symptoms for 2 days (but not fever alone): runny nose, stuffy or blocked nose or noisy breathing, cough, fever, sore throat, or sneezing Safety: examined whether the use of hand sanitiser was associated with an increased risk of any skin reactions during the intervention period. Skin reactions: dryness, redness, flakiness, itchiness, eczema, and any other skin reactions
Notes	The period study conducted: 27 April to 25 September 2009 Funding: government (Health Research Council of New Zealand)

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Priest 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Stata/MP 10.1 for Windows was used to generate the random numbers"
Allocation concealment (selection bias)	Low risk	Done by trial statistician provided with school codes and district and randomised the schools to either "A" or "B"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Outcome assessors were blinded to the group allocation until the analysis was completed.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to the group allocation until the analysis was completed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The flow diagram gives a clear account on follow-up, with numbers of those lost to follow-up and those who discontinued the intervention along with the reasons for doing so. No child was excluded from the analysis. Only PP analysis was reported.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the published protocol were reported in the study. The exception was "1 planned secondary outcome (that is irrelevant to our study) that was not collected and 2 collected secondary outcomes that were not planned in the original protocol".

Priest 2014

Study characteristics	
Methods	A cluster-RCT
Participants	Study included children aged 5 to 11 years at 68 primary schools in New Zealand. Schools were randomised to hand sanitiser + education session arm (34 schools and 8859 children) and education session arm (34 schools and 7386 children). Inclusion criteria: School-level inclusion: at least 100 children of primary school age (school years 1 to 6; children will generally range in age from 5 years to 11 years) at November 2008. Schools that are not currently using hand sanitiser products or are willing to not use them for the period of the trial. Schools are within the City boundaries of Christchurch, Dunedin, or Invercargill in New Zealand. The principal of the school consents to the school being included in the trial. Not ‘‘special schools’’ (e.g. schools for children with deafness or disability) and either not currently using hand sanitiser products or willing to not use them for the period of the trial if they were randomised to the control group were eligible to participate in the trial. Student-level inclusion (follow-up children): children were eligible to participate in the follow-up group, for whom more detailed information on absences was collected, if they attended a school year 1 to 6 class in 1 of the included schools at the beginning of the second school term in 2009 (the end of April), and their caregivers completed the consent form indicating that they were willing to be telephoned following their child’s absences and that they were able to take part in telephone interviews in English

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Priest 2014 *(Continued)*

	Exclusion criteria: School-level exclusion: special needs schools Student-level exclusion (follow-up children): children of the principal investigators and study personnel of the trial. Or, children of families that the principal of the primary school directs us not to approach
Interventions	Hand sanitiser provision (in addition to hand hygiene education session also provided to control group) in schoolchildren. See Table 1 for details.
Outcomes	Laboratory: none Effectiveness: Primary outcome: the incidence rate of absence episodes from school (reported by the parents during telephone calls) due to any illness during the study period (winter term) Secondary outcomes: assessing whether hand sanitiser was effective in reducing the: 1. incidence rate of respiratory illness absence episodes, 2. incidence rate of gastrointestinal illness absence episodes, 3. incidence rate of absence for any reason, 4. length of illness episode, 5. length of illness absence episode, and 6. incidence rate of subsequent illness amongst other children or adults in the household. Definition of respiratory illness: at least 2 of the following caregiver-reported symptoms for 1 day, or 1 of the following symptoms for 2 days (but not fever alone): runny nose, stuffy or blocked nose or noisy breathing, cough, fever, sore throat, or sneezing Safety: examined whether the use of hand sanitiser was associated with an increased risk of any skin reactions during the intervention period. Skin reactions: dryness, redness, flakiness, itchiness, eczema, and any other skin reactions
Notes	The period study conducted: 27 April to 25 September 2009 Funding: government (Health Research Council of New Zealand)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Stata/MP 10.1 for Windows was used to generate the random numbers"
Allocation concealment (selection bias)	Low risk	Done by trial statistician provided with school codes and district and randomised the schools to either "A" or "B"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Outcome assessors were blinded to the group allocation until the analysis was completed.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to the group allocation until the analysis was completed.
Incomplete outcome data (attrition bias)	Unclear risk	The flow diagram gives a clear account on follow-up, with numbers of those lost to follow-up and those who discontinued the intervention along with the

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Priest 2014 *(Continued)*

All outcomes		reasons for doing so. No child was excluded from the analysis. Only PP analysis was reported.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the published protocol were reported in the study. The exception was "1 planned secondary outcome (that is irrelevant to our study) that was not collected and 2 collected secondary outcomes that were not planned in the original protocol".

Radonovich 2019

Study characteristics	
Methods	Cluster-RCT, multicentre, pragmatic effectiveness trial
Participants	Study included 280 clusters randomly assigned to N95 respirators (189 clusters and 1993 HCPs) and medical masks (191 clusters and 2058 HCPs). All participants in a cluster worked in the same outpatient clinic or outpatient setting. All participants were permitted to participate for 1 or more years and gave written consent for each year of participation. Inclusion criteria: healthcare workers in outpatient settings serving adult and paediatric patients with a high prevalence of acute respiratory illness. Participants were aged at least 18 years and employed at 1 of the 7 participating health systems, and self-identified as routinely positioned within 6 feet (1.83 m) of patients. Participants were full-time employees (defined as direct patient care for approximately ≥ 24 hours weekly) and worked primarily at the study site (defined as ≥ 75% of working hours). Exclusion criteria: medical conditions precluding safe participation or anatomic features that could interfere with respirator fit, such as facial hair or third-trimester pregnancy. Participants self-identified race and sex using fixed categories; these variables were collected because facial anthropometrics related to race and sex may influence N95 respirator fit.
Interventions	Fit-tested N95 respirators versus medical masks when near patients with respiratory illness. See Table 1 for details.
Outcomes	Laboratory. Primary outcome: the incidence of laboratory-confirmed influenza, defined as: 1. detection of influenza A or B virus by RT-PCR in an upper respiratory specimen collected within 7 days of symptom onset; 2. detection of influenza from a randomly obtained swab from an asymptomatic participant; and 3. influenza seroconversion (symptomatic or asymptomatic), defined as at least a 4-fold rise in haemagglutination inhibition antibody titres to influenza A or B virus between pre-season and postseason serological samples deemed not attributable to vaccination. Effectiveness. Secondary outcomes: the incidence of 4 measures of viral respiratory illness or infection as follows: 1. acute respiratory illness with or without laboratory confirmation; 2. laboratory-detected respiratory infection, defined as detection of a respiratory pathogen by PCR or serological evidence of infection with a respiratory pathogen during the study surveillance period(s), which was added to the protocol prior to data analysis; 3. laboratory-confirmed respiratory illness, identified as previously described (defined as self-reported acute respiratory illness plus the presence of at least PCR–confirmed viral pathogen in a specimen collected from the upper respiratory tract within 7 days of the reported symptoms and/or at least a 4-fold rise from pre-intervention to postintervention serum antibody titres to influenza A or B virus; and 4. influenza-like illness, defined as temperature of at least 100 °F (37.8 °C) plus cough and/or a sore throat, with or without laboratory confirmation.

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Radonovich 2019 *(Continued)*

	Safety: no serious study-related adverse events were reported. 19 participants reported skin irritation or worsening acne during years 3 and 4 at 1 site in the N95 respirator group.
Notes	The study was conducted from September 2011 to May 2015, with final follow-up on 28 June 2016. Funding: government Compliance: adherence was reported on daily surveys 22,330 times in the N95 respirator group and 23,315 times in the medical mask group. “Always” was reported 14,566 (65.2%) times in the N95 respirator group and 15,186 (65.1%) times in the medical mask group; “sometimes” 5407 (24.2%) times in the N95 respirator group and 5853 (25.1%) times in the medical mask group; “never” 2272 (10.2%) times in the N95 respirator group and 2207 (9.5%) times in the medical mask group; and “did not recall” 85 (0.4%) times in the N95 respirator group and 69 (0.3%) times in the medical mask group. Participant-reported adherence could not be assessed in 784 participants (31.2%) in the N95 respirator group and 822 (30.8%) in the medical mask group (P = 0.84) because of lack of response to surveys or lack of adherence opportunities (i.e. participants did not encounter an individual with respiratory signs or symptoms). Analysed post hoc, participant adherence was reported as always or sometimes 89.4% of the time in the N95 respirator group and 90.2% of the time in the medical mask group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequences by an individual not involved in the study implementation and data analyses. Used stratified randomisation
Allocation concealment (selection bias)	Low risk	Used constrained randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants cannot be blinded, but it seems that all the measures otherwise were the same with meticulous follow-up. Besides, the primary outcome was lab based (an objective outcome), which is unlikely to be affected by of lack of blinding. Investigators were blinded to the randomisation until completion of the study and analysis.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome is laboratory-confirmed diagnosis.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Missing outcomes were imputed using standard multiple imputation techniques, creating multiple imputed data sets with no missing values for each analysis"
Selective reporting (reporting bias)	Low risk	Reported study outcomes matched the published protocol. Every outcome was accounted for.

Radonovich 2019

Study characteristics

Methods	Cluster-RCT, multicentre, pragmatic effectiveness trial
Participants	Study included 280 clusters randomly assigned to N95 respirators (189 clusters and 1993 HCPs) and medical masks (191 clusters and 2058 HCPs).

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Radonovich 2019 *(Continued)*

	All participants in a cluster worked in the same outpatient clinic or outpatient setting. All participants were permitted to participate for 1 or more years and gave written consent for each year of participation. Inclusion criteria: healthcare workers in outpatient settings serving adult and paediatric patients with a high prevalence of acute respiratory illness. Participants were aged at least 18 years and employed at 1 of the 7 participating health systems, and self-identified as routinely positioned within 6 feet (1.83 m) of patients. Participants were full-time employees (defined as direct patient care for approximately ≥ 24 hours weekly) and worked primarily at the study site (defined as ≥ 75% of working hours). Exclusion criteria: medical conditions precluding safe participation or anatomic features that could interfere with respirator fit, such as facial hair or third-trimester pregnancy. Participants self-identified race and sex using fixed categories; these variables were collected because facial anthropometrics related to race and sex may influence N95 respirator fit.
Interventions	Fit-tested N95 respirators versus medical masks when near patients with respiratory illness. See Table 1 for details.
Outcomes	Laboratory. Primary outcome: the incidence of laboratory-confirmed influenza, defined as: 1. detection of influenza A or B virus by RT-PCR in an upper respiratory specimen collected within 7 days of symptom onset; 2. detection of influenza from a randomly obtained swab from an asymptomatic participant; and 3. influenza seroconversion (symptomatic or asymptomatic), defined as at least a 4-fold rise in haemagglutination inhibition antibody titres to influenza A or B virus between pre-season and postseason serological samples deemed not attributable to vaccination. Effectiveness. Secondary outcomes: the incidence of 4 measures of viral respiratory illness or infection as follows: 1. acute respiratory illness with or without laboratory confirmation; 2. laboratory-detected respiratory infection, defined as detection of a respiratory pathogen by PCR or serological evidence of infection with a respiratory pathogen during the study surveillance period(s), which was added to the protocol prior to data analysis; 3. laboratory-confirmed respiratory illness, identified as previously described (defined as self-reported acute respiratory illness plus the presence of at least PCR–confirmed viral pathogen in a specimen collected from the upper respiratory tract within 7 days of the reported symptoms and/or at least a 4-fold rise from pre-intervention to postintervention serum antibody titres to influenza A or B virus; and 4. influenza-like illness, defined as temperature of at least 100 °F (37.8 °C) plus cough and/or a sore throat, with or without laboratory confirmation. Safety: no serious study-related adverse events were reported. 19 participants reported skin irritation or worsening acne during years 3 and 4 at 1 site in the N95 respirator group.
Notes	The study was conducted from September 2011 to May 2015, with final follow-up on 28 June 2016. Funding: government Compliance: adherence was reported on daily surveys 22,330 times in the N95 respirator group and 23,315 times in the medical mask group. “Always” was reported 14,566 (65.2%) times in the N95 respirator group and 15,186 (65.1%) times in the medical mask group; “sometimes” 5407 (24.2%) times in the N95 respirator group and 5853 (25.1%) times in the medical mask group; “never” 2272 (10.2%) times in the N95 respirator group and 2207 (9.5%) times in the medical mask group; and “did not recall” 85 (0.4%) times in the N95 respirator group and 69 (0.3%) times in the medical mask group. Participant-reported adherence could not be assessed in 784 participants (31.2%) in the N95 respirator group and 822 (30.8%) in the medical mask group (P = 0.84) because of lack of response to surveys or lack of adherence opportunities (i.e. participants did not encounter an individual with respiratory signs or symptoms). Analysed post hoc, participant adherence was reported as always or sometimes 89.4% of the time in the N95 respirator group and 90.2% of the time in the medical mask group.
Risk of bias	

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Radonovich 2019 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequences by an individual not involved in the study implementation and data analyses. Used stratified randomisation
Allocation concealment (selection bias)	Low risk	Used constrained randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants cannot be blinded, but it seems that all the measures otherwise were the same with meticulous follow-up. Besides, the primary outcome was lab based (an objective outcome), which is unlikely to be affected by of lack of blinding. Investigators were blinded to the randomisation until completion of the study and analysis.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome is laboratory-confirmed diagnosis.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Missing outcomes were imputed using standard multiple imputation techniques, creating multiple imputed data sets with no missing values for each analysis"
Selective reporting (reporting bias)	Low risk	Reported study outcomes matched the published protocol. Every outcome was accounted for.

Ram 2015

Study characteristics	
Methods	RCT
Participants	377 household compounds (index cases) completed the study. Control arm has 184 compounds with 1607 contacts, and intervention group has 193 compounds with 1814 contacts. Final analysis was performed on 193 index cases and 1661 contacts in the intervention group and 184 index cases and 1498 contacts in the control group. In 2009, index case-patients with symptom onset within 7 days preceding enrolment were eligible. Eligibility criteria changed in 2010 to include index case-patient with symptom onset within 48 hours preceding enrolment. Inclusion criteria: 1. Individuals ≥ 5 years old: ILI, defined as history of fever and either cough or sore throat with fever onset within the previous 24 hours. 2. Individuals < 5 years old: any child with acute fever with onset within the previous 24 hours. 3. Return to home within 24 hours of presentation to Upazilla Health Complex, Jahurul Islam Medical College Hospital or the local pharmacies, i.e. the index case cannot be admitted for treatment. If admitted, the patient would not be eligible. 4. No fever in any bari resident during the 7 days preceding the patient's presentation to hospital (see definition below). 5. At least 2 individuals (in addition to the index case-patient) who intend to reside in the bari during the subsequent 20 days. 6. Residence within 30 minutes travel time (1-way) from the Upazilla Health Complex or Jahurul Islam Medical College Hospital or the local pharmacy. Exclusion criteria: compounds were excluded if any compound member(s) was reported to have fever within 3 days before index case-patient enrolment. At another time point, compounds were excluded

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Ram 2015 *(Continued)*

	if any primary household member was reported to have fever (fever occurring within 48 hours prior to enrolment recorded).
Interventions	Promoting intensive hand-washing in households to prevent transmission of ILI. See Table 1 for details.
Outcomes	Laboratory: PCR for influenza A and B, with further subtyping of influenza A isolates for all ILI amongst contacts Effectiveness: incidence of ILI. An age-based definition of ILI was used as follows. 1. For individuals > 5 years old, ILI was defined as history of fever with cough or sore throat. 2. For children < 5 years old, ILI was defined as fever (the authors used this relatively liberal case definition in order to include influenza cases with atypical presentations in children). Safety: no safety data planned or reported by investigators
Notes	Inclusion/exclusion criteria changed 3 times during the study conduct. The period study conducted: June 2009 to December 2010 Funding: government

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation, with a block size of 4, in order to promote random and even allocation of household compounds to the 2 treatment arms. The list of random assignments was generated by an investigator with no contact with the participants.
Allocation concealment (selection bias)	Low risk	Once baseline data collection was complete, the data collector notified the field research officer, who consulted the block randomisation list to make the assignment of the household compound to intervention or control.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Relied on symptom reporting from the head of family. Inclusion/exclusion criteria changed 3 times during the study conduct. Given the provision of a hand-washing station as part of the intervention, it was not possible to ensure blinding of participants, intervention staff, or data collectors.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Relied on symptom reporting from the head of family. Inclusion/exclusion criteria changed 3 times during the conduct of the study. Given the provision of a hand-washing station as part of the intervention, it was not possible to ensure blinding of participants, intervention staff, or data collectors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow chart followed all households an individuals from recruitment to analysis.
Selective reporting (reporting bias)	Low risk	The specified outcomes are clearly accounted for. Investigators report all outcomes for each modified enrolment.

Ram 2015

Study characteristics

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Ram 2015 *(Continued)*

Methods	RCT
Participants	377 household compounds (index cases) completed the study. Control arm has 184 compounds with 1607 contacts, and intervention group has 193 compounds with 1814 contacts. Final analysis was performed on 193 index cases and 1661 contacts in the intervention group and 184 index cases and 1498 contacts in the control group. In 2009, index case-patients with symptom onset within 7 days preceding enrolment were eligible. Eligibility criteria changed in 2010 to include index case-patient with symptom onset within 48 hours preceding enrolment. Inclusion criteria: 1. Individuals ≥ 5 years old: ILI, defined as history of fever and either cough or sore throat with fever onset within the previous 24 hours. 2. Individuals < 5 years old: any child with acute fever with onset within the previous 24 hours. 3. Return to home within 24 hours of presentation to Upazilla Health Complex, Jahurul Islam Medical College Hospital or the local pharmacies, i.e. the index case cannot be admitted for treatment. If admitted, the patient would not be eligible. 4. No fever in any bari resident during the 7 days preceding the patient's presentation to hospital (see definition below). 5. At least 2 individuals (in addition to the index case-patient) who intend to reside in the bari during the subsequent 20 days. 6. Residence within 30 minutes travel time (1-way) from the Upazilla Health Complex or Jahurul Islam Medical College Hospital or the local pharmacy. Exclusion criteria: compounds were excluded if any compound member(s) was reported to have fever within 3 days before index case-patient enrolment. At another time point, compounds were excluded if any primary household member was reported to have fever (fever occurring within 48 hours prior to enrolment recorded).
Interventions	Promoting intensive hand-washing in households to prevent transmission of ILI. See Table 1 for details.
Outcomes	Laboratory: PCR for influenza A and B, with further subtyping of influenza A isolates for all ILI amongst contacts Effectiveness: incidence of ILI. An age-based definition of ILI was used as follows. 1. For individuals > 5 years old, ILI was defined as history of fever with cough or sore throat. 2. For children < 5 years old, ILI was defined as fever (the authors used this relatively liberal case definition in order to include influenza cases with atypical presentations in children). Safety: no safety data planned or reported by investigators
Notes	Inclusion/exclusion criteria changed 3 times during the study conduct. The period study conducted: June 2009 to December 2010 Funding: government

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation, with a block size of 4, in order to promote random and even allocation of household compounds to the 2 treatment arms. The list of random assignments was generated by an investigator with no contact with the participants.

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Ram 2015 *(Continued)*

Allocation concealment (selection bias)	Low risk	Once baseline data collection was complete, the data collector notified the field research officer, who consulted the block randomisation list to make the assignment of the household compound to intervention or control.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Relied on symptom reporting from the head of family. Inclusion/exclusion criteria changed 3 times during the study conduct. Given the provision of a hand-washing station as part of the intervention, it was not possible to ensure blinding of participants, intervention staff, or data collectors.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Relied on symptom reporting from the head of family. Inclusion/exclusion criteria changed 3 times during the conduct of the study. Given the provision of a hand-washing station as part of the intervention, it was not possible to ensure blinding of participants, intervention staff, or data collectors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow chart followed all households an individuals from recruitment to analysis.
Selective reporting (reporting bias)	Low risk	The specified outcomes are clearly accounted for. Investigators report all outcomes for each modified enrolment.

Roberts 2000

Study characteristics	
Methods	Open cluster-RCT carried out between March and November 1996 (the Southern Hemisphere winter season) in 23 childcare centres caring for a minimum of 50 children 10 hours a day, 5 days a week in Australia. The study assessed the effects of an Australian national hand-washing programme compared to standard procedure. Randomisation was according to a random-number table, and cluster coefficients are reported.
Participants	Children (299 in the intervention arm and 259 in the control arm) aged 3 or younger attending the centres at least 3 days a week. Attrition was 51 children in the intervention arm and 72 children in the control arm due mainly to staff leaving the centres.
Interventions	Hand-washing programme with training for staff and children. It is unclear whether any extra hand-cleansing agents were used, as GloGerm (?) is mentioned when it was used in a preliminary study.
Outcomes	Laboratory: N/A Effectiveness: ARI (runny nose, cough, and blocked nose) Follow-up was via a parental phone interview every 2 weeks. Safety: N/A
Notes	Risk of bias: low (cluster coefficients and analysis by unit of randomisation) Note: the authors conclude that although there was no overall decrease in respiratory illness (RR 0.95, 95% CI 0.89 to 1.01), in children up to 24 months the decrease was statistically significant (RR 0.90, 95% CI 0.83 to 0.97). The authors speculated that this was because maximum benefits are likely from this age group due to their limited ability to wipe their nose and hands without a structured programme. Analyses by 3 compliance levels are also reported. A so-so reported and well-conducted trial
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

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Roberts 2000 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomisation was according to a random-number table.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was not possible to blind the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The observer was not informed of the content of the training sessions or the intervention status of the centres."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Recruitment rate 88% (23 of 26 CCCs); loss to follow-up not clear, as no denominator given
Selective reporting (reporting bias)	Low risk	Centres were comparable at baseline.

Sandora 2005

Study characteristics	
Methods	Single-blind, cluster-RCT carried around the Boston area, USA, in the period of November 2002 to April 2003. The trial tested the effects of using a hand sanitiser and a programme of instruction on the transmissions of GI infections (data not extracted) and ARIs in families. Units of randomisation were child-care centres and were carried out on enrolment by an investigator using random block size generated by computer. Assignment was single-blind (i.e. investigator blinded to the status of the centre). Cluster correlation was 0.01.
Participants	292 families with 1 or more children aged 6 months to 5 years who were in child care for 10 or more hours a week 155 children in 14 centres were allocated to the intervention arm and 137 children in 12 centres to the control arm**.** The mean age was 3 to 2.7 years. Attrition was respectively 15 (3 lost to follow-up and 12 who discontinued the intervention) and 19 (8 lost to follow-up and 11 who discontinued the intervention). ITT analysis was carried out.
Interventions	Alcohol-based hand sanitiser with biweekly hand hygiene educational materials over 5 months versus biweekly educational material on healthy diet
Outcomes	Effectiveness: ARI (2 of the following symptoms for 1 day or 1 of the following symptoms for 2 days: runny nose, cough, sneezing, stuffy or blocked nose, fever, sore throat). An illness episode had to be separated by 2 symptom-free days from a previous episode. A secondary illness was when it followed a similar illness in another family member by 2 to 7 days. Follow-up was by means of biweekly phone calls to caregivers. Safety: dry skin (71 reports), stinging (11 reports), bad smell (7 reports), dislike (2 reports), allergic reaction (2 reports), slippery feel (1 report), and irritation (20 reports)
Notes	Risk of bias: low Note: the authors conclude that although the rate of GI illnesses was significantly lower in the intervention group, the IRR was not significantly different for ARIs (0.97, 95% CI 0.72 to 1.30). Compliance and droplet route spread may account for this apparent lack of effect. A well-reported trial

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Sandora 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random assignments were generated by computer using a permuted-blocks design with random block sizes."
Allocation concealment (selection bias)	Low risk	"Assignments were concealed in opaque envelopes, and centers were assigned to control or intervention groups by a study investigator as they were enrolled."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Teachers in the intervention classrooms were responsible for encouraging the use of the disinfecting wipes and hand sanitizer according to the study protocol ... Given that no placebo was provided and sanitizer use was recorded, neither families nor data collectors could be blinded as to the group assignment of the family."
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Given that no placebo was provided and sanitizer use was recorded, neither families nor data collectors could be blinded as to the group assignment of the family."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 15 in intervention arm (3 lost to follow-up and 12 who discontinued the intervention) and 19 in the control arm (8 lost to follow-up and 11 who discontinued the intervention). ITT analysis was carried out.
Selective reporting (reporting bias)	Unclear risk	Well-reported

Sandora 2008

Study characteristics

Methods	Cluster-RCT carried out in a single elementary school system located in Avon, Ohio, USA to assess the effectiveness of a multifactorial infection-control intervention, including alcohol-based hand sanitiser and surface disinfection, in reducing absenteeism caused by gastrointestinal and respiratory illnesses amongst elementary school students. The study also aimed to describe the viral and bacterial contamination of common surfaces in the school classroom and to assess the impact of an environmental disinfectant on the presence of selected viruses and bacteria on these surfaces. Clustering was described as "teams of 3-4 classes depending on the class year".
Participants	A total of 363 students in 15 different classrooms were eligible to participate and received letters about the study. A sample of 285 of these students provided written informed consent and were randomly assigned to the intervention group (146) or to the control group (139) and contributed to final analysis. No students were lost to follow-up or discontinued the intervention during the study period. Baseline demographic characteristics were similar in the intervention and control groups. Most families were white and non-Hispanic and in excellent or very good health at baseline.
Interventions	Alcohol-based hand sanitiser to use at school and quaternary ammonium wipes to disinfect classroom surfaces daily for 8 weeks versus usual hand-washing and cleaning practices
Outcomes	Laboratory: Serological evidence: no Swabs for bacteria and viruses from 3 types of classroom surfaces were taken.

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Sandora 2008 *(Continued)*

	Effectiveness: Respiratory illness defined as days absent as measured by a (blinded) school worker who routinely recorded reason for absenteeism either for gastrointestinal or respiratory causes. Safety: N/A
Notes	The authors conclude that the multifaceted intervention that included alcohol-based hand sanitiser use and disinfection of common classroom surfaces reduced absenteeism from gastrointestinal illness amongst elementary school students. The intervention did not impact on absenteeism from respiratory illness. In addition, norovirus was detected less frequently on classroom surfaces in the group receiving the intervention. The study is of good quality with low risk of bias. The authors checked compliance by counting discarded wipes. Reasons given for the apparent lack of effect against ARIs but good effect on GI illness are that disinfecting the classroom surfaces (daily at lunchtime with alkali) was important, as were the alcohol wipes. The authors measured the norovirus concentration on surfaces and found this to be reduced. Other reasons may be that droplets are not affected by this method, or that contamination of hands by respiratory infections is likely to be continuous (in orofaecal transmission is mostly at the time of defecation).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The allocation sequence was generated by computer ..."
Allocation concealment (selection bias)	Unclear risk	"...and teams were assigned to study groups by a study investigator (Dr Shih)." Blinding of allocation cannot be guaranteed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All of the students absences were recorded in the usual fashion by the school employee who normally answers this dedicated telephone line. This employee was blinded to the group assignment of the child."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No students were lost to follow-up or discontinued the intervention during the study period.
Selective reporting (reporting bias)	Unclear risk	Well-reported

Satomura 2005

Study characteristics

Methods	RCT. Randomisation was achieved by simple computer-generated random digit. Allocation was concealed using sealed, opaque envelopes. Not clear if there was a central randomisation centre. Post hoc exchange of envelopes was prevented by writing both the name of each participant and the number on the envelope he/she drew before breaking the seal. Participants were not blinded to the intervention; however, disease incidence was determined by 1 study physician who was not informed of the results of assignment. Analysis was done based on the intention-to-treat principle. The study targeted community healthcare all over Japan and was conducted between December 2002 and March 2003 for a follow-up period of 60 days.

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Satomura 2005 *(Continued)*

Participants	387 participants at 18 sites were recruited, 384 were included in the analysis: water gargling (N = 122), povidone-iodine gargling (N = 132), and control (N = 130). Follow-up was completed on 338 participants. Attrition was fully explained for URTI analysis; however, 2 participants were not accounted for in the ILI analysis. 46 participants did not complete the follow-up due to either discontinuation of diary use (n = 9) or contracting ILI (n = 37). Of the 37 participants with ILI, 11 were in the povidone-iodine group, 12 in the water group, and 14 in the control group. Analysis was performed on 35 participants (Kitamura 2007).
Interventions	Participants were randomised to 1 of the following: water gargling, n = 122 (20 mL of water for about 15 seconds 3 times consecutively, at least 3 times a day); povidone-iodine gargling, n = 133 (20 mL of 15 to 30 times diluted 7% povidone-iodine (as indicated by the manufacturer) in the same way as water gargling); and control, n = 132 (retain their previous gargling habits). All groups were asked to fill a daily gargling diary (standardised form to record: gargling habits, hand-washing, and influenza complaints). The frequency of gargling in the water group was higher (3.6); the frequency of hand-washing was similar amongst the 3 groups. URTI symptom was classified according to Jackson methods. Diary recording was continued throughout the follow-up period and for 1 week after the onset of URTI. ILI was reported separately.
Outcomes	Laboratory: none Effectiveness: Primary outcome: incidence of first URTI. Index cases were defined as all of the following conditions: 1. both nasal and pharyngeal symptoms, 2. severity of at least 1 symptom increased by 2 grades or more, and 3. worsening of a symptom of 1 increment or more for > 3 days. Secondary outcome: severity of URTI of the incident cases was assessed by grading each symptom during the initial 7 days after the onset of URTI in numeric scores: none = 0, mild = 1, moderate = 2, and severe = 3 ILI was defined as both developing a fever of 38 °C or higher and worsening arthralgia in addition to some respiratory symptoms (Kitamura 2007). Safety: no harm was reported. However, 2 participants in the povidone-iodine group switched to water gargling (analysed in their assignment group).
Notes	The authors concluded that simple water gargling is effective in preventing URTIs amongst healthy people. However, no statistically significant difference was observed against ILIs. The study was well-conducted; blinding would have added to the validity of the results. In addition, the study was not powered enough to detect a statistically significant preventative effect against ILI. The study demonstrates that in addition to hand-washing, simple gargling even with water can reduce URTI, but not ILI. However, during periods of endemic influenza, multiple inexpensive and simple modalities (hand-washing, masks, gargling) can be utilised together to reduce infection and transmission. Overall, the reporting of the 2 combined studies together is highly confusing. In the first study (Satomura 2005), the main outcome is URTI defined as fever and arthralgia. The second study (which is a presentation of further data from the 2005 publication in the guise of a short report) introduces the outcome ILI with a definition similar to that of URTI in the first study but referring to the earlier outcome as common cold. Also of note is reporting of significance without confidence intervals. Overall, this potentially important study should be repeated with a larger denominator. Unclear risk of bias because of confused reporting and absence of double-blinding

Risk of bias

Bias	Authors' judgement	Support for judgement

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Satomura 2005 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Group assignment was based on simple computer-generated random digits..."
Allocation concealment (selection bias)	Low risk	"By an individual drawing of sealed opaque envelopes, subjects were randomly assigned to the following three groups" "allocation was completely concealed from study administrators"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"To prevent post hoc exchange of the envelopes, local administrators wrote down both the name of each subject and the number on the envelope he/she drew before breaking the seal."
Incomplete outcome data (attrition bias) All outcomes	Low risk	338 of 385 randomised followed up; reasons reported.
Selective reporting (reporting bias)	Unclear risk	Confusing reporting

Savolainen-Kopra 2012

Study characteristics	
Methods	Open cluster-RCT, 3-arm intervention trial
Participants	A total of 21 clusters (683 individuals) were randomised to implement hand hygiene with soap and water (257 individuals), alcohol-based hand rub (202 individuals), or control (224 individuals). The study was conducted in distinct office work units in 6 corporations in the Helsinki Region that together employed some 10,000 staff. All employees (age ≥ 18 years, both genders) were contacted by email survey. Inclusion criteria: "Volunteers working in defined units" Exclusion criteria: "Persons with open wounds or chronic eczema in hands" The designated 21 study clusters were identified as operationally distinct working units, each containing at least 50 people.
Interventions	Hand hygiene with soap and water and standardised instructions on how to limit the transmission of infections. Usual hand hygiene (control). See Table 1 for details.
Outcomes	Laboratory: "Between November 2008 and May 2010, the seven occupational health clinics serving the six participating corporations were advised to collect, using standard techniques, two to three respiratory samples per week from typical RTI patients and also faecal samples from a few representative patients with gastrointestinal symptoms when a GIT outbreak was suspected. The samples could originate from the study participants and also from work units not included in the study. In the laboratory, viral nucleic acids were extracted with well-characterized commercial kits and tested by validated real-time PCR methods to detect influenza A and B viruses, respiratory syncytial virus, parainfluenza virus types 1, 2, and 3, adenoviruses, human rhinoviruses and human enteroviruses from respiratory specimens, and norovirus from faecal specimens (detailed descriptions of the test procedures are available from the authors)."

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Savolainen-Kopra 2012 *(Continued)*

	Effectiveness: Predefined primary endpoints: 1. Number of reported infection episodes in a cluster per total reported weeks. 2. Number of reported sick leave episodes in a cluster per total reported weeks. Secondary endpoints and outcome measures: 1. Number of days with reported symptoms of RTI and/or GTI in a cluster within a time frame of 100 reporting weeks. 2. Number of days-off due to own RTI or GTI in a cluster within a time frame of 100 reporting weeks. Safety: reported 0 adverse events
Notes	The period study conducted: January 2009 to May 2010 Funding: government

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Low risk	"clusters were matched and randomized prior to onset of the interventions"
Blinding of participants and personnel (performance bias) All outcomes	High risk	The interventions were not blinded to any party involved (i.e. the study group, participants, or the occupational health services). Subjective reporting of disease episodes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Subjective reporting of disease episodes
Incomplete outcome data (attrition bias) All outcomes	High risk	24% loss to follow-up. However, new recruiting in most clusters; the total number of reporting participants at the end of the trial was 91.7% compared to that at the beginning. Attrition was reported, and 76% of volunteers who started reporting continued to do so until the end of the study. Because of new recruiting in most clusters, the total number of reporting participants at the end of the trial was 626, or 91.7%, compared to that at the beginning. This means that 15.7% of the participants were replaced during the study!!! Raw data on the effects of the interventions on the occurrence of respiratory infections and vomiting/diarrhoea diseases were not reported. Zero adverse effects were reported.
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.

Roberts 2000

Study characteristics

Methods	Open cluster-RCT carried out between March and November 1996 (the Southern Hemisphere winter season) in 23 childcare centres caring for a minimum of 50 children 10 hours a day, 5 days a week in

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Roberts 2000 *(Continued)*

	Australia. The study assessed the effects of an Australian national hand-washing programme compared to standard procedure. Randomisation was according to a random-number table, and cluster coefficients are reported.
Participants	Children (299 in the intervention arm and 259 in the control arm) aged 3 or younger attending the centres at least 3 days a week. Attrition was 51 children in the intervention arm and 72 children in the control arm due mainly to staff leaving the centres.
Interventions	Hand-washing programme with training for staff and children. It is unclear whether any extra hand-cleansing agents were used, as GloGerm (?) is mentioned when it was used in a preliminary study.
Outcomes	Laboratory: N/A Effectiveness: ARI (runny nose, cough, and blocked nose) Follow-up was via a parental phone interview every 2 weeks. Safety: N/A
Notes	Risk of bias: low (cluster coefficients and analysis by unit of randomisation) Note: the authors conclude that although there was no overall decrease in respiratory illness (RR 0.95, 95% CI 0.89 to 1.01), in children up to 24 months the decrease was statistically significant (RR 0.90, 95% CI 0.83 to 0.97). The authors speculated that this was because maximum benefits are likely from this age group due to their limited ability to wipe their nose and hands without a structured programme. Analyses by 3 compliance levels are also reported. A so-so reported and well-conducted trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was according to a random-number table.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was not possible to blind the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The observer was not informed of the content of the training sessions or the intervention status of the centres."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Recruitment rate 88% (23 of 26 CCCs); loss to follow-up not clear, as no denominator given
Selective reporting (reporting bias)	Low risk	Centres were comparable at baseline.

Sandora 2005

Study characteristics

Methods	Single-blind, cluster-RCT carried around the Boston area, USA, in the period of November 2002 to April 2003. The trial tested the effects of using a hand sanitiser and a programme of instruction on the transmissions of GI infections (data not extracted) and ARIs in families. Units of randomisation were child-care centres and were carried out on enrolment by an investigator using random block size generated

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Sandora 2005 *(Continued)*

	by computer. Assignment was single-blind (i.e. investigator blinded to the status of the centre). Cluster correlation was 0.01.
Participants	292 families with 1 or more children aged 6 months to 5 years who were in child care for 10 or more hours a week 155 children in 14 centres were allocated to the intervention arm and 137 children in 12 centres to the control arm**.** The mean age was 3 to 2.7 years. Attrition was respectively 15 (3 lost to follow-up and 12 who discontinued the intervention) and 19 (8 lost to follow-up and 11 who discontinued the intervention). ITT analysis was carried out.
Interventions	Alcohol-based hand sanitiser with biweekly hand hygiene educational materials over 5 months versus biweekly educational material on healthy diet
Outcomes	Effectiveness: ARI (2 of the following symptoms for 1 day or 1 of the following symptoms for 2 days: runny nose, cough, sneezing, stuffy or blocked nose, fever, sore throat). An illness episode had to be separated by 2 symptom-free days from a previous episode. A secondary illness was when it followed a similar illness in another family member by 2 to 7 days. Follow-up was by means of biweekly phone calls to caregivers. Safety: dry skin (71 reports), stinging (11 reports), bad smell (7 reports), dislike (2 reports), allergic reaction (2 reports), slippery feel (1 report), and irritation (20 reports)
Notes	Risk of bias: low Note: the authors conclude that although the rate of GI illnesses was significantly lower in the intervention group, the IRR was not significantly different for ARIs (0.97, 95% CI 0.72 to 1.30). Compliance and droplet route spread may account for this apparent lack of effect. A well-reported trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random assignments were generated by computer using a permuted-blocks design with random block sizes."
Allocation concealment (selection bias)	Low risk	"Assignments were concealed in opaque envelopes, and centers were assigned to control or intervention groups by a study investigator as they were enrolled."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Teachers in the intervention classrooms were responsible for encouraging the use of the disinfecting wipes and hand sanitizer according to the study protocol ... Given that no placebo was provided and sanitizer use was recorded, neither families nor data collectors could be blinded as to the group assignment of the family."
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Given that no placebo was provided and sanitizer use was recorded, neither families nor data collectors could be blinded as to the group assignment of the family."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 15 in intervention arm (3 lost to follow-up and 12 who discontinued the intervention) and 19 in the control arm (8 lost to follow-up and 11 who discontinued the intervention). ITT analysis was carried out.
Selective reporting (reporting bias)	Unclear risk	Well-reported

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Sandora 2008

Study characteristics	
Methods	Cluster-RCT carried out in a single elementary school system located in Avon, Ohio, USA to assess the effectiveness of a multifactorial infection-control intervention, including alcohol-based hand sanitiser and surface disinfection, in reducing absenteeism caused by gastrointestinal and respiratory illnesses amongst elementary school students. The study also aimed to describe the viral and bacterial contamination of common surfaces in the school classroom and to assess the impact of an environmental disinfectant on the presence of selected viruses and bacteria on these surfaces. Clustering was described as "teams of 3-4 classes depending on the class year".
Participants	A total of 363 students in 15 different classrooms were eligible to participate and received letters about the study. A sample of 285 of these students provided written informed consent and were randomly assigned to the intervention group (146) or to the control group (139) and contributed to final analysis. No students were lost to follow-up or discontinued the intervention during the study period. Baseline demographic characteristics were similar in the intervention and control groups. Most families were white and non-Hispanic and in excellent or very good health at baseline.
Interventions	Alcohol-based hand sanitiser to use at school and quaternary ammonium wipes to disinfect classroom surfaces daily for 8 weeks versus usual hand-washing and cleaning practices
Outcomes	Laboratory: Serological evidence: no Swabs for bacteria and viruses from 3 types of classroom surfaces were taken. Effectiveness: Respiratory illness defined as days absent as measured by a (blinded) school worker who routinely recorded reason for absenteeism either for gastrointestinal or respiratory causes. Safety: N/A
Notes	The authors conclude that the multifaceted intervention that included alcohol-based hand sanitiser use and disinfection of common classroom surfaces reduced absenteeism from gastrointestinal illness amongst elementary school students. The intervention did not impact on absenteeism from respiratory illness. In addition, norovirus was detected less frequently on classroom surfaces in the group receiving the intervention. The study is of good quality with low risk of bias. The authors checked compliance by counting discarded wipes. Reasons given for the apparent lack of effect against ARIs but good effect on GI illness are that disinfecting the classroom surfaces (daily at lunchtime with alkali) was important, as were the alcohol wipes. The authors measured the norovirus concentration on surfaces and found this to be reduced. Other reasons may be that droplets are not affected by this method, or that contamination of hands by respiratory infections is likely to be continuous (in orofaecal transmission is mostly at the time of defecation).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The allocation sequence was generated by computer ..."
Allocation concealment (selection bias)	Unclear risk	"...and teams were assigned to study groups by a study investigator (Dr Shih)." Blinding of allocation cannot be guaranteed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible

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Sandora 2008 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All of the students absences were recorded in the usual fashion by the school employee who normally answers this dedicated telephone line. This employee was blinded to the group assignment of the child."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No students were lost to follow-up or discontinued the intervention during the study period.
Selective reporting (reporting bias)	Unclear risk	Well-reported

Satomura 2005

Study characteristics	
Methods	RCT. Randomisation was achieved by simple computer-generated random digit. Allocation was concealed using sealed, opaque envelopes. Not clear if there was a central randomisation centre. Post hoc exchange of envelopes was prevented by writing both the name of each participant and the number on the envelope he/she drew before breaking the seal. Participants were not blinded to the intervention; however, disease incidence was determined by 1 study physician who was not informed of the results of assignment. Analysis was done based on the intention-to-treat principle. The study targeted community healthcare all over Japan and was conducted between December 2002 and March 2003 for a follow-up period of 60 days.
Participants	387 participants at 18 sites were recruited, 384 were included in the analysis: water gargling (N = 122), povidone-iodine gargling (N = 132), and control (N = 130). Follow-up was completed on 338 participants. Attrition was fully explained for URTI analysis; however, 2 participants were not accounted for in the ILI analysis. 46 participants did not complete the follow-up due to either discontinuation of diary use (n = 9) or contracting ILI (n = 37). Of the 37 participants with ILI, 11 were in the povidone-iodine group, 12 in the water group, and 14 in the control group. Analysis was performed on 35 participants (Kitamura 2007).
Interventions	Participants were randomised to 1 of the following: water gargling, n = 122 (20 mL of water for about 15 seconds 3 times consecutively, at least 3 times a day); povidone-iodine gargling, n = 133 (20 mL of 15 to 30 times diluted 7% povidone-iodine (as indicated by the manufacturer) in the same way as water gargling); and control, n = 132 (retain their previous gargling habits). All groups were asked to fill a daily gargling diary (standardised form to record: gargling habits, hand-washing, and influenza complaints). The frequency of gargling in the water group was higher (3.6); the frequency of hand-washing was similar amongst the 3 groups. URTI symptom was classified according to Jackson methods. Diary recording was continued throughout the follow-up period and for 1 week after the onset of URTI. ILI was reported separately.
Outcomes	Laboratory: none Effectiveness: Primary outcome: incidence of first URTI. Index cases were defined as all of the following conditions: 1. both nasal and pharyngeal symptoms, 2. severity of at least 1 symptom increased by 2 grades or more, and 3. worsening of a symptom of 1 increment or more for > 3 days. Secondary outcome: severity of URTI of the incident cases was assessed by grading each symptom during the initial 7 days after the onset of URTI in numeric scores: none = 0, mild = 1, moderate = 2, and severe = 3

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Satomura 2005 *(Continued)*

	ILI was defined as both developing a fever of 38 °C or higher and worsening arthralgia in addition to some respiratory symptoms (Kitamura 2007). Safety: no harm was reported. However, 2 participants in the povidone-iodine group switched to water gargling (analysed in their assignment group).
Notes	The authors concluded that simple water gargling is effective in preventing URTIs amongst healthy people. However, no statistically significant difference was observed against ILIs. The study was well-conducted; blinding would have added to the validity of the results. In addition, the study was not powered enough to detect a statistically significant preventative effect against ILI. The study demonstrates that in addition to hand-washing, simple gargling even with water can reduce URTI, but not ILI. However, during periods of endemic influenza, multiple inexpensive and simple modalities (hand-washing, masks, gargling) can be utilised together to reduce infection and transmission. Overall, the reporting of the 2 combined studies together is highly confusing. In the first study (Satomura 2005), the main outcome is URTI defined as fever and arthralgia. The second study (which is a presentation of further data from the 2005 publication in the guise of a short report) introduces the outcome ILI with a definition similar to that of URTI in the first study but referring to the earlier outcome as common cold. Also of note is reporting of significance without confidence intervals. Overall, this potentially important study should be repeated with a larger denominator. Unclear risk of bias because of confused reporting and absence of double-blinding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Group assignment was based on simple computer-generated random digits..."
Allocation concealment (selection bias)	Low risk	"By an individual drawing of sealed opaque envelopes, subjects were randomly assigned to the following three groups" "allocation was completely concealed from study administrators"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"To prevent post hoc exchange of the envelopes, local administrators wrote down both the name of each subject and the number on the envelope he/she drew before breaking the seal."
Incomplete outcome data (attrition bias) All outcomes	Low risk	338 of 385 randomised followed up; reasons reported.
Selective reporting (reporting bias)	Unclear risk	Confusing reporting

Savolainen-Kopra 2012

Study characteristics

Methods	Open cluster-RCT, 3-arm intervention trial
Participants	A total of 21 clusters (683 individuals) were randomised to implement hand hygiene with soap and water (257 individuals), alcohol-based hand rub (202 individuals), or control (224 individuals).

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Savolainen-Kopra 2012 *(Continued)*

	The study was conducted in distinct office work units in 6 corporations in the Helsinki Region that together employed some 10,000 staff. All employees (age ≥ 18 years, both genders) were contacted by email survey. Inclusion criteria: "Volunteers working in defined units" Exclusion criteria: "Persons with open wounds or chronic eczema in hands" The designated 21 study clusters were identified as operationally distinct working units, each containing at least 50 people.
Interventions	Hand hygiene with soap and water and standardised instructions on how to limit the transmission of infections. Usual hand hygiene (control). See Table 1 for details.
Outcomes	Laboratory: "Between November 2008 and May 2010, the seven occupational health clinics serving the six participating corporations were advised to collect, using standard techniques, two to three respiratory samples per week from typical RTI patients and also faecal samples from a few representative patients with gastrointestinal symptoms when a GIT outbreak was suspected. The samples could originate from the study participants and also from work units not included in the study. In the laboratory, viral nucleic acids were extracted with well-characterized commercial kits and tested by validated real-time PCR methods to detect influenza A and B viruses, respiratory syncytial virus, parainfluenza virus types 1, 2, and 3, adenoviruses, human rhinoviruses and human enteroviruses from respiratory specimens, and norovirus from faecal specimens (detailed descriptions of the test procedures are available from the authors)." Effectiveness: Predefined primary endpoints: 1. Number of reported infection episodes in a cluster per total reported weeks. 2. Number of reported sick leave episodes in a cluster per total reported weeks. Secondary endpoints and outcome measures: 1. Number of days with reported symptoms of RTI and/or GTI in a cluster within a time frame of 100 reporting weeks. 2. Number of days-off due to own RTI or GTI in a cluster within a time frame of 100 reporting weeks. Safety: reported 0 adverse events
Notes	The period study conducted: January 2009 to May 2010 Funding: government

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Low risk	"clusters were matched and randomized prior to onset of the interventions"
Blinding of participants and personnel (performance bias) All outcomes	High risk	The interventions were not blinded to any party involved (i.e. the study group, participants, or the occupational health services). Subjective reporting of disease episodes
Blinding of outcome assessment (detection bias)	High risk	Subjective reporting of disease episodes

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Savolainen-Kopra 2012 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	24% loss to follow-up. However, new recruiting in most clusters; the total number of reporting participants at the end of the trial was 91.7% compared to that at the beginning. Attrition was reported, and 76% of volunteers who started reporting continued to do so until the end of the study. Because of new recruiting in most clusters, the total number of reporting participants at the end of the trial was 626, or 91.7%, compared to that at the beginning. This means that 15.7% of the participants were replaced during the study!!! Raw data on the effects of the interventions on the occurrence of respiratory infections and vomiting/diarrhoea diseases were not reported. Zero adverse effects were reported.
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported.

Simmerman 2011

Study characteristics	
Methods	Randomised controlled study
Participants	Study recruited 348 households and 885 members and randomised them as follows: 1. Control (index household = 119, with 302 family members) 2. Hand-washing (index household = 119, with 292 family members) 3. Hand-washing and face mask (index household = 110, with 291 family members) The household members of children (index cases) presenting with ILI at the outpatient department of the Queen Sirikit National Institute of Child Health (QSNICH) in Bangkok, the largest public paediatric hospital in Thailand Inclusion criteria: For index cases: children aged 1 month through 15 years, residents of the Bangkok metropolitan area, and had an onset of illness < 48 hours before respiratory specimens tested positive for influenza by an RIDT that was later confirmed by qualitative real-time RT-PCR (rRT-PCR) Eligible index cases' households must have had at least 2 other members aged ≥ 1 month who planned to sleep inside the house for a period of at least 21 days from the time of enrolment. Exclusion criteria: For index cases: children at high risk for severe influenza complications (e.g. chronic lung disease, renal disease, and long-term aspirin therapy) and those treated with influenza antiviral medications Excluded households: those with any member reporting an ILI that preceded the index case by 7 days or less and households where any member had received influenza vaccination during the preceding 12 months
Interventions	Hand-washing, or hand-washing plus paper surgical face mask, or control. See Table 1 for details.
Outcomes	Laboratory: To identify index cases: QuickVue Influenza A+B rapid diagnostic kit (Quidel Co., San Diego, CA, USA), followed by rRT-PCR for influenza viral RNA Index cases and contacts tested with nasal swab and throat swab both processed for rRT-PCR.

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Simmerman 2011 *(Continued)*

	2 blood samples for antibody seroconversion collected on Days 1 and 21 (seroconversion defined as a fourfold rise in HI titre between paired sera for any of the antigens assayed). Effectiveness: Laboratory-confirmed secondary influenza virus infections amongst household members described as the secondary attack rate (SAR). A secondary influenza virus infection was defined as a positive rRT-PCR result on Days 3 or 7 or a fourfold rise in influenza HI antibody titres with the virus type and sub-type matching the index case. SAR for ILI defined by the WHO as fever plus cough or sore throat, based on self-reported symptoms. Safety: no safety measures planned or reported by the investigators Adherence: participants in the control arm reported an average of 3.9 hand-washing episodes/day (on Day 7), whilst participants in the hand-washing arm reported an average of 4.7 hand-washing episodes/day (95% CI 4.3 to 5.0; P = 0.002 compared to controls), and participants in the hand-washing plus face mask arm reported 4.9 episodes/day (95% CI 4.5 to 5.3; P < 0.001 compared to controls). In the intervention arms, parents had the highest reported daily hand-washing frequency (5.7, 95% CI 5.3 to 6.0) followed by others (4.8, 95% CI 4.3 to 5.3), siblings (4.3, 95% CI 3.7 to 4.8), and the index cases (4.1, 95% CI 3.8 to 4.4). There was no difference in the average amount of soap used in a week in the hand-washing arm (54 mL per person) and the hand-washing plus face mask arm (58.1 mL per person) (P = 0.15). 289 participants in the hand-washing plus face mask arm used an average of 12 masks per person per week (median 11, IQR 7 to 16) and reported wearing a face mask a mean of 211 minutes/day (IQR 17 to 317 minutes/day). Parents wore their masks for a median of 153 (IQR 40 to 411) minutes per day, far more than other relations (median 59; IQR 9 to 266), the index patients themselves (median 35; IQR 4 to 197), or their siblings (median 17; IQR 6 to 107). The study authors note that differences in average usage may be an attenuated measure of appropriate use in relation to the actual unmeasured exposure risk such as proximity to the index case.
Notes	The period study conducted: April 2008 and August 2009 Funding: government

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was achieved using a block randomization method using a list of blocks each with 12 household IDs, four of which were assigned to each of the three study arms."
Allocation concealment (selection bias)	Unclear risk	"A study coordinator assigned each household to one study arm after consent was obtained"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Recruiting clinicians were blinded to the allocation of the specific intervention. The participants were not blinded, but it is unlikely that the outcome would have been affected by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The primary outcome is a laboratory-confirmed influenza.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Household flow chart provided with reasons for exclusions, all numbers provided. Analysis was done by ITT and PP.
Selective reporting (reporting bias)	Low risk	All outcomes are accounted for in the ITT analysis of the results.

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Stebbins 2011

Study characteristics	
Methods	Cluster-RCT, open-label
Participants	Study included 3360 students from 10 Pittsburgh elementary schools. Intervention arm (5 schools, 1695 people) and control arm (5 schools, 1665 people) No inclusion or exclusion criteria were provided.
Interventions	Training in hand and respiratory (cough) hygiene. Hand sanitiser was provided and encouraged to be used regularly. See Table 1 for details.
Outcomes	Laboratory: Primary outcome: laboratory-confirmed influenza (RT-PCR) amongst children presenting with ILIs leading to their absence from school 2 nasal swabs were obtained using test manufacturer-approved sterile Dacron swabs. 1 swab was employed for influenza testing using the QuickVue Influenza A+B test (Quidel Corp, San Diego, CA). The second nasal swab was delivered on cold pack to the University of Pittsburgh Medical Center Clinical Virology Laboratory, Pittsburgh, PA for RT-PCR testing (performed within 48 hours). The RT-PCR used viral nucleic acid extract (EasyMag; bioMerieux, Durham, NC) and primer/probe sequences for influenza A, influenza B, and influenza A H1 and H3 subtypes (CDC, Atlanta GA). Effectiveness: Secondary outcome: absence episodes and cumulative days of absence due to ILI, any illness, and all causes Safety: none mentioned
Notes	The period study conducted: 1 November 2007 through 24 April 2008 Funding: unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"constrained randomization algorithm"
Allocation concealment (selection bias)	Low risk	"Random allocation of schools to two arms was created by Dr. Cummings and concealed until intervention assignment". "At the beginning of the school year parents and guardians were given the opportunity to decline participation"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	In 76% and 78% of illness in intervention and control group were laboratory confirmed. ILI is objectively defined.

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Stebbins 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Only episodes of identified causes were analysed. Causes of absence episodes in 66% of the study participants were not identified (2092 in the intervention group and 2232 in the control group). The parents could be contacted in only 34% cases of absence. About half of them had an illness, and in one-third of these cases the illness met the criteria of ILI (361 cases (33%)). Of these, 279 (77%) were tested for influenza.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to judge

Stebbins 2011

Study characteristics	
Methods	Cluster-RCT, open-label
Participants	Study included 3360 students from 10 Pittsburgh elementary schools. Intervention arm (5 schools, 1695 people) and control arm (5 schools, 1665 people) No inclusion or exclusion criteria were provided.
Interventions	Training in hand and respiratory (cough) hygiene. Hand sanitiser was provided and encouraged to be used regularly. See Table 1 for details.
Outcomes	Laboratory: Primary outcome: laboratory-confirmed influenza (RT-PCR) amongst children presenting with ILIs leading to their absence from school 2 nasal swabs were obtained using test manufacturer-approved sterile Dacron swabs. 1 swab was employed for influenza testing using the QuickVue Influenza A+B test (Quidel Corp, San Diego, CA). The second nasal swab was delivered on cold pack to the University of Pittsburgh Medical Center Clinical Virology Laboratory, Pittsburgh, PA for RT-PCR testing (performed within 48 hours). The RT-PCR used viral nucleic acid extract (EasyMag; bioMerieux, Durham, NC) and primer/probe sequences for influenza A, influenza B, and influenza A H1 and H3 subtypes (CDC, Atlanta GA). Effectiveness: Secondary outcome: absence episodes and cumulative days of absence due to ILI, any illness, and all causes Safety: none mentioned
Notes	The period study conducted: 1 November 2007 through 24 April 2008 Funding: unclear

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"constrained randomization algorithm"

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Stebbins 2011 *(Continued)*

Allocation concealment (selection bias)	Low risk	"Random allocation of schools to two arms was created by Dr. Cummings and concealed until intervention assignment". "At the beginning of the school year parents and guardians were given the opportunity to decline participation"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	In 76% and 78% of illness in intervention and control group were laboratory confirmed. ILI is objectively defined.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only episodes of identified causes were analysed. Causes of absence episodes in 66% of the study participants were not identified (2092 in the intervention group and 2232 in the control group). The parents could be contacted in only 34% cases of absence. About half of them had an illness, and in one-third of these cases the illness met the criteria of ILI (361 cases (33%)). Of these, 279 (77%) were tested for influenza.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to judge

Suess 2012

Study characteristics	
Methods	Cluster-RCT, open-label, parallel design
Participants	Study sample included 84 households randomised as follows: 1. 30 control (index cases = 30, household contact = 82) 2. 26 mask group (index cases = 26, household contact = 69) 3. 28 mask and hand hygiene group (index cases = 28, household contact = 67) Inclusion criteria: patients presenting to general practitioners or family physicians at the study sites within 2 days of symptom onset; had a positive rapid antigen test for influenza (later to be confirmed by quantitative RT-PCR (qRT-PCR); and was at least 2 years old. Index cases also had to be the only household member suffering from respiratory disease within 14 days prior to symptom onset. Exclusion criteria were pregnancy, severely reduced health status, and HIV infection. 1-person households were also not eligible or inclusion.
Interventions	Quote: "facemask and practising intensified hand hygiene (MH group), wearing facemask only (M group) and none of the 2 (control group)". See Table 1 for details.
Outcomes	Primary outcomes: SAR of laboratory-confirmed (qRT-PCR) influenza infection amongst household members (secondary infection cases) presenting with ILI within the observation period (8 days from the date of onset). ILI was defined as fever (> 38.0 °C) + cough or sore throat. Nasal wash specimens (or if these were not possible, nasal swabs) from all participating household members Effectiveness: Secondary outcomes: laboratory-confirmed influenza infection in a household contact (secondary infection cases). The study authors defined a symptomatic secondary influenza virus infection as a laboratory-confirmed influenza infection in a household member who developed fever (> 38.0 °C), cough, or sore throat during the observation period. They termed all other secondary cases as subclinical. A

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Suess 2012 *(Continued)*

	secondary outcome measure was the occurrence of ILI as defined by WHO as fever plus cough or sore throat. Safety: study reported that the majority of participants (107/172, 62%) did not report any problems with mask-wearing. This proportion was significantly higher in the group of adults (71/100, 71%) compared to the group of children (36/72, 50%) (P = 0.005). The main problem reported by participants (adults as well as children) was "heat/humidity" (18/34, 53% of children; 10/29, 35% of adults) (P = 0.1), followed by "pain" and "shortness of breath" when wearing a face mask.
Notes	Period study conducted: November 2009 to April 2011 Funding: governmental Adherence: in general, daily adherence was good, reaching a plateau of over 50% in nearly all groups (M and MH groups; 2009/10 and 2010/11) from the third day on (by then the intervention had been implemented in all households). A gradual decline towards lower adherence began around the sixth day of the index patient's illness.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"prepared lists of random numbers with Microsoft Excel 2003 (Mircosoft™ Cooperation, Seattle, USA) which were divided between the three intervention groups. Each participating physician received a list of random numbers with the interventions represented in a 1:1:1 ratio"
Allocation concealment (selection bias)	Low risk	"the participating physician received a list of random numbers with the interventions represented in a 1:1:1 ratio. Eligible index patients were randomly assigned a number, which was then communicated to the study center. The resulting intervention was only communicated to the households with the physicians. Intervention material was given to the study sites in closed boxes marked only with the randomisation number. Recruiting physicians were not aware of the allocation of the numbers to the interventions and the boxes for the three intervention arms looked identical. After randomisation, participants were given their box by the physician's assistants"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Outcomes are very objective and therefore unlikely to be influenced by lack of blinding. In addition, “physicians (as well as laboratory personnel) blinded from the randomisation results”.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	“physicians (as well as laboratory personnel) blinded from the randomisation results”. Outcomes are very objective and therefore unlikely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. Daily follow-up home visits over the short period of data collection (8 days)
Selective reporting (reporting bias)	Low risk	The follow-up period is very short (8 days) with very good coverage, and the criteria for defining the outcome are highly objective. All planned outcomes were reported.

Suess 2012

Study characteristics

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Suess 2012 *(Continued)*

Methods	Cluster-RCT, open-label, parallel design
Participants	Study sample included 84 households randomised as follows: 1. 30 control (index cases = 30, household contact = 82) 2. 26 mask group (index cases = 26, household contact = 69) 3. 28 mask and hand hygiene group (index cases = 28, household contact = 67) Inclusion criteria: patients presenting to general practitioners or family physicians at the study sites within 2 days of symptom onset; had a positive rapid antigen test for influenza (later to be confirmed by quantitative RT-PCR (qRT-PCR); and was at least 2 years old. Index cases also had to be the only household member suffering from respiratory disease within 14 days prior to symptom onset. Exclusion criteria were pregnancy, severely reduced health status, and HIV infection. 1-person households were also not eligible or inclusion.
Interventions	Quote: "facemask and practising intensified hand hygiene (MH group), wearing facemask only (M group) and none of the 2 (control group)". See Table 1 for details.
Outcomes	Primary outcomes: SAR of laboratory-confirmed (qRT-PCR) influenza infection amongst household members (secondary infection cases) presenting with ILI within the observation period (8 days from the date of onset). ILI was defined as fever (> 38.0 °C) + cough or sore throat. Nasal wash specimens (or if these were not possible, nasal swabs) from all participating household members Effectiveness: Secondary outcomes: laboratory-confirmed influenza infection in a household contact (secondary infection cases). The study authors defined a symptomatic secondary influenza virus infection as a laboratory-confirmed influenza infection in a household member who developed fever (> 38.0 °C), cough, or sore throat during the observation period. They termed all other secondary cases as subclinical. A secondary outcome measure was the occurrence of ILI as defined by WHO as fever plus cough or sore throat. Safety: study reported that the majority of participants (107/172, 62%) did not report any problems with mask-wearing. This proportion was significantly higher in the group of adults (71/100, 71%) compared to the group of children (36/72, 50%) (P = 0.005). The main problem reported by participants (adults as well as children) was "heat/humidity" (18/34, 53% of children; 10/29, 35% of adults) (P = 0.1), followed by "pain" and "shortness of breath" when wearing a face mask.
Notes	Period study conducted: November 2009 to April 2011 Funding: governmental Adherence: in general, daily adherence was good, reaching a plateau of over 50% in nearly all groups (M and MH groups; 2009/10 and 2010/11) from the third day on (by then the intervention had been implemented in all households). A gradual decline towards lower adherence began around the sixth day of the index patient's illness.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"prepared lists of random numbers with Microsoft Excel 2003 (Mircosoft™ Co-operation, Seattle, USA) which were divided between the three intervention groups. Each participating physician received a list of random numbers with the interventions represented in a 1:1:1 ratio"
Allocation concealment (selection bias)	Low risk	"the participating physician received a list of random numbers with the interventions represented in a 1:1:1 ratio. Eligible index patients were randomly assigned a number, which was then communicated to the study center. The resulting intervention was only communicated to the households with the

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Suess 2012 *(Continued)*

		physicians. Intervention material was given to the study sites in closed boxes marked only with the randomisation number. Recruiting physicians were not aware of the allocation of the numbers to the interventions and the boxes for the three intervention arms looked identical. After randomisation, participants were given their box by the physician's assistants"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Outcomes are very objective and therefore unlikely to be influenced by lack of blinding. In addition, "physicians (as well as laboratory personnel) blinded from the randomisation results".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"physicians (as well as laboratory personnel) blinded from the randomisation results". Outcomes are very objective and therefore unlikely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. Daily follow-up home visits over the short period of data collection (8 days)
Selective reporting (reporting bias)	Low risk	The follow-up period is very short (8 days) with very good coverage, and the criteria for defining the outcome are highly objective. All planned outcomes were reported.

Talaat 2011

Study characteristics	
Methods	Cluster-RCT
Participants	Children (N = 44,451) in the first 3 primary grades from 60 governmental elementary schools in Cairo, Egypt were included and randomised to 30 schools in the intervention arm (N = 20,882 students) and 30 control schools (N = 23,569 students). No exclusion criteria provided.
Interventions	Students were required to wash their hands at least twice during the school days for about 45 seconds, followed by proper rinsing and drying on a clean towel. Campaign material was developed, and posters were placed near sinks in the classroom and playground to encourage hand-washing with soap and water upon arriving at school, before and after meals, using the bathroom, and after coughing and sneezing. See Table 1 for details.
Outcomes	Laboratory: point-of-care influenza A and B viruses using QuickVue (QuickVue; Quidel Corp., San Diego, CA, USA). School nurses collected nasal swabs from children who visited the school clinic with ILI, and only for students who had prior written approval of a parent. Effectiveness: rates of absenteeism caused by ILI and laboratory-confirmed influenza. ILI defined as fever > 38 °C and either cough or sore throat. Safety: none planned or reported by the investigators
Notes	The period study conducted: 16 February to 12 May 2008 Funding: unclear

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

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Talaat 2011 *(Continued)*

Random sequence generation (selection bias)	Low risk	"computer-generated random number table"
Allocation concealment (selection bias)	Unclear risk	No information given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The participants and study personnel were not blinded, although lack of blinding is unlikely to have influenced the outcome. Laboratory-confirmed influenza was only conducted only for students who had prior written approval of a parent.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	“Differential interest of study teams may have contributed to the low rate of testing in students who were absent because of ILI in the control schools compared to the intervention schools (12% vs 22%)”
Incomplete outcome data (attrition bias) All outcomes	High risk	No flow chart of clusters flow during the study period. No information on withdrawal. Differential interest of study teams may have contributed to the low rate of testing in students who were absent because of ILI in the control schools compared to the intervention schools (12% vs 22%) incomplete or loss of data. The total number ILI episodes could be an underestimate, as there is no proactive method to look for symptoms of ILI amongst the students; it depends on the student being absent or in class with symptoms that are picked up by the teachers at school.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to judge

Talaat 2011

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Notes	The period study conducted: 16 February to 12 May 2008 Funding: unclear

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Talaat 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated random number table"
Allocation concealment (selection bias)	Unclear risk	No information given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The participants and study personnel were not blinded, although lack of blinding is unlikely to have influenced the outcome. Laboratory-confirmed influenza was only conducted only for students who had prior written approval of a parent.
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Selective reporting (reporting bias)	Unclear risk	Insufficient information to judge

Temime 2018

Study characteristics	
Methods	2-arm cluster-RCT
Participants	All residents and staff of 27 privately held chains of nursing homes owned by Korian. 26 nursing homes (13 per arm), with an average of 80 residents per nursing home, were included in the study.
Interventions	"The intervention was based on a bundle of HH-related measures aimed at NH staff, residents, visitors, and outside care providers. These measures included facilitated access to handrub solution using pocket-sized containers and new dispensers, a campaign to promote HH with posters and event organization, the formation of local work groups in each NH to work on HH guidelines, and staff education using e-learning on infection control and HH training performed by the same nurse for all NHs." See Table 1 for details.
Outcomes	Laboratory: none used Effectiveness: Primary outcomes: incidence rate of ARIs and AGE reported in the context of episodes of clustered cases, defined as at least 5 cases within 4 days amongst nursing home residents or staff. ARIs were defined as the combination of at least 1 respiratory symptom with 1 symptom of systemic infection. AGE was defined as the sudden onset of diarrhoea or vomiting in the absence of a non-infectious aetiology.

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Temime 2018 *(Continued)*

	Secondary endpoints were mortality rate, hospitalisation rate, and antibiotic prescription rate (measured in defined daily doses (DDDs) per 100 resident days). Safety: no adverse event surveillance planned or reported by the investigators
Notes	The period study conducted: 1 April 2014 to 1 April 2015 Funding: private (Institute of Ageing Well Korian (Institut du bien vieillir Korian), which runs the nursing homes included in the study)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"simple" randomisation is used
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"we suspected that underreporting occurred. The data were verified qualitatively after the end of the intervention through individual phone interviews with each participating NH. Based on these interviews, ARI clustered cases episodes had actually occurred in 12 out of 13 control NHs; however, only 1 had been notified to health authorities. No unreported clustered cases episodes were identified in the intervention NHs"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Data were collected at NH level and reported to centralised by the NH group headquarters in Paris through computerised databases. There was underreporting of ARI and AGE in the control groups. The trial authors suspected that underreporting occurred. Primary outcome: high risk. Secondary outcomes: low risk
Incomplete outcome data (attrition bias) All outcomes	High risk	For the primary outcome, there was underreporting of ARI and AGE in the control groups; no study flow chart was provided; and no reporting on any exclusions. Surveillance is based on voluntary and standardised notifications to health authorities of any AGE or ARI clustered case episode.
Selective reporting (reporting bias)	Low risk	Reported outcomes match planned outcomes published in the protocol.

Temime 2018

Study characteristics

Methods	2-arm cluster-RCT
Participants	All residents and staff of 27 privately held chains of nursing homes owned by Korian. 26 nursing homes (13 per arm), with an average of 80 residents per nursing home, were included in the study.
Interventions	"The intervention was based on a bundle of HH-related measures aimed at NH staff, residents, visitors, and outside care providers. These measures included facilitated access to handrub solution using pocket-sized containers and new dispensers, a campaign to promote HH with posters and event organization, the formation of local work groups in each NH to work on HH guidelines, and staff education using e-learning on infection control and HH training performed by the same nurse for all NHs."

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Temime 2018 *(Continued)*

	See Table 1 for details.
Outcomes	Laboratory: none used Effectiveness: Primary outcomes: incidence rate of ARIs and AGE reported in the context of episodes of clustered cases, defined as at least 5 cases within 4 days amongst nursing home residents or staff. ARIs were defined as the combination of at least 1 respiratory symptom with 1 symptom of systemic infection. AGE was defined as the sudden onset of diarrhoea or vomiting in the absence of a non-infectious aetiology. Secondary endpoints were mortality rate, hospitalisation rate, and antibiotic prescription rate (measured in defined daily doses (DDDs) per 100 resident days). Safety: no adverse event surveillance planned or reported by the investigators
Notes	The period study conducted: 1 April 2014 to 1 April 2015 Funding: private (Institute of Ageing Well Korian (Institut du bien vieillir Korian), which runs the nursing homes included in the study)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"simple" randomisation is used
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"we suspected that underreporting occurred. The data were verified qualitatively after the end of the intervention through individual phone interviews with each participating NH. Based on these interviews, ARI clustered cases episodes had actually occurred in 12 out of 13 control NHs; however, only 1 had been notified to health authorities. No unreported clustered cases episodes were identified in the intervention NHs"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Data were collected at NH level and reported to centralised by the NH group headquarters in Paris through computerised databases. There was underreporting of ARI and AGE in the control groups. The trial authors suspected that underreporting occurred. Primary outcome: high risk. Secondary outcomes: low risk
Incomplete outcome data (attrition bias) All outcomes	High risk	For the primary outcome, there was underreporting of ARI and AGE in the control groups; no study flow chart was provided; and no reporting on any exclusions. Surveillance is based on voluntary and standardised notifications to health authorities of any AGE or ARI clustered case episode.
Selective reporting (reporting bias)	Low risk	Reported outcomes match planned outcomes published in the protocol.

Turner 2004a

Study characteristics

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Turner 2004a *(Continued)*

Methods	Double-blind RCT conducted by Hill Top Research, Inc., Winnipeg, Canada, to assess the efficacy of acids with virucidal activity for the inactivation of virus and prevention of experimental rhinovirus colds. Participants in good health, aged 18 to 60, were recruited from Winnipeg and surrounding communities for participation. Qualified participants were randomised to treatment with vehicle (62% ethanol, 1% ammonium lauryl sulphate, and 1% Klucel), vehicle containing 3.5% salicylic acid, or vehicle containing 1% salicylic acid and 3.5% pyroglutamic acid. The volunteers' hands were disinfected, and then test product was applied to both hands of participant. 15 minutes after application, the fingerprints of each hand were contaminated with rhinovirus type 39. The volunteers touched conjunctiva and the nasal mucosa only with the right hand. Viral contamination of the fingers was assessed in the left hands of the volunteers, and viral infection was assessed by culture of nasal lavage specimens and blood samples.
Participants	85 volunteers; 31 control group, 27 used vehicle with 3.5% salicylic acid, 27 used vehicle with 1% salicylic acid and 3.5% pyroglutamic acid
Interventions	Use of salicylic acid versus salicylic acid and pyroglutamic acid versus "placebo" substance
Outcomes	Laboratory: yes Effectiveness: rhinovirus type 39 infection Safety: N/A
Notes	Risk of bias: unclear (no description of randomisation process, concealment or allocation) Note: the authors concluded that organic acids commonly used in over-the-counter skin care and cosmetic products have substantial virucidal activity against rhinovirus. These preparations provided effective residual antiviral activity on the hands. The virucidal effect of these hand treatments resulted in a reduction in the incidence of rhinovirus infection in the treated volunteers (P = 0.025). The utility of this observation in the natural setting remains to be determined. The volunteers were not allowed to use their hands in the interval between the hand treatment and the virus challenge, so the effect of normal use of the hands on the virucidal activity of these organic acids is not known. Similarly, the virus challenge method used in these experiments may not simulate the natural setting in all aspects. The effect of nasal secretions that would be transferred with the virus in the natural setting on the activity of the acids or on the transmission of virus was not tested in the model. We are unsure as to the practical significance of this study and the generalisability of its results to the real world. Poorly reported study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised" Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double blind", but no description
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double blind", but no description
Incomplete outcome data (attrition bias) All outcomes	Low risk	All accounted for (short study).

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Turner 2004a *(Continued)*

Selective reporting (reporting bias)	High risk	Poorly reported

Turner 2004b

Study characteristics

Methods	Double-blind RCT conducted by Hill Top Research, Inc., Winnipeg, Canada, to assess the residual virucidal activity of a skin cleanser wipe and its effectiveness in preventing experimental rhinovirus colds. Participants in good health, aged 18 to 60 years, were recruited from Winnipeg and surrounding communities for participation. The residual activity of a skin cleanser wipe containing 4% pyroglutamic acid formulated with 0.1% benzalkonium chloride was tested. The negative control treatment was 62% ethanol. Benzalkonium chloride had been previously tested and was found to have no virucidal activity. Volunteers were randomly assigned to use the control preparation or the active preparation. The study material was applied to hands with a towelette. 15 minutes later, when the fingers were completely dry, the fingertips of each hand of the control participants and the volunteers in the active treatment group were contaminated with rhinovirus type 39. An additional volunteer in the active group was challenged with virus 1 hour after application, and the final group of volunteers was challenged 3 hours after application. Viral infection was assessed by culture of nasal lavage specimens and blood samples.
Participants	122 volunteers; 30 in control group, 92 in active group (30 tested after 15 minutes, 30 after 1 hour, 32 after 2 hours)
Interventions	Use of a skin cleanser wipe containing 4% pyroglutamic acid formulated with 0.1% benzalkonium chloride versus skin cleanser wipe containing ethanol
Outcomes	Laboratory: yes Effectiveness: rhinovirus type 39 infection Safety: N/A
Notes	Risk of bias: unclear (no description of randomisation process, concealment or allocation)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised" Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double blind", but no description given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double blind", but no description given
Incomplete outcome data (attrition bias) All outcomes	Low risk	All accounted for (short study).

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Turner 2004b *(Continued)*

Selective reporting (reporting bias)	High risk	Poorly reported

Turner 2012

Study characteristics

Methods	Randomised controlled clinical trial
Participants	A total of 212 participants were enrolled (116 in the treatment group, 96 in the control group). Healthy adult volunteers aged > 18 years from the University of Virginia community Written informed consent was obtained, and volunteers were compensated for participation. Exclusion: individuals with skin conditions that would interfere with safety evaluations or medical conditions that could impact the person's well-being or affect study results, and those whose occupations required frequent hand-washing
Interventions	Antiviral hand treatment containing 2% citric acid, 2% malic acid, and 62% ethanol (n = 116) or to a no-treatment control group (n = 96). The hand treatment was applied every 3 hours and after hand-washing whilst the participants were awake. See Table 1 for details.
Outcomes	Laboratory: PCR using AmpliTaq Gold DNA Polymerase from Applied Biosystems Effectiveness: reduction of rhinovirus-induced common colds; comparison of the number of RV-associated illnesses per 100 participants in the control group with that in the treatment group over 9 weeks. Definitions: a common cold illness was defined as the presence of any of the symptoms of nasal obstruction, rhinorrhoea, sore throat, or cough on at least 3 consecutive days. Illnesses separated by at least 3 symptom-free days were considered to be separate illnesses. Rhinovirus infection was defined as the detection of RV in nasal lavage. All volunteers were seen weekly for nasal lavage, and specimens were assayed by PCR for the presence of RV. PCR–positive specimens separated by at least 8 days and at least 1 negative PCR specimen were considered to be separate infections. RV-associated illnesses were based on detection of RV either at the time of the illness or at the first weekly visit after the illness. Safety: hand irritation occurred in 11 of the 116 volunteers (9%) in the treatment group, which met protocol criteria for removal from the study. An additional 8 participants who did not meet these protocol criteria voluntarily withdrew due to hand irritation. There was no hand irritation in the control group. No other adverse effects of the study treatment were noted.
Notes	The period study conducted: August 2009 to November 2009 Funding: The Dial Corporation - a Henkel Company, Scottsdale, Arizona, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A randomization code generated using commercially available software was provided by the sponsor"
Allocation concealment (selection bias)	Low risk	"staff at the study site assigned sequential subject numbers as they enrolled volunteers into the study, and treatment assignment was determined by the subject number."
Blinding of participants and personnel (performance bias)	Low risk	The outcomes are unlikely to be influenced by lack of blinding.

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Turner 2012 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Personnel who conducted the laboratory assays were blinded to study groups and to whether the specimen was from a routine or illness related visit"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition (and reasons for it) was reported. Study outcomes reported as ITT and PP.
Selective reporting (reporting bias)	Low risk	All planned outcomes in study protocol were reported on.

Turner 2004a

Study characteristics	
Methods	Double-blind RCT conducted by Hill Top Research, Inc., Winnipeg, Canada, to assess the efficacy of acids with virucidal activity for the inactivation of virus and prevention of experimental rhinovirus colds. Participants in good health, aged 18 to 60, were recruited from Winnipeg and surrounding communities for participation. Qualified participants were randomised to treatment with vehicle (62% ethanol, 1% ammonium lauryl sulphate, and 1% Klucel), vehicle containing 3.5% salicylic acid, or vehicle containing 1% salicylic acid and 3.5% pyroglutamic acid. The volunteers' hands were disinfected, and then test product was applied to both hands of participant. 15 minutes after application, the fingerprints of each hand were contaminated with rhinovirus type 39. The volunteers touched conjunctiva and the nasal mucosa only with the right hand. Viral contamination of the fingers was assessed in the left hands of the volunteers, and viral infection was assessed by culture of nasal lavage specimens and blood samples.
Participants	85 volunteers; 31 control group, 27 used vehicle with 3.5% salicylic acid, 27 used vehicle with 1% salicylic acid and 3.5% pyroglutamic acid
Interventions	Use of salicylic acid versus salicylic acid and pyroglutamic acid versus "placebo" substance
Outcomes	Laboratory: yes Effectiveness: rhinovirus type 39 infection Safety: N/A
Notes	Risk of bias: unclear (no description of randomisation process, concealment or allocation) Note: the authors concluded that organic acids commonly used in over-the-counter skin care and cosmetic products have substantial virucidal activity against rhinovirus. These preparations provided effective residual antiviral activity on the hands. The virucidal effect of these hand treatments resulted in a reduction in the incidence of rhinovirus infection in the treated volunteers (P = 0.025). The utility of this observation in the natural setting remains to be determined. The volunteers were not allowed to use their hands in the interval between the hand treatment and the virus challenge, so the effect of normal use of the hands on the virucidal activity of these organic acids is not known. Similarly, the virus challenge method used in these experiments may not simulate the natural setting in all aspects. The effect of nasal secretions that would be transferred with the virus in the natural setting on the activity of the acids or on the transmission of virus was not tested in the model. We are unsure as to the practical significance of this study and the generalisability of its results to the real world. Poorly reported study

Risk of bias

Bias	Authors' judgement	Support for judgement

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Turner 2004a *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"randomised" Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double blind", but no description
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double blind", but no description
Incomplete outcome data (attrition bias) All outcomes	Low risk	All accounted for (short study).
Selective reporting (reporting bias)	High risk	Poorly reported

Turner 2004b

Study characteristics	
Methods	Double-blind RCT conducted by Hill Top Research, Inc., Winnipeg, Canada, to assess the residual virucidal activity of a skin cleanser wipe and its effectiveness in preventing experimental rhinovirus colds. Participants in good health, aged 18 to 60 years, were recruited from Winnipeg and surrounding communities for participation. The residual activity of a skin cleanser wipe containing 4% pyroglutamic acid formulated with 0.1% benzalkonium chloride was tested. The negative control treatment was 62% ethanol. Benzalkonium chloride had been previously tested and was found to have no virucidal activity. Volunteers were randomly assigned to use the control preparation or the active preparation. The study material was applied to hands with a towelette. 15 minutes later, when the fingers were completely dry, the fingertips of each hand of the control participants and the volunteers in the active treatment group were contaminated with rhinovirus type 39. An additional volunteer in the active group was challenged with virus 1 hour after application, and the final group of volunteers was challenged 3 hours after application. Viral infection was assessed by culture of nasal lavage specimens and blood samples.
Participants	122 volunteers; 30 in control group, 92 in active group (30 tested after 15 minutes, 30 after 1 hour, 32 after 2 hours)
Interventions	Use of a skin cleanser wipe containing 4% pyroglutamic acid formulated with 0.1% benzalkonium chloride versus skin cleanser wipe containing ethanol
Outcomes	Laboratory: yes Effectiveness: rhinovirus type 39 infection Safety: N/A
Notes	Risk of bias: unclear (no description of randomisation process, concealment or allocation)
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

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Turner 2004b *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"randomised" Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double blind", but no description given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double blind", but no description given
Incomplete outcome data (attrition bias) All outcomes	Low risk	All accounted for (short study).
Selective reporting (reporting bias)	High risk	Poorly reported

Turner 2012

Study characteristics	
Methods	Randomised controlled clinical trial
Participants	A total of 212 participants were enrolled (116 in the treatment group, 96 in the control group). Healthy adult volunteers aged > 18 years from the University of Virginia community Written informed consent was obtained, and volunteers were compensated for participation. Exclusion: individuals with skin conditions that would interfere with safety evaluations or medical conditions that could impact the person's well-being or affect study results, and those whose occupations required frequent hand-washing
Interventions	Antiviral hand treatment containing 2% citric acid, 2% malic acid, and 62% ethanol (n = 116) or to a no-treatment control group (n = 96). The hand treatment was applied every 3 hours and after hand-washing whilst the participants were awake. See Table 1 for details.
Outcomes	Laboratory: PCR using AmpliTaq Gold DNA Polymerase from Applied Biosystems Effectiveness: reduction of rhinovirus-induced common colds; comparison of the number of RV-associated illnesses per 100 participants in the control group with that in the treatment group over 9 weeks. Definitions: a common cold illness was defined as the presence of any of the symptoms of nasal obstruction, rhinorrhoea, sore throat, or cough on at least 3 consecutive days. Illnesses separated by at least 3 symptom-free days were considered to be separate illnesses. Rhinovirus infection was defined as the detection of RV in nasal lavage. All volunteers were seen weekly for nasal lavage, and specimens were assayed by PCR for the presence of RV. PCR–positive specimens separated by at least 8 days and at least 1 negative PCR specimen were considered to be separate infections. RV-associated illnesses were based on detection of RV either at the time of the illness or at the first weekly visit after the illness. Safety: hand irritation occurred in 11 of the 116 volunteers (9%) in the treatment group, which met protocol criteria for removal from the study. An additional 8 participants who did not meet these protocol

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Turner 2012 *(Continued)*

	criteria voluntarily withdrew due to hand irritation. There was no hand irritation in the control group. No other adverse effects of the study treatment were noted.
Notes	The period study conducted: August 2009 to November 2009 Funding: The Dial Corporation - a Henkel Company, Scottsdale, Arizona, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A randomization code generated using commercially available software was provided by the sponsor"
Allocation concealment (selection bias)	Low risk	"staff at the study site assigned sequential subject numbers as they enrolled volunteers into the study, and treatment assignment was determined by the subject number."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The outcomes are unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Personnel who conducted the laboratory assays were blinded to study groups and to whether the specimen was from a routine or illness related visit"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition (and reasons for it) was reported. Study outcomes reported as ITT and PP.
Selective reporting (reporting bias)	Low risk	All planned outcomes in study protocol were reported on.

White 2001

Study characteristics

Methods	Double-blind, placebo-controlled, cluster-RCT that took place in 3 schools in California during March to April 1999. The study assessed the incremental value of using an alcohol hand rub together with water-and-soap hand-washing. Both arms were administered an educational programme beginning 2 weeks prior to start of the trial. Randomisation was by classroom, and the placebo hand rub was indistinguishable from the active ingredient. Details of randomisation are not given.
Participants	Of the 72 classes originally recruited, lack of compliance (use of supplementary product at least 3 times a day) reduced the classes to 32 (16 in both arms) and a total of 769 participants aged 5 to 12 (381 students who received the sanitiser, and 388 who received the placebo).
Interventions	Pump-activated antiseptic hand rub with benzalkonium chloride (SAB) (Woodward Laboratories) or inert placebo that "virtually" looked the same in batches of 4 colour-coded bottles. School staff, parents, and participants were blinded.
Outcomes	Laboratory: testing of virucidal and bactericidal activity of the active compound Effectiveness: ARI (cough, sneezing, sinus trouble, bronchitis, fever, red eye, headache, mononucleosis, acute exacerbations of asthma) Gastrointestinal and other illnesses (data not extracted) Follow-up and observation was carried out by classroom staff, and illnesses were described by parents.

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White 2001 *(Continued)*

	Safety: 7 students dropped out because of mild sensitivity to the rub
Notes	Risk of bias: high (no description of randomisation; partial reporting of outcomes, numerators and denominators) Note: the authors conclude that addition of the rub led to a 30% to 38% decrease of illness and absenteeism (RR for illness absence incidence 0.69, RR for absence duration 0.71). Very high attrition, unclear randomisation procedure, educational programme and use of placebo hand rub make generalisability of the results debatable. No confidence intervals reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised trial", but sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"To distinguish content, both the active and placebo formulations were distributed in four color-coded groups of 1oz spritz bottles. The content were and distribution patters were only know to the researchers and were indecipherable by the school staff or students."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Teachers were responsible for recording attendance for each day during the study"
Incomplete outcome data (attrition bias) All outcomes	High risk	Partial reporting of outcomes, numerators and denominators
Selective reporting (reporting bias)	High risk	Poor reporting

Yeung 2011

Study characteristics

Methods	Clustered-RCT of a hand hygiene intervention involving pocket-sized containers of alcohol-based hand rub for the control of infections in long-term care facilities. Staff hand hygiene adherence was directly observed, and residents' infections necessitating hospitalisation were recorded. After a 3-month preintervention period, long-term care facilities (LTCFs) were randomised to receive pocket-sized containers of alcohol-based gel, reminder materials, and education for all HCWs (treatment group) or to receive basic life support education and workshops for all HCWs (control group). A 2-week intervention period (1 to 15 April 2007) was followed by 7 months of postintervention observations.
Participants	6 out of 7 community-based, private or semiprivate, residential LTCFs in Hong Kong agreed to participate and were randomised to: 1. hand hygiene group (3 LTCFs, 73 nursing staff and 244 residents analysed); or 2. control group (3 LTCFs, 115 nursing staff and 379 residents analysed). All were nursing homes serving an elderly population. All LTCFs were situated in different regions of Hong Kong, including urban and rural areas. The targets of the intervention were all full- and part-time HCWs at these LTCFs.

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Yeung 2011 *(Continued)*

	The LTCFs employed 3 types of HCWs: nurses, nursing assistants, and physiotherapists.
Interventions	Pocket-sized containers of alcohol-based gel, reminder materials, and education (intervention group) or basic life-support education and workshop (control group). See Table 1 for details.
Outcomes	Rates of infection (requiring hospitalisation) Outbreaks Death due to infection Diagnoses of infection coded into 6 categories, all of which were common endemic infections in LTCFs: 1. pneumonia, 2. urinary tract infection, 3. septicaemia, 4. skin or soft-tissue infection (including cellulitis or pressure sores), 5. gastroenteritis, and 6. fever. Infections recorded in death certificates were also included, regardless of whether the resident had been hospitalised. The causes of death were categorised as due to infection, not due to infection, or unknown. If the primary or the secondary diagnosis on the death certificate belonged to 1 of the 6 endemic infection categories, the death was coded as due to infection. No safety outcomes reported.
Notes	University and industry funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available

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Zomer 2015

Study characteristics	
Methods	Cluster-RCT
Participants	71 daycare centres (36 intervention DCCs, and 35 control) in Rotterdam-Rijnmond, Gouda and Leiden in the Netherlands Study enrolled 545 children (intervention = 278, control = 267). Inclusion/exclusion criteria: children who attended the DCC at least 2 days a week; were aged between 6 months and 3.5 years at start of the trial; intended to attend the DCC throughout the study period; and if their parents consented, were Dutch-speaking, and had access to email or regular post. Children were excluded if they had a chronic illness or medication that predisposed them to infection, a sibling taking part in the trial (i.e. 1 child per family could be included), or if they started attending CCC after the beginning of the trial).
Interventions	4 components: 1. HH products, paper towel dispensers, soap, alcohol-based hand sanitiser, and hand cream were provided for 6 months. 2. Training and a booklet outlining the training. 3. 2 team training sessions aimed at specific HH improvement activities. 4. Posters and stickers for caregivers and children as reminders. See Table 1 for details.
Outcomes	Laboratory: none Effectiveness: incidence of respiratory infections in children monitored by parents. The common cold was defined as a blocked or runny nose with at least 1 of the following symptoms: coughing, sneezing, fever, sore throat, or earache. Safety: none planned or reported by the investigators
Notes	The period study conducted: September 2011 to April 2012 Funding: mixed. The Netherlands Organisation for Health Research and Development (ZonMw). Dispensers and refills were sponsored by SCA Hygiene Products, Sweden.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Stratified randomization is performed by assigning each DCC to one of six strata based on size (i.e. small < 46 children per day versus large ≥ 46 children per day) and geographic location (i.e. highly urban versus urban versus slightly/non-urban). DCCs are assigned to either intervention or control group by means of computer generation with a 1:1 ratio in each of the strata"
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Outcome is subjective.
Blinding of outcome assessment (detection bias)	High risk	Symptoms were reported by parents, no validation.

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Zomer 2015 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Very few children were excluded or lost to follow-up (reasons for exclusions provided).
Selective reporting (reporting bias)	Low risk	All planned outcomes are reported. However, between published protocol and the paper, secondary outcomes became the primary outcome in the published paper!

AEs: adverse events
AFH: Armed Forces Hospital
AGE: acute gastroenteritis
ALRI: acute lower respiratory infection
ARI: acute respiratory infection
ASR: adverse skin reactions
A&E: accident and emergency
BIPAP: bilevel positive airway pressure
CCC: childcare centre
CDC: Centers for Disease Control and Prevention
CG: control group
CHG: chlorhexidine gluconate
CI: confidence interval
CMF: citric acid: malic acid: sodium lauryl sulphate (a virucidal mixture added to tissue paper)
CoV: coronavirus
cluster-RCT: cluster-randomised controlled trial
CRI: clinical respiratory illness
CXR: chest X-ray
DCC: daycare centre
EG: experimental group
FRI: febrile respiratory illness
GI: gastrointestinal
GTI: gastrointestinal infection
GP: general practitioner
HCW: healthcare worker
HFH: Hanoi French Hospital
HH: hand hygiene
HR: high risk
HSG: hand sanitiser group
ICD-9: International Classification of Disease, 9th Revision, Clinical Modification
ICU: intensive care unit
ILI: influenza-like illness
IQR: interquartile range
IRR: incident rate ratio
ITT: intention-to-treat
LRTI: lower respiratory tract infection
LTCF: long-term care facility
MCU: medical convalescent unit
MDCK: Madin Darby canine kidney cell line
M group: face mask group
MH group: face mask and hand hygiene group
MS: monkey-derived cell line
N/A: not applicable
NAT: nucleic acid testing
NH: nursing home
NICU: neonatal intensive care unit
NOS: Newcastle-Ottawa Scales
NTS: nasal and throat swab
OR: odds ratio
PCR: polymerase chain reaction

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PCU: physical conditioning unit
POCT: point-of-care testing
PP: per protocol
PPE: personal protective equipment
QNAF: Qatar National Research Fund
RCT: randomised controlled trial
RDS: respiratory distress syndrome
RI: respiratory infection
RIDT: rapid influenza diagnostic test
RNA: ribonucleic acid
RR: risk ratio
rRT-PCR: real-time reverse transcription-polymerase chain reaction
RTI: respiratory tract infection
RT-PCR: reverse-transcriptase polymerase chain reaction
RSV: respiratory syncytial virus
RV: rhinovirus
SAB: surfactant, allantoin, and benzalkonium chloride
SAR: secondary attack rate
SARS: severe acute respiratory syndrome
SCBU: special care baby unit
SD: standard deviation
SHEWA-B: Sanitation, Hygiene Education and Water Supply in Bangladesh
SOB: shortness of breath
SOPs: standard operating procedures
S/S: signs/symptoms
SSTI: skin and soft-tissue infection
STH: soil-transmitted helminth
SWG: soap and water group
TIDieR: Template for Intervention Description and Replication
UHR-I: ultra high-risk infection
UHR-S: ultra high-risk SARS
URI: upper respiratory infection
URTI: upper respiratory tract infection
WBC: white blood cell
WHO: World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abou El Hassan 2004	Topic completely extraneous
Amirav 2005	Randomised controlled trial of aerosol treatment
Anderson 2004	Mathematical model with interesting discussion of interaction between public health measures
Anonymous 2002	News item
Anonymous 2004	News item
Anonymous 2005a	News item
Anonymous 2005b	News item
Anonymous 2005c	News item
Apisarnthanarak 2009	Intervention bundle not broken down.
Apisarnthanarak 2010	Participants took antivirals.

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Study	Reason for exclusion
Aragon 2005	Descriptive paper (non-comparative). Has no viral outcomes
Azor-Martinez 2014	Results reported as respiratory and gastrointestinal infections. No extractable respiratory data
Barros 1999	Correlational study between incidence of URTI and factors such as overcrowding
Bauer 2009	Historical comparison with RSV gammaglobulin amongst interventions
Bell 2004	Has unpublished entry exit screening data and extensive references but no comparative data
Bellissimo-Rodrigues 2009	Intervention is chlorhexidine.
Ben-Abraham 2002	Exclude - bacterial illness only
Black 1981	Diarrhoea only outcome
Borkow 2010	No human beings involved.
Bouadma 2010	Hospital-based ventilator routine
Bowen 2007	Outcomes of composite infections. Respiratory infections are not reported separately.
Breugelmans 2004	Description of risk factors in aircraft
Cai 2009	Compliance study
Cantagalli 2010	Outcome outside inclusion criteria
Carbonell-Estrany 2008	Immunoglobulin intervention and descriptive review
Carter 2002	News item
Castillo-Chavez 2003	Editorial
Cava 2005a	Survey of quarantinees' views
Cava 2005b	Personal experiences of quarantine
CDC 2003a	Case reports
CDC 2003b	No data presented.
Chai 2005	Letter - about MRSA
Chami 2012	Outcomes of composite infections. Respiratory infections are not reported separately.
Chaovavanich 2004	Case report
Chau 2003	No original retrievable data. Mathematical model fitting expected to observed cases with quarantine in the SARS of Hong Kong
Chau 2008	Audit of infection control procedures and compliance with guidelines
Chen 2007	An assessment of the impact of different hand-washing teaching methods. No clinical outcomes

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Study	Reason for exclusion
Cheng 2010	Confounded by antiviral use for postexposure prophylaxis
Chia 2005	Knowledge survey
Clynes 2010	Letters
Cowling 2007	Epidemiology, non-comparative, non-interventions study
Daniels 2010	Commentary
Daugherty 2008	No free data presented.
Davies 1994	Antibody titres as outcomes with so many biases that interpretation of study is problematic
Day 1993	No acute respiratory infection outcome data
Day 2006	Mathematical model; no new data
Dell'Omodarme 2005	Probabilistic and Bayesian mathematical model of screening at entry
Denbak 2018	Outcomes of composite infections. Respiratory infections are not reported separately.
Desenclos 2004	Description of transmission
DiGiovanni 2004	Qualitative study of compliance factors in quarantine
Doebbeling 1992	RCT respiratory data not present. Only 3 viruses isolated in total with no viral typing available.
Dwosh 2003	Case series
Edmonds 2010	Lab study
Fendler 2002	Cohort study badly biased with differential health profiles and healthcare workers dependency in intervention and control semi-cohorts. No attempt to adjust for confounders was made. No de-nominators available.
Flint 2003	Description of spread in aircraft and non-comparative data
Fung 2004	Non-comparative
Garcia 2010	Commentary
Gaydos 2001	Editorial linked to Ryan 2001. (Ryan 2001 was an included trial in the previous version of this review (2011). Non-RCTs were removed in this 2020 update).
Gensini 2004	Interesting historical review
Girou 2002	Non-clinical outcomes
Glass 2006	Mathematical model - no original data presented
Goel 2007	Non-comparative study
Gomersall 2006	Non-comparative study

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Study	Reason for exclusion
Gore 2001	Summary of Dyer 2000. (Dyer 2000 was a prospective, cluster open-label cross-over cohort study included in the previous version of this review (2011). Non-RCTs were removed in this 2020 update).
Gostin 2003	Not an analytical study
Gralton 2010	Review
Guinan 2002	It would appear that 9 classes took part and "acted as their own controls", but it is not clear if there was cross-over of classes or not. In addition, the outcome is combined gastrointestinal/respiratory. The clue lies in the presence of a nested economic analysis which shows considerable savings in time for staff and pupils if the soap is used: in other words this is a (covert) publicity study.
Gupta 2005	Economic model - no new data
Gwaltney 1982	No breakdown of cases given by arm.
Han 2003	Non-comparative
Hayden 1985	This is an RCT with laboratory-induced colds, small numbers, and uncertain numerators, but almost certainly because of the unique laboratory conditions (placebo tissues not being a placebo at all) of impossible generalisation. It was a pilot to the far bigger trial by Farr 1988a; Farr 1988b.
Hendley 1988	Inappropriate intervention
Hens 2009	Model
Heymann 2009	Already included in review as Heymann 2004. (Heymann 2004 was a controlled before and after study included in the previous version of this review (2011). Non-RCTs were removed in this 2020 update).
Hilburn 2003	No ARI/viral outcomes (e.g. URTIs)
Hilmarsson 2007	Animal study
Hirsch 2006	Study tested pharmacological interventions.
Ho 2003	Descriptive review
Hsieh 2007	Mathematical model
Hugonnet 2007	Letter without any data
Jiang 2003	2 papers that are probably different versions of the same paper: Jiang SP, Huang LW, Wang JF, Wu W, Yin SM, Chen WX, et al. A study of the architectural factors and the infection rates of healthcare workers in isolation units for severe acute respiratory syndrome. Chung-Hua Chieh Ho Ho Hu Hsi Tsa Chih [Chinese Journal of Tuberculosis & Respiratory Diseases]. 26(10):594-7, 2003 Oct
Johnson 2009	Outcomes are non-clinical.
Jones 2005	Historical account
Kaydos-Daniels 2004	Not an analytical study
Kelso 2009	Model

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Study	Reason for exclusion
Khaw 2008	Assessing the efficacy of O_2 delivery
Kilabuko 2007	Aetiological study
Kosugi 2004	Non-comparative study
Lam 2004	Outcomes were generic (infection rates). No laboratory data available for viral diagnosis.
Lange 2004	No data presented.
Larson 2004a	Inappropriate outcomes
Larson 2004b	Inappropriate outcomes
Larson 2005	Cluster-RCT comparing the effects of 2 hand hygiene regimens on infection rates and skin condition and microbial counts of nurses' hands in neonatal intensive care units. Outcomes were generic (e.g. pneumonia and microbial counts of participants' skin). No laboratory data available for viral diagnosis.
Lau 2004	Attitude survey
Lau 2005	Herbal remedy effectiveness assessment
Lee 2005	Descriptive study of risk and protective factors of transmission in households. No assignment took place.
Lee 2010	Cohort study; unclear numbers were vaccinated against influenza
Lennell 2008	Measured absenteeism due to non-specific infection
Lipsitch 2003	Mathematical model fit to evidence
Luckingham 1984	Historical report on Tucson experience during Spanish flu pandemic
Ma 2004	Case-control study of risk factors for SARS
MacIntyre 2010	Commentary on Cowling 2009
Malone 2009	Model
Marin 1991	Viral resistance study
McSweeny 2007	Historical description
Mielke 2009	Review
Mikolajczyk 2008	No intervention
Monsma 1992	Non-comparative study
Nandrup-Bus 2009	The trial had only 2 clusters.
Nishiura 2009	Model

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Study	Reason for exclusion
O'Callaghan 1993	Letter linked to Isaacs 1991. (Isaacs 1991 was a retrospective and prospective cohort study included in the previous version of this review (2011). Non-RCTs were removed in this 2020 update).
Olsen 2003	Description of transmission
Ooi 2005	Descriptive study, but with interesting organisational chart
Orellano 2010	Confounded by antiviral use
Panchabhai 2009	Pharma intervention
Pang 2004	Descriptive study of Beijing outbreak. Some duplicate data in common with Pang 2003. (Pang 2003 was an eclogical study included in the previous version of this review (2011). Non-RCTs were removed in this 2020 update).
Patel 2012	Although within each district the participating schools and households were randomly selected, the allocation of districts to the intervention and comparison arms was not randomly assigned.
Pittet 2000	Analysis of relationship between hand-washing compliance campaign and nosocomial bacterial infections (e.g. MRSA)
Prasad 2004	Letter about retrospective cohort - behavioural
Rabenau 2005	In vitro test of several disinfectants
Reynolds 2008	Describes the psychological effects of quarantine
Richardson 2010	Non-clinical study
Riley 2003	Mathematical model fit to evidence
Rodriguez 2009	A “reasonable attempt at minimizing bias” (see inclusion criteria) does not include absenteeism
Rosen 2006	Non-specific outcome. Measured absenteeism
Rosenthal 2005	Outcomes were generic (e.g. pneumonia, URTIs). No laboratory data available for viral diagnosis.
Safiulin 1972	Non-comparative set of studies with no clinical outcomes
Sandrock 2008	Review
Sattar 2000	Experiment assessing virucidal activity of fingertip surface - no clinical outcome data
Schull 2007	Describes the impact of SARS in a Toronto study
Seal 2010	Lab study
Seale 2009	Study looking at whether using respirators in A&E department is feasible
Sizun 1996	This is a review; no original data presented.
Slayton 2016	Compares hand-washing plus (antibacterial) towel versus hand-washing without towel
Stebbins 2009	Attitude survey

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Study	Reason for exclusion
Stedman-Smith 2015	Composite outcome. No data on separate respiratory illnesses reported.
Stoner 2007	No study data available.
Stukel 2008	Impact of the SARS disruption on care/mortality for other pathologies (e.g. acute myocardial infarction). There are no interventions, and outcomes are unrelated to acute respiratory infections.
Svoboda 2004	Descriptive study with before-and-after data but shifting denominators
Tracht 2010	Model
Ueno 1990	Experimental study. No clinical intervention
Uhari 1999	No respiratory illness data to be extracted
van der Sande 2008	Laboratory study without any clinical outcomes
Vessey 2007	Composite outcome. No data on separate respiratory illnesses reported.
Viscusi 2009a	Lab study
Viscusi 2009b	Lab study
Wang 2003	Descriptive study
Wang 2005	Case-control study of susceptibility factors
Weber 2004	Editorial linked to Larson 2004a
Wen 2010	Lab study
White 2005	Redundant publication of White 2003. (White 2003 was a prospective, open, cohort study included in the previous version of this review (2011). Non-RCTs were removed in this 2020 update).
Wilczynski 1997	Clinical trial of the effects of breastfeeding
Wilder-Smith 2003	Description of risk factors in aircraft
Wilder-Smith 2005	Descriptive review
Wong 2005	Attitude survey
Yen 2010	Model
Yu 2004	Description of transmission
Zamora 2006	Head-to-head comparison of 2 sets of PPEs with no controls and no clinical outcomes
Zhai 2007	Non-comparative study
Zhao 2003	CCT of SARS treatment

A&E: accident and emergency
ARI: acute respiratory infection
CCT: controlled clinical trial

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MRSA: methicillin-resistant *Staphylococcus aureus*
RCT: randomised controlled trial
RSV: respiratory syncytial virus
PPE: personal protective equipment
SARS: severe acute respiratory syndrome
URTI: upper respiratory tract infection

Characteristics of ongoing studies *[ordered by study ID]*

NCT03454009

Study name	Appropriate time-interval application of alcohol hand gel on reducing influenza-like illness among preschool children: a randomized, controlled trial
Methods	This is a comprehensive randomised cluster hand-hygiene improvement intervention to reduce self-reported ARI/ILI and GI illness, absenteeism, presenteeism and related behavioural and attitudinal change over a 90-day trial. The intervention group will receive hand hygiene supplies and a variety of educational materials, including environmental posters in common areas. The control group will perform their usual hygiene activities and will not receive an intervention. Identical weekly surveys will be administered to the intervention and control groups to measure self-reported illness, absenteeism, presenteeism, along with behaviour and attitudes measured at specified intervals during the study. The intervention and control groups were randomised by work floors before the onset of the enrolment period. It is hypothesised that employees in the intervention group will experience reduced self-reported illness, absenteeism, and presenteeism along with improved protective hygiene behaviours and related attitudes, relative to those in the control group over the 90-day trial.
Participants	Inclusion criteria: 1. At least 18 years of age or older 2. No known allergies to alcohol or surface disinfecting wipes 3. Works at least 30% of office hours at the study host site 4. Consent to receiving emails from Kent State University Exclusion criteria: 1. Under 18 years of age 2. Known allergies to alcohol or surface disinfecting wipes 3. Works less than 30% of office hours at the study host site 4. Does not consent to receiving emails from Kent State University
Interventions	The intervention group will receive hand hygiene supplies and a variety of educational materials, including environmental posters in common areas. The control group will perform their usual hygiene activities and will not receive an intervention.
Outcomes	Self-reported ARI/ILI and GI illness, absenteeism, presenteeism and related behavioural and attitudinal change over a 90-day trial
Starting date	5 February 2018
Contact information	Maggie Stedman-Smith, PhD, Kent State University College of Public Health
Notes	Recruitment completed. Last update in ClinicalTrials.gov was 1 May 2019. NCT03454009

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NCT04267952

Study name	Hand hygiene intervention program on primary school students' health outcomes and absenteeism in school
Methods	Study Type: interventional (clinical trial) Estimated enrolment: 200 participants Allocation: randomised Intervention model: parallel assignment Masking: single (participant) Masking description: participation will not know whether they are in the experimental or control group
Participants	Inclusion criteria: primary school student (especially third- and fourth-class student) Exclusion criteria: people with chronic disease
Interventions	Experimental: first group Hand hygiene intervention programme prepared by using planned behaviour theory will be applied to the students in this group. Active comparator: second group Students in this group will be given classic hand hygiene training.
Outcomes	Primary outcome measure: children with symptoms of infection will be referred to the family physician to have a rapid antigen test and to report the result to the researcher. 10 identified upper respiratory tract symptoms (fever, sore throat, runny nose, etc.) will be recorded weekly by family of children. The researcher will receive symptom information from the family via weekly SMS. The number of days the child does not attend school due to illness and the percentage of absenteeism 1. Group A streptococcal infections in rapid antigen test (time frame: total 20 weeks) 2. Incidence of symptoms of acute upper respiratory tract infection (time frame: total 20 weeks) 3. School absenteeism (time frame: total 20 weeks) Secondary outcome measures: Glogerm gel applied hands will shine areas containing micro-organisms. Contamination rate will be calculated by taking a photo of the hands and performing brightness analysis in Adobe Photoshop program. 1. Pollution rate of hands (time frame: from date of randomisation until the date of first documented progression assessed up to 7 months)
Starting date	9 September 2019
Contact information	Contact: Uyanık +905068949969; gulcinyelten@hotmail.com
Notes	Recruitment is ongoing. Last update in ClinicalTrials.gov was 13 February 2020. NCT04267952

NCT04296643

Study name	Medical masks vs N95 respirators for COVID-19

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NCT04296643 *(Continued)*

Methods	A RCT in which nurses will be randomised to either medical masks or N95 respirators when providing medical care to patients with COVID-19. This Canadian multicentre RCT will assess whether medical masks are non-inferior to N95 respirators when nurses provide care involving non-aerosol generating procedures. Nurses will be randomised to either use of a medical mask or to a fit-tested N95 respirator when providing care for patients with febrile respiratory illness. The primary outcome is laboratory confirmed COVID-19 amongst nurse participants.
Participants	Inclusion criteria: 1. Nurses who work > 37 hours per week in medical, emergency, paediatric units Exclusion criteria: 1. Nurses with 1 or more comorbidities 2. Nurses who cannot pass an N95 respirator fit-test
Interventions	Experimental: medical mask Medical mask worn when providing care to patient with febrile respiratory illness Active comparator: N95 respirator N95 respirator worn when providing care to patient with febrile respiratory illness
Outcomes	Primary outcome measures: 1. Number of participants with RT-PCR confirmed COVID-19 infection 2. RT-PCR confirmed COVID-19 infection (time frame: 6 months) Secondary outcome measures: 1. Number of participants with acute respiratory illness 2. Number of participants with absenteeism 3. Number of participants with lower respiratory infection 4. Number of participants with pneumonia 5. Number of participants with ICU admission 6. Number of participants needing mechanical ventilation 7. Number of participants that died
Starting date	Started 2 April 2020
Contact information	Contact: Mark Loeb, MD, 9053340010; loebm@mcmaster.ca
Notes	NCT04296643

NCT04337541

Study name	Reduction in COVID-19 infection using surgical facial masks outside the healthcare system
Methods	Parallel RCT
Participants	18 years of age and older. The participants recruited are people working outside of their home, who have not previously been infected with COVID-19 and who do not wear facial masks (e.g. healthcare personnel) when working. They will be randomised for: 1. normal behaviour according to the authority's recommendations; or

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NCT04337541 *(Continued)*

	2. normal behaviour according to the authority's recommendations and use of facial masks.
Interventions	All participants will follow authority recommendations and be randomised to either wear facial masks or not. They will perform swab-test if they experience symptoms during the study as well as at the end of study. Participants will be instructed in using the facial mask consistently when outside their home (and at home when receiving visits from others). The instruction is given in writing and via an instruction video. The participants will be contacted once weekly to optimise compliance. It will be registered if the participants are diagnosed with COVID-19. Participants will perform antibody screening at study start and end. Participants who do not test positive for COVID-19 during the study period will perform a swab self-test if experiencing symptoms or when the study ends (instruction video).
Outcomes	Primary outcome: reduction in COVID-19 infection frequency Secondary outcome: number of participants testing positive in antibody screening at study start and study end, respectively
Starting date	2 April 2020
Contact information	Prof Henning Bundgaard, DMSc +4526112290; henning.bundgaard@regionh.dk
Notes	NCT04337541. Published *Annals of Internal Medicine*, https://www.acpjournals.org/doi/10.7326/M20-6817, 18 Nov 2020).

NCT04471766

Study name	Evaluation of locally produced cloth face mask on COVID-19 and respiratory illnesses prevention at the community level - a cluster-RCT
Methods	Study type: interventional (clinical trial) Estimated enrolment: 66,000 participants Allocation: randomised Intervention model: parallel assignment Masking: single (outcomes assessor) Primary purpose: prevention
Participants	Ages eligible for study: 10 years and older (child, adult, older adult) Sexes eligible for study: all Accepts healthy volunteers: no Criteria Inclusion criteria: 1. Household resident 2. Age 10 years and older Exclusion criteria: 1. Refusal to participate
Interventions	Experimental: certified cloth face mask plus preventive information

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NCT04471766 *(Continued)*

	Active comparator: information on COVID-19 prevention
Outcomes	Self-reported main symptoms of COVID-19 (3 or more of fever, cough, fatigue, shortness of breath, loss of smell/taste) Consultation for COVID-19 like illness or reported positive test, or both Self reported COVID-19 like illness plus hospitalisation or death Any death during the follow-up period: 1. Reported COVID-19 like illness (time frame: 4 months' follow-up) 2. Consultation (time frame: 4 months' follow-up) 3. Severe illness (time frame: 4 months' follow-up) 4. Mortality (time frame: 4 months' follow-up)
Starting date	Estimated study start date: July 2020
Contact information	Amabelia Rodrigues, PhD, 00245966078659; a.rodrigues@bandim.org
Notes	The number of cases of COVID-19 is still increasing, and transmission of SARS-CoV-2 seems to occur mainly through person-to-person transmission through respiratory droplets, indirect contact with infected people and surfaces. The use of face masks is recommended as a public health measure, but in many settings only domestic cloth made masks are available to the majority of the people. However, masks can be of different quality, and very little is known about the utility of cloth face masks at the community level. In Bandim Health Project's Health and Demographic Surveillance System we will evaluate the effect of providing locally produced cloth face masks on the severity of COVID-19 like illness and mortality in an urban population. The locally produced cloth mask is made according to a laboratory-certified model and will be provided to the intervention group alongside information of how the risk of transmission can be reduced. The control group will receive information alone. Follow-up will be implemented through telephone calls and postepidemic home visits.

Wang 2015

Study name	A cluster-RCT to test the efficacy of face masks in preventing respiratory viral infection among Hajj pilgrims
Methods	Cluster-randomised trial, randomising worshippers' accommodation tents during several seasons of the Hajj pilgrimage in Saudi Arabia. In the intervention tents, free face masks will be distributed to be worn for 7 days.
Participants	Pilgrims to the Hajj
Interventions	Standard surgical masks distributed free of charge to pilgrims in the intervention accommodation tents. Control group receives no intervention.
Outcomes	Flu-like illness, recorded in diaries, with laboratory confirmation where possible
Starting date	
Contact information	
Notes	Australian New Zealand Clinical Trials Registry (ANZCTR), ACTRN12613001018707

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ARI: acute respiratory tract infections
ICU: intensive care unit
ILI: influenza-like illness
GI: gastrointestinal
RCT: randomised controlled trial
RT-PCR: reverse-transcriptase polymerase chain reaction

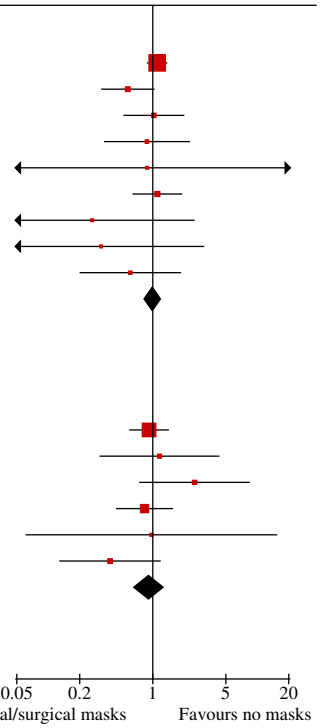
DATA AND ANALYSES

Comparison 1. Randomised trials: medical/surgical masks versus no masks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Viral illness	9		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1.1 Influenza-like illness	9	3507	Risk Ratio (IV, Random, 95% CI)	0.99 [0.82, 1.18]
1.1.2 Laboratory-confirmed influenza	6	3005	Risk Ratio (IV, Random, 95% CI)	0.91 [0.66, 1.26]
1.2 Influenza-like illness in healthcare workers	2	1070	Risk Ratio (IV, Random, 95% CI)	0.37 [0.05, 2.50]

Analysis 1.1. Comparison 1: Randomised trials: medical/surgical masks versus no masks, Outcome 1: Viral illness

Study or Subgroup	log[RR]	SE	Medical/surgical masks Total	No masks Total	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 Influenza-like illness						
Aiello 2012	0.095	0.115	392	370	64.5%	1.10 [0.88 , 1.38]
Barasheed 2014	-0.55	0.3	75	89	9.5%	0.58 [0.32 , 1.04]
Canini 2010	0.025	0.342	148	158	7.3%	1.03 [0.52 , 2.00]
Cowling 2008	-0.128	0.483	61	205	3.7%	0.88 [0.34 , 2.27]
Jacobs 2009	-0.126	1.83	17	15	0.3%	0.88 [0.02 , 31.84]
MacIntyre 2009	0.1	0.28	186	100	10.9%	1.11 [0.64 , 1.91]
MacIntyre 2015	-1.335	1.15	580	458	0.6%	0.26 [0.03 , 2.51]
MacIntyre 2016	-1.139	1.16	302	295	0.6%	0.32 [0.03 , 3.11]
Suess 2012	-0.494	0.571	26	30	2.6%	0.61 [0.20 , 1.87]
Subtotal (95% CI)			**1787**	**1720**	**100.0%**	**0.99 [0.82 , 1.18]**
Heterogeneity: Tau² = 0.00; Chi² = 7.29, df = 8 (P = 0.51); I² = 0%						
Test for overall effect: Z = 0.13 (P = 0.90)						
1.1.2 Laboratory-confirmed influenza						
Aiello 2012	-0.083	0.223	392	370	51.6%	0.92 [0.59 , 1.42]
Cowling 2008	0.148	0.674	61	205	6.0%	1.16 [0.31 , 4.34]
MacIntyre 2009	0.92	0.6225	186	100	7.0%	2.51 [0.74 , 8.50]
MacIntyre 2015	-0.182	0.32	580	458	25.8%	0.83 [0.45 , 1.56]
MacIntyre 2016 (1)	-0.03	1.414	302	295	1.4%	0.97 [0.06 , 15.51]
Suess 2012	-0.942	0.57	26	30	8.3%	0.39 [0.13 , 1.19]
Subtotal (95% CI)			**1547**	**1458**	**100.0%**	**0.91 [0.66 , 1.26]**
Heterogeneity: Tau² = 0.00; Chi² = 5.08, df = 5 (P = 0.41); I² = 1%						
Test for overall effect: Z = 0.58 (P = 0.56)						



Footnotes
(1) Both MacIntyre studies reported on laboratory confirmed respiratory virus infection

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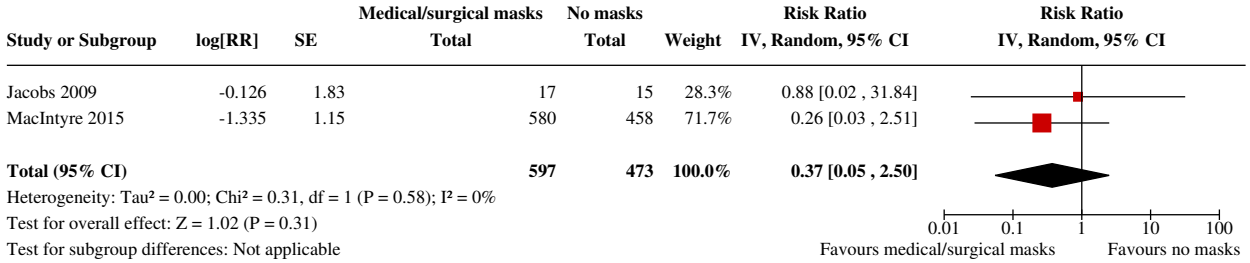
Analysis 1.2. Comparison 1: Randomised trials: medical/surgical masks versus no masks, Outcome 2: Influenza-like illness in healthcare workers



Comparison 2. Randomised trials: N95 respirators compared to medical/surgical masks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Viral illness	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.1.1 Clinical respiratory illness	3	7799	Risk Ratio (IV, Random, 95% CI)	0.70 [0.45, 1.10]
2.1.2 Influenza-like illness	5	8407	Risk Ratio (IV, Random, 95% CI)	0.82 [0.66, 1.03]
2.1.3 Laboratory-confirmed influenza	5	8407	Risk Ratio (IV, Random, 95% CI)	1.10 [0.90, 1.34]
2.2 Viral illness in healthcare workers	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.2.1 Clinical respiratory illness	3	7799	Risk Ratio (IV, Random, 95% CI)	0.70 [0.45, 1.10]
2.2.2 Influenza-like illness	4	8221	Risk Ratio (IV, Random, 95% CI)	0.81 [0.59, 1.11]
2.2.3 Laboratory-confirmed influenza	4	8221	Risk Ratio (IV, Random, 95% CI)	1.05 [0.79, 1.40]

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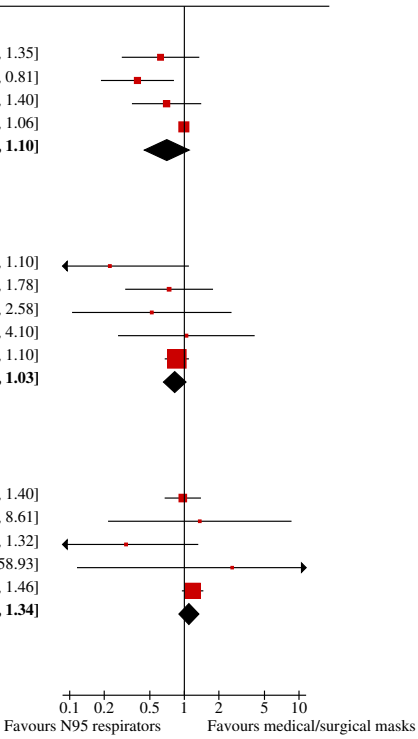
Analysis 2.1. Comparison 2: Randomised trials: N95 respirators compared to medical/surgical masks, Outcome 1: Viral illness

Study or Subgroup	log[RR]	SE	N95 respirators Total	Medical/surgical masks Total	Weight	Risk Ratio IV, Random, 95% CI
2.1.1 Clinical respiratory illness						
MacIntyre 2011	-0.478	0.397	949	492	18.5%	0.62 [0.28 , 1.35]
MacIntyre 2013	-0.942	0.374	581	286	19.7%	0.39 [0.19 , 0.81]
MacIntyre 2013 (1)	-0.357	0.355	516	286	20.8%	0.70 [0.35 , 1.40]
Radonovich 2019	-0.01	0.035	2243	2446	41.0%	0.99 [0.92 , 1.06]
Subtotal (95% CI)			**4289**	**3510**	**100.0%**	**0.70 [0.45 , 1.10]**
Heterogeneity: Tau² = 0.13; Chi² = 8.37, df = 3 (P = 0.04); I² = 64%						
Test for overall effect: Z = 1.54 (P = 0.12)						
2.1.2 Influenza-like illness						
Loeb 2009	-1.496	0.81	210	212	2.0%	0.22 [0.05 , 1.10]
MacIntyre 2009	-0.306	0.45	92	94	6.6%	0.74 [0.30 , 1.78]
MacIntyre 2011	-0.654	0.817	949	492	2.0%	0.52 [0.10 , 2.58]
MacIntyre 2013	0.04	0.7	1097	572	2.7%	1.04 [0.26 , 4.10]
Radonovich 2019	-0.151	0.124	2243	2446	86.7%	0.86 [0.67 , 1.10]
Subtotal (95% CI)			**4591**	**3816**	**100.0%**	**0.82 [0.66 , 1.03]**
Heterogeneity: Tau² = 0.00; Chi² = 3.19, df = 4 (P = 0.53); I² = 0%						
Test for overall effect: Z = 1.68 (P = 0.09)						
2.1.3 Laboratory-confirmed influenza						
Loeb 2009	-0.031	0.186	210	212	27.7%	0.97 [0.67 , 1.40]
MacIntyre 2009 (2)	0.31	0.94	92	94	1.2%	1.36 [0.22 , 8.61]
MacIntyre 2011	-1.171	0.74	949	492	1.9%	0.31 [0.07 , 1.32]
MacIntyre 2013	0.96	1.59	1097	572	0.4%	2.61 [0.12 , 58.93]
Radonovich 2019	0.166	0.11	2243	2446	68.8%	1.18 [0.95 , 1.46]
Subtotal (95% CI)			**4591**	**3816**	**100.0%**	**1.10 [0.90 , 1.34]**
Heterogeneity: Tau² = 0.00; Chi² = 4.15, df = 4 (P = 0.39); I² = 4%						
Test for overall effect: Z = 0.89 (P = 0.37)						



Footnotes

(1) MacIntyre 2013 includes 2 comparisons: N95 vs surgical masks and targeted N95 vs surgical masks

(2) MacIntyre 2009 reported on outcome laboratory confirmed infections

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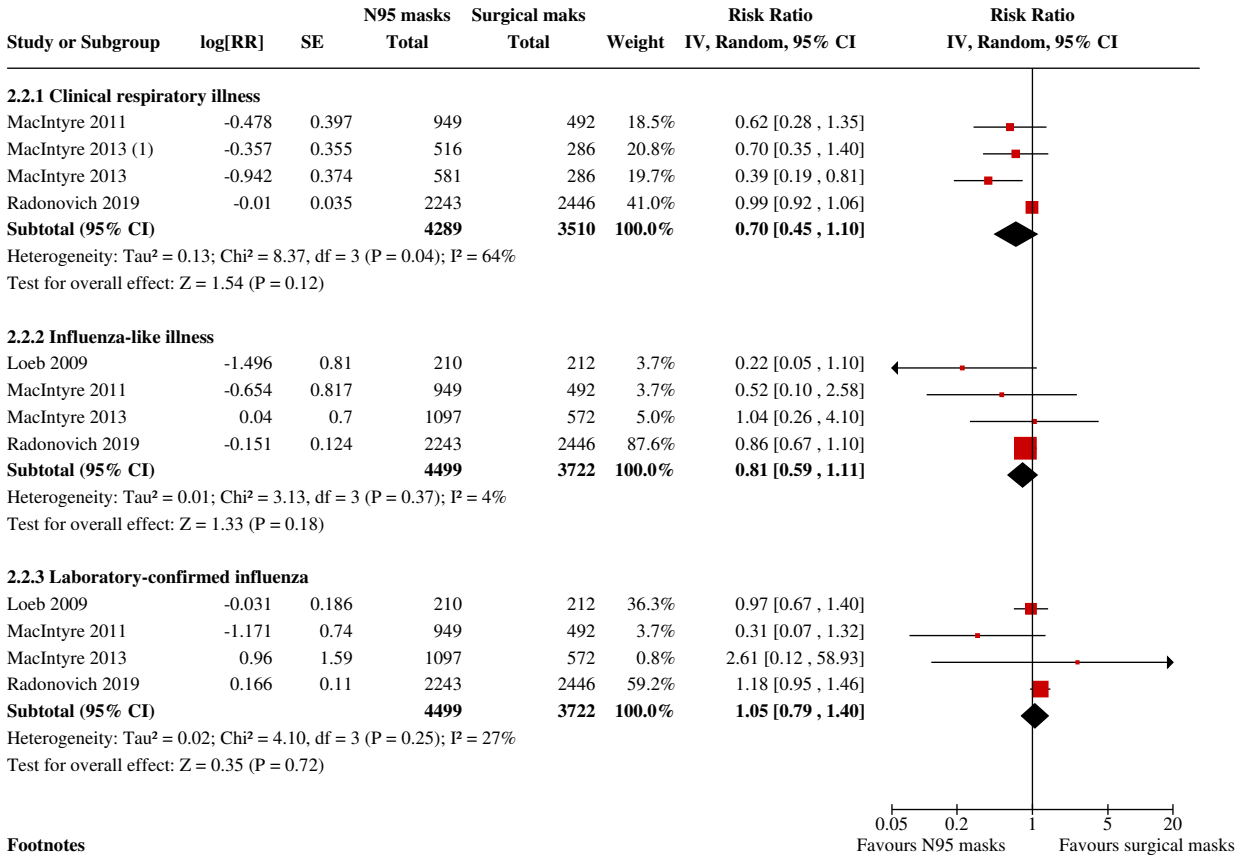
Analysis 2.2. Comparison 2: Randomised trials: N95 respirators compared to medical/surgical masks, Outcome 2: Viral illness in healthcare workers



Footnotes

(1) MacIntyre 2013 includes 2 comparisons: N95 vs surgical masks and targeted N95 vs surgical masks

Comparison 3. Randomised trials: hand hygiene compared to control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Viral illness	16		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.1.1 Acute respiratory illness	7	44129	Risk Ratio (IV, Random, 95% CI)	0.84 [0.82, 0.86]
3.1.2 Influenza-like illness	10	32641	Risk Ratio (IV, Random, 95% CI)	0.98 [0.85, 1.13]
3.1.3 Laboratory-confirmed influenza	8	8332	Risk Ratio (IV, Random, 95% CI)	0.91 [0.63, 1.30]
3.2 ARI or ILI or influenza (including outcome with most events from each study)	16	61372	Risk Ratio (IV, Random, 95% CI)	0.89 [0.84, 0.95]
3.3 Influenza or ILI: sensitivity analysis including outcomes with the most precise and unequivocal definitions	11	26343	Risk Ratio (IV, Random, 95% CI)	0.92 [0.80, 1.05]
3.4 ARI or ILI or influenza: subgroup analysis	16	61372	Risk Ratio (IV, Random, 95% CI)	0.89 [0.84, 0.95]

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Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.4.1 Children	9	21283	Risk Ratio (IV, Random, 95% CI)	0.92 [0.84, 1.01]
3.4.2 Adults	7	40089	Risk Ratio (IV, Random, 95% CI)	0.85 [0.79, 0.92]
3.5 Absenteeism	3	3150	Risk Ratio (IV, Random, 95% CI)	0.64 [0.58, 0.71]

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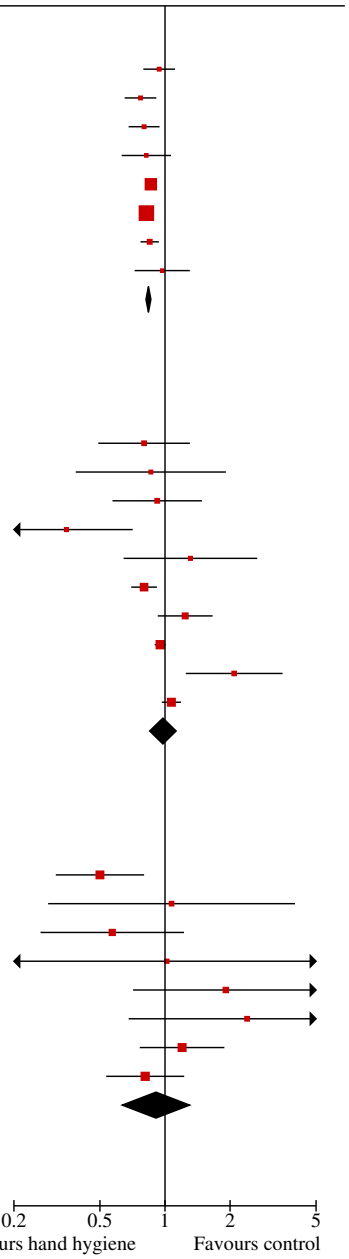
Analysis 3.1. Comparison 3: Randomised trials: hand hygiene compared to control, Outcome 1: Viral illness

Study or Subgroup	log[RR]	SE	Hand hygiene Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
3.1.1 Acute respiratory illness						
Azor-Martinez 2018	-0.062	0.086	274	149	2.4%	0.94 [0.79 , 1.11]
Azor-Martinez 2018 (1)	-0.261	0.086	339	149	2.4%	0.77 [0.65 , 0.91]
Correa 2012	-0.223	0.084	794	933	2.5%	0.80 [0.68 , 0.94]
Larson 2010	-0.199	0.134	946	904	1.0%	0.82 [0.63 , 1.07]
Little 2015	-0.151	0.02	8241	8667	35.2%	0.86 [0.83 , 0.89]
Millar 2016	-0.198	0.016	10000	10000	48.7%	0.82 [0.80 , 0.85]
Nicholson 2014	-0.163	0.05	847	833	6.9%	0.85 [0.77 , 0.94]
Sandora 2005	-0.03	0.15	602	451	0.8%	0.97 [0.72 , 1.30]
Subtotal (95% CI)			**22043**	**22086**	**100.0%**	**0.84 [0.82 , 0.86]**
Heterogeneity: Tau² = 0.00; Chi² = 7.51, df = 7 (P = 0.38); I² = 7%						
Test for overall effect: Z = 13.09 (P < 0.00001)						
3.1.2 Influenza-like illness						
Biswas 2019	-0.223	0.249	5077	5778	6.1%	0.80 [0.49 , 1.30]
Cowling 2008	-0.151	0.408	84	205	2.7%	0.86 [0.39 , 1.91]
Cowling 2009	-0.083	0.243	257	279	6.3%	0.92 [0.57 , 1.48]
Hubner 2010	-1.05	0.36	64	65	3.4%	0.35 [0.17 , 0.71]
Larson 2010	0.271	0.363	946	904	3.4%	1.31 [0.64 , 2.67]
Little 2015	-0.223	0.07	8241	8667	18.7%	0.80 [0.70 , 0.92]
Ram 2015	0.215	0.149	193	184	11.5%	1.24 [0.93 , 1.66]
Roberts 2000	-0.051	0.03	299	259	21.8%	0.95 [0.90 , 1.01]
Simmerman 2011	0.737	0.263	292	302	5.6%	2.09 [1.25 , 3.50]
Zomer 2015	0.068	0.052	278	267	20.3%	1.07 [0.97 , 1.19]
Subtotal (95% CI)			**15731**	**16910**	**100.0%**	**0.98 [0.85 , 1.13]**
Heterogeneity: Tau² = 0.02; Chi² = 32.18, df = 9 (P = 0.0002); I² = 72%						
Test for overall effect: Z = 0.31 (P = 0.76)						
3.1.3 Laboratory-confirmed influenza						
Biswas 2019	-0.693	0.24	508	689	19.8%	0.50 [0.31 , 0.80]
Cowling 2008	0.07	0.671	84	205	6.0%	1.07 [0.29 , 4.00]
Cowling 2009	-0.562	0.39	257	279	12.7%	0.57 [0.27 , 1.22]
Hubner 2010	0.02	0.834	64	65	4.2%	1.02 [0.20 , 5.23]
Larson 2010	0.648	0.504	946	904	9.2%	1.91 [0.71 , 5.13]
Ram 2015	0.875	0.644	193	184	6.4%	2.40 [0.68 , 8.48]
Simmerman 2011	0.182	0.23	292	302	20.4%	1.20 [0.76 , 1.88]
Stebbins 2011	-0.211	0.212	1695	1665	21.4%	0.81 [0.53 , 1.23]
Subtotal (95% CI)			**4039**	**4293**	**100.0%**	**0.91 [0.63 , 1.30]**
Heterogeneity: Tau² = 0.11; Chi² = 13.58, df = 7 (P = 0.06); I² = 48%						
Test for overall effect: Z = 0.53 (P = 0.60)						



Footnotes

(1) Azor 2018 included 2 hand-washing groups: one using soap and water (RR 0.94) and the other using hand sanitizer (RR 0.77)

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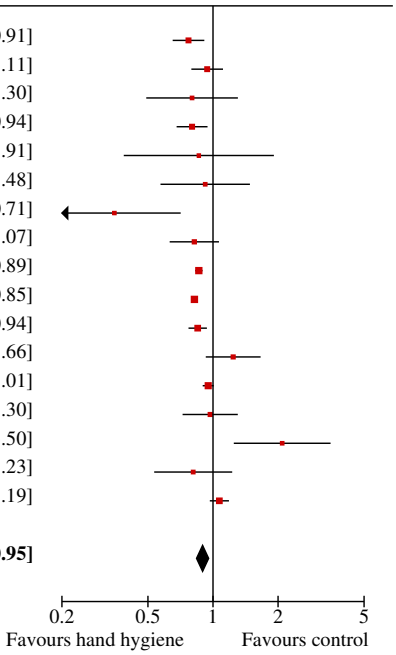
Analysis 3.2. Comparison 3: Randomised trials: hand hygiene compared to control, Outcome 2: ARI or ILI or influenza (including outcome with most events from each study)

Study or Subgroup	log[RR]	SE	Hand hygiene Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Azor-Martinez 2018	-0.261	0.086	339	149	7.1%	0.77 [0.65 , 0.91]
Azor-Martinez 2018 (1)	-0.062	0.086	274	149	7.1%	0.94 [0.79 , 1.11]
Biswas 2019	-0.223	0.249	5077	5778	1.5%	0.80 [0.49 , 1.30]
Correa 2012	-0.223	0.084	794	933	7.2%	0.80 [0.68 , 0.94]
Cowling 2008	-0.151	0.408	84	205	0.6%	0.86 [0.39 , 1.91]
Cowling 2009	-0.083	0.243	257	279	1.6%	0.92 [0.57 , 1.48]
Hubner 2010	-1.05	0.36	64	65	0.8%	0.35 [0.17 , 0.71]
Larson 2010	-0.199	0.134	946	904	4.2%	0.82 [0.63 , 1.07]
Little 2015	-0.151	0.02	8241	8667	13.1%	0.86 [0.83 , 0.89]
Millar 2016	-0.198	0.016	10000	10000	13.3%	0.82 [0.80 , 0.85]
Nicholson 2014	-0.163	0.05	847	833	10.4%	0.85 [0.77 , 0.94]
Ram 2015	0.215	0.149	193	184	3.6%	1.24 [0.93 , 1.66]
Roberts 2000	-0.051	0.03	299	259	12.3%	0.95 [0.90 , 1.01]
Sandora 2005	-0.03	0.15	602	451	3.5%	0.97 [0.72 , 1.30]
Simmerman 2011	0.737	0.263	292	302	1.4%	2.09 [1.25 , 3.50]
Stebbins 2011	-0.211	0.212	1695	1665	2.0%	0.81 [0.53 , 1.23]
Zomer 2015	0.068	0.052	278	267	10.2%	1.07 [0.97 , 1.19]
Total (95% CI)			**30282**	**31090**	**100.0%**	**0.89 [0.84 , 0.95]**

Heterogeneity: Tau² = 0.01; Chi² = 65.64, df = 16 (P < 0.00001); I² = 76%
Test for overall effect: Z = 3.38 (P = 0.0007)
Test for subgroup differences: Not applicable

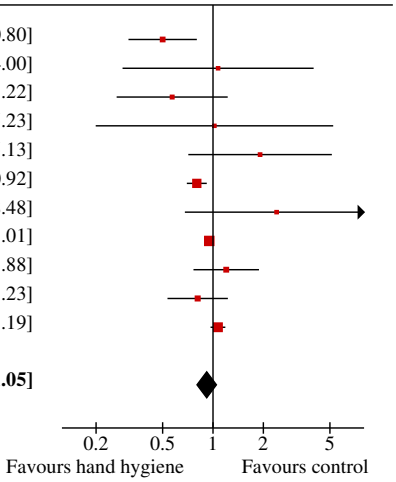


Footnotes
(1) Azor 2018 included 2 treatment groups: soap and water (RR 0.94); and hand sanitizer (RR 0.77)

Analysis 3.3. Comparison 3: Randomised trials: hand hygiene compared to control, Outcome 3: Influenza or ILI: sensitivity analysis including outcomes with the most precise and unequivocal definitions

Study or Subgroup	log[RR]	SE	Hand hygiene Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Biswas 2019	-0.693	0.24	508	689	6.2%	0.50 [0.31 , 0.80]
Cowling 2008	0.07	0.671	84	205	1.0%	1.07 [0.29 , 4.00]
Cowling 2009	-0.562	0.39	257	279	2.7%	0.57 [0.27 , 1.22]
Hubner 2010	0.02	0.834	64	65	0.7%	1.02 [0.20 , 5.23]
Larson 2010	0.648	0.504	946	904	1.7%	1.91 [0.71 , 5.13]
Little 2015	-0.223	0.07	8241	8667	21.6%	0.80 [0.70 , 0.92]
Ram 2015	0.875	0.644	193	184	1.1%	2.40 [0.68 , 8.48]
Roberts 2000	-0.051	0.03	299	259	26.6%	0.95 [0.90 , 1.01]
Simmerman 2011	0.182	0.23	292	302	6.7%	1.20 [0.76 , 1.88]
Stebbins 2011	-0.211	0.212	1695	1665	7.5%	0.81 [0.53 , 1.23]
Zomer 2015	0.068	0.052	278	267	24.1%	1.07 [0.97 , 1.19]
Total (95% CI)			**12857**	**13486**	**100.0%**	**0.92 [0.80 , 1.05]**

Heterogeneity: Tau² = 0.02; Chi² = 25.77, df = 10 (P = 0.004); I² = 61%
Test for overall effect: Z = 1.27 (P = 0.20)
Test for subgroup differences: Not applicable



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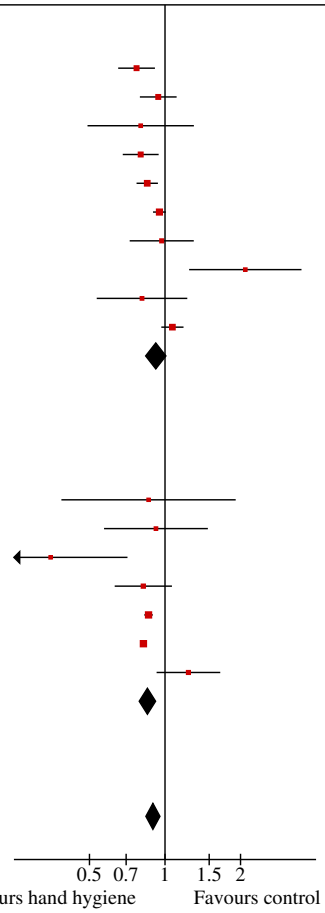
Analysis 3.4. Comparison 3: Randomised trials: hand hygiene compared to control, Outcome 4: ARI or ILI or influenza: subgroup analysis

Study or Subgroup	log[RR]	SE	Hand hygiene Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
3.4.1 Children						
Azor-Martinez 2018 (1)	-0.261	0.086	339	149	7.1%	0.77 [0.65 , 0.91]
Azor-Martinez 2018	-0.062	0.086	274	149	7.1%	0.94 [0.79 , 1.11]
Biswas 2019	-0.223	0.249	5077	5778	1.5%	0.80 [0.49 , 1.30]
Correa 2012	-0.223	0.084	794	933	7.2%	0.80 [0.68 , 0.94]
Nicholson 2014	-0.163	0.05	847	833	10.4%	0.85 [0.77 , 0.94]
Roberts 2000	-0.051	0.03	299	259	12.3%	0.95 [0.90 , 1.01]
Sandora 2005	-0.03	0.15	602	451	3.5%	0.97 [0.72 , 1.30]
Simmerman 2011	0.737	0.263	292	302	1.4%	2.09 [1.25 , 3.50]
Stebbins 2011	-0.211	0.212	1695	1665	2.0%	0.81 [0.53 , 1.23]
Zomer 2015	0.068	0.052	278	267	10.2%	1.07 [0.97 , 1.19]
Subtotal (95% CI)			**10497**	**10786**	**62.8%**	**0.92 [0.84 , 1.01]**
Heterogeneity: Tau² = 0.01; Chi² = 29.46, df = 9 (P = 0.0005); I² = 69%						
Test for overall effect: Z = 1.79 (P = 0.07)						
3.4.2 Adults						
Cowling 2008	-0.151	0.408	84	205	0.6%	0.86 [0.39 , 1.91]
Cowling 2009	-0.083	0.243	257	279	1.6%	0.92 [0.57 , 1.48]
Hubner 2010	-1.05	0.36	64	65	0.8%	0.35 [0.17 , 0.71]
Larson 2010	-0.199	0.134	946	904	4.2%	0.82 [0.63 , 1.07]
Little 2015	-0.151	0.02	8241	8667	13.1%	0.86 [0.83 , 0.89]
Millar 2016	-0.198	0.016	10000	10000	13.3%	0.82 [0.80 , 0.85]
Ram 2015	0.215	0.149	193	184	3.6%	1.24 [0.93 , 1.66]
Subtotal (95% CI)			**19785**	**20304**	**37.2%**	**0.85 [0.79 , 0.92]**
Heterogeneity: Tau² = 0.00; Chi² = 16.39, df = 6 (P = 0.01); I² = 63%						
Test for overall effect: Z = 4.22 (P < 0.0001)						
Total (95% CI)			**30282**	**31090**	**100.0%**	**0.89 [0.84 , 0.95]**
Heterogeneity: Tau² = 0.01; Chi² = 65.64, df = 16 (P < 0.00001); I² = 76%						
Test for overall effect: Z = 3.38 (P = 0.0007)						
Test for subgroup differences: Chi² = 1.59, df = 1 (P = 0.21), I² = 37.2%						

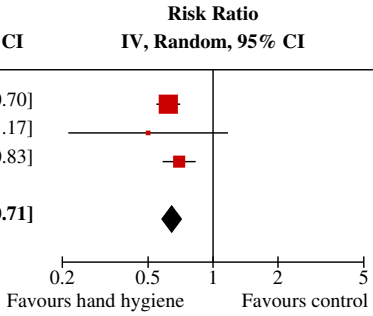


Footnotes

(1) Azor 2018 includes 2 intervnetion groups: soap and water (RR 0.94) and hand sanitizer (RR 0.77)

Analysis 3.5. Comparison 3: Randomised trials: hand hygiene compared to control, Outcome 5: Absenteeism

Study or Subgroup	log[RR]	SE	Hand Hygiene Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Azor-Martinez 2016	-0.478	0.065	621	720	64.8%	0.62 [0.55 , 0.70]
Hubner 2010	-0.693	0.435	64	65	1.4%	0.50 [0.21 , 1.17]
Nicholson 2014	-0.362	0.09	847	833	33.8%	0.70 [0.58 , 0.83]
Total (95% CI)			**1532**	**1618**	**100.0%**	**0.64 [0.58 , 0.71]**
Heterogeneity: Tau² = 0.00; Chi² = 1.43, df = 2 (P = 0.49); I² = 0%						
Test for overall effect: Z = 8.45 (P < 0.00001)						
Test for subgroup differences: Not applicable						



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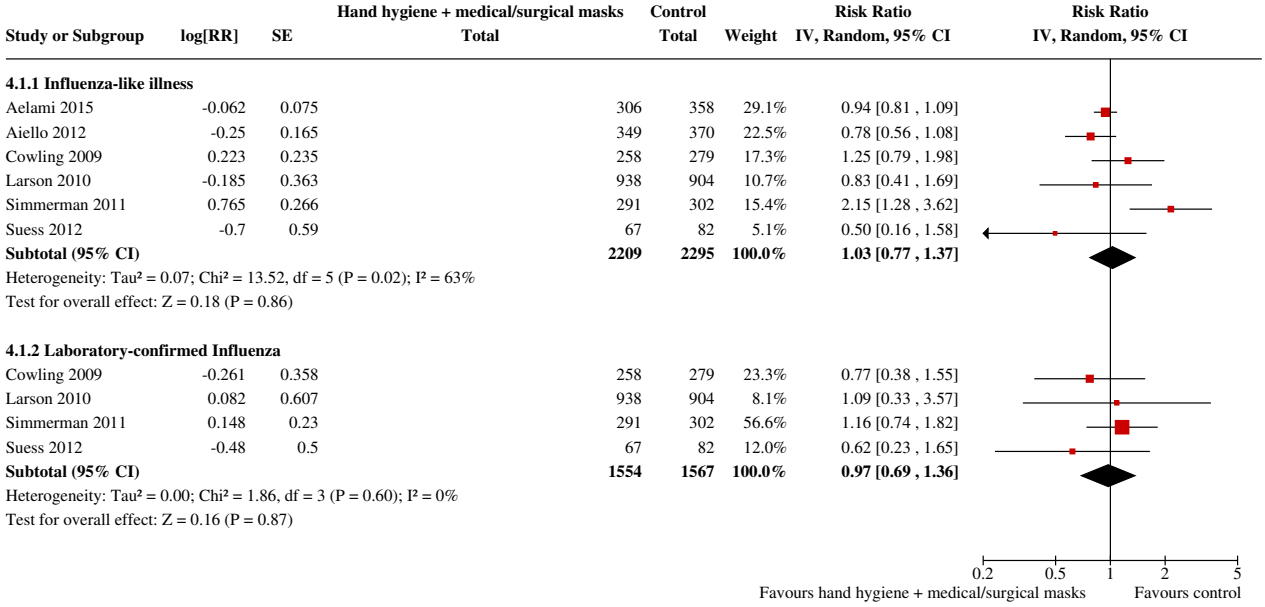
Comparison 4. Randomised trials: hand hygiene + medical/surgical masks compared to control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Viral illness	6		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.1.1 Influenza-like illness	6	4504	Risk Ratio (IV, Random, 95% CI)	1.03 [0.77, 1.37]
4.1.2 Laboratory-confirmed Influenza	4	3121	Risk Ratio (IV, Random, 95% CI)	0.97 [0.69, 1.36]

Analysis 4.1. Comparison 4: Randomised trials: hand hygiene + medical/surgical masks compared to control, Outcome 1: Viral illness



Comparison 5. Randomised trials: hand hygiene + medical/surgical masks compared to hand hygiene

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Viral illness	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.1.1 Influenza-like illness	3	2982	Risk Ratio (IV, Random, 95% CI)	1.03 [0.69, 1.53]
5.1.2 Laboratory-confirmed influenza	3	2982	Risk Ratio (IV, Random, 95% CI)	0.99 [0.69, 1.44]

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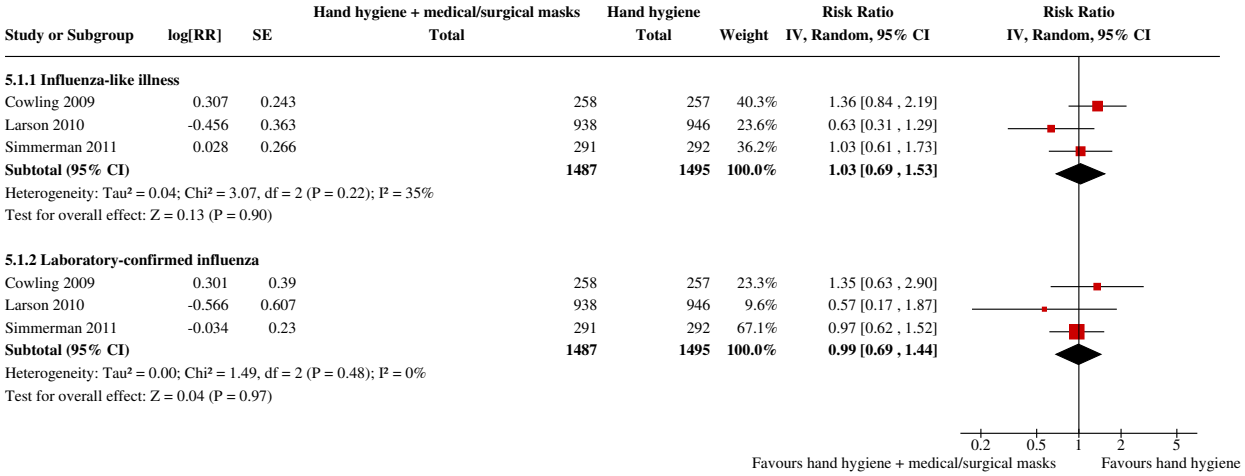
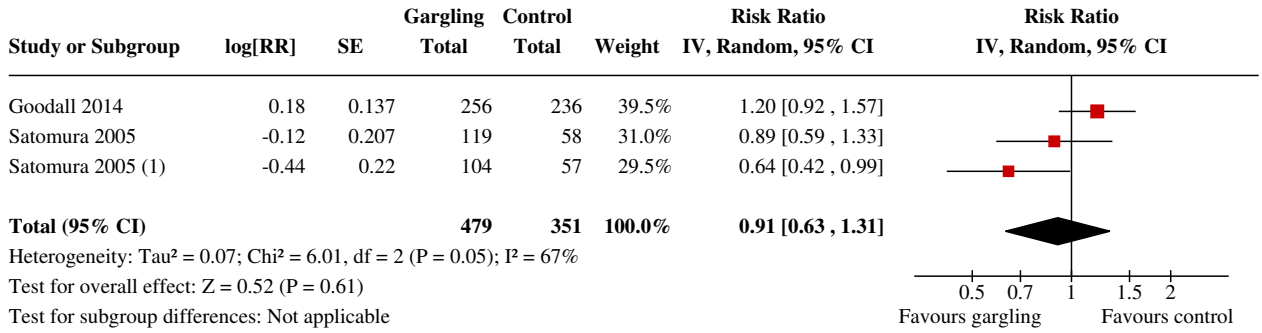
Analysis 5.1. Comparison 5: Randomised trials: hand hygiene + medical/surgical masks compared to hand hygiene, Outcome 1: Viral illness



Comparison 6. Randomised trials: gargling compared to control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Viral illness	2	830	Risk Ratio (IV, Random, 95% CI)	0.91 [0.63, 1.31]

Analysis 6.1. Comparison 6: Randomised trials: gargling compared to control, Outcome 1: Viral illness



Footnotes

(1) Satomura 2005 included 2 intervention groups

ADDITIONAL TABLES

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist

Author, year	Brief name	Recipient	Why	What (materials)	What (procedures)	Who provided	How	Where	When and how much	Tailoring	Modification of intervention throughout trial	Strategies to improve or maintain intervention fidelity	Extent of intervention fidelity
Masks compared to either no masks or different mask types													
Barasheed 2014	Supervised mask use	Religious pilgrims ≥ 15 years	Prevent respiratory virus infections at mass gatherings through mask use	Plain surgical face masks (3M Standard Tie-On Surgical Mask, Cat No: 1816) manufactured by 3M company, USA; 5 masks per day Written instructions on face mask use Special polythene bags for disposal	Masks provided to index case and their contacts with advice on mask use (before prayers, in seminars, and after meals). Written instructions provided on face mask use, need to change them, and disposal.	Not described, presumably the medical researchers	Face-to-face provision of masks, instructions, and reminders	Tents of pilgrimage site (Mina Valley, Saudi Arabia)	Advice on mask use given throughout pilgrimage stay (5 days)	None reported.	None reported.	The medical researchers followed pilgrims each day to remind participants about recording their mask usage in health diary.	Face mask use: mask group: 56/75 (76%), control group: 11/89 (12%) (P < 0.001) 76% of intervention tents wore masks. 10 of 75 (13%) pilgrims in 'mask' tents wore face masks during sleep.
Canini 2010	Surgical face masks	Householders (over 5 years)	Limit transmission of influenza transmission by large	Initial supply of 30 masks: for adults and children > 10: surgery masks with earloops, 3 plys, anti fog (AEROKYN, LCH medical products, Paris, France)	Masks given immediately on home visit by attending general practitioner with demonstration of proper use	General practitioners	Face-to-face individually	Households in France	One-off provision of masks worn for 5 days	None described.	None described.	Not described, but reported mask usage was measured	34/51 (66%) wore masks > 80% of the duration.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

			droplets produced during coughing in households	Children 5 to 10: face mask KC47127, (Kimberly-Clark, Dallas, TX, USA) Closed plastic bags for disposal	and instruction to be worn for 5 days in presence of another household member or in confined space (e.g. car) and to change every 3 hours or if damaged.								Reported mask-wearing: 11 ± 7.2 masks during 4.0 ± 1.6 days with an average use of 2.5 ± 1.3 masks per day and duration of use of 3.7 ± 2.7 hours/day
Jacobs 2009	Face masks	Hospital healthcare providers (nurses, doctors, and co-medical personnel)	Decrease risk of infection through limiting droplet spread through masks	Hospital-standard disposable surgical Mask MA-3 (Ozu Sangyo, Tokyo, Japan); quantity not specified	Provision of masks and instructions for use	Not described, presumably research team	Face-to-face	Tertiary care hospital in Tokyo, Japan Face masks worn whilst on hospital property.	77 days	None described.	None described.	Self-reported compliance	Self-reported compliance for both groups reported as good, with full compliance by 84.3% and remainder complying 79.2% to 98.7%.
Loeb 2009	2 active interventions A. sur-	Healthcare workers (nurses)	Reduce transmission of influenza in healthcare settings through coughing	A. Surgical masks B. N95 respirators	Provision of masks or N95 respirators Instruction in use and proper placement of devices	Provided by research team (not further	In-person face-to-face	Tertiary hospitals in Ontario,	1 influenza season (12 weeks) Use of mask as required[2] when pro-	Fit-testing of nurses not already	Ceased before end of season	Compliance audits during peak of season by trained auditor who stood	18 episodes: N95: 6/7 participants (85.7%) wearing assigned

Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	gical masks B. N95 respirators		or sneezing with protective masks		Fit-testing and demonstration of positioning of N95 using standard protocol and procedure (details provided) Qualitative fit-testing using saccharin or Bitrex protocol[1]	described) Fit-testing by technician for N95		Canada	viding care to or within 1 m of patient with febrile respiratory illness, ≥ 38 °C, and new or worsening cough or shortness of breath Nurses to wear N95 when caring for patients with "febrile respiratory illness"	fit-tested		short distance from patient isolation room	device versus 100% for masks
MacIntyre 2009	2 active interventions in addition to infection control guidelines A. Surgical masks (SM)	Householders with a child with fever and respiratory symptoms	Prevent or reduce respiratory virus transmission in the community through non-pharmaceutical interventions	A. 3M surgical mask, catalogue no. 1820; St Paul, MN, USA for adults B. P2 masks (3M flat-fold P2 mask, catalogue no. 9320; Bracknell, Berkshire, UK) A and B: health guidelines and pamphlets about infection control	Provision of masks and pamphlets and education about infection prevention and mask use Telephone calls and exit interviews to record adherence to mask use All groups: health guidelines, pamphlets about infection control were provided	Not described, presumably research team	Face-to-face and by telephone	Households in Sydney, Australia	2 winter seasons (3 months and 6 months) 2 weeks of follow-up Masks to be worn at all times when in same room as index child, regardless of distance from child	None described.	None described.	Daily telephone calls to record mask use throughout day Exit interviews about adherence	Reported mask use: Day 1 SM: 36/94 (38%) P2: 42/92 (46%) stated wearing "most or all" of the time. Other participants were wearing face masks rarely or never. Day 5:

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	B. P2 masks (P2)												SM: 29/94 (31%) P2: 23/92 (25%)
MacIntyre 2011	3 active interventions A. Medical masks B. N95 respirators fit-tested C. N95 respirators non-fit-tested	Healthcare workers	Protect HCWs by preventing transmission of influenza and other respiratory viruses from patients through mask wearing	Daily supply of A. 3 medical masks (3M medical mask, catalogue number 1820, St Paul, MN, USA) 2 respirators: B. N95 fit-tested mask (3M flat-fold N95 respirator, catalogue number 9132) fit-tested with 3M FT-30 Bitrex Fit Test kit according to manufacturer's instructions (3M, St Paul, MN, USA) C. N95 non-fit-tested mask (3M flat-fold N95 respirator, catalogue number 9132) Diary cards for usage recording	Supply of masks or respirators. Instruction in when to wear it, correct fitting, and storage (in paper bag in personal locker) Instruction in importance of hand hygiene before and after removal For fit-tested group: fit-testing procedure	Masks provided to hospitals. Training of staff provided by 1 member of research team.	Masks and training provided face-to-face, not described if training was individually or in groups.	Emergency departments and respiratory wards in hospitals in Beijing, China	Entire work shift for 4 weeks	Taken off for toilet and meal breaks and at end of shift	None described.	Mask/respirator use monitored by: (i) observed compliance by head ward nurse recorded daily; (ii) self-report diary cards carried during day recording; (i) no. hours; (ii) usage. Exit interviews	Adherence for usage was high for all and not significantly different amongst arms. Medical mask: 76%, 5 hours N95 fit-tested: 74%, 5.2 hours N95 non-fit-tested: 68%, 4.9 hours
MacIntyre 2013	3 active interventions A. N95 respirators at all times	Healthcare workers (nurses and doctors)	Protect HCWs from respiratory infections from patients through mask use	Daily supply of: A. and B. 2 respirators (3M Health Care N95 Particulate Respirator; catalogue number 1860) 3M FT-30 Bitrex Fit Test Kit C. 3 masks 3 masks	Supply of respirators Instructions in use including times and fit Fit-testing procedure according to the manufacturer's instructions (3M) For targeted N95:	3M supplied respirators and masks. Provider of instructions	Masks and training provided face-to-face, not described	Emergency departments and respiratory wards of ter-	For 4 weeks, A and B worn at all times on shift; B. targeted (intermittent) use of N95 respirators only whilst	None described.	None described.	Self-reported daily record of number of hours worked, mask or respirator use, number of high-	Compliance highest for targeted N95 (82%; 422/516) versus N95 (57%; 333/581) versus medical mask

Physical interventions to interrupt or reduce the spread of respiratory viruses (Review)
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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	B. N95 respirators targeted use C. Medical masks			(3M Standard Tie-On Surgical Mask catalogue number mask 1817; 3M, St Paul, MN, USA) Pocket-sized diary card with tick boxes for mask use	checklist of defined high-risk procedures, including common aerosol-generating procedures	not specified.	if training was individually or in groups.	tiary hospitals in Beijing, China	performing high-risk procedures or barrier.			risk procedures undertaken collected by study staff.	(66%; 380/572).
MacIntyre 2015	2 active interventions A. Cloth masks B. Medical masks	Hospital healthcare workers	Prevent respiratory infections in HCWs from patients through mask-wearing	A. 5 cloth masks for study duration (2- layer, cotton) B. 2 medical masks daily for each 8-hour shift for study duration (3 layers, non-woven material) All masks locally manufactured. Written instructions on cleaning cloth masks	Cloth or medical masks to be worn at all times on shift. Cloth masks to be washed with soap and water daily after shifts, and the process of cleaning to be documented. Provision of written instructions for cloth mask cleaning	Researchers arranged supply of masks and instructions and any training of staff assisting the delivery.	Masks and written instructions provided face-to-face.	Hospital wards in Vietnam	4 weeks (25 days) of face mask use	Masks not worn while in the toilet or during tea or lunch breaks.	None described.	Monitored compliance with mask use by self-report diary card and exit survey and interviews with a sub-sample (ACTRN12610000823757)	Mask-wearing compliance: cloth mask: 56.8%; medical mask: 56.6%; Reported cloth mask washing: 23/25 days (92%)
MacIntyre 2016	Medical mask use	Sick householders with ILI (index	Protect well people in the community from transmission of res-	21 medical masks (3M 1817 surgical mask) Diary cards for mask use	Supply of masks Instructions for mask wearing and hand-washing protocol Provision of diary cards	Study staff member provided masks and	Masks and instructions provided face-	Fever clinics of major hospitals in	3 masks/day for 21 days Mask wearing: whenever in the same	Allowed to remove their masks during	None reported.	Self-reported daily record of mask use using diary card	Mask use: mask group: 4.4 hours; control group: 1.4 hours

Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

			cases) and their well contacts of the same household	piratory pathogens by contacts with ILI through mask use			in-structions in use.	to-face and indi-vidu-ally.	Bei-jing, Chi-na	room as a household member or a visi-tor to the household Hand-washing: before putting on and after taking off	meal-times and whilst asleep and to cease wear-ing once symp-toms re-solved	
Radonovich 2019	2 ac-tive inter-ven-tions A. N95 res-pira-tors (N95) B. Med-ical masks (MM)	Health-care per-son-nel of out-pa-tient sites with-in med-ical cen-tres	Prevent HCP from acquiring workplace viral respi-ratory in-fections and trans-mitting them to others by effective respira-tory pro-tection by N95 respira-tors which reduce aerosol exposure and in-halation of small airborne particles, meet fil-tration	A. N95 respirators: 3M Corporation 1860, 1860S, and 1870 (St Paul, MN, USA) or Kim-berly Clark Technol Flu-idshield PFR95-270, PFR95-274 (Dallas, TX, USA) B. Medical mask Precept 15320 (Arden, NC, USA) or Kimberly Clark Technol Fluidshield 47107 (Dal-las, TX, USA). Reminder signs posted at each site A portable comput-er equipped with da-ta recording software (HandyAudit; Toronto, Canada) to document	Participants in-structed to wear assigned pro-tective devices whenever they were positioned within 6 feet (1.83 m) of patients with sus-pected or con-firmed respiratory ill-ness and to don a new N95/MM with each patient in-teraction. Hand hygiene recommended to all participants in accordance with Centers for Disease Control	Cen-tres pro-vided de-vice sup-plied by study to HCP. Study per-son-nel post-ed re-minder signs and emails and con-duct-ed ad-	Face-to-face indi-vid-ual pro-vi-sion of de-vices and ad-her-ence ob-ser-va-tions On-site post-ing of signs Oth-er re-minders	Out-pa-tient sites with-in med-ical cen-tres in USA	As in-structed, for each new pa-tient in-teraction during 12-week peri-od of peak viral respi-ratory ill-ness each year for 4 years (to-tal of 48 weeks)	Fit-ting of N95 masks	None de-scribed.	Reminder signage posted at study sites, and emails sent by study per-son-nel. Self-re-ported daily de-vice wear-ing of “al-ways”, “some-times”, “never”, or “did not recall" Observa-tion of de-vice-wear-ing behav-iours as partici-pants en-tered and	Device wearing: N95: 89.4% re-ported “al-ways” or “some-times” versus MM: 90.2% “Never” N95: 10.2% MM: 9.5%

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

			require-ments, and fit tightly	adherence (Radonovich 2016)	and Prevention guidelines. Infection preven-tion policies were followed at each study site. Reminder signs posted at sites and emails sent. Annual fit-testing conducted for all participants. Filtration testing performed on the device models in the study. Further details in proto-col (Radonovich 2016).	her-ence ob-ser-va-tions.	by email					exited care rooms conduct-ed dur-ing unan-nounced, inconspic-uous vis-its to ran-domly selected sites docu-mented on portable computer	
Hand hygiene													
Alza-her 2018	Hand hy-giene work-shop	Pri-mary school girls	Target-ed school children to improve hand hy-giene to reduce school ab-sences due to up-per res-pirato-ry infec-tion and spread of infection in schools	6-minute video-clip of 2 siblings that attended school-based health ed-ucation about hand hy-giene Short interactive lecture about: common infections in schools, methods of transmis-sion, hand-washing pro-cedure using soap and water including when to wash hands	Delivery of work-shop and distri-bution of sup-porting materi-als (games and posters) to school and students	Study in-vesti-gator deliv-ered work-shop.	De-liv-ered face-to-face in group for-mat for the work-shop	2 pri-mary girls' schools in Sau-di Ara-bia	1-hour once-off workshop; posters and games provided to school	Not de-scribed	Not de-scribed	Posters in restrooms as re-minders of hand-washing hygiene during 5-week fol-low-up pe-riod after workshop	Not re-ported

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

			and to families	Puzzle games related to hand hygiene Posters with cartoon princesses' picture promoting hand-washing										
Arbogast 2016	Multimodal hand hygiene intervention programme in addition to control of brief video	Office buildings and the employees of health insurance company	Reduce hand-to-mouth germ transmission from shared workspaces and workplace facilities and thereby healthcare claims and absenteeism through improved workplace hand hygiene	Alcohol-based hand sanitiser (PURELL Advanced, GOJO Industries Inc, Akron, OH, USA) installed as wall-mounted dispensers, stands, or free-standing bottles One 8-ounce bottle of hand sanitiser (PURELL Advanced) per cubicle One 100-count canister of hand wipes (PURELL Wipes) per cubicle Replenishment products stored in supply room (in addition to existing foam hand wash (GOJO Green Certified Foam Handwash) and an alcohol-based hand sanitiser foam wall-mounted dispenser (PURELL, GOJO Industries) already provided near the restroom exits prior to intervention) Identical soap in all restrooms Intervention and control group: brief (< 1-minute educational video) about	Hand hygiene supplies installed in offices. Replenishment product was made easily available to individual employees upon request via a simple process. Monitoring of product shipments into sites Physical collection and full replacement of soap, sanitiser, and wipes Intervention and control group: educational video embedded at end of baseline online knowledge survey	Not described, presumably study investigators arranged installations	Hand hygiene supplies provided in office environments and individually at staff cubicles/offices. Video provided individually via email.	High-traffic common areas of 2 US health insurance company offices (e.g. near elevators, at entrances) and appropriate public spaces (e.g. coffee area, break rooms,	13.5 months overall One-off email video 11 days before study hand hygiene supplies installed. 13 months of provision of supplies 2 times evening collection and full replacement of products	Sanitiser installed in high-use areas of the offices.	Not described	Employee survey at 4 months included questions about hand hygiene practice compliance. Monitoring of product shipments into the sites and physical collection of the soap, sanitiser, and wipes products 2 times in the study; collected samples were measured and usage rates were estimated	Intervention group employees: reported 40% more cleaning of work area regularly; significantly more likely to keep the hand sanitiser with them and use it throughout the day; significant increases in hand sanitiser use for at-risk activities[3] Estimated use by average employee from sample collection:

Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

				proper hand hygiene technique, for both washing and sanitising hands ''Wash Your Hands'', signage promoting hand hygiene compliance, was already posted next to restroom exits at both the control and intervention sites.				con-ference rooms, train-ing rooms, lob-bies, re-cep-tion ar-eas); indi-vid-ual staff cubi-cles of most-ly open plan of-fices (av-erage 309 square feet). Of-fice re-strooms				sanitiser 1.8 to 3.0 times/day, soap 2.1 to 4.4 times/day, wipes at their desk 1.4 to 1.5 times/ week
Azor-Mar-tinez 2016	Hand-wash-ing pro-gramme	Pri-mary school chil-dren and their	Prevent transmis-sion of up-per respi-ratory in-fections in schools	Brochure about hand-washing awareness and habits Workshop content mate-rials	Brochure sent to parents by mail with study infor-mation sheet.	Brochure sent by school ad-min-	Brochure sent by mail to in-di-vid-	Pri-mary school class-es in Spain (de-	8 months overall One-off brochure and instal-lation of	Su-per-vi-sion and ad-min-	Not de-scribed	Daily re-inforce-ment by teachers of hand hygiene	Self-re-ported correct hand-washing included in analy-

Physical interventions to interrupt or reduce the spread of respiratory viruses (Review)
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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	parents and teachers	and to families through non-pharmaceutical intervention of handwashing programme in schools	Stories, songs, and classroom posters about hand hygiene and infection transmission Hand sanitiser (ALCO ALOE GEL hand sanitiser by Americo Govantes Burguete, S.L. Madrid, Spain containing 0.2% chlorhexidine digluconate, 1% phenoxyethanol, 0.1% benzalkonium chloride, 5% aloe barbadensis, 70% denat ethyl alcohol, excipients quantity sufficient for 100 mL alcohol 70%, pH 7.0 to 7.5) Informational poster about when and how to wash hands Written and verbal guidance to teachers, parents, and students on properties, possible side effects, and precautionary measures for gel use and storage	Workshop provided for pupils and teachers: frequent infections in schools, transmission and prevention, instructions on correct handwashing (water and soap, soaping > 20 s, drying hands), use of hand sanitisers and possible side effects Classroom activities linked to hand hygiene and infection transmission Reinforcement of hand hygiene by teachers Hand sanitiser dispensers fixed to walls with an informational poster about hand-washing Supervision of younger children when using hand sanitiser and administration of sanitiser if needed Instruction of children in handwashing procedure	istration. Workshop and verbal and written information presumably provided by the study research assistant. Classroom activities provided by research assistant and teachers. Supervision	ual parents. Workshops and classroom activities delivered in groups face-to-face. Teacher reinforcement of hand hygiene provided to class face-to-face. Hand sanitiser use supervision was	tails not provided)	hand sanitiser dispensers 2-hour workshop held 1 month before study commencement Fortnightly classroom activities As required, teacher supervision and administration of hand sanitiser Daily reinforcement of hand hygiene by teachers	istration of hand sanitiser as needed by teachers, especially for younger children	Fortnightly support by research assistant promoting handwashing Self-reported correct handwashing procedure (water and soap, soaping > than 20 s, drying hands)	sis but not separately reported.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					dures after toilet and when dirty and correct hand sanitiser use[4]	and administration of hand sanitiser for younger children by teachers	provided individually and face-to-face.						
Azor-Martinez 2018	Educational and hand hygiene programme 2 active interventions: A. soap and water B. hand sanitiser	Day care centres and their attending children, their parents, and DCC staff	Prevent transmission of respiratory infections by improved hand hygiene of children, parents, and staff through handwashing practices and use of hand sanitiser due to its bactericide and virucide properties	A. Liquid soap (no specific antibacterial components (pH = 5.5)) OR B. Hand sanitiser (70% ethyl alcohol (pH = 7.0 to 7.5)) for home use and in dispensers for school classroom Workshop content handout Stories, songs, and posters about hand hygiene and infection transmission	Installation of liquid soap or hand sanitiser dispensers in classrooms Supervision and administration of hand sanitiser if required 3 hand hygiene workshops for parents and DCC staff: 1. Hand-washing practices, hand sanitiser use, possible side effects and precautionary measures (HSG only) 2. RIs and their treatments	Workshop delivered by researchers Research assistant provided hand hygiene materials to DCCs and parents. Parents and staff	Workshops delivered face-to-face in groups to parents and staff. Workshop content emailed to attendees individually.	Classroom of DCCs (in Spain) for child interventions Workshops provided at DCCs.	8 months overall Initial 1-hour workshop 1 month before study commencement 3 further identical sessions/DCC provided again 1 month apart Fortnightly classrooms and DCC activities	Administration of hand sanitiser in the case of young children DCC staff could attend training at other DCC if unable to attend	Not described	Not described Reported that no monitoring of compliance through continuous observation of hand hygiene behaviours was done, but amount of hand sanitiser was measured	Families or DCC staff, or both, used 1660 L of hand sanitiser, estimated use by each child of dose 6 to 8 times/day.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					3. Fever Instructions to children, parents, and DCC staff on usual hand-washing practices and protocol [5] Classroom activities (stories and songs) about hand hygiene and infection transmission	supervised and administered sanitiser where indicated.	Individual face-to-face supervision of hand sanitiser use, as indicated	One-off installation of dispensers As-needed supervision of hand sanitiser use Dose of sanitiser: 1 to 2 mL/ disinfection	at own DCC.			
Biswas 2019	Hand sanitiser and respiratory hygiene education	Primary schools and their students and staff	Reduce community-wide influenza virus transmission by improving handwashing and respiratory hygiene and use of sanitiser in schoolchildren as contributors to community-wide virus transmission	Hand sanitiser (63% ethyl alcohol) in colourless, transparent 1.5-litre local plastic bottles (manufactured by a local pharmaceutical company and was available commercially in Bangladesh (price: USD 5.75/L)) Video clip on respiratory hygiene practices Behavioural change materials – 3 colour posters (see Appendix of paper) Curriculum materials for hygiene classes	Installation of hand sanitiser in wall dispensers in all classrooms and outside all toilets, refilled by field staff as needed Encouragement of use of sanitiser at 5 key times during the day[6] Hand and respiratory hygiene education provided.[7] Integration of hygiene messages into school's hygiene curriculum Delivery of video clip on respirato-	Selected teachers responsible for dissemination of intervention messages throughout were trained over 2 days	Hand sanitiser and education materials provided to schools. Education provided in classrooms in groups and	Primary schools (in Bangladesh) Sanitiser in each classroom and outside toilets Education in classroom	10 weeks Intervention messages conveyed in classrooms 3 times/ week.	Refills provided as needed.	Not described	Structured field observation by 2 field staff of 5 hours/ school observing handwashing and respiratory hygiene behaviours of children at 2 different locations in a classroom or outside Every other day, field staff measured the level	Handwashing observed opportunities: IG 604/921 (66%) vs CG 171/802 (21%) Hand sanitiser used in 91% of observed handwashing events in intervention schools. Average

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

								of hand sanitiser in the morning and in the afternoon to calculate amount of hand sanitiser used/day/school and enrolled children.	consumption of hand sanitiser/child/day: 4.3 mL Observation of proper cough or sneeze etiquette: IG: 33% vs CG: 2%

ry hygiene practice

Behaviour change materials distributed and placed around schools.

Use of sanitiser by classroom teachers after training

Training of selected teachers in consultation with head of school and management committee in key messages

Communication of key messages by the selected teachers to other teachers

in these messages, behaviour change communication, sanitiser use, and practices for preventing spread of respiratory secretions.

Classroom teachers conveyed intervention messages during regular face-to-face.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					hy- giene class- es. Field staff re- placed sup- plies as need- ed.								
Cor- rea 2012	Alco- hol-based hand rubs	Child- care cen- tres and their staff and chil- dren	Reduce in- cidence and trans- mission of infection in chil- dren by improved hand hy- giene where water is scarce includ- ing pro- vision of ABH and training in hand hygiene teach- ing tech- niques	Dispensers of alco- hol-based hand rubs with ethanol 62.0% (PURELL, GOJO Indus- tries, Akron, OH, USA) Workshop materials[8] Visual reminders on ABH techniques in bath- rooms and next to dis- pensers	ABH and training on proper use to staff and children Pre-trial ABH use workshop to teachers that followed rec- ommended HH teaching tech- niques and in- structed teach- ers to add ABH to routine HH and give preference to hand-wash- ing with soap and water if hands visibly soiled Continuous refill- ing of ABH ABH technique refresher work- shops (8/centre) Monitoring of safety, proper use	Local rep- re- sen- ta- tive of GO- JO In- dus- tries Inc. pro- vided dis- pensers and dis- penser in- stal- la- tions free of charge.	Face- to- face train- ing and pro- vi- sion of ma- teri- als; group train- ing	Child- care cen- tres in Colom- bia (cen- tres or com- mu- nity homes) ABH in cen- tres, class- rooms, and com- mon areas de- pend- ing on size	8 months overall 1 ABH dis- penser per centre with < 14 children; 1 per classroom in larger centres; 1 per class- room + 1 for com- mon areas in centres with > 28 children 1 work- shop pre- trial to staff Monthly 30-minute ABH tech- nique re-	Re- filled ABH as need- ed	Not de- scribed	Visual re- minders and monthly refresher training Monitor- ing of safe- ty, prop- er use of ABH, amount of ABH used Se- mi-struc- tured sur- vey on comple- tion of teachers' percep- tions about changes in HH prac- tices and use of	Teachers at 7 interven- tion cen- tres re- ported al- most complete substi- tution of HSW with ABH, and HSW de- creased from 3 times per day to 1 per day, and ABH rose to 6 per day. Teach- ers at re- maining 14 centres report- ed par- tial substi-

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					of ABH, amount of ABH used	Field-work team deliv-ered other com-po-nents.	Visu-al re-minders in bath-rooms and next to dis-pensers Work-shops and train-ing pre-sum-ably pro-vid-ed in cen-tres.	fresher training (8 per cen-tre) Biweekly monitor-ing			HSW and ABH. Measure-ment of consump-tion of re-sources and costs related to ABH use and HSW	tution of HSW with ABH. Controls report-ed HSW 3 times per day. Median number of ABH ap-plications per child rose from 3.5 to 4.5 in preschools and 3.5 to 5.5 in commun-ity centres.
Di-Vita 2011	House-hold hand-wash-ing pro-mo-tion	House-hold-ers with index pa-tient with ILI	Prevent influen-za trans-mission in house-holds in re-source-poor settings through provision of hand-washing facilities and use of them at critical	Hand-washing stations with soap	Provision of hand-washing stations Hand-washing motivation to wash at criti-cal times for pathogen trans-mission (e.g. af-ter coughing or sneezing)	Not specif-ical-ly de-scribed, pre-sum-ably the re-searchers	Face-to-face pro-vi-sion of fa-cili-ties in house-holds "Mo-tiva-tion" not	House-hold in Bangladesh	Over 2 in-fluenza seasons One-off provision of hand-washing facilities Frequen-cy of "mo-tivation" not de-scribed	Not de-scribed	Not de-scribed	Not de-scribed	Not de-scribed

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

			times for pathogen transmission				described						
Feldman 2016	2 active interventions A. Hand disinfection with chlorhexidine gluconate + hygiene education B. Hygiene education	Naval ships and their sailors	Reduced infection transmission and improved hand hygiene in sailors who are at increased risk due to closed environments, contact with shared surfaces, and poor HH culture	Septadine solution (Floris, Misgav, Israel) 70% alcohol and 0.5% CHG; inactive materials: purified water, glycerin, propylene glycol, and methylene blue	Installation of CHG disinfection devices on ships alongside regular soap and water Supply and replenishment of CHG (sent to ships regardless of replenishment demands) Hygiene instruction by a naval physician (to both intervention groups and study control group)	Provision of CHG presumably by study team and funds Hygiene instruction by naval physician	CHG sent to ships directly. Mode of hygiene instruction not described.	Navy fast missile boats and patrol boats of naval base in Israel Dispensers installed in key locations onboard (adjacent to heads (toilets), mess decks (dining rooms), common	4 months Unlimited supply of CHG replenished on demand for 4 to 5 months. Automatic amount dispensed: 3 mL	CHG replenished on demand.	Not described	Total amount of CHG dispensed was tallied.	Mean volume CHG: 8.2 mL per sailor per day (projected yearly cost USD 45 per sailor)

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

								areas).					
Gwaltney 1980	A. Virucidal hand preparation B. Placebo (no control)	Healthy young adults	Reduce infection rates by interrupting viral spread by hand or self-inoculation route	A. Virucidal hand preparation: aqueous iodine (2% iodine and 4% potassium iodide) B. Placebo: aqueous solution of food colours (Kroger; Kroger Co., Cincinnati, OH, USA) mixed to resemble the colour of iodine with 0.01% iodine and 0.02% potassium iodide to give an odour of iodine Masks	Immersion of each finger and thumb of both hands to proximal interphalangeal joint (interphalangeal joint of thumb) into designated preparation for 5 seconds then air-dried for 5 to 6 min Exposure of recipients to donors either immediately after treatment or after 2-hour delay by hand contact with donor stroking fingers for 10 s Masks worn by donors and recipients during procedure. Recipients placed in single isolation rooms after second exposure till end of experiment.	Researchers	Face-to-face and individually	US university	Exposure to donors on 3 consecutive days (days 2, 3, and 4) after initial exposure	Not described	Not described	Reported knowledge of hand preparation use as active, placebo, or don't know	Active (n = 24): 6 active 2 placebo 16 don't know Placebo (n = 22): 6 active 7 placebo 9 don't know
Hubner 2010	Alcoholic hand disin-	Employees (admin-	Reduce absenteeism and spread of	2 alcohol-based hand rubs (500 mL bottles) for desktop use to ensure minimal effort for use:	Provision of hand rub and instruction on use as needed at work only and in ac-	Presumably provid-	In person to staff	Administration of-	12 months overall Hand rub used as	Hand rub use especially	Not described	Self-reported compliance with hand hy-	Reported mean hand disinfection frequency

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	fection	istrative officers)	infection in administration employees with frequent customer contact and work with paper documents through improved hand hygiene	1. Amphisept E (Bode Chemie, Hamburg, Germany) ethanol (80% w/w) based formula with antibacterial, antifungal, and limited virus inactivating activity. 2. For participants with skin problems: Sterillium (Bode Chemie, Hamburg, Germany) 2-propanol (45% w/w), 1-propanol (30% w/w), and mecetronium etilsulfate (0.2% w/w), with a refatting effect and has activity against bacteria, fungi and enveloped viruses. Hand cream: Baktolan balm, water-in-oil emulsion with no non-antibacterial properties (Bode Chemie, Hamburg, Germany)	cordance with prevailing standard[7]: at least 5 times per day, especially after toileting, blowing nose, before eating, and after contact with ill colleagues, customers, and archive material	ed or arranged by study team	fices in Germany Hand rubs used at desk or work (not outside of work).	much needed for complete wetting of the hands (at least 3 mL or a palmful)[8] at least 5 times per day.	after toileting, blowing nose, before eating, and after contact with ill colleagues, customers, and archive material		giene measures	times per day: > 5: 19% 3 to 5: 59.8% 1 to 2: 20.5% < 1: 0.7%
Ladegaard 1999 (translated from Danish)	Hand hygiene programme	Daycare centres and their staff, children, and parents of children	Reduce risk of infection in child care through increased hygienic education of daycare professionals, motivation of daycare facilities for regular	Personnel guide on recommendations for: hygiene, ventilation, out-of-stay care, stricter hygienic regulations in cases with selected diseases Fairy tale and poster "The Princess Who Won't Wash Hands" Colouring in drawings "Wash hands" song and rhymes	Staff meeting in each DCC and training in microbiological cause of infection spread guided by National Board of Health and Hygiene Education of children in handwashing (about bacteria and why and when to wash hands)	Research team presumably provided training.	Face-to-face with training and activities by group with staff and children	On-site in DCCs	2-month intervention period 1-hour training of children	None described.	None described.	None described.	None reported.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

			hand hygiene, and informing parents about hand hygiene	T-shirt for children with the inscription "Clean hands - yes thank you" Diploma for children and book "The Princess Who Won't Wash Hands" to also be used by parents with their child Informational leaflet for parents in envelope	Practical handwashing classes with 4 to 5 children at a time Provision of t-shirt, book, and diploma to children Provision of leaflet for parents		Information sent home to parents via children.					
Little 2015	Web-based handwashing intervention	Householders (over 18) who were general practice patients	Prevent transmission of respiratory tract infections through improved hand hygiene to reduce spread via close contact (via droplets) and hand-to-face contact	Website-based programme: provided information about the importance of influenza and role of hand-washing; developed a plan to maximise intention formation for hand-washing; reinforced helpful attitudes and norms; addressed negative beliefs (URL provided for demonstration version no longer active; see www.lifeguideonline.org)	Provision of link to website for direct log in Automated emails prompted participants to use sessions and complete monthly questionnaires and maintain hand-washing.	Researchers delivered web-based programme and emails.	Online individually	Households in England	4 months overall 4 weekly web-based sessions Monthly email questions to maintain handwashing over 4 months	Tailored feedback provided within web programme	None described.	Emailed questions monthly to maintain handwashing	None reported.
Luby 2005	Handwashing promotion at neighbourhood	Neighbourhoods and their households	Improve handwashing and bathing with soap in settings where communicable dis-	Slide shows, videotapes, and pamphlets illustrating health problems from contaminated hands and specific hand-washing instructions Soaps: 90-gram white bars without brand	Hand-washing promotion to neighbourhoods: Neighbourhood meetings of 10 to 15 householders (mothers) from nearby homes	Research team in collaboration with Health	Face-to-face in small groups and individually	Neighbourhoods and homes in Karachi, Pakistan	1-year weekly household visits 30- to 45-minute neighbourhood meet-	Soap replaced regularly.	None described.	None described, though soap use measured.	Households' mean use of study soap per week: 3.3 bars Average use per

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	level with 2 interventions at household level A. Antibacterial soap B. Plain soap	eases are leading causes of childhood morbidity and mortality	names or symbols, same smell with identical generic white wrappers with serial numbers matched to households A. Households: 2 to 4 white bars of 90-gram antibacterial soap containing 1.2% triclocarban (Safeguard Bar Soap: Procter & Gamble Company (Cincinnati, OH, USA) B. Households: plain soap (no triclocarban) Soap packets	and monthly meetings for men Soap to households Fieldworker home visits: discussed importance of and correct hand-washing (wet hands, lather them completely with soap, rub them together for 45 seconds, and rinse off completely) technique and promote regular hand-washing habits[11] Encouragement of daily bathing with soap and water	Oriented Preventive Education (HOPE)[12] Fieldworkers were trained in interviewing and handwashing promotion.		ings 2 to 3 times/week first 2 months then weekly for months 2 to 9, then monthly Monthly men's meetings first 3 months Weekly household visits			resident per day: 4.4 g
Millar 2016 additional details from Ellis 2010	Skin and soft-tissue infection prevention intervention in addition to	Military trainees	Improve personal hygiene practices to prevent infection, especially acute respiratory infection in military trainees who are at increased risk	A. Enhanced standard: supplemental materials (a pocket card and posters in the barracks) B. CHG: CHG-based body wash (Hibiclens, Mölnlycke Heath Care, Norcross, GA, USA)	Provision of education and hygiene-based measures in addition to standard SSTI prevention brief upon entry: Enhanced standard: supplemental materials CHG: as for enhanced standard	Not described, presumably the researchers	Face-to-face and individually for body wash and pocket card Mode of	US military training base	One-off education on entry to training CHG: use of wash 1 per week for entire training period (14 weeks)	None described.	None described.	None described.	None described.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	SSTI brief on entry also provided to control A. Enhanced standard B. Chlorhexidine				group, plus a CHG-based body wash and instructions for use				ed-uca-tion not de-scribed.				
Mor-ton 2004	Healthy hands (alco-hol gel as hand-wash-ing ad-junct)	Ele-men-tary schools and their chil-dren and staff	Prevent infections in ele-mentary school-age children who are particu-larly vul-nerable through adjunct use of al-cohol gel and ed-ucation based on Health Be-lief Mod-el (HBM) (Kirscht 1974)	Alcohol gel and dis-pensers: AlcoSCRUB (60% eth-yl alcohol) supplied by Erie Scientific Company, Portsmouth, NH, USA ''Healthy Hands Rules'' protocol[13] (Figure 3 in paper) Healthy Hand Resource Manual for school nurse, available for parents Monthly newsletters to parents ''Healthy Hands'' refrig-erator magnet for fam-ilies (see Figure 2 in pa-per) Informational letter to local primary care	Healthy hands protocol in-troduced after "Germ unit" edu-cation in classes Daily reminders to children on public address system (in first week) then week-ly reminders Review of proto-col in each class-room after vaca-tion by school nurse 2 classroom vis-its from school nurse "Healthy Hands" magnet provid-	Gel pro-vid-ed by sup-pli-ers. Re-search team pro-vided ed-uca-tion-al as-pects. Class-room teach-ers re-spon-sible	Face-to-face train-ing in class-es and indi-vid-ual infor-ma-tion giv-ing and mon-itor-ing	Ele-men-tary schools in USA Wall-mount-ed near door en-trance of each class-room at age-ap-pro-pri-ate height	46 days 0.5 mL dis-pensed per appli-cation. Use of "special soap" ac-cording to "Healthy Hands Proto-col" (Fig-ure 3 in paper)	Rein-force-ment teach-ing pro-vided if gel us-age indi-cated that it was need-ed. Germ unit ed-uca-tion tai-lored for	1 stu-dent was con-cerned gel was mak-ing her sick, so school nurse pro-vided addi-tion-al class-room vis-it to allay con-cerns.	Usage of gel calcu-lated.	5 gel ap-plications per day 1 dis-penser lasted 1 month.

Physical interventions to interrupt or reduce the spread of respiratory viruses (Review)
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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

				providers, paediatricians, family practitioners, and advanced practice nurses "Germ Unit" curriculum and materials including Germ models and Glo Germ	ed to parents and guardians. "Hand Checks on Wednesdays" to identify adverse effects of gel	for encouraging use of gel and reinforcing protocol School nurse assisted in monitoring and hand checks for adverse effects.				each grade level.		
Nicholson 2014	Handwashing with soap	Households with 5-year-olds and their mothers	Targeted 5-year-old children and their mothers as change agents to reduce incidence of respiratory infections (and diarrhoeal disease) through	Initial supply of 5 bars of free soap (90-gram Lifebuoy bars) replenished on submission of empty wrappers. Environmental cue reminders (wall hangers, danglers) Rewards (e.g. stickers, coins, toy animals)	Provision of soap and social marketing programme (Sidibe 2009) (Lifebuoy branding) to educate, motivate, and reward children for HWWS at key times Weeks 1 to 17: hand-washing occasions, germ education, soap's	Dedicated team of "promoters" delivered education and home	Face-to-face in groups Individually by mother to child	"Classrooms" held in community buildings Home visits of households	41 weeks Weekly "classrooms" after school and home visits HWWS encouraged 5 key occasions: after defecation, be-	Mothers were asked to provide and share handwashing tips with other	Technical difficulties with "soap acceleration sensors" to measure	Registers for "classrooms" and home visits where 3-week gaps in attendance triggered supervisors to ask participants to resume	Soap consumption: IG vs CG: 235 g vs 45 g

Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	hand-washing using behaviour change principles (Claessen 2008), including social norms for child and mother (Perkins 2003), using fear of contamination and disgust (Curtis 2001), peer pressure (Sidibe 2003), morale boosting, and networking support	importance in germ removal Week 18 onward: encouragement of HWWS on 5 key occasions supported by environmental cues "Classrooms" for children Home visits for mothers Parents' evenings to boost morale, build networks, and run competition for compliance, assignment completion, and folder decoration Establishment of a "Good Mums" club for sharing HWWS tips Rewards provided by mothers. Children encouraged to advocate HWWS within families before meals. Establishment of social norms for child and mother with pledges in front of peers	visits. Mothers provided supplied rewards.	in Mumbai, India	fore each of 3 meals, and during bathing. Week 18 onward: handwashing on 5 occasions for 10 consecutive days 6 weekly parents' meetings	mothers, competitions held for mothers.	HWWS behaviours prevented successful use.	or be withdrawn Monitoring of soap resale on open market by use of unique identifiers on soap wrappers and twice weekly checks in local shops Collection of used soap wrappers as soap consumption measure

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

Pan-de-jpong 2010	3 active interventions (no control) different time-interval applications of alcohol hand gel A. Every 60 min B. Every 120 min C. Once before lunch	Preschool classes (students and teachers) and their parents	Targeted preschool children who can have high infection rates in ILI; have close interaction so at risk of airborne, droplet, and contact transmission; and are of increasingly younger ages through hand gel as a single strategy of convenient and effective disinfection	1 container of alcohol hand gel per classroom (active ingredients: ethyl alcohol, 70%; chlorhexidine gluconate,1%; Irgasan (triclosan), 0.3%) Cost of hand gel every 60 minutes was USD 6.39 per child per 12-week period Leaflet describing risk factors for ILI for each family	Teachers instructed to: assist each child with dispensing hand gel at required time interval, store hand gel properly, and refill gel as needed. Monitoring of hand gel use at specified times	Teachers supervised, stored, and refilled hand gel. Instructions to teachers presumably provided by researchers. Leaflets distributed through school. Monitoring of use by 2 research assistants	Face-to-face to schools, teachers and children Individual assistance to children with hand gel Leaflets given to each family.	Kindergarten school in Bangkok, Thailand	12 weeks overall 1 pump of gel per child per disinfection round at 1 of 3 time intervals of school day: A. every 60 min B. every 120 min C. once only before lunch, the school standard for hand hygiene	None described.	Students whose families declined to participate were not asked to use alcohol hand gel. These students remained in their classrooms and continued to follow the school standard for hand	2 research assistants monitored hand gel use every 60 or 120 minutes for the duration of study. Classroom teachers were required to co-sign after each disinfection round.	Reported that compliance was ensured for each intervention group Cost of hand gel every 60 minutes was USD 6.39 per child per 12-week period.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

											hy-giene.		
Priest 2014	Hand sanitiser provision (in addition to hand hygiene education session also provided to control group)	Primary schools and their students, teachers, and administrative staff	Reduce person-to-person community transmission of infectious disease by targeting improved and additional hand hygiene of school children through supervised hand sanitiser provision as an alternative to improving and maintaining bathroom facilities	‘‘No touch’’ dispensers (> 60% ethanol) for each classroom that dispensed dose when hands were placed under an infrared sensor Supply of top-up sanitiser as needed	Dispensers installed into each classroom. Teachers asked to ensure that the children used sanitiser at particular times and to oversee general use (McKenzie 2010). Weekly classroom visits to top-up of sanitiser and measure quantity used 30-minute in-class hand hygiene education session provided (also to control group) plus instruction in hand sanitiser use.	School liaison research assistants topped-up sanitiser. Teachers	Installation of dispensers to classrooms Supervision of children by teachers delivered face-to-face individually and as a class.	City schools in New Zealand	20 weeks (2 school terms) Sanitiser to be used by students at least after coughing/sneezing, blowing their nose, and as they leave for morning break and for lunch break. Approximately 0.45 mL of sanitiser dispensed per wash. Weekly top-up of sanitiser	Children were able to use the sanitiser at any time they wished as well as at key times (McKenzie 2010).	Change of sanitiser after week 10 to flavourless type of the same % ethanol in 41 of 396 classrooms (10%) (in 9 of 34 schools) due to children tasting it when eating, affecting use.	Weekly classroom visits by school liaison research assistants who recorded quantity of sanitiser used Total amount of sanitiser per classroom was measured. Compliance defined as dispensing a volume equivalent to at least 45 mL per child of hand sanitiser solution over the trial period.	100% dispensing 45 mL per child Average hand sanitiser dispensed/child for 34 schools: 94 mL Median classroom difference in sanitiser usage between first 10 weeks and second 10 weeks amongst classes that switched products was 220 mL.

Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

Ram 2015	Soap and intensive hand-washing promotion	Household compounds and its householders (adults and children) that had a householder with ILI	Reduce household transmission of ILI and influenza by promoting hand-washing in households with householder with ILI as other householders who are well are at highest risk of exposure due to crowded and poorly ventilated homes. Followed constructs of Social Cognitive Theory and the Health Belief Model (Glanz 2008) and behaviour change communication using social	Hand-washing station in central location of each compound using: large water container with a tap; plastic case for soap; bar of soap. Cue cards depicting critical times for hand-washing: after coughing or sneezing; after cleaning one's nose or child's nose, after defecation; after clearing a child who has defecated; before food preparation or serving; before eating.	Hand-washing station in each compound Didactic and interactive group-level education and skills training describing influenza symptoms, transmission, and prevention, promoting health and non-health benefits of hand-washing with soap and identification of barriers and proposed solutions to hand-washing with soap Daily surveillance including weighing of soap and replacing if ≥ 20 g and resupply of water in container if needed Posting of cue cards Asking householders to demonstrate hand-washing with soap technique	Intervention staff arranged provision of hand-washing station and presumably provided education. Intervention staff conducted daily surveillance and reinforcement visits.	All elements delivered face-to-face but at compound (facilities), group (education), and individual levels (reinforcement).	Household compounds in a rural area of Bangladesh consisting of several households with common courtyard, shared latrine, water source, and cooking facilities	Initiation of intervention within 18 hours of study enrolment, then daily visits until 10 days following resolution of index case patient's symptoms Day 1 set up of hand-washing station	Daily surveillance included observation of individual hand-washing reinforcement and modelling as needed.	None described.	Daily surveillance of facilities and reinforcement and modelling of hand-washing behaviours including observed hand-washing Cue cards in common areas of courtyard Presence or absence of soap during each of first 10 days of surveillance from 180 household compounds Patterns and amount of soap use measured.[14]	Soap present for at least 7 days in all compounds and on all 10 days in 133 compounds (74%). Soap and water together were present 7 or more of first 10 days in 99% of compounds, with water and soap observed together on all 10 days in 99 compounds (55%) Soap consumption per capita: median: 2.3 g maximal: 5 g (on Day 7)

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

			marketing concepts										
Roberts 2000	Education about infection control measures, handwashing, and aseptic nose wiping	Childcare centres and their staff and children	Reduce transmission of respiratory infections in childcare centres through improved infection control procedures	GloGerm (GloGerm, Moab, UT, USA) Newsletters to staff Songs and rhymes on hand-washing Plastic bags (sandwich bags available at supermarkets) to cover hand for nose wiping	Staff training in good health (developed by Kendrick 1994) and practical exercise of handwashing with GloGerm Fortnightly visits and newsletter to reinforce training and to communicate techniques Recommended hand-washing technique as per guidelines of the time[15] and after toileting, before eating, after changing diaper (staff and child), and after wiping nose unless barrier used Teaching of technique to children and wash hands for infants	Training and reinforcement activities provided by 1 of the researchers Teachers delivered training to children based on their training.	Face-to-face in groups for training and classes and individually as needed to children or staff	Childcare centres in Canberra, Australia	8 months overall 3-hour training in evening or 1-hour during lunch for new staff after study start Duration of handwashing: "count to 10" to wash and "count to 10" to rinse	Training for new staff provided as needed.	None described.	6-weekly compliance measured by recorded observation of recommended practice for 3 hours in morning in each centre, graded by quantiles of frequency of recommended handwashing by children.	Compliance was reported only in relation to analysis of outcomes. High compliance reported for nose wiping and child handwashing.
Sandora 2005	Healthy Hands Healthy Families	Families with an index child in out-of-	Reduce illness transmission in the home through multifactorial campaign centred on	Alcohol-based hand sanitiser: active ingredient: 62% ethyl alcohol (PURELL Instant Hand Sanitizer; GOJO Industries, Inc, Akron, OH, USA)	Supply of hand sanitiser and hand hygiene materials Biweekly telephone calls	Study investigator	Not stated whether materials mailed or	Homes in USA Sanitiser use in home	5 months overall Biweekly educational materials	None described.	None described.	Recorded amount of hand sanitiser used (as reported by the primary caregiver)	Median frequency of reported times of hand sanitiser use: 5.2 per day

Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

		home child-care	hand hygiene education and hand sanitiser	Hand hygiene educational materials at home (fact sheets, toys, games)	Biweekly educational materials		delivered in person	Sanitiser dispensed 1 mL each pump.				38% used > 2 ounces of hand sanitiser per fortnight = 4 to 5 uses per day
Savolainen-Kopra 2012 further details from Savolainen-Kopra 2010	STOPFLU Enhanced hygiene 2 active interventions IR1. Soap and water wash IR2. Alcohol-based hand rub	Office workers of office work units	Prevent transmission of respiratory infections in workplaces through enhanced hand hygiene with behavioural recommendations to reduce transmission by droplets during coughing or sneezing	IR1: Liquid hand soap ("Erisan Nonsid" by Farmos Inc., Turku, Finland) IR2: in addition: Alcohol-based hand rub, 80% ethanol ("LV" by Berner Inc., Helsinki, Finland) Bottles of hand hygiene product (free of charge) to be used at home and in the office (IR2). Written instructions on hygiene for further reference	Toilets equipped with liquid hand soap (all groups) or alcohol-based hand rub (IR2). Guidance on other ways to limit transmission of infections, e.g. frequent handwashing in office and at home, coughing, sneezing into disposable handkerchief or sleeve, avoiding handshaking Visits to work clusters and monitoring of materials availability Monthly electronic "information spot" about viral diseases for motivation to maintain hygiene habits Adherence activities	In collaboration with occupational health clinics servicing the corporation Specially trained research nurse provided guidance and visited worker	In-person provision of soap or hand rub Guidance and written instructions given personally. Face-to-face visits by study nurse	Office work units in corporations in Helsinki, Finland	15 to 16 months overall Monthly visits by nurse throughout	Nurses assisted with any practical problems with intervention as they arose. New employees received guidance on hand hygiene and habits.	None described.	Adherence assessed by an electronic self-report survey of transmission-limiting habits 3 times (more details in protocol). Use of soap (IR1) and alcohol-based disinfectant (IR2) for personal use was recorded. Study nurse checked availability of soap and alcohol rub.	Avoiding handshaking became more common and remained high in both groups. Recorded use for personal use smaller than predicted use based on hand hygiene instructions. Soap or disinfectant usage per participant: IR1: 6.1 IR2: 6.9

Physical interventions to interrupt or reduce the spread of respiratory viruses (Review)
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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					clusters throughout intervention period.								
Stebbins 2011	"WHACK the Flu" (hand sanitiser and training in hand and respiratory hygiene)	Elementary schools and their students and homeroom teachers	Targeted school-aged children as important sources of influenza transmission through improved cough etiquette and hand hygiene in schools including sanitiser as potential inexpensive non-pharmaceutical interventions	Hand sanitiser dispensers with 62% alcohol-based hand sanitiser from PURELL (GOJO Industries, Inc, Akron, OH, USA) automatically dispensing 1 dose	Delivery of grade-specific presentations on "WHACK the Flu" concepts and proper handwashing technique and sanitiser use: (W)ash or sanitise your hands often; (H)ome is where you stay when you are sick; (A)void touching your eyes, nose and mouth; (C)over your coughs and sneezes; and (K)eep your distance from sick people (provided URL no longer active) Desired frequency of hand wash use taught to student (see When and how much)	Project staff provided education. Homeroom teachers reinforced message and monitored proper use of sanitiser.	Face-to-face at schools, presumably as a group in classes	Elementary schools (Pittsburgh, USA) Dispensers installed in each classroom and all major common areas.	Whole intervention over 1 influenza season One-off installation of hand sanitiser dispensers One-off 45-minute education presentation and one-off refresher training at onset of influenza season Goal of use of 1 dose (0.6 mL) of sanitiser 4 times per day[16]	Encouraged to wash hands or use additional doses of hand sanitiser, or both, as needed	None reported.	Monthly teacher surveys of observed NPI-related behaviour in their students before, during, and after influenza season Measurement of hand sanitiser use at 2-week intervals throughout the intervention period	Teacher surveys of observed classroom NPI behaviour indicated successful adoption and maintenance of behaviours throughout influenza season. Average sanitiser use: 2.4 times per day

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					Installation of hand sanitiser dispensers Refresher training at each school Reinforcement of message and monitoring of sanitiser								
Talaat 2011	Intensive hand hygiene campaign	Schools and their students, teachers, and parents	Reduce or prevent transmission of influenza viruses amongst children through intensive hand hygiene intervention campaign	Soap supplied as needed. Grade-specific student booklets each including a set of 12 games and fun activities that promoted hand-washing Hand hygiene activities materials including: games (e.g. how to escape from the germs); puzzles; soap activities (e.g. soap drawing); song specially developed to promote hand hygiene Teachers' guidebook including detailed description of the students' activities and methods to encourage students to practice these activities. Posters with messages to wash hands with soap and water upon arriv-	Establishment of a hand hygiene team in each school Provision of hand hygiene activities: weekly exercises (e.g. games, aerobics, songs, experiments); school activities, (e.g. obligatory hand-washing under supervision, morning broadcast, parent meetings, students-parents information transfer); specific school initiatives: (e.g. competitions and awards, hand-washing committee, school trips to soap factory	Hand hygiene team (3 teachers from social studies, arts, and sports and the school nurse) ensured that all predesigned activities for the hand hy-	Delivered face-to-face in groups and individually	Elementary schools (grades 1 to 3) in Cairo, Egypt In school environment and classrooms Poster near sinks in classrooms and on playground	12 weeks overall Weekly hand hygiene campaign activities Weekly visits by social workers Twice-daily obligatory supervised hand-washing required by students for about 45 seconds, followed by proper rinsing and drying with a clean	Soap and hand-drying material provided by school administration if children did not bring their own as was the custom or families could	None described.	Observation by social workers of hand hygiene activities, availability of soap and drying material, and students' hand-washing during the day Schools created own activities to improve compliance.	About 93% of the students had soap and drying material available. All but 2 intervention schools "had a rigorous system of ensuring that school-children were washing their hands at least twice daily".

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	ing at school, before and after meals, after using the bathroom, and after coughing or sneezing. Informational flyers for parents reinforcing the messages delivered at the schools.	and water purification plant) More details in Table 1 of paper Song played regularly. Social worker weekly visits Distribution of flyers to parents	giene campaign were implemented. 6 independent social workers visited the schools.	cloth towel.	not afford it. Schools could create own motivating activities such as selecting a weekly hand hygiene champion, developing theatre plays, and launching school contests for drawings and songs.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

Temime 2018	Multifaceted hand hygiene programme (including alcohol-based hand rub)	Nursing home staff, residents, visitors, and outside care providers	Nursing homes and their residents, staff, and visitors and external providers have an increased risk of person-to-person transmission of pathogens, and HH is a simple and cost-effective tool for infection control; however, compliance with HH is poor in nursing homes.	Dispensers and pocket-sized containers of hand rub solution Posters promoting hand hygiene Developed local HH guidelines eLearning module on infection control and HH training with online quizzes requiring sufficient performance	Facilitated access to hand rub solution Campaign to promote HH with posters and event organisation Formation of local work groups in each NH Development of local HH guidelines Staff education using eLearning Monitoring of quantity of hand rub solution used	Same nurse provided HH training for all NHs. Provision of hand rub by NH Local work group developed guideline. eLearning module and posters presumably developed by research team.	Provision of materials face-to-face Education and quizzes via eLearning	Nursing homes in France	1 year overall One-off provision of hand rub One-off eLearning repeated if unsatisfactory performance.	If staff did not score sufficiently on online quiz, they were invited to repeat the eLearning.	None described.	Estimated mean amount of hand rub solution used per resident per day assessed as proxy for HH frequency, based on quantity of hand rub solution bought by NH (which was routinely monitored in all the NHs).	Hand rub solution used: baseline quantity of consumed hand rub solution was 4.5 mL per resident per day. Over the 1 year, mean quantity consumed was significantly higher in intervention NH (7.9 mL per resident per day) than control (5.7 per resident per day).

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

Turner 2004a Clinical trial 1	3 active interventions (no control) Product: A. Ethanol B. Salicylic acid C. Salicylic acid with pyroglutamic acid	Healthy volunteers	Assess the residual virucidal activity of organic acids used in currently available over-the-counter skin products for the prevention of experimental rhinovirus colds	1.7 mL of hand products: A. 62% ethanol, 1% ammonium lauryl sulphate, and 1% Klucel) B. 3.5% salicylic acid, or vehicle containing C. 1% salicylic acid and 3.5% pyroglutamic acid	Disinfection of hands then application of test product then allowed to dry. 15 min later, fingertips of each hand contaminated with 155 $TCID_{50}$ of rhinovirus type 39 in a volume of 100 µL. Hands air-dried for 10 min. Intentional attempted inoculation with virus by contact with fingers, conjunctiva, and nasal mucosa with fingers of right hand. Left hand eluted in 2 mL of virus-collecting broth.	Researchers	Face-to-face individually	Communities in Manitoba, Canada	1.7 mL of product applied. See What for timing	Not described	Not described	Not described	Not described
Turner 2004b Clinical trial 2	2 active interventions (no control) Skin cleaner wipe	Healthy volunteers	Assess the residual virucidal activity of organic acids used in currently available over-the-counter skin products for	Skin cleanser wipe containing: A. 4% pyroglutamic acid formulated with 0.1% benzalkonium chloride B. 62% ethanol	Application of product to hands with towelette then allowed to dry. 15 min later, fingertips of each hand contaminated with 106 $TCID_{50}$	Researchers	Face-to-face individually	Communities in Manitoba, Canada	Dose not reported; see What for timing Additional group challenged 1 h after application; final group chal-	Not described	Not described	Not described	Not described

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	product: A. Pyroglutamic acid B. Ethanol	the prevention of experimental rhinovirus colds		of rhinovirus type 39 in a volume of 100 µL. Intentional attempted inoculation with virus by contact with fingers, conjunctiva, and nasal mucosa with fingers of right hand. Left hand eluted in 2 mL of virus-collecting broth.				lenged 3 h after application (remained at study site and not allowed to use or wash hands between).				
Turner 2012	Antiviral hand lotion	Healthy adults	Reduce rhinovirus infection and illness through hand disinfection with ethanol and organic acid sanitiser	Lotion containing 62% ethanol, 2% citric acid, and 2% malic acid Daily diary	Provision of lotion and instructions for use Meetings with participants to check compliance	Staff of study site presumably supplied lotion. Study site staff met with participants.	Face-to-face and presumably individually, but not specified	Study site at university community in the USA	9 weeks Every 3 hours whilst awake and after handwashing for 9 weeks Compliance meetings twice weekly for first 5 weeks then weekly meetings with participants	None reported.	None reported.	Self-reported daily diary of time of each product application Twice weekly for 5 weeks then weekly meetings with participants to reinforce compliance with treatment	"All subjects … applied at least 90% of the expected amount of hand treatment" (p.1424)

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

Yeung 2011	Multifaceted hand hygiene programme (including alcohol-based hand rub)	Long-term care facilities and their healthcare workers	Promote use of alcohol-based hand rub by staff in LTCFs as an effective, timely, and low-irritant method of hand hygiene in a high-risk environment	Free supply of pocket-sized containers of alcohol-based antiseptic hand rub (either WHO formulation I (80% ethanol) or II (80% propanol) carried by each HCW (supplier: Vickmans Laboratories) Replacement hand rub as required Hand hygiene seminar content Reminder materials (3 to 5 posters and specially designed ballpoint pens)	Provision of materials Provision of hand hygiene seminars to HCWs covering: indications, proper method, and importance of antiseptic hand rubbing and washing according to WHO 2006a) guidelines Provision of feedback session Direct, unobtrusive observation of hand hygiene adherence Training of observation staff	Study team delivered the materials, seminars, and observer training. Administrative staff of LTCF provided replacement hand rub and communicated with HCWs. 6 registered nurses	Delivered face-to-face and individually for hand rub and pens; not described if education was individually or by group, but seminar implies as a group	LTCFs in Hong Kong Posters posted in common areas. Adherence observations occurred in common rooms and resident rooms but not bathing or toilet areas.	7 months overall Initial 2-week intervention period, then 7 months of hand rub provision and reminders 3 identical seminars at start of intervention; each staff member to attend once Feedback session 3 months after start of intervention 2-hour training of observers Adherence observations either 9 am to 12 pm or 3 pm to 6 pm, 1 LTCF at a time	Replacement of hand rub as required	As adherence dropped off in the middle months, the feedback session was delivered.	Direct observation of HCW adherence to handwashing and antiseptic hand rubbing (recorded separately and anonymously) during bedside procedures or physical contact with residents 3300 hand hygiene opportunities during 248.5 hours of observation on 92 days	90% attendance of seminars Hand rubbing with gel increased significantly from 1.5% to 15.9%. Handwashing decreased significantly from 24.3% to 17.4%. Control: 30% Overall handwashing adherence increased from 25.8% to 33.3%.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

						conducted direct observation of adherence after 2-hour training (100% inter-rater reliability).							
Zomer 2015	Hand hygiene products and training	Day-care centres and their caregivers (staff)	Reduce infections in children attending DCCs through improved access to HH materials (Zomer 2013a) and compliance of their DCC caregivers to hand hygiene guidelines based on	HH products: dispensers for paper towels, soap, alcohol-based hand sanitiser, and hand cream, with refills for 6 months Reminder posters and stickers for children and DCC caregivers Training materials including booklet	Provision of free HH products sponsored by SCA Hygiene Products, Sweden. Provision of posters and stickers for children and staff Provision of training about RIVM 2011 for mandatory HH[18] Distribution of training booklet	Study team arranged supply of HH products and presumably provided training.	Products provided to DCCs in person for staff use. Mode of training not specified.	DCCs in regions of the Netherlands	6 months overall Initial one-off supply of products 3 training sessions with 1-month interval 2 team training sessions	Replacement hand hygiene provided as required.	None described.	6-month follow-up observation of whether intervention dispensers and posters/ stickers in use Survey of DCC caregivers HH guidelines compliance observed	2 DCCs did not use any HH products. Sanitiser products used in at least 1 of 2 groups in 94%, 89%, 86%, and 45% of intervention DCCs. Posters used in 86%, stickers in 74%.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

				socio-cognitive and environmental determinants of caregivers' HH behaviour[17] (Zomer 2013b)	Team training sessions aimed at goal-setting and formulating HH improvement activities (Erasmus 2011; Huis 2013)						at 1, 3, and 6 months' follow-up: no. of HH actions/no. of opportunities	DCC survey results: 79% attended at least 1 training session; 77% received HH guidelines booklet. HH compliance at 6 months: IG: 59% vs CG: 44% (Zomer TP, et al, unpublished data) All intervention DCCs received guidelines training; all but 2 received at least 1 team training.
Hang hygiene and masks													
Aelami 2015	Hygienic education and	Religious pilgrims	Prevent influenza-like illness by reduced infection	Hygiene package of: alcohol-based hand rub (gel or spray) surgical masks	Not clearly described, but it appears that packages may have been distributed by trained physi-	Not specifically described	Not described, but it appears	Not described if before de-	One-off during Hajj season	Not described	Not described	Not described	None described

Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	package		transmission through personal hygiene measures	soap paper handkerchiefs user instructions	cians before departure to or on site of country of pilgrimage		that packages were distributed face-to-face and individually	parture (from Iran) or on site (in Saudi Arabia)					
Aiello 2010	2 active interventions: A. Face mask (FM) B. Face mask and hand hygiene (FM + HH)	Students living in university residences	Reduce the incidence of and mitigate ILI by use of non-pharmaceutical interventions of personal protection measures	7 face masks (standard medical procedure masks with ear loops TECNOL procedure masks; Kimberly-Clark) 7 resealable plastic bags for mask storage when not in use (e.g. eating) and for disposal Alcohol-based hand sanitiser (62% ethyl alcohol in a gel base, portable 2-ounce squeeze bottle, 8-ounce pump) Hand hygiene education (proper hand hygiene practices and cough etiquette) via emailed video, study website, written materials detailing appropriate hand sanitiser and mask use	Weekly supply of masks through student mailboxes Provision of basic hand hygiene education through an email video link, the study website, and written materials; instruction to wear mask as much as possible; education in correct mask use, change of masks daily, use of provided resealable bags for mask storage and disposal Provision of replacement supplies which students signed for upon receipt	Not described, except education provided via study website (URL not provided) "Trained staff" for compliance monitoring	Education via email and study website; provision of masks and sanitiser in person to residences	University residence halls in the USA	One-off education, 6 weeks (excluding spring break) of face mask and/or hand hygiene measures which commenced at "the beginning of the influenza season just after identification of the first case of influenza on campus" (p.496). Replacement supplies pro-	Mask wearing during sleep optional and encouraged outside of residence.	University spring break occurred during weeks 4 and 5 of the study, with most students leaving campus and travelling; they were not	Weekly web-based student survey included: self-reported average number of times hands washed/day and average duration of hand-washing to obtain composite "optimal hand-washing" score (at least 20 s ≥ 5/day); average no. of mask hours/	Average mask use hours/day: FM + HH 2.99 vs FM 3.92 Average hand-washing times/day: FM + HH 6.11 vs FM 8.18 vs control group 8.75 Daily washing seconds/day: FM + HH 20.65 vs FM 23.15 vs control 22.35

Physical interventions to interrupt or reduce the spread of respiratory viruses (Review)
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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

						Study-affiliated residence hall staff provided replacement supplies.			vided as needed.		re-quired to continue protective measures at that time.	day/week; average hand sanitiser use/day/week and amount used. Trained staff in residence hall common areas observed silently and anonymously improper mask use, instances of hand sanitiser use.	Hand sanitiser use times/day: FM + HH: 5.2 vs FM 2.31 vs control 2.02 No. of proper mask wearing participants/hour of observation: FM + HH 2.26 vs FM 1.94
Aiello 2012	2 interventions: A. Face mask (FM) B. Face mask and hand sanitiser (FM + HH)	Students living in university residences	Prevent ILI and laboratory-confirmed influenza by use of non-pharmaceutical interventions of personal protection measures (e.g. face masks and hand hygiene)	Packets of 7 standard medical procedure masks with ear loops (TECNOL procedure masks, Kimberly-Clark, Roswell, GA, USA) and plastic bags for storage during interruptions in mask use (e.g. whilst eating, sleeping) and for daily disposal Hand sanitiser (2-ounce squeeze bottle, 8-ounce pump bottle with 62% ethyl alcohol in a gel base)	Intervention materials and educational video provided. Supply of masks and instructions on wearing Provision of replacement masks or sanitisers as needed on site	Trained study staff available at tables in each residence hall for surplus masks and sanitiser	Hygiene packs delivered to student mailboxes; face-to-face supply also available	University residence halls in the USA	One-off educational video at start Weekly supply of hygiene packs Masks to be worn at least 6 hours/day Study staff available onsite with re-	Students encouraged but not obliged to wear masks outside of residence hall.	1-week university spring break during the study when majority of students left	Weekly student survey including compliance (e.g. masks hours/day, frequency and amount of sanitiser use, number of hand washes/day, duration of hand-	Self-reported mask wearing: no significant difference Sanitiser use: significantly more in FM + HH than FM or control groups

Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

				Replacement face masks and hand sanitiser Educational video: proper hand hygiene and use of standard medical procedure face masks				and for observing compliance		placement supplies as needed for duration of intervention (6 weeks, excluding spring break)		campus	washing (seconds) Observed compliance completed by trained study staff who daily and anonymously observed mask wearing in public areas of residences.	More results in S1 of paper. Staff observed an average of 0.0007 participants properly wearing a mask for each hour of observation.
Cowling 2009	2 active interventions in addition to control of lifestyle education: A. Enhanced hand hygiene (HH)	Householders with index patient with influenza	Reduce transmission of influenza in households through personal protective measures	A. and B. Liquid soap for each kitchen and bathroom: 221 mL Ivory liquid hand soap (Proctor & Gamble, Cincinnati, OH, USA) Alcohol hand rub in individual small bottles (100 mL) WHO recommended formulation I, 80% ethanol, 1.45% glycerol, and 0.125% hydrogen peroxide (Vickmans Laboratories, Hong Kong, China) B. Adults: box of 50 surgical face masks (Tecnol–The Lite One (Kimberly-Clark, Roswell, GA, USA) to each household member or C. Children 3	Home visits Provision of soap, hand rub, and masks as applicable and when to use them HH: education about efficacy of hand hygiene Demonstration of proper handwashing and antisepsis techniques + FM: education about efficacy of surgical face masks in reducing disease spread to household contacts if	Trained study nurse provided interventions.	Face-to-face to householders	Households in Hong Kong	Initial home visit scheduled within 2 days (ideally 12 h) of index case identification. Further home visits day 3 and 6, 7-day follow-up HH: use of liquid soap after every washroom visit, sneezing or	Not described	Not described	Monitoring of adherence during home visits Evaluation of adherence on final visit by interview or self-reported practices and counting of amount of soap and rub left in bottles and remaining masks for FM group	Most initial visits completed within 12 h. Intervention groups "reported higher adherence … than the control group. Self-reported data were consistent with measurements of amount of soap,

Physical interventions to interrupt or reduce the spread of respiratory viruses (Review)
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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	B. Face masks and enhanced hygiene (FM + HH)			to 7: box of 75 paediatric masks	all parties wear masks Demonstration of proper wearing and hygienic disposal All groups: provision of education about the importance of a healthy diet and lifestyle, both in terms of illness prevention (for household contacts) and symptom alleviation (for the index case)				coughing, when their hands were soiled. Use rub when first returning home and immediately after touching any potentially contaminated surfaces FM: masks worn as often as possible at home (except eating or sleeping) and when the index patient was with the household members outside of the household				alcohol hand rub, and face masks used" (p.443) (see Table 6 in paper). "Adherence to the hand hygiene intervention was slightly higher in the hand hygiene group than the face mask plus hand hygiene group." Median masks used: Index: 9 Contact: 4 More details in paper and Appendices
Larson 2010	2 active interventions	Hispanic households	Reduce incidence and sec-	A. and B.	Provision of materials and instructions for	4 trained bilin-	Face-to-face	Households in	19-month follow-up	Change masks be-	None described.	RA home visits for adherence	Sanitiser use (mean

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	ventions in addition to control of URI education: A. Alcohol-based hand sanitiser (HS) B. Face masks and hand sanitiser (FM + HS)	holders with at least 1 preschool or elementary school child	ondary transmission of URIs and influenza through non-pharmaceutical household level interventions	2-month supply of hand sanitiser in 8-, 4-, and 1-ounce containers: PURELL (Johnson & Johnson, Morris Plains, NJ, USA) B. 2-month supply of masks: Procedure Face Masks for adults and children (Kimberly-Clark, Roswell, GA, USA) Replacement supplies at least once every 2 months Disposable thermometers Educational materials about URI prevention, treatment, and vaccination (written in Spanish or English language)	when to use including demonstration of use and observation of return demonstration by householder A. Mask worn when householder had: "temperature of ≥37.8°C and cough and/or sore throat in the absence of a known cause other than influenza" (CDC definition of influenza-like illness at the time). Home visits to reinforce adherence, replenish supplies and record use, answer questions B. Telephone calls to reinforce mask use All groups received URI educational materials.	gual research assistants (RAs) with minimum baccalaureate degree and experience in community-based research; procedures were practised with each other until demonstrated proficiency	to householders	New York, USA	Initial home visit, then at least every 2 months Sanitiser for use at home, work, and school B. Telephone calls days 1, 3, 6 Masks worn for 7 days when within 3 feet of person with ILL or no symptoms.	tween interactions with person with ILL Householders' questions and misconceptions addressed on home visits.	with random accompaniment by project manager, who also made random calls to householders Telephone calls to reinforce mask use Used bottles or face masks, or both, monitored for usage.	ounces/month) HH: 12.1 FM + HH: 11.6 Mask compliance was "poor": 22/44 (50%) used within 48 hours of onset. Mask users reported mean mask use of 2.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

Simmerman 2011	2 active interventions: A. Handwashing education and handwashing kit (HW) B. Handwashing education, handwashing kit, and face masks (HW + FM)	Households with a febrile, influenza-positive child	Decrease influenza virus transmission in household with a febrile influenza-positive child through promoted use of handwashing or handwashing with face mask use	A. and B. Hand-washing kit per household including graduated dispenser with standard unscented liquid hand soap (Teepol brand. Active ingredients: linear alkyl benzene sulfonate, potassium salt, and sodium lauryl ether sulphate) Replacement soap as needed Written materials from education including pamphlets and posters attached near sinks in household. B. Box of 50 standard paper surgical face masks and 20 paediatric face masks (Med-con company, Thailand #14IN-20AMB-30IN)	A. and B. Provision of intensive handwashing education on initial home visit to household members with 5 approaches: discussion, individual hand-washing training, self-monitoring diary, provision of soap, and provision of written materials (Kaewchana 2012) Individual handwashing training ("why to wash", "when to wash", and "how to wash" in 7 handwashing steps described in Thailand Ministry of Public Health guidelines) B. Provision of education of benefits of and appropriate face mask wearing Soap replaced as needed. More details (Kaewchana 2012)	Study nurse conducted home visits, provided education and monitoring activities.	Education provided face-to-face as a group to household member and individually for handwashing training.	In homes (in Bangkok, Thailand)	One-off provision of kits at initial home visit conducted within 24 hours of enrolment Subsequent home visits on days 3, 7, and 21 90-day supply of handwashing supplies 30-minute education provided at initial home visit	B. No face masks whilst eating or sleeping as impractical and could hinder breathing in ill child Impromptu education and training provided by nurses as questions arose.	None described.	Self-monitoring diary recording handwashing frequency > 20 s and face mask use for that group Reinforcement of messages by nurses on subsequent home visits Amount of household liquid soap and number of face masks used	Reported average handwashing episodes/day: HW: 4.7 HW + FM: 4.9 Parents had highest frequency (5.7), others (4.8), siblings (4.3), index cases (4.1). Average soap used/week: HW: 54 mL/person HW + FM: 58.1 mL/person B. Mask use: 12/person/week Mask wearing median min-

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

													utes/day: 211 Parents 153, other relations 59, index patients 35, siblings 17
Suess 2012	2 active interventions in addition to written information: A. Mask/hygiene (MH) B. Mask (M)	Households with an influenza-positive index case in the absence of further respiratory illness within the preceding 14 days	Prevent influenza transmission in households through easily applicable and accessible non-pharmaceutical interventions such as face masks or hand hygiene measures	A. Alcohol-based hand rub (Sterilium, Bode Chemie, Germany) A. and B. Surgical face masks in 2 different sizes: children < 14 years (Child's Face Mask, Kimberly-Clark, USA) and adults (Aérokyn Masques, LCH Medical Products, France) Written information provided on correct use of intervention and on infection prevention (Seuss 2011) (Tips and information on the new flu A/H1N1) (URL provided is no longer active) Digital tympanic thermometer General written information on infection prevention	A. Provision of hand rub and masks A. and B. Provision of masks only Provision of thermometer and how to use it Mask fit assessed (at first household visit) Information provided by telephone and written instructions at home visit on proper use of interventions and recommendations to sleep in a different room than the index patient, not to take meals with the index patient, etc. (Seuss 2011)	Study personnel arranged provision of materials, rang the participants, visited the homes, demonstrated and assessed fit of masks.	Provision of materials in person to households Initial telephone delivery of information Face-to-face home visits	Households in Berlin, Germany	Over 2 consecutive flu seasons Day 1 households received all necessary material instructions. Household visits no later than 2 days after symptom onset of the index case, then days 2, 3, 4, 6, 8 (5 times) or on days 3, 4, 6, 8 (4 times) depending on the day	Adult masks worn if masks for under 14-year-olds did not fit properly. If other household members developed fever (> 38.0 °C),	In the season 2010/11 participants also recorded number of masks used per day.	Self-reported daily adherence with face masks, i.e. if they wore masks "always", "mostly", "sometimes", or "never" as instructed. Participants of the MH households additionally noted the number of hand disinfections per day. Exit questionnaire about	Face mask use (median/individual): MH: 12.6 M: 12.9 Daily adherence was good, reaching a plateau of over 50% in nearly all groups from the third day on. MH hand rub use (median): 87 mL (Seuss 2011) MH mean frequency of daily

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	In-person demonstration of interventions at first home visit All participating households received general written information on infection prevention.		of recruitment Hand rub use: after direct contact with the index patient (or other symptomatic household members), after at-risk activities or contact[19] Mask use: at all times when index patient and/or any other household member with respiratory symptoms were together in 1 room Regular change of face masks, not worn during the night or	cough, or sore throat, they were asked to adopt the same preventive behaviour as the index patient.	(preventive) behaviour during the past 8 days, general attitudes towards NPI, the actual amount of used intervention materials, and, if applicable, problems with wearing face masks. Used intervention material per household member was calculated by dividing the amount used per household by the number of household members. See paper and Suess 2011 for	hand disinfection: 7.6 (SD 6.4) times per day See paper and Suess 2011 for more results.	

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

									outside the household			more details.	
Hand hygiene and surface/object disinfection													
Ban 2015	Hand hygiene and surface cleaning or disinfection	Kindergartens and the families of their students	Reduce transmission of infection in young children from contaminated surfaces or hands through hand hygiene and surface cleaning or disinfection	Antibacterial products for hand hygiene and surface cleaning or disinfection: liquid antimicrobial soap for hand-washing (0.2% to 0.3% parachlorometaxylenol). Instant hand sanitiser for hand disinfecting (72% to 75% ethanol), antiseptic germicide (4.5% to 5.5% parachlorometaxylenol, diluting before use). Bleach (4.5% to 5.0% sodium hypochlorite, diluting before use) for surface disinfecting. Produced by Whealthfields Lohmann (Guangzhou) Company Ltd.	Provision of products to kindergartens and families Instruction of parents or guardians and teachers in hand hygiene techniques and use of antibacterial products Daily cleaning of kindergartens with products At least twice/week cleaning of homes and weekly cleaning or disinfecting of items such as children's toys, house furnishings, frequently touched objects (doorknobs, tables or desks), kitchen surfaces (utensils, cutlery, countertops, chopping boards, sinks, floors, etc.), bathroom surfaces (toilet, sink, floor, etc.)	Research team provided products and instructions and monitoring.	Materials provided to kindergartens and families in person and presumably instructions in person to families and staff.	In kindergartens (hard surfaces) and families' homes (Xiantao, China)	1 year overall Daily handwashing with soap before eating, after using bathroom, nose blowing, and outdoor activities Hand sanitiser carried daily. Kindergarten cleaning daily Home cleaning at least twice/week	Families and teachers could contact study management at any time as needed. Exchange of empty bottles for new ones at any time	Not described	Close contact with teachers and families for monitoring, e.g. unscheduled parents' meetings, quarterly home visits, phone interviews, and monthly cell phone messages Monthly survey of consumption of products by volume, total usage, person usage	Consumption of products by person (mL/person/day). Liquid soap: 7.7 Sanitiser: 1.4 Bleach: 25.0 Antiseptic-germicide: 12.5

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					Monitoring activities								
Carabin 1999	Hygiene programme	Day-care centres and their staff and children	Reduce infections in at-risk children (under 3 years old) in DCCs with inexpensive, easily implementable and practical interventions	Hygiene materials and documents, e.g. colouring books, hand-washing posters, hygiene videotapes Materials for training Reimbursement of equivalent of 1 full-time educator's salary Bleach (diluted 1:10) for toy and play area cleaning	Provision of comprehensive hygiene training session to entire DCC staff, especially the educators of participating classrooms Training in recommendations for hygiene practices: i. toy cleaning ii. hand-washing technique and schedule iii. use of creative reminder cues for hand-washing iv. open window for daily period v. sandbox and play area cleaning Payment of salary of educator for the day to encourage participation DCC meetings to discuss training session with all staff	Training appears to have been provided by study team.	Appears staff trained as a group, i.e. "entire DCC staff"	Day-care centres in Canada Location of training not described, except may have been off-site from DCCs since 1 DCC did not "send" staff to training.	15-month trial One-off 1-day training Toy cleaning at least every 2 days Hand-washing at least after DCC arrival, after outside play, after bathroom, before lunch Open windows at least 30 min/day Biweekly cleaning of sandbox/play area	Teachers to use creative reminder cues for hand-washing with children	Not described	Follow-up telephone questionnaire for DCC directors about following training recommendations	Use of materials: colouring book: 22/24 poster: 23/24 videotapes: 18/24 staff meetings: 19/24 Increased frequency of toy cleaning: 6/24 Use of rake and shovel for sandpit: 17/24 Frequency of cleaning sandbox: 14/24

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

Kotch 1994	Hygiene	Caregivers at child day-care centres (CDCCs)	Develop feasible, multicomponent hygienic intervention to reduce infections in children at CDCCs who are at increased risk	Hygiene curriculum for caregivers Availability of soap, running water, and disposable towels Waterless disinfectant scrub (Cal Stat) used only if alternative was not washing at all. Handouts posted in CDCC.	Delivery of hygiene curriculum to caregivers through initial training session which required demonstration of participants' hand-washing and diapering skills Local procedures: Hand-washing of children and staff Disinfection of toilet and diapering areas Physical separation of diapering areas from food preparation and serving areas Hygienic diaper disposal Daily washing and disinfection of toys, sinks, kitchen and bathroom floors Daily laundering of blankets, sheets, dress-up clothes Hygienic preparation, serving, and clean up of food	Research team delivered training. Scrub donated by Calgon Vetal Laboratories.	Face-to-face training and follow-up group and individually	Classrooms of child day-care centres in the USA	8 months overall 3-hour initial training session Cleaning schedules as described in column What (procedures) Onsite follow-up training 1 week and 5 weeks later	Follow-up sessions addressed questions and local adaptations to procedures. As required induction training	During intervention, research team encouraged directors to address physical barrier to hygiene practice, such as distance between sink and diapering areas and sink access in rooms.	Follow-up sessions reinforced training. Meeting with directors 5 weekly unobtrusive recorded observation by training staff	Rate of compliance to barrier modification was better in younger centres, which were more likely to have written guidelines.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					Separate training of food handlers As-required induction training for new staff Onsite follow-up training reinforcing adaptations, demonstrations and discussion of hygiene techniques, responding to questions, and review of handouts Monthly meeting with centre directors to encourage leadership and support								
McConeghy 2017	Multifaceted handwashing and surface-cleaning intervention	Nursing homes and their staff	Reduce exposure to pathogens and person-person transmission in high-risk facility of close environment and potentially contaminated surfaces through multifaceted inter-	Education and launch materials Online module for certified nursing assistants about: infection prevention, product, and monitoring "Essential bundle" of hygiene products supplied at no cost: - hand sanitiser gel and foam - antiviral facial tissues - disinfecting spray - hand and face wipes Plus additional:	Pre-intervention: NH administrators required to: - identify a "Heroes In Prevention" champion and team - allow all staff participation in education - iPad use for staff in each floor or community - ask staff to incorporate intervention into workflow	Study personnel equipped staff with knowledge and tools and support. NH staff (e.g. champion, hy-	Face-to-face interaction with staff for planning and some aspects and delivery of products	Nursing homes in the USA On-site and at unit/team levels On-line training	6 months overall: training period: 3 months 1-hour launch event 1 or 2 hygiene monitors/site 1 champion/site 1-hour online module for selected	Sites could use existing comparable products from another vendor and fill in any gaps with study	2 sites retrained due to low training participation rate.	Cloud-based audit and feedback system via secure login to web browsers on NHs' existing computers or via iPads included weekly product consumption to get measure:	Online training participation rates: > 90% for 3/5 sites, 13% and 23% for 2/5 Administrators demonstrated high fidelity in reporting measures of

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	vention equipping staff to protect residents from infection within the "culture" of care	- 4 skin cream and wipe products iPads for compliance audits Newsletters for support during intervention	Delivery of 3 components: - education - cleaning products - compliance audit and feedback Education: Launch event for all staff to publicise programme and explain roles Intensive training of "hygiene monitors" for data collection and compliance audit and feedback tool Training of site champion Training of select group of certified nursing assistants (online module) Audit and feedback activities Ongoing support during intervention: - newsletter with best practices - teleconferences with each NH	giene monitors, nursing assistants) delivered aspects of interventions after specific training.	Some aspects delivered online (e.g. nursing modules, compliance auditing)	nursing assistants iPads for each community or floor Weekly teleconferences initially decreased in frequency over time. Weekly measurement of product consumption	products. New staff provided with education, as needed and came onboard. Retraining of sites with low training participation rates	weekly count of product units consumed x no. of hand hygiene occasions	handwashing (> 80% of time). Handwashing rates in Figure 1B in paper reported as "relatively constant" and "not ideal in the first few months", but improved significantly over time.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					- "onboarding" education of new staff								
Sandora 2008	Multifactorial intervention, including alcohol-based hand sanitiser and surface disinfection	Elementary school and its students	Reduce transmission of infections in schoolchildren through improved hand hygiene and environmental disinfection	1 container of disinfecting wipes (Clorox Disinfecting Wipes (The Clorox Company, Oakland, CA, USA); active ingredient, 0.29% quaternary ammonium chloride compound) Pre-labeled 1.7-ounce containers of alcohol-based hand sanitiser (AeroFirst non-aerosol alcohol-based foaming hand sanitiser (DEB SBS Inc, Stanley, NC, USA, for The Clorox Company); active ingredient, 70% ethyl alcohol) Receptacle in classrooms for empty containers	Sanitiser and wipes provided to classroom/teacher with instructions for use. Teachers disinfected desks once daily. Hand sanitiser to be used: before and after lunch, after use of the restroom (on return to the classroom; hand hygiene with soap and water occurred in the restroom, because sanitisers were not placed there), after any contact with potentially infectious secretions (e.g. after exposure to other ill children or shared toys that had been mouthed)	Research team arranged supply of materials and instructed teachers on use. Teachers instructed in use of materials and in collecting empty containers and distrib-	Products provided to schools. Instruction provided face-to-face to teachers and children.	Elementary schools and their classrooms in the USA	8-week period Desks disinfected once a day.	Products replenished as needed.	None described.	Individually labelled containers collected every 3 weeks from the classroom to assess adherence.	Product usage: average wipes used/week: 897 (128 wipes/classroom/week) Average bottles of hand sanitiser used per week: 8.75 (1.25 bottles/classroom/week)

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

						uting new product.							
Quarantine													
Miyaki 2011	Quarantine from work (stay-at-home order)	Employees	Prevent spread of influenza in workplaces by quarantining workers who had a cohabitating family member with an ILI	Full wages to employee	Non-compulsory asking of workers whose family members developed an ILI to stay at home voluntarily on full wages. Daily measuring of temperature before leaving work. Where symptoms were doubtful, industrial physician made judgement. Company doctors provided input on cancelling of stay-at-home orders as required.	Health management department oversaw the procedures and decisions.	Mode of advice to employees not described.	Car industries in Japan	Stay-at-home order for 5 days after resolution of ILI symptoms or 2 days after alleviation of fever over 7.5 months	Strict standard for cancelling of stay-at-home orders described.	None described.	Recording of compliance with stay-at-home request	100% compliance to stay at home reported.
Other (miscellaneous) interventions													
Farr 1988a trial 1	2 active interventions in addition to control	Families	Reduce transmission of viruses from hand contamination via hand-to-hand contact or large-	3-ply tissues with: A. 5.1 mg/inch^2 (2.54 cm^2) of the virucidal mixture (58.8% citric acid, 29.4% malic acid, 11.8% sodium lauryl sulphate) B. 3 mg/inch^2 (2.54 cm^2) of saccharin	Family visits to distribute tissues Weekly contact of mother Families instructed to only use supplied tissues.	Nurse epidemiologist visited families.	Face-to-face visits to families and individuals in	Communities in the USA	6 months overall Monthly family visits Weekly contact with mother	Not described	Not described	Family visits and weekly contact with mother to encourage compliance	Not described

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	of no tissues: A. Virucidal nasal tissues B. Placebo tissues		particle aerosol through tissues for nose blowing and coughs and sneezes	applied uniformly to all 3 plies of the tissue Tissues prepared by Kimberly-Clark Corporation, Neenah, WI, USA.				families (especially mothers)				
Farr 1988b trial 2	2 active interventions (no control): A. Virucidal nasal tissues B. Placebo tissues	Families	Reduce transmission of viruses from hand contamination via hand-to-hand contact or large-particle aerosol through tissues for nose blowing and coughs and sneezes	2-ply tissues containing: A. 4.0 mg/inch^2 (2.54 cm^2) of antiviral mixture (53.3% citric acid, 26.7% malic acid, 20% sodium lauryl sulphate) B. 3 mg/inch^2 (2.54 cm^2) of succinic acid, malic acid, sodium hydroxide, and polyethylene glycol Tissues prepared by Kimberly-Clark Corporation, Neenah, WI, USA.	Family visits to distribute tissues and encourage compliance Weekly contact of mother Families instructed to only use supplied tissues.	Nurse epidemiologist visited families monthly. Study monitor visited bimonthly.	Face-to-face visits to families and individuals in families (especially mothers)	Communities in the USA	6 months overall Monthly family visits Weekly contact with mother Bimonthly study monitor visit	None described.	None described.	Bimonthly study monitor visits to encourage compliance as well as monthly and weekly contact by nurse	In 124/222 families, 1 or more family members reported not using the tissues regularly and/or reported having side effects from the tissues.
Longini 1988	2 active interventions (no	Households and their families	Prevent intrafamilial transmission of viral agents in a	Treated tissues of 3-ply material identified with no specific identifiers (Kimberly-Clark Corporation)	Tissues delivered to households with specific instructions on use (all purposes, when blowing	Tissues assigned by study	Supply of tissues throughout	Households in the USA	5 months' overall supply	Resupply of tissues	None described.	Reported use of tissues "not at all, some of the time,	Reported use "all of the time": A. vs B.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

	control): A. Virucidal nasal tissues B. Placebo tissues	community setting	with inside layer containing: A. citric and malic acid plus sodium lauryl sulphate; B. succinic acid.	nose, coughing or sneezing) and to discard after use and to help young children use tissues if develop a cold.	sponsor (Kimberly-Clark Corporation).	5-month trial period			as required	most of the time, or all of the time"	82% vs 71%
Chard 2019 (additional details from Chard 2018)	Water, Sanitation, and Hygiene for Health and Education in Laotian Primary Schools (WASH HELPS)	Primary schools and their students	Prevent the spread of pathogens within schools through improved water supply and hygiene facilities and improved WASH habits in children at home and throughout the life course	For each school: Water supply for school compound: (borehole, protected dug well with pump, or gravity-fed system) Water tank to supply toilet and hand-washing station School sanitation facilities (3 toilet compartments) Hand-washing facilities: 2 sinks with tapped water and supply of soap available (1 bar of soap/pupil) 3 group hand-washing tables with soap and water At least 1 drinking water filter per classroom	Provision of school: Water supply, sanitation facilities, hand-washing facilities (individual and group), drinking water filters Behaviour change education and promotion including daily group hygiene activities Daily hand-washing and cleaning schedules	UNICEF paid for materials. School and teachers conducted daily hand-washing activities with children. Students participat-	Facilities provided within schools. Children participated in group hand-washing and cleaning.	Primary schools and their classrooms (in Laos)	One-off provision of water and hygiene facilities Daily hand-washing activities and cleaning for 1 school year Cleaning schedules posted in at least 1 classroom near toilet.	Water supply tailored to the school requirements/environment. Sanitation facilities provided as needed and desig-	Rain water tank provision affected by rain water supply, so changed to tanks with motorised hand pumps or gravity-fed wa-	Unannounced visits every 6 to 8 weeks for structured observations to measure fidelity and adherence Fidelity Index score (0 to 20): for hardware provided see Table 1 in paper and protocol Adherence index: student report of behavioural out-	Fidelity: 30.9% across all schools and visits Adherence: 29.4% Hardware provision: 87.8% of schools School-level adherence: 61.4% Group compound cleaning: 94.8%, toilet use: 75.5%, group toilet cleaning: 68.3%,

Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

				Schedules of daily group hand-washing, compound and toilet cleaning Cost per school: USD 13,000 to 17,500		ed in daily group cleaning activities.				nated for boys, girls, and students with disabilities.	ter supply systems. Theft and animal consumption of supplied soap reduced supply.	comes index score (0 to 4)	group hand-washing: 48.7%, individual hand-washing with soap after toilet use: 23.9%. Further details (Chard 2018)
Hartinger 2016	Integrated environmental home-based intervention package (IHIP)	Households and their householders including children	Reduce infections and improve child growth in households in rural communities with limited facilities through a multicomponent, low-cost environmental intervention to improve drinking water,	Per household: "OPTIMA-improved stove": improved ventilated solid-fuel stove Kitchen sink with in-kitchen water connection providing piped water Point-of-use water quality intervention applying solar disinfection to drinking water	Community engagement with local and regional stakeholders in design and development Provision of stoves, kitchen sinks, and plastic bottles for solar water treatment, and hygiene education Training of mothers/caretakers in: - solar drinking-water disinfection (SODIS)[20] ac-	Health promoters hired local elementary school teachers and implemented and promoted the inter-	Face-to-face and to individual households; mode of delivery of training as individual or group not	Households in rural communities in Peru	Stoves and sinks installed over initial 3 months. Monthly reinforcement over 12 months of SODIS, child and kitchen hygiene Weekly spot checks of compliance	Tailored to particular household facilities and environments as needed and to local beliefs and	Not described	Weekly spot-check observations of household hygiene and environmental health conditions (e.g. presence of SODIS bottles on the roof or kitchen) using a checklist Monthly self-report by	SODIS use: 60% initially and 10% at end of study Self-reported use by mothers: 90% with slight decrease at end Self-reported stove use: 90% daily Sink use: 66% daily

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

				sanitation, personal hygiene, and household air quality developed in pilot (Hartinger 2011; Hartinger 2012) using a participatory approach that addressed local beliefs and cultural views	cording to standard procedures - hand hygiene (washing own and children's hands with soap at critical times[21]) - advice to separate animals and their excreta from the kitchen environment Project-initiated repairs	ventions. 4 teams of field staff conducted spot-check observations.	described	Repairs after 9 months Environmental samples test middle and end of 12-month surveillance.	cultural customs Repairs to stoves as needed and checked at 9 months		mothers of stove and sink use	35% of stoves needed minor repairs, 1% needed major repairs. Best-functioning stoves achieved mean 45% and 27% reduction of $PM_{2.5}$ and CO, respectively, in mothers' personal exposure.
Huda 2012	Sanitation Hygiene Education and Water Supply in Bangladesh (SHEWA-B)	Villages and their households with a child < 5 years old	Reduce illness in children < 5 years by improving hygiene practices, sanitation and water supply and treatment in their household	Materials for training of community hygiene promoters and promotion activities including flip charts and flash cards with messages alerting participants to presence of unobservable "germs" and practices to minimise germs See Box 1 in paper for 11 key messages.[22]	Engaging local residents under guidance of local NGOs to develop community action plans addressing: Latrine coverage and usage Access to and use of arsenic-free water Improved hygiene practices, especially handwashing with soap	Community hygiene promoters (local residents with at least 10 years' schooling trained for 10	Face-to-face delivery to groups (villages and households) and individuals	Villages and households in districts of Bangladesh Community activities held in villages.	18 months overall Expected household visit and courtyard meeting every 2 months Handwashing opportunities: after own or child's defecation,	Community action plans developed for and by local residents.	Not described	Structured observation of handwashing and child faeces disposal behaviour in households and spot checks of type of household water and sanitation facilities	HW: Food-related: No significant difference from baseline to 18 months; IG versus CG After anus cleaning: 36% versus 27%

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					Recruitment and appointment of community hygiene promoters Household visits, courtyard meetings, and social mobilisation activities (e.g. water, sanitation and hygiene fairs, village theatre, group discussions in tea stalls (the social meeting point for village men)) by community promoters Structured observation in households	days on behaviour change communication in water, sanitation, and hygiene)	Meetings held in courtyards of groups of households. Household visits	prior to preparing and serving food, prior to eating and feeding a child				Defecation: 30% versus 23% No access to latrine decreased from 10.3% to 6.8%. No significant improvement in access to improved latrines, solid waste disposal, drainage systems, and covered containers for water storage
Ibfelt 2015	Disinfection of toys	Daycare nurseries	Reduce transmission of pathogens via shared toys in daycare environment through regular disinfection treatment	Disinfectants: Turbo Oxysan (Ecolab, Valby, Denmark) for washing machines Sirafan M, Ecolab (1% to 3% benzalkonium chloride, 1% to 3% didecyldimethylammonium chloride, and 5% to 7% alcohol ethoxylates) for immersion or wiping	Collection and commercial cleaning of toys from nurseries: - linen and toys suitable for washing machines were washed at 46 °C and subsequently disinfected - toys not suitable for washing machines immersed	Commercial cleaning company: Berendsen A/S, Søborg, Denmark	Cleaning companies collected the toys and linen and cleaned them	Daycare nurseries in Denmark Commercial industrial clean-	2 to 3 months overall Cleaning every 2 weeks	Staggered cleaning to ensure children had toys to play with whilst oth-	None described.	None described.	None described.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

					in disinfectant or wiped with microfibre cloth		off-site, then returned them.	ing facility		ers were being cleaned		
Najnin 2019 (see also Qadri 2015 for further details)	2 active interventions: A. Combined cholera vaccine and 'behaviour change communication' intervention B. Cholera vaccine-alone group	Low-income households and compounds	Prevent or reduce transmission of respiratory illness based on the Integrated Behavioural Model for Water Sanitation and Hygiene (IBM-WASH) theoretical framework (Dreibelbis 2013; Hulland 2013)	A. and B. Cholera vaccine ShanChol™ (Shantha Biotechnics-Sanofi, India) A. Following hardware per compound: a. Hand-washing hardware: (i) Bucket with a tap (provided free of charge) (ii) Soapy water bottle (mixture of a commercially available sachet of powdered detergent (~USD 0.03) with 1.5 L of water in a plastic bottle with a hole punched in the cap) supplied by participating compounds (iii) Bowl to collect rinse water after washing hands (see photo in text or in Najnin 2017 doi.org/10.1093/ije/dyx187) b. Water treatment hardware:	A. and B. Provision of cholera vaccine (2 doses at least 14 days apart) Provision of hand-washing hardware and behaviour change communication activities Encouragement of hand-washing after defecation, after cleaning child's anus, and before preparing food Encouragement to add chlorine to own water vessels Benefits were again explained. Follow-up visits by health promoters	Dushtha Shasthya Kendra (DSK), an NGO, delivered the hardware and behavioural intervention (through community health promoters). Separate data collectors observed soap avail-	Handwashing and water treatment hardware mostly delivered at the compound level in person. Behaviour change communication messages were delivered both at	Households and compounds (where several households share a common water source, kitchen, and toilets) in Bangladesh	Behaviour change communication messages delivered first (within 3 months of cholera vaccination). Point-of-use water hardware provided 3 months later. Follow-up health promoter visits 3 times in 2 months after hardware installation, then 2 times/month (over nearly 2 years).	Hardware-related problems (breakage/leakage) were addressed on health promoter follow-up visits.	None described.	Unannounced home visits by data collectors who observed presence of soap/soapy water and water in most convenient place for handwashing (either reserved in a container or available at the tap) Residual chlorine was measured indicating uptake of chlorine dispenser.	Presence of soap / soapy water and water: A. Handwashing group compounds: 45% (1,729 / 3,886); B. Vaccine-only group compound: 22% (438 / 1,965); C. Control: 28% (556 / 1991) Residual chlorine present in stored drinking water of 4% (160/3886) of households in the vac-

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

				Dispenser containing liquid sodium hypochlorite See Figure 2 in Najnin 2017 for photos of both doi.org/10.1093/ije/dyx187 and more details. Participants own water vessels for water treatment Print materials for behaviour change to compounds and households		ability.	compound and household levels.					cine-plus-behaviour-change compound and none in the other 2 compounds.
Gargling													
Goodall 2014	2 active interventions: A. Vitamin D_3 supplementation B. Gargling water	University students	Decrease the incidence of URTI through increased vitamin D levels (associated with greater frequency and severity of URTI) and gargling (as preventative measure against URTI)	A. Vitamin D_3: container of 8 capsules of 10,000 IU (purchased from Euro-Pharm International Canada Inc.) Weekly email reminder B. Gargling: 30 mL of tap water 2/day	A. Vitamin D: instructed to take 1 pill weekly B. Gargling: instructed to gargle twice daily for 30 seconds All participants received general lifestyle and health advice on sleep, nutrition, hand hygiene, and exercise.	Not specified, presumably the researchers including a study pharmacist	Vitamin D_3 supplied individually, but no further details. Method of lifestyle and health advice provision	In university student housing (in residences or off-campus) in Canada	2 months overall Vitamin D_3: weekly supplementation and email reminder Gargling: 30 mL of water for 30 seconds twice daily	None described.	None described.	None described.	None described.

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Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

							also not described.						
Ide 2014	2 active interventions (no control): A. Green tea gargling B. Water gargling	High school students	Prevent influenza spread and infection in high school students who are at increased risk from close interaction through gargling as a non-pharmaceutical intervention, specifically green tea containing highly bioactive catechin (-)-epigallocatechin gallate, with possible anti-influenza virus properties	A. Bottled green tea (500 mL) containing a catechin concentration of 37 ± 0.2 mg/dL, including approximately 18% (-)-epigallocatechin gallate (manufactured by the Kakegawa Tea Merchants Association). Concentration measured by high-performance liquid chromatography based on the average concentration in 10 bottles from the same production lot (September 2011) used for gargling in the study. B. Tap water	A. Provision of green tea B. Advice to gargle with tap water and not to gargle green tea during study A. and B. Advice to gargle at least 3 times/day (after arriving at school, after lunch, and after school) Consumption of green tea and other tea was not restricted for either group. Safety monitoring carried out throughout the study (not further described).	Materials supplied by researchers. High schools' vice principals and head teachers assisted with safety monitoring.	Green tea supplied individually to students. Mode of gargling advice not described.	High schools in Japan	Gargling 3 times/day for 90 days	None described.	None described.	Daily questionnaire included questions about daily adherence to gargling regimen. Adherence rate of gargling at or above 75%, and absence of green tea gargling when in the water gargling group.	Gargling adherence rate: green tea group: 73.7%; water group: 67.2%
Satomura 2005	2 active inter-	Healthy adults	Prevent URTIs through	A. Water B. 15 to 30 times diluted 7% povidone-iodine (as	Local administrators instructed participants to:	Local project ad-	Not specified,	18 healthcare	60 days overall	If diluted povi-	3 partici-	Completion of gargling	9 participants did not com-

Table 1. Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist *(Continued)*

ventions: A. Water gargling B. Povidone-iodine gargling	gargling water alone, which may wash out pathogens from the pharynx and oral cavity through whirling water or through chlorine, or povidone-iodine for its perceived virucidal properties	indicated by manufacturer)	- gargle dose of water or povidone-iodine 3 times/day; - maintain hand-washing routine; - not change other hygiene habits; - not take any cold remedies; - complete gargling diary. Weekly monitoring of hygienic actions and encouragement to keep up assigned intervention every week	ministrators (18 healthcare professionals) provided instructions and monitoring and encouragement.	but likely to have been face-to-face and individually, at least initially for instructions	sites in Japan (4 in northern region, 9 in central region, 5 in western region)	1. Water gargling: 20 mL for 15 s at least 3 times/day 2. Povidone-iodine gargling: 20 mL of dilution 3 times/day	done-iodine caused serious discomfort or was not available, participants were allowed to gargle with water instead.	pants assigned to povidone-iodine gargled with water instead as the povidone-iodine "did not agree with them".	diary: frequency of gargling and hand-washing Weekly monitoring and encouragement by local administrators	plete diary. Average frequency of gargling / person / day: With water: A: 3.6 B: 0.8 Control: 0.9 With povidone-iodine: A.: <0.1 B: 2.9 Control: 0.2

ABH: alcohol-based rub
ARI: acute respiratory infection
CDC: Centers for Disease Control and Prevention
CG: control group
CHG: chlorhexidine gluconate
CO: carbon monoxide
DCCs: daycare centres
FM: face masks
HCP: healthcare personnel
HCW: healthcare worker
HH: hand hygiene
HSG: hand sanitiser group
HSW: hand-washing with soap and water
HWWS: hand-washing with soap
IG: intervention group
IHIP: integrated environmental home-based intervention package

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ILI: influenza-like illness
IU: international units
LTCFs: long-term care facilities
NGOs: non-governmental organisations
NH: nursing home
no.: number
NPIs: non-pharmaceutical interventions
PM2.5: particulate matter of less than 2.5 microns
RAs: research assistants
RIs: respiratory infections
RTIs: respiratory tract infections
SD: standard deviation
SSTI: skin and soft-tissue infection
SWG: soap-and-water group
TCID: tissue-culture infectious dose
URTI: upper respiratory tract infection
WHO: World Health Organization
wk: week
w/w: weight for weight

[1]: Occupational Safety and Health Administration (OSHA). OSHA technical manual: section VIII: chapter 2: respiratory protection. US Department of Labor. www.osha.gov/dts/osta/otm/otm_viii/otm_viii_2.html (accessed 21 April 2020).

[2]: Ministry of Health and Long-Term Care, Public Health Division, Provincial Infectious Diseases Advisory Committee. Preventing respiratory illnesses: protecting patient and staff: infection control and surveillance standards for febrile respiratory illness (FRI) in non-outbreak conditions in acute care hospitals [September 2005] http://www.health.gov.on.ca/english/providers/program/infectious/diseases/best_prac/bp_fri_080406.pdf (accessed September 11 2009). [URL inactive]

[3]: Before eating, after sneezing, coughing, handling money, using restroom, returning to desk and interacting with others who may be sick

[4]: after coming into classroom, before and after lunch, after break, after physical education, when they went home and after coughing, sneezing or blowing their noses

[5]: after toileting and when visibly dirty plus a protocol for particular circumstances: after coming into the classroom; before and after lunch; after playing outside; when they went home; after coughing, sneezing, or blowing their noses; and after diapering

[6]: 1) when entering into the classroom; 2) after sneezing, coughing, or blowing their nose; 3) after using the toilet/washroom; 4) before eating any food; and 5) when leaving the school at the end of the day

[7]: what to do if hands were dirty, why students should wash their hands, benefits of washing hands and using hand sanitizer, procedure for washing hands using hand sanitizer, to cover mouth and nose with upper part of sleeve while coughing and/or sneezing

[8]: Boyce JM, Pittet D, Healthcare Infection Control Practices Advisory Committee, HICPAC/ SHEA/APIC/IDSA Hand Hygiene Task Force. Guideline for hand hygiene in healthcare settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/ IDSA Hand Hygiene Task Force. MMWR Recommendations and Reports 2002;51(RR-16):1–45. www.cdc.gov/mmwr/preview/mmwrhtml/rr5116a1.htm (accessed 21 April 2020). International Bank for Reconstruction and Development/ World Bank, Bank-Netherlands Water Partnership, Water and Sanitation Program. Hand washing manual: a guide for developing a hygiene promotion program to increase handwashing with soap. http://go.worldbank.org/PJTS4A53C0 (Accessed 16 May 2007). *[URL inactive]* California State Department of Education. *Techniques for Preventing the Spread of Infectious Diseases*. Sacramento (CA): California State Department of Education, 1983. Geiger BF, Artz L, Petri CJ, Winnail SD, Mason JW. *Fun with Handwashing Education*. Birmingham (AL): University of Alabama, 2000. Roberts A, Pareja R, Shaw W, Boyd B, Booth E, Mata JI. A tool box for building health communication capacity. www.globalhealthcommunication.org/tools/29 (Accessed 10 October 2007). *[URL inactive]* Stark P. *Handwashing Technique. Instructor's Packet. Learning Activity Package*. Sacramento (CA): California State Department of Education, 1982.

[9]: DIN EN 1500: Chemische Desinfektionsmittel und Antiseptika, Hygienische Händedesinfektion, Prüfverfahren und Anforderungen (Phase 2/Stufe 2). Brüssel (Belgium): CEN, European Comittee for Standardization 1997;1-20.

[10]: DIN EN 12791: Chemische Desinfektionsmittel und Antiseptika, Chirugische Händedesinfektionsmittel - Prüfverfahren und Anforderungen (Phase 2/Stufe 2). Brüssel (Belgium): CEN, European Comittee for Standardization 2005;1-31.

[11]: after defaecation, after cleaning an infant who had defaecated, before preparing food, before eating, and before feeding infants

[12]: non-governmental organisation that supports community-based health and development initiatives

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[13]: “Healthy Hands” Rules (from Figure 3 in paper): Do use “special soap” when arrive to school, before lunch, after go to bathroom (only if soap and water not available), if rub nose or eyes or if fingers in mouth, if teacher asks. Do not: use “special soap” if hand dirt on them, put “special soap” on another student, play with ‘special soap”, put hands near eyes after using “special soap”.
[14]: Calculated by subtracting each day’s soap weight from the previous day’s weight. Maximum number of grams of soap consumed for each compound was identified and the day on which the maximum soap consumption was recorded. A per capita estimate of daily soap consumption was calculated
[15]: National Health and Medical Research Council. Staying Healthy in Child Care. Canberra (Australia): Australian Government Publishing Service, 1994
[16]: upon arrival, before and after lunch, and prior to departure
[17]: knowledge and awareness of HH guidelines, perceived importance of performing HH, perceived behavioural control (i.e. perceived ease or difficulty of performing the behaviour), and habit
[18]: “According to the Dutch national guidelines, HH is mandatory for caregivers before touching/preparing food, before caregivers themselves ate or assisted children with eating, and before wound care; and after diapering, after toilet use/wiping buttocks, after caregivers themselves coughed/sneezed/wiped their own nose, after contact with body fluids (e.g. saliva, vomit, urine, blood, or mucus when wiping children’s noses), after wound care, and after hands were visibly soiled.” (p. 2495)
[19]: having touched household items being used by the index patients and/or other symptomatic household contacts, and after coughing/sneezing, before meals, before preparing meals and when returning home
[20]: SODIS: www.sodis.ch/index_EN.html
[21]: after defecation, after changing diapers, before food preparation and before eating
[22]: 1. Wash both hands with water and soap before eating/ handling food 2. Wash both hands with water and soap/ash after defecation 3. Wash both hands with water and soap/ash after cleaning baby’s bottom 4. Use hygienic latrine by all family members including Children 5. Dispose of children’s faeces into hygienic latrines 6. Clean and maintain latrine 7. Construct a new latrine if the existing one is full and fill the pit with soil/ash. 8. Safe collection and storage of drinking water 9. Draw drinking water from arsenic safe water point 10. Wash raw fruits and vegetables with safe water before eating and cover food properly 11. Manage menstruation period safely (p.605)

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Table 2. Results from trials of hand hygiene compared to control

Study	Comparison (see Table 1 for details of interventions)	Reported outcomes	Results
Alzaher 2018 cluster-RCT Saudi Arabia	Hand-washing workshop and posters vs usual practice	% absence days due to URI	0.39% and 0.72% in intervention group schools; 0.86% and 1.39% in control schools
Arbogast 2016 cluster-RCT USA	Hand sanitiser + wipes + hand foam vs none Both groups received education + signage about hand-washing	1. Health insurance claims for preventable illnesses per employee 2. Absences per employee	1. 0.30 claims in intervention; 0.37 in control (27% relative reduction; P = 0.03) 2. 1.45 in intervention; 1.53 in control (5.0% relative reduction in intervention; P = 0.30)
Azor-Martinez 2016 RCT Spain	Hand-washing with soap and water plus hand sanitiser vs usual hand-washing practices	% absence days due to URI	1.15% in intervention; 1.68% in control. Significantly lower in intervention (P < 0.001)
Azor-Martinez 2018 cluster-RCT Spain	Education and hand hygiene with soap and water vs hand hygiene with sanitiser vs usual hand-washing procedures	1. URI incidence rate ratio (primary) 2. Percentage difference in absenteeism days	1. HH soap vs control 0.94 (95% CI 0.82 to 1.08); HH sanitiser vs control 0.77 (95% CI 0.68 to 0.88); HH soap vs HH sanitiser 1.21 (95% CI 1.06 to 1.39) 2. HH soap 3.9% vs control 4.2% (P < 0.001); HH sanitiser 3.25% vs control 4.2% (P = 0.026); HH soap 3.9% vs HH sanitiser 3.25% (P < 0.001)
Biswas 2019 cluster-RCT Bangladesh	Hand sanitiser and respiratory hygiene education and cough/sneeze hygiene vs no intervention	1. ILI incidence rate (at least 1 episode) 2. Laboratory-confirmed influenza	1. 22 per 1000 student-weeks in intervention; 27 per 1000 student-weeks in control, not statistically significantly different 2. 3 per 1000 student-weeks in intervention; 6 per 1000 student-weeks in control, P = 0.01
Correa 2012 cluster-RCT Colombia	Alcohol-based hand sanitiser in addition to hand-washing vs usual hand-washing practice	ARIs in 3rd trimester of follow-up	Hazard ratio for intervention to control 0.69 (95% CI 0.57 to 0.83)
Cowling 2008 cluster-RCT Hong Kong	Hand hygiene (36 households) vs face mask (mask) vs education (control)	Secondary attack rate for: 1. laboratory-confirmed influenza; 2. ILI definition 1; 3. ILI definition 2; 4. ILI definition 3.	1. HH 0.06; mask 0.07; control 0.06 2. HH 0.18; mask 0.18; control 0.18 3. HH 0.11; mask 0.10; control 0.11 4. HH 0.04; mask 0.08; control 0.04
Cowling 2009 cluster-RCT Hong Kong	Hand hygiene (HH) vs face mask + hand hygiene (HH + mask) vs education (control)	Secondary attack rate for: 1. laboratory-confirmed influenza;	1. HH 5; HH + mask 7; control 10 2. HH 16; HH + mask 21; control 19 3. HH 4; HH + mask 7; control 5

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Table 2. Results from trials of hand hygiene compared to control *(Continued)*

		2. ILI definition 1; 3. ILI definition 2.	
DiVita 2011 (conference abstract) RCT Bangladesh	Hand-washing stations with soap and motivation vs none	1. SAR for laboratory-confirmed influenza 2. SAR for ILI	1. SAR higher in intervention group (11.0% vs 7.5%) 2. SAR higher in intervention group (14.2% vs 11.9%)
Feldman 2016 cluster-RCT Israel	Hand disinfection + soap and water installed vs none	1. Number of respiratory infections 2. Number of off-duty days	1. 11 in each group 2. 112 in intervention; 104 in control
Gwaltney 1980 RCT USA	Virucidal hand wash vs placebo	1. Number with illness after immediate exposure 2. Number with illness after 2-hour delay in exposure	1. 0 of 8 in intervention; 7 of 7 in control 2. 1 of 10 in intervention; 6 of 10 in control
Hubner 2010 RCT Germany	Hand disinfection provided vs none	Odds ratios (95% CI) (intervention:control) 1. Influenza 2. Common cold 3. Sinusitis 4. Sore throat 5. Fever 6. Cough	1. 1.02 (0.20 to 5.23) 2. 0.35 (0.17 to 0.71) 3. 1.87 (0.52 to 6.74) 4. 0.62 (0.31 to 1.25) 5. 0.38 (0.14 to 0.99) 6. 0.45 (0.22 to 0.91)
Ladegaard 1999 RCT Denmark	Hand hygiene and education vs none	Sick days during the "effect period"	22 days/child in the intervention group vs 36 days/child in the control group
Larson 2010 cluster-RCT USA	Education vs education with alcohol-based hand sanitiser vs education with hand sanitiser and face masks	Incidence rate ratios (episodes per 1000 person-weeks) for: 1. URI; 2. ILI; 3. influenza; Secondary attack rates for: 4. URI/ILI/influenza; 5. ILI/influenza.	1. HS 29; HS + masks 39; control 35 2. HS 1.9; HS + masks 1.6; control 2.3 3. HS 0.6; HS + masks 0.5; control 2.3 4. HS 0.14; HS + masks 0.12; control 0.14 5. HS 0.02; HS + masks 0.02; control 0.02
Little 2015 RCT England	Bespoke automated web-based hand hygiene motivational intervention with tailored feedback vs none	Number of participants with 1 or more episodes of URI	Risk ratio for intervention to control 0.86 (95% CI 0.83 to 0.89; P < 0.001)

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Table 2. Results from trials of hand hygiene compared to control *(Continued)*

Luby 2005 RCT Pakistan	Antibacterial soap and education about hand-washing vs plain soap and education vs none	1. Cough or difficulty breathing in children < 15 yrs (episodes/100 person-weeks) 2. Congestion or coryza in children < 15 yrs (episodes/100 person-weeks) 3. Pneumonia in children < 5 yrs (episodes/100 person-weeks)	All outcomes significantly lower than control 1. 4.21 in antibacterial soap group; 4.16 in plain soap group; 8.50 in control group 2. 7.32 in antibacterial soap group; 6.87 in plain soap group; 14.78 in control group 3. 2.42 in antibacterial soap group; 2.20 in plain soap group; 4.40 in control group
Millar 2016 cluster-RCT USA	Standard educational promotion of hand-washing vs enhanced promotion vs promotion plus a once-weekly application of chlorhexidine-based body wash	Incidence rates of ARI over 20 months	37.7 enhanced + body wash; 29.3 enhanced; 35.3 standard; RR for enhanced + body wash to standard 1.07 (95% CI 1.03 to 1.11); RR for enhanced to enhanced + body wash 0.78 (95% CI 0.75 to 0.81)
Morton 2004 cluster-RCT Cross-over study USA	Alcohol gel plus education vs regular hand-washing	Absence due to infectious illness	Results not stated numerically
Nicholson 2014 cluster-RCT India	Combination hand-washing promotion with provision of free soap vs none	Target children: 1. Episodes of ARI (per 100 person-weeks) 2. School absence episodes (per 100 person-days) Families: 3. Episodes of ARI	1. 16 in intervention; 19 in control 2. 1.2 in intervention; 1.7 in control 3. 10 in intervention; 11 in control
Priest 2014 cluster-RCT New Zealand	Hand hygiene education and hand sanitiser vs education alone	1. % absence days due to respiratory illness 2. % absence days due to any illness	1. 0.84% in intervention group; 0.80% in control (P = 0.44) 2. 1.21% in intervention group; 1.16% in control (P = 0.35)
Ram 2015 RCT Bangladesh	Education to promote intensive hand-washing in households plus soap provision vs none	1. Secondary attack ratio for intervention to control for ILI 2. Laboratory-confirmed influenza	1. 1.24 (95% CI 0.93 to 1.65) 2. 2.40 (95% CI 0.68 to 8.47)
Roberts 2000 cluster-RCT Australia	Hand-washing programme with training for staff and children vs none	Incidence rate ratio for ARI	IRR 0.92 for intervention to control (95% CI 0.86 to 0.99)
Sandora 2008 cluster-RCT USA	Hand sanitiser and education vs none	Incidence rates for ARI (episodes per person-month)	0.43 in intervention; 0.42 in control

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Table 2. Results from trials of hand hygiene compared to control *(Continued)*

Savolainen-Kopra 2012 cluster-RCT Finland	Hand hygiene with soap and water (IR1 group) vs with alcohol-based hand rub (IR2 group) vs control (none); intervention groups also received education	1. Number of respiratory infection episodes/week 2. Number of reported infection episodes/week 3. Number of reported sick leave episodes/week	1. 0.076 in IR1; 0.085 in IR2; 0.080 in control, NS 2. 0.097 in IR1; 0.107 in IR2; 0.104 in control, NS 3. 0.042 in IR1; 0.035 in IR2; 0.035 in control. Significantly higher in IR1 compared with control
Simmerman 2011 cluster-RCT Thailand	Hand-washing (HW) vs hand-washing plus paper surgical face masks (HW + FM) vs control (none)	Odds ratios for secondary attack rates for influenza	OR for HW: control 1.20 (95% CI 0.76 to 1.88) OR for HW + masks: control 1.16 (95% CI 0.74 to 1.82) OR for HW + masks: HW 0.72 (95% CI 0.21 to 2.48)
Stebbins 2011 cluster-RCT USA	Training in hand and respiratory (cough) hygiene + hand sanitiser vs none	Incidence rate ratios for intervention to control for: 1. laboratory-confirmed influenza (RT-PCR); 2. influenza-A; 3. absence.	1. IRR 0.81 (95% CI 0.54 to 1.23) 2. IRR 0.48 (95% CI 0.26 to 0.87) 3. IRR 0.74 (95% CI 0.56 to 0.97)
Talaat 2011 cluster-RCT Egypt	Mandatory hand-washing intervention + education vs none	1. Number of absence days due to ILI 2. Number of absence days	1. 917 in intervention; 1671 in control (P < 0.001) 2. 13,247 in intervention; 19,094 in control (P < 0.001)
Temime 2018 cluster-RCT France	Hand hygiene with alcohol-based hand rub, promotion, staff education, and local work groups vs none	Incidence rate of ARI clusters (5 or more people in same nursing home)	2 ARI clusters in intervention; 1 in control
Turner 2012 RCT USA	Antiviral hand treatment vs no treatment	1. Number of rhinovirus infections 2. Common cold infections 3. Rhinovirus-associated illnesses	1. 49 in intervention; 49 in control, NS 2. 56 in intervention; 72 in control, NS 3. 26 in intervention; 24 in control, NS
White 2001 DB-RCT USA	Hand rub with benzalkonium chloride (hand sanitiser) vs placebo	ARI symptoms Laboratory: testing of virucidal and bactericidal activity of the product	30% to 38% decrease of illness and absenteeism (RR for illness absence incidence 0.69; RR for absence duration 0.71)
Yeung 2011 cluster-RCT Hong Kong	Alcohol-based hand gel + materials + education vs control (basic life support workshop)	Difference between pre-study period and poststudy in pneumonia infections recorded in residents	0.63/1000 reduction in intervention group; 0.16/1000 increase in control
Zomer 2015 cluster-RCT Netherlands	4 components: 1. Hand hygiene products, paper towel dispensers, soap, alcohol-based hand sanitiser,	Incidence rate ratio for intervention to control for common cold	IRR 1.07 (95% CI 0.97 to 1.19) 8.2 episodes per child-year in intervention; 7.4 episodes per child-year in control

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Table 2. Results from trials of hand hygiene compared to control *(Continued)*

	and hand cream provided for 6 months 2. Training and booklet 3. 2 team training sessions aimed at hand hygiene improvement 4. Posters and stickers for caregivers and children as reminders Combination vs usual practice		

ARI: acute respiratory infection
CI: confidence interval
cluster-RCT: cluster-randomised controlled trial
DB-RCT: double-blind randomised controlled trial
HH: hand hygiene
HS: hand sanitiser
HW: hand-washing
ILI: influenza-like illness
IRR: incidence rate ratio
NS: non-significant
OR: odds ratio
RCT: randomised controlled trial
RR: risk ratio
RT-PCR: reverse-transcriptase polymerase chain reaction
SAR: secondary attack rate
URI: upper respiratory infection
yrs: years

Table 3. Results from trials of hand hygiene + medical/surgical masks compared to control

Study	Comparison (see Table 1 for details of interventions)	Reported outcomes	Results
Aelami 2015 (conference abstract) RCT Saudi Arabia	Hand hygiene education + alcohol-based hand rub + soap + surgical masks vs none	Proportion with ILI (defined as presence of ≥ 2 of the following during their stay: fever, cough, and sore throat)	52% in intervention; 55.3% in control (P < 0.001)
Aiello 2010 cluster-RCT USA	Face mask use (FM) vs face masks + hand hygiene (FM + HH) vs control Note that this study is not included in meta-analysis as each treatment group included only 1 cluster.	1. ILI 2. Laboratory-confirmed influenza A or B	Significant reduction in ILI cases in both intervention groups compared with control over weeks 3 to 6 No significant differences between FM and FM + HH
Aiello 2012 cluster-RCT USA	Face mask use (FM) vs face masks + hand hygiene (FM + HH) vs control	1. Clinical ILI 2. Laboratory-confirmed influenza A or B	1. Non-significant reductions in FM group compared with control over all weeks. Significant reduction in FM + HH group compared with control in weeks 3 to 6

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Table 3. Results from trials of hand hygiene + medical/surgical masks compared to control *(Continued)*

			2. Non-significant reductions in both intervention groups compared with control
Cowling 2009 cluster-RCT Hong Kong	Hand hygiene (HH) vs hand hygiene plus face masks (HH + mask) vs control	Secondary attack ratio for: 1. laboratory-confirmed influenza; 2. ILI definition 1; 3. ILI definition 2.	1. HH 5; HH + mask 7; control 10 2. HH 16; HH + mask 21; control 19 3. HH 4; HH + mask 7; control 5
Larson 2010 cluster-RCT USA	Education (control) vs education with alcohol-based hand sanitiser (HS) vs education + HS + face masks (HS + mask)	Incidence rate ratios (episodes per 1000 person-weeks) for: 1. URI; 2. ILI; 3. influenza. Secondary attack rates for: 4. URI/ILI/influenza; 5. ILI/influenza.	1. HS 29; HS + mask 39; control 35 2. HS 1.9; HS + mask 1.6; control 2.3 3. HS 0.6; HS + mask 0.5; control 2.3 4. HS 0.14; HS + mask 0.12; control 0.14 5. HS 0.02; HS + mask 0.02; control 0.02
Simmerman 2011 cluster-RCT Thailand	Control vs hand-washing (HW) vs hand-washing + paper surgical face masks (HW + mask)	Odds ratio for secondary attack rates for influenza	OR for HW: control 1.20 (95% CI 0.76 to 1.88) OR for HW + mask: control 1.16 (95% CI 0.74 to 1.82) OR for HW + mask: HW 0.72 (95% CI 0.21 to 2.48)
Suess 2012 cluster-RCT Germany	Face mask + hand hygiene (mask + HH) vs face masks only (mask) vs none (control)	Secondary attack rates in household contacts: 1. Laboratory-confirmed influenza 2. ILI	1. Mask 9; mask + HH 15; control 23 2. Mask 9; mask + HH 9; control 17

CI: confidence interval
cluster-RCT: cluster-randomised controlled trial
FM: face mask
HH: hand hygiene
HS: hand sanitiser
HW: hand-washing
ILI: influenza-like illness
OR: odds ratio
RCT: randomised controlled trial
URI: upper respiratory infection

Table 4. Results from trials of soap + water compared to hand sanitisers

Study	**Comparison** (see Table 1 for details of interventions)	**Reported outcomes**	**Results**
Azor-Martinez 2018 cluster-RCT Spain	Education and hand hygiene with soap and water (HH soap) vs hand hygiene with sanitiser (HH sanitiser) vs usual hand-washing procedures	1. URI incidence rate ratio (primary) 2. Percentage difference in absenteeism days	1: HH soap vs control 0.94 (95% CI 0.82 to 1.08); HH sanitiser vs control 0.77 (95% CI 0.68 to 0.88); HH soap vs HH sanitiser 1.21 (95% CI 1.06 to 1.39) 2: HH soap 3.9% vs control 4.2% (P < 0.001); HH sanitiser 3.25% vs control 4.2% (P = 0.026); HH soap 3.9% vs HH sanitiser 3.25% (P < 0.001)
Pandejpong 2012	Alcohol hand gel applied every 60 minutes vs every 120 minutes vs once before lunch (3 groups).	Absent days due to confirmed ILI/present days	0.017 in every hour group; 0.025 in every 2 hours group; 0.026 in before lunch group. Statistically significant difference between every hour group and

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Table 4. Results from trials of soap + water compared to hand sanitisers *(Continued)*

cluster-RCT Thailand			before lunch group, and between every hour and every 2 hours groups
Savolainen-Kopra 2012 cluster-RCT Finland	Hand hygiene with soap and water (IR1 group) vs with alcohol-based hand rub (IR2 group) vs control (none); intervention groups also received education	1. Number of respiratory infection episodes/week 2. Number of reported infection episodes/week 3. Number of reported sick leave episodes/week	1. 0.076 in IR1; 0.085 in IR2; 0.080 in control, NS 2: 0.097 in IR1; 0.107 in IR2; 0.104 in control, NS 3: 0.042 in IR1; 0.035 in IR2; 0.035 in control. Significantly higher in IR1 compared with control
Turner 2004a and-Turner 2004b RCT Canada	Study 1. Ethanol vs salicylic acid 3.5% vs salicylic acid 1% and pyroglutamic acid 3.5% Study 2. Skin cleanser wipe vs ethanol (control)	% of volunteers infected with rhinovirus	7% in each intervention group; 32% in control (study 1) 22% in intervention, 30% in control (study 2)

CI: confidence interval
cluster-RCT: cluster-randomised controlled trial
HH: hand hygiene
ILI: influenza-like illness
NS: non-significant
RCT: randomised controlled trial
URI: upper respiratory infection

Table 5. Results from trials of surface/object disinfection (with or without hand hygiene) compared to control

Study	**Comparison** (see Table 1 for details of interventions)	**Reported outcomes**	**Results**
Ban 2015 cluster-RCT China	Hand hygiene products, surface cleaning and disinfection provided to families and kindergartens vs none	1. Respiratory illness 2. Cough and expectoration	1. OR 0.47 for intervention to control (95% CI 0.38 to 0.59) 2. OR 0.56 (95% CI 0.48 to 0.65)
Carabin 1999 cluster-RCT Canada	One-off hygiene education and disinfection of toys with bleach vs none	Difference in incidence rate for URTI (cluster-level result)	0.28 episodes per 100 child-days lower in intervention group (95% CI 1.65 lower to 1.08 higher); URTI incidence rate IRR 0.80 (95% CI 0.68 to 0.93)
Ibfelt 2015 cluster-RCT Denmark	Disinfectant washing of linen and toys by commercial company every 2 weeks vs usual care	Presence of respiratory viruses on surfaces	Statistically significant reduction in intervention group in adenovirus, rhinovirus, RSV, metapneumovirus, but not other viruses including coronavirus
Kotch 1994 RCT USA	Training in hand-washing and diapering and disinfection of surfaces vs none	Respiratory illness incidence rate in: 1. children < 24 months; 2. children >= 24 months.	1. 14.78 episodes per child-year in intervention; 15.66 in control 2. 12.87 in intervention; 11.77 in control

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Table 5. Results from trials of surface/object disinfection (with or without hand hygiene) compared to control *(Continued)*

McConeghy 2017 RCT USA	Staff education, cleaning products, and audit of compliance and feedback vs none	Infection rates	Upper respiratory infections not reliably recorded or reported.
Sandora 2008 cluster-RCT USA	Hand sanitiser and disinfection of classroom surfaces vs materials about good nutrition (control)	Absence due to respiratory illness (multivariable analysis)	Rate ratio 1.10 for intervention to control (95% CI 0.97 to 1.24)

CI: confidence interval
cluster-RCT: cluster-randomised controlled trial
IRR: incident rate ratio
OR: odds ratio
RCT: randomised controlled trial
RSV: respiratory syncytial virus
URTI: upper respiratory tract infection

Table 6. Results from trials of complex interventions compared to control

Study	**Comparison** (see Table 1 for details of interventions)	**Reported outcomes**	**Results**
Complex hygiene and sanitation interventions compared to control			
Chard 2019 cluster-RCT Laos	Complex sanitation intervention and education vs none	Pupil-reported symptoms of respiratory infection over 1 week	NS difference between groups. 29% of intervention group; 32% control group; adjusted risk ratio 1.08 (95% CI 0.95 to 1.23)
Hartinger 2016 cluster-RCT Peru	Cooking and sanitation provision and education vs none	Number of ARI episodes per child-year	NS difference between groups. Risk ratio for intervention to control 0.95 (95% CI 0.82 to 1.10)
Huda 2012 cluster-RCT Bangladesh	Sanitation provision and education vs none	Respiratory illness	12.6% in intervention group; 13.0% in control group. Not adjusted for multiple outcome measurements. No CIs reported.
Najnin 2019 cluster-RCT Bangladesh	Sanitation and behaviour change intervention (plus cholera vaccine) vs none	Respiratory illness in past 2 days	2.8% in intervention group; 2.9% in control group

ARI: acute respiratory infection
CI: confidence interval
cluster-RCT: cluster-randomised controlled trial
NS: non-significant
RCT: randomised controlled trial

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Table 7. Results from trials of virucidal tissues compared to control

Study	Comparison	Reported outcomes	Results
Virucidal tissues compared with placebo or no tissues			
Farr 1988a and Farr 1988b cluster-RCT USA Trial 1 and Trial 2	Trial 1. Virucidal nasal tissues vs placebo vs none Trial 2. Virucidal nasal tissues vs placebo	Respiratory illnesses per person over 24 weeks Trial 1 Trial 2	Trial 1: 3.4 in tissues group; 3.9 in placebo group; 3.6 in no-tissues group Trial 2: 3.4 in tissues group; 3.6 in placebo group NS
Longini 1988 DB-PC RCT USA	Virucidal nasal tissues vs placebo	Secondary attack rate of viral infections (number of infections in household members of index case)	10.0 in intervention; 14.3 in placebo; NS

cluster-RCT: cluster-randomised controlled trial
DB-PC: double-blind, placebo-controlled
NS: non-significant
RCT: randomised controlled trial
vs: versus

Table 8. Summary of main results of the review for the primary outcomes

Interventions	RCT/cluster-RCT (N = 67)
Medical/surgical masks	**Masks (medical/surgical) compared to no masks** 9 trials no effect on ILI (RR 0.99, 0.82 to 1.18) (Aiello 2010; Barasheed 2014; Canini 2010; Cowling 2008; Jacobs 2009; MacIntyre 2009; MacIntyre 2015; MacIntyre 2016; Suess 2012); 6 trials no effect on laboratory-confirmed influenza 95% CI RR 0.84 (0.61 to 1.17) (Aiello 2012; Cowling 2008; MacIntyre 2009; MacIntyre 2015; MacIntyre 2016; Suess 2012); 2 trials in HCWs no effect on ILI (RR 0.37, 0.05 to 2.50) (Jacobs 2009; MacIntyre 2015). **Medical/surgical masks vs other (non-N95) masks:** 1 trial more ILI with cloth mask (RR 13.25, 1.74 to 100.97) (MacIntyre 2015); 1 trial no effect of catechin-treated masks on influenza (adjusted OR 2.35, 0.40 to 13.72) (Ide 2016).
N95 respirator	**N95 respirators compared to medical/surgical masks** 3 trials no difference for clinical respiratory illness (RR 0.70, 0.45 to 1.10) (MacIntyre 2011; MacIntyre 2013; Radonovich 2019); 4 trials no difference for ILI (95% CI RR 0.81, 0.62 to 1.05) (Loeb 2009; MacIntyre 2009; MacIntyre 2011; Radonovich 2019); 4 trials no difference for laboratory-confirmed influenza (95% CI RR 1.06, 0.81 to 1.38) (Loeb 2009; MacIntyre 2009; MacIntyre 2011; Radonovich 2019). 4 studies conducted in HCWs, 3 trials no difference for clinical respiratory illness (RR 0.70, 0.45 to 1.10) (MacIntyre 2011; MacIntyre 2013; Radonovich 2019); 3 trials no difference for ILI (RR 0.64, 0.32 to 1.31) (Loeb 2009; MacIntyre 2011; Radonovich 2019); 3 trials no difference for laboratory-confirmed ILI (RR 1.02, 0.73 to 1.43) (Loeb 2009; MacIntyre 2011; Radonovich 2019).
Hand hygiene	**Hand hygiene compared to control** 16 trials found effect on combined outcome (ARI or ILI or influenza) (RR 0.89, 0.84 to 0.95) (Azor-Martinez 2018; Biswas 2019; Correa 2012; Cowling 2008; Cowling 2009; Hubner 2010; Larson 2010; Little 2015; Millar 2016; Nicholson 2014; Ram 2015; Roberts 2000; Sandora 2005; Simmerman 2011; Stebbins 2011; Zomer 2015); 7 trials effect on ARI (RR 0.84, 0.82 to 0.86) (Azor-Martinez 2018; Correa 2012; Larson 2010; Little 2015; Millar 2016; Nicholson 2014; Sandora 2005); 10 trials no effect on ILI

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Table 8. Summary of main results of the review for the primary outcomes *(Continued)*

	(RR 0.98, 0.85 to 1.13) (Biswas 2019; Cowling 2008; Cowling 2009; Hubner 2010; Larson 2010; Little 2015; Ram 2015; Roberts 2000; Simmerman 2011; Zomer 2015); 8 trials no effect on laboratory-confirmed influenza (RR 0.91, 95% CI 0.63 to 1.30) (Biswas 2019; Cowling 2008; Cowling 2009; Hubner 2010; Larson 2010; Ram 2015; Simmerman 2011; Stebbins 2011)
Hand hygiene + medical/surgical masks	**Hand hygiene + medical/surgical masks compared to control** 7 trials no effect on ILI (95% CI RR 0.97, 0.80 to 1.19) (Aelami 2015; Aiello 2010; Aiello 2012; Cowling 2009; Larson 2010; Simmerman 2011; Suess 2012); 4 trials no effect on laboratory-confirmed influenza (RR 0.97, 0.69 to 1.36) (Cowling 2009; Larson 2010; Simmerman 2011; Suess 2012). **Hand hygiene + medical/surgical masks compared to hand hygiene** 3 trials no effect on ILI (RR 1.03, 0.69 to 1.53) or laboratory-confirmed influenza (RR 0.99, 0.69 to 1.44) (Cowling 2009; Larson 2010; Simmerman 2011).
Soap + water compared to sanitiser, and comparisons of different types of sanitiser	**Soap + water compared to sanitiser, and comparisons of different types of sanitiser** 1 trial hand sanitiser was more effective than soap and water (Azor-Martinez 2018); 1 trial there was no difference (Savolainen-Kopra 2012). 2 trials in children antiseptic was more effective (Morton 2004; White 2001); 1 trial in children antiseptic = soap (Luby 2005). 1 trial hand sanitisers were better than placebo, but no difference between sanitisers (Turner 2004a); 1 trial no difference between different wipes (Turner 2004b).
Surface/object disinfection (with or without hand hygiene) compared to control	**Surface/object disinfection compared to control** 2 trials were effective on ARI (Ban 2015; Carabin 1999); 1 trial was effective for viruses detected on surface (Ibfelt 2015); 2 trials showed no difference in ARIs (Kotch 1994; McConeghy 2017).
Disinfection of living quarters	-
Complex interventions	**Complex interventions compared to control** 4 trials in low-income countries found no effect on respiratory viral illness (Chard 2019; Hartinger 2016; Huda 2012; Najnin 2019).
Physical interventions (masks, gloves, gowns combined)	-
Gloves	-
Gowns	-
Physical distancing	-
Quarantine in the community	**Quarantine compared to control** 1 trial effective for influenza (Cox hazard ratio 0.799, 95% CI 0.66 to 0.97) (Miyaki 2011).
Eye protection	-
Gargling	**Gargling compared to control** 1 trial gargling with tap water was effective, povidone-iodine was not effective (Satomura 2005); 1 trial gargling with green tea was not more effective than tap water (Ide 2014); 1 trial gargling with water was not effective (Goodall 2014); pooling of 2 trials no effect of gargling (RR 0.91, 95% CI 0.63 to 1.31) (Goodall 2014; Satomura 2005).
Virucidal tissues	**Virucidal tissues compared to control**

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Table 8. Summary of main results of the review for the primary outcomes *(Continued)*

	1 trial had a small effect (Farr 1988a) ("The study authors conclude that virucidal tissues have only a small impact upon the overall rate of natural acute respiratory illnesses"); 2 trials non-significant difference (Farr 1988b; Longini 1988).
Nose wash	-

ARI: acute respiratory infection
CI: confidence interval
HCW: healthcare worker
ILI: influenza-like illness
OR: odds ratio
RCT: randomised controlled trial
RR: risk ratio

Table 9. Trial authors' outcome definitions

	Study	Outcomes definitions
Masks (n = 13)		
1.	Cowling 2008 cluster-RCT Hong Kong	Laboratory: QuickVue Influenza A+B rapid test Viral culture on MDCK (Madin-Darby canine kidney cells) Samples were harvested using NTS, but the text refers to a second procedure from June 2007 onwards with testing for influenza viruses on index participants with a negative QuickVue result but a fever ≥ 38 °C who were also randomised and further followed up. Data on clinical signs and symptoms were collected for all participants, and an additional NTS was collected for later confirmation of influenza infection by viral culture. It is noteworthy that dropout was higher in households of index participants who had a negative result on the rapid influenza test (25/44, 57%) compared to those who had a positive result (45/154, 29%). Effectiveness: secondary attack ratios (SAR): SAR is the proportion of household contacts of an index case who subsequently were ill with influenza (symptomatic contact individuals with at least 1 NTS positive for influenza by viral culture or PCR) 3 clinical definitions were used for secondary analysis: 1. fever ≥ 38 °C or at least 2 of the following symptoms: headache, coryza, sore throat, muscle aches and pains; 2. at least 2 of the following S/S: fever ≥ 37.8 °C, cough, headache, sore throat and muscle aches and pains; and 3. fever of ≥ 37.8 °C plus cough or sore throat. Safety: harms were not mentioned as an outcome in the methods, but it was reported in the results that there were no adverse events.
2.	Jacobs 2009 RCT Japan	Laboratory-confirmation not reported. Effectiveness: URTI is defined on the basis of a symptom score with a score > 14 being a URTI according to Jackson's 1958 criteria ("Jackson score"). These are not explained in text, although the symptoms are listed in Table 3 (any, sore throat, runny nose, stuffy nose, sneeze, cough, headache, earache, feel bad) together with their mean and scores (SD) by intervention arm. Safety: the text does not mention or report harms. These appear to be indistinguishable from URTI symptoms (e.g. headache, which is reported as of significantly longer duration in the intervention arm). Compliance is self-reported as high (84.3% of participants).

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Table 9. Trial authors' outcome definitions *(Continued)*

3.	Loeb 2009 cluster-RCT HCW Canada	Clinical respiratory illness, influenza-like illness, and laboratory-confirmed respiratory virus infection. 1. Clinical respiratory illness, defined as 2 or more respiratory symptoms or 1 respiratory symptom and a systemic symptom. 2. Influenza-like illness, defined as fever ≥ 38 °C plus 1 respiratory symptom. 3. Laboratory-confirmed viral respiratory infection. Laboratory confirmation was by nucleic acid detection using multiplex RT-PCR for 17 respiratory viruses. Safety: harms were not mentioned as an outcome in the methods, but it is stated in the results that no adverse events were reported by participants.
4.	MacIntyre 2009 cluster-RCT Australia	Eligibility criteria were stipulated as follows: 1. the household contained > 2 adults > 16 years of age and 1 child 0 to 15 years of age; 2. the index child had fever (temperature > 37.8 °C) and either a cough or sore throat; 3. the child was the first and only person to become ill in the family in the previous 2 weeks; 4. adult caregivers consented to participate in the study; and 5. the index child was not admitted to the hospital. Definitions used for outcomes: 1. ILI defined by the presence of fever (temperature > 37.8 °C), feeling feverish or a history of fever, > 2 symptoms (sore throat, cough, sneezing, runny nose, nasal congestion, headache), or 1 of the symptoms listed plus laboratory confirmation of respiratory viral infection. 2. Laboratory confirmation: multiplex RT-PCR tests to detect influenza A and B and RSV, PIV types 1–3, picornaviruses (enteroviruses or rhinoviruses), adenoviruses, coronaviruses 229E and OC43, and hMPV plus ≥ 1 sym Effectiveness: presence of ILI or a laboratory diagnosis of respiratory virus infection within 1 week of enrolment. Safety: harms not mentioned as an outcome in the methods, but it is reported in the results that more than 50% of participants reported concerns with mask wearing, mainly that wearing a face mask was uncomfortable, but there were no significant differences between the P2 (N95) and surgical mask groups. Other concerns were that the child did not want the parent wearing a mask.
5.	Aiello 2010 cluster-RCT USA	Laboratory details are described in appendix. Effectiveness: ILI, defined as cough and at least 1 constitutional symptom (fever/feverishness, chills, headache, myalgia). ILI cases were given contact nurses phone numbers to record the illness and paid USD 25 to provide a throat swab. 368 participants had ILI, 94 of which had a throat swab analysed by PCR. 10 of these were positive for influenza (7 for A and 3 for B), respectively by arm 2, 5 and 3 using PCR, 7 using cell culture. Safety: no outcomes on harms planned or reported.
6.	Canini 2010 cluster-RCT USA	The primary endpoint was the proportion of household contacts who developed an ILI during the 7 days following inclusion. Exploratory cluster-level efficacy outcome, the proportion of households with 1 or more secondary illness in household contacts. A temperature over 37.8 °C with cough or sore throat was used as primary clinical case definition. The authors also used a more sensitive case definition based on a temperature over 37.8 °C or at least 2 of the following: sore throat, cough, runny nose, or fatigue.

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Table 9. Trial authors' outcome definitions *(Continued)*

		Safety: adverse reactions due to mask wearing were reported, with 38 (75%) participants in the intervention arm experiencing discomfort with mask use due to warmth (45%), respiratory difficulties (33%), and humidity (33%). Children wearing children face masks reported feeling pain more frequently than other participants wearing adult face masks (P = 0.036).
7.	Aiello 2012 cluster-RCT in halls of residence in the USA	Clinically verified ILI - case definition (presence of cough and at least 1 or more of fever/feverishness, chills, or body aches) Laboratory-confirmed influenza A or B. Throat swab specimens were tested for influenza A or B using real-time PCR. Safety: no outcomes on harms planned or reported.
8.	Barasheed 2014 cluster-RCT Saudi Arabia	Laboratory: 2 nasal swabs from all ILI cases and contacts. 1 for influenza POCT using the QuickVue Influenza (A+B) assay (Quidel Corporation, San Diego, USA) and 1 for later NAT for influenza and other respiratory viruses. However, there was a problem with getting POCT on time during Hajj. Effectiveness: to assess the effectiveness of face masks in the prevention of transmission of ILI. ILI was defined as subjective (or proven) fever plus 1 respiratory symptom (e.g. dry or productive cough, runny nose, sore throat, shortness of breath). Safety: no outcomes on harms planned or reported.
9.	MacIntyre 2011 cluster-RCT China	Clinical respiratory illness Influenza-like illness Laboratory-confirmed viral respiratory infection Laboratory-confirmed influenza A or B 1. Clinical respiratory illness, defined as 2 or more respiratory or 1 respiratory symptom and a systemic symptom. 2. Influenza-like illness, defined as fever ≥ 38 °C plus 1 respiratory symptom (i.e. cough, runny nose, etc.). 3. Laboratory-confirmed viral respiratory infection (detection of adenoviruses, human metapneumovirus, coronavirus 229E/NL63, parainfluenza viruses 1, 2, and 3, influenza viruses A and B, respiratory syncytial virus A and B, rhinovirus A/B and coronavirus OC43/HKU1 by multiplex PCR). 4. Laboratory-confirmed influenza A or B. 5. Adherence with mask/respirator use. Safety: adherence and adverse effects of mask wearing were collected at exit interviews 4 weeks' poststudy. Significantly higher adverse events with N95 respirator compared to medical mask for discomfort, headache, difficulty breathing, nose pressure, trouble communicating, not wearing, and unspecified "other" side effects. Over 50% of those wearing N95 respirators reported adverse events. Of those wearing medical masks versus N95 respirators, 85.5% (420/491) versus 47.4% (447/943) reported no adverse events (P < 0.001), respectively.
10.	MacIntyre 2013 cluster-RCT China	Laboratory: 1. Laboratory-confirmed viral respiratory infection in symptomatic participants, defined as detection of adenoviruses; human metapneumovirus; coronaviruses 229E/NL63 and OC43/HKU1; parainfluenza viruses 1, 2, and 3; influenza viruses A and B; respiratory syncytial viruses A and B; or rhinoviruses A/B by NAT using a commercial multiplex PCR (Seegen, Inc., Seoul, Korea). 2. Laboratory-confirmed influenza A or B in symptomatic participants.

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Table 9. Trial authors' outcome definitions *(Continued)*

		3. Laboratory-confirmed bacterial colonisation in symptomatic participants, defined as detection of *Streptococcus pneumoniae*, *Legionella*, *Bordetella pertussis*, *Chlamydia*, *Mycoplasma pneumoniae*, *or Haemophilus influenzae* type B by multiplex PCR (Seegen, Inc.). Effectiveness: clinical respiratory illness defined as 2 or more respiratory symptoms or 1 respiratory symptom and a systemic symptom. ILI defined as fever (38 °C) plus 1 respiratory symptom. Safety: adverse effects measured using a semi-structured questionnaire. Investigators stated that there was higher reported adverse effects and discomfort of N95 respirators compared with the other 2 arms. In terms of comfort, 52% (297 of 571) of the medical mask arm reported no problems, compared with 62% (317 of 512) of the targeted arm and 38% (217 of 574) of the N95 arm (P < 0.001).
11.	MacIntyre 2015 cluster-RCT Vietnam	Clinical respiratory illness, influenza-like illness, and laboratory-confirmed respiratory virus infection. 1. Clinical respiratory illness, defined as 2 or more respiratory symptoms or 1 respiratory symptom and a systemic symptom. 2. Influenza-like illness, defined as fever ≥ 38 °C plus 1 respiratory symptom. 3. Laboratory-confirmed viral respiratory infection. Laboratory confirmation was by nucleic acid detection using multiplex RT-PCR for 17 respiratory viruses. Safety: adverse events associated with face mask use were reported in 40.4% (227/562) of HCWs in the medical/surgical mask arm and 42.6% (242/568) in the cloth mask arm (P = 0.45). The most frequently reported adverse events were: general discomfort (35.1%; 397/1130) and breathing problems (18.3%; 207/1130). The rate of ILI was higher in the cloth mask arm compared to medical/surgical masks (RR 13.25, 95% CI 1.74 to 100.97).
12.	MacIntyre 2016 cluster-RCT China	Clinical respiratory illness, influenza-like illness, and laboratory-confirmed viral respiratory infection. 1. Clinical respiratory illness, defined as 2 or more respiratory symptoms (cough, nasal congestion, runny nose, sore throat, or sneezes) or 1 respiratory symptom and a systemic symptom (chill, lethargy, loss of appetite, abdominal pain, muscle or joint aches). 2. Influenza-like illness, defined as fever ≥ 38 °C plus 1 respiratory symptom. 3. Laboratory-confirmed viral respiratory infection, defined as detection of adenoviruses, human metapneumovirus, coronaviruses 229E/NL63 and OC43/HKU1, parainfluenza viruses 1, 2, and 3, influenza viruses A and B, respiratory syncytial virus A and B, or rhinovirus A/B by NAT using a commercial multiplex PCR. Safety: no outcomes on harms planned or reported.
13.	Radonovich 2019 cluster-RCT USA	Laboratory. Primary outcome: incidence of laboratory-confirmed influenza, defined as: 1. detection of influenza A or B virus by RT-PCR in an upper respiratory specimen collected within 7 days of symptom onset; 2. detection of influenza from a randomly obtained swab from an asymptomatic participant; and 3. influenza seroconversion (symptomatic or asymptomatic), defined as at least a 4-fold rise in haemagglutination inhibition antibody titres to influenza A or B virus between pre-season and postseason serological samples deemed not attributable to vaccination. Effectiveness. Secondary outcomes: incidence of 4 measures of viral respiratory illness or infection as follows:

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Table 9. Trial authors' outcome definitions *(Continued)*

		1. acute respiratory illness with or without laboratory confirmation; 2. laboratory-detected respiratory infection, defined as detection of a respiratory pathogen by PCR or serological evidence of infection with a respiratory pathogen during the study surveillance period(s), which was added to the protocol prior to data analysis; and 3. laboratory-confirmed respiratory illness, identified as previously described (defined as self-reported acute respiratory illness plus the presence of at least PCR–confirmed viral pathogen in a specimen collected from the upper respiratory tract within 7 days of the reported symptoms and/or at least a 4-fold rise from pre-intervention to postintervention serum antibody titres to influenza A or B virus). Influenza-like illness, defined as temperature of at least 100 °F (37.8 °C) plus cough and/or a sore throat, with or without laboratory confirmation. Safety: 19 participants reported skin irritation or worsening acne during years 3 and 4 at 1 site in the N95 respirator group.
Hand and hygiene (n = 32)		
14.	Alzaher 2018 cluster-RCT Saudi Arabia	Episode of URI was defined as having 2 of the following symptoms for a day or 1 of the symptoms for 2 or more consecutive days: 1) a runny nose, 2) a stuffy or blocked nose or noisy breathing, 3) sneezing, 4) a cough, 5) a sore throat, and 6) feeling hot, having a fever or a chill.
15.	Arbogast 2016 cluster-RCT USA	ICD-9 used: 46611: acute bronchiolitis due to respiratory syncytial virus, 46619: acute bronchiolitis due to other infectious organisms, 4800: pneumonia due to adenovirus, 4809: viral pneumonia, unspecified, 4870: influenza with pneumonia, 07999: unspecified viral infection, 4658: acute upper respiratory infections of other multiple sites, 4659: acute upper respiratory infections of unspecified site, 4871: influenza with other respiratory manifestations.
16.	Azor-Martinez 2016 RCT Spain	Upper respiratory illness was defined as 2 of the following symptoms during 1 day, or 1 of the symptoms for 2 consecutive days: (1) runny nose; (2) stuffy or blocked nose or noisy breathing; (3) cough; (4) feeling hot or feverish or having chills; (5) sore throat; or (6) sneezing.
17.	Azor-Martinez 2018 RCT Spain	Respiratory illness (RI) was defined as the presence of 2 of the following symptoms during 1 day or the presence of 1 of the symptoms for 2 consecutive days: (1) runny nose, (2) stuffy or blocked nose or noisy breathing, (3) cough, (4) feeling hot or feverish or having chills, (5) sore throat, or (6) sneezing. ICD-10 and ICD-9 diagnosis codes used: nonspecific upper respiratory tract infection (465.9), otitis media (382.9), pharyngotonsillitis (463), lower respiratory tract infections (485 and 486), acute bronchitis (490), and bronchiolitis (466.19). Study authors combined the bronchopneumonia code (485) and pneumonia code (486) under the label "lower respiratory tract infections." If > 1 antibiotic was prescribed during an episode, they used the first prescription for analysis. The final diagnosis was done by the medical researchers on the basis of the symptoms described above and a review of the medical history of children with RIs.
18.	Biswas 2019 cluster-RCT Bangladesh	Influenza-like illness: an ILI episode was defined as measured fever > 38 °C or subjective fever and cough. Laboratory-confirmed influenza Nasal swabs for real-time RT-PCR.
19.	Correa 2012	Acute respiratory infection was defined as 2 or more of the following symptoms for at least 24 hours, lasting at least 2 days: runny, stuffy, or blocked nose or noisy

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Table 9. Trial authors' outcome definitions *(Continued)*

	cluster-RCT Colombia	breathing; cough; fever, hot sensation, or chills; and/or sore throat. Ear pain alone was considered ARI alternately.
20.	Cowling 2009 cluster-RCT Hong Kong	Laboratory-confirmed of influenza virus infection by RT-PCR for influenza A and B virus. Clinical influenza-like illness: used 2 clinical definitions of influenza based on self-reported data from the symptom diaries as secondary analyses. The first definition of clinical influenza was at least 2 of the following signs and symptoms: temperature 37.8 °C or greater, cough, headache, sore throat, and myalgia; the second definition was temperature 37.8 °C or greater plus cough or sore throat.
21.	DiVita 2011 (conference abstract) RCT Bangladesh	Influenza-like illness was defined as fever in children < 5 years old and fever with cough or sore throat in individuals > 5 years old.
22.	Feldman 2016 cluster-RCT Israel	Infectious diseases grouped into diarrhoeal, respiratory, and skin infection. Based on ICD-9, but no supplementary material was accessible for further definition (Supplementary Material C lists all ICD-9 diagnoses tallied in this "outcome").
23.	Gwaltney 1980 RCT USA	Viral cultures and serology if rhinovirus in laboratory-inoculation
24.	Hubner 2010 RCT Germany	Assessing illness rates due to common cold and diarrhoea. Collecting data on illness symptoms (common cold, sinusitis, sore throat, fever, cough, bronchitis, pneumonia, influenza, diarrhoea) and associated absenteeism at the end of every month. Definitions of symptoms were given to the participants as part of the individual information at the beginning of the study. Whilst most symptoms are quite self-explanatory, "influenza" and "pneumonia" are specific diagnoses that were confirmed by professional diagnosis only. Similarly, (self-) diagnosis of "fever" required objective measurement with a thermometer.
25.	Ladegaard 1999 RCT Denmark	Laboratory: serological evidence Effectiveness: influenza-like illness (described as fever, history of fever or feeling feverish in the past week, myalgia, arthralgia, sore throat, cough, sneezing, runny nose, nasal congestion, headache). However, a positive laboratory finding for influenza converts the ILI definition into one of influenza.
26.	Larson 2010 cluster-RCT USA	Study goals: rates of symptoms and secondary transmission of URIs, incidence of virologically confirmed influenza, knowledge of prevention and treatment strategies for influenza and URIs, and rates of influenza vaccination. 1. Laboratory-confirmed influenza: nasal swabs to test for influenza types A and B as well as other common respiratory viruses by rapid culture (R-Mix, Diagnostic Hybrids, Inc., Athens, OH, USA). PCR and subtyping of the samples was done during the second half of the second year of the study. 2. Influenza-like illness: CDC definition of ILI from the Sentinel Physicians' Network was used to determine when masks should be worn: "temperature of ≥37.8°C and cough and/or sore throat in the absence of a known cause other than influenza".

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Table 9. Trial authors' outcome definitions *(Continued)*

		3. Episodes of URI = upper respiratory infection: not clear, no explicitly stated definition, reported that the most commonly reported URI symptoms are cough or rhinorrhoea.
27.	Little 2015 RCT England	Respiratory tract infections defined as 2 symptoms of an RTI for at least 1 day or 1 symptom for 2 consecutive days. For reported ILI, study authors did not use WHO or CDC definitions because these definitions require measured temperature, and thus were not appropriate (participants were not included after a clinical examination), and they did not use the European Centre for Disease Prevention and Control definition (1 systemic and 1 respiratory symptom) because, according to the international influenza collaboration, this definition does not necessarily differentiate ILI from a common cold. Influenzanet suggests making high temperature a separate element. Their pragmatic definition of ILI therefore required a high temperature (feeling very hot or very cold; or measured temperature > 37.5 °C), a respiratory symptom (sore throat, cough, or runny nose), and a systemic symptom (headache, severe fatigue, severe muscle aches, or severe malaise).
28.	Luby 2005 RCT Pakistan	Defined pneumonia in children according to the WHO clinical case definition: cough or difficulty breathing with a raised respiratory rate (> 60 per minute in individuals younger than 60 days old, > 50 per minute for those aged 60 to 364 days, and > 40 per minute for those aged 1 to 5 years)
29.	Millar 2016 cluster-RCT USA	Medically attended, outpatient cases of acute respiratory infection in the study population. The case definition was any occurrence of the following International Classification of Disease, 9 Revision, Clinical Modification (ICD-9) symptom or disease-specific codes: 460-466, 480-488, and specifically 465.9, 482.9, 486, and 487.1. **Acute respiratory infections (460 to 466)** 460 Acute nasopharyngitis (common cold) 461 Acute sinusitis 462 Acute pharyngitis 463 Acute tonsillitis 464 Acute laryngitis and tracheitis 465 Acute upper respiratory infections of multiple or unspecified sites 466 Acute bronchitis and bronchiolitis **Pneumonia and influenza (480 to 488)** 480 Viral pneumonia 481 Pneumococcal pneumonia (*Streptococcus pneumoniae* pneumonia) 482 Other bacterial pneumonia 483 Pneumonia due to other specified organism 484 Pneumonia in infectious diseases classified elsewhere 485 Bronchopneumonia, organism unspecified 486 Pneumonia, organism unspecified 487 Influenza 488 Influenza due to identified avian influenza virus 465.9 Acute upper respiratory infections of unspecified site

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Table 9. Trial authors' outcome definitions *(Continued)*

		482.9 Bacterial pneumonia NOS 487.1 Diagnosis of influenza with other respiratory manifestations
30.	Morton 2004 cluster-RCT Cross-over study USA	Respiratory illnesses defined by symptoms of upper respiratory infections such as nasal congestion, cough, or sore throat, in any combination, with or without fever
31.	Nicholson 2014 cluster-RCT India	Acute respiratory infections Operational definitions for all the illnesses were taken from Black's Medical Dictionary. ARIs defined as "Pneumonia, cough, fever, chest pain and shortness of breath, cold, inflammation of any or all of the airways, that is, nose, sinuses, throat, larynx, trachea and bronchi".
32.	Pandejpong 2012 cluster-RCT Thailand	Influenza-like illness defined if 2 or more symptoms of stuffy nose, cough, fever or chills, sore throat, headache, diarrhoea, presence of hand, foot, or mouth ulcers.
33.	Priest 2014 cluster-RCT New Zealand	Respiratory illness was defined as an episode of illness that included at least 2 of the following caregiver-reported symptoms for 1 day, or 1 of these symptoms for 2 days (but not fever alone): runny nose, stuffy or blocked nose or noisy breathing, cough, fever, sore throat, or sneezing.
34.	Ram 2015 RCT Bangladesh	Influenza-like illness Age-specific definitions of ILI. For individuals ≥ 5 years old, ILI was defined as history of fever with cough or sore throat. For children < 5 years old, ILI was defined as fever; study authors used this relatively liberal case definition in order to include influenza cases with atypical presentations in children. Laboratory-confirmed influenza infection Oropharyngeal swabs from index case patients for laboratory testing for influenza. All swabs were tested by PCR for influenza A and B, with further subtyping of influenza A isolates.
35.	Roberts 2000 cluster-RCT Australia	The symptoms of acute upper respiratory illness elicited from parents were: a runny nose, a blocked nose, and cough. Study authors used a definition of colds based on a community intervention trial of virucidal impregnated tissues. A cold was defined as either 2 symptoms for 1 day or 1 of the respiratory symptoms for at least 2 consecutive days, but not including 2 consecutive days of cough alone. Study authors defined a new episode of a cold as the occurrence of respiratory symptoms after a period of 3 symptom-free days.
36.	Sandora 2005 cluster-RCT USA	The overall rates of secondary respiratory and GI illness. Respiratory illness was defined as 2 of the following symptoms for 1 day or 1 of the symptoms for 2 consecutive days: (1) runny nose; (2) stuffy or blocked nose or noisy breathing; (3) cough; (4) fever, feels hot, or has chills; (5) sore throat; and (6) sneezing. An illness was considered new or separate when a period of at least 2 symptom-free days had elapsed since the previous illness. An illness was defined as a secondary case when it began 2 to 7 days after the onset of the same illness type (respiratory or GI) in another household member.

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Table 9. Trial authors' outcome definitions *(Continued)*

37.	Savolainen-Kopra 2012 cluster-RCT Finland	Nasal and pharyngeal stick samples from participants with respiratory symptoms
38.	Simmerman 2011 cluster-RCT Thailand	Influenza-like illness defined by WHO as fever plus cough or sore throat, based on self-reported symptoms. Laboratory-confirmed secondary influenza virus infections amongst household members described as the secondary attack rate. The secondary influenza virus infection was defined as a positive rRT-PCR result on days 3 or 7 or a four-fold rise in influenza HI antibody titres with the virus type and subtype matching the index case.
39.	Stebbins 2011 cluster-RCT USA	The primary outcome was an absence episode associated with an influenza-like illness that was subsequently laboratory confirmed as influenza A or B. The following CDC definition for ILI was used: fever ≥ 38 °C with sore throat or cough.
40.	Talaat 2011 cluster-RCT Egypt	Nasal swab for QuickVue test for influenza A and B viruses. Influenza-like illness (defined as fever > 38 °C and either cough or sore throat).
41.	Temime 2018 cluster-RCT France	ARIs were defined as the combination of at least 1 respiratory symptom and 1 symptom of systemic infection.
42.	Turner 2004b RCT Canada	Virologic assays
43.	Turner 2012 RCT USA	Laboratory-confirmed rhinovirus infection by PCR assay. Common cold illness was defined as the presence of any of the symptoms of nasal obstruction, rhinorrhoea, sore throat, or cough on at least 3 consecutive days. Illnesses separated by at least 3 symptom-free days were considered as separate illnesses.
44.	Yeung 2011 cluster-RCT Hong Kong	Pneumonia
45.	Zomer 2015 cluster-RCT Netherlands	Incidence of gastrointestinal and respiratory infections in children monitored by parents. The common cold was defined as a blocked or runny nose with at least 1 of the following symptoms: coughing, sneezing, fever, sore throat, or earache.
Hand hygiene and masks (n = 6)		
46.	Aelami 2015 (conference abstract)	Influenza-like illness was defined as the presence of at least 2 of the following during their stay: fever, cough, and sore throat.

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Table 9. Trial authors' outcome definitions *(Continued)*

	RCT Saudi Arabia	Safety: no outcomes on harms planned or reported.
47.	Aiello 2010 cluster-RCT USA	Influenza-like illness case definition (presence of cough and at least 1 constitutional symptom (fever/feverishness, chills, or body aches). Safety: no outcomes on harms planned or reported.
48.	Cowling 2009 cluster-RCT Hong Kong	2 clinical definitions of influenza. First definition was at least 2 of the following signs and symptoms: temperature 37.8 °C or greater, cough, headache, sore throat, and myalgia. The second was temperature 37.8 °C or greater plus cough or sore throat. Safety: no outcomes on harms planned or reported.
49.	Larson 2010 cluster-RCT USA	Study goals: rates of symptoms and secondary transmission of URIs, incidence of virologically confirmed influenza, knowledge of prevention and treatment strategies for influenza and URIs, and rates of influenza vaccination. 1. Laboratory-confirmed influenza: nasal swabs to test for influenza types A and B as well as other common respiratory viruses by rapid culture (R-Mix, Diagnostic Hybrids, Inc., Athens, OH, USA). PCR and subtyping of the samples was done during the second half of the second year of the study. 2. Influenza-like illness: CDC definition of ILI from the Sentinel Physicians' Network was used to determine when masks should be worn: "temperature of ≥37.8°C and cough and/or sore throat in the absence of a known cause other than influenza". 3. Episodes of URI = upper respiratory infection: not clear, no explicitly stated definition, reported that the most commonly reported URI symptoms are cough or rhinorrhoea. Safety: no outcomes on harms planned or reported.
50.	Simmerman 2011 cluster-RCT Thailand	Laboratory-confirmed secondary influenza virus infections amongst household members described as the secondary attack rate. The secondary influenza virus infection was defined as a positive rRT-PCR result on days 3 or 7 or a four-fold rise in influenza HI antibody titres with the virus type and subtype matching the index case. Influenza-like illness defined by WHO as fever plus cough or sore throat, based on self-reported symptoms. Safety: no outcomes on harms planned or reported.
51.	Suess 2012 cluster-RCT Germany	Quantitative RT-PCR for samples of nasal wash. Influenza virus infection as a laboratory-confirmed influenza infection in a household member who developed fever (> 38.0 °C), cough, or sore throat during the observation period. Also secondary outcome measure of the occurrence of ILI as defined by WHO as fever plus cough or sore throat. Safety: the study reported that the majority of participants (107/172, 62%) did not report any problems with mask wearing. This proportion was significantly higher in the group of adults (71/100, 71%) compared to the group of children (36/72, 50%) (P = 0.005). The main problem stated by participants (adults and children) was "heat/humidity" (18/34, 53% of children; 10/29, 35% of adults) (P = 0.1), followed by "pain" and "shortness of breath" when wearing a face mask.
Surface/object disinfection (with or without hand hygiene)(n = 8)		

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Table 9. Trial authors' outcome definitions *(Continued)*

52.	Ban 2015 cluster-RCT China	Acute respiratory illness classified as the appearance of 2 or more of the following symptoms: fever, cough and expectoration, runny nose and nasal congestion.
53.	Carabin 1999 cluster-RCT Canada	The presence of nasal discharge (runny nose) accompanied by 1 or several of the following symptoms: fever, sneezing, cough, sore throat, ear pain, malaise, irritability. A URTI was defined as a cold for 2 consecutive days.
54.	Chard 2019 cluster-RCT Laos	Pupils were considered to have symptoms of respiratory infection if they reported cough, runny nose, stuffy nose, or sore throat.
55.	Ibfelt 2015 cluster-RCT Denmark	Laboratory confirmation of 16 respiratory viruses: influenza A; influenza B; coronavirus NL63229E, OC43 and HKU1; parainfluenza virus 1, 2, 3, and 4; rhinovirus; RSV A/B; adenovirus; enterovirus; parechovirus; and bocavirus using quantitative PCR
56.	Kotch 1994 RCT USA	Respiratory symptoms include coughing, runny nose, wheezing or rattling in the chest, sore throat, or earache.
57.	McConeghy 2017 RCT USA	Classified infections as lower respiratory tract infections (i.e. pneumonia, bronchitis, or chronic obstructive pulmonary disease exacerbation) or other.
58.	Sandora 2008 cluster-RCT USA	RI was defined as an acute illness that included > 1 of the following symptoms: runny nose, stuffy or blocked nose, cough, fever or chills, sore throat, or sneezing.
59.	White 2001 DB-RCT USA	RI was defined as: cough, sneezing, sinus trouble, bronchitis, fever alone, pink-eye, headache, mononucleosis, and acute exacerbation of asthma.
Other (miscellaneous) interventions (n = 4)		
60.	Hartinger 2016 cluster-RCT Peru	ARI was defined as a child presenting cough or difficulty breathing, or both. ALRI was defined as a child presenting cough or difficulty breathing, with a raised respiratory rate > 50 per minute in children aged 6 to 11 months and > 40 per minute in children aged > 12 months on 2 consecutive measurements. An episode was defined as beginning on the first day of cough or difficulty breathing and ending with the last day of the same combination, followed by at least 7 days without those symptoms.
61.	Huda 2012 cluster-RCT Bangladesh	Study authors classified acute respiratory illness as having cough and fever or difficulty breathing and fever within 48 h prior to interview.

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Table 9. Trial authors' outcome definitions *(Continued)*

62.	Najnin 2019 cluster-RCT Bangladesh	Classified participants as having respiratory illness if they reported having fever plus either cough or nasal congestion or fever plus breathing difficult.
63.	Satomura 2005 RCT Japan	Upper respiratory tract infection defined as all of the following conditions: 1. both nasal and pharyngeal symptoms; 2. severity of at least 1 symptom increased by 2 grades or more; and 3. worsening of a symptom of 1 increment or more for > 3 days. Because of the difference in the mode of transmission, study authors excluded influenza-like diseases featured by moderate or severe fever; anti-influenza vaccination in the preseason and arthralgia, and treated them separately. The incidence was determined by 1 study physician who was blinded to group assignment.
Virucidal tissues (n = 2)		
64.	Farr 1988a cluster-RCT USA trial 1 and trial 2	RI defined as: occurrence of at least 2 respiratory symptoms on the same day or the occurrence of a single respiratory symptom on 2 consecutive days (except for sneezing). The respiratory symptoms were as follows: sneezing, nasal congestion, nasal discharge, sore throat, scratchy throat, hoarseness, coughing, malaise, headache, feverishness, chilliness and myalgia.
65.	Longini 1988 DB-PC RCT USA	Respiratory illness defined as 1 or more of the following symptoms occurring during the course of acute episode: coryza, sore throat or hoarseness, earache, cough, pain on respiration, wheezy breathing or phlegm from the chest.

ALRI: acute lower respiratory infection
ARIs: acute respiratory infections
CDC: Centers for Disease Control and Prevention
CI: confidence interval
cluster-RCT: cluster-randomised controlled trial
CRI: clinical respiratory illness
DB-PC: double-blind, placebo-controlled
DB-RCT: double-blind randomised controlled trial
GI: gastrointestinal
HCW: healthcare workers
HI: haemagglutinin
hMPV: human metapneumo virus
ICD-9: International Classification of Disease, 9th Revision, Clinical Modification
ICD-10: International Classification of Disease, 10th Revision, Clinical Modification
ILI: influenza-like illness
NAT: nucleic acid testing
NOS: not otherwise specified
NTS: nasal and throat swab
PCR: polymerase chain reaction
PIV: parainfluenza virus
POCT: point-of-care testing
RCT: randomised controlled trial
RI: respiratory infection
RR: risk ratio
rRT-PCR: real-time reverse transcriptase polymerase chain reaction
RSV: respiratory syncytial virus
RTI: respiratory tract infection
RT-PCR: reverse transcriptase polymerase chain reaction
SAR: secondary attack ratios

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SD: standard deviation
S/S: signs and symptoms
URI: upper respiratory infection
URTI: upper respiratory tract infection
WHO: World Health Organization

APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials (CENTRAL) search string

([mh "Influenza, Human"] OR [mh "Influenzavirus A"] OR [mh "Influenzavirus B"] OR [mh "Influenzavirus C"] OR Influenza:ti,ab OR [mh "Respiratory Tract Diseases"] OR Influenzas:ti,ab OR “Influenza-like”:ti,ab OR ILI:ti,ab OR Flu:ti,ab OR Flus:ti,ab OR [mh ^"Common Cold"] OR "common cold":ti,ab OR colds:ti,ab OR coryza:ti,ab OR [mh coronavirus] OR [mh "sars virus"] OR coronavirus:ti,ab OR Coronaviruses:ti,ab OR [mh "coronavirus infections"] OR [mh "severe acute respiratory syndrome"] OR "severe acute respiratory syndrome":ti,ab OR "severe acute respiratory syndromes":ti,ab OR sars:ti,ab OR [mh "respiratory syncytial viruses"] OR [mh "respiratory syncytial virus, human"] OR [mh "Respiratory Syncytial Virus Infections"] OR "respiratory syncytial virus":ti,ab OR "respiratory syncytial viruses":ti,ab OR rsv:ti,ab OR parainfluenza:ti,ab OR “Respiratory illness”:ti,ab OR ((Transmission) AND (Coughing OR Sneezing)) OR ((respiratory:ti,ab AND Tract) AND (infection:ti,ab OR Infections:ti,ab OR illness:ti,ab)))
AND
([mh "Hand Hygiene"] OR handwashing:ti,ab OR “hand-washing”:ti,ab OR ((Hand:ti,ab OR Alcohol:ti,ab) AND (wash:ti,ab OR Washing:ti,ab OR Cleansing:ti,ab OR Rinses:ti,ab OR hygiene:ti,ab OR rub:ti,ab OR Rubbing:ti,ab OR sanitizer:ti,ab OR sanitiser:ti,ab OR cleanser:ti,ab OR disinfected:ti,ab OR Disinfectant:ti,ab OR Disinfect:ti,ab OR antiseptic:ti,ab OR virucid:ti,ab)) OR [mh "gloves, protective"] OR Glove:ti,ab OR Gloves:ti,ab OR [mh Masks] OR [mh "respiratory protective devices"] OR facemask:ti,ab OR Facemasks:ti,ab OR mask:ti,ab OR Masks:ti,ab OR respirator:ti,ab OR respirators:ti,ab OR [mh ^"Protective Clothing"] OR [mh "Protective Devices"] OR "patient isolation":ti,ab OR ((school:ti,ab OR Schools:ti,ab) AND (Closure:ti,ab OR Closures:ti,ab OR Closed:ti,ab)) OR [mh Quarantine] OR quarantine:ti,ab OR "Hygiene intervention":ti,ab OR [mh Mouthwashes] OR gargling:ti,ab OR "nasal tissues":ti,ab OR [mh "Eye Protective Devices"] OR Glasses:ti,ab OR Goggle:ti,ab OR "Eye protection":ti,ab OR Faceshield:ti,ab OR Faceshields:ti,ab OR Goggles:ti,ab OR "Face shield":ti,ab OR "Face shields":ti,ab OR Visors:ti,ab)
AND
([mh "Communicable Disease Control"] OR [mh "Disease Outbreaks"] OR [mh "Disease Transmission, Infectious"] OR [mh "Infection Control"] OR "Communicable Disease Control":ti,ab OR "Secondary transmission":ti,ab OR ((Reduced:ti,ab OR Reduce:ti,ab OR Reduction:ti,ab OR Reducing:ti,ab OR Lower:ti,ab) AND (Incidence:ti,ab OR Occurrence:ti,ab OR Transmission:ti,ab OR Secondary:ti,ab))

Appendix 2. PubMed search string

("Influenza, Human"[Mesh] OR "Influenzavirus A"[Mesh] OR "Influenzavirus B"[Mesh] OR "Influenzavirus C"[Mesh] OR Influenza[tiab] OR "Respiratory Tract Diseases"[Mesh] OR "Bacterial Infections/transmission"[Mesh] OR Influenzas[tiab] OR “Influenza-like”[tiab] OR ILI[tiab] OR Flu[tiab] OR Flus[tiab] OR "Common Cold"[Mesh:NoExp] OR "common cold"[tiab] OR colds[tiab] OR coryza[tiab] OR coronavirus[Mesh] OR "sars virus"[Mesh] OR coronavirus[tiab] OR Coronaviruses[tiab] OR "coronavirus infections"[Mesh] OR "severe acute respiratory syndrome"[Mesh] OR "severe acute respiratory syndrome"[tiab] OR "severe acute respiratory syndromes"[tiab] OR sars[tiab] OR "respiratory syncytial viruses"[Mesh] OR "respiratory syncytial virus, human"[Mesh] OR "Respiratory Syncytial Virus Infections"[Mesh] OR "respiratory syncytial virus"[tiab] OR "respiratory syncytial viruses"[tiab] OR rsv[tiab] OR parainfluenza[tiab] OR “Respiratory illness”[tiab] OR ((Transmission[tiab]) AND (Coughing[tiab] OR Sneezing[tiab])) OR ((respiratory[tiab] AND Tract[tiab]) AND (infection[tiab] OR Infections[tiab] OR illness[tiab])))
AND
("Hand Hygiene"[Mesh] OR handwashing[tiab] OR hand-washing[tiab] OR ((Hand[tiab] OR Alcohol[tiab]) AND (wash[tiab] OR Washing[tiab] OR Cleansing[tiab] OR Rinses[tiab] OR hygiene[tiab] OR rub[tiab] OR Rubbing[tiab] OR sanitizer[tiab] OR sanitiser[tiab] OR cleanser[tiab] OR disinfected[tiab] OR Disinfectant[tiab] OR Disinfect[tiab] OR antiseptic[tiab] OR virucid[tiab])) OR "gloves, protective"[Mesh] OR Glove[tiab] OR Gloves[tiab] OR Masks[Mesh] OR "respiratory protective devices"[Mesh] OR facemask[tiab] OR Facemasks[tiab] OR mask[tiab] OR Masks[tiab] OR respirator[tiab] OR respirators[tiab] OR "Protective Clothing"[Mesh:NoExp] OR "Protective Devices"[Mesh] OR "patient isolation"[tiab] OR ((school[tiab] OR Schools[tiab]) AND (Closure[tiab] OR Closures[tiab] OR Closed[tiab])) OR Quarantine[Mesh] OR quarantine[tiab] OR “Hygiene intervention”[tiab] OR "Mouthwashes"[Mesh] OR gargling[tiab] OR “nasal tissues”[tiab] OR "Eye Protective Devices"[Mesh] OR Glasses[tiab] OR Goggle[tiab] OR “Eye protection”[tiab] OR Faceshield[tiab] OR Faceshields[tiab] OR Goggles[tiab] OR “Face shield”[tiab] OR “Face shields”[tiab] OR Visors[tiab])
AND
("Communicable Disease Control"[Mesh] OR "Disease Outbreaks"[Mesh] OR "Disease Transmission, Infectious"[Mesh] OR "Infection Control"[Mesh] OR Transmission[sh] OR “Prevention and control”[sh] OR "Communicable Disease Control"[tiab] OR “Secondary transmission”[tiab] OR ((Reduced[tiab] OR Reduce[tiab] OR Reduction[tiab] OR Reducing[tiab] OR Lower[tiab]) AND (Incidence[tiab] OR Occurrence[tiab] OR Transmission[tiab] OR Secondary[tiab])))
AND

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(Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab])
NOT
(Animals[Mesh] not (Animals[Mesh] and Humans[Mesh]))
NOT
("Case Reports"[pt] OR Editorial[pt] OR Letter[pt] OR Meta-Analysis[pt] OR "Observational Study"[pt] OR "Systematic Review"[pt] OR "Case Report"[ti] OR "Case series"[ti] OR Meta-Analysis[ti] OR "Meta Analysis"[ti] OR "Systematic Review"[ti])

Appendix 3. Embase (Elsevier) search string

('influenza'/exp OR Influenza:ti,ab OR 'Respiratory Tract Disease'/exp OR Influenzas:ti,ab OR Influenza-like:ti,ab OR ILI:ti,ab OR Flu:ti,ab OR Flus:ti,ab OR 'Common Cold'/de OR "common cold":ti,ab OR colds:ti,ab OR coryza:ti,ab OR 'coronavirus'/exp OR 'SARS coronavirus'/exp OR coronavirus:ti,ab OR Coronaviruses:ti,ab OR 'coronavirus infection'/exp OR 'severe acute respiratory syndrome'/exp OR "severe acute respiratory syndrome":ti,ab OR "severe acute respiratory syndromes":ti,ab OR sars:ti,ab OR 'Pneumovirus'/exp OR 'Human respiratory syncytial virus'/exp OR "respiratory syncytial virus":ti,ab OR "respiratory syncytial viruses":ti,ab OR rsv:ti,ab OR parainfluenza:ti,ab OR "Respiratory illness":ti,ab OR ((Transmission) AND (Coughing OR Sneezing)) OR ((respiratory:ti,ab AND Tract) AND (infection:ti,ab OR Infections:ti,ab OR illness:ti,ab)))
AND
('hand washing'/exp OR handwashing:ti,ab OR hand-washing:ti,ab OR ((Hand:ti,ab OR Alcohol:ti,ab) AND (wash:ti,ab OR Washing:ti,ab OR Cleansing:ti,ab OR Rinses:ti,ab OR hygiene:ti,ab OR rub:ti,ab OR Rubbing:ti,ab OR sanitizer:ti,ab OR sanitiser:ti,ab OR cleanser:ti,ab OR disinfected:ti,ab OR Disinfectant:ti,ab OR Disinfect:ti,ab OR antiseptic:ti,ab OR virucid:ti,ab)) OR 'protective glove'/exp OR Glove:ti,ab OR Gloves:ti,ab OR 'mask'/exp OR 'gas mask'/exp OR facemask:ti,ab OR Facemasks:ti,ab OR mask:ti,ab OR Masks:ti,ab OR respirator:ti,ab OR respirators:ti,ab OR 'protective clothing'/de OR 'protective equipment'/exp OR "patient isolation":ti,ab OR ((school:ti,ab OR Schools:ti,ab) AND (Closure:ti,ab OR Closures:ti,ab OR Closed:ti,ab)) OR 'Quarantine'/exp OR quarantine:ti,ab OR "Hygiene intervention":ti,ab OR 'mouthwash'/exp OR gargling:ti,ab OR "nasal tissues":ti,ab OR 'eye protective device'/exp OR Glasses:ti,ab OR Goggle:ti,ab OR "Eye protection":ti,ab OR Faceshield:ti,ab OR Faceshields:ti,ab OR Goggles:ti,ab OR "Face shield":ti,ab OR "Face shields":ti,ab OR Visors:ti,ab)
AND
('Communicable Disease Control'/exp OR 'epidemic'/exp OR 'disease transmission'/exp OR 'Infection Control'/exp OR "Communicable Disease Control":ti,ab OR "Secondary transmission":ti,ab OR ((Reduced:ti,ab OR Reduce:ti,ab OR Reduction:ti,ab OR Reducing:ti,ab OR Lower:ti,ab) AND (Incidence:ti,ab OR Occurrence:ti,ab OR Transmission:ti,ab OR Secondary:ti,ab)))
AND
(random* OR factorial OR crossover OR placebo OR blind OR blinded OR assign OR assigned OR allocate OR allocated OR 'crossover procedure'/exp OR 'double-blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single-blind procedure'/exp NOT ('animal'/exp NOT ('animal'/exp AND 'human'/exp)))

Appendix 4. CINAHL (EBSCO) search string

((MH "Influenza, Human+") OR (MH "Orthomyxoviridae+") OR TI Influenza OR AB Influenza OR (MH "Respiratory Tract Diseases+") OR TI Influenzas OR AB Influenzas OR TI Influenza-like OR AB Influenza-like OR TI ILI OR AB ILI OR TI Flu OR AB Flu OR TI Flus OR AB Flus OR (MH "Common Cold+") OR TI "common cold" OR AB "common cold" OR TI colds OR AB colds OR TI coryza OR AB coryza OR (MH "coronavirus+") OR (MH "sars virus+") OR TI coronavirus OR AB coronavirus OR TI Coronaviruses OR AB Coronaviruses OR (MH "coronavirus infections+") OR (MH "severe acute respiratory syndrome+") OR TI "severe acute respiratory syndrome" OR AB "severe acute respiratory syndrome" OR TI "severe acute respiratory syndromes" OR AB "severe acute respiratory syndromes" OR TI sars OR AB sars OR (MH "respiratory syncytial viruses+") OR TI "respiratory syncytial virus" OR AB "respiratory syncytial virus" OR TI "respiratory syncytial viruses" OR AB "respiratory syncytial viruses" OR TI rsv OR AB rsv OR TI parainfluenza OR AB parainfluenza OR TI "Respiratory illness" OR AB "Respiratory illness" OR ((Transmission) AND (Coughing OR Sneezing)) OR ((TI respiratory OR AB respiratory AND Tract) AND (TI infection OR AB infection OR TI Infections OR AB Infections OR TI illness OR AB illness)))
AND
((MH "Handwashing+") OR TI handwashing OR AB handwashing OR TI hand-washing OR AB hand-washing OR ((TI Hand OR AB Hand OR TI Alcohol OR AB Alcohol) AND (TI wash OR AB wash OR TI Washing OR AB Washing OR TI Cleansing OR AB Cleansing OR TI Rinses OR AB Rinses OR TI hygiene OR AB hygiene OR TI rub OR AB rub OR TI Rubbing OR AB Rubbing OR TI sanitizer OR AB sanitiser OR TI sanitizer OR AB sanitiser OR TI cleanser OR AB cleanser OR TI disinfected OR AB disinfected OR TI Disinfectant OR AB Disinfectant OR TI Disinfect OR AB Disinfect OR TI antiseptic OR AB antiseptic OR TI virucid OR AB virucid)) OR (MH "gloves+") OR TI Glove OR AB Glove OR Gloves OR (MH "Masks+") OR (MH "respiratory protective devices+") OR TI facemask OR AB facemask OR TI Facemasks OR AB Facemasks OR TI mask OR AB mask OR TI Masks OR AB Masks OR TI respirator OR AB respirator OR TI respirators OR AB respirators OR (MH "Protective Clothing") OR (MH "Protective Devices+") OR TI "patient isolation" OR AB "patient isolation" OR ((TI school OR AB school OR TI Schools OR AB Schools) AND (TI Closure OR AB Closure OR TI Closures OR AB Closures OR TI Closed OR AB Closed)) OR (MH "Quarantine+") OR TI quarantine OR AB quarantine OR TI "Hygiene intervention" OR AB "Hygiene intervention" OR (MH "Mouthwashes+") OR TI gargling OR AB gargling OR TI "nasal tissues" OR AB "nasal tissues" OR (MH "Eye Protective Devices+") OR TI Glasses OR AB Glasses OR TI Goggle OR AB Goggle OR TI "Eye protection" OR AB "Eye protection" OR TI Faceshield OR AB Faceshield OR TI Faceshields OR AB Faceshields OR TI Goggles OR AB Goggles OR TI "Face shield" OR AB "Face shield" OR TI "Face shields" OR AB "Face shields" OR TI Visors OR AB Visors)
AND

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((MH "Infection Control+") OR (MH "Disease Outbreaks+") OR (MH "Infection Control+") OR TI "Communicable Disease Control" OR AB "Communicable Disease Control" OR TI "Secondary transmission" OR AB "Secondary transmission" OR ((TI Reduced OR AB Reduced OR TI Reduce OR AB Reduce OR TI Reduction OR AB Reduction OR TI Reducing OR AB Reducing OR TI Lower OR AB Lower) AND (TI Incidence OR AB Incidence OR TI Occurrence OR AB Occurrence OR TI Transmission OR AB Transmission OR TI Secondary OR AB Secondary)))
AND
((MH "Clinical Trials+") OR (MH "Quantitative Studies") OR TI placebo* OR AB placebo* OR (MH "Placebos") OR (MH "Random Assignment") OR TI random* OR AB random* OR TI ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*)) OR AB ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*)) OR TI clinic* trial* OR AB clinic* trial* OR PT clinical trial)

Appendix 5. Previous search strategies (pre-2010)

Details of the 2010 update and the search strategy used in the original review and the 2009 search strategy updates for MEDLINE, CENTRAL, EMBASE and CINAHL

In the 2010 update we searched, as we have done previously, the Cochrane Central Register of Controlled Trials (CENTRAL) 2010, Issue 3, which includes the Acute Respiratory Infections Group's Specialised Register, MEDLINE (April 2009 to October week 2, 2010), EMBASE (April 2009 to October 2010) and CINAHL (January 2009 to October 2010). Details of previous searches are in Appendix 1. In addition, to include more of the literature of low-income countries in this update, we ran searches in LILACS (2008 to October 2010), Indian MEDLARS (2008 to October 2010) and IMSEAR (2008 to October 2010).

We used the following search strategy (updated to include new and emerging respiratory viruses) to search MEDLINE and CENTRAL. We combined the MEDLINE search strategy with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Ovid format) (Lefebvre 2011). We also included an additional search strategy based on the work of Fraser, Murray and Burr (Fraser 2006) to identify observational studies.

1 Influenza, Human/
2 exp Influenzavirus A/
3 exp Influenzavirus B/
4 Influenzavirus C/
5 (influenza* or flu).tw.
6 Common Cold/
7 common cold*.tw.
8 Rhinovirus/
9 rhinovir*.tw.
10 adenoviridae/ or mastadenovirus/ or adenoviruses, human/
11 adenoviridae infections/ or adenovirus infections, human/
12 adenovir*.tw.
13 coronavirus/ or coronavirus 229e, human/ or coronavirus oc43, human/ or infectious bronchitis virus/ or sars virus/
14 coronavir*.tw.
15 coronavirus infections/ or severe acute respiratory syndrome/
16 (severe acute respiratory syndrome* or sars).tw.
17 respiratory syncytial viruses/ or respiratory syncytial virus, human/
18 Respiratory Syncytial Virus Infections/
19 (respiratory syncytial virus* or rsv).tw.
20 Pneumovirus Infections/
21 parainfluenza virus 1, human/ or parainfluenza virus 3, human/
22 parainfluenza virus 2, human/ or parainfluenza virus 4, human/
23 (parainfluenza* or para-influenza* or para influenza).tw.
24 enterovirus a, human/ or exp enterovirus b, human/ or enterovirus c, human/ or enterovirus d, human/
25 Enterovirus Infections/
26 enterovir*.tw.
27 Human bocavirus/
28 bocavirus*.tw.
29 Metapneumovirus/
30 metapneumovir*.tw.
31 Parvovirus B19, Human/
32 parvoviridae infections/ or erythema infectiosum/
33 parvovirus*.tw.
34 Parechovirus/
35 parechovirus*.tw.
36 acute respiratory tract infection*.tw.
37 acute respiratory infection*.tw.
38 or/1-37

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39 Handwashing/
40 (handwashing or hand washing or hand-washing).tw.
41 hand hygiene.tw.
42 (sanitizer* or sanitiser*).tw.
43 (cleanser* or disinfectant*).tw.
44 gloves, protective/ or gloves, surgical/
45 glov*.tw.
46 masks/ or respiratory protective devices/
47 (mask or masks or respirator or respirators).tw.
48 Protective Clothing/
49 Protective Devices/
50 Patient Isolators/
51 Patient Isolation/
52 patient isolat*.tw.
53 (barrier* or curtain* or partition*).tw.
54 negative pressure room*.tw.
55 ((reverse barrier or reverse-barrier) adj3 (nurs* or unit or isolation)).tw.
56 Cross Infection/pc [Prevention & Control]
57 (cross infection* adj2 prevent*).tw.
58 Communicable Disease Control/
59 Infection Control/
60 (school* adj3 (clos* or dismissal*)).tw.
61 temporary closur*.tw.
62 mass gathering*.tw.
63 (public adj2 (gathering* or event*)).tw.
64 (bans or banning or banned or ban).tw.
65 (outbreak adj3 control*).tw.
66 distancing*.tw.
67 Quarantine/
68 quarantine*.tw.
69 (protective adj2 (cloth* or garment* or device* or equipment)).tw.
70 ((protective or preventive) adj2 (procedure* or behaviour* or behavior*)).tw.
71 personal protect*.tw.
72 (isolation room* or isolation strateg*).tw.
73 (distance adj2 patient*).tw.
74 ((spatial or patient) adj separation).tw.
75 cohorting.tw.
76 or/39-75
77 38 and 76
78 (animals not (animals and humans)).sh.
79 77 not 78

Ovid MEDLINE

1 Influenza, Human/
2 exp Influenzavirus A/
3 exp Influenzavirus B/
4 Influenzavirus C/
5 (influenza* or flu).tw.
6 Common Cold/
7 common cold*.tw.
8 Rhinovirus/
9 rhinovir*.tw.
10 adenoviridae/ or mastadenovirus/ or adenoviruses, human/
11 adenoviridae infections/ or adenovirus infections, human/
12 adenovir*.tw.
13 coronavirus/ or coronavirus 229e, human/ or coronavirus oc43, human/ or infectious bronchitis virus/ or sars virus/
14 coronavir*.tw.
15 coronavirus infections/ or severe acute respiratory syndrome/
16 (severe acute respiratory syndrome* or sars).tw.
17 respiratory syncytial viruses/ or respiratory syncytial virus, human/
18 Respiratory Syncytial Virus Infections/

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19 (respiratory syncytial virus* or rsv).tw.
20 Pneumovirus Infections/
21 parainfluenza virus 1, human/ or parainfluenza virus 3, human/
22 parainfluenza virus 2, human/ or parainfluenza virus 4, human/
23 (parainfluenza* or para-influenza* or para influenza).tw.
24 enterovirus a, human/ or exp enterovirus b, human/ or enterovirus c, human/ or enterovirus d, human/
25 Enterovirus Infections/
26 enterovir*.tw.
27 Human bocavirus/
28 bocavirus*.tw.
29 Metapneumovirus/
30 metapneumovir*.tw.
31 Parvovirus B19, Human/
32 parvoviridae infections/ or erythema infectiosum/
33 parvovirus*.tw.
34 Parechovirus/
35 parechovirus*.tw.
36 acute respiratory tract infection*.tw.
37 acute respiratory infection*.tw.
38 or/1-37
39 Handwashing/
40 (handwashing or hand washing or hand-washing).tw.
41 hand hygiene.tw.
42 (sanitizer* or sanitiser*).tw.
43 (cleanser* or disinfectant*).tw.
44 gloves, protective/ or gloves, surgical/
45 glov*.tw.
46 masks/ or respiratory protective devices/
47 (mask or masks or respirator or respirators).tw.
48 Protective Clothing/
49 Protective Devices/
50 Patient Isolators/
51 Patient Isolation/
52 patient isolat*.tw.
53 (barrier* or curtain* or partition*).tw.
54 negative pressure room*.tw.
55 ((reverse barrier or reverse-barrier) adj3 (nurs* or unit or isolation)).tw.
56 Cross Infection/pc [Prevention & Control]
57 (cross infection* adj2 prevent*).tw.
58 Communicable Disease Control/
59 Infection Control/
60 (school* adj3 (clos* or dismissal*)).tw.
61 temporary closur*.tw.
62 mass gathering*.tw.
63 (public adj2 (gathering* or event*)).tw.
64 (bans or banning or banned or ban).tw.
65 (outbreak adj3 control*).tw.
66 distancing*.tw.
67 Quarantine/
68 quarantine*.tw.
69 (protective adj2 (cloth* or garment* or device* or equipment)).tw.
70 ((protective or preventive) adj2 (procedure* or behaviour* or behavior*)).tw.
71 personal protect*.tw.
72 (isolation room* or isolation strateg*).tw.
73 (distance adj2 patient*).tw.
74 ((spatial or patient) adj separation).tw.
75 cohorting.tw.
76 or/39-75
77 38 and 76
78 (animals not (animals and humans)).sh.
79 77 not 78

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Embase.com search strategy, October 2010
The search strategy was broadened in 2010 to be more inclusive of new and emerging viruses.

#3 #1 AND #25899
#2 766172
#2.8 #2.3 NOT #2.7766172
#2.7 #2.4 NOT #2.6
#2.6 #2.4 AND #2.5
#2.5 'human'/de AND [embase]/lim
#2.4 'animal'/de OR 'nonhuman'/de OR 'animal experiment'/de AND [embase]/lim
#2.3 #2.1 OR #2.2
#2.2 random*:ab,ti OR placebo*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR allocat*:ab,ti OR trial:ti OR (doubl* NEXT/1 blind*):ab,ti AND [embase]/lim
#2.1 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp AND [embase]/lim

#1 74545
#1.65 #1.28 AND #1.6474545
#1.64 #1.29 OR #1.30 OR #1.31 OR #1.32 OR #1.33 OR #1.34 OR #1.35 OR
#1.36 OR #1.37 OR #1.38 OR #1.39 OR #1.40 OR #1.41 OR #1.42 OR #1.43
OR #1.44 OR #1.45 OR #1.46 OR #1.47 OR #1.48 OR #1.49 OR #1.50 OR
#1.51 OR #1.52 OR #1.53 OR #1.54 OR #1.55 OR #1.56 OR #1.57 OR #1.58
OR #1.59 OR #1.60 OR #1.61 OR #1.62 OR #1.63
#1.63 cohorting:ab,ti OR 'cohort isolation':ab,ti AND [embase]/lim
#1.62 ((spatial OR patient*) NEAR/2 separation):ab,ti AND [embase]/lim
#1.61 (distance NEAR/2 patient*):ab,ti AND [embase]/lim
#1.60 (isolation NEXT/1 (room* OR strateg*)):ab,ti AND [embase]/lim
#1.59 'personal protection':ab,ti AND [embase]/lim
#1.58 ((protective OR preventive) NEAR/2 (procedure* OR behaviour* OR behavior*)):ab,ti AND [embase]/lim
#1.57 (protective NEAR/2 (cloth* OR garment* OR device* OR equipment)):ab,ti AND [embase]/lim
#1.56 quarantin*:ab,ti AND [embase]/lim
#1.55 distancing:ab,ti AND [embase]/lim
#1.54 ((outbreak* OR transmission OR infection*) NEAR/2 control):ab,ti AND [embase]/lim
#1.53 bans:ab,ti OR banning:ab,ti OR banned:ab,ti OR ban:ab,ti AND [embase]/lim
#1.52 (public NEAR/2 (gathering* OR event*)):ab,ti AND [embase]/lim
#1.51 'mass gathering':ab,ti OR 'mass gatherings':ab,ti AND [embase]/lim
#1.50 (temporar* NEAR/2 closur*):ab,ti AND [embase]/lim
#1.49 (school* NEAR/3 (clos* OR dismissal*)):ab,ti AND [embase]/lim
#1.48 'infection control'/de AND [embase]/lim
#1.47 'epidemic'/dm_pc AND [embase]/lim
#1.46 (('cross infection' OR 'cross infections') NEAR/2 prevent*):ab,ti AND [embase]/lim
#1.45 'cross infection'/dm_pc AND [embase]/lim
#1.44 (('reverse barrier' OR 'reverse-barrier') NEAR/3 (nurs* OR unit OR isolat*)):ab,ti AND [embase]/lim
#1.43 'negative pressure room':ab,ti OR 'negative pressure rooms':ab,ti AND [embase]/lim
#1.42 barrier*:ab,ti OR curtain*:ab,ti OR partition*:ab,ti AND [embase]/lim
#1.41 (patient* NEAR/2 isolat*):ab,ti AND [embase]/lim
#1.40 'patient isolator'/de AND [embase]/lim
#1.39 'protective equipment'/de AND [embase]/lim
#1.38 'protective clothing'/de AND [embase]/lim
#1.37 facemask*:ab,ti OR mask:ab,ti OR masks:ab,ti OR goggles:ab,ti
OR respirator*:ab,ti OR respirators:ab,ti AND [embase]/lim
#1.36 'face mask'/exp OR 'mask'/de OR 'surgical mask'/de AND [embase]/lim
#1.35 glov*:ab,ti AND [embase]/lim
#1.34 'surgical glove'/de AND [embase]/lim
#1.33 cleanser*:ab,ti OR disinfect*:ab,ti OR antiseptic*:ab,ti OR virucid*:ab,ti AND [embase]/lim
#1.32 sanitizer*:ab,ti OR sanitiser*:ab,ti AND [embase]/lim
#1.31 (alcohol NEAR/2 rub*):ab,ti AND [embase]/lim
#1.30 handwash*:ab,ti OR (hand* NEAR/2 (wash* OR cleans* OR hygiene)):ab,ti AND [embase]/lim
#1.29 'hand washing'/de AND [embase]/lim
#1.28 #1.1 OR #1.2 OR #1.3 OR #1.4 OR #1.5 OR #1.6 OR #1.7 OR #1.8 OR #1.9 OR #1.10 OR #1.11 OR #1.12 OR #1.13 OR #1.14 OR #1.15 OR
#1.16 OR #1.17 OR #1.18 OR #1.19 OR #1.20 OR #1.21 OR #1.22 OR #1.23
OR #1.24 OR #1.25 OR #1.26 OR #1.27

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#1.27 (respiratory NEAR/2 (infect* OR illness* OR virus* OR pathogen* OR acute)):ab,ti AND [embase]/lim
#1.26 parechovirus*:ab,ti AND [embase]/lim
#1.25 'parechovirus'/de AND [embase]/lim
#1.24 parvovirus*:ab,ti AND [embase]/lim
#1.23 'parvovirus infection'/de OR 'erythema infectiosum'/exp AND [embase]/lim
#1.22 'parvovirus'/de OR 'human parvovirus b19'/de AND [embase]/lim
#1.21 'human metapneumovirus'/de OR 'human metapneumovirus infection'/de AND [embase]/lim
#1.20 'bocavirus'/de OR 'bocavirus infection'/de AND [embase]/lim
#1.19 enterovir*:ab,ti AND [embase]/lim
#1.18 'enterovirus infection'/de OR 'coxsackie virus infection'/de OR 'echovirus infection'/de AND [embase]/lim
#1.17 'enterovirus'/de OR 'coxsackie virus'/exp OR 'echo virus'/de AND [embase]/lim
#1.16 parainfluenza:ab,ti OR 'para influenza':ab,ti OR 'para-influenza':ab,ti AND [embase]/lim
#1.15 'parainfluenza virus'/exp AND [embase]/lim
#1.14 'pneumovirus infection'/de AND [embase]/lim
#1.13 'respiratory syncytial virus':ab,ti OR 'respiratory syncytial viruses':ab,ti OR rsv:ab,ti AND [embase]/lim
#1.12 'respiratory syncytial pneumovirus'/de OR 'respiratory syncytial virus infection'/exp AND [embase]/lim
#1.11 coronavir*:ab,ti OR sars:ab,ti OR 'severe acute respiratory syndrome':ab,ti AND [embase]/lim
#1.10 'coronavirus infection'/de OR 'severe acute respiratory syndrome'/de AND [embase]/lim
#1.9 'coronavirus'/de OR 'human coronavirus nl63'/de OR 'sars coronavirus'/de OR 'transmissible gastroenteritis virus'/de
#1.8 adenovir*:ab,ti AND [embase]/lim
#1.7 'adenovirus infection'/de OR 'human adenovirus infection'/de OR 'human adenovirus'/exp AND [embase]/lim
#1.6 rhinovir*:ab,ti AND [embase]/lim
#1.5 'rhinovirus infection'/de OR 'human rhinovirus'/de AND [embase]/lim
#1.4 'common cold':ab,ti OR 'common colds':ab,ti OR coryza:ab,ti OR colds:ab,ti AND [embase]/lim
#1.3 'common cold'/de OR 'common cold symptom'/de AND [embase]/lim
#1.2 influenza*:ab,ti OR flu:ab,ti AND [embase]/lim
#1.1 'influenza'/exp AND [embase]/lim

CINAHL (EBSCO) search strategy, October 2010
The search strategy was broadened in 2010 to be more inclusive of new and emerging viruses.

S54 S32 and S53
S53 S44 or S52
S52 S45 or S46 or S47 or S48 or S49 or S50 or S51
S51 TI observational stud* or AB observational stud*
S50 TI cohort stud* or AB cohort stud*
S49 (MH "Cross Sectional Studies")
S48 (MH "Nonconcurrent Prospective Studies")
S47 (MH "Correlational Studies")
S46 (MH "Case Control Studies+")
S45 (MH "Prospective Studies")
S44 S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43
S43 TI allocat* N1 random* or AB allocat* N1 random*
S42 (MH "Quantitative Studies")
S41 TI placebo* or AB placebo*
S40 (MH "Placebos")
S39 TI random* allocation* or AB random* allocation*
S38 (MH "Random Assignment")
S37 TI (randomised control* trial* or randomized control* trial*) or AB (randomised control* trial* or randomized control* trial)
S36 TI ((singl* W1 blind*) or (singl* W1 mask*) or (doubl* W1 blind*) or (doubl* W1 mask*) or (trebl* W1 blind*) or (trebl* W1 mask*) or (tripl* W1 blind*) or (tripl* W1 mask*)) or AB ((singl* W1 blind*) or (singl* W1 mask*) or (doubl* W1 blind*) or (doubl* W1 mask*) or (trebl* W1 blind*) or (trebl* W1 mask*) or (tripl* W1 blind*) or (tripl* W1 mask*))
S35 TI clinic* W1 trial* or AB clinic* W1 trial*
S34 PT clinical trial
S33 (MH "Clinical Trials+")
S32 S15 and S31
S31 S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30
S30 TI (bans or banning or banned or ban or "outbreak control" or "outbreak controls" or distancing* or quarantine* or "protective clothing" or "protective garment" or "protective garments" or "protective gown" or "protective gowns" or "protective device" or "protective devices" or "protective equipment" or "protective behaviour" or "protective behavior" or "protective behaviours" or "protective behaviors" or "protective procedure" or "protective procedures" or "preventive behaviours" or "preventive behaviour" or "preventive behavior" or "preventive behaviors" or "preventive procedure" or "preventive procedures" or "personal protective" or

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"isolation room" or "isolation rooms" or "isolation strategy" or "isolation strategies" or "patient distance" or "patient distancing" or "patient separation" or "spatial separation") or AB (handwashing or "hand washing" or hand-washing or "hand hygiene" or sanitizer or sanitiser or cleanser* or disinfectant* or glov* or mask or masks or respirator or respirators or "patient isolation" or "patient isolators" or barrier* or curtain* or partition* or "negative pressure room" or "negative pressure rooms" or "reverse barrier nursing" or "reverse barrier unit" or "reverse barrier isolation" or "cross infection" or "infection control" or "disease control" or "school closure" or "school closures" or "school dismissal" or "school dismissals" or "temporary closure" or "temporary closures" or "mass gathering" or "mass gatherings" or "public gathering" or "public gatherings" or "public event" or "public events")
S29 TI (handwashing or "hand washing" or hand-washing or "hand hygiene" or sanitizer or sanitiser or cleanser* or disinfectant* or glov* or mask or masks or respirator or respirators or "patient isolation" or "patient isolators" or barrier* or curtain* or partition* or "negative pressure room" or "negative pressure rooms" or "reverse barrier nursing" or "reverse barrier unit" or "reverse barrier isolation" or "cross infection" or "infection control" or "disease control" or "school closure" or "school closures" or "school dismissal" or "school dismissals" or "temporary closure" or "temporary closures" or "mass gathering" or "mass gatherings" or "public gathering" or "public gatherings" or "public event" or "public events") or AB (handwashing or "hand washing" or hand-washing or "hand hygiene" or sanitizer or sanitiser or cleanser* or disinfectant* or glov* or mask or masks or respirator or respirators or "patient isolation" or "patient isolators" or barrier* or curtain* or partition* or "negative pressure room" or "negative pressure rooms" or "reverse barrier nursing" or "reverse barrier unit" or "reverse barrier isolation" or "cross infection" or "infection control" or "disease control" or "school closure" or "school closures" or "school dismissal" or "school dismissals" or "temporary closure" or "temporary closures" or "mass gathering" or "mass gatherings" or "public gathering" or "public gatherings" or "public event" or "public events")
S28 (MH "Sterilization and Disinfection")
S27 (MH "Quarantine")
S26 (MH "Area Restriction (Iowa NIC)") OR (MH "Infection Protection (IowaNIC)")
S25 (MH "Infection Control")
S24 (MH "Cross Infection/PC")
S23 (MH "Isolation, Reverse")
S22 (MH "Patient Isolation")
S21 (MH "Protective Devices")
S20 (MH "Protective Clothing")
S19 (MH "Respiratory Protective Devices")
S18 (MH "Masks")
S17 (MH "Gloves")
S16 (MH "Handwashing+")
S15 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14
S14 TI ("acute respiratory tract infection" or "acute respiratory tract infections" or "acute respiratory infection" or "acute respiratory infections") or AB (influenza* or flu or "common cold" or "common colds" or rhinovir* or adenovir* or coronavir* or sars or "severe acute respiratory syndrome" or "respiratory syncytial virus" or "respiratory syncytial viruses" or rsv or pneumovir* or parainfluenza* or "para influenza" or para-influenza or enterovir* or bocavir* or metapneumovir* or parvovir* or parechovir*)
S13 TI (influenza* or flu or "common cold" or "common colds" or rhinovir* or adenovir* or coronavir* or sars or "severe acute respiratory syndrome" or "respiratory syncytial virus" or "respiratory syncytial viruses" or rsv or pneumovir* or parainfluenza* or "para influenza" or para-influenza or enterovir* or bocavir* or metapneumovir* or parvovir* or parechovir*) or AB (influenza* or flu or "common cold" or "common colds" or rhinovir* or adenovir* or coronavir* or sars or "severe acute respiratory syndrome" or "respiratory syncytial virus" or "respiratory syncytial viruses" or rsv or pneumovir* or parainfluenza* or "para influenza" or para-influenza or enterovir* or bocavir* or metapneumovir* or parvovir* or parechovir*)
S12 (MH "Respiratory Tract Infections+")
S11 (MH "Parvovirus Infections+")
S10 (MH "Enterovirus Infections+")
S9 (MH "Enteroviruses+")
S8 (MH "Respiratory Syncytial Virus Infections")
S7 (MH "Respiratory Syncytial Viruses")
S6 (MH "SARS Virus")
S5 (MH "Severe Acute Respiratory Syndrome")
S4 (MH "Coronavirus Infections+")
S3 (MH "Coronavirus+") OR (MH "Coronavirus Infections")
S2 (MH "Common Cold")
S1 (MH "Influenza+") OR (MH "Influenza A H5N1") OR (MH "Influenza A

LILACS (Latin America and Caribbean) search strategy
(mh:"Influenza, Human" OR "Gripe Humana" OR "Influenza Humana" OR influenza* OR flu OR grippe OR gripe OR mh:"Influenzavirus A" OR mh:b04.820.545.405* OR mh:b04.909.777.545.405* OR mh:"Influenzavirus B" OR mh:b04.820.545.407* OR mh:b04.909.777.545.407* OR "influenzavirus B" OR mh:"Influenzavirus C" OR "Influenzavirus C" OR mh:"Common Cold" OR "common cold" OR "common colds" OR "Resfriado Común" OR "Resfriado Comum" OR coryza OR "Coriza Aguda") AND (mh:handwashing OR "Lavado de Manos" OR "Lavagem de Mãos" OR "Desinfección de Manos" OR "Desinfecção de Mãos" OR "Higienização de Mãos Pré-Cirúrgica" OR handwash* OR "hand washing" OR "hand hygiene" OR "hand cleaning" OR "hand cleanse" OR "hand cleansing" OR higiene OR sanitizer* OR

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sanitiser* OR cleanser* OR disinfect* OR esteriliza* OR desinfectar* OR virucid* OR antiseptic* OR mh:"Gloves, Protective" OR "protective glove" OR "protective gloves" OR "Guantes Protectores" OR "Luvas Protetoras" OR mh:e07.700.600.400* OR mh:j01.637.215.600.400* OR mh:j01.637.708.600.400* OR glov* OR guantes OR luvas OR mh:masks OR mask* OR máscaras OR mascarillas OR facemask* OR goggles OR respirator* OR mh:"Respiratory Protective Devices" OR "Dispositivos de Protección Respiratoria" OR "Dispositivos de Proteção Respiratória" OR mh:"Protective Clothing" OR "Ropa de Protección" OR "Roupa de Proteção" OR mh:e07.700.600* OR mh:j01.637.215.600* OR mh:j01.637.708.600* OR mh:"Protective Devices" OR "Equipos de Seguridad" OR "Equipamentos de Proteção" OR mh:e07.700* OR mh:j01.637.708* OR mh:vs2.006.001.001* OR mh:vs4.002.001.001.007.002.002* OR mh:"Patient Isolation" OR "patient isolation" OR "Aislamiento de Pacientes" OR "Isolamento de Pacientes" OR mh:"Patient Isolators" OR "patient isolators" OR "Aisladores de Pacientes" OR "Isoladores de Pacientes" OR barrier* OR curtain* OR partition* OR barrera OR barreira OR cortina OR tabique OR mh:"Cross Infection" OR "cross infection" OR "Infección Hospitalaria" OR "Infecção Hospitalar" OR "Infecciones en Hospitales" OR "Infecciones Nosocomiales" OR "Infecções Nosocomiais" OR mh:"Infection Control" OR mh:n06.850.780.200.450* OR "Control de Infecciones" OR "Controle de Infecções" OR mh:"Communicable Disease Control" OR "Control de Enfermedades Transmisibles" OR "Controle de Doenças Transmissíveis" OR mh:n06.850.780.200* OR mh:sp8.946.819.811* OR mh:"Disease Outbreaks/prevention & control" OR mh:quarantine OR cuarentena OR quarentena OR "personal protection" OR "isolation room" OR "sala de aislamiento" OR "quarto de isolamento" OR "patient distance" OR "distancia del paciente" OR "spatial separation" OR cohort* OR ban OR bans OR banning OR banned OR prohibici* OR proibi* OR "outbreak control" OR distanc* OR "school closure" OR "school closures" OR "temporary closure" OR "temporary closures" OR "cierre de la escuela" OR "fechamento da escola" OR "public gathering" OR "public gatherings" OR "reunion publica" OR "reverse barrier nursing" OR "reverse barrier unit" OR "reverse barrier isolation" OR "negative pressure room" OR "negative pressure rooms" OR "patient separation") AND db:("LILACS") AND type_of_study:("clinical_trials" OR "cohort" OR "case_control")

Indian MEDLARS search strategy
(influenza$ or flu or common cold$ or rhinovir$ or coronavir$ or adenovir$ or severe acute respiratory syndrome$ or sars or respiratory syncytial virus$ or rsv or parainfluenza$ or enterovir$ or metapneumovir$ or parvovir$ or bocavir$ or parechovir$) and (handwashing or hand washing or mask$ or glov$ or protect$ or isolat$ or barrier$ or curtain$ or partition$ or cross infection$ or infection control$ or disease control$ or school$ or quarantine$ or ban$ or cohort$ or distanc$ or spatial separation$)
IMSEAR (Index Medicus for the South East Asia Region) search strategy
(influenza or flu or common cold or rhinovirus or coronavirus or adenovirus or severe acute respiratory syndrome or sars or respiratory syncytial virus or rsv or parainfluenza or enterovirus or bocavirus or metapneumovirus or parvovirus or parechovirus) and (handwashing or hand washing or hand hygiene or sanitizer or sanitiser or cleanser or disinfectant or gloves or masks or mask or protective clothing or protective devices or patient isolation or barrier or curtain or partition or cross infection or disease control or infection control or school or schools or bans or banning or banned or ban or distancing or quarantine or isolation or spatial separation or cohorting or cohort isolation)

In the first publication of this review we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2006, issue 4); MEDLINE (1966 to November 2006); OLDMEDLINE (1950 to 1965); EMBASE (1990 to November 2006) and CINAHL (1982 to November 2006). The MEDLINE search terms were modified for OLDMEDLINE, EMBASE and CINAHL.

In this 2009 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2009, issue 2); Ovid MEDLINE (2006 to May Week 1 2009); OLDMEDLINE (1950 to 1965); Ovid EMBASE (2006 to Week 18, 2009) and Ovid CINAHL (2006 to May Week 1 2009).

Ovid MEDLINE
1 exp Influenza/
2 influenza.tw.
3 flu.tw.
4 exp Common Cold/
5 common cold.tw.
6 exp Rhinovirus/
7 rhinovirus*.tw.
8 exp Adenoviridae/
9 adenovirus*.tw.
10 exp Coronavirus/
11 exp Coronavirus Infections/
12 coronavirus*.tw.
13 exp Respiratory Syncytial Viruses/
14 exp Respiratory Syncytial Virus Infections/
15 respiratory syncytial virus*.tw.
16 respiratory syncythial virus.tw.
17 exp Parainfluenza Virus 1, Human/
18 exp Parainfluenza Virus 2, Human/
19 exp Parainfluenza Virus 3, Human/
20 exp Parainfluenza Virus 4, Human/
21 (parainfluenza or para-influenza or para influenza).tw.
22 exp Severe Acute Respiratory Syndrome/

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23 (severe acute respiratory syndrome or SARS).tw.
24 acute respiratory infection*.tw.
25 acute respiratory tract infection*.tw.
26 or/1-25 (59810)
27 exp Hand Washing/
28 (handwashing or hand washing or hand-washing).tw.
29 hand hygiene.tw.
30 (sanitizer* or sanitiser*).tw.
31 (cleanser* or disinfectant*).tw.
32 exp Gloves, Protective/
33 exp Gloves, Surgical/
34 glov*.tw.
35 exp Masks/
36 mask*1.tw.
37 exp Patient Isolators/
38 exp Patient Isolation/
39 patient isolat*.tw.
40 (barrier* or curtain* or partition*).tw.
41 negative pressure room*.tw.
42 reverse barrier nursing.tw.
43 Cross Infection/pc [Prevention]
44 school closure*.tw.
45 (clos* adj3 school*).tw.
46 mass gathering*.tw.
47 public gathering*.tw.
48 (ban or bans or banned or banning).tw.
49 (outbreak* adj3 control*).tw.
50 distancing.tw.
51 exp Quarantine/
52 quarantine*.tw.
53 or/27-49
54 26 and 53
55 (animals not (humans and animals)).sh.
56 54 not 55

CENTRAL search strategy
#1 MeSH descriptor Influenza, Human explode all trees
#2 influenza:ti,ab,kw
#3 flu:ti,ab,kw
#4 MeSH descriptor Common Cold explode all trees
#5 "common cold":ti,ab,kw
#6 MeSH descriptor Rhinovirus explode all trees
#7 rhinovirus*:ti,ab,kw
#8 MeSH descriptor Adenoviridae explode all trees
#9 adenovirus*:ti,ab,kw
#10 MeSH descriptor Coronavirus explode all trees
#11 MeSH descriptor Coronavirus Infections explode all trees
#12 coronavirus*:ti,ab,kw
#13 MeSH descriptor Respiratory Syncytial Viruses explode all trees
#14 MeSH descriptor Respiratory Syncytial Virus Infections explode all trees
#15 respiratory syncytial virus*:ti,ab,kw
#16 respiratory syncythial virus*:ti,ab,kw
#17 MeSH descriptor Parainfluenza Virus 1, Human explode all trees
#18 MeSH descriptor Parainfluenza Virus 2, Human explode all trees
#19 MeSH descriptor Parainfluenza Virus 3, Human explode all trees
#20 MeSH descriptor Parainfluenza Virus 4, Human explode all trees
#21 (parainfluenza or para-influenza or para influenza):ti,ab,kw
#22 MeSH descriptor Severe Acute Respiratory Syndrome explode all trees
#23 (severe acute respiratory syndrome or SARS):ti,ab,kw
#24 acute respiratory infection*:ti,ab,kw
#25 acute respiratory tract infection*:ti,ab,kw

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#26 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25)
#27 MeSH descriptor Handwashing explode all trees
#28 (handwashing or hand washing or hand-washing):ti,ab,kw
#29 hand hygiene:ti,ab,kw
#30 (sanitizer* or sanitiser*):ti,ab,kw
#31 (cleanser* or disinfectant*):ti,ab,kw
#32 MeSH descriptor Gloves, Protective explode all trees
#33 MeSH descriptor Gloves, Surgical explode all trees
#34 glov*:ti,ab,kw
#35 MeSH descriptor Masks explode all trees
#36 mask*:ti,ab,kw
#37 MeSH descriptor Patient Isolators explode all trees
#38 MeSH descriptor Patient Isolation explode all trees
#39 (barrier* or curtain* or partition*):ti,ab,kw
#40 negative NEXT pressure NEXT room*:ti,ab,kw
#41 "reverse barrier nursing":ti,ab,kw
#42 MeSH descriptor Cross Infection explode all trees with qualifier: PC
#43 school NEXT closure*:ti,ab,kw
#44 (clos* NEAR/3 school*):ti,ab,kw
#45 mass NEXT gathering*:ti,ab,kw
#46 public NEXT gathering*:ti,ab,kw
#47 ("ban" or "bans" or banned or banning):ti,ab,kw
#48 (outbreak* NEAR/3 control*):ti,ab,kw
#49 distancing:ti,ab,kw
#50 MeSH descriptor Quarantine explode all trees
#51 quarantine*:ti,ab,kw
#52 (#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51)
#53 (#26 AND #52)

Ovid EMBASE search strategy
1 exp Influenza/
2 influenza.tw.
3 flu.tw.
4 exp Common Cold/
5 common cold.tw.
6 exp Human Rhinovirus/
7 rhinovirus*.tw.
8 exp Adenovirus/
9 adenovirus*.tw.
10 exp Coronavirus/
11 coronavirus*.tw.
12 exp Respiratory Syncytial Pneumovirus/
13 respiratory syncytial virus*.tw.
14 respiratory syncythial virus.tw.
15 (parainfluenza or para-influenza or para influenza).tw.
16 exp Severe Acute Respiratory Syndrome/
17 (severe acute respiratory syndrome or SARS).tw.
18 acute respiratory infection*.tw.
19 acute respiratory tract infection*.tw.
20 or/1-19
21 exp Hand Washing/
22 (handwashing or hand washing or hand-washing).tw.
23 hand hygiene.tw.
24 (sanitizer$ or sanitiser$).tw.
25 (cleanser$ or disinfectant$).tw.
26 exp Glove/
27 exp Surgical Glove/
28 glov*.tw.
29 exp Mask/
30 mask*1.tw.

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31 patient isolat*.tw.
32 (barrier* or curtain* or partition*).tw.
33 negative pressure room*.tw.
34 reverse barrier nursing.tw.
35 Cross Infection/pc [Prevention]
36 school closure*.tw.
37 (clos* adj3 school*).tw.
38 mass gathering*.tw.
39 public gathering*.tw. (5)
40 (ban or bans or banned or banning).tw.
41 (outbreak* adj3 control*).tw.
42 distancing.tw.
43 quarantine*.tw.
44 or/21-43
45 20 and 44

EBSCO CINAHL search strategy
S26 S10 and S24
S25 S10 and S24
S24 S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or 23 or S24
S23 TI outbreak* N3 control* or AB outbreak* N3 control*
S22 TI (school closure* or mass gathering* or public gathering* or ban or bans or banned or banning or distancing or quarantine*) or AB (school closure* or mass gathering* or public gathering* or ban or bans or banned or banning or distancing or quarantine*)
S21 TI (patient isolat* or barrier* or curtain* or partition* or negative pressure room* or reverse barrier nursing) or AB (patient isolat* or barrier* or curtain* or partition* or negative pressure room* or reverse barrier nursing)
S20 TI (glov* or mask*) or AB (glov* or mask*)
S19 TI (handwashing or hand washing or hand-washing or hand hygiene) or AB (handwashing or hand washing or hand-washing or hand hygiene)
S18 (MH "Quarantine")
S17 (MM "Cross Infection")
S16 (MH "Isolation, Reverse")
S15 (MH "Patient Isolation+")
S14 (MH "Respiratory Protective Devices")
S13 (MH "Masks")
S12 (MH "Gloves")
S11 (MH "Handwashing+")
S10 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9
S9 TI (influenza or flu or rhinovirus* or adenovirus* or coronavirus* or respiratory syncytial virus* or respiratory syncythial virus* or parainfluenza or para-influenza or para influenza or severe acute respiratory syndrome or SARS or respiratory viral infection* or viral respiratory infection*) or AB (influenza or flu or rhinovirus* or adenovirus* or coronavirus* or respiratory syncytial virus* or respiratory syncythial virus* or parainfluenza or para-influenza or para influenza or severe acute respiratory syndrome or SARS or respiratory viral infection* or viral respiratory
infection*)TI (influenza or flu or rhinovirus* or adenovirus* or coronavirus* or respiratory syncytial virus* or respiratory syncythial virus* or parainfluenza or para-influenza or para influenza or severe acute respiratory (syndrome or SARS or respiratory viral infection* or viral respiratory infection*) or AB (influenza or flu or rhinovirus* or adenovirus* or coronavirus* or respiratory syncytial virus* or respiratory syncythial virus* or parainfluenza or para-influenza or para influenza or severe acute respiratory syndrome or SARS or respiratory viral infection* or viral
respiratory infection*)
S8 (MH "SARS Virus")
S7 (MH "Severe Acute Respiratory Syndrome")
S6 (MH "Respiratory Syncytial Virus Infections")
S5 (MH "Respiratory Syncytial Viruses")
S4 (MH "Coronavirus+")
S3 (MH "Coronavirus Infections+")
S2 (MH "Common Cold")
S1 (MH "Influenza+")

WHAT'S NEW

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Date	Event	Description
1 April 2020	New citation required and conclusions have changed	There is now sufficient randomised controlled trial (RCT) evidence to show that hand hygiene is likely to provide a modest-benefit. Uncertainty remains for the other interventions. Further RCT evidence is needed.
1 April 2020	New search has been performed	Searches updated. In this 2020 update we only searched for RCTs and cluster-RCTs. We included 44 new trials (Aelami 2015; Aiello 2012; Alzaher 2018; Arbogast 2016; Azor-Martinez 2016; Azor-Martinez 2018; Ban 2015; Barasheed 2014; Biswas 2019; Canini 2010; Chard 2019; Correa 2012; DiVita 2011; Feldman 2016; Goodall 2014; Hartinger 2016; Hubner 2010; Huda 2012; Ibfelt 2015; Ide 2014; Ide 2016; Little 2015; MacIntyre 2011; MacIntyre 2013; MacIntyre 2015; MacIntyre 2016; McConeghy 2017; Millar 2016; Miyaki 2011; Najnin 2019; Nicholson 2014; Pandejpong 2012; Priest 2014; Radonovich 2019; Ram 2015; Savolainen-Kopra 2012; Simmerman 2011; Stebbins 2011; Suess 2012; Talaat 2011; Temime 2018; Turner 2012; Yeung 2011; Zomer 2015). We excluded 12 new trials (Azor-Martinez 2014; Bowen 2007; Chami 2012; Denbak 2018; Lennell 2008; Nandrup-Bus 2009; Patel 2012; Rosen 2006; Slayton 2016; Stedman-Smith 2015; Uhari 1999; Vessey 2007). We identified 5 new ongoing trials (NCT03454009; NCT04267952; NCT04296643; NCT04337541; Wang 2015) one of which – NCT04337541 - published as this review was going to press. We focused on RCTs and cluster-RCTs only and removed observational studies from this update.

HISTORY

Protocol first published: Issue 4, 2006
Review first published: Issue 4, 2007

Date	Event	Description
22 October 2010	New search has been performed	Searches conducted. We included 7 new trials: 4 randomised controlled trials and 3 non-randomised comparative studies. We excluded 36 new trials.
22 October 2010	New citation required but conclusions have not changed	We updated the review again at the behest of the World Health Organization (WHO). External sources of support amended. External support from the WHO. The WHO interim guidelines document on 'Infection Prevention and Control of Epidemic and Pandemic Prone Acute Respiratory Diseases in Health Care' was published in 2007 to provide infection control guidance to help prevent the transmission of acute respiratory diseases in health care. The update of these guidelines will be evidence-based, and an update of this review was requested to assist in informing the evidence base for the revision of the WHO guidelines. Dr John Conly, Dr Mark Jones, and Sarah Thorning joined the review team.
7 May 2009	New search has been performed	For the 2009 update, we included 3 cluster-randomised controlled trials, Cowling 2009; MacIntyre 2009; Sandora 2008, and 1

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Date	Event	Description
		individual randomised controlled trial (Satomura 2005, with its linked publication Kitamura 2007). We also included 1 retrospective cohort study (Foo 2006), 1 case-control study (Yu 2007), and 2 prospective cohort studies (Wang 2007; Broderick 2008). The content and conclusions of the 2007 review changed little, but the additional 8 studies add more information and certainty. Our meta-analysis remains unchanged as there were no new studies for pooling.
30 April 2009	New citation required but conclusions have not changed	New author joined the review team.
8 July 2008	Amended	Converted to new review format.
20 August 2007	Amended	Review first published Issue 4, 2007.

CONTRIBUTIONS OF AUTHORS

Tom Jefferson (TOJ), Chris Del Mar (CDM), and Liz Dooley (LD) were responsible for drafting the protocol.
TOJ, Eliana Ferroni (EF), Bill Hewak (BH), and Adi Prabhala (AP) extracted study data, and Sree Nair (SN) performed the analyses in the original review.

TOJ, EF, Lubna A Al-Ansary (LA), Ghada A Bawazeer (GB), and CDM adjudicated in data extraction in the 2009 update. Mieke van Driel (MvD) assisted in writing the review, updating with the most recent studies, and additional tables (apart from TiDIER). MvD constructed the summary of results table which was removed in the 2020 review update.

TOJ and John Conly (JMC) extracted data, and CDM checked extractions and arbitrated in the 2010 update. All three review authors checked the search strategy terms. Sarah Thorning (ST) designed and carried out the searches. All 2010 review authors contributed to the final report.

For the 2020 update:
Updated searches: ST
Co-ordinated the update: LD
Updated Background section: CDM
Designed Excel forms for extracting study characteristics and tested their usefulness/applicability: MJ
Screened titles and abstracts, excluded irrelevant citations: MJ
Excluded irrelevant citations based on title and text in the trial registry entry: ST
Excluded irrelevant citations based on titles/abstracts and the full-text articles: GB
Selection of studies: MvD, MJ, GB, JC
Data extraction and management: MJ, EF, LA, GB, TOJ, TH, EB
Assessment of risk of bias in the included studies: TOJ, EB, LA, GB, MJ, EF
Adjudicated data extraction: MJ
Data analysis: MJ, EB
Wrote the update: MJ, TOJ, LD, LA, JMC, EB, MVD, GB, TH, CDM, PG

DECLARATIONS OF INTEREST

Tom Jefferson: Tom Jefferson's full disclosure is available at restoringtrials.org/competing-interests-tom-jefferson/.
Chris B Del Mar: a grant from WHO paid to Bond University and a grant from UK National Institute for Health Research (NIHR) to be paid to Bond University on publication of the review in the Cochrane Library. Funding from National Health and Medical Research Council (NHMRC) for research on antibiotic resistance.
Liz Dooley: a grant from the World Health Organization (WHO) paid to Bond University and a grant from UK NIHR to be paid to Bond University on publication of the review in the Cochrane Library.
Eliana Ferroni: none known.
Lubna A Al-Ansary: none known.
Ghada A Bawazeer: none known.

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Mieke L van Driel: Dr van Driel has acted as a consultant for Therapeutic Guidelines Ltd and NPS Medicinewise, for which fees have been paid to her institution.
Mark A Jones: a grant from WHO paid to Bond University and a grant from UK NIHR to be paid to Bond University on publication of the review in the Cochrane Library.
Sarah Thorning: none known.
Elaine M Beller: this review was supported in part by research grants from the NHMRC, Australia, to the Institute for Evidence-Based Healthcare, Bond University.
Justin Clark: none known.
Tammy Hoffmann: a grant from WHO paid to Bond University and a grant from UK NIHR to be paid to Bond University on publication of the review in the Cochrane Library. Funding from NHMRC for research on antibiotic resistance.
Paul Glasziou: none known.
John M Conly: John Conly holds grants from the Canadian Institutes for Health Research on acute and primary care preparedness for COVID-19 in Alberta, Canada and was the primary local Investigator for a *Staphylococcus aureus* vaccine study funded by Pfizer for which all funding was provided only to the University of Calgary. He also received support from the Centers for Disease Control and Prevention (CDC) to attend an Infection Control Think Tank Meeting.

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  2020/1011941
- World Health Organization, Geneva, Switzerland

  Requested and provided support to The Cochrane Collaboration for the 2011 update
- National Institute of Health Research (NIHR), UK

  This study/project is funded by the NIHR Incentive Scheme Award Reference 130721. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.
- World Health Organization, Geneva, Switzerland

  Provided financial support for the 2020 update of this review. Reference number 2020/1011941

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the title of the review in 2010 (see Published notes below).

For this 2020 update, we added one additional outcome: adverse events related to the intervention, and we split the outcomes into primary and secondary outcomes. We also focused only on RCTs and cluster-RCTs and removed observational studies.

NOTES

In Issue 1, 2010, the title of the review was changed from 'Interventions for the interruption or reduction of the spread of respiratory viruses' to 'Physical interventions to interrupt or reduce the spread of respiratory viruses'.

The original review was subsequently published as Jefferson T, Foxlee R, Del Mar C, Dooley L, Ferroni E, Hewak B, Prabhala A, Nair S, Rivetti A. Physical interventions to interrupt or reduce the spread of respiratory viruses: systematic review. BMJ 2008;336:77-80 and Jefferson T, Del Mar C, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, van Driel ML, Foxlee R, Rivetti A. Physical interventions to interrupt or reduce the spread of respiratory viruses: systematic review. BMJ 2009;339:b3675. DOI: 10.1136/bmj.b3675.

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Nonpharmaceutical Measures for Pandemic Influenza in Nonhealthcare Settings—Personal Protective and Environmental Measures

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There were 3 influenza pandemics in the 20th century, and there has been 1 so far in the 21st century. Local, national, and international health authorities regularly update their plans for mitigating the next influenza pandemic in light of the latest available evidence on the effectiveness of various control measures in reducing transmission. Here, we review the evidence base on the effectiveness of nonpharmaceutical personal protective measures and environmental hygiene measures in nonhealthcare settings and discuss their potential inclusion in pandemic plans. Although mechanistic studies support the potential effect of hand hygiene or face masks, evidence from 14 randomized controlled trials of these measures did not support a substantial effect on transmission of laboratory-confirmed influenza. We similarly found limited evidence on the effectiveness of improved hygiene and environmental cleaning. We identified several major knowledge gaps requiring further research, most fundamentally an improved characterization of the modes of person-to-person transmission.

Influenza pandemics occur at irregular intervals when new strains of influenza A virus spread in humans (*1*). Influenza pandemics cause considerable health and social impact that exceeds that of typical seasonal (interpandemic) influenza epidemics. One of the characteristics of influenza pandemics is the high incidence of infections in all age groups because of the lack of population immunity. Although influenza vaccines are the cornerstone of seasonal influenza control, specific vaccines for a novel pandemic strain are not expected to be available for the first 5–6 months of the next pandemic. Antiviral drugs will be available in some locations to treat more severe infections but are unlikely to be available in the quantities that might be required to control transmission in the general community. Thus, efforts to control the next pandemic will rely largely on nonpharmaceutical interventions.

Most influenza virus infections cause mild and self-limiting disease; only a small fraction of case-patients require hospitalization. Therefore, influenza virus infections spread mainly in the community. Influenza virus is believed to be transmitted predominantly by respiratory droplets, but the size distribution of particles responsible for transmission remains unclear, and in particular, there is a lack of consensus on the role of fine particle aerosols in transmission (*2*,*3*). In healthcare settings, droplet precautions are recommended in addition to standard precautions for healthcare personnel when interacting with influenza patients and for all visitors during influenza seasons (*4*). Outside healthcare settings, hand hygiene is recommended in most national pandemic plans (*5*), and medical face masks were a common sight during the influenza pandemic in 2009. Hand hygiene has been proven to prevent many infectious diseases and might be considered a major component in influenza pandemic plans, whether or not it has proven effectiveness against influenza virus transmission, specifically because of its potential to reduce other infections and thereby reduce pressure on healthcare services.

In this article, we review the evidence base for personal protective measures and environmental hygiene measures, and specifically the evidence for the effectiveness of these measures in reducing transmission of laboratory-confirmed influenza in the community. We also discuss the implications of the evidence base for inclusion of these measures in pandemic plans.

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Methods and Results

We conducted systematic reviews to evaluate the effectiveness of personal protective measures on influenza virus transmission, including hand hygiene, respiratory etiquette, and face masks, and a systematic review of surface and object cleaning as an environmental measure (Table 1). We searched 4 databases (Medline, PubMed, EMBASE, and CENTRAL) for literature in all languages. We aimed to identify randomized controlled trials (RCTs) of each measure for laboratory-confirmed influenza outcomes for each of the measures because RCTs provide the highest quality of evidence. For respiratory etiquette and surface and object cleaning, because of a lack of RCTs for laboratory-confirmed influenza, we also searched for RCTs reporting effects of these interventions on influenza-like illness (ILI) and respiratory illness outcomes and then for observational studies on laboratory-confirmed influenza, ILI, and respiratory illness outcomes. For each review, 2 authors (E.Y.C.S. and J.X.) screened titles and abstracts and reviewed full texts independently.

We performed meta-analysis for hand hygiene and face mask interventions and estimated the effect of these measures on laboratory-confirmed influenza prevention by risk ratios (RRs). We used a fixed-effects model to estimate the overall effect in a pooled analysis or subgroup analysis. No overall effect would be generated if there was considerable heterogeneity on the basis of I^2 statistic ≥75% (*6*). We performed quality assessment of evidence on hand hygiene and face mask interventions by using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (*7*). We provide additional details of the search strategies, selection of articles, summaries of the selected articles, and quality assessment (Appendix, https://wwwnc.cdc.gov/EID/article/26/5/19-0994-App1.pdf).

Personal Protective Measures

Hand Hygiene

We identified a recent systematic review by Wong et al. on RCTs designed to assess the efficacy of hand hygiene interventions against transmission of laboratory-confirmed influenza (*8*). We used this review as a starting point and then searched for additional literature published after 2013; we found 3 additional eligible articles published during the search period of January 1, 2013–August 13, 2018. In total, we identified 12 articles (*9*–*20*), of which 3 articles were from the updated search and 9 articles from Wong et al. (*8*). Two articles relied on the same underlying dataset (*16*,*19*); therefore, we counted these 2 articles as 1 study, which resulted in 11 RCTs. We further selected 10 studies with >10,000 participants for inclusion in the meta-analysis (Figure 1). We excluded 1 study from the meta-analysis because it provided estimates of infection risks only at the household level, not the individual level (*20*). We did not generate an overall pooled effect of hand hygiene only or of hand hygiene with or without face mask because of high heterogeneity in individual estimates (I^2 87 and 82%, respectively). The effect of hand hygiene combined with face masks on laboratory-confirmed influenza was not statistically significant (RR 0.91, 95% CI 0.73–1.13; I^2 = 35%, p = 0.39). Some studies reported being underpowered because of limited sample size, and low adherence to hand hygiene interventions was observed in some studies.

We further analyzed the effect of hand hygiene by setting because transmission routes might vary

Table 1. Summary of literature searches for systematic review on personal and environmental nonpharmaceutical interventions for pandemic influenza*

Types of interventions	No. studies identified	Study designs included†	Main findings
Hand hygiene	12	RCT	The evidence from RCTs suggested that hand hygiene interventions do not have a substantial effect on influenza transmission.
Respiratory etiquette	0	NA	We did not identify research evaluating the effectiveness of respiratory etiquette on influenza transmission.
Face masks	10	RCT	The evidence from RCTs suggested that the use of face masks either by infected persons or by uninfected persons does not have a substantial effect on influenza transmission.
Surface and object cleaning	3	RCT, observational studies	There was a limited amount of evidence suggesting that surface and object cleaning does not have a substantial effect on influenza transmission.

*NA, not available; RCT randomized controlled trial.
†In these systematic reviews, we prioritized RCTs, and only considered observational studies if there were a small number of RCTs. Our rationale was that with evidence from a larger number of RCTs, additional evidence from observational studies would be unlikely to change overall conclusions.

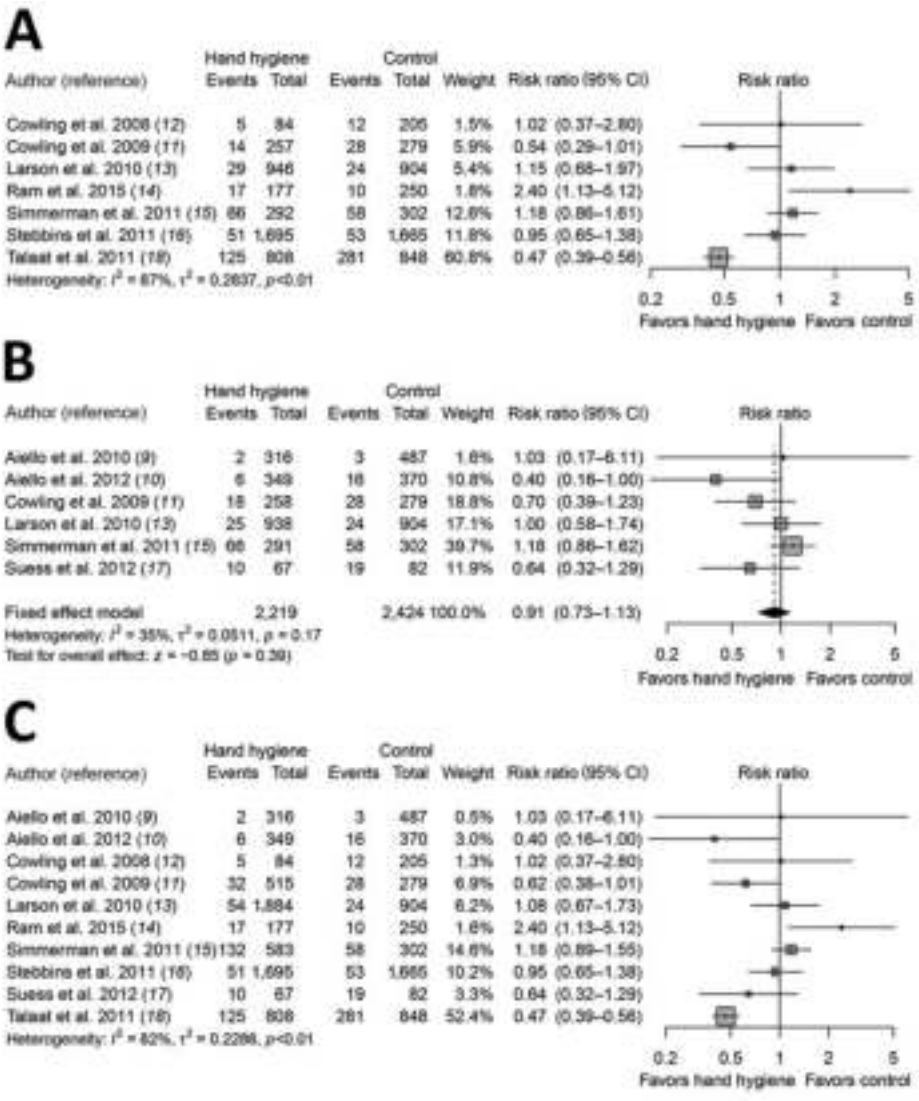

Figure 1. Meta-analysis of risk ratios for the effect of hand hygiene with or without face mask use on laboratory-confirmed influenza from 10 randomized controlled trials with >11,000 participants. A) Hand hygiene alone; B) hand hygiene and face mask; C) hand hygiene with or without face mask. Pooled estimates were not made if there was high heterogeneity (I^2 ≥75%). Squares indicate risk ratio for each of the included studies, horizontal line indicates 95% CIs, dashed vertical line indicates pooled estimation of risk ratio, and diamond indicates pooled estimation of risk ratio. Diamond width corresponds to the 95% CI.

in different settings. We found 6 studies in household settings examining the effect of hand hygiene with or without face masks, but the overall pooled effect was not statistically significant (RR 1.05, 95% CI 0.86–1.27; I^2 = 57%, p = 0.65) (Appendix Figure 4) (*11*–*15*,*17*). The findings of 2 studies in school settings were different (Appendix Figure 5). A study conducted in the United States (*16*) showed no major effect of hand hygiene, whereas a study in Egypt (*18*) reported that hand hygiene reduced the risk for influenza by >50%. A pooled analysis of 2 studies in university residential halls reported a marginally significant protective effect of a combination of hand hygiene plus face masks worn by all residents (RR 0.48, 95% CI 0.21–1.08; I^2 = 0%, p = 0.08) (Appendix Figure 6) (*9*,*10*).

In support of hand hygiene as an effective measure, experimental studies have reported that influenza virus could survive on human hands for a short time and could transmit between hands and contaminated surfaces (*2*,*21*). Some field studies reported that influenza A(H1N1)pdm09 and influenza A(H3N2) virus RNA and viable influenza virus could be detected on the hands of persons with laboratory-confirmed influenza (*22*,*23*), supporting the potential of direct and indirect contact transmission to play a role in the spread of influenza. Other experimental studies also demonstrated that hand hygiene could reduce or remove infectious influenza virus from human hands (*24*,*25*). However, results from our meta-analysis on RCTs did not provide evidence to support a protective effect of hand hygiene against transmission of laboratory-confirmed influenza. One study did report a major effect, but in this trial of hand hygiene in schools in Egypt, running water had to be installed and soap and hand-drying

material had to be introduced into the intervention schools as part of the project (*18*). Therefore, the impact of hand hygiene might also be a reflection of the introduction of soap and running water into primary schools in a lower-income setting. If one considers all of the evidence from RCTs together, it is useful to note that some studies might have underestimated the true effect of hand hygiene because of the complexity of implementing these intervention studies. For instance, the control group would not typically have zero knowledge or use of hand hygiene, and the intervention group might not adhere to optimal hand hygiene practices (*11*,*13*,*15*).

Hand hygiene is also effective in preventing other infectious diseases, including diarrheal diseases and some respiratory diseases (*8*,*26*). The need for hand hygiene in disease prevention is well recognized among most communities. Hand hygiene has been accepted as a personal protective measure in >50% of national preparedness plans for pandemic influenza (*5*). Hand hygiene practice is commonly performed with soap and water, alcohol-based hand rub, or other waterless hand disinfectants, all of which are easily accessible, available, affordable, and well accepted in most communities. However, resource limitations in some areas are a concern when clean running water or alcohol-based hand rub are not available. There are few adverse effects of hand hygiene except for skin irritation caused by some hand hygiene products (*27*). However, because of certain social or religious practices, alcohol-based hand sanitizers might not be permitted in some locations (*28*). Compliance with proper hand hygiene practice tends to be low because habitual behaviors are difficult to change (*29*). Therefore, hand hygiene promotion programs are needed to advocate and encourage proper and effective hand hygiene.

Respiratory Etiquette

Respiratory etiquette is defined as covering the nose and mouth with a tissue or a mask (but not a hand) when coughing or sneezing, followed by proper disposal of used tissues, and proper hand hygiene after contact with respiratory secretions (*30*). Other descriptions of this measure have included turning the head and covering the mouth when coughing and coughing or sneezing into a sleeve or elbow, rather than a hand. The rationale for not coughing into hands is to prevent subsequent contamination of other surfaces or objects (*31*). We conducted a search on November 6, 2018, and identified literature that was available in the databases during 1946–November 5, 2018. We did not identify any published research on the effectiveness of respiratory etiquette in reducing the risk for laboratory-confirmed influenza or ILI. One observational study reported a similar incidence rate of self-reported respiratory illness (defined by >1 symptoms: cough, congestion, sore throat, sneezing, or breathing problems) among US pilgrims with or without practicing respiratory etiquette during the Hajj (*32*). The authors did not specify the type of respiratory etiquette used by participants in the study. A laboratory-based study reported that common respiratory etiquette, including covering the mouth by hands, tissue, or sleeve/arm, was fairly ineffective in blocking the release and dispersion of droplets into the surrounding environment on the basis of measurement of emitted droplets with a laser diffraction system (*31*).

Respiratory etiquette is often listed as a preventive measure for respiratory infections. However, there is a lack of scientific evidence to support this measure. Whether respiratory etiquette is an effective nonpharmaceutical intervention in preventing influenza virus transmission remains questionable, and worthy of further research.

Face Masks

In our systematic review, we identified 10 RCTs that reported estimates of the effectiveness of face masks in reducing laboratory-confirmed influenza virus infections in the community from literature published during 1946–July 27, 2018. In pooled analysis, we found no significant reduction in influenza transmission with the use of face masks (RR 0.78, 95% CI 0.51–1.20; I^2 = 30%, p = 0.25) (Figure 2). One study evaluated the use of masks among pilgrims from Australia during the Hajj pilgrimage and reported no major difference in the risk for laboratory-confirmed influenza virus infection in the control or mask group (*33*). Two studies in university settings assessed the effectiveness of face masks for primary protection by monitoring the incidence of laboratory-confirmed influenza among student hall residents for 5 months (*9*,*10*). The overall reduction in ILI or laboratory-confirmed influenza cases in the face mask group was not significant in either studies (*9*,*10*). Study designs in the 7 household studies were slightly different: 1 study provided face masks and P2 respirators for household contacts only (*34*), another study evaluated face mask use as a source control for infected persons only (*35*), and the remaining studies provided masks for the infected persons as well as their close contacts (*11*–*13*,*15*,*17*). None of the household studies reported a significant reduction in secondary laboratory-confirmed influenza virus infections in the face

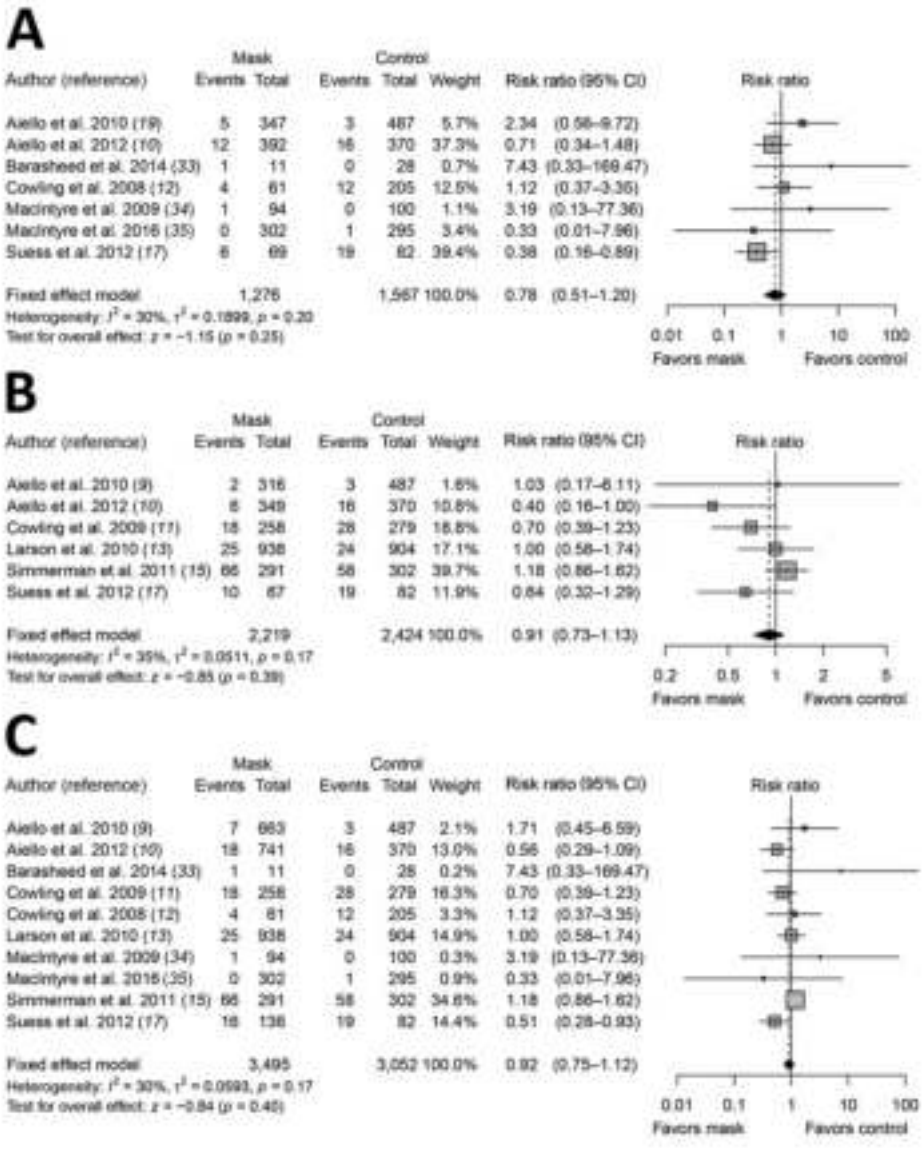

Figure 2. Meta-analysis of risk ratios for the effect of face mask use with or without enhanced hand hygiene on laboratory-confirmed influenza from 10 randomized controlled trials with >6,500 participants. A) Face mask use alone; B) face mask and hand hygiene; C) face mask with or without hand hygiene. Pooled estimates were not made if there was high heterogeneity (I^2 ≥75%). Squares indicate risk ratio for each of the included studies, horizontal lines indicate 95% CIs, dashed vertical lines indicate pooled estimation of risk ratio, and diamonds indicate pooled estimation of risk ratio. Diamond width corresponds to the 95% CI.

mask group (*11*–*13*,*15*,*17*,*34*,*35*). Most studies were underpowered because of limited sample size, and some studies also reported suboptimal adherence in the face mask group.

Disposable medical masks (also known as surgical masks) are loose-fitting devices that were designed to be worn by medical personnel to protect accidental contamination of patient wounds, and to protect the wearer against splashes or sprays of bodily fluids (*36*). There is limited evidence for their effectiveness in preventing influenza virus transmission either when worn by the infected person for source control or when worn by uninfected persons to reduce exposure. Our systematic review found no significant effect of face masks on transmission of laboratory-confirmed influenza.

We did not consider the use of respirators in the community. Respirators are tight-fitting masks that can protect the wearer from fine particles (*37*) and should provide better protection against influenza virus exposures when properly worn because of higher filtration efficiency. However, respirators, such as N95 and P2 masks, work best when they are fit-tested, and these masks will be in limited supply during the next pandemic. These specialist devices should be reserved for use in healthcare settings or in special subpopulations such as immunocompromised persons in the community, first responders, and those performing other critical community functions, as supplies permit.

In lower-income settings, it is more likely that reusable cloth masks will be used rather than

disposable medical masks because of cost and availability (*38*). There are still few uncertainties in the practice of face mask use, such as who should wear the mask and how long it should be used for. In theory, transmission should be reduced the most if both infected members and other contacts wear masks, but compliance in uninfected close contacts could be a problem (*12*,*34*). Proper use of face masks is essential because improper use might increase the risk for transmission (*39*). Thus, education on the proper use and disposal of used face masks, including hand hygiene, is also needed.

Environmental Measures

Surface and Object Cleaning

For the search period from 1946 through October 14, 2018, we identified 2 RCTs and 1 observational study about surface and object cleaning measures for inclusion in our systematic review (*40*–*42*). One RCT conducted in day care nurseries found that biweekly cleaning and disinfection of toys and linen reduced the detection of multiple viruses, including adenovirus, rhinovirus, and respiratory syncytial virus in the environment, but this intervention was not significant in reducing detection of influenza virus, and it had no major protective effect on acute respiratory illness (*41*). Another RCT found that hand hygiene with hand sanitizer together with surface disinfection reduced absenteeism related to gastrointestinal illness in elementary schools, but there was no major reduction in absenteeism related to respiratory illness (*42*). A cross-sectional study found that passive contact with bleach was associated with a major increase in self-reported influenza (*40*).

Given that influenza virus can survive on some surfaces for prolonged periods (*43*), and that cleaning or disinfection procedures can effectively reduce or inactivate influenza virus from surfaces and objects in experimental studies (*44*), there is a theoretical basis to believe that environmental cleaning could reduce influenza transmission. As an illustration of this proposal, a modeling study estimated that cleaning of extensively touched surfaces could reduce influenza A infection by 2% (*45*). However, most studies of influenza virus in the environment are based on detection of virus RNA by PCR, and few studies reported detection of viable virus.

Although we found no evidence that surface and object cleaning could reduce influenza transmission, this measure does have an established impact on prevention of other infectious diseases (*42*). It should be feasible to implement this measure in most settings, subject to the availability of water and cleaning products. Although irritation caused by cleaning products is limited, safety remains a concern because some cleaning products can be toxic or cause allergies (*40*).

Discussion

In this review, we did not find evidence to support a protective effect of personal protective measures or environmental measures in reducing influenza transmission. Although these measures have mechanistic support based on our knowledge of how influenza is transmitted from person to person, randomized trials of hand hygiene and face masks have not demonstrated protection against laboratory-confirmed influenza, with 1 exception (*18*). We identified only 2 RCTs on environmental cleaning and no RCTs on cough etiquette.

Hand hygiene is a widely used intervention and has been shown to effectively reduce the transmission of gastrointestinal infections and respiratory infections (*26*). However, in our systematic review, updating the findings of Wong et al. (*8*), we did not find evidence of a major effect of hand hygiene on laboratory-confirmed influenza virus transmission (Figure 1). Nevertheless, hand hygiene might be included in influenza pandemic plans as part of general hygiene and infection prevention.

We did not find evidence that surgical-type face masks are effective in reducing laboratory-confirmed influenza transmission, either when worn by infected persons (source control) or by persons in the general community to reduce their susceptibility (Figure 2). However, as with hand hygiene, face masks might be able to reduce the transmission of other infections and therefore have value in an influenza pandemic when healthcare resources are stretched.

It is essential to note that the mechanisms of person-to-person transmission in the community have not been fully determined. Controversy remains over the role of transmission through fine-particle aerosols (*3*,*46*). Transmission by indirect contact requires transfer of viable virus from respiratory mucosa onto hands and other surfaces, survival on those surfaces, and successful inoculation into the respiratory mucosa of another person. All of these components of the transmission route have not been studied extensively. The impact of environmental factors, such as temperature and humidity, on influenza transmission is also uncertain (*47*). These uncertainties over basic transmission modes and mechanisms hinder the optimization of control measures.

Table 2. Knowledge gaps for personal protective and environmental nonpharmaceutical interventions for pandemic influenza*

Intervention	Knowledge gaps	Suggested studies
Hand hygiene	There are major gaps in our knowledge of the mechanisms of person-to-person transmission of influenza, including the role of direct and indirect contact, the degree of viral contamination on hands and various types of surfaces in different settings, and the potential for contact transmission to occur in different locations and under different environmental conditions. There is little information on whether greater reductions in transmission could be possible with combinations of personal intervention (e.g., isolation away from family members as much as possible, plus using face masks and enhancing hand hygiene).	Additional high-quality RCTs of efficacy of hand hygiene against laboratory-confirmed influenza in other nonhealthcare settings, except households and university residential halls, would be valuable. In particular, studies in school settings are needed to solve the discrepancy between the two studies from the United States and Egypt.
Respiratory etiquette	There is no evidence about the quantitative effectiveness of respiratory etiquette against influenza virus.	RCTs of interventions to demonstrate the effectiveness of respiratory etiquette in reducing influenza transmission would be valuable.
Face mask	There are major gaps in our knowledge of the mechanisms of person-to-person transmission of influenza, including the importance of transmission through droplets of different sizes including small particle aerosols, and the potential for droplet and aerosol transmission to occur in different locations and with environmental conditions.	Additional high-quality RCTs of efficacy of face masks against laboratory-confirmed influenza would be valuable. Effectiveness of face masks or respirator use to prevent influenza prevention in special subpopulation, such as immunocompromised persons, would be valuable.
Surface and object cleaning	The effectiveness of different cleaning products in preventing influenza transmission–in terms of cleaning frequency, cleaning dosage, cleaning time point, and cleaning targeted surface and object material–remains unknown.	RCTs of interventions to demonstrate the effectiveness of surface and object cleaning in reducing influenza transmission would be valuable. Studies that can demonstrate the reduction of environmental detection of influenza virus through cleaning of surfaces and objects would also be valuable.

*RCT, randomized control trial.

In this review, we focused on 3 personal protective measures and 1 environmental measure. Other potential environmental measures include humidification in dry environments (*48*), increasing ventilation (*49*), and use of upper-room UV light (*50*), but there is limited evidence to support these measures. Further investigations on the effectiveness of respiratory etiquette and surface cleaning through conducting RCTs would be helpful to provide evidence with higher quality; evaluation of the effectiveness of these measures targeting specific population groups, such as immunocompromised persons, would also be beneficial (Table 2). Future cost-effectiveness evaluations could provide more support for the potential use of these measures. Further research on transmission modes and alternative interventions to reduce influenza transmission would be valuable in improving pandemic preparedness. Finally, although our review focused on nonpharmaceutical measures to be taken during influenza pandemics, the findings could also apply to severe seasonal influenza epidemics. Evidence from RCTs of hand hygiene or face masks did not support a substantial effect on transmission of laboratory-confirmed influenza, and limited evidence was available on other environmental measures.

This study was conducted in preparation for the development of guidelines by the World Health Organization on the use of nonpharmaceutical interventions for pandemic influenza in nonmedical settings.

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GLOBAL INFLUENZA PROGRAMME

Non-pharmaceutical public health measures for mitigating the risk and impact of epidemic and pandemic influenza

Annex: Report of systematic literature reviews

World Health Organization

1559

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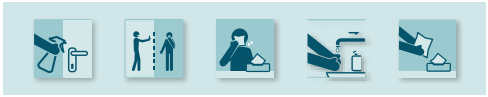

Non-pharmaceutical public health measures for mitigating the risk and impact of epidemic and pandemic influenza

Annex: Report of systematic literature reviews

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Abbreviations and acronyms

ACH	air changes per hour
CI	confidence interval
EDR	excess death rate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ILI	influenza-like illness
ITIS	infrared thermal image scanner
NPI	non-pharmaceutical intervention
PCR	polymerase chain reaction
PICTs	Pacific Island Countries and Territories
RCT	randomized controlled trial
RNA	ribonucleic acid
RR	risk ratio
SC	school closure
UV	ultraviolet
WC	workplace closure
WHO	World Health Organization

Glossary

Contact tracing	Identification and follow-up of persons who may have come into contact with an infected person.
Closure	Halting the operation of an institution or business.
Isolation	Separation or confinement of a person who has or is suspected of having influenza virus infection, to prevent further infections.
Non-pharmaceutical /non-pharmacological interventions	Interventions that do not include pharmacological measures such as vaccines and antiviral drugs.
Personal protective measures	Measures to reduce personal risk of infection, such as hand washing and face masks.
Quarantine	Separation or restriction of the movement of persons who may be infected, based either on exposure to other infected people or on a history of travel to affected areas.
Movement restriction	Limitation on the movements of a person who has or is suspected of having an infection

EXECUTIVE SUMMARY

New influenza A viruses emerge in humans from time to time, causing global pandemics. The most recent influenza pandemic began in 2009 with the influenza A(H1N1)pdm09 virus. Public health measures against pandemic influenza include vaccines, antiviral drugs and non-pharmaceutical measures. Given that vaccines against novel pandemic strains are unlikely to be available in the early months of an influenza pandemic, and antiviral drugs are in short supply in many locations, non-pharmaceutical public health measures are often some of the most accessible interventions for community mitigation of a pandemic. Non-pharmaceutical interventions (NPIs) also have an important role in mitigating interpandemic influenza epidemics, which occur each winter in temperate locations and at varying times of the year in tropical and subtropical locations. These measures could reduce individuals' risk of infection, delay the epidemic peak, reduce the "height" of the epidemic peak, and spread cases over a long time period; each of these outcomes would contribute to reducing the overall impact of a pandemic or epidemic.

Here, we systematically review and evaluate the evidence base on the effectiveness and impact of community mitigation measures for pandemic and interpandemic influenza. This evidence base will contribute to updated public health guidelines for community mitigation measures for influenza. The scope of this review includes evidence on the effectiveness of interventions such as personal protective measures, environmental measures, social distancing measures, and travel-related measures. Consideration is also given to the feasibility of each intervention, including potential ethical issues.

We found that there is a limited evidence base on the effectiveness of non-pharmaceutical community mitigation measures. There are a number of high-quality randomized controlled trials demonstrating that personal measures (e.g. hand hygiene and face masks) have at best a small effect on transmission, with the caveat that higher compliance in a severe pandemic might improve efficacy. However, there are few randomized trials for other NPIs, and much of the evidence base is from observational studies and computer simulations. School closures can reduce transmission, but would need to be carefully timed to achieve mitigation objectives, while there may be ethical issues to consider. Travel-related measures are unlikely to be successful in most locations because current screening tools such as thermal scanners cannot identify presymptomatic and asymptomatic infections, and travel restrictions and travel bans are likely to have prohibitive economic consequences.

INTRODUCTION

Non-pharmacological interventions (NPIs) are often the most accessible interventions when a new pandemic influenza virus emerges and begins to spread, because of limited availability of antiviral drugs and delays in the availability of vaccines against the pandemic strain (1). These community mitigation measures may be able to slow the spread of infections in the community, delaying the peak in infections, reducing the size of the peak and spreading infections over a longer period of time (Fig. 1) (*2, 3*). Each of these consequences should contribute to reducing the overall impact of the epidemic or pandemic. Given that in some locations there could be limited surge capacity in hospitals (and particularly in intensive care beds), spreading infections over a longer time period could save lives, even if the total number of infections remained the same.

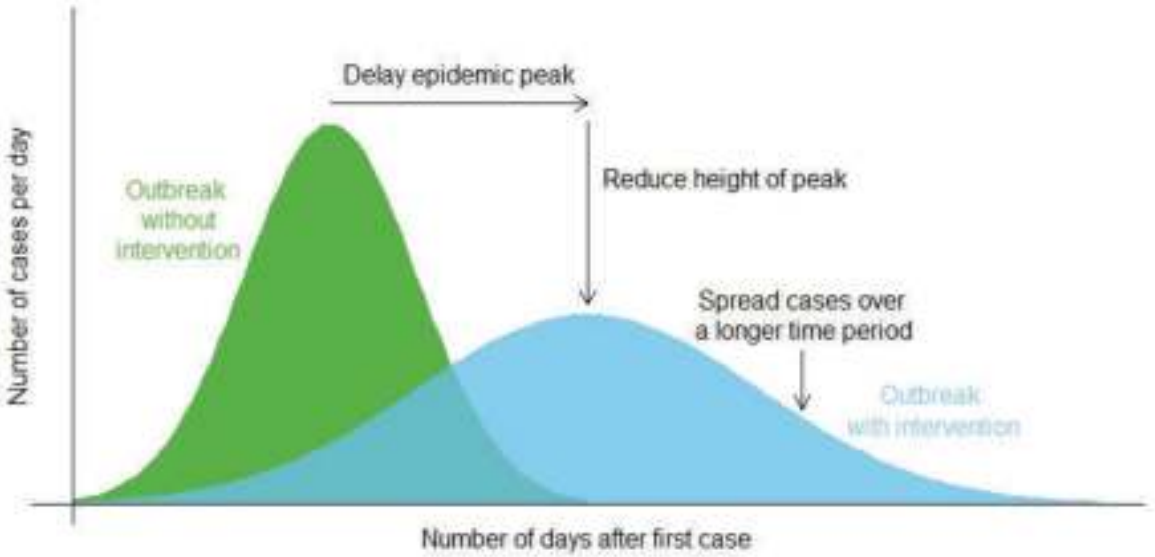

Fig. 1. Intended impact of non-pharmaceutical interventions on an influenza epidemic or pandemic by reducing person-to-person transmission

NPIs in non-health care settings usually focus on: reducing transmission by personal or environmental protective measures (e.g. hand hygiene); reducing the spread in the community populations (e.g. isolating and treating patients; closing schools and cancelling mass gatherings); limiting the international spread on travelling (e.g. travel screening and restriction); and public advice to the community (*4*). A number of health authorities have recently updated their reviews and guidelines on NPIs, including the United States (US) Centers for Disease Control and Prevention (CDC) (*2*), the European Centre for Disease Prevention and Control (*3*), the Australian Government Department of Health (*5*), the United Kingdom Department of Health (*6*), the Singapore Ministry of Health (*7*) and the Government of New Zealand (*8*).

This review examines the evidence base on each of the NPIs in community settings. While our focus is on the effectiveness of NPIs for mitigation of an influenza pandemic, the same measures may also be used in interpandemic influenza epidemics, which occur each winter in temperate locations and at varying times of the year in tropical and subtropical locations. In addition to NPIs in community settings, health authorities may also intervene in health care settings and systems, for example by establishing special influenza outpatient clinics, improving triage and isolation in hospitals, and cancelling non-essential surgeries. Health care system interventions are outside the scope of the present review of community mitigation measures.

The list of community mitigation measures is shown below. For each of the 18 listed NPIs, we first determined whether any systematic review had been published within the past 5 years (i.e. since January 2014), If there was a recently published review, we conducted a systematic review limited to studies published more recently than that review (starting from 1 year prior to the publication date), and updated that existing review. If we could not identify a systematic review of the NPI within the past 5 years, we conducted a full systematic review for the NPI. For the review of peer-reviewed articles, two independent reviewers screened all titles of studies identified by the search strategy for each of the NPIs, then reviewed the abstracts of the potentially relevant studies. If the studies described that NPI and its effectiveness against influenza transmission, the reviewers read the full-length text and extracted relevant data. Further discussion with a third reviewer was held if a consensus was not reached. We also evaluated the methodological quality of each of the studies using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (*9*), based on the question of whether NPIs can reduce influenza transmission in the community. The quality of evidence was ranked for each study as high, moderate, low or very low, based on its risk of bias, consistency, directness, precision of the results and publication bias. Hence, we set the highest priority on randomized controlled trials (RCTs), then on observational studies and finally on simulation studies. If RCTs were reported, as a general principle we did not review observational studies or simulation studies, and if observational studies were reported, as a general principle we did not review simulation studies.

This report describes the evidence base on the effectiveness of each NPI. The specific targets of the evidence include but are not limited to reducing transmission, delaying the peak of the epidemic, spreading out infections over a longer time period, and reducing the total number of infections. This review of the evidence base will support the development of guidance on the use of NPIs for community mitigation. The NPIs reviewed in this report are listed below.

LIST OF NON-PHARMACEUTICAL PUBLIC HEALTH MEASURES

NPI	DEFINITION
Personal protective measures	**Personal hygiene measures to reduce the risk of acquiring or spreading respiratory infections.**
1. Hand hygiene	A personal measure aiming to reduce influenza transmission via direct or indirect contact by washing hands with soap and water or alcohol-based hand cleaners.
2. Respiratory etiquette	A personal measure aiming to reduce influenza transmission via respiratory droplets by covering nose and mouth with disposable tissues while coughing or sneezing.
3. Face masks	A personal measure aiming to reduce influenza transmission by wearing face mask of different types, including home-made masks, surgical and medical masks, or respirators with higher filtration rates. Masks can be worn by symptomatic or exposed persons to reduce onwards transmission (source control), or by uninfected persons in the community to reduce their risk of infection.

LIST OF NON-PHARMACEUTICAL PUBLIC HEALTH MEASURES

NPI	DEFINITION
Environmental measures	**Environmental hygiene measures to reduce the risk of acquiring or spreading influenza within an area.**
4. Surface and object cleaning	Routine cleaning of frequently used surfaces and objects to reduce influenza transmission.
5. Other environmental measures	Other measures to reduce risk of influenza transmission through the environment.
Social distancing measures	**Social measures to reduce the risk of acquiring or spreading respiratory infections in various community settings (e.g. homes, workplaces, schools, health care settings etc.)**
6. Contact tracing	The identification and follow-up of persons who may have come into contact with an infected person, usually in combination with quarantine of identified contacts.
7. Isolation of sick individuals	Reduction in virus transmission from an ill person to others by confining symptomatic individuals for a defined period either in a special facility or at home.
8. Quarantine of exposed individuals	Isolation of individuals who contacted a person with proven or suspected influenza, or travel history to an affected area, for a defined period after last exposure. Quarantined cases may be isolated.
9. School closure	Closure of schools either when virus transmission is observed in the school or community, or an early planned closure of schools before influenza transmission initiates.
10. Workplace closure	Closure of workplaces when virus transmission is observed in the workplace, or an early planned closure of workplaces before influenza transmission initiates.
11. Workplace measures	Measures to reduce influenza transmission in the workplace, or on the way to and from work, by decreasing frequency and length of social interactions.
12. Avoiding crowding	Measures to reduce influenza transmission in crowded areas (e.g. large meetings, conferences, and religious pilgrimages, national and international events).
Travel-related measures	**Measures including the provision of travel health advice, screening of travellers and restriction of travellers.**
13. Travel advice	Official government travel advice with legal and economic implications.
14. Entry and exit screening	Screening travellers for influenza symptoms to reduce the number of infectious individuals entering or leaving a country with infection, respectively, in order to delay the international spread of infection.

LIST OF NON-PHARMACEUTICAL PUBLIC HEALTH MEASURES

NPI	DEFINITION
15. Internal travel restrictions	Prevent or limit influenza transmission by restricting travel within a country.
16. Border closures	Prevent influenza entering a country by restricting travel to or from an affected area, in order to delay the international spread of infection.

SUPPORTING EVIDENCE FOR NPIS

Search strategy

Systematic reviews of NPIs were conducted using four databases (PubMed, EMBASE, MEDLINE and Cochrane Library) and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy for each topic is given below.

MEASURES	SEARCH TERMS
1. Hand hygiene	#1: "hand hygiene" OR "hand washing" OR "handwashing" OR "hand-washing" OR "hand-wash" OR "hand wash" OR "handwash" OR "hand sanitize" OR "hand sanitizers" OR "hand sanitizer" OR "hand rub" OR "handrub" OR "hand rubbing" OR "hand cleansing" OR "hand cleans" OR "hand cleanser" OR "hand disinfectant" OR "hand disinfectants" OR "hand disinfection" OR "hand soap" OR "hand wipe" #2: "influenza" OR "flu" #3: #1 AND #2
2. Respiratory etiquette	#1: "respiratory hygiene" OR "cough etiquette" OR "respiratory etiquette" #2: "influenza" OR "flu" #3: #1 AND #2
3. Face masks	#1: "facemask" OR "facemasks" OR "mask" OR "masks" OR "respirator" OR "respirators" #2: "influenza" OR "flu" #3: #1 AND 2
4. Surface and object cleaning	#1: "surface" OR "surfaces" OR "object" OR "objects" OR "fomite" OR "fomites" OR "environment" OR "environmental" #2: "clean" OR "cleans" OR "cleaning" OR "cleanse" OR "cleansing" OR "disinfect" OR "disinfects" OR "disinfection" OR "disinfecting" OR "wipe" OR "wipes" OR "sanitize" OR "sanitizes" OR "sanitizing" OR "sanitation" OR "sterilize" OR "sterilizes" OR "sterilizing" OR "sterilization" OR "sterilise" OR "sterilises" OR "sterilising" OR "sterilisation" OR "decontaminate" OR "decontaminates" OR "decontaminating" OR "decontamination" #3: "influenza" OR "flu" #4: #1 AND #2 AND #3

MEASURES	SEARCH TERMS
5. Other environmental measures	UV light #1: "ultraviolet" OR "UVGI" OR "UV" OR "UVC" OR "far-UVC" OR "UV-C" #2: "influenza" OR "flu" #3: #1 AND #2 Ventilation and humidity #1: "ventilation" OR "temperature" OR "humidity" OR "environment" #2: "indoor" OR "room" #3: "influenza" OR "flu" #4: #1 AND #2 AND #3
6. Contact tracing	#1: "contact tracing" OR "trace contact" OR "trace contacts" OR "identify contact" OR "identify contacts" OR "case detection" OR "detect cases" OR "case finding" OR "find cases" OR "early detection" #2: "influenza" OR "flu" #3: #1 AND #2
7. Isolation of sick individuals	#1: "patient isolation" OR "case isolation" OR "voluntary isolation" OR "home isolation" OR "social isolation" OR "self-isolation" #2: "influenza" OR "flu" #3: #1 AND #2
8. Quarantine of exposed individuals	#1: "quarantine" #2: "influenza" OR "flu" #3: #1 AND #2
9. School closure	#1: "school closure" OR "class dismissal" OR "school holiday" OR "community mitigation" OR "social distancing" #2: "influenza" OR "flu" #3: #1 AND #2
10. Workplace closure	#1: "workplace" OR "work site" OR "business" OR "organization" OR "office" #2: "closure" OR "close" #3: "influenza" OR "flu" #4: #1 AND #2 AND #3
11. Workplace measures	#1: "telework" OR "leave" OR "social mixing" OR "social distancing" OR "community mitigation" OR "non-pharmaceutical" OR "nonpharmaceutical" #2: "influenza" OR "flu" #3: #1 AND #2
12. Avoiding crowding	#1: "event" OR "meeting" OR "sport" OR "concert" OR "pilgrimage" OR "park" OR "conference" OR "mass" OR "public" OR "community" OR "large" OR "general" OR "church" #2: "gather*" OR "crowd*" #3: "influenza" OR "flu" #4: #1 AND #2 AND #3

MEASURES	SEARCH TERMS
13. Travel advice	#1: "travel" OR "traveler" OR "travelers" OR "traveller" OR "travellers" #2: "advice" OR "restrict" OR "restriction" OR "prohibit" OR "prohibition" #3: "influenza" OR "flu" #4: #1 AND #2 AND #3
14. Entry and exit screening	#1: "travel" OR "traveler" OR "travelers" OR "traveller" OR "travellers" #2: "screen" OR "screening" OR "entry screening" OR "exit screening" OR "entry-exit screening" OR "mass screening" OR "border screening" OR "detect" OR "detecting" OR "detection" #3: "influenza" OR "flu" #4: #1 AND #2 AND #3
15. Internal travel restriction	#1: "travel" OR "traveler" OR "travelers" OR "traveller" OR "travellers" #2: "domestic" OR "internal" #3: "restrict" OR "restriction" OR "prohibit" OR "prohibition" OR "limit" OR "limitation" OR "control" #4: "influenza" OR "flu" #5: #1 AND #2 AND #3 AND #4
16. Border closure	#1: "travel" OR "traveler" OR "travelers" OR "traveller" OR "travellers" #2: "border" OR "international" #3: "restrict" OR "restriction" OR "prohibit" OR "prohibition" OR "limit" OR "limitation" OR "control" OR "closure" #4: influenza" OR "flu" #5: #1 AND #2 AND #3 AND #4

1. PERSONAL PROTECTIVE MEASURES

1.1. Hand hygiene

Terminology
The definitions of relevant hand hygiene practices and products, and common terminology, are shown in Table 1 below.

Table 1. Definitions of hand hygiene terms

TERM	DEFINITION
Hand hygiene practices	
Hand hygiene	A general term referring to any action of hand cleansing, e.g. handwashing, antiseptic handwash, antiseptic hand rub, or surgical hand antisepsis (*10, 11*)
Hand cleansing	Action of performing hand hygiene for the purpose of physically or mechanically removing dirt, organic material, and/or microorganisms (*10*)
Handwashing	Washing hands with plain or antimicrobial soap and water (*10*)
Antiseptic handwashing	Washing hands with soap and water, or other detergents containing an antiseptic agent (*10*)
Antiseptic handrubbing (or handrubbing)	Applying an antiseptic handrub to all surfaces of the hands to reduce or inhibit the growth of microorganisms without the need for an exogenous source of water and requiring no rinsing or drying with towels or other devices (*10, 11*)
Hand disinfection	Hand disinfection is extensively used as a term in some parts of the world and can refer to antiseptic handwash, antiseptic handrubbing, hand antisepsis / decontamination / degerming, handwashing with an antimicrobial soap and water, hygienic hand antisepsis, or hygienic handrub (*10*)
Hand hygiene products	
Alcohol-based (hand) rub (or hand sanitizer)	An alcohol-containing preparation (liquid, gel or foam) designed for application to the hands to inactivate microorganisms and/or temporarily suppress their growth. Such preparations may contain one or more types of alcohol, other active ingredients with excipients, and humectants (*10*)

TERM	DEFINITION
Antimicrobial (medicated) soap	Soap (detergent) containing an antiseptic agent at a concentration sufficient to inactivate microorganisms and/or temporarily suppress their growth. The detergent activity of such soaps may also dislodge transient microorganisms or other contaminants from the skin to facilitate their subsequent removal by water (*10*)
Antiseptic hand wipe	A piece of fabric or paper pre-wetted with an antiseptic used for wiping hands to inactivate and/or remove microbial contamination. They may be considered as an alternative to washing hands with non-antimicrobial soap and water but, because they are not as effective at reducing bacterial counts on health care workers' hands as alcohol-based handrubs or washing hands with an antimicrobial soap and water, they are not a substitute for using an alcohol-based handrub or antimicrobial soap (*10*)
Plain soap	Plain soap refers to detergents that do not contain antimicrobial agents or contain low concentrations of antimicrobial agents that are effective solely as preservatives (*11*)
Other	
Visibly soiled hands	Hands showing visible dirt or visibly contaminated with proteinaceous material, blood, or other body fluids (e.g. faecal material or urine) (*11*)

Methods

We conducted a review of systematic reviews. PubMed, Medline, EMBASE and CENTRAL were searched for reviews until 1 August 2018. Review selection criteria were systematic reviews within 5 years studying the effect of hand hygiene interventions on prevention of laboratory-confirmed influenza in non-health care settings, regardless of language.

After identifying the most recent published systematic review (see below), we updated the search done in that published review in the same four databases through to 14 August 2018 using the same search terms. Study selection criteria were RCTs comparing the effect of hand hygiene interventions with no intervention in laboratory-confirmed influenza prevention in community settings. Study participants or clusters of participants were assigned prospectively into intervention and control groups using random allocation. A community setting was defined as an open setting without confinement or special care for the patients. Articles describing any hand hygiene related interventions were included. No language limits were applied.

Because of the availability of a reasonable number of randomized trials of hand hygiene, we did not extend the search to observational studies, but we did note the findings from earlier systematic reviews of observational studies of hand hygiene (*12-14*).

After data extraction, quality assessment of the evidence was done for included studies based on the GRADE framework. The research question was to study the effect of hand hygiene intervention on laboratory-confirmed influenza prevention.

Two independent reviewers (ZX and ES) reviewed retrieved titles and subsequent relevant abstracts independently. Titles or abstracts with any one of the reviewers' decision to include were included in next step. After title and abstract screening, two reviewers reviewed the full text based on the selection criteria. Data extraction and evidence quality assessment were also done by the reviewers. If a consensus was not reached, further discussion was held or opinion was obtained from the third independent reviewer.

Risk ratios (RRs) and their 95% confidence intervals (95% CIs) were calculated to estimate the effect of hand hygiene intervention on prevention of laboratory-confirmed influenza. Heterogeneity of each pooled and subgroup analysis was assessed by I2 statistics. The overall effect of each pooled and subgroup analysis was estimated by fixed-effect model. If the heterogeneity was high (I2 ≥ 75%), we did not estimate an overall pooled effect.

Results

We identified 225 reviews through the database search with our search terms, of which 172 reviews were screened out during by title and abstract screening. 46 reviews were excluded after full-text assessment that were not systematic reviews, not within the past 5 years, not based on RCTs, or had no hand hygiene intervention or no laboratory-confirmed influenza outcome. In total, seven reviews were included in our analysis, from which we identified nine eligible articles. The most recent systematic review and meta-analysis was published in 2014; it reviewed and analysed RCTs to study the effect of hand hygiene on the prevention of laboratory-confirmed influenza (*15*). The process of identifying these review articles is shown in Fig. 2.

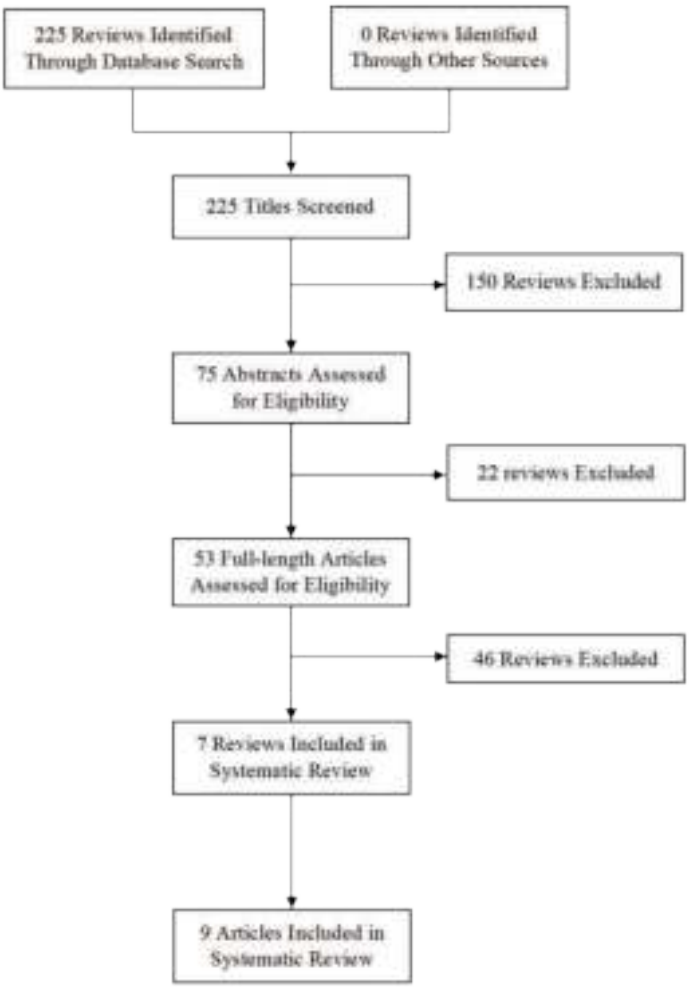

Fig. 2. The flow chart of hand hygiene review selection

In the additional search to update the systematic review by Wong et al. (*15*) that was published in 2014, 352 articles were identified from 1 January 2013 to 14 August 2018. At total of 319 articles were excluded in the title and abstract screening. 30 articles were excluded that were not RCTs, not done outside of health care settings, did not have a hand hygiene intervention or did not have a laboratory-confirmed influenza outcome. Three additional articles were identified since the publication of the review by Wong et al. (*15*). In total, 12 articles (11 studies; Azman et al. (*16*) and Stebbins et al. (*17*) were the same project during the same period but studied different questions) were included in our systematic review and 11 articles (10 studies; Levy et al. (*18*) only had household level secondary infection data but no individual level data) were included in the meta-analysis. The article selection flow is shown in Fig. 2.

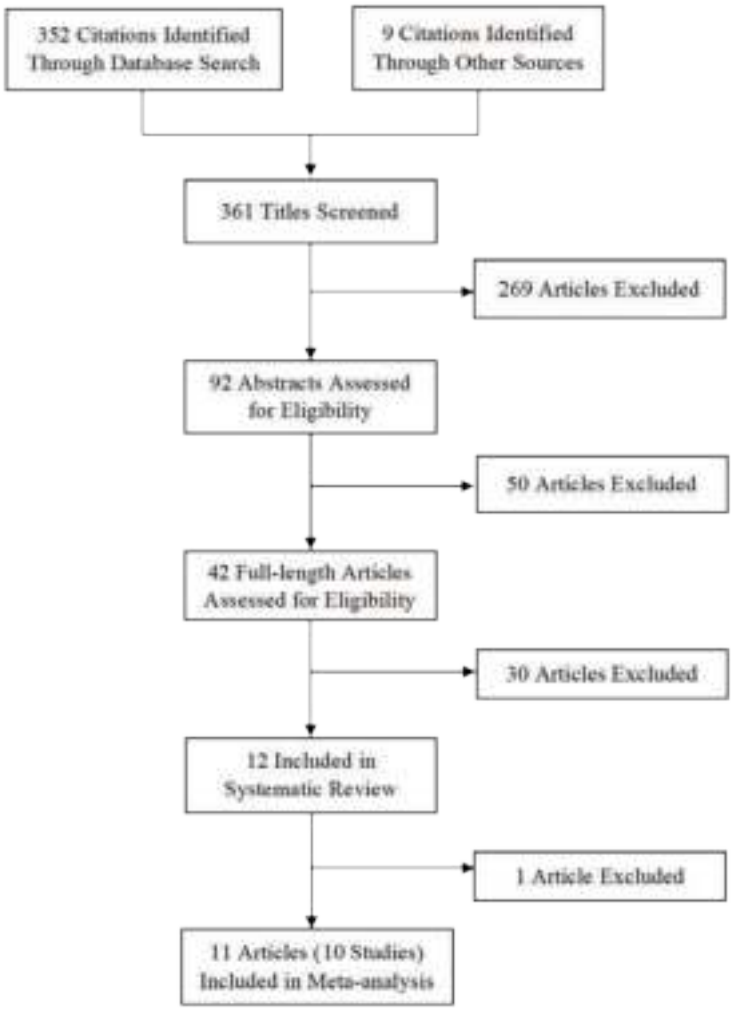

Fig. 3. The flow chart of hand hygiene article selection

Table 2. Basic characteristics of included studies

CHARACTERISTICS	NO. OF STUDIES (%)
Country	
Developed	7 (64)
Developing	4 (36)
Setting	
Household	7 (64)
Elementary school	2 (18)
University residential hall	2 (18)
Transmission mode	
Primary	5 (45)
Secondary	6 (55)
Intervention evaluated[a]	
Hand sanitizer and education	3 (20)
Hand sanitizer, soap and education	1 (7)
Hand sanitizer and face mask	3 (20)
Hand sanitizer, face mask and education	2 (13)
Soap	3 (20)
Soap and education	1 (7)
Soap and face mask	2 (13)
Outcome assessed	
Laboratory-confirmed influenza	11 (100)

[a] More than one intervention for some studies.

Among the 11 included studies, 7 studies were in household settings, two in elementary schools and two in university residential halls. Included study information is shown in Table 2, and detailed study description and evidence quality assessment are shown in Table 3. The evidence profile for the outcomes is summarized in Table 4.

In the pooled analysis, hand hygiene with face mask (RR = 0.91, 95% CI: 0.73–1.13, p = 0.39, I2 = 35%) did not have a statistically significant protective effect in non-health care settings (Fig. 4) *(19-24)*. Some published studies noted that poor adherence to hand hygiene may lead to underestimation of the true effect of the intervention (*19, 21, 22*).

The relative importance of transmission modes of influenza may vary in different settings. In school settings, no total effect was generated due to high heterogeneity (Fig. 5) (*17, 25*). In a study in the United States of America (USA), there was no significant effect of hand hygiene with a point estimate of the risk ratio close to 1, whereas a large trial in Egypt reported a reduction of more than 50% in influenza cases in the intervention group.

Hand hygiene with face mask intervention contributed to 52% relative risk reduction (RR = 0.48, 95% CI: 0.21–1.08, p = 0.08, marginally significant, I2 = 0%) of laboratory-confirmed influenza infection in university residential hall (Fig. 6) (*20, 23*).

The efficacy of hand hygiene with or without face mask was insignificant (RR = 1.05, 95% CI: 0.86–1.27, p = 0.65, I2 = 57%) in household setting in the analysis (Fig. 7) (*19, 21, 22, 24, 26, 27*). Although the pooled analysis did not identify a significant effect of hand hygiene overall, some household transmission studies reported that implementing hand hygiene intervention earlier after onset in the index case might be more effective in preventing secondary cases in the household (*19, 24*).

Experimental studies found that influenza virus could not survive long on human hands (*28, 29*). Viable influenza virus could be transmitted from contaminated surfaces to human hands by rubbing (*30*). Simmerman cultured live influenza virus from a finger swab sample from a laboratory-confirmed influenza patient (*31*). This evidence suggested the biological plausibility of indirect contact transmission via contaminated hands of influenza. Experimental studies also claimed that hand hygiene practice (e.g. handwashing with water and soap, and handrubbing with alcohol-based handrub) is effective to inactivate or reduce viable influenza virus on human hands (*32-34*). These results highlighted the importance of hand hygiene and suggested that hand hygiene may be initiative to prevent influenza transmission.

Ethical considerations

There are no major ethical issues. Alcohol-based handrub might be not available in some locations due to religious objections, such as the situation of incompliance of hand hygiene recommendation among Muslim health care workers (35). Skin irritation by alcohol handrub is possible, although the irritant potential of alcohol-based handrub is very low (*36*). Low adherence to hand hygiene intervention was observed in some studies (*19, 21, 22, 26*).

Knowledge gaps

Our review identified 10 RCTs of hand hygiene against laboratory-confirmed influenza. The pooled estimate of the effectiveness of hand hygiene in household settings was close to the null, with a fairly narrow confidence interval (Fig. 7), and future studies are unlikely to move the pooled estimate far from the null even if individual trials done in the future show protective efficacy of hand hygiene. In schools, there are only two published trials, and there is a clear need for additional studies to resolve the discrepancy between those two studies from the USA and Egypt (*17, 25*), one of which showed a considerable effect of hand hygiene (Fig. 5).

A more basic knowledge gap is on mechanisms of person-to-person transmission of influenza, including virus survival on hands and different types of surfaces, and the potential for contact transmission to occur in different locations and with different environmental conditions. Randomized trials of hand hygiene can contribute to determining modes of influenza transmission because hand hygiene would primarily act against one specific mode of transmission (indirect contact) but not other modes (respiratory droplets of varying sizes) (*37*).

Table 3. Description of studies included in the review of hand hygiene

STUDY	STUDY DESIGN	STUDY PERIOD	POPULATION & SETTING	TRANSMISSION MODE	INTERVENTION	OUTCOME & FINDING	QUALITY OF EVIDENCE
Azman AS, 2013 (*16*)	Cluster-RCT School level	2007–2008 influenza season	3360 students from 10 elementary schools in Pittsburgh, USA	Primary and secondary	Hand sanitizer, soap and education	The primary transmission outcome refers to Stebbins, S. 2011; no significant difference in secondary ILI attack rate between intervention group and control group	Moderate
Levy JW, 2014 (*18*)	Cluster-RCT Household level	2009–2010	191 households with index children recruited from a public paediatric hospital in Bangkok, Thailand	Secondary	Handwashing; handwashing and face mask	Less secondary influenza infections in households in the intervention group than control group, but not statistically significant; handwashing reduces surface influenza RNA contamination	Moderate
Ram PK, 2015 (*27*)	Cluster-RCT Household level	2009–2010	384 households with index case-patients recruited from a hospital in Kishoregoni, Bangladesh	Secondary	Handwashing with soap and education	Handwashing promotion did not prevent secondary influenza infection in household setting	Moderate
Aiello AE, 2010 (*20*)	Cluster-RCT University residence hall level	2006–2007 influenza season	1297 participants recruited from7 residential halls in Michigan, USA	Primary	Hand sanitizer and face mask; face mask	The laboratory-confirmed influenza protective effect of intervention is not significant; but the intervention is significant in ILI reduction	Moderate
Aiello AE, 2012 (*23*)	Cluster-RCT University residence hall level	2007–2008 influenza season	1111 participants recruited from 5 residential halls in Michigan, USA	Primary	Hand sanitizer and face mask; face mask	Reductions in the rates of influenza in the intervention groups, but not significant; significant reduction in the rates of ILI	High
Cowling BJ, 2008 (*26*)	Cluster-RCT Household level	2007	198 households with index subjects recruited from outpatient clinics in Hong Kong SAR, China	Secondary	Hand sanitizer and education; face mask and education	No significant difference between intervention groups and control group in laboratory-confirmed influenza and clinical secondary attack rate	Moderate

STUDY	STUDY DESIGN	STUDY PERIOD	POPULATION & SETTING	TRANSMISSION MODE	INTERVENTION	OUTCOME & FINDING	QUALITY OF EVIDENCE
Cowling BJ, 2009 (*19*)	Cluster-RCT Household level	2008	259 households with index subjects recruited from outpatient clinics in Hong Kong SAR, China	Secondary	Hand sanitizer and education; hand sanitizer, face mask and education	Hand hygiene and face mask intervention prevent influenza transmission, but not statistically significant; among the households implementing interventions within 36 hours symptom onset of index cases, the interventions significantly reduce influenza transmission	Moderate
Larson EL, 2010 (*21*)	Cluster-RCT Household level	2006–2008	509 households were recruited in New York, USA	Primary	Hand sanitizer and education; hand sanitizer, face mask and education	There is no detectable benefit of hand hygiene, face mask and education intervention on influenza prevention	Moderate
Simmerman JM, 2011 (*22*)	Cluster-RCT Household level	2008–2009	442 households with index children recruited from a public paediatric hospital in Bangkok, Thailand	Secondary	Handwashing; handwashing and face mask	Hand hygiene and face mask intervention did not reduce influenza transmission	Moderate
Stebbins S, 2011 (*17*)	Cluster-RCT School level	2007–2008 influenza season	3360 students from 10 elementary schools in Pittsburgh, USA	Primary	Hand sanitizer, soap and education	"WHACK the Flu" programme did not reduce laboratory-confirmed influenza infection, but reduced absence episodes and laboratory-confirmed influenza A	Moderate
Suess T, 2011 (*24*)	Cluster-RCT Household level	2009–2010 pandemic season 2010–2011 influenza season	84 households with one influenza positive index case were recruited by general practitioners or paediatricians in Berlin, Germany	Secondary	Hand sanitizer and face mask; face mask	The interventions could reduce influenza transmission in household setting when implemented early and use properly	Moderate
Talaat M, 2011 (*25*)	Cluster-RCT School level	2008	44 451 students were enrolled from 60 elementary schools in Cairo, Egypt	Primary	Handwashing	Hand hygiene campaign effectively reduced different kinds of infectious disease, including laboratory-confirmed influenza	Moderate

ILI: influenza-like illness; RCT: randomized controlled trial; RNA: ribonucleic acid; SAR: Special Administrative Region; USA: United States of America.

Table 4. Grade evidence profile for hand hygiene

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hand hygiene with or without face mask	versus control	Risk ratio	Quality	Importance
Effect of hand hygiene intervention on prevention of laboratory-confirmed influenza											
10	Randomized trial [1]	No serious risk of bias [2,3,4]	Serious [5]	No serious indirectness [6]	Serious [7]	Strong association [8]	434/6442 (6.7%)	504/5392 (9.3%)	Risk ratio cannot be generated because of high heterogeneity	Moderate	Important

1 All studies were randomized trials.
2 All studies were cluster-RCTs at household, school and university residence level.
3 Five studies reported blinding of study staff including clinical staff, laboratory staff or recruiting physicians. Subjects of all studies were not blinded due to the nature of the study design.
4 Allocation concealment was adequate in all trials. Three studies used block randomization and seven studies used simple randomization.
5 High heterogeneity was observed in the pooled analysis (I2 > 50%).
6 Laboratory-confirmed influenza was the outcome for all studies.
7 Cowling B.J. 2008 and Suess T. 2011 reported insufficient number of participants. Cowling B.J. 2009 reported insufficient statistical power. Larson E.L. 2010 reported lower rate of illness was found compared to initial assumption. Simmerman J.M. 2011 reported did not reach the recruitment target. Talaat M. 2011 reported low rate of testing of students who were absent due to ILI.
8 Aiello AE (2012), rated as high-quality study, showed a large effect in favouring hand hygiene intervention – RR = 0.4.

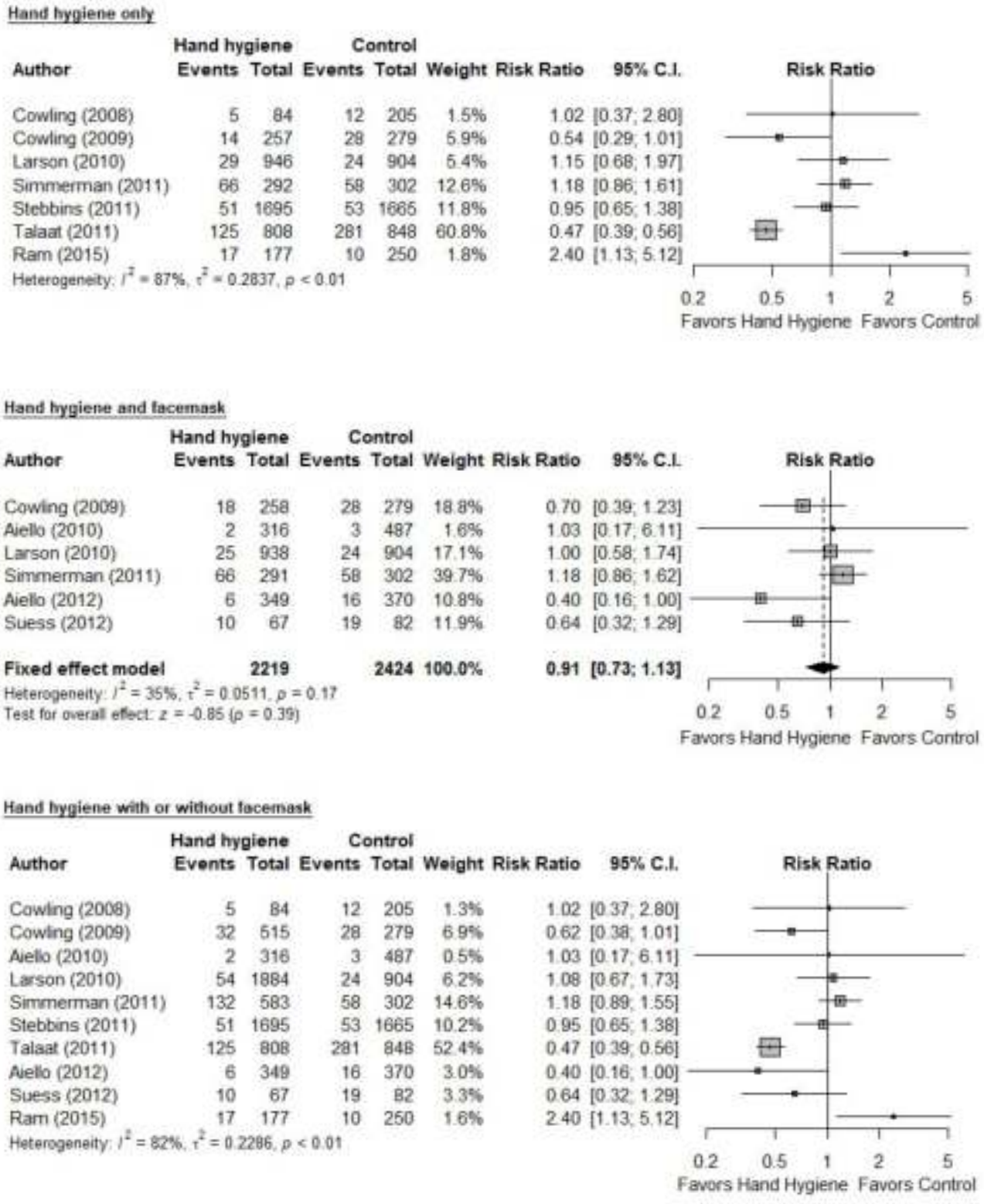

Fig. 4. Risk ratios for the effect of hand hygiene interventions with or without face mask on laboratory-confirmed influenza (pooled analysis)

Note: Total effect would not be estimated when heterogeneity is high (I2 ≥75%).

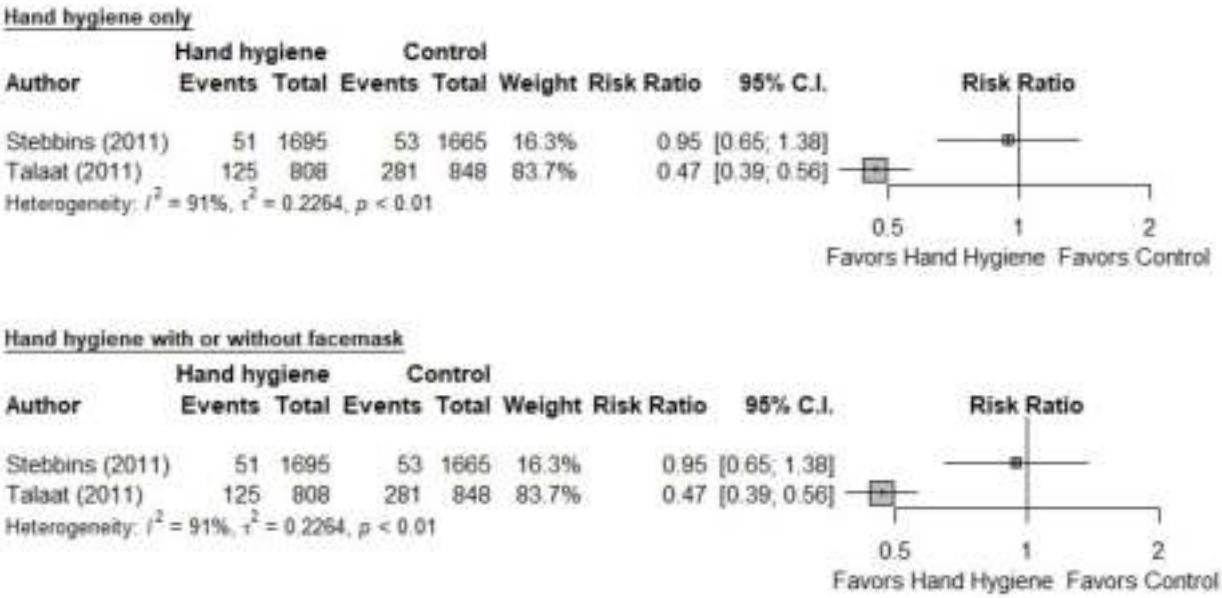

Fig. 5. Risk ratios for the effect of hand hygiene interventions with or without face mask on laboratory-confirmed influenza in elementary school setting

Note: Total effect would not be estimated when heterogeneity is high (I2 ≥ 75%).

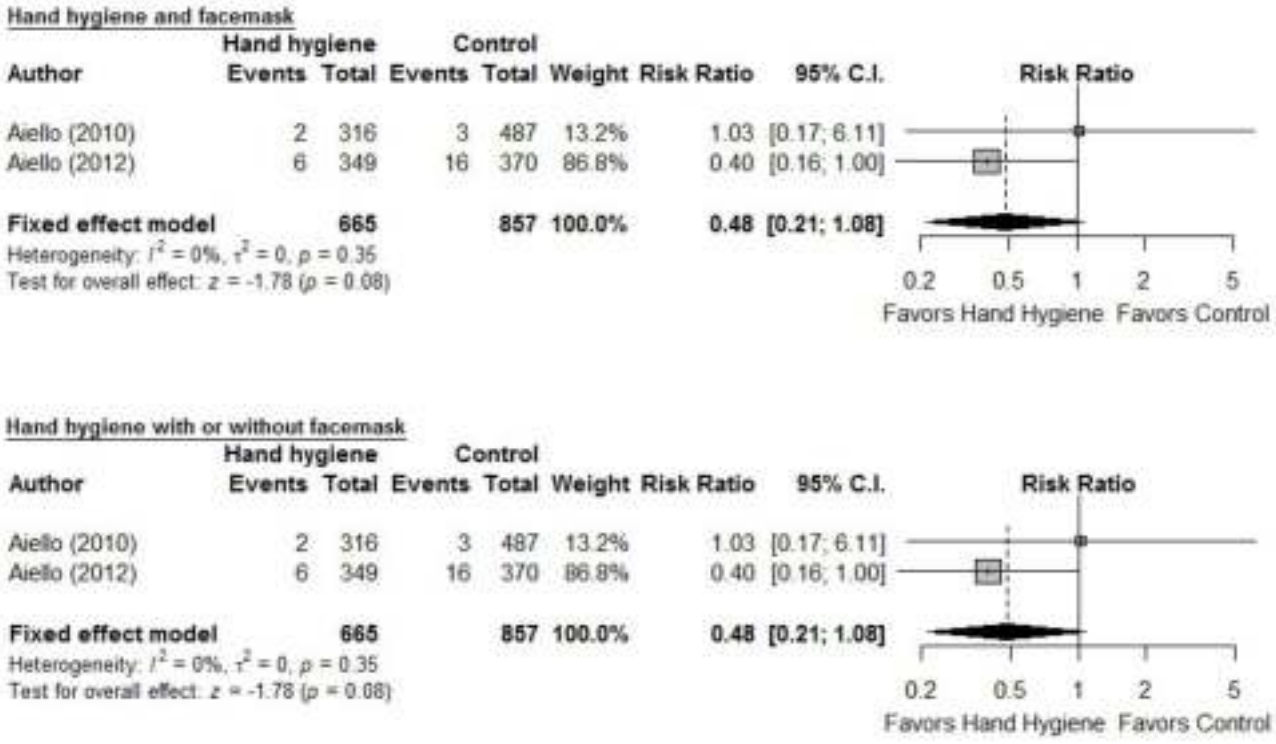

Fig. 6. Risk ratios for the effect of hand hygiene interventions with or without face mask on laboratory-confirmed influenza in university residential hall setting

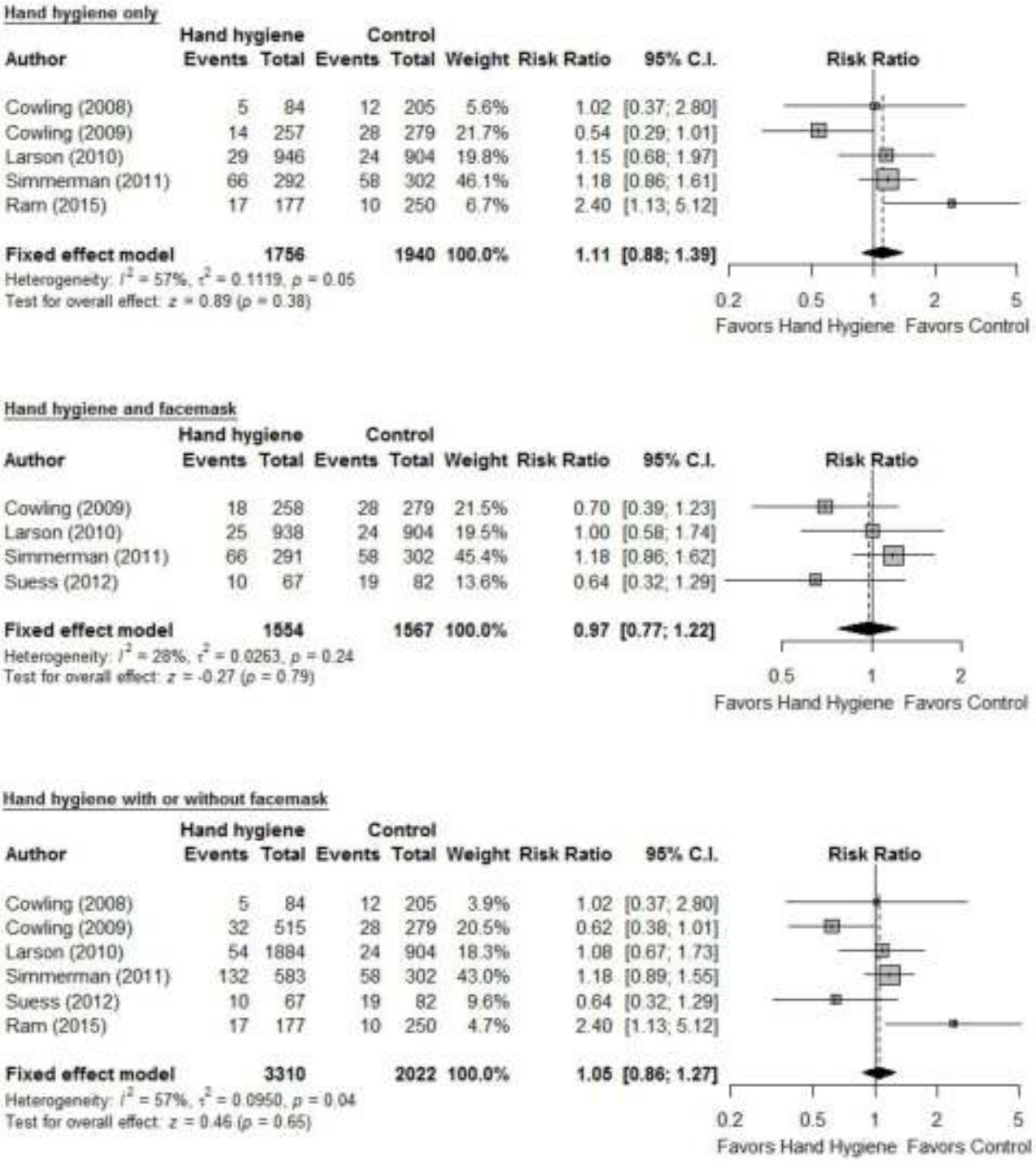

Fig. 7. Risk ratios for the effect of hand hygiene interventions with or without face mask on laboratory-confirmed influenza in household setting

1.2. Respiratory etiquette

Terminology

Definitions of respiratory etiquette are shown in Table 5.

Table 5. Definitions of respiratory etiquette terms

TERM	DEFINITION
Respiratory etiquette	Respiratory etiquette is also known as 'cough etiquette' (*38*). It is a simple hygiene practice to prevent person-to-person transmission of respiratory infections. Measures include (*39*): 1) Cover the mouth and nose with a tissue when coughing or sneezing 2) Find the nearest waste basket to dispose the used tissue immediately 3) Wash hands after touching respiratory secretions and/or contaminated objects

Methods

On 6 November 2018, we conducted a literature search in four databases: Medline (January 1946 to October 2018), PubMed (January 1950 to October 2018), EMBASE (1980 to October 2018), and CENTRAL (The Cochrane Library, 2018, Issue 5). Reference lists of retrieved articles were also reviewed for additional potential articles for this review. Articles of all languages were reviewed. Studies were selected if they investigated specifically the use of respiratory/ cough etiquette as the intervention along with the study outcome of laboratory-confirmed influenza virus infection. Studies that reported use of face mask as part of the respiratory etiquette were excluded because they will be covered in Section 1.3. Two independent reviewers (ES and SG) reviewed retrieved titles and subsequent relevant abstracts independently.

Results

A total of 80 articles were retrieved from four electronic databases after removing duplicate publications. Titles, abstract content and full text were subsequently reviewed for inclusion; 35 abstracts were selected for screening and then 18 full-text articles were assessed for eligibility. No studies were identified for this review to quantify the efficacy of respiratory etiquette with the outcome of laboratory-confirmed influenza. The flow chart is shown Fig. 8.

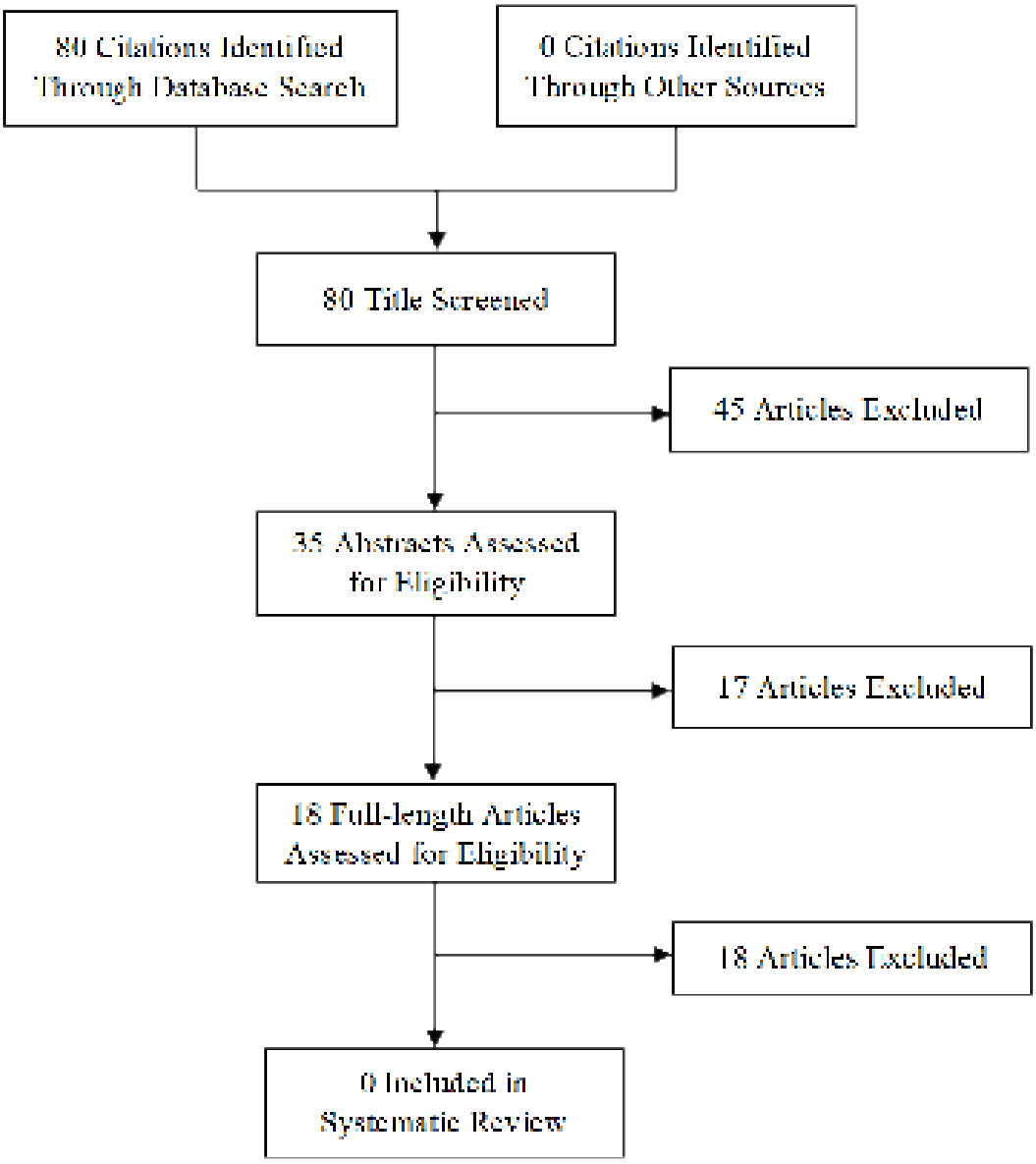

Fig. 8. Flow chart of the process and results of study selection

Balaban et al. reported a 2% reduction of self-reported respiratory illnesses, defined by one or more symptoms in cough, congestion, sore throat, sneezing or breathing problems, with the practice of cough etiquette among US pilgrims in the 2009 Hajj (*40*). Zayas et al. conducted an observational study to determine the effectiveness of respiratory etiquette manoeuvres in blocking the release of droplets or aerosols during coughing (*38*). They concluded the common respiratory etiquette (using surgical mask and hand, arm or sleeve, tissue) is not effective in blocking different diameter droplets to the surrounding environment and the majority of droplets dispersed to the environment when practicing the manoeuvre were < 1 µm.

Ethical considerations

No major ethical considerations. Cultural contexts may need to be considered when recommending specific actions such as covering coughs with hands or tissues.

Knowledge gaps

There is a need for further research in the best measures of respiratory etiquette for reducing influenza transmission (38).

1.3. Face masks

Terminology
Relevant terminology relating to face masks is shown in Table 6.

Table 6. Definitions of masks terms

TYPES OF MASKS	TERMINOLOGY
Clothing, scarf or rags tied over the nose and mouth	These are referred as alternative barriers to medical masks, but there is insufficient information available on their effectiveness *(41)*.
Cloth mask Face mask	Cloth masks can be referred to 'reusable masks made of cloth or any other fabric, including cotton, silk or muslin'*(42)* . Fitness of fabric and number of layers of a cloth mask determine its filtration capacity *(42)*. Cloth masks should be cleaned thoroughly between each use *(43)*. Washing with household detergent at normal temperature will be sufficient *(43)*.
Respirator	A face mask, also known as surgical, isolation, dental or medical procedure masks, is a loose-fitting, disposable device that covers the mouth and nose of the user, and helps block large-particle droplets, splashes, sprays or splatter that may contain infectious agents *(44)*. Face masks may also help reduce exposure of user's saliva and respiratory secretions to others *(44)*. They may come with or without a face shield and are not designed to be shared *(44)*. They are not designed to protect against breathing in small-particle aerosols that may contain viruses. Face masks should be used once and then disposed in the trash *(45)*. Respirator, also known as filtering facepiece respirator, is a personal protective device that covers the nose and mouth of the user, and helps reduce the risk of inhaling hazardous airborne particles (including dust particles and infectious agents), gases, or vapours on the user *(46)*. NIOSH in the USA certifies N, R and P series particulate filtering respirator types 95, 99 and 100 with minimum filtration efficiencies of 95, 99 and 99.97%, respectively. This certification is recognized by countries like Canada, Mexico and Chile. Several countries including Canada, Mexico and Chile. In Europe, respirators marked with 'Conformité Européen' (CE) such as FFP1 (class P1), FFP2 (class P2) and FFP3 (class P3) types meet minimum filtration efficiencies of 80, 94 and 99%, respectively *(47)*. A label 'NIOSH' is required to be printed on the NIOSH-approved products with other information including part, lot number and company name; A label 'CE' on the product indicates EC conformity *(47)*.

EC: European Community; NIOSH: National Institute for Occupational Safety and Health; USA: United States of America.

Methods

On 28 July 2018, we conducted a literature search in four databases: Medline (January 1946 to June 2018), PubMed (January 1950 to July 2018), EMBASE (1980 to June 2018), and CENTRAL (The Cochrane Library, 2018, Issue 5). Reference lists of retrieved articles were also reviewed for additional potential articles for this review. Articles of all languages were reviewed. Studies were selected if they were conducted in RCT in community settings such as households and schools, evaluated the use of face masks with or without the combination of other intervention as one intervention, and included the incidence of laboratory-confirmed influenza case as study outcome. Two independent reviewers (ES and ZX) reviewed retrieved titles and subsequent relevant abstracts independently.

Qualities of studies were assessed by GRADE with an aim to evaluate the efficacy of community-based face mask use in the prevention of laboratory-confirmed influenza virus infections.

Results

A total of 1100 articles were retrieved from four electronic databases after removing duplicate records. Titles, abstract content and full text were subsequently reviewed for inclusion; 10 relevant studies were identified for this review and meta-analysis to quantify the efficacy of community based use of face masks after excluding 89 articles by full-text assessment. The flow chart is shown in Fig. 9. Of 10 studies, seven were conducted in household settings (*19, 21, 22, 24, 26, 48, 49*), with two studies conducted in university residence halls (*20, 23*), and one study conducted in Hajj pilgrims (*50*). Nearly half of the studies evaluated the effect of face mask use with the practice of handwashing, therefore results were analysed in two groups: comparison of control group with intervention group of face mask use only; and comparison of control group with intervention group of face mask use with or without handwashing.

Among the 10 selected studies, two studies by MacIntyre et al. had a slightly different study design. One study enrolled families in which one person had laboratory-confirmed influenza, and only required the household contacts to wear face masks or P2 masks (equivalent to a N95 respirator) (48), whereas the other study required only the ill members to wear face mask to evaluate the protective effect of face mask if worn by the ill individual (i.e. source control) (*49*). In the remaining eight studies, every participant in the face mask intervention group was supposed to wear a face mask.

MacIntyre et al. compared the protective effect of face mask and P2 mask but found no significant difference in influenza-like illness (ILI) and laboratory-confirmed respiratory infections (influenza A and B virus, respiratory syncytial virus [RSV], human metapneumovirus [hMPV], adenovirus, human parainfluenza virus [PIV], coronavirus, rhinovirus, enterovirus or picornovirus); however, they reported a significant reduction in ILI if the mask was worn with good compliance in a secondary analysis (*48*).

Two studies by Aiello et al. were conducted in residence hall settings (*20, 23*). They randomized university residents by cluster (each residential hall forming a cluster unit) to face masks, enhanced hand hygiene, or both. They then measured the incidence of laboratory-confirmed influenza in students in each hall. The authors reported no significant difference in ILI and laboratory-confirmed influenza in these three randomized groups; however, they observed a significant reduction in ILI in the combined face mask and hand hygiene intervention group during the latter half of the study period in a secondary analysis.

Seven studies were conducted in household settings where a person with laboratory-confirmed influenza was recruited as a household index case, and the rate of secondary infections in the education group (control), mask group and/or hand hygiene group was monitored for illnesses and infections. All studies found no significant differences in the rate of laboratory-confirmed

influenza virus infections in contacts in the face mask arms, and some studies reported that low compliance of the use of NPIs could affect the results (*21*). One study reported a significant reduction in laboratory-confirmed influenza virus infections in contacts in the face mask and hand hygiene group in the subset of households where the intervention was applied within 36 hours of symptom onset in the index case (*24*).

Ten studies were pooled to conduct a meta-analysis to quantify the efficacy of community based use of face masks in the reduction of laboratory-confirmed influenza virus infection (Table 7). In the pooled analysis, there was a non-significant relative risk reduction of 22% (RR = 0.78, 95% CI: 0.51–1.20, I2 = 30%, p = 0.25) in the face mask group and 8% in the face mask group regardless of the addition of practice of hand hygiene (RR = 0.92, 95% CI: 0.75–1.12, I2 = 30%, p = 0.40). The evidence profile for face masks outcome is summarized in Table 8.

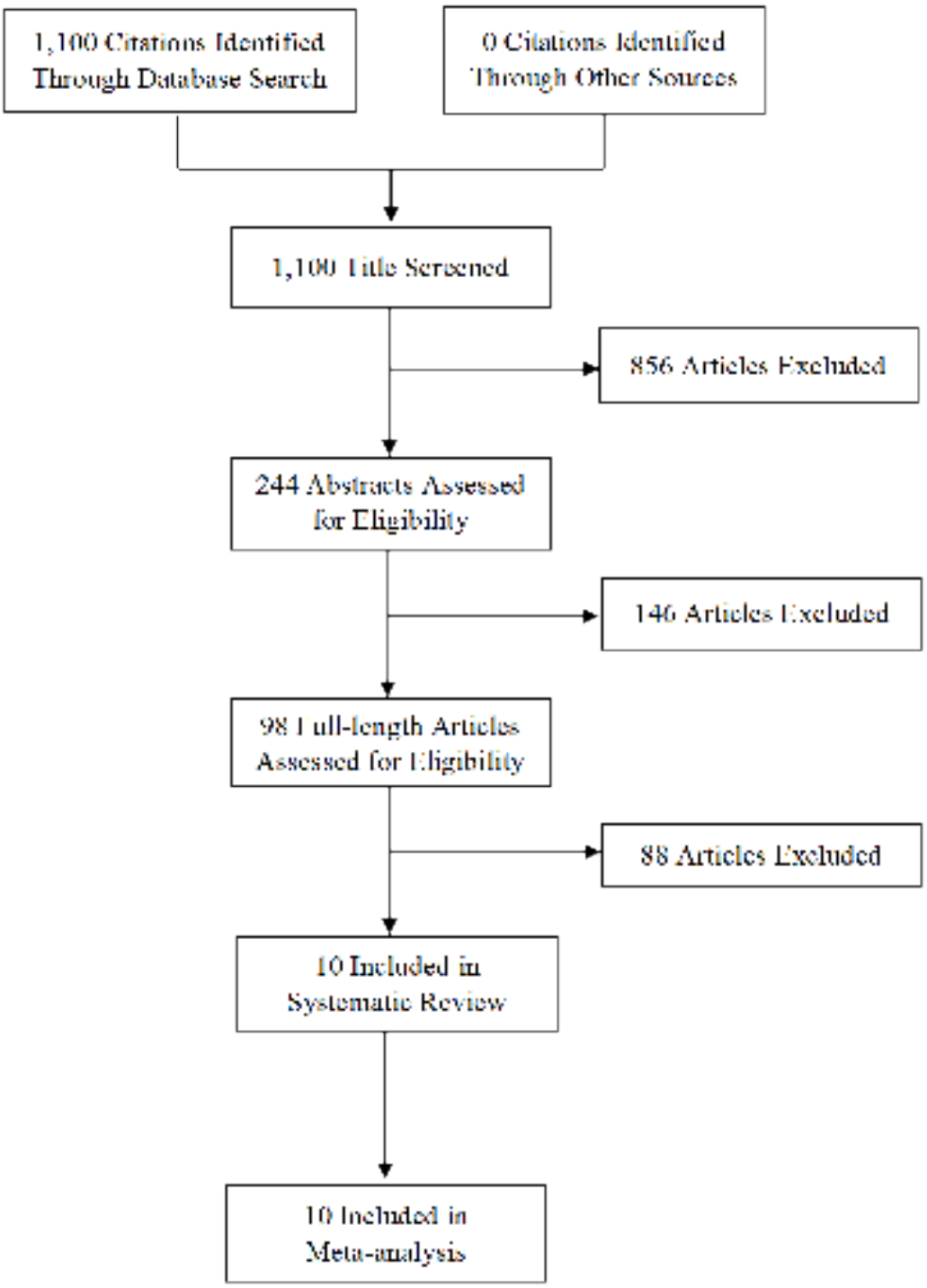

Fig. 9. The flow chart of the process and results of study selection

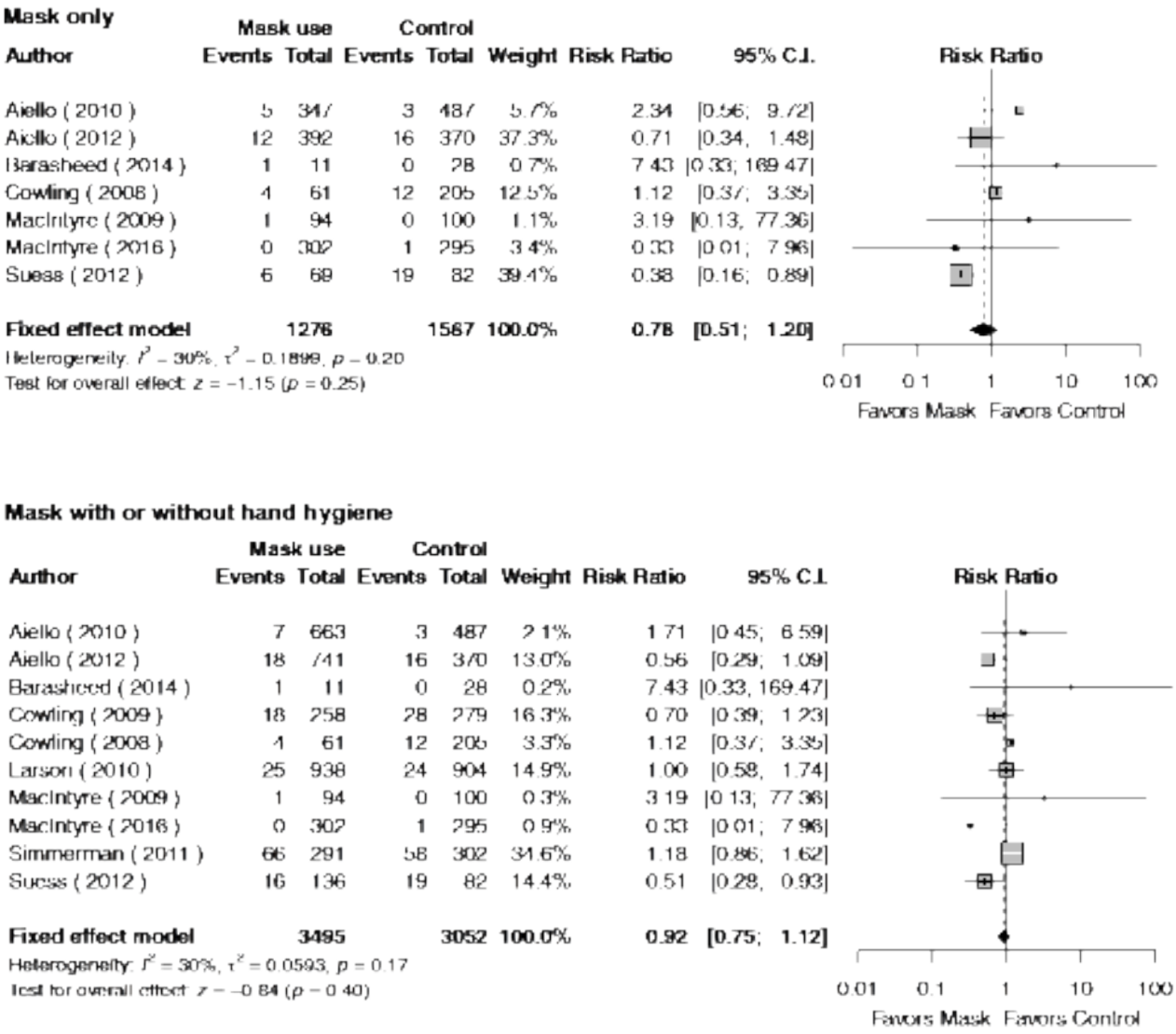

Fig. 10. Effects of face mask use interventions with or without enhanced hand hygiene on laboratory-confirmed influenza in 10 studies

Ethical considerations

No major ethical considerations. Masks may be more culturally acceptable in some locations than others, and a variety of factors may affect compliance.

Knowledge gaps

In the studies of face mask use with or without hand hygiene, the pooled estimate of the risk reduction against laboratory-confirmed influenza was 0.90 (95% CI: 0.75–1.12), which suggests that additional randomized trials would be less likely to identify a substantial protective efficacy of face masks. However, the majority of these studies were conducted in households in which at least one person was infected, and exposure levels might be relatively higher. Additional studies of face mask use in the general community would be valuable. While respirators should provide better protection against respiratory infections compared to face masks because of their higher filtration efficiency, a household randomized controlled study showed no difference in their effect on ILIs and laboratory-confirmed influenza virus infection (*48*). One issue is that respirators require fit testing for optimal performance, but fit testing facilities are not widely available in the community.

Table 7. Description of studies included in the review of face masks

STUDY	STUDY DESIGN	STUDY PERIOD	POPULATION & SETTING	INTERVENTION	OUTCOME & FINDING	QUALITY OF EVIDENCE
Aiello AE, 2010 (20)	Cluster-randomized intervention trial	Nov 2006 – Mar 2007	1437 university hall residents (USA)	Mask; Mask + Hand hygiene; control	Significant reduction in ILI during weeks 4–6 in mask and hand hygiene group compared to control; No significant reduction in ILI in mask and hand group or mask-only group or control	Moderate
Aiello AE, 2012(*23*)	Cluster-randomized interventional trial	Nov 2007 – Mar 2008	1178 university hall residents (USA)	Mask; Mask + Hand hygiene; control	No significant reduction in rates of laboratory-confirmed influenza in mask and hand group or mask-only group or control group	Moderate
Barasheed O, 2014 (*50*)	Non-blinded cluster-randomized trial	Nov 2011 – Nov 2011	164 Australian pilgrims (Saudi Arabia)	Mask; control	No significant difference in laboratory-confirmed influenza in two arms; protective effect against syndromic ILI compared to controls (31% versus 53%, p = 0.04)	Moderate
Cowling BJ, 2008 (*26*)	Cluster-randomized intervention trial	Feb 2007 – Sep 2007	198 laboratory-confirmed influenza case and their household contacts	Mask; Hand hygiene; control	No significant reduction in the secondary influenza attack rate in control, mask or hand group	Moderate
Cowling BJ, 2009 (*19*)	Cluster-randomized intervention trial	Jan 2008 – Sep 2008	407 laboratory-confirmed influenza case and 794 household members	Mask; Mask + Hand hygiene; control	No significant difference in rates of laboratory-confirmed influenza in hand-only or mask and hand group	Moderate
Larson EL, 2010 (*21*)	Cluster-randomized intervention trial	Nov 2006 – Jul 2008	617 households	Mask + Hand hygiene; Hand hygiene; control	No significant reduction in rates of laboratory-confirmed influenza in control, hand, mask or hand group	Moderate
MacIntyre CR, 2009 (*48*)	Cluster-randomized intervention trial	Aug 2006 – Oct 2006 & Jun 2007 – Oct 2007	145 laboratory-confirmed influenza case and their adult household contacts	Surgical mask; P2 mask; control	No significant difference in rate of laboratory-confirmed influenza in control, face mask or P2 mask group	Moderate
MacIntyre CR, 2016 (*49*)	Cluster-randomized intervention trial	Nov 2013 – Jan 2014	245 ILI index case and 597 household contacts	Mask; control	Clinical respiratory illness, ILI and laboratory-confirmed viral infections were lower in the mask arm compared to control, but results were not statistically significant	Moderate
Simmerman JM, 2011) (*22*)	Cluster-randomized intervention trial	Apr 2008 – Aug 2009	465 laboratory-confirmed influenza case and their household contacts	Mask + Hand hygiene; hand hygiene; control	No significant reduction in rate of secondary influenza infection in control, hand, mask or hand group	Moderate
Suess (2012) (*24*)	Cluster-randomized intervention trial	Nov 2009 – Jan 2010 & Jan 2011 – Apr 2011	84 laboratory-confirmed influenza case and 218 household contacts	Mask; Mask + Hand; control	No significant difference in rate of laboratory-confirmed influenza in control, mask, mask or hand group	Moderate

ILI: influenza-like illness; USA: United States of America.

Table 8. Grade evidence profile for face masks

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mask	Control	Risk ratio	Quality	Importance
10	RCT [1,2]	No serious risk of bias [3,4]	No serious inconsistency [5]	No serious indirectness	Serious [6]	None	156/3495	161/3052	0.92 (0.75,1.12)	Moderate	Important

RCT: randomized controlled trial.

1 All studies were randomized trials.
2 All studies were cluster-RCTs at household and university residence level.
3 Eight studies reported blinding of study staffs including clinical staff, laboratory staff or recruiting physicians. Subjects of all studies were not blinded.
4 Three studies used block randomization; six studies used computer program to generate the randomization order and one study used ticket-picking for selection.
5 Moderate heterogeneity was observed in the pooled analysis.
6 Six studies did not have sufficient sample size in each intervention group; 3 studies reported insufficient statistical power; one study reported insufficient detection of influenza case.

2. ENVIRONMENTAL MEASURES

2.1. Surface and object cleaning

Methods

We conducted a systematic review on the effect of surface and object cleaning in preventing influenza virus infections in non-health care settings. PubMed, Medline, EMBASE and CENTRAL were searched for articles on 15 October 2018.

Study selection criteria were studies reporting the effect of surface and object cleaning intervention with no intervention in preventing influenza virus infections in community settings. RCTs and other types of epidemiological studies were included if they aimed to study the effect of surface and object cleaning on laboratory-confirmed influenza, ILI or respiratory illness. Simulation studies, recommendations, and commentaries or editorials were excluded. A community setting was defined as an open setting without confinement and special care for the patients. Articles describing any surface and object cleaning related interventions were included. No language limits were applied.

Two independent reviewers (ZX and ES) reviewed titles, abstracts and full texts. After confirmed included studies, data extraction and evidence quality assessment were performed by the reviewers. The GRADE framework was used to evaluate the effect of surface and object cleaning on influenza.

Results

There were 484 articles retrieved through database search. 462 articles were excluded through title and abstract screening. In the full-text assessment, 19 articles were screened out due to no surface and object cleaning intervention or no specific respiratory infection outcome. Finally, three articles were included in the systematic review to study the effectiveness of surface and object cleaning to prevent influenza infection. The article selection flow is shown in Fig. 11.

A cross-sectional study showed that bleach use in households was significantly associated with an increased in the rate of self-reported influenza (influenza data were obtained from self-administered questionnaires and the paper did not specify whether it was laboratory-confirmed influenza or ILI), and the authors hypothesized that this might due to the immunosuppressive properties of bleach (*51*). An RCT with disinfection of toys and linen in day care nurseries found a reduction in the detections of viruses in the environment, but no significant effect on influenza virus specifically and no significant reduction in acute respiratory illnesses among children *(52)*. Another RCT conducted in elementary schools demonstrated that hand hygiene with alcohol-based hand sanitizer and surface disinfection with quaternary ammonium wipes intervention could reduce gastrointestinal illness absenteeism, but not respiratory illness absenteeism (*53*). Detailed data extraction is shown in Table 9 below.

Experimental studies found that laboratory-grown influenza virus could survive on common surfaces and objects (e.g. stainless steel, wood, plastic, cloth and banknotes) from community settings for a few hours and up to 1 week (*28, 30, 54-56*). Influenza virus RNA could be detected by polymerase chain reaction (PCR) on surfaces and objects in household, school and airport settings in the field studies (*31, 52, 57-60*). Killingley et al. found viable influenza virus in the environment with laboratory-confirmed influenza individuals (*59*). These results suggested the biological plausibility that influenza virus could transmit via the fomite route. And the results from some experimental studies showed that disinfection process with different disinfection products (e.g. ethanol and 1-propanol) was effective to inactivate or reduce infectious influenza virus on surfaces (*61-63*), which suggested the importance of surface and object cleaning in influenza transmission prevention.

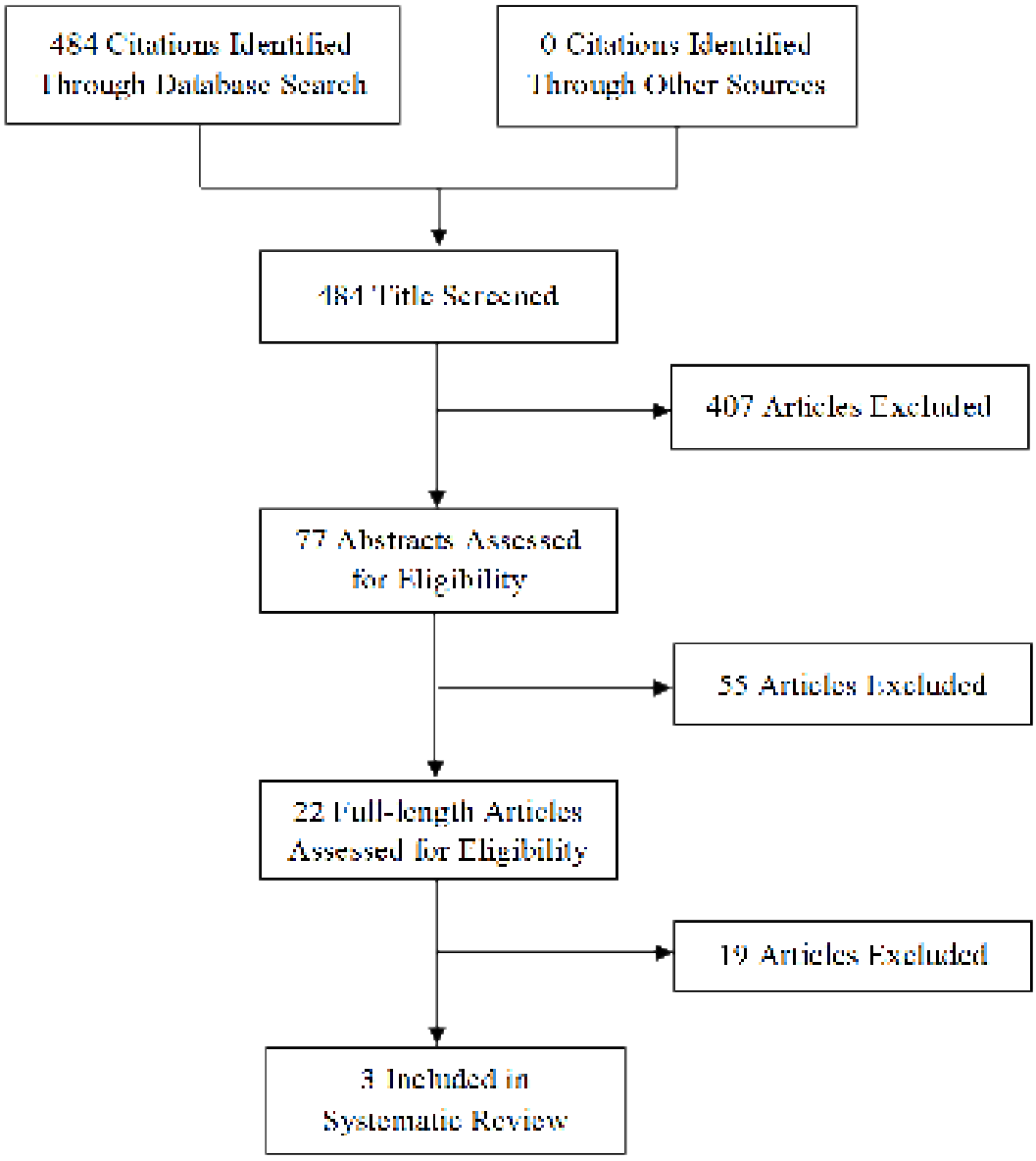

Fig. 11. The flow chart of surface and object cleaning articles selection

Ethical considerations

Disinfection product selection is a major issue, especially in public settings. Some disinfectants are irritants and may lead to adverse effect in sensitive population (*51*), and some disinfectants with alcohol may not be applicable in some countries or regions due to religious objections (*35*). In addition, the safety of cleaning personnel should also be considered. Proper training should be provided for the cleaning personnel, including proper use of the disinfectant (usage, dosage and time) and precautions before cleaning, such as wearing protective clothing.

Knowledge gaps

Only three studies were included in our systematic review and only two of them were RCTs. More trials are needed to study the effect of surface and object cleaning on influenza prevention. The best evidence for pandemic preparedness would be provided by studies in which the outcome is laboratory-confirmed influenza, rather than acute respiratory infections. Studies in various settings (e.g. household, school, workplace and public place) are also needed. The effect of different disinfection products to prevent influenza virus infection in terms of disinfection frequency, disinfection dosage, disinfection time point, and disinfection targeted surface and object material remained unknown.

Table 9. Description of studies included in the review of surface and object cleaning

STUDY	STUDY DESIGN	STUDY PERIOD	POPULATION & SETTING	INTERVENTION	OUTCOME MEASURE	MAIN FINDING	QUALITY OF EVIDENCE
Casas L, 2015 (*51*)	Cross-sectional study	2008–2010	9102 students from schools in Spain, Netherlands and Finland	Environment cleaning with bleach	Self-reported influenza	Passive contact with cleaning bleach in the household may increase the risk of respiratory and other infections in children, which may adversely affect the health of school-age children	Very low
Ibfelt T, 2015 (*52*)	Cluster-RCT	Autumn 2012 – April 2013	Twelve day-care nurseries (caring for 587 children) in Copenhagen, Denmark	Disinfection of toys	Respiratory infections and surface sample influenza virus detection	Frequently disinfection of toys could reduce environmental microbial presence, but not significantly reduce respiratory sickness of nursery children	Low
Sandora TJ, 2008 (*53*)	Cluster-RCT	March-May 2006	285 students from elementary schools in Avon, Ohio, USA	Hand hygiene and surface cleaning	Respiratory illness	Surface disinfection reduced gastrointestinal related absenteeism among school-age children, but not respiratory illness-related ones	Low

RCT: randomized controlled trial; USA: United States of America.

2.2. (*1*) Other environmental measures (UV light)

Terminology

The definition of ultraviolet (UV) light is shown in Table 10.

Table 10. Definition of UV light terms

TERM	DEFINITION
Ultraviolet light (UV light)	UV light is electromagnetic radiation that can be categorized into three groups by wavelength bands *(64)*: 1) UV-A (400–315 nm): It can be used for various purposes like pest control or identifying counterfeit banknotes. 2) UV-B (315–280 nm): It is known for the development of skin cancer. 3) UV-C (280–100 nm): It is used for disinfection of drinking water and sterilization of apparatus.
Ultraviolet germicidal irradiation (UVGI)	It is a mean of disinfection which breaks down microorganisms and can be used to prevent the spread of certain infectious diseases (*65*)

Methods

On 25 September 2018, we conducted a literature search in four databases: Medline (January 1946 to September 2018), PubMed (January 1950 to September 2018), EMBASE (1980 to September 2018), and CENTRAL (The Cochrane Library, 2018, Issue 5). Articles of all languages were included. Reference lists of retrieved articles were also reviewed for additional potential articles for this review. Studies were selected if they mentioned the use of UV light in community setting and reported laboratory-confirmed influenza virus infections as a study outcome. Two independent reviewers (ES and ZX) reviewed retrieved titles and subsequent relevant abstracts independently.

Results

A total of 1155 articles were retrieved from four electronic databases after removing duplicate publications. Titles, abstract content and full text were subsequently reviewed for inclusion; 67 abstracts were selected for subsequently screening and eventually 39 full texts were assessed for eligibility. No studies were identified in this review to quantify the efficacy of UV light with the laboratory-confirmed influenza outcome. The flow chart is shown in Fig. 12.

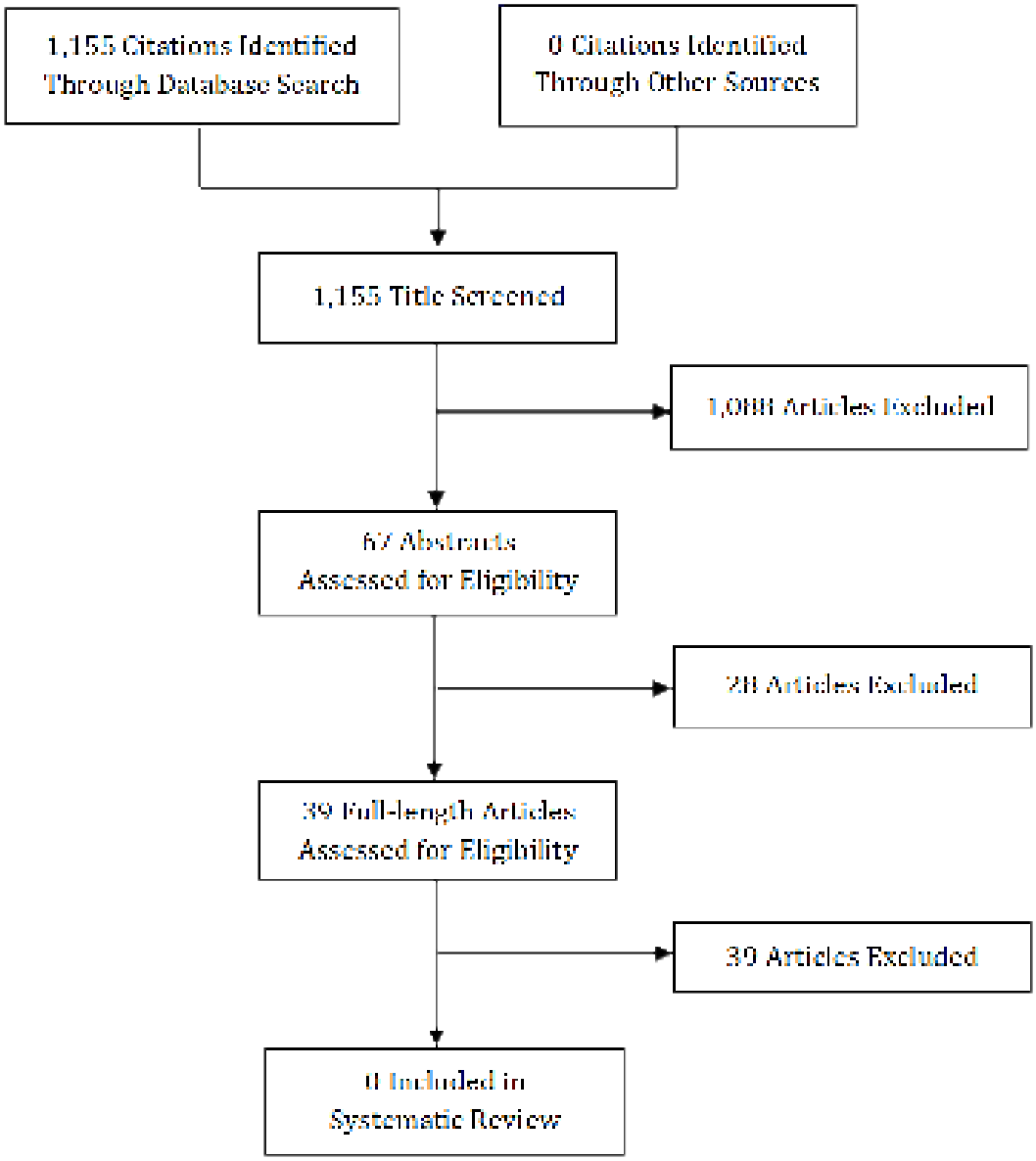

Fig. 12. The flow chart of the process and results of study selection

Ethical considerations

Exposure to UV light at certain wavelengths can increase the risk of skin cancer and cataracts; one study estimated that up to 20% of cataracts were due to UV overexposure (*64*). The use of UV light in occupied areas would need to be implemented carefully to control risks.

Knowledge gaps

The effectiveness of UV light in reducing the incidence of influenza virus infections still requires more evidence. Potential safety issues are also an important issue. Welch et al. reported that a low dose of far-UV-C light could inactivate aerosolized influenza H1N1 virus in a test chamber, and they reported an harmless effect on exposed mammalian skin (*66*), but more evidence is needed to confirm the impact of far-UV-C light in natural settings.

2.2. (*2*) Other environmental measures (ventilation)

Terminology
Definitions of ventilation are shown in Table 11 (*67*).

Table 11. Definition of ventilation terms

TERM	DEFINITION
Ventilation	Ventilation moves outdoor air into a building or a room, and distributes the air within the building.
Natural ventilation	Natural forces such as winds exchange the air in the building through windows, doors, solar chimneys, wind towers or trickle ventilators.
Mechanical ventilation	Mechanical ventilation uses mechanical fans to drive the outdoor air into the building at a designed flow rate.
	Mechanical ventilation can be integrated with air-conditioning system to control the indoor air temperature and humidity.
Hybrid (mixed-mode) ventilation	Combination of both mechanical and natural ventilation.
Air changes per hour (ACH)	The volume of air supplied to a room, in m3/hour, divided by the room volume, in m^3.

Methods
On 25 September 2018, we conducted a literature search in four databases: Medline (January 1946 to September 2018), PubMed (January 1950 to September 2018), EMBASE (1980 to September 2018), and CENTRAL (The Cochrane Library, 2018, Issue 5). Articles of all languages were included. Reference lists of retrieved articles were also reviewed for additional potential articles for this review. Studies that used modelling or simulation to describe the impact of ventilation on the rate of influenza virus infection in community settings were included. Two independent reviewers (ES and ZX) reviewed retrieved titles and subsequent relevant abstracts independently.

Results
A total of 630 articles were retrieved from four electronic databases after removing duplicate publications. Titles, abstract content and full text were subsequently reviewed for inclusion; 35 abstracts were selected for screening and then 18 full texts were assessed for eligibility. Three studies were identified for this review to evaluate the contribution of ventilation in influenza infection in community settings, both from the same author. The flow chart is shown in Fig. 13. and the description for each study is shown in Table 12.

A stimulation study modelled the transmission potential levels in an elementary school and predicted a reduction of R0 (from 11.38 to 3.97) with an increase in air changes per hour (ACH) from 0.5 to 2 (*68*).

Another stimulation study on an influenza outbreak, with consideration of possible airborne transmission in a community predicted a 40% reduction of peak daily-infected ratio by increasing the ventilation from 1 ACH to 9 ACH, and the peak would delay from Day 30 to Day 240 by increasing the ventilation from 1 ACH to 7 ACH (*69*). The authors further predicted that the overall attack rate during an epidemic would reduce from 100% to 3.3% if the ACH increased

from 1 to 7. They further studied the effectiveness of ventilation in another study, and predicted that doubling or tripling the ventilation rate could reduce the peak infection rate by over 60% under the assumption of equal contribution of airborne and close contact transmission; the authors concluded that an overall 30% reduction of peak infections was possible, even if airborne transmission only contributed to 20% of total infections (*70*).

Ethical considerations

No major ethical considerations.

Knowledge gaps

Mathematical models can only provide an indication of the potential spread of respiratory infections, and results can vary depending on the model assumptions. Experimental studies such as RCTs would provide more compelling evidence on the efficacy of increasing ventilation in reducing influenza transmission.

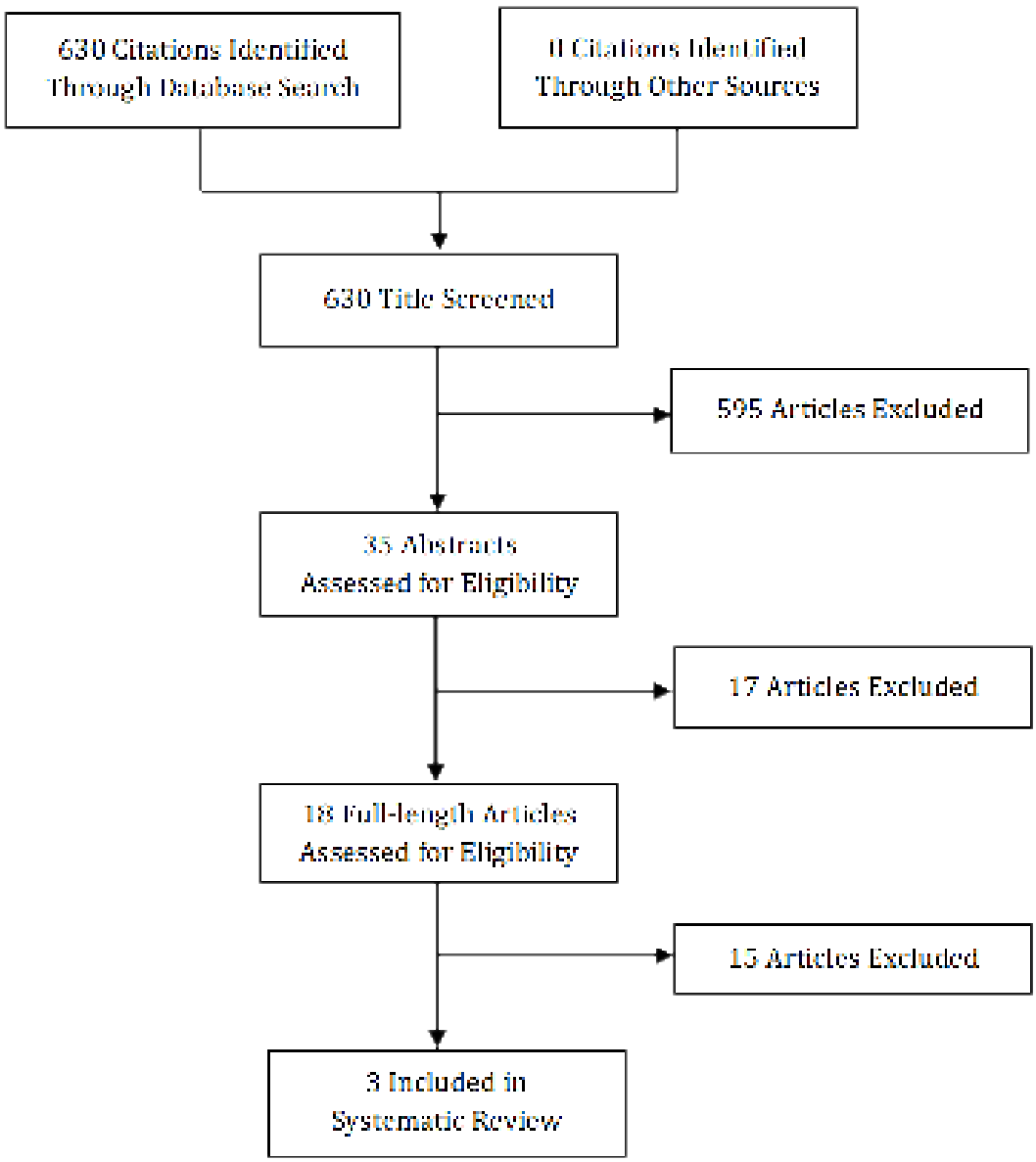

Fig. 13. The flow chart of the process and results of study selection

Table 12. Description of simulation studies included in the review of ventilation

STUDY	STUDY POPULATION	STUDY DESIGN	INTERVENTION	OUTCOME
Chen S, 2007 (*68*)	494 students (60 kindergarten and 434 elementary students) in an elementary school in Taipei City, Taiwan	Mathematical modelling	ACH, ACH + mask, 80% vaccination rate + 80% mask + 1.5 ACH	R0 is estimated to reduce from 11.38 to 3.97 for enhanced 0.5 and 2 ACH
Gao XL, 2009 (*69*)	Hong Kong SAR data in 2007	Mathematical modelling at community level	ACH, ACH + mask, ACH + UVGI, ACH + HEPA filter	Peak daily-infected ratio was reduced from 43% at 1 ACH to 21% at 3 ACH, 10% at 5 ACH, 3% at 7 ACH and 0.2% at 9 ACH; when ACH were increased from 1 to 5 ACH and 7 ACH, the disease attack rate was reduced from 100% to 69.8% and 3.3% respectively
Gao X, 2016 (*70*)	8 population groups (home stayers, office workers, classroom attendees, food service workers, shop workers, drivers, public space workers and other)	Mathematical modelling at 7 locations in communities	Ventilation, Ventilation + mask	Increasing ACH by doubling or tripling could reduce the peak infection rate by 65% and 83%; peak infection rate could reduce by about 34%, and outbreak could be delayed by over 50 days if applying a higher ventilation rate and masks for ill person

ACH: air changes per hour; HEPA: high-efficiency particulate air; R0: basic reproductive number; SAR: Special Administrative Region; UVGI: ultraviolet germicidal irradiation.

2.2. (*3*) Other environmental measures (humidity)

Terminology

Definitions of humidity are shown in Table 13.

Table 13. The definition of humidity terms

TERMS	TERMINOLOGY
Absolute humidity	A measure of actual amount of water vapour in the air, regardless of the air's temperature (expressed as grams of water per cubic metre volume of air) (*71*)
Relative humidity	A measure of amount of water vapour but relative to the temperature of air (expressed as a percentage) (*71*)

Methods
On 25 September 2018, we conducted a literature search in four databases: Medline (January 1946 to September 2018), PubMed (January 1950 to September 2018), EMBASE (1980 to September 2018), and Cochrane Library databases and the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2018, Issue 5). Articles of all languages were included. Reference lists of retrieved articles were also reviewed for additional potential articles for this review. Studies that evaluated the impact of humidification in respect to the reduction of number of infected individuals in community settings were included.

Results
A total of 631 articles were retrieved from four electronic databases after removing duplicated publications. Titles, abstract content and full text were subsequently reviewed for inclusion; 16 abstracts were selected for subsequent screening, and eventually three full texts were assessed for eligibility. No studies were identified in Fig. 14.

Reiman et al. studied the effect of elevated humidification on influenza virus survival in preschool classrooms with the outcome measure being the detection of influenza virus in air and fomites *(72)*. They reported a significant reduction of influenza A virus in air and on fomite (markers and wooden toys) in humidified preschool classrooms compared to control rooms. Detection rate of influenza A virus in air and fomites were 20% at humidified rooms (humidification maintained at 9.89 millibar) compared to 14.5% at control rooms (at 6.33millibar); the differences in influenza detection were statistically significant in both air and fomites. Myatt et al. simulated the airborne survival of influenza virus with the impacts of home humidification with the CONTAM a multi-zone indoor air quality model, and described a 17.5% to 31.6% reduction of influenza virus survival in rooms with a humidifier operating (*73*). Noti et al. used a manikin to stimulate coughs containing influenza virus and assessed the viral infectivity under various levels of relative humidity in the examination room (*74*), and found that total virus during a 1-hour collection remained at about 70% infectivity at RH ≤ 23% but only about18% at RH ≥ 43% .

Ethical considerations
No major ethical considerations.

Knowledge gaps
The exact mechanism of how humidity affects the survival of the influenza virus is not clear (*72, 75*). Many studies have studied the effect under laboratory conditions, but very few have tested in natural settings.

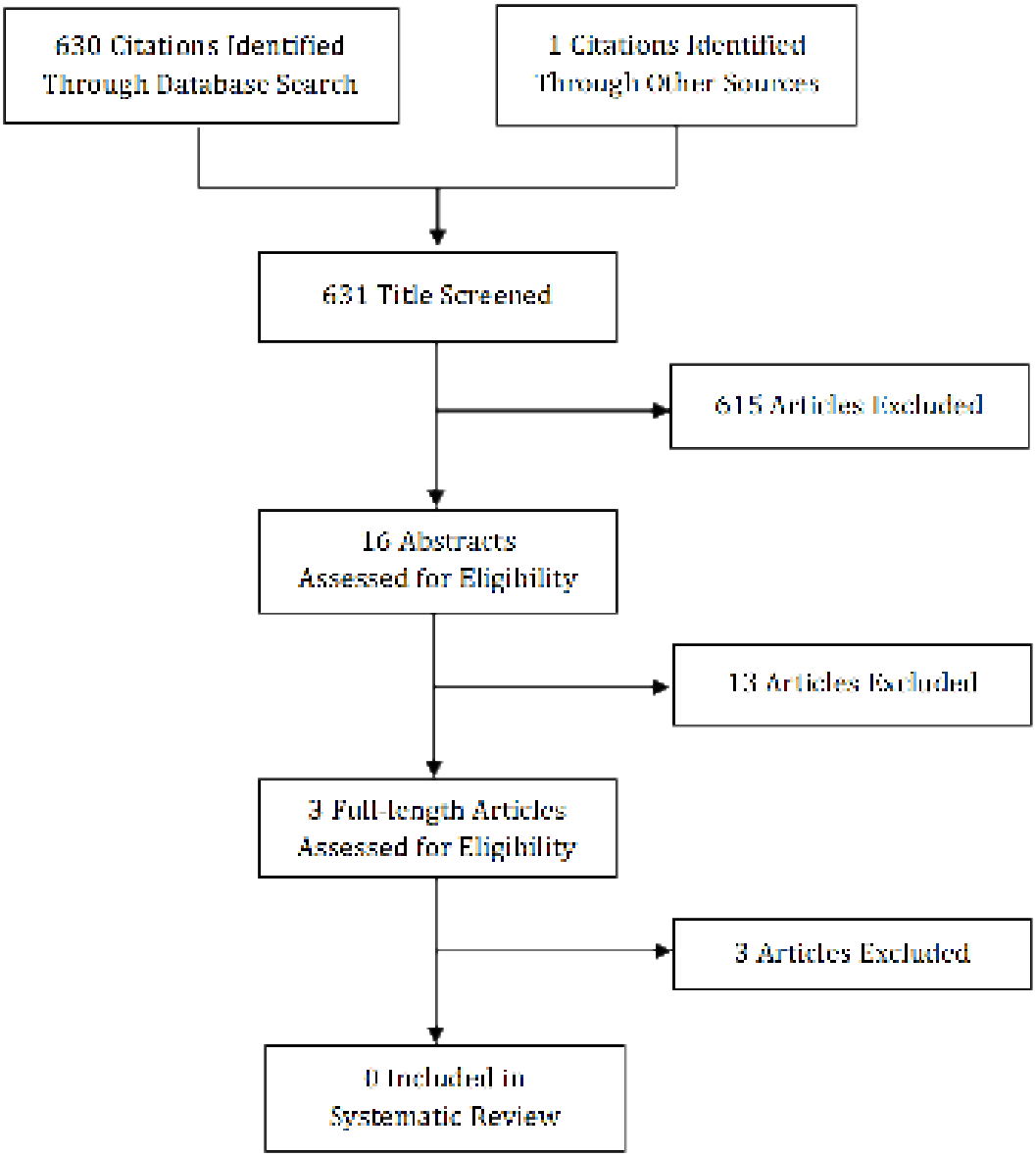

Fig. 14. The flow chart of the process and results of study selection

3. SOCIAL DISTANCING MEASURES

3.1. Contact tracing

Terminology

Contact tracing is the identification and follow-up of persons who may have come into contact with an infected person (76). Although contact tracing is often coupled with quarantine or provision of antiviral prophylaxis to exposed contacts, the term "contact tracing" does not involve these processes.

Methods

A literature search was conducted using PubMed, MEDLINE, EMBASE and CENTRAL (search date 12 November 2018). No language limit was applied for the literature search; however, literatures in languages other than English were excluded during full-text screening. The inclusion criteria were studies reporting the effectiveness of contact tracing on the control of influenza in non-health care settings. No limitation on study design was applied for study inclusion because preliminary works have identified no RCTs for this topic. Systematic reviews and meta-analyses, as well as studies involving clinical settings were excluded. Two reviewers independently (MF and SG) screened the titles, abstracts and full texts to identify articles for inclusion. Quality assessment of evidence was not conducted because no epidemiological study was included in this systematic review.

Results

The initial database search yielded 1188 articles, of which 75 were selected for full-text screening based on their title and abstract contents. Of these, 71 articles were excluded; the main reasons for exclusion of these articles include absence of discussion on effectiveness of contact tracing and irrelevance. The study selection process is detailed in Fig.15.

All four studies were simulation studies (*77-80*). None studied contact tracing as a single intervention; instead, this measure was studied in combination with other interventions, such as quarantine, isolation and provision of antiviral drugs (Table 14). Such combinations of interventions have been suggested to reduce transmission and delay the epidemic peak (*77, 79, 80*).

Reduction of impact

Wu et al. suggested in their simulation model of an influenza pandemic with a reproductive number (R_0) of 1.8 that the combination of contact tracing, quarantine, isolation and antivirals reduced the infection attack rate to 34% from the baseline of 74% (*77*). However, the addition of contact tracing on top of quarantine and isolation measures was suggested to provide only modest benefit, while at the same time greatly increasing the proportion of quarantined individuals. On the other hand, Fraser et al. found that it would be difficult to control influenza even with 90% contact tracing and quarantine, due to the presumed high level of presymptomatic or asymptomatic transmission in influenza (*79*).

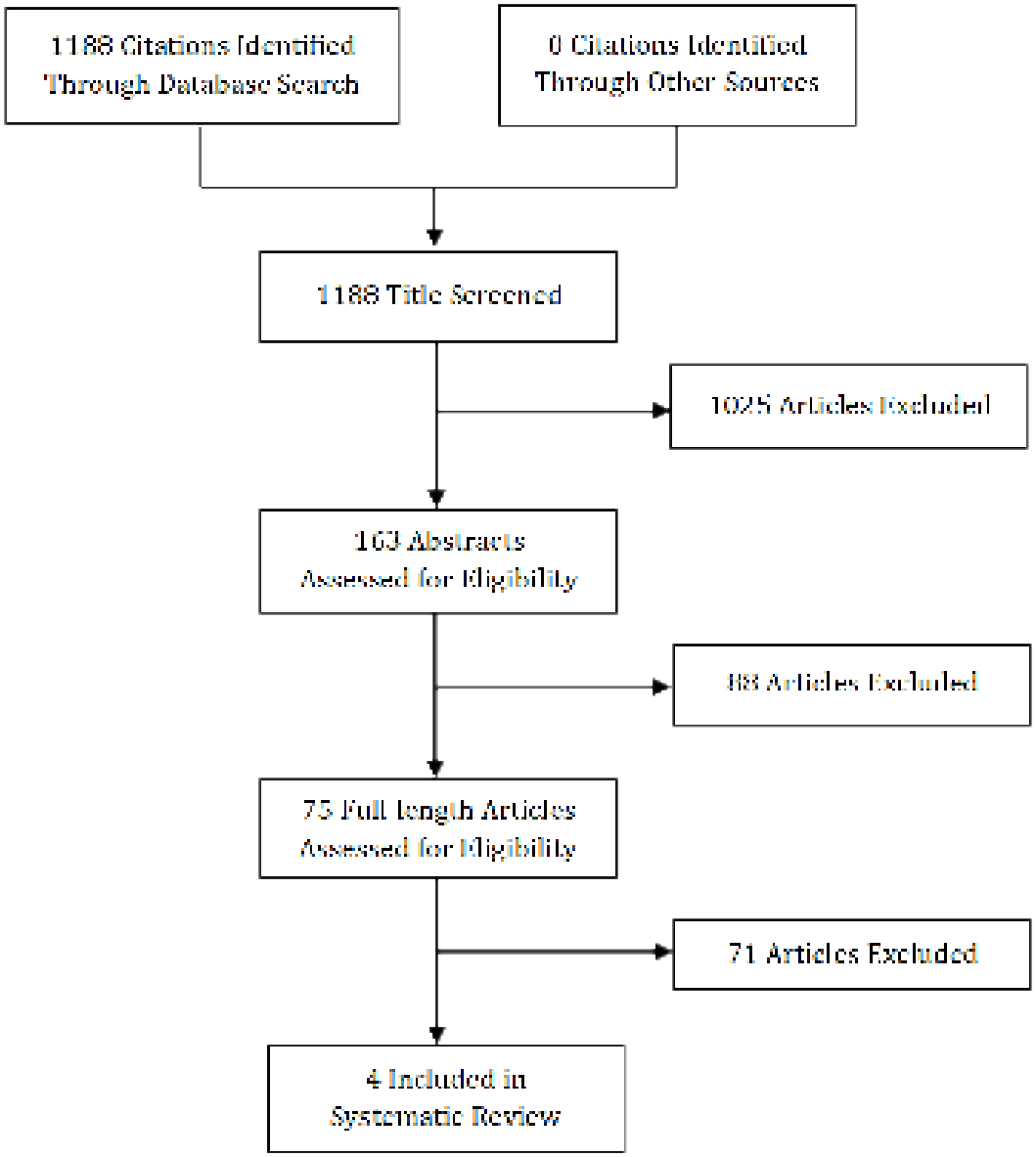

Fig. 15. The flow chart of contact tracing

Delay of epidemic peak

A combination of isolation, treatment of cases, contact tracing, quarantine and post-exposure prophylaxis for both community and household contacts, in addition to some household-focused measures, have been suggested to bring about delay in epidemic peak for up to 6 weeks, assuming a case detection rate of 10–30% (*80*). The study was set in the population structure of Germany in an epidemic with an R0 of 1.58. The authors assumed that the above combination of measures would be 75% effective in reducing secondary cases, while household-focused measures would be 50% effective.

Table 14. Summary of included studies

AUTHOR, YEAR PUBLISHED	TRANSMISSIBILITY OF THE INFLUENZA STRAIN (R_0)	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS
Wu JT, 2006 (*77*)	1.80	(1) Model based on distribution of household sizes and average numbers of children in household of different sizes in Hong Kong SAR (2) Constant introduction of 1.5 infected individuals per day per 100 000 people for 365 days (3) 70% of transmission occur outside home (in schools and workplaces)	Combination of contact tracing with other interventions such as quarantine, isolation and antivirals. When contact tracing was in effect, each compliant adult member of a household named on average five members of their peer group. Contacts were traced with a mean delay of 1 day. Contacts were asked to take precautionary measures. Interventions were active before arrival of infected individuals in the city	Combination of quarantine, isolation and antivirals reduce the baseline infection attack rate of 74% to 40%. Addition of contact tracing further reduce infection attack rate to 34%, but increase proportion of population in quarantine considerably
Peak CM, 2017 (*78*)	1.54	Initial infected population of 1000 individuals in early epidemic phase, assuming no substantial depletion of susceptible within first few generations of transmission	Symptomatic contacts were isolated immediately, contacts who were asymptomatic when identified were placed under either quarantine or symptom monitoring (at high performance, delay in contact tracing was 0.5 ± 0.5 days, 90% of contacts were traced, 50% were truly infected among traced contacts)	Combination of contact tracing with quarantine is more effective in reducing reproduction number than combination of contact tracing with symptom monitoring
Fraser C, 2004 (*79*)	Upper bound of R0 was 21	(1) Disease outbreak in its early stages in a community of homogenous mixing (2) Proportion of presymptomatic transmission is 30–50%	Isolation of symptomatic individuals, contact tracing and quarantine of a proportion of contacts that are infected prior to isolation of symptomatic individual. Isolation and quarantine were implemented without delay. Efficacy of isolation of symptomatic individuals considered were 75%, 90%, and 100%; contact tracing and isolation of infected contacts were 100% effective	Control of influenza is very difficult even at 90% quarantine and contact tracing, due to the high level of presymptomatic transmission
an der Heiden M, 2009 (*80*)	1.34, 1.58, 2.04	(1) Model based on the age distribution and size of the population of Germany: 71 000 000 adult population and 11 000 000 children (< 15 years old), entire population is fully susceptible at onset of the epidemic (2) Children are 2.06 times as susceptible as adults, 86% of infected individuals become symptomatic	(1) Intensive case-based measures (CCM1; consisting of isolation and therapy of cases, contact tracing, quarantine and post-exposure prophylaxis of selected contacts in- and outside of the household) (2) Less-intensive measures (CCM2; isolation and therapy of cases, quarantine and post-exposure prophylaxis of household contacts); CCM1 and CCM2 were set to be 75% and 50% effective in reducing secondary cases	(1) When the first 500 cases are managed with CCM1 followed by 10 000 cases managed by CCM2, the peak of epidemic is delayed for up to 6 weeks (R0 1.58, 5 imported cases per day, case detection rate 10–30%). If only CCM1 was adopted without CCM2, delay was estimated to be 6–20 days (case detection rate 10–30%). (2) Effectiveness of these combination of interventions is affected by the R0 of the influenza strain and case detection rate, i.e. higher R0 causes interventions to be ineffective at an earlier time point

CCM: combination of case-based methods; R0: basic reproductive number; SAR: Special Administrative Region.

Reduction in transmissibility

Peak et al. compared the combination of contact tracing with quarantine or symptom monitoring in the early phase of an epidemic with an R0 of 1.54 (*78*). The study suggested that contact tracing combined with quarantine was more effective than a combination with symptom monitoring in reducing transmission.

Ethical considerations

There are no major ethical issues. Identification of contacts of infected individuals does bring about privacy concerns; however, this may be justified because contact tracing does allow identification of persons at-risk and timely provision of treatment and care (81, 82). There may be more ethical concerns when contact tracing is coupled with measures such as household quarantine, discussed further in Section 3.3. As discussed in the results section above, contact tracing is able to increase substantially the proportion of people quarantined, but may not offer much additional benefit to existing interventions (*77*). A considerable amount of resources is also needed for contact tracing is these circumstances. Wu et al. suggested addition of contact tracing to existing interventions is only justified when the R0 can be reduced below 1 (*77*).

Methods

A literature search was conducted using PubMed, MEDLINE, EMBASE and CENTRAL (search on 5 August 2018). No language limit was applied for the literature search; however, literatures in languages other than English were excluded during full-text screening. The inclusion criterion is studies reporting the effectiveness of isolation on control of influenza in non-health care settings. No limitation on study design was applied for study inclusion as preliminary works have identified no RCT for this topic. Systematic review and meta-analyses, as well as studies involving clinical settings were excluded. Two reviewers independently (MF and SG) screened the titles, abstracts and full texts to identify articles for inclusion. Quality assessment of evidence was conducted for epidemiological studies for effectiveness of isolation on mitigation of influenza.

Results

The initial database search yielded 588 articles, of which 70 were selected for full-text screening based on their title and abstract contents. Of these, 56 articles were excluded; the main reasons for exclusion of relevant articles included absence of discussion on effectiveness of isolation and focus on health care setting. One other study for inclusion was identified through snowball searches. The study selection process is detailed in Fig.16.

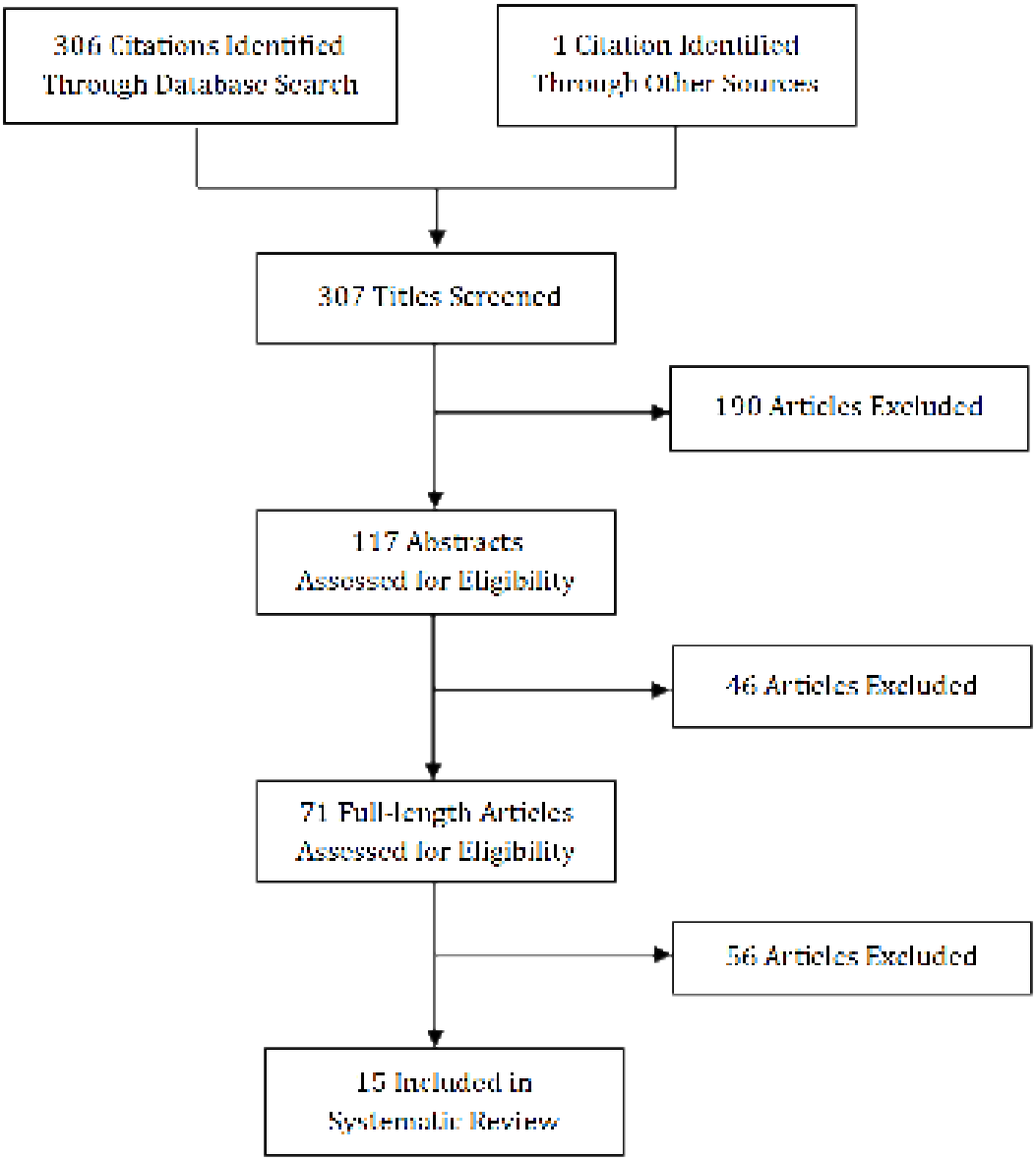

Fig. 16. The flow chart of isolation

Of the 15 included studies, four were epidemiological studies, of which one was an analysis of historical data from the 1918–1919 pandemic in 43 cities in the USA and three were outbreak investigations that occurred in a home for the elderly in France, a training camp in China and a Peruvian navy ship, respectively (Table 15) (*83-86*). The remaining 11 were simulation studies (Table 16) (*77, 79, 87-94*). Case isolation was implemented in the outbreaks as a combination with various other interventions, such as antiviral prophylaxis and use of face mask. Case isolation was also studied as a single intervention or combined with other interventions in the 11 simulation studies. It is of note that the simulation studies were conducted based on a wide range of assumptions; for example, asymptomatic fraction and contact rate reduction brought forth by isolation, hence providing wide-ranging insights on effectiveness of isolation in different scenarios. These included studies focused mostly on reduction of attack rate, epidemic size, transmissibility and delay in epidemic peak as outcomes of interest. All but one study suggested a favourable impact of isolation, or combination of isolation with other interventions in epidemics with R0 1.5–2.0.

Reduction of impact

Eight studies suggested a decrease in attack rate brought about by implementation of case isolation (*77, 83, 86-91*). An individual-based simulation model for the United Kingdom and the USA suggested rapid case isolation could reduce the cumulative clinical attack rate from 34% to 27% for a pandemic with R_0 2.0, assuming uniform reductions in contact rates in schools, workplaces and households (*87*). Kelso and colleagues reported similar findings, in which case isolation alone was able to prevent an epidemic (<10% infected) in a community of 30 000 persons with R_0 1.5, when 90% of cases are isolated and such a measure is implemented within 3 weeks from the introduction of an initial case (*90*). While isolation alone has been suggested to be more impactful than other interventions, combination with other interventions further improved the effectiveness (*77, 89-91*). In addition, the increase in isolation rate is quasi-linearly correlated with the decrease in attack rate of influenza (*88*).

A reduction in the cumulative incidence of infections due to an isolation policy was also recorded during an influenza A(H1N1)pdm09 outbreak on a navy ship (86). A combination of isolating ILI cases, and use of masks and hand sanitizers was implemented. The clinical attack rate of the outbreak was 23.9%, a significant reduction from the 97% projected in the absence of any intervention. This also corresponded to a reduction in the effective reproduction number (R) from 1.55 to 0.7 with the intervention. Chu et al. reported similar findings in an outbreak in a physical training camp, in which the final attack rate recorded was about one quarter of the projected attack rate of 81% in absence of previous exposure, immunity and any interventions (*83*). In the 1918–1919 pandemic, excess death rates due to pneumonia and influenza decreased in New York City and Denver after isolation and quarantine were implemented (*85*).

On the contrary, Fraser et al. discussed the difficulty in controlling influenza even with high level of case isolation combined with contact tracing and quarantine, due to high proportion of asymptomatic transmission of influenza (*79*). The probability of isolation without increased public health effort by individuals in the community have also been suggested to be high, at 50% and 90% for adult and children respectively (*90*).

Delay of epidemic peak

The study by Flauhault et al. suggested that case isolation would have the strongest impact on global spread of a pandemic involving 52 cities, as compared to air-travel restrictions and antiviral treatment, such that isolation of 40% of cases would delay the epidemic by 83 days as compared to absence of any intervention (*88*). A combination of isolation of 10% of symptomatic cases with 60% reduction in air traffic, on the other hand, would delay the start of epidemics in each city by an average of 19 days, with considerable case reduction (88). The study by Wang et al. showed a similar effect, albeit focusing on arrival time of influenza pandemic, in which isolation of a moderate proportion of cases delayed the arrival of the pandemic in a subpopulation for about a month, in the circumstance of high compliance and early implementation (*92*). Delay in response will reduce significantly the effectiveness. Combined intervention with quarantine, school closure (SC), community-contact reduction, and personal protective measures further augmented the effect (*91*).

Table 15. Summary of epidemiological studies

AUTHOR, YEAR PUBLISHED	INFLUENZA STRAIN OR TRANSMISSIBILITY (R_0)	TYPE OF STUDY	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS	GRADE EVIDENCE
Chu C, 2012 (*83*)	A(H1N1)pdm09	Outbreak investigation	Outbreak in a physical training camp in China with 3256 persons	Combination of isolation with other interventions including oseltamivir treatment and prophylaxis, cancellation of training and group activities, face mask usage, ventilation and disinfection (implemented within a few days of surge in ILI)	(1) 72.7% clinical cases were reported before intervention, 27.3% after intervention. (2) The clinical attack rate recorded for the outbreak was 18.2%, while the projected attack rate in absence of previous exposure, immunity and any interventions was 80.9%	Very low
Gaillat J, 2008 (*84*)	Seasonal	Outbreak investigation	Outbreak in elderly home with 81 residents in summer (recorded attack rate of 39.5%)	Sick residents were immediately isolated and used face masks, oseltamivir treatment and post-exposure prophylaxis were given to residents and staffs	No new case was reported among residents and staffs within 2 days of implementation of intervention	Very low
Markel H, 2007 (*85*)	1918 pandemic H1N1	Analysis of historical data	43 large cities in the USA; utilized historical mortality data from the US Census Bureau and other historical archival documents	Combination of SC, public gathering bans, and isolation and quarantine (enforced and mandated respectively)	(1) All 43 cities implemented at least one intervention, and 15 cities implemented all three interventions. Cities that started implementation earlier had lower peak mortality and total mortality. (2) Excess death rate in New York decreased to baseline when isolation and quarantine were implemented, similarly in Denver when SC, isolation and quarantine were implemented	Very low
Vera DM, 2014 (*86*)	A(H1N1)pdm09	Outbreak investigation, stochastic model	Outbreak on a navy ship with 355 crews	Suspected ILI cases were placed in isolation, active case finding, face mask usage and hand hygiene, and antiviral provision	(1) Significant reduction in reproduction number during implementation of interventions (54.4%, from 1.55 to 0.7). The projected reproduction number without isolation was 4.5. (2) Clinical attack rate recorded was 23.9%, while the projected rate was 97%.	Very low

GRADE: Grading of Recommendations Assessment, Development and Evaluation; ILI: influenza-like illness; R0: basic reproductive number; SC: school closure; USA: United States of America.

Table 16. Summary of simulation studies

AUTHOR, YEAR PUBLISHED	TRANSMISSIBILITY OF THE INFLUENZA STRAIN (R_0)	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS
Flahault A, 2006 (*88*)	Constant (3.1) in tropical zone, 0.3–3.24 elsewhere with seasonal differences	(1) Spread of influenza pandemic to 52 cities globally from Hong Kong SAR via air transport (2) 25% of the population has pre-existing immunity, 60% of cases are symptomatic	(1) Combination of isolation (exclusion of 10% of symptomatic individuals from simulation) and 60% air traffic reduction (implemented since day 1) (2) Combination of (1) with antiviral treatment and vaccination	(1) Isolation reduced case number by 9% (2) Combination of isolation and air traffic reduction delayed time to reach epidemic status (1/100 000) in each city by an average of 19 days (3) Increasing isolation proportion to 40% delayed epidemic by an average of 83 days; combination of isolation, air traffic reduction, antiviral, vaccination reduced case number by 65%
Fraser C, 2004 (*79*)	Upper bound of R_0 was 21	(1) Disease outbreak in its early stages in a community of homogenous mixing (2) Proportion of presymptomatic transmission is 30–50%	Isolation of symptomatic individuals, contact tracing and quarantine of a proportion of contacts that are infected prior to isolation of symptomatic individual. Isolation and quarantine were implemented without delay. Efficacy of isolation of symptomatic individuals considered were 75%, 90%, and 100%; contact tracing and isolation of infected contacts were 100% effective.	Control of influenza is very difficult even at 90% quarantine and contact tracing, due to the high level of presymptomatic transmission.
Halloran ME, 2008 (89)	1.9–2.1, 2.4 and 3.0	(1) Model based on population of Chicago (8.6 million people) (2) 67% of influenza infections are symptomatic, case ascertainment levels are 60–80%	Combination of home isolation of ascertained cases (compliance 60% or 90%; isolated in but not from household members) with quarantine and other social distancing measures, implemented at intervention threshold of 1, 0.1, and 0.01%	At R_0 of 1.9–2.1, 60% ascertainment and 90% compliance, intervention threshold of 0.1%, attack rate was 0.17–1.2%, as compared to baseline scenario of 42.4–46.8%
Kelso JK, 2009 (*90*)	1.5, 2.5, and 3.5	(1) Population of 30 000, grouped into hubs of schools, workplaces and other facilities. Other contacts were biased towards meetings between neighbouring individuals (2) Asymptomatic fraction matched seasonal influenza	(1) Isolation (assumed isolated individuals only made household contacts, 90% and 100% chance respectively for adults and children to be compliant) (2) Combination of isolation with SC, workplace non-attendance and community-contact reduction	(1) At R_0 of 1.5, case isolation implemented within 3 weeks was the only single intervention capable of preventing an epidemic (≥10% attack rate), daily attack rate reduced from 90/10,000 to < 35 if introduced within a month (2) Combination of all four measures reduced attack rate from baseline of 33% to 9%, influenza control is more difficult at higher R_0

AUTHOR, YEAR PUBLISHED	TRANSMISSIBILITY OF THE INFLUENZA STRAIN (R_0)	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS
Saunders-Hastings P, 2017 (*91*)	1.5–2.5	(1) Model based on population of Ottawa–Gatineau census metropolitan area in 2011	Combination of isolation with other interventions including vaccination, antiviral treatment, prophylaxis, SC, community-contact reduction, personal protective measures and quarantine; best guess for adherence for voluntary isolation is 30%	(1) Combination of isolation and quarantine resulted in reduction of attack rate to 33.9%, from the baseline of 53.4%, lowest among all interventions studied. (2) Combination of isolation, quarantine, SC, community-contact reduction and personal protective measures reduced attack rate to 15.2% and delayed pandemic peak to more than 100 days
Zhang Q, 2015 (*94*)	2.5	(1) A community of households with distribution of household sizes based on Australian census data in 2001 (2) Chances of infection from community contacts is negligible as compared to infection from household member	Self-isolation or combination with antiviral prophylaxis (self-isolation assumed to have no impact on household contacts)	Self-isolation is able to overcome negative effect of delay in antiviral drug provision of 1 and 2 days by reducing household reproduction number, albeit compliance for self-isolation have to be significantly higher for 2-days delay
Zhang Q, 2014 (*93*)	1.5	(1) Stable population with homogenous mixing (2) Asymptomatic fraction is 0.5, and symptomatic cases are twice as infectious	Isolation or combination with antiviral prophylaxis	(1) Case isolation reduced reproduction number to below one (2) Combination of isolation and antiviral prophylaxis reduced substantially the cumulative number of infected individuals
Ferguson NM, 2006 (*87*)	1.4–2.0	(1) Model based on population density data and data on travel patterns of the USA and United Kingdom (2) 30% of transmission occurred in household, the rest in general community, workplaces and schools; asymptomatic fraction was 0.5	Rapid case isolation (assumed uniform reduction of contact including household contacts)	Rapid case isolation reduced cumulative attack rates from 34% to 27% for R0 2.0 if 90% of cases were isolated
Wu JT, 2006 (*77*)	1.80	(1) Model based on distribution of household sizes and average numbers of children in household of different sizes in Hong Kong SAR (2) Constant introduction of 1.5 infected individuals per day per 100 000 people for 365 days (3) 70% of transmission occur outside home (e.g. in schools and workplaces)	Combination of isolation and voluntary quarantine. Interventions were active before arrival of infected individuals in the city.	Combination of isolation and voluntary quarantine reduced the baseline attack rate of 74% to 43%.

AUTHOR, YEAR PUBLISHED	TRANSMISSIBILITY OF THE INFLUENZA STRAIN (R_0)	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS
Wang L, 2012 (*92*)	1.75	International spread of influenza to cities at early stage of a pandemic outbreak	Isolation (implemented by removing some infectious individuals from the simulation model)	Isolation of a moderate proportion of cases delayed the arrival of the pandemic for about a month, in the circumstance where cases were fully compliant and intervention was started at the first instance of the pandemic
Yasuda H, 2009 (*95*)	A(H1N1)pdm09	Community of 8800 individuals, with family structures based on Japanese census data	Home isolation of one in three adults and 70–90% of school-aged children	Total number of infections reduced by 33% when one in three adults and all children were isolated at home compared to baseline situation

R_0: basic reproductive number; SC: school closure; United Kingdom: United Kingdom of Great Britain and Northern Ireland; USA: United States of America.

Reduction in transmissibility

Zhang et al. showed in their simulation studies that isolation of cases can reduce the household reproduction number to below one, and compensate for a delay in antiviral drug distribution by 1 to 2 days. Compliance for self-isolation has to be significantly higher to offset longer delays (*93, 94*). An outbreak in a home for the elderly in France reported an abrupt cessation of outbreak after case isolation, antiviral treatment and prophylaxis were implemented (*84*). Reduction in eproduction number was also recorded in the navy ship outbreak previously described, by 54% from 1.55 to 0.7 with a combination of interventions (*86*). The projected reproduction number without implementation of isolation was 4.5.

Ethical considerations

Home isolation is commonly done voluntarily by ill individuals who do not feel well enough to work or engage in other daily activities (*88, 90*). Some ethical concerns may arise when isolation interventions are mandated, of which the main concern is freedom of movement (*96*). Studies on acceptability of isolation as an intervention to control influenza have also suggested the potential of social stigma as a concern for some individuals (97). Home isolation may also bring about increased risks of infection among household members, in the circumstances in which the contact rate between the infected individual with household members increase due to home isolation. Such risks can be reduced by adopting good precautionary measures such as wearing a face mask or employing hand hygiene. Such concern is more significant when concurrent quarantine of household members is mandated.

Knowledge gaps

Most currently available studies on effectiveness of isolation are simulation studies, which have a low strength of evidence. Available epidemiological studies studied isolation together with other interventions, or did not use laboratory confirmation as the outcome of interest. Although it is difficult to study isolation in an RCT, robust findings from such studies would be very valuable. In addition, in some of the relevant simulation studies, assumptions have been used to predict the effect of isolation on social contact rate, which in turn affect the transmission dynamics and control of influenza. Limited information exists at present for this aspect, as well as other commonly used assumptions including asymptomatic fraction, and dynamicity due to the nature of compliance behaviour, resource planning and distribution capacity (*77*).

3.2. Quarantine of exposed individuals

Terminology

Terms relevant to quarantine are defined in Table 17.

Table 17. Definition of terms relevant to quarantine

TERM	DEFINITION
Quarantine	Imposed separation or restriction of movement of persons who are exposed, who may or may not be infected but are not ill, and may become infectious to others (*98*).
Household quarantine	Confinement (commonly at home) of non-ill household contacts of a person with proven or suspected influenza (*2, 98*).
Home quarantine	Home confinement of non-ill contacts of a person with proven or suspected influenza.
Self-quarantine	Voluntary confinement of non-ill contacts of a person with proven or suspected influenza.

TERM	DEFINITION
Work quarantine	1) Measures taken by workers who have been exposed and who work in a setting where the disease is especially liable to transmit (or where there are people at higher risk from infection), e.g. people working in elderly homes and nurses in high risk units (*98*). 2) Measures taken by health care workers who chose to stay away from their families when off-duty so as not to carry the infection home (*98*).
Maritime quarantine	Monitoring of all passengers and crew for a defined period before disembarking from a ship is permitted in a jurisdiction (*99*).
Onboard quarantine	Monitoring of all passengers and crew for a defined period before disembarking from a flight is permitted (100). Also known as 'airport quarantine' (*100*).

Methods

Literature search was conducted using PubMed, MEDLINE, EMBASE and CENTRAL (search date 24 July 2018). No language limit was applied for the literature search; however, literatures in languages other than English were excluded during full-text screening. Studies reporting the effectiveness of quarantine on the control of influenza in non-health care settings were included. No limitation on study design was applied for study inclusion as preliminary works identified no RCT for this topic. Systematic review and meta-analyses, as well as studies involving clinical settings, were excluded. Two reviewers (MF and SG) independently screened the titles, abstracts and full texts to identify articles for inclusion. Quality assessment of evidence was conducted for epidemiological studies for effectiveness of quarantine on mitigation of influenza.

Results

The initial database search yielded 1873 articles, of which 120 were selected for full-text screening based on their title and abstract contents. Of these, 104 articles were excluded; the main reasons for exclusion of relevant articles include absence of discussion on effectiveness of quarantine and focus on health care setting. The study selection process is detailed in Fig.17.

The included studies were comprised of 10 simulation studies (Table 19) (*77, 80, 87, 89, 91, 101-105*). The epidemiological studies included one modelling study based on pandemic influenza A(H1N1)pdm09 transmission in Beijing (106), two analyses of historical data (1918–19 influenza pandemic in the USA and South Pacific, respectively) (*85, 99*), two observational studies and one a quasi-cluster-RCT in Japan (Table 18) (*100, 107, 108*). Quarantine measures studied include home quarantine, household quarantine, border quarantine as well as maritime quarantine. Quarantine were studied as a single intervention or as combination with other interventions, commonly with isolation and antiviral prophylaxis. These included studies focused mostly on reduction of attack rate, transmissibility and delay in epidemic peak as outcomes of interest.

Reduction of impact

Five studies suggested reduction in attack rate with implementation of household quarantine measures (77, 87, 89, 91, 107). Miyaki and colleagues conducted a quasi-cluster RCT in Japan in 2009–2010, which involved two clusters of company workers; the intervention was voluntary waiting at home on full pay if a family member was experiencing ILI. The intervention reduced risk and number of infections for members of the cluster and in the workplace involved (107).

Ferguson et al. reported in their simulation study that household quarantine were effective in reducing attack rate at R0 1–4.2, especially at low values (87). Combination of quarantine with other interventions such as household isolation with prophylaxis, SC and workplace distancing were suggested to further reduce the cumulative incidence of infections (77, 87, 89).

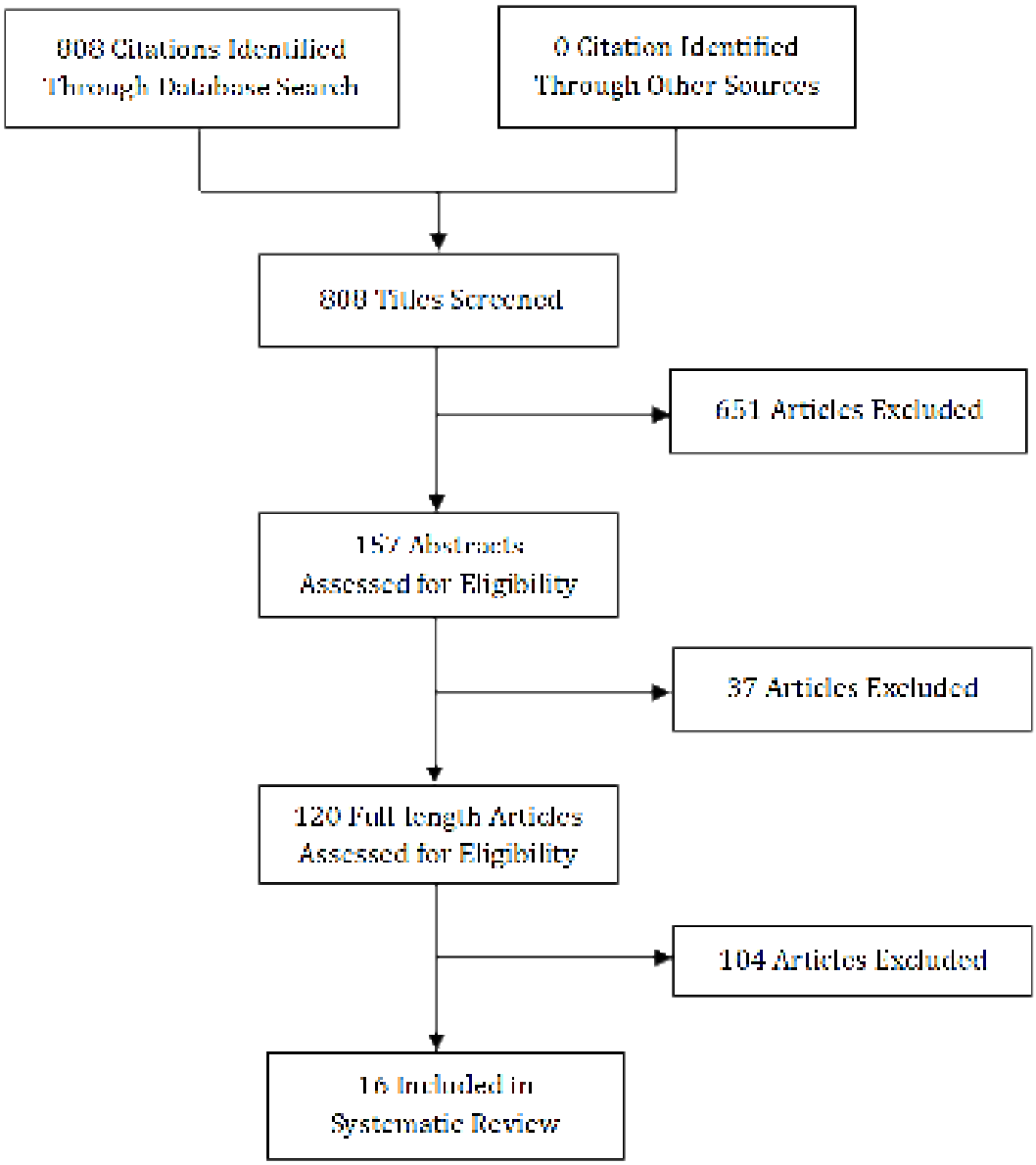

Fig. 17. The flow chart of quarantine

Household quarantine has also been suggested to be highly effective in reducing peak and total number of cases in a pandemic, provided that compliance is high (*105*). Longini et al. reported similar findings; that is, the effectiveness of household quarantine in reducing number of cases is conditioned by high compliance at 70% and relatively low R0, in addition to early implementation *(101)*. On the other hand, border quarantine has been suggested to cause minimal impact on reduction of number of cases (*104*).

Both analyses of historical data of the 1918–19 pandemic studied the effectiveness of interventions on mortality (*85, 99*). When a combination of isolation and quarantine was implemented, excess death rates due to pneumonia and influenza were shown to decrease in New York City and Denver (*85*). Maritime quarantine in the pacific islands have also delayed or prevented arrival of the epidemic, indirectly reducing mortality in the region (*99*).

Transmissibility

Both household quarantine and border quarantine have been suggested to reduce transmissibility, albeit with moderate effectiveness (*100, 102, 103*). Fujita et al. reported in their assessment of onboard quarantine inspection in Japan during the 2009 H1N1 pandemic, minimal impact in detecting and preventing entry of cases; however, following up with passengers thereafter was found to be effective in preventing secondary infection in the community from travellers (*100*). Nishiura and colleagues also suggested that border quarantine of 9 days would prevent 99% of entry of infectious travellers into small island nations (*102*).

Increased risk to household contacts

While reducing risk and number of infections in the intervention cluster, the quasi-cluster RCT of Miyaki et al. also reported that more individuals fell ill in the intervention group when there was an ill family member (*107*). The likelihood of a household contact (concurrently quarantined with an isolated individual) becoming a secondary case has been estimated to increase with each day of quarantine (*108*).

Table 18. Summary of epidemiological studies

AUTHOR, YEAR PUBLISHED	INFLUENZA STRAIN OR TRANSMISSIBILITY (R_0)	TYPE OF STUDY	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS	GRADE EVIDENCE
Markel H, 2007 (*85*)	1918 pandemic H1N1	Analysis of historical data	43 large cities in the USA; utilized historical mortality data from the US Census Bureau and other historical archival documents	Combination of SC, public gathering bans, and isolation and quarantine (enforced and mandated respectively)	(1) All 43 cities implemented at least one intervention, and 15 cities implemented all 3 together. Cities that started implementation earlier have lower peak mortality and total mortality; (2) Excess death rate in New York decreased to baseline when isolation and quarantine were implemented, similarly in Denver when SC, isolation and quarantine were implemented	Very low
Fujita M, 2011 (*100*)	A(H1N1)pdm09	Observational	Japan (passengers at Narita International Airport for onboard quarantine and Japan at-large for the outbreak)	Onboard quarantine was conducted for 500 flights carrying 120 069 passengers in Narita International Airport over 25 days. Patients identified by positive rapid test, and persons seated around them were isolated. If patient was subsequently confirmed of their infection by PCR, patient was isolated while persons seated around them were quarantined	Onboard quarantine detected few cases and was not effective in preventing virus entry into the country, however onboard quarantine improved traceability of travellers. Upon monitoring after travellers are in town, onward transmission/ secondary infection is prevented	Very low
Li X, 2013 (*106*)	A(H1N1)pdm09	Model based on epidemiologic dynamics of influenza A(H1N1)pdm09	Beijing (N = 20 million); utilized data of daily confirmed cases reported by Beijing Municipal Bureau of Health (May-July 2009)	Mandatory quarantine for all close contacts	Reduced number of cases at peak of epidemic to 5 times less than the projected scenario in which mandatory quarantine was not conducted, and delayed epidemic peak. Pandemic size remained the same and authors discussed on high economic and social costs of quarantine	Very Low

CI: confidence interval; GRADE: Grading of Recommendations Assessment, Development and Evaluation; ILI: influenza-like illness; PCR: polymerase chain reaction; R0: basic reproductive number; RCT: randomized controlled trial; SC: school closure; USA: United States of America.

Table 18. Summary of epidemiological studies

AUTHOR, YEAR PUBLISHED	INFLUENZA STRAIN OR TRANSMISSIBILITY (R_0)	TYPE OF STUDY	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS	GRADE EVIDENCE
McLeod MA, 2008 (*99*)	1918 pandemic H1N1	Analysis of historical data	South Pacific islands (including Australia); utilized archival data from national archives of relevant countries, government departments and international organizations	Maritime quarantine (monitoring all passengers and crew for on average 5–7 days before allowing disembarkation)	Strict maritime quarantine have delayed or prevented arrival of the pandemic in said jurisdictions, and associated with reduced mortality rate. Partial quarantine (routine release, without quarantine of asymptomatic passengers) in Fiji and Tahiti was unsuccessful, as in other jurisdictions that did not adopt any border control interventions	Very low
Miyaki K, 2011 (*107*)	A(H1N1)pdm09	Quasi-cluster-RCT	15 134 general employees (aged 19–72 years) of two sibling companies in Japan	Employees in intervention group were asked to stay home voluntarily if any co-habiting family members showed signs of ILI, until 5 days had passed since the resolution of ILI symptoms or 2 days after alleviation of fever, while on full pay. Employees in the control group reported to work as usual even if a household member developed ILI	Infection in workplace is significantly reduced among intervention group, however participants in this group are at higher risks of getting infected when there is an infected household member	Low
van Gemert C, 2011 (*108*)	A(H1N1)pdm09	Retrospective cross-sectional	Confirmed cases reported to the Victorian Department of Health, Australia from May-June 2009 (n = 36 index case-patients, 131 household contacts)	Antiviral drug usage (treatment and prophylaxis) and household quarantine	Odds of a household contact who was concurrently quarantined with the index case-patient becoming a secondary case-patient increased for each additional day (adjusted odds ratio 1.25, 95% CI 1.06–1.47)	Very low

CI: confidence interval; GRADE: Grading of Recommendations Assessment, Development and Evaluation; ILI: influenza-like illness; PCR: polymerase chain reaction; R0: basic reproductive number; RCT: randomized controlled trial; SC: school closure; USA: United States of America.

Table 19. Summary of simulation studies

AUTHOR, YEAR PUBLISHED	TRANSMISSIBILITY OF THE INFLUENZA STRAIN (R_0)	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS
an der Heiden M, 2009 (*80*)	1.34, 1.58, 2.04	(1) Model based on the age distribution and size of the population of Germany: 71 000 000 adult population and 11 000 000 children (< 15 years old), entire population is fully susceptible at onset of the epidemic; (2) Children are 2.06 times as susceptible as adults, 86% of infected individuals become symptomatic	(1) Intensive case-based measures (CCM1; consisting of isolation and therapy of cases, contact tracing, quarantine and post-exposure prophylaxis of selected contacts in- and outside of the household); (2) Less-intensive measures (CCM2; isolation and therapy of cases, quarantine and post-exposure prophylaxis of household contacts); CCM1 and CCM2 were set to be 75% and 50% effective in reducing secondary cases	(1) When the first 500 cases are managed with CCM1 followed by 10 000 cases managed by CCM2, the peak of epidemic is delayed for up to 6 weeks (R0 1.58, 5 imported cases per day, case detection rate 10–30%). If only CCM1 was adopted without CCM2, delay was estimated to be 6–20 days (case detection rate 10–30%); (2) Effectiveness of these combination of interventions is affected by the R0 of the influenza strain and case detection rate (i.e. higher R0 causes interventions to be ineffective at an earlier time point).
Saunders-Hastings P, 2017 (*91*)	1.5–2.5	(1) Model based on population of Ottawa–Gatineau census metropolitan area in 2011	Combination of quarantine with other interventions including vaccination, antiviral treatment, prophylaxis, SC, community-contact reduction, personal protective measures and isolation; best guess for adherence for quarantine is 15%	(1) Combination of quarantine and isolation resulted in reduction of attack rate to 33.9%, from the baseline of 53.4%, lowest among all interventions studied. (2) Combination of quarantine, isolation SC, community-contact reduction and personal protective measures reduced attack rate to 15.2% and delayed pandemic peak to more than 100 days
Ferguson NM, 2006(*87*)	1.4–2.0	(1) Model based on population density data and data on travel patterns of the USA and United Kingdom; (2) 30% of transmission occurred in household, the rest in general community, workplaces and schools; asymptomatic fraction was 0.5	Voluntary household quarantine for 14 days (assumed 50% compliance, external contact rates reduced by 75% and intra-household contact rate increased by 100%)	Voluntary household quarantine was effective in reducing attack rates in the community and delaying epidemic peak, in the circumstance where compliance is high. A combination of household quarantine and antiviral prophylaxis provision will further strengthen the effect, at the same time alleviate the ethical dilemma of household quarantine

AUTHOR, YEAR PUBLISHED	TRANSMISSIBILITY OF THE INFLUENZA STRAIN (R_0)	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS
Wu JT, 2006 (*77*)	1.80	(1) Model based on distribution of household sizes and average numbers of children in household of different sizes in Hong Kong SAR; (2) Constant introduction of 1.5 infected individuals per day per 100 000 people for 365 days; (3) 70% of transmission occur outside home (in schools and workplaces)	Combination isolation and voluntary quarantine (household quarantine of on average 7.5–8.2 days). Interventions were active before arrival of infected individuals in the city	Combination of isolation and voluntary quarantine reduced the baseline infection attack rate of 74% to 43%
Halloran ME, 2008 (89)	1.9–2.1, 2.4 and 3.0	(1) Model based on population of Chicago (8.6 million people); (2) 67% of influenza infections are symptomatic, case ascertainment levels are 60–80%	Combination of household quarantine (for 10 days with compliance of 30%, 60% or 90%) with isolation, and other social distancing measures, implemented at intervention threshold of 1, 0.1, and 0.01%	At R_0 1.9–2.1, 60% ascertainment and 90% compliance, intervention threshold of 0.1%, attack rate was 0.17–1.2%, as compared to baseline scenario of 42.4–44.7%
Sato H, 2010 (104)	2.3	(1) Population of 100 000 individuals (2) Transmission caused by cases undetected by onboard quarantine	Onboard quarantine combined with SC and home quarantine (with compliance of 10%, 30% and 50%; quarantined individuals were assumed to have no contact with infectious individuals for 3, 7 or 14 days)	The interventions were effective in reducing maximum number of daily asymptomatic cases and delaying the epidemic peak. Such effectiveness depends heavily on compliance; low compliance result in minimal impact. Home quarantine for 14 days with compliance of 50%, starting on day 6 was the most effective, which reduced number of cases by 44% and delayed the epidemic peak by 17 days
Longini IM Jr, 2005 (101)	1.4	Population of 500 000 individuals, with age and household sizes based on the Thai 2000 census (rural Thailand)	Household quarantine (contact probabilities within households and household clusters were doubled for quarantined individuals)	Household quarantine alone was effective in reducing number of cases. Early implementation and high compliance are needed for successful intervention

AUTHOR, YEAR PUBLISHED	TRANSMISSIBILITY OF THE INFLUENZA STRAIN (R_0)	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS
Nishiura H, 2009 (*102*)	1.67	Disease-free small island nation, which permitted arrival of 20 aircraft with a total of 8000 incoming individuals before closing all airports	Border quarantine – all incoming individuals were placed into routine quarantine on arrival, and were monitored for onset of symptoms. All infected individuals who develop influenza symptoms were successfully detected. Quarantine security was assumed to be fully effective and that no secondary transmission would occur in the quarantine facility	Reduction of 99% of risks of introducing infectious individuals into small island nations with quarantine period of 9 days. Combination with rapid diagnostic testing can reduce the quarantine period to 6 days
Roberts MG, 2007 (*103*)	2.0	(1) Population of one million persons (2) Proportion of symptomatic infective 67%, asymptomatic individuals have 50% infectivity as compared to symptomatic individuals	(1) Home quarantine (70% compliance) for 6 days, hence 56% of all transmission from those infected within their household is prevented. (2) Home quarantine (50% compliance), hence 40% of transmission from household contacts is prevented (3) Combination of home quarantine with SC, and targeted antiviral prophylaxis	Home quarantine alone was successful in reducing the reproduction number, as well as proportion of population infected. At higher transmissibility, R0 3.0, only the combination of home quarantine with SC and targeted antiviral prophylaxis is effective in preventing an epidemic
Yang Y, 2011 (*105*)	1.79	(1) Population of 8382 persons, with population and social structure based on the city of Eemnes	(1) Household quarantine (stay at home at all times with compliance 25%, 50%, 75%, and 100%). (2) Combination of household quarantine with SC and refrain from social activities; Delay between interventions and out-break threshold was less than one day	At 50% compliance, household quarantine reduced 22.4% and 20.8% total number of cases and peak cases respectively, as well as delayed epidemic peak. A combination of all 3 interventions did not add much benefit in reducing the total number of cases, however reduced the peak cases by 56%, and delayed the epidemic peak

CCM: combination of case-based methods; R0: basic reproductive number; SAR: Special Administrative Region; SC: school closure; United Kingdom: United Kingdom of Great Britain and Northern Ireland; USA: United States of America.

Delay of epidemic peak

Five studies reported the effectiveness of household quarantine, border quarantine and maritime quarantine in delaying peak of epidemic (*80, 91, 99, 104, 106*). As previously described, analysis of historical data suggested maritime quarantine effectively delayed or prevented arrival of the 1918–1919 pandemic in the pacific islands. Similarly, a model based on the 2009 H1N1 pandemic in Beijing reported delay in epidemic peak as compared to a projected scenario without mandatory quarantine (*106*). Combination with other interventions may improve effectiveness of quarantine (80). Saunders-Hastings et al. reported in their simulation study that a combination of quarantine with seven other interventions including voluntary isolation, SC, and personal protective measures can delay peak of pandemic for more than 100 days (*91*). On the other hand, as for reduction of impact, Sato et al. suggested minimal impact of border quarantine in delaying epidemic peak, mainly due to the low detection rate of cases (*104*).

Ethical considerations

As with isolation, the main concern of quarantine is freedom of movement of individuals (*106*). However, such concern is more significant for quarantine, because currently available evidence on effectiveness of quarantine varies and it involves restriction of movement of some healthy or non-ill individuals. Mandatory quarantine considerably increases such ethical concern as compared to voluntary quarantine (*96*). In addition, household quarantine can increase the risks of household members becoming infected, and such risk increases with the duration of quarantine (*87, 107, 108*). A combined policy of household quarantine with household prophylaxis has been suggested to be able to alleviate such concerns (*87*). Maritime quarantine and border quarantine are subject to similar concerns. On the other hand, onboard quarantine involves a shorter duration of restriction of movement, but currently available evidence has suggested the intervention to have low cost–effectiveness and minimal impact on influenza control.

Knowledge gaps

Most of the currently available evidence on effectiveness of quarantine on influenza control was drawn from simulation studies, which have very low strength of evidence. Available epidemiological studies did not rely fully on laboratory-confirmed influenza as the outcome of interest. While acknowledging the difficulties of studying quarantine in an RCT, robust data from experimental studies would be valuable. In addition, as part of simulation studies, assumptions have been used in various aspects of model construction, of which many still require more robust evidence, such as the asymptomatic fraction among all infections, as well as the possibility of superspreaders and the nature of compliance behaviour (*77, 102*).

3.3. School closures

Terminology

Closure of schools include scenarios either when virus transmission is observed in the school, or an early planned closure of schools before influenza transmission initiates. Types of closure are shown in Table 20 (*109*).

Table 20. The definition of SC terms

TERM	DEFINITION
School closure	School is closed to all children and staff.
Class dismissal	School campus remains open with administrative staff, but most children stay home.
Reactive Closure/ Dismissal	School is closed after a substantial incidence of ILI is reported among children and/or staff in that school.
Proactive Closure/ Dismissal	School is closed before a substantial transmission among children and staff is reported.

ILI: influenza-like illness.

Methods

The latest systematic review to review the effects of SCs on influenza outbreaks was published in 2013 by Jackson et al. (*110*). We conducted an additional search to update the systematic in PubMed, Medline, EMBASE and CENTRAL from 1 January 2011 to 4 September 2018. Inclusion criteria included study designs of RCTs, epidemiological studies and modelling studies reporting the effectiveness of SC in non-health care settings. Studies that described one or more influenza outbreaks, as well as the combination of SC and other NPIs, were also included. Modelling studies were included only if they used influenza surveillance data to evaluate the effectiveness of SC. Modelling studies based on stimulated data and/or on avian influenza virus, studies without school-specific data and studies published other than full report were excluded. Articles published other than English were also excluded after full-text screening. Two reviewers (SG and MF) independently screened titles, abstracts and full texts to identify the eligible articles. The quality of evidence was evaluated based on GRADE to assess the overall effectiveness of SC in mitigating influenza pandemics or epidemics, with seven specific metrics: reducing the epidemic peak, reducing overall attack rate, reducing incidence, reducing duration of the epidemic, reducing transmission, delaying the epidemic peak and reducing school absenteeism.

Results

The most recent systematic review was published in 2013, Jackson et al. identified 79 epidemiological studies on SCs and summarized the evidence as demonstrating that this intervention could reduce the transmission of pandemic and seasonal influenza among schoolchildren, but owing to the heterogeneity in the available data, the optimum strategy (e.g. the length of closure, reactive or proactive closure) remained unclear (*110*). The flow chart of study selection is shown in Fig. 19.

In the additional search to update the systematic review that was published by Jackson et al. in 2013, 287 papers were identified from the four databases and 12 citations were found from other sources, resulting in total of 299 citations for screening. Of these, 101 full-length articles were assessed for eligibility and 22 additional articles were identified. In total, 101 articles were included in our systematic review. The flow chart of study selection is shown in Fig. 18. The quality of evidence was assessed to be very low according to the GRADE criteria.

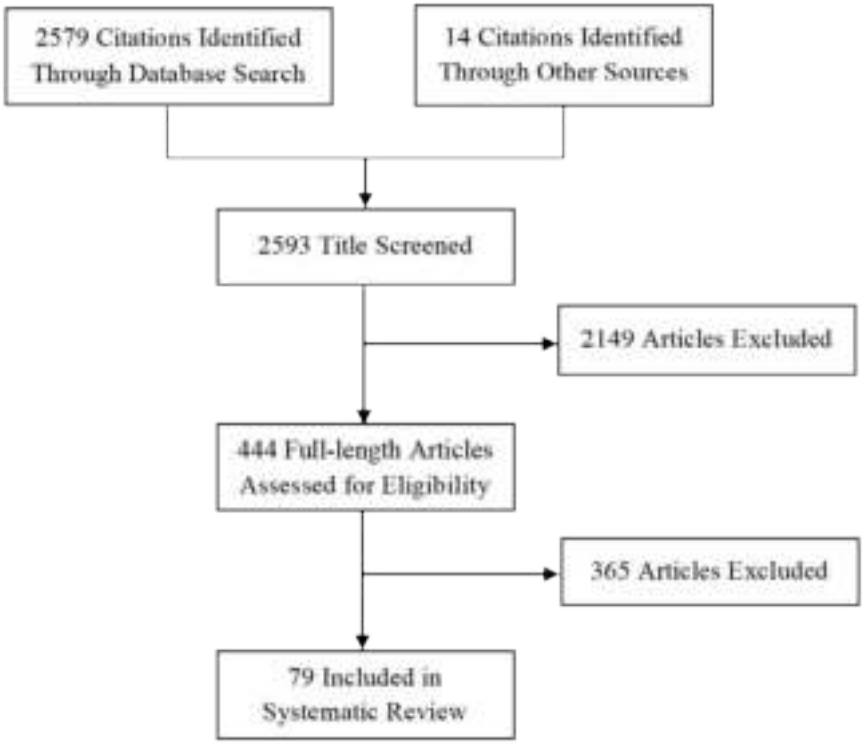

Fig. 18. The flow chart of systematic review by Jackson

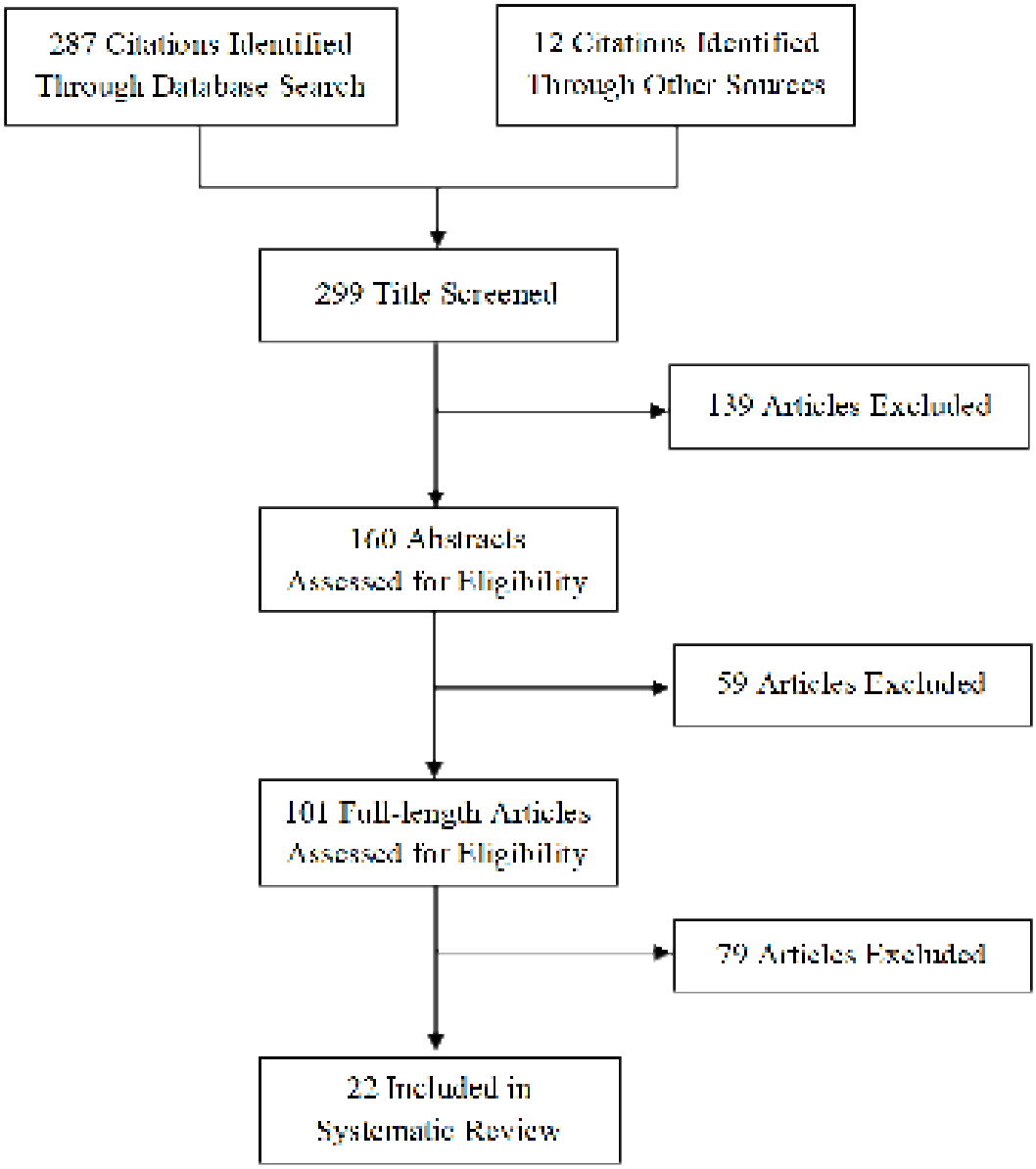

Fig. 19. The flow chart of updated studies in school closures

Among the included 101 articles, 16 articles presented data on reactive SCs (111-126), 13 articles examining proactive SCs (*85, 127-138*), 28 articles examined the impact of regular school holidays on transmission (*123, 125, 136, 139-163*), and 47 articles were related to outbreak reports or teachers' strike (*164-210*). The basic characteristic of the studies is shown in Table 21.

Table 21. Basic characteristic of the studies

	Number of studies (n=101)
Type of influenza strain	
Seasonal	30
1918 pandemic	7
1968 pandemic	1
2009 pandemic	62
Seasonal and 2009 pandemic	1
Study setting	
Asia	30
Europe	26
America	38
Africa	1
Australia	6
Nature of closure[a]	
Outbreak report or teachers' strike	47
Planned holiday	28
Reactive closure	16
Proactive closure	13
Duration of closure[b]	
7–13 days	40
14–20 days	24
≥ 21 days	22
< 7 days	13
Varied	8
Not clear	5

[a] A single article can contain different types of closure.

[b] Each study may present more than one dataset for which the durations of closure differed.

A total of 16 studies demonstrated that reactive SC could be a useful control measure during influenza epidemics or pandemics, with impacts that included reducing the incidence and reducing the peak size (Table 22). Several studies reported a reduction in number of confirmed or ILI cases (*114, 115, 117, 119, 123, 125, 126*). One study also showed a reduction in total infected cases by 32.7% (total reduced number of cases from 127.1 to 85.5) (*122*). Another observational study suggested a reduction in the peak of influenza epidemic curve by 24% during the 4-day closure, and also a reduction of the total number of infected students by 8% (*118*). However, two observational studies in China did not identify a significant difference on total attack rate between the control (SC not implemented) and intervention group (school closed) (*112, 113*). Two studies in the USA showed that absenteeism was lower after school reopening compared to before SC (*120, 121*).

Effectiveness of SCs can also be assessed by evaluating the transmission rate; that is, reproduction number. Hens el at. showed a reduction of the reproduction number from 1.33 (95% CI: 1.11–1.56) to 0.43 (95% CI: 0.35–0.52) after SC (116). An observational study from Japan reported that SC was more effective than class closure (dismissal of that particular class with substantial increase in influenza incidence) (126). In another study from Japan, a 2-day SC in the outbreak situation

(after a 10% of absentee occurrence in a school) was also shown to associate with the interruption of an outbreak within a week (124). One detailed study of transmission in a school in Pennsylvania identified no effect of the reactive closure that was implemented when 27% of students already had symptoms (*111*).

Effectiveness of proactive SC was studied in 13 articles (Table 23). A study showed that proactive SC had an advantage in delaying the epidemic peak for more than a week, affecting the modelled mean peak, and reducing the overall attack rate from 9.7% to 8.6% (*127*). Bootsma et al. estimated that early and sustained interventions, including SCs, reduced overall mortality by up to 25% in some cities (128). Hatchett et al. and Markel et al. also examined NPIs in the 1918–1919 pandemic, reporting that the combined use of NPIs including SCs were able to delay the time to peak mortality, and to reduce peak mortality and overall mortality (*85, 135*).

One study estimated a 29–37% reduction in influenza transmission by the 18-day period of mandatory SCs and other social distancing measures including closure of restaurants and theatres, and cancellation events (130). A study in Mexico City estimated that effective reproduction ratio declined from 1.6 before closure to less than 1 during closure (134). Wu et al. estimated that the reproduction number was reduced from 1.7 to 1.5 during the proactive closures and to 1.1 during the rest of the summer holiday (*138*). One study in Mexico showed a 80% reduction of contact rate during closure period and a subsequent planned holiday (*136*). However, closing kindergartens and primary schools for 2 weeks in Hong Kong SAR did not show any significant effect on community transmission, although the incidence remained low after the peak during proactive closure (133).

A total of 28 studies monitored the change of influenza incidence across planned school holidays (e.g. the scheduled winter holiday each year), to estimate the impact of SC on influenza transmission (Table 24). Eight of these studies illustrated that planned holidays could reduce influenza transmission (*136, 139, 141, 147, 148, 150, 159, 163*). One study demonstrated that school holidays reduced the R0 of influenza A(H1N1)pdm09 by 14–27% in different regions of India compared with non-holiday period (139). One study also reported an association of school holiday with a reduction of 63% to 100% in transmission in Canada (148). Another study reported a reduction of R0 from 1.25 to 0.79 during the 8 days-national holidays in China, but reported that the 8-week summer school holiday had a limited effect on incidence of ILI (*163*). Two studies in the United Kingdom and Mexico showed that SCs could reduce contact rate by around 48–80% (*136, 141*). Two studies in Belgium and the Netherlands suggested that holidays delayed the epidemic peak by more than 1 week, and reduced the peak incidence by 4–27% (*155, 160*). A study from the USA showed that absenteeism in Adrian reduced by approximately 6% (*157*), whereas Rodriguez et al. reported no difference between closed schools and those that did not close (*158*).

Observational studies also reported a reduction in incidence of influenza associated with planned school holidays (*123, 125, 140, 142-146, 149, 150, 152-154, 156, 159, 161, 162*). Studies showed that summer or winter holidays were associated with the reduction of ILI incidences by showing significant changes of ILI incidence rate ratios of schoolchildren to adults during the breaks (*143, 145, 153*). A study based on national surveillance data in France showed that routine school holidays prevented 18% of seasonal influenza cases (18–21% in children) (*142*). Another study in Japan estimated a 38% reduction in number of medically attended clinical ILI cases (*152*). Wheeler et al. suggested that planned holidays could prevent or delay potential influenza cases among school-age children by around 42% (*161*). In comparison, a systematic of simulation studies that reviewed the effects of SCs on influenza outbreaks found that this intervention can be a useful control measure during an influenza pandemic (*211*).

A study conducted a review on social distancing interventions in schools other than SC (212). A total of 16 articles met the inclusion criteria, and 16 states in the USA mentioned school practices to promote social distancing in the published guideline documents. The most frequent categories of school measures included cancelling or postponing after-school activities, increasing space among students, cancelling classes or activities, and reducing mixing during transport.

A simulation study showed that classroom restrictions (the children must remain seated while in their classroom) were the best single intervention at lower infection probabilities. At higher transmission rates, staggered shifts (each classroom follows one of three different schedules put forth by the school: the current schedule, a shift of 45 minutes, and a shift of 90 minutes) is the best single intervention (*213*). A study by Cooley et al. reported that a 3-day weekend for schools could be effective at reducing peak attack rate, and would be less detrimental than sustained SC (*214*). Closing the playground and other common areas could significantly reduce the total number of infected students (*215*). However, the evidence is limited on the effectiveness of school measures.

Ethical considerations

Apart from a potential health impact, SCs can have a substantial social impact by requiring parents to make other arrangements for care or supervision of their children, which can be particularly challenging for some families and for prolonged closures. In addition there may be social equity concerns; for example, because of access to subsidized or free food at school for lower income families (*121*).

Knowledge gaps

More research is needed on the best trigger factors, timing and duration of SCs in order to maximize the impact of this disruptive intervention.

Table 22. Summary table of reactive closure

AUTHOR, YEAR	REDUCE PEAK	REDUCE OVERALL ATTACK RATE	REDUCE INCIDENCE	REDUCE DURATION	REDUCE TRANSMISSION	REDUCE ABSENTEEISM
Cauchemez S, 2011 (*111*)	–	–	–	–	Reproduction number remained unchanged during SC and after the reopening of school (R = 0.3)	–
Chen T, 2017 (*112*)	–	Total attack rate of 1–3 week of SC were close to that for no intervention	–	Duration of outbreak was prolonged	–	–
Chen T, 2018 (*113*)	–	Total attack rate of 1–3 week of SC were close to that for no intervention	–	Duration of outbreak was prolonged	–	–
Davis BM, 2015 (114) [a]	–	–	ILI rate ratio changed from 3.13 (3 weeks before peak), to 2.75 (at peak) and 1.79 (3 weeks after the peak)	–	–	–
Egger JR, 2012 (115)	–	–	7.1% reduction in ILI case over the outbreak period	–	–	–
Hens N, 2012 (116)	–	–	–	– –	Influenza case reproduction number decreased from 1.33 (during outbreak before SC) to 0.43 (after SC)	–
Janjua NZ, 2010 (117)	–	–	Daily number of ILI cases declined during SC	–	–	–

ILI: influenza-like illness (fever plus cough and/or sore throat); SC: school closure.

AUTHOR, YEAR	REDUCE PEAK	REDUCE OVERALL ATTACK RATE	REDUCE INCIDENCE	REDUCE DURATION	REDUCE TRANSMISSION	REDUCE ABSENTEEISM
Kawano S, 2015 (*118*)[b]	Number of infected students in a SC decreased by 24% at its peak	Cumulative number of infected students decreased by 8.0%	–	–	–	–
Loustalot F, 2011 (*119*)	–	–	Incidence remained low during closure	–	–	–
Miller JC, 2010 (*120*)	–	–	–	–	–	Absenteeism was lower after reopening compared to before closure
Russell ES, 2016 (*121*)	–	–	–	–	Closing schools after a widespread ILI activity did not reduce ILI transmission	Absenteeism changed from 1% (baseline), to 3.62% (during SC), and 0.68% (after school reopening)
Sato T, 2013 (*122*)	–	Total number of infected persons decreased from 127.1 to 85.5; the maximum number of infected cases decreased from 63.7 to 53.1	–	–	–	–
Sonoguchi T, 1985 (*123*)	–	–	Number of cases declined from 16 on the day before closure to almost 13, 5 and 0 on the three days of closure in high school	–	–	–
Sugisaki K, 2013 (*124*)	–	–	–	Outbreak duration decreased by 4.98 days if the class is closed for 2 days upon the observed 10% ILI-related absentee rate	–	–
Uchida M, 2011 (*125*)	–	–	Incidence declined during closure period	–	–	–
Uchida M, 2012 (*126*)[c]	–	–	At elementary school, subsequent peak of H1N1 case showed up despite school or class closure (Fig. 1); at junior high school, SC significant reduced the number of H1N1 case but not in class closure (Fig. 2)	–	–	–

ILI: influenza-like illness (fever plus cough and/or sore throat); SC: school closure.
[a] ILI rate ratio is compared at school district level, with 51–100% of schools being closed, compared with district level, with 1–50% of schools being closed.
[b] Author mentioned the recommended period of SC is > 4 days.
[c] Closure duration is significantly related with the number of cases within the 7-day of school opening.

Table 23. Summary table of proactive closure

AUTHOR, YEAR	REDUCE PEAK	REDUCE OVERALL ATTACK RATE	DELAY TIME TO PEAK	REDUCE INCIDENCE	REDUCE TRANSMISSION
Bolton, 2012 (*127*)	–	Overall attack rate decreased from 9.7% to 8.6%[a]	Epidemic peak would be delayed by over a week	–	–
Bootsma MC, 2007 (*128*)[b]	Earlier intervention may reduce peak mortality	Earlier intervention may reduce total mortality	–	–	–
Caley P, 2008 (*129*)[b]	–	–	–	–	Transmission reduced by 38% during period of social distancing
Chowell G, 2011 (*130*)[b]	–	–	–	–	Reproduction number decreased from 2.2 (before SC) to 1.0 (during SC); transmission rate is estimated to reduce by 29.6% during the intervention period
Copeland DL, 2013 (*131*)	–	–	–	Incidence rate of ARI increased from 0.6% (before closure), to 1.2% (during SC) and dropped to 0.4% (after school reopening)	–
Cowling BJ, 2008 (*133*)[c]	–	–	–	–	Not found a substantial effect on community transmission
Cowling BJ, 2010 (*216*)[c]	–	–	–	–	The estimated reproduction number changed from 1.5 (initial peak) to below 1 (during proactive closure), and fluctuated between 0.8 and 1.3 through the school vacations
Cruz-Pacheco G, 2009 (*134*)[b]	–	–	–	Incidence increased to peak then decreased gradually during closure period	Effective reproductive ratio R(t) declined from 1.6 before to < 1 during closure

ARI: acute respiratory infection (presence of at least 2 of the following symptoms: fever, cough, sore throat and runny nose);
ILI: influenza-like illness (fever plus cough and/or sore throat); SC: school closure.
[a] Assuming schools were closed for 4 weeks and the attack rate in children was threefold higher than in adults.
[b] SC combined with other interventions.
[c] Proactive closure followed by planned holidays.

AUTHOR, YEAR	REDUCE PEAK	REDUCE OVERALL ATTACK RATE	DELAY TIME TO PEAK	REDUCE INCIDENCE	REDUCE TRANSMISSION
Hatchett RJ, 2007 (135)[b]	Earlier intervention reduced peak weekly excess pneumonia and influenza death rate	–	–	–	–
Herrera-Valdez MA, 2011 (*136*) [b]	–	–	–	–	Reduced contact rates by around 80% during closure period
Markel H, 2007 (85) [b]	Earlier intervention reduced peak excess death rate	Earlier and increased duration of intervention reduced total excess death	Earlier interventions increased time to epidemic peak	–	–
Tinoco Y, 2009 (*137*)	–	–	–	Number of ILI cases decreased throughout closure period	–
Wu JT, 2010 (*138*) [c]					The reproduction number was reduced from 1.7 to 1.5 during the proactive closures and to 1.1 during the rest of the summer holiday

[a] Assuming schools were closed for 4 weeks and the attack rate in children was threefold higher than in adults.

[b] SC combined with other interventions.

[c] Proactive closure followed by planned holidays.

Table 24. Summary table of planned holidays

AUTHOR, YEAR	REDUCE PEAK	DELAY PEAK	REDUCE OVERALL ATTACK RATE	REDUCE INCIDENCE	REDUCE TRANSMISSION	REDUCE ABSENTEEISM
Ali ST, 2013 (*139*)	–	–	–	–	Reproduction number reduced by 14–27% in different regions of India	–
Baguelin M, 2010 (*140*)	–	–	–	Incidence declined throughout the closure period	–	–
Birrell PJ, 2011 (*141*)	–	–	–	–	Reduce contact rate among 5–14 years old by 72% (summer holiday) and 48% (half term holiday)	–
Cauchemez S, 2008 (*142*)	–	–	–	Routine school holidays prevented 18% of seasonal influenza cases (18–21% in children)	–	–
Chowell G, 2011 (*144*)	–	–	–	Number of confirmed cases declined throughout closure period	–	–
Chowell,G, 2014 (*143*)[a]	–	–	–	Schoolchildren-to-adult ratios decreased by 40–68% during the 2-week period immediately preceding the winter break	–	–
Chu Y, 2017 (*145*)	–	–	–	ILI incidence rate ratio of age 5–14 (schoolchildren) to adult (aged above 60) declined by 13.3% during summer break	–	–
Davies JR, 1988 (*146*)	–	–	–	Clinical influenza cases increased during closure period	–	–
Eames KT, 2012 (*147*)	–	–	–	–	The initial growth rate of the epidemic during holidays would be 35% lower than during term time (from 1.57 to 1.07)	–

AUTHOR, YEAR	REDUCE PEAK	DELAY PEAK	REDUCE OVERALL ATTACK RATE	REDUCE INCIDENCE	REDUCE TRANSMISSION	REDUCE ABSENTEEISM
Earn DJ, 2012 (*148*)	_	_	_	_	Reduction in transmission rate in school-age children was 63%, 100% and 86% as a result of schools closing for the summer in Calgary, Edmonton and the province of Alberta as a whole respectively	_
Evans B, 2011 (*149*)	_	_	_	Estimated number of ILI cases declined during school holiday	_	_
Ewing A, 2017 (*150*)[b]	_	Fig. 5A suggested a peak delay	_	Fig. 5B illustrated a reduction of influenza incidence	Influenza transmission decreased by approximately 15% (from 1.1 to 0.9) in most seasons and decreased to < 1 immediately following Christmas	_
Flasche S, 2011 (*151*)	_	_	_	_	No evidence found of a relationship between the effective reproduction number and the start of school holidays	_
Fujii H, 2002 (*152*)	_	_	_	Number of ILI cases declined by 38% during the first week of closure (from 191 to 118 cases), then increased to 173 cases during the second week of closure	_	_
Garza RC, 2013 (*153*)	_	_	_	ILI incidence rate ratio reduced by 37% among children 5–14 years of age during the week after the winter school break	_	_
Herrera-Valdez MA, 2011 (*136*)[c]	_	_	_	_	Reduced contact rates by around 80% during closure period	_

AUTHOR, YEAR	REDUCE PEAK	DELAY PEAK	REDUCE OVERALL ATTACK RATE	REDUCE INCIDENCE	REDUCE TRANSMISSION	REDUCE ABSENTEEISM
Louie JK, 2007 (*154*)	_	_	_	ILI incidence declined throughout closure; laboratory-confirmed declined slightly first, then increased	_	_
Luca G, 2018 (*155*)[d]	Peak incidence reduced by 4%	All holidays delay the peak time of 1.7 weeks	Epidemic size reduced by approximately 2%	_	_	_
Merler S, 2011 (*156*)[e]	_	_	_	Incidence declined during closure	_	_
Monto AS, 1970 (*157*)	_	_	_	_	_	Absenteeism reduced by approximately 6% in Adrin
Rodriguez CV, 2009 (*158*)	_	_	_	_	_	No difference in post-break absenteeism in schools on holidays compared with schools that remained open at the same times (relative rate = 1.07, 95% CI = 0.96–1.20)
Smith S, 2011 (*159*)	_	_	_	Consultation rates decreased in school-aged children	Transmission of influenza may be interrupted in that school-age group	_
Sonoguchi T, 1985 (*123*)	_	_	_	Case number remained low during closure period in middle school	_	_
Te Beest DE, 2015 (*160*)	Epidemic peak is lowered by 27%	Peak is delayed for approximately 1 week	_	_	_	_

AUTHOR, YEAR	REDUCE PEAK	DELAY PEAK	REDUCE OVERALL ATTACK RATE	REDUCE INCIDENCE	REDUCE TRANSMISSION	REDUCE ABSENTEEISM
Uchida M, 2011 (*125*)	_	_	_	Incidence declined during closure period	_	_
Wheeler CC, 2010 (*161*)	_	_	Daily number of ILI cases declined during SC	Prevent or delay around 42% of potential influenza cases among school-age children	_	_
Wu J, 2010 (*162*)	_	_	_	Cumulative incidence of confirmed cases increased during SC	_	_
Yu H, 2012 (*163*)	_	_	_	_	Reproduction number changed from 1.25 (before National Day holiday), to < 1 (during that holiday), and 1.23 (after that holiday); National day holiday reduced the reproduced number by 37%	_

CI: confidence interval; ILI: influenza-like illness; SC: school closure.

[a] Decline in ratio is caused by a decrease in ILI rates among schoolchildren and the average reduction in ILI incidence among schoolchildren in the 2 weeks during the winter break compared with the 2 weeks before.

[b] The holiday model combined the changes associated with both the SC and travel models.

[c] All holidays included Fall holiday, Christmas holiday, Winter holiday and Easter holiday.

[d] Mainly planned holidays, some reactive closures.

[e] SC combined with other interventions.

Table 25. Summary of outbreak reports and teachers' strike

AUTHOR,YEAR	OUTCOME
Armstrong C, 1921 (*164*)	Number of cases peaked on the day following closure and declined thereafter
Baker MG, 2009 (*165*)	Start of the school holidays in New Zealand reduced influenza transmission and that the return to school slightly accelerated the epidemic
Briscoe JH, 1977 (*166*)	Number of clinical cases declined during closure
Calatayud L, 2010 (*167*)	Cases decline after the half way of SC
Carrillo-Santisteve P, 2010 (*168*)	Number of confirmed and probable cases declined during closure
Cashman P, 2007 (*169*)	A planned SC may have contributed to controlling the outbreak without quantitative information
Chieochansin T, 2009 (*170*)	Laboratory-confirmed cases declined throughout period of closure
Cohen NJ, 2011 (*171*)	Number of respiratory illness cases were lower on the first day of closure compared to previous days, increased during closure and then declined
Danis K, 2004 (*172*)	Number of ILI cases declined during closure period
Echevarria-Zuno S, 2009 (*173*)	Epidemic continued while schools were closed and peaked around 1 week after closure
Effler PV, 2010 (*174*)	Number of confirmed cases declined during closure period
Engelhard D, 2011 (*175*)	ILI rate peaked and declined during closure
Farley TA, 1992 (*176*)	Absenteeism remained low after school reopening
Glass RI, 1978 (*177*)	School absenteeism was lower after the holiday than before
Gomez J, 2009 (*178*)	Number of pneumonia cases decreased from 130 cases at peak to around 40 during closure
Grilli EA, 1989 (*179*)	During the mid-term break there were a further 15 ILI cases (daily cases not provided)
Guinard A, 2009 (*180*)	No further cases during SC period, but epidemic appear to be over before the school was closed

AUTHOR, YEAR	OUTCOME
Health Protection Agency West Midlands H1N1v Investigation Team, 2009 (*181*)	Confirmed number of cases declined during closure period
Heymann A, 2004 (*182*)[a]	Significant decreases in the rate of diagnoses of respiratory infections (42%), visits to physician (28%) and emergency departments (28%) and medication purchases (35%)
Heymann AD, 2009 (*183*)[a]	Decease in ratio of 14.7% for 6–12 years old associated with teachers' strike
Hsueh PR, 2010 (*184*)	Number of class suspensions or SC generally associated with the number of hospitalizations
Huai Y, 2010 (*185*)	Number of confirmed cases peak at 30 cases on the first day of closure, then declined during closure period
Janusz KB, 2011 (*186*)	Absenteeism changed from 8% (baseline), to 15% (2-days before school outbreak), and 13% (post-school outbreak)
Johnson AJ, 2008 (*187*)	Number of parentally-reported ILI cases decline because of SC
Jordan EO, 1919 (*188*)	Incidence declined from 19 cases to 15 cases the following week in elementary school, and declined from 16 to 5 cases in high school
Kawaguchi R, 2009 (*189*)	Number of confirmed cases declined throughout closure period
Lajous M, 2010 (*190*)	Planned holiday was followed by a slight decrease in ILI case numbers
Leonida DDJ, 1970 (*191*)	Absenteeism continued decline during second SC
Lessler J, 2009 (*192*)	Both confirmed H1N1 influenza and self-reported ILI declined through closure period
Leung YH, 2011 (*193*)	Number of laboratory-confirmed cases increased during first two days of closure and then declined
Lo JY, 2003 (*204*)	Change in proportion of positive specimens were 50–100% lower in April-June than the average because of community control measures
Marchbanks TL, 2011 (*194*)	Number of ILI cases increased during first two days of closure and then declined
Miller DL, 1969 (*195*)	In children aged 5–14 years, rates of influenza declined during the Christmas holidays

[a] Articles related to teachers' strike.

AUTHOR,YEAR	OUTCOME
Nishiura H, 2009 (*196*)	Number of laboratory-confirmed cases declined throughout the closure
Olson JG, 1980 (*197*)	School absenteeism (all-cause) declined in Girls Teachers' Colleges Primary School; absenteeism very similar before and after closure in Taipei American School
Paine S, 2010 (*198*)	Case numbers peaked and declined during holiday, effective reproduction number declined before holiday and continued to decrease during the holiday
Petrovic V, 2011 (*199*)	Weekly incidence rate of ILI and the number of hospitalized cases decreased after the SC
Poggensee G, 2010 (*200*)	Practice index was associated with vacation density
Rajatonirina S, 2011 (*201*)	Only few cases continued to occur during closure period
Shaw C, 2006 (*202*)	Absenteeism was lower after closure than before closure in both reactive closure and planned holiday
Shimada T, 2009 (*203*)	Number of new confirmed cases decreased after SCs
Smith A, 2009 (*206*)	Number of ILI cases declined during closure period
Strong M, 2010 (*207*)	Number of self-reported ILI cases declined during closure period
van Gageldonk-Lafeber AB, 2011 (*208*)	Possible reduced incidence, or slowed epidemic growth
Wallensten A, 2009 (*209*)	Absenteeism almost not changed before and after closure
WHO, 2009 (*205*)	School absenteeism in the following weeks did not increase after school reopening
Winslow CEA, 1920 (*210*)	Cities with SCs had higher deaths rates; timing and duration of closure were not stated

ILI: influenza-like illness; SC: school closure.

3.4. Workplace closures

Methods

PubMed, Medline, EMBASE and CENTRAL were searched until 18 September 2018. No language limits were applied but papers in languages other than English were excluded in screening. The inclusion criteria included RCTs, epidemiological studies and simulation studies reporting the effectiveness of workplace closure (WC) in non-health care settings, as well as the combination of WC and other NPIs. The exclusion criteria included the following: studies in health care settings; studies do not have specific data related to WC; review, letter, news or summary articles; studies related to avian influenza; and the language of articles not in English. Two reviewers (SG and ES) independently screened titles, abstracts and full texts to identify eligible articles.

Results

A total of 475 citations were identified through database search and other sources, of which 18 full-length articles assessed for eligibility and six articles were selected for this systematic review. The flow chart of study selection is shown in Fig. 20.

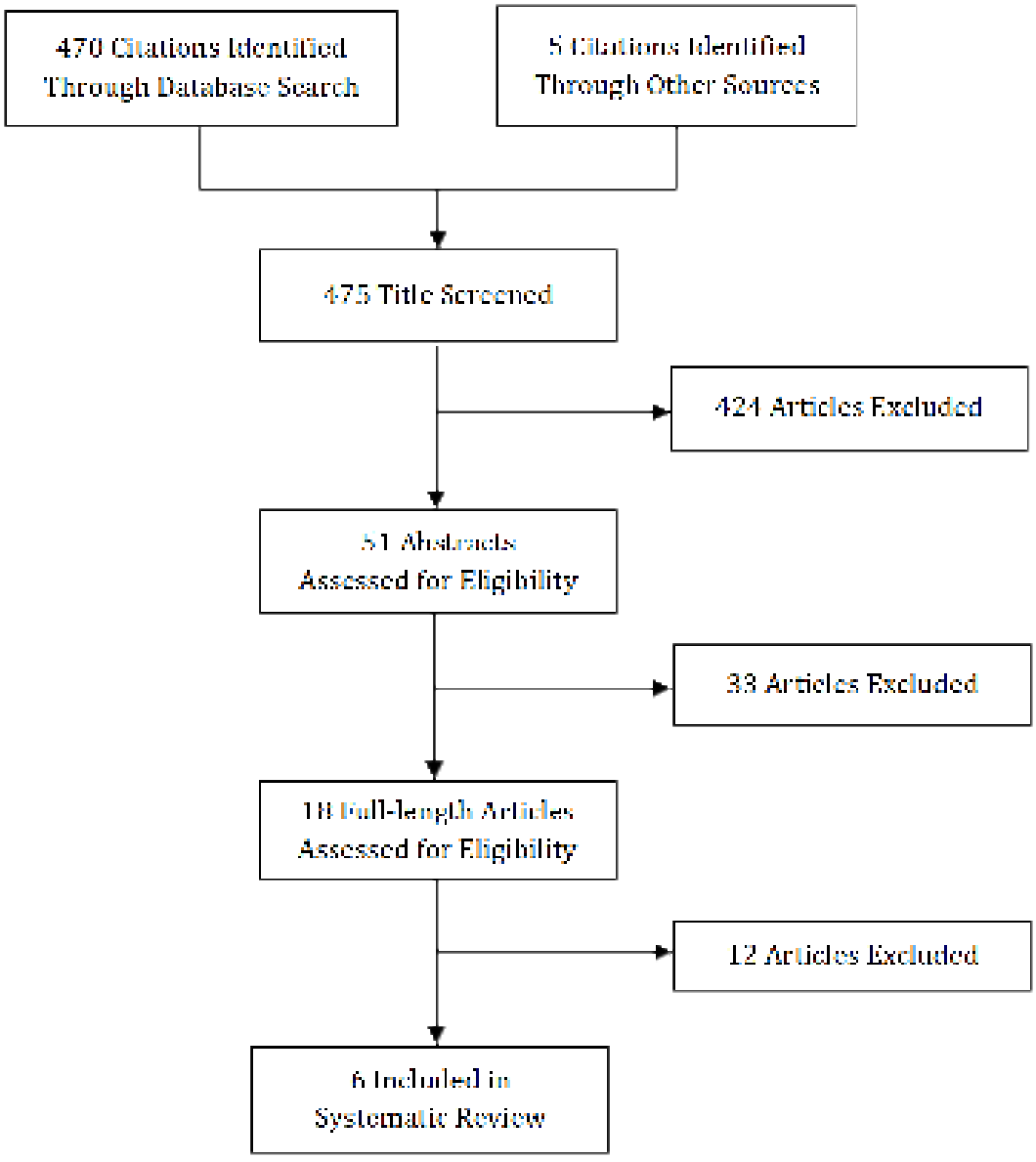

Fig. 20. The flow chart of workplace closure

Among these six studies, four were measured with SC, one targeted different single and multiple strategies, and another evaluated the effectiveness of WC alone (Table 26). All six studies represented simulation studies that met the inclusion criteria and the main outcome include the reduction of attack rate, peak number and delay of epidemic peak.

Predicted effects reduction

Five studies suggested the reduction in attack rate, infected duration or peak number. In the studies by Ferguson et al. (*87*) and Xia et al. (*217*), WC resulted in a small reduction in cumulative attack rate, while Carrat et al. (218) and Mao et al. (*219*) suggested an obvious decrease when assessing the effect of combining intervention. The study by Carrat et al. simulated individual and community level model in France, which suggested a decline of the cumulative attack rate from 46.8% to 1.1%, assuming the R0 of 2.07 (*218*). Mao et al. used an agent-based stochastic simulation model with R0 = 1.3–1.4 in the USA, and predicted a decline of overall attack rates from 18.6% to 11.9% with 100% SC and 10% WC, and from 18.6% to 4.9% with 100% SC and 33% WC (*219*).

A heuristic model using R0 of 1.7 and 2.0 suggested a small reduction in cumulative attack rate but a more substantial reduction in peak attack rates (up to 40%) when 100% SC and 10% WC was implemented. It also suggested that effectiveness could increase if 50% of workplaces were closed, but this would have a higher economic cost (*87*). A simulation model for the control of influenza in an isolated geographical region by Roberts et al. suggested the single WC strategy could not prevent the epidemic (with R0 = 2.0).

Delay the time of peak occurrence

Delaying the epidemic peak is another factor to consider the effectiveness of this intervention. A simulation study using individual-based model suggested that nationwide closure of schools and workplaces for weeks would delay the time of peak occurrence by 5–8 days, depending on the R0 = 1.4, 1.7 and 2.0 (*220*). However, the study by Mao et al. suggested that 100% SC and 33% WC could advance the peak by approximately 1 week (*219*).

Ethical considerations

Apart from a potential health impact, WC can have a substantial impact on the economy and productivity of the society (*221*).

Knowledge gaps

As with SCs, more research is needed on the best trigger factors, timing and duration of WCs in order to maximize the impact of this disruptive intervention.

Table 26. Description of studies included in the review of WCs

STUDY	INFLUENZA STRAIN & TRANSMISSIBILITY (R_0)	STUDY SETTING AND POPULATION	STUDY DESIGN	CLOSURE DURATION	CLOSURE PROPORTION	CLOSURE THRESHOLD	INTERVENTION	OUTCOME
Carrat F, 2006 (*218*)	Future pandemic strain; R_0 = 2.07	General population in France (n = 10 000)	Simulation both individual and community level	N/A	N/A	5 infections per 1000 subjects	SC + WC	Mean accumulation infection rate reduced from 46.8% (42.3–50.5%) to 1.1% (0.6–2.1%)
Ciofi degli Atti ML, 2008 (*220*)	Future pandemic strain; R_0 = 1.4, 1.7, 2	General population in Italy (n = 56 995 744)	Global SEIR model for importation of cases with an individual-based model	4 weeks	N/A	N/A	SC + WC	Nationwide closure could delay the time of peak occurrence by 5–8 days, based on various scenarios
Ferguson NM, 2006 (*87*)	Future pandemic strain; R_0 = 1.7, 2.0	300 million in USA, 58.1 million in United Kingdom	Heuristic model	N/A	Varied: 10%, 50%	N/A	100% SC + varied WC (10%, 50%)	100% SC + 10% WC could slightly reduce the cumulative attack rate, and might reduce the peak attack rate of up to 40%; 50% of WC could further improve the effectiveness with a higher economic cost
Mao L, 2011 (*219*)	Future pandemic strain; R_0 = 1.3–1.4	Urbanized area of Buffalo, NY, USA (n = 985 001)	Agent-based stochastic simulations	N/A	Varied: 10%, 33%	N/A	1) 100% SC + varied (10%, 33%) WC; 2) 100% SC + varied (10%, 33%) WC + preventive behaviour	1) Overall attack rates declined from 18.6% to 11.9% (10% WC) and 4.9% (33% WC), respectively 2); overall attack rate reduced to 3.99% (10% WC) and 1.83% (33% WC), respectively
Roberts MG, 2007 (*103*)	Future pandemic strain; R_0 = 1.1, 2.0 and 3.0	Isolated geographical region (n = 1 000 000)	A model based on published parameters	N/A	70%	N/A	1) WC; 2) WC + SC; 3) WC + SC + antiviral treat + 70% home quarantine	The single strategy of WC is not successful, the combination of four strategies would prevent the epidemic
Xia H, 2015 (*217*)	Simulate H1N1; R_0 = 1.35, 1.40, 1.45, 1.60 (all similar to R_0 = 1.35)	Delhi, India (over 13 million)	Realistic individual-based social contact network and agent-based modelling	3 weeks	60%	Over 0.1% population are infected	Single: WC	Intervention could reduce the attack rate and peak number, and delay the time of peak occurrence; single WC is the most ineffective method among vaccination, antiviral drugs, SC and WC

N/A: not applicable; NY: New York; R0: basic reproductive number; SC: school closure; SD: standard deviation; SEIR: susceptible–exposed–infectious–recovered; United Kingdom: United Kingdom of Great Britain and Northern Ireland; USA: United States of America; WC: workplace closure.

3.5. Workplace measures

Methods

The latest systematic review to review the effects of workplace measures in reducing influenza virus transmission was published by Ahmed et al. in 2018 (*222*). We conducted an additional search in PubMed, Medline, EMBASE and CENTRAL from 1 January 2017 to 28 September 2018. Workplace measures includes teleworking, flexible leave policies, working from home, weekend extension, segregation into smaller groups and social distancing at workplaces. All RCTs, epidemiological studies or simulation studies in non-health care workplaces were included in this review. Review, commentary, editorial articles, studies on WC and studies on generic social distancing not in workplace were excluded from our review. The following outcomes were extracted from the studies: cumulative attack rate, peak attack rate, occurrence of peak and other effects. Two reviewers (SG and ZX) worked independently. The GRADE method was used to evaluate the quality of evidence for the effectiveness of workplace measures in reducing influenza transmission.

Results

The most recent systematic review was published in 2018; Ahmed et al. identified 15 epidemiological or simulation studies (from 14 articles) on workplace measures. In the additional search to update the systematic review that was published by Ahmed et al., 81 articles were identified from the databases and one paper from other sources, resulting in total of 82 for title screening. Ten full-length articles were assessed for eligibility and four additional articles were identified. In total, 19 studies (18 articles) were included in our systematic review. The flow charts of study selection are shown in Fig. 21 and Fig. 22.

Among the included 19 studies, there were six epidemiological studies (Table 27) (*107, 223-227*). A cross-sectional study that randomly selected US adults from the Knowledge Networks online research panel showed that those who could not work from home from 7 to 10 days were more likely to have ILI symptoms compared to those who could (*223*). Another cohort study suggested that respondents who could work from home had a 30% lower rate of attending work with severe ILI symptoms compared to employees without such ability, which may be able to reduce employee-to-employee transmission (*225*). A cohort study in Singapore estimated that the intervention of enhanced surveillance and segregation of units into smaller working subgroups had significant lower serologically confirmed infections compared to those with standard pandemic plan (17% versus 44%) (*224*). A RCT study evaluated the effectiveness of voluntary waiting at home on full pay measure against influenza A(H1N1)pdm09 transmission in workplaces showed an overall risk reduction by 20% (*107*). Piper et al. (*227*) and Asfaw et al. (*226*) used the resources data from nationally representative survey in the USA, and illustrated that adults with paid sick days had a higher probability of staying at home and hence reduced the face-to-face transmission in workplace.

The remaining 13 studies were simulation studies (*89-91, 228-236*). The 12 simulation studies from the review by Ahmed et al. suggested that the workplace measure alone reduced the cumulative attack rate by 23%, as well as delaying and reducing the peak influenza attack rate (*89, 90, 228-236*). A study in Ottawa suggested that working from home measure combined with other interventions could reduce the illness attack rate from 55% to 8% (*91*).

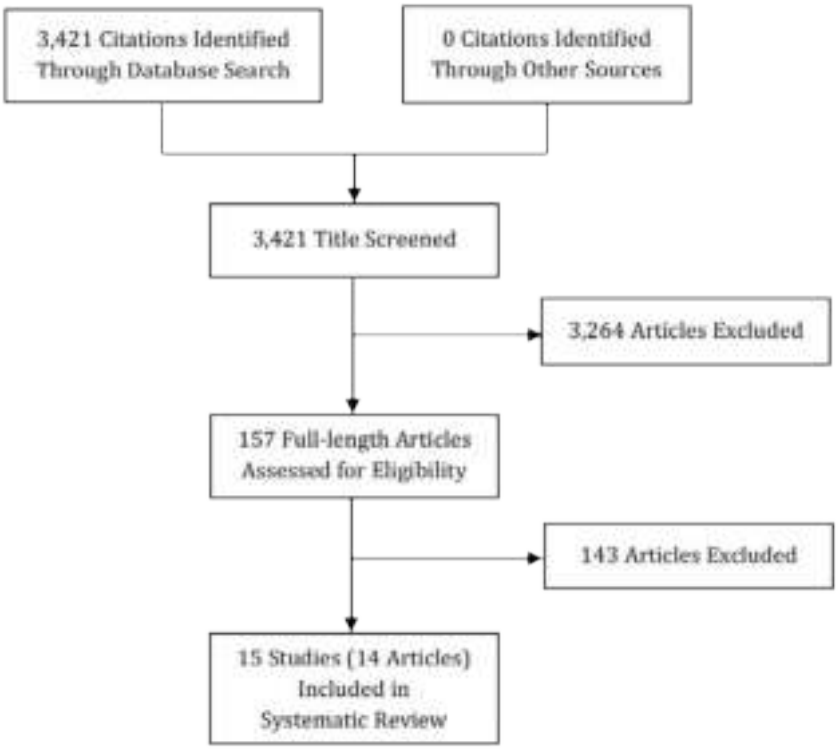

Fig. 21. The flow chart of systematic review by Ahmed

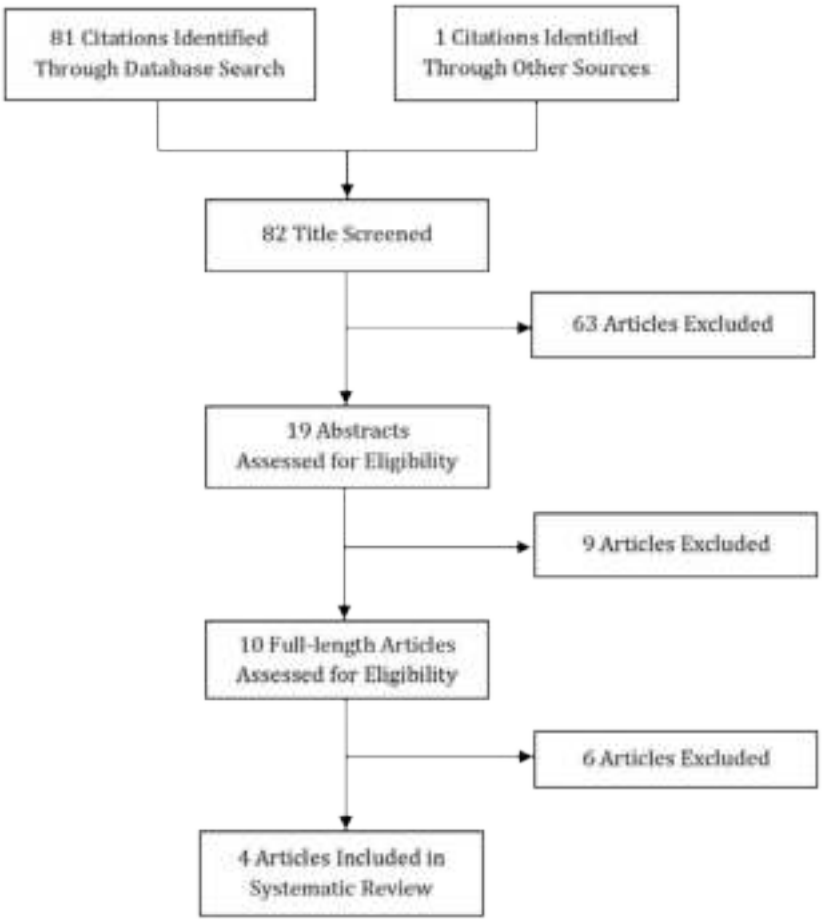

Fig. 22. The flow chart of updated studies in workplace measures

Ethical considerations
Similar to WC, workplace measures could affect the economy and productivity of the society.

Knowledge gaps
A comprehensive review of the ethical issues of workplace measures is lacking, as is a comparison of the benefits and costs of implementing the measures. Other workplace measures have not been studied in depth, such as providing separate studios for people with ILI. In addition, the studies on feasibility and scope of implementation of workplace measures, and the potential impact on families and society transmission are limited.

Table 27. Description of epidemiological studies included in the review of workplace measures

STUDY	STUDY DESIGN	INFLUENZA STRAIN	POPULATION AND SETTING	INTERVENTION	OUTCOME	QUALITY OF EVIDENCE
Asfaw A, 2017 (*226*)	National representative survey	Influenza A(H1N1)pdm09	71 200 people in the USA	Single: paid sick leave	Employees with paid sick leave have a 32% higher probability of staying at home than workers without paid sick leave, which might reduce the transmission of influenza	Very low
Kumar S, 2012 (*223*)	Cross-sectional study	Influenza A(H1N1)pdm09	Nationally representative sample (n = 2079) of USA	Single: can work from home	The people who unable to work at home were more likely to have had ILI (P< 0.05)	Very low
Lee V, 2010 (*224*)	Cohort study	Influenza A(H1N1)pdm09	Singapore military personnel (n = 437 in control group and n = 470 in intervention group)	Multiple: enhanced surveillance and segregation of units into smaller working subgroups	Confirmed infections were significantly (p< 0.001) lower in intervention group (17%) than in the control group (44%)	Very low
Miyaki K, 2011 (*107*)	Quasi-cluster-RCT	Influenza A(H1N1)pdm09	Two sibling companies (Cohort 1 n = 6634, Cohort 2 n = 8500) in Kanagawa Prefecture, Japan	Single: Voluntary waiting at home on full pay if the family became ILI	The intervention reduced around 20% of overall infection risk in the workplace	Low
Rousculp M, 2010 (*225*)	Cohort study	2007–2008 seasonal influenza	793 employees with ILI in three large US companies	Single: can work from home	Employees who could telework had a 29.7% lower rate of attending work with severe ILI symptoms, which indicated that implement teleworking policies may be able to reduce employee-to-employee transmission	Very low
Piper K, 2017 (*227*)	National representative survey (3 rounds interviews in 2009)	Influenza A(H1N1)pdm09	12 044 employees over 16 years old in the USA	Single: paid sick days	Individuals with paid sick leave are more likely to stay at home in order to reduce the influenza transmission in workplace	Very low

ILI: influenza-like illness; RCT: randomized controlled trial; USA: United States of America.

3.6. Avoiding crowding

Methods

The citations were identified from PubMed, Medline, EMBASE and CENTRAL until 18 October 2018. Two reviewers (SG and ES) screened each title, abstract and article that met the criteria in full. Both epidemiological and simulation studies relative to the effectiveness of avoiding crowding (e.g. cancellation or postpone of events and limitation of attendance) in public area are included. Studies that only report an outbreak event in a crowded area or perceptions on mass gathering but without specific data related to the effectiveness of avoid crowding and studies published in review, letter, news or summary articles were excluded. The effectiveness of cancelling, postponing or limiting attendance in reducing influenza transmission was used when examined the quality of evidence by GRADE.

Results

We identified three studies for the systematic review after reviewing 815 titles and 121 abstracts identified from databases and other sources. The flow chart is shown as Fig. 23. Among these three articles, two of them were based on the 1918 influenza pandemic and one focused on World Youth Day gathering in 2008 (details shown in Table 28).

Hachett et al. and Markel et al. reported a strong association between the early implementation of interventions and the mitigation of pandemic influenza. The study by Markel et al. showed three major categories for NPI: SC, cancellation of public gatherings, and isolation or quarantine in 43 cities in the USA. SC combined with a ban on public gatherings was the most common intervention with a median duration of 4 weeks, which can significantly reduce weekly excess death rate (EDR). Also, early implementation led to greater delays in reaching peak mortality (Spearman $\rho = -0.74$, $P < 0.001$), lower peak mortality rates (Spearman $\rho = 0.31$, $P = 0.02$) and lower total mortality (Spearman $\rho = 0.37$, $P = 0.008$) (*85*). There was a statistically significant association between increased duration of interventions and a reduction in total mortality burden (Spearman $\rho = -0.39$, $P = 0.005$) (*85*). Another study by Hatchett et al. also emphasized the early bans on public gathering, closure public places implementation in reducing the EDR (135). In addition, the basic group accommodation for 1 week during World Youth Day was described by Staff el at. (*237*). People accommodated in a single large place (17.2%) had a significantly higher attack rate compared with people who lived in small classrooms (9.2%) in the context of mass gatherings ($p < 0.01$) (*237*).

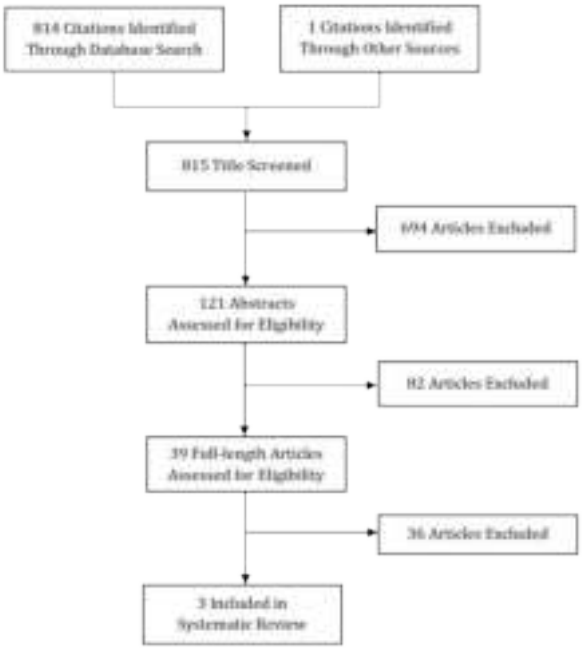

Fig. 23. The flow chart of avoiding crowding

Table 28. Description of studies included in the review of avoiding crowding

STUDY	INFLUENZA	INTERVENTION	OUTCOME	QUALITY OF EVIDENCE
Hatchett RJ, 2007 (*135*)	1918 Pandemic	Early church closure, theatre closure and bans on public gathering	Associated with lower peak excess death rates (Spearman $\rho = 0.56$, $\rho = 0.56$, $\rho = 0.46$ separately)	Very low
Markel H, 2007 (*85*)	1918 Pandemic	Multiple: SC + cancellation of public gatherings + isolation and quarantine.	Implemented earlier and longer duration are significantly associated with the reduction of influenza transmission	Very low
Staff M, 2011 (*237*)	World Youth Day 2008 pilgrims	1 group of pilgrims was accommodated as a large group in a gymnasium and another group was sub-divided into smaller groups and accommodated in classrooms for 1 week.	The attack rate was significantly ($p< 0.01$) higher among pilgrims accommodated in the gymnasium (17.2%) than those staying in the classrooms (9.2%)	Very low

SC: school closure.

Ethical considerations

In urban locations it can be difficult to avoid crowding without considerable social costs. Modification, postponement or cancellation of mass gatherings may have cultural or religious considerations, in addition to public health aspects.

Knowledge gaps

There are still major gaps in our understanding of person-to-person transmission dynamics. Reducing mass gatherings is likely to reduce transmission in the community, but the potential effects are difficult to predict with accuracy. Large-scale RCTs are unlikely to be feasible.

4. TRAVEL-RELATED MEASURES

4.1. Travel advice

Terminology
Travel advice refers to advice from official government to help members of the public to make informed decisions when they are planning to travel, and offer them an objective assessment of risk (*238*). Travel bans are more extreme, and discussed separately. Travel advice can increase travellers' awareness of the travel risk in pandemic countries or areas and may affect decisions to travel.

Methods
The databases including PubMed, Medline, EMBASE and Cochrane Library were searched until September 2018. Inclusion criteria were primary research evaluating travel advice for influenza in the community setting. Studies had to demonstrate any effectiveness following travel advice to the public. We excluded studies conducting at the health care settings, animal-related studies, systematic reviews and/or meta-analysis without updated evidences, not measuring effectiveness of travel advice to the community, and article type of letter, commentary or news. Two reviewers (SR and SG) contributed to the title, abstract and full-text screening.

Results
A total of 168 records were identified and included in the title and abstract screening, and 146 of the records were excluded. Twelve full-text records were evaluated for eligibility and all were excluded. No full-length articles were included in this systematic review. The flow chart of study selection is shown in Fig. 24.

Ethical considerations
Policy decisions and justification should be open to the public, so that the public awareness of influenza can be increased, and public trust to follow travel advice can be maintained (239).

Regarding the impact for the global economy through the public avoidance of travel or trade, travel advice may develop financial loss of the public (*239*).

Knowledge gaps
There is still no evidence measuring the quantitative effect of travel advice on influenza pandemic, which may hamper the development of policy in this area. Because the outcomes of effectiveness may vary by reproduction number, study of the level of infectivity and travel restriction, influenza strain-specific travel advice can be considered.

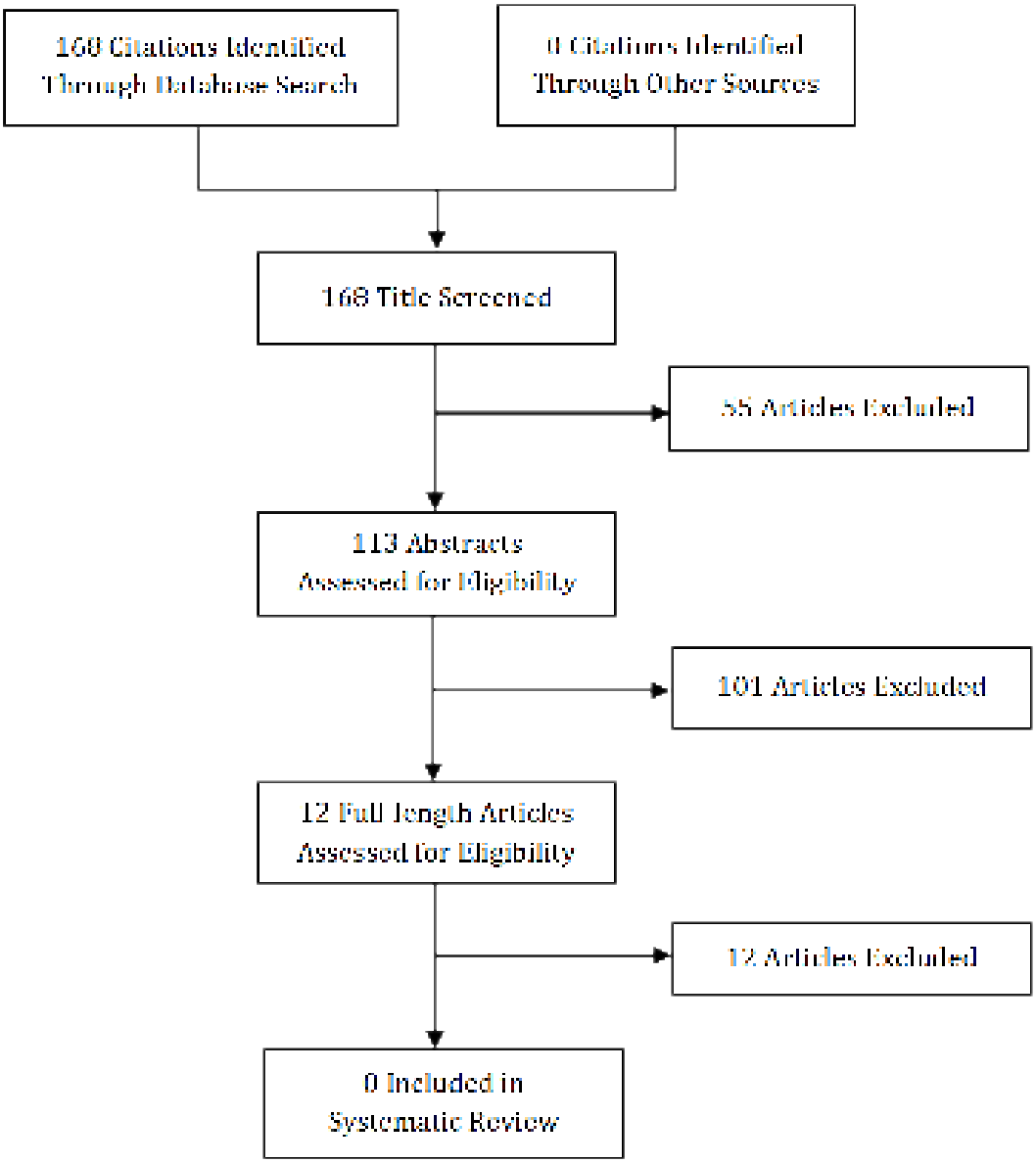

Fig. 24. The flow chart of travel advice

4.2. Entry and exit screening

Terminology

The aim of screening travellers for influenza is to reduce the number of infectious individuals entering or leaving a country. Screening measures include health declarations, visual inspection, and thermography to detect individuals with influenza-related symptoms (*240*). These measures can be conducted at arrival terminal (entry screening) or at departure terminal departure (exit screening) (*241*).

Methods

The databases PubMed, Medline, EMBASE and Cochrane Library were searched until September 2018. Inclusion criteria were primary research evaluating entry and/or exit screening for influenza in the community setting. Studies had to demonstrate any effectiveness following entry and/or exit screening in the community. We excluded studies conducting at health care settings, animal-related studies, systematic reviews and/or meta-analysis without updated evidence, not

measuring effectiveness of travel advice to the community, and article type of letter, commentary or news. Two reviewers (SR and SG) contributed to the title, abstract and full-text screening. The quality of evidence was measured using the GRADE approach. The rating was made for the overall effectiveness of entry and exit screening by two independent reviewers.

Results

A total of 297 records were identified and included in the title and abstract screening, and 230 were excluded; 31 full texts were evaluated for eligibility and 19 full texts were excluded. Ten full-length articles were included in this systematic review. A flow chart of study selection shown in Fig. 25. Study details are shown in Table 29, Table 30, Table 31 and Table 32.

A simulation study in the USA estimated that entry screening can detect 50% of infected travellers and is likely to lower the predicted pandemic influenza attack rate by less than 1% (*242*). Furthermore, several simulation studies showed that screening international travellers may help to delay the epidemic by a few days (0–12 days) (*163, 242-244*). However, several observational studies that were conducted at international airports demonstrated that the sensitivity of entry screening was low (5.8% at New Zealand, 6.6% at Japan and 1.1% at USA) (*245-247*), and half of international travel-related case-patients were identified more than a day after arrival by passive case finding and contact tracing in the community, although 37% of international travel-related cases of influenza were screened at the border entry site (*163*). Simulation studies predicted that screening of travellers may not prevent case import and local epidemics (*243*, *244*).

Fig. 25. The flow chart of entry and exit screening

Sensitivity of screening can affect the effectiveness of travellers' screening. One of the major criteria for screening influenza infected travellers is fever, because it is a relatively specific sign of influenza compared with other signs or symptoms. Infrared thermometers have been used for border screening in many locations due to the instantaneous and non-invasive nature. One study showed that the sensitivity and specificity of infrared thermometer were 50.8–70.4% and 63.6–81.7% respectively during influenza A(H1N1)pdm09 in Japan (*248*). An infrared thermal image scanner (ITIS) is another screening tool for the massive number of travellers. A study conducted in New Zealand demonstrated that the sensitivity and specificity of ITIS ranged from 84–86% and 31–71%, respectively (*249*).

Molecular diagnostics can be used, but will be expensive and resource intensive if used in a large population (*250*). Point-of-care antigen detection tests might be more feasible but would still be costly (*250*).

Considering the incubation period of influenza virus infection of 1–2 days (*163*), the variation of symptom presentation and imperfect screening methods (*251*), screening travellers to prevent the introduction of influenza still has limitations. Furthermore, the public health resources including trained staff, screening devices and laboratory resources are limited (247); thus, screening targeted travellers from and to high risk area should be carefully considered.

Although exit screening has been recommended in the past, we did not identify any reports of the actual implementation of exit screening in the literature.

Ethical considerations

Screening should be conducted voluntarily as much as possible, and compulsory screening should be considered very carefully (*239*). Informed consent from the traveller for the screening of specimen-collection including nasal swabs should be obtained in accordance with the International Health Regulations (*252*).

Knowledge gaps

There were no high-quality studies on the effectiveness of entry and exit screening. Quantitative study for the implementation of screening programmes at different times, different combinations, and different pathogens are required to understand the potential advantage of screening (*251*).

Table 29. Summary of epidemiological studies included in the review

STUDY	INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	NO. OF TRAVELLERS HAD MEDICAL ASSESSMENT	CASE DEFINITION FOR SCREENING AND NO. OF TRAVELLERS MET	LABORATORY TEST FOR THE CASE AND NO. OF SPECIMENS ANALYSED	OUTCOME	COMMENTS AND LIMITATIONS	QUALITY OF EVIDENCE
Hale MJ, et al. 2012 (*245*)	• Influenza A(H1N1)pdm09 • R_0 = N/A	• Cross-sectional study • Auckland international airport, New Zealand. • 456 518 international travellers including flight passenger and crew member arriving between 27 April and 22 June 2009	• Entry screening - In-flight announcement - Locator card completion - Travel advisory information - Self presentation	• 409 (0.09%)	• ILI • 109 (27% of medical assessment)	• RT-PCR from 109 respiratory swab	• 4 were positive. • 69 travellers were confirmed as cases passed through airport. • Sensitivity of screening: 5.8% (95% CI: 2.3–14.0%)	• Low sensitivity of entry screening • Mild illness might not see a doctor or did not diagnosed. • The number of cases who passed through the airport was based on estimated fraction of data from the first 100 cases	Very low
Priest PC, et al. 2013 (*247*)	Seasonal influenza	• Cross-sectional study • Christchurch airport, New Zealand. • 23 513 international travellers including flight passenger and crew member arriving between 23 June and 12 September 2008	• Entry screening - In-flight questionnaire (symptoms)	• 1358 (17%)	• Traveller who reported 1 or more of: cough, sore throat, sneezing, fever or chill, runny or blocked nose, muscle aches or pains, feeling generally unwell, chest discomfort or breathing difficulties	• Commercial EasyPlex multiplexed tandem PCR kit from respiratory swab No. of Case and non-case:1331 and 2438	• 60 were positive (51, type B; 8, type A; 1 type A&B) • Estimated prevalence: 1.13% (95% CI: 0.77–1.48)	• Either resource intensive or ineffective • Symptom based screening • Not report symptom	Very low
Sakaguchi H, et al. 2009 (*246*)	• Influenza A(H1N1) pdm09; • R_0 = N/A	• Cross-sectional study • Narita airport, Japan • 471 933 international travellers including flight passenger and crew member visited affected countries arriving between 28 April and 18 June 2008	• Entry screening – Screening surface body temperature using infrared thermal scanners	N/A	• Traveller who visited influenza affected countries with 2 symptoms or more of 4 symptoms (1. Nasal discharge or nasal obstruction; 2. Sore throat; 3. Cough; 4. Fever or feeling feverish and chills) or travellers with body temperature > 38°c	• Rapid influenza diagnostic test and RT-PCR from 805 respiratory specimens	• 9 were positive. • 141 travellers were found during the community containment measures. • Sensitivity of screening: 6.6%	• Require large amount of human resources • Mild illness travellers were not examined • Not report symptom	Very low
Yu H, et al. 2012 (*163*)	• Influenza A(H1N1)pdm09; • R_0 = N/A	• Retrospective cohort study • China (193 sentinel hospital, 30 provinces) • 7 1 665 persons with confirmed A (H1N1) pdm09 virus between 7 May and 30 November 2009.	• Entry screening – active surveillance at the border and medical monitoring	N/A	• Confirmed case: ARI with laboratory evidence of influenza A(H1N1) pdm09 • ARI: fever (≥ 37.3), and/or recent onset of 1 or more of the following: rhinorrhea, nasal congestion, sore throat or cough	• RT-PCR	• 932 were related to international travel. • 37% of int'l travel-related cases identified at the border. • Half (468/932) were identified 1 or more days after their arrival. • Detection rate of case identified at the entry screening: fever + before arrival: 76%, fever- before arrival 63%	• Epidemic likely delayed by 4 days (100% of screening sensitivity) • Mild illness or subclinical infection might not be examined • Case-based surveillance	Very low

ARI: acute respiratory infection; CI: confidence interval; ILI: influenza-like illness; N/A: not applicable; PCR: polymerase chain reaction; R0: basic reproductive number; RT: reverse transcription.

Table 30. Summary of simulation studies included in the review

STUDY	INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	NO. OF TRAVELLERS HAD MEDICAL ASSESSMENT	SCENARIO	OUTCOME	COMMENTS AND LIMITATIONS	QUALITY OF EVIDENCE
Malone JD, 2009 (*242*)	• Pandemic influenza • R0 = 2.4 (Europe), 2.1 (Latin America), and 2.0 (Canada and USA)	• Stochastic discrete event simulation model • 18 US international airport	• Entry screening	• 409 (0.09%)	• 50% of passengers predicted to be infected and high detection rate of 80% for symptomatic travellers for the screening • 100% of passengers infected and 80% of detection rate from screening • 50% of passengers infected and < 50% of detection rate from the screening	• Lowest number of arriving infected passengers (peak day 45–980); attack rate of without and with screening: 30.7% and 30.4% • Peak days 24 and 45 arrive; attack rate of without and with screening: 30.8% and 30.5% • Highest number of arriving Peak day 45–1600 arrive; attack rate of without and with screening: 30.9% and 30.6%	• Entry screening lower the attack rate by less than 1% • Possible variation by airline patterns, screening effectiveness and test accuracy of RT-PCR.	Very low
Cowling BJ, 2010 (*244*)	•R0 = influenza H1N1 N/A	• Bootstrapping • 35 countries had reported to WHO by 6 July 2009 • 100 confirmed cases	• Entry screening - Temperature check prior to disembarkation - Health declaration forms - Observation of symptoms by staffs - Body temperature scan by thermal scanners	N/A	• No screening • a) Medical check before disembarkation • b) Health declaration forms • c) Symptom screening • d) Thermal scanning • e) b) OR c) OR d) • f) b) AND c) AND d)	• Median interval with inter quartile range between first imported case and first local case: 22 days (0, 22days) • a) 21 days (14, 28) • b) 22 days (13, 34) • c) 33 days (7, 41) • d) 22 days (7, 33) • e) 22 days (7, 35) • f) 23 days (9, 35)	• Entry screening did not delay significantly in local transmission • Mild illness or self-limiting nature may affect the result • Did not consider the size of local epidemics.	Very low
Caley P, 2007 (*243*)	• New pandemic influenza •R0 = 1.5, 2.5, and 3.5	• Simulation study • 100% sensitivity for detecting symptomatic infection, • 12 hours of travel	• Exit screening • Entry screening – Screening surface body temperature using infrared thermal scanners	N/A	• Traveller who visited influenza affected countries with 2 symptoms or more of 4 symptoms (1. Nasal discharge or nasal obstruction; 2. Sore throat; 3. Cough; 4. Fever or feeling feverish and chills) or travellers with body temperature > 38°c	• Rate of evading screening: 0.26 (R0 = 1.5), 0.45(R0 = 2.5), 0.59 (R0 = 3.5) • Median delay from 57 to 60 days by screening (R0 = 1.5, 400 travellers / day); natural median delay 57 days * Time delay: the start of an influenza pandemic and its subsequent initiation in other countries	• Delay effect by implementing screening is small compare with natural delay • In-flight transmission not fully considered.	Very low

N/A: not applicable; PCR: polymerase chain reaction; R0: basic reproductive number; RT: reverse transcription; USA: United States of America; WHO: World Health Organization.

Table 29. Summary of epidemiological studies included in the review

STUDY	INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	NO. OF TRAVELLERS HAD MEDICAL ASSESSMENT	CASE DEFINITION FOR SCREENING AND NO. OF TRAVELLERS MET	LABORATORY TEST FOR THE CASE AND NO. OF SPECIMENS ANALYSED	OUTCOME	COMMENTS AND LIMITATIONS	QUALITY OF EVIDENCE
Nishiura H, 2011 (*248*)	• Influenza including A(H1N1)pdm09 and other • R_0 = N/A	• Observational study • A) 471 733 travellers including flight passengers and crew members from 28 April 2009 to 18 June 2009 • B) 9 140 435 flight passengers from 1 September 2009 to 31 January 2010	• Entry screening	• a) 805 • b) 1049	• a) (1) contract in Canada, Mexico or USA, or (2) fever ≥ 38°C or 2≥ acute upper respiratory symptoms • b) (a) self-reported symptoms, (2) relatives or friends of (1) or identified by an infrared thermal scanner	• a) RT-PCR from 805 respiratory swab	• a) sensitivity of entry screening: 22% (18/805) • b) sensitivity and specificity of infrared thermal scanners in detecting hyperthermia: 50.8–70.4% and 63.6–81.7%. PPV: 37.3–68.0%	• Fever screening as a sole measure of entry screening is insufficient • Used non-randomized dataset • Confounding factors including age and outdoor temperature should be considered for the performance of infrared thermal scanners	Very low
Priest PC, 2011 (*249*)	Seasonal influenza	• Observational study • Christchurch airport, New Zealand. • 8020 travellers including flight passengers and crew members from 2008	• Entry screening - In-flight questionnaire (symptoms)	• 5274 questionnaires returned • 823 were symptomatic • 1281 were measured temperature using tympanic and ITIS.	• Traveller who reported 1 or more of: cough, sore throat, sneezing, fever or chill, runny or blocked nose, muscle aches or pains, feeling generally unwell, chest discomfort or breathing difficulties.	• MT-PCR	• Sensitivity and specificity of ITIS (84–86% and 42–72%)	• Fever screening using ITIS is insufficient to detect influenza infection • Majority of travellers in this population was afebrile. • Some of infected travellers had anti-pyretic before arrival	Very low

ITIS: infrared thermal image scanner; MT: multiplexed tandem; N/A: not applicable; PCR: polymerase chain reaction; PPV: positive predictive value; R0: basic reproductive number; RT: reverse transcription; USA: United States of America.

Table 32. Summary of studies of PCR assay included in the review

STUDY	INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	NO. OF TRAVELLERS HAD MEDICAL ASSESSMENT	CASE DEFINITION FOR SCREENING AND NO. OF TRAVELLERS MET	LABORATORY TEST FOR THE CASE AND NO. OF SPECIMENS ANALYSED	OUTCOME	COMMENTS AND LIMITATIONS	QUALITY OF EVIDENCE
Chen J, 2018 (*250*)	• Seasonal influenza • R_0 = N/A	• Observational study • Xiamen international airport China • 1 540 076 incoming travellers between May 2015 and May 2016	• Entry screening	• 1224	• ILI (fever≥ 37.5°C, either cough, rhinorrhea, sore throat and/or gastrointestinal discomfort)	• Flu Dot-ELISA • Viral culture	• Sensitivity of Flu Dot-ELISA: 96.6% (95% CI: 92.7–98.7)	• suitable to use rapid influenza test (Flu Dot-ELSIA) • Missed detection of asymptomatic travellers • Sensitivity of viral culture is less than 100%	Very low

ILI: influenza-like illness; PCR: polymerase chain reaction; R0: basic reproductive number.

4.3. Internal travel restrictions

Terminology

Because airports and land transportation are associated with long-distance spread of influenza (*253*), travel restrictions are considered as a measure to reduce regional and international spread (*254*). Although a previous quantitative expert survey study suggests that this travel restriction is likely to be ineffective due to its limited evidence (1), internal travel restriction to prevent domestic travel of persons to influenza is still considered as an NPI.

Methods

The most recent systematic review of travel restriction was published in 2014 by Mateus et al. (*255*). They identified eight studies, which found that internal travel restriction has limited effectiveness and remained unclear. This review included few simulation studies and several reviews of simulation studies, and was intended to measure the overall travel restriction including internal and international restriction. Instead of using this previous review, we conducted a new search in the databases PubMed, Medline, EMBASE and Cochrane Library, until September 2018. Inclusion criteria were primary research evaluating internal travel restriction for influenza pandemic in the community setting. Studies had to demonstrate any effectiveness following internal travel restriction to the public. We excluded studies conducting at the health care settings, animal-related studies, systematic reviews and/or meta-analysis without updated evidence, not measuring effectiveness of travel advice to the community, and article type of letter, commentary or news. Two reviewers (SR and SG) contributed to the title, abstract and full-text screening. The quality of evidence was measured using the GRADE approach. The rating was made for the overall effectiveness of internal travel restrictions by two independent reviewers. The flow chart of study selection is shown in Fig. 26.

Results

At total of 67 records were identified and included in the title and abstract screening, and 56 were excluded; 11 full-text articles were evaluated for eligibility and six of these were excluded; thus, five full-length articles were included in this systematic review. The summary is shown in Table 33.

A time series analysis study conducted in the USA showed that frequency of domestic airline travel is temporally associated with the rate of influenza spread and following September 11 2001, had markedly delayed the epidemic peak 13 days later than the average for other years (*256*). A simulation study predicted that implementation of strict travel restriction (95% travel restriction and enforced for 4 weeks) could reduce the ILI peak by 12% and moderate restriction (50% travel restriction and enforced for 2–4 weeks) could delay the pandemic peak between 1 and 1.5 weeks (127). Another simulation study predicted that more than 80% of internal travel restriction is beneficial (R0 = 1.5; 80% and 99% restriction delayed median days of 22–32 and 52, respectively, until 20 infectious persons arrivals in the designated city) (254). One simulation study estimated that strict internal travel restrictions (90%) could have some impact in delaying the epidemic peak by 2 weeks in the United Kingdom and by less than 1 week in the USA; however, 75% travel restriction would be ineffective (*87*).

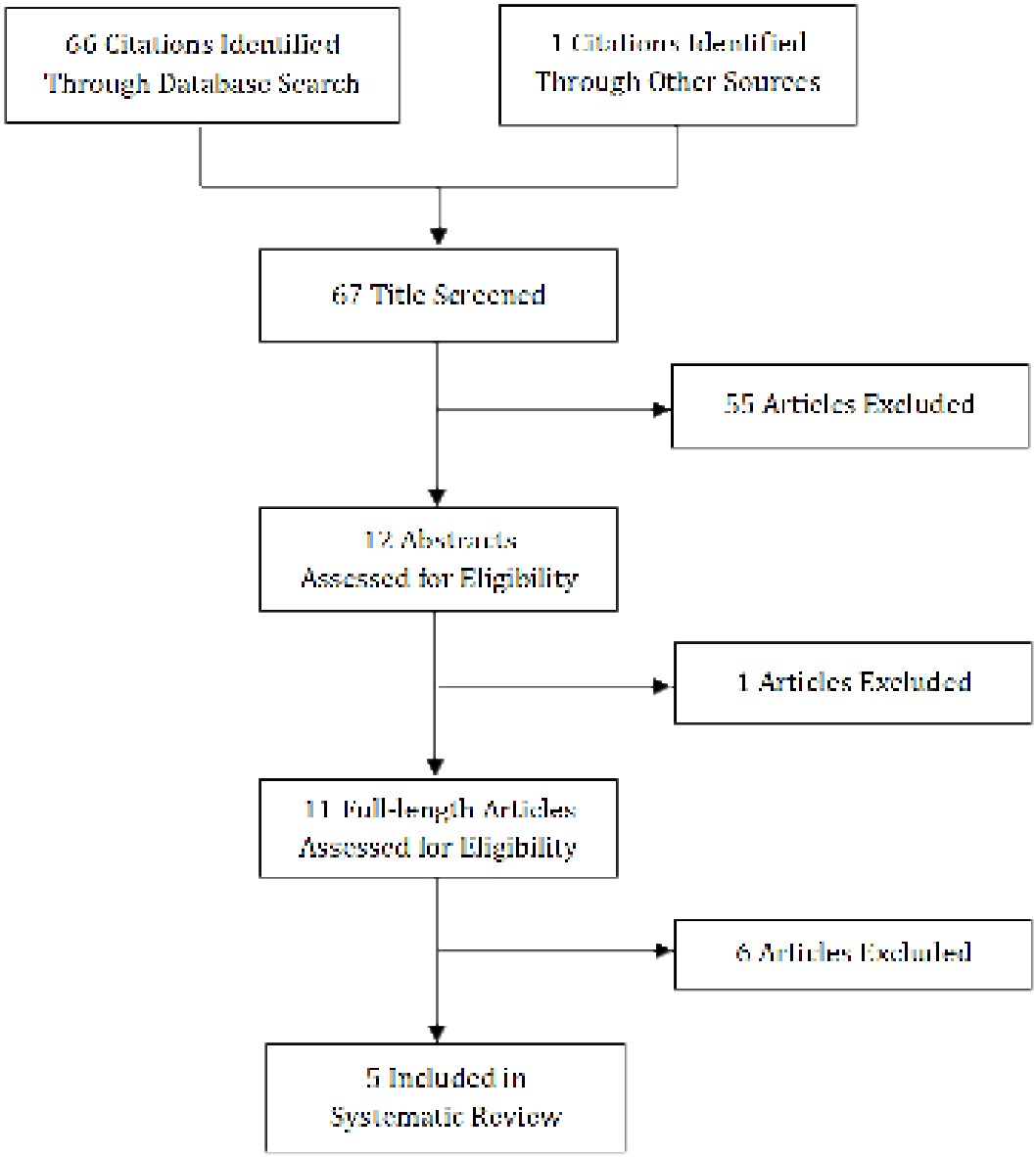

Fig. 26. The flow chart of internal travel restriction

Ethical considerations

Travel restriction should be voluntarily applied as much as possible, and compulsory intervention should be involved as a last resort (*239*). Furthermore, governments should pay close attention to adverse economic consequences, particularly on vulnerable populations including workers who have frequent travel and individuals who need to have immediate medical treatment (*239*).

Knowledge gaps

Although most of the literature on this topic results from simulation studies and natural experiments, it is unlikely that large trials will ever be done. Improved understanding of transmission dynamics of influenza would be advantageous; for example, on how environmental or other factors can affect influenza transmission and seasonality (*256*).

Table 33. Summary of studies included in the review

STUDY	STUDY DESIGN INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	OUTCOME	COMMENTS AND IMITATIONS	EVIDENCE QUALITY RATING
Brownstein JS, 2006 (*256*)	• Seasonal influenza • R_0 = N/A	• Time series analysis • USA • Weekly mortality from pneumonia and influenza for 9 influenza seasons (from 1996–1997 to 2004–2005)	• N/A	• Following September 11 2001, had markedly delayed peak 13 day later than average	• Domestic air travel affects the influenza spread in USA • Study used the data from voluntarily reporting system • Study used influenza mortality time series data which may not correspond to influenza activity	Very low
Bolton KJ, 2012 (*127*)	• Seasonal influenza • R_0 = around 2	• Stochastic, compartmental patch model of SEIR • Mongolia	• Travel restriction - 50% reduction in mean travel volume in early epidemic	• Delayed the pandemic peak by about 1.5 weeks if maintained for 4 weeks of restriction and by about 1 week if maintained for 2 weeks of restriction • Reduced the attack rates by less than 0.1% when travel volume was reduced by 95%	• Benefit of travel restriction may be limited • Not considered the transmission at the level of household	Very low
Wood JG, 2007 (*254*)	• Seasonal influenza • R_0 = 1.5–3.5	• Stochastic SIR model • Australia • Average daily volumes of domestic air travel between Sydney, Melbourne and Darwin	• 80%, 90% and 99% of travel restriction • Median time between the day when the no. infected person first reached 20	• Scenario (Sydney to Melbourne) Beginning of epidemic was delayed in 22–32 days (80% restriction), and 52 days (99% restriction)	• Strict travel restriction required to delay the time • Seasonal variation and further importation of influenza was not considered	Very low
Ferguson NM, 2006 (87)	• Seasonal influenza • R_0 = 1.4–2.0	• Stochastic mathematical individual-based model • United Kingdom and USA	• Reactive movement restrictions in a 20 km exclusion zone around every case – 75 and 90% restriction • Peak time delay	• Delaying the peak of the epidemic by less than 1 week in USA (without int'l travel restriction) – 90% restriction have some effect on the delaying the peak, but 75% restriction have almost none effect	• Internal travel restriction must be highly strict to have impact • Not considered the effect of personal protective measures on transmission	Very low
Germann TC, 2006 (*257*)	• Seasonal influenza H5N1 • R_0 = 1.6, 1.9, 2.1, and 2.4	• Stochastic agent-based discrete-time simulation model • USA	• 90% of travel restriction	• Epidemic peak delayed few days • 0.2% of increase of cumulative incidence (R_0 = 1.6) • 0.5% of increase of cumulative incidence (R_0 = 1.9)	• The combination of intervention such as social distancing and vaccination may increase the effectiveness of travel restriction	Very low

N/A: not applicable; R0: basic reproductive number; SEIR: susceptible–exposed–infectious–recovered; SIR: susceptible–infectious–recovered; United Kingdom: United Kingdom of Great Britain and Northern Ireland; USA: United States of America.

4.4. Border closures

Terminology
International travel can cause infectious disease cross-border transmission; thus, border closure, one of the measures that can be rapidly implemented, may reduce the epidemic spread of influenza. The transportation of international travel includes ship, bus, train and aeroplane.

Methods
The databases (PubMed, Medline, EMBASE and Cochrane Library) were searched until September 2018. Inclusion criteria were primary research evaluating border closure for influenza pandemics in the community setting. Studies had to demonstrate any effectiveness following border closure in the community. We excluded studies conducted in health care settings, animal-related studies, systematic reviews and/or meta-analysis without updated evidence, not measuring effectiveness of travel advice to the community, and article type of letter, commentary or news. Two reviewers (SR and SG) contributed to the title, abstract and full-text screening. The quality of evidence was measured using the GRADE approach. The rating is made for the overall effectiveness of border closure by two independent reviewers.

Results
A total of 327 records were identified and included in the title and abstract screening, and 314 were excluded; 13 full texts were assessed for eligibility and 11 full-length articles were identified for inclusion in the systematic review. The flow chart of study selection is shown in Fig. 27.
The description of the studies shown in Table 34.

An epidemiological study demonstrated that international airline travel could significantly reduce the mortality impact of a pandemic (*256*). Another simulation study estimated that a 99% restriction of border travel between Hong Kong SAR and mainland China may delay the epidemic peak compare with non-travel restriction (sole air restriction, 2 week–delay; both air and land, 3.5 week–delay; all air, land and sea, 12 weeks) (*258*). However, international travel restrictions of other modes of transportation such as land and sea would have less impact (2–3 day delay of the epidemic peak) (*258*). Implementing border crossing travel restrictions within three months of identification of first global case could reduce the seven–month cumulative attack rate by around 2% (*258*). However, implementing travel restrictions after the 5 months of arrival of the first global case would not be expected to be effective (*258*).

Another simulation study reported that international air-travel restriction could delay the peak of epidemic by about 1–3 weeks depending on the transmission rate (1.4, 1.7, or 2) and the level of restriction (90% or 99%), although the attack rate was not significantly affected (*220*). Furthermore, global-scale simulation study reported that travel restrictions could delay the epidemics by about 2 to 3 weeks (*259*) and significantly delay global spread by 5–133 days (*260*).

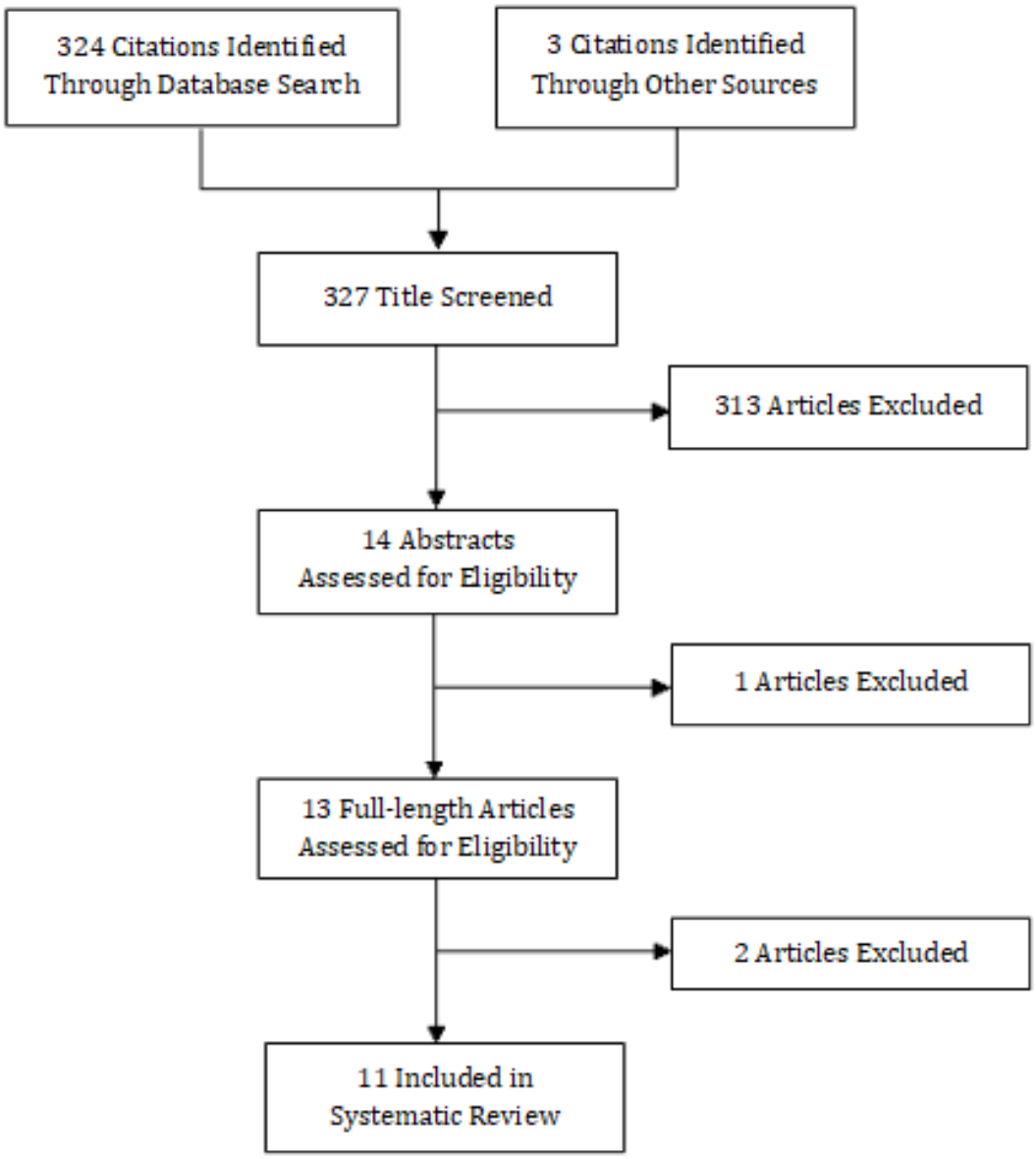

Fig. 27. The flow chart of border closures

A simulation study predicted that 99.9% border control could delay the epidemic peak by 6 weeks (90% and 99% of border control would delay 1.5 and 3 weeks, respectively) (87). Another study estimated that international travel restrictions would slow the importation of cases, and an 80–99% travel restriction would delay of the exportation of cases range 6.6–133 days; however, it did not reduce the magnitude of spread (*261*). Another simulation study predicted that children-selective restriction could be helpful to delay epidemic for a few weeks (*262*).

A simulation study based on travel data from Pacific Island Countries and Territories (PICTs), only six PICTs would be likely to prevent importation of influenza pandemic by 99% of travel restriction through border control. In PICTs, critical necessity such as food and medical supplies are largely dependent on importation, so that strict border closure was carefully considered in PICTs (*263*). Although 99% of travel restriction of all mode of transportation has delayed the epidemic peak, the magnitude of the epidemic was reduced less than 10% in this study. Another observational study in South Pacific Island jurisdictions, during the influenza pandemic which began in 1918,

reported that strict maritime quarantine reduced attributable mortality rate from pandemic influenza between 0 and 840 (crude mortality rate per 1000 population) (*99*).

Border closure such as travel restriction is a measure that can be rapidly implemented and it may decelerate the epidemic growth; however, this may not be effective at limiting the magnitude of influenza epidemics (*258*).

Ethical considerations

The human rights of mobility should be considered (*239*). Therefore, as with internal travel restriction, border controls should be voluntarily applied as much as possible, and compulsory intervention should be involved as a last resort (*239*). Furthermore, the stigmatization and discrimination of individuals from influenza affected areas, and economic consequences by implementing border closures should also be considered (*239*, *264*).

Knowledge gaps

Although most of the literature on this topic results from simulation studies and natural experiments, it is unlikely that large trials will ever be done. Improved understanding of transmission dynamics of influenza would be advantageous; for example, on how environmental or other factors can affect influenza transmission and seasonality (*256*).

Table 33. Summary of studies included in the review

STUDY	STUDY DESIGN INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	OUTCOME	COMMENTS AND IMITATIONS	EVIDENCE QUALITY RATING
Brownstein JS, 2006 (*256*)	• Seasonal influenza • R_0 = N/A	• Time series analysis • USA • Weekly mortality from pneumonia and influenza for 9 influenza seasons (from 1996–1997 to 2004–2005)	• N/A	• September 11 2001 affected international flight volume decreased by 27%, and the peak of influenza mortality was delayed by 2 weeks	• Decrease in travel volume was associated with a delayed and prolonged influenza season. • Study used the data from voluntarily reporting system • Study used influenza mortality time series data which may not correspond to influenza activity	Very Low
Chong KC, 2012 (*258*)	• Influenza H1N1 pandemic • R_0 = 1.4	• Stochastic SEIR model • Hong Kong SAR and mainland China	• Travel restriction – 90%, and 99% travel restriction on different mode transportation (air, land, sea) • Measure the first passage time (first global case onset ~ first local case report)	• 99% of international air-travel restriction delayed the interval between the first imported case and one hundred infected case passed the border by a week and the epidemic peak delayed by two weeks • 99% of restriction of both air and land travel delayed the interval (passage time) by an additional one to two weeks and the epidemic peak delayed about 3.5 weeks • 99% restriction of all mode of transportation delayed the interval by additional 2 months, and delayed the epidemic peak time for about 12 weeks • Travel restriction 3 month after the arrival of first global case reduce the 7-months cumulative attack rate around 2%	• Travel restriction may not be effective • Not considered the infection risk for the out bound susceptible travellers • No adjustment of multi-step journey	Very Low
Ciofi degli Atti ML, 2008 (*220*)	• Pandemic influenza • R_0 = 1.4, 1.7, 2.0	• Global deterministic SEIR model • Italy	• Incoming international flight restriction (90% or 99%)	• Int'l air-travel restriction delayed the interval between first global case report and the importation of the first cases by 7–37 days. Furthermore, the pandemic peak delayed by 6–39 days. The attack rate was reduced less than 0.1%	• Air-travel restrictions can delay 1 to 3 weeks in delaying the epidemic.	Very Low

Table 34. Summary table of studies included in the review

STUDY	STUDY DESIGN INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	OUTCOME	COMMENTS AND IMITATIONS	EVIDENCE QUALITY RATING
Epstein JM, 2007 (*259*)	• Pandemic influenza • R_0 = 1.4, 1.7, 2.0	• Global influenza transmission model • Global (Hong Kong SAR, London and Sydney)	• Travel restriction (90%, 95%, and 99%) • The interval between the outbreaks occurred in Hong Kong SAR or London and the case-passage time to USA	• First passage time is delayed from 18 days to 31 days (outbreak originated from Hong Kong SAR), and from 7 days to 27 days (from London) with R_0 = 1.7 The delays are larger for smaller R_0	• Air-travel restrictions can delay 2 to 3 weeks in delaying the epidemic. • Model is based on the largest metropolitan areas	Very Low
Cooper BS, 2006 (*260*)	• Pandemic influenza • R_0 = 1.8–5	• Metapopulation model • Global (Hong Kong SAR, London, Sydney)	• Air-travel restriction from affected cities (50, 90, 99 and 99.9%) • Susceptibility (10%, 60%, and 100%)	• Median epidemic peak delay can be ranged between 7–102 days	• Banning flight from affected region would be effective delaying global spread	Very Low
Ferguson NM, 2006 (*87*)	• Seasonal influenza • R_0 = 1.4–2.0	• Stochastic spatially structured mathematical model • USA	• 90, 99% or 99.9% border control in USA	• Imported infections might delay the epidemic peak of USA by 1.5 weeks (90% border control), 3 weeks (99%), and 6 weeks (99.9%)	• Combing travel restriction measure including internal and international have more impact delaying epidemic peak	Very Low
Hollingsworth TD, 2006 (*261*)	• Pandemic influenza • R_0 = N/A • Pandemic influenza	• Simple mathematical SEIR model of an epidemic in a source country with cases exported to other countries	• 80, 99, or 99% of travel restriction • Peak time delay	• The mean time delay exporting the infected case is 5.3 days (80% of restriction), 11.7 days (90%), and 131.7 days (99%)	• Restriction on travel may have limited benefit of global spread of pandemic influenza	Very Low

Table 34. Summary table of studies included in the review

STUDY	STUDY DESIGN INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	OUTCOME	COMMENTS AND IMITATIONS	EVIDENCE QUALITY RATING
Eichner M, 2009 (*263*)	• R_0 = 1.5, 2.25, and 3.0	• Probalistic model • PICTs	• 79% or 99% of travel restriction • Assess the probability that an island either occur epidemics or escape the pandemic	• Among 17 PICTs, with 99% travel restriction, six countries (with R_0 = 1.5) and four to five countries (with $R_0 \geq$ 2.25) would be likely escaped the pandemic influenza with more than 50% probability. However, with 79% of travel restriction, only one country (with R_0 = 1.5) and no country (with R0≥ 2.25) was likely escaped the pandemic	• Border control can benefit only a few PICTs for avoiding pandemic influenza • Some of data used in this analysis was missing and suboptimal	Very Low
McLeod MA, 2008 (*99*)	• Pandemic influenza • R_0 = N/A	• Epidemiological study • 11 South Pacific Island jurisdictions	• 5–7 days' maritime quarantine • Death rate	• Arrival of pandemic and death rates attributed to influenza per 1000 population was significantly delayed and reduced compare with the other Pacific Island Jurisdiction - American Samoa (1920, no death reported) - Australia (early January 1919, death rate = 2.4) - Tasmania (August 1919, death rate = 0.81) - New Caledonia (1921, death rate less than 11)	• Strict border control in the island can be advantage to delay the pandemic and reduce the mortality • Confounding factors including pre-existing immunity may affect this result	Very Low
Lam ET, 2011 (*262*)	• Pandemic influenza • R_0 = 1.2, 1.6, 2.0	• Simple stochastic model • Hong Kong SAR	• 100% border crossing travel restriction among children	• Children-selective travel restriction delayed the epidemic for a 19–35 days (R_0 = 1.2), and less than 15 days (R_0 = 1.6 and 2.0)	• The intervention was assumed to implemented after pandemic declared	Very low
Bajardi P, 2011 (*265*)	• Pandemic influenza • R_0 = 1.7 with generation interval 3.6 days	• SEIR-like Global Epidemic and Mobility model	• 40% and 90% of int'l travel restriction to and from Mexico	• Mean delay of the arrival of infection from other countries was less than 3 days (40% of restriction), and about 2 weeks (90% of restriction)	• The intervention was assumed to implemented at the early stage of the outbreak (by 3 months)	Very low

N/A: not applicable; PICTs: Pacific Island Countries and Territories; R0: basic reproductive number; SAR: Special Administrative Region; SEIR: susceptible–exposed–infectious–recovered; USA: United States of America.

SUMMARY OF EVIDENCE

Personal protective measures

Personal hygiene measures such as hand hygiene, respiratory etiquette and face masks are widely used as non-pharmaceutical intervention measures to reduce the risk of acquiring or spreading respiratory infections, and for mitigating pandemic influenza. However, our review identified a lack of compelling evidence for the effectiveness of hand hygiene, respiratory etiquette and face masks against influenza transmission in the community. There are still gaps in the evidence base which further research would help to fill.

Environmental measures

Environmental measures including surface and object cleaning are generally conducted to limit the risk of acquiring or spreading respiratory infections within an area. The evidence for the effect of surface and object cleaning on influenza prevention is limited, and no significant reductions in influenza infections were observed by surface and object cleaning intervention; studies provided very low to low quality evidence. Other environmental measures including UV light as air disinfection, ventilation as increasing air change and humidity as amount of water vapour in the air were limited. Therefore, additional research is required to confirm whether these measures could be of value in mitigating pandemic influenza.

Social distancing measures

Social distancing measures including contact tracing, isolation and quarantine of influenza affected individuals, closures of school and workplace, and avoiding crowding reduce the risk of influenza transmission in community settings. Evidence for the overall effectiveness of contact tracing is very limited. Only one study discussed the benefit of adding contact tracing to isolation and quarantine. The addition of contact tracing is estimated to provide at most modest benefit; however, it will increase considerably the proportion of individuals in quarantine. For isolation, currently available evidence showed that even as a single intervention isolation is effective. Compliance of individuals and timeliness of intervention do affect the effectiveness of isolation in mitigation of influenza. Quality of evidence based on GRADE assessment is, however, very low. More robust evidence drawn from epidemiological studies is needed. The effectiveness of quarantine in mitigation of influenza varies. Household quarantine is suggested to be effective in reducing the impact and transmissibility, and in delaying the epidemic peak; the combination of quarantine with other interventions such as case isolation and SC will further strengthen the effectiveness. There is also an increased risk of infection in individuals quarantined concurrently with an isolated individual. Hence, ethical concerns arise for mandated quarantine. Onboard quarantine, on the other hand, has a minimal impact, based on a very low quality of evidence. More robust evidence drawn from epidemiological studies is needed.

SC can reduce the spread of the influenza; however, the threshold for closing time and duration are uncertain. The combination of SC with other interventions is more effective in reducing the spread of infection. Unlike the evidence of effectiveness of SC, evidence on WCs is limited and all six studies for this effectiveness measure were simulation models (i.e. the quality of evidence is very low). Five of these studies suggested that reductions in attack rate, duration of infection or peak numbers occurred because of the WC. The combination with other interventions may enhance the effectiveness of the individual measures. Workplace measures are effective and feasible during a pandemic. Avoiding crowding, which includes separating people into small groups or cancellation of public gatherings, is effective as an intervention in preventing transmission of influenza as well. However, the quality of evidence is very low based on the GRADE approach.

Travel-related measures

Travel-related measures including travel advice, traveller screening, travel restriction and border closures have been used in previous pandemics to limit international spread. The evidence of travel advice against influenza transmission is still uncertain. The effectiveness of screening incoming and/or outbound travellers against influenza spread is also controversial. However, travel restriction and border closure may slow the spread of influenza at the community level, although all the evidence available was of very low quality.

Table 35. Quality of evidence and summary of results for each NPI

MEASURES	QUALITY OF EVIDENCE		RESULTS
1. Hand hygiene	Moderate (lack of effectiveness in reducing influenza transmission)		Eleven RCTs were included in this review. While hand hygiene was not effective against laboratory-confirmed influenza in meta-analysis in community settings and university halls, it was effective in one of two trials conducted in schools.
2. Respiratory etiquette	**None**		No scientific studies were identified for inclusion in this review.
3. Face masks	Moderate (lack of effectiveness in reducing influenza transmission)		Ten RCTs were included in meta-analysis, and there was no evidence that face masks are effective in reducing transmission of laboratory-confirmed influenza.
4. Surface and object cleaning	Low (lack of effectiveness in reducing influenza transmission)		Two RCTs and one cross-sectional study were included in the systematic review. There was evidence that surface and object cleaning could reduce detections of virus in the environment, but there was no evidence of effectiveness against laboratory-confirmed influenza virus infection.
5. Other environmental measures	**UV light**	**None**	No scientific studies were identified for inclusion in this review.
	Ventilation	Very low (effective)	In simulation studies, increasing the ventilation rate reduced influenza transmission.
	Humidity	**None**	No scientific studies were identified for inclusion in this review.
6. Contact tracing	Very low (unknown)		Evidence for overall effectiveness of contact tracing was limited. All included studies were simulation models. Only one study suggested the benefit of adding contact tracing on top of isolation and quarantine. Such addition was estimated to provide at most modest benefit, at the same time this would considerably increase the number of quarantined individuals.

MEASURES	QUALITY OF EVIDENCE	RESULTS
7. Isolation of sick individuals	Very low (effective)	Simulation studies suggested that isolation of sick individuals can reduce transmission in epidemics and pandemics. The overall effectiveness of the measure is moderate and combination with other interventions may improve the effectiveness.
8. Quarantine of exposed individuals	Very low (variable effectiveness)	We identified 6 epidemiological studies and 10 simulation studies eligible for inclusion in our review. Quarantine is generally effective in reducing burden of disease, transmissibility and delaying epidemic peak.
9. SCs	Very low (variable effectiveness)	The effect of reactive SC in reducing influenza transmission varied but was generally limited. Proactive closures and planned school holidays had a moderate impact on transmission. While SCs alone might have an impact, combination with other interventions further improved the effectiveness.
10. WCs	Very low (effective)	The strength of evidence on WC is very low since the identified studies are all simulation studies. Large-scale WCs could delay the epidemic peak for more than one week, and small-scale closures may have a modest impact on attack rate or peak number.
11. Workplace measures	Very low (effective)	The included studies indicated that workplace measures could reduce overall and the peak number of influenza cases, as well as delaying the peak occurrence. While the overall effectiveness and feasibility of workplace measures is modest, combination with other interventions can further improve its effectiveness.
12. Avoiding crowding	Very low (unknown)	Avoiding crowding including separating people into small groups or cancelling public gatherings is an effective intervention to prevent the spread of influenza. However, the effects of measures to avoid crowding in reducing transmission is uncertain.

Table 35. Quality of evidence and summary of results for each NPI

MEASURES	QUALITY OF EVIDENCE	RESULTS
13. Travel advice	**None**	No scientific studies were identified for inclusion in this review.
14. Entry and exit screening	Very low (lack of effectiveness in reducing influenza transmission)	Ten studies were included in this review. Considering the asymptomatic period of infected patients and the sensitivity of screening devices, the effectiveness of screening travellers is likely to be very limited.
15. Internal travel restrictions	Very low (effective)	The effectiveness of internal travel restriction is dependent on the level of restriction, and only very strict restrictions would be expected to have an impact on influenza transmission.
16. Border closures	Very low (variable effectiveness)	Eleven studies were included in this review. Generally, only strict border closures are expected to be effective within small island nations. For island nations, border closure should be carefully considered because it may affect the supply of essential items to the population.

NPI: non-pharmaceutical intervention; RCT: randomized controlled trial; SC: school closure; UV: ultraviolet; WC: workplace closure.

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The Practice of Wearing Surgical Masks during the COVID-19 Pandemic

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To the Editor: We read with interest the meta-analysis conducted by Xiao et al. (*1*) that found no significant reduction in influenza transmission with the use of surgical masks in the community, based on 10 randomized controlled trials. Nevertheless, mechanistic studies found that surgical masks could prevent transmission of human coronavirus and influenza virus infections if worn by infected persons (*2*). The authors pointed out the limitations of their study: small sample size and suboptimal adherence in the mask-wearer group (*1*). Recommendations on masks in the community vary across countries during the coronavirus disease (COVID-19) pandemic (*3*); studies have reported mixed results (*2*,*4*,*5*).

Epidemiologic data may provide an alternative insight. As of April 3, 2020, Taiwan recorded 348 COVID-19 cases (1.46/100,000 population), of which 48 (13.8%) were local cases. Singapore recorded 1,114 cases (19.07/100,000 population), of which 572 (51.3%) were local cases. Taiwan and Singapore both employed stringent measures. Taiwan recommended the use of masks early in the pandemic. In contrast, Singapore did not recommend the use of masks until April 3 and initiated its Stay Home policy on April 7.

Before the 2003 severe acute respiratory syndrome coronavirus epidemic in Taiwan, only persons with open tuberculosis wore masks in public. During the epidemic, wearing a mask in public was stigmatized. Thereafter, we educated the public to wear masks as a practice of respiratory hygiene. Although evidence is limited for their effectiveness in preventing transmission of severe acute respiratory syndrome coronavirus 2, either for source control or to reduce exposure, the wearing of masks by healthy persons may prevent potential asymptomatic or presymptomatic transmission (*3*). This marginal reduction in transmission may produce substantial results, particularly when it is implemented early. Taiwan had the foresight to create a large stockpile of medical and surgical masks; other countries or regions might now consider doing so as part of future pandemic plans (*3*).

About the Author

Mr. Chiang is a medical student at National Taiwan University. His primary research interests are epidemiology and prevention of communicable diseases.

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The role of community-wide wearing of face mask for control of coronavirus disease 2019 (COVID-19) epidemic due to SARS-CoV-2

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SUMMARY

Background: Face mask usage by the healthy population in the community to reduce risk of transmission of respiratory viruses remains controversial. We assessed the effect of community-wide mask usage to control coronavirus disease 2019 (COVID-19) in Hong Kong Special Administrative Region (HKSAR).

Methods: Patients presenting with respiratory symptoms at outpatient clinics or hospital wards were screened for COVID-19 per protocol. Epidemiological analysis was performed for confirmed cases, especially persons acquiring COVID-19 during mask-off and mask-on settings. The incidence of COVID-19 per million population in HKSAR with community-wide masking was compared to that of non-mask-wearing countries which are comparable with HKSAR in terms of population density, healthcare system, BCG vaccination and social distancing measures but not community-wide masking. Compliance of face mask usage in the HKSAR community was monitored.

Findings: Within first 100 days (31 December 2019 to 8 April 2020), 961 COVID-19 patients were diagnosed in HKSAR. The COVID-19 incidence in HKSAR (129.0 per million population) was significantly lower ($p<0.001$) than that of Spain (2983.2), Italy (2250.8), Germany (1241.5), France (1151.6), U.S. (1102.8), U.K. (831.5), Singapore (259.8), and South Korea (200.5). The compliance of face mask usage by HKSAR general public was 96.6% (range: 95.7% to 97.2%). We observed 11 COVID-19 clusters in recreational 'mask-off' settings compared to only 3 in workplace 'mask-on' settings ($p=0.036$ by Chi square test of goodness-of-fit).

Conclusion: Community-wide mask wearing may contribute to the control of COVID-19 by reducing the amount of emission of infected saliva and respiratory droplets from individuals with subclinical or mild COVID-19.

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Introduction

Coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is closely related to bat SARS related coronaviruses,[1] is the second pandemic of the 21st century following the influenza A H1N1 pandemic of 2009. With the rapidly galloping epidemic due to globalization and international travel, World Health Organization (WHO) declared COVID-19 to be a pandemic on 11 March 2020,[2] which is 72 days after the first official announcement of clusters of patients with community-acquired pneumonia in Wuhan, Hubei Province of China on 31 December 2019 (day 1).[3] As of 8 April 2020 (day 100), over 1.35 million people have been infected worldwide with nearly 80,000 deaths.[4] In response, proactive infection control measures have been implemented in hospital settings.[5,6] In addition, non-pharmaceutical public health interventions including border control or closure, quarantine and testing of all incoming travelers or returnees, massive reverse-transcription polymerase chain reaction (RT-PCR) testing for case detection, rapid contact tracing and quarantine, frequent hand hygiene, and later social distancing measures

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including school closure, home office, cancelation of all mass gatherings, later stay-at-home order, and cessation of all socioeconomic activities except essential services, were also adopted to various degrees and at different time points in different geographical areas to reduce the risk of community transmission. Many of these measures had been used for the control of community transmission of severe acute respiratory syndrome (SARS) in 2003 and pandemic influenza A H1N1 in 2009 in Hong Kong Special Administrative Region of China (HKSAR) and other parts of the world.[7,8] However, the efficacy of community-wide masking of the population during these past epidemics or the present COVID-19 pandemic has not been clearly investigated. Unlike 2003 SARS which was generally manifested with high fever and progressive pneumonia with a mortality of about 10%, COVID-19 can be associated with very mild symptoms and a mortality of less than 4%. Thus subclinical or asymptomatic SARS-CoV-2 shedders may play an important role in perpetuating the pandemic.[9,10] We hypothesized that community-wide masking in HKSAR may break the chain of transmission of SARS-CoV-2 by reducing the infectiousness of the subclinical virus shedders while also offering some protection to the susceptible population.

In HKSAR, community-wide masking was practiced by the general population at an early stage of the local COVID-19 epidemic. Here, we described the comparative epidemiology of COVID-19 during the first 100 days. We also analyzed the incidence of COVID-19 in geographical areas with or without community-wide masking for most individuals, and also the number of COVID-19 clusters of COVID-19 in relation to workplace (mask-on setting) or non-workplace recreational settings (mask-off setting) of HKSAR.

Methods

Community control measures against COVID-19 in HKSAR

HKSAR is a cosmopolitan city of 7.45 million people in Southern China. Occupying only 1104 square-kilometers, it is the third most densely populated area in the world with around 6700 people per square-kilometer. Soon after the official announcement of a cluster of patients with community-acquired pneumonia in Wuhan by the National Health Commission of the People's Republic of China, on 31 December 2019 (day 1), the center for Health Protection (CHP) of the Department of Health, the HKSAR government alerted members of the public to maintain good personal and environmental hygiene, with specific emphasis on hand hygiene, refraining from work or attending class at school, avoiding crowded places, seek medical advice promptly and wear a surgical mask if they develop respiratory symptoms.[3] Step-wise introduction of other community interventions later to control the spread of COVID-19 was described. As an objective parameter of community-wide preparedness, compliance of face mask usage by the general public monitored by staff working in Infection Control Unit, and Department of Microbiology, Queen Mary Hospital for three consecutive days from 6 April to 8 April 2020 (day 98 to day 100). Each staff member would count the number of persons not wearing a mask among the first 50 persons encountered in the street during their morning commute. The residential district of the staff was recorded.

Epidemiology of COVID-19 in HKSAR

A multi-pronged screening strategy to identify patients infected with SARS-CoV-2 was implemented.[5,6] The epidemiology of newly confirmed cases was announced in the daily press conference jointly held by CHP and Hospital Authority. Major clusters arising from mask-on (workplace) and mask-off (recreational) settings were analyzed to evaluate the efficacy of wearing face masks.

Comparing the epidemiology of COVID-19 in HKSAR and other parts of the world

The epidemiology of COVID-19 of HKSAR was compared to that of the representative countries in North America, Europe, and Asia using publicly accessible information from the website of WHO to understand the overall effect of our control measures used in HKSAR. Countries with well-established healthcare system, where face mask usage was not universally adopted in the community, and having over 100 confirmed cases at day 72 when WHO declared a pandemic were selected for comparison.

Laboratory diagnosis of SARS-CoV-2

Clinical specimens including nasopharyngeal aspirates, nasopharyngeal swabs, throat swab, saliva, sputum, endotracheal aspirates, or bronchoalveolar lavage were subjected to nucleic acid extraction by the eMAG extraction system (bioMérieux, Marcy-l'Étoile France) as we previously described.[5,6] The presence of SARS-CoV-2 RNA in specimens was first determined by the Light-Mix Modular SebeccoV E-gene commercial kit (TIB Molbiol, Berlin, Germany) at all public hospitals under the Hospital Authority and the Public Health Laboratory Service of the Department of Health, and further confirmed by in-house real-time RT-PCR assay targeting the SARS-CoV-2 RNA-dependent RNA polymerase/helicase gene as described.[11]

Statistical analysis

Incidence rates were compared using the exact Poisson test using R software. Proportions were compared using the chi-squared test. A p value of <0.05 was considered statistically significant.

Results

Community response to COVID-19 in HKSAR

Due to the prior experience of the SARS outbreak in 2003, the general public of HKSAR was on high alert after the official announcement of a cluster of pneumonia cases of unknown etiology in Wuhan on 31 December 2019 (day 1), because a total of 1755 infected persons with 299 (17.0%) deaths over 133 days (11 February 2003 to 23 June 2003) was recorded during this past SARS epidemic. When the causative agent of COVID-19 was identified on 9 January 2020 (day 10), and named as SARS-CoV-2 on 12 February 2020 (day 44), this emerging pathogen was perceived to be as detrimental as 2003 SARS-CoV by the HKSAR general public. Even though initially HKSAR government only advocated people with respiratory symptoms to wear a surgical mask according to the recommendations of WHO and Centers for Disease Control and Prevention (CDC) of the United States, the general public volunteered to wear face mask quite compliantly from the pre-pandemic to pandemic phase of COVID-19.

Sixty-seven staff members (9 from Infection Control Unit, and 58 from Department of Microbiology), residing in all 18 administrative districts in HKSAR, recorded the number of persons not wearing face mask among the first 50 people they encountered during their morning commute to Queen Mary Hospital (located in Southern district) between 7:00am to 9:00am over three consecutive days from 6 April to 8 April 2020 (day 98 to day 100). A total of 10,050 persons were observed. Only 337 (3.4%) persons did not wear face mask. The daily compliance of face mask usage was 97.2%, 97.1%, and 95.7% over three consecutive days in all 18 administrative districts in HKSAR.

Besides proactive infection control measures implemented by public hospitals under the governance of Hospital Authority,[5,6]

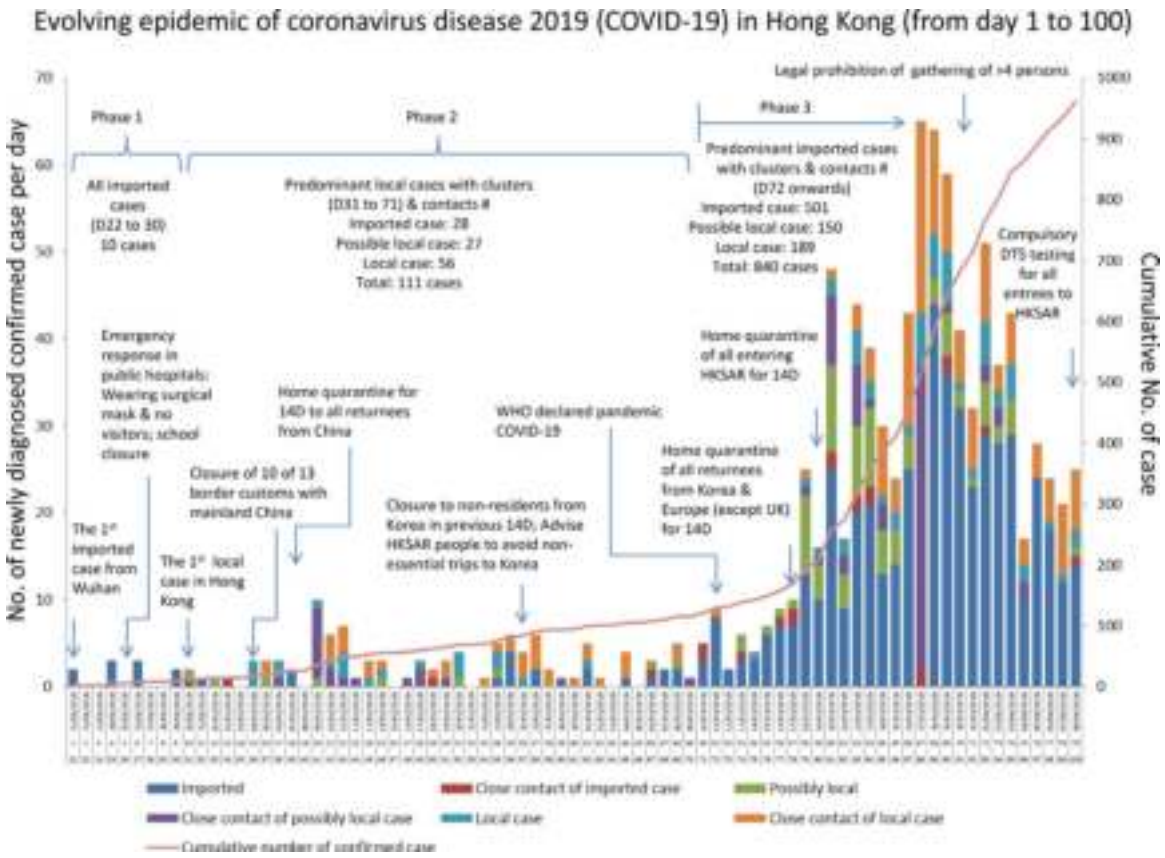

Fig. 1. Evolving epidemic of coronavirus disease 2019 (COVID-19) in Hong Kong (from day 1 to 100).
Note. #including their close contacts
COVID-19, coronavirus disease 2019; DTS, deep throat saliva; WHO, World Health Organization.

step-wise introduction of epidemiological measures by the HKSAR government were enforced. They included border controls to reduce imported SARS-CoV-2 cases from mainland China on 4 February 2020 (day 36). This was followed by imposing home quarantine order for 14 days to all entrees from mainland China on 8 February 2020 (day 40). Subsequently, the quarantine order was progressively imposed to all entrees into HKSAR on and after 19 March 2020 (day 80) (Fig. 1). All entrees were compulsorily tested for SARS-CoV-2 by collecting their posterior oropharyngeal saliva with effect from 8 April 2020 (day 100). As in other localities, isolation of confirmed case, contact tracing and quarantine, closure of affected or high risk premises, and social distancing measures such as home-office and school closure were instituted.

Epidemiology of COVID-19 in HKSAR

Up to day 100 of the epidemic, a total of 961 cases of COVID-19 were confirmed in HKSAR. Transmission of COVID-19 was divisible into four phases: phase 0 (from day 1 to 21) with no confirmed cases of COVID-19 in HKSAR; phase 1 (from day 22 to 30) with 10 imported cases; phase 2 (from day 31 to 71) with 111 cases (predominantly local cases) and; phase 3 (from day 72, WHO declared COVID-19 pandemic, onwards) with 840 cases (predominantly imported cases with local clusters of cases) (Fig. 1). Among the 961 confirmed cases, there were 11 clusters of 113 persons that were directly engaged in mask-off activities such as dining and drinking in restaurant or bar, singing at karaoke, and exercise in fitness clubs. There were only three clusters involving 11 persons engaged in mask-on settings at the workplace. Using the chi-square test of goodness-of-fit with Williams' continuity correction, there were significantly more COVID-19 clusters involving mask-off settings than might be expected assuming that the null hypothesis of equal number of clusters involving mask-on and mask-off settings was true ($p = 0.036$).

Comparing the epidemic progression of COVID-19 in HKSAR with other parts of the world

The incidence and cumulative number of COVID-19 cases in HKSAR and the representative countries or areas since the first laboratory-confirmed case of SARS-CoV-2 are illustrated in Fig. 2a& 2b. The incidence of COVID-19 in HKSAR was significantly less than that of the selected countries (with well-established healthcare system and having over 100 confirmed cases at day 72 when WHO declared a pandemic) in Asia, Europe, and North America, where face mask usage was not universally adopted in the community (Table 1). Singapore's land area and population density are comparable to HKSAR.[4] On day 100 (8 April 2020), the incidence of COVID-19 per million population in Singapore was significantly higher than that in HKSAR (259.8 per million population vs 129.0 per million population, $p < 0.001$) (Table 2). In South Korea, the number of molecular diagnostic tests per million population was comparable to HKSAR. The proportion of local cases in South Korea related to mask-off settings was significantly higher than that in HKSAR [5150/10,384 (49.6%) vs 113 / 961 (11.8%), $p < 0.001$] because of super-spreading events at a church which was also a mask-off setting (Table 2).

Discussion

Evidence for using face masks to prevent transmission of respiratory viruses in the community remains limited to a few stud-

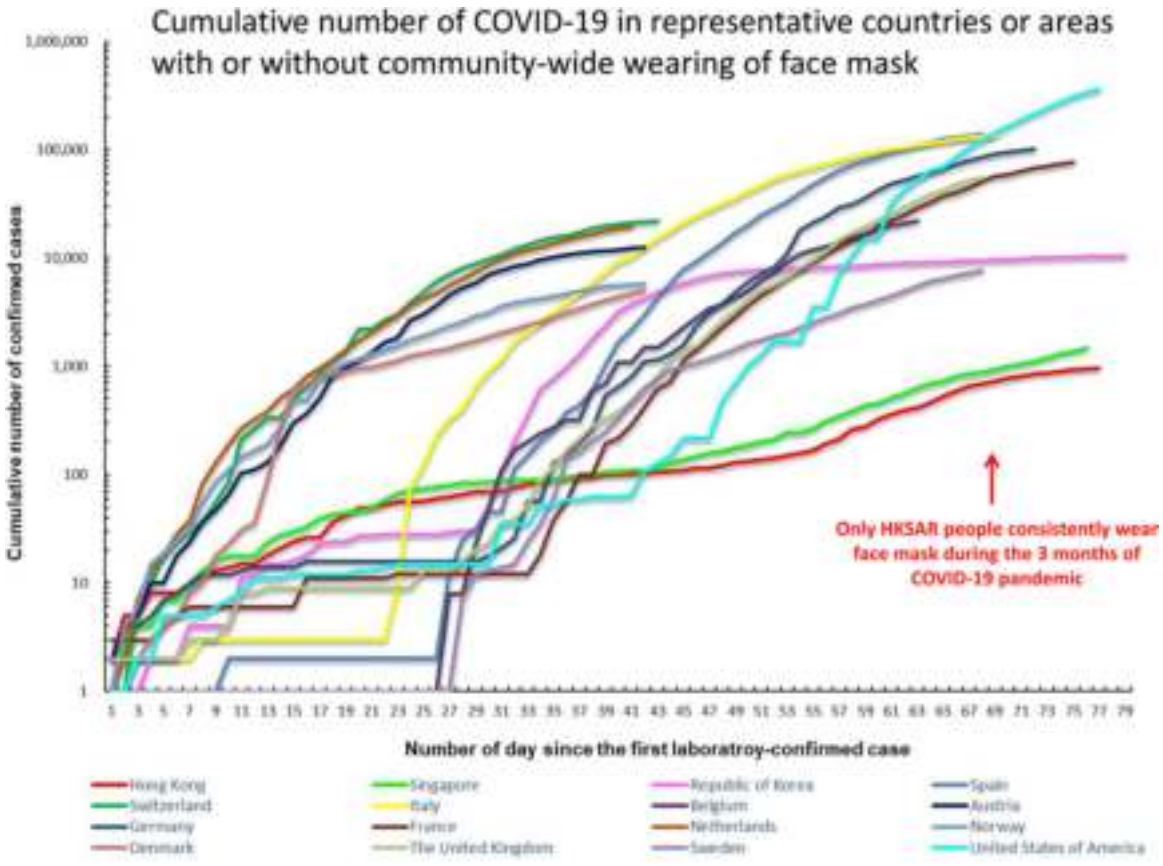

Fig. 2a. Cumulative number of COVID-19 in representative countries or areas with or without community-wide wearing of face mask
Note. The x-axis denotes the number of days since the first laboratory-confirmed case in the representative countries or areas.
The date of first laboratory-confirmed case in Hong Kong (21 January 2020), Singapore (24 January 2020), South Korea (21 January 2020), Spain (1 February 2020), Switzerland (26 February 2020), Italy (31 January 2020), Belgium (06 February 2020), Austria (27 February 2020), Germany (28 January 2020), France (25 January 2020), Netherlands (28 February 2020), Norway (27 February 2020), Denmark (27 February 2020), The United Kingdom (1 February 2020), Sweden (01 February 2020) and United States of America (23 January 2020).

ies conducted in the household setting.[12,13] Although there is no expert consensus on this issue, universal masking is voluntarily adopted by people in our HKSAR community soon after the first imported case of COVID-19 was reported. This public action was linked to the painful experience of the 2003 SARS outbreak (1755 cases with 299 deaths in 6.73 million population) when HKSAR people adopted universal masking in addition to other non-pharmaceutical interventions such as hand hygiene, social distancing and school closure.[7] These community hygienic measures during the SARS outbreak resulted in a significant reduction of positive specimens of all circulating respiratory viruses including influenza viruses in 2003 compared with preceding periods.[14] In a case-control study conducted in Beijing during 2003 SARS, consistent wearing of a face mask outdoors was associated with a 70% risk reduction, compared to those not wearing a face mask.[15]

HKSAR is the only area practicing universal masking despite the recommendation of WHO and CDC that mask should be reserved for those with symptoms and in healthcare settings. We therefore compared the number of COVID-19 clusters in mask-on settings at workplace with that of the mask-off settings such as dining and drinking in restaurant or bar, singing at karaoke, and exercising in gymnasium, where there was a large gathering of people sharing food, drinks, and instruments. In effect, these mask-off settings allowed the sharing of their saliva and respiratory droplets, which may contain a viral load of 100 million per ml, directly or indirectly.[16,17] In HKSAR hospitals, wearing face masks is mandatory during the pandemic. It is also the practice among many community service providers and those who are working indoors. Since the supply of face mask was tight in the community as well as in the healthcare setting, it is the practice of our general public not to use more than one face mask per person per day. We observed that the overall compliance of face mask usage was 97% in all administrative districts in the morning. Thus we have the reason to believe that their compliance to face mask usage would remain high throughout the day at the workplace. It is therefore not surprising that the number of COVID-19 clusters was significantly higher in the mask-off recreational settings in HKSAR.

Universal masking in the community may mitigate the extent of transmission of COVID-19 and may be a necessary adjunctive public health measure in a densely populated city like HKSAR, with an average of 170,000 people entering HKSAR from Mainland and overseas per day.[18] Our incidence of COVID-19 was also lower than that of other areas with local transmission, vindicating this approach. In particular, our incidence of COVID-19 was significantly lower than that of Singapore, a city comparable with HKSAR in terms of area, population density, healthcare infrastructure, BCG vaccination,[19] as well as adopting social distancing strategies and SARS-CoV-2 testing infrastructure.[20] Besides a lower ambient temperature and a higher risk of importation of COVID-19 cases from the mainland which are factors promoting COVID-19 transmission in HKSAR, the most important difference between the two cities is the community-wide usage of face masks in HKSAR but not in Singapore. Moreover, 50% of local transmission of COVID-19 in South Korea was attributed to religious activities where face mask usage

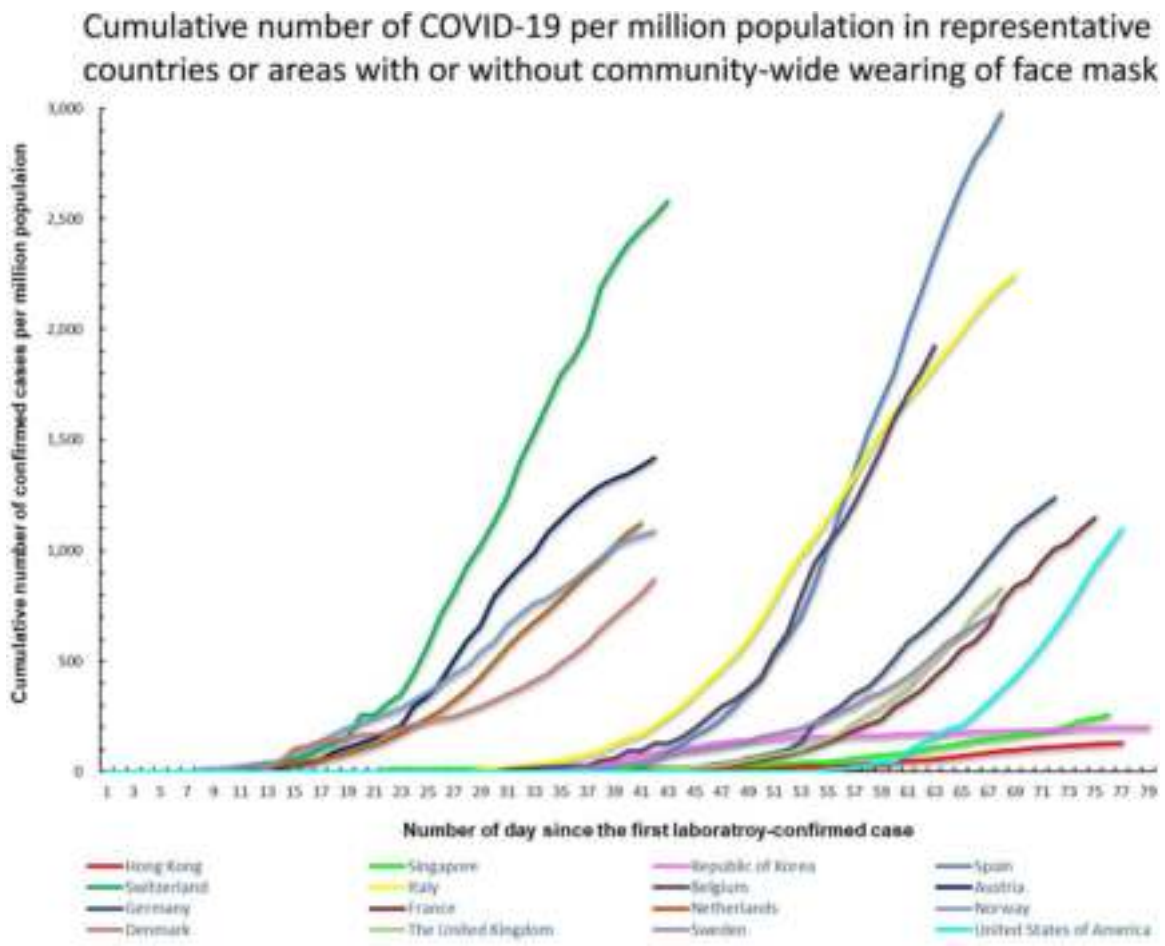

Fig. 2b. Cumulative number of COVID-19 per million population in representative countries or areas with or without community-wide wearing of face mask
Note. The x-axis denotes the number of day since the first laboratory-confirmed case in the representative countries or areas.
The date of first laboratory-confirmed case in Hong Kong (21 January 2020), Singapore (24 January 2020), South Korea (21 January 2020), Spain (1 February 2020), Switzerland (26 February 2020), Italy (31 January 2020), Belgium (06 February 2020), Austria (27 February 2020), Germany (28 January 2020), France (25 January 2020), Netherlands (28 February 2020), Norway (27 February 2020), Denmark (27 February 2020), The United Kingdom (1 February 2020), Sweden (01 February 2020) and United States of America (23 January 2020).

was discouraged. Mask-off activities clearly have potential implications for COVID-19 transmission in the community.

However, the use of face mask in the community remains controversial.[21,22] WHO issued an interim guideline regarding the use of masks in the context of COVID-19 on 6 April 2020, stating no evidence that wearing a mask by healthy persons in the wider community setting can prevent acquisition of COVID-19.[23] European Centre for Disease Prevention and Control issued a technical report on 8 April 2020 that the use of face masks in the community could be considered, especially when visiting busy, closed spaces, despite not knowing how much the use of masks in the community can contribute to a decrease in transmission in addition to the other counter measures.[24] On 3 April 2020, CDC recommended the use of cloth face coverings, especially in areas of significant community-based transmission.[25] The shift of paradigm from not recommending to promoting the use of face masks was based on the rationale of pre-symptomatic shedding of SARS-Cov-2 and presence of asymptomatic patients with high viral load in the community.[9,26] The use of face mask may serve as source control by preventing dispersal of droplets during talking, sneezing, and coughing,[27] and also reduce the risk of environmental contamination by SARS-CoV-2. Despite some supporters of WHO recommendation speaking against universal masking in our local medical community, most opinion leaders in the clinical microbiology and infectious disease specialties of HKSAR openly championed this measure for the control of community transmission of COVID-19.[28] Masking is a continuous form of protection to stop the spreading of saliva and respiratory droplets to others or from others, and to the environment or from the environment to the susceptible by hands through touching of nose, mouth and eye. Touching nose and mouth is a subconscious behavior.[29] Hand hygiene is always the cornerstone to prevent transmission of COVID-19 but it is a one-off discontinuous process where hand contamination may occur easily between each alcoholic handrubbing or hand washing. Although we have successfully implemented directly observed hand hygiene (DOHH) by regular delivery of alcohol-based hand rub to conscious hospitalized patients and persons in residential care homes for the elderly before meal and medication rounds,[30–32] it may be difficult to practice DOHH in the community. Studies have also shown that wearing a mask with frequent hand hygiene significantly reduced transmission of seasonal influenza virus in the community setting. But once the effect of the use of surgical mask was removed, the effect of hand hygiene became insignificant.[33] With the understanding that the supply of face masks should primarily be reserved for usage in healthcare settings, we believe that it is still advisable to encourage people to wear face masks in the public based on the precautionary principles.[34] Moreover, wearing a cloth mask with less filtration efficiency may still be better than no mask at all in communities of high transmission.

Table 1
Incidence of coronavirus disease 2019 (COVID-19) infection in Hong Kong Special Administrative Region (HKSAR) as compared with that of selected countries as of 8 April 2020 (at day 100 after official announcement of pneumonia outbreak in Wuhan, Hubei Province, China)[a].

Countries or city	Population (million)[b]	Cumulative number of confirmed case[c]	Number (percentage) of death	Incidence per million population[d]	P value (incidence compared with HKSAR)	Population density: population per km^2 (rank in the world)[e]
Hong Kong SAR[f]	7.45	961	4 (0.4%)	129.0	Not applicable	6782 (3rd)
Western Pacific Region						
Singapore	5.70	1,481	6 (0.4%)	259.8	P<0.001	7894 (2nd)
South Korea	51.78	10,384	200 (1.9%)	200.5	P<0.001	517 (13th)
European Region						
Spain	47.10	140,510	13,798 (9.8%)	2,983.2	P<0.001	93 (89th)
Switzerland	8.59	22,164	641 (2.9%)	2,580.2	P<0.001	208 (48th)
Italy	60.24	135,586	17,129 (12.6%)	2,250.8	P<0.001	200 (51st)
Belgium	11.52	22,194	2,035 (9.2%)	1,926.6	P<0.001	376 (22nd)
Austria	8.90	12,640	243 (1.9%)	1,420.2	P<0.001	106 (76th)
Germany	83.15	103,228	1,861 (1.8%)	1,241.5	P<0.001	233 (41st)
France	67.06	77,226	10,313 (13.4%)	1,151.6	P<0.001	123 (68th)
Netherlands	17.44	19,580	2,101 (10.7%)	1,122.7	P<0.001	420 (16th)
Norway	5.37	5,863	69 (1.7%)	1,091.8	P<0.001	17 (171st)
Denmark	5.82	5,071	203 (4.0%)	871.3	P<0.001	135 (64th)
The United Kingdom	66.44	55,246	6,159 (11.1%)	831.5	P<0.001	274 (32nd)
Sweden	10.33	7,693	591 (7.7%)	744.7	P<0.001	23 (159th)
Region of Americas						
United States of America	329.45	363,321	10,845 (3.0%)	1,102.8	P<0.001	34 (145th)

[a] Developed countries with well-established healthcare system and reached more than 100 confirmed cases at day 72 (WHO declare pandemic COVID-19) were selected for comparison.
[b] The population of country or city were retrieved from the website of World Health Organization.
[c] Infection retrieved from situation report - 79 of World Health Organization issued on 8 April 2020 (day 100 after the official announcement of clusters of community-acquired pneumonia in Wuhan, Hubei Province, China.
[d] The sequence of countries was listed as descending order in accordance with the incidence of COVID-19 per million population.
[e] Information retrieved from Wikipedia - List of countries and dependencies by population density. https://en.wikipedia.org/wiki/List_of_countries_and_dependencies_by_population_density (Accessed 12 April 2020).
[f] The number of confirmed case was based on the official announcement daily by HKSAR, China.

Table 2
Comparison of the epidemiology and community responses against coronavirus disease 2019 (COVID-19) in Hong Kong SAR, Singapore, and South Korea.

Epidemiology parameter as of 8 April 2020	Hong Kong SAR	Singapore	South Korea
Total number of confirmed case	961	1,481	10,384
Number of imported cases	517 (53.8%)	567 (38.3%)[a]	NM
Number of RT-PCR performed per million population	~15,000	~12,800[b]	~9,900[c]
Number of local cases related to mask-off setting (i.e. religious activities, dining and drinking in restaurant or bar, singing at karaoke, and exercise in gymnasium)	113 (11.8%)	NM	5150 (49.6%)[c,d]
Number of local cases related to family (other than mask-off setting described above)	41 (4.3%)	NM	NM
Number of local cases related to mask-on setting (i.e. workplace)	11 (1.4%)	NM	NM
Date of border restrictions	25 March 2020[e]	23 March 2020, 2359[f]	1 April 2020[g]
Average of ambient temperature range in the first 100 days of COVID-19 transmission	18 °C to 22 °C[h]	24 °C to 31 °C[i]	1 °C to 9 °C[j]
Routine childhood BCG immunization program[k]	Yes	Yes	Yes

Note. NM, not mentioned.
[a] Daily report on COVID-19. Minister of Health, Singapore. https://www.moh.gov.sg/docs/librariesprovider5/local-situation-report/situation-report-1-apr-2020.pdf. Accessed 12 April 2020.
[b] Information obtained from Minister of Health, Singapore. https://www.moh.gov.sg/covid-19. Accessed 12 April 2020.
[c] Information obtained from Coronavirus Disease-19, Republic of Korea. http://ncov.mohw.go.kr/en/. Accessed 12 April 2020.
[d] These patients were all related to a cohort of participants involving in religious activities - wearing face masks was discouraged. These were the believer of Olive Tree, a Christian new religious movement, originally known as Jesus Christ Congregation Revival Association of Korea, founded in Republic of Korea by Park Tae Son. https://en.wikipedia.org/wiki/Olive_Tree_(religious_movement). Accessed 12 April 2020.
[e] Deny entry of non-Hong Kong resident.
[f] All short-term visitors (from anywhere in the world) will not be allowed to enter or transit through Singapore.
[g] All passengers are subject to mandatory self-quarantine for 14 days, except for airline crew. https://en.wikipedia.org/wiki/Travel_restrictions_related_to_the_2019%E2%80%9320_coronavirus_pandemic. Accessed 12 April 2020.
[h] https://www.hko.gov.hk/en/wxinfo/pastwx/mws/mws.htm. Accessed 12 April 2020.
[i] https://www.climatestotravel.com/climate/singapore. Accessed 12 April 2020.
[j] https://www.climatestotravel.com/climate/south-korea. Accessed 12 April 2020.
[k] There is postulation of countries with BCG vaccination program tends to have lower incidence and death due to COVID-19[19].

SARS-CoV-2 is a highly transmissible respiratory virus which causes upper and lower respiratory tract infection leading to a high viral load in respiratory secretions and saliva as shown in clinical studies and transmission studies by close contact in animal models.[35] Moreover, SARS-CoV-2 can suppress the host innate immune response in terms of interferon and cytokine response which in turn leads to a higher level of viral replication than that by the 2003 SARS-CoV in an *ex vivo* lung tissue explant model.[10] These *ex vivo* findings supported the suggestion that an important proportion of COVID-19 patients may be pre-symptomatic or mildly symptomatic virus shedders. These groups of patients are unlikely to be tested or isolated and may contribute to the perpetuation of

the pandemic. Therefore community-wide mask usage irrespective of symptoms may reduce the infectivity of these silent COVID-19 cases to the susceptible individuals.

There are several limitations in our study. First, we did not analyze the mask-off settings in the family because the modes of transmission among close household contacts can be more diverse. If the 15 family clusters were also counted within the mask-off settings, the difference would be even more significant ($p<0.001$). Second, the type of mask used in the community cannot be controlled. The compliance of wearing face mask in terms of not touching the external surface of mask or face, and hand hygiene before or after touching the mask cannot be assessed. Third, we cannot count the mask compliance directly for every community settings. Nevertheless, in the absence of effective antiviral and vaccines, the pandemic spread COVID-19 to many countries provide an unique opportunity to study the effectiveness of this non-pharmaceutical control measures. As of 27 February 2020 (day 38 since the first reported case in South Korea), South Korea government has started to distribute face masks to the public amid the outbreak of the COVID-19,[36] which was associated with a flattening of the epidemic curve. As of 14 April 2020 (day 82 since the first reported case in Singapore), Singapore government has started to enforce a penalty of 300 Singapore dollar for anyone going out from home without a mask.[37] Further studies on this important non-pharmaceutical control measure are warranted. In order to live with emerging infectious diseases and seasonal influenza epidemics, every individual should have personalized reusable mask, gown, and gloves made of self-disinfecting fabrics, and even reusable anti-fog face shield within their own set of Epidemic Combat Kit for their personal protection.

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Declaration of Competing Interest

All authors report no conflicts of interest relevant to this article.

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Effectiveness of non-pharmaceutical interventions on COVID-19 transmission in 190 countries from 23 January to 13 April 2020

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ABSTRACT

Background: To evaluate and compare the effectiveness of four types of non-pharmaceutical interventions (NPIs) to contain the time-varying effective reproduction number (Rt) of coronavirus disease-2019 (COVID-19).

Methods: This study included 1,908,197 confirmed COVID-19 cases from 190 countries between 23 January and 13 April 2020. The implemented NPIs were categorised into four types: mandatory face mask in public, isolation or quarantine, social distancing and traffic restriction (referred to as mandatory mask, quarantine, distancing and traffic hereafter, respectively).

Results: The implementations of mandatory mask, quarantine, distancing and traffic were associated with changes (95% confidence interval, CI) of −15.14% (from −21.79% to −7.93%), −11.40% (from −13.66% to −9.07%), −42.94% (from −44.24% to −41.60%) and −9.26% (from −11.46% to −7.01%) in the Rt of COVID-19 when compared with those without the implementation of the corresponding measures. Distancing and the simultaneous implementation of two or more types of NPIs seemed to be associated with a greater decrease in the Rt of COVID-19.

Conclusion: Our study indicates that NPIs can significantly contain the COVID-19 pandemic. Distancing and the simultaneous implementation of two or more NPIs should be the strategic priorities for containing COVID-19.

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Introduction

The coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in Wuhan, China, in December 2019. The World Health Organization (WHO) declared it as a pandemic on 12 March 2020. As of 28 May 2020, there are more than 5.5 million confirmed cases of COVID-19 and 353,373 related deaths worldwide (World Health Organization, 2020). Many countries have implemented a series of non-pharmaceutical interventions (NPIs), such as traffic restriction and social distancing, to contain the outbreak of this disease (Jon Cohen, 2020; Lewnard and Lo, 2020).

Owing to the rapid transmission of COVID-19 worldwide and the lack of an efficient vaccine or treatment for this novel infectious disease, NPIs are among the few approaches to cope with the resulting pandemic. There is an urgent need to understand whether these NPIs are effective and which of these NPIs are more efficient. However, the information on this topic is limited.

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Most previous studies have focused on evaluating a single NPI within a single city or country using a modelling method, and the results of these studies are inconsistent. Few studies have investigated the simultaneous implementation of multiple NPIs and compared the effectiveness of different NPIs (Lai et al., 2020; Min et al., 2020). To the best of our knowledge, no study has examined the association between various NPIs and the time-varying effective reproduction number (Rt) of COVID-19 on the global scale. Therefore, we investigated and compared the effectiveness of four types of NPIs, namely mandatory face mask in public, isolation or quarantine, social distancing and traffic restriction, on the transmission of COVID-19 in 190 countries between 23 January and 13 April 2020.

Method

Study design and setting

This ecological study included a total of 415 sites (comprising 235 cities from 10 countries and 180 countries) between 23 January and 13 April 2020. Information on the daily number of confirmed COVID-19 cases was extracted from a data repository sourced from Johns Hopkins University Center for Systems Science and Engineering and the Wind Financial database, which archive data from the official websites of health ministries worldwide (Dong et al., 2020; Wind, 2020).

Data pertaining to the implementation of NPIs during the study period were obtained from official webpages of high-circulation newspapers published in the 415 cities/countries. In brief, we first recorded any legal NPIs announced by the government of each site and its implementation date [i.e., start date and end date (if applicable before the study end date)]. Then, we categorised the NPIs into the following four types: 'mandatory face mask in public' (referred to as mandatory mask hereinafter), 'isolation or quarantine' (referred to as quarantine hereinafter), 'social distancing' (referred to as distancing hereinafter) and 'traffic restriction' (referred to as traffic hereinafter). Details pertaining to the process of categorising the NPIs are summarised in Table S1. If any NPI of a type was deemed officially announced as being in force at a site on any day of the study period, then that NPI type was treated as 'on' for that site on that day in our data analysis. In contrast, if no NPI of a type was found to be effective at a site on any day of the study period, the NPI type was treated as 'off' in our data analysis.

Moreover, we collected demographic and socioeconomic status data for each site. Data on population size (number of persons), population density (persons per square km) and median age (years) were obtained from United Nations, Department of Economic and Social Affairs, Population Division (Elaboration of data by United Nations, 2019) and/or statistics bureau of the countries studied. Data on the percentage of populations aged 65 years or older were obtained from the World Bank data portal (2019 revision). Information about the Global Health Security Index (GHSI) was collected from the GHSI report (Johns Hopkins, 2019). Because only country-level GHSI data were available, we applied them to all cities within a given country.

Calculation of time-varying effective reproduction number (Rt)

We used Rt, which represents the average number of secondary infected cases generated by a primary infected individual at time t, to estimate the changes in COVID-19 transmissibility. Rt >1 indicates an expansionary trend of the epidemic, whereas Rt <1 indicates a contractionary trend of the epidemic. We calculated the Rt and its 95% credible interval for each day by applying the method developed by Cori et al. (2013) through a 7-day moving average. We assumed that the serial interval distribution of COVID-19 followed a gamma distribution with a mean of 3.96 days and a standard deviation (SD) of 4.75 days (Du et al., 2020).

Data analysis

First, we used the generalised linear mixed model (GLMM) to assess the effectiveness of the four types of NPIs on the transmission of COVID-19 separately. The implementation status (on/off) of each type of NPI (i.e., mandatory mask, quarantine, distancing and traffic) at each site on each day was included in the model as an independent variable. The dependent variable was Rt, which was log-transformed to normalise before data analysis and then retransformed to the original scale for presentation. Effect estimations were reported as percentage differences in the Rt between sites with a given type of NPI and sites without the corresponding type of NPI as the reference. A city/country-level random intercept was included in the model to control for clustering effects within the same city/country. Two models were developed. Model 1 included the following covariates: calendar time to control seasonal and long-term trends over the study period; Rt of the previous day to account for temporal autocorrelation; public health response time, which was defined as the number of days between the date of activation of the first NPI and the date on which the first case was reported; an indicator for the day of the week and public holidays to account for weekly or periodic variations in the number of people who underwent the SARS-CoV-2 test; duration for which a type of NPI was implemented to control for the potential effects of implementation duration; population density to account for a higher transmission rate in regions with high population density; median age to account for higher incidence rates among the elderly; and GHSI to account for countries' capacity to prevent and mitigate epidemics and pandemics. Model 2 was further mutually adjusted for the other three types of NPIs, for example, adjusted for quarantine, distancing and traffic to determine the association between the 'mandatory mask' type of NPI and Rt.

Second, we compared the effectiveness of the different types of NPIs implemented. We classified the 415 sites into the following 16 mutually exclusive groups: no implementation of NPIs; implementation of any one type of NPIs, namely mandatory mask only, quarantine only, distancing only or traffic only; implementation of any two types of NPIs, namely 'distancing + mandatory mask', 'distancing + quarantine', 'traffic + mandatory mask', 'traffic + quarantine', 'traffic + distancing' or 'quarantine + mandatory mask'; implementation of any three types of NPIs, namely 'distancing + quarantine + mandatory mask', 'traffic + quarantine + mandatory mask', 'traffic + distancing + mandatory mask' or 'traffic + distancing + quarantine'; and implementation of all four types of NPIs, that is, 'traffic + distancing + quarantine + mandatory mask'. We applied the GLMM mentioned above with the same covariates as those used in Model 1. The reference group was 'no implementation of NPIs'.

Third, stratified analyses were performed to investigate whether these associations were modified by WHO regions, population density and GHSI.

Finally, we performed three sensitivity analyses to examine the robustness of the estimated associations and the lag effects: (1) We used the Rt on the third day (Lag 3), the seventh day (Lag 7) and the 14th day (Lag 14) as the dependent variable to examine the lag effect; (2) we investigated the associations by excluding Hubei province in China, which was a significant outlier in the model; and (3) we investigated the associations by adjusting for percentages of populations aged 65 years or older instead of median age to consider the effects of age structure.

All data analyses were performed using R 3.6.1 (R Core Team, Vienna, Austria). A two-tailed P value of <0.05 was considered statistically significant.

Result

A total of 415 sites (i.e., 235 cities from 10 countries and 180 countries) were included in this study. Table S2 summarises the relevant information on COVID-19 and the NPIs implemented in the 190 countries during the study period. As of 13 April 2020, 1,908,197 cases of COVID-19 infection were reported. The highest number of cases was reported in the United States of America [577,165 (30.25% of the total number of cases reported worldwide)], followed by Spain, Italy, France, Germany, the United Kingdom, China, Iran, Turkey and Belgium.

Table 1 shows the data pertaining to the implementation of NPIs at the study sites over the study period. No official NPIs were ever implemented in 382 sites. In many sites, two or more types of NPIs were implemented simultaneously during the study period. The common types of NPIs or combinations of NPI types that were implemented across the sites were 'traffic only' (138 sites), 'traffic + quarantine' (130 sites), 'traffic + distancing' (177 sites) and 'traffic + distancing + quarantine' (218 sites). The implementation durations of each type of NPI or each combination of NPI types ranged from 4 to 38 days. Relatively long median durations of implementation were observed for 'traffic only' (12.5 days), 'distancing + mandatory mask' (16 days), 'traffic + quarantine' (33 days), 'traffic + distancing' (19 days), 'traffic + quarantine + mandatory mask' (38 days), 'traffic + distancing + quarantine' (24 days) and 'traffic + distancing + quarantine + mandatory mask' (37 days).

Table 2 presents the associations between each type of NPI and the Rt of COVID-19. The implementations of any type of NPI were significantly associated with a decrease in the Rt of COVID-19. Mutual adjustments substantially diluted these associations. The implementations of mandatory mask, quarantine, distancing and traffic were associated with changes of −15.14% (from −21.79% to −7.93%), −11.40% (from −13.66% to −9.07%), −42.94% (from −44.24% to −41.60%) and −9.26% (from −11.46% to −7.01%) in the Rt of COVID-19, respectively, when compared with the Rt in the sites without the implementation of the corresponding measures.

Table 3 shows the comparisons of the effectiveness of different NPIs on the Rt of COVID-19. 'Distancing only' led to a greater decrease in the Rt of COVID-19 than 'traffic only' and 'quarantine only'. The combinations of other types of NPIs with distancing were generally associated with a greater decrease in the Rt when compared with the combinations without distancing. The combinations with more types of NPIs were generally associated with a greater decrease in the Rt. No significant associations were observed for 'mandatory mask only', 'distancing + mandatory mask', 'traffic + mandatory mask' and 'traffic + distancing + mandatory mask'.

As shown in Table 4, subgroup data analysis generally yielded similar results. The association strengths differed slightly for some subgroups, that is, greater decreases in the Rt were observed for the subgroups of 'higher population density' and 'lower GHSI'. No significant associations were observed for some subgroups.

Tables S3-S5 summarise the results of our sensitivity analyses. The decreased magnitudes in the Rts were generally smaller on days Lag 3, Lag 7 and Lag 14 when compared with those on the current day (Table S3). Similar results were obtained by excluding the outlier province (Hubei, China) (Table S4) and by adjusting for percentages of subjects aged ≥65 years instead of median age (Table S5).

Discussion

This comprehensive ecological study covering 190 countries indicated that the implementation of any type of NPI, namely traffic, distancing, mandatory mask or quarantine was significantly associated with a decrease in the Rt of COVID-19. All NPI implementations involving distancing were associated with a greater decrease in the Rt of COVID-19 than those not involving distancing. Accordingly, combinations with more types of NPIs seemed to be associated with a greater decrease in the Rt of COVID-19.

Most previous studies have investigated the effectiveness of a single NPI rather than a group of NPIs despite the fact that two or more NPIs are commonly implemented simultaneously (Auger et al., 2020; Chinazzi et al., 2020; Hernandez et al., 2020; Milne and Xie, 2020). The results of our study were consistent with those of the studies, which concluded that the implementation of NPIs was

Table 1
Non-pharmaceutical interventions implemented in the 190 countries between 23 January 2020 and 13 April 2020 (N = 415).

Type of NPIs	No. of sites that implemented the NPIs (%)	Median duration (range) of NPI implementation (days)
0 NPIs	382 (92.05%)	N/A
Any one type of NPI		
Mandatory mask only	1 (0.24%)	4 (N/A)
Quarantine only	48 (11.57%)	7 (1–53)
Distancing only	40 (9.64%)	4 (1–31)
Traffic only	138 (33.25%)	12.5 (1–75)
Any two types of NPIs		
Distancing + mandatory mask	1 (0.24%)	16 (N/A)
Distancing + quarantine	21 (5.06%)	6 (1–35)
Traffic + mandatory mask	1 (0.24%)	4 (N/A)
Traffic + quarantine	130 (31.33%)	33 (1–72)
Traffic + distancing	177 (42.65%)	19 (1–38)
Quarantine + mandatory mask	0 (0.00%)	N/A
Any three types of NPIs		
Distancing + quarantine + mandatory mask	2 (0.48%)	8.5 (1–16)
Traffic + quarantine + mandatory mask	36 (8.67%)	38 (2–42)
Traffic + distancing + mandatory mask	1 (0.24%)	7 (N/A)
Traffic + distancing + quarantine	218 (52.53%)	24 (2–49)
All four types of NPIs		
Traffic + distancing + quarantine + mandatory mask	60 (14.46%)	37 (1–75)

NPIs: Non-pharmaceutical interventions.
%: Percentage of sites implementing corresponding types of NPI among the 415 included sites.
N/A: not applicable.

Table 2
Associations of individual type of non-pharmaceutical intervention with the Rt of COVID-19.

Type of NPI	Model 1		Model 2	
	Difference (95% CI)	*P*	Difference (95% CI)	*P*
Mandatory mask (Yes vs. No)	−33.35% (-39.07 to -27.09)	<0.001	−15.14% (-21.79 to -7.93)	<0.001
Quarantine (Yes vs. No)	−32.98% (-34.59 to -31.33)	<0.001	−11.40% (-13.66 to -9.07)	<0.001
Distancing (Yes vs. No)	−46.46% (-47.63 to -45.27)	<0.001	−42.94% (-44.24 to -41.60)	<0.001
Traffic (Yes vs. No)	−29.09% (-30.73 to -27.42)	<0.001	−9.26% (-11.46 to -7.01)	<0.001

NPIs: Non-pharmaceutical interventions.
Sites without the corresponding type of NPI as the reference.
Results are presented as percentage differences in the Rt with [95% Confidence Interval (CI)].
Model 1: Adjusted for the calendar time, Rt on the previous day, public health response time defined as the time in days between the activation of the first NPI and the date of reporting of the first case, an indicator of the day of the week and public holidays, implementation duration of NPIs, population density, median age and GHSI.
Model 2: Further mutually adjusted for the other three types of NPIs, for example, adjusted for quarantine, distancing and traffic in the model for the association between 'mandatory mask' type of NPI and Rt.

Table 3
Comparison of effectiveness of different NPI types or combinations on the Rt of COVID-19.

Type of NPIs	Difference (95% CI)	*P*
Any one type of NPIs		
Mandatory mask only	−34.06% (-60.78 to 10.87)	0.116
Quarantine only	−10.6% (-15.31 to -5.64)	<0.001
Distancing only	−23.03% (-28.43 to -17.22)	<0.001
Traffic only	−9.64% (-12.21 to -7.00)	<0.001
Any two types of NPIs		
Distancing + mandatory mask	53.30% (-2.50–141.03)	0.064
Distancing + quarantine	−38.58% (-44.23 to -32.37)	<0.001
Traffic + mandatory mask	−66.58% (-92.67 to 52.41)	0.157
Traffic + quarantine	−17.83% (-20.07 to -15.53)	<0.001
Traffic + distancing	−44.11% (-46.37 to -41.76)	<0.001
Any three types of NPIs		
Distancing + quarantine + mandatory mask	−69.73% (-82.48 to -47.69)	<0.001
Traffic + quarantine + mandatory mask	−17.06% (-24.99 to -8.29)	<0.001
Traffic + distancing + mandatory mask	−54.32% (-79.59 to 2.24)	0.057
Traffic + distancing + quarantine	−54.12% (-55.63 to -52.56)	<0.001
All four types of NPIs		
Traffic + distancing + quarantine + mandatory mask	−62.81% (-66.27 to -58.98)	<0.001

NPIs: Non-pharmaceutical interventions.
Sites with No NPI implementation are the reference.
Results are presented as percentage differences in the Rt with [95% Confidence Interval (CI)].
Adjusted for calendar time, Rt on the previous day, public health response time defined as the number of days between the date of activation of the first NPI and the date of reporting of the first case, an indicator of the day of the week and public holidays, implementation duration of a type of NPI, population density, median age and GHSI.

associated with a decrease in transmissibility, such as the studies in mainland China showing that travel restrictions might delay the progression of the COVID-19 epidemic by 3–5 days (Chinazzi et al., 2020; Tian et al., 2020), and the study in New York showing that wearing a mask could reduce daily deaths by 17%–45% over 2 months (Eikenberry et al., 2020). Moreover, two studies reported social distancing to be an effective NPI (Hernandez et al., 2020; Zhang et al., 2020). A study conducted in China showed that social distancing and epicentre lockdown might reduce the number of new infection cases by up to 98.9% (Zhang et al., 2020), while another study indicated that social distancing reduced the growth rate of confirmed cases in five countries (Austria, Belgium, Italy, Malaysia and South Korea) by 52.37% on average (SD 13.37%) (Hernandez et al., 2020). A few studies investigated the effectiveness of multiple NPIs in China (Cowling et al., 2020; Lai et al., 2020; Milne and Xie, 2020; Pan et al., 2020), European countries (Flaxman et al., 2020), the United Kingdom (Davies et al., 2020) and Singapore (Koo et al., 2020). Their results showed that the implementation of multiple NPIs was associated with a reduction in the transmission of COVID-19. In contrast, a study conducted in 20 European countries revealed that stay-at-home orders, closure of all non-essential businesses and wearing of face masks in public were not significantly associated with the incidence rate of confirmed cases (Hunter et al., 2020). It is difficult to directly compare the results of our study with those of previous studies owing to multiple reasons, such as differences in study design and period, targeted populations and transmissibility parameters. Moreover, most previous studies used modelling methods to simulate the epidemic with the implementation of NPIs. In contrast, we used the data published on the official webpages of the governments of 190 countries to provide direct evidence about the effectiveness of NPI implementation on COVID-19 transmission. Nevertheless, our study and most previous studies support the implementation of NPIs as a measure for containing the global pandemic of COVID-19.

Few studies have compared the effectiveness of different NPIs and their combinations for containing COVID-19. Our results showed that the NPI of distancing and its combinations with other NPI types are associated with a greater decrease in the Rt of COVID-19, suggesting that distancing should be adopted as a priority NPI for COVID-19 containment. This is in line with a modelling study in China, which also suggested that social distancing seemed to have a greater impact on the containment of COVID-19 outbreak than travel restrictions (Lai et al., 2020). Moreover, our study indicated

Table 4
Subgroup analysis of association between non-pharmaceutical interventions and the Rt of COVID-19 transmission.

Types of NPIs	Subgroup analysis			
	Stratified by continents			
	European	American	Asia	African
Comparison of individual types of NPIs[a]				
Mandatory mask (Yes vs. No)	−1.33% (-13.02–11.94)	−23.68% (-41.5 to -0.45)	−0.26% (-6.15 to 6.01)	−28.56% (-48.8 to -0.31)
Quarantine (Yes vs. No)	−18.27% (-22.14 to -14.21)	−4.23% (-10.07 to 1.99)	−4.55% (-8.47 to -0.46)	−10.72% (-16.04 to -5.07)
Distancing (Yes vs. No)	−39.4% (-42.07 to -36.59)	−42.87% (-45.37 to -40.27)	−17.76% (-20.56 to -14.85)	−16.05% (-21.33 to -10.41)
Traffic (Yes vs. No)	−11.26% (-15.18 to -7.17)	−8.34% (-13.75 to -2.58)	−8.62% (-11.95 to -5.17)	−30.86% (-34.83 to -26.66)
Comparison of combinations of NPI types[b]				
Any one type of NPI				
Mandatory mask only	−41.49% (-65.82 to 0.16)	N/A	N/A	N/A
Quarantine only	−20.21% (-27.00 to -12.79)	0.84 % (-10.00–12.98)	−11.62% (-18.83 to -3.76)	−4.01% (-15.45 to 8.97)
Distancing only	−38.35% (-45.64 to -30.09)	−33.33% (-42.93 to -22.12)	−18.8% (-30.30 to -5.41)	11.55 % (-3.32 to 28.71)
Traffic only	−9.21% (-13.65 to -4.54)	−15.12% (-22.68 to -6.81)	−12.58% (-16.2 to -8.81)	−24.60% (-30.13 to -18.62)
Any two types of NPIs				
Distancing + mandatory mask	N/A	N/A	7.27 % (-26.61 to 56.77)	N/A
Distancing + quarantine	−48.75% (-56.37 to -39.80)	−50.46% (-63.40 to -32.95)	−20.51% (-34.83 to -3.06)	−15.48% (-26.91 to -2.27)
Traffic + mandatory mask	N/A	N/A	N/A	−74.36% (-96.01–64.91)
Traffic + quarantine	−42.60% (-48.81 to -35.65)	−11.70% (-15.46 to -7.78)	−9.24% (-13.91 to -4.31)	−34.84% (-40.35 to -28.83)
Traffic + distancing	−49.10% (-52.82 to -45.08)	−38.73% (-44.72 to -32.1)	−17.13% (-22.00 to -11.96)	−41.59% (-46.93 to -35.71)
Any three types of NPIs				
Distancing + quarantine + mandatory mask	14.41 % (-34.75–100.60)	N/A	−41.40% (-66.30 to1.90)	N/A
Traffic + quarantine + mandatory mask	−35.98% (-56.39 to -6.02)	−31.04% (-74.06–83.34)	−5.07% (-11.73 to 2.09)	N/A
Traffic + distancing + mandatory mask	N/A	N/A	−28.19% (-64.91 to 46.93)	N/A
Traffic + distancing + quarantine	−55.24% (-58.04 to -52.26)	−50.94% (-53.41 to -48.34)	−26.66% (-31.42 to -21.55)	−48.26% (-53.16 to -42.85)
All four types of NPIs				
Traffic + distancing + quarantine + mandatory mask	−54.03% (-60.16 to -46.94)	−62.40% (-71.60 to -50.24)	−30.90% (-35.65 to -25.79)	−57.91% (-69.86 to -41.21)
	Stratified by population density		Stratified by GHSI	
	≤ 110.5 pears/km^2	> 110.5 pears/km^2	≤ 58.5	>58.5
Comparison of individual types of NPIs[a]				
Mandatory mask (Yes vs. No)	0.33 % (-8.71 -10.26)	−24.22% (-33.10 to -14.16)	−24.64% (-30.01 to -18.86)	−17.85% (-41.76 to 15.88)
Quarantine (Yes vs. No)	−8.09% (-11.03 to -5.06)	−20.38% (-23.80 to -16.80)	−22.16% (-24.61 to -19.63)	21.06 % (14.22–28.31)
Distancing (Yes vs. No)	−42.58% (-44.30 to -40.80)	−43.00% (-45.01 to -40.91)	−41.40% (-43.1 to -39.64)	−39.37% (-41.82 to -36.82)
Traffic (Yes vs. No)	−11.46% (-14.05 to -8.79)	−3.93% (-8.04 to 0.36)	−13.32% (-15.8 to -10.77)	−27.64% (-32.22 to -22.75)
Comparison of combinations of NPI[b]				
Any one type of NPI				
Mandatory mask only	−32.62% (-60.74 to 15.66)	N/A	−40.27% (-64.91 to 1.68)	N/A
Quarantine only	2.11 % (-4.02–8.64)	−35.8% (-41.93 to -29.01)	−27.97% (-32.60 to -23.02)	30.17 % (20.21–40.96)
Distancing only	−17.39% (-26.00 to -7.77)	−30.13% (-36.64 to -22.96)	−32.09% (-37.69 to -25.99)	−8.65% (-21.22 to 5.93)
Traffic only	−11.61% (-14.64 to -8.49)	−5.10% (-10.11 to 0.18)	−12.86% (-15.64 to -10.00)	−26.96% (-33.39 to -19.91)
Any two types of NPIs				
Distancing + mandatory mask	N/A	40.99 % (-10.17–121.29)	21.86 % (-21.3–88.7)	N/A
Distancing + quarantine	−34.91% (-44.27 to -23.98)	−41.29% (-48.06 to -33.64)	−46.29% (-51.7 to -40.27)	−31.53% (-49.42 to -7.32)
Traffic + mandatory mask	−68.2% (-94.53–84.7)	N/A	−70.57% (-93.53 to 33.82)	N/A
Traffic + quarantine	−18.25% (-20.99 to -15.42)	−21.94% (-25.62 to -18.08)	−30.81% (-33.99 to -27.48)	−10.56% (-14.78 to -6.13)
Traffic + distancing	−40.23% (-43.34 to -36.94)	−47.4% (-50.75 to -43.82)	−48.01% (-50.53 to -45.37)	−44.41% (-49.82 to -38.43)
Any three types of NPIs				
Distancing + quarantine + mandatory mask	37.89 % (-20.47–139.08)	−81.93% (-90.65 to -65.08)	−79.01% (-88.57 to -61.46)	N/A
Traffic + quarantine + mandatory mask	6.79 % (-5.37 to 20.51)	−38.47% (-46.73 to -28.93)	−42.60% (-47.41 to -37.35)	−7.17% (-63.86–138.44)
Traffic + distancing + mandatory mask	−52.9% (-79.49 to 8.13)	N/A	−59.44% (-81.96 to -8.79)	N/A
Traffic + distancing + quarantine	−53.76% (-55.64 to -51.8)	−55.27% (-57.74 to -52.65)	−58.75% (-60.70 to -56.69)	−48.26% (-50.58 to -45.82)
All four types of NPIs				
Traffic + distancing + quarantine + mandatory mask	−54.29% (-59.07 to -48.96)	−71.21% (-75.22 to -66.54)	−72.36% (-74.83 to -69.65)	−56.94% (-70.12 to -37.95)

N/A: not applicable due to no sites implemented the corresponding type of NPIs.
Results are presented as percentage differences in the Rt with [95% Confidence Interval (CI)].

[a] Sites without the corresponding type of NPI as the reference. Adjusted for calendar time, Rt on the previous day, public health response time defined as the number of days between the date of activation of the first NPI and the date of reporting of the first case, an indicator of day of the week and public holidays, implementation duration of a type of NPI, population density, median age and GHSI and mutually adjusted for the other three types of NPIs, for example, adjusted for quarantine, distancing, and traffic in the model for the association between the 'mandatory mask' type of NPI and Rt.

[b] Sites with No NPI implementation are the reference. Adjusted for calendar time, Rt on the previous day, public health response time defined as the number of days between the date of activation of the first NPI and the date of reporting of the first case, an indicator of the day of the week and public holidays, implementation duration of a type of NPI, population density, median age and GHSI

that the simultaneous implementation of two or more NPI types seems to be associated with a greater decrease in the Rt of COVID-19.

In the comparisons of the effectiveness of different NPIs and their combinations, we found non-significant associations for 'mandatory mask only' and the combinations 'distancing + mandatory mask', 'traffic + mandatory mask' and 'traffic + distancing + mandatory mask' (Table 3). Non-significant associations were also found in some subgroup analyses (Table 4), which were inconsistent with previous studies reporting that the face mask was associated with reduced risk of COVID-19 infection (Cheng et al., 2020; Chu et al., 2020; Eikenberry et al., 2020). The lack of statistical significance for these associations in our study may be ascribed to the small number of cities or countries that implemented the above NPI types and combinations.

Our study has several important strengths. First, we captured the available data on confirmed cases of COVID-19 infection and legal NPIs implemented from 190 countries, which suggests that our findings are applicable in most countries worldwide. The large sample size allowed us to obtain more stable estimates and conduct a series of subgroup and sensitivity analyses, which generally yielded similar results, indicating that the associations observed in our study are robust. Second, we adjusted for a series of important confounders in the model, including socio-demographics and health security capacities. Finally, this study is the first to present a comprehensive and quantitative comparison of the effectiveness of various NPIs and their combinations at a global scale, which may provide timely evidence for policymakers to adopt appropriate NPIs in different countries to control the outbreak of COVID-19.

Several limitations should be noted. First, we treated an NPI as 'on' in the data analysis if the NPI was officially announced as being in force by a government. We were unable to account for the intensity of enforcement and people's compliance, which might have varied across countries and cities. Also, contents of each NPI at different sties might be somewhat different. However, we included a city-level random intercept that may control the between-city variations in intensity and compliance. Second, we considered four types of NPIs that were legally and officially announced by the governments of countries and cities considered in this study. A few NPIs, such as knowledge promotion, voluntary isolation and voluntarily wearing a mask were not considered. Moreover, some cultural factors such as personal hygiene, social habits and family size may influence the spread of COVID-19. Further investigations are warranted to assess the effects of these factors. Third, the information of testing capacities in each site was not available. However, we already adjusted for GHSI, which is an important indicator reflecting testing capacity. Fourth, although our results show non-significant associations of Rt with 'mandatory mask only' and the combinations 'distancing + mandatory mask', 'traffic + mandatory mask' and 'traffic + distancing + mandatory mask', we should interpret with caution because these estimates came from only a few sites. Fifth, because all the cities or countries took action to separate infected persons from uninfected persons at the outset, the effects of not separating infected persons remain unknown. Additionally, the effects of different NPIs may be highly correlated because they commonly, synchronously occurred and were jointly implemented, which may contradict the assumption of independent covariates in GLMM model. However, the results could also be affected by other NPIs if only one type of NPIs was considered. Thus, we gradually introduced two models and presented them separately in Table 2. The two models will allow us to compare the potential influences of additional three other NPIs on the effect of an individual NPI. Furthermore, mutually adjusted for the other three types of NPIs did not materially affect the conclusion.

In conclusion, we found that any type of NPI, namely mandatory face mask in public, isolation or quarantine, social distancing and traffic restriction, may reduce the spread of COVID-19. Social distancing seems more effective than the other three types of NPIs. The simultaneous implementation of two or more types of NPIs may be more effective for containing the spread of COVID-19.

Conflict of interests

None declared.

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Ethical approval

No ethical approval was required.

Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.10.066.

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By Wei Lyu and George L. Wehby

Community Use Of Face Masks And COVID-19: Evidence From A Natural Experiment Of State Mandates In The US

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ABSTRACT State policies mandating public or community use of face masks or covers in mitigating the spread of coronavirus disease 2019 (COVID-19) are hotly contested. This study provides evidence from a natural experiment on the effects of state government mandates for face mask use in public issued by fifteen states plus Washington, D.C., between April 8 and May 15, 2020. The research design is an event study examining changes in the daily county-level COVID-19 growth rates between March 31 and May 22, 2020. Mandating face mask use in public is associated with a decline in the daily COVID-19 growth rate by 0.9, 1.1, 1.4, 1.7, and 2.0 percentage points in 1–5, 6–10, 11–15, 16–20, and 21 or more days after state face mask orders were signed, respectively. Estimates suggest that as a result of the implementation of these mandates, more than 200,000 COVID-19 cases were averted by May 22, 2020. The findings suggest that requiring face mask use in public could help in mitigating the spread of COVID-19.

One of the most contentious issues being debated worldwide in the response to the coronavirus disease 2019 (COVID-19) pandemic is the value of wearing masks or face coverings in public settings.[1] A key factor fueling the debate is the limited direct evidence thus far on how much widespread community use would affect COVID-19 spread. However, there is now substantial evidence of asymptomatic transmission of COVID-19.[2,3] For example, a recent study of antibodies in a sample of customers in grocery stores in New York State reported an infection rate of 14.0 percent by March 29 (projected to represent more than 2.1 million cases), which substantially exceeds the number of confirmed COVID-19 cases.[4] Moreover, all public health authorities call on symptomatic people to wear masks to reduce transmission risk. Even organizations that at the time of our study had not yet recommended widespread community use of face masks for COVID-19 mitigation (that is, everyone without symptoms should use a face mask outside of their home), such as the World Health Organization, strongly recommend that symptomatic individuals wear them.[5] Because mask wearing by infected people can reduce transmission risk, and because of the high proportion of asymptomatic infected individuals and transmissions, there appears to be a strong case for the effectiveness of widespread use of face masks in reducing the spread of COVID-19. However, there is no direct evidence thus far on the magnitude of such effects, especially at a population level.

Researchers have been reviewing evidence from previous randomized controlled trials for other respiratory illnesses, examining mask use and types among people at higher risk of contracting infections (such as health care workers or people in infected households). Systematic reviews and meta-analyses of such studies have provided suggestive, although generally weak, evidence.[6] The estimates from the meta-analyses

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based on randomized controlled trials suggest declines in transmission risk for influenza or influenza-like illnesses to mask wearers, although estimates are mostly statistically insignificant possibly because of small sample sizes or design limitations, especially those related to assessing compliance.[7–9] There is also a relationship between increased adherence to mask use, specifically, and effectiveness of reducing transmission to mask wearers: In one randomized study of influenza transmission in infected households in Australia, transmission risk for mask wearers was lower with greater adherence.[10] Further, the evidence is mixed from randomized studies on types of masks and risk for influenza-like illness transmission to mask wearers; for example, a recent systematic review and meta-analysis comparing N-95 respirators versus surgical masks found a statistically insignificant decline in influenza risk with N-95 respirators.[11]

Positions on widespread face mask use have differed worldwide but are changing over time. In the US, public health authorities did not recommend widespread face mask use in public at the start of the pandemic. The initially limited evidence on asymptomatic transmission and concern about mask shortages for the health care workforce and people caring for patients contributed to that initial decision. On April 3, 2020, the Centers for Disease Control and Prevention (CDC) issued new guidance advising everyone to wear cloth face covers in public areas where close contact with others is unavoidable, citing new evidence on virus transmission from asymptomatic or presymptomatic people.[12] Guidelines differ between countries, and some, including Germany, France, Italy, Spain, China, and South Korea, have mandated the use of face masks in public.[13–16]

This study adds complementary evidence to the literature on the impacts of widespread community use of face masks on COVID-19 spread from a natural experiment based on whether or not US states had mandated the use of face masks in public for COVID-19 mitigation as of May 2020. Fifteen states plus Washington, D.C., issued mandates for face mask use in public between April 8 and May 15.

We identified the effects of state mandates for the use of face masks in public on the daily COVID-19 growth rate, using an event study that examined the effects over different periods. We considered the impact of mandates for mask use targeted only to employees in some work settings, as opposed to communitywide mandates. This evidence is critical, as states and countries worldwide begin to shift to "reopening" their economies and as foot traffic increases. Mandating the public use of masks has become a socially and politically contentious issue, with multiple protests and even acts of violence directed against masked employees and those asking customers to wear face masks.[17] Face cover recommendations and mandates are part of the current set of measures, following earlier social distancing measures such as school and nonessential business closures, bans on large gatherings, and shelter-in-place orders being considered by states and local governments, especially as regions of the country reopen. For example, during Virginia's phase one reopening, begun May 22, 2020, everyone in the state was required to wear a face mask in public where people congregate.[18] Even though more states have issued such orders since the study was completed, it is critical to provide direct evidence on this question not only for public health authorities and governments but also for educating the public.

Study Data And Methods

DATA We collected information on statewide face cover mandate orders from public data sets on such policies and from searching and reviewing all state orders issued between April 1 and May 21, 2020. Our study focused on state executive orders or directives signed by governors that mandate use. Recommendations or guidelines from state departments of public health were not included, as these largely follow the CDC guidelines and might not necessarily add further information or impact. See online appendix A for a more detailed description of the data sources and measuring of the mandates.[19]

States differ in whether or not they require their citizens to wear face masks (covers) to limit COVID-19 spread. Between April 8 and May 15, governors of fifteen states and the mayor of Washington, D.C., signed orders mandating all individuals who can medically tolerate the wearing of a face mask do so in public settings (for example, public transportation, grocery stores, pharmacies, or other retail stores) where maintaining six feet of "social distance" might not always be practicable. These sixteen jurisdictions also have specific mandates requiring employees in certain professions to wear masks at all times while working.

In addition to these sixteen jurisdictions, twenty additional states have employee-only mandates (but no community mandate) requiring that some employees (for example, close-contact service providers such as in barber shops and nail salons) wear a face mask at all times while providing services. The face mask defined in these orders primarily refers to cloth face coverings or nonmedical masks. The state orders

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strongly discourage the use of any medical or surgical masks and N-95 respirators, which should be reserved for health care workers and first responders. The orders also clearly specify that the face masks are not a replacement for any other social distancing protocols. More information on dates and links to these state orders are in appendix exhibit A1 and appendices D and E.[19] Fifteen states had not yet issued community or employee mandates when we performed the study.

The main model used publicly available daily county-level data of confirmed COVID-19 cases from March 25 through May 21.[20] The data covered all states plus Washington, D.C., and the analytical sample included 2,930 unique counties plus New York City (five boroughs combined). See appendix A for a more detailed description of COVID-19 data.[19]

STATISTICAL ANALYSIS We employed an event study, which is generally similar to a difference-in-differences design, to examine whether statewide mandates to wear face masks in public affect the spread of COVID-19 based on the state variations noted earlier. This design allowed us to estimate the effects in the context of a natural experiment, comparing the pre-post mandate changes in COVID-19 spread in the states with mandates versus changes in COVID-19 spread in the states that did not pass these mandates, over time. The model also tested whether states issuing these mandates had differential pre-event trends in COVID-19 rates before they were issued. This is a critical assumption of the validity of an event study that must be upheld under testing. In addition, the model allowed us to control for a wide range of time-invariant differences between states and counties, such as population density and socioeconomic and demographic factors, plus time-variant differences between states and counties, such as other mitigation and social distancing policies, in addition to state-level COVID-19 testing rates.

We estimated the effects of face cover mandates on the daily county-level COVID-19 growth rate, which is the difference in the natural log of cumulative COVID-19 cases on a given day minus the natural log of cumulative cases in the prior day, multiplied by 100.[21] This measure gives the daily growth rate in percentage points.

The reference period for estimating the face cover mandate effects was 1–5 days before signing the order. We examined how effects change over five post-event periods: 1–5, 6–10, 11–15, 16–20, and 21 or more days. The model also tested for pre-event trends over the course of 6–10, 11–15, and 16 or more days before signing the mandate. For all counties in the analytical sample, the main model included daily data from March 31 (seven days before the first state signed a face cover mandate) through May 22. The models were estimated by least squares weighted by the county's 2019 population with heteroscedasticity-robust and state-clustered standard errors.

As noted earlier, all of the fifteen states plus Washington, D.C., that mandated face cover use in public also mandated employee mask use. To assess the effects of employee face cover mandates, we employed another event study model that focused solely on the employee face cover mandate as the policy intervention. In this analysis, we excluded the sixteen jurisdictions that enacted both public and employee face cover mandates and focused on the twenty states that enacted an employee-only mandate and the fifteen states with neither a public nor an employee mandate.

LIMITATIONS We were unable to measure face cover use in the community (that is, compliance with the mandate). As such, the estimates represent the intent-to-treat effects of these mandates—that is, their effects as passed and not the individual-level effect of wearing a face mask in public on one's own COVID-19 risk. Related, we did not measure enforcement of the mandates, which might affect compliance. We also did not have data on county-level mandates for wearing face masks in public. In some states without state-level mandates at the time of our study, such as California,[22] Texas,[23] and Colorado,[24] multiple counties had enacted such mandates. These county-level mandates did not bias the intent-to-treat estimates of effects of state-level mandates as actually passed, but they added local-level heterogeneity not directly accounted for in the model. We did examine the robustness of estimates to the exclusion of some of these states. Finally, we were able to examine only confirmed COVID-19 cases. However, there is evidence of a higher infection rate in the community than is reflected in the number of confirmed cases.[25]

Study Results

EFFECTS OF MANDATES FOR FACE COVERING IN PUBLIC Exhibit 1 plots the event study estimates of effects of state mandates for community face covering in public on the county-level daily growth rate of COVID-19 cases, with 95 percent confidence intervals, obtained from the main regression model (in appendix B),[19] using county-level daily data from March 31 through May22; appendix exhibit C1 (column 1) reports the exact estimates. The effects are shown over the course of five periods after signing the orders, relative to the five days before signing (which is the reference period). Also shown

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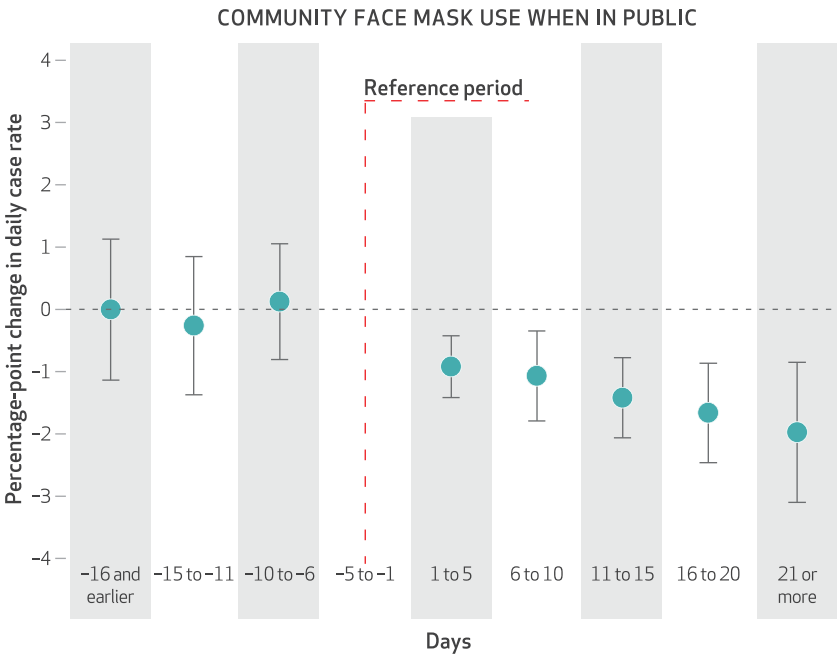
EXHIBIT 1

Event study estimates of the effects of states mandating community face mask use in public on the daily county-level growth rate of COVID-19 cases, 2020



SOURCE Authors' analysis of US county-level COVID-19 case data between March 31 and May 22, 2020. **NOTES** Event study estimates (dots) and 95% confidence intervals (bars) of the effects of states mandating community use of face covers or masks when people are in public on the county-level daily growth rate of COVID-19 cases over different periods before and after the mandate order was signed. The reference period was the first five days before the mandate order was signed. The model controlled for major COVID-19 mitigation policies as time-varying (closure of K–12 schools, county-level or statewide shelter-in-place orders, nonessential business closure, closure of restaurants for dining in, closure of gyms or movie theaters), COVID-19 tests per 100,000 people, county fixed effects, and day fixed effects. The model was estimated by least squares weighted by the county 2019 population, and the standard errors were robust to heteroscedasticity and clustered at the state level.

are estimated differences in daily COVID-19 growth rates between states with and without the mandates over the course of three periods before the reference period.

There was a significant decline in daily COVID-19 growth rate after the mandating of face covers in public, with the effect increasing over time after the orders were signed. Specifically, the daily case rate declined by 0.9, 1.1, 1.4, 1.7, and 2.0 percentage points within 1–5, 6–10, 11–15, 16–20, and 21 or more days after signing, respectively. All of these declines were statistically significant ($p < 0.05$ or less). In contrast, the pre-event trends in COVID-19 case growth rates were small and statistically insignificant.

We also projected the number of averted COVID-19 cases with the mandates for face mask use in public by comparing actual cumulative daily cases with daily cases predicted by the model if none of the states had enacted the public face cover mandate at the time they did (see details in appendix B).[19] The main model estimates suggested that because of these mandates, 230,000–450,000 cases may have been averted by May 22. Estimates of averted cases should be viewed cautiously and only as general approximations.

ROBUSTNESS CHECKS We estimated multiple extensions of the main event study model to assess the robustness of estimates to different model specifications and sample choices. These checks started the event study on March 26; added flexible controls for social distancing measures, state reopening measures, employee face mask use mandates, and county-specific time trends; and allowed time trends to vary by sociodemographic indicators. Other checks used the mandate effective date instead of the signing date, used hyperbolic sine transformation to account for zero cases, included states as the unit instead of counties, included only urban counties, and excluded some states without state-level mandates but with multiple counties having local mandates. The detailed description and results of these robustness checks are in appendix C.[19] The results were robust across these checks; effects were smaller when we used the effective dates instead of the signing dates, which differ by about two to three days, on average, suggesting earlier compliance, and when we used states as the unit of analysis. But the estimates remained meaningful and statistically significant in all checks.

EFFECTS OF EMPLOYEE-ONLY FACE COVER MANDATES As noted earlier, we also directly assessed the effects of states mandating only that certain employees wear face masks. Twenty states issued employee use mandates but not community use mandates. We reestimated the event study model described earlier for an employee-only mandate including those twenty states (issued between April 17 and May 9) and the fifteen states without mandates, and excluding the sixteen jurisdictions that issued both public and employee use mandates. Exhibit 2 plots the event study estimates of changes in county-level daily COVID-19 growth rates with the employee-only face cover mandates and their 95 percent confidence intervals. All pre- and postmandate estimates were small and insignificant. Overall, these results indicate no evidence of declines in daily COVID-19 growth rates with employee-only mandates.

Discussion

Around the world, governments have been fighting COVID-19 spread through a mix of policies and mitigation measures such as school and nonessential business closures and shelter-in-place orders. Some countries have also recommended or mandated widespread community use of face

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masks as a mitigation measure. However, the effectiveness of this measure is highly debated. The debate and uncertainty are fueled by the limited direct empirical evidence available on the magnitude of the effects of widespread face mask use in public on COVID-19 mitigation. There is a critical need for empirical evidence on the magnitude of these effects from natural experiments.[8] This evidence is especially relevant as governments reopen their economies and loosen social distancing restrictions while new infections continue to occur and while there is no vaccine or widely accessible or effective treatments in sight.

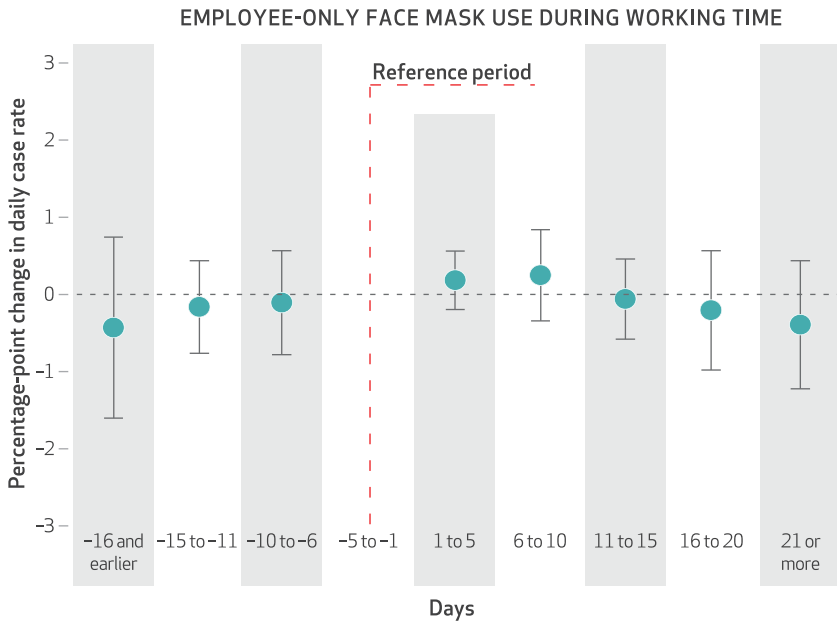
The study provides direct evidence on the effectiveness of widespread community use of face masks from a natural experiment that evaluated the effects of state government mandates in the US for face mask use in public on COVID-19 spread. Fifteen states plus Washington, D.C., mandated face mask use between April 8 and May 15. Using an event study that examined daily changes in county-level COVID-19 growth rates, the study found that mandating public use of face masks was associated with a reduction in the COVID-19 daily growth rate. Specifically, we found that the average daily county-level growth rate decreases by 0.9, 1.1, 1.4, 1.7, and 2.0 percentage points in 1–5, 6–10, 11–15, 16–20, and 21 or more days after signing, respectively.

These estimates are not small; they represent nearly 16 percent to 19 percent of the effects of other social distancing measures (school closures; bans on large gatherings; shelter-in-place orders; and closures of restaurants, bars, and entertainment venues) after similar periods from their enactment.[21] The estimates suggest that the effectiveness of and benefits from these mandates increase over time. By May 22, 2020, the estimates suggest that 230,000–450,000 COVID-19 cases may have been averted on the basis of when states passed these mandates. Again, the estimates of averted cases should be viewed cautiously, as they are sensitive to assumptions and different approaches to transforming the changes in the daily growth rate estimates to cases.

The early declines in the daily growth rate over the course of five days after signing the order are broadly consistent with the timing of the effects of other social distancing measures such as business closures.[21] Although the median incubation period is estimated to be around five days,[26] there is a wide range from 2.2 days (2.5th percentile) to 11.5 days (97.5th percentile), which suggests that for many people, symptoms may appear relatively early. Further, people may become aware of the mandates early through governors' briefings and related media reports, or they may be anticipating them.

EXHIBIT 2

Event study estimates of effects of states mandating only employee use of face masks during working time on daily county-level growth rate of COVID-19 cases



SOURCE Authors' analysis of US county-level COVID-19 case data between March 31 and May 22, 2020. **NOTES** Event study estimates (dots) and 95% confidence intervals (bars) of the effects of states mandating employee use of face covers or masks on the county-level daily growth rate of COVID-19 cases over different periods before and after the mandate order was signed. This model excluded fifteen states plus Washington, D.C., that made the use of face covering mandatory for both the general public and employees. The reference period was the first five days before the mandate order was signed. The model controlled for major COVID-19 mitigation policies as time-varying (closure of K–12 schools, county-level or statewide shelter-in-place orders, nonessential business closure, closure of restaurants for dining in, and closure of gyms or movie theaters), COVID-19 tests per 100,000 people, county fixed effects, and day fixed effects. The model was estimated by least squares weighted by the county 2019 population, and the standard errors were robust to heteroscedasticity and clustered at state level.

There is no evidence of differential pre-mandate COVID-19 trends with respect to issuing these mandates. The estimates represent the intent-to-treat effects of the statewide face cover mandates as passed, conditional on other national and local measures. In that way, the effects are independent of the CDC national guidance to wear face masks that was issued April 3, 2020.[12] These effects were robust to several model checks. The study provides evidence from a natural experiment on the effectiveness of mandating public use of face masks in mitigating the spread of COVID-19. We found no evidence for effects of states mandating employee face mask use, perhaps because many businesses themselves already required their employees to wear masks.[27,28] In that case, mandating employee mask use reinforce what many businesses already choose to do on their own.

Although the intent-to-treat estimates are of interest for understanding the effectiveness of

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these policies in limiting COVID-19 spread at the community and population levels, understanding how their effects change with compliance and enforcement strategies is important for designing effective policies. Our study has built the first step in estimating the overall effect of these policies as enacted. However, these policies vary in their strictness and the consequences of noncompliance. The mandates generally require wearing a face mask in public whenever the social distance cannot be maintained. States such as Delaware, Maryland, Massachusetts, and Maine clarify what "public" areas are (for example, indoor space in retail establishments, outdoor space in busy parking lots and waiting areas for take-out services, semi-enclosed areas such as at public transportation stops, and enclosed spaces such as in taxis and other public transportation). The language on enforcement and penalties for noncompliance also vary. In states such as Delaware, Hawaii, Maryland, and Massachusetts, the face mask orders state that they have the force and effect of law, with a willful violation subject to a criminal offense with penalties. For example, the order in Maryland states that "a person who knowingly and willfully violates this order is guilty of a misdemeanor and on conviction is subject to imprisonment not exceeding one year or a fine not exceeding $5,000 or both."[29] In contrast, the orders of other states such as Connecticut, Maine, and Pennsylvania, although clearly mandating the wearing of a face mask in public, do not appear to clearly specify that violations of the order are subject to criminal offense or penalties. Future work should examine whether and how differences in strictness and enforcement modify the effects of these mandates.

Compliance and enforcement may also differ across contextual factors (such as other social distancing measures, workforce distribution, population demographics, and socioeconomic and cultural factors). In that regard, it is important to clarify that the suggested benefits from mandating face mask use are not substitutes for other social distancing measures; the effects are conditional on the other enacted social distancing measures and how communities are complying with them. It is also important to extend the evidence into additional measures of exposure to the virus in the community as data become available, such as from serological testing for antibodies. Finally, future work can examine effects on deaths, which lag cases and change not only with the number of cases but also with case severity.

Conclusion

The study provides evidence that US states mandating the use of face masks in public had a greater decline in daily COVID-19 growth rates after issuing these mandates compared with states that did not issue mandates. These effects were observed conditional on other existing social distancing measures and were independent of the CDC recommendation to wear face covers issued April 3, 2020. As international and state governments begin to relax social distancing restrictions, and considering the high likelihood of a second COVID-19 wave in the fall and winter of 2020,[30] requiring the use of face masks in public could help in reducing COVID-19 spread. ■

An unedited version of this article was published online June 16, 2020, as a Fast Track Ahead Of Print article. That version is available in the online appendix.

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Trends in COVID-19 Incidence After Implementation of Mitigation Measures — Arizona, January 22–August 7, 2020

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Mitigating the spread of SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19), requires individual, community, and state public health actions to prevent person-to-person transmission. Community mitigation measures can help slow the spread of COVID-19; these measures include wearing masks, social distancing, reducing the number and size of large gatherings, pausing operation of businesses where maintaining social distancing is challenging, working from or staying at home, and implementing certain workplace and educational institution controls (*1*–*4*). The Arizona Department of Health Services' (ADHS) recommendations for mitigating exposure to SARS-CoV-2 were informed by continual monitoring of patient demographics, SARS-CoV-2 community spread, and the pandemic's impacts on hospitals. To assess the effect of mitigation strategies in Arizona, the numbers of daily COVID-19 cases and 7-day moving averages during January 22–August 7, 2020, relative to implementation of enhanced community mitigation measures, were examined. The average number of daily cases increased approximately 151%, from 808 on June 1, 2020 to 2,026 on June 15, 2020 (after stay-at-home order lifted), necessitating increased preventive measures. On June 17, local officials began implementing and enforcing mask wearing (via county and city mandates),* affecting approximately 85% of the state population. Statewide mitigation measures included limitation of public events; closures of bars, gyms, movie theaters, and water parks; reduced restaurant dine-in capacity; and voluntary resident action to stay at home and wear masks (when and where not mandated). The number of COVID-19 cases in Arizona peaked during June 29–July 2, stabilized during July 3–July 12, and further declined by approximately 75% during July 13–August 7. Widespread implementation and enforcement of sustained community mitigation measures informed by state and local officials' continual data monitoring and collaboration can help prevent transmission of SARS-CoV-2 and decrease the numbers of COVID-19 cases.

ADHS supports surveillance and investigation efforts of local public health departments, compiles surveillance and investigation information across counties, and provides infrastructure statewide to support infectious disease surveillance. Data on laboratory-confirmed and probable (*5*) COVID-19 cases (based on the Council of State and Territorial Epidemiologists case definitions)† were collected in the centralized Medical Electronic Disease Surveillance Intelligence System (MEDSIS),§ which is used by state, tribal, and county public health agencies to report human-based diseases in Arizona. Information was submitted to or entered into MEDSIS by health care providers, laboratories, local health departments, tribal entities, and ADHS. Multiple laboratory tests submitted for a single patient were combined into a single record. Specimen collection date was used for confirmed cases, and symptom onset date was used for probable cases.

Temporal trends were examined by comparing the number of daily COVID-19 cases (as of September 1)¶ and 7-day moving averages before, during, and after implementation of enhanced community mitigation measures, defined as the following: limitations on persons' time away from their place of residence except for essential activities; certain business closures and service limitations (e.g., occupancy limitations, curbside pickup, and delivery of goods); enhanced sanitation practices**; social distancing, employee mask wearing, and symptom screenings for all businesses operating a physical location; limitations on the occurrence and size of public events; and local mandates enforcing mask use. The 7-day moving average was calculated after the cumulative case count exceeded 20 cases and is presented to describe COVID-19 trends.

On March 11, 2020, Arizona declared a public health state of emergency to prepare for, prevent, respond to, and mitigate the spread of SARS-CoV-2. Additional guidance was provided to local officials, businesses, communities, and individual persons to implement social distancing and close schools statewide

* Mandates and ordinances varied and were county- and city-specific. Enforcement types included educating persons on the dangers of COVID-19 spread, issuing fines to persons and businesses who refused to comply with mandates, and loss of licenses for businesses not enforcing rules or mandates.

† https://cdn.ymaws.com/www.cste.org/resource/resmgr/ps/positionstatement2020/Interim-20-ID-02_COVID-19.pdf.

§ https://azdhs.gov/preparedness/epidemiology-disease-control/infectious-disease-services/index.php#medsis-faqs.

¶ https://www.azdhs.gov/preparedness/epidemiology-disease-control/infectious-disease-epidemiology/covid-19/dashboards/index.php.

** Based on guidance from ADHS, CDC, and the Department of Labor, and Occupational Safety and Health Administration to limit and mitigate the spread of COVID-19, including promoting healthy hygiene practices; and intensifying cleaning, disinfection and ventilation practices.

(March 15); postpone and limit large gatherings to fewer than 50 persons; recommend telework options; restrict access to congregate settings; require restaurants to provide dine-out options only; and close all bars, gyms, and movie theaters in counties with confirmed COVID-19 cases (March 19) (Table). Based on Arizona data and CDC guidance (*1*,*2*), ADHS also recommended limiting persons' time away from their place of residence except for essential activities (i.e., stay-at-home order, "Stay Home, Stay Healthy, Stay Connected")†† (March 31).

During April 1–May 15, the 7-day moving average of daily cases ranged from 154 to 443 (Figure). During April 29–May 11, Arizona initiated a phased approach for retail shops and stores, cosmetologists, and barbers to reopen and operate, and for restaurants to resume dine-in services; the stay-at-home order ended May 15.

Average daily cases increased 151% from June 1 (808) to June 15 (2,026), necessitating an increased focus on preventive measures by businesses, communities, and individual persons. Updated guidance from state officials provided local governments the authority to implement mask policies (June 17) and enforcement measures tailored to local public health needs (local policies were applicable to approximately 85% of the total Arizona population). Before June 17, mask wearing had not been widely mandated or enforced. Arizona limited organized public events to fewer than 50 persons (with some exceptions); closed bars, gyms, movie theaters, and water parks and recreational tubing facilities (June 29); and limited restaurants' indoor dining to <50% capacity, with at least 6 feet of separation between patrons (July 9). The 7-day moving average of daily cases peaked during June 29–July 2 (range = 4,148–4,377), stabilized during July 3–12 (range = 3,609–4,160), and subsequently decreased 75% from July 13 (3,506) to August 7 (867). Mitigation measures put in place in June were extended through August to further limit transmission.

Discussion

Quantitative data on the effectiveness of community mitigation measures at suppressing the spread of COVID-19 are limited. The primary goal of implementing widespread enhanced mitigation measures in Arizona was to protect and save lives and maintain capacity in the health care system. A combination of voluntary and enforceable measures is more effective than any single measure (*6*). Mitigation measures mandated through public policy can effectively increase social distancing (*7*), and wearing masks has prevented transmission of SARS-CoV-2 (*8*). In Arizona, decreases in daily COVID-19

†† https://www.azdhs.gov/preparedness/epidemiology-disease-control/infectious-disease-epidemiology/index.php#novel-coronavirus-admin-orders; https://azgovernor.gov/executive-orders.

TABLE. Public policies to implement and enforce COVID-19 community mitigation measures and dates of issue/reissue* — Arizona, March 11–August 7, 2020

Mitigation measure	Date of issue/reissue
Declaration of emergency	Mar 11
School closure (on-site learning)	Mar 15
Limits on senior living facilities visitation	Mar 19
Expanded availability and coverage for telemedicine for persons, pets, and animals	Mar 25, Apr 1
Deferred requirements to renew driver license	Mar 20
Stay-at-home order	Mar 30–May 15
Business/Service closures	
Bars	Mar 19, Jun 29, Jul 23
Movie theaters	Mar 19, Jun 29, Jul 23
Indoor gyms and fitness clubs	Mar 19, Jun 29, Jul 23
Restaurants, on-site dining	Mar 19
Pools	Mar 19
Water parks and recreational tubing facilities	Jun 29, Jul 23
Business/Service limits (requirements)	
All businesses operating a physical location (enhanced sanitation,† social distancing, employee mask wearing, symptom screenings)	Jun 17
Retail (limited capacity, social distancing, enhanced sanitation)	Apr 29
Barbers and cosmetologists (employee mask wearing, spaced appointments, enhanced sanitation)	May 4
Restaurants (social distancing, limited capacity, employee mask wearing, patron mask wearing [when not eating or drinking], employee screening, enhanced sanitation)	May 4, Jul 9
Public pools (e.g., at hotels; limited capacity)	Jun 29, Jul 23
Private pools in public areas (e.g., multihousing complexes; limited capacity)	Jun 29, Jul 23
Public events (<50 persons)	Mar 15, Jun 29, Jul 23
Wearing masks (mandatory)	
Local officials able to mandate and enforce wearing masks	Jun 17
Yuma County	Jun 18
Maricopa County	Jun 19
Pima County	Jun 19
Santa Cruz County	Jun 19
Coconino County	Jun 20
>40 other cities/tribal communities	Jun 17–25§

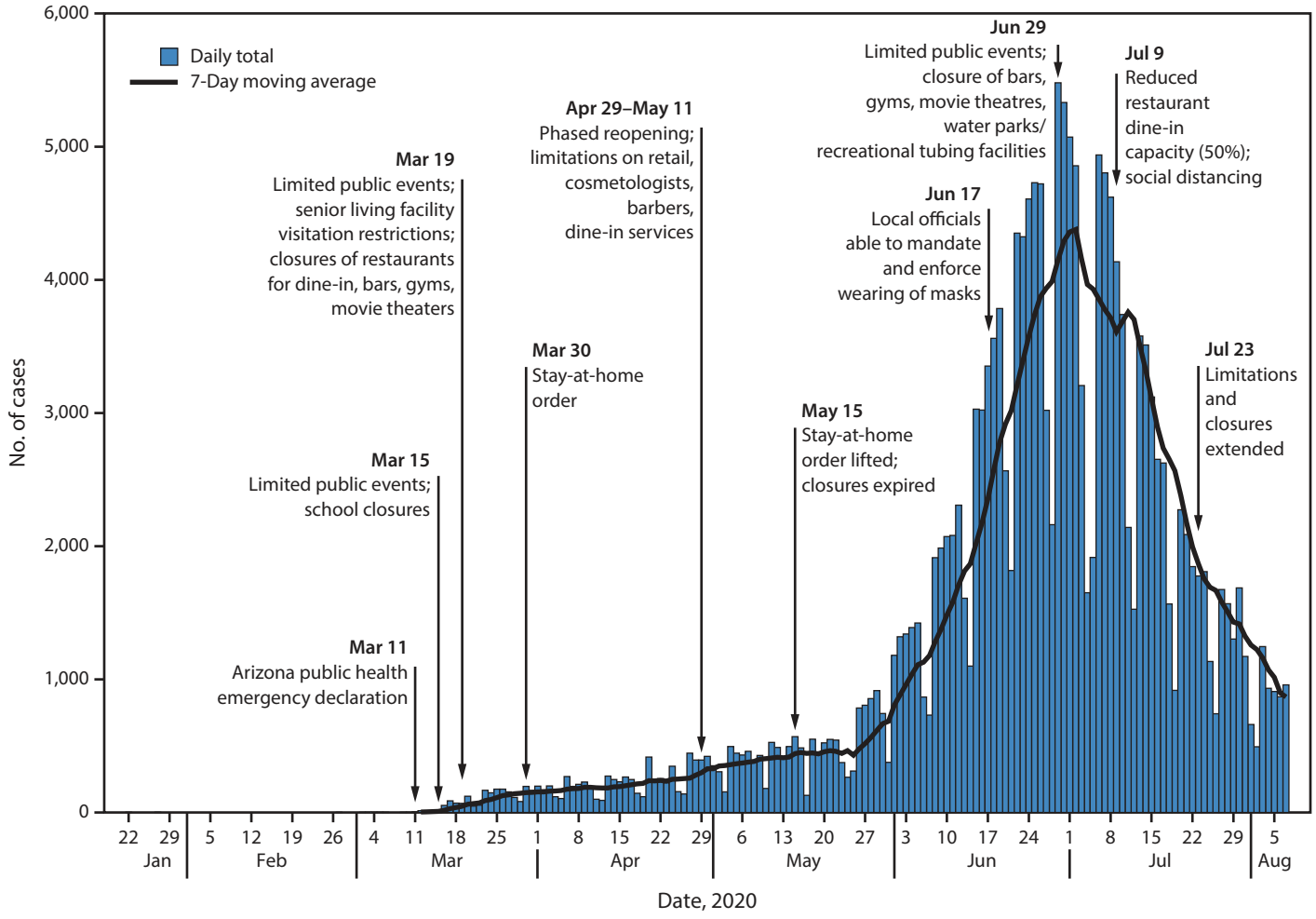
Abbreviation: COVID-19 = coronavirus disease 2019.

* Issue dates are the dates the issuing official signed the order implementing the mandatory mitigation measure. In some instances, mitigation measures were effective either immediately or within 1 to 3 days of issue. https://www.azdhs.gov/preparedness/epidemiology-disease-control/infectious-disease-epidemiology/index.php#novel-coronavirus-admin-orders; https://azgovernor.gov/executive-orders.

† Based on guidance from the Arizona Department of Health Services, CDC, Department of Labor, and Occupational Safety and Health Administration (OSHA) to limit and mitigate the spread of COVID-19 including promoting healthy hygiene practices; and intensifying cleaning, disinfection and ventilation practices.

§ Other tribal communities with mask mandates (issued June 18–23) included Fort McDowell Yavapai Nation, Gila River Indian Community, Navajo Nation, Salt-River Pima-Maricopa Indian Community, Tohono O'Odham Nation. Other cities with mask mandates (issued June 17–25) included Avondale, Bisbee, Buckeye, Carefree, Casa Grande, Chandler, Clarkdale, Clifton, Coolidge, Cottonwood, Douglas, Flagstaff, Fountain Hills, Gila Bend, Gilbert, Glendale, Globe, Goodyear, Guadalupe, Jerome, Kingman, Litchfield Park, Mammoth, Mesa, Miami, Nogales, Oro Valley, Paradise Valley, Payson, Peoria, Phoenix, San Luis, Sedona, Scottsdale, Somerton, Superior, Surprise, Tempe, Tolleson, Tucson, Youngtown, Yuma. Several other tribal communities and cities encouraged but did not mandate wearing masks.

FIGURE. Selected community mitigation measures* and COVID-19 case counts† and 7-day moving averages§ — Arizona, January 22–August 7, 2020



Abbreviation: COVID-19 = coronavirus disease 2019.

* Issue dates are the dates the issuing official signed the order implementing the mandatory mitigation measure. In some instances, mitigation measures were effective either immediately or within 1 to 3 days of issue. https://www.azdhs.gov/preparedness/epidemiology-disease-control/infectious-disease-epidemiology/index.php#novel-coronavirus-admin-orders; https://azgovernor.gov/executive-orders.

† As of September 1, 2020. Specimen collection date was used for confirmed cases, and symptom onset date was used for probable cases.

§ Plotting of 7-day moving average began when cumulative case count exceeded 20 cases.

cases were observed after widespread sustained community mitigation measures that promoted social distancing, limited large gatherings, paused operations of businesses where mask use and social distancing were difficult to maintain, mandated and enforced mask wearing, and promoted voluntary resident actions to stay at home and wear masks (when and where not mandated). The number of COVID-19 cases stabilized and began to decrease approximately 2 weeks after local officials began mandating mask wearing (throughout several counties and cities) and enhanced sanitation practices. Additional declines in case counts were associated with implementation of statewide limitations and closures sustained throughout July and extended into August.

The findings in this report are subject to at least four limitations. First, the relationship between mitigation measures and changes in case counts are temporal correlations and should not be interpreted to infer causality. Other factors that might have influenced the rate of change (e.g., travel restrictions, neighboring state mitigation measures, and individual choices to reduce movement before implementation of mandates) cannot be ruled out. Second, health centers run by tribal entities and federal health facilities (i.e., Indian Health Service, Veteran's Administration, and Department of Defense) in the state are requested but not required to comply with state reporting rules. Many of these health centers and federal health facilities complied with reporting, but the completeness of reporting by these entities is unknown. Third, adherence to

Summary

What is already known about this topic?

Community mitigation measures can help slow the spread of COVID-19.

What is added by this report?

The number of COVID-19 cases in Arizona stabilized and then decreased after sustained implementation and enforcement of statewide and locally enhanced mitigation measures, beginning approximately 2 weeks after implementation and enforcement of mask mandates and enhanced sanitations practices began on June 17; further decreases were observed during July 13–August 7, after statewide limitations and closures of certain services and businesses.

What are the implications for public health practice?

Widespread implementation and enforcement of sustained community mitigation measures, including mask wearing, informed by state and local officials' continual data monitoring and collaboration can help prevent transmission of SARS-CoV-2 and decrease the numbers of COVID-19 cases.

mitigation measures was not assessed, nor could the extent to which each individual measure affected the number of incident COVID-19 cases be established. Finally, Arizona might not be representative of other U.S. states, and community mitigation measures might have a different impact in more populous or densely populated states; thus, these findings are not necessarily generalizable to other settings.

Enhanced mitigation measures should be implemented by communities and persons to slow COVID-19 spread, particularly before a vaccine or therapeutic treatment becomes widely available. State, local, and tribal officials are best positioned to continually monitor data and collaborate to determine the level and types of enhanced mitigation required. Mitigation measures, including mask mandates, that are implemented and enforced statewide appear to have been effective in decreasing the spread of COVID-19 in Arizona.

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Mask Wearing and Control of SARS-CoV-2 Transmission in the United States

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Introduction: Cloth face coverings and surgical masks have become commonplace across the United States in response to the SARS-CoV-2 epidemic. While evidence suggests masks help curb the spread of respiratory pathogens, research is limited. Face masks have quickly become a topic of public debate as government mandates have started requiring their use. Here we investigate the association between self-reported mask wearing, social distancing and community SARS-CoV-2 transmission in the United States, as well as the effect of statewide mandates on mask uptake. **Methods:** Serial cross-sectional surveys were administered June 3 through July 27, 2020 via web platform. Surveys queried individuals' likelihood to wear a face mask to the grocery store or with family and friends. Responses (N=378,207) were aggregated by week and state and combined with measures of the instantaneous reproductive number (R_t), social distancing proxies, respondent demographics and other potential sources of confounding. We fit multivariate logistic regression models to estimate the association between mask wearing and community transmission control (R_t<1) for each state and week. Multiple sensitivity analyses were considered to corroborate findings across mask wearing definitions, R_t estimators and data sources. Additionally, mask wearing in 12 states was evaluated two weeks before and after statewide mandates. **Results:** We find an upward trend in mask usage across the U.S., although uptake varies by geography and demographic groups. A multivariate logistic model controlling for social distancing and other variables found a 10% increase in mask wearing was associated with a 3.53 (95% CI: 2.03, 6.43) odds of transmission control (R_t<1). We also find that communities with high mask wearing and social distancing have the highest predicted probability of a controlled epidemic. These positive associations were maintained across sensitivity analyses. Segmented regression analysis of mask wearing found no statistical change following mandates, however the positive trend of increased mask wearing over time was preserved. **Conclusion:** Widespread utilization of face masks combined with social distancing increases the odds of SARS-CoV-2 transmission control. Mask wearing rose separately from government mask mandates, suggesting supplemental public health interventions are needed to maximize mask adoption and disrupt the spread of SARS-CoV-2, especially as social distancing measures are relaxed.

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Introduction

In December 2019, SARS-CoV-2 and the resulting COVID-19 disease were first identified in Wuhan, China[1]. The disease has spread globally since its identification, causing widespread morbidity and mortality[2,3]. In the absence of a vaccine or curative therapy, governments in the United States and worldwide have adopted numerous approaches to curb the virus's continued transmission[4,5]. Despite widespread implementation, the efficacy of various nonpharmaceutical interventions has been intensely debated[6], resulting in significant individual and community heterogeneity in the acceptance of these interventions[7], including the use of face masks and respirators[8].

Evidence strongly supports N95 respirators as an effective method to prevent viral respiratory transmission, but supply chain shortages necessitate their preferential allocation to high-risk, front-line medical personnel[9,10]. Consequently, cloth face coverings and surgical masks (henceforth collectively, "face masks") are recommended as an alternative for the general public[11]. Following the initial spread of the virus in the United States, many local and state jurisdictions have mandated the use of face masks in public settings[5]. These masks are intended to serve as a mechanical barrier that absorbs virus-laden droplets expelled by the user[12]. Therefore, their purpose is to reduce transmission events by the user, rather than protect the individual from infection. Accordingly, face masks are advocated as a source of collective benefit, akin to herd immunity with vaccination, which is most successful with high levels of adoption[13].

Real-world evidence on the effectiveness of face masks at preventing respiratory transmission of SARS-CoV-2 is limited but growing[11,14]. While work on other respiratory infections[15] and two recent case reports[16,17] suggest mask usage may be effective, a recent global analysis found a limited marginal effect of mask mandates in the presence of other interventions[18]. Here, we use an ecological approach to assess mask compliance directly, irrespective of mandates. We combine survey data on personal mask wearing habits across the United States with a time varying measure of transmission control, as quantified by the effective reproductive number (R_t) in each state. We then evaluate the association of a change in mask wearing with the timing of mask mandates to better understand the conflicting evidence.

Materials and Methods

Survey Description

A web survey hosted on SurveyMonkey.com was deployed and promoted in conjunction with COVIDNearYou (a Boston Children's Hospital based digital surveillance platform), as part of an effort to increase participatory syndromic surveillance for COVD-19[19–21]. The survey data were collected through SurveyMonkey's "end page river sampling" [www.surveymonkey.com/mp/survey-methodology]. Briefly, over 2 million people around the world complete surveys designed by individuals, community groups, and businesses using the SurveyMonkey online survey platform every day. At the completion of these surveys, respondents in the United States are randomly offered to participate in the COVIDNearYou web survey. The river sample is not a stochastic probability sample of the entire population; however, it reaches respondents with diverse geographic and demographic backgrounds to ensure broad representativeness. Responses to this questionnaire were collected between June 3, 2020 and July 27, 2020 in all 50 states and the District of Columbia. Respondents were not provided incentives to complete the questionnaire. This study was approved by the Boston Children's Hospital Institutional Review Board.

Survey responses were analyzed using crude data (unweighted) and survey weights that reflect the demographic composition of the United States. Survey weights standardize for age, race,

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sex, education, and geography using the Census Bureau's American Community Survey. Also included was an additional smoothing parameter for political party identification based on aggregates of SurveyMonkey research surveys, refreshed weekly with rolling two-week aggregated data. Weights are generated daily for weekday surveys and once after weekend surveys.

Mask Wearing Exposure

Survey respondents were asked a range of questions (full survey: www.surveymonkey.com/r/COVIDNearYouSurveyMonkey) including how likely they were to wear a mask while "grocery shopping" or "visiting family and friends" on a 4-point scale, from "very likely" to "not likely at all". A composite exposure of consistent self-reported face mask wearing (referred to as *mask wearing*) is defined as the percentage of respondents who replied "very likely" to both questions. The percentage of respondents who replied "very likely" to each question, separately, was also evaluated in sensitivity analyses. Surveys without responses to either question (N=4,186) were excluded. For validation, the exposure was aggregated by county (limited to those with over 50 observations, N = 324) between July 2 and July 14, 2020 and compared against cross-sectional New York Times and Dynata interviews on mask wearing[8] completed during this time period.

Social Distancing Exposure

Population-level social distancing by state and by week was quantified as the duration of time spent at home compared to baseline (defined as January 3, 2020 - February 6, 2020)[22]. Duration of time spent at home was estimated with the Google community "residential time" mobility measure[23], which was estimated using anonymized and aggregated data from individual Google users who opted into location history on their mobile devices[24]. A measure of social distancing from Facebook's COVID-19 symptom survey[25] was included in a sensitivity analysis. Individuals were asked "In the past 24 hours, with how many people have you had direct contact, outside of your household," in a variety of settings. The number of self-reported contacts at "social gatherings" (censored outlier responses) was aggregated over each week and state utilizing Facebook's weighted sampling scheme[25].

Community Transmission Control Outcome

The daily estimated instantaneous reproductive number (R_t) – the number of secondary cases arising from a single case for a given day – was used to measure state-specific community transmission control. R_t was aggregated to the week and dichotomized as epidemic slowing (1 if $R_t < 1$) or maintenance/growth (0 if $R_t \geq 1$). R_t estimates were extracted from rt.live, which was fit to case data from The COVID Tracking Project (method and adaptation previously described[26–28]). Sensitivity analyses were performed with R_t values extracted from epiforecasts.io[29,30] (available through July 19, 2020) and with R_t dichotomized at different cutoffs.

Modelling Mask Effectiveness on Transmission Control

We fit multivariate logistic regression models using *R* (version 3.6.2) to predict the community transmission control outcome (dichotomized R_t) using state- and week-specific estimates of mask wearing (crude and survey-weighted) and social distancing (relative residential time). State population density was included as a potential confounder given the association between population structure and SARS-CoV-2 transmission[31,32] as well as the association between urban versus rural regions and face mask usage[8]. Percent non-white was included as a confounder due to the relationship with epidemiological indicators of SARS-CoV-2[33] and uptake of non-pharmaceutical interventions[34]. A linear weekly time trend was also modeled.

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To address the potential of reverse causation, where high previous transmission induced elevated mask wearing as well as lower potential R_t (due to reduced effective contact availability), we included each state's peak R_t from March-May 2020 as a confounder in a sensitivity analysis. We also evaluated an interaction between the exposures of mask wearing and social distancing.

For each model, influential observations (up to n = 24) with a Cook's distance over 4/N were excluded[35]. The influential observations removed varied between models, except for observations from New Jersey (characterized by high mask wearing, very high social distancing, and high community transmission control) which were repeatedly excluded for influence. Serial correlation was assessed in the final models but was abated following the aggregation of data.

Two additional modeling frameworks were utilized in sensitivity analyses. While each survey consisted of an independent sample of respondents, a mixed model with a random intercept for state and the same fixed effects as reported in the crude logistic model (model 1) was fit to account for the potential hierarchical structure of the observations. Additionally, an ordinal logistic regression was fit to measure the association of mask wearing with multiple, ordered categories of R_t.

Mask Mandates

The date for each statewide mask mandate was extracted from the masks4all.org database[36]. To assess the effect of mask mandates on mask wearing, segmented regression[37] was run comparing the 2 weeks preceding and 2 weeks following each state's intervention.

Results

Self-reported mask wearing was evaluated using N=378,207 survey responses recorded between June 3, 2020 and July 27, 2020. Most (84.6%) reported "very likely" to wearing a face mask to the grocery store, while just under half (40.2%) did so to visit friends and family. A similar number (39.8%) reported they were very likely to wear a mask to the grocery store and with family and friends. Very few (4.7%) reported they were "not likely [to wear a mask] at all" in either situation. The percentage of individuals in each county who reported "always" wearing a mask in the New York Times interviews was correlated with those who reported they were "very likely" to wear a mask to the grocery store (Spearman's ρ = .80, p<0.0001), with family and friends (Spearman's ρ = .57, p<0.0001), and the composite score (Spearman's ρ = .57, p<0.0001).

Mask wearing was higher among women, elderly, non-white or Hispanic, and lower income respondents (p<0.0001, **Table 1**). There was substantial geographic heterogeneity in survey responses (**Figure 1**, **A.**), with the highest percentage of mask wearers along the coasts and southern border, as well as in large urban areas. There was a general trend of increased mask use across U.S. Census Divisions throughout the survey period (**Figure 1**, **B.**) and the West North Central Census Division reported the lowest mask usage across the entire period surveyed.

We find a negative relationship between the mean percentage of people that report wearing a mask and the instantaneous reproductive number (**Figure 2)**. In a multivariate logistic regression model adjusting for confounders, social distancing and a time trend, there is a significant association between percent reporting mask wearing and community transmission control (i.e. R_t<1) with an OR = 1.14 [95% CI: 1.07,1.20] (**Table 2, Model 1**). A 10% increase in mask wearing was associated with an over three-fold increase in odds of transmission control [OR = 3.53, 95% CI: 2.03, 6.43]. The association between mask wearing and community

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transmission control was robust to changes in definitions of mask wearing, R_t estimated from epiforecasts.io, control for peak R_t, and survey-weight standardization (**Table 2, Models 2-6**). When adjusting for community self-reported contacts instead of mobility, the association between one percent change in mask wearing and community transmission control was attenuated [OR = 1.09, 95% CI: 1.02, 1.16], but remained significant (**Figure S1**). Mask wearing was also significantly associated with reduced transmission across multiple R_t dichotomization thresholds (**Figure S2**) and when categorized as an ordinal variable (**Figure S3**). A mixed model with a random intercept for state found a stronger association of mask wearing on community transmission control [OR = 1.18, 95% CI: 1.07, 1.30].

Communities with high levels of mask wearing and social distancing are predicted by the model to have the highest probability of community transmission control (**Figure 3**). States with the highest percentage of reported mask wearing but lowest levels of social distancing have less than a 35% probability of community transmission control, though there are wide confidence intervals. The interaction between social distancing and mask wearing was not statistically significant (**Table 2, Model 7**).

We evaluated the change in mask wearing in the 2 weeks before and after statewide mask mandates for 12 states (**Figure 4**). While there was a general trend of increased mask usage across these states over time, the linear segmented regression models resulted in no significant change in slope in crude, β = .04 [95% CI: -.47, .54], or weighted, β = .31 [95% CI: -.28, .91], mask usage following the interventions. There was a non-significant 2.2% [95% CI: -2.1%,6.5%] change in average mask usage following the mandate in the unweighted model and a 2.31% [95% CI: -2.76%,7.38%] change in the weighted model.

Discussion

The effect of mask wearing on community transmission of SARS-CoV-2 has been the subject of substantial debate, despite evidence from detailed transmission studies and population-wide data from other respiratory pathogens. Here we present findings from over 300,000 serial cross-sectional surveys administered daily in June and July 2020 that confirm a high percentage of reported face mask wearing is associated with a higher probability of transmission control in U.S. states. Face mask wearing was more commonly reported among certain socio-economic groups (especially non-white and lower-income respondents). However, the impact of face mask wearing on lowering the instantaneous reproductive number below one – the threshold required for transmission control – remained despite adjusting for demographics, social distancing and prior peak transmissibility.

Mask wearing is shown to increase the odds of transmission control across all levels of social distancing, suggesting that any intervention to improve this community-based behavior may be worthwhile. The absence of a statistical change in mask wearing the two weeks following state-wide mandates highlights the point that regulation alone may not drive increased masking behavior. However, we found that there is a general increase in mask wearing prior to the implementation of these policies and mask mandates may be important tools in maintaining this trend. Masking behavior assessed from anonymous surveys may provide insight into where education or other interventions should be directed. These results are consistent with case studies of mask wearing in the United States[16,17], and potentially provide some insight into why one report found no substantial effect of mask mandates in conjunction with other interventions[18]. The data presented here may highlight a gap between governmental policy and actual user behavior, but more research is needed.

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Our evidence supports the role of mask wearing in controlling SARS-CoV-2 transmission; however, this ecological study cannot inform questions of causality. It is difficult to disentangle individuals' engagement in mask wearing from their adoption of other preventative hygiene practices, and mask wearing may be serving as a proxy for other risk avoidance behaviors not queried (e.g. avoiding indoor spaces) – especially considering the magnitude of the reported effects. While our findings remained despite controlling for individual-level contacts from the Facebook survey, a proxy that likely includes other aspects of risk reduction, the possibility of residual confounding is likely. Additionally, observations from smaller states are overrepresented when results are aggregated at the state-level and further observations from survey respondents may not reflect the general population. However, our findings were consistent even with application of US census-based survey-weights.

A state that demonstrates social distancing may also be subject to additional non-modeled but impactful interventions including gathering size reductions, travel limitations, and the closing of businesses[38]. While the social distancing proxy used here captures the broad activity level that would result from the implementation of these policies, future research should focus on incorporating data from disaggregated interventions with empirical assessments of mask wearing. Additionally, potential R_t and mask wearing within a state may be the result of prior transmission. While we showed the effect of mask wearing was robust to peak R_t in the first wave of the epidemic, our methods do not control for time-dependent confounding or variations in mask usage by susceptibility status.

The validity of epidemiologic parameters of transmission are only as accurate as the incidence data to which the models are fit. If states reporting low mask wearing also underreport incidence (e.g. limited testing), we may be underestimating the true effect of mask wearing. Conversely, instantaneous R_t estimations of transmission are subject to uncertainty, especially towards the end of the time-series before reports are complete[27]. While our results were robust to different estimators, our model does not account for estimation error. Additionally, mask wearing measures, social distancing and R_t all exhibit significant temporal autocorrelation. To combat this, we dichotomized R_t and aggregated our exposures by week, but further analyses may consider complex time-series models, mechanistic and quasi-experimental methods to estimate the effect of face masks.

We find a community benefit for "face masks" which collectively include masks of various hypothesized efficacies[39]. We did not query specific mask type or the use of face shields in conjunction with masks. The reported association may understate the maximum potential for face masks to curb respiratory transmission, which can only be realized through increasing the utilization of superior mask materials (i.e. choosing surgical masks over fleece gaiters). Additional study of effect modification by mask type is necessary to estimate true causal effects.

When considering the various challenges the US population has faced in slowing the spread of SARS-CoV-2, evidence on the impact of nonpharmaceutical interventions is paramount. Our data suggest widespread use of face masks by the general public may aid in limiting the SARS-CoV-2 epidemic as social distancing restrictions are rolled back around the United States. Given mixed evidence on the effect of mask mandates, but a strengthening body of evidence on the effect of masks, policy makers should consider innovative strategies for evaluating and increasing mask usage to help control the epidemic.

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Contributions

BMR, LFW and JSB conceived of the study. BMR, LFW, CMA and JSB wrote the first draft of the manuscript. BMR, LFW, MRB, and CMA contributed to the data analysis. JC, JB and JC oversaw and implemented data collection. All authors contributed to the interpretation of the data and editing of the final manuscript. All authors have seen and approved the manuscript.

Declaration of Interests

LB sits on the board of Ending Pandemics and the Skoll Foundation.

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Table 1. Characteristics of Unweighted Survey Respondents by Mask Wearing Status

Characteristics of Unweighted Survey Respondents by response to the question, “how likely are you to wear a face mask to visit family and friends.” For each response, N (row %) and p-value from χ^2 test is presented. Overall N (column %) also included for each category.

How Likely Are You To Wear a Face Mask To Visit Family and Friends?

	Very Likely No. 152,158	Somewhat Likely No. 81,596	Not So Likely No. 73,723	Not Likely At All No. 67,832	Total No. 375,309	P-value
Sex						< 0.0001
Female	103,624 (42%)	54,314 (22%)	47,825 (19%)	40,908 (17%)	246,671 (66%)	
Male	46,543 (38%)	26,374 (21%)	25,226 (20%)	25,910 (21%)	124,053 (33%)	
Missing	1,991 (43%)	908 (20%)	672 (15%)	1,014 (22%)	4,585 (1%)	
Age						< 0.0001
13-17	7 (33%)	4 (19%)	5 (24%)	5 (24%)	21 (0%)	
18-24	6,328 (33%)	4,626 (24%)	4,564 (24%)	3,895 (20%)	19,413 (5%)	
25-34	15,943 (35%)	9,790 (22%)	9,955 (22%)	9,629 (21%)	45,317 (12%)	
35-44	25,679 (36%)	14,938 (21%)	14,339 (20%)	15,503 (22%)	70,459 (19%)	
45-54	32,138 (40%)	17,505 (22%)	15,778 (19%)	15,755 (19%)	81,176 (22%)	
55-64	35,005 (44%)	17,697 (22%)	14,915 (19%)	12,772 (16%)	80,389 (21%)	
65+	35,763 (48%)	15,874 (21%)	13,114 (18%)	9,372 (13%)	74,123 (20%)	
Missing	1,295 (29%)	1,162 (26%)	1,053 (24%)	901 (20%)	4,411 (1%)	
Race/Ethnicity						< 0.0001
White	91,105 (35%)	58,395 (22%)	58,303 (22%)	55,380 (21%)	263,183 (70%)	
Black	26,904 (62%)	8,638 (20%)	4,579 (11%)	2,955 (7%)	43,076 (11%)	
Hispanic	8,858 (57%)	3,237 (21%)	2,166 (14%)	1,309 (8%)	15,570 (4%)	
Other	16,510 (49%)	7,314 (22%)	5,513 (16%)	4,202 (13%)	33,539 (9%)	
Missing	8,781 (44%)	4,012 (20%)	3,162 (16%)	3,986 (20%)	19,941 (5%)	
Household Income						< 0.0001
<$50,000	47,847 (44%)	23,025 (21%)	19,373 (18%)	17,927 (17%)	108,172 (29%)	
$50,000-$99,000	43,380 (39%)	24,601 (22%)	22,285 (20%)	20,707 (19%)	110,973 (30%)	
>$100,000	51,010 (38%)	29,095 (22%)	27,951 (21%)	25,954 (19%)	134,010 (36%)	
Missing	9,921 (45%)	4,875 (22%)	4,114 (19%)	3,244 (15%)	22,154 (6%)	
Census Division						< 0.0001
New England	10,747 (48%)	5,421 (24%)	3,838 (17%)	2,518 (11%)	22,524 (6%)	
Middle Atlantic	20,939 (45%)	10,336 (22%)	8,407 (18%)	6,826 (15%)	46,508 (12%)	
East North Central	17,206 (35%)	11,205 (23%)	10,723 (22%)	10,117 (21%)	49,251 (13%)	
West North Central	7,692 (28%)	6,168 (23%)	6,557 (24%)	6,762 (25%)	27,179 (7%)	
East South Central	7,508 (35%)	4,484 (21%)	4,530 (21%)	4,838 (23%)	21,360 (6%)	
West South Central	15,332 (40%)	7,883 (21%)	7,490 (20%)	7,417 (19%)	38,122 (10%)	
South Atlantic	34,688 (42%)	17,453 (21%)	15,610 (19%)	14,218 (17%)	81,969 (22%)	
Pacific	27,244 (48%)	11,989 (21%)	9,878 (17%)	8,028 (14%)	57,139 (15%)	
Mountain	10,802 (35%)	6,657 (21%)	6,690 (21%)	7,108 (23%)	31,257 (8%)	

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Table 2. Regression Results

Estimated odds ratios [95% confidence intervals] from multivariable logistic regression models. Model 1 reports the association of the outcome of community transmission control (R_t<1) with the percentage of surveys reporting “very likely” to wear a mask to the grocery store and to visit family and friends, aggregated by state and week. Model 1 controls for a weekly time trend, social distancing (relative Google mobility “residential time”), percentage non-white and population density. We evaluated the association using survey weights (Model 2), alternative estimators of R_t (Model 3), and alternative definitions of mask usage (Models 4 and 5). Model 6 accounts for each states peak R_t prior to the start of the study and model 7 includes an interaction of mask wearing with social distancing.

	1. Association with R_t (Low)	2. Weighted Sample	3. Association with R_t (epiforecasts)	4. Alternative Mask Definition 1	5. Alternative Mask Definition 2	6. Accounting for Prior Transmission	7. With Interaction Term
Mask Wearing (%, Composite)	1.14 ***	1.13 ***	1.10 ***			1.14 ***	1.17 **
	[1.07, 1.20]	[1.07, 1.20]	[1.04, 1.16]			[1.08, 1.21]	[1.05, 1.32]
Time Trend (Week)	1.38 ***	1.35 ***	1.27 ***	1.37 ***	1.40 ***	1.38 ***	1.35 ***
	[1.17, 1.59]	[1.16, 1.57]	[1.11, 1.45]	[1.19, 1.58]	[1.20, 1.63]	[1.18, 1.59]	[1.17, 1.56]
Social Distancing (%, Proxy)	1.42 ***	1.43 ***	1.37 **	1.41 ***	1.52 ***	1.39 **	1.77
	[1.18, 1.74]	[1.17, 1.75]	[1.13, 1.66]	[1.15, 1.72]	[1.24, 1.86]	[1.13, 1.72]	[0.88, 3.15]
Non-White (%)	0.91 ***	0.91 ***	0.94 ***	0.91 ***	0.93 ***	0.90 ***	0.95 ***
	[0.91, 0.96]	[0.91, 0.97]	[0.92, 0.97]	[0.91, 0.96]	[0.93, 0.96]	[0.90, 0.95]	[0.92, 0.97]
Density (1000 people/sq mi)	0.08 **	0.08 ***	0.30 *	0.08 **	0.08 ***	0.05 ***	0.10 **
	[0.02, 0.26]	[0.02, 0.31]	[0.10, 0.86]	[0.02, 0.26]	[0.02, 0.22]	[0.01, 0.15]	[0.03, 0.41]
Mask Wearing (%, With Friends)				1.14 ***			
				[1.08, 1.21]			
Mask Wearing (%, Grocery)					1.07 **		
					[1.02, 1.12]		
State Peak R_t (March - May)						2.60 ***	
						[1.49, 4.58]	
Mask*Socia Distancing							0.99
							[0.98, 1.01]
N	376	376	379	376	382	381	392
AIC	347.78	362.83	383.84	347.10	366.59	346.54	353.53
Pseudo R2	0.39	0.38	0.31	0.40	0.35	0.41	0.37

*** p < 0.001; ** p < 0.01; * p < 0.05

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Figure 1. Mask wearing across three-digit zip code and time

The percentage of individuals who responded they were very likely to wear a mask to the grocery store and with family and friends was averaged across the entire study period and each 3-digit ZCTA prefix (fuzzy matched with reported zip code) in the United States (Panel A). ZCTA clusters with less than 50 responses are shown in gray. Observations of mask wearing were also aggregated at the daily level across each Census division for the study period (Panel B).

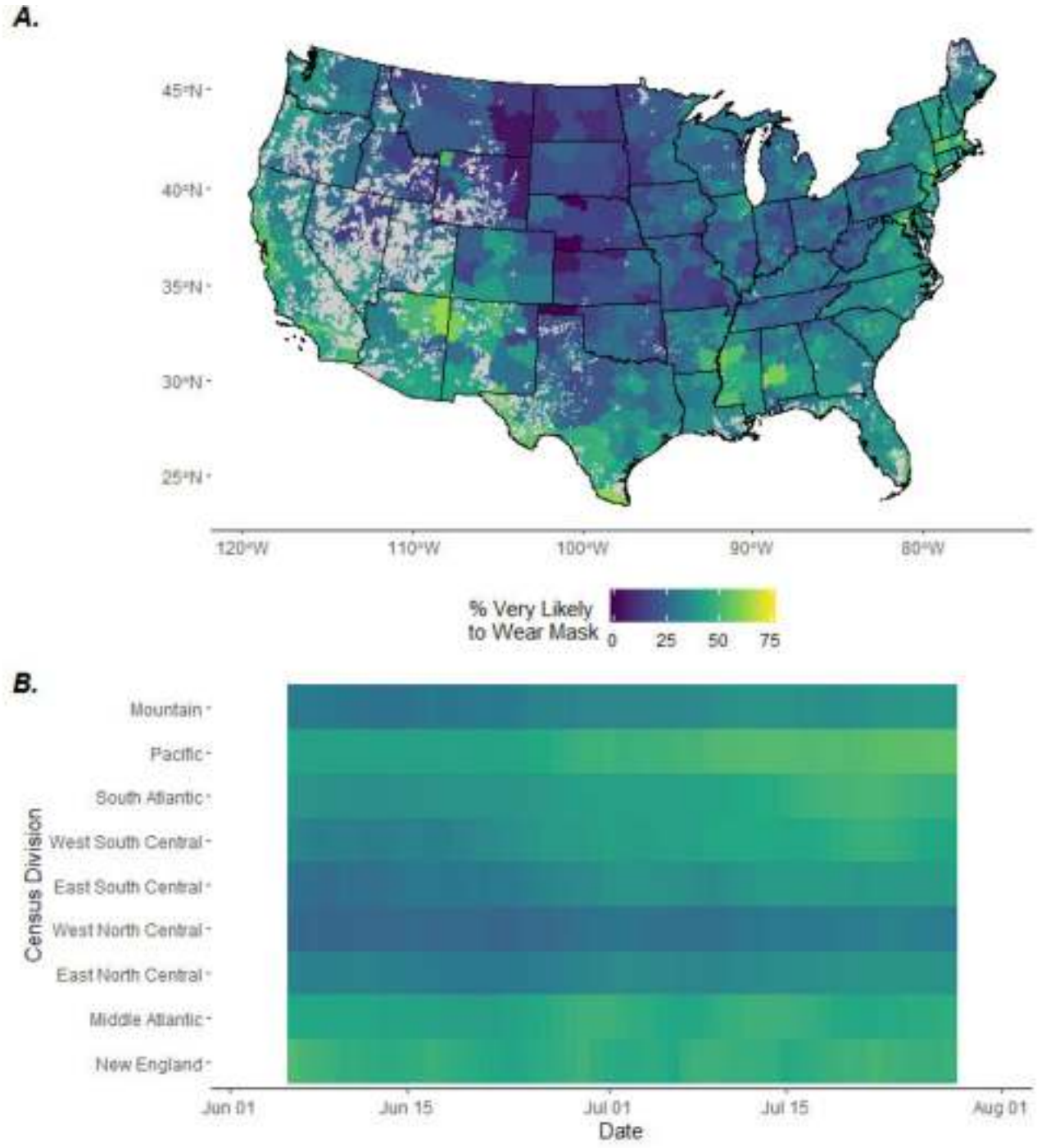

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Figure 2. Mask Wearing and the Effective Reproductive Number

Box (median and IQR) and whiskers (minimum and maximum excluding outliers) of R_t estimates (rt.live) for each week and state (grey circles). Plot is stratified by quartiles (Q1: 28.8%, Q2: 36.6%, and Q3: 45.2%) of the percentage of individuals that report they are very likely to wear a mask with family/friends and to the grocery store.

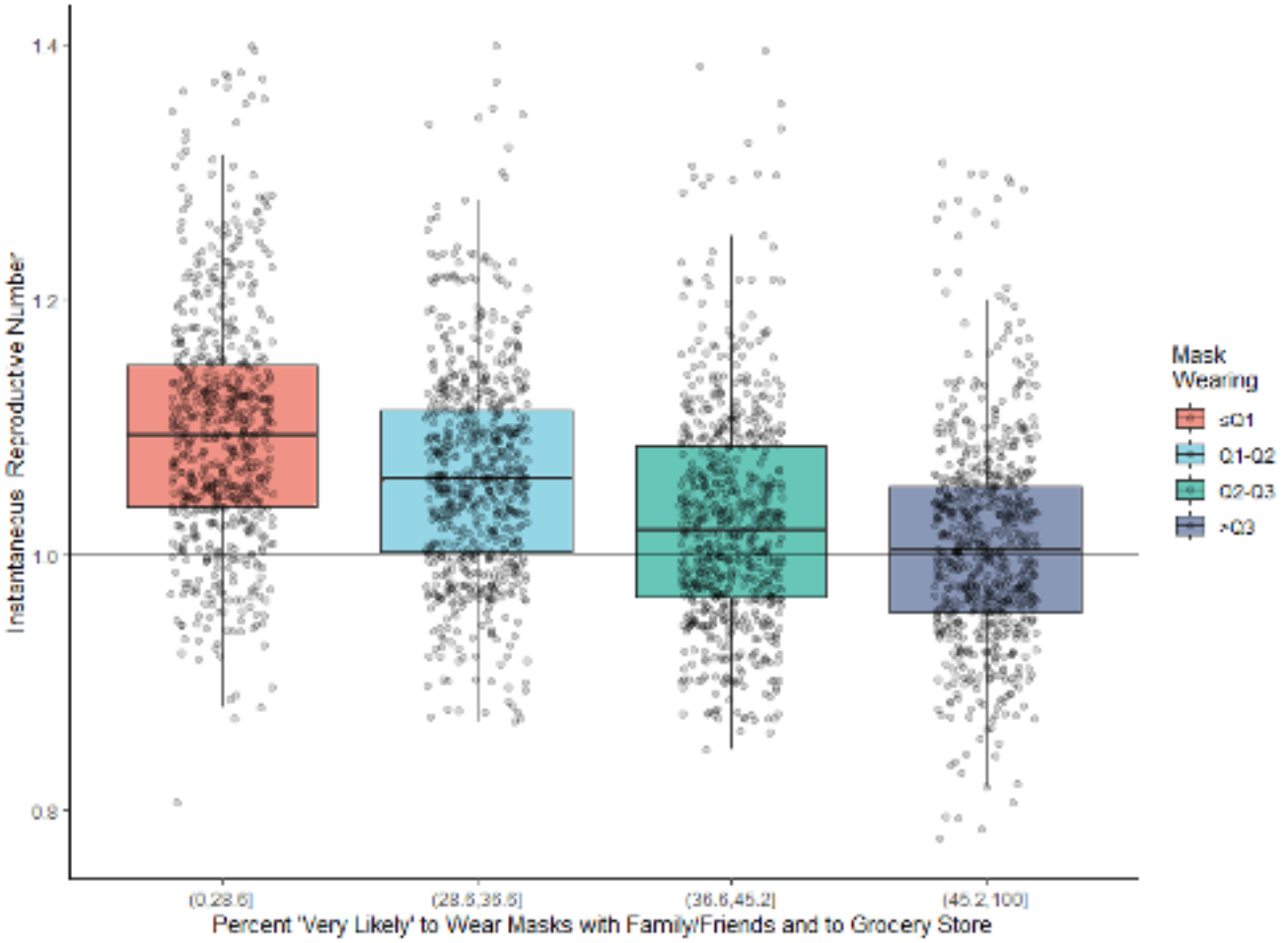

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Figure 3. Mask Wearing, Social Distancing and the Predicted Probability of R_t below 1

Projected values from a logistic regression model measuring the association of community transmission control (R_t <1) with mask-wearing and social distancing in US states adjusting for population density, percent non-white and a time trend (Model 1). Values of social distancing are from the Google Community reports of relative residential time and represent no change from baseline, the national median during the study period (June 3 – July 31, 2020), and 97.5th percentile observed during the study period. Observed mask wearing was between 8.1%-73.7%, so estimates outside this range are model-based extrapolations. Horizontal line placed at 80% probability of community transmission control, though the desired % may be higher.

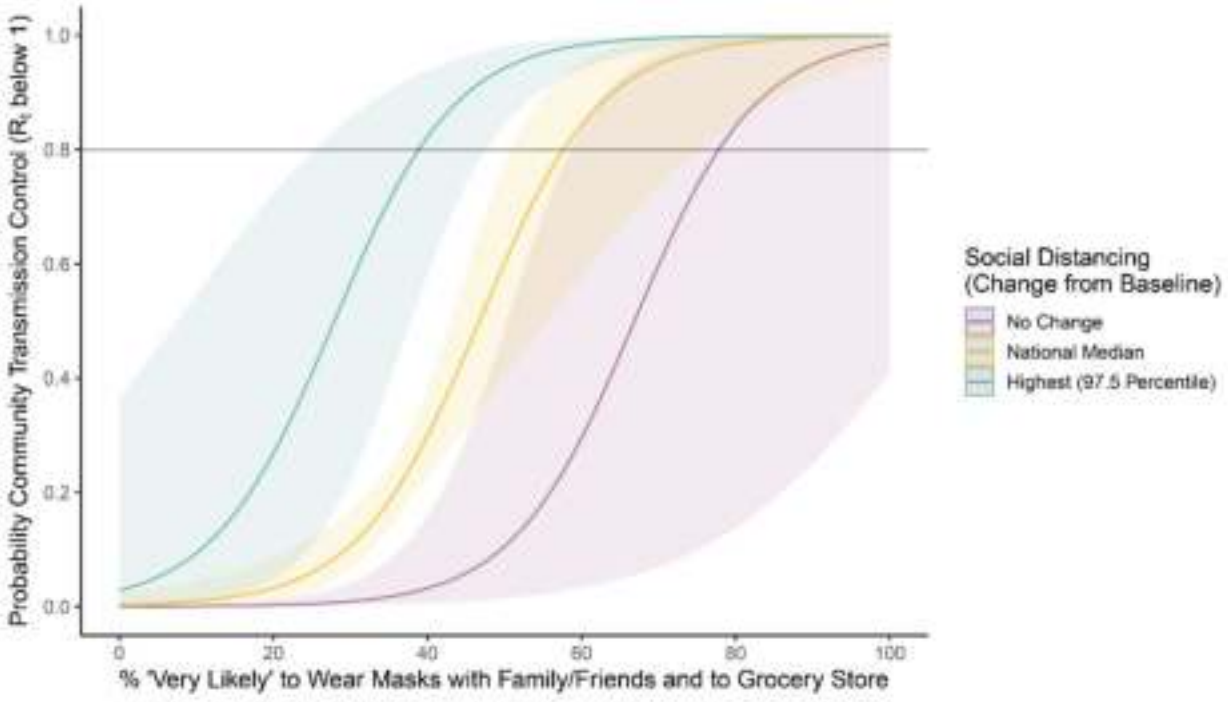

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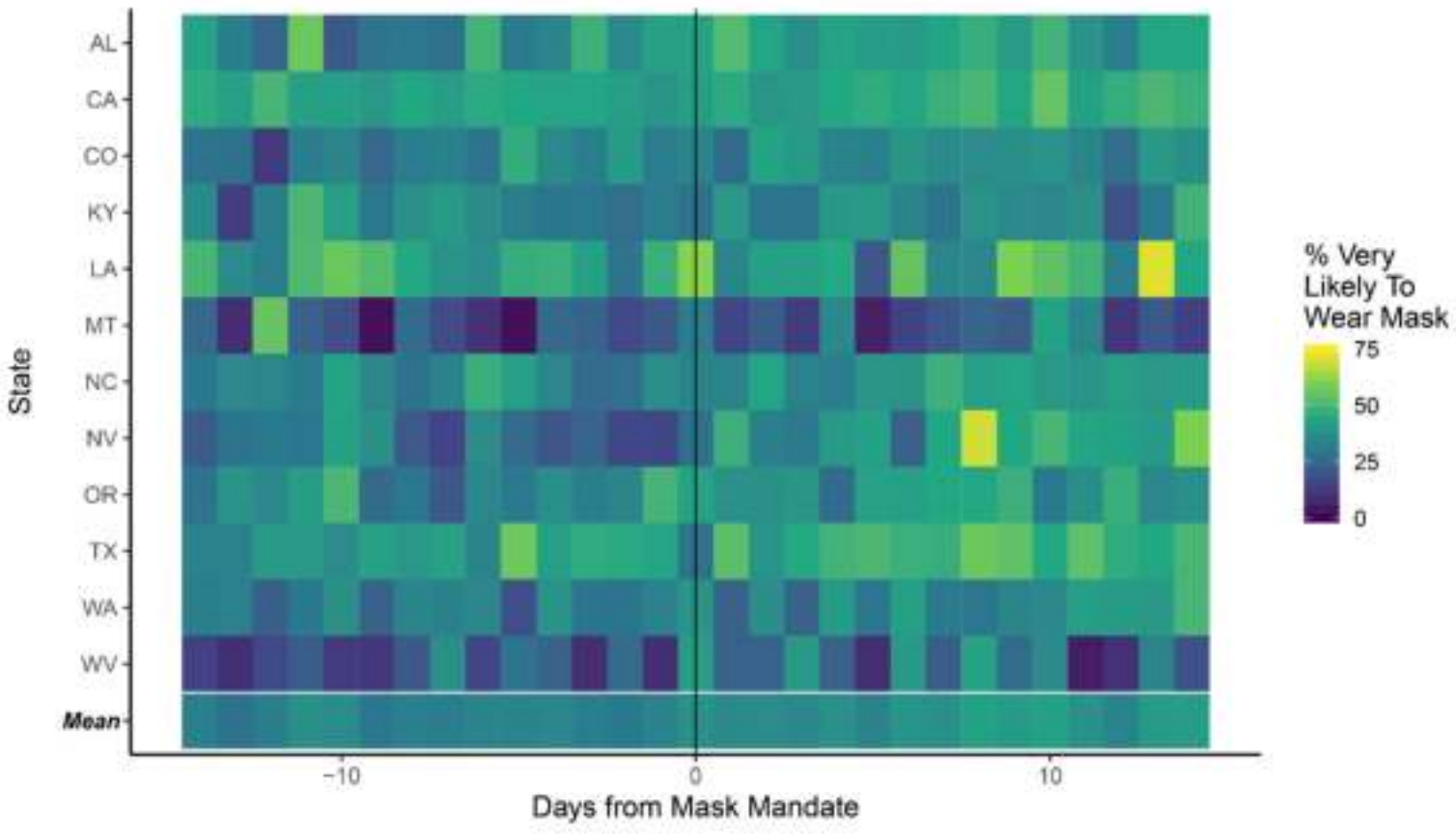
Figure 4. Mask Wearing in 14 Days Preceding and Following Statewide Mask Mandates

Daily measure of the percentage of individuals that report they are very likely to wear a mask with family/friends and to the grocery store in 12 states. Values are for the 14 days preceding and following each state's institution of a statewide mask mandate. The mean daily value across all states is presented for the same timeframe.



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Supplementary Materials

Figure S1. Mask Wearing, Social Contacts and the Predicted Probability of *Rt* below 1

Projected values from a logistic regression model measuring the association of community transmission control (R_t <1) with mask-wearing and social contacts in US states adjusting for population density, percent non-white and a time trend (Model 1). The number of self-reported contacts at "social gatherings" from Facebooks' COVID-19 symptom survey was aggregated over each week and state utilizing a weighted sampling scheme.

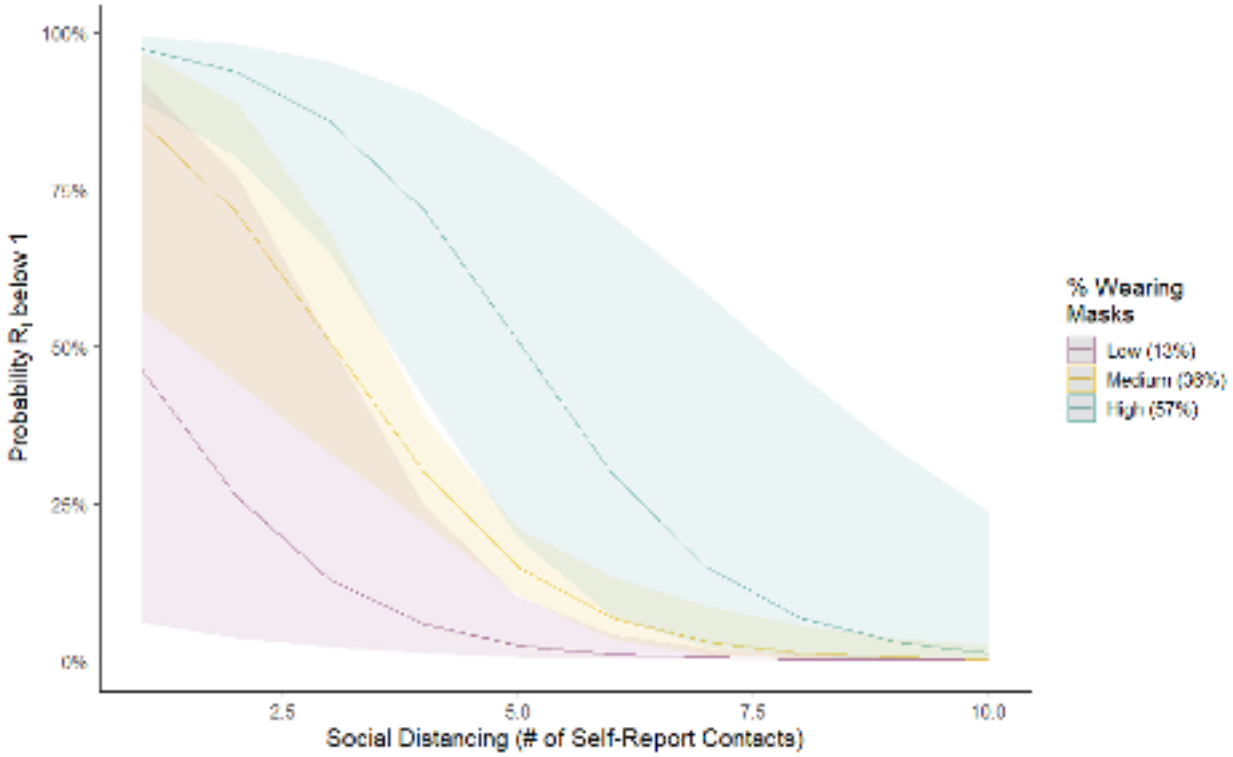

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Figure S2. Association of mask wearing with R_t at different dichotomization cutoffs

Results from a logistic regression model measuring the association of community transmission control ($R_t < x$) with mask-wearing adjusting for social distancing, population density, percent non-white and a time trend. Model was repeated as cutoff for R_t dichotomization (x) was varied. The odds ratio (point) and 95% confidence interval (-) for mask wearing that resulted from each iteration is shown.

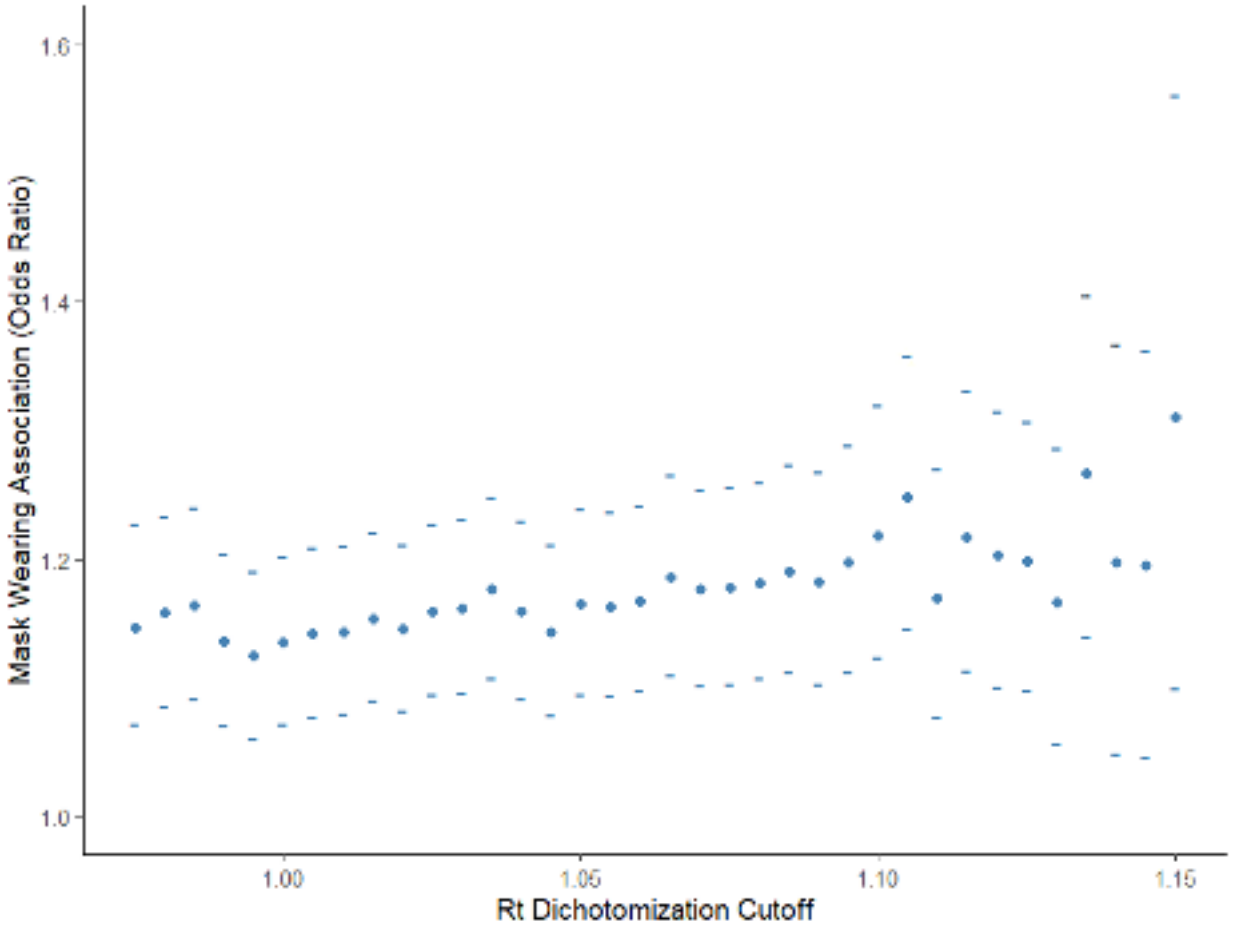

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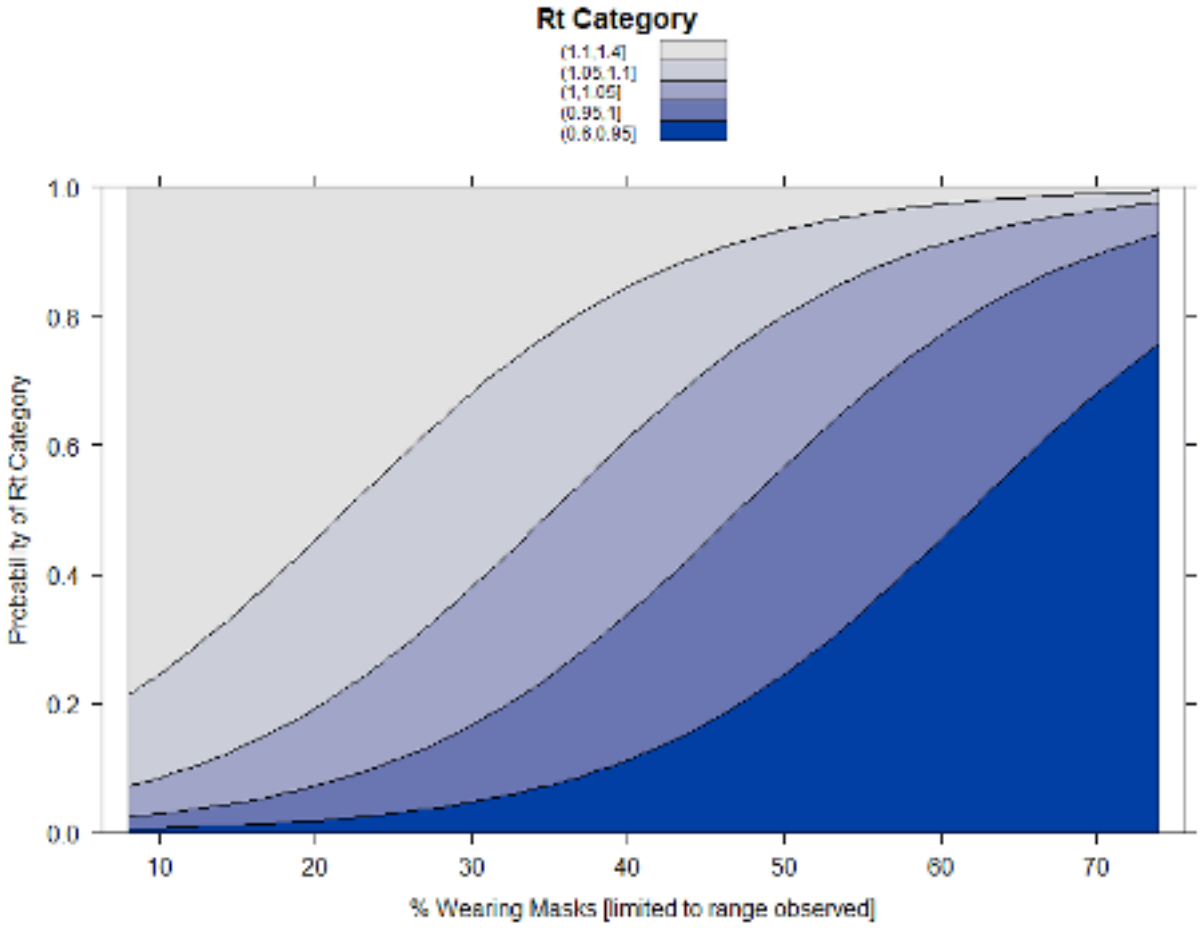
Figure S3. Association of mask wearing with categorical R_t

Projected probabilities from an ordinal logistic regression model measuring the association of community transmission control (R_t) with mask-wearing adjusting for social distancing, population density, percent non-white and a time trend. Observed mask wearing was between 8.1%-73.7%.



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Title: Strong impact of closing schools, closing bars and wearing masks during the COVID-19 pandemic: results from a simple and revealing analysis

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Abstract: Many complex mathematical and epidemiological methods have been used to model the Covid-19 pandemic. We took a different approach. Making no assumptions, we simply plotted cases, hospitalizations and deaths, on a $\log_2$ Y axis and a linear date-based X axis, and analyzed them using segmented regression. The data fit straight lines with correlation coefficients ranging from 92% - 99%, and these lines broke at interesting intervals, revealing that school closings dropped infection rates in half, lockdowns dropped the rates 3 to 4 fold, and other actions (such as closing bars and mandating masks) brought the rates even further down. Hospitalizations and deaths lagged, but paralleled cases. The graphs, which are easy to read, have several implications for modeling and policy development during this and future pandemics. Overall three interventions had the most impact: closing schools, closing bars and wearing masks: a message easily understood by the public.

One Sentence Summary: Regression analysis showed that closing schools, closing bars, and wearing masks had major effects on infections, hospitalizations and death rates in the US during the Covid-19 pandemic.

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Main Text: As of August 1st, 2020, the Covid-19 pandemic has been in effect for about six months in the US. Infection rates have climbed, fallen and climbed again, as different state governments ordered interventions to fight the pandemic, rescinded them to open their economies, and then (in some cases) reinstituted them as infections resurged. In this study, we analyzed the effects of those interventions using a simple approach. We started by asking if a pandemic in its earliest stages, when the population is completely naïve, might be described by simple kinetics similar to those that model chemical reactions in their earliest stages, before the increasing concentrations of reaction products begin to impinge on the reaction rate. Making no assumptions, we simply plotted the data for Covid-19 cases in several states in the USA as the pandemic evolved. We confined our analysis to the USA for several reasons. First, we did not think it wise to compare countries with different types of health systems. Second, in the absence of a coordinated federal response, different states made different policy decisions, on different dates; allowing for detailed local comparisons of states with strict and early lockdowns, states with no restrictions at all, and states with similar policies implemented at different times. Because of these state-to-state differences, we thought that an analysis done at the granular state level might be able to distinguish the results of different interventions from one another, and show which were most effective.

Our earliest plots indicated that the daily increases in cases during the initial days of the pandemic follow a purely exponential trajectory, regardless of country, state or county. We therefore plotted the data on a $\log_2$ Y axis, choosing $\log_2$, rather than the more standard $\log_{10}$, because it makes the doubling time easy to calculate (e.g. if a plot of new cases per day is a straight line and passes through three horizontal lines [2^3] in a period of 15 days, then the doubling time is 5 days. We also saw that the curves could be rendered as a series of straight lines that visually seemed to "break" into new straight lines with new slopes that seemed to correlate with changing government policies. To add rigor to our visual results, we used segmented regression analysis, a statistical method for determining discontinuous changes in slope. We found, for the first few months of the pandemic, that the data fit straight lines with R values usually greater than 92% - 99%, and that the breaks (slope changes) occurred at interesting and revealing intervals. For example, school closings reduced the rate of infections by half or more, with a 6-14 day delay. Lockdowns reduced the rates of infections by 2 to 4 fold, with a similar delay. Further actions (such as mandating masks or closing bars) similarly brought the rates further down with somewhat more variable lag times. Deaths, as expected, were a lagging indicator, but closely paralleled the other two main parameters (cases and hospitalizations) about one week later. This method remained useful even in later stages of the pandemic, as the country began to open up, as it enabled visualization of the effects of relaxing restrictions, and showed the mitigating effects of late interventions. The graphs, which are easy to read, show how various individual policy decisions reduced or increased the rates of new Covid cases, hospitalizations and deaths; and can potentially serve as the groundwork for future policy decisions during this and future pandemics.

Results:

Outlining the process for one state

We begin here with data from a single state, Maryland (MD), the home of the NIH, where we assumed we would have access to precise data (an issue with some states). We graphed cases, hospitalizations and deaths on a $\log_2$ Y axis, and applied segmented regression analysis to evaluate the accuracy of the visually estimated slopes and breakpoints.

Figure 1 displays a progression of graphs for the state from March 6, 2020, when the first three cases were reported, to April 15th. This simple method appeared to be adequate to model the data during this initial stage of the pandemic, and revealed some features that were not obvious from

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other, more commonly used plots, most of which are plotted on linear Y axes[1-2] or, at best, on axes of Log_{10} (ref 3).

Because the total number of Covid-19 cases (Figure 1A, solid green line) tended to increase exponentially, resulting in a fairly straight line on the log_2 scale, we were able to determine from the slope (dashed green line) that the initial doubling time was 2.5 days. This rapid rate lasted until March 29, at which time it slowed to a doubling time of 4.7 days. This change occurred 15 days after schools closed, 12 days after bars and restaurants closed, and one day before the state lockdown, suggesting that the effect of one or both of the first two policy decisions was to reduce the doubling rate of cases to slightly more half of the original rate. Figure 1B shows that the slopes for hospitalizations and deaths followed the same pattern, with lag times of about three and eight days longer respectively than the lag times of positive cases. Figure 1C shows the effect of the lockdown in MD, which was followed twelve days later by an additional threefold change in doubling time, from 4.7 to 12.8 days, and similar rate reductions in hospitalizations and deaths with additional lags of 2 and 6 days respectively. Segmented regression analysis showed that the combined broken lines fit the data remarkably well, with R values well over 99 for total cases (99.89), for total hospitalizations (99.85) and total deaths (99.42). Figure 1D shows the data for daily new cases, whose slopes tend to change within a day of those for total cases, and undergo greater changes.

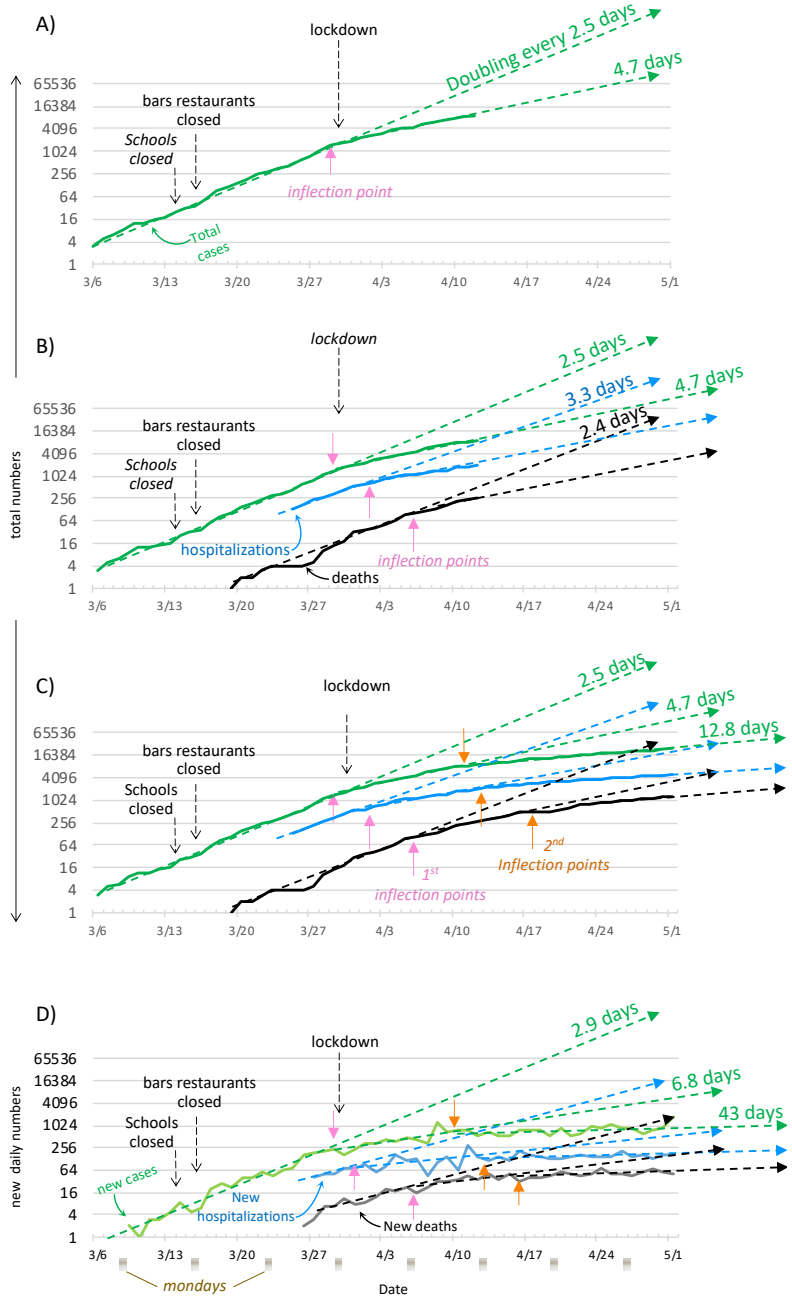

Figure 1) Laying out the process for one state (Maryland). (A-C) Graphs for total accumulating cases, hospitalizations and deaths. **(D)** graph of new daily cases, hospitalizations and deaths. Pink and Orange arrows =1st and 2nd inflection points respectively.
A) First rate drop: Initially Covid-19 cases double every 2.5 days. Then, 15 days after schools, bars & restaurants are closed (and one day before lockdown), the doubling rate slows to every 4.7 days.
B) Other parameters also drop. Hospitalization and death rates drop, 3 and 8 days respectively after the decline in cases.
C) 2nd rate drop: the lockdown is followed by a second rate decline to a doubling time of 12.8 days, for cases, hospitalizations and deaths at 12, 14 and 18 days later respectively
D) New daily cases: new cases, new hospitalizations and new deaths follow similar patterns. The data are less smooth, partly due to the smaller numbers and partly because reporting is lower on Sundays and Mondays (brown arrows) and rebound later in the week.

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The fact that the inflection points for daily new cases often occur one day before those for total cases, rather than on the same day, and that the correlation coefficient value (96.99) is slightly lower than that for total cases, is likely due to the fact that daily new cases have a periodic dip on Sundays and Mondays, and then rebound slightly as the reporting catches up during the week. This variability results in a greater "fuzziness" that creates an uncertainty in the break points and a somewhat lower accuracy in the slopes. Nevertheless, the high correlation coefficients suggest that these slopes are good representations of the trends in the data.

Effects of School Closings and of Lockdowns

Because Maryland closed bars and restaurants just three days after closing schools, it was impossible to separate the effects of those two actions from each other. A recent study on closing schools[4] ran into the same problem. In fact, the near simultaneous execution of several different interventions by many states and countries has made it difficult to assess the value of any one particular intervention. We therefore asked if any state had witnessed changes in slopes after closing schools but before taking any other major action, such as closing bars and restaurants, closing essential businesses, or giving "stay at home" orders. We found three states with no mask mandates (Georgia, Tennessee, Mississippi), that had spaced their other interventions far enough apart to enable us to examine the effects of each by itself. (Fig2)

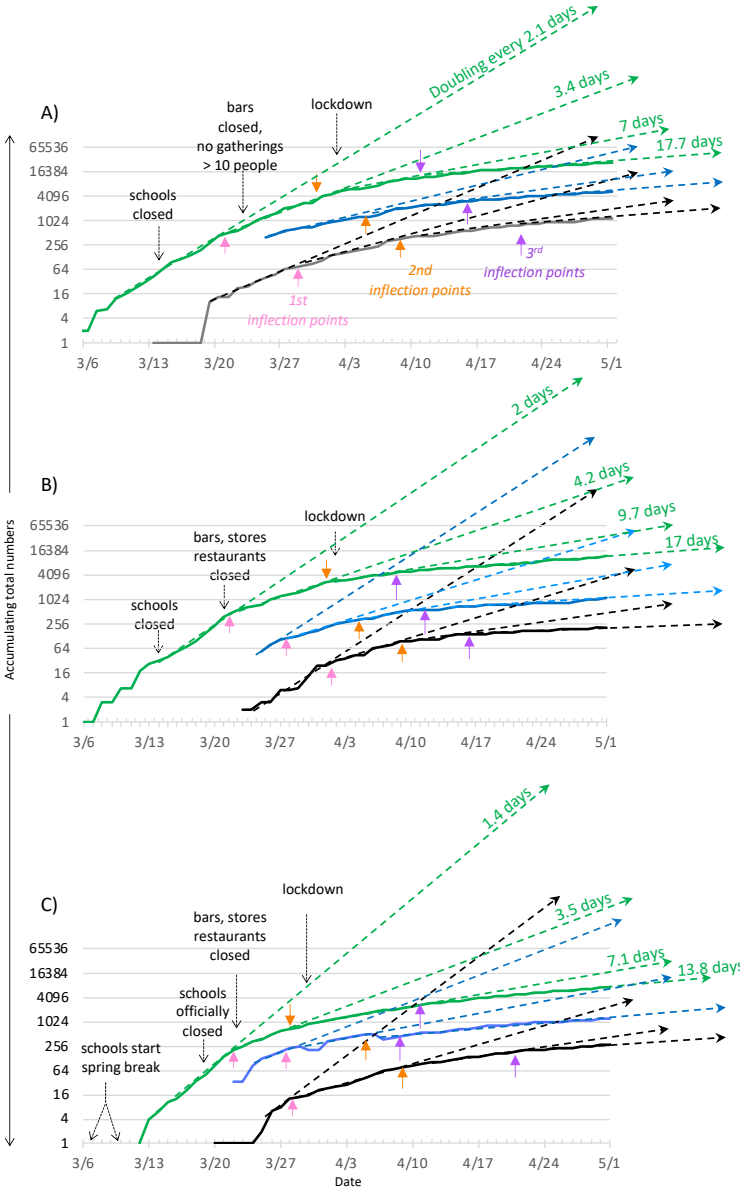

Figure 2: the effect of closing schools: graphs cover three states from 3/6/2020 to 5/1/2020. Colored arrows point to inflection points. Pink = 1st, orange = 2nd and purple = 3rd inflection point.
A) **Georgia:** Total cases and death rates decline 8 and 14 days, respectively, after school closings. Cases, hospitalizations and deaths drop again 11, 14 and 17 days, respectively, after closing bars, and again, with similar lag times, after lockdown. **B) Tennessee:** Total cases decline 8 days after school closings, again 11 days after non-essential businesses close, and again 7 days after lockdown. Hospitalizations and deaths follow with typical lag times. **C) Mississippi:** Case rates drop about 2 days after official school closings (10-12 days after the start of spring break), again 10 days after non-essential businesses close, and again 14 days after the lockdown. Hospitalizations and deaths follow with variable lag times.

Georgia (Figure 2A) officially closed schools on March 16[9]. However, the 16th was a Monday, and we therefore chose to specify Saturday, March 14th, as the school closing date, as this was the first day that children did not attend school. Seven days later, on March 21st, Georgia's initial doubling rate of 2.2 days for total positive cases dropped to a doubling time of 3.5 days. Two days after that, Georgia closed bars and restaurants, and this was followed eight days later

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by a second change to a doubling time of 7.6 days. Two days after this second rate drop, the governor ordered a lockdown[11], which was followed by a third decline in the slopes after a lag of nine days. The observation that each change in doubling times occurred before the next government intervention suggests that each intervention is followed by its own rate change and that additional interventions have additional effects.

Two days after this second rate drop, the governor ordered a lockdown[11], which was followed by a third decline in the slopes, after a lag of nine days, to a doubling time of 17.7 days. The observation that each change in doubling times occurred before the next government intervention suggests that each intervention is followed by its own rate change and that additional interventions have additional effects.

Tennessee (Figure 2B) also closed schools on March 14th and saw a twofold drop 8 days later, the same day that bars, restaurants and non-essential business were closed. This second intervention was followed eleven days later by another twofold drop in rate. One day after this second drop, the governor issued a "stay at home" order[14], which correlated with a third drop 7 days later.

Mississippi (Figure 2C) was a puzzle at first, because the first rate drop occurred only two days after the official order to close schools[5]. Rather than dismiss this as a simple outlier - it was the only state among the 50 that had such a short lag time - we delved into other possible explanations, thinking that perhaps we were simply wrong, and some aspect of human behavior other than school closings was responsible for the first sets of rate reductions. Perhaps, Americans had simply started going out less, as suggested by the phone mobility data from Apple, Google and Cuebiq[6-8].

However, an analysis of the mobility data for Mississippi in comparison with other states (Supplemental Figure 1), showed no change in mobility that could underlie Mississippi's early rate change. We therefore looked for other factors, and discovered that spring breaks for Mississippi colleges[9] and K-12 schools[10] had almost all begun earlier than other states, with slightly variable start dates from March 6 to March 10. Although the K-12 breaks normally last only one week, the governor asked schools to extend their spring breaks because of the virus[11], and nearly all of the schools did not go back into session before he officially closed them on the 18th of March[5,12]. Consequently, the drop in the rate of cases that occurred on March 20th most likely resulted from the fact that children had stopped attending school 10-14 days earlier, rather than from the March 20th executive order to close schools.

Thus, for states that separated their government actions by a week or more, we were able to assess the effects of those actions individually. Closing schools appeared to cut the rate of infections in half, beginning 8-14 days post-closure, and similarly reduced hospitalizations, but with lag times 2-4 days longer than for positive infections. Deaths followed suit, lagging an additional 7-11 days.

Closing bars and restaurants and ordering lockdowns similarly reduced the rates of infections, with similar lag times. Cumulatively, these interventions resulted in 7-10 fold drops in the rates of infections, hospitalizations and deaths. Nevertheless, even when combined, these effects were frequently insufficient to result in a steady decrease in the daily tallies of new infections. For that we needed masks.

Mask Mandates

Although the federal government never mandated masks, and many government officials continued to eschew them, a few state governors wrote orders for their constituents to wear

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masks. Unlike school closings, which occurred all over the US in the space of about two weeks, from March 6 (Mississippi) to March 23rd (Idaho), mask mandates were put in place over a longer time period, from March to July. This gave us an opportunity to evaluate both early and late mandates. We found that they were about equally effective (Figures 3 and 4).

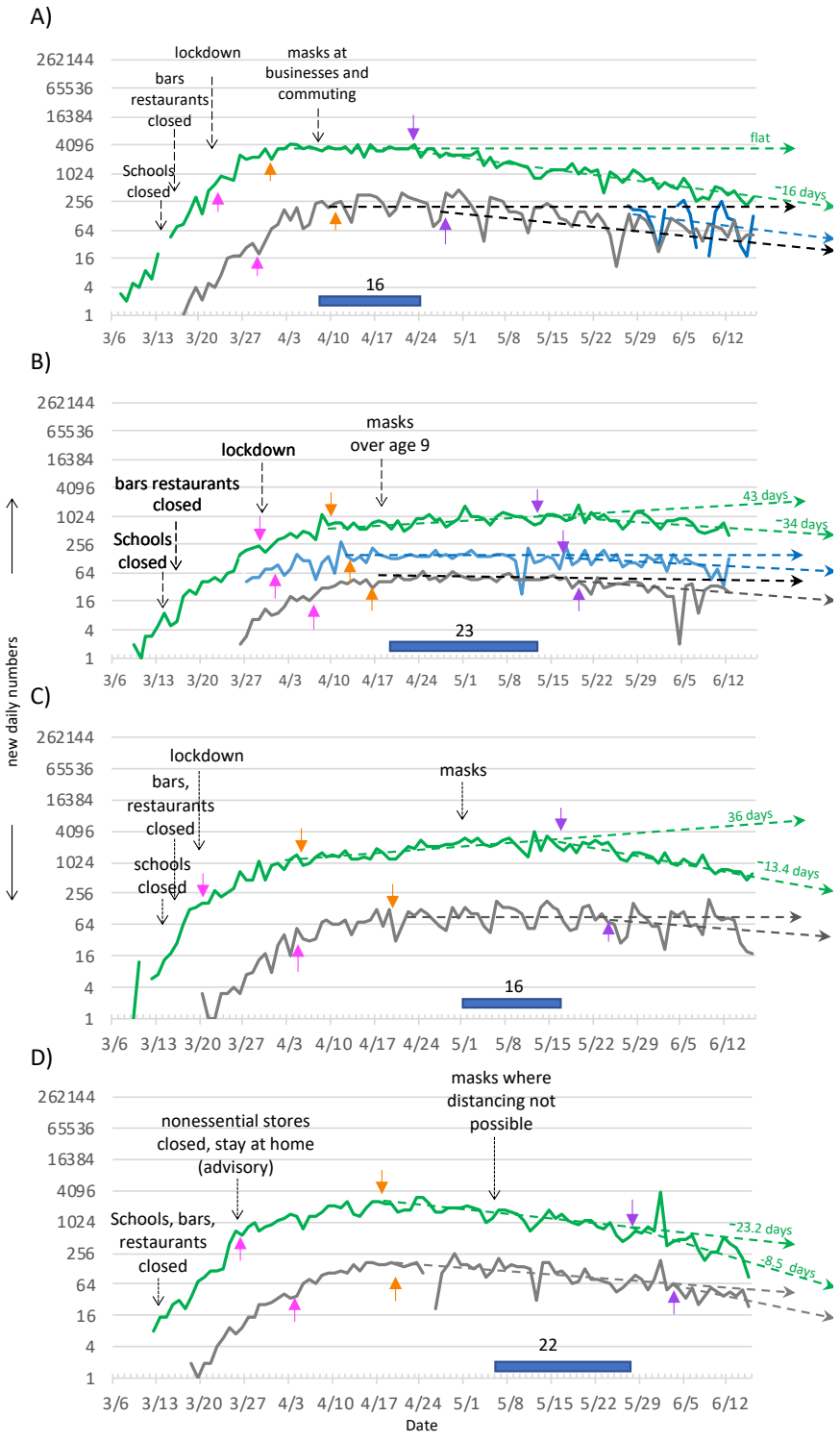

Figure 3 shows the effects of early mask mandates from four states that ordered the use of masks at times spanning a month, from April 8th to May 6th. We depict new daily numbers, as total numbers were high enough by this time to be slow to show intervention effects. Each state's mandate was followed by a drop in the rates of infections, and then by drops in the rates of hospitalizations (where reported) and deaths, showing that the effect of mandating masks is to drop the slopes about 2 fold. As the mandates stepped through time, the rate reductions followed in concert, with later mandates correlating with later inflection points. This supports the view that these rate reductions were due to wearing masks, rather than other potential changes in mobility[6-8] or behavior.

Figure 3: the effect of wearing masks: graphs depict new daily numbers for four states that mandated masks at different times from April 8 to May 6, 2020. Pink, orange and purple arrows point respectively to 1st, 2nd, 3rd inflections points. **A) New Jersey:** 16 days after mask mandate on 4/8 the slope drops about 2 fold. After this point, daily new cases drop by half every 16 days**. B) Maryland:** 23 days after mask mandate, on 4/18 the slope drops 1.5 fold to a halving rate of 34 days**. C) Illinois:** 18 days after mask mandate on 5/1 the slope declines about 2 fold, to a halving rate of 13.4 days**. D) Massachusetts:**18 days after mask mandate on 5/6, an already declining slope drops about 2 fold further, to a halving rate of 8.5 days.

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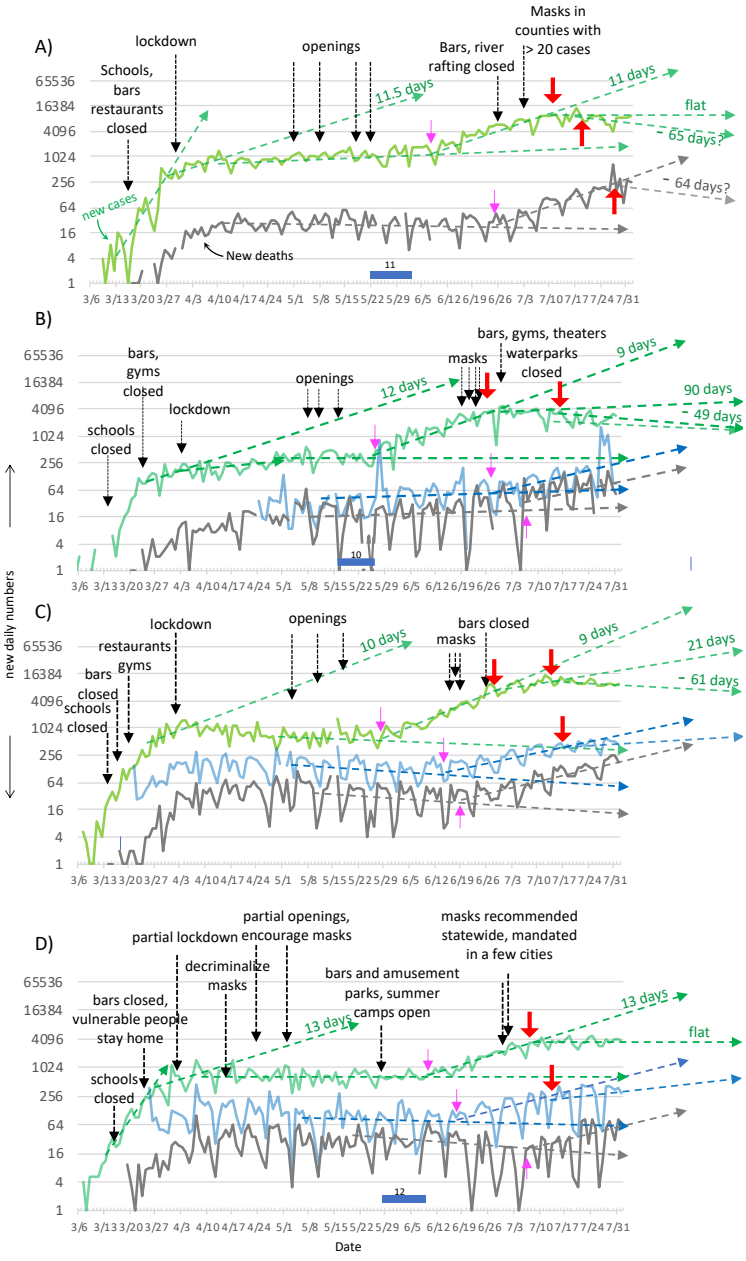
The lag times for the effect of masks (16-23 days, as indicated by dark blue bars near the X axis) seemed somewhat longer than those that followed closing schools, bars and restaurants, or ordering lockdowns, perhaps because it takes time for people to obtain masks and get into the habit of wearing them, whereas a school or a business can be closed in a day.

An exception to the effectiveness of mask wearing was seen in New York, which implemented a mask mandate during its lockdown, when new daily cases were already being cut in half every

Openings

As states reopened their economies, and experienced surges in new infections, we found that the new infection rates showed the effects of previous interventions that remained operational, as well as clear effects of interventions that were implemented later. For example, figure 4 shows data for four states (Texas, Arizona, Florida and Georgia) that opened in the middle of May. We chose these four because they had not previously mandated masks, in order to determine the effect of late mask mandates. These states had flattened or even reversed their slopes by closing schools, bars and restaurants, and non-essential businesses. All but Georgia had also implemented strict stay-at-home orders (Figure 4A - C)



The first effect we observed was the lasting impact of school closings. As infection rates surged following reopening of state economies, the benefit from having closed the schools persisted. In all four states, as schools remained shuttered for the summer, the rates of new infections never recouped the initial doubling times of 2-3 days, instead returning to the slower doubling times of 9-11 days that had followed the school closings, despite the fact that all other restrictions had been lifted. This suggests that the effect of each intervention endures as long as that intervention remains place, regardless of other actions that may be implemented or rescinded.

Figure 4: infection rates after opening mimic post-school-closing rates, and are flattened by wearing masks and closing bars. Small pink and large red arrows point respectively to beginnings of surges and reductions in infections. **A) Texas:** May1: opening almost everything (but not bars). May 8: personal care services open. May 18: gyms open. May 22: bars. On 6/16 Texas suddenly added 14 open. **B) Arizona openings**: May 8: many businesses open. May 11: restaurants open. May 16: everything else opens (including bars). **C) Florida openings**: May1: some counties open. May 11: Palm beach opens. May 18: Miami-Dade and Broward counties open. **D) Georgia openings**: April 24: personal services, gyms open. May 1: opening just about everything except bars and amusement parks. May 28: Bars, amusement parks, overnight camping open.

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The second thing we noticed was that the post-opening surges seemed to be strongly correlated with the opening of bars. Regardless of the timing or sequence of other relaxations, opening bars was followed 11-12 days later by surging infection rates. Texas, for example (Figure 4A), opened many businesses, including restaurants from May 1st to May 18th, with little repercussions on infection rates. On May 22nd, bars were opened (along with aquariums, zoos, rodeos, bowling alleys, bingo halls and skating rinks) and 11 days later, infection rates surged.

Arizona (Figure 4B) opened everything over an 8 day period, with bars opening only on the last day (May 18th). As with Texas, Arizona's surge of new cases also began 11 days later. Georgia (Figure 4D) carefully opened its economy over a period of more than a month, with no ill effects until it opened bars on the last day, along with amusement parks and overnight camping. It saw a surge starting 12 days later. In Florida each county decided individually when to open, making it impossible to determine the effect of opening bars in the Sunshine State, but for the other three states, the lag from opening bars to surges in infection rates was remarkably consistent (11-12 days), with only 1 day's difference among the three.

Thirdly, the data suggested that the simple combination of closing bars and wearing masks was a highly effective way to clamp down on surging infection rates. Each of these measures brought the infection rates down by twofold, for a cumulative reduction of fourfold in new infection rates. States that implemented both interventions, put surging infection rates into decline. Texas, Arizona and Florida (Figure 4 A-C) all carried out both interventions, though in different orders. In all three states, surging doubling times of 9-11 days sank to halving times ranging from 49 (Arizona) to 65 (Texas) days.

In contrast to the other three surging states, Georgia's governor neither closed bars nor mandated masks (Figure 4 D). However, he did encourage mask wearing, and several mayors mandated them for their cities, covering about 20% of the state's population. This mask mandate was followed about ten days later by a twofold reduction in the rate of new cases. Nonetheless, new cases did not go into decline, but instead flatlined. The major difference between Georgia and the three states that dropped their post-opening surge rates to declining ones is that the more successful states not only mandated mask wearing, they also closed their bars.

Together the data from these four states suggest that bringing cases down to manageable levels might not require shutting down an entire economy. The combination of closing schools, closing bars, and wearing masks may be enough.

Discussion

As countries and states debate the best way to prevent Covid-19 infections, and as they contemplate re-opening schools in the fall, the analysis of the information thus far gleaned about this new pandemic is vital to those decisions. There have been several previous attempts to correlate various government interventions with rates of SARS-Cov-2 infections, and predict which might be most effective[13-18]. These studies, however, have mostly taken a global view, and this is not necessarily the most productive for the US. Although a global view has the advantage of large numbers, it has the disadvantage of combining disparate interventions, done at different times in different places, into one global soup, in an attempt to find common themes.

We honed down instead to the granular data at the state - and sometimes city - level, painstakingly combing governors' executive orders and press releases (and those of mayors when necessary) to find examples of states that had implemented each of their interventions sufficiently far apart to enable us to distinguish the effect(s) of each individual intervention.

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A second difference between this and previous studies is the method we used. A maxim among scientists is to use the simplest method that explains the data. Our decision to plot the data, as they came, without any assumptions, on a Log_2 Y axis, allowed us to see the straight lines in the data, find the slopes of those lines, and the inflection or "break" points where those slopes changed. The human eye, coupled with human intuition is a powerful tool, and can guide a simple mathematical approach. We therefore used segmented regression analysis to test our visually-based hypotheses about breakpoints, slopes and doubling times. The high R values for the segmented slopes highlight the accuracy of the visually based breakpoints, despite the variability of the data of new daily cases known to occur because of the "weekend effect" of low reporting, and of low initial numbers.

The results, demonstrate that, other than full lockdowns, three government interventions had the most impact on the rates of Covid-19 infections: closing schools, closing bars and wearing masks.

Schools: Closing schools not only flattened the early curves of rapidly rising numbers of infections in March (Figure 2), it prevented a return to those initial rates after states opened up their economies in mid-summer - a time when schools remained closed (figure 4). This demonstrates that the effect of a particular intervention lasts as long as that intervention is in place, regardless of other interventions that might be mandated and/or rescinded.

Although it could be argued that the mid-summer surging rates of infections were lower than the initial rates in March because of increased resistance in the US population, this is unlikely. At the time (early to mid-June), the number of confirmed cases in the US – just under 2 million - constituted a mere 0.6 percent of the population[19]. Even if the true infection rate were 8-10 times higher, as underscored by a recent study[20], the increase to 6% would still be too small to account for the reduced rates of post-opening infections, which closely mimicked the early post-school-closing rates.

These findings help to resolve the conflicting conclusions of two previous reports. In contrast to two early predictive models suggesting that closing schools would bring down Covid-19 infection rates, a study covering the effects of government interventions in six countries[21] concluded that closing schools had no effect in the US. However, the authors analyzed each of those countries as a whole, which is not useful in the case of the US, which had no national policy on the matter. The second study[22] analyzed individual states, and concluded that closing schools had a major impact. However, in evaluating all the states together, the authors noted that they were unable to discount the potential effects of other interventions. Our study, like theirs, shows that closing schools had a major effect, and supports this idea with the results from the small set of states (Figure 3), where the effect could not be explained by other interventions.

Bars: The effect of closing and opening bars became evident in those states that opened their economies in stages (Figure 4). Although most states closed bars and restaurants simultaneously during their early shutdowns, some opened them at different times during the re-openings. We found that, regardless of other relaxations, new infections surged beginning 11-12 days after bars were opened, and fell once again about 8 days after bars were re-shuttered. This suggests that closing (and re-opening) settings that might not be conducive to social distancing has more impact on new infection rates than would opening other types of businesses (dog groomers, markets, hardware stores; even restaurants).

Masks. Akin to school closings, the beneficial effect of wearing masks was evident during the early period when states were closing down (Figure 3), and also later during post-opening surges. Under

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both conditions, those states that mandated masks[23] saw about a twofold reduction in the rate of new cases. Although political controversy reduced the proportion of the population that wears masks, those states that combined masks with bar closures saw their post-opening surge rates drop to declining ones (Figure 4). We surmise that better adherence to the mask mandates would likely have generated even larger decreases in infection rates.

One exception to the effect of early mask mandates was evident in the data from New York (Supplemental figure 2), which mandated masks after it had already turned its rapidly rising infection numbers into declining ones. The mask mandate had no further suppressive effect on infections. However, when New York later opened its economy, and infections began to rise, that increase was remarkably lower than those of states that opened without mask mandates in place (figure 3), suggesting that the early mask mandate had a long lasting effect.

Several studies suggested that early interventions have more effect than later ones. However, our data show that late interventions can be just as effective as early ones. Compare, for example, the twofold reductions in infection rates that follow early mask mandates in Figure 3, with the similar reductions seen in figure 4 - with mandates made months later. Although the numbers of cases at the time of a late intervention may be larger, setting a higher baseline, the proportional rate reductions are about the same. Whether flattening a curve at 10 or1000 new cases per day, these interventions have a major effect that can lead, with time, to lowering infections to the same level.

Finally, Figures 1-4 show that rates of new daily hospitalizations and new deaths seem to parallel those of new cases, with lag times of about three days to a week for hospitalizations, and a further lag of 3 - 10 days for deaths. Although improvements in medical care may start to change this picture[24-26], it currently appears that a fairly constant proportion of infected people will become ill and die. To counter this, we need a global set of effective policies to reduce new infections, as reductions in hospitalizations and deaths will follow. In the absence of a uniform US federal policy, we have been able to use the different state policies to determine the value of different interventions. Our analysis shows that, when combined, the three most powerful interventions - closing schools, closing bars and wearing masks - successfully flattened initial infection rates, and turned post-opening surges into declining ones, suggesting that the country could perhaps open up its economy safely if it kept bars and schools closed, and required the strict wearing of masks in public

Coda: If, in a future pandemic with a new infectious agent, governing bodies decide to base decisions on analyses of rates of infections, hospitalizations and deaths, we will need to eliminate the weekend effect, which results in underreporting on weekends and Mondays, and over-reporting later in the week, in every state examined. This can delay the determination of a rate change for a week or more, because many data points must accumulate to reliably assign a breakpoint and new slope. As there is already a biological delay from infection to the onset of symptoms, and a further delay before testing, any additional delay prevents the timely implementation of needed interventions. In a rapidly evolving pandemic, reliable data are crucial to the outcome, and every day counts.

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Supplementary Materials:

Materials and Methods

Data acquisition: Data for different US states were taken from those published online by the individual State Health Departments, from "the Covid Tracking Project"[27] at the Atlantic under a Creative Commons CC BY-NC-4.0 license, from Statista[28] and from the IHME[29]. For school closings, mobility data, and other government actions, we also relied on GitHub[30] and then verified the dates with the various governors' orders. If the date of official school closing was a Monday, we used the Saturday before as the first date that students were not in school. For Mississippi, we found that Colleges and Universities, and most K-12 districts had gone on spring break about a week and a half before the official Governor's order to close the schools. We contacted the Mississippi department of Education, and most of the individual school districts, to find which, if any, had gone back to school in the interim between spring break and the official closing order, covering 97.2% of students in the state, and discovered that >87% of those students had not gone back to school, mostly because of local decisions by their mayors, school boards or boards of health. We consequently used the first day of spring break as the date of school closing in Mississippi.
For deaths, we report the combined "confirmed plus probable" when available.

Data analysis:

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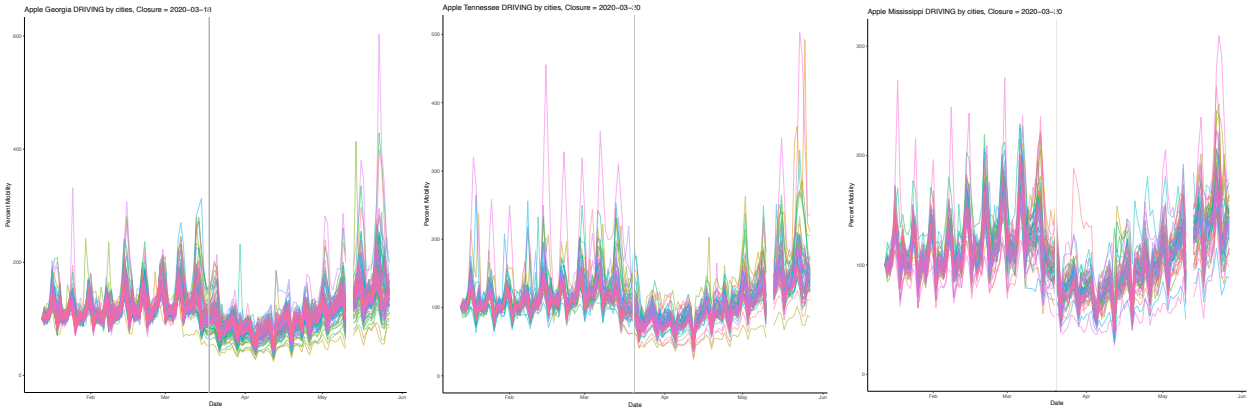
Data were analyzed in two ways. First by visualization on a plot using a Log2 Y axis to find the approximate dates of breakpoints in the lines. Second, using segmented linear regression to find and estimate the breakpoints, and to compute regression slopes and confidence intervals. To this end, trends in the number of new cases, total cases and total deaths were estimated by segmented regression using the "segmented" package library in R following its authors instructions[31]. The independent variable (X) was always "number of days" starting from March 3rd as Day 1. March 3rd was chosen because none of the states examined had any COVID-19 cases, hospitalizations or deaths reported prior to March 3rd. Initial values for either 2 or 3 segment breakpoints were provided using the 33rd, 50th, and 66th percentiles of date numbers spanning the range of the total deaths reported from that particular state. Total deaths were chosen because they typically had the smallest range of dates, so initial values chosen from the range of total deaths would usually work for the positive cases and the hospitalizations. If only 2 breakpoints were needed, then only 33rd and 66th percentiles were used. In rare cases where these initial values would not work to fit a particular variable (e.g. hospitalization or new cases), initial values would be chosen manually based on the date range of that variable. Estimated breakpoints were generally robust to the initial values chosen, and would typically yield the same estimated breakpoints even when substantially different initial values were provided. Estimated breakpoints were reported in number of days with their standard errors and their predicted date. Slopes for the resulting 3 or 4 regression segments were also reported with their adjusted 95% confidence intervals and their doubling times, calculated as 1/slope. The 95% confidence intervals can be compared against zero, to determine if slopes are increasing or decreasing, and they can be compared against each other to determine if one slope has significantly flattened or significantly increased relative to the previous slope.

Visualizations: Graphs follow the principles of Edward Tufte[32] as closely as possible.

Supplemental data

Supplemental Figure 1) Apple Mobility data for Georgia, Tennessee and Mississippi: Graphs show how much cell phones moved by driving each day. Different colors represent different counties in each state. Overall, phones in all 50 states started moving less in mid march. (the small spike in mid February is Valentine's day weekend). There is no obvious difference im the mobility data for the three states.



Georgia Tennessee Mississippi

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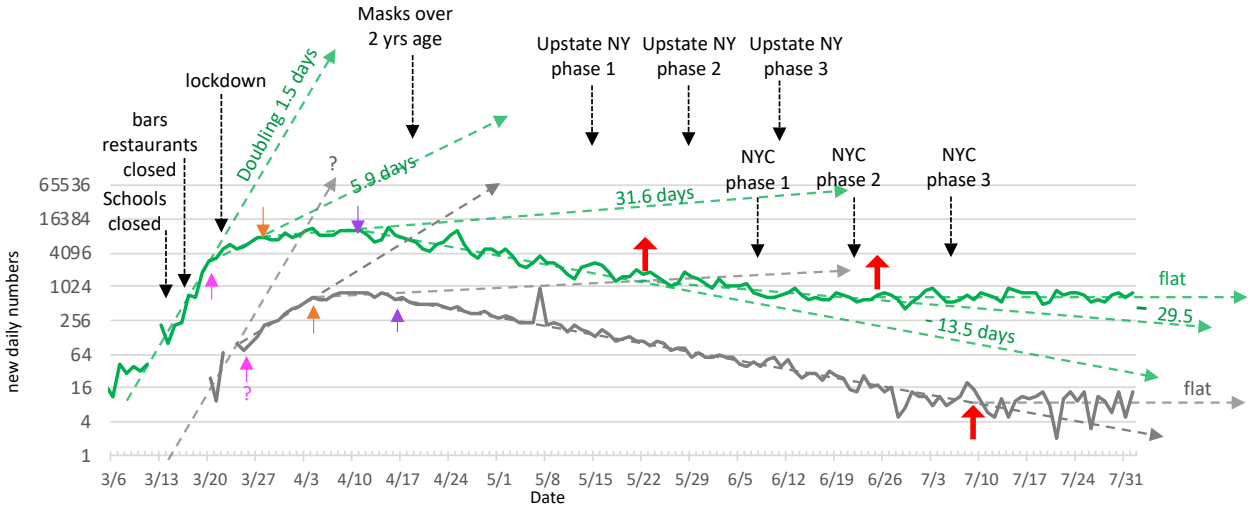
Supplemental Figure 2) New York new daily cases and deaths: pink, orange and purple arrows point respectively to 1st, 2nd, 3rd inflection points found during early stages of pandemic. Larger red arrows point to inflection points during the state's economic openings. Question marks indicate slope and inflection point where the estimate is questionable because of lack of sufficient data points.



1) Things to note from supplemental Figure 2:
   1) Closing schools, restaurants and bars dropped the infection rate about four fold, seemingly a combination of the individual effects of closing bars and closing schools seen in states that ordered those separately.
   2) The effect of closing schools eateries is as strong here, at a time when daily new infections were close to a thousand, as they were in other states with daily new infection rates in the tens, supporting the idea that the proportional effect of a particular mandate is about the same whether implemented early or late.
   3) As with other states, opening the economy stopped the decline in infections. Opening in stages resulted in staged increases in slope.
   4) Mandating masks had no apparent immediate effect during the lockdown, as the previous mandates had already sent infection rates into decline. However, when the state opened up, it did not return to the post-school closing doubling rate of 5.9 days, as was seen in states that had not required masks (Figure 3), but instead to the lower rates that resulted from late-post-opening mask mandates. Thus, like the effect of closing schools, the effect of mandating masks seems to last as long as the mandate is in place.

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Widespread use of face masks in public may slow the spread of SARS CoV-2: an ecological study

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Word Count: 1753

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Abstract

Background

The reasons for the large differences between countries in the sizes of their SARS CoV-2 epidemics is unknown. Individual level studies have found that the use of face masks was protective for the acquisition and transmission of a range of respiratory viruses including SARS CoV-1. We hypothesized that population level usage of face masks may be negatively associated SARS CoV-2 spread.

Methods

At a country level, linear regression was used to assess the association between COVID-19 diagnoses per inhabitant and the national promotion of face masks in public (coded as a binary variable), controlling for the age of the COVID-19 epidemic and testing intensity.

Results

Eight of the 49 countries with available data advocated wearing face masks in public – China, Czechia, Hong Kong, Japan, Singapore, South Korea, Thailand and Malaysia. In multivariate analysis face mask use was negatively associated with number of COVID-19 cases/inhabitant (coef. -326, 95% CI -601- -51, P=0.021). Testing intensity was positively associated with COVID-19 cases (coef. 0.07, 95% CI 0.05-0.08, P<0.001).

Conclusion

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Whilst these results are susceptible to residual confounding, they do provide ecological level support to the individual level studies that found face mask usage to reduce the transmission and acquisition of respiratory viral infections.

Keywords: SARS CoV-2; COVID-19; face masks; prevention; epidemiology; Asia

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Background

SARS CoV-2, the viral cause of COVID-19, has spread rapidly to over 190 countries [1]. There has, however, been remarkable variation in how extensively it has spread and in the national responses to this spread [1, 2]. For example, although the virus is thought to have first emerged in China, European countries such as Italy and Spain have reported roughly 30-fold higher number of infections per capita than China [1, 2]. Understanding the reasons underpinning this heterogeneity in spread is crucial to ongoing prevention efforts. The cornerstones of prevention efforts have included extensive testing, contact tracing and isolation and various forms of social distancing/quarantining [3, 4]. Whilst there have been important differences in how these were implemented in different countries, arguably the most striking difference in approach has been in the use of universal face masks in public. Whereas a number of predominantly Asian countries have promoted this practice, the World Health Organization (WHO) and most European and North American countries have not promoted this strategy [5, 6]. The head of the Chinese Center for Disease Control and Prevention has stated that the biggest mistake that Europe and the US were making in tacking COVID-19 was their failure to promote the widespread usage of face masks in public [7]. The WHO argues against universal face mask use based on a lack of evidence to support the practice, as well as a concern that using face masks will provide users with a false sense of security which may result in poorer hand hygiene and hence increased transmission [3, 5, 8]. The US Centers for Disease Control and Prevention does not recommend that people who are well wear a face mask to protect themselves from respiratory diseases, including COVID-19 [5]. In fact, the US Surgeon General stated that facemasks “are not effective in

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preventing (the) general public from catching coronavirus" and urged people to stop buying face masks [5].

Advocates of universal usage of face masks point to four types of evidence. Firstly, SARS CoV-1 and -2 are spread mainly through contact- and droplet- but also through airborne-transmission [6, 9]. Detailed environmental and epidemiological investigations from the large Amoy Gardens outbreak of SARS CoV-1 revealed that airborne transmission played an important role in the outbreak [10, 11]. Likewise in vitro studies demonstrate that SARS CoV-2 can be aerosolized and remain viable in the air in this form for at least 3 hours [12]. Although viral viability was not assessed, air samples from hospital rooms and toilets used by COVID-19 patients as well as from a crowded entrance to a department store tested positive for SARS CoV-2 [13]. Even if we discount the evidence of airborne transmission, face masks could play a major role in reducing droplet and possibly contact (via reduced digital-oral interactions) transmission. The second type of evidence is that from epidemiological studies showing that masks do provide this protective effect. One systematic review on the efficacy of face masks to prevent influenza, found evidence that face masks were effective in preventing the transmission to others and weaker evidence that they prevented influenza acquisition [14]. Likewise, a systematic review and metanalysis in health care workers found that mask wearing was associated with a lower incidence of clinical respiratory infections [15]. A Cochrane review of different physical measures to prevent the acquisition of respiratory viruses found face masks to be the most effective of all measures investigated - including social distancing [16]. The results were similar for studies limited to SARS CoV-1 transmission, with the authors concluding: 'wearing a surgical mask or a N95 mask is the measure with

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the most consistent and comprehensive supportive evidence' [16]. Thirdly, there is increasing evidence that a large proportion of SARS CoV-2 transmission occurs from pauci- or asymptomatic individuals. An estimated 30% of infections are truly asymptomatic and 80% mild infections [17]. Evidence is also mounting that infected individuals are infectious prior to the onset of symptoms [18]. Taken together these findings provide an explanation for why epidemiological studies have found that nondocumented infections were the infection source for 79% of documented cases in Wuhan, China [18]. In this setting limiting masks to confirmed infections is far less likely to have an impact on transmission than universal use. The key argument for universal use is thus preventing transmission and a secondary argument is preventing acquisition [7, 9].

These considerations provided the motivation for the current analysis where we assessed if there was ecological level evidence that countries that promoted face mask usage in public had a lower number of COVID-19 diagnoses per capita.

Methods

Dependent variable:

The *cumulative number of cases of COVID-19* infection per million inhabitants on 29 March 2020 per country. This data was obtained from the European Centre for Disease Prevention and Control (ECDC) data repository: https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases

Independent variables:

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Universal face mask. A binary variable equal to 1 or 0 according to whether or not national policies promote the wearing of face masks in public regardless of symptoms. Countries were classified according to a narrative review of official national documents and other sources (STable 1).

Testing intensity. Cumulative number of nucleic acid amplification SARS CoV-2 tests conducted per country per million inhabitants up till 29 March 2020. This data was extracted from the Wikipedia COVID-19 testing site on 29 March 2020: https://en.wikipedia.org/wiki/COVID-19_testing

Age of epidemic. The date the first case of COVID-19 was diagnosed in each country. This was measured in days after the first COVID-19 case was officially reported in China (10 January 2020). This data was obtained from the ECDC data repository on 29 March 2020: https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases

Data analysis

Linear regression was used to analyze the association between the independent and dependent variables. We controlled for the fact that SARS CoV-2 epidemic is at different stages in different countries via two methods. Firstly, the 'age of the epidemic' variable was included in all analyses. Secondly, we only included countries with at least 500 cumulative cases and countries whose first case was reported before 7 March 2020. Countries with missing data were dropped from the analyses. The analysis was performed in STATA version 16 (Stata Corp, College Station, Tx). Although Hong Kong is a part of China it was included as a separate data point in

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keeping with its population size and relative autonomy as regards public health responses. Because Czechia was the only country to introduce universal face masks late in the epidemic (18 March 2020), we repeated the analyses excluding Czechia [19, 20].

Results

Forty-nine countries were found with complete data, epidemics older than 7 March 2020 and more that 500 cases/million inhabitants (STable 1). Large variations were evident in the number of COVID-19 cases per million inhabitants (median 158, interquartile range [IQR] 20-486), testing per million (median 1723, IQR 307-4802) and the date of the first case (median 24 February, IQR 28 January – 28 February; STable 1). Only 8 of these countries advocated wearing face masks in public – China, Czechia, Hong Kong, Japan, Singapore, South Korea, Thailand and Malaysia. These countries tended to have older epidemics. Seven of the 8 were in the group of countries with the 10 oldest epidemics (STable 1).

In multivariate analysis face mask use was negatively associated with number of COVID-19 cases (coef. -326, 95% CI -601- -51, P=0.021; Table 1). Testing intensity was positively associated with COVID-19 cases (coef. 0.07, 95% CI 0.05-0.08, P<0.001).

Repeating the analyses excluding Czechia strengthened the association between COVID-19 cases and face mask usage slightly (STable 2).

Discussion

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In this ecological study we found that countries that promoted widespread face mask usage had lower cumulative numbers of COVID-19 diagnosed after controlling for testing intensity and age of the epidemic. It is important to note that this association may be entirely explained by unmeasured confounders. For example, if countries promoting universal face masking also conducted more effective contact tracing and isolation than other countries and this was responsible for the slower spread, our study design would have falsely attributed this effect to using face masks. We did not have accurate data to control for these confounders. We did however control for testing intensity which is an important potential confounder. We also controlled for the age of the epidemic which is an obvious independent determinant of the size of the epidemic. A further limitation of our study was that we were unable to quantitate the intensity of face mask use per country. This resulted in a rather crude binary classification of face mask usage per country.

At this albeit early phase of the pandemic it is important to explore why the virus has spread more extensively in many European countries than China and neighboring countries where the outbreak appeared to have commenced. This is difficult in the absence of data that quantitates national competency in terms of the various components of successful national COVID-19 response plans. Narrative reviews of the features that resulted in the success of countries such as China, Hong Kong, Japan, Singapore and Taiwan have noted a number of common features. These include: rapid response, extensive testing, contact isolation and the widespread usage of face masks in public [4, 21].

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There are a number of countries in Western European such as Italy that have conducted intensive screening, contact tracing, isolation, social distancing and widespread lockdowns and yet have amongst the largest COVID-19 epidemics in the world [2]. A striking omission from this response-list if we compare it to the responses in China and other Asian countries with lower COVID-19 incidence is that the widespread use of face masks in public was not promoted. The only European country to adopt this strategy was Czechia, and it did so at a relatively late stage in the epidemic [19, 20]. Early indications suggest that despite higher testing rates than the average for western European countries, the number of new infections is lower in Czechia [1]. Future studies will however be crucial to evaluate the impact of this intervention in Czechia and elsewhere. These studies may benefit from including data from Taiwan and Macau where use of face masks in public has been high and the cumulative number of infections has remained so low that they did not meet the 500 case threshold for inclusion in this study (Taiwan 283 and Macau 34 cumulative cases as of 29 March) [1].

It is likely that a single intervention is not sufficient to suppress the spread of COVID-19 [2]. The safest approach in the middle of this epidemic may be to introduce the full package of interventions that have been proven to work in Asian countries and then scale back according to new findings [3, 9]. Our analysis provides further evidence that this package should include widespread usage of face masks in public. Currently the only European country that can be considered to be doing this is Czechia.

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Authors' contributions

CK conceptualized the study, was responsible for the acquisition, analysis and interpretation of data and wrote the analysis up as a manuscript.

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Nil

Conflict of interest

The author declares that he/she has no competing interests.

Ethical approval

The analysis involved a secondary analysis of public access ecological level data. As a result, no ethics approval was necessary.

Informed consent

Not applicable

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252 Table 1. Country level, multivariate linear regression of factors associated with
253 cumulative number of COVID-19 diagnoses per million inhabitants (N=49).

254

	Coef.	95% CI	P-value
Testing intensity	0.069	0.05-0.08	<0.001
Face masks	-326	-601 - -51	0.021
Date of epidemic	-3.59	-9.31 – 2.11	0.211

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Association of County-Wide Mask Ordinances with Reductions in Daily CoVID-19 Incident Case Growth in a Midwestern Region Over 12 Weeks

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Abstract

Importance: This study assessed the longitudinal impact of new COVID-19 cases when a mask ordinance was implemented in 2 of a 5-county Midwestern U.S. metropolitan region over a 3-month period of time. Reduction in case growth was significant and reduced infection inequities by race and population density.

Objective: The objective of this study was to assess the impact that a mandatory mask wearing requirement had on the rate of COVID-19 infections by comparing counties with a mandatory policy with those neighboring counties without a mandatory masking policy.

Design: This was a quasi-experimental longitudinal study conducted over the period of June 12-September 25, 2020.

Setting: This study was a population-based study. Data were abstracted from local health department reports of COVID-19 cases.

Participants: Raw cases reported to the county health departments and abstracted for this study; census-level data were synthesized to address county-level population, income and race.

Intervention(s) (for clinical trials) or Exposure(s) (for observational studies): The essential features of this intervention was an instituted mask mandate that occurred in St. Louis City and St. Louis County over a 12 week period.

Main Outcome(s) and Measure(s): The primary study outcome measurement was daily COVID-19 infection growth rate. The mask mandate was hypothesized to lower daily infection growth rate.

Results: Over the 15-week period, the average daily percent growth of reported COVID-19 cases across all five counties was 1.81% (±1.62%). The average daily percent growth in incident COVID-19 cases was similar between M+ and M- counties in the 3 weeks prior to implementation of mandatory mask policies (0.90% [±0.68] vs. 1.27% [±1.23%], respectively, p=0.269). Crude modeling with a difference-in-difference indicator showed that after 3 weeks of mask mandate implementation, M+ counties had a daily percent COVID-19 growth rate that was 1.32 times lower, or a 32% decrease. At 12 weeks post-mask policy implementation, the average daily COVID-19 case growth among M- was 2.42% (±1.92), and was significantly higher than the average daily COVID case growth among M+ counties (1.36% (±0.96%)) (p<0.001). A significant negative association was identified among counties between percent

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growth of COVID-19 cases and percent racial minorities per county ($p<0.001$), as well as population density ($p<0.001$).

Conclusions and Relevance: These data demonstrate that county-level mask mandates were associated with significantly lower incident COVID-19 case growth over time, compared to neighboring counties that did not implement a mask mandate. The results highlight the swiftness of how a mask ordinance can impact the trajectory of infection rate growth. Another notable finding was that following implementation of mask mandates, the disparity of infection rate by race and population density was no longer significant, suggesting that regional-level policies can not only slow the spread of COVID-19, but simultaneously create more equal environment.

Key Points

Question: How are local mask ordinances associated with growth of COVID-19 cases among adjacent counties?

Findings: Ecological longitudinal analysis reveals a significant slowing of daily COVID-19 case growth after mask ordinance implementation among counties.

Meaning: Local-level policy of mask ordinances are shown to be an effective COVID-19 mitigation strategy even within locations of diverse populations.

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Introduction

COVID-19 has claimed over 210,000 lives in the U.S.[1] While urgent policies have been implemented to reduce COVID-19 infections throughout the pandemic, there has been significant variability across state and local governments. In particular, due to the difficulty in maintaining social distancing guidelines and in an attempt to allow the economy to recover by opening businesses, some elected officials have issued mask mandates for the public to reduce COVID-19 transmission. Research has demonstrated the effectiveness of masks in preventing the spread of infectious diseases through airborne droplets,[2] yet the majority of a community would need to be masked in order to reduce infection rates. Several governors have avoided state-level mandates by rationalizing that within-state variations of COVID-19 infection rates call for more localized public health policymaking than state-wide orders.[3]

While studies found mask policies to be effective in reducing infection growth rates early in the pandemic, there is an urgent need to know how the impact of such policy persists over time; in addition, the impact on unequal infection rates such as higher rates reported among African-American/Black and Hispanic/Latinx populations.[1] Mask wearing has transitioned to a politically nuanced behavior, and this has been particularly true in the region surrounding the Midwestern city of St. Louis, providing a natural experiment to understand the longitudinal impact of a variable mask mandate policies has on county-level changes in incident CoVID-19 rates over a 12-week period.

Methods

This ecological study evaluated the effects of a public mask mandate on the daily cumulative case growth of COVID-19 infections among five neighboring counties within the metropolitan statistical area of Saint Louis, Missouri: City of St. Louis, St. Louis County, Jefferson County, Saint Charles County, and Franklin County. The study period included a three-week period prior

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to the implementation of a mandatory mask order in St. Louis City and County on July 3, 2020, and a 12-week post-implementation period, for a total of 15 weeks.

Outcome of Interest

The primary outcome of interest was the cumulative daily percent change of reported COVID-19 cases by county. Daily incident COVID-19 cases were sourced from publicly available data provided by the Missouri Department of Health and Senior Services.

Primary Predictor and Covariates

Presence of a mask ordinance was the primary predictor of interest. Among the five counties, two implemented a mask ordinance during the study period for individuals entering public indoor spaces; the City and County of Saint Louis[4] (M+), with three counties having no such mandate during the study period (M-).

As COVID-19 infections occur more often among areas with higher county-level population density per square mile, higher proportion of residents identifying as non-white, and lower median annual household income,[25,6] these variables were included from the 2018, 5-year American Community Survey to control for variations in COVID-19 case growth.

Statistical Analysis

Data were constructed with daily percent changes in COVID-19 cases as a function of time (daily) and location (county), with 530 unique observations from June 12, 2020 to September 25, 2020. The average percent change in cases per day was calculated across M+ and M- counties to understand the pattern of COVID-19 growth throughout the study period. Kendal's tau-b rank correlation test was employed to identify associations among county-level demographics and percent daily growth of COVID-19 cases.

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A difference-in-difference (DID) framework was employed to evaluate the effect of mask ordinances on percent daily growth in COVID-19 prevalence. Specific to this study, a DID estimator (δ) was calculated using binary dummy variables for both treatment (M+ or M-) at time (prior to mask ordinance implementation and after implementation). The calculated DID estimator was then applied to a linear probability model to determine the effects of a mask ordinance on COVID-19 case growth. Four adjusted models were constructed, accounting for county-level characteristics, each at 3 week intervals past the implementation date.

Statistical analyses were completed using R 4.0 software with significance determined at $\alpha = 0.05$.

Results

Over the 15-week period, the average daily percent growth of reported COVID-19 cases across all five counties was 1.81%(±1.62%). A total of 44,294 cases were reported throughout this period among a total estimated population of just over 2,000,000 residents, which is approximately one-third of the population within the state of Missouri.

The average daily percent growth in incident COVID-19 cases was similar between M+ and M- counties in the 3 weeks prior to implementation of mandatory mask policies (0.90%[±0.68] vs. 1.27%[±1.23%], respectively, p=0.269) (Figure 1). Prior to the mandate implementation a there was no association between percent growth of COVID-19 cases and percent racial minorities, population density, nor median income per county.

At 12 weeks post-implementation, the average daily COVID-19 case growth among M- was 2.42%(±1.92), significantly higher than the average daily COVID case growth among M+ counties (1.36%[±0.96%], p<0.001).

In adjusted linear probability models (Table 1), the mask mandate was found to be significantly associated with slowing the reported growth of daily COVID-19 cases across the study period.

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From 3 weeks pre-policy to 3 weeks post-policy, M+ counties had a daily average COVID-19 growth rate of 44% less than M- counties (1.08/2.44). At week 6, 9, and 12 assessments, modeling revealed a continuing significant reduction in COVID-19 cases in counties with mask mandates. From pre-policy to 12 weeks post-policy (Figure 2), M+ counties had a daily average COVID-19 growth rate of 40% less than of M- counties (0.47/1.16). Using the DID linear probability equation, a counterfactual line is estimated, indicating probable growth of counties with mask mandate had a mask mandate not been implemented. Within the adjusted models, accounting for the DID estimator, proportion non-white population and population density were negatively associated with increased daily growth rate, yet median income did not contribute significantly to any of the calculated models.

Discussion

This longitudinal study demonstrates that the implementation of county-level mask mandates lowered incident COVID-19 case growth over time, compared to neighboring counties with no such mask mandate. Importantly, the results highlight the swiftness of such impact, with significant effects seen at just 3 weeks post-implementation. As time progressed, this impact was slightly reduced, possibly due to the arbitrary political borders of counties and states, which do not necessarily constrain transmission as mobility across mask mandate and non-mandated regions occurs. Although broader state or national mandatory mask ordinances would likely have a significant reduction in COVID-19 infections, in their absence, support for governors and elected officials to minimize the interactions across these borders may be beneficial.

Furthermore, implementation of a mask mandate may have reduced the unequal burden on African American/Black and Hispanic/Latinx individuals, as well as areas with higher population density. COVID-19 has highlighted the impact and swiftness of racial and ethnic inequities through higher rates of COVID-19 morbidity and mortality among non-white communities. In particular, many individuals were unable to abide by stay-at-home orders that protected middle

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and high-income communities as a result of “essential” employment in grocery stores, health care support positions, and public transportation. These jobs, often lacking PPE and paid sick leave, are more often filled by people of color, living in higher population density and lower socioeconomic areas.[7] The mask policy that was enacted in many communities may have provided a more equal approach to reducing COVID-19 infections, as it occurred in St. Louis, Missouri.

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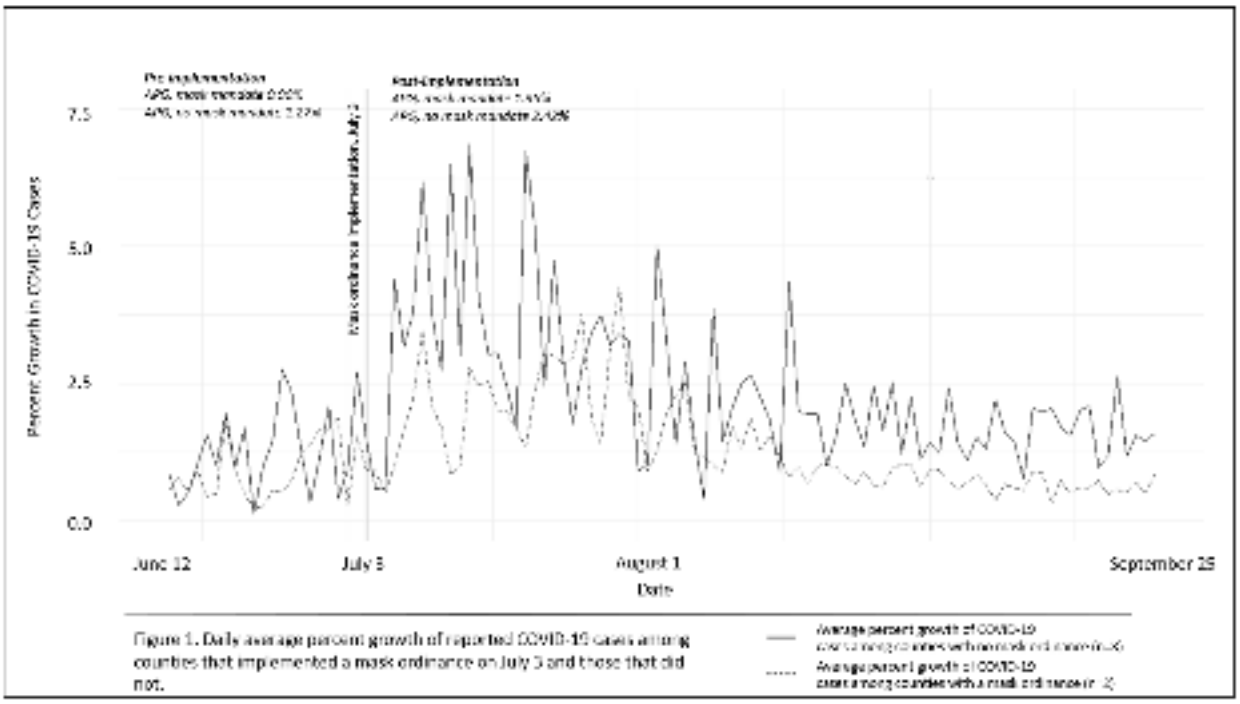

Figure 1. Daily average percent growth of reported COVID-19 cases among counties that implemented a mask ordinance on July 3 and those that did not.

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Table 1. Covariate associations 3 weeks prior to mask mandate and 12 weeks after mask mandate[a]				
	3 weeks prior to mask mandate, June 12 to July 3		12 weeks prior to mask mandate, July 3 to September 25	
	τ	p value	τ	p value
Percent population non-white	-0.04	0.623	-0.22	<0.001
Median annual household income ($)	-0.01	0.849	<0.01	0.977
Population density (mi^2)	-0.08	0.282	-0.26	<0.001
a. Kendal's tau-b rank correlation				

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Table 2. Linear probability models predicting percent growth in reported COVID-19 cases among five counties in Missouri

	3 Weeks Post Mask Policy		6 Weeks Post Mask Policy		9 Weeks Post Mask Policy		12 Weeks Post Mask Policy	
	β	Std. E	β	Std. E	β	Std. E	β	Std. E
DID estimator[a]	-1.36**	0.45	-0.77*	0.40	-0.72*	0.36	-0.69*	0.3
Percent population non-white[b]	0.10	0.32	-0.08	0.27	-0.07	0.22	-0.04	0.1
Median annual household income($)[c]	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.0
Population density (mi^2)[d]	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.0

a. adjusted R^2 0.32, b. adjusted R^2 0.21, c. adjusted R^2 0.15, d. adjusted R^2 0.13
Significance reported t *0.05, **0.01, ***0.001

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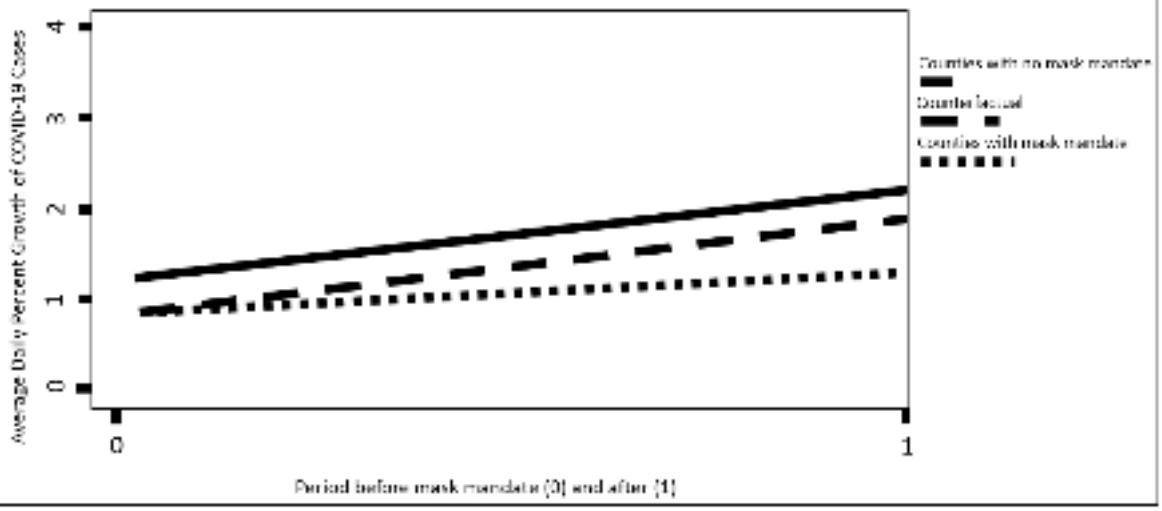
Figure 2. Plotting of Y=β0+ β1[time]+ β2[presence of mask ordinance]+ β3[DID estimator]+ ε from model results in table 1. Effect of a mask mandate among counties is depicted in the difference between the dotted mask line and the dotted/dashed counterfactual line.



Occupational Medicine
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SHORT REPORT

Effects of universal masking on Massachusetts healthcare workers' COVID-19 incidence

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Background	Healthcare workers (HCWs) and other essential workers are at risk of occupational infection during the COVID-19 pandemic. Several infection control strategies have been implemented. Evidence shows that universal masking can mitigate COVID-19 infection, though existing research is limited by secular trend bias.
Aims	To investigate the effect of hospital universal masking on COVID-19 incidence among HCWs compared to the general population.
Methods	We compared the 7-day average incidence rates between a Massachusetts (USA) healthcare system and Massachusetts residents statewide. The study period was from 17 March (the date of first incident case in the healthcare system) to 6 May (the date Massachusetts implemented public masking). The healthcare system implemented universal masking on 26 March, we allotted a 5-day lag for effect onset and peak COVID-19 incidence in Massachusetts was 20 April. Thus, we categorized 17–31 March as the pre-intervention phase, 1–20 April the intervention phase and 21 April to 6 May the epidemic decline phase. Temporal incidence trends (i.e. 7-day average slopes) were compared using standardized coefficients from linear regression models.
Results	The standardized coefficients were similar between the healthcare system and the state in both the pre-intervention and epidemic decline phases. During the intervention phase, the healthcare system's epidemic slope became negative (standardized β: −0.68, 95% CI: −1.06 to −0.31), while Massachusetts' slope remained positive (standardized β: 0.99, 95% CI: 0.94 to 1.05).
Conclusions	Universal masking was associated with a decreasing COVID-19 incidence trend among HCWs, while the infection rate continued to rise in the surrounding community.
Key words	Hospital; infection control; infectious disease; personal protective equipment; SARS-CoV-2.

Introduction

COVID-19 is an occupational risk for healthcare workers (HCWs) essential to maintaining health and hospital systems [1]. Evidence supports HCWs' infection risk due to direct exposure to co-workers, patients and contaminated environments [2]. Accumulating research suggests that optimal infection control strategies, including personal protective equipment (PPE), can minimize the risk of SARS-CoV-2 transmission to HCWs [3,4]. Among now established mitigation measures, universal masking is thought to be one of the most effective means to protect HCWs. However, existing evidence of universal masking efficacy is largely based on self-comparison results (i.e. comparing pre- and post-masking phases) [5] instead of comparing HCWs with a reference population, and thus

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Key learning points

What is already known about this subject:

- Healthcare workers are occupationally exposed to SARS-CoV-2.
- Protecting healthcare workers and other essential workers is important to maintain healthcare and other essential businesses.
- Optimal personal protective equipment use can minimize workers' risk of being affected by COVID-19.

What this study adds:

- Additional evidence that universal masking is associated with decreased incident COVID-19 infections among healthcare workers.
- Universal masking in the healthcare setting protects healthcare workers.

What impact this may have on practice or policy:

- Timely universal masking policy should be implemented and maintained in healthcare settings during the COVID-19 pandemic.
- Our study indirectly supports universal masking with procedure masks or similar medical masks by other essential workers and within indoor businesses when social distancing and ventilation may be inadequate.

subject to secular trend bias. Therefore, we conducted this study to investigate the effect of universal masking in a Massachusetts (USA) healthcare system, using the statewide population as a comparison group.

Methods

This time-series study examined the daily COVID-19 incidence trends among the Massachusetts statewide population and the HCWs of a Massachusetts community healthcare system that tested symptomatic employees since the initial outbreak. The statewide data were derived from the Massachusetts Department of Public Health [6]. More than 95% of the system's HCWs (4449 out of 4673) resided within Massachusetts, almost all in the seven counties of the greater Boston area, which are also home to 84% of the statewide population [7]. The HCW cohort of the healthcare system and related ethical statement are described in our previous paper [8]. In the present study, the total number of HCW incident cases is different due to a longer observation period. We calculated 7-day moving average COVID-19 incidence to smooth daily fluctuation. Each incident case was assigned the date when that HCW called the occupational health 'hotline' for triage. For state population cases, we assigned the reported date.

We defined the study period as from 17 March 2020, when the first case in the healthcare system was identified, to 6 May 2020. The study period was divided into three phases: pre-intervention (17–31 March), intervention (1–20 April) and epidemic decline (21 April to 6 May). Date cut-offs were determined as follows. First, the healthcare system implemented universal masking on 26 March and we allowed five more days for the policy to take effect based on the average COVID-19 incubation period. The policy included securing N95s for all direct-care staff managing confirmed/suspect COVID-19 patients and providing procedure masks to all other clinical and non-clinical staff. Second, Massachusetts reached the peak of COVID-19 incidence on 20 April (Figure 1), and the effects of universal masking are more detectable when the surrounding community secular trend is increasing. Finally, Massachusetts implemented a statewide masking policy on 6 May.

We built linear regression models to investigate the temporal trends for each cohort's 7-day average incidence within each of the three phases. Standardized beta coefficients and 95% confidence intervals (95% CIs) were calculated and presented to account for the different scales between the healthcare system and the state. The analyses were performed using R software (version 3.6.3) and SAS software (version 9.4, SAS Institute).

Results

During the study period, incident cases in the healthcare system and the state were 142 and 75 493, respectively. Pre-intervention, both the healthcare system and the state had strong increasing trends in the 7-day average COVID-19 incidence (Figure 1; Table 1) with overlapping slopes (0.96 (0.80 to 1.13) and 0.99 (0.92 to 1.07), respectively). While the temporal trend among Massachusetts residents kept increasing with a similar slope in the intervention phase (0.99 (0.94 to 1.05)), that of the healthcare system decreased and was negative (−0.68 (−1.06 to −0.31)). During epidemic decline, following the states' pandemic peak, both populations' incidence showed overlapping negative slopes (−0.90 (−1.19 to −0.60) and −0.99 (−1.07 to −0.92)) (Figure 1; Table 1).

Discussion

Our study provides additional evidence of the protective effect of universal masking in healthcare settings. The HCW's epidemic curve was flattened, and in fact, demonstrated a decreasing daily incidence trend after

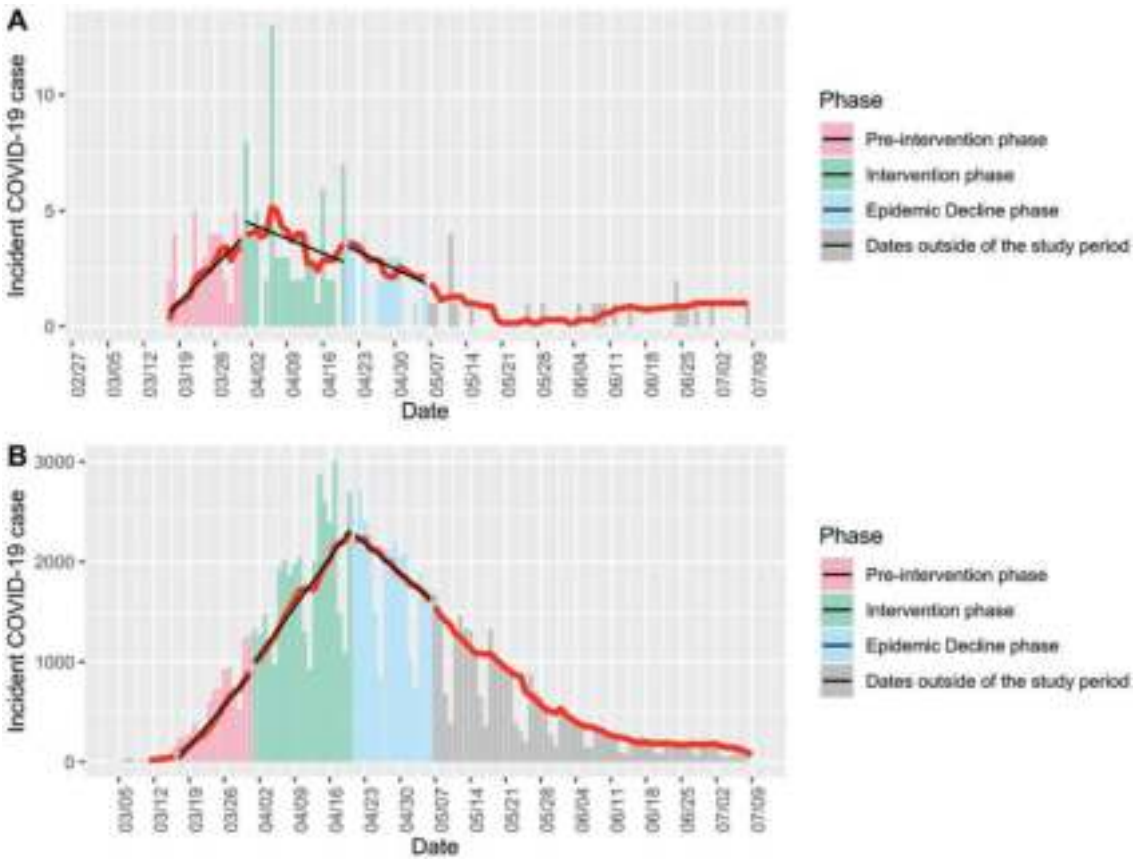

Figure 1. Temporal distribution of COVID-19 incidence among the (A) healthcare system employees and (B) Massachusetts residents statewide. Bars indicate the absolute number of daily cases. The red line denotes the 7-day average of new cases. The black lines show linear regression slopes in each specific phase. The phases were categorized based on the implementation date of universal masking policy by the healthcare system (pre-intervention phase, 17–31 March; intervention phase, 1–20 April; epidemic decline phase, 21 April to 6 May).

Table 1. The standardized beta coefficients of 7-day average COVID-19 incident cases regressed on days during the three study phases

	Pre-intervention phase (17–31 March)	Intervention phase (1–20 April)	Epidemic decline phase (21 April to 6 May)
The healthcare system	0.96 (0.80 to 1.13)	−0.68 (−1.06 to −0.31)	−0.90 (−1.19 to −0.60)
Massachusetts statewide	0.99 (0.92 to 1.07)	0.99 (0.94 to 1.05)	−0.99 (−1.07 to −0.92)

Beta coefficient (95% CI) derived from linear regression models in each phase.

implementing universal masking, while the statewide infection rate continued to increase during the same time period. The findings are in agreement with a recently published study using HCW self-comparison [5], finding a significant decrement in the SARS-CoV-2 positivity rate after the implementation of universal masking. We confirmed this effect by including a comparison group, eliminating potential secular trend bias that limits before and after time-series studies.

Evidence supports that PPE can prevent HCWs from being infected [9]. Two studies conducted in Wuhan, China investigated 278 and 420 front-line HCWs with optimal PPE protection from different healthcare systems, respectively, and reported no infections [3,10]. In contrast, 10 out of 213 HCWs without appropriate masking protection sustained nosocomial infection [10]. In accordance with the existing evidence [5], our results further support masking's protective effects from the perspective of hospital infection prevention.

The current study has several strengths such as the use of a comparable reference group, a validated outcome and a distinct intervention. Nonetheless, there are some limitations. First, the current study is limited by the small sample size of HCWs, the short intervention period and individual HCW compliance with the masking policy and PPE use were not measured. The relatively small sample size during the post-intervention, epidemic decline period prevented us from detecting potential additional effects of universal masking, as statewide incidence was also strongly decreasing. In part, this was likely due to

the increased use of masks within the community for grocery shopping and similar activities. Therefore, additional larger-scale studies of masking are warranted. Second, the 5-day interval assumed for the policy to take effect was not precise, but reasonable because the median lag time between symptom development and infection is 5 days [11]. Finally, there could be unmeasured confounding, such as improved social distancing, hand hygiene and isolation of COVID-19 patients. However, we found significant differences between incidence curves, with HCWs' changing from positive to negative slopes shortly after universal masking, which is unlikely to be entirely biased.

In conclusion, our results suggest that universal masking significantly mitigates COVID-19 incidence in the healthcare setting, which may be applicable to other essential workers and indoor businesses.

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Competing interests

S.N.K. has received COVID-19-related consulting fees from Open Health. All other authors declare no competing interests.

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Mask-Wearing During the COVID-19 Pandemic

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Mask-Wearing During the COVID-19 Pandemic

Abstract

Background
Masks have been widely recommended as a precaution against COVID-19 transmission. Several studies have shown the efficacy of masks at curbing droplet dispersion in lab settings. Using individual response data from the Imperial College London — YouGov personal measures survey, this study investigates reported mask use and its association with the spread of COVID-19.

Methods
We examine the association of reported mask-wearing in a population within a country with the growth rate of active cases COVID-19 cases. The analysis uses country-wide data from weekly surveys of individuals' mask-wearing behavior in public places, as well as other concurrently implemented non-pharmaceutical interventions, mobility changes, new cases of COVID-19 data and other control variables. The mask-wearing data were obtained from the Imperial College — YouGov multi-country survey of people's personal habits before and during COVID-19. Because mask-wearing showed substantial variation across countries and over time, we use a reduced form econometric model to relate population-wide changes in mask-wearing to the growth rate in COVID-19.

Results
The results indicate that reported mask-wearing could play an important role in mitigating the growth of COVID-19. Widespread mask-wearing within a country associates with an expected 7% (95% CI: 3.94% — 9.99%) decline in the growth rate of daily active cases of COVID-19 in the country. This daily decline equates to an expected 88.5% drop in the growth of daily active cases over a 30-day period when compared to zero percent mask-wearing, all else held equal. The decline in daily growth rate due to the combined effect of reported mask-wearing, reduced social mobility, and non-pharmaceutical interventions averages 28.1% (95% CI: 24.2%-32%). These estimates remain robust across multiple sensitivity analyses.

Conclusions
Face mask usage as a preventative measure against the transmission of COVID-19 varies widely across countries. This observational study uses data from 24 countries and finds that reported face mask usage associates with a decline in new COVID-19 cases. Even though the model controls for a large variety of variables that affect spread, and we run a number of robustness checks, it remains possible that some of the decline associated with face masks is related to confounding variables not included in the model. In summary, due to the confounding variables and the variations in the type of mask and its usage, randomized control trials of mask usage in populations are needed to determine the true effect of mask–wearing on mitigating the transmission of infectious respiratory diseases.

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1. Introduction

In response to the COVID-19 pandemic, multiple countries curbed the spread of the disease by enforcing strict policy measures such as lockdowns and shelter-in-place orders [1]. The non-pharmaceutical interventions (NPIs) included closures of school, restaurants, bars, retail outlets and other non-essential businesses, as well as shelter-in-place policies and the prohibition of large gatherings (e.g., limited to 10 people) [2]. These institutional measures aimed to reduce the exposure of susceptible individuals to symptomatic and asymptomatic infected individuals by decreasing social mobility (e.g., going out to movies, concerts and restaurants, assembling in large groups) and encouraging social distancing. (e.g., 1m-2m physical distancing) [3,4].

Unlike the widespread and proactive implementation of lockdowns and physical distancing measures, the usage of masks varied widely across countries. Some countries quickly adopted guidelines for mask usage (e.g., Malaysia, Singapore, Taiwan, and Thailand) while others did not recommend using face mask unless sick [5,6,7]. Indeed, the World Health Organization updated its mask-wearing guidelines only on June 5, 2020 [8], to recommend that "The general public should wear non-medical masks where there is widespread transmission and when physical distancing is difficult, such as on public transport, in shops or in other confined or crowded environments.". Due to these changing guidelines and uneven implementations, mask-wearing varied dramatically across countries and over time [9].

Multiple studies have investigated the impact of various governmental NPIs [3,10,11,12], that encourage physical distancing and the wearing of face masks [13,14,15]. In each case they find that NPIs, physical distancing, and face mask usage reduce the transmission of COVID-19. However, the interventions, government policies, and individual measures seldom act in isolation. Treating these measures in isolation could lead to under- or over-estimation of their effectiveness at reducing the spread of the disease, biasing the assessments of the measure's impact. In this study, we investigate the association of population-wide mask-wearing with the number of COVID-19 cases, concurrent with other individual and institutional measures. Specifically, we expand on the current stream of research by simultaneously considering the effects of NPIs and social mobility along with a population's reported usage of face masks in public places in a reduced-form econometric model (see examples in [3] and [10]). Using data from 24 countries, we identify the effect of each measure by exploiting the country-wise differences in the (1) percentage of the population who report wearing a face masks in public places (YouGov Survey Data [9]), (2) social mobility across multiple categories such as Parks and Transit Locations (using Google Mobility Reports [16]) and NPI implementations (using CoronaNet-Project [1])

2. Methods

This study is a cross-sectional analysis of the effects of personal and governmental measures across 24 countries on mitigating COVID-19 disease spread. The data used in this study were collected from February 21, 2020 to July 8, 2020, representing 139 days of data for each country. All analysis presented in this paper uses publicly available data. Subsequently, we first present the data and then the model-based analysis.

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Key Variables of Interest

Mask-Wearing: Survey data released by the Institute of Global Health Innovation (IGHI) at Imperial College London and YouGov [9] provide reported mask-wearing across multiple countries. The survey covers 26 countries (as of July 8, 2020), with around 21,000 people interviewed each week. We restrict our analysis to 24 countries, because two countries – China and Hong Kong – do not have publicly available data on the social mobility dimensions we control for in this study. The data present global insights on people's reported behavior in response to COVID-19. The dataset provides the percentage of population in each country who report to wear a mask in public places. Because these surveys were conducted at an interval of several days, we interpolate (linearly) to estimate the percentage of the population that would wear masks in public spaces for days when the data were unavailable (Figure 1). We use the significant variation of mask-wearing across countries to measure the association of people reporting mask wearing and the spread of COVID-19.

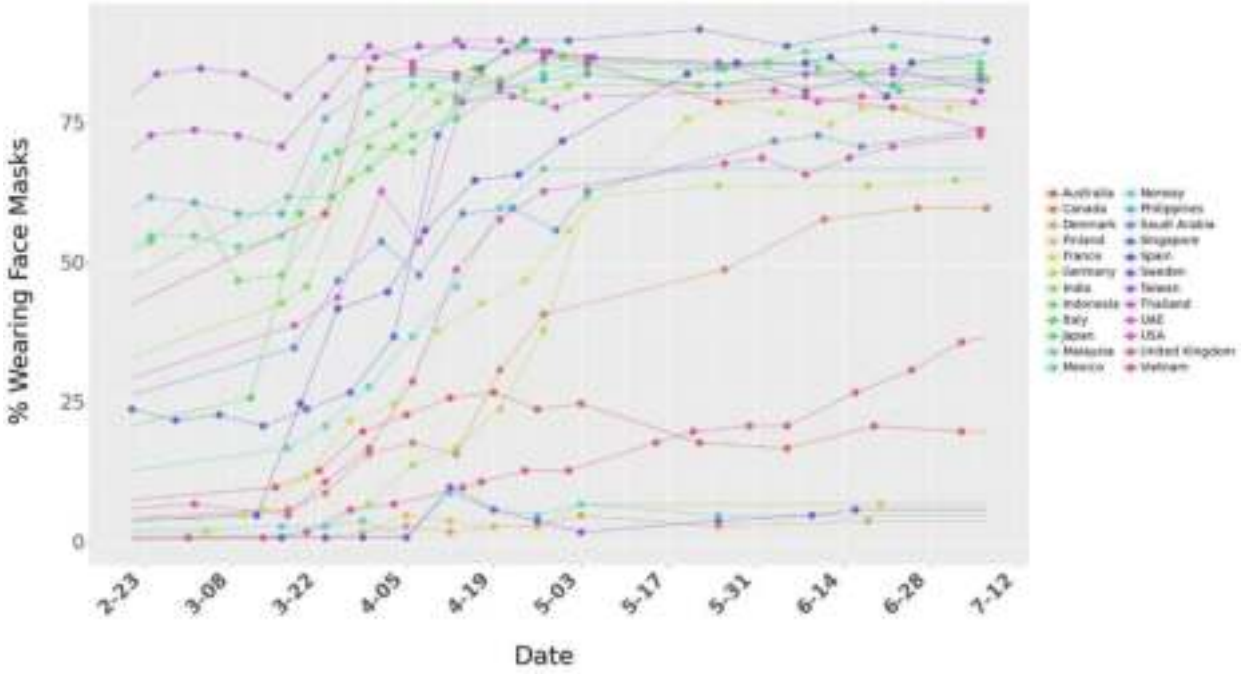

Figure 1. Percentage of people who say they are wearing a face mask in public spaces

Social Mobility: Google Community Mobility Reports provide data on relative mobility changes with respect to an internal baseline across multiple categories namely, retail and recreation, groceries and pharmacies, parks, transit stations, workplaces, and residential (Figure 2). A summary for the community mobility is shown in Table S2 in the Supplement. Apart from the Google Mobility reports, we also utilize mobility data from Apple to test the robustness of the model to different measures of mobility. We note that neither Google nor Apple provide absolute measures of mobility, but rather present relative changes with respect to benchmarks they use internally. Finally, drops in mobility could be driven by both individual actions (e.g., cautious behavior) as well as institutional actions due to NPIs enacted by governments. To control for mobility declines due to institutional actions, we also include country-specific interventions enacted both nationally and provincially.

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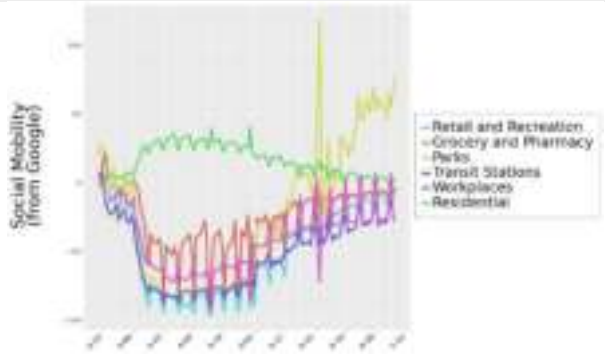

Figure 2 (a) Social Mobility for Italy from Google Community Mobility Reports

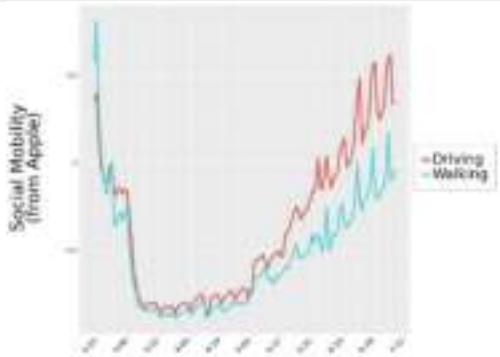

Figure 2 (b) Social Mobility for Italy from Apple Community Mobility Reports

Figure 2. Social mobility from Google Mobility Reports and Apple Mobility Reports for Italy. Social mobility for all the 24 countries is shown in Figure S8 in Supplementary.

Non-Pharmaceutical Interventions: Governments across the 24 countries enforced different policies to control the spread of COVID-19. Prior research has shown that these policies played a significant role in reducing human to human physical contacts and led to a slowdown in the spread of the disease. However, these policies were implemented in different ways, some nationally, some provincially. We use data from COVID-19 Government Response Event Dataset [1] to control for government policies in estimating the effect of masks. Figure S10 lists the types and counts of national and provincial government policies implemented across the 24 countries we consider in this study. The dataset contains 5,816 entries on policies at National and Provincial level. Finally, inclusion of these interventions helps control for some of the observed drops in mobility that are not necessarily associated with individual actions but by the presence of institutional policies. Detailed information about the interventions are included in the Supplement (Section S2.5).

Covariates

Because the data span multiple countries and weeks, we include time and country fixed effects in the model. The model controls for country-level heterogeneity using fixed-effects, where the variable for a country assumes a value of one if the data considered are specific to that country, and zero otherwise. This allows for control of country-level characteristics that are not in the model and helps reduce the errors due to omitted variables in our analysis. In addition to country-level differences, we also control for time-based differences (e.g., people are more aware and cautious over time) by incorporating time-fixed effects, where the variable $Week_t$ takes a value of 1 if the data are from week 't' (where t =1 in the first week for a given country in the data). In addition, we control for each country's testing capability (Figure 3a) by accounting for the total number of daily tests in the country. Finally, we also control for actions people take to educate themselves by including the Google Trends (Figure 3b) data for the search term 'coronavirus'.

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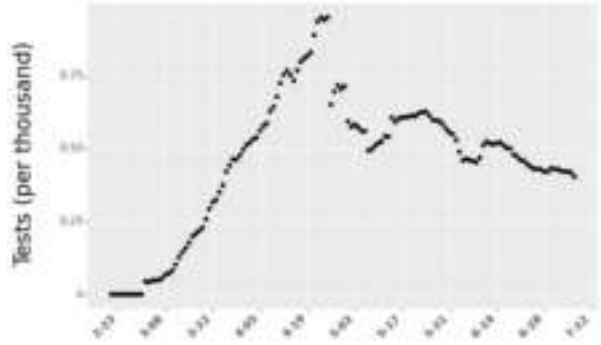

Figure 3 (a) Number of COVID-19 Tests per Thousand People in Italy

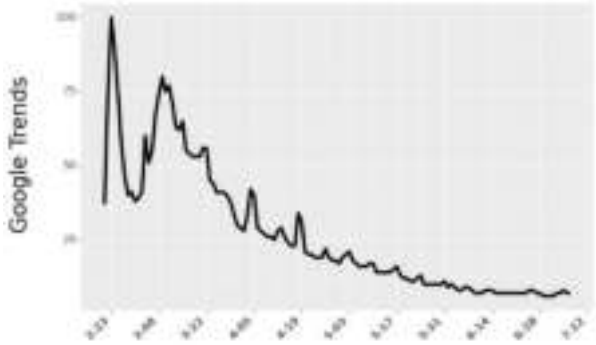

Figure 3 (b) Google Trends for Search Term *coronavirus* in Italy.

Figure 3. Number of COVID-19 Tests and Google Trends (per thousand people) for Italy. Data for all the 24 countries is shown in Figure S13 and Figure S14 respectively in Supplementary.

Outcome Variable

Data for the number of active daily cases in each country were obtained from the Johns Hopkins University School of Public Health [17]. We use a seven-day moving average of cumulative confirmed cases and cumulative recovered cases to compute daily active cases and daily growth rate. The dataset aggregates this information across multiple national, state, and local health departments within each country. The daily growth rate is then related, by means of a reduced-form econometric model, to the independent variables described earlier. We describe the derivation in the Supplement (Section S1.1). We illustrate the daily cases and growth rate for one country, Italy, in Figure 4.

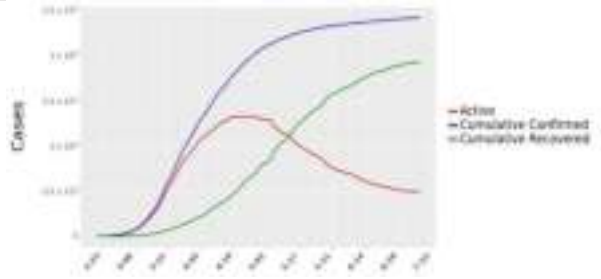

Figure 4 (a) CoVID-19 Cases in Italy.

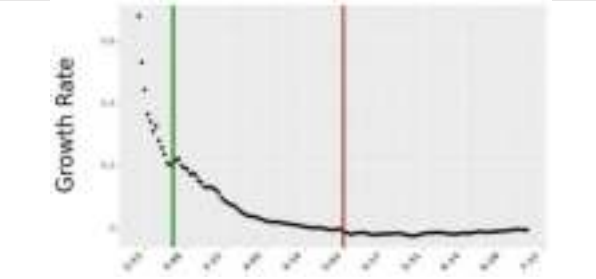

Figure 4 (b) Growth rate in Italy.

Figure 4. Daily Active cases and growth rate in Active cases for Italy. Vertical green line in (b) shows the start of data collection for Italy. Vertical red line in (b) shows the end of 60 days of data collection for Italy. Data for all the 24 countries is shown in Figure S6 and Figure S7 respectively in the Supplement.

Analysis

A reduced form econometrics model was used to relate the growth rate of daily active infections to the independent variables described earlier. Similar models have been used by [3] to determine the effect of anti-contagion policies on the spread of COVID-19. In brief, the model assumes that the daily growth rate (ratio of active infections today to active infections the day before) is affected by the institutional measures such as NPIs as well as individual measures such as social mobility and mask-wearing. The covariates listed above help control for other factors

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that could affect growth over time. Because the epidemiological parameters for new diseases such as COVID-19 might not be well understood, reduced form techniques allow for the estimation of the impact of governmental and personal measures to help contain the spread of the virus. The model we use initializes when a country reaches 20% of peak new cases as observed by July 8, 2020 to filter out the high variation in growth rates when the number of cases is very low at the beginning of the pandemic. For robustness, we also test other starting times in the Supplement and find results in line with the ones presented here. The Supplement also provides further details about the methodological approach as well as information on the model formulation used.

We provide some brief notes on the operationalization of the independent variables and the model initialization below:

1. Responses to the survey about mask-wearing are subject to biases. For example, individuals might overestimate the efficacy of their mask or their wearing pattern. To alleviate some of these concerns, we compute the natural log of the mask-wearing variable to discount its impact on the growth of cases. This transformation yields a curve that grows at a slower rate as the values of mask-wearing increase, thereby diminishing the impact of higher levels of mask-wearing. We also test for other functional forms (square-root and linear) and present those results in the Supplement (Table S7).
2. Due to the high correlation across the different mobility data categories obtained from Google, we only include *Mobility: Parks* and *Mobility: Transit Stations* in the model. Because we are interested in determining the impact of mobility in general, the two mobility variables suffice in capturing the individual's movement patterns during this time. In Supplement S3.4, we present results including other types of mobility, and also run the model with Apple Mobility data in the place of Google Mobility Reports.
3. The CoronaNet dataset from [1] collected information on all the government policies introduced by different countries across the world. They categorized the policies into 19 different policy-types. We use their categorization in the model. From February 21, 2020 to July 8, 2020, we check if a policy p was implemented in a country j on day t. If the policy was implemented, we assign a value of 1 to $s_{j,t,p}$, where s represents the level of policy coverage. If the policy was introduced at a provincial level, we $s_{j,t,p}$ by the population of the state. Because several policies were introduced at the same time or close together, they too suffered from collinearity issues. To minimize multicollinearity issues, we choose only a specific set of policies to include in the analysis. The Supplement (Section S2.5) discusses this selection mechanism.
4. Due to uncertainty of the lag in COVID-19 incidences and the difficulties in detection during the early days of the disease (Woloshin et al 2020), similar to prior research we tested the focal model across multiple lag periods (*shift*) from zero to 14 days and for different initialization thresholds (*th*) for each country (zero percent to 20% of a country's peak daily cases). We chose the best *shift* and *th* values using a k-fold cross-validation process (k=5). The chosen model had the highest maximum likelihood estimate of the data as well as the lowest prediction error. We discuss this procedure in the Supplement (Section S4.1). The results presented in the next section correspond to a model with a shift of nine days and a *th* of 20% of peak new cases by July 12, 2020. Finally, the model was estimated on 1,422 observations across 24 countries, averaging 60 observations per country. We restrict our analysis to the first 60 days. However, we test

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the robustness of the findings for other lengths of data. This allows for greater variation in mask usage within the data.

In the next section, we describe our results and their policy implications.

3. Results

The results indicate that individual (mask-wearing, social mobility) and institutional measures (NPIs) could play a role in mitigating the growth of COVID-19. The estimates from the focal reduced form model for these measures and their corresponding confidence intervals are shown in Figure 5. The full table of results, along with results for all robustness checks are provided in Supplement (Section 3). We first list the results of the key measures we consider and then discuss their implications.

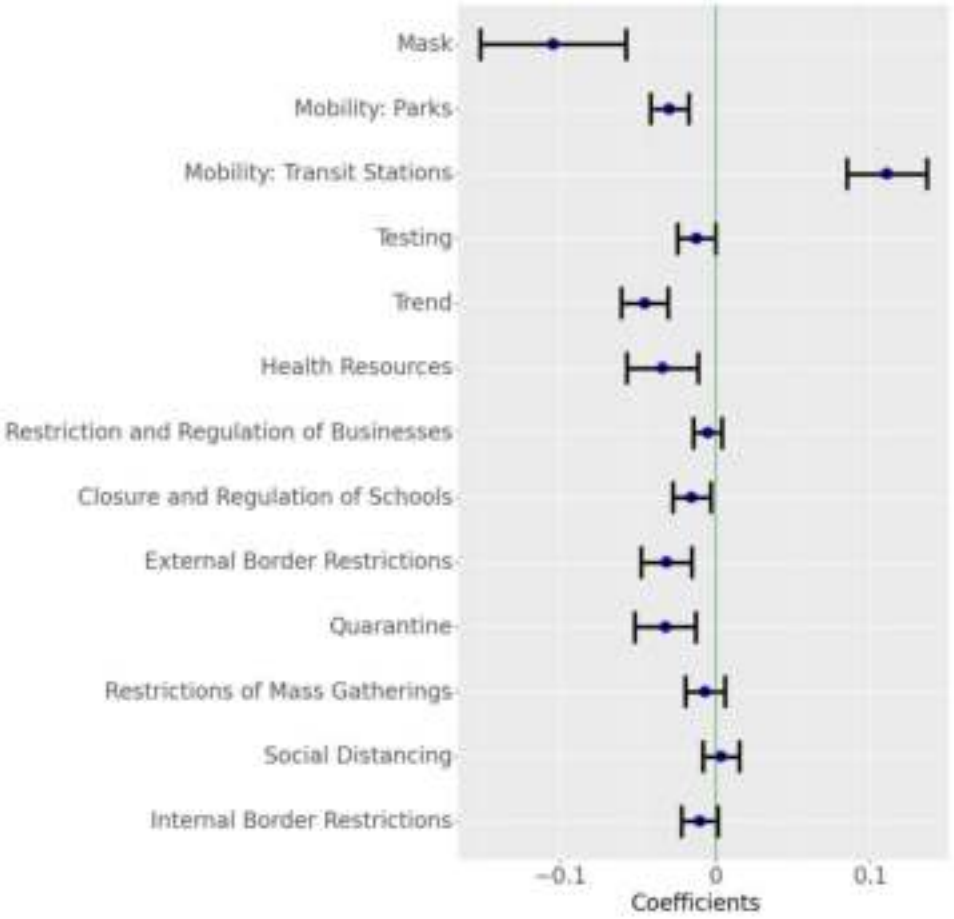

Figure 5. Parameter estimates for the Growth rate model. The blue dot indicates the point estimates and the horizontal lines indicate 95% confidence interval around the estimate (Masks transformed as ln(1+mask)). Results for different transformations of Mask and other covariates is shown in Figure S16.

Masks. The model finds that a reported mask wearing of 100% is associated with an average 7% (95% CI: 3.94% — 9.99%) drop in daily COVID-19 cases. While this daily effect appears small over a 30 day period, 100% reported mask-wearing leads to approximately 88.5% (95% CI:

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68.7% — 89.2%) decline in active cases when compared to the situation where 0% of the people report wearing masks (all else remaining the same across the two scenarios). Modifying the functional form of the mask variable did not appreciably change the association. For example, in the linear model, masks are associated with an average 8.69% (95% CI: 5.63% — 11.66%) drop in daily growth rate and for the square root model the expected daily drop in growth rate was 7.89% (95% CI: 4.81% — 10.87%). The stability of the results seems to indicate that mask-wearing can potentially play a significant role in mitigating the spread of the disease. Figure 6 plots the ratio of active cases under different proportions of respondents who claim to wear masks as against no mask wearing.

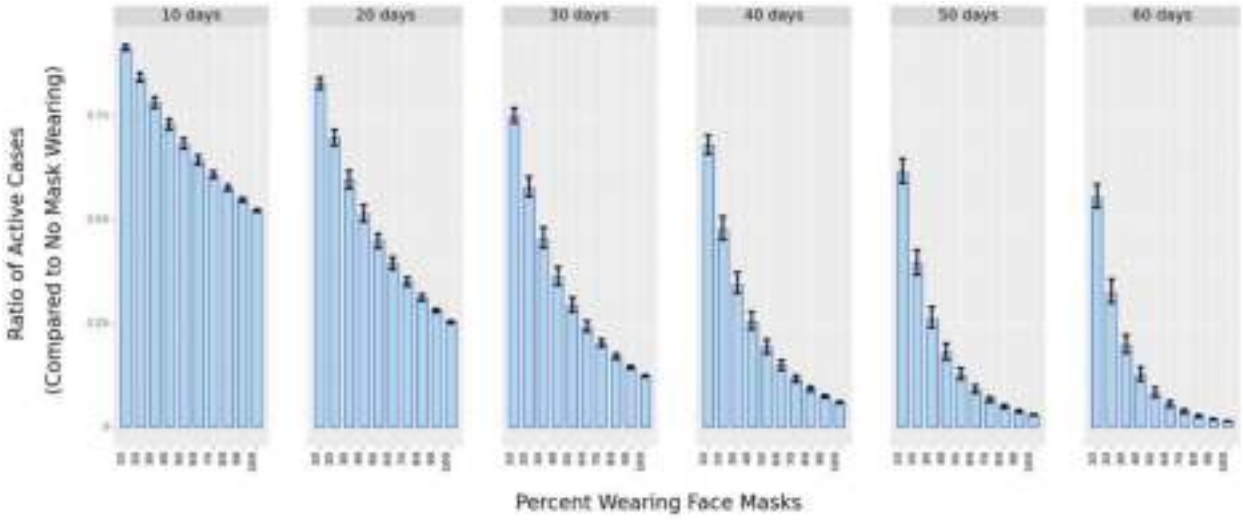

Figure 6. Ratio of Active cases under different percentage of mask wearing in public spaces as compared to 0 mask wearing over different periods (in days) . The shaded bars represents in ratio while the black vertical lines represent the 25th and 75th percentile of the ratio (from simulations using Krinsky-Robb method)

Mobility and NPIs. As expected, the model finds that a rise in mobility links with a rise in the number of cases. Specifically, the selected mobility variables associate with a combined 8.1% (95% CI: 5.6% - 10.6%) drop in daily case numbers. Similarly, we find that the implementation of NPIs also associate with a drop in daily growth rates across countries. After accounting for mobility declines, the NPI measures 'Quarantine, 'External Border Restrictions,' and 'Closure and Regulation of Schools' link with the highest declines in the growth of cases. Overall, all NPIs included in the model led to a decrease in the growth rate of COVID-19. This finding confirms multiple studies that investigated the effects of NPIs at limiting the spread of COVID-19 [10,18]. Overall, we find that if the NPIs were enacted uniformly across the whole country, then the combined association of the NPIs with the decline of growth in daily cases of COVID-19 would average 13% (95% CI: 9.2% - 16.2%). We determine the combined effect using the Krinsky-Robb method, a Monte Carlo simulation used to draw samples from a multivariate normal distribution. Supplement S3.1 provides more details on this method.

Control Functions and Robustness Checks

Due to nearly concurrent enactments and blanket coverage of policies and precautionary behaviors within countries, the individual (e.g., masks, limiting mobility) and institutional (NPIs)

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measures correlate in time. This precludes causal identification of each measure's individual effect on disease mitigation. In other words, because mask-wearing, mobility reductions, and NPIs occur at similar times, their effects are intertwined and difficult to determine separately. For some variables such as mobility and NPIs, we lack the necessary data to fully control for some of these issues. In the case of mask-wearing, even though we cannot eliminate the simultaneity, we attempt to reduce the effects of confounding variables by employing control functions [19]. In addition, [20] note that control functions make the intervention exogenous in a regression equation. To create a control function, we use country mortality data for SARS, H1N1, and MERS to predict the propensity of mask-wearing in each country (see Supplement S4.5.2 for more details). Next, we compute the control function by determining the predicted mask-wearing residuals (Predicted Mask-Wearing minus Actual Stated Mask-Wearing), allowing for better identification of the effect of reported mask-wearing on COVID-19 case numbers.

Using this procedure, we find that if 100% of the population claimed to wear masks, then mask-wearing relates with an average 4.95% (95% CI: 2.26% — 7.53%) drop in daily growth rate (nine days later), when compared to zero percent reported mask-wearing. While we are careful to note that this estimate could still be affected by confounding variables, this result lends further support to the estimate presented earlier. In summary, widespread mask-wearing could lead to a significant decline in the growth of COVID-19.

To help determine the accuracy of the results we run several robustness checks (see Supplement S4):

(1) We vary the lag period (*shift*) from 0 to 14 days. The results show that the estimates of the individual and institutional measures are relatively stable.
(2) We also vary the length of time we consider in the analysis. The model considered 60 days of data for each country. We vary this to estimate the model on 35, 45, 55, 65, 75 and 85 days of data. We find that the results remain consistent to these changes.
(3) We replace Google mobility data with Apple mobility data. The model estimates remain robust to this change.
(4) We vary the functional form of how mask-wearing relates to the growth of COVID-19. The results do not vary appreciably with respect to this to this change.
(5) We also test the robustness of the analysis by modifying the data using exponential smoothing. Specifically, for any day *t*, the focal model in Equation (1) ignores the value of the independent variables from days *t-shift+1* to t (discussed in Figure S1). In the model we use for the robustness check, we do not ignore values between *t-shift* and *t* and use exponential smoothing to average the intervening data. Finally, we also modify the interpolation method from linear (current) to quadratic. We find that the results are stable to all these modifications.

The Supplement details all the robustness checks and simulations as well as their results.

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4. Discussion

Over the past few months, several studies have investigated the efficacy of masks at minimizing droplet dispersion [21,22] and the potential consequences of their use [14,23] in the general population. Although no randomized control trial on the efficacy of face mask usage in the general population exists, [15,14] provide compelling evidence for the use of face masks through a systematic review of the multiple observational studies and the evidence thus far. Both studies project that the use of face masks reduces the transmission of disease. While the type of face mask as well as the timing and length of use can affect its efficacy, its use as a precautionary principle has been strongly advised [24]. Despite this preponderance of evidence, face mask use, in the US remains controversial [25,26]. Additionally, as observed in the data, even in countries where masks do not face similar headwinds and as support for mask usage gathers further evidence, face mask use is not as common place (e.g., Denmark, Norway, Sweden, Finland, Australia), even as a precautionary principle.

This study links the growth in active cases of COVID-19 in a country, to a population's reported wearing of face masks in public places over time. The model also includes other measures that could simultaneously impact the growth of the disease as face mask usage changes over time. After accounting for these measures and controlling for other covariates, the results indicate that reported face mask use is associated with a decline in the growth of COVID-19. More precisely, if 100% of the population claimed to wear masks, then mask-wearing is associated with an average 7% decline in the growth of COVID-19. This association persists across multiple robustness checks and model formulations. A decline of 7% corresponds to an 88.5% drop in the number of active cases 30 days later. Taken together with the other measures (mobility changes, NPIs), the combined association obtained via the Krinsky-Robb method of individual and institutional measures on the decline in the daily growth of COVID-19 is 28.1% (95% CI: 24.2%-32%).

Limitations

This study has several limitations. First, countries enacted multiple NPIs simultaneously. This precludes us from identifying the effectiveness of NPIs separately. Second, the mobility data provided by Google and Apple are only indicative of the relative changes from a benchmark, so their association with disease spread should be interpreted with precaution.

Third, even though we consider multiple NPIs and mobility measures and control for population-wide awareness, testing, and country and time differences, there could be several variables that we do not or cannot include due to the lack of data. For example, one of the NPIs we consider relates to health announcements (e.g., handwashing, coughing into one's elbow, etc.). However, the model only notes the NPI and not the adoption of these practices in the general population. While some data (e.g. sale of soap, cleansers, etc.) could approximate this, multiple confounding variables still exist and thus limit the extent to which we can apply any causal interpretation of the results. We attempt to provide better insights using a control function approach, however, stop short of making causal claims.

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Fourth, our analysis was conducted at the country level due to data restrictions. However, mask usage, mobility changes as well as the implementation of NPIs most likely vary within the country. Nevertheless, the analyses in this study are helpful at understanding the practical implementation of mask usage policy within a country.

Finally, we rely on the accuracy of data collected by third parties. Inconsistencies in testing, reporting, and recording of the data could lead to errors in the results obtained. Additionally, mask-types and mask-wearing patterns could vary across countries, individuals, and over time. This limitation affects all observational COVID-19 population-based studies. Randomized control trials of mask usage in populations are needed to determine the true effect of mask–wearing on mitigating the transmission of infectious respiratory diseases.

5. Conclusions

The population-wide usage of face masks as a preventative measure against the transmission of COVID-19 varies widely across countries. Using data from 24 countries, this study finds that reported face mask usage associates with a decline in the growth rate of COVID-19. Even though we control for multiple variables that could affect spread and include multiple robustness checks, it remains possible that some of the decline associated with face masks may be related with other confounding variables not included in our model.

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Impact of universal masking in health care and community on SARS-CoV-2 spread

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Abstract

Universal masking the health care setting and in the community to contain the spread of SARS-CoV-2 has been recently recommended by the WHO, but supporting data are rare. The City of Jena was the first community in Germany to issue an order on mandatory public masking. Here, we report the development of the number of novel infections in our hospital and in the city of Jena after implementation of universal masking in our hospital and the city.

Introduction

There are only a few studies on universal masking during the flu season in hospitals (Esposito et al. 2020), and, to the best of our knowledge, there are no studies investigating the efficacy of universal masking in healthy individuals to prevent SARS-CoV-2 transmissions. At least, for seasonal human corona virus infection, it was shown that exhaled droplets with a diameter of ≤5 µm containing viral particles can completely be withheld by surgical masks when worn by an infected person (Leung et al. 2020). Arguments against universal masking include a global supply shortage of medical masks, the insufficient filtration of alternative cloth masks compared to medical masks (MacIntyre et al. 2015), a false sense of protection by wearing a mask that may result in failing to maintain physical distance from others, and the risk imposed by incorrect usage of masks by non-trained carriers, *e.g.* transmitting pathogens from contaminated hands to the mask. Here, we report effects of universal masking that were observed after implementation of (*i*) mandatory universal masking in the Jena University Hospital (JUH) and (*ii*) of mandatory community masking in the city of Jena.

Impact of hospital-wide universal masking

The JUH is a tertiary academic hospital with about 1,400 beds and 5,600 employees providing care for about 53,000 inpatients per year. The first detected COVID-19 case in Jena was a physician returning from Austria. Upon his return, he immediately reported to the hospital occupational health department, was tested and isolated at home on 11th March

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2020. On 16th March, a nurse that had returned from skiing in Northern Italy became the source of the first nosocomial outbreak involving four patients and two health care workers (HCW). Consequently, extensive screening was conducted on 1,311 HCW – representing one third of the total work force in direct patient care- between 11th March and 12th May resulting in 31 positive cases until 19th March, approximately one week after the first confirmed case (***Figure 1***). As a consequence, mandatory masking for all personnel involved in patient care was implemented on 20th March. Continued routine staff screening revealed only four HCWs tested positive between 20th March and 12th May. This corresponds to a substantial drop in the rate of new infections among HCWs from 10.1% (31 of 306 screened HCW in this period) before to 0.4% (4 of 1,005 HCW screened in this period) after implementation of universal masking. In addition, a strict containment system was introduced on 5th April, which included placing all patients in single rooms upon admission and SARS-CoV-2 screening regardless of their admitting chief complaint. Thereafter, HCW screening did not reveal any further positive case.

Impact of community-wide universal masking

Jena is the second largest city in Thuringia, Germany, with approximately 111,400 inhabitants. Despite thorough contact tracing and isolation of confirmed COVID-19 positive cases by the authorities, a rapid increase in numbers was observed after patient zero (***Figure 1***). The governmental containment (closing of stores, schools, kindergartens, churches etc.) together with social distancing measures was strictly implemented on 20th March in Jena and four days later in the entire Federal State of Thuringia. As novel infections continued to occur, Jena authorities were the first in Germany to introduce universal community-wide masking*, i.e.* mandatory covering of the mouth and nose in public buildings and public transport accepting also cloth masks or scarfs. On 24th April, a state-wide recommendation for community-wide masking in combination with first relaxations of the strict lockdown was issued.

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We also assessed the effectiveness of mandatory community-wide masking in Jena in comparison with the nearby city of Erfurt (***Figure 1***). Both cities exhibit a similar university as well as socioeconomic structure. Erfurt introduced masking four weeks after Jena, simultaneously with the first relaxation of the lockdown measures.

As shown in ***Figure 1,*** there were no new COIVD-19 cases in Jena five days after implementation, which is in line with the average incubation time of SARS-CoV-2. While in Erfurt, COVID-19 continued to spread and only ceased after the same community-wide masking was imposed.

We are aware that mere association is not causation and that our conclusions are limited by the observational nature of the data. However, it is uncertain whether an ethically sound trial on the controversial issue of mandatory community-wide masking will ever be performed. Therefore, our observations support the notion to implement universal masking in both health care as well as community settings as considering the ensuing reduced infection-rates. Given the risk-benefit ratio, we consider universal masking combined with social distancing as a suitable measure to contain the spread of SARS-CoV-2.

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Conflicts of interest
The authors do not report any conflict of interest.

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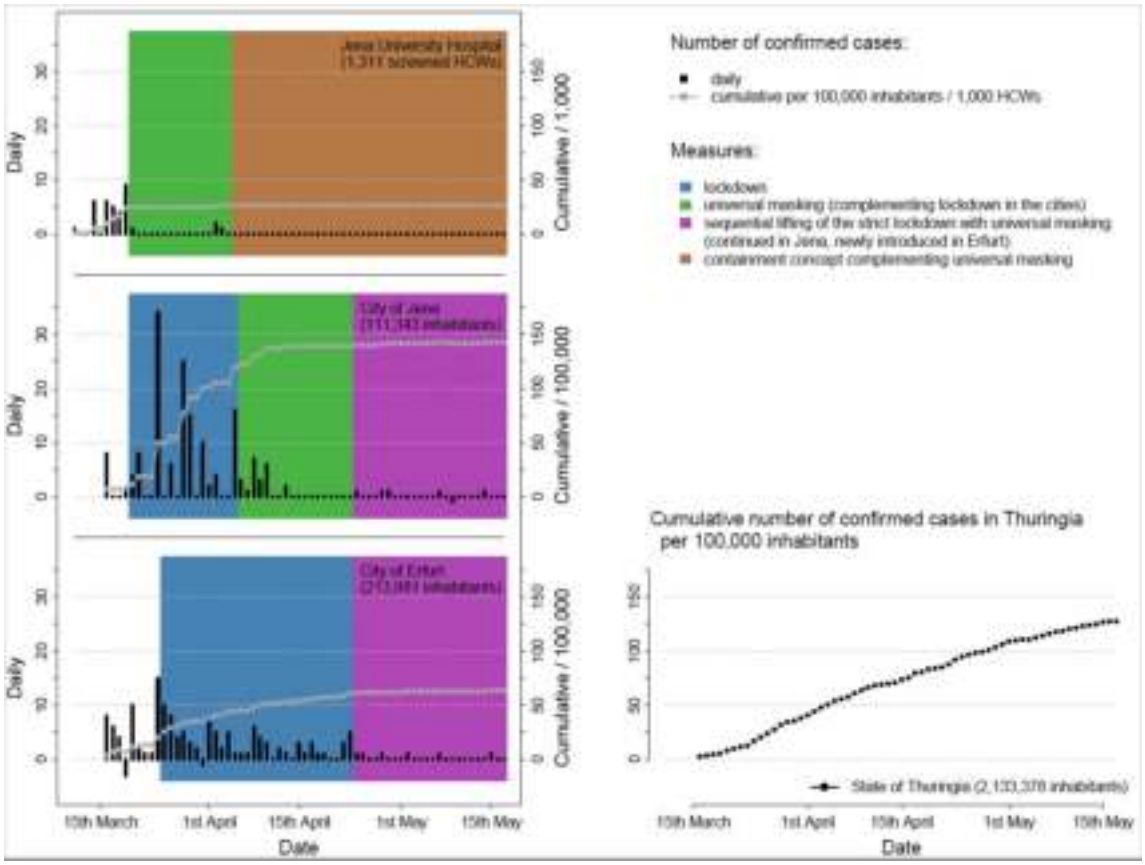
113 **FIGURE**



114

115 **Figure 1:** Daily reported number of novel confirmed SARS-CoV-2 infections and
116 corresponding cumulative numbers per 1,000 health care workers (HCW) of Jena University
117 Hospital (JUH, 1,500 beds) as well as per 100,000 inhabitants of the Thuringian cities Jena
118 and Erfurt (left panel). All reported cases comprise only the first SARS-CoV-2 test results.
119 Results of multiple testing are excluded because all infected subjects are reported by full
120 name and address to the respective Public Health Departments. For comparison, the
121 cumulative number per 100,000 inhabitants in the State of Thuringia is provided (right panel).
122 The measures implemented at the JUH and in the cities are color-coded. Please note,
123 "negative" bars for daily reported novel infections in Jena and Erfurt are explained by re-
124 classification of individual COVID-19 cases as non-COVID-19 after quality control of the
125 respective data and laboratory reports by the State Health Department of Thuringia. The
126 number of inhabitants (on 31st December 2019) were taken from the Thuringian State Office
127 of Statistics.

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Title: Impact of nonpharmaceutical governmental strategies for prevention and control of COVID-19 in São Paulo State, Brazil.

Abbretiaved title: COVID-19: nonpharmaceutical strategies.

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Abstract

Interrupted time series analyses (ITSA) were performed to measure the impact of social distancing policies (instituted 22/03/2020) and subsequent mandatory masking in the community (instituted 04/05/2020) on the incidence and effective reproductive number (Rt) of COVID-19 in São Paulo State, Brazil. Overall, the impact of social distancing both on incidence and Rt was greater than the incremental effect of mandatory masking. Those findings may reflect either a small impact of face masking or the loosening of social distancing after mandatory use of masks.

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Text

São Paulo state reported the first case of COVID-19 in Brazil, on 25 February 2020 [1]. While this manuscript is being written (as of 23 August 2020), the number of laboratory-confirmed cases in Brazil approaches 3 million, with circa 115 thousand deaths (https://covid.saude.gov.br/). Circa 20.5% of both cases and deaths occurred in São Paulo, Brazil's most populous state (44 million inhabitants). Geographic modeling[2] and ecological analyses[3] documented patterns of disease spread from the metropolitan area, where 39 cities harbor 21 million inhabitants, to the remaining 606 municipalities located in the inner areas of the state.

To contain the spread of SARS-Cov-2, The government of São Paulo decreed the closure of non-essential services and the restriction of public transport from 22 March. Even though evidence for the effectiveness of that measure in preventing deaths and intensive care units (ICU) admissions was reported[4], data on its impact in the inner areas of the state is still lacking. Furthermore, a second decree from May 4th made the use of face masks in community settings mandatory.

Out study was a natural experiment using ecological approach. We aimed at analyzing the impact of both control measures cited above on daily incidence rates (per 100,000 inhabitants) and daily estimates of the effective reproductive number (R_t) of laboratory-confirmed COVID-19 cases in the metropolitan and inner areas of São Paulo State. Daily incidence from 1 March through 4 July were obtained from São Paulo State Epidemiological Surveillance Center database (www.cve.saude.sp.gov.br), and population data for year 2020 was recovered from the São Paulo State Foundation for Data Analysis (SEADE, https://www.seade.gov.br/). The time series of cases was used to estimate R_t, as described by Wallinga & Lipsitch[5].

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Interrupted time series (ITS) analysis[6] was performed using STATA 14 (Statacorp, College Station, TX), with models that included both successive interventions (social distancing [#1] and universal masking [#2]). Those models fitted linear trends for each period (pre-intervention #1, between interventions, and post-intervention #2). Both immediate impact and sustained changes in trends were assessed.

Results are presented in **Table 1** and **Figure 1**. Social distancing had immediate beneficial impact on incidence in all the state, but trend changes were significant only for inner municipalities. As symmetric result was detected for R_t: overall immediate impact, but sustained trend changed only in the metropolitan area. The incremental impact of universal masking was not immediate, but a significant change downwards in incidence trends was generally detected. As for the R_t, only an immediate impact in inner municipalities was statistically significant.

São Paulo state did not experience a lockdown in the strict sense of the word. Instead, the March 22nd decree attempted to induce social distancing by closing non-essential services (e.g., stores) and restricting public transport (subway, metropolitan railways, and buses). ITS analysis demonstrates a variable but generally beneficial impact of that measure. This is in agreement with previous reports and modeling predictions[4,7]. The incremental benefit of mandatory universal masking was subtle, with impact on incidence rates but not on daily R_t series. This finding contrasts with recent reports from the US [8].

As with all analyzes of natural experiments, our study is subject to confounding bias. The most important is the gradual loosening of restrictive policies (the so-called São Paulo Plan, available at https://www.saopaulo.sp.gov.br/planosp/). Briefly, those measures, initiated in 1 June 2020 were slowly and heterogeneously applied. The State was divided in 22 administrative areas, which could open 0 to 40% of non-essential services, depending on standards of COVID-19 incidence and mortality, availability and occupation of Intensive Care Unit beds.

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Municipalities were also allowed to implement additional restrictive measures, as aspect which increased the heterogeneity of the preventive policies. Recommendations changed every two weeks, depending on novel epidemiological data. To assess that slowly applied, geographically heterogeneous and time-varying strategy was beyond the scope of this study. Also, the continuous rise in population mobility (as detected from movement of mobile phones and reported in the São Paulo Government homepage, https://www.saopaulo.sp.gov.br/coronavirus/) was not included in our models, since we had access only to incomplete data. Also, the increasing availability of laboratory testing may have influenced our findings. However, as previously reported, that increase was greater during the first months of pandemics in Brazil, so they were expected to underestimate the impact of the first intervention [9]. Even though those aspects might confound the impact of nonpharmaceutical measures, they are real life phenomena inherent to studies of effectiveness (as opposed to efficacy).

Another limitation of our study was its ecological approach. Obviously, we did not assess the impact of staying at home or using cloth masks on individual risks of being infected by SARS-Cov-2. Our main objective was to study the collective impact of governmental policies.

A systematic review of nonpharmaceutical measures to prevent COVID-19, based solely on observational studies, concluded that social distancing, use of masks and eye protection were beneficial [10]. Unfortunately, those results are limited by the heterogeneity of settings (healthcare and community) and of interventions. The analysis of benefits from use of masks is particularly challenging. Previous studies point to an expected greater efficacy of N95 respirators and surgical masks than that of cloth and/or homemade masks. It is worth noting that a recent systematic review with meta-analysis or randomized clinical trials found general protective impact of face masks [11]. However, protection was greater in healthcare settings than in the community. Also, the included studies assessed influenza and other respiratory

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viruses, and most of them tested surgical masks. Therefore, inferences have been largely based on analogy, and the benefits of cloth masks are far from straightforward.

In conclusion, we found that governmental strategies based on nonpharmaceutical intervention were generally effective in slowing the evolution of pandemics in São Paulo State, Brazil. The effectiveness was greater for the first intervention (social distancing), with some incremental impact of mandatory use of face masks. Those findings may reflect either a small impact of face masking or the loosening of social distancing after mandatory use of masks. Either way, they contribute for directing public policies against COVID-19 in Brazil and other countries, in a period when the world is still far from achieving control of the current pandemics.

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Data availability statement

All data used for our analysis is available in two supplementary files uploaded with the manuscript.

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Table 1. Interrupted time series analysis (ITSA) of the impact of governmental interventions for social distancing (March 22nd, 2020) and mandatory universal masking (May 4th, 2020) on trends of incidence and effective reproduction number (R_t) of laboratory-confirmed COVID-19 cases in the metropolitan area and inner municipalities of São Paulo State, Brazil.

ITSA variables	Metropolitan area (*circa* 21 million inhabitants)	Inner state (*circa* 24 million inhabitants)
	Coefficient (95% Confidence Interval)	*Coefficient (95% Confidence Interval)*
Impact on incidence rates		
General time trend (days)	**0.11 (0.08 to 0.13)**	**0.09 (0.07 to 0.10)**
Social distancing, immediate impact	0.19 (-0.15 to 0.53)	**- 0.41 (-0.69 to - 0.13)**
Social distancing, impact on trend	**-0.08 (-0.10 to -0.05)**	**-0.06 (-0.08 to - 0.05)**
Universal masking, immediate impact	0.40 (0.01 to 0.79)	0.16 (-0.11 to 0.43)
Universal masking, impact on trend	**-0.04 (-0.05 to -0.02)**	**-0.03 (-0.04 to -0.02)**
Impact on reprodutive number (R_t)		
General time trend (days)	0.00 (-0.03 to 0.04)	**-0.04 (-0.07 to -0.01)**
Social distancing, immediate impact	**- 1.50 (-1.88 to -1.11)**	**-1.17 (-1.57 to - 0.77)**
Social distancing, impact on trend	**- 0.02 (-0.05 to -0.01)**	**0.03 (0.01 to 0.05)**
Universal masking, immediate impact	0.13 (-0.01 to 0.27)	**- 0.47 (-0.11 to - 0.20)**
Universal masking, impact on trend	**0.13 (0.01 to 0.02)**	-0.001 (-0.002 to 0.004)

Note. Results with p-value <0.05 are presented in boldface. Daily incidence rate and R_t were analyzed from March 1st until July 4th , 2020.

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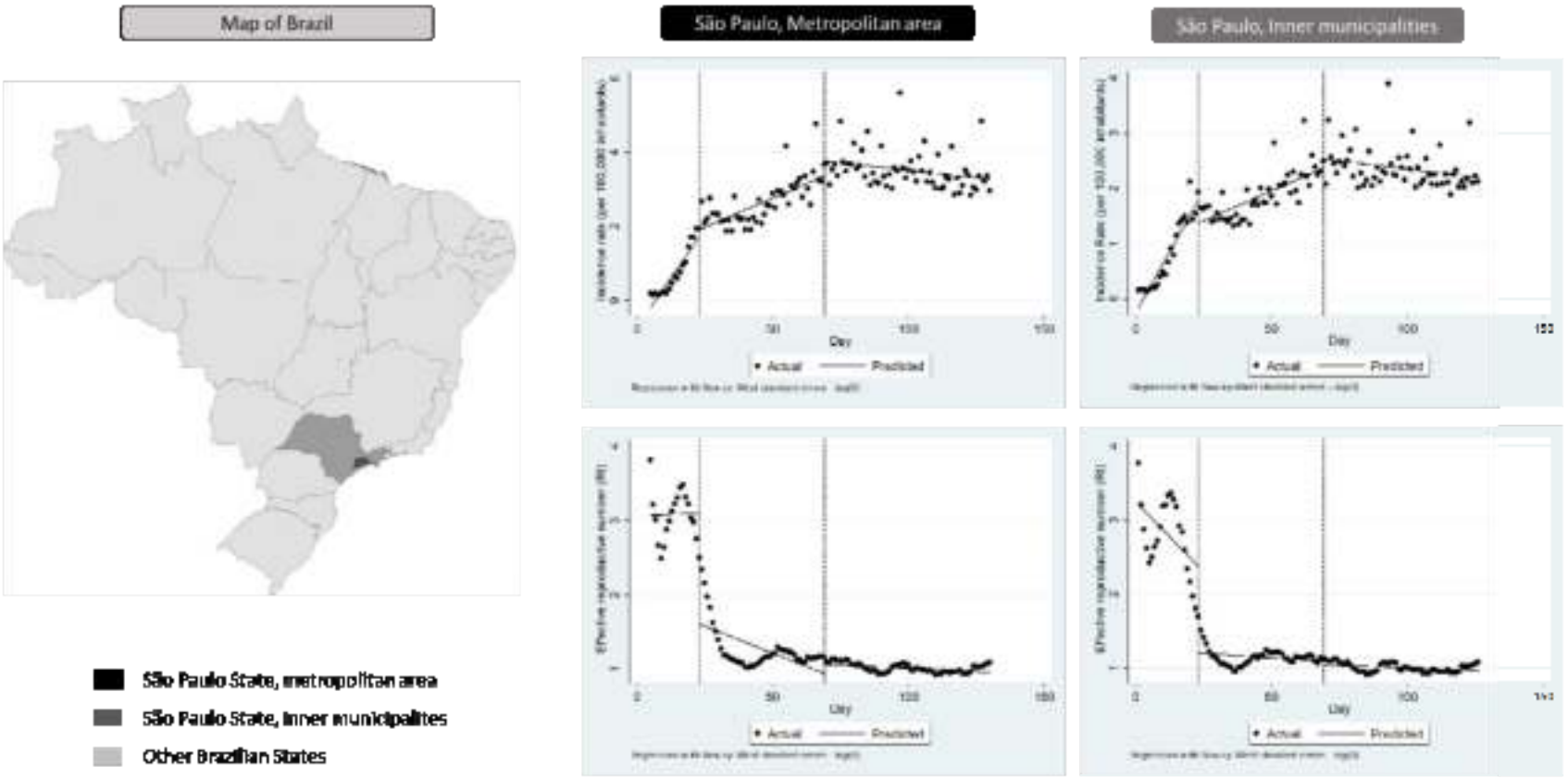

Figure 1. Graphical presentation of the impact of governmental interventions for social distancing and mandatory universal masking on trends of incidence and effective reproduction number (R_t) of laboratory-confirmed COVID-19 cases in the metropolitan area and inner municipalities of São Paulo State, Brazil.
Note. The two dashed vertical lines in the graphs represent, respectively, government decrees of social restriction (22 March) and universal use of masks in the community (4 May).

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Face Masks, Public Policies and Slowing the Spread of COVID-19: Evidence from Canada*

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September 24, 2020

Abstract

We estimate the impact of mask mandates and other non-pharmaceutical interventions (NPI) on COVID-19 case growth in Canada, including regulations on businesses and gatherings, school closures, travel and self-isolation, and long-term care homes. We partially account for behavioral responses using Google mobility data. Our identification approach exploits variation in the timing of indoor face mask mandates staggered over two months in the 34 public health regions in Ontario, Canada's most populous province. We find that, in the first few weeks after implementation, mask mandates are associated with a reduction of 25 percent in the weekly number of new COVID-19 cases. Additional analysis with province-level data provides corroborating evidence. Counterfactual policy simulations suggest that mandating indoor masks nationwide in early July could have reduced the weekly number of new cases in Canada by 25 to 40 percent in mid-August, which translates into 700 to 1,100 fewer cases per week.

Keywords: COVID-19, face mask mandates, non-pharmaceutical interventions, counterfactuals
JEL codes: I18, I12, C23

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1 Introduction

When government policies to stem the spread of COVID-19 were introduced in early 2020, the best available evidence supporting them was provided by studies of previous epidemics, epidemiological modeling, and case studies (OECD, 2020). Even when the efficacy of a given precaution in reducing COVID-19 transmission has been established, significant doubts regarding the usefulness of specific policy measures may persist due to uncertainty regarding adherence to the rules and other behavioral responses. For example, even though several observational studies, mostly in medical setting, have shown that face masks reduce the transmission of COVID-19 and similar respiratory illnesses (see Chu et al. (2020) for a comprehensive review), a face mask mandate may not be effective in practice if it fails to increase the prevalence of mask wearing (compliance), or if it leads to increased contacts due to a false sense of security. It is therefore important to directly evaluate and quantify the relationship between various policy measures and the rate of propagation of COVID-19.

The low cost and high feasibility of mask mandates relative to other containment measures for COVID-19 has generated keen interest worldwide for studying their effectiveness. This attention has been compounded by substantial variation, across jurisdictions and over time, in official advice regarding the use of masks. Figure B1 in the Appendix plots self-reported mask usage in select countries (Canada, United States, Germany and Australia) in the left panel, and across Canadian provinces in the right panel. The figure shows large differences in mask usage, both across countries and within Canada.[1]

We estimate and quantify the impact of mask mandates and other non-pharmaceutical interventions (NPI) on the growth of the number of COVID-19 cases in Canada. Canadian data has the important advantage of allowing two complementary approaches to address our objective. First, we estimate the effect of mask mandates by exploiting within-province geographic variation in the timing of indoor face mask mandates across 34 public health regions (PHUs) in Ontario, Canada's most populous province with a population of nearly 15 million or roughly 39% of Canada's population (Statistics Canada, 2020). The advantage of this approach is that it exploits variation over a relatively small geographic scale (PHU), holding all other province-level policies or events constant. In addition, the adoption of indoor face mask mandates in these 34 sub-regions was staggered over approximately two months, creating sufficient intertemporal policy variation across the PHUs.

[1]We show mask usage for the U.S. and Germany because related work by Chernozhukov et al. (2020) and Mitze et al. (2020) studies the effect of mask mandates in these countries respectively. We show Australia as an example of a country which did not mandate mask usage, except for Melbourne in late July. See Hatzius et al. (2020) for more cross-country comparisons of mask usage.

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Second, we evaluate the impact of NPIs in Canada as a whole, by exploiting variation in the timing of policies across the country's ten provinces. By studying inter-provincial variation, we are able to analyze the impact of not only mask mandates, but also other NPIs, for which there is little or no variation across Ontario's PHUs (regulations on businesses and gatherings, schooling, travel and long-term care). In addition, our province-level data include both the closing period (March-April) and the gradual re-opening period (May-August), providing variation from both the imposition and the relaxation of policies.

Our panel-data estimation strategy broadly follows the approach of Chernozhukov, Kasahara and Schrimpf (2020), hereafter CKS (2020), adapted to the Canadian context. We allow for behavioural responses (using Google Community Mobility Reports geo-location data as proxy for behaviour changes and trends), as well as lagged outcome responses to policy and behavioral changes. Our empirical approach also allows current epidemiological outcomes to depend on past outcomes, as an information variable affecting past policies or behaviour, or directly, as in the SIR model framework.

We find that, in the first few weeks after their introduction, mask mandates are associated with an average reduction of 25 to 31% in the weekly number of newly diagnosed COVID-19 cases in Ontario, holding all else equal. We find corroborating evidence in the province-level analysis, with a 36 to 46% reduction in weekly cases, depending on the empirical specification. Furthermore, using survey data, we show that mask mandates increase self-reported mask usage in Canada by 30 percentage points, suggesting that the policy has a significant impact on behaviour. Jointly, these results suggest that mandating indoor mask wear in public places is a powerful policy measure to slow the spread of COVID-19, with little associated economic disruption at least in the short run.[2]

Counterfactual policy simulations using our empirical estimates suggest that mandating indoor masks nationwide in early July could have reduced weekly new cases in Canada by 25 to 40% on average by mid-August relative to the actually observed numbers, which translates into 700 to 1,100 fewer cases per week.

We also find that the most stringent restrictions on businesses and gatherings observed in our data are associated with a decrease of 48 to 57% in weekly cases, relative to a lack of restrictions. The business/gathering estimates are, however, noisier than our estimates for mask mandates and do not retain statistical significance in all specifications; they appear driven by the smaller provinces and the re-opening period (May to August). School closures and travel restrictions are associated with a large decrease in weekly case growth in the

[2]Hatzius et al. (2020) estimate that a national mask mandate in the USA could replace alternative restrictions costing 5% of GDP.

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closing period. Our results on business/gathering regulations and school closure suggest that reduced restrictions and the associated increase in business or workplace activity and gatherings or school re-opening can offset, in whole or in part, the estimated effect of mask mandates on COVID-19 case growth, both in our sample and subsequently.

An additional contribution of this research project is to assemble, from original official sources only, and make publicly available a complete dataset of COVID-19 cases, deaths, tests and policy measures in all 10 Canadian provinces.[3] To this end, we constructed, based on official public health orders and announcements, time series for 17 policy indicators regarding face masks, regulations on businesses and gatherings, school closures, travel and self-isolation, and long-term care homes.

Our paper relates most closely to two recent empirical papers on the effects of mask mandates using observational data.[4] CKS (2020) and Mitze et al. (2020) study the effect of mask mandates in the United States and Germany, respectively. CKS (2020), whose estimation strategy we follow, exploit U.S. state-level variation in the timing of mask mandates for employees in public-facing businesses, and find that these mandates are associated with 9 to 10 percentage points reduction in the weekly growth rate of cases. This is substantially smaller that our estimates, possibly because the mask mandates that we study are much broader: they apply to all persons rather than just employees, and most apply to all indoor public spaces rather than just businesses. Mitze et al. (2020) use a synthetic control approach and compare the city of Jena and six regions in Germany that adopted a face mask policy in early to mid April 2020, before their respective state mandate. They find that mandatory masks reduce the daily growth rate of cases by about 40%.

Our paper has several advantages compared to the above two papers. First, we exploit both regional variation within the same province (like Mitze et al., 2020) and provincial variation in the whole country (like CKS, 2020), and find similar results, which strengthens the validity of our findings. Second, we show that self-reported mask usage has increased after introducing mask mandates. We view this "first-stage" result on mask usage as informative, as the effectiveness of any NPI or public policy critically depends on the compliance rate. Moreover, this result mitigates possible concerns that the estimated mask mandate effect on COVID-19 case growth may be caused by factors other than mask policy. Third, a key

[3] All data are available for download at https://github.com/C19-SFU-Econ. The COVID-19 cases, deaths and tests data that we collected and use in this paper incorporate all official ex-post revisions as of mid-August, unlike data from the Government of Canada COVID-19 website or other aggregator websites.

[4] Howard et al. (2020), a comprehensive review of the medical literature, stresses that "no randomized controlled trial (RCT) on the use of masks as source control for SARS-CoV-2 has been published." It is unlikely that an RCT on masks' effectiveness against COVID-19 will be feasible or ethical during the pandemic.

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difference between our paper and CKS (2020) is that we evaluate the effect of *universal* (or *community*) mandatory indoor mask wearing for the public rather than the effect of mandatory mask wearing for *employees only*.[5] While other factors such as differences in mask wear compliance between Canada and the U.S. may contribute to the different estimated magnitude of the policy impact, our results suggest that more comprehensive mask policies can be more effective in reducing the case growth rate.

Other Related Literature

Abaluck et al. (2020) discuss the effectiveness of universal adoption of homemade cloth face masks and conclude that this policy could yield large benefits, in the \$3,000–\$6,000 per capita range, by slowing the spread of the virus. The analysis compares countries with pre-existing norms that sick people should wear masks (South Korea, Japan, Hong Kong and Taiwan) and countries without such norms.[6]

In the medical literature, Prather et al. (2020) argue that masks can play an important role in reducing the spread of COVID-19. Howard et al. (2020) survey the medical evidence on mask efficiency and recommend public use of masks in conjunction with existing hygiene, distancing, and contact tracing strategies. Greenhalgh et al. (2020) provide evidence on the use of masks during non-COVID epidemics (influenza and SARS) and conclude that even limited protection could prevent some transmission of COVID-19. Leung et al. (2020) study exhaled breath and coughs of children and adults with acute respiratory illness and conclude that the use of surgical face masks could prevent the transmission of the human coronavirus and influenza virus from symptomatic individuals. Meyerowitz et al. (2020) present a recent comprehensive review of the evidence on transmission of the virus and conclude that there is strong evidence from case and cluster reports indicating that respiratory transmission is dominant, with proximity and ventilation being key determinants of transmission risk, as opposed to direct contact or fomite transmission.

Our paper also complements recent work on COVID-19 policies in Canada. Mohammed et al. (2020) use public opinion survey data to study the effect of changes in mask-wear policy recommendations, from discouraged to mandatory, on the rates of mask adoption and public trust in government institutions. They show that Canadians exhibit high compliance with mask mandates and trust in public health officials remained consistent across time. Yuksel et al. (2020) use an outcome variable constructed from Apple mobility data along

[5] Lyu and Wehby (2020) provide suggestive evidence that community mask mandates are more effective than employees-only mandates.

[6] The authors report average daily case growth rate of 18% in countries with no pre-existing mask norms vs. 10% in countries with such norms. On a weekly basis, this translates to a reduction of 49 log points ($100(\log(1.18^7) - \log(1.1^7))$) in case growth, or 39% reduction in weekly cases.

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with weather data and lagged COVID-19 cases or deaths as dependent variables to study compliance with social distancing measures.

2 Data

We use three main data sources, respectively for epidemiological variables, NPI and mask mandates, and behavioral responses. The time period is from the start of detected community transmission in Canada in March to mid-August, 2020.

We located and accessed the original official sources to collect a complete dataset of COVID-19 cases, deaths, tests and policy measures in all ten Canadian provinces.[7] In addition, our data include cases and policy measure indicators for each of the 34 public health units (PHUs) in Ontario. A detailed description is provided in the data source files shared at the project's Github webpage.

Implementation dates of NPIs and other public policies were collected from government websites, announcements, public health orders and staged re-opening plans collected from their official sources. In the national data, the raw policy measures data contain the dates or enactment and relaxation (if applicable) of 17 policy indicators including: mandatory mask wear; closure and re-opening of retail and non-essential businesses, restaurants, recreation facilities, and places of worship; school closures; limits on events and gatherings; international and domestic travel restrictions and self-isolation requirements; restrictions on visits and staff movement in long-term care homes. All policy indicator variables are defined in Table C1 in the Appendix.[8] Since many of these indicators are highly correlated with each other, we combine them into five policy aggregates in the empirical analysis (see Table A17 and Section 3.2). In the Ontario PHU data, the implementation dates of mask mandates and the relaxation dates of policies for businesses and gatherings vary across PHUs. Decisions about the former were made at the PHU level, while decisions about the latter were made by the province, which classified PHUs into three groups, with some exceptions.

Regarding behavioral responses, we use the Google COVID-19 Community Mobility Reports, which summarize daily cellphone geo-location data for each province as indices calculated relative to the median value for the same day of the week in the five-week baseline

[7]The provinces differ in the ease of accessibility of their official time series of COVID-19 cases, deaths and test numbers. In some cases, we located and used the hidden json sources feeding the public dashboard charts. In few instances in which data were not available, we used the numbers reported in the daily provincial government announcements. All COVID-19 outcome data sources are referenced and web-linked in Appendix Table C3.

[8]Additional survey data on mask usage is described and used in Section 4.4.

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period January 3 to February 6, 2020.[9] In Ontario, these location data are available for each of the 51 first-level administrative divisions (counties, regional municipalities, single-tier municipalities and districts).[10]

3 Empirical method

We follow the approach of CKS (2020), but modify and adapt it to the Canadian context. The empirical strategy uses the panel structure of the outcome, policy and behavioral proxy variables, and includes lags of outcomes as information, following the causal paths suggested by the epidemiological SIR model (Kermack and McKendrick, 1927). Specifically, we estimate the effect of policy interventions on COVID-19 outcomes while controlling for information and behaviour. In contrast to CKS (2020) and Hsiang et al. (2020), who study variation in NPIs across U.S. states or across countries, our identification strategy exploits policy variation at the sub-provincial level (Ontario's PHUs) in addition to cross-province variation, and our data captures both the closing down and gradual re-opening stages of the epidemic.

3.1 Estimation strategy

The main data used in our empirical analysis are summarized below; Section 3.2 describes the variables in detail. Everywhere i denotes province for national analysis, and health region (PHU) for Ontario analysis, and t denotes time measured in days.

1. Outcomes, Y_{it} – growth rate of weekly cases or deaths.

2. Information, I_{it} – lagged outcomes, i.e. past levels or growth rate of cases (or deaths). We also consider a specification that includes the past cases/deaths and case/death growth at the national level as additional information variables.

3. Behavioral responses, B_{it} – Google mobility data capturing changes in people's geolocation relative to a baseline period in January-February.

4. Policy/NPIs, P_{it} – for the national analysis, five policy aggregates by province and date; for the Ontario analysis, two policy variables (mask mandates and regulation on business and gathering) by PHU and date.

[9] The reports are available for download at https://www.google.com/covid19/mobility/.

[10] Each of these divisions is either entirely (in most cases) or predominantly located within a single PHU. In cases where a PHU corresponds to multiple divisions, 2016 Census population counts were used as weights to compute the PHU's mobility index.

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5. Controls, W_{it} – province or PHU fixed effects, growth rate of weekly new COVID-19 tests, and a time trend.

To assess and disentangle the impact of NPIs and behavioral responses on COVID-19 outcomes, we estimate the following equation:

$$Y_{it} = \alpha B_{it-l} + \pi P_{it-l} + \mu I_{it} + \delta_Y W_{it} + \varepsilon_{it}^Y \tag{1}$$

where l denotes a time lag measured in days. Equation (1) models the relationship between COVID-19 outcomes, Y_{it}, and lagged behaviour, B_{it-l}, lagged policy measures, P_{it-l} and information (past outcomes), $I_{it} = Y_{it-l}$. For case growth as the outcome, we use $l = 14$. For deaths growth as the outcome, we use $l = 28$.[11] The choice of these lags is discussed in Appendix D.

By including lagged outcomes, our approach allows for possible endogeneity of the policy interventions P_{it}, that is, the introduction or relaxation of NPIs based on information on the level or growth rate of cases or deaths. Also, past cases may be correlated with (lagged) government policies or behaviors that may not be fully captured by the policy and behaviour variables.

In Appendix Table A18, we also report estimates of the following equation:

$$B_{it} = \beta P_{it} + \gamma I_{it} + \delta_B W_{it} + \varepsilon_{it}^B \tag{2}$$

which models the relationship between policies P_{it}, information, I_{it} (weekly levels or growth of cases or deaths) and behaviour, B_{it}. It is assumed that behaviour reacts to the information without a significant lag. We find strong correlation between policy measures and the Google mobility behavioral proxy measure.

Equation (1) captures both the direct effect of policies on outcomes, with the appropriate lag, as well as the potential indirect effect on outcomes from changes in behaviour captured by the changes in geo-location proxy B_{it-l}. In Appendix Tables A19 and A20, we also report estimates of equation (1) without including the behavioral proxy, that is, capturing the total effect of policies on outcomes. Since our estimates of the coefficient α in equation (1) are not significantly different from zero, the results without controlling for the behavioral proxy are very similar to those from estimating equation (1).

[11] Our lag for deaths is one week longer than that used by CKS (2020). The difference is due to additional evidence from the medical literature and the construction of the weekly variables (see Appendix D).

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3.2 Variables and descriptive analysis

Outcomes. Our main outcome of interest is the growth rate of weekly new positive COVID-19 cases as defined below.[12] We use weekly outcome data to correct for the strong day-of-the-week effect present in COVID-19 outcome data.[13] Weekly case growth is a metric that can be helpful in assessing trends in the spread of COVID-19, and it is highlighted in the World Health Organization's weekly epidemiological updates (see, for example, World Health Organization (2020)).

Specifically, let C_{it} denote the cumulative case count up to day t and define ΔC_{it} as the weekly COVID-19 cases reported for the 7-day period ending at day t:

$$\Delta C_{it} \equiv C_{it} - C_{it-7}.$$

The weekly case (log) growth rate is then defined as:

$$Y_{it} = \Delta \log(\Delta C_{it}) = \log(\Delta C_{it}) - \log(\Delta C_{it-7}), \tag{3}$$

that is, the week-over-week growth in cases in region i ending on day t.[14] The weekly death growth rate is defined analogously, using cumulative deaths data.

Policy. In the Ontario analysis, we exploit regional variation in the timing of indoor mask mandates staggered over two months in the province's 34 regions ("public health units" or PHUs). Figure 1 displays the gradual introduction of mask mandates across the 34 PHUs in Ontario. The exact implementation dates of the mask mandates are reported in Table C2. Mandatory indoor masks were introduced first in the Wellington-Dufferin-Guelph PHU on June 12 and last in the Northwestern PHU on August 17.[15]

[12] We also report results using the growth rate of deaths as supplemental analysis in Section 4.6.

[13] Figures B9 and B10 in the Appendix respectively display the weekly and daily cases, deaths and tests in each Canadian province over time. There are markedly lower numbers reported on weekends or holidays.

[14] To deal with zero weekly values, which mostly occur in the smaller regions, as in CKS (2020), we replace log(0) with -1. We also check the robustness of our results by adding 1 to all ΔC_{it} observations before taking logs, by replacing log(0) with 0, and by using population weighted least squares; see Tables A5 and A8.

[15] There is no PHU-wide mask mandate in Lambton as of August 31, but its main city, Sarnia, enacted a mask mandate on July 31.

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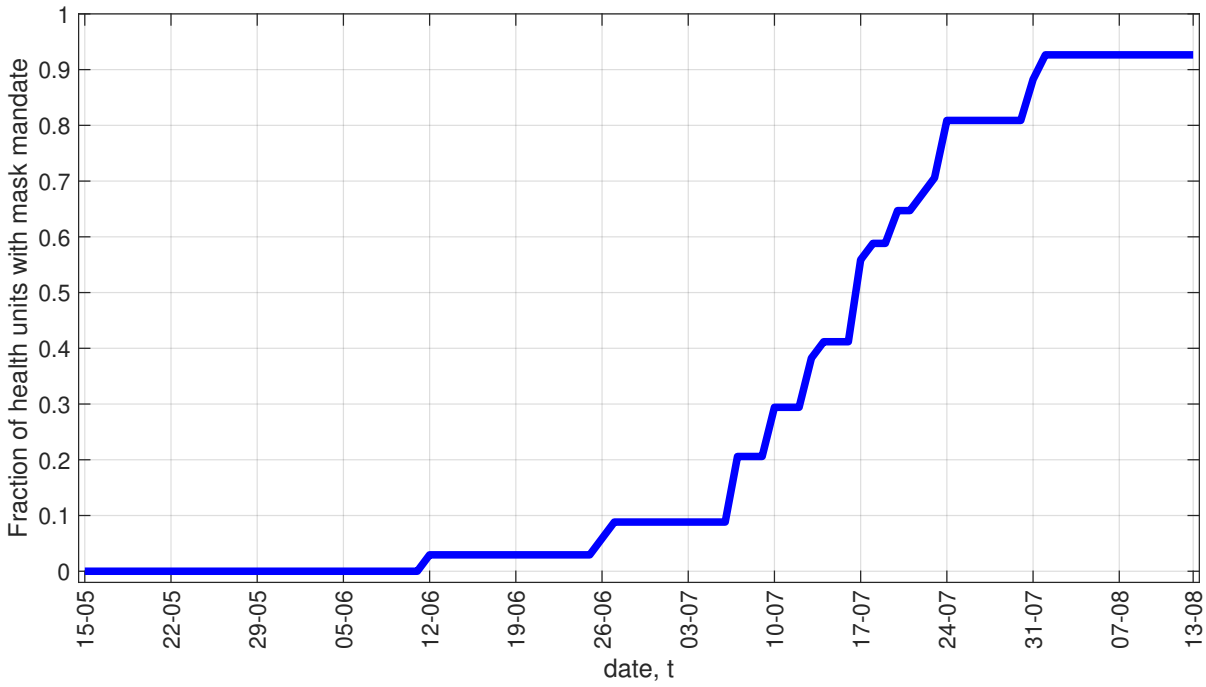
Figure 1: Ontario - mask mandates over time



Notes: There are a total of 34 public health units (PHU) in Ontario. See Table C2 for the exact date of mask mandate implementation in each PHU.

In the province-level analysis, we assign numerical values to each of the 17 policy indicators listed in Table C1 in Appendix C. The values are on the interval [0,1], with 0 meaning no or lowest level of restrictions and 1 meaning maximal restrictions. A policy value between 0 and 1 indicates partial restrictions, either in terms of intensity (see more detail and the definitions in Table C1) or by geographical coverage (in large provinces). The numerical values are assigned at the daily level for each region (PHU or province, respectively for the Ontario and national results), while maintaining comparability across regions.

Many NPIs were implemented at the same time, both relative to each other and/or across regions (especially during the March closing-down period), which causes many of the policy indicators to be highly correlated with each other (see Appendix Table A4). To avoid multi-collinearity issues, we group the 17 policy indicators into 5 policy aggregates via simple averaging: (i) *travel*, which includes international and domestic travel restrictions and self-isolation rules; (ii) *school*, which is an indicator of provincial school closure; (iii) *business/gathering*, which comprises regulations and restrictions on non-essential businesses and retail, personal businesses, restaurants, bars and nightclubs, places of worship, events,

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gyms and recreation, and limits on gathering; (iv) *long-term care (LTC)*, which includes NPIs governing the operation of long-term care homes (visitor rules and whether staff are required to work on a single site) and (v) *mask* which takes value 1 if an indoor mask mandate has been introduced, 0 if not, or value between 0 and 1 if only part of a province has enacted such policy.[16]

The five policy aggregates are constructed at the daily level and capture both the closing-down period (an increase in the numerical value from 0 toward 1) and the re-opening period (decrease in the numerical value toward zero). In comparison, the policy indicators compiled by Raifman (2020) for the USA used in CKS (2020) are binary "on (1)"/"off (0)" variables.[17] For consistency with the weekly outcome and information variables and the empirical model timing, we construct the policy aggregates P_{it}^{j} used in the regressions (where j denotes policy type) by taking a weekly moving average of the raw policy data, from date $t-6$ to date t.

Figure 2 plots the values of the 5 policy aggregates over time for each of the 10 provinces. Travel restrictions, school closures (including Spring and Summer breaks) and business closures were implemented in a relatively short period in the middle of March. There is some variation in the travel policy aggregate since some Canadian provinces (the Atlantic provinces and Manitoba) implemented inter-provincial domestic travel or self-isolation restrictions in addition to the federal regulations regarding international travel. Restrictions on long-term care facilities were introduced more gradually. In the re-opening period (May-August), there is also more policy intensity variation across the provinces, especially in the business and gatherings category, as the different provinces implemented their own re-opening plans and strategies. Mask mandates were first introduced in Ontario starting from June in some smaller PHUs and early July in the most populous PHUs such as Toronto, Ottawa and Peel (see Appendix Table C2). In Quebec, indoor masks were mandated province-wide on July 18. Nova Scotia and Alberta's two main cities implemented mask mandates on July 31 and August 1, respectively.

[16] We do not use provincial declarations of emergency in our analysis as they are mostly legal tools enabling other restrictions rather than restrictions *per se*.

[17] The daily numerical values for each of the 17 basic policy indicators and the 5 policy aggregates for each province and date are available on the project's Github repository.

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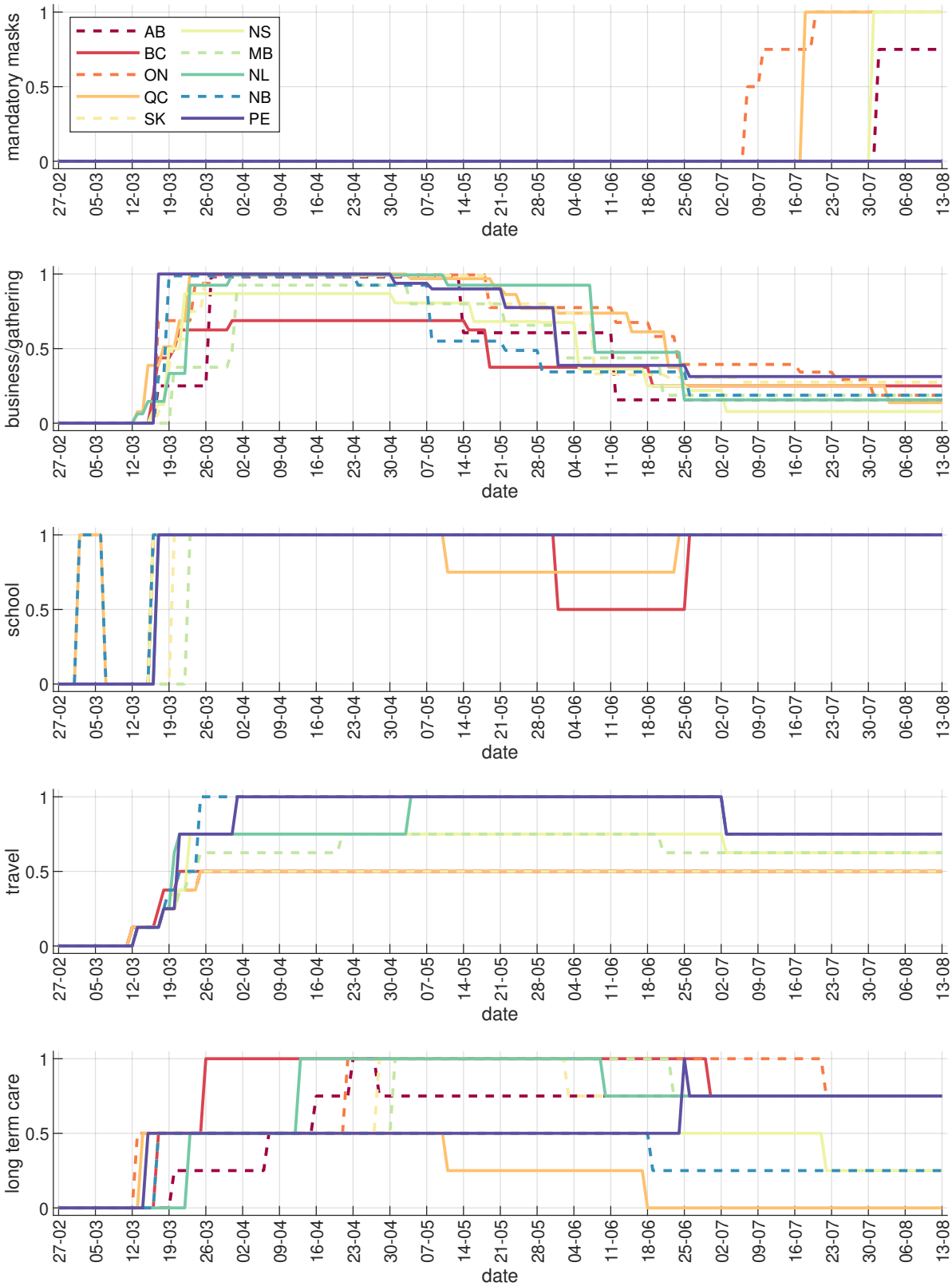
Figure 2: Policy aggregates - Canada



Notes: The figure plots the numerical values of the 5 policy aggregates (Mask, Business /gathering, School, Travel and Long-term care, LTC) over time, for each of the 10 provinces. The mask policy values for ON reflect the gradual adoption of mandates and the respective PHUs population sizes.

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There are two empirical challenges specific to our Canadian context and data. The first challenge is the presence of small provinces and sub-regions with very few COVID-19 cases or deaths. In Section 4.3, we perform a number of robustness checks using different ways of handling the observations with very few cases (in particular zero cases). The second data limitation is that there are only 10 provinces in Canada and 34 public health units in Ontario, unlike the 51 U.S. jurisdictions in CKS (2020). To account for the resulting small number of clusters in the estimation, we compute and report wild bootstrap standard errors and p-values, as proposed by Cameron et al. (2008).[18] On the flip side, our data has the advantage of a longer time horizon (March to August) and non-binary, more detailed policy variables compared to Raifman et al. (2020).

Behaviour proxy. We follow CKS (2020) and other authors in interpreting the location change indices from the Google Community Mobility reports as proxies for changes in people's behaviour during the pandemic, keeping in mind that location is only one aspect of behaviour relevant to COVID-19. The general pattern in the data (see Figure B3) shows sharply reduced frequency of recorded geo-locations in shops, workplaces and transit early in the pandemic (March), with a subsequent gradual increase back toward the baseline (except for transit), and a flattening out in July and August.

Several of the six location indicators (retail, grocery and pharmacy, workplaces, transit, parks and residential) are highly correlated with each other (see Tables A1 and A2) and/or contain many missing observations for the smaller provinces. To address these data limitations and the possible impact of collinearity on the estimation results, we use as proxy for behavioral changes the simple average of the following three mobility indicators: "retail", "grocery and pharmacy" and "workplaces". To be consistent with the weekly outcome variables and to mitigate day-of-week behavioural variation, we construct the Behaviour proxy B_{it} by taking a weekly moving average of the $\frac{1}{3}$ (retail + grocery and pharmacy + workplaces) data, from date $t-6$ to date t.[19,20] As a result, our empirical analysis uses weekly totals (for cases, tests and deaths) or weekly moving averages (for policies and the behaviour proxy) of all variables recorded on daily basis.[21]

[18] Alternative methods for computing the standard errors are explored in Section 4.3.

[19] We drop the "transit", "parks", and "residential" location indicators because, respectively, 10.6%, 13.7%, and 2.8% of the observations are missing in the provincial data, and 20.7%, 52.1%, and 11.1% are missing in the Ontario data. The "transit" and "residential" variables are also highly correlated with the three indicators we include in our aggregate behaviour proxy B_{it}. Furthermore, the "parks" indicator does not have clear implication for COVID-19 outcomes.

[20] In the Ontario analysis, 1.4% of the B_{it} values are imputed via linear interpolation.

[21] In estimation equation (1), we take moving average from date $t-14$ to date $t-20$ for policies and behaviour when the outcome is weekly case growth, and from date $t-28$ to date $t-34$ if the outcome is

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Tables A3 and A4 display the correlation between our behaviour proxy B_{it} and the five NPI policy aggregates P_{it}^{j}. Importantly, the behaviour proxy and mask mandate variables are not highly correlated, suggesting that the effect of mask mandates on COVID-19 outcomes should be independent of location behaviour changes.

Information. We use the weekly cases and case growth variables defined above, ΔC_{it} and Y_{it}, to construct the information variables I_{it} in equation (1). Specifically, we use as information the lagged value of the weekly case growth rate Y_{it-l} $(= \Delta \log(\Delta C_{it-l})$ and the log of past weekly cases, $\log(\Delta C_{it-l})$. We also use the lagged provincial (Ontario analysis) or national (Canada analysis) case growth rate and log of weekly cases as additional information variables in some specifications. A two-week information lag $l = 14$ is used in the baseline results. In the supplementary regressions using the death growth rate as the outcome, we use information on past deaths and a four-week lag (see Section 4.6).

Control variables. In all regressions, we control for region fixed effects (PHU or province) and the weekly COVID-19 tests growth rate $\Delta \log(\Delta T_{it})$, where T_{it} denotes cumulative tests in region i until date t and ΔT_{it} is defined analogously to ΔC_{it} above. We include a time trend: our baseline uses a cubic polynomial in days, but we also report results with no time trend and with week fixed effects. Robustness checks also include news or weather variables as controls (see Section 4.3).

Time period. We use the period May 15 to August 13 for the analysis with Ontario PHU level data and the period March 11 to August 13 for the national analysis with provincial data. The end date reflects data availability at the time of empirical analysis and writing. The start date for the Ontario sample (May 15) is approximately two weeks after the last restrictive measures were implemented and four weeks before the first mask mandate was introduced in Ontario. Robustness checks with different initial dates (May 1, June 1 and June 15) are reported in Section 4.3, with our results remaining stable. The initial date for the national sample (March 11) was chosen as the first date on which each province reported at least one COVID-19 test (so that cases could be potentially reported). Again, alternative initial dates are explored in Section 4.3.

deaths growth. Alternative lags are explored in Section 4.3.

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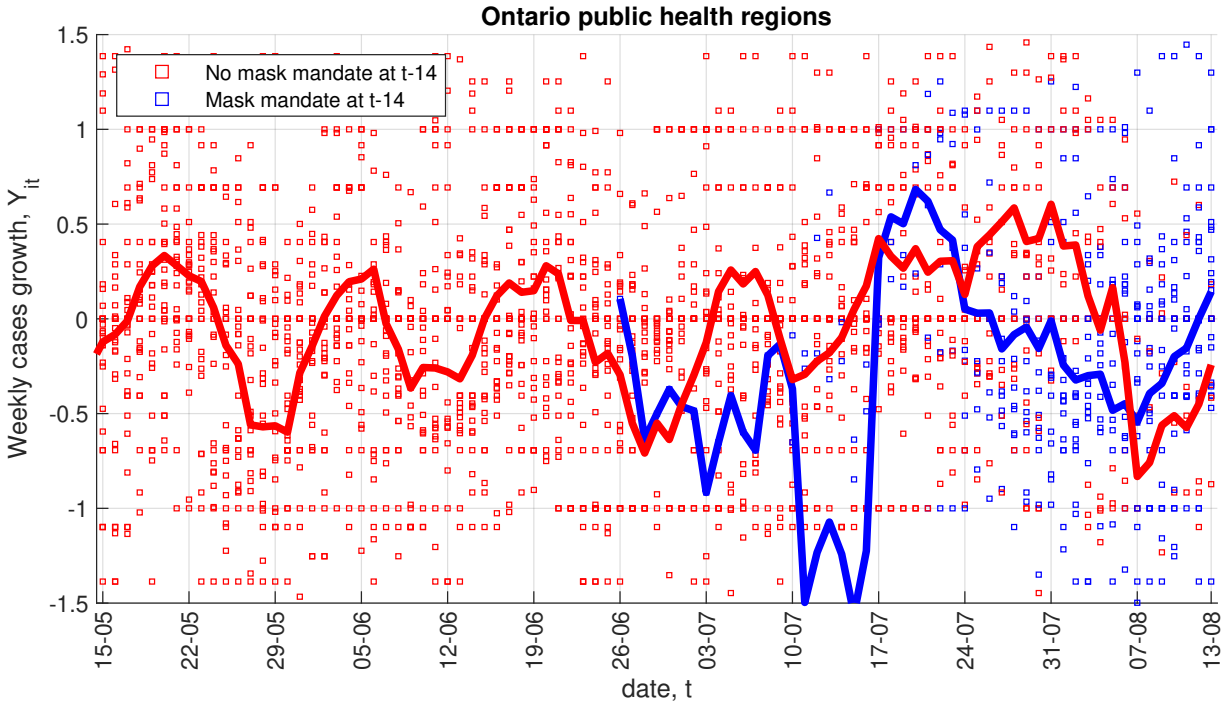
4 Results

4.1 Mask mandates in Ontario public health regions

We start with a simple graphical illustration of the effect of mask mandates on COVID-19 cases growth. Figure 3 displays the average log case growth, $Y_{it} = \Delta \log(\Delta C_{it})$ in Ontario PHUs with or without mask mandates. It shows that, on average, the PHUs with a mask mandate two weeks prior have lower case growth than the PHUs without a mask mandate two weeks prior.

Figure 3: Ontario - mask mandates and weekly case growth



Notes: The figure plots the average log weekly case growth $\Delta\log(\Delta C)$ in the PHUs with mask mandate (blue) vs. without (red) mask mandate 14 days prior.

Table 1 shows the estimates of equation (1), in which we control for other policies, behaviour and information, as explained in Section 3.1.[22] We report wild bootstrap p-values clustered at the PHU level to account for the small number of clusters.[23] The odd-numbered

[22]Mask mandates and regulations on business and gatherings vary at the PHU level. Long-term care policy changed only province-wide. The other policies (schooling and travel) do not vary during the sample period and hence are omitted from the regressions with Ontario PHU data.

[23]Table A6 in the Appendix reports alternative standard error specifications: regular clustering at the PHU level (Stata command "cluster"), wild bootstrap standard errors clustered at the PHU level, and wild

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columns in Table 1 use lagged cases and lagged cases growth at the PHU level as information; the even-numbered columns also include lagged cases and lagged case growth at the province level as additional information variables. In the tables, *Variable*_14 indicates a 14-day lag of *Variable*.

We present estimates of equation (1) from three specifications that handle possible time effects differently. Columns (1) and (2) in Table 1 are the most basic specifications, without including a time trend. The estimates in columns (1) and (2) suggest that, controlling for behavioural changes, mandatory indoor face masks reduce the growth rate of infections by 29–32 log points ($p < 0.05$), which is equivalent to a 25–28% reduction in weekly cases.[24]

In order to control for potential province-wide factors affecting the spread of COVID-19 such as income support policies or adaptation to the pandemic over time (so-called COVID fatigue), we also estimate (1) with a cubic time trend in days from the beginning of the sample, in columns (3) and (4) of Table 1, and with week fixed effects, in columns (5) and (6). Columns (3)-(6) show that our estimates of the mask mandate policy remain robust to the inclusion of a cubic time trend or week fixed effects. The results indicate that, depending on the specification, mask mandates are associated with a reduction of up to 38 log points in weekly case growth or, equivalently, a 31% reduction in weekly cases. The magnitude of the mask policy estimate is not very sensitive to whether lagged province-level data are included as additional information.

The results in Table 1 suggest that indoor mask mandates can be a powerful preventative measure in the COVID-19 context. Our estimates of the mask mandate impact across Ontario's PHUs are equivalent to a 25–31% reduction in weekly cases. This estimate is larger than the 9–10% reduction estimated by CKS (2020) for the U.S. One possible explanation is that Ontario's mask policy is more comprehensive: we evaluate the effect of *universal* indoor mask-wearing for the public rather than the effect of mask wearing for *employees only* in CKS (2020). Differences in the compliance rate may also contribute to this difference; we discuss this potential channel in Section 4.4.

The results in Table 1 also show a statistically significant negative association between information (log of past cases, log(ΔC)_14) and current weekly case growth ($p < 0.01$ in all specifications), indicating that a higher level of cases two weeks prior is correlated with lower current case growth. While B_{it} allows for behavioural responses to information, the negative estimate on log(ΔC)_14 in Table 1 suggests that our location-based proxy does not capture

bootstrap standard errors clustered by both PHU and date. Our results are robust to alternative ways of calculating standard errors.

[24] Using equation (3), a coefficient of x translates into a $1-\exp(x)$ reduction in weekly cases $\Delta C_{it}/\Delta C_{it-7}$.

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Table 1: Main Results - Ontario public health regions

	Outcome: weekly case growth Y_{it}=$\Delta\log(\Delta C_{it})$					
	(1)	(2)	(3)	(4)	(5)	(6)
	no time trend		cubic time trend		week fixed effects	
Mask_14	-0.291 **	-0.323 **	-0.366 **	-0.376 ***	-0.319 **	-0.327 **
	[0.017]	[0.016]	[0.010]	[0.008]	[0.021]	[0.019]
Business/gathering_14	-0.625	-0.457	-0.137	0.279	-0.098	0.054
	[0.209]	[0.473]	[0.877]	[0.689]	[0.890]	[0.935]
Long-term care_14	0.643	0.544	0.747	-0.097	-1.044	-1.997
	[0.463]	[0.549]	[0.677]	[0.930]	[0.388]	[0.102]
Behaviour proxy_14	-0.020	-0.016	-0.018	-0.018	-0.016	-0.014
	[0.160]	[0.215]	[0.266]	[0.272]	[0.302]	[0.352]
$\Delta\log(\Delta C)$_14	0.030	0.029	0.024	0.028	0.013	0.012
	[0.614]	[0.649]	[0.692]	[0.665]	[0.817]	[0.834]
$\log(\Delta C)$_14	-0.214 ***	-0.214 ***	-0.203 ***	-0.209 ***	-0.199 ***	-0.201 ***
	[0.000]	[0.000]	[0.001]	[0.001]	[0.001]	[0.001]
$\Delta\log(\Delta PC)$_14		0.287		0.184		0.543 **
		[0.307]		[0.566]		[0.046]
$\log(\Delta PC)$_14		-0.028		0.528		0.112
		[0.907]		[0.124]		[0.744]
$\Delta\log(\Delta T)$	-0.313 *	-0.409 *	-0.260	-0.382	-0.230	-0.480
	[0.087]	[0.058]	[0.287]	[0.125]	[0.492]	[0.138]
R-squared	0.046	0.050	0.051	0.058	0.091	0.094
N	3,094	3,094	3,094	3,094	3,094	3,094
public health unit FE	X	X	X	X	X	X
cubic time trend (days)			X	X		
week fixed effects					X	X

Notes: The sample time period is May 15 to August 13, 2020. P-values from wild bootstrap (cgmwildboot) standard errors clustered by public health unit (PHU) with 5000 repetitions are reported in the square brackets. Mask_14, Business/gathering_14, Behaviour_14, $\Delta\log(\Delta C)$_14, and $\log(\Delta C)$_14 are measured at the PHU level, while Long-term care_14, $\Delta\log(\Delta PC)$_14, $\log(\Delta PC)$_14, and $\Delta\log(\Delta T)$ are measured at the province level. PC denotes provincial total cases. ***, ** and * denote 10%, 5% and 1% significance level respectively. Missing values (1.3% of all observations) for Behaviour proxy_14 are imputed via linear interpolation.

important aspects of behaviour, such as frequent hand-washing or physical distancing. In fact, our coefficient estimate on the behavioral proxy B_{it} is very close to zero (both in Table

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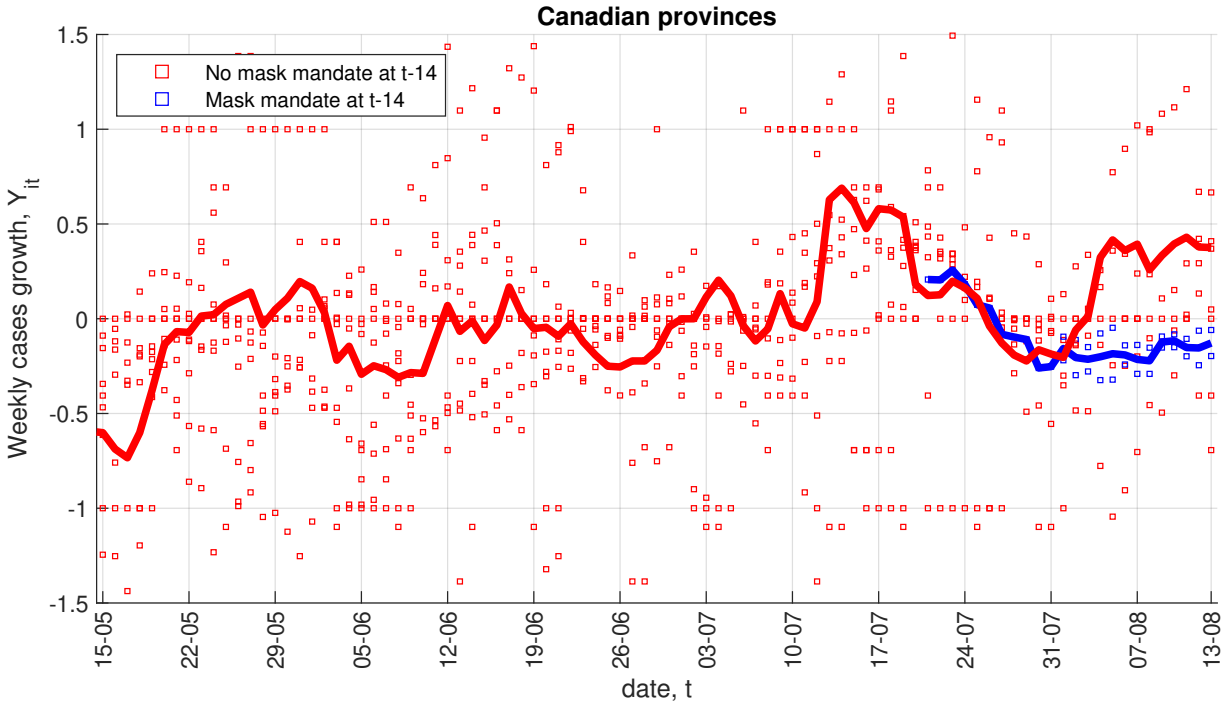
1 and in Section 4.2's province-level results), unlike in CKS (2020).[25] In Appendix Table A18, we find strong contemporaneous correlations between the policy measures, log cases, and the Google mobility behavioral proxy from estimating equation (2). This suggests that the information (lagged cases) and the lagged policy variables included in equation (1) may absorb lagged behavioral responses proxied by B_{it-l} or other latent behavioral changes not captured by B_{it-l}.

4.2 Province-level results

We next evaluate the impact of NPIs on COVID-19 cases growth in Canada as a whole by exploiting variation in the timing of policies across the 10 provinces. Here, we examine NPIs for which there is no variation across Ontario's PHUs (i.e., schooling, travel, and LTC) in addition to mask mandates. Also, provincial data contain variation in the timing of policy changes in both the closing and re-opening phases, allowing us to study both the imposition and relaxation of restrictions.

Figure 4: Canada - mask mandates and weekly case growth



Notes: The figure plots the average weekly case growth $\Delta \log(\Delta C)$ in the provinces with mask mandate (blue) vs. without mask mandate (red) 14 days prior.

[25] We also tried including each location change measure separately and the results are similar (not shown).

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As in the Ontario analysis, we begin with a graphical illustration of mask mandates and COVID-19 case growth across Canadian provinces, in the period March 11 to August 13, 2020. Figure 4 plots the average log weekly case growth in the provinces with vs. without mask mandates. While mask mandates are implemented relatively late in our sample period, average case growth in the provinces with a mask mandate (Ontario and Quebec) diverged from the average case growth in the provinces without a mandate begin roughly four weeks after the mandates are imposed.[26]

Table 2 displays the estimates of equation (1) for weekly case growth, along with wild bootstrap p-values, clustered at the province level (see Table A9 for other methods of computing the standard errors). The odd-numbered columns use lagged cases and lagged case growth at the provincial level as information while the even-numbered columns include in addition lagged cases and case growth at the national level as additional information variables.

As in the Ontario analysis, we present in Table 2 estimates from three specifications: no time trend (columns (1)-(2)), including cubic time trend in days (columns (3)-(4)) and including week fixed effects (columns (5)-(6)). The most robust result is the estimated effect of mask mandates: they are associated with a large reduction in weekly case growth of 45 to 62 log points, which is equivalent to a 36 to 46% reduction in weekly cases across the different specifications. The estimates are statistically significantly different from zero in all cases, with a p-value of less than 0.001 in columns (1)-(4). It is reassuring that these results regarding mask mandates are consistent with the Ontario analysis in the previous section.

Table 2 further shows that restrictions on businesses and gatherings are associated with a reduction in the weekly case growth of 65 to 85 log points or, vice versa, that relaxing business/gathering restrictions is associated with higher case growth. The estimate is equivalent to a 48 to 57% decrease in weekly cases in our sample period. The business/gathering estimates are, however, more noisy than our estimates for mask mandates and do not retain statistical significance in the specifications with week fixed effects ($p = 0.15$ and 0.14). Tables A8 and A15 further suggest that the results on business and gathering NPIs are driven by the smaller provinces and the re-opening period (May to August). Still, these results suggest that lowered restrictions and the associated increase in business/workplace activity or gatherings can be an important offsetting factor for the estimated effect of mask mandates on COVID-19 case growth, both in our sample and in the future.

We also find that school closures (the School_14 variable in Table 2) can be negatively

[26]Figure 4 assumes a July 7 mask mandate implementation date for Ontario (when its most populous PHU, Toronto, adopted a mask mandate, along with Ottawa), and July 18 for Quebec (province-wide mandate).

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Table 2: Main Results – Canada

	Outcome: weekly case growth Y_{it}=$\Delta\log(\Delta C_{it})$					
	(1)	(2)	(3)	(4)	(5)	(6)
	no time trend		cubic time trend		week fixed effects	
Mask_14	-0.446 ***	-0.484 ***	-0.618 ***	-0.613 ***	-0.581 **	-0.567 **
	[0.000]	[0.000]	[0.000]	[0.000]	[0.030]	[0.026]
Business/gathering_14	-0.654 **	-0.827 **	-0.835 **	-0.846 **	-0.648	-0.694
	[0.018]	[0.019]	[0.031]	[0.033]	[0.146]	[0.137]
School_14	-0.336	-0.480	-0.425 **	-0.433 **	-0.261	-0.347
	[0.352]	[0.196]	[0.015]	[0.019]	[0.235]	[0.130]
Travel_14	-0.585	-0.772	-0.375	-0.412	-0.396	-0.553
	[0.146]	[0.118]	[0.613]	[0.636]	[0.695]	[0.559]
Long-term care_14	-0.052	-0.119	0.023	0.032	0.063	0.056
	[0.824]	[0.715]	[0.958]	[0.920]	[0.889]	[0.898]
Behaviour proxy_14	-0.009	-0.008	-0.001	0.000	-0.003	0.001
	[0.257]	[0.350]	[0.880]	[0.972]	[0.858]	[0.935]
$\Delta\log(\Delta C)$_14	-0.061	-0.062	-0.078 *	-0.072	-0.055	-0.054
	[0.177]	[0.262]	[0.090]	[0.198]	[0.449]	[0.459]
$\log(\Delta C)$_14	-0.223 ***	-0.244 ***	-0.227 **	-0.227 *	-0.224	-0.232
	[0.000]	[0.003]	[0.019]	[0.090]	[0.102]	[0.113]
$\Delta\log(\Delta NC)$_14		0.015		-0.107		-0.050
		[0.895]		[0.631]		[0.807]
$\log(\Delta NC)$_14		0.141		0.055		0.302 **
		[0.326]		[0.825]		[0.048]
$\Delta\log(\Delta T)$	0.112	0.166 *	0.172 **	0.169 *	0.158	0.166 *
	[0.170]	[0.074]	[0.043]	[0.056]	[0.110]	[0.073]
R-squared	0.406	0.410	0.414	0.414	0.430	0.433
N	1,560	1,560	1,560	1,560	1,560	1,560
province fixed effects	X	X	X	X	X	X
cubic time trend (days)			X	X		
week fixed effects					X	X

Notes: The time period is March 11 to August 13, 2020. P-values from wild bootstrap (cgmwildboot) standard errors clustered by province with 5000 repetitions are reported in the square brackets. ***, ** and * denote 10%, 5% and 1% significance level respectively. NC denotes national total cases.

associated with case growth. However, the estimates are statistically significant from zero only in the specifications with cubic time trend (columns (3) and (4)). As seen in Figure

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2, provincial school closures occurred in a very short time interval during March, so we may lack statistical power to separately identify its effect from other NPIs (especially the travel-related). Hence, we interpret this result with caution.

As in Table 1, the level of past cases, $\log(\Delta C)$, is negatively and statistically significantly associated with current weekly case growth in columns (1)-(4).

Since the specification with cubic time trend in Tables 1 and 2 allows for possible non-monotonic aggregate time trends in case growth in a parsimonious way, we choose it as our baseline specification with which to perform robustness checks in the next section. Robustness checks with the other specifications are available upon request.

4.3 Robustness

Policy collinearity

A possible concern about our data for the national analysis is that some NPIs (e.g. international travel restrictions or closing of schools) were implemented within a very short time interval.[27] Thus, we may lack enough regional variation to distinguish and identify the separate effect of each policy.[28] Collinearity could also affect the standard errors and the signs of the estimated coefficients.

To check robustness with respect to potential collinearity in the NPI policies, Tables A7 and A10 report estimates from our baseline specification, omitting one policy at a time, for Ontario and Canada respectively. First, it is reassuring that the mask mandate estimates are hardly affected by omitting any of the other policies. This is expected since mask mandates were imposed during a period where other NPIs changed little (see Figure 2). Similarly, the effects of business/gathering regulations and school closures in Table A10 are not sensitive to omitting other policies one at a time, which suggests that there is sufficient statistical power and variation to identify them in the national analysis.

Treatment of zero weekly cases

Another concern for our empirical strategy is that the usual formula for our dependent variable, $\Delta \log(\Delta C_{it})$, cannot be applied when the weekly case total ΔC_{it} is zero. We follow CKS (2020) and replace ln(0) with -1 in our baseline specifications in Tables 1 and 2. We now check the robustness of our estimates to alternative treatments of zero weekly cases.

For easier comparison, the first two columns in Table A5 repeat columns (3) and (4)

[27] For example, Table A4 shows a correlation of 0.61 between the Travel and School policy aggregates.

[28] Aggregating the 17 basic policy indicators into five groups mitigates this issue. Here, we test whether any remaining collinearity poses a problem.

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from Table 1 for Ontario.[29] Our main results on mask mandates across Ontario PHUs are robust to replacing log(0) with 0 and to adding 1 to all ΔC_{it} observations before taking logs, as shown in columns (3)-(6) of Table A5. Another way to mitigate the issue of PHUs with very few cases is to estimate a weighted least squares regression where PHUs are weighted by population. Columns (7) and (8) in Table A5 show that the resulting mask estimate has a slightly smaller magnitude and, due to the reduced effective sample size, weaker statistical significance.

Similarly, Table A8 shows that our province-level estimates, in particular for mask mandates, are also robust to the same manipulations as above.[30] In columns (9) and (10) of Table A8, we restrict the sample to only the largest 4 provinces (British Columbia, Ontario, Quebec and Alberta), which have only 0.3% (2 out of 624) zero observation cases. Again, the estimated mask effects are little changed.

Alternative dates

Figure B4 shows that our estimates and confidence intervals for the effect of mask mandates in the Ontario baseline regressions do not vary much by the initial date of the sample. Similarly, Figure B5 shows that, in the national analysis, our results about mask mandates and business/gathering restrictions are also robust to alternative sample start dates.

Alternative lags

We explore alternative time lags, either shorter or longer in duration, centered around the baseline value of 14 days. Figure B6 (with Ontario data) and Figure B7 (with province-level data) plot the estimates and confidence intervals from the baseline regressions and show that our mask effect estimates remain fairly consistent for different lags.

Omitted variables

Our behaviour proxy variable (Google geo-location trends) likely misses some aspects of behaviour relevant for COVID-19 transmission. One factor that may meaningfully impact behaviour is weather. For example, good weather could entice more people to spend time outside, lowering the chance of viral transmission. Columns (3) and (4) in Table A11 report national estimates with lagged weather variables (daily maximum and minimum temperatures and precipitation for the largest city in each province[31]) as additional regressors. Our NPI estimates, in particular mask mandates, are little changed from the baseline results in columns (1) and (2).

[29] 535 out of 3,094 observations (17%) had to be replaced.

[30] 230 out of 1,560 observations (15%) had to be replaced.

[31] Vancouver, BC; Calgary, AB; Saskatoon, SK; Winnipeg, MB; Toronto, ON; Montreal, QC; Moncton, NB; Halifax, NS; Charlottetown, PE; and St. John's, NL.

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Another possible concern is that our information variables, lagged cases and lagged case growth, may not fully capture the information based on which people react or adjust their behaviour, possibly affecting the observed weekly case growth. Columns (5) and (6) in Table A11 add a national-level "news" variable to the baseline specification. The news variable is defined as the number of daily search results from a news aggregator website (*Proquest Canadian Newsstream*) for the terms "coronavirus" or "COVID-19" (see Appendix C for more details). In column (6), the lagged news variable approaches the 10% significance level ($p = 0.103$). Our estimates on masks and business/gathering remain very close to those in the baseline.

4.4 Self-reported mask usage

The effectiveness of any NPI or public policy crucially depends on whether it affects behaviour. In this section, we use self-reported data on mask usage to examine whether mask mandates indeed increase mask use in Canada ("first-stage" analysis).

We use data from the YouGov COVID-19 Public Monitor, which includes multiple waves of public opinion surveys fielded regularly since early April in many countries.[32] Here, we focus on inter-provincial comparison within Canada. Our variable of interest is based on responses to the question "Thinking about the last 7 days, how often have you worn a face mask outside your home (e.g. when on public transport, going to a supermarket, going to a main road)?" The answer choices are "Always", "Frequently", "Sometimes", "Rarely", and "Not at all". We create a binary variable taking value 1 if the response is "Always" and 0 otherwise, as well as another variable taking value of 1 if the respondent answered either "Always" or "Frequently" and 0 otherwise.

We begin with a simple illustration of self-reported mask usage in Canada from April to August 2020. Figure B2 plots the average self-reported mask usage (the response "Always") in the provinces with and without mask mandates.[33] The figure clearly shows that self-reported mask usage is higher, by up to 50 percentage points, in the provinces with a mask mandate than in the provinces without mask mandates. Since Figure B2 does not account for compositional changes in the data, we formally estimate equation (2), using self-reported mask usage as the behavioral outcome.[34]

[32] The YouGov data can be accessed at: https://yougov.co.uk/covid-19.

[33] As on Figure 4, we use July 7 as the mask mandate implementation date in Ontario.

[34] Since mask usage is reported only for specific dates within each survey wave, we use our mask policy variable daily values for these same dates instead of the weekly moving average.

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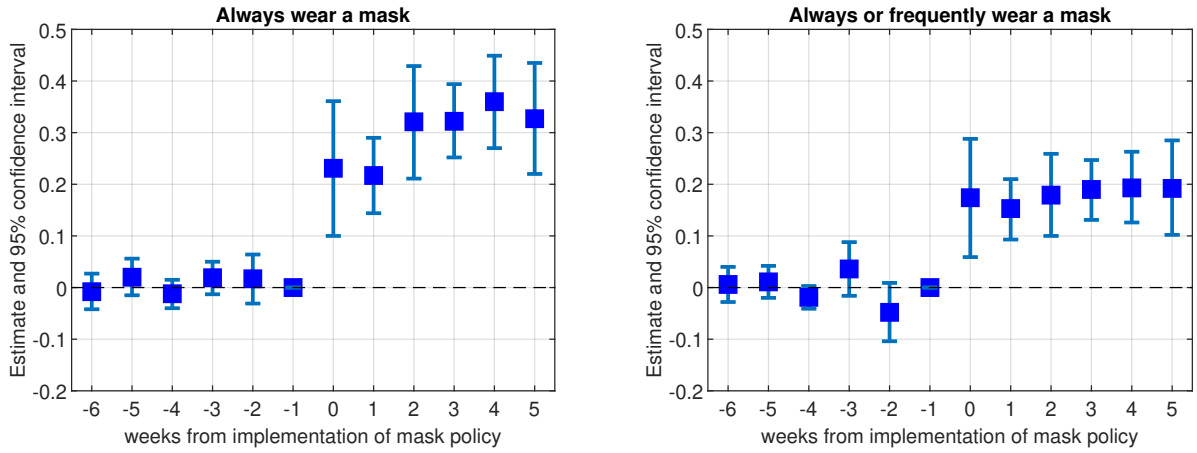
Figure 5: Event Study of Self-reported Mask Usage – Canada



Notes: The data source is YouGov. The outcome is a binary variable taking value 1 if the respondent respectively answered "Always" (in the left panel) or "Always" or "Frequently" (in the right panel) to "Thinking about the last 7 days, how often have you worn a face mask outside your home?" The figure plots the estimates from a version of equation (2) where the mask policy variable is replaced by the interaction of the variables corresponding to being in the treatment group (imposed mask mandate) and a series of dummies for each week, ranging from 6 weeks before the mask mandate to 6 weeks after ($T = -6$ to $+5$, where $T = 0$ is the mandate implementation date). The reference point is 1 week before the implementation ($T = -1$). Wild bootstrap (cgmwildboot) standard errors clustered by province with 5000 repetitions are used to construct the confidence intervals. Sample weights are used.

Figure 5 shows a graphical event study analysis on mask mandates and changes in mask usage. The event study approach is appropriate for the mask usage outcome variable, since the policy impact is expected to be immediate, unlike the other outcomes we study, for which any impact is expected to occur with a lag and we use weekly totals or moving averages. We replace the mask policy variable in equation (2) by the interaction of variables corresponding to being in the treatment group (i.e. under a mask mandate), and a series of dummies for each week, ranging from 6 weeks before the mask mandate to 5 weeks after the mask mandate ($T = -6$ to $+5$, where $T = 0$ is the implementation date of the mask mandate). The reference point is one week before the implementation of the mask mandate ($T = -1$), and we use the same y-axis scale on both panels.

The left and right panels of Figure 5 present the results from the event study analysis for the "Always" and "Always" or "Frequently" mask usage answers, respectively. We make several observations. First, neither panel shows a pre-trend – the estimates are close to zero before the mask mandates. This addresses the potential concern that provinces that implemented mask mandates may have had a different trend in mask usage than provinces that did not. Second, the effect of mask mandates on mask usage is immediate: an increase

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of roughly 20 percentage points as soon as the mask policy is implemented at ($T = 0$). Third, the effect appears persistent rather than transitory, since mask usage after $T = 0$ does not revert to its level before $T = 0$.

Table 3: Self-reported mask usage – Canada

	Outcome: "Always wear mask"					
	(1)	(2)	(3)	(4)	(5)	(6)
	no time trend		cubic time trend		week fixed effects	
Mask	0.404 ***	0.396 ***	0.304 ***	0.315 ***	0.310 ***	0.310 ***
	[0.000]	[0.000]	[0.000]	[0.000]	[0.000]	[0.000]
$\Delta\log(\Delta C)$	-0.017	-0.006	-0.008	-0.006	-0.004	-0.008
	[0.663]	[0.611]	[0.524]	[0.595]	[0.656]	[0.464]
$\log(\Delta C)$	-0.025	0.015 **	0.004	0.006	0.006	0.007
	[0.127]	[0.025]	[0.662]	[0.544]	[0.504]	[0.502]
$\Delta\log(\Delta NC)$		-0.106 *		-0.023		0.191
		[0.054]		[0.324]		[0.108]
$\log(\Delta NC)$		-0.089 ***		-0.028		-0.068
		[0.000]		[0.669]		[0.582]
R-squared	0.157	0.169	0.172	0.172	0.173	0.174
N	8,859	8,859	8,859	8,859	8,859	8,859
individual characteristics	X	X	X	X	X	X
province fixed effects	X	X	X	X	X	X
cubic time trend (days)			X	X		
week fixed effects					X	X
† average mask usage rate without mask mandate = 0.298						

Notes: The time period is April 2 to August 13, 2020. P-values from wild bootstrap (cgmwildboot) standard errors clustered by province with 5000 repetitions are reported in the square brackets. NC denotes national total cases. The data source is YouGov. The outcome is a dummy which takes value 1 if the respondent answered "Always" to the survey question "Thinking about the last 7 days, how often have you worn a face mask outside your home?" Sample weights are used. Individual characteristics include a gender dummy, age dummy (in years), dummies for each household size, dummies for each number of children, and dummies for each employment status. ***, ** and * denote 10%, 5% and 1% significance level respectively.

Table 3 displays the estimates on self-reported mask usage (answer "Always") in equation (2) along with wild bootstrap p-values clustered at the province level. The odd-numbered columns use lagged cases and lagged case growth at the provincial level as information while the even-numbered columns include in addition lagged cases and case growth at the national level as additional information variables. As in Table 1 and Table 2, we present estimates

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without time trend, including cubic time trend (in days), and including week fixed effects. Our preferred specification with cubic time trend, column (4) of Table 3, shows that mask mandates are associated with 31.5 percentage point increase in self-reported mask usage ($p < 0.001$), from a base of self-reported mask usage without mask mandate of 29.8%.[35,36]

These "first-stage" results show that mask mandates exhibit significant compliance in Canada and establish a basis for the significant impact of mask mandates on the spread of COVID-19 that we find. That said, given that mask mandates do not change everyone's behaviour, our estimates in Tables 1 and 2 represent intent-to-treat effects. The full effect of the entire population shifting from not wearing to wearing masks is likely significantly larger.[37]

There is a heated debate on whether community use of masks may create a false sense of security that reduces adherence to other preventive measures. We also investigate this question using YouGov survey data. As Tables A13 and A14 indicate, we find no evidence that mask mandates in Canada have had an offsetting effect on other preventive measures such as hand washing, using sanitizer, avoiding gatherings, and avoiding touching objects in public during the period we study. On the contrary, mask mandates may slightly increase social distancing in one out of the eight precaution categories (avoiding crowded areas) ($p < 0.10$).[38]

4.5 Counterfactuals

We evaluate several counterfactuals corresponding to replacing the actual mask policy in a province or Canada-wide with a counterfactual policy, including absence of mask mandate.

Letting t_0 be the implementation date of a counterfactual policy, we set the counterfactual weekly case count, ΔC_{it}^c, equal to ΔC_{it} for all $t < t_0$. For each date $t \geq t_0$, using the definition of Y_{it} from (3), we then compute the counterfactual weekly cases, ΔC_{it}^c and the counterfactual

[35]Similarly, in Table A12, column (4) shows that "Always" or "Frequent" mask usage increases by 21.5 percentage points. The finding that the increase in mask usage among the "Always" respondents is larger than among the "Always" or "Frequent" respondents is consistent with some people switching from wearing masks "frequently" to "always."

[36]Hatzius et al. (2020) document that state mask mandates in the US increased mask usage roughly by 25 percentage points in 30 days. The compliance with mask mandates may differ across countries or regions based on social norms, peer effects, political reasons or the consequences of noncompliance (e.g., fines).

[37]If we take the increase of about 30 percentage points in reported mask usage induced by mask mandates at face value, the full effect of mask wearing (treatment-on-the-treated effect) would be roughly triple our estimates. It could be larger still if there is desirability bias in answering the mask usage survey question, so that the actual increase in mask use may be smaller than our estimate.

[38]Consistent with this result, Seres et al. (2020) find that wearing masks increased physical distancing based on a randomized field experiment in stores in Germany.

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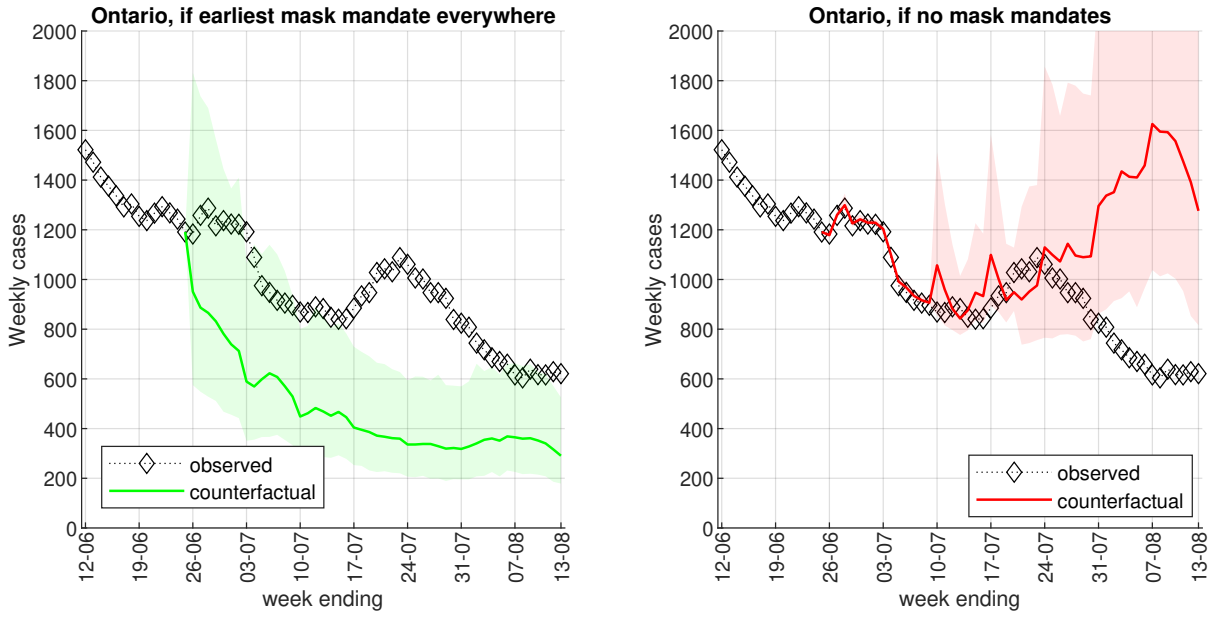
case growth rate, Y_{it}^c, as follows:

$$\Delta C_{it}^c = \exp(Y_{it}^c)\left(\Delta C_{it-7}^c\right) \text{ and}$$

$$Y_{it}^c = \hat{Y}_{it} + \beta_{Mask_14}\left(\text{Mask}^c_14 - \text{Mask_14}\right) + \beta_{log_dC_14}\left(\ln(\Delta C_{it-14}^c) - \ln(\Delta C_{it-14})\right),$$

where $\hat{Y}_{it}$ is the regression-fitted value of weekly case growth; β_{Mask_14} is the coefficient estimate on the mask mandate variable Mask_14 in baseline specification (4) in Table 1 or 2, depending on the counterfactual; Mask^c_14 is the counterfactual mask policy (e.g. different implementation date, wider geographic coverage or absence of mask mandate); and $\beta_{log\Delta C_14}$ is the coefficient estimate (-0.227 or -0.209) on lagged cases log(ΔC)_14 in Table 1 or 2, column 4. The coefficient $\beta_{log\Delta C_14}$ adjusts the counterfactual case growth rate for the negative statistically significant association between the weekly case total two weeks prior and time-t case growth. This effect may be due to people being more careful when they perceive the risk of infection to be higher or less careful vice versa.

Figure 6: Counterfactuals - Ontario public health regions



Notes: The left panel assumes that mask mandates were adopted in all PHUs on June 12 (date of the first mask mandate in ON). The right panel assumes that mask mandates were not adopted in any PHU. We use the mask estimate (-0.376) from column (4) of Table 1.

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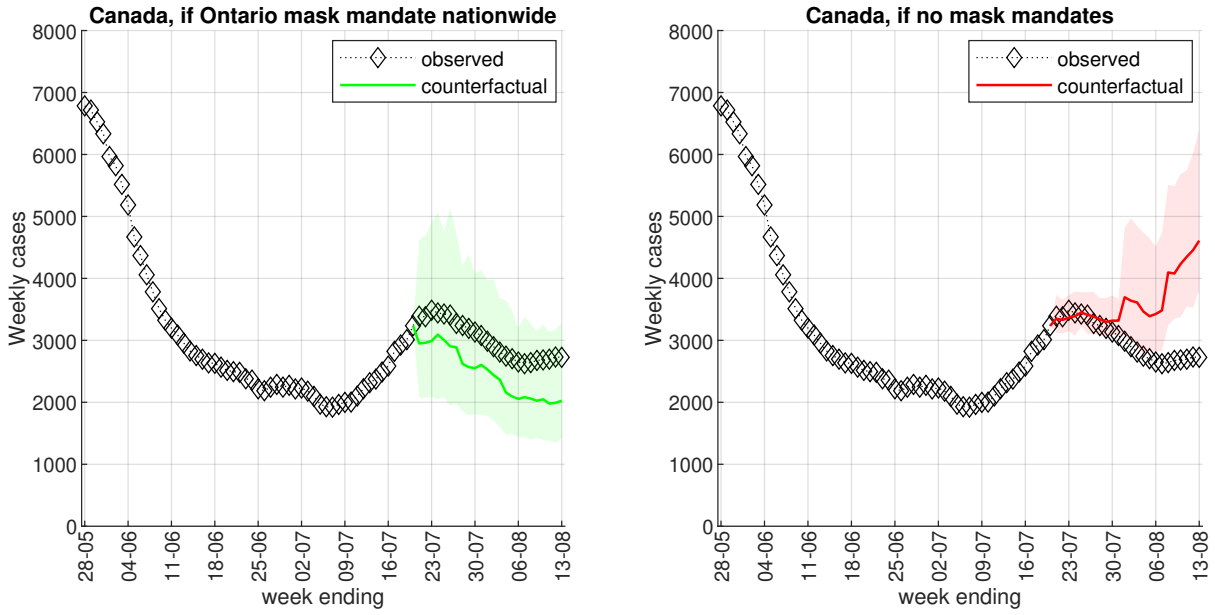
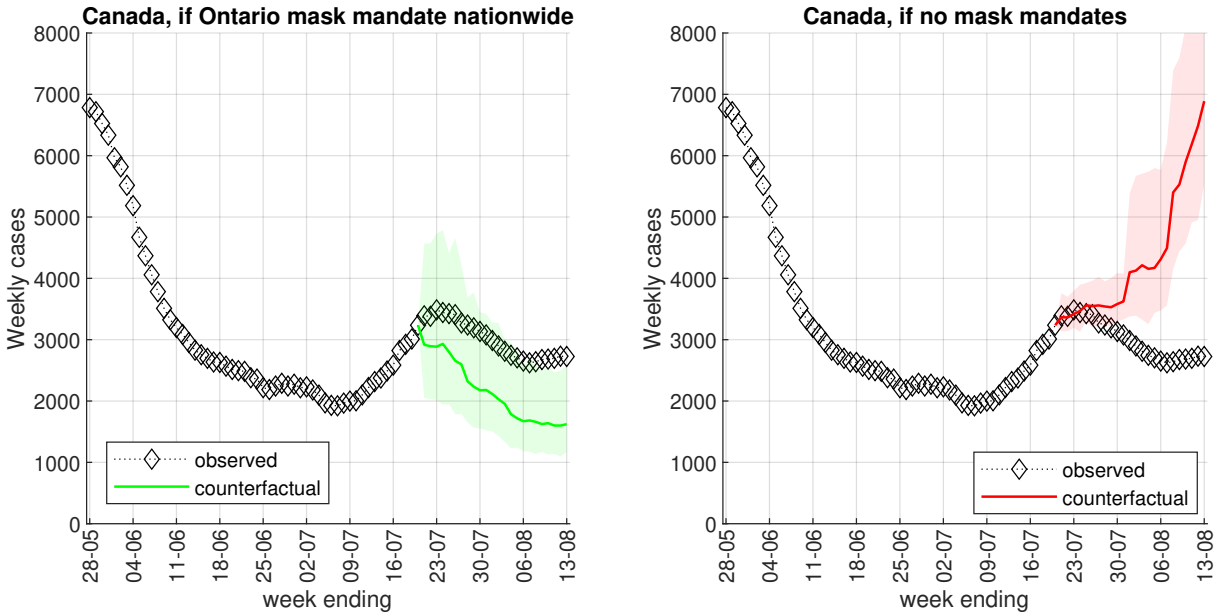
Figure 7: Counterfactuals – Canada (Table 1 mask estimate)



Notes: The left panel assumes that mask mandates were adopted in all provinces on July 7 (the adoption date in Toronto and Ottawa). The right panel assumes that mask mandates were not adopted in any province. We use the mask estimate (-0.376) from column (4) of Table 1.

Figure 8: Counterfactuals – Canada (Table 2 mask estimate)



Notes: The left panel assumes that mask mandates were adopted in all provinces on July 7 (the adoption date in Toronto and Ottawa). The right panel assumes that mask mandates were not adopted in any province. We use the mask estimate (-0.613) from column (4) of Table 2.

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Figures 6, 7 and 8 show results from two counterfactual policy evaluations. The first exercise, depicted in the left-hand side panel of the figures, assumes that masks are adopted everywhere at the earliest date observed in the data. Specifically, Figure 6 considers the counterfactual of all Ontario PHUs adopting mask mandates on June 12, while Figures 7 and 8 assume that all provinces adopt a mask mandate on July 7.[39]

Using our mask policy estimate from Table 1, Figure 6 shows that an earlier face mask mandate across Ontario PHUs could have lead to an average reduction of about 300 cases per week as of August 13, holding all else equal. For Canada as a whole, a nation-wide adoption of mask mandates in early July is predicted to reduce total cases per week in the country by 700 to 1,100 cases on average as of August 13, depending on whether we use the more conservative mask estimate (-0.376) from column (4) of Table 1 (see Figure 7) or the larger estimate (-0.613) from column (4) of Table 2 (see Figure 8). In all cases, the indirect feedback effect via $\beta_{log\Delta C_14}$ (lagged cases as information) starts moderating the decrease in cases two weeks after the start of the counterfactual mask policy.

In the right-hand side panel of Figures 6, 7 and 8, we perform the opposite exercise, namely assuming instead that mask mandates were *not* adopted in any Ontario PHU or any Canadian province. Our estimates imply that the counterfactual absence of mask mandates would have led to a large increase in new cases, both in Ontario and Canada-wide, especially when using the larger mask coefficient estimate from Table 2 (see Figure 8).

Finally, in Figure B11 in the Appendix, we also evaluate the counterfactual in which British Columbia and Alberta, the third and fourth largest Canadian provinces by population, adopt province-wide mask mandates on July 15. The results, using the Mask_14 estimate from Table 2, suggest a reduction of about 300 cases per week in each province by mid-August.

The counterfactual simulations assume that all other variables, behaviour and policies (except the mask policy and $t-14$ cases) remain fixed, as observed in the data. This is a strong assumption, but it may be plausible over the relatively short time period that we analyze. Moreover, the counterfactuals assume that regions without a mask mandate would react in the same way, on average, as the regions that imposed a mandate. Therefore, these results should be interpreted with caution and only offer a rough illustration and projection of the estimated effect of mask mandates on COVID-19 cases.

[39] June 12 is the date of the earliest mask mandate in Ontario. For the national analysis, July 7, the effective date for Toronto and Ottawa, is considered Ontario's first significant date of mask mandate enactment: PHUs with earlier mandates account for less than 10% of Ontario's population.

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4.6 Additional analysis

Closing and re-opening sub-periods

We investigate whether policy impact varied in different phases of the pandemic by splitting the full sample period into two sub-periods: "closing" (March 11 to May 14) and "re-opening" (May 15 to August 13). The dividing date of May 15 (referring to the NPIs in place around May 1) was chosen because very few policies were relaxed before May 1, and very few non-mask policies were tightened after May 1 in our sample period (see Figure 2).

In Table A15, we report estimates and wild bootstrap standard errors using our baseline specification with cubic time trend, separately for the closing and re-opening periods. We find that the imposition of school closures and travel restrictions early in the closing period is associated with a very large subsequent reduction in weekly case growth, as can be also seen on Figure B8 – the average observed log growth rate of cases $\Delta \log(\Delta \text{C})$ falls from 2.4 (ten-fold growth in weekly cases) to -0.4 (33% decrease in weekly cases) between March 15 and April 5. Long-term care restrictions are also associated with reduced case growth two weeks later during the March to May closing period. We interpret these results with caution, however, since many of these policy measures and restrictions were enacted in a brief time interval during March and there is not much inter-provincial variation (see Figure 2). No mask mandates were present in the closing period.

In the re-opening period, our results in Table A15 are in line with our full-sample results for mask mandates and business/gathering regulations (Table 2), with slightly larger coefficient estimates and less statistically significant p-values, possibly due to the smaller sample. Travel and school closures are not statistically significant in the re-opening period. This is unsurprising: relaxation of travel policies was minor and endogenous (only re-open to safe areas within Canada), and the schools that re-opened (in parts of Quebec and, on a part-time basis, in British Columbia) did so on voluntary attendance basis, yielding smaller class sizes.

Deaths

We also examine the weekly death growth as an outcome. We only have access to disaggregated deaths data at the province level (not at PHU levels in Ontario). We thus estimate regression equation (1) using $Y_{it} = \Delta \log(\Delta D_{it})$ for each province i as the dependent variable. In addition, we use a 28-day lag for the policy, behaviour proxy, and information variables to reflect the fact that deaths occur on average about two weeks after case detection; see Appendix D for details and references.[40]

[40] In Table 4, *Variable*_28 denotes the *Variable* lagged by 28 days.

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Table 4 reports the estimates from the same specifications as those for case growth in Table 2. In all specifications, mask mandates are associated with a large reduction in the observed weekly deaths growth rate four weeks later (more than 90 log points, or equivalently more than 60% reduction in weekly deaths). These results are larger than our case growth results, but consistent with them given the substantial uncertainty. See also Figure B12, which plots the average weekly death growth in the provinces without a mask mandate four weeks prior vs. that for Ontario, the only province with mask mandate four weeks prior in our sample period.

The robustness checks in Table A16, however, show that, unlike for case growth, the mask mandate estimates in Table 4 are not robust to weighing by population or to restricting the sample to the largest 4 provinces. This suggests that the estimated effect is largely driven by observations from the small provinces, which have a disproportionately larger number of zero or small weekly death totals.[41] Furthermore, given the 28-day lag, there are only 9 days with observations (from Ontario only) for which the mask mandate variable takes value of 1. Due to these serious data limitations, the relation between mask mandates and COVID-19 deaths in Table 4 is suggestive at best, and we urge caution in interpreting or extrapolating from these results.

That said, our main findings about the growth in cases may have implications about future growth in deaths, particularly if the affected demographics become less skewed toward the young in later periods.

[41] 205 out of the 1,470 observations (14%) had log(0) replaced by -1.

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Table 4: Canada – deaths growth rate and policies

	Outcome: weekly deaths growth, $\Delta\log(\Delta D)$					
	(1)	(2)	(3)	(4)	(5)	(6)
	no time trend		cubic time trend		week fixed effects	
Mask_28	-1.391 ***	-1.453 ***	-0.922 **	-0.983 **	-0.904 **	-0.915 **
	[0.000]	[0.000]	[0.022]	[0.032]	[0.036]	[0.045]
Business/gathering_28	0.241	0.271	-0.134	-0.224	-0.279	-0.268
	[0.529]	[0.521]	[0.762]	[0.748]	[0.712]	[0.732]
School_28	0.002	0.018	0.441	0.440	0.624	0.630
	[0.974]	[0.924]	[0.317]	[0.341]	[0.114]	[0.113]
Travel_28	-0.176	-0.287	-0.005	-0.027	-0.191	-0.161
	[0.553]	[0.432]	[0.972]	[0.935]	[0.638]	[0.718]
Long-term care_28	-0.091	-0.140	-0.035	-0.036	-0.024	-0.017
	[0.592]	[0.600]	[0.900]	[0.900]	[0.936]	[0.948]
Behaviour proxy_28	0.003	0.000	0.002	0.003	0.005	0.005
	[0.718]	[1.000]	[0.815]	[0.737]	[0.675]	[0.695]
$\Delta\log(\Delta D)$_28	0.151	0.175	0.141	0.152	0.154	0.153
	[0.194]	[0.245]	[0.361]	[0.345]	[0.266]	[0.266]
$\log(\Delta D)$_28	-0.238 ***	-0.248 ***	-0.216 ***	-0.220 ***	-0.229 ***	-0.227 ***
	[0.000]	[0.000]	[0.000]	[0.000]	[0.000]	[0.000]
$\Delta\log(\Delta ND)$_28		-0.110		-0.121		-0.019
		[0.471]		[0.476]		[0.806]
$\log(\Delta ND)$_28		-0.015		0.018		-0.053
		[0.743]		[0.858]		[0.557]
$\Delta\log(\Delta T)$	0.081	0.018	-0.038	-0.051	-0.037	-0.037
	[0.409]	[0.922]	[0.758]	[0.735]	[0.752]	[0.748]
R-squared	0.233	0.239	0.251	0.254	0.286	0.286
N	1,470	1,470	1,470	1,470	1,470	1,470
province fixed effects	X	X	X	X	X	X
cubic trend in days			X	X		
week fixed effects					X	X

Notes: The time period is March 11 to August 13, 2020. P-values from wild bootstrap (cgmwildboot) standard errors clustered by province with 5000 repetitions are reported in the square brackets. ***, ** and * denote 10%, 5% and 1% significance level respectively. ND denotes national total deaths.

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5 Conclusion

The wearing of face masks by the general public has been a very contentious policy issue during the COVID-19 pandemic, with health authorities in many countries and the World Health Organization giving inconsistent or contradictory recommendations over time. "Conspiracy theories" and misinformation surrounding mask wear abound in social media, fuelled by some individuals' perception that mask mandates constitute significant restrictions on individual freedoms. Given the absence of large-scale randomized controlled trials or other direct evidence on mask effectiveness in preventing the spread of COVID-19, quantitative observational studies like ours are essential for informing both public policy and the public opinion.

We estimate the impact of mask mandates and other public policy measures on the spread of COVID-19 in Canada. We use both within-province and cross-province variation in the timing of mask mandates and find a robust and significantly negative association between mask mandates and subsequent COVID-19 case growth – 25 to 46% average reduction in weekly cases in the first several weeks after adoption, depending on the data sample and empirical specification used. These results are supported by our analysis of survey data on compliance with the mask mandates, which show that the mandates increase the proportion of reporting as always wearing a mask in public by around 30 percentage points. However, our sample period does not allow us to determine whether their effect lasts beyond the first few weeks after implementation. We conclude that mask mandates can be a powerful policy tool for at least temporarily reducing the spread of COVID-19.

Mask mandates were introduced in Canada during a period where other policy measures were relaxed, as part of the economy's re-opening. Specifically, we find that relaxed restrictions on businesses or gatherings are positively associated with subsequent COVID-19 case growth – a factor that could offset and obscure the health benefits of mask mandates. Past case totals were also found to matter for subsequent COVID-19 outcomes, suggesting that riskier behaviour based on favourable lagged information may limit how low mask mandates and other restrictions – short of a lockdown – can push the number of new cases.

We have deliberately abstained from studying the direct economic impacts of COVID-19, focusing instead on the unique features of the Canadian data for identifying the effect of NPIs, in particular mask mandates, on COVID-19 case growth. Future research combining epidemiological finding with the economic benefits and costs of various public policies or restrictions would enrich the ongoing policy debate and provide further guidance.

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Appendix A. Additional tables

Table A1: Ontario – Correlations between the Google mobility indicators

category	retail	grocery	workplaces	transit	residential	parks	N
retail	1						3,008
grocery	0.82	1					3,064
workplaces	0.39	0.26	1				3,082
transit	0.57	0.47	0.65	1			2,453
residential	-0.54	-0.38	-0.92	-0.69	1		2,751
parks	0.50	0.31	0.40	0.40	-0.47	1	1,483

Notes: The time period is May 1 to July 30 (two weeks before the May 15 - August 13 sample period). Daily PHU-level data.

Table A2: Canada – Correlations between the Google mobility indicators

category	retail	grocery	workplaces	transit	residential	parks	N
retail	1						1,560
grocery	0.84	1					1,560
workplaces	0.69	0.53	1				1,560
transit	0.82	0.60	0.86	1			1,394
residential	-0.80	-0.58	-0.91	-0.85	1		1,516
parks	0.53	0.43	0.19	0.25	-0.46	1	1,347

Notes: The time period is February 26 to July 30 (two weeks before the March 11 - August 13 sample period). Daily province-level data.

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Table A3: Ontario – Correlations between policies and location behaviour

	Behaviour proxy	Mask	Business/gathering	LTC
Behaviour proxy	1			
Mask	0.17	1		
Business/gathering	-0.55	-0.63	1	
Long-term care (LTC)	-0.27	-0.75	0.66	1

Notes: The time period is May 15 to August 13 ($N = 3,094$). Each variable is a 7-day moving average. All variables are at the PHU level, except LTC which is measured at the province level.

Table A4: Canada – Correlations between policies and location behaviour

	Behaviour proxy	Mask	Business/gathering	School	Travel	LTC
Behaviour proxy	1					
Mask	0.09	1				
Business/gathering	-0.86	-0.23	1			
School	-0.37	0.08	0.37	1		
Travel	-0.14	-0.09	0.30	0.61	1	
Long-term care (LTC)	-0.14	-0.11	0.24	0.44	0.22	1

Notes: The time period is March 11 to August 13 ($N = 1,560$). Province-level, 7-day moving averages.

Table A5: Ontario – Robustness (treatment of zero weekly cases)

	Outcome: weekly case growth, $\Delta\log(\Delta C)$							
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
	Baseline		Alternative 1		Alternative 2		Alternative 3	
p-values in [ ] brackets	replace log(0) by -1		replace log(0) by 0		add 1 before taking log		weighted by population	
Mask_14	-0.366 **	-0.376 ***	-0.310 **	-0.315 ***	-0.272 **	-0.280 **	-0.249 *	-0.259 *
	[0.010]	[0.008]	[0.010]	[0.008]	[0.017]	[0.013]	[0.096]	[0.082]
Business/	-0.137	0.279	0.021	0.290	-0.006	0.270	0.350	0.529 *
gathering_14	[0.877]	[0.689]	[0.945]	[0.613]	[1.000]	[0.616]	[0.226]	[0.092]
Long-term care_14	0.747	-0.097	-0.003	-0.568	0.196	-0.327	-1.652	-1.927 *
	[0.677]	[0.930]	[0.973]	[0.667]	[0.908]	[0.782]	[0.137]	[0.070]
Behaviors_14	-0.018	-0.018	-0.016	-0.016	-0.013	-0.014	-0.008	-0.009
	[0.266]	[0.272]	[0.188]	[0.194]	[0.278]	[0.270]	[0.416]	[0.418]
$\Delta\log(\Delta C)$_14	0.024	0.028	0.043	0.045	0.028	0.030	0.038	0.038
	[0.692]	[0.665]	[0.330]	[0.322]	[0.520]	[0.494]	[0.578]	[0.562]
$\log(\Delta C)$_14	-0.203 ***	-0.209 ***	-0.184 ***	-0.188 ***	-0.164 ***	-0.169 ***	-0.223 ***	-0.231 ***
	[0.001]	[0.001]	[0.001]	[0.000]	[0.001]	[0.001]	[0.000]	[0.000]
$\Delta\log(\Delta PC)$_14		0.184		0.132		0.094		0.066
		[0.566]		[0.647]		[0.722]		[0.696]
$\log(\Delta PC)$_14		0.528		0.302		0.437		0.300
		[0.124]		[0.302]		[0.101]		[0.257]
$\Delta\log(\Delta T)$	-0.260	-0.382	-0.189	-0.266	-0.129	-0.215	-0.012	-0.063
	[0.287]	[0.125]	[0.361]	[0.203]	[0.486]	[0.242]	[0.942]	[0.677]
R-squared	0.051	0.058	0.059	0.062	0.057	0.063	0.066	0.069
N	3,094	3,094	3,094	3,094	3,094	3,094	3,094	3,094
PHU fixed effects	X	X	X	X	X	X	X	X
cubic time trend	X	X	X	X	X	X	X	X
population weighted	No	No	No	No	No	No	Yes	Yes

Notes: The time period is May 15 to August 13, 2020. P-values from wild bootstrap (cgmwildboot) standard errors clustered by public health unit (PHU) with 5000 repetitions are reported in the square brackets. Columns (1) and (2) repeat columns (3) and (4) from Table 1 where we replace log(0) with -1. Columns (3) and (4) replace log(0) with 0, and columns (5) and (6) add 1 to all ΔC_{it} observations. Columns (7) and (8) report estimates from a weighted least squares regression with weights equal to the PHU population sizes. ***, ** and * denote 10%, 5% and 1% significance level respectively.

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Table A6: Ontario – Robustness (standard errors)

Outcome: weekly case growth $\Delta\log(\Delta C)$				
	(1)		(2)	
Mask_14	-0.366		-0.376	
	(0.014)	**	(0.012)	**
	[0.010]	**	[0.008]	***
	{0.022}	**	{0.016}	**
Business/gathering_14	-0.137		0.279	
	(0.849)		(0.688)	
	[0.877]		[0.689]	
	{0.887}		{0.703}	
Long-term care_14	0.747		-0.097	
	(0.657)		(0.951)	
	[0.677]		[0.930]	
	{0.702}		{0.935}	
Behaviour proxy_14	-0.018		-0.018	
	(0.183)		(0.197)	
	[0.266]		[0.272]	
	{0.281}		{0.272}	
R-squared	0.054		0.060	
N	3,094		3,094	
$\Delta\log(\Delta C)$_14	X		X	
$\log(\Delta C)$_14	X		X	
$\Delta\log(\Delta PC)$_14			X	
$\log(\Delta PC)$_14			X	
$\Delta\log(\Delta T)$	X		X	
PHU fixed effects	X		X	
cubic time trend	X		X	

Notes: The time period is May 15 - August 13. P-values from standard clustering by PHU (Stata command cluster) in the ( ) parentheses, wild bootstrap with one-way clustering by PHU and 5000 repetitions in the [ ] square brackets, and wild bootstrap with two-way clustering by PHU and day with 5000 repetitions in the { } curly braces. PC denotes provincial cases.

Table A7: Ontario – Robustness (policy collinearity)

	Outcome: weekly case growth $\Delta\log(\Delta C)$							
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
	Baseline		Drop Mask_14		Drop Business/gathering_14		Drop LTC_14	
Mask_14	-0.366 **	-0.376 **			-0.362 **	-0.382 ***	-0.363 **	-0.376 ***
	[0.010]	[0.008]			[0.012]	[0.009]	[0.010]	[0.008]
Business/gathering_14	-0.137	0.279	-0.041	0.398			-0.047	0.260
	[0.877]	[0.689]	[0.976]	[0.565]			[0.947]	[0.682]
Long-term care (LTC)_14	0.747	-0.097	0.650	-0.271	0.653	0.229		
	[0.677]	[0.930]	[0.728]	[0.836]	[0.682]	[0.890]		
Behaviour proxy_14	-0.018	-0.018	-0.014	-0.014	-0.017	-0.019	-0.018	-0.018
	[0.266]	[0.272]	[0.323]	[0.336]	[0.199]	[0.174]	[0.268]	[0.268]
$\Delta\log(\Delta C)$_14	0.024	0.028	0.035	0.039	0.025	0.027	0.027	0.027
	[0.692]	[0.665]	[0.541]	[0.512]	[0.696]	[0.676]	[0.678]	[0.669]
log(ΔC)_14	-0.203 ***	-0.209 ***	-0.215 ***	-0.221 ***	-0.202 ***	-0.210 ***	-0.206 ***	-0.209 ***
	[0.001]	[0.001]	[0.001]	[0.001]	[0.001]	[0.001]	[0.000]	[0.001]
$\Delta\log(\Delta PC)$_14		0.184		0.217		0.122		0.174
		[0.566]		[0.485]		[0.722]		[0.611]
log(ΔPC)_14		0.528		0.486		0.544		0.532
		[0.124]		[0.158]		[0.115]		[0.132]
$\Delta\log(\Delta T)$	-0.260	-0.382	-0.243	-0.367	-0.263	-0.364	-0.239	-0.382
	[0.287]	[0.125]	[0.322]	[0.136]	[0.291]	[0.162]	[0.287]	[0.125]
R-squared	0.051	0.058	0.049	0.054	0.054	0.060	0.053	0.060
N	3,094	3,094	3,094	3,094	3,094	3,094	3,094	3,094
public health unit FE	X	X	X	X	X	X	X	X
cubic time trend	X	X	X	X	X	X	X	X

Notes: The time period is May 15 to August 13, 2020. P-values from wild bootstrap (cgmwildboot) standard errors clustered by public health unit (PHU) with 5000 repetitions are reported in the square brackets. Columns (1) and (2) repeat columns (3) and (4) from Table 1. We drop each policy at at time in columns (3)-(8). ***, ** and * denote 10%, 5% and 1% significance level respectively.

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Table A8: Canada - Robustness (treatment of zero weekly cases)

	Outcome: Weekly case growth, $\Delta\log(\Delta C)$									
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
	Baseline		Alternative 1		Alternative 2		Alternative 3		Alternative 4	
	Replace log(0) by -1		Replace log(0) by 0		Add 1 before taking log		Weighted by population		4 largest provinces	
Mask_14	-0.618 ***	-0.613 ***	-0.599 ***	-0.591 ***	-0.594 ***	-0.587 ***	-0.618 ***	-0.613 ***	-0.593 ***	-0.588 ***
	[0.000]	[0.000]	[0.000]	[0.000]	[0.000]	[0.000]	[0.000]	[0.000]	[0.000]	[0.000]
Business / gathering_14	-0.835 **	-0.846 **	-0.794 *	-0.812 *	-0.698 **	-0.711 *	-0.224	-0.216	0.049	0.160
	[0.031]	[0.033]	[0.076]	[0.070]	[0.046]	[0.055]	[0.513]	[0.615]	[0.754]	[0.509]
School_14	-0.425 **	-0.433 **	-0.393 **	-0.410 **	-0.366 **	-0.381 **	-0.148	-0.211 **	-0.029	-0.060
	[0.015]	[0.019]	[0.023]	[0.020]	[0.050]	[0.042]	[0.278]	[0.010]	[0.599]	[0.478]
Travel_14	-0.375	-0.412	-0.499	-0.565	-0.283	-0.338	-1.513 *	-1.811 *	-2.368	-4.980 ***
	[0.613]	[0.636]	[0.446]	[0.437]	[0.646]	[0.630]	[0.077]	[0.071]	[0.358]	[0.000]
LTC_14	0.023	0.032	0.093	0.108	0.051	0.063	0.097	0.119	-0.054	-0.076
	[0.958]	[0.920]	[0.772]	[0.746]	[0.866]	[0.831]	[0.360]	[0.274]	[0.626]	[0.132]
Behaviour_14	-0.001	0.000	-0.002	0.000	0.001	0.002	-0.015 *	-0.013	-0.025 ***	-0.030 ***
	[0.880]	[0.972]	[0.864]	[0.946]	[0.910]	[0.692]	[0.054]	[0.100]	[0.000]	[0.000]
$\Delta\log(\Delta C)$_14	-0.078 *	-0.072	-0.034	-0.025	-0.042	-0.035	0.002	0.005	0.036	0.023
	[0.090]	[0.198]	[0.456]	[0.599]	[0.221]	[0.359]	[1.000]	[0.942]	[0.611]	[0.746]
$\log(\Delta C)$_14	-0.227 **	-0.227 *	-0.236 ***	-0.236 ***	-0.209 ***	-0.210 **	-0.265 ***	-0.276 ***	-0.281	-0.290 ***
	[0.019]	[0.090]	[0.000]	[0.000]	[0.000]	[0.012]	[0.000]	[0.000]	[0.109]	[0.000]
$\Delta\log(\Delta NC)$_14		-0.107		-0.180		-0.144		-0.174 ***		-0.297 ***
		[0.631]		[0.335]		[0.384]		[0.000]		[0.000]
$\log(\Delta NC)$_14		0.055		0.100		0.085		0.255		0.615 ***
		[0.825]		[0.738]		[0.731]		[0.295]		[0.000]
$\Delta\log(\Delta T)$	0.172 **	0.169 *	0.098 *	0.093	0.113 *	0.109	0.079	0.074	0.072	0.071
	[0.043]	[0.056]	[0.094]	[0.130]	[0.075]	[0.109]	[0.776]	[0.781]	[0.754]	[0.639]
R-squared	0.414	0.414	0.483	0.484	0.471	0.471	0.651	0.653	0.804	0.813
N	1,560	1,560	1,560	1,560	1,560	1,560	1,560	1,560	624	624
Province FE	X	X	X	X	X	X	X	X	X	X
Cubic trend	X	X	X	X	X	X	X	X	X	X
Weighted	No	No	No	No	No	No	Yes	Yes	No	No

Notes: The time period is March 11 to August 13, 2020. P-values from wild bootstrap (cgmwildboot) standard errors clustered by province with 5000 repetitions in the square brackets. Columns (1) and (2) repeat columns (3) and (4) from Table 2 where we replace log(0) with -1. Columns (3) and (4) replace log(0) with 0, and columns (5) and (6) add 1 to all ΔC_{it} observations. Columns (7) and (8) report results from a weighted least squares regression with the province populations as weights. Finally, columns (9) and (10) restrict the sample to only the largest 4 provinces (BC, ON, QC, and AB) which have only 0.3% zero observation cases. ***, ** and * denote 10%, 5% and 1% significance level respectively.

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Table A9: Canada – Robustness (standard errors)

Outcome: weekly case growth $\Delta\log(\Delta C)$				
	(1)		(2)	
Mask_14	-0.618		-0.613	
	(0.014)	**	(0.014)	**
	[0.000]	***	[0.000]	***
	{0.000}	***	{0.000}	***
Business/gathering_14	-0.835		-0.846	
	(0.027)	**	(0.023)	**
	[0.031]	**	[0.033]	**
	{0.035}	**	{0.039}	**
School_14	-0.425		-0.433	
	(0.042)	**	(0.025)	**
	[0.015]	**	[0.019]	**
	{0.015}	**	{0.014}	**
Travel_14	-0.375		-0.412	
	(0.526)		(0.534)	
	[0.613]		[0.636]	
	{0.612}		{0.637}	
Long-term care_14	0.023		0.032	
	(0.948)		(0.926)	
	[0.958]		[0.920]	
	{0.958}		{0.920}	
Behaviour proxy_14	-0.001		0.000	
	(0.857)		(0.962)	
	[0.880]		[0.972]	
	{0.878}		{0.972}	
R-squared	0.406		0.410	
N	1,560		1,560	
$\Delta\log(\Delta C)$_14	X		X	
$\log(\Delta C)$_14	X		X	
$\Delta\log(\Delta NC)$_14			X	
$\log(\Delta NC)$_14			X	
$\Delta\log(\Delta T)$	X		X	
province fixed effects	X		X	
cubic time trend	X		X	

Notes: The time period is March 11 - August 13. P-values from standard clustering by province in the ( ) parentheses, wild bootstrap with one-way clustering by province and 5000 repetitions in the [ ] square brackets, and wild bootstrap with two-way clustering by province and day with 5000 repetitions in the { } curly braces.

Table A10: Canada - Robustness (policy collinearity)

	Outcome: weekly case growth, $\Delta\log(\Delta C)$									
	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
	drop Mask_14		drop Business /gathering_14		drop School_14		drop Travel_14		drop LTC_14	
Mask_14			-0.621 ***	-0.614 ***	-0.588 ***	-0.592 ***	-0.635 ***	-0.636 ***	-0.618 ***	-0.614 ***
			[0.000]	[0.000]	[0.006]	[0.004]	[0.000]	[0.004]	[0.000]	[0.000]
Business/	-0.837 **	-0.847 **			-0.827 **	-0.847 **	-0.895 **	-0.909 **	-0.829 **	-0.837 **
gathering_14	[0.033]	[0.040]			[0.031]	[0.034]	[0.012]	[0.013]	[0.035]	[0.030]
School_14	-0.389 **	-0.406 **	-0.413 **	-0.434 **			-0.494 ***	-0.476 **	-0.419 **	-0.424 **
	[0.040]	[0.041]	[0.019]	[0.042]			[0.008]	[0.018]	[0.013]	[0.036]
Travel_14	-0.421	-0.472	-0.571	-0.623	-0.525	-0.502			-0.383	-0.422
	[0.548]	[0.566]	[0.378]	[0.411]	[0.445]	[0.556]			[0.544]	[0.562]
LTC_14	0.024	0.033	-0.075	-0.069	-0.041	-0.028	0.061	0.068		
	[0.961]	[0.908]	[0.842]	[0.848]	[0.918]	[0.926]	[0.850]	[0.821]		
Behaviour_14	-0.001	0.000	0.007	0.008	0.003	0.003	0.001	0.001	-0.002	0.000
	[0.883]	[0.982]	[0.527]	[0.338]	[0.767]	[0.704]	[0.826]	[0.814]	[0.856]	[0.930]
$\Delta\log(\Delta C)$_14	-0.074	-0.069	-0.059	-0.055	-0.084 *	-0.077	-0.089 **	-0.083 *	-0.078 *	-0.072
	[0.110]	[0.217]	[0.180]	[0.302]	[0.069]	[0.184]	[0.043]	[0.095]	[0.078]	[0.172]
$\log(\Delta C)$_14	-0.227 **	-0.228 *	-0.230 ***	-0.232 *	-0.227 **	-0.223	-0.214 ***	-0.211 **	-0.228 ***	-0.228 **
	[0.019]	[0.090]	[0.007]	[0.068]	[0.036]	[0.107]	[0.002]	[0.040]	[0.000]	[0.034]
$\Delta\log(\Delta NC)$_14		-0.122		-0.092		-0.071		-0.063		-0.106
		[0.572]		[0.659]		[0.755]		[0.820]		[0.642]
$\log(\Delta NC)$_14		0.080		0.083		-0.036		-0.022		0.054
		[0.743]		[0.742]		[0.893]		[0.932]		[0.823]
$\Delta\log(\Delta T)$	0.170 *	0.167 *	0.153 *	0.151	0.174 **	0.169 *	0.180 *	0.176 *	0.173 **	0.170 **
	[0.055]	[0.072]	[0.080]	[0.102]	[0.048]	[0.060]	[0.060]	[0.070]	[0.024]	[0.037]
R-squared	0.410	0.411	0.408	0.408	0.412	0.412	0.413	0.413	0.414	0.414
N	1,560	1,560	1,560	1,560	1,560	1,560	1,560	1,560	1,560	1,560
Province FE	X	X	X	X	X	X	X	X	X	X
Cubic in days	X	X	X	X	X	X	X	X	X	X

Notes: The time period is March 11 to August 13, 2020. P-values from wild bootstrap (cgmwildboot) standard errors clustered by province with 5000 repetitions are reported in the square brackets. We drop each policy one at a time in columns (3)-(12). ***, ** and * denote 10%, 5% and 1% significance level respectively.

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Table A11: Canada – Robustness (news and weather)

	Outcome: weekly case growth $\Delta\log(\Delta C)$					
	(1)	(2)	(3)	(4)	(5)	(6)
	baseline		add weather		add news	
Mask_14	-0.618 ***	-0.613 ***	-0.676 **	-0.666 **	-0.629 ***	-0.616 ***
	[0.000]	[0.000]	[0.020]	[0.026]	[0.000]	[0.002]
Business/ gathering_14	-0.835 **	-0.846 **	-0.903 *	-0.912 *	-0.884 **	-0.892 **
	[0.031]	[0.033]	[0.078]	[0.070]	[0.018]	[0.024]
School_14	-0.425 **	-0.433 **	-0.497 *	-0.528 *	-0.297	-0.292
	[0.015]	[0.019]	[0.068]	[0.085]	[0.205]	[0.111]
Travel_14	-0.375	-0.412	-0.242	-0.318	-0.302	-0.415
	[0.613]	[0.636]	[0.777]	[0.727]	[0.687]	[0.627]
Long-term care_14	0.023	0.032	0.052	0.063	0.043	0.056
	[0.958]	[0.920]	[0.908]	[0.884]	[0.900]	[0.881]
Behaviour proxy_14	-0.001	0.000	-0.002	-0.001	-0.001	0.002
	[0.880]	[0.972]	[0.868]	[0.962]	[0.918]	[0.814]
$\Delta\log(\Delta C)$_14	-0.078 *	-0.072	-0.083 *	-0.078	-0.071	-0.072
	[0.090]	[0.198]	[0.068]	[0.170]	[0.118]	[0.202]
$\log(\Delta C)$_14	-0.227 **	-0.227 *	-0.221 *	-0.224	-0.216 *	-0.221
	[0.019]	[0.090]	[0.054]	[0.120]	[0.090]	[0.110]
$\Delta\log(\Delta NC)$_14		-0.107		-0.136		-0.066
		[0.631]		[0.470]		[0.774]
$\log(\Delta NC)$_14		0.055		0.130		0.338
		[0.825]		[0.612]		[0.332]
$\Delta\log(\Delta T)$	0.172 **	0.169 *	0.189 **	0.187 *	0.161 *	0.158 *
	[0.043]	[0.056]	[0.033]	[0.052]	[0.064]	[0.078]
Rain_14			0.053	0.054		
			[0.189]	[0.177]		
Max temp_14			0.037	0.039		
			[0.434]	[0.389]		
Min temp_14			-0.031	-0.034		
			[0.562]	[0.519]		
News_14					-0.003	-0.007
					[0.278]	[0.103]
R-squared	0.414	0.414	0.419	0.419	0.415	0.416
N	1,560	1,560	1,560	1,560	1,560	1,560
Province FE	X	X	X	X	X	X
Cubic in days	X	X	X	X	X	X
Weather			X	X		
News					X	X

Notes: The time period is March 11 to August 13, 2020. P-values from wild bootstrap (cgmwildboot) standard errors clustered by province with 5000 repetitions are reported in the square brackets. Columns (1) and (2) repeat columns (3) and (4) from Table 2. Columns (3) and (4) report estimates with lagged weather variables as additional controls. Columns (5) and (6) add a "news" variable to the baseline specification (see Appendix C for more details). ***, ** and * denote 10%, 5% and 1% significance level respectively.

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Table A12: Self-reported Mask Usage ("Always" or "Frequently") – Canada

	Outcome: Wear mask "Always" or "Frequently"					
	(1)	(2)	(3)	(4)	(5)	(6)
	no time trend		cubic time trend		week fixed effects	
Mask	0.371 ***	0.354 ***	0.217 ***	0.215 ***	0.212 ***	0.211 ***
	[0.000]	[0.000]	[0.002]	[0.006]	[0.000]	[0.000]
$\Delta\log(\Delta C)$	-0.029	-0.015	-0.017 **	-0.015 *	-0.016 **	-0.019 **
	[0.503]	[0.164]	[0.032]	[0.086]	[0.047]	[0.021]
$\log(\Delta C)$	-0.037 *	0.028 ***	0.015 ***	0.015 **	0.016 ***	0.016 **
	[0.079]	[0.004]	[0.000]	[0.031]	[0.002]	[0.012]
$\Delta\log(\Delta NC)$		-0.158 **		-0.044		0.185
		[0.036]		[0.236]		[0.132]
$\log(\Delta NC)$		-0.148 ***		0.025		-0.024
		[0.000]		[0.582]		[0.907]
R-squared	0.132	0.162	0.173	0.173	0.174	0.175
N	8,859	8,859	8,859	8,859	8,859	8,859
mean wo mask mandates	0.464	0.464	0.464	0.464	0.464	0.464
individual characteristics	X	X	X	X	X	X
province fixed effects	X	X	X	X	X	X
cubic time trend (days)			X	X		
week fixed effects					X	X

Notes: The time period is April 2 to August 13, 2020. P-values from wild bootstrap (cgmwildboot) standard errors clustered by province with 5000 repetitions are reported in the square brackets. NC denotes national total cases. The data source is YouGov. The outcome is a dummy which takes one for the respondent who answers "Always" or "Frequently" to the survey question "Thinking about the last 7 days, how often have you worn a face mask outside your home?" Sample weights are used. Individual characteristics include a gender dummy, dummies for each age (in years), dummies for each household size, dummies for each number of children, and dummies for each employment status. ***, ** and * denote 10%, 5% and 1% significance level respectively.

Table A13: Self-reported precautions – Canada

	Outcome: "Always" response							
	(1) wash hands	(2) use sanitizer	(3) avoid going out in general	(4) avoid small gatherings	(5) avoid medium gatherings	(6) avoid large gatherings	(7) avoid crowded areas	(8) avoid touching objects
Mask	-0.013	-0.013	0.014	0.047	0.015	0.058	0.083 *	0.030
	[0.560]	[0.864]	[0.452]	[0.122]	[0.766]	[0.386]	[0.069]	[0.417]
$\Delta\log(\Delta C)$	0.006	0.006	0.003	0.002	0.011	0.007	0.021 **	-0.003
	[0.348]	[0.512]	[0.607]	[0.914]	[0.385]	[0.562]	[0.016]	[0.748]
$\log(\Delta C)$	-0.011 *	-0.005	0.013 **	0.019 *	0.011	0.011	0.011	0.011
	[0.071]	[0.523]	[0.021]	[0.056]	[0.556]	[0.348]	[0.388]	[0.162]
$\Delta\log(\Delta NC)$	-0.031	-0.025	-0.028	0.069 ***	-0.012	0.008	-0.030	-0.038
	[0.333]	[0.518]	[0.420]	[0.000]	[0.740]	[0.726]	[0.296]	[0.264]
$\log(\Delta NC)$	0.063 ***	0.066	-0.014	-0.012	0.043	0.004	0.051	0.033
	[0.002]	[0.256]	[0.725]	[0.806]	[0.461]	[0.937]	[0.424]	[0.525]
R-squared	0.045	0.049	0.048	0.133	0.146	0.126	0.081	0.042
N	8,859	8,859	8,859	8,859	8,859	8,859	8,859	8,859
individual characteristics	X	X	X	X	X	X	X	X
province FE	X	X	X	X	X	X	X	X
cubic trend (in days)	X	X	X	X	X	X	X	X
average w/o mask mandate	0.719	0.477	0.274	0.470	0.601	0.770	0.654	0.491
survey item # (i12_)	health_2	health_3	health_6	health_12	health_13	health_14	health_15	health_20

Notes: The time period is April 2 to August 13, 2020. P-values from wild bootstrap (cgmwildboot) standard errors clustered by province with 5000 repetitions are reported in the square brackets. NC denotes national total cases. The data source is YouGov. The outcome is a dummy which takes value 1 if the respondent answered "Always" to each survey question listed in Table C4. Sample weights are used. Individual characteristics include a gender dummy, age dummy (in years), dummies for each household size, dummies for each number of children, and dummies for each employment status. ***, ** and * denote 10%, 5% and 1% significance level respectively.

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Table A14: Self-reported precautions – Canada (continued)

	Outcome: "Always" or "Frequently" response							
	(1) wash hands	(2) use sanitizer	(3) avoid going out in general	(4) avoid small gatherings	(5) avoid medium gatherings	(6) avoid large gatherings	(7) avoid crowded areas	(8) avoid touching objects
Mask	-0.005	0.003	0.035	0.046	0.009	0.050	0.074 ***	0.016
	[0.858]	[0.899]	[0.272]	[0.192]	[0.869]	[0.140]	[0.009]	[0.717]
$\Delta\log(\Delta C)$	-0.001	0.002	-0.006	-0.010	-0.004	-0.005	0.006	-0.005
	[0.716]	[0.775]	[0.568]	[0.167]	[0.688]	[0.614]	[0.291]	[0.666]
$\log(\Delta C)$	0.000	-0.004	0.018 ***	0.017 ***	0.012	0.005	0.009	-0.001
	[0.938]	[0.596]	[0.000]	[0.000]	[0.168]	[0.536]	[0.288]	[0.760]
$\Delta\log(\Delta NC)$	-0.004	-0.004	-0.094	-0.089	-0.075 *	0.038	0.001	-0.047
	[0.912]	[0.933]	[0.265]	[0.102]	[0.072]	[0.382]	[0.963]	[0.052]
$\log(\Delta NC)$	0.011	0.074	0.029	0.073	0.100 *	0.002	-0.001	0.056
	[0.578]	[0.177]	[0.533]	[0.285]	[0.085]	[0.972]	[0.998]	[0.092]
R-squared	0.076	0.050	0.074	0.109	0.101	0.089	0.079	0.046
N	8,859	8,859	8,859	8,859	8,859	8,859	8,859	8,859
individual characteristics	X	X	X	X	X	X	X	X
province FE	X	X	X	X	X	X	X	X
cubic trend (in days)	X	X	X	X	X	X	X	X
average wo mask mandate	0.929	0.755	0.629	0.696	0.777	0.869	0.859	0.796
survey item # (i12_)	health_2	health_3	health_6	health_12	health_13	health_14	health_15	health_20

Notes: The time period is April 2 to August 13, 2020. P-values from wild bootstrap (cgmwildboot) standard errors clustered by province with 5000 repetitions are reported in the square brackets. NC denotes national total cases. The data source is YouGov. The outcome is a dummy which takes value 1 if the respondent answered "Always" or "Frequently" to each survey question in Table C4. Sample weights are used. Individual characteristics include a gender dummy, age dummy (in years), dummies for each household size, dummies for each number of children, and dummies for each employment status. ***, ** and * denote 10%, 5% and 1% significance level respectively.

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Table A15: Canada – Closing vs. Re-opening Sub-periods

	Outcome: weekly case growth $\Delta\log(\Delta C)$			
	Closing: March 11 - May 14		Re-opening: May 15 - August 13	
	(1)	(2)	(3)	(4)
Mask_14	n.a.	n.a.	-0.788 *	-0.797 *
	n.a.	n.a.	[0.070]	[0.056]
Business/gathering_14	-0.045	-0.095	-1.115 **	-1.148 *
	[0.914]	[0.874]	[0.038]	[0.056]
School_14	-0.998 ***	-1.041 ***	0.005	-0.016
	[0.000]	[0.000]	[1.000]	[0.939]
Travel_14	-2.433 ***	-2.623 ***	0.910	0.929
	[0.000]	[0.000]	[0.351]	[0.376]
Long-term care_14	-0.803 ***	-0.906 **	-0.260	-0.264
	[0.006]	[0.010]	[0.578]	[0.563]
Behaviour proxy_14	-0.036 *	-0.034	-0.012	-0.013
	[0.087]	[0.139]	[0.841]	[0.834]
$\Delta\log(\Delta C)$_14	0.075	0.076	-0.156	-0.157
	[0.184]	[0.250]	[0.105]	[0.136]
$\log(\Delta C)$_14	-0.399 ***	-0.413 ***	-0.221	-0.221
	[0.000]	[0.000]	[0.148]	[0.161]
$\Delta\log(\Delta NC)$_14		-0.120		-0.346
		[0.535]		[0.709]
$\log(\Delta NC)$_14		0.285		0.494
		[0.312]		[0.657]
$\Delta\log(\Delta T)$	0.110	0.099	0.233	0.261
	[0.256]	[0.299]	[0.479]	[0.423]
R-squared	0.689	0.689	0.169	0.170
N	650	650	910	910
province fixed effects	X	X	X	X
cubic time trend (days)	X	X	X	X

Notes: P-values from wild bootstrap (cgmwildboot) standard errors clustered by province with 5000 repetitions are reported in the square brackets. ***, ** and * denote 10%, 5% and 1% significance level respectively. NC denotes national total cases. No mask mandates are present in the closing period.

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Table A16: Canada – Deaths growth (treatment of zero weekly deaths)

	Outcome: weekly deaths growth $\Delta\log(\Delta D)$					
	(1)	(2)	(3)	(4)	(5)	(6)
	baseline		4 largest provinces		population weighted	
Mask_28	-0.922 **	-0.983 **	0.139	0.009	-0.260	-0.480
	[0.022]	[0.032]	[0.762]	[0.762]	[0.592]	[0.488]
Business/gathering_28	-0.134	-0.224	-2.067 ***	-2.277 ***	-1.300	-1.442
	[0.762]	[0.748]	[0.000]	[0.000]	[0.102]	[0.106]
School_28	0.441	0.440	0.599	0.601	0.355	0.371
	[0.317]	[0.341]	[0.381]	[0.255]	[0.500]	[0.557]
Travel_28	-0.005	-0.027	1.645	2.101	0.906	0.741
	[0.972]	[0.935]	[0.259]	[0.244]	[0.216]	[0.405]
Long-term care_28	-0.035	-0.036	-0.024	-0.088	-0.053	-0.056
	[0.900]	[0.900]	[0.878]	[0.762]	[0.896]	[0.808]
Behaviour proxy_28	0.002	0.003	-0.012	-0.001	-0.009	-0.001
	[0.815]	[0.737]	[0.244]	[0.861]	[0.500]	[0.958]
$\Delta\log(\Delta D)$_28	0.141	0.152	-0.037 ***	0.006	0.010	0.065
	[0.361]	[0.345]	[0.000]	[0.599]	[0.818]	[0.344]
$\log(\Delta D)$_28	-0.216 ***	-0.220 ***	-0.139	-0.164	-0.164 *	-0.181
	[0.000]	[0.000]	[0.381]	[0.253]	[0.056]	[0.100]
$\Delta\log(\Delta ND)$_28		-0.121		-0.197		-0.262 *
		[0.476]		[0.244]		[0.065]
$\log(\Delta ND)$_28		0.018		0.203		0.147
		[0.858]		[0.125]		[0.448]
$\Delta\log(\Delta T)$	-0.038	-0.051	0.194 ***	0.125	0.176	0.130
	[0.758]	[0.735]	[0.000]	[0.255]	[0.050]	[0.124]
R-squared	0.251	0.254	0.474	0.480	0.496	0.507
N	1,470	1,470	588	588	1,470	1,470
Province FE	X	X	X	X	X	X
cubic time trend (days)	X	X	X	X	X	X
population weighted	No	No	Yes	Yes	No	No

Notes: The time period is March 11 to August 13, 2020. P-values from wild bootstrap (cgmwildboot) standard errors clustered by province with 5000 repetitions are reported in the square brackets. Columns (1) and (2) repeat columns (3) and (4) from Table 4. Columns (3) and (4) report results from a weighted least squares regression with the province populations used as weights. Columns (5) and (6) restrict the sample to only the largest 4 provinces (BC, ON, QC, and AB) with only 5% (29 out of 588) observations with zero weekly deaths. ***, ** and * denote 10%, 5% and 1% significance level respectively. ND denotes national total deaths.

Table A17: Canada - Correlations between the policy indicators

Policy	indicator	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17
Mask	P1. mandatory indoor masks	1																
	P2. non-essential business/retail	-0.11	1															
	P3. personal services	-0.18	0.67	1														
	P4. restaurants	-0.14	0.64	0.83	1													
Business/	P5. bars/nightclubs	-0.14	0.55	0.75	0.84	1												
gathering	P6. religious worship	-0.05	0.66	0.76	0.80	0.77	1											
	P7. events gathering	-0.07	0.65	0.81	0.84	0.76	0.79	1										
	P8. recreation/parks/gyms	-0.17	0.74	0.78	0.78	0.73	0.75	0.81	1									
	P9. gathering maximum index	-0.02	0.56	0.70	0.72	0.71	0.79	0.76	0.64	1								
School	P10. no school	0.05	0.18	0.27	0.26	0.41	0.27	0.42	0.20	0.51	1							
	P11. travel ban international	0.04	0.16	0.27	0.26	0.43	0.34	0.41	0.16	0.57	0.77	1						
Travel	P12. travel ban domestic	-0.09	0.09	0.07	-0.02	0.14	0.04	-0.01	0.06	0.15	0.15	0.14	1					
	P13. self-isolation international	0.04	0.16	0.27	0.23	0.38	0.30	0.40	0.13	0.53	0.72	0.86	0.15	1				
	P14. self-isolation domestic	-0.14	0.12	0.20	0.07	0.19	0.21	0.06	0.07	0.26	0.24	0.23	0.63	0.23	1			
LTC	P15. LTC visits	-0.16	0.40	0.56	0.58	0.59	0.54	0.57	0.48	0.54	0.35	0.35	0.13	0.32	0.33	1		
	P16. LTC single site	0.05	-0.23	-0.17	-0.08	-0.13	-0.20	-0.05	-0.20	-0.03	0.18	0.25	-0.15	0.26	-0.23	-0.06	1	
	P17. provincial emergency	-0.07	0.21	0.33	0.39	0.56	0.44	0.42	0.30	0.51	0.55	0.63	0.16	0.57	0.26	0.40	0.01	1

Notes: The time period is Feb 26 to July 30 (two weeks before the March 11 - August 13 sample period). Daily province-level data.

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Table A18: Canada – Location behaviour and policies

	Outcome: location behaviour							
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
	Retail		Grocery		Workplaces		Behaviour proxy, B_{it}	
Mask	-4.204	-4.175	-0.670	-0.810	-0.385	-0.403	-1.753	-1.796
	[0.440]	[0.429]	[0.814]	[0.770]	[0.806]	[0.795]	[0.563]	[0.514]
Business/gathering	-18.959 *	-14.359 *	-12.243 **	-8.640	-12.110 *	-7.636	-14.437 **	-10.212
	[0.055]	[0.092]	[0.044]	[0.153]	[0.084]	[0.195]	[0.049]	[0.150]
School	-16.524 **	-8.927	-7.111 **	-1.894	-24.795 ***	-17.613 **	-16.143 ***	-9.478
	[0.020]	[0.297]	[0.013]	[0.663]	[0.004]	[0.028]	[0.003]	[0.114]
Travel	-15.648	-10.505	-18.913 ***	-13.735 **	-7.354	-2.029	-13.971 *	-8.756
	[0.162]	[0.340]	[0.000]	[0.019]	[0.174]	[0.607]	[0.058]	[0.223]
Long-term care	0.131	-0.717	-0.237	-1.088	-1.987	-2.864 *	-0.698	-1.556
	[0.980]	[0.914]	[0.960]	[0.768]	[0.480]	[0.079]	[0.873]	[0.610]
$\Delta\log(\Delta C)$	1.614 **	1.235 *	1.905 ***	1.397 ***	1.134 *	0.707	1.551 ***	1.113 **
	[0.023]	[0.051]	[0.000]	[0.004]	[0.075]	[0.132]	[0.004]	[0.034]
$\log(\Delta C)$	-2.545 ***	-2.062 ***	-1.935 ***	-1.537 ***	-1.387 **	-0.912 *	-1.956 ***	-1.504 ***
	[0.005]	[0.000]	[0.007]	[0.006]	[0.013]	[0.075]	[0.007]	[0.000]
$\Delta\log(\Delta NC)$		5.462 **		8.543 ***		6.511 ***		6.839 ***
		[0.034]		[0.000]		[0.000]		[0.000]
$\log(\Delta NC)$		-9.372 ***		-7.206 **		-9.076 ***		-8.551 ***
		[0.004]		[0.018]		[0.000]		[0.000]
R-squared	0.935	0.942	0.866	0.880	0.910	0.925	0.927	0.938
N	1,560	1,560	1,560	1,560	1,560	1,560	1,560	1,560
province fixed effects	X	X	X	X	X	X	X	X
cubic time trend (days)	X	X	X	X	X	X	X	X

Notes: The time period is March 11 to August 13, 2020. P-values from wild bootstrap (cgmwildboot) standard errors clustered by province with 5000 repetitions are reported in the square brackets. The behaviour proxy B_{it} in columns (7) and (8) is the unweighted average of the "retail", "grocery" and "workplaces" Google mobility indices. ***, ** and * denote 10%, 5% and 1% significance level respectively. NC denotes national total cases.

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Table A19: Ontario – Policies and information only

	Outcome: weekly case growth $\Delta\log(\Delta C)$					
	(1)	(2)	(3)	(4)	(5)	(6)
	no time trend		cubic time trend		week fixed effects	
Mask_14	-0.228 *	-0.286 **	-0.333 **	-0.341 **	-0.286 **	-0.298 **
	[0.050]	[0.036]	[0.025]	[0.025]	[0.036]	[0.028]
Business/gathering_14	0.041	0.132	0.039	0.512	0.128	0.256
	[0.816]	[0.710]	[0.937]	[0.437]	[0.824]	[0.670]
Long-term care_14	0.467	0.366	0.799	-0.240	-1.022	-2.033 *
	[0.570]	[0.670]	[0.653]	[0.856]	[0.393]	[0.099]
$\Delta\log(\Delta C)$_14	0.028	0.026	0.027	0.030	0.014	0.014
	[0.645]	[0.682]	[0.676]	[0.652]	[0.804]	[0.825]
$\log(\Delta C)$_14	-0.198 ***	-0.202 ***	-0.200 ***	-0.207 ***	-0.195 ***	-0.198 ***
	[0.002]	[0.001]	[0.001]	[0.000]	[0.001]	[0.001]
$\Delta\log(\Delta PC)$_14		0.391		0.260		0.572 **
		[0.170]		[0.401]		[0.038]
$\log(\Delta PC)$_14		-0.045		0.462		0.128
		[0.841]		[0.168]		[0.712]
$\Delta\log(\Delta T)$	-0.363 **	-0.481 **	-0.209	-0.343	-0.194	-0.464
	[0.050]	[0.028]	[0.381]	[0.169]	[0.564]	[0.144]
R-squared	0.046	0.050	0.051	0.058	0.091	0.094
N	3,094	3,094	3,094	3,094	3,094	3,094
public health unit FE	X	X	X	X	X	X
cubic time trend (days)			X	X		
week fixed effects					X	X

Notes: The time period is May 15 to August 13, 2020. P-values from wild bootstrap (cgmwildboot) standard errors clustered by public health unit (PHU) with 5000 repetitions are reported in the square brackets. ***, ** and * denote 10%, 5% and 1% significance level respectively.

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Table A20: Canada – Policy and Information only

	Outcome: weekly case growth, $\Delta\log(\Delta C)$					
	(1)	(2)	(3)	(4)	(5)	(6)
	no time trend		cubic time trend		week fixed effects	
Mask_14	-0.413 ***	-0.416 ***	-0.629 ***	-0.618 ***	-0.567 ***	-0.561 ***
	[0.000]	[0.000]	[0.000]	[0.002]	[0.000]	[0.004]
Business /gathering_14	-0.288	-0.425	-0.665	-0.716 **	-0.500	-0.579
	[0.112]	[0.165]	[0.103]	[0.032]	[0.138]	[0.112]
School_14	-0.244	-0.381	-0.431	-0.443 *	-0.250	-0.353
	[0.461]	[0.334]	[0.144]	[0.066]	[0.258]	[0.137]
Travel_14	-0.509	-0.794	-0.293	-0.368	-0.430	-0.592
	[0.270]	[0.106]	[0.579]	[0.580]	[0.612]	[0.481]
Long-term care_14	-0.100	-0.193	0.027	0.037	0.081	0.064
	[0.67]	[0.494]	[0.917]	[0.904]	[0.805]	[0.849]
$\Delta\log(\Delta C)$_14	-0.024	-0.010	-0.040	-0.026	-0.017	-0.015
	[0.56]	[0.824]	[0.385]	[0.555]	[0.772]	[0.797]
$\log(\Delta C)$_14	-0.182 ***	-0.208 ***	-0.197 ***	-0.200 **	-0.201 *	-0.214 *
	[0.000]	[0.000]	[0.000]	[0.01]	[0.064]	[0.067]
$\Delta\log(\Delta NC)$_14		-0.073		-0.221		-0.106
		[0.636]		[0.291]		[0.581]
$\log(\Delta NC)$_14		0.121		0.012		0.281 *
		[0.359]		[0.938]		[0.090]
$\Delta\log(\Delta T)$	0.139	0.187 *	0.185 *	0.176 *	0.155	0.162 *
	[0.107]	[0.052]	[0.069]	[0.080]	[0.131]	[0.100]
R-squared	0.382	0.386	0.391	0.393	0.414	0.416
N	1,560	1,560	1,560	1,560	1,560	1,560
province fixed effects	X	X	X	X	X	X
cubic time trend (days)			X	X		
week fixed effects					X	X

Notes: The time period is March 11 to August 13, 2020. P-values from wild bootstrap (cgmwildboot) standard errors clustered by province with 5000 repetitions are reported in the square brackets. ***, ** and * denote 10%, 5% and 1% significance level respectively.

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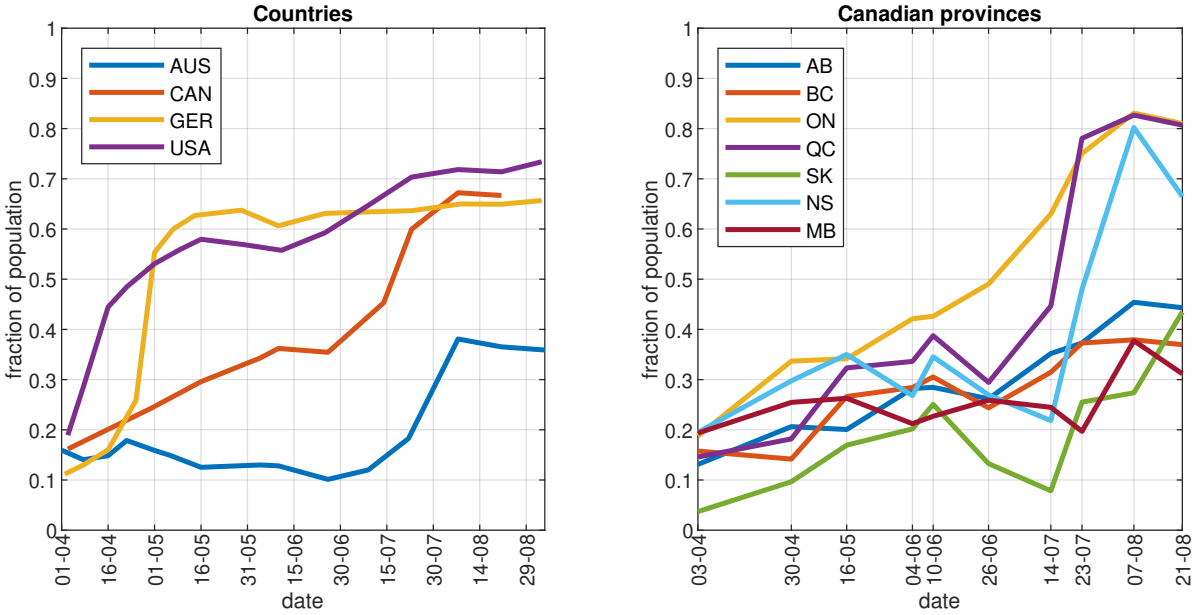
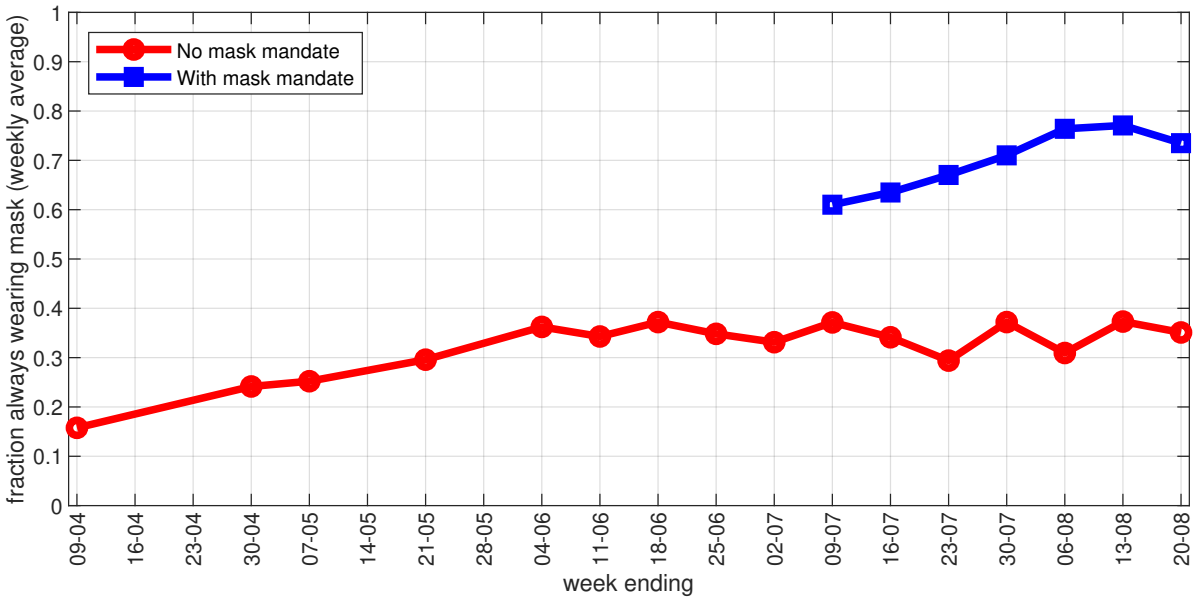
Appendix B. Additional Figures

Figure B1: Self-reported mask usage in selected countries and Canadian provinces



Notes: The data source is YouGov. The outcome equals 1 if the respondent answered "Always" to the question "Worn a face mask outside your home" and 0 otherwise. The sample weights are used to construct the country and provincial averages.

Figure B2: Canada - mask mandates and self-reported mask usage



Notes: The data source is YouGov. The figure plots the average self-reported mask usage by week (the fraction of respondents who answered "Always" to the survey question "Worn a face mask outside your home") in the provinces with vs. without mask mandates. Sample weights used to compute the averages.

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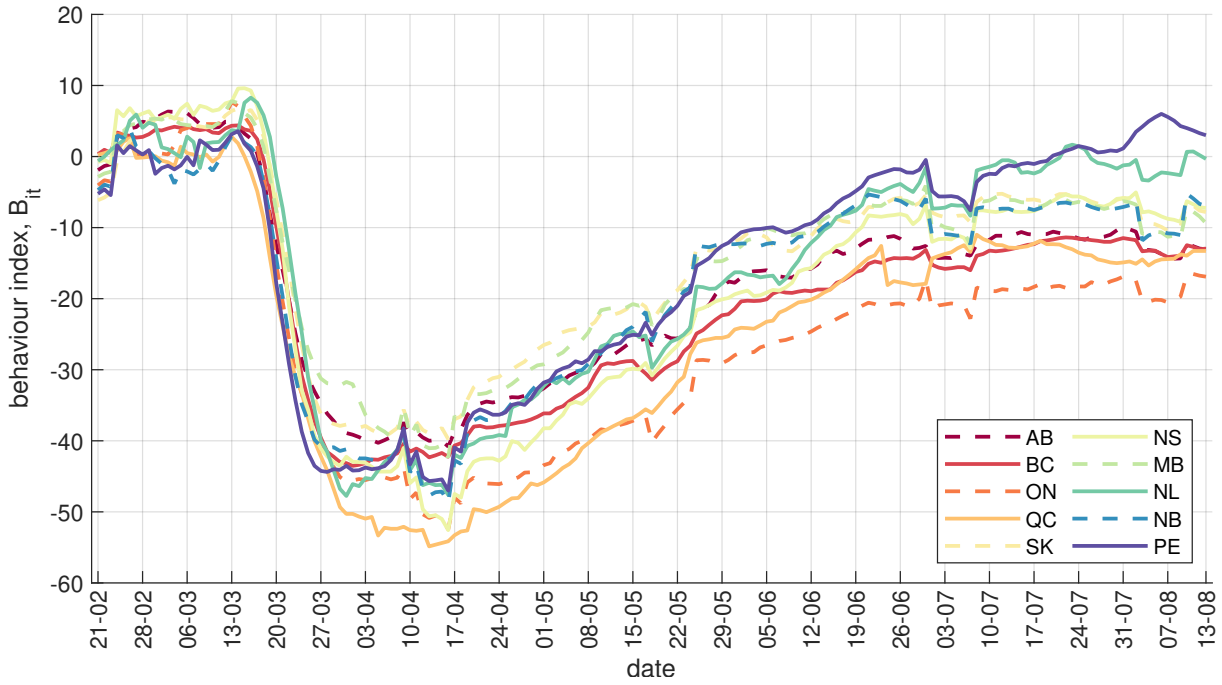
Figure B3: Canada - Behaviour proxy, B_{it}



Notes: The Behaviour proxy B_{it} is the average of the "retail", "grocery and pharmacy", and "workplaces" Google mobility indicators. Province-level 7-day moving averages are plotted.

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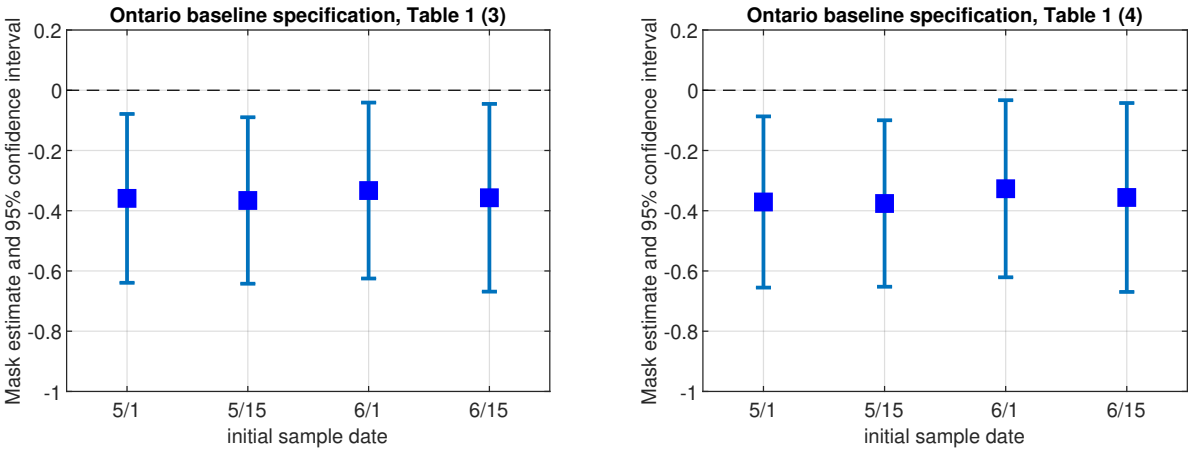
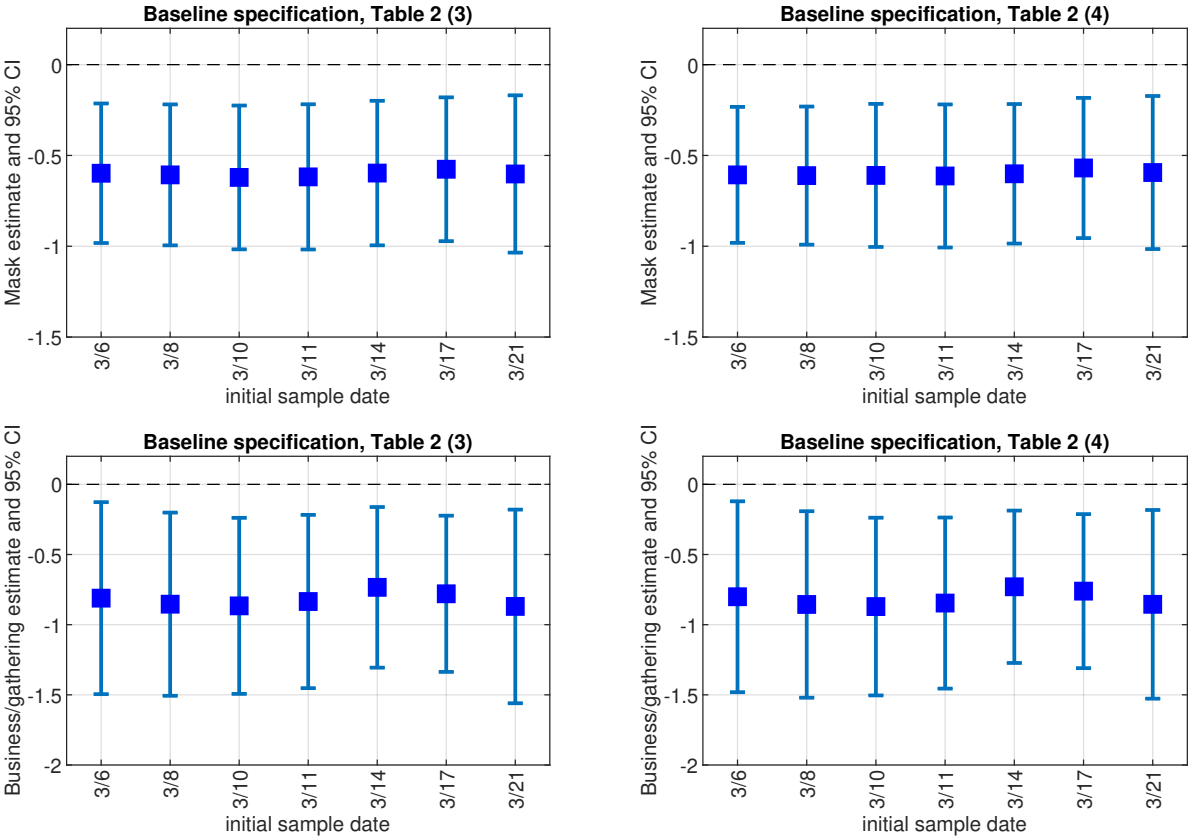
Figure B4: Ontario - different initial dates



Notes: We plot the coefficient estimates on mask policy, with 95% confidence intervals, from equation (1), for different initial dates of the sample. The initial sample date in the baseline specifications reported in Table 1 is May 15. The left panel corresponds to baseline column (3) in Table 1, the right column corresponds to column (4) in Table 1.

Figure B5: Canada - different initial dates



Notes: We plot the coefficient estimates on mask policy, with 95% confidence intervals, in the upper panel and the estimates on business/gathering policy in the lower panel, from equation (1) for different initial dates of the sample. The initial date in our baseline specification (Table 2) is March 11. The left panels correspond to column (3) in Table 2; the right panels correspond to column (4) in Table 2.

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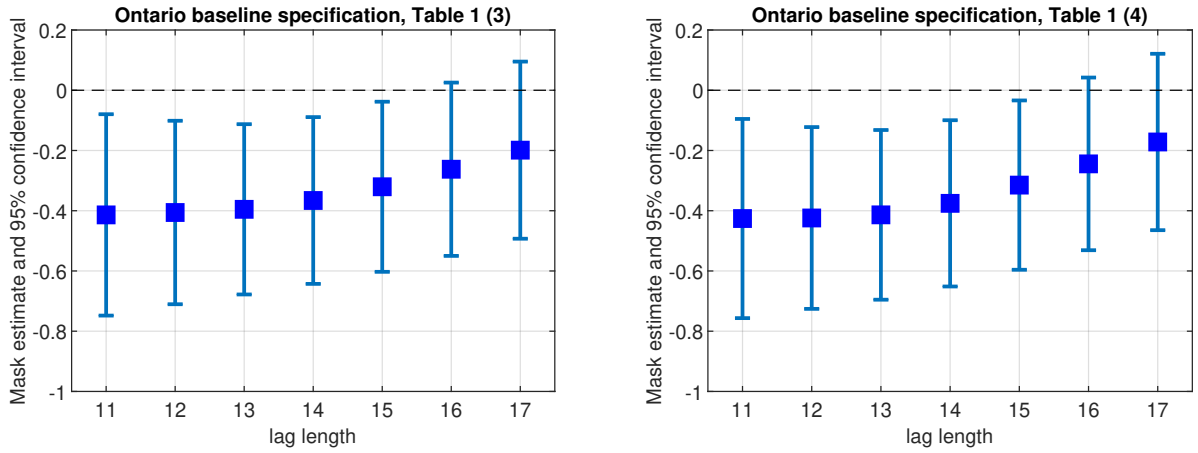
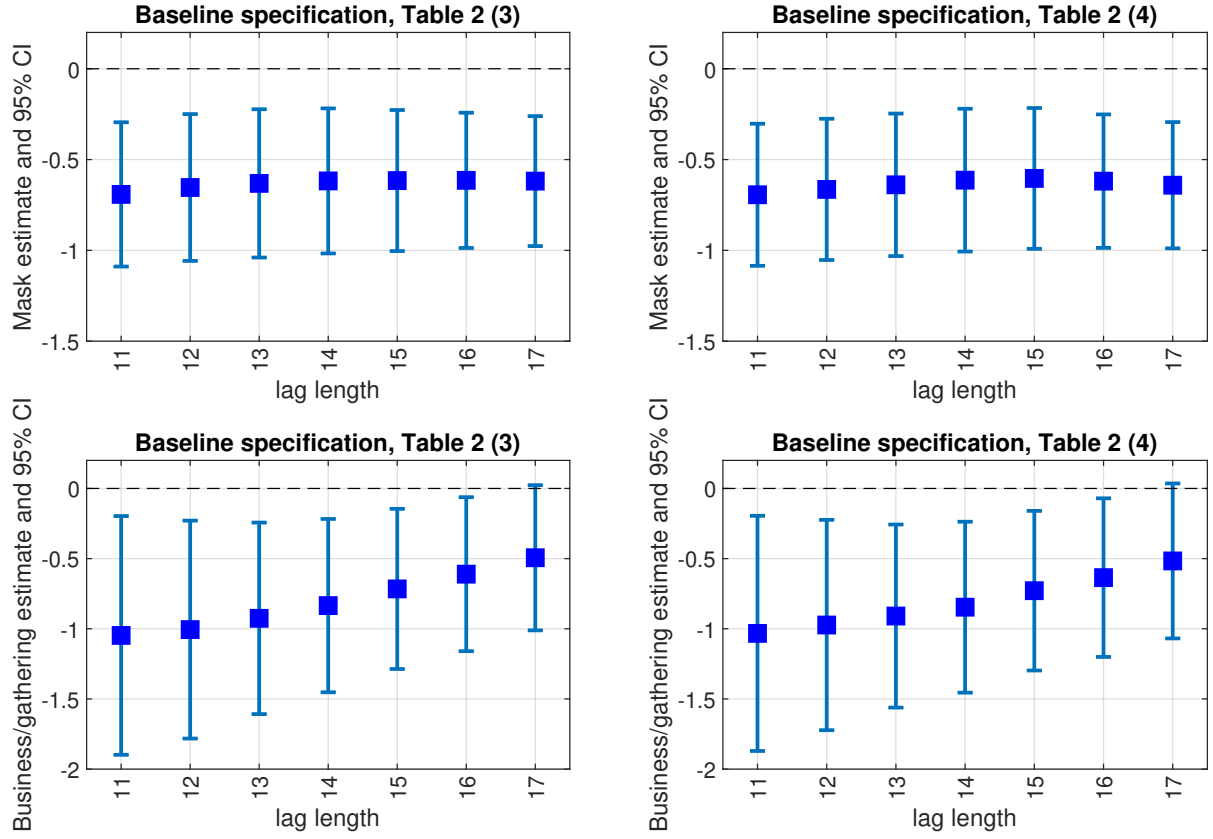
Figure B6: Ontario - different lags



Notes: We plot the coefficient estimates on mask policy, with 95% confidence intervals, in equation (1) for different lag values. The lag used in the baseline specifications in Table 1 is 14 days. The left panel corresponds to column (3) in Table 1, the right column corresponds to column (4) in Table 1.

Figure B7: Canada - different lags



Notes: We plot the estimates on mask policy in the upper panel and the business/gathering policy in the lower panel, in equation (1) for different lag values. The lag in our baseline specification (Table 2) is 14 days. The left panels correspond to column (3) in Table 2; the right panels correspond to column (4) in Table 2.

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Figure B8: Canada – Weekly cases, deaths and tests (growth rate)

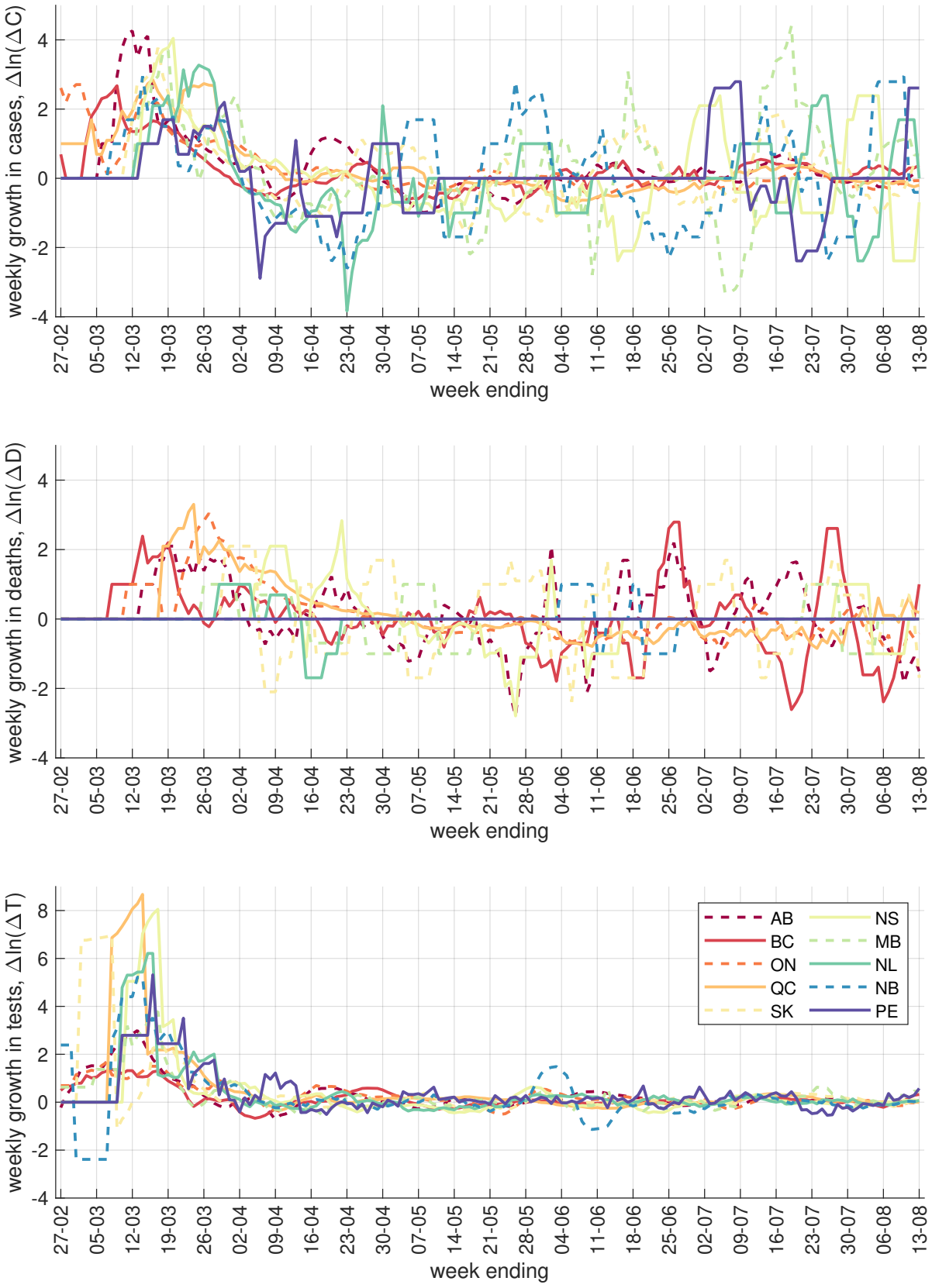

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Figure B9: Canada – Weekly cases, deaths and tests (level)

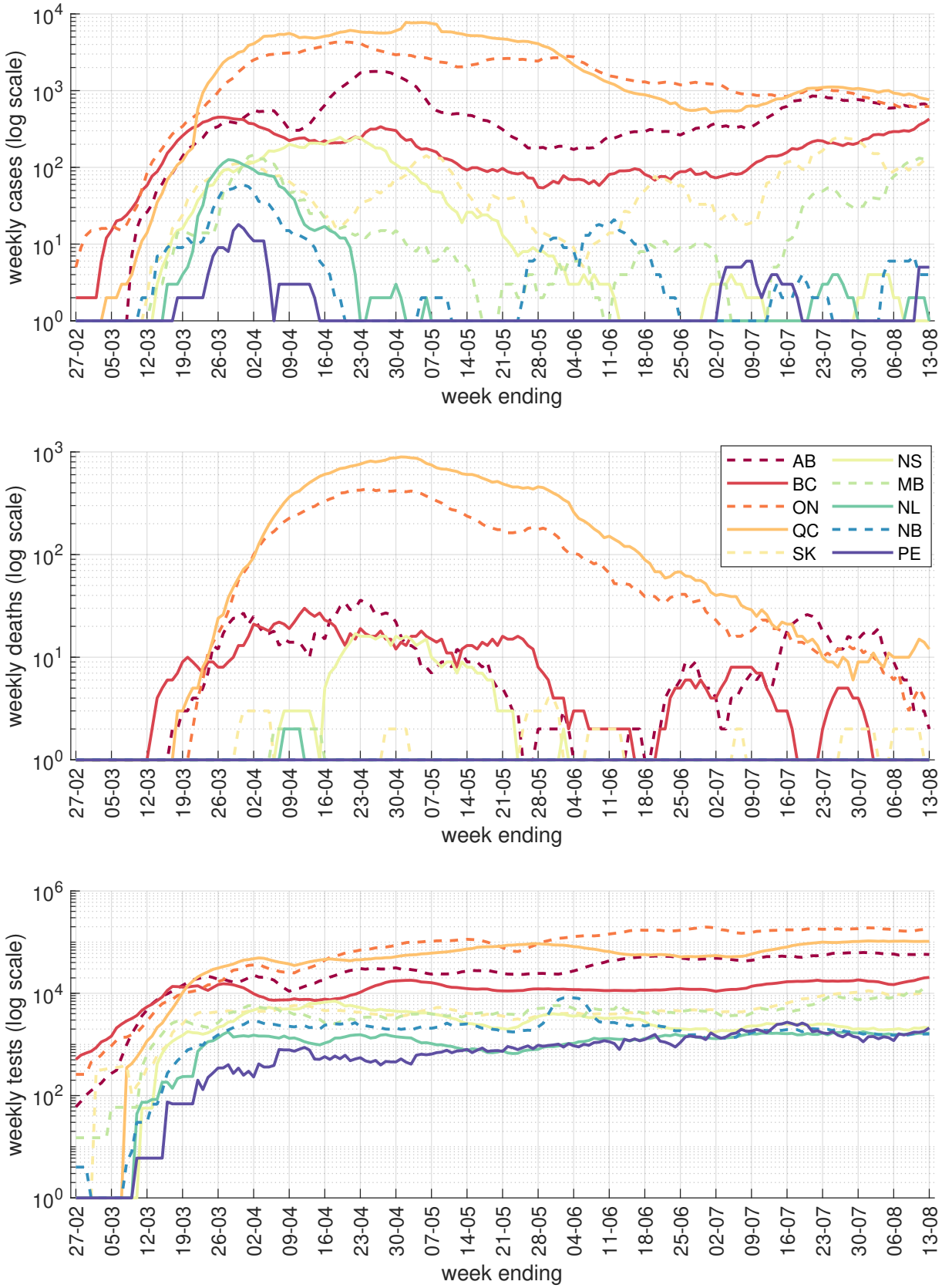

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Figure B10: Canada – Daily cases, deaths and tests

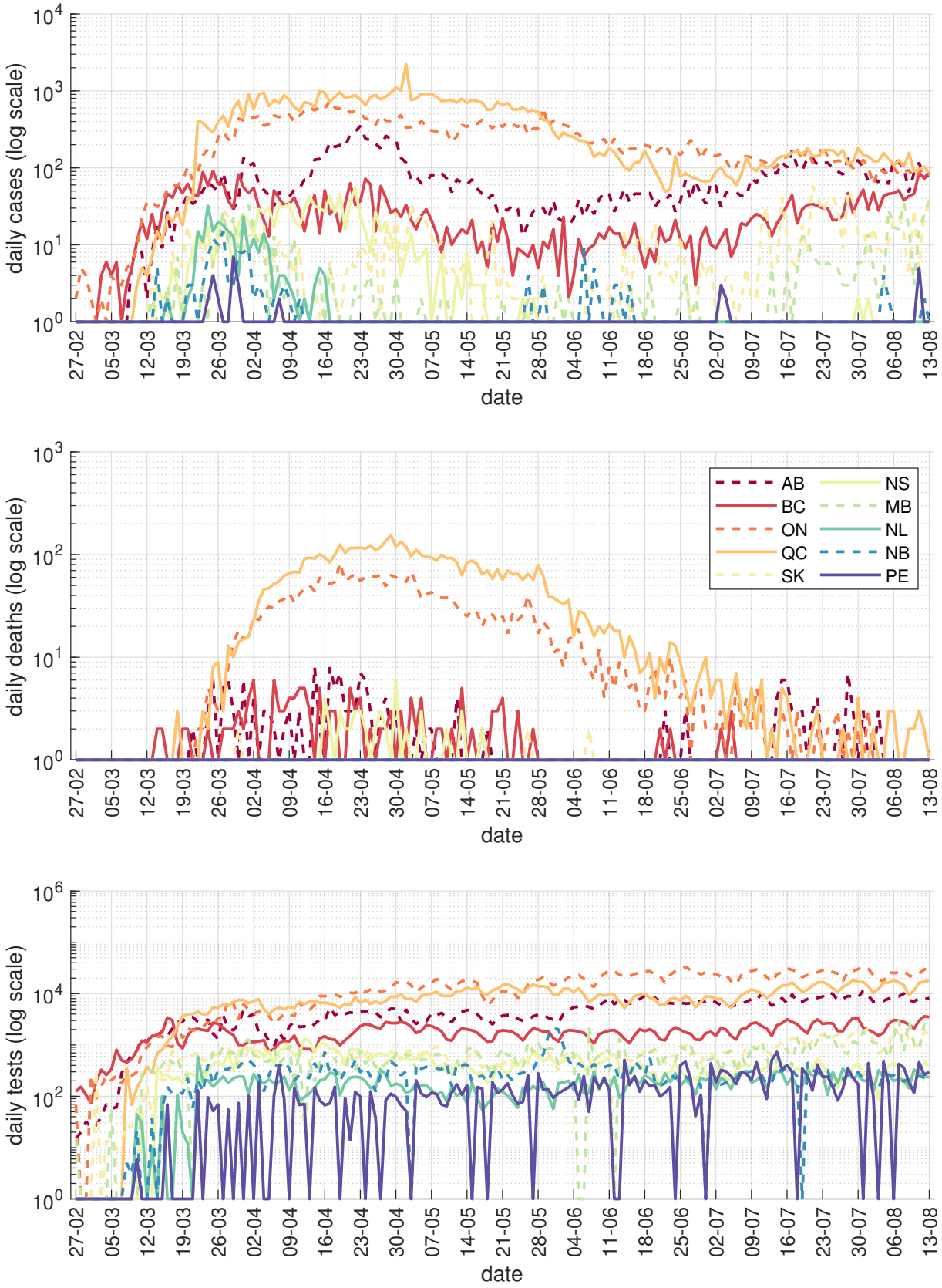

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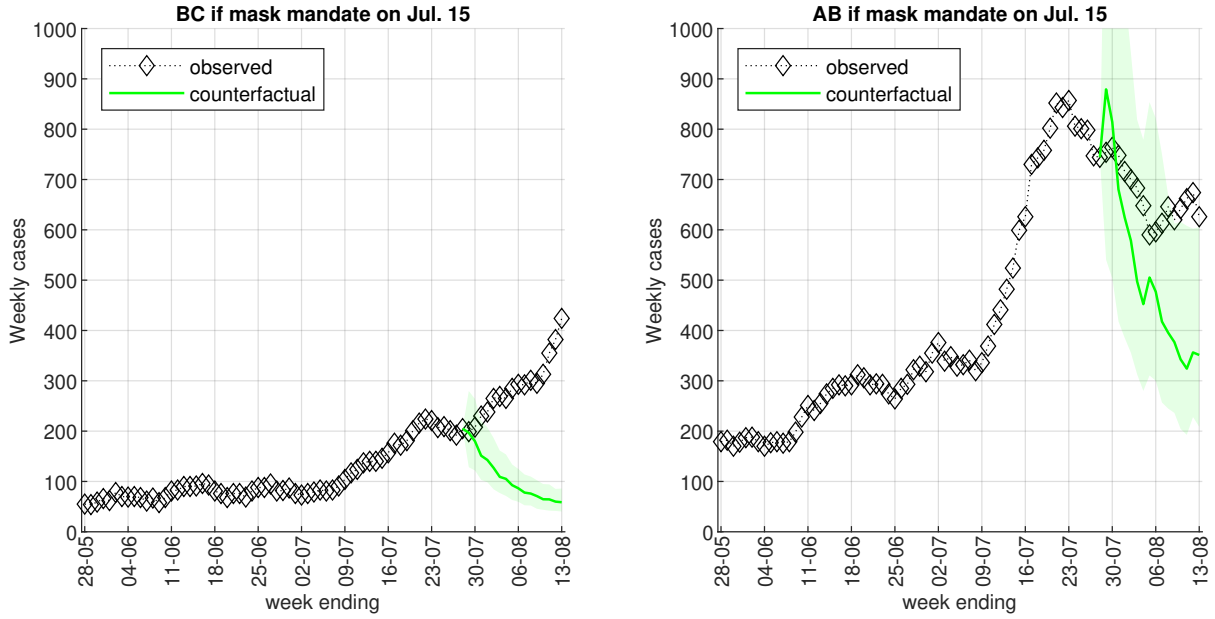
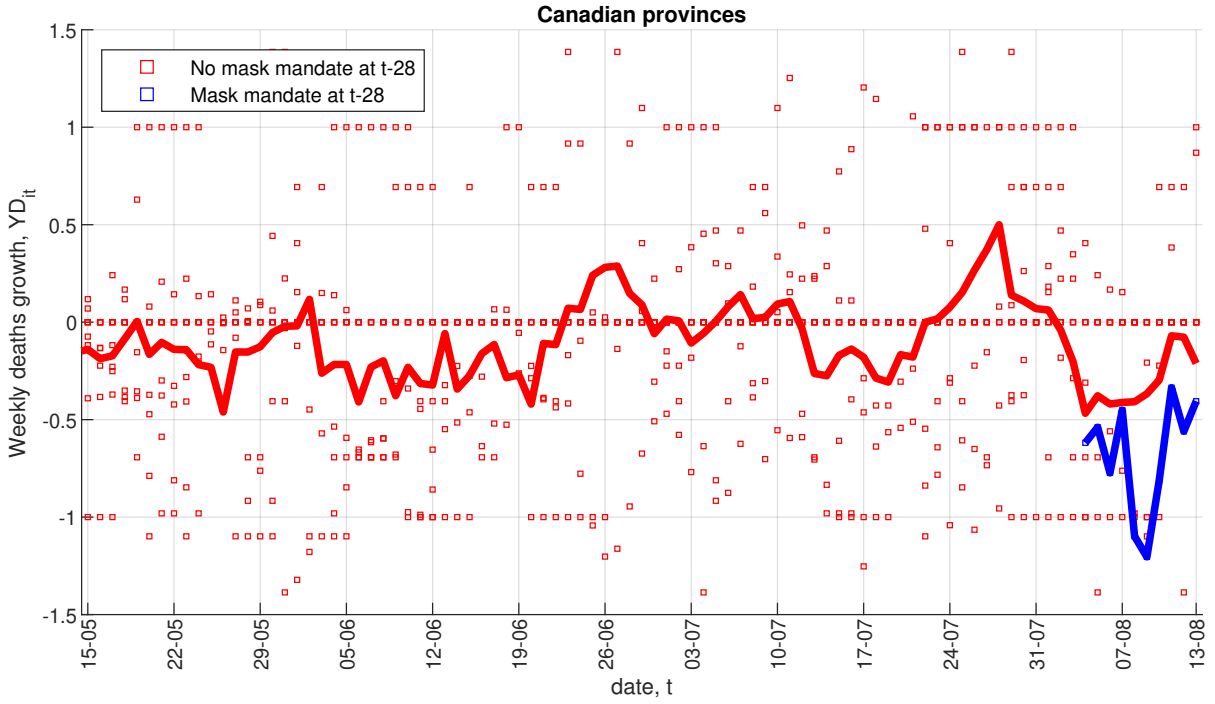
Figure B11: Counterfactuals – Mask mandates in Alberta and British Columbia



Notes: The figure assumes mask adoption on July 15 for two provinces that have not yet adopted mask mandates, specifically British Columbia (BC, left panel) and Alberta (AB, right panel). The counterfactual uses the mask mandate estimate -0.613 from Table 2, column (4).

Figure B12: Canada - mask mandates and weekly deaths growth



Notes: Average log weekly death growth in provinces with vs. without mask mandates 28 days prior.

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Appendix C. Definitions and data sources

Table C1: Policy indicators and aggregates

Non-Essential Travel	
restrictions - international	1: travelers that are neither citizens nor residents 0.5: same as 1, but US citizens allowed
restrictions - inter-provincial	1: residents of all other provinces 0.5: residents of some other provinces
self-isolation - international	1: required (by provincial or federal government) 0.5: recommended (by provincial or federal government)
self-isolation - inter-provincial	1: required of residents of all other provinces 0.5: required of residents of some other provinces, or recommended
Primary and Secondary Schools	
schools closed	1: no classes (includes Spring and Summer breaks) 0.5: part-time classes; 0: classes in session
Business and Gathering Regulations	
non-essential and retail business personal services business restaurants bars and nightclubs places of worship events and gatherings recreation, gyms and parks	0: no or lowest restrictions; 1: strictest restrictions; values between 0 and 1: partial restrictions
indoor gatherings maximum	1: no gathering allowed; $x \in [0.5, 1]$: limit of $100(1-x)$ $x \in [0, 0.5]$: limit of $25/x$
Long-Term Care (LTC) Regulations	
visiting restrictions	1: no visits (with limited exceptions such as end of life) 0.5: number of visitors restricted
single-site work requirement[1]	1: requirement in effect 0.5: requirement with explicit later implementation deadline
Mandatory Masks	
indoor public places[2]	1: mask mandate in effect; 0: no mandate
provincial declaration of emergency	1: in effect; 0: not in effect

Notes: 1. We do not consider recommendations or requirements limited to outbreak facilities. 2. We do not consider limited mask mandates such as applying only to transit or personal service establishments.

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Table C2: Ontario public health regions and date of mask mandate

1	Algoma Public Health Unit	July 17, 2020
2	Brant County Health Unit	July 20, 2020
3	Chatham-Kent Health Unit	August 14, 2020
4	Durham Region Health Department	July 10, 2020
5	Eastern Ontario Health Unit	July 07, 2020
6	Grey Bruce Health Unit	July 17, 2020
7	Haldimand-Norfolk Health Unit	August 01, 2020
8	Haliburton, Kawartha, Pine Ridge District Health Unit	July 13, 2020
9	Halton Region Health Department	July 22, 2020
10	Hamilton Public Health Services	July 20, 2020
11	Hastings and Prince Edward Counties Health Unit	July 10, 2020
12	Huron Perth District Health Unit	July 17, 2020
13	Kingston, Frontenac and Lennox & Addington Public Health	June 27, 2020
14	Lambton Public Health	July 31, 2020*
15	Leeds, Grenville and Lanark District Health Unit	July 07, 2020
16	Middlesex-London Health Unit	July 18, 2020
17	Niagara Region Public Health Department	July 31, 2020
18	North Bay Parry Sound District Health Unit	July 24, 2020
19	Northwestern Health Unit	August 17, 2020
20	Ottawa Public Health	July 07, 2020
21	Peel Public Health	July 10, 2020
22	Peterborough Public Health	August 01, 2020
23	Porcupine Health Unit	July 23, 2020
24	Region of Waterloo, Public Health	July 13, 2020
25	Renfrew County and District Health Unit	July 14, 2020
26	Simcoe Muskoka District Health Unit	July 13, 2020
27	Southwestern Public Health	July 31, 2020
28	Sudbury & District Health Unit	July 17, 2020
29	Thunder Bay District Health Unit	July 24, 2020
30	Timiskaming Health Unit	July 24, 2020
31	Toronto Public Health	July 07, 2020
32	Wellington-Dufferin-Guelph Public Health	June 12, 2020
33	Windsor-Essex County Health Unit	June 26, 2020
34	York Region Public Health Services	July 17, 2020

*Lambton Public Health did not enact a mask mandate as of the end of August 2020. However, the City of Sarnia, which has 58 % of Lambton's population according to the 2016 Census, enacted a mask mandate on July 31, 2020. The mask variable for Lambton is coded as 0.5 from July 31, 2020 onward.

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Table C3: Canada COVID-19 official data sources

Province	Cases	Deaths	Tests
Alberta (AB)	link	link	link
British Columbia (BC)	link	link	link
Ontario (ON)	link	link	link
Quebec (QC)	link	link	link
Saskatchewan (SK)	link[1]	link	link
Nova Scotia (NS)	link	link	link
Manitoba (MB)	link	link	link[2]
Newfoundland and Labrador (NL)	link[1]	link	link
New Brunswick (NB)	link	link	link
Prince Edward Island (PE)	link	link	link

Notes: 1. Saskatchewan and Newfoundland and Labrador do not revise their posted data series. We made data adjustments based on subsequent revisions announced in government bulletins; 2. The Manitoba tests numbers were manually collected from the COVID-19 provincial government bulletins.

Weather – we downloaded historical weather data for the largest city in each province from the Weather Canada website. The data provide daily information on 11 variables: maximum temperature (C), minimum temperature (C), mean temperature (C), heating degree-days, cooling degree-days, total rain (mm), total snow (cm), total precipitation (mm), snow on the ground (cm), direction of maximum wind gust (tens of degrees), and speed of maximum wind gust (km/h). We only use the temperature and precipitation data in Table A11 as possible factors determining outside vs. inside activity.

News – we collected data from *Proquest Canadian Newsstream*, a subscription service to all major and small-market daily or weekly Canadian news sources. We recorded the number of search results for each day from Feb 1, 2020 to Aug 20, 2020 by searching the database for the keywords "Coronavirus" or "COVID-19". We only counted the results with source listed as "newspaper" since other sources, such as blogs or podcasts, tend to duplicate the same original content.

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Table C4: YouGov Survey Questions

Survey item	Question
i12_health_2	Washed hands with soap and water
i12_health_3	Used hand sanitiser
i12_health_6	Avoided going out in general
i12_health_12	Avoided small social gatherings (not more than 2 people)
i12_health_13	Avoided medium-sized social gatherings (between 3 and 10 people)
i12_health_14	Avoided large-sized social gatherings (more than 10 people)
i12_health_15	Avoided crowded areas
i12_health_20	Avoided touching objects in public (e.g. elevator buttons or doors)

Notes: the data source is YouGov. Possible responses to each survey item are "Always", "Frequently", "Sometimes", "Rarely", and "Not at all". For Table A13, we create a binary variable taking value 1 if the response is "Always" and 0 otherwise. For Table A14, we create a binary variable taking value of 1 if the respondent answered either "Always" or "Frequently" and 0 otherwise.

All data used in the paper are available at https://github.com/C19-SFU-Econ/data.

Appendix D. Lags Determination

As discussed in Section 3.1, we assume a lag of 14 days between a change in policy or behaviour and its hypothesized effect on weekly case growth, and a lag of 28 days between such a change and its effect on weekly death growth.

First, we consider the lag between infection and a case being reported. As most identified cases of COVID-19 in Canada are symptomatic, we focus on symptomatic individuals. For most provinces cases are listed according to the date of report to public health. In provinces where the dates instead refer to the public announcement, we shifted them back by one day, as announcements typically contain the cases reported to public health on the previous day. The relevant lag therefore has two components:

1. Incubation period: Most studies suggest an average incubation period of 5-6 days (e.g. 5.2 days in Li et al. (2020), 5.5 days in Lauer et al. (2020), 5.6 days in Linton et al. (2020), 6.4 days in Backer et al. (2020)).

2. Time between symptoms onset and reporting of the case to public health: the Ontario data contain an estimate of the symptom onset date ("episode date") for each case. For our sample period the average difference between the date of report and the episode date is 4.8 days (median: 4 days) including only values from 1 to 14 days, and 6.3

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days (median: 5 days) including only values from 2 to 28 days. We assume that the lags in Ontario and in other provinces are similar, and use a value of 5-6 days between symptom onset and report to public health authorities.

Adding these together implies that the typical lag between infection and a positive case being reported to public health is around 11 days.

Second, we consider the effect of weekly averaging on the appropriate lag for our analysis. Suppose a policy or behavioural change starts on date t, impacting the daily growth in infections between dates $t-1$ and t and in each subsequent day. Then, assuming a lag of 11 days between infection and case reporting, case counts C are affected from date t+11 onward. Our outcome variable $\Delta \log(\Delta \mathrm{C})$ thus would react to the original policy or behavioral change on date $t+11$. The change is complete on $t+23$, when the week from $t+17$ to $t+23$ is compared to the week from $t+10$ to $t+16$. The midpoint of the change is $t+17$.

Choosing a lag of l days implies that the policy/behaviour variable phases in from $t+l$ to $t+l+6$. To match the midpoint of this phase-in to the midpoint of the change in the outcome variable, we set $l=14$. The chosen lag matches the lag used by other authors who study COVID-19 policy interventions, e.g., CKS (2020). We explore sensitivity to alternative lags in Section 4.3.

With respect to deaths, our data are, in most cases, backdated (revised by the authorities ex-post) to the actual date of death. The medical literature suggests that the mean time from symptom onset to death is around 19 days (20 days in Wu et al. (2020), 17.8 days in Verity et al. (2020), 20.2 days when accounting for right truncation in Linton et al. (2020), 16.1 days in Sanche et al. (2020), etc.), that is, two weeks longer than our estimate of the time from symptom onset to reporting of a positive test result. We correspondingly set the lag used in our analysis of the death growth rate (Section 4.6) to 28 days.

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Face mask wearing rate predicts country's COVID-19 death rates

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Abstract

Identification of biomedical and socioeconomic predictors for the number of deaths by COVID-19 among countries will lead to the development of effective intervention. While previous multiple regression studies have identified several predictors, little is known for the effect of mask non-wearing rate on the number of COVID-19-related deaths possibly because the data is available for limited number of countries, which constricts the application of traditional multiple regression approach to screen a large number of potential predictors. In this study, we used the hypothesis-driven regression to test the effect of limited number of predictors based on the hypothesis that the mask non-wearing rate can predict the number of deaths to a large extent together with age and BMI, other relatively independent risk factors for hospitalized patients of COVID-19. The mask non-wearing rate, percentage of age ≥ 80 (male), and male BMI showed Spearman's correlations up to about 0.8, 0.7, and 0.6 with the number of deaths per million from 22 countries from mid-March to mid-June, respectively. The observed number of deaths per million were significantly correlated with the numbers predicted by the lasso regression model including four predictors, age ≥ 80 (male), male BMI, and mask non-wearing rates from mid-March and late April to early May (Pearson's coefficient = 0.918). The multiple linear regression models including the mask non-wearing rates, age, and obesity-related predictors explained up to 79% variation of the number of deaths per million. Furthermore, 56.8% of the variation of mask non-wearing rate in mid-March, the strongest predictor of the number of deaths per million, was predicted by age ≥ 80 (male) and male BMI, suggesting the confounding role of these predictors. Although further verification is needed to identify causes of the national differences in COVID-19 mortality rates, these results highlight the importance of the mask, age, and BMI in predicting the COVID-19-related deaths, providing a useful strategy for future regression analyses that attempt to contribute to the mechanistic understanding of COVID-19.

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Introduction

There have been considerable differences in the number of deaths by COVID-19 among countries. Western countries (Europe and the United States), in particular, have been suffered from the high number of deaths and the high death rate compared to East Asian countries. Several regression studies have identified predictors, or candidates for true risk factors, for the difference among countries such as age, obesity, and previous BCG vaccination (Jeet et al., 2020; Bellali, Chtioui, & Chahed, 2020; Leung, Bulterys, & Bulterys, 2020; Squalli, 2020; Knittel & Ozaltun, 2020). However, it is important to continue characterizing novel and known predictors under various biomedical and socioeconomic contexts for potential future intervention to counteract with the ongoing COVID-19 pandemic.

Leffler et al. (2020) used the issued dates for each government's mandates or recommendations for face mask wearing as a predictor in their analysis. By their multivariable linear regression, duration of infection in the country, duration of wearing masks, and percentage of the population over age 60 significantly predicted each country's COVID-19 mortality rate. Also, a systematic review and meta-analysis identifying 172 observational studies indicated that face mask use could result in a large reduction in risk of COVID-19 (Chu et al., 2020). These findings, along with the big difference in face mask wearing rates between Western and other East Asian countries, suggest that the importance of mask wearing rate can be a significant predictor for the number of deaths by COVID-19. However, to our knowledge, there has been no analytical studies including the face mask wearing rate in regression models. This is possibly because the common regression approach uses a large number of samples and predictors to achieve the high prediction rates. The mask wearing rate is available only for limited number of countries.

Other studies identified age, BMI, and male sex as provisional and relatively independent risk factors for hospitalized patients of COVID-19 (Palaiodimos et al., 2020). In 5279 patients with laboratory confirmed COVID-19 patients in New York City, age is the strongest risk factor associated with hospital admission, while the critical illness after admission was associated with age, heart failure, BMI >40, and male sex (Petrilli et al., 2020). Docherty et al. (2020) reported using data from 20133 patients admitted to hospital with COVID-19 in the United Kingdom that independent risk factors are increasing age, male sex, and chronic comorbidity, including obesity.

In this study, we employed the hypothesis-driven regression approach to identify predictors for the number of deaths by COVID-19 across countries based on the hypothesis that the mask non-wearing rate can predict the number of deaths to a large extent together with age and BMI, other relatively independent risk factors for hospitalized patients of COVID-19. This approach uses limited number of a priori determined predictors based on a certain hypothesis. The hypothesis-driven regression is especially useful in providing biological insights related to the association with small number of samples, while the implication is restricted to the hypothesis, and has been used in various fields of research (Klein et al., 2013; Sabuncu et al., 2016; Carriedo et al., 2020). Based on the results we discussed the cultural factors for the observed difference among countries, which may have lowered

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the number of COVID-19-related deaths in East Asian countries.

Methods

Data collection

All data was collected from publicly available secondary sources. Analyses in the present study included UK, France, Italy, USA, Spain, Mexico, Germany, Malaysia, Canada, Sweden, China, Saudi Arabia, India, Indonesia, Philippines, Norway, Finland, Japan, Denmark, Australia, Singapore, and Thailand. These countries were chosen because of the availability for mid-March mask-wearing data. The face mask wearing rates in mid-March (3/9-18) 2020 and late April to early May (4/26-5/1) 2020 across countries were derived from "% of people in each country who say they are: Wearing a face mask when in public spaces" in Smith (2020). Total COVID death per million were obtained from Ritchie (2020). BMI data was obtained from Global Status Report on Noncommunicable Diseases 2014. 5 Oct. 2015, www.who.int/nmh/publications/ncd-status-report-2014/en/. Population percent by age data was obtained from Kose et al. (2020).

Data analysis

R version 3.6.2 was used for all statistical analyses. Pearson's and Spearman's correlations were calculated by cor and cor.test fuctions. Lasso regression was used to find potential effects of predictors on the number of deaths per million (Tibshirani, 2011). Multiple linear regression models were built using the lm function.

Results

Spearman's correlations

We first calculated Spearman's correlations between the number of deaths per million from various dates and parameters related to the mask non-wearing rate, age, and obesity (Fig. 1). The correlation coefficients between the number of deaths per million and mask non-wearing rates (both mid-March and late April to early May) showed time-dependent increases, reaching the apparent plateau in early May. The mask non-wearing rate in mid-March generally showed higher correlation coefficients than those that determined in late April to early May. The highest correlation of 0.79 was observed between the mid-March mask non-wearing rate and the number of deaths per million on June 6, 2020 ($P = 6.865e-06$).

Age-related predictors were also highly correlated with the number of deaths per million with Spearman's correlation coefficients of up to ~0.68. In both sexes, correlation coefficients were lower in younger age groups (age 65–69) compared to those of higher age groups, and the highest

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correlations were found in age ≥ 80 groups. In contrast to the mask non-wearing rate, correlations between the number of deaths and age-related predictors were highest in mid-May and decreased thereafter.

In general BMI showed lower correlations with the number of deaths per million with a clear sex-dependent difference. Male BMI was more closely associated with the number of deaths per million than female BMI.

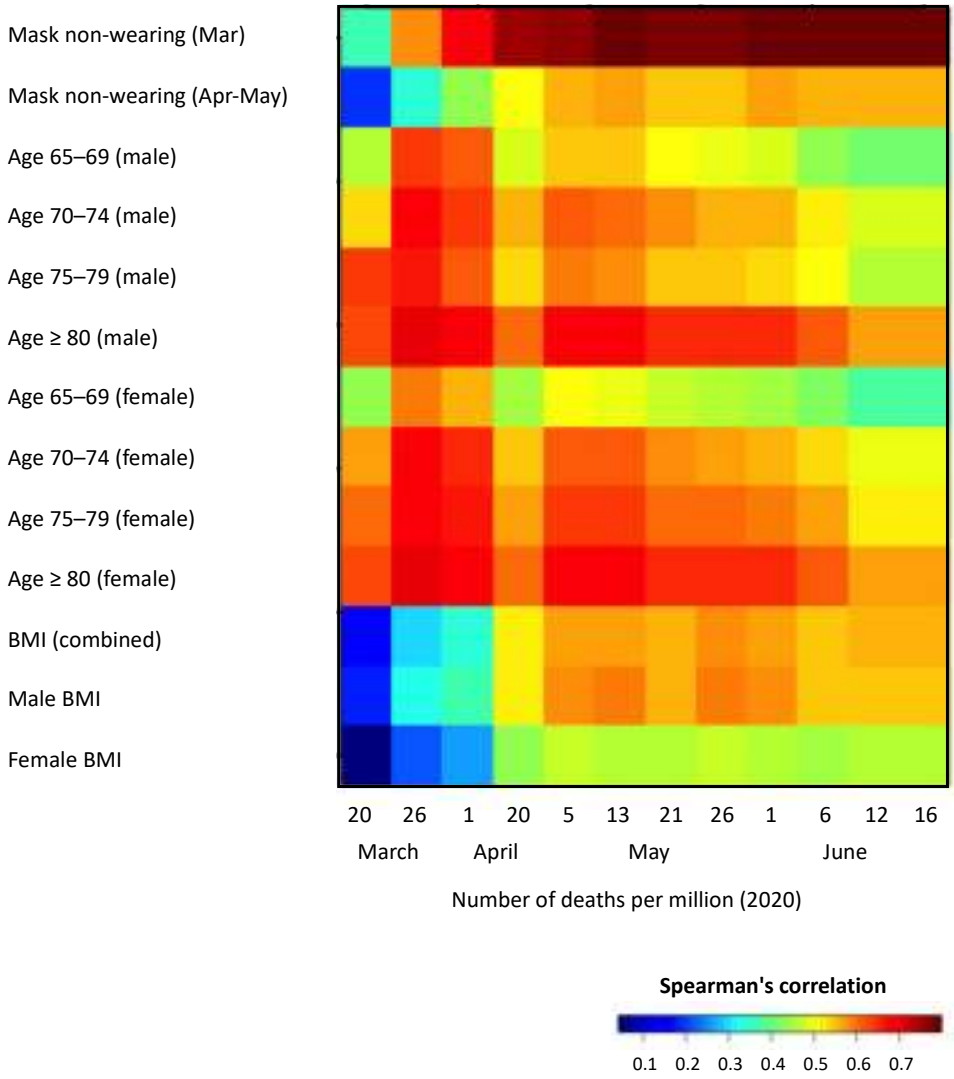

Fig. 1. Spearman's correlation (over time) among parameters related to COVID19 deaths, obesity, age, and mask non-wearing rate.

Time course profiles for Spearman's correlation coefficients of several highly correlated parameters demonstrated the unique feature of age ≥ 80 (male) among parameters used (Fig. 2). Spearman's correlation coefficients for this parameter remained almost constant throughout the study period,

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whereas those for other three parameters showed time-dependent increase and reached the apparent plateau around day 50 (mid-May).

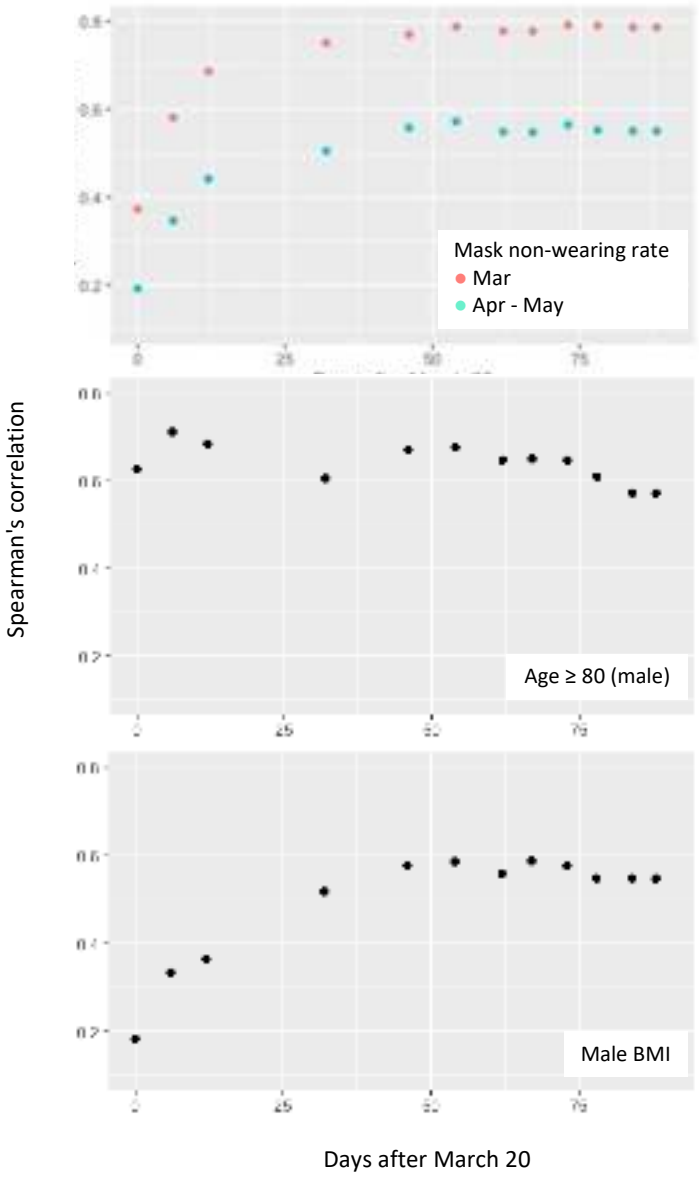

Fig. 2. Time-dependent changes in Spearman's correlations between the number of deaths per million on May 13 and mask non-wearing rates (mid-March and late April to early May), age ≥ 80, and male BMI.

Scatter plots

We subsequently made scatter plots showing the relationship between the number of deaths per million and predictors that showed high Spearman's correlation (Fig. 3). The number of deaths per million on May 13 was used because it showed the highest correlations with most important

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predictors including the mask non-wearing rates (mid-March), age ≥ 80 (male), and male BMI. As expected, the number of deaths per million did not show a clear correlation with the mask non-wearing rate (late April to early May). The number of deaths per million showed exponential type increases in most plots, in particular with the mask non-wearing rate (mid-March).

We therefore applied the logarithmic transformation to the number of deaths per million. The transformed number of deaths per million on May 13 showed significant linear correlation with the mask non-wearing rate in mid-March (r = 0.865, P = 9.739e-08), mask non-wearing rate in late April to early May (r = 0.530, P = 0.009296), age ≥ 80 (male) (r = 0.658, P = 0.0008717), and BMI (male) (r = 0.682, P = 0.0004762). The relationship between the number of deaths per million (May 13) and age ≥ 80 (female) appeared to be similar in the scatter plot (data not shown), but their linear correlation did not reach the statistical significance with a lower Pearson correlation coefficient compared to that of age ≥ 80 of males (r = 0.416, P = 0.05381).

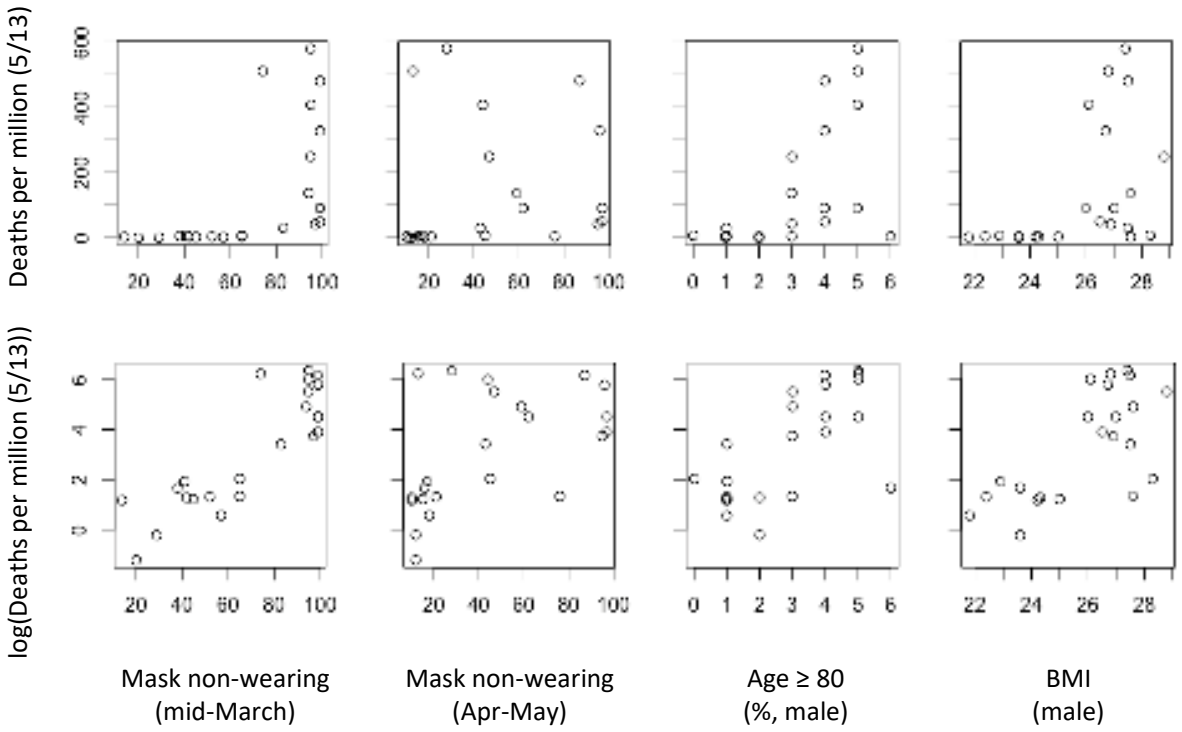

Fig. 3. Scatter plots showing the correlations among parameters related to COVID19 deaths, obesity, age, and mask non-wearing rate. The number of deaths per million on May 13 was used with (bottom panels) and without (top panels) logarithmic transformation.

Lasso regression

Next, we used the least absolute shrinkage and selection operator (lasso) regression to find the potential effects of these predictors on the log-transformed number of deaths per million. The lasso regression estimates the regression coefficients with the lasso penalty terms, retaining important

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explanatory variables, while less important variables are removed from the regression (Tibshirani, 2011). When all parameters in Fig. 2 were included together with age ≥ 80 (female), the lasso regression selected BMI (male) (beta = 0.21610188), age ≥ 80 (male) (0.34906818), the mask non-wearing rate (mid-March) (0.06019861), and the mask non-wearing rate in late April to early May (-0.02008978) with an intercept of -6.65720405. Age ≥ 80 (female) was omitted from the regression. The observed number of deaths per million showed high correlation with the number predicted by the lasso regression model (Fig. 4; Pearson's coefficient = 0.918, P = 1.635e-09).

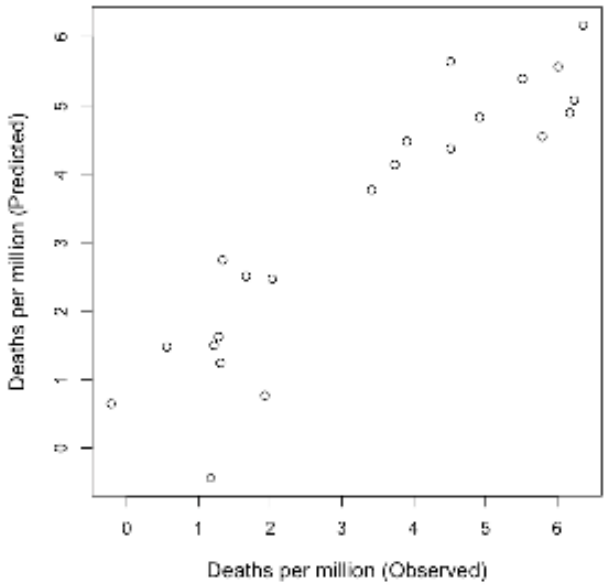

Fig. 4. Pearson's correlation between observed and predicted values of log-transformed number of deaths per million. The minimum lambda of 0.02511886 was used for the lasso regression. Pearson's coefficient = 0.918, P = 1.635e-09.

Multiple linear regression

We performed a hypothesis-driven linear regression using three or two of predictors selected by the lasso regression. Because the mask non-wearing rate is available only for 22 countries (Supplementary File 1), we first selected BMI (male), age ≥ 80 (male), and the mask non-wearing rate in mid-March for this regression (Table 1, model 1). This multiple regression model explained 76.0% variation of the number of deaths per million on May 13 (P = 2.075e-06), identifying the significant effects of mask non-wearing rate in mid-March and age ≥ 80 (male). BMI (male) also showed a trend for association, but the association was not statistically significant.

Other combinations of three predictors also resulted in significant associations between the number of deaths per million on May 13 and the selected predictors with ~0.7 adjusted R square values (Table 1). We found several important features in the multiple regressions. First, the effect of mask non-wearing rate in mid-March was significant in all regressions tested with low P values, and exclusion

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of this predictor markedly decreased the adjusted R square (model 2). Second, BMI (male) showed a relatively low association with the number of deaths on May 13, being significant only when the strongest predictor, mask non-wearing rate in mid-Match, was not included the regression (model 3). Third, the highest adjusted R square of 0.7934 was obtained when we include predictors age ≥ 80 (male) and mask non-wearing rates of mid-March and late April to early May (model 4). All regression coefficients were statistically significant in this model.

Regressions including two predictors also underscored the importance of the mask non-wearing rate in mid-March as the predictor for the number of deaths per million on May 13. Namely, the mask non-wearing rate in mid-March was always a significant predictor (models 5–7) with adjusted R square of up to ~0.75. While BMI (male) and age ≥ 80 (male) were also significantly associated with the number of deaths per million on May 13, exclusion of the mask non-wearing rate in mid-March dropped the adjusted R square to ~0.65.

Table 1. Multiple linear regressions for predicting the number of deaths per million (May 13) using three or two predictors

Model	Predictors	Beta (standard error)	P value	Adjusted R2 (overall P)
1	BMI (male)	0.21212 (0.16368)	0.21137	0.7603 (2.075e-06)
	Age ≥ 80 (male)	0.39160 (0.15572)	0.02163*	
	Mask non-wearing rate (Mar)	0.04163 (0.01330)	0.00579**	
	Intercept	-6.26822 (3.68145)	0.10584	
2	BMI (male)	0.539400 (0.175061)	0.00644**	0.631 (9.438e-05)
	Age ≥ 80 (male)	0.600767 (0.176575)	0.00318**	
	Mask non-wearing rate (Apr-May)	0.002544 (0.010958)	0.81900	
	Intercept	-12.468384 (4.223399)	0.00853**	
3	BMI (male)	0.19276 (0.16627)	0.2615	0.751 (2.908e-06)
	Mask non-wearing rate (Mar)	0.07963 (0.01567)	7.77e-05***	
	Mask non-wearing rate (Apr-May)	-0.02649 (0.01138)	0.0318*	
	Intercept	-6.13726 (3.74871)	0.1190	
4	Age ≥ 80 (male)	0.33405 (0.14491)	0.03328*	0.7934 (5.529e-07)
	Mask non-wearing rate (Mar)	0.07551 (0.01354)	2.71e-05***	

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	Mask non-wearing rate (Apr-May)	-0.02292 (0.01043)	0.04124*	
	Intercept	-1.99613 (0.62727)	0.00516**	
5	Age ≥ 80 (male)	0.371983 (0.157729)	0.0292*	0.7517
	Mask non-wearing rate (Mar)	0.053365 (0.009917)	3.42e-05***	(6.898e-07)
	Intercept	-1.570567 (0.654079)	0.0267*	
6	BMI (male)	0.17211 (0.18432)	0.362153	0.6931
	Mask non-wearing rate (Mar)	0.05656 (0.01347)	0.00048***	(5.163e-06)
	Intercept	-5.16465 (4.13573)	0.226911	
7	Mask non-wearing rate (Mar)	0.08907 (0.01351)	2.6e-06***	0.7465
	Mask non-wearing rate (Apr-May)	-0.02579 (0.01147)	0.0366*	(8.407e-07)
	Intercept	-1.86463 (0.69196)	0.0144*	
8	BMI (male)	0.5608 (0.1450)	0.00104**	0.6494
	Age ≥ 80 (male)	0.6091 (0.1685)	0.00185**	(1.832e-05)
	Intercept	-12.9298 (3.6328)	0.00209**	

* P < 0.05, ** P < 0.01

Single regression

Because the mask non-wearing rate in mid-March showed the strong association with the number of deaths on May 13, we also built several single linear regression models for predicting the number of deaths from other dates using this predictor (Table 2). Overall, changes in adjusted R square showed the similar tendency with those of the Spearman's correlation coefficients (Fig. 1), in which the value gradually increased during March and April, reaching the plateau in mid-May. Overall, the mask non-wearing rate in mid-March explained up to 72% of variations of the number of deaths per million.

Table 2. Linear regressions for predicting the log-transformed number of deaths per million from various dates using the mask non-wearing date in mid-March as the single predictor

Model	Number of deaths per million	Beta (standard error) P value	Intercept (standard error) P value	Adjusted R2 (overall P)
1	March 26	0.04089 (0.01706)	-2.89183 (1.30653)	0.1843

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		P = 0.0264*	P = 0.0387*	(0.02641)
2	April 1	0.05149 (0.01513) P = 0.00282**	-2.68139 (1.15891) P = 0.03144*	0.335 (0.002824)
3	April 20	0.06303 (0.01127) P = 1.79e-05***	-1.84714 (0.86336) P = 0.0449*	0.5903 (1.794e-05)
4	May 5	0.065157 (0.009786) P = 1.76e-06***	-1.492568 (0.749481) P = 0.0603	0.6736 (1.755e-06)
5	May 13	0.065560 (0.009377) P = 8.75e-07***	-1.362001 (0.718190) P = 0.0724	0.6951 (8.754e-07)
6	May 21	0.066014 (0.00915) P = 5.61e-07***	-1.290532 (0.701396) P = 0.0807	0.7082 (5.609e-07)
7	May 26	0.065582 (0.008961) P = 4.48e-07***	-1.195657 (0.686308) P = 0.0968	0.7145 (4.484e-07)
8	June 1	0.065597 (0.008839) P = 3.64e-07***	-1.130428 (0.676922) P = 0.111	0.7203 (3.641e-07)
9	June 6	0.065558 (0.008759) P = 3.21e-07***	-1.072095 (0.670825) P = 0.126	0.7238 (3.21e-07)
10	June 12	0.065304 (0.008685) P = 2.99e-07***	-1.000452 (0.665144) P = 0.148	0.7256 (2.995e-07)
11	June 16	0.06495 (0.00866) P = 3.11e-07***	-0.94215 (0.66326) P = 0.171	0.7246 (3.111e-07)

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Prediction of mask non-wearing rates

Lastly, we examined the relationship between the mask non-wearing rate, age ≥ 80 (male), and male BMI (Fig. 5). The mask non-wearing rate in mid-March showed significant correlations with both age ≥ 80 (male) and male BMI. Multiple linear regressions found both age ≥ 80 (male) and male BMI as significant predictors of the mask non-wearing rate with regression coefficients of 5.224 (P = 0.042559) and 8.377 (P = 0.000682), respectively, with an interception of -160.020 (P = 0.006040). This multiple regression model explained 56.8% variation of the mask non-wearing rate in mid-March

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(P = 0.0001325).

Compared to the mask non-wearing rate in mid-March, that in late April to early May showed a weak association with age ≥ 80 (male) and male BMI (Fig. 5). Accordingly, in the following multiple linear regression analysis, age ≥ 80 (male) and male BMI explained only 29.4% variation of the mask non-wearing rate although the regression was still statistically significant (P = 0.01419), The regression coefficients of men BMI and age ≥ 80 (male) were 8.422 and 3.270, respectively (P = 0.0141 and 0.3776, respectively).

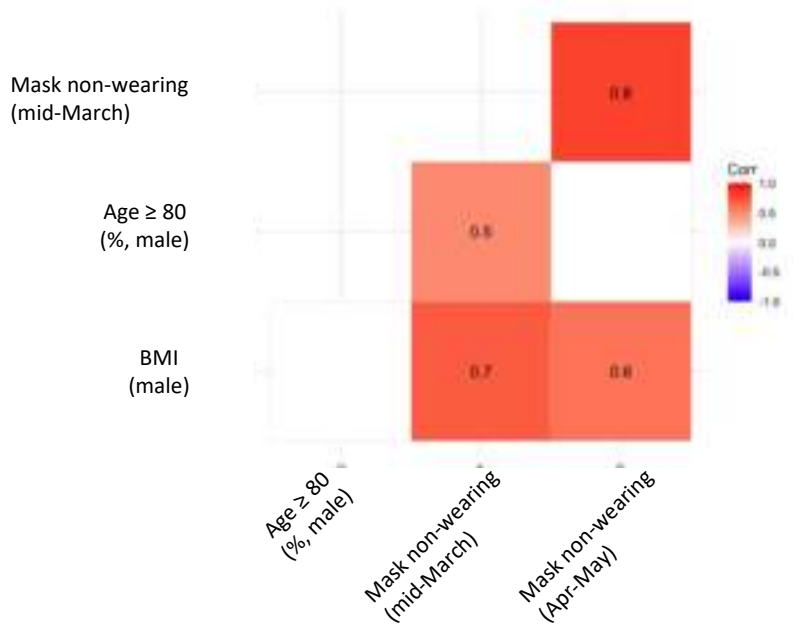

Fig. 5. Pearson's correlation matrix between mask non-wearing rate, age ≥ 80 (male), and mae BMI. Only significant correlations are shown (P < 0.05).

Discussion

The number of deaths per million on a certain date highly depends on when the epidemic began in the country, in particular in the early stages of the pandemic. In this study, we have tentatively determined March 20 as the start date of a global pandemic. It is likely that this assumption is a reasonable approximation for our hypothesis because all employed predictors (mask non-wearing rates, age and BMI) tended to show weak correlations with the number of deaths per million at the onset of the pandemic followed by marked increases as the progress of the pandemic. These features enabled us to select a specific date (May 13), at which most parameters showed the high correlations with the number of deaths per million, and to build regression models that well explain the variation of the response variable with limited number of predictors. On the other hand, it is noteworthy that the age-related predictors were highly correlated to the number of deaths per million from the very beginning

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of the pandemic and then remained constant or gradually declined. Below we discuss the potential biomedical and socioeconomic mechanisms by which each predictor affects the number of deaths by COVID-19.

Obesity

We have proposed possible mechanisms by which obesity could be a risk factor for the severity of COVID-19 and H1N1 influenza infections (Miyazawa, 2020). Namely, respiratory failure is the most important pathology that contributes to the severity of both COVID-19 and H1N1 influenza infections. Since obese patients generally show a restrictive breathing pattern and reduced lung volumes, the obesity-hypoventilation syndrome can lead to respiratory failure in COVID-19 patients, being a risk factor especially for patients with severe symptoms. Also, obesity has been reported to be a risk factor for the development of acute respiratory distress syndrome (Zhi et al, 2016), which is a serious clinical manifestation of COVID-19 (Simonnet et al., 2020). According to Moriconi et al. (2020), in patients of COVID-19, inflammatory markers were higher in obese group than non-obese group at admission, and obese group showed a worse pulmonary clinical picture, with lower PaO2. Thus, obesity could be a risk factor for already hospitalized COVID-19 patients or even for those with serious symptoms.

These potential mechanisms may explain the reason why the association of BMI (male) and the number of deaths increased May to June 2020. Typical COVID-19 patients are hospitalized a few days to a week after infection and in some cases the symptom become severe a few weeks after hospitalization. If the obesity affects the last phase of the transition of the disease, there must be some delay in the increase in correlations between BMI and the number of deaths per million compared to the spread of COVID-19. However, we cannot rule out the possibility that obese people have high chance to be infected because obese adults are known to inhale air average 50% more per day than non-obese adults (Brochu, 2014), which may lead to increase the chance to inhale the virus.

Age

In contrast to BMI, age ≥ 80 (male) was correlated with the number of deaths from the onset of the global pandemic. This may reflect the common etiological feature that old people are more susceptible to infection and have higher risk of death after infection compared to young people because of the dysfunction of immunity.

The precise reason why older age contributes to the number of COVID-19-related deaths remains to be elucidated, while the immune dysfunction has been proposed as a potential mechanism (Mueller, McNamara, & Sinclair, 2020). Meanwhile, it is controversial whether the reduced immunity simply contributes to the higher mortality after infection. Excessive immunity could cause the cytokine storm and ARDS in COVID-19 in some cases (Ye, Wang, & Mao, 2020). Furthermore, two patients with X-

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linked agammaglobulinemia have recovered from COVID-19, suggesting that B-cell response may not be necessary for the recover from this disease (Soresina et al., 2020). While other dysfunction of immunity, such as age-related T-cell dysfunction, may be involved in the severity of COVID-19 (Minato, Hattori, & Hamazaki, 2020), the mechanism should be carefully investigated.

Along with immune dysfunction, old individuals tend to provoke unwanted inflammation, which may contribute to the severity of COVID-19 (Mueller, McNamara, & Sinclair, 2020). This tendency can be seen in SARS-CoV-infected old nonhuman primate (Smits et al., 2010). Also, To et al. (2020) reported that older age is correlated with the higher salivary viral load, which is highest during the first week after symptom onset. Furthermore, as in the case of obese patients, decreased respiratory function of elderly could also be the reason. In elder individual, both forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) decrease dramatically (Falaschetti et al., 2004), to almost half of their lifetime maximum values, especially in males (Leem et al., 2019).

Sex differences

We identified a clear sex-dependent difference in the Spearman's correlation coefficients between the number of deaths per million and obesity-related parameters. This is in line with the fact that males are more susceptible to severe outcomes from COVID-19 than females (Montopoli et al., 2020; Grandi , Facchinetti, & Bitzer, 2020). It has been proposed that estrogen may be protective against COVID-19 in females (Grandi , Facchinetti, & Bitzer, 2020), while androgens may worsen COVID-19 in males (Montopoli et al., 2020). It is also possible that smoking, which is more common in males globally, may play a role in worsening COVID-19 (Grandi , Facchinetti, & Bitzer, 2020). Also, females generally have more fear to COVID-19 and tend to take more preventive behaviors than males (Yıldırım, 2020)

Face mask

Face masks are considered to be effective in preventing transmission of COVID-19 to others, and also have a protective effect in preventing transmission from others. A recent simulation study showed that universal masking at 80% adoption suppresses COVID-19 deaths significantly more than maintaining a lockdown. Comparison between the validated modeling results and empirical data from Asian regions showed an almost perfect correlation between early universal masking and successful suppression of COVID-19 outbreaks (Kai et al., 2020). Also, Zhang et al. (2020) reported that face mask alone could have reduced the number of infections by over 78,000 in Italy from April 6 to May 9 and over 66,000 in New York City from April 17 to May 9, claiming that the failure in containing the propagation of COVID-19 pandemic worldwide is largely attributed to the unrecognized importance of airborne virus transmission.

Likewise, the mask non-wearing rate in mid-March was found to be the strongest predictor for the

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number of deaths per million in this study, even the single regression by which explained more than 70% of the variation of the response variable.

There was a big difference in face mask wearing rates between Western countries and Asian countries (especially East Asian countries). The county's policy for wearing face mask alone cannot explain this big difference because, for example, face mask has never been mandated in Japan, despite its high face mask wearing rate. We speculate that the cultural may be the major reason for the difference. Many Japanese wear surgical masks on a daily basis not for shedding infections or pollens, but also for achieving anonymity just like westerners wearing sunglasses, which is referred to as "mask dependency" in excessive cases (Li, 2017). However, while people may hope to achieve anonymity, most of them want to avoid making others uncomfortable, and there is a regional difference in what people feel uncomfortable. Jack, Caldara, & Schyns (2012) mentioned that "whereas Western Caucasian internal representations predominantly featured the eyebrows and mouth, East Asian internal representations showed a preference for expressive information in the eye region" . This tendency may be the major reason why it is more considered rude wearing sunglasses among East Asia (Gesteland, 2020), whereas it is considered more suspicious to wear face masks in Western countries. Yamanaka (2020) wonders if Japan has an "X-factor" that led to the low rates of COVID-19 deaths. Although the present study is not intended to show the causal role of face mask wearing rate, future attempts for intervention may consider the face mask wearing rate as the major candidate for the "X-factor".

Additionally, most Japanese keep silent while using public transportation, because loud chatter in the public transportation is considered rude in Japan (Baseel, 2020). This may also be able to reduce the case of COVID-19 because more aerosols are exhaled from asymptomatic individuals during speaking than breathing (Buonanno, Stabile, & Morawska, 2020) and it is considered to contribute largely to spread of COVID-19 (Prather, Wang, & Schooley, 2020). Also aerosols' viral density should be different between speaking and breathing, because origin of the aerosols should be different, mainly from lung or mouth. Aerosols from mouth than lung may contain more virus in asymptomatic individuals. Long et. al (2020) noted that although virus shedding does not equate with viral infectivity, the asymptomatic group had a significantly longer duration of viral shedding than the symptomatic group.

Correlation between variables

There was a significant positive correlation between male BMI and mask non-wearing rate in mid-March. Although this does not simply indicate that obese people tend not to wear masks, it is possible to speculate that when people become more obese, they feel more uncomfortable to wear masks since obese adult inhale air average 50% more per day than non-obese adults (Brochu, 2014). Also, body temperature is positively associated with obesity (Bastardot, 2019), and face masks could rise body temperature (Yip, 2005; Hayashi 2004). Therefore, obese people may feel more heat and discomfort

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(Li, 2005) when wearing face masks depending on the temperature and humidity. The small size of universal face masks may be a simple reason for the correlation.

There was a significant positive correlation between age ≥ 80 (male) and mask non-wearing rate in mid-March. Due to the lack of data on mask wearing rates by age, this cannot be fully discussed either. It has been reported that age was correlated with fear and were related to preventive behaviors (Yıldırım, 2020). Face mask wearing in public correlates with the proportion of people who are afraid of COVID-19, except for Scandinavian countries and United Kingdom (Smith, 2020). These facts are inconsistent with the correlation found in this study. Further data is required for detailed investigation.

Conclusion

The mask non-wearing rate in mid-March alone explained up to 72% of variations of the number of deaths per million. The fact that the face mask non-wearing rate in mid-March, the early phase of the pandemic, more strongly predicted the total number of deaths per population over the entire three-month course of the pandemic than the face mask non-wearing rate in late April to early May may suggest that face mask wearing from the early phase of the pandemic may be very important for suppressing COVID-19-related deaths, if mask wearing is assumed to be an independent risk factor.

In the lasso regression, four factors, BMI (male), age ≥ 80 (male), the mask non-wearing rate (mid-March), and the mask non-wearing rate in late April to early May were chosen, and the observed and predicted model of number of deaths per million showed high correlation (Pearson's coefficient = 0.918, P = 1.635e-09). Although this has not been proven at this time to be the cause of the differences in COVID-19 mortality by country, it may be a useful method for predicting COVID-19 mortality.

The death rate of the country in the early stages of a pandemic could be further predicted if factors such as the timing and number of infected people entering the country from abroad are taken into account.

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Face masks considerably reduce COVID-19 cases in Germany

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We use the synthetic control method to analyze the effect of face masks on the spread of COVID-19 in Germany. Our identification approach exploits regional variation in the point in time when wearing of face masks became mandatory in public transport and shops. Depending on the region we consider, we find that face masks reduced the number of newly registered severe acute respiratory syndrome coronavirus 2 infections between 15% and 75% over a period of 20 days after their mandatory introduction. Assessing the credibility of the various estimates, we conclude that face masks reduce the daily growth rate of reported infections by around 47%.

COVID-19 | public health measures | face masks | synthetic control method

Many countries have experimented with several public health measures to mitigate the spread of COVID-19. One particular measure that has been introduced are face masks. It is of obvious interest to understand the contribution made by such a measure in reducing infections.

The effect of face masks on the spread of infections has been studied for a long time. The usefulness of facial protection for clinical personnel is beyond dispute, even though there are many questions left open (1). There is also evidence that face masks helped in mitigating the spread of earlier epidemics such as SARS 2003 (severe acute respiratory syndrome 2003) or influenza (see *SI Appendix*, section E for a brief literature survey). The impact of face masks worn in public on the spread of COVID-19 has yet to be systematically analyzed. This is the objective of this paper.

There is a general perception in Germany that the mandatory use of face masks in public reduces COVID-19 incidences considerably. This perception stems mainly from the city of Jena. After face masks became mandatory between 1 April and 10 April 2020 the number of new infections fell almost to zero. Jena is not the only region in Germany, however, that introduced face masks. Six further regions made masks compulsory before the introduction at the federal state level. Eventually, face masks became mandatory in all federal states between 20 April and 29 April 2020 (see *SI Appendix*, section A for background).

We quantify the effectiveness of face masks by employing the synthetic control method (SCM; refs. 2–5). Our identification approach exploits this regional variation in the point in time when face masks became mandatory. We use data for 401 regions in Germany (municipal districts) to estimate the effect of this particular policy intervention on the development of registered infections with COVID-19. We consider the timing of mandatory face covering as an exogenous event to the local population: Masks were imposed by local authorities and were not the outcome of some process in which the population was involved. We compare the COVID-19 development in various regions to their synthetic counterparts. The latter are constructed as weighted averages of control regions that are structurally similar to treated regions. Structural dimensions considered include prior COVID-19 cases, the demographic composition, and the local health care system.

A detailed analysis of the timing of all public health measures in the regions we study guarantees that we correctly attribute our findings to face masks (and not erroneously to other public health measures). We also employ a standard SIR (susceptible–infected–removed) model and undertake an analysis of the distribution of the lag between infection and reporting date. This allows us to provide a precise interpretation of our empirical effectiveness measure and to pin down the point in time when the effects of face masks should be visible in the data.

We find statistically significant and sizeable support for the general perception that the public wearing of face masks in Jena strongly reduced the number of incidences. We obtain a synthetic control group that closely follows the COVID-19 trend before the introduction of mandatory masks in Jena. The difference between Jena and this group becomes significant thereafter. Our findings indicate that the early introduction of face masks in Jena has resulted in a drop in newly registered COVID-19 cases of around 75% after 20 d. Put simply, if the control region observes 100 new infections over a period of 20 d, the mask region observes only 25 cases. This drop is greatest, by more than 90%, for the age group 60 y and above. Our results are robust to different sensitivity checks, among which are placebo-in-space and placebo-in-time analyses.

As a means to verify the generalizability of our findings for Jena, we move from a single- to a multiple-treatment approach and estimate average treatment effects of introducing face masks

Significance

Mitigating the spread of COVID-19 is the objective of most governments. It is of utmost importance to understand how effective various public health measures are. We study the effectiveness of face masks. We employ public regional data about reported severe acute respiratory syndrome coronavirus 2 infections for Germany. As face masks became mandatory at different points in time across German regions, we can compare the rise in infections in regions with masks and regions without masks. Weighing various estimates, we conclude that 20 d after becoming mandatory face masks have reduced the number of new infections by around 45%. As economic costs are close to zero compared to other public health measures, masks seem to be a cost-effective means to combat COVID-19.

Author contributions: T.M., R.K., J.R., and K.W. designed research, performed research, contributed new reagents/analytic tools, analyzed data, and wrote the paper.

The authors declare no competing interest.

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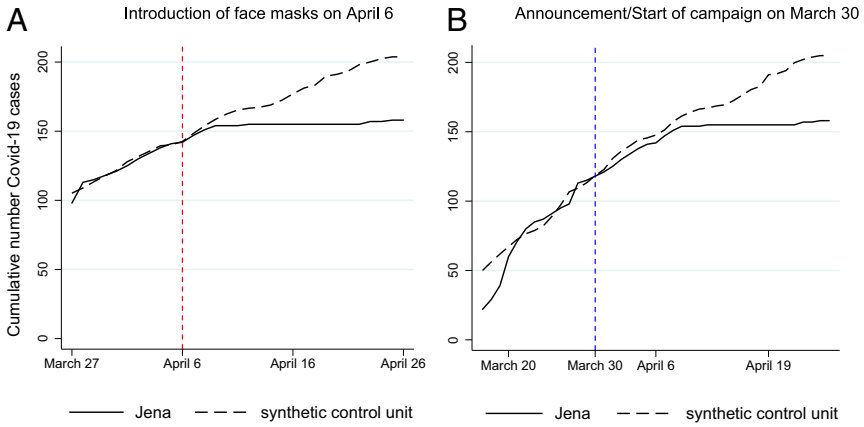

Fig. 1. Treatment effects of the mandatory introduction of face masks (6 April) and of its announcement (30 March) in Jena. The figure shows the development of the cumulative number of COVID-19 cases in Jena (treated region, black solid line) compared to a synthetic control group (gray dashed line) over time. (Details on the construction of the synthetic control group and SCM estimation are given in *Method and Data*.) Both panels distinguish between a pretreatment and treatment period. In *A*, the treatment period starts on 6 April when face masks became mandatory in public transport and shops. The start of the treatment period is indicated by the dashed vertical line (red). In *B*, the treatment period is set to begin on 30 March as starting date of the local campaign in Jena to wear face masks in public. The start of the treatment period is indicated by the dashed vertical line (blue). The panels show that the conclusion is independent of the starting dates: Face masks strongly reduced the number of COVID-19 cases in Jena.

on the spread of COVID-19 for all regions that introduced masks by 22 April (~8% of all German regions). Although the estimated average treatment effect is smaller compared to the one found for Jena, it is still statistically significant and sufficiently large to support our point that wearing face masks is an effective and cost-efficient measure for fighting COVID-19. When we summarize all of our findings in one single measure (*SI Appendix*, section D.2), we conclude that the daily growth rate of COVID-19 cases in the treatment group falls by around 47% due to mandatory mask-wearing relative to the synthetic control group.*

Our findings can be aligned with earlier evidence on face masks, public health measures, and the epidemic spread of COVID-19, although consolidated scientific knowledge is limited (*SI Appendix*, section E). While there is a growing consensus from clinical studies that face masks significantly reduce the transmission risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and COVID-19 (7, 10), nonclinical evidence on the effectiveness of face masks is still largely missing. Ref. 11 surveys evidence on the population impacts of a widespread community mask use and stresses that "no randomized control trials on the use of masks … has been published." The study which is "the most relevant paper" for ref. 11 is one that analyzed "exhaled breath and coughs of children and adults with acute respiratory illness" (ref. 12, p. 676), that is, used a clinical setting. Concerning the effect of masks on community transmissions, the survey needs to rely on pre–COVID-19 studies.

Ref. 13 is among the first to estimate the population impact of face masks on SARS-CoV-2 infections.† The authors track the development of COVID-19 in three pandemic epicenters, Wuhan, Italy, and New York City, between 23 January and 9 May 2020 and find sizable mitigating effects of face masks on epidemic spread. While their study offers important insights into the population effects of face masks, a methodical limitation is that estimates are only carried out in a "before–after" manner with no use of a strict control group approach. This may limit the causal interpretation of results. We therefore follow the spirit of ref. 4 and provide causal evidence identifying the population impact of mandatory face masks on the spread of COVID-19.

Results: The Effects of Face Masks on the Spread of COVID-19

All results are obtained by applying the synthetic control method. It is described briefly in *Method and Data* and in more detail in *SI Appendix*, section B.

Results for Jena. Face masks became mandatory in Jena in three steps between 1 and 10 April. The most important measure (in the sense of having the largest impact measured in terms of social contacts) requires face masks in public transports and shops and entered into force on 6 April (see *SI Appendix*, section A for detailed information). We therefore center our discussion on this date.

Fig. 1*A* shows the SCM results for the introduction of face masks in Jena on 6 April. The visual inspection of the development of cumulative COVID-19 cases shows that the trend development of the synthetic control group is very similar to Jena before the treatment, indicating a good fit.‡ The difference in the cumulated registered COVID-19 cases between Jena and its corresponding synthetic control group after the start of the treatment on 6 April can be interpreted as the treatment effect on the treated [see *SI Appendix*, section C.3 for (post)estimation details].

Fig. 1*A* clearly shows a gradually widening gap in the cumulative number of COVID-19 cases between Jena and its synthetic control group. The size of the effect 20 d after the start of the treatment (6 April) amounts to a decrease in the number of cumulative COVID-19 cases of 23%, which corresponds to a drop in newly registered cases of roughly 75%. Expressed differently, the daily growth rate of the number of infections decreases by 1.28 percentage points per day (see *SI Appendix*, section D.2 for computational details and an overview of all

*The main channel through which masks reduce transmission of SARS-CoV-2 is the limiting effect for the spread of exhaled air, as argued by ref. 6. Refs. 6 and 7 argue that aerosols (as opposed to larger droplets) are filtered only by high-quality masks. Droplets are also filtered by home-made masks. Earlier work includes ref. 8 that was recently extended by ref. 9. Ref. 9 finds that all face covers (without an outlet valve) "reduce the front flow through jet by more than 90%." As surgical and hand-made masks generally do not tightly fit, they generate backward and downward jets.

†Ref. 10 conducts a systematic review and meta-analysis. They do not report a study (see their table 1) that analyzes the entire population of a country.

‡As a measure for the quality of the fit between the treated region and its synthetic control group, the pretreatment root-mean-square prediction error (RMSPE) can be calculated and compared to a reference case. For Jena the pretreatment RMSPE is 3.145. This is considerably lower than an average RMSPE of 6.669 for all other 400 regions and their synthetic controls in the pretreatment period until 6 April. This points to the relatively good fit of the synthetic control group for Jena in this period.

measures). If we look at the estimated differences by age groups, *SI Appendix*, Fig. S7 indicates that the largest effects occur for individuals above 60 y of age. Here the reduction in cumulative cases even exceeds 50%, which corresponds to a drop in newly registered SARS-CoV-2 infections by more than 90%. The significant drop can be explained by the introduction of face masks in elderly and nursing homes, which had already started on 1 April. For the other two age groups the decrease in the number of cumulative cases lies between 10% and 20%.

If we consider a median time lag of 10.5 d from infection until registration (see *SI Appendix*, section A.3), the occurrence of a gradually widening gap between Jena and its synthetic control in the first week after the introduction of mandatory face masks seems fast. One might conjecture that an announcement effect played a role. As shown in *SI Appendix*, section C.6.1, online searches for (purchasing) face masks peaked on 22 April, when it was announced that face masks would become compulsory in all German federal states.[§] Another peak in online searches, almost as large (70% of the peak of 22 April), appeared on 31 March. This marks the date of the regulation making masks compulsory between 1 and 10 April in Jena. The regulation was accompanied by a campaign "*Jena zeigt Maske*," communicating the necessity to wear face masks in public, that started on 30 March.[#]

Fig. 1*B* plots the estimated effect size when we define the start of the treatment period by the start of the campaign on 30 March. The visual inspection of the difference between Jena and its synthetic control group points to the presence of a small anticipation effect. Yet, the gap to the synthetic control significantly widens only ∼10 to 12 d after the announcement and then grows considerably over time. As this temporal transmission channel appears plausible given a median time lag between infection and registration of almost equal length, we take this as first evidence for a face mask effect in the reduction of SARS-CoV-2 infections.

Robustness Checks. Obviously, the estimated difference in COVID-19 development in Jena vis-à-vis the synthetic Jena is only convincing if 1) the requirements of the SCM are fulfilled and 2) potentially concurrent policies other than masks can be ruled out. The role of the first set of robustness checks consists of understanding the sensitivity to the length of the preintervention period (*Cross-Validation Tests*) and to the composition of the control pool (*Changing the Donor Pool*).[‖] In a second step, we rule out unobserved macro effects shared by many regions (*Placebo-in-Space Tests*) and test for anticipation effects potentially caused by other public health measures (*Placebo-in-Time Tests*). The second step also comprises difference-in-difference estimation as a further test for latent concurrent policies that go beyond observable policies (displayed in *SI Appendix*, Fig. S2).

Cross-validation tests. We study the sensitivity of our estimates with respect to the length of the training and validation period before the start of the treatment. We accordingly alter the imposed lag structure for predictors that have a time dimension, that is, the number of cumulative and newly registered COVID-19 cases. The set of time-constant predictors is kept unchanged by this test. As shown in *SI Appendix*, section C.7, we do not find a systematic estimation bias of our baseline SCM specification compared to alternative ones with longer lag structures (up to 7 d) and accordingly shorter trainings periods. Given that regional COVID-19 cases developed very dynamically and nonlinearly in the pretreatment period, this is an important finding in terms of the robustness of our results.

We also test for the sensitivity of the estimated treatment effects to changes in the set of time-constant predictors. We do so by sequentially excluding individual variables from the set of predictors. As shown in *SI Appendix*, section C.7, the estimated trajectories for the respective synthetic control groups follow a very similar trend. All of them identify a reduction in the number of cumulative COVID-19 cases in Jena vis-à-vis the synthetic Jena that widens over time. We conclude from these results that using the full set of predictors is the most reasonable approach.

Changing the donor pool. This may be equally important as our baseline specification includes the region of Heinsberg in the donor pool used to construct the synthetic Jena (with a weight of 4.6%; compare *SI Appendix*, Table S5). As Heinsberg is one of the German regions that was significantly affected by the COVID-19 pandemic during the Carnival season, one may expect that this leads to an overestimation of the effects of face masks. Accordingly, *SI Appendix*, section C.8 presents estimates for alternative donor pools. Again, we do not find evidence for a significant bias in our baseline specification. By tendency, the treatment effect becomes larger, particularly if we compare Jena only to other regions in Thuringia (to rule out macroregional trends) and to a subsample of larger cities (*kreisfreie Städte*). The latter comparison reduces the degree of latent regional heterogeneity, for instance, with regard to social interactions. Both subsamples exclude Heinsberg. We also run SCM for subsamples excluding Thuringia (to rule out spatial spillover effects) and for East and West German regions only (again to test for specific macro regional trends). Generally, these sensitivity tests underline the robustness of the estimated treatment effect for Jena.

Placebo-in-space tests. These tests check whether other cities that did not introduce face masks on 6 April have nonetheless experienced a similar decline in the number of registered COVID-19 cases. If this had been the case, the treatment effect might have been driven by other latent factors rather than by face masks. Such latent factors may, for instance, be related to the macroregional dynamics of COVID-19 in Germany. Therefore, *SI Appendix*, section C.9 reports pseudo-treatment effects for similarly sized cities in the federal state of Thuringia assuming that they had introduced face masks on 6 April—although, in fact, they did not. As the figure illustrates, these cities show either a significantly higher or a similar development of registered COVID-19 cases compared to their synthetic controls. This result provides further empirical support for a relevant effect in the case of Jena.

As a more comprehensive test, we run placebo-in-space tests for all other regions that did not introduce face masks on 6 April or closely afterward. Again, we estimate the same model on each untreated region, assuming it was treated at the same time as Jena. The empirical results in Fig. 2 indicate that the reduction in the reported number of COVID-19 cases in Jena clearly exceeds the trend in most other regions—both for the overall sample in Fig. 2*A* and the subsample of large cities (*kreisfreie Städte*) in Fig. 2*B*.

One advantage of these tests is that they allow us to conduct inference on the significance of the estimated treatment effects for Jena. Accordingly, Fig. 2 *C* and *D* visualize the estimated treatment effects together with 90% confidence intervals. Intervals have been calculated on the basis of (one-sided) *P* values (pretreatment match quality adjusted) reported in Fig. 2 *E* and *F*.[**] The latter indicate the probability that the reduction in the number of COVID-19 cases was observed by chance given the distribution of pseudo-treatment effects in the other German regions (see ref. 18). In both panels, the reported confidence intervals and underlying *P* values indicate that the reduction in

[§]For a German-wide news report see, for example, ref. 14.

[#]See local newspaper reports, for instance ref. 15.

[‖]Further requirements, that are less central to our application, are listed in *Method and Data* and are discussed in *SI Appendix*, section B.

[**]We follow the method proposed in ref. 16 to calculate confidence intervals from P values. As pointed out in ref. 17, the interpretation of confidence intervals and P values is restricted to the question of whether or not the estimated effect of the actual treatment is large relative to the distribution of placebo effects.

STATISTICS

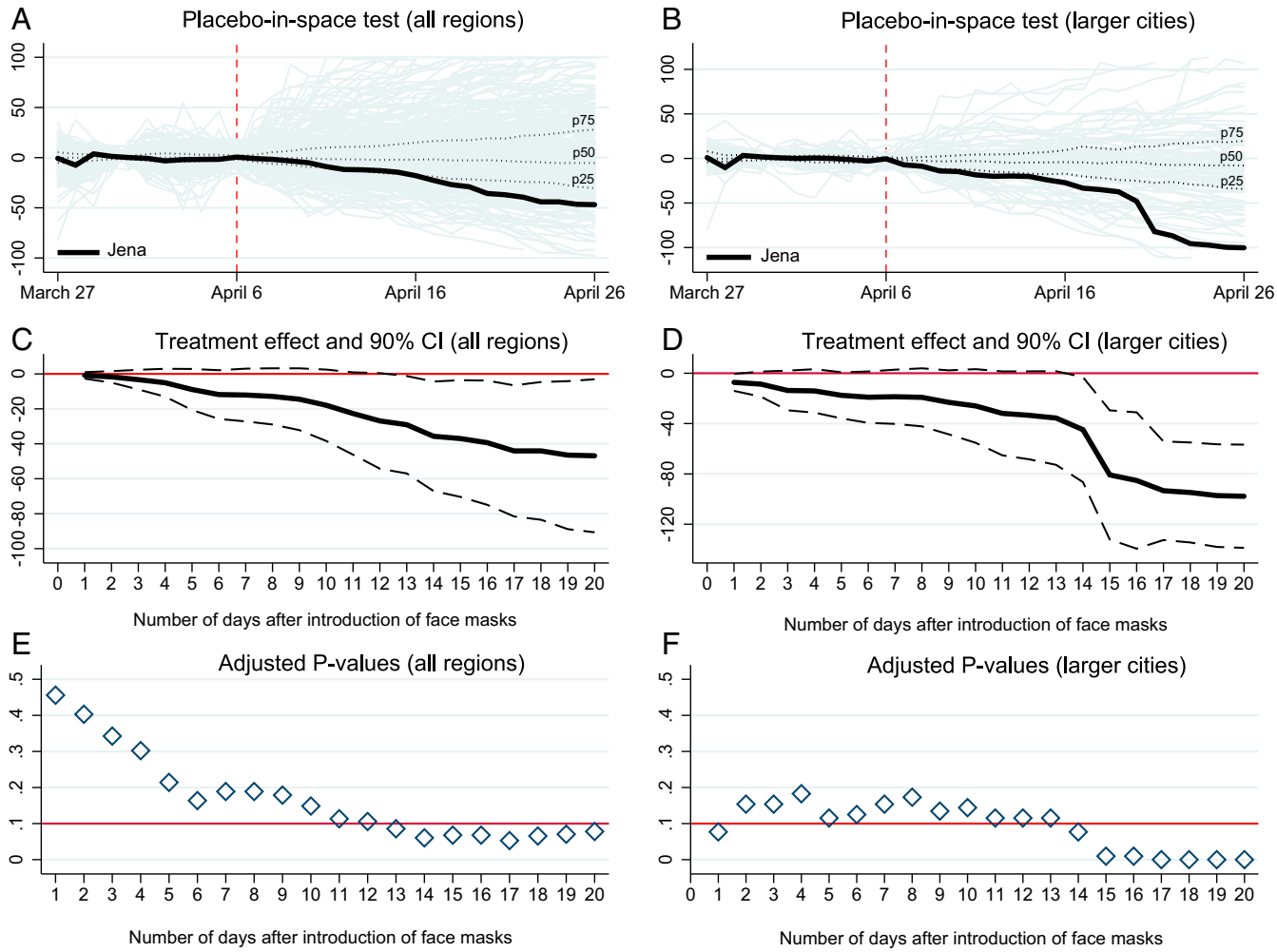

Fig. 2. Comprehensive placebo-in-space tests for the effect of face masks on COVID-19 cases. The figure compares the difference in the cumulative number of COVID-19 cases between Jena and its synthetic control group with the differences between all other regions in the donor pool and their respective controls over time. Differences have been calculated for the treatment period after 6 April when Jena de facto introduced mandatory face masks. For all other regions, the reported differences in the treatment period constitute pseudo-treatment effects since these regions had not introduced face masks back then. In *A*, the black solid line measures the treatment effect for Jena. The solid gray lines measure the pseudo-treatment effects for all other German regions in the donor pool (see *Method and Data* for details on the specification of the donor pool). Plots are shown for donor regions with an acceptable pretreatment root-mean-square prediction error (RMSPE), that is, less than 10 times the RMSPE of Jena; dotted lines indicate the median (p50), 25th percentile (p25), and 75th percentile (p75) of pseudo-treatment effects. In *B*, the donor pool is reduced to comprise only larger cities (*kreisfreie Städte*). *C* and *D* also plot the treatment effect for Jena and 90% confidence intervals (gray dashed lines) for the full sample of regions and the subsample of larger cities, respectively. Confidence intervals are constructed on the basis of pseudo *P* values as shown in *E* and *F* for the first 20 d after the introduction of face masks in Jena. These *P* values are adjusted for the pretreatment match quality (see *Method and Data* for details). The red horizontal line in *E* and *F* indicates a threshold *P* value of 0.1.

the number of COVID-19 cases was not a random event. In larger cities (Fig. 2*D*), the reduction due to the introduction of face masks is clearly visible 2 wk after the start of the treatment. Again, this timing is in line with our above argument that a sufficiently long incubation time and testing lags need to be considered in the evaluation of treatment effects.[††]

Placebo-in-time tests. As for the case of placebo-in-space tests, it is important for the validity of results that we do not observe significant treatment effects for Jena prior to the introduction of face masks on 6 April or its announcement on 30 March. To rule out such anticipation effects, we have systematically reviewed all general decrees published by the local administration in Jena. Of particular interest are those decrees that significantly differ with respect to their timing from those at the federal state level in Thuringia.

Looking at *SI Appendix*, Fig. S2, Jena and Thuringia passed at least 40 public health measures before the end of April 2020. Jena implemented 27 of these 40 either earlier than Thuringia or on its own. Examples of earlier implementation include the closing of bars, cafés, and restaurants or quarantine rules for travelers returning home. Relevant regions included foreign countries but also other German federal states, among which were Bavaria, Baden-Wurttemberg, and North-Rhine Westphalia. Measures

[††]We analyze a measure that is introduced for the first time in this region. One might conjecture that our estimation measures both the true effect of a face mask but also any other change in behavior (washing hands, limiting interactions, staying at home more, etc.) that was triggered by this policy. This change in behavior is known as the Hawthorn effect. Individuals in this pioneer region might take the crisis more seriously than in the other areas. Although German health authorities had been strongly recommending such behavioral changes in daily life since mid-March, we cannot fully rule out this mixing of effects. Mobility data for federal states in *SI Appendix*, section C.6.2 show that federal states moved in a relatively coordinated way in this respect. Unfortunately, mobility data for Jena are not easily available.

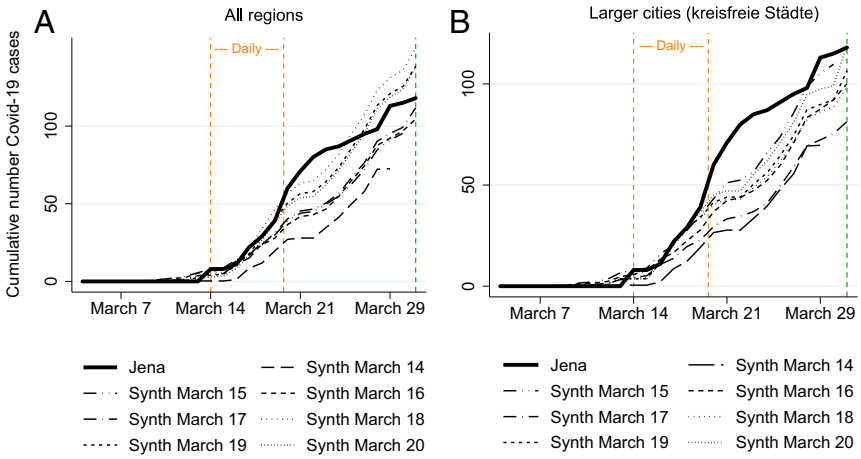

Fig. 3. Placebo-in-time tests for (pseudo) treatment effects in the period 14 to 20 March. The figure shows the empirical development of the cumulative number of COVID-19 cases in Jena (treated region, black solid line) and the estimated development in different synthetic control groups over time. The key difference between these synthetic control groups lies in the starting point of the (pseudo) treatment period. The starting point varies on a daily basis between 14 and 20 March. In *A*, the full sample of German regions is used as the donor pool for the construction of synthetic control groups (see *Method and Data* for details on the specification of the donor pool). Vertical dashed lines (orange) indicate the time corridor in which the respective (pseudo) treatment periods start. In *B*, the donor pool is reduced to comprise only larger cities (*kreisfreie Städte*). Again, vertical dashed lines (orange) indicate the time corridor in which the respective (pseudo) treatment periods start.

imposed by Jena only include the complete closing of hotels (in contrast to closing of hotels for tourism only in Thuringia) and a curfew (which lasted for only 2 wk, though).

As these major health decrees were accompanied by smaller ones on an almost daily basis until 20 March, we run a series of SCM estimations using each day between 14 and 20 March as a (pseudo) treatment period.[‡‡] The results for the full donor pool including all other German regions and the subsample of larger cities are shown in Fig. 3 *A* and *B*. Results are reported until 30 March when the mandatory introduction of face masks was announced.

To take an example, consider the graph with the long dashes in Fig. 3*A* denoted "Synth March 14." It shows the cumulative number of COVID-19 cases for a synthetic control group for Jena extracted from the full donor pool under the assumption that some treatment had started on 14 March. Similarly, "Synth March 15" (and so on) show the evolution of COVID-19 cases for a starting date of 15 March. Hence, each SCM estimation starts at a different point in time.

The visual inspection of the relative development of COVID-19 cases in Jena vis-à-vis its synthetic Jena does not indicate a clear treatment effect in terms of reducing COVID-19 cases prior to 1 April. The results are particularly clear-cut for the sample of larger cities in Fig. 3*B*, indicating that earlier public health measures alone did not significantly suppress the number of COVID-19 cases in Jena in the first 2 wk after their introduction.

Difference-in-difference tests. The reported trajectories of synthetic Jena in Fig. 3*A* leave us with some degree of ambiguity, though. To explicitly test for a potential trend reversal in the development of COVID-19 cases prior to the introduction of face masks, we further run an alternative robustness test on the basis of incremental difference-in-difference (DiD) estimation. The DiD estimator is particularly well-suited to estimate dynamic treatment effects in the context of limited information about the exact length of transmission lags before individual policy interventions show measurable effects (a detailed description is given in *SI Appendix*, section F). As the results clearly show, treatment effects from public health measures in Jena in terms of a reduction in COVID-19 cases only become statistically significant roughly 2 wk after the introduction of face masks on 6 April. If we resort to the estimated incubation and reporting lag as shown in *SI Appendix*, section A.3, this result supports our main SCM findings that the relative reduction in the cumulative number of COVID-19 cases is mainly attributable to the timing of introducing face masks. The incremental DiD results also support our main SCM findings in terms of the magnitude of the treatment effect.

Results for Other Regions. Jena may be a unique case. We therefore also study treatment effects for other individual regions that introduced face masks earlier than other regions. Further single-unit treatment analyses are shown in *SI Appendix*, section D.1. SCM estimation for multiple treated units can be undertaken as not only did some individual regions introduce face masks earlier than their federal states (see Fig. 5, below the time line) but also some federal states (Saxony and Saxony-Anhalt) before the remaining German federal states (*SI Appendix*, Fig. S1). To ensure a sufficiently long treatment period, we consider all regions as treated which introduced face masks on or before 22 April. We estimate average treatment effects in a multiple treatment SCM approach for 1) all of these regions and 2) a subset consisting of larger cities (*kreisfreie Städte*) only. In the former case we have a total of 32 treated units, and in the latter there are 8 treated units. The donor pool of control regions (all regions in Germany and only larger cities, respectively) is specified such that the minimum time lag in the introduction of face masks between treated and control regions ranges between 5 and 13 d.

The results, visible in Fig. 4, point to a significant face mask effect in the reduction of SARS-CoV-2 infections over a period of 20 d after the introduction. The temporal evolution of the average number of cumulative COVID-19 cases for treated regions and their corresponding synthetic control groups are shown in Fig. 4 *A* and *B*, respectively. The reported 90% confidence intervals in Fig. 4 *C* and *D* calculated on the basis of adjusted *P* values shown in Fig. 4 *E* and *F* indicate that the estimated treatment effects are not random for both samples. While treatment effects of face masks turn significant after roughly 1 wk for the overall sample, the emergence of a reduction in the subsample of larger cities is fast and points to early anticipation effects of face masks in urban areas, particularly during the period when local economies were gradually reopened after 20 April.

[‡‡]Alternatively, we have also tested for pseudo-treatment effects in Jena over a period of 20 d before the introduction of face masks. This period is equally split into a pre- and pseudo posttreatment period. As *SI Appendix*, Fig. S11*B* shows, there is no strong deviation from the path of the synthetic control group.

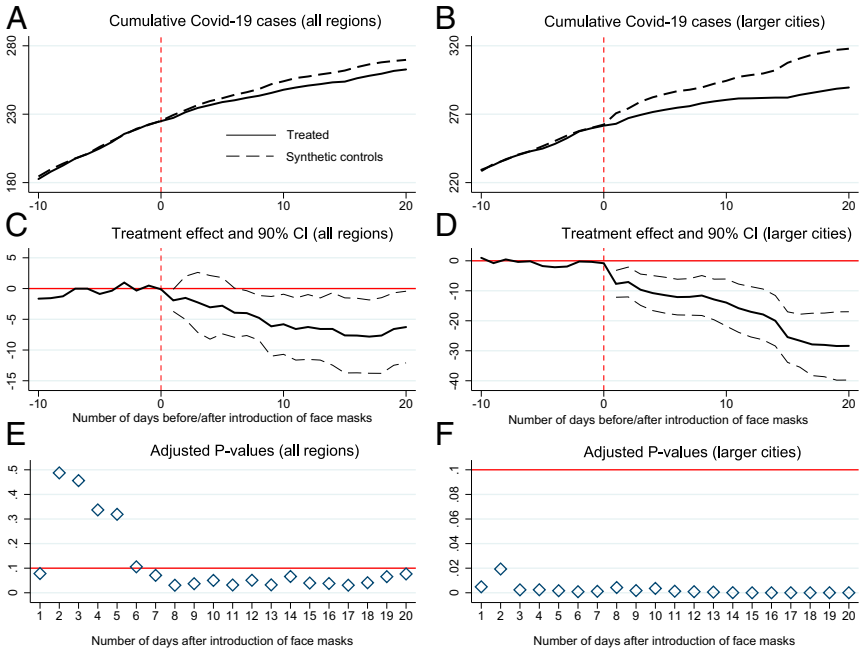

Fig. 4. Average treatment effects for the introduction of face masks with multiple treated units. The figure shows the average development of the cumulative number of COVID-19 cases for treated units (defined as all regions that introduced face masks on or before 22 April), for their synthetic control groups and estimated treatment effects. *A* plots the average number of cumulative COVID-19 cases in treated regions (black solid line) and synthetic controls (black dashed line) for the full sample of German regions in the donor pool (see *Method and Data* for details on the specification of the donor pool). The horizontal axis plots the number of days before and after the start of the treatment (mandatory introduction of face masks). The vertical dashed line (red color) indicates the start of the treatment period, which is allowed to vary by treated regions. In *B*, the number of treated and the donor pool for control regions is limited to larger cities (*kreisfreie Städte*). *C* and *D* plot the estimated average treatment effects, that is, average reduction in the cumulative number of COVID-19 cases (black solid lines) over time joint with 90% confidence intervals (gray dashed lines) for the two samples. Confidence intervals are constructed on the basis of pseudo *P* values as shown in *E* and *F* for the first 20 d after the start of the treatment. These (one-sided) *P* values are adjusted for the pretreatment match quality (see *Method and Data* for details). Inference has been conducted on the basis of a randomly drawn sample of 1 million placebo averages. The red horizontal line in *E* and *F* indicates a threshold *P* value of 0.1.

Importantly, however, the trend development for larger cities as shown in Fig. 4 not only indicates a drop in the number of newly registered COVID-19 cases around the immediate timing of the introduction of face masks but also points to the presence of dynamic treatment effects as the average gap between treated regions and their synthetic control groups widens over time. This hints at the role played by mandatory face masks in avoiding a new wave of new infections once the economy and labor market is reopened. As Fig. 4*B* highlights, such an avoidance effect may be particularly important in larger cities with higher population density and accordingly higher intensity of social interaction[§§]

Taken together, over a period of 20 d, we observe an average reduction of 28.4 cases between treated and control regions in the context of urban areas. Relative to the average number of cumulative COVID-19 cases on 11 May in control regions (317.9), this amounts to a reduction of 8.9% in the cumulative number of COVID-19 cases and a reduction of 51.2% in newly registered cases. The difference in the daily growth rate of the number of infections correspondingly amounts to 0.46 percentage points. For the full sample, this difference is estimated to be 0.13 percentage points (see *SI Appendix*, section D.2 for an overview of all measures and *Method and Data* for theoretical background). This smaller magnitude in the latter sample including all municipal districts has to be evaluated against the background of a considerable degree of structural heterogeneity, for instance, related to the composition of the local population but also the local COVID-19 spread. We argue that the latter should thus be interpreted as a lower bound for the true treatment effects.

[§§]This is perfectly in line with ref. 7 given the reduction in aerosols and droplets via using masks.

Discussion

We set out by analyzing the effect of face masks on the spread of COVID-19 for a comparative case study of the city of Jena. Our quasi-experimental control group approach using SCM shows that the introduction of face masks on 6 April reduced the number of newly registered COVID-19 cases over the next 20 d by 75% relative to the synthetic control group. Comparing the daily growth rate in the synthetic control group with the observed daily growth rate in Jena, the latter shrinks by around 70% due to the introduction of face masks. This is a sizeable effect. The introduction of mandatory face masks and the associated signal to the local population to take the risk of person-to-person transmissions seriously apparently helped considerably in reducing the spread of COVID-19. Looking at average treatment effects for all other regions puts this result in some perspective. The reduction in the daily growth rate of infections amounts to 14% only. By contrast, when we focus on larger cities, we find a reduction in the daily growth rate of infections by roughly 47%.

What would we reply if we were asked what the effect of introducing face masks would have been if they had been made mandatory all over Germany? The answer depends, first, on which of the percentage measures we found above is the most convincing and, second, on the point in time when face masks are made compulsory. The second aspect is definitely not only of academic interest but would play a major role in the case of a second wave.[##]

[##]We implicitly assume that compliance to rules in Germany is sufficiently homogenous. Some field observations in this respect would be very useful, especially across federal states in Germany and worldwide. Ref. 19 reports that compliance for distancing rules rises when masks are worn. As a first guess and assuming a compliance of 100% in our treated regions, one would expect that a reduction in compliance by x% of the population leads to a reduction of the effects of masks by x%.

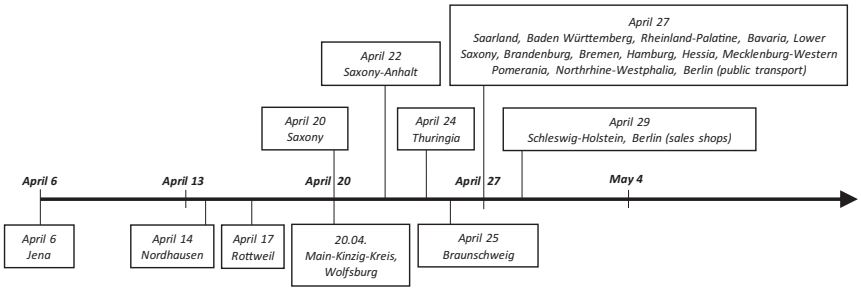

Fig. 5. The timing of mandatory face mask wearing in German federal states (*Top*) and individual regions (*Bottom*). The figure shows the regional variation in the introduction of face masks in public transport and shops over time. While text boxes above the timeline on the horizontal axis indicate the timing when the wearing of face masks became compulsory in the respective federal states (NUTS1 level), text boxes below the timeline identify individual NUTS3 regions that have anteceded the general introduction of face masks at the federal state level. The first NUTS3 region that introduced mandatory face masks in Germany was Jena on 6 April. By 29 April face masks had become mandatory in all German regions. (See *SI Appendix*, section A.1 for more background.)

We believe that the reduction in the daily growth rates of infections between 47% and 70% is our best estimate of the effects of face masks. Arguments in favor of the high 70% stress that Jena introduced face masks before any other region did so. It announced face masks as the first region in Germany while in our posttreatment period hardly any other public health measures were introduced or eased. Hence, it provides the most clear-cut quasi-experimental setting for studying its effects. Second, as described in *Method and Data*, Jena is a fairly representative region of Germany in terms of COVID-19 cases. Third, the smaller treatment effects observed in the multiple-treatment analysis may also result from the fact that—by the time that other regions followed the example of Jena—behavioral adjustments in Germany's population had already taken place. Wearing face masks gradually became more common and more and more people started to adopt their usage even when it was not yet required. The results for the subsample of larger cities are, however, quantitatively similar to Jena.

Arguments for the lower 47% state that the stronger impact of face masks on the infectious in Jena may thereby partly be driven by a Hawthorn effect. The population in this pioneer region might have reacted very strongly to the mandatory introduction of face masks by taking the other imposed public health measures and hygiene rules (washing hands, limiting interactions, staying at home more, etc.) more seriously.

Concerning the point in time (or better, the point in the epidemic cycle) when face masks become mandatory, all of our estimates might actually be modest. The daily growth rates in the number of infections when face masks were introduced in Jena was around 2 to 3%. These are low growth rates compared to the early days of the epidemic in Germany, where daily growth rates lay above 50% (20). One might therefore conjecture that the effects might have been even greater if masks had been introduced earlier.

This timing effect might also explain the difference between Jena estimates and lower estimates for other regions. By the time Jena introduced face masks on 6 April, the general trend in development of COVID-19 cases was still relatively dynamic across German regions. In mid-April, when other regions followed the example of Jena and introduced face masks before the general introduction at the federal state level, overall daily growth rates were already lower.

We simultaneously stress the need for further complementary analyses. First, Germany is only one specific country. Different regulations, norms (which relate to compliance), or climatic conditions might change the empirical picture for other countries. Second, we ignored the impact of the number of tests on reported infections. While we do not believe that this matters for Germany as rules for testing are homogenous across regions, this might play a bigger role for international comparisons. Third, we have ignored spatial dependencies in the epidemic diffusion of COVID-19. This might also matter. Fourth, there are various types of face masks. We cannot identify differential effects since mask regulations in German regions do not require a certain type. Finally, economic costs should be taken into account. When we compare masks with other common measures,*** the implied economic costs for community masks seem comparatively low. This applies to disposable masks and reusable nonmedical masks. Yet, the cost of information campaigns should be taken into account. While a detailed cost–benefit analysis is needed, we would expect that a comparison with other policy actions would speak in favor of face masks. [See *SI Appendix*, section E.3 for a brief introduction to the literature. We estimate that costs (of households only) for face masks amount to 1.4 to 2.5% of disposable income.]

Method and Data

Variation in Timing. Six regions in Germany (municipal districts, equivalent to the European Union nomenclature of territorial units for statistics, NUTS, level 3 categorization) made face masks mandatory before their respective federal states. They are displayed in Fig. 5. The figure also shows differences across federal states in the timing of introducing mandatory face masks.

Statistical Method. We estimate treatment effects from introducing face masks by means of the SCM for single and multiple treated units. (All analyses are undertaken in Stata. The corresponding files plus data are available in *SI Appendix*.) The SCM has become increasingly popular for policy evaluations that rely on comparative case studies. The intuition of SCM estimation can briefly be described as follows (see ref. 2–5 and *SI Appendix*, section B for more background).

First, the method can be applied to policy interventions (thereafter treatment) which only target a small number of treated units (in our case, one or a few regions). Treatment effects are identified by comparing the development of outcomes in treated and control regions during the treatment period. For causal inference, the proper selection and weighting of control regions is crucial to credibly estimate what outcome would have been observed in the treated region in the absence of the treatment. To establish this counterfactual, the SCM approach constructs a synthetic control group as weighted average of regions in the donor pool of controls. Weights for individual control regions vary between 0 and 1, sum up to 1 over all control regions, and are determined on the basis of a minimum distance approach. The latter involves a set of predictor variables chosen by the researcher as to closely match the outcome of the treated region prior to the treatment (predictors used here are listed in *SI Appendix*, Table S4 and selected weights for control regions are displayed in *SI Appendix*, Table S5).

Second, statistical significance of the estimated treatment effect is based on permutation. The SCM estimates a series of placebo treatment effects for all regions in the donor pool, that is, each region in the donor pool is treated

***Common measures can be grouped inter alia into closures (of, e.g., restaurants or hotels, educational institutions or clubs, and leisure facilities), contact bans (for individuals, faith groups, or visits to hospitals or retirement homes), and contact rules (social distancing or quarantines after traveling).

STATISTICS

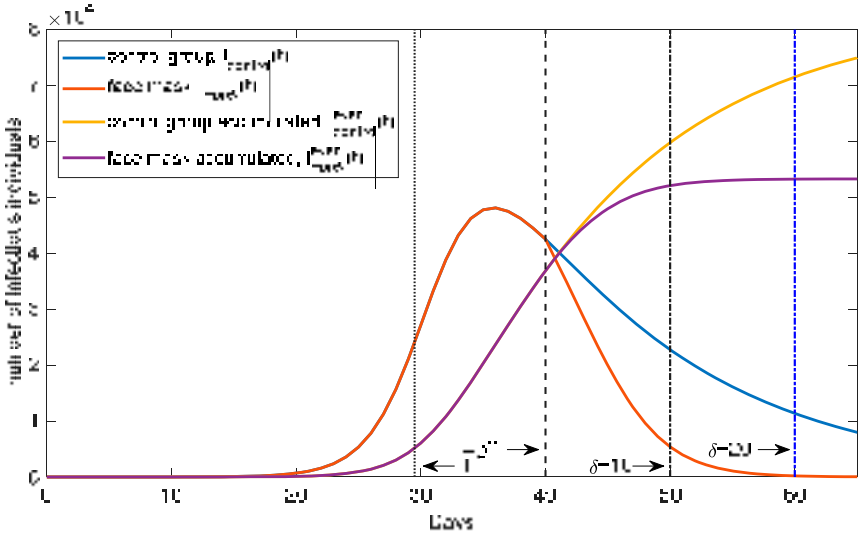

Fig. 6. Theoretical effects of face masks on the number of infectious individuals I(t) and on the accumulated number of infectious individuals I^{ever}(t). The horizontal axis plots time and the vertical axis the number of infectious individuals, both new cases (blue and red curves) and accumulated cases (yellow and purple curves). The curves show time paths following from a standard SIR model. We let an intervention take place on day $T = 29$. After a delay of D^m days, where D^m is the median of the delay between infection and reporting, the effect of the intervention is visible. Waiting 10 or 20 d then allows us to quantify the effect of the intervention.

as if it had been treated. The distribution of placebo effects is then compared with the treatment effect for the treated region. If the magnitude of the latter effect is large relative to the distribution of the placebo effects, the treatment effect is considered not to be observed by chance, that is, it is deemed to be significant.

Third, the effective use of SCM relies on contextual requirements: 1) A donor pool of controls is available, that is, not all regions receive the treatment during the period of the study; 2) predictor values of the treated region are not extreme relative to those of controls, that is, the treated region lies in the convex hull of control regions; 3) data are available for a sufficiently long time horizon before and after the start of the treatment; 4) spillover effects of the treatment on controls are absent; and 5) there are no early anticipation effects. Implications of these requirements for our analysis are discussed in *SI Appendix*, section B and we apply a series of robustness tests to check if the requirements hold in our data settings (reported in *Robustness Checks*).

Finally, as we also employ DiD estimation, we briefly touch upon the relationship between these two approaches. Similar to SCM, the DiD approach estimates treatment effects by contrasting changes in outcomes between a pretreatment and treatment period for treated and nontreated (control) regions. An attractive feature of the DiD approach is its flexibility in estimating dynamic treatment effects, that is, those that build up over time potentially determined by (unobserved) interventions starting at different time periods. (This is the reason why we employed DiD above.) By contrast, DiD has its limits when only one or a few treated regions are available as heteroscedastic errors might occur (see ref. 21). DiD estimation also relies strongly on the validity of the parallel trends assumption: It requires that treated and control regions would have followed parallel trajectories over time if treatment had not occurred. Given the highly dynamic development of regional COVID-19 cases and the likely presence of macroregional trends, the validity of the common trend assumption is questionable in our data settings. For SCM estimation, we do not need to impose this assumption as the presence of common trends between treated and control regions is in itself a favorable factor for finding an appropriate counterfactual trajectory (2, 3, 22).

Data. We use the official German statistics on reported COVID-19 cases from the Robert Koch Institute (23). We build a balanced panel for 401 NUTS level 3 regions and 105 d spanning the period from 28 January to 11 May 2020 (42,105 observations). We use the cumulative number of registered COVID-19 cases in each district and the number of cumulative COVID-19 cases per 100,000 inhabitants as main outcome variables. We estimate overall effects for these variables together with disaggregated effects by age groups (persons aged 15 to 34 y, 35 to 59 y, and 60+ y). We also employ regional data to inter alia identify control regions. *SI Appendix*, Table S4 shows summary statistics.

Face masks are clearly not the only public health measures to mitigate the spread of COVID-19. Identification of the face mask effect therefore needs to take the timing of other public health measures into account. To this end, we built a database for all public health measures in Jena and Thuringia and for face masks in all other federal states. See *SI Appendix*, sections A.1 and A.2 for details. The database indicates that our results indeed capture the effects of face masks and not of other public health measures.

Conceptional Background. To facilitate the interpretation of our findings, we employ a standard SIR model with three states: susceptible, infectious, and removed (see *SI Appendix*, section A.4 for more details.) Imagine we study a region where face masks are not mandatory. The time path $I(t)$ of infections individuals in this (synthetic) control group is displayed in Fig. 6 as $I_{control}$(t). The time path for I^{ever}(t) in the control group is denoted by $I^{ever}_{control}$(t). Now consider the introduction of mandatory face masks at T (set to 29.5 in Fig. 6).[†††] Mandatory masks reduce the infection rate (via a parameter r in the SIR model). Given a (median) delay of D^m between infection and reporting to authorities (estimated at 10.5 d in *SI Appendix*, section A.3), we model this delay by effectively reducing r at $T + D^m$. Hence, as of $T + D^m$, the number of infectious individuals falls faster, see "face masks I_{mask}(t)," and the number of individuals ever infected rises less quickly, as visible when looking at I^{ever}_{mask}(t). Note the qualitative similarity between the yellow and purple curve here and the corresponding curves in Figs. 1*A* and 4 *A* and *B*.

Now imagine we want to quantify the effect of face masks. The model suggests that the effect of face masks can be described by the reduction in the total number of individuals ever infected. As an example, consider time $T + D^m + \delta$, that is, δ days after face masks became effective. The difference between the control region and the face-mask region is given by $I^{ever}_{control}(T + D^m + \delta) - I^{ever}_{mask}(T + D^m + \delta)$. Hence, the introduction of face masks reduced the number of COVID-19 cases by

[†††]We chose $T = 29.5$ as this yields a date when masks show an effect in the data on $T + D^m = 40$ where the epidemic is already beyond its peak in our simple model. This is consistent with Jena, where the incidence had already been declining when face masks became mandatory. Numerical solutions are computed in MATLAB. The code is available in *SI Appendix*.

$$\textit{reduction over } \delta \textit{ days } = \frac{I^{ever}_{control}(T + D^m + \delta) \; - \; I^{ever}_{mask}(T + D^m + \delta)}{I^{ever}_{control}(T + D^m + \delta) \; - \; I^{ever}_{control}(T + D^m)} * 100\%. \quad [1]$$

This equation produces the numbers we report to quantify the effects of face masks. *SI Appendix*, section D.2 describes our measures based on daily growth rates.

Data Availability. Public health data have been deposited in FigShare (https://doi.org/10.6084/m9.figshare.13065920). All study data are included in the paper and *SI Appendix*.

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Title: Mask mandates can limit COVID spread: Quantitative assessment of month-over-month effectiveness of governmental policies in reducing the number of new COVID-19 cases in 37 US States and the District of Columbia

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ABSTRACT

Introduction: SARS-CoV-2 is the beta-coronavirus responsible for COVID-19. Facemask use has been qualitatively associated with reduced COVID-19 cases, but no study has quantitatively assessed the impact of government mask mandates (*MM*) on new COVID-19 cases across multiple US States.

Data and Methods: We utilized a non-parametric machine-learning algorithm to test the *a priori* hypothesis that *MM* were associated with reductions in new COVID-19 cases. Publicly available data were used to analyze new COVID-19 cases from 37 States and the District of Columbia (i.e., "38 States"). We conducted confirmatory All-States and State-Wise analyses, validity analyses [e.g., leave-one-out (LOO) and bootstrap resampling], and covariate analyses.

Results: No statistically significant difference in the daily number of new COVID-19 infections was discernable in the All-States analysis. In State-Wise LOO validity analysis, 11 States exhibited reductions in new COVID-19 and the reductions in four of these States (AK, MA, MN, VA) were significant in bootstrap resampling. Only the Social Capital Index predicted *MM* success (training $p<0.028$ and LOO $p<0.013$).

Conclusion: Results obtained when studying the impact of *MM* on COVID-19 cases varies as a function of the heterogeneity of the sample being considered, providing clear evidence of Simpson's Paradox and thus of confounded findings. As such, studies of *MM* effectiveness should be conducted on disaggregated data. Since transmissions occur at the individual rather than at the collective level, additional work is needed to identify optimal social, psychological, environmental, and educational factors which will reduce the spread of SARS-CoV-2 and facilitate *MM* effectiveness across diverse settings.

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INTRODUCTION

The significance of respiratory droplets and airborne viral particles in the spread of SARS-CoV-2 and propagation of the COVID-19 pandemic gained early attention.[1] Asymptomatic carriage of SARS-CoV-2 is important to community spread because these individuals can transmit the virus in exhaled breath.[2, 3] Corollary research reported that face masks are protective[4-7] and may limit the severity of COVID-19 among individuals who become infected.[8] Indeed, the Centers for Disease Control and Prevention (CDCP) has advocated wearing a facemask when social isolation is impossible or impractical,[9] and recently reported that dining-out is among the riskiest known activities during the coronavirus pandemic—since face masks *are not used* when people are eating and drinking.[10] Other activities associated with an increased risk of SARS-CoV-2 transmission include singing[11] and aerosol generating procedures in the healthcare setting.[12] Small droplet formation, which can lead to aerosolization of the virus, is a major driver of infection risk,[13] thus wearing a facemask is expected to reduce inhalation of aerosolized virus.[4] Indeed, low rates of positive serology were observed (i.e., < 4% n=1/27) when healthcare workers followed aerosol minimizing procedures *and* used personal protective equipment to perform deep respiratory sampling in patients with COVID-19.[14] Thus, there is consensus in the scientific, clinical, and business communities that appropriate wearing of facemasks is a "best-practice" personal behavior, which can reduce the chances of being infected by, or of infecting others with, SARS-CoV-2 and other airborne disease-causing microbes.

Mathematical and time-series models of COVID-19 data collected in the US investigated salutary effects of masking on reducing the spread of the pandemic.[15, 16] These models suggest that a consistent application of best-practice public-health orders and citizen behaviors is needed to slow the spread of the pandemic.[17] A hybrid modeling approach used by the Institute for Health Metrics and Evaluation predicted that if 95% of people in the US wore masks outside their homes, the number of projected deaths from COVID-19 would drop by half within four months.[18] Thus, experts hypothesize that Mask Mandate

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(*MM*) orders should result in reduced COVID-19 transmission and fatalities—assuming that the individuals in the community adhere to the *MM*.

Encouraged by research findings that wearing masks reduces the number of new COVID-19 cases, and motivated to intervene by increasing numbers of cases, Governors of 37 US States and the District of Columbia (hereafter called the "38 States") issued *MM* orders. However, the lack of clear, consistent Global, Federal, and State guidance on the use of face coverings (e.g., mandates *vs*. recommendations), and on who should be using masks (e.g., essential workers *vs*. private citizens), has initiated a nation-wide naturalistic experiment.[15] In the absence of clear guidance and direct leadership, variations in *MM* acceptance and enforcement have arisen within and between US States.[17, 19-22]

Promulgating and exacerbating confusion regarding the effectiveness of wearing face masks, adjudicating the effectiveness of *MM* orders has largely been left to *qualitative interpretations* and *visual/numerical inspections* of the epidemic curves depicting the number of new cases over time. Qualitative assessment cannot objectively test the *a priori* hypothesis that wearing a mask in public spaces reduces the incidence of COVID-19 cases. Accordingly, using publicly-available data, we employ non-parametric maximum-accuracy machine-learning to *quantitatively* test the confirmatory (*a priori*) hypothesis that imposing a *MM reduced* daily number of new COVID-19 cases in the month *after vs*. *before* the *MM*.

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METHODS

Hypotheses

First, merging data from all 38 States in which the Governor issued a *MM*, we test the *a priori* hypothesis that "*All-States*" imposition of a *MM reduced* the daily number of new COVID-19 cases in the month *after vs*. in the month *before* the *MM*. States were included if State leadership (e.g., Governors) had mandated the use of facemasks by all public-facing employees.

Second, considering each State individually, we test the *a priori* hypothesis that "*State-Wise"* imposition of *MM reduced* the daily number of new COVID-19 cases in the month *after vs*. in the month *before* the *MM*.

Data

The daily number of new COVID-19 cases was obtained separately for each State in the month *before* the *MM* was made (maximum of 30 days), and in the month *after* the *MM* was made (maximum of 31 days). Case reports occurring before the *MM* were dummy-coded as class=0, and case reports occurring after the *MM* were coded as class=1. Data from The New York Times, based on reports from State and local health agencies, were initially downloaded from GitHub on August 8, 2020 (data re-confirmed on September 23, 2020)[23] and cross referenced against the COVID-19 State Policy Database (data through June 1, 2020) for dates that *MM* were issued in each State.[24]

Our decision to compare daily number of new cases in the month before *vs*. the month after the *MM* was based on methodological and statistical considerations. First, *MM* orders were made because the day-over-day increases in the number of new cases threatened the ability of available health care resources to meet patient and healthcare worker needs. Therefore, the month following the *MM* naturally offers great opportunity for increased mask wearing to meaningfully reduce the number of new cases. Second, some amount of time is required after the *MM* is made for citizens (who wish to comply) to obtain masks, learn

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how and when to wear them, and how to care for them, and for new infections occurring in the two-week period prior to the *MM* to develop symptoms after the *MM* was made. Third, to maximize the available statistical power of our analyses for estimating short-term effects (see *Statistical Analysis*), we extracted the number of cases for up to 30 days before and up to 31 days after the *MM* was implemented (yielding a maximum of n=61 data points for each state).

Additional attributes, obtained for individual States, were used in an attempt to discriminate States for which a *MM* did *vs*. did not reduce the number of new COVID-19 cases. Numerical attributes included population estimates,[26] gross domestic product (State and per capita),[27] age (with arbitrary brackets of 0-18, 18-25, 26-34, 35-54, 55-64, and 65+),[28] pre-pandemic (January 2020) number of unemployed persons and rate,[29] homelessness,[30] shelter beds,[31] incarceration number and rate,[32] number of nursing home residents,[33] population density (people per square mile in 2015),[34] urban overcrowding (number of houses having >1 person per room),[35] severe urban overcrowding (number of houses having >1.5 people per room),[35] ethnicity (white, black, and Hispanic categories),[36] Social Capital Index (a measure of social cohesion, where higher positive numbers indicate greater societal cohesion),[37] and obesity.[38] Categorical attributes included if the State's Governor wore a mask in public after the *MM* was made (0=Did not wear mask, 1=wore mask) which was assessed using media reports and public database image searches, the Governor's political party (0=Republican, 1=Democrat),[39] and the Governor's gender (0=Female, 1=Male).[40]

Statistical Analysis

We used confirmatory *O*ptimal *D*iscriminant (or *D*ata) *A*nalysis (ODA) to ascertain the *predictive accuracy* attained by using maximum-accuracy models to evaluate the *hypothesized reduction in the number of new cases* occurring subsequent to the *MM*.[41-43] ODA is the moniker of the statistically-motivated non-parametric machine-learning algorithm which identifies the cut-point for an ordered *attribute* (i.e., "independent variable"), or the assignment rule for a categorical attribute, which yields the

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133 *strongest achievable accuracy* in discriminating between two or more class categories (i.e., "dependent
134 variable") for a given sample and hypothesis.[41-43] In the present study all hypotheses were confirmatory.[42]
135 For both the All-States (38-State) and the State-Wise analysis, the *a priori* hypothesis was that the *MM*
136 (up to 31 days) reduced the number of new cases.[44, 45]

137 An ODA model is obtained by iterating through every possible different assignment rule that is consistent
138 with the *a priori* hypothesis, and identifying the model achieving the highest effect strength for sensitivity
139 (ESS) statistic.[41, 42] An index of classification accuracy adjusted to remove the effect of chance, ESS is a
140 function of the mean sensitivity of the model achieved across class categories, standardized such that 0
141 represents the discriminatory accuracy which is expected by chance, 100 represents errorless (perfect)
142 discrimination, and values of $-100 \leq ESS < 0$ represent accuracy which is worse than expected by chance.
143 For a two-category *class variable* such as studied herein (i.e., month before *MM*=class 0 *vs*. month after
144 *MM*=class 1),

145 Mean Classification Accuracy (%) = 100 x [(sensitivity for class 0 + sensitivity for class 1)/2], (1)
146 and
147 ESS = 100 x [(Mean Classification Accuracy–50)/50]. (2)

148 A nonparametric permutation test which requires no distributional assumptions is used to assess the
149 statistical significance (p value) of the achieved ESS.[41, 44, 45] Point estimates of p values for tests of
150 statistical hypotheses reported herein are indicated as being statistically significant ($p \leq 0.05$) at either the
151 *experimentwise* (confirmatory $p \leq p_{Bonferroni}$) or the *per-comparison* (confirmatory $p \leq 0.05$) criterion.[42]

152 Internal model validation was conducted using bootstrap resampling[46, 47] (n=25,000) of the State-Wise
153 models within the *ODA* package for R.[48] Specifically, resampling with 50% replacement was conducted
154 using the LOO (i.e., validity) ODA model confusion matrix for each State. Exact discrete 95% confidence
155 intervals (CI) for the given ODA model ("Model") and for randomly scrambled observations from the

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model ("Chance") were obtained.[46] Graphical depictions of new cases organized across days, and histograms of bootstrapped 95% CIs, were created using *ggplot2* for R.[49]

Potential generalizability of the ODA model applied to classify an independent random sample is assessed using a one-sample "leave-one-out" (LOO) jackknife analysis.[42] The sample size offers greater than 90% power to identify an ODA model of moderate strength (i.e., 25≤ESS<50).[50]

Exploratory ODA analyses were conducted to model the association of inter-State differences 28 variables (e.g., age, wealth, population density) conceivably capable of discriminating States which did *vs*. did not exhibit the predicted decline in number of new cases in the month following a *MM* (see *Data Supplement*).[42]

Sensitivity analyses were conducted comparing the initial data (obtained August 8, 2020) to the data obtained September 23, 2020. The percentage difference between the two datasets were calculated for each value [i.e., 100 x ($data_{new}$-$data_{old}$) / $data_{old}$] to quantify differences between datasets. In sensitivity analyses, any differences between datasets were compared according to the ODA model cut-points obtained using the initial data to determine whether the model was invariant to new (updated) data.

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RESULTS

All-States Analysis

The *mean* number of new COVID-19 cases before *vs*. after the *MM* for the sample of 38 States was 654 (N=1138, SD=1357) *vs*. 639 (N=1177, SD=975), respectively. In three instances, the daily report of new cases appeared to be outliers (GA 4/12/20, LA 5/29/20, and VA 5/6/20) and were coded as missing (i.e., coded as -999). Confirmatory ODA was used to test the *a priori* hypothesis that imposition of a *MM* reduced the *number* of new COVID-19 cases (the attribute) one-month *after vs*. one-month *before* the *MM* (the class variable). The confirmatory ODA model was: if >4 new cases-per-day then predict pre-*MM*; otherwise if ≤4 new cases-per-day, then predict post-*MM*. In training (using all observations from the sample) analysis, this model correctly classified 98.1% of the pre-*MM* cases, and 6.1% of the post-*MM* cases: ESS=4.1 (a weak effect), $p<0.13$.

Thus, when considering all 38 States having a *MM* as a single sample, there was no statistically significant difference in the daily number of new COVID-19 infections in the month before *vs*. the month after the *MM*.

State-Wise Analysis

As seen in Table 1, after the *MM* the *mean* number of new daily cases was numerically *lower* in 13 States (AK, GA, HI, LA, MA, MI, MN, NY, VA, VT, WA, WV, WY) post-*MM*, and numerically *higher* in the remaining 25 States. Table 2 gives the findings of ODA used to test the *a priori* hypothesis that State-Wise imposition of a *MM* (made by 38 different State Governors) *reduced the number of new COVID-19 cases* in the month *after vs*. in the month *before* the *MM*—with each State considered individually. In each State-Wise analysis, the class variable was a binary coded variable signifying the period before *vs*. after the *MM* occurred, and the attribute was the daily number of new cases. In Table 2, the States are ordered from strongest to weakest ESS of the confirmatory ODA model in training analysis.

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193 Among all 38 States, training data for Minnesota (MN, the first State in Table 2) offer the greatest support
194 for the *a priori* hypothesis. The ODA model is: if >480 new cases-per-day, then predict pre-*MM*;
195 otherwise if ≤480 cases-per-day, then predict post-*MM*. This ODA model correctly classified 28 of 30
196 (93.3%) of the pre-*MM* days, and 27 of 31 (87.1%) of the post-*MM* days, thereby yielding a *strong*[42]
197 ESS=80.4, $p<0.0001$. However, this model showed modest instability in LOO jackknife analysis
198 (*relatively strong*[42] ESS=73.9, $p<0.0001$). In contrast, data for Alaska (AK, second row in Table 2) had
199 the second-strongest training effect (*strong* ESS=80.3, $p<0.0001$), which was stable in LOO analysis.
200 Among all 38 States, only AK returned a *strong* confirmation of the *a priori* hypothesis in training and
201 LOO analysis.

202 Of the total of 38 States included in this study, 11 (23.7%) achieved confirmatory $p<0.05$ at the
203 experimentwise criterion, and two (5.3%) achieved confirmatory $p<0.05$ at the per-comparison criterion[42]
204 (Table 2). Three States (MN, AK, HI) yielded a training model indicating a *strong* confirmation[42] (i.e.,
205 ESS≥75) of the *a priori* hypothesis. Five States (MA, VT, VA, MI, NY) yielded a training model
206 indicating a *relatively strong* confirmation[42] (i.e., 50≤ESS<75). And, three States (LA, WA, WY) yielded
207 a training model indicating a *moderate* confirmation[42] (i.e., 25≤ESS<50) of the *a priori* hypothesis.

208 Except for GA and WY, States having a numerically greater *mean* number of new daily cases pre- *vs.*
209 post-*MM* (Table 1) also had statistically-significant (at either the experimentwise or the per-comparison
210 criterion[42]) confirmatory (Table 2) and LOO (Table 3) ODA models supporting the *a priori* hypothesis.

211 For all 11 States in Table 2 having training $p<0.05$, Table 3 presents 95% exact discrete CIs obtained for
212 model and for chance.[46] For AK, VA, MA, and MN, the *lower bound* of the 95% exact discrete CI *for*
213 *model* is greater than the *upper bound* of the 95% exact discrete CI *for chance*—therefore the result is
214 statistically significant. For the remaining seven States, the upper bound for chance exceeded the lower
215 bound for the model, so the result was not statistically significant in bootstrap validity analysis.

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For example, the daily number of new COVID-19 cases one-month pre- and one-month post-*MM* is illustrated in Figure 1.A for MN. Figure 1.B is a graphical summary of the model and chance bootstrap results: the blue histogram represents chance, the red histogram represents the model, the Y axis is frequency of the result in the Bootstrap analysis, and the X axis is training ESS. The dashed vertical lines inside the Figure represent the lower 95% CI for the model (red dashes), and the upper 95% CI for chance (blue dashes). When the blue dashes are on the same side as the blue histogram, and the red dashes are on the same side as the red histogram, the effect is statistically significant. Thus, evaluating MN in training analysis, the *a priori* hypothesis is accepted with experimentwise $p<0.05$.

In contrast, Figure 2.A presents the daily number of new COVID-19 cases one-month pre- and one-month post-*MM* for WA, and Figure 2.B is a graphical summary of the model and chance bootstrap results. Since the blue dashes are on the side of the red histogram, and the red dashes are on the side of the blue histogram, the hypothesized effect is not statistically significant for WA.

Modeling Success *vs*. Failure of a *MM* Order in Reducing the Number of New COVID-19 Cases

Finally, ODA was used to discriminate the four States (AK, MA, MN, VA) having a significantly lower number of new cases after the *MM vs*. the 34 States which did not support the *a priori* hypothesis. The only attribute which met the per-comparison criterion for statistical significance[42] was SCI, a measure of societal cohesion and the closeness of social ties.[51] The ODA model was: if SCI≤0.311, then predict the *MM did not reduce* the number of new cases of COVID-19; otherwise if SCI>0.311 then predict the *MM reduced* the number of new cases. In training ($p<0.028$) and LOO ($p<0.013$) analysis this model correctly classified all four States in which the *MM* reduced the number of new cases, and 25 of 35 (71.43%) States in which the *MM* failed to reduce the number of new cases. This level of classification accuracy corresponds to ESS=71.43, indicating a relatively strong effect.[42]

Sensitivity analyses

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239 The dataset obtained on August 8, 2020 to was compared to a dataset obtained on September 23, 2020
240 and after exclusion of outliers (n=3), case numbers in the new dataset matched the original dataset (i.e.,
241 0% difference) for all states except Oregon (n=12/61) and Virginia (n=5/12), for which the new data fell
242 within ±6% of the original data. These numerical changes in data values (none of which were near the
243 ODA model cut-points) did not change the ODA model, the accuracy (ESS), or statistical significance (p)
244 of the model in training or LOO analysis for any model.

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DISCUSSION

An *All-States* analysis was conducted using merged data for 38 US States. Results indicated *no statistically significant decrease* in the number of new daily COVID-19 cases in the month before *vs*. after the *MM* was made. In contradistinction, a *State-Wise* analysis identified *clear evidence of State-specific MM effectiveness in reducing the number of new cases within one month of enactment* for multiple States (Tables 2 and 3). Such clear inconsistency is attributable to improper analysis of merged samples creating an analytic anomaly called *Simpson's Paradox*—which may identify spurious relationships, may fail to identify actual relationships, and/or may over- or under-weight the strength of effects—in every area of quantitative empirical science.[42, 47] *Paradoxical confounding* exists when the finding obtained by statistical analysis conducted for a combined sample is different than the finding obtained by the same analysis conducted separately for the constituent samples.[52] In the setting of a public health emergency, such as the current pandemic, accurate knowledge of the effectiveness of public health interventions is essential so that public health authorities can communicate this to the public.

Combining disparate groups is the primary operating procedure in government, scientific, and media discussions about the number of new and cumulative daily, monthly, and total number of COVID-19 cases and fatalities. Examples of such combined groups include global (the maximum-possible combined group), regional (e.g., the northern hemisphere), continental (e.g., Europe, Africa), and country (e.g., China, US, India, Brazil, France, UK, Israel) daily and cumulative case counts.[53] However, disparities in regional increases in numbers of new cases prompted some analysts to issue a warning against focusing on National trends.[54] Findings presented herein—that four of 38 (10.5%) States reliably demonstrated the hypothesized reduction in number of new cases in the month after the *MM* was made—similarly suggest a warning against focusing on State trends. Cognizance of the need to combine groups in a manner that prevents invalid statistical conclusions begs the question of how small must a "catchment area" be to count new cases so as to prohibit paradoxical confounding. Unfortunately, it has been shown that Simpson's Paradox can even occur for single-subject, "N-of-1" designs.[55] Thus, while accurate case

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counts and definitions are important for tracking the epidemiology of the pandemic, such measures do not necessarily reflect the "reality on the ground" in any specific community, nor can they reliably discern the individual effectiveness of public health interventions.

The current methodology of conducting after-the-fact pandemic accounting for convenient and familiar (statistically unmotivated) groups is obviously inadequate when it is considered from a problem-solving perspective that focuses on getting (and staying) ahead of the pandemic curve. Others have argued, early in the pandemic, that rapid and comprehensive contact tracing will empower understanding of the situations and the processes underlying new COVID-19 infections.[56] As is the case in fighting a wildfire, progress is made by going to the active location each day, extinguishing blazes, and reducing available fuel, rather than by assessing the number of acres which burned the day before. However, contact tracing is most effective when community spread is low, so multifaceted interventions are needed to control the spread of the pandemic and presently wearing a mask is the most efficacious known means of slowing the pandemic.[5, 6, 8, 15, 16]

Temporal counts of the number of new cases are an imprecise measure—including the month-over-month methodology used presently—for multiple reasons. Even with perfect *MM* compliance, there is an up to 14-day lag time between infection and presentation of symptoms, and potentially an even longer lag between infection and presentation at a healthcare facility. After a *MM* order is made, there are logistical problems in getting masks to people, and there is a learning curve for users—where, when and how to wear and care for masks. *MM* compliance is imperfect, and enforcement is difficult. Indeed, individual *MM* compliance is expected to be heterogeneous based on experimental evidence from behavioral psychology. Individuals are susceptible to cognitive biases and often use heuristics to address complex problems when uncertainty is high. Examples of such biases and heuristics related to *MM* use include availability bias (e.g., knowing someone who is sick *vs.* not), anchoring bias (e.g., fixation on initial recommendations to avoid mask use to preserve PPE), and substitution heuristics (e.g., physical

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discomfort with wearing a mask is substituted for mask efficacy).[57] The impact of these and other biases and heuristics on mask effectiveness is currently understudied.

Because transmissions occur at the level of the individual, rather than at a State or National level, governments should emphasize best-practice personal behaviors, adequate contact tracing, and minimization of high-risk exposures. Indeed, we posit that the efficacy of mask wearing is not at question as this depends only on the use of the mask. Instead, the effectiveness of *MM* can be eroded by multiple factors including asymptomatic carriage, willful ignorance of *MM* and lack of knowledge of how and when to wear masks. Moreover, our State-Wise analysis supports the *a priori* hypothesis that *MM* do indeed have a significant salutary effect on the spread of the pandemic, but more work is needed to define the social, psychological, environmental, and educational facilitators that maximize *MM* effectiveness.

Experimentally speaking, the best test of public health intervention effectiveness (e.g., *MM*)—using a methodology called an "A (before intervention), B (after intervention)" design—would involve simultaneous uniform application, enforcement, and education around the intervention, coupled with exacting real-time contact-tracing. A science-based, consistent approach to disease management could reduce public misunderstanding in this realm, and diminish mistrust of the other public health interventions (e.g., vaccines currently under development).[58] Our analysis is limited because we were not able to utilize a rigorous AB analytic framework to test our *a priori* hypotheses. Rather, we took advantage of the naturalistic experiment created by the heterogeneous response to the pandemic across States to highlight the paradoxical results obtained when applying an All-States followed by a State-Wise analytic approach. Our analysis was limited to testing our *a priori* hypothesis and it is worth considering the time-dependent impact of *MM*. Additional work is needed to evaluate the impact of *MM* on the growth of the pandemic. Our analysis is conservative in that we focused only on reductions in new cases and may underestimate the true impact of *MM*. Future studies should evaluate the impact of MM on new deaths. Large-scale serological studies may provide more insights into the spread of SARS-CoV-2 *MM* in States with vs. those without early *MM*.

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Finally, we found that SCI, a measure of social closeness and ties,[51] was a relatively strong predictor of *MM* effectiveness. This finding is notable in that SCI could be a facilitating factor that makes mandated public health interventions more efficient. For example, populations with higher levels of social cohesion are inherently more likely to work together when faced with a common problem based on a shared sense of identity and social bonds. However, this finding has limitations. States with higher SCI should not be interpreted as being inherently better at reducing new SARS-CoV-2 cases, but rather we believe this finding also supports a new corollary hypothesis that States with lower SCI may require different and multifaceted interventions to address the pandemic.

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CONCLUSION

We identified paradoxical confounding whereby the effect of *MM* orders when analyzed using the pooled data from all 38 States available differed when compared to a State-Wise analysis. Overemphasis placed on National or State-level trends may obscure the true effectiveness of important public health interventions such as mask wearing, because transmission events are stochastic and occur at the level of individuals. Thus, greater emphasis on the impact of personal behaviors on *MM* effectiveness and thorough contact tracing are needed to combat the pandemic. While societal factors reflected by measures like the SCI may facilitate the efficiency of interventions like *MM* in select regions, more work is needed to define the optimal set of interventions that reduce SARS-CoV-2 transmission for socially diverse populations. Finally, optimal experimental designs, measurements, and analytic approaches are needed to provide the public with a clearer understanding of the evolution of the pandemic, and feedback on how current public health interventions are performing, in order to begin to restore broad-based trust in the scientific method.

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Table 1: State-Wise Descriptive Statistics for Number of New Cases Pre- *vs*. Post-Mask Mandate (*MM*)

	Before *MM* (n≤30)		After *MM* (n≤31)	
State	Mean	SD	Mean	SD
AK	9.8	4.8	2.4	2.0
AL	229.4	64.1	390.3	158.0
AR	93.7	75.4	205.0	114.8
AZ	245.6	88.2	547.7	355.1
CA	1417.9	390.6	2147.9	464.8
CO	338.6	81.2	421.1	148.5
DC	68.0	52.3	155.3	52.7
DE	147.2	100.1	153.7	69.2
FL	754.3	263.8	863.7	305.2
GA	704.1	315.6	653.4	218.1
HI	17.1	9.4	3.4	4.3
IL	1564.2	504.7	2182.9	668.9
IN	530.7	134.4	559.0	132.2
KY	159.5	87.9	178.8	85.7
LA	760.2	606.1	399.2	237.0
MA	1925.7	718.4	1041.5	660.5
MD	385.2	292.1	911.0	240.9
ME	26.4	12.6	39.7	16.7
MI	1147.5	344.6	572.2	255.6
MN	637.7	116.4	383.6	101.5
MS	222.9	68.5	277.7	81.8
NE	179.6	152.3	296.1	109.6
NH	59.3	17.4	80.8	29.6
NJ	1480.3	1528.0	2936.7	808.8
NM	117.1	47.0	146.3	51.3
NV	120.8	38.8	124.9	42.7
NY	7479.5	2836.8	4170.2	2206.4
OH	503.5	288.7	574.1	106.9
OR	61.0	14.9	59.9	29.0
PA	1051.8	605.8	1150.4	355.1
RI	138.1	120.7	278.0	87.1
TX	923.8	222.6	1266.6	380.9
UT	65.9	56.0	137.8	34.7
VA	933.2	243.9	656.0	230.7
VT	25.1	16.2	5.5	5.2
WA	299.2	132.8	252.7	108.5
WV	31.8	17.7	28.4	19.5
WY	14.6	12.9	11.1	6.6

Legend: SD=Standard Deviation

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Table 2: Maximum-Accuracy Confirmatory Models Assessing State-Wise Mask Mandate (*MM*) Effectiveness

					Training		LOO[d]	
State	Pre-*MM*	Sensitivity (%)[a]	Post-*MM*	Specificity (%)[b]	*p*<	ESS (%)[c]	*p*<	ESS (%)[c]
MN	>480 Cases	28/30 (93.3)	≤480 Cases	27/31 (87.1)	0.0001	80.4	0.0001	73.9
AK	>4 Cases	27/30 (90.0)	≤4 Cases	28/31 (90.3)	0.0001	80.3	0.0001	80.3
HI	>6 Cases	26/30 (86.7)	≤6 Cases	28/31 (90.3)	0.0001	77.0	0.0001	64.0
MA	>1174 Cases	29/30 (96.7)	≤1174 Cases	23/31 (74.2)	0.0001	70.9	0.0001	64.3
VT	>14 Cases	23/30 (76.7)	≤14 Cases	29/31 (93.6)	0.0001	70.2	0.0001	66.8
VA	>691 Cases	27/29 (93.1)	≤691 Cases	23/31 (74.2)	0.0001	67.3	0.0001	67.3
MI	>732 Cases	26/30 (86.7)	≤732 Cases	24/31 (77.4)	0.0001	64.1	0.0001	50.8
NY	>4762 Cases	26/30 (86.7)	≤4762 Cases	22/31 (71.0)	0.0001	57.6	0.0001	51.0
LA	>340 Cases	26/30 (86.7)	≤340 Cases	17/30 (56.7)	0.0027	43.3	0.0037	36.7
WA	>294 Cases	17/30 (56.7)	≤294 Cases	25/31 (80.6)	0.011	37.3	0.0028	37.3
WY	>15 Cases	13/30 (43.3)	≤15 Cases	27/31 (87.1)	0.036	30.4	0.04	24.0
PA	>1389 Cases	12/30 (40.0)	≤1389 Cases	26/31 (83.4)	0.16	23.9	0.07	20.5
OR	>41 Cases	28/30 (93.3)	≤41 Cases	8/31 (25.8)	0.25	19.1	0.23	9.5
GA	>886 Cases	8/29 (27.6)	≤886 Cases	28/31 (90.3)	0.34	17.9	0.21	11.0
WV	>36 Cases	11/30 (36.7)	≤36 Cases	25/31 (80.6)	0.31	17.3	0.18	14.0
DE	>203 Cases	6/30 (20.0)	≤203 Cases	28/31 (90.3)	0.65	10.3	0.34	7.0
OH	>768 Cases	4/30 (13.3)	≤768 Cases	30/31 (96.8)	0.68	10.1	0.30	6.8
KY	>64 Cases	28/30 (93.3)	≤64 Cases	5/31 (16.1)	0.7	9.5	0.30	9.5
IN	>396 Cases	27/30 (90.0)	≤396 Cases	6/31 (19.4)	0.72	9.4	0.38	6.1
NV	>189 Cases	3/30 (10.0)	≤189 Cases	30/31 (96.8)	0.81	6.8	0.99	-77.1
NE	>455 Cases	3/30 (10.0)	≤455 Cases	30/31 (96.8)	0.81	6.8	0.82	-3.0
AL	>107 Cases	30/30 (100)	≤107 Cases	2/31 (6.4)	0.84	6.4	0.52	3.1
NJ	>4296 Cases	1/30 (3.33)	≤4296 Cases	31/31 (100)	0.94	3.3	0.88	-3.1
TX	>477 Cases	30/30 (100.0)	≤477 Cases	1/31 (3.2)	0.96	3.2	0.51	3.2
FL	>534 Cases	25/30 (83.3)	≤534 Cases	6/31 (19.4)	0.97	2.7	0.77	-3.9
NM	>216 Cases	2/30 (6.7)	≤216 Cases	29/31 (93.6)	0.98	0.2	0.94	-6.3
MS	>138 Cases	28/30 (93.3)	≤138 Cases	2/31 (6.4)	0.99	-0.2	0.95	-6.8
UT	>176 Cases	2/30 (6.7)	≤176 Cases	28/31 (90.3)	0.99	-3.0	0.99	-12.8
DC	>224 Cases	1/30 (3.3)	≤224 Cases	29/31 (93.6)	0.99	-3.1	0.88	-3.1
MD	>1154 Cases	1/30 (3.3)	≤1154 Cases	29/31 (93.6)	0.99	-3.1	0.94	-6.3
CO	>210 Cases	28/30 (93.3)	≤210 Cases	1/31 (3.2)	0.99	-3.4	0.89	-3.4
NH	>34 Cases	28/30 (93.3)	≤34 Cases	1/31 (3.23)	0.99	-3.4	0.95	-6.8
ME	>61 Cases	1/30 (3.3)	≤61 Cases	27/31 (87.1)	0.99	-9.6	0.99	-93.4
IL	>1133 Cases	26/30 (86.7)	≤1133 Cases	1/31 (3.2)	0.99	-10.1	0.98	-10.1
AR	>34 Cases	24/30 (80.0)	≤34 Cases	1/31 (3.2)	0.99	-16.8	0.99	-20.1
AZ	>161 Cases	24/30 (80.0)	≤161 Cases	1/31 (3.2)	0.99	-16.8	0.99	-20.1
RI	>273 Cases	9/30 (30.0)	≤273 Cases	16/31 (51.6)	0.99	-18.4	0.99	-41.7
CA	>2315 Cases	2/30 (6.7)	≤2315 Cases	21/31 (67.7)	0.99	-25.6	0.99	-32.2

Footnotes: a) Sensitivity gives the results for the predicted (numerator) and the actual (denominator) number of new cases after *MM*. b) Specificity gives the results for predicted (numerator) and actual (denominator) number of new cases before *MM*. c) ODA models explicitly maximize classification (i.e., predictive) accuracy adjusted for chance, which is assessed

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by the effect strength for sensitivity (ESS) statistic: ESS=0 is the accuracy expected by chance; ESS<25 is a relatively weak effect; ESS<50 is a moderate effect; ESS<75 is a relatively strong effect; ESS<90 is a strong effect; and -100≤ESS<0 is accuracy which is worse than expected by chance. In this column, MN has a training model with an ESS that provides the strongest support for the *a priori* hypothesis and is statistically significant whereas CA has a training model that provides the least support for this hypothesis and is not significant. d) Classification performance in validity analysis was computed using a one-sample leave-one-out (LOO) jackknife validity assessment. In this column, AK has a validity model with an ESS that provides the strongest support for the *a priori* hypothesis and is statistically significant whereas ME has a validity model that provides the least support for this hypothesis and is not significant.

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Table 3: LOO Confirmatory *p*, and Bootstrap 95% CI for LOO ESS, for 11 States Demonstrating Mask Mandate (*MM*) Effectiveness vis-à-vis Training $p<0.05$

State	$p <$	Chance 95% CI[a]	Model 95% CI[a]	95% CI overlap[b]
AK	0.0001	-36.1 – 35.9	64.6 – 100	No
VA	0.0001	-35.8 – 35.9	49.9 – 100	No
MA	0.0001	-35.0 – 34.8	41.7 – 92.9	No
MN	0.0001	-35.9 – 36.1	40.3 – 95.2	No
HI	0.0001	-36.1 – 35.9	34.9 – 91.7	Yes
VT	0.0001	-35.7 – 34.9	30.3 – 86.7	Yes
NY	0.0001	-36.1 – 35.8	25.5 – 86.1	Yes
LA	0.0037	-34.8 – 35.7	25.0 – 84.6	Yes
MI	0.0001	-35.8 – 36.1	11.1 – 76.6	Yes
WA	0.0028	-34.4 – 35.0	0.00 – 68.4	Yes
WY	0.04	-33.3 – 33.5	-10.1 – 58.3	Yes

Footnotes: a) Exact Discrete 95% Confidence Intervals (CIs) for Model and Chance ESS were estimated using bootstrap resampling of the ODA model confusion matrix from each respective State obtained in LOO analysis. b) For a given State, if the upper bound (UB) of the CI for chance falls *beneath* the lower bound (LB) of the CI for the model, this column indicates NO 95% CI overlap—so the confirmatory hypothesis is *accepted* (i.e., the *MM* reduced the number of new cases). And, for a given State, if the UB of the CI for chance falls *above* the LB of the CI for the model, this column indicates YES 95% CI overlap—so the confirmatory hypothesis is *rejected* (i.e., the *MM* did not reduce the number of new cases). In other words, if the exact discrete CIs for model and chance do not overlap, then the ODA model identified in LOO analysis is considered statistically robust and the findings are likely to be generalizable.

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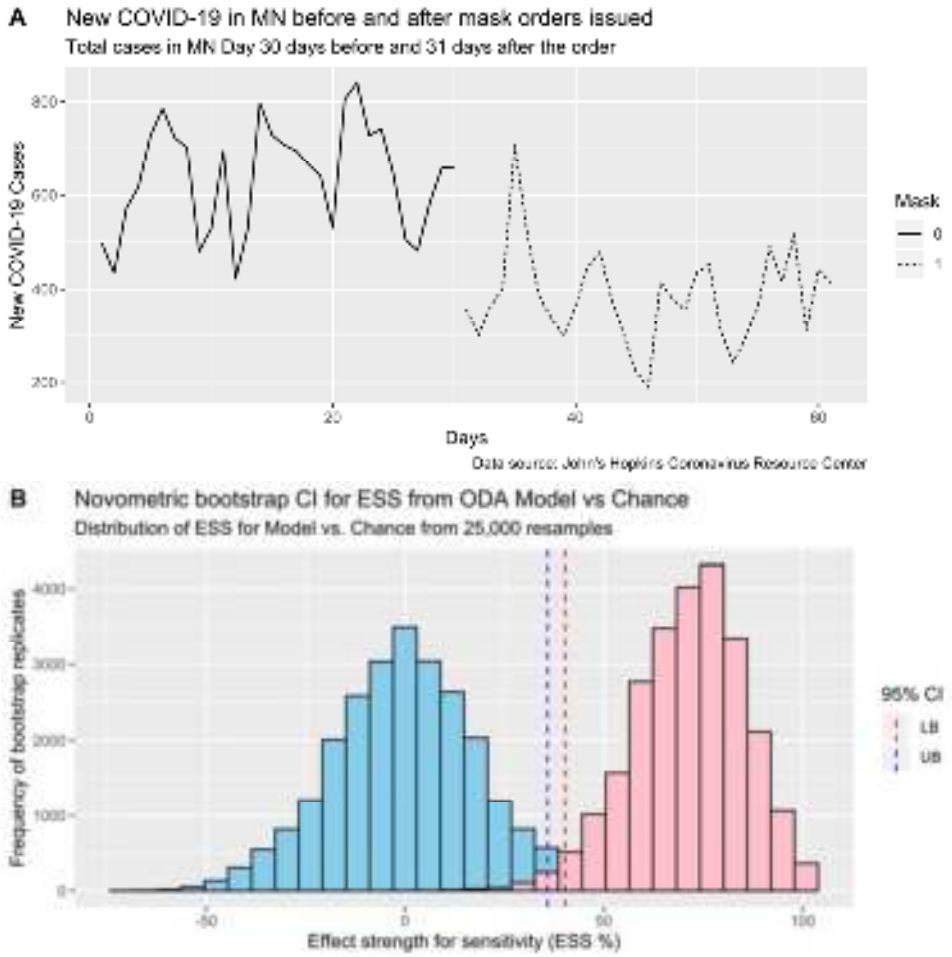
Figure 1. Representative state (MN) with a strong impact of Mask Mandate (*MM*) orders



Legend:

Panel A. Number of new COVID-19 cases reported within MN daily in the month before (solid black line) *vs*. daily in the month after (broken black line) *MM* orders were issued.

Panel B. Distribution of bootstrap replicates for model and chance for the LOO analysis for MN by ODA. Here, the ODA model was resampled using bootstrap resampling with replacement (n=25,000 resamples with 50% replacement) for the LOO model confusion matrix (see Table 3) as well as for chance (i.e., the final model predictions randomly scrambled relative to the class variable). The lack of overlap between the Chance UB and Model LB is denoted by the alignment (rather than reversal) of the dashed lines with the corresponding Chance (blue) and Model (red) bootstrap distributions.

Abbreviations: LB = lower bound of the 95% CI (i.e., 2.5th percentile); UB = upper bound of the 95% CI (i.e., 97.5th percentile); LOO = leave-one-out one-sample jackknife.[42]

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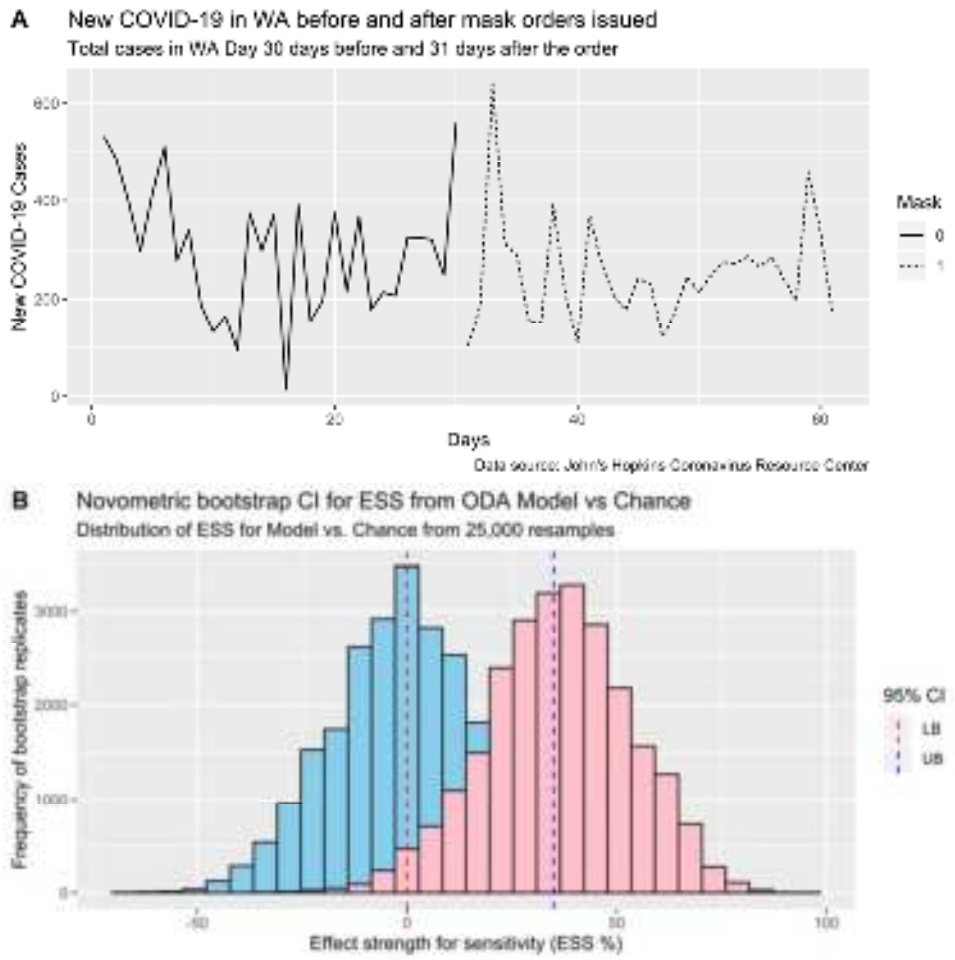
Figure 2. Representative state (WA) with a moderate impact of Mask Mandate (*MM*) orders



Legend:

Panel A. Number of new COVID-19 cases reported within WA daily in the month before (solid black line) *vs*. daily in the month after (broken black line) *MM* orders were issued.

Panel B. Distribution of bootstrap replicates for model and chance for the LOO analysis for WA by ODA. Here, the ODA model was resampled using bootstrap resampling with replacement (n=25,000 resamples with 50% replacement) for the LOO model confusion matrix (see Table 3) as well as for chance (i.e., the final model predictions randomly scrambled relative to the class variable). The overlap between the Chance UB and Model LB is denoted by the reversal (rather than alignment) of the dashed lines with the corresponding Chance (blue) and Model (red) bootstrap distributions.

Abbreviations: LB = lower bound of the 95% CI (i.e., 2.5th percentile); UB = upper bound of the 95% CI (i.e., 97.5th percentile); LOO = leave-one-out one-sample jackknife.[42]

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How Policies on Restaurants, Bars, Nightclubs, Masks, Schools, and Travel Influenced Swiss COVID-19 Reproduction Ratios

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Summary. The role of complete lockdowns in reducing the reproduction ratios (R_t) of COVID-19 is now established. However, the persisting reality in many countries is no longer a complete lockdown, but restrictions of varying degrees using different choices of Non-pharmaceutical interaction (NPI) policies. A scientific basis for understanding the effectiveness of these graded NPI policies in reducing the R_t is urgently needed to address the concerns on personal liberties and economic activities. In this work, we develop a systematic relation between the degrees of NPIs implemented by the 26 cantons in Switzerland during March 9 – September 13 and their respective contributions to the R_t. Using a machine learning framework, we find that R_t which should ideally be lower than 1.0, has significant contributions in the post-lockdown scenario from the different activities - restaurants (0.0523 (CI. 0.0517-0.0528)), bars (0.030 (CI. 0.029-0.030)), and nightclubs (0.154 (CI. 0.154-0.156)). Activities which keep the land-borders open (0.177 (CI. 0.175-0.178)), and tourism related activities contributed comparably 0.177 (CI. 0.175-0.178). However, international flights with a quarantine did not add further to the R_t of the cantons. The requirement of masks in public transport and secondary schools contributed to an overall 0.025 (CI. 0.018-0.030) reduction in R_t, compared to the baseline usage even when there are no mandates. Although causal relations are not guaranteed by the model framework, it nevertheless provides a fine-grained justification for the relative merits of choice and the degree of the NPIs and a data-driven strategy for mitigating R_t.

Keywords. COVID-19; Non-pharmaceutical interventions; Lockdown; Policy; Reproduction ratio Switzerland;

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1. Introduction.

COVID-19 has caused over a million deaths, and many millions of infections globally. Despite the intense global efforts, there is no scalable treatment or vaccine yet. This problem is compounded by the fact that the epidemiology of COVID-19 is very unique [2] and that it spreads efficiently, with an estimated 44% [3] to 69% [4] of the transmissions before the onset of symptoms. Non-pharmaceutical interventions (NPI) have been the only successful method of mitigating the spread of infections [5-7]. In addition to the initial recommendations on social-distancing and sanitizing, complete lockdowns and restricted opening of businesses had been implemented in various degrees. There have been several demonstrations of the effectiveness of the lockdowns in successfully reducing the reproduction ratio (R_t) and mitigating the spread of COVID-19 [8-11].

NPIs performing a balancing act. The goal of NPIs is to flatten the infection curve [12] until there is a change in the infection landscape due to a scalable vaccine, therapeutic intervention, or a mutation in the virus which reduces the case fatality rate. However, since NPIs affect both personal liberties and economic welfare, it is important to know the effectiveness of the different NPIs for evidence-based public health planning. The impact of the two extremes of the NPI spectrum [8-11], no restrictive measures and a complete lockdown are relatively easy to understand. However, many policies changes, such as the compulsory use of masks, different degrees of opening of the restaurants or bars have been applied simultaneously, and it has not been easy to quantify the effectiveness of the contributions from these different factors. To the best of our knowledge, there have not been any examples of deciphering the contributions of the policies to the R_t.

In this work, we apply a recently developed formalism [13] to decipher the role of the different NPI policies adopted by Switzerland. Until April, Switzerland had the highest per-capita COVID-19 infections globally, however Switzerland could open up most of its activities staring May. During May-July period, the number daily new infections was less than 100, and it was followed by increasing infections as well as tightening of regulations. The few cases together with an efficient infrastructure for contact tracing [14] helped isolate all potentially infected persons, and helped in mitigating the spread of infections. However, as the daily new cases crossed 1,000 the fears that the efficiency of the contact tracing are reaching the limits begins to resound. Further, another complicated aspect of the epidemiology of COVID-19 has been that the infections need not always be attributable to a symptomatic person. The ability to understand the overall impact of an NPI policy on the overall infections, which implicitly includes the secondary infections, asymptomatic transmissions is thus needed and is the focus of the present article.

2. Results.

2.1 Relating the policies to reproduction ratios

2.1.1 Determinants - NPI Policy data.

To perform a quantitative analysis, the different degrees of non-pharmaceutical intervention policies were curated and codified. Media reports published in english language were used for this curation and the policies were cross-checked with the official press releases of the Federal and Cantonal authorities. The following codes were employed:

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- *BarbersSalonSpa*: Everything closed (0), Beauty salons, Barbers shops etc allowed to operate with the stipulated norms (1), Pre-lockdown level (2)
- *Bars*: Closed (0), Opened with limited capacity and restrictions on standing customers (1), Opened with full capacity while respecting social distancing (2), Pre-lockdown level (3)
- *Mask*: No mask requirement (0), Mask usage is mandatory in public transport (1), Mask usage is mandatory in shops (2)
- *Nightclubs and Discos*: Closed (0), Opened with contact tracing and checking the ID or with a limited audience of 50 to 100 (1), Opened with an audience of over 100 up to 300 (2), Pre-lockdown level (3)
- *Restaurants*: Closed (0), Takeaway only (1), restaurant occupancy limited to 50 (2), restaurant occupancy of 100 (3), Unrestricted but respecting social distancing (4), Pre-lockdown level (5)
- *Retail*: All non-essentials closed (0), Opening do-it stores (1), Opening all retail stores (2), Pre-lockdown level (3)
- *Schools*. Closed (0), Open with mask-requirements on pupils in all secondary-schools or when the distance between pupils is less than 2.25 meters (1), Open with no mask-requirements
- *Tourism potential.* The number of hotel rooms available in the cantons, invariable with time. This can be a surrogate for the general mobility and associated economic activity in the regions
- *Travel restrictions*: All travel from outside Switzerland is restricted (0), Travel by road to the cantons having a road-entry to Schengen countries is opened (1), In addition to the road travel from Schengen countries, International travel is permitted with a quarantine requirement upon arrival (2)

In this work we use the NPIs and R_t's with the resolution of a week [15]. Each NPI policy code was assumed to be the same for an entire week starting from Monday to Sunday. The data was applied over 26 weeks between March 9 to September 13. Several exceptional cases have not been included in the choice of the policy variables. Manufacturing was shutdown specifically in the early lockdown phase in Ticino (TI) canton. The states in USA had two major differences – "stay at home" versus "safe at home". The Swiss policies reflected more the latter, and unlike some states of USA or Italy had not restricted outdoor activities. Hence the permission for outdoor activities was not included in the analysis.

2.1.2 Consequences - Reproduction rates (R_t).

Time varying reproduction rate, R_t ($=\alpha_t/\gamma$) was estimated using the rates of transmission (α_t) and recovery from the infection (γ). The infected and recovered data was obtained from *https://www.corona-data.ch/*. We estimated the average recovery time in for Switzerland to be around 14 days, and $\gamma=1/14$. Using the number of active infections (I_{active}), and the number of daily new infections on a given day (dI/dt), the weekly averaged transmission rates were calculated as, $\alpha_t=\langle 1/I_{active} . (dI/dt)\rangle$.

2.1.3 Model - Interpretable Artificial Intelligence.

Our goal is to develop a model relating the controlling NPIs and the consequent reproduction ratios by a model, and to understand the relative contributions of the NPIs to the R_t. The NPIs of any week are assumed to affect the reproduction rate in the following week. To not restrict the model to linearity and maintain the generality, we used an artificial intelligence model. The data from 26 weeks and 26 cantons used, with 20% for testing and 80% for training. A 5-fold cross validation was used to further validate the results. The daily rates, their weekly averages α_t and how they change over the weeks is illustrated in Figure 2 and demonstrates a dynamic scenario.

The artificial intelligence (AI) model was developed using the *XGBoost* library in Python. 80% of the complete data set was used as the training set and 20% as the test set. The parameters for the AI model (*learning_rate*=0.08, *n_estimators*=525, *max_depth*=7, *min_child_weight*=5, *gamma*=0, *subsample*=0.85, *colsample_bytree*=0.75, *reg_alpha*=1) were obtained using *RandomizedSearchCV*. With these parameters, the predictions of the reproduction rates for the Cantons were good as shown in Table 1. Each model's

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predictive ability is evaluated using a 5-fold cross-validation analysis and the best set of parameters is selected based on the average of mean squared error for the validation sets. The quality of prediction seemed to be robust against changes in the training set as shown by the 5-fold cross-validation analysis.

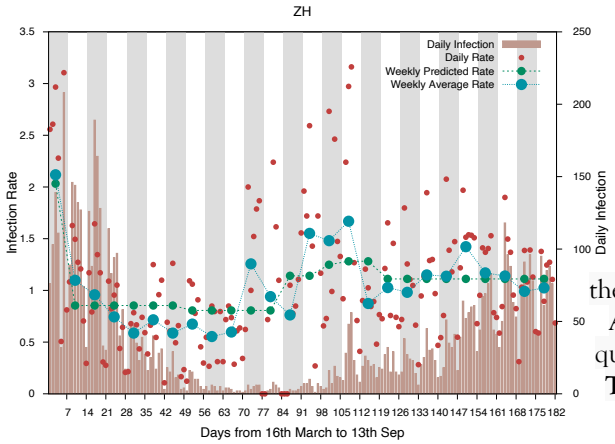

Figure 1. Comparing the observations and estimations from Zurich canton. The number of daily infection cases, the daily instantaneous R_t, and its weekly average are shown. Also shown is the R_t predicted using our AI model. The quality of predictions for the different cantons are shown in **Table 1**.

Canton	Cases until 13 September	R^2 from a single model	R^2 from 5-fold Cross Validation	Canton	Cases until 13 September	R^2 from a single model	R^2 from 5-fold Cross Validation
VD	8795	0.673117037	0.647847665	NE	985	0.25887226	0.21571116
GE	7616	0.627418522	0.625777595	SO	744	0.210001297	0.187173494
ZH	7008	0.598277452	0.586055896	TG	640	0.389502291	0.410028348
TI	3577	0.29952398	0.283008382	SZ	527	-0.07411167	-0.126575857
BE	2852	0.368545109	0.379780423	ZG	392	0.247699512	0.199368169
VS	2505	0.459523001	0.449849909	JU	289	0.137647876	0.120101292
AG	2364	0.618817663	0.640935414	SH	177	0.369710129	0.369761684
FR	2106	0.431110605	0.387268328	GL	168	0.140084061	0.13367399
SG	1414	0.384846143	0.374026311	AR	139	-0.01352006	-0.021623142
BS	1272	0.236721344	0.243603321	NW	139	0.035126862	0.068942698
BL	1137	0.341130146	0.33396309	UR	138	0.146536746	0.172496426
LU	1115	0.535569715	0.534524372	OW	108	-0.21602673	-0.20605954
GR	1049	0.311370476	0.328251839	AI	26	-0.67085668	-0.49664838

Table 1. Quality of predictions for the cantons. The co-efficient of determination R^2 is used as a metric to understand if the model results, including training and test, compare well with the R_t estimates. The results are good when the number of cases recorded were more than 1000. The uncertainties in both the estimation of R_t from the epidemiological data, and the predictions using a model are both expected when the number of infections are fewer.

2.2 Decoupling the contributions from the different NPIs.

2.2.1 Interpretable AI for relative contributions

We performed a retrospective analysis to understand the relation between the different non-pharmaceutical interventions policies imposed by each canton in every week between March 9 to September 13, which we codified as discussed above, and the reproduction ratios (R_t). To decouple the relative contributions from the individual NPIs to each of the weekly predictions, we post-processed the results of our AI model using an interpretable AI framework based on SHapley Adaptive exPlanation (SHAP) [16]. A Python implementation of SHAP (https://github.com/slundberg/shap) was used for our interpretable AI analyses. The SHAP analyses was repeated with a 5-Fold Cross-Validation and the variances were found to be minimal. The role of many NPIs with significant contributions to R_t are discussed below.

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2.2.2 Dine and drink.

The contributions to R_t from the different graded openings of the restaurants is shown in Figure 2A. The x-axis represents the different grades of opening of the restaurants: restaurants are closed (0), open with up to 50 clients (2), open with up to 100 clients (3), unrestricted clientele but following social distancing norms (4), pre-lockdown level (5). The restaurant-component to R_t from the predictions for the 26 cantons and 26 weeks (y-axis) is organized by the restaurant opening degree and displayed. The color of these points was used to represent the overall R_t in that canton in that week. The data shows a clear pattern of increasing contributions to the R_t from the increasing degrees of restaurant openings. Leaving the pre-lockdown conditions (code 5), which lacked sanitization, social-distancing measures, the maximum R_t one can expect because of opening restaurants at level 4 relative to a complete closure is 0.0523 (CI. 0.0517-0.0528). Similar analysis shows that different graded openings of the bars (Figure 2B) between a full opening of the bars (code 2) a complete closure (code 0) contribute 0.030 (CI. 0.029-0.030) to R_t. Nightclubs (Figure 2C) with more than 100 clients allowed (code 3) contributes 0.154 (CI. 0.154-0.156) to the R_t relative to their complete closure, and is the only case in all of our analysis where the R_t contribution is comparable to the contributions from the pre-lockdown period.

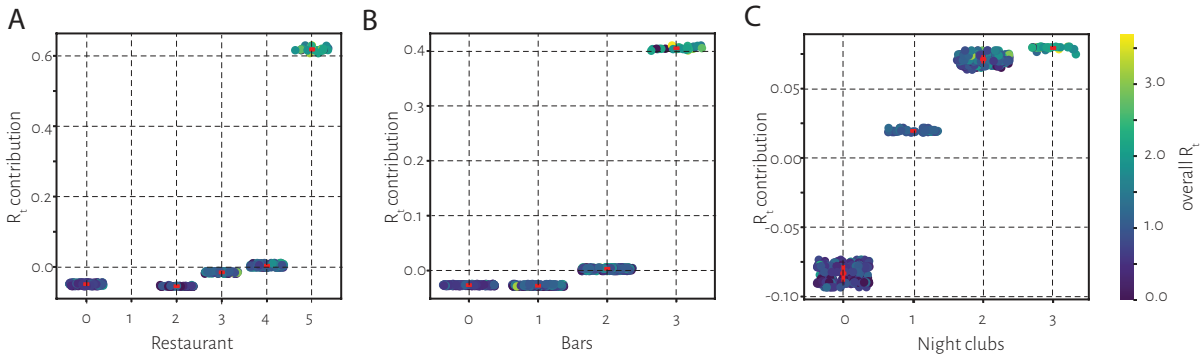

Figure 2. Impact of restrictive measures on dine and drink. The contributions to the R_t from the different restrictive policies for operating *A.* Restaurants *B.* Bars and *C.* Nightclubs are shown. Each point in the three graphs represents the contribution to the R_t from a specific week in one of the 26 cantons, and the colorbar represents the value of the R_t. In all three graphs, 0 on the x-axis represents the complete closure, and the highest value the pre-lockdown operational levels. The red lines indicate the confidence interval in each category.

2.2.3 Travel and tourism.

In March, Switzerland had closed entry access via road to Schengen countries as well as via air travel. Starting from mid-June, the road access to Schengen countries was opened (code 1 for cantons sharing borders with neighboring countries) and air-travel was permitted with a quarantine requirement upon arrival (code 2 for cantons with international airports). The contributions to R_t from this ease-of-access descriptor shown in Figure 3A, shows an additional R_t of 0.177 (CI. 0.175-0.178) due to opening of the land-borders. The international air-travel with a quarantine requirement did not contribute any further to the R_t. An additional factor that was included in the analysis was the tourism potential quantified by the number of hotel rooms in the canton, which of course remains constant during the 26 weeks of analysis. The variable contributed 0.179 (CI. 0.172-0.187) to the R_t. The tourism potential is neither the actual number of travels made in this year, nor an NPI policy, but a factor which remained a constant for each canton. However, given the magnitude of its contribution, it requires an interpretation, possibly of the surrogate it represents. Specifically, the cantons JU (code 102), AR (code 122) which have lower number of hotels are near the borders and have a high cross-border commuter traffic which is probably being captured in the analysis.

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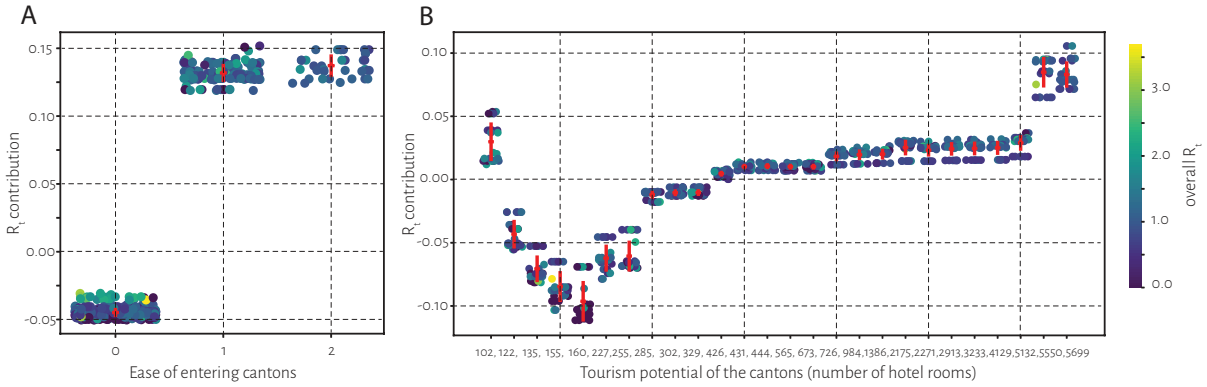

Figure 3. Impact of mobility. The contributions to R_t depending on *A.* the ease of entering the cantons by road or air travel where the codes 0 – no travel allowed, 1 – opening of Schengen borders, 2 – opening of international airports with quarantine on travelers were applied and *B.* Tourism potential, represented by the number of hotel rooms in the different cantons are indicated. The non-intuitive higher contributions to R_t in cantons with lower tourism potential, can be understood by the borders they share with other Schengen countries. At this moment, because of the lack of access to the actual travel data within Switzerland, it is not easy to infer whether this pattern is due to the commuters or domestic tourism.

2.2.4 Mask requirements.

Swiss Federal government made the use of masks in all public transport mandatory (code 1) since July 6. In subsequent weeks, many cantons made the use of a mask to enter the shops (code 2) compulsory. Compared to the no-mask requirement from the pre-lockdown period, a mandatory mask in public transport contributed to a reduction of 0.0139 (CI. 0.0132-0.0144) (Figure 4A). An additional requirement of using the masks in the shops when a requirement in public transport is already mandated (code 2) did not reduce R_t further. The use of mask in secondary schools was also made compulsory in some cantons (code 1), and its additional benefit relative to a scenario with schools not requiring masks (code 2) could be seen in Figure 4B. A reduction of R_t 0.011 (CI. 0.008-0.0127) was estimated because of the use of the masks in school. The combined effect of the use of mask in public transport and at schools is thus a reduction in R_t of 0.025 (CI. 0.018-0.030). It must be noted that the compliance in general may be different from the policy itself, where more people use the mask even if there is no recommendation. This will lead to underestimation of the beneficial effects of the use of the mask.

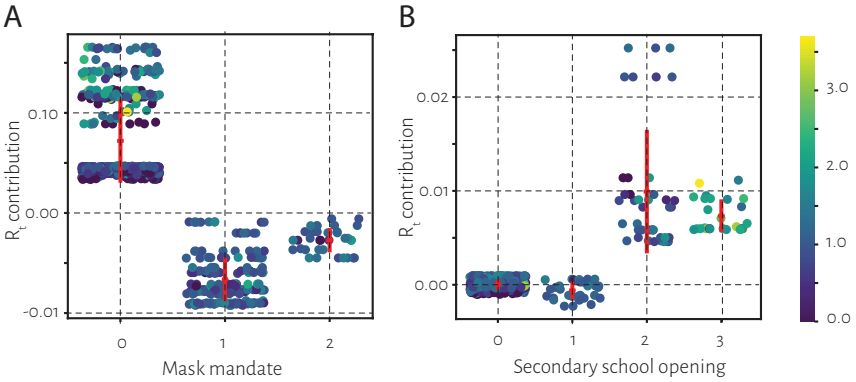

Figure 4. Impact of mask mandates. The mask imposition in *A.* public transport (code 1) and shops (code 2) and *B.* secondary schools (code1), and no-mask restrictions in schools (code 2) are compared. In both the settings the role of imposing a mask is clear.

3. Discussion

3.1 First estimates for the measure of effectiveness of individual NPIs.

Epidemiological scenario calculations forecast the number of infections and critical-care requirements for the various R_t's which are in-turn influenced by the NPIs. With an objective to understand how the different NPIs influence the reproduction ratios, the present work addresses the interesting and practically relevant zone between the extremes of a complete lockdown and no restrictions whose role on R_t is obvious. The present work attempts to decipher the contribution of each individual NPI

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implemented at a certain degree of restrictiveness. To the best of our knowledge there has been no precedence on the decomposition of the effectiveness of the different NPIs.

If we consider a mask mandate, there is no evidence for its effectiveness other than referring to the widespread use of masks in the Asian countries where the R_t's have been low. The efficacy of masks in reducing aerosol transmission under laboratory conditions [17] are cited as alternative evidences, although their relevance for real scenarios of mask usage in daily life and the impact on the transmission of the disease rather than aerosols is not clear. Our work which interprets what happened in real-life mask usage in public transport and in schools contributed to the reduction R_t is a better reflection of how the NPI policies affected COVID-19 transmission. These theoretical inferences for the individual NPI effectiveness are important as it is not easy to design randomized control trials which study each of the individual policies [18].

3.2 Overall effectiveness including all implicit transmissions.

Switzerland had employed a very efficient contact tracing system [14] which had identified several clusters of infections arising in different business interactions or in social contexts. However, the overall transmissions also include secondary transmissions or via asymptomatic persons, which may not be traced easily. Further, beyond a certain number of daily cases the infrastructure may not support efficient contact tracing. The method we propose here, while may appear redundant when the number of daily infections are few and contact tracing is efficient, will maintain its validity by identifying all potential downstream infections including those by asymptomatics. Although the method will not be helpful in identifying or isolating the infected, it can in principle quantify the impact of NPIs even when the contact-tracing is limited.

3.2 Non-causal impact of NPIs.

While we underscore the importance of decoupling the contributions using AI in this work, or alternatively by any other model, we also understand that these relations do not necessarily imply causality. The SHAP method identifies the best way of assigning the contributions to the different factors, in each individual prediction, but may not interpreted as causal. Despite this lacuna, the interpretable AI formulation of SHAP designed with the intent of creating "controllable knobs" which can be tuned to achieve the desirable result can be a helpful guide for the "evidence-based" or "data-driven" [19] NPI policies.

3.3 Bringing epidemiology and policy-making together using AI.

Our work integrates three different perspectives which attempt to understand the mitigation of COVID-19. Policy experts quantify the "stringency" of the Government policies to understand if the response is adequate [20], however, those studies typically do not quantify the consequences of the policies making a discussion on adequacy irrelevant. Epidemiological scenario studies discuss various scenarios of how the critical care requirements are for different possible the reproduction rates, and underscore the importance of maintaining lower reproduction rates without providing a prescription for how it can be achieved. Artificial intelligence has been used to make forecasts, such as predictions of the peaks. However, the predictions hold meaning for a shorter time until either the Government policy or behavioral patterns change. Thus, without addressing the root cause which is the relation between the NPIs and the reproduction ratios, the predictions lose relevance very quickly. In our work we attempt to bring together the policy principles, epidemiological interest in R_t, within the framework of AI to achieve this evidence for the effectiveness of the different NPI policies.

3.4 Learning from data and moving forward.

As the "new-normal" with COVID-19 appears to last long, it is important to understand the relative effectiveness of different NPIs for prioritizing them. For example, as per our analysis, and given the behavioral patterns until September, the effectiveness of keeping the borders closed is comparable to the

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effectiveness of restricting the nightclubs. However, their impacts on the overall society and economy may be completely different and can be weighed in other studies. The model is a first attempt at identifying the contributions of the different NPIs to the R_t. However, with time more data and considering newer scenarios such as seasonal changes, variable compliances to the NPIs, the model can be trained better. The model should be a living-model, which is regularly updated for reflecting the scenarios better.

4. Conclusions.

As the COVID-19 pandemic continues to persist for foreseeable future, drastic complete lockdowns may not be a sustainable option. The need for tailored and evidence-based non-pharmaceutical intervention policies which achieve an optimal balance between effectiveness in mitigation and inconvenience in other spheres requires an understanding of the effectiveness of individual policies. The model developed here for deciphering the individual contributions of the various simultaneously imposed non-pharmaceutical intervention policies to the time varying reproduction ratio is a first attempt for such understanding. While the model has to be constantly updated to stay relevant, it paves the possibility for an evidence-based or data-driven policy making where educated, scientifically justifiable and impactful choice of the non-pharmaceutical interventions can be made.

Author contributions. CKS, MRB performed the machine learning calculations; MRB, HJ, BS extracted the epidemiological data and performed analyses of rates; CKS, MRB, HJ, BS, MKP analyzed the results; MKP conceived the project, curated the data on government policies and wrote the paper;

Supplementary Data Availability. The source data, and figures for all states are available at https://github.com/meherpr/SwissRt

Competing interests statement. The authors declare no competing interests

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Association of County-Wide Mask Ordinances with Reductions in Daily CoVID-19 Incident Case Growth in a Midwestern Region Over 12 Weeks

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Abstract

Importance: This study assessed the longitudinal impact of new COVID-19 cases when a mask ordinance was implemented in 2 of a 5-county Midwestern U.S. metropolitan region over a 3-month period of time. Reduction in case growth was significant and reduced infection inequities by race and population density.

Objective: The objective of this study was to assess the impact that a mandatory mask wearing requirement had on the rate of COVID-19 infections by comparing counties with a mandatory policy with those neighboring counties without a mandatory masking policy.

Design: This was a quasi-experimental longitudinal study conducted over the period of June 12-September 25, 2020.

Setting: This study was a population-based study. Data were abstracted from local health department reports of COVID-19 cases.

Participants: Raw cases reported to the county health departments and abstracted for this study; census-level data were synthesized to address county-level population, income and race.

Intervention(s) (for clinical trials) or Exposure(s) (for observational studies): The essential features of this intervention was an instituted mask mandate that occurred in St. Louis City and St. Louis County over a 12 week period.

Main Outcome(s) and Measure(s): The primary study outcome measurement was daily COVID-19 infection growth rate. The mask mandate was hypothesized to lower daily infection growth rate.

Results: Over the 15-week period, the average daily percent growth of reported COVID-19 cases across all five counties was 1.81% (±1.62%). The average daily percent growth in incident COVID-19 cases was similar between M+ and M- counties in the 3 weeks prior to implementation of mandatory mask policies (0.90% [±0.68] vs. 1.27% [±1.23%], respectively, p=0.269). Crude modeling with a difference-in-difference indicator showed that after 3 weeks of mask mandate implementation, M+ counties had a daily percent COVID-19 growth rate that was 1.32 times lower, or a 32% decrease. At 12 weeks post-mask policy implementation, the average daily COVID-19 case growth among M- was 2.42% (±1.92), and was significantly higher than the average daily COVID case growth among M+ counties (1.36% (±0.96%)) (p<0.001). A significant negative association was identified among counties between percent

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growth of COVID-19 cases and percent racial minorities per county ($p<0.001$), as well as population density ($p<0.001$).

Conclusions and Relevance: These data demonstrate that county-level mask mandates were associated with significantly lower incident COVID-19 case growth over time, compared to neighboring counties that did not implement a mask mandate. The results highlight the swiftness of how a mask ordinance can impact the trajectory of infection rate growth. Another notable finding was that following implementation of mask mandates, the disparity of infection rate by race and population density was no longer significant, suggesting that regional-level policies can not only slow the spread of COVID-19, but simultaneously create more equal environment.

Key Points

Question: How are local mask ordinances associated with growth of COVID-19 cases among adjacent counties?

Findings: Ecological longitudinal analysis reveals a significant slowing of daily COVID-19 case growth after mask ordinance implementation among counties.

Meaning: Local-level policy of mask ordinances are shown to be an effective COVID-19 mitigation strategy even within locations of diverse populations.

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Introduction

COVID-19 has claimed over 210,000 lives in the U.S.[1] While urgent policies have been implemented to reduce COVID-19 infections throughout the pandemic, there has been significant variability across state and local governments. In particular, due to the difficulty in maintaining social distancing guidelines and in an attempt to allow the economy to recover by opening businesses, some elected officials have issued mask mandates for the public to reduce COVID-19 transmission. Research has demonstrated the effectiveness of masks in preventing the spread of infectious diseases through airborne droplets,[2] yet the majority of a community would need to be masked in order to reduce infection rates. Several governors have avoided state-level mandates by rationalizing that within-state variations of COVID-19 infection rates call for more localized public health policymaking than state-wide orders.[3]

While studies found mask policies to be effective in reducing infection growth rates early in the pandemic, there is an urgent need to know how the impact of such policy persists over time; in addition, the impact on unequal infection rates such as higher rates reported among African-American/Black and Hispanic/Latinx populations.[1] Mask wearing has transitioned to a politically nuanced behavior, and this has been particularly true in the region surrounding the Midwestern city of St. Louis, providing a natural experiment to understand the longitudinal impact of a variable mask mandate policies has on county-level changes in incident CoVID-19 rates over a 12-week period.

Methods

This ecological study evaluated the effects of a public mask mandate on the daily cumulative case growth of COVID-19 infections among five neighboring counties within the metropolitan statistical area of Saint Louis, Missouri: City of St. Louis, St. Louis County, Jefferson County, Saint Charles County, and Franklin County. The study period included a three-week period prior

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to the implementation of a mandatory mask order in St. Louis City and County on July 3, 2020, and a 12-week post-implementation period, for a total of 15 weeks.

Outcome of Interest

The primary outcome of interest was the cumulative daily percent change of reported COVID-19 cases by county. Daily incident COVID-19 cases were sourced from publicly available data provided by the Missouri Department of Health and Senior Services.

Primary Predictor and Covariates

Presence of a mask ordinance was the primary predictor of interest. Among the five counties, two implemented a mask ordinance during the study period for individuals entering public indoor spaces; the City and County of Saint Louis[4] (M+), with three counties having no such mandate during the study period (M-).

As COVID-19 infections occur more often among areas with higher county-level population density per square mile, higher proportion of residents identifying as non-white, and lower median annual household income,[25,6] these variables were included from the 2018, 5-year American Community Survey to control for variations in COVID-19 case growth.

Statistical Analysis

Data were constructed with daily percent changes in COVID-19 cases as a function of time (daily) and location (county), with 530 unique observations from June 12, 2020 to September 25, 2020. The average percent change in cases per day was calculated across M+ and M- counties to understand the pattern of COVID-19 growth throughout the study period. Kendal's tau-b rank correlation test was employed to identify associations among county-level demographics and percent daily growth of COVID-19 cases.

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A difference-in-difference (DID) framework was employed to evaluate the effect of mask ordinances on percent daily growth in COVID-19 prevalence. Specific to this study, a DID estimator (δ) was calculated using binary dummy variables for both treatment (M+ or M-) at time (prior to mask ordinance implementation and after implementation). The calculated DID estimator was then applied to a linear probability model to determine the effects of a mask ordinance on COVID-19 case growth. Four adjusted models were constructed, accounting for county-level characteristics, each at 3 week intervals past the implementation date.

Statistical analyses were completed using R 4.0 software with significance determined at $\alpha = 0.05$.

Results

Over the 15-week period, the average daily percent growth of reported COVID-19 cases across all five counties was 1.81%(±1.62%). A total of 44,294 cases were reported throughout this period among a total estimated population of just over 2,000,000 residents, which is approximately one-third of the population within the state of Missouri.

The average daily percent growth in incident COVID-19 cases was similar between M+ and M- counties in the 3 weeks prior to implementation of mandatory mask policies (0.90%[±0.68] vs. 1.27%[±1.23%], respectively, p=0.269) (Figure 1). Prior to the mandate implementation a there was no association between percent growth of COVID-19 cases and percent racial minorities, population density, nor median income per county.

At 12 weeks post-implementation, the average daily COVID-19 case growth among M- was 2.42%(±1.92), significantly higher than the average daily COVID case growth among M+ counties (1.36%[±0.96%], p<0.001).

In adjusted linear probability models (Table 1), the mask mandate was found to be significantly associated with slowing the reported growth of daily COVID-19 cases across the study period.

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From 3 weeks pre-policy to 3 weeks post-policy, M+ counties had a daily average COVID-19 growth rate of 44% less than M- counties (1.08/2.44). At week 6, 9, and 12 assessments, modeling revealed a continuing significant reduction in COVID-19 cases in counties with mask mandates. From pre-policy to 12 weeks post-policy (Figure 2), M+ counties had a daily average COVID-19 growth rate of 40% less than of M- counties (0.47/1.16). Using the DID linear probability equation, a counterfactual line is estimated, indicating probable growth of counties with mask mandate had a mask mandate not been implemented. Within the adjusted models, accounting for the DID estimator, proportion non-white population and population density were negatively associated with increased daily growth rate, yet median income did not contribute significantly to any of the calculated models.

Discussion

This longitudinal study demonstrates that the implementation of county-level mask mandates lowered incident COVID-19 case growth over time, compared to neighboring counties with no such mask mandate. Importantly, the results highlight the swiftness of such impact, with significant effects seen at just 3 weeks post-implementation. As time progressed, this impact was slightly reduced, possibly due to the arbitrary political borders of counties and states, which do not necessarily constrain transmission as mobility across mask mandate and non-mandated regions occurs. Although broader state or national mandatory mask ordinances would likely have a significant reduction in COVID-19 infections, in their absence, support for governors and elected officials to minimize the interactions across these borders may be beneficial.

Furthermore, implementation of a mask mandate may have reduced the unequal burden on African American/Black and Hispanic/Latinx individuals, as well as areas with higher population density. COVID-19 has highlighted the impact and swiftness of racial and ethnic inequities through higher rates of COVID-19 morbidity and mortality among non-white communities. In particular, many individuals were unable to abide by stay-at-home orders that protected middle

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and high-income communities as a result of “essential” employment in grocery stores, health care support positions, and public transportation. These jobs, often lacking PPE and paid sick leave, are more often filled by people of color, living in higher population density and lower socioeconomic areas.[7] The mask policy that was enacted in many communities may have provided a more equal approach to reducing COVID-19 infections, as it occurred in St. Louis, Missouri.

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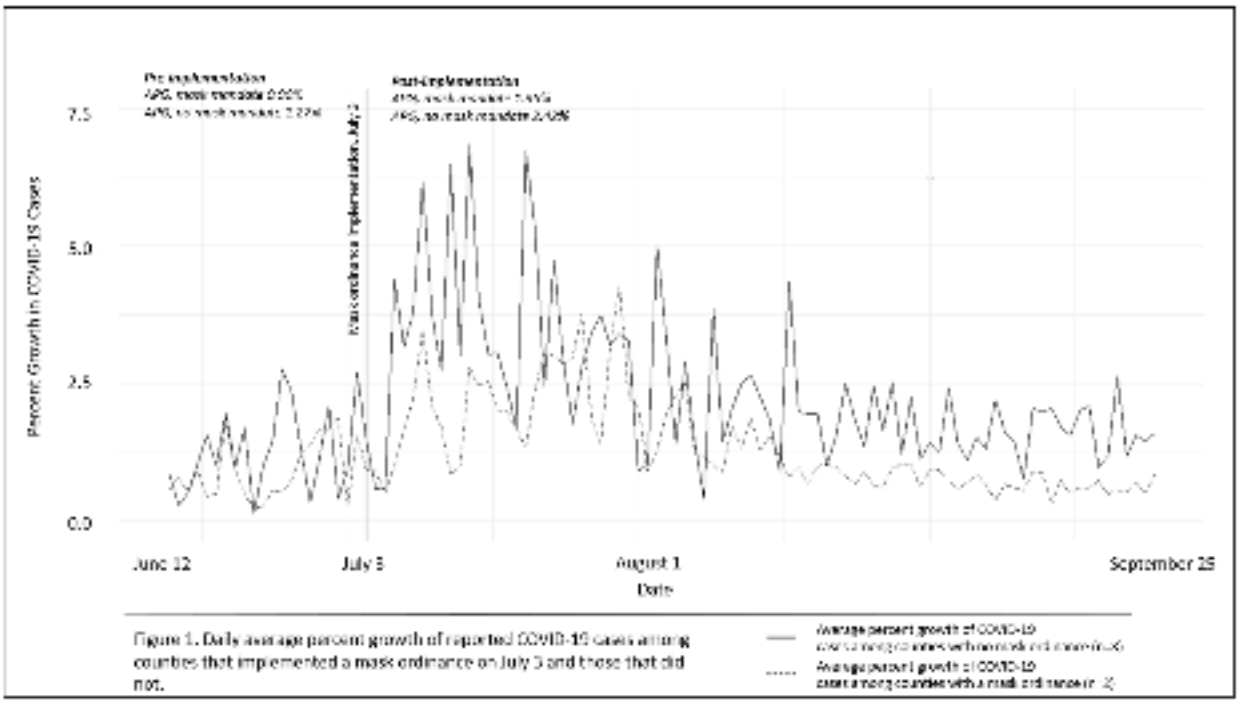

Figure 1. Daily average percent growth of reported COVID-19 cases among counties that implemented a mask ordinance on July 3 and those that did not.

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Table 1. Covariate associations 3 weeks prior to mask mandate and 12 weeks after mask mandate[a]				
	3 weeks prior to mask mandate, June 12 to July 3		12 weeks prior to mask mandate, July 3 to September 25	
	τ	p value	τ	p value
Percent population non-white	-0.04	0.623	-0.22	<0.001
Median annual household income ($)	-0.01	0.849	<0.01	0.977
Population density (mi^2)	-0.08	0.282	-0.26	<0.001
a. Kendal's tau-b rank correlation				

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Table 2. Linear probability models predicting percent growth in reported COVID-19 cases among five counties in Missouri

	3 Weeks Post Mask Policy		6 Weeks Post Mask Policy		9 Weeks Post Mask Policy		12 Weeks Post Mask Policy	
	β	Std. E	β	Std. E	β	Std. E	β	Std. E
DID estimator[a]	-1.36**	0.45	-0.77*	0.40	-0.72*	0.36	-0.69*	0.3
Percent population non-white[b]	0.10	0.32	-0.08	0.27	-0.07	0.22	-0.04	0.1
Median annual household income($)[c]	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.0
Population density (mi^2)[d]	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.0

a. adjusted R^2 0.32, b. adjusted R^2 0.21, c. adjusted R^2 0.15, d. adjusted R^2 0.13
Significance reported t *0.05, **0.01, ***0.001

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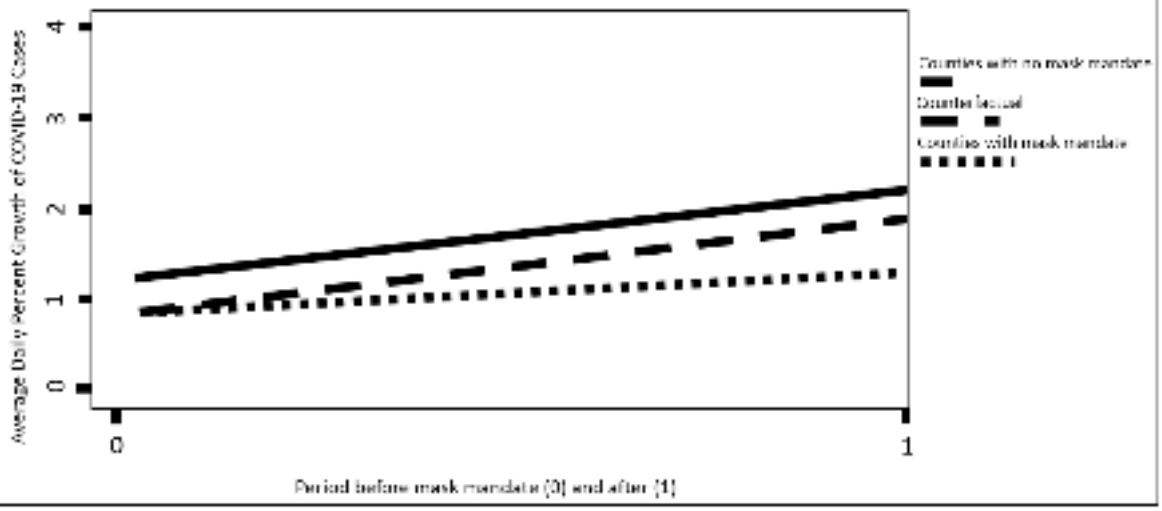
Figure 2. Plotting of Y=β0+ β1[time]+ β2[presence of mask ordinance]+ β3[DID estimator]+ ε from model results in table 1. Effect of a mask mandate among counties is depicted in the difference between the dotted mask line and the dotted/dashed counterfactual line.



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Causal impact of masks, policies, behavior on early covid-19 pandemic in the U.S.

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ABSTRACT

The paper evaluates the dynamic impact of various policies adopted by US states on the growth rates of confirmed Covid-19 cases and deaths as well as social distancing behavior measured by Google Mobility Reports, where we take into consideration people's voluntarily behavioral response to new information of transmission risks in a causal structural model framework. Our analysis finds that both policies and information on transmission risks are important determinants of Covid-19 cases and deaths and shows that a change in policies explains a large fraction of observed changes in social distancing behavior. Our main counterfactual experiments suggest that nationally mandating face masks for employees early in the pandemic could have reduced the weekly growth rate of cases and deaths by more than 10 percentage points in late April and could have led to as much as 19 to 47 percent less deaths nationally by the end of May, which roughly translates into 19 to 47 thousand saved lives. We also find that, without stay-at-home orders, cases would have been larger by 6 to 63 percent and without business closures, cases would have been larger by 17 to 78 percent. We find considerable uncertainty over the effects of school closures due to lack of cross-sectional variation; we could not robustly rule out either large or small effects. Overall, substantial declines in growth rates are attributable to private behavioral response, but policies played an important role as well. We also carry out sensitivity analyses to find neighborhoods of the models under which the results hold robustly: the results on mask policies appear to be much more robust than the results on business closures and stay-at-home orders. Finally, we stress that our study is observational and therefore should be interpreted with great caution. From a completely agnostic point of view, our findings uncover predictive effects (association) of observed policies and behavioral changes on future health outcomes, controlling for informational and other confounding variables.

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1. Introduction

Accumulating evidence suggests that various policies in the US have reduced social interactions and slowed down the growth of Covid-19 infections.[1] An important outstanding issue, however, is how much of the observed slow down in the spread is attributable to the effect of policies as opposed to a voluntarily change in people's behavior out of fear of being infected. This question is critical for evaluating the effectiveness of restrictive policies in the US relative to an

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[1] See Courtemanche et al. (2020), Hsiang et al. (2020), Pei et al. (2020), Abouk and Heydari (2020), and Wright et al. (2020).

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alternative policy of just providing recommendations and information such as the one adopted by Sweden. More generally, understanding people's dynamic behavioral response to policies and information is indispensable for properly evaluating the effect of policies on the spread of Covid-19.

This paper quantitatively assesses the impact of various policies adopted by US states on the spread of Covid-19, such as non-essential business closure and mandatory face masks, paying particular attention to how people adjust their behavior in response to policies as well as new information on cases and deaths.

We present a conceptual framework that spells out the causal structure on how the Covid-19 spread is dynamically determined by policies and human behavior. Our approach explicitly recognizes that policies not only directly affect the spread of Covid-19 (e.g., mask requirement) but also indirectly affect its spread by changing people's behavior (e.g., stay-at-home order). It also recognizes that people react to new information on Covid-19 cases and deaths and voluntarily adjust their behavior (e.g., voluntary social distancing and hand washing) even without any policy in place. Our causal model provides a framework to quantitatively decompose the growth of Covid-19 cases and deaths into three components: (1) direct policy effect, (2) policy effect through behavior, and (3) direct behavior effect in response to new information.

Guided by the causal model, our empirical analysis examines how the weekly growth rates of confirmed Covid-19 cases and deaths are determined by (the lags of) policies and behavior using US state-level data. To examine how policies and information affect people's behavior, we also regress social distancing measures on policy and information variables. Our regression specification for case and death growths is explicitly guided by a SIR model although our causal approach does not hinge on the validity of a SIR model.

As policy variables, we consider mandatory face masks for employees in public businesses, stay-at-home orders (or shelter-in-place orders), closure of K-12 schools, closure of restaurants except take out, closure of movie theaters, and closure of non-essential businesses. Our behavior variables are four mobility measures that capture the intensity of visits to "transit", "grocery", "retail", and "workplaces" from Google Mobility Reports. We take the lagged growth rate of cases and deaths and the log of lagged cases and deaths at both the state-level and the national-level as our measures of information on infection risks that affects people's behavior. We also consider the growth rate of tests, month dummies, and state-level characteristics (e.g., population size and total area) as confounders that have to be controlled for in order to identify the causal relationship between policy/behavior and the growth rate of cases and deaths.

Our key findings from regression analysis are as follows. We find that both policies and information on past cases and deaths are important determinants of people's social distancing behavior, where policy effects explain more than 50% of the observed decline in the four behavior variables.[2] Our estimates suggest that there are both large policy effects and large behavioral effects on the growth of cases and deaths. Except for mandatory masks, the effect of policies on cases and deaths is indirectly materialized through their impact on behavior; the effect of mandatory mask policy is direct without affecting behavior.

Using the estimated model, we evaluate the dynamic impact of the following three counterfactual policies on Covid-19 cases and deaths: (1) mandating face masks, (2) allowing all businesses to open, and (3) not implementing a stay-at-home order. The counterfactual experiments show a large impact of those policies on the number of cases and deaths. They also highlight the importance of voluntary behavioral response to infection risks when evaluating the dynamic policy effects.

Our estimates imply that nationally implementing mandatory face masks for employees in public businesses on March 14th would have reduced the growth rate of cases and that of deaths by approximately 10 percentage points in late April. As shown in Fig. 1, this leads to reductions of 21% and 34% in cumulative reported cases and deaths, respectively, by the end of May with 90 percent confidence intervals of [9, 32]% and [19, 47]%, which roughly implies that 34 thousand lives could have been saved. This finding is significant: given this potentially large benefit of reducing the spread of Covid-19, mandating masks is an attractive policy instrument especially because it involves relatively little economic disruption. These estimates contribute to the ongoing efforts towards designing approaches to minimize risks from reopening (Stock, 2020b).

Fig. 2 illustrates how never closing any businesses (no movie theater closure, no non-essential business closure, and no closure of restaurants except take-out) could have affected cases and deaths. We estimate that business shutdowns have roughly the same impact on growth rates as mask mandates, albeit with more uncertainty. The point estimates indicate that keeping all businesses open could have increased cumulative cases and deaths by 40% at the end of May (with 90 percent confidence intervals of [17, 78]% for cases and [1, 97]% for deaths).

Fig. 3 shows that stay-at-home orders had effects of similar magnitude as business closures. No stay-at-home orders could have led to 37% more cases by the start of June with a 90 percent confidence interval given by 6% to 63%. The estimated effect of no stay-at-home orders on deaths is a slightly smaller with a 90 percent confidence interval of −7% to 50%.

We also conducted sensitivity analysis with respect to changes to our regression specification, sample selection, methodology, and assumptions about delays between policy changes and changes in recorded cases. In particular, we examined whether certain effect sizes can be ruled out by various more flexible models or by using alternative timing assumptions that define forward growth rates. The impact of mask mandates is more robustly and more precisely estimated than that of business closure policies or stay-at-home orders, and an undesirable effect of increasing the weekly

[2] The behavior accounts for the other half. This is in line with theoretical study by Gitmez et al. (2020) that investigates the role of private behavior and negative external effects for individual decisions over policy compliance as well as information acquisition during pandemics.

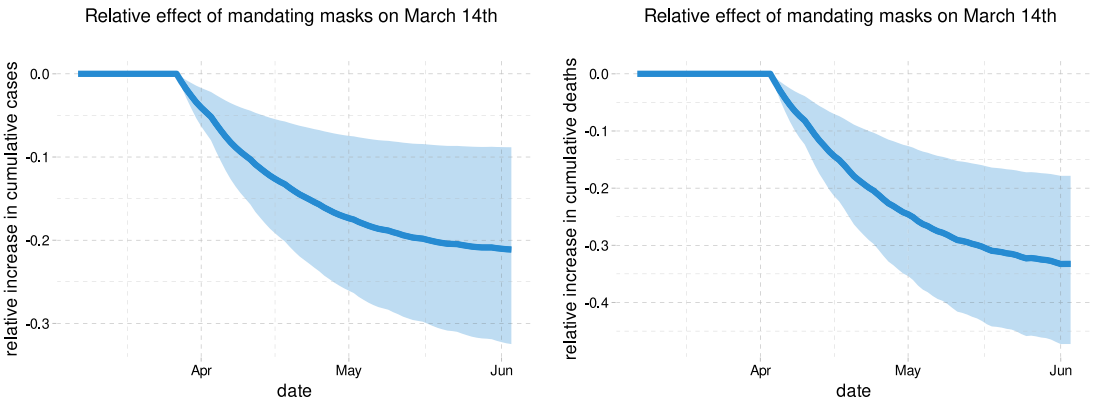

Fig. 1. Relative cumulative effect on confirmed cases and fatalities of nationally mandating masks for employees on March 14th in the US. This figure shows the estimated relative change in cumulative cases and deaths if all states had mandated masks on March 14th. The thick blue line is the estimated change in cumulative cases or deaths relative to the observed number of cases or deaths. The shaded region is a pointwise 90% confidence band.

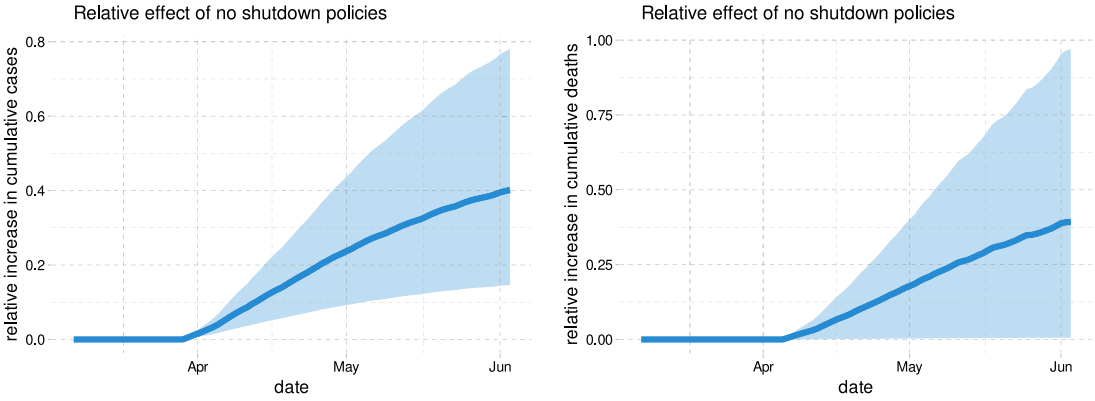

Fig. 2. Relative cumulative effect of no business closure policies on cases and fatalities in the US. This figure shows the estimated relative change in cases and deaths if no states had ever implemented any business closure policies. The thick blue line is the estimated change in cumulative cases or deaths relative to the observed number of cumulative cases or deaths. The shaded region is a pointwise 90% confidence band.

death growth by 5 percentage points is ruled out by all of the models we consider.[3] This is largely due to the greater variation in the timing of mask mandates across states. The findings of shelter-in-place and business closures policies are considerably less robust. For example, for stay-at-home mandates, models with alternative timing and richer specification for information set suggested smaller effects. Albeit after application of machine learning tools to reduce dimensionality, the range of effects $[0, 0.15]$ could not be ruled out. A similar wide range of effects could not be ruled out for business closures.

We also examine the impact of school closures. Unfortunately, there is very little variation across states in the timing of school closures. Across robustness specifications, we obtain point estimates of the effect of school closures as low as 0 and as high as -0.6. In particular, we find that the results are sensitive to whether the number of past national cases/deaths is included in a specification or not. This highlights the uncertainty regarding the impact of some policies versus private behavioral responses to information.

A growing number of other papers have examined the link between non-pharmaceutical interventions and Covid-19 cases.[4] Hsiang et al. (2020) estimate the effect of policies on the growth rate of cases using data from the United States, China, Iran, Italy, France, and South Korea. In the United States, they find that the combined effect of all policies they consider on the growth rate is -0.347 (0.061). Courtemanche et al. (2020) use US county level data to analyze the effect of interventions on case growth rates. They find that the combination of policies they study reduced growth rates by 9.1

[3] This null hypothesis can be generated by looking at the meta-evidence from RCTs on the efficacy of masks in preventing other respiratory cold-like deceases. Falsely rejecting this null is costly in terms of potential loss of life, and so it is a reasonable null choice for the mask policy from decision-theoretic point of view.

[4] We refer the reader to Avery et al. (2020) for a comprehensive review of a larger body of work researching Covid-19; here we focus on few quintessential comparisons on our work with other works that we are aware of.

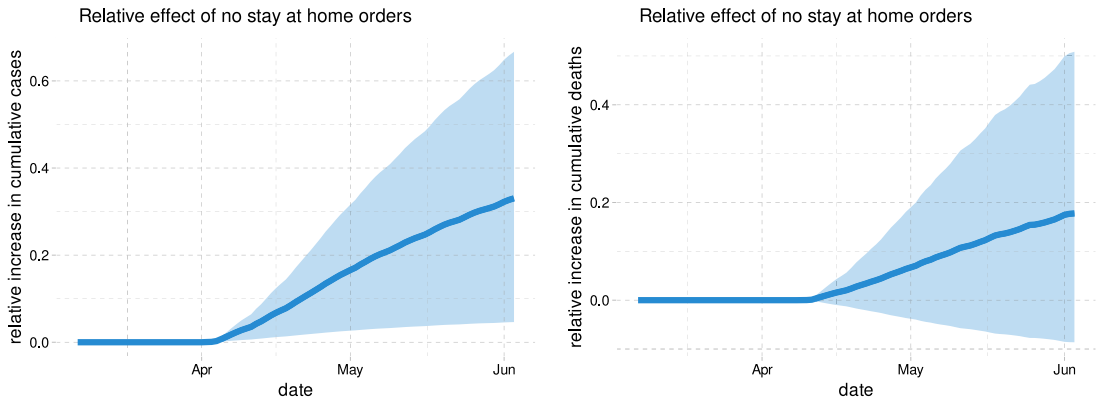

Fig. 3. Relative cumulative effect of not implementing stay-at-home order on cases and fatalities in the US. This figure shows the estimated relative change in cases and deaths if no states had ever issued stay at home orders. The thick blue line is the estimated change in cumulative cases or deaths relative to the observed number of cumulative cases or deaths. The shaded region is a point wise 90% confidence band.

percentage points 16–20 days after implementation, out of which 5.9 percentage points are attributable to shelter in place orders. Both Hsiang et al. (2020) and Courtemanche et al. (2020) adopt a reduced-form approach to estimate the total policy effect on case growth without using any social distancing behavior measures.[5]

Existing evidence for the impact of social distancing policies on behavior in the US is mixed. Abouk and Heydari (2020) employ a difference-in-differences methodology to find that statewide stay-at-home orders have strong causal impacts on reducing social interactions. In contrast, using data from Google Mobility Reports, Maloney and Taskin (2020) find that the increase in social distancing is largely voluntary and driven by information.[6] Another study by Gupta et al. (2020) also found little evidence that stay-at-home mandates induced distancing by using mobility measures from PlaceIQ and SafeGraph. Using data from SafeGraph, Andersen (2020) shows that there has been substantial voluntary social distancing but also provide evidence that mandatory measures such as stay-at-home orders have been effective at reducing the frequency of visits outside of one's home.

Pei et al. (2020) use county-level observations of reported infections and deaths in conjunction with mobility data from SafeGraph to conduct simulation of implementing all policies 1–2 weeks earlier and found that it would have resulted in reducing the number of cases and deaths by more than half. However, their study does not explicitly analyze how policies are related to the effective reproduction numbers.

Epidemiologists use model simulations to predict how cases and deaths evolve for the purpose of policy recommendation. As reviewed by Avery et al. (2020), there exists substantial uncertainty about the values of key epidemiological parameters (see also Atkeson, 2020a; Stock, 2020a). Simulations are often done under strong assumptions about the impact of social distancing policies without connecting to the relevant data (e.g., Ferguson et al., 2020). Furthermore, simulated models do not take into account that people may limit their contact with other people in response to higher transmission risks.[7] When such a voluntary behavioral response is ignored, simulations would necessarily exhibit exponential spread and over-predict cases and deaths. In contrast, as cases and deaths rise, a voluntary behavioral response may possibly reduce the effective reproduction number below 1, potentially preventing exponential spread. Our counterfactual experiments illustrate the importance of this voluntary behavioral change.

Whether wearing masks in public place should be mandatory or not has been one of the most contested policy issues with health authorities of different countries providing contradictory recommendations. Reviewing evidence, Greenhalgh et al. (2020) recognize that there is no randomized controlled trial evidence for the effectiveness of face masks, but they state "indirect evidence exists to support the argument for the public wearing masks in the Covid-19 pandemic".[8] Howard et al. (2020) also review available medical evidence and conclude that "mask wearing reduces the transmissibility per contact by reducing transmission of infected droplets in both laboratory and clinical contexts". The laboratory findings in Hou et al. (2020) suggest that the nasal cavity may be the initial site of infection followed by aspiration to the lung, supporting the argument "for the widespread use of masks to prevent aerosol, large droplet, and/or mechanical exposure

5 Using a synthetic control approach, Cho (2020) finds that the cases would have been lower by 75 percent had Sweden adopted stricter lockdown policies.

6 Specifically, they find that of the 60 percentage point drop in workplace intensity, 40 percentage points can be explained by changes in information as proxied by case numbers, while roughly 8 percentage points can be explained by policy changes.

7 See Atkeson (2020b) and Stock (2020a) for the implications of the SIR model for Covid-19 in the US. Fernández-Villaverde and Jones (2020) estimate a SIRD model in which time-varying reproduction numbers depend on the daily deaths to capture feedback from daily deaths to future behavior and infections.

8 The virus remains viable in the air for several hours, for which surgical masks may be effective. Also, a substantial fraction of individual who are infected become infectious before showing symptom onset.

to the nasal passages". He et al. (2020) examined temporal patterns of viral shedding in COVID-19 patients and found the highest viral load at the time of symptom onset; this suggests that a significant portion of transmission may have occurred before symptom onset and that universal face masks may be an effective control measure to reduce transmission.[9] Ollila et al. (2020) provide a meta-analysis of randomized controlled trials of non-surgical face masks in preventing viral respiratory infections in non-hospital and non-household settings, finding that face masks decreased infections across all five studies they reviewed.[10]

Given the lack of experimental evidence on the effect of masks in the context of COVID-19, conducting observational studies is useful and important. To the best of our knowledge, our paper is the first empirical study that shows the effectiveness of mask mandates on reducing the spread of Covid-19 by analyzing the US state-level data. This finding corroborates and is complementary to the medical observational evidence in Howard et al. (2020). Analyzing mitigation measures in New York, Wuhan, and Italy, Zhang et al. (2020b) conclude that mandatory face coverings substantially reduced infections. Abaluck et al. (2020) find that the growth rates of cases and of deaths in countries with pre-existing norms that sick people should wear masks are lower by 8 to 10% than those rates in countries with no pre-existing mask norms.[11] The Institute for Health Metrics and Evaluation at the University of Washington assesses that, if 95% of the people in the US were to start wearing masks from early August of 2020, 66,000 lives would be saved by December 2020 (IHME, 2020), which is largely consistent with our results. Our finding is also independently corroborated by a completely different causal methodology based on synthetic control using German data in Mitze et al. (2020).[12]

Our empirical results contribute to informing the economic-epidemiological models that combine economic models with variants of SIR models to evaluate the efficiency of various economic policies aimed at the gradual "reopening" of various sectors of economy.[13] For example, the estimated effects of masks, stay-home mandates, and various other policies on behavior, and of behavior on infection can serve as useful inputs and validation checks in the calibrated macro, sectoral, and micro models (see, e.g., Alvarez et al., 2020; Baqaee et al., 2020; Fernández-Villaverde and Jones, 2020; Acemoglu et al., 2020; Keppo et al., 2020; McAdams, 2020 and references therein). Furthermore, the causal framework developed in this paper could be applicable, with appropriate extensions, to the impact of policies on economic outcomes replacing health outcomes (see, e.g., Chetty et al., 2020; Coibion et al., 2020).

Finally, our causal model is framed using the language of structural equations models and causal diagrams of econometrics (Wright, 1928; Haavelmo, 1944; Tinbergen, 1940; Wold, 1954; Pearl, 1995) and genetics (Wright, 1923),[14] with natural unfolding potential/structural outcomes representation (Rubin, 1974; Tinbergen, 1930; Neyman, 1925; Imbens and Rubin, 2015). The work on causal graphs has been modernized and developed by Pearl (1995), Greenland et al. (1999), Pearl (2009), Pearl and Mackenzie (2018) and many others (e.g., Pearl and Mackenzie, 2018; White and Chalak, 2009; Robins et al., 2020; Peters et al., 2017; Bareinboim et al., 2020; Hernán and Robins, 2020), with applications in computer science, genetics, epidemiology, and econometrics (see, e.g., Heckman and Pinto, 2013; Hünermund and Bareinboim, 2019; White and Chalak, 2009 for applications in econometrics). The particular causal diagram we use has several "mediation" components, where variables affect outcomes directly and indirectly through other variables called mediators; these structures go back at least to Wright (1923, see Figure 6); see, e.g., Baron and Kenny (1986), Hines et al. (2020), Robins et al. (2020) for modern treatments.

2. The causal model for the effect of policies, behavior, and information on growth of infection

2.1. The causal model and its structural equation form

We introduce our approach through the Wright-style causal diagram shown in Fig. 4. The diagram describes how policies, behavior, and information interact together:

- The *forward* health outcome, $Y_{i,t+\ell}$, is determined last, after all other variables have been determined;
- The adopted policies, P_{it}, affect health outcome $Y_{i,t+\ell}$ either directly, or indirectly by altering human behavior B_{it};

9 Lee et al. (2020a) find evidence that viral loads in asymptomatic patients are similar to those in symptomatic patients. Aerosol transmission of viruses may occur through aerosols particles released during breathing and speaking by asymptomatic infected individuals; masks reduce such airborne transmission (Prather et al., 2020). Anfinrud et al. (2020) provide visual evidence of speech-generated droplet as well as the effectiveness of cloth masks to reduce the emission of droplets. Chu et al. (2020) conduct a meta-analysis of observational studies on transmission of the viruses that cause COVID-19 and related diseases and find the effectiveness of mask use for reducing transmission.

10 Whether wearing masks creates a false sense of security and leads to decrease in social distancing is also a hotly debated topic. A randomized field experiment in Berlin, Germany, conducted by Seres et al. (2020) finds that wearing masks actually increases social distancing, providing no evidence that mandatory masks leads to decrease in social distancing.

11 Miyazawa and Kaneko (2020) find that country's COVID-19 death rates are negatively associated with mask wearing rates.

12 Our study was first released in ArXiv on May 28, 2020 whereas Mitze et al. (2020) was released at SSRN on June 8, 2020.

13 Adda (2016) analyzes the effect of policies reducing interpersonal contacts such as school closures or the closure of public transportation networks on the spread of influenza, gastroenteritis, and chickenpox using high frequency data from France.

14 The father and son, P. Wright (economist) and S. Wright (geneticist) collaborated to develop structural equation models and causal path diagrams; P. Wright's key work represented supply–demand system as a directed acyclical graph and established its identification using exclusion restrictions on instrumental variables. We view our work as following this classical tradition.

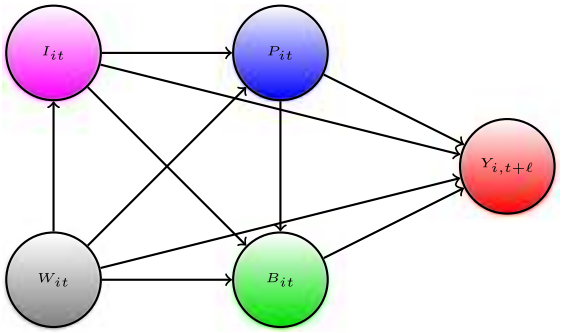

Fig. 4. S. & P. Wright type causal path diagram for our model.

- Information variables, I_{it}, such as lagged values of outcomes can affect human behavior and policies, as well as outcomes;
- The confounding factors W_{it}, which vary across states and time, affect all other variables.

The index i denotes observational unit, the state, and t and $t+\ell$ denotes the time, where ℓ is a positive integer that represents the time lag between infection and case confirmation or death.

Our main outcomes of interest are the growth rates in Covid-19 cases and deaths, behavioral variables include proportion of time spent in transit, shopping, and workplaces, policy variables include mask mandates, stay-at-home orders, and school and business closures, and the information variables include lagged values of outcome. We provide a detailed description of these variables and their timing in the next section.

The causal structure allows for the effect of the policy to be either direct or indirect — through behavior or through dynamics; all of these effects are not mutually exclusive. The structure also allows for changes in behavior to be brought by change in policies and information. These are all realistic properties that we expect from the contextual knowledge of the problem. Policies such as closures of schools, non-essential business, and restaurants alter and constrain behavior in strong ways. In contrast, policies such as mandating employees to wear masks can potentially affect the Covid-19 transmission directly. The information variables, such as recent growth in the number of cases, can cause people to spend more time at home, regardless of adopted state policies; these changes in behavior in turn affect the transmission of Covid-19. Importantly, policies can have the informational content as well, guiding behavior rather than constraining it.

The causal ordering induced by this directed acyclical graph is determined by the following timing sequence:

(1) information and confounders get determined at t,
(2) policies are set in place, given information and confounders at t;
(3) behavior is realized, given policies, information, and confounders at t;
(4) outcomes get realized at $t+\ell$ given policies, behavior, information, and confounders.

The model also allows for direct dynamic effects of information variables on the outcome through autoregressive structures that capture persistence in growth patterns. As highlighted below, realized outcomes may become new information for future periods, inducing dynamics over multiple periods.

Our quantitative model for causal structure in Fig. 4 is given by the following econometric structural (or potential) outcomes model:

$$\begin{aligned} Y_{i,t+\ell}(b,p,\iota) &:= \alpha' b + \pi' p + \mu' \iota + \delta_Y' W_{it} + \varepsilon_{it}^y, \\ B_{it}(p,\iota) &:= \beta' p + \gamma' \iota + \delta_B' W_{it} + \varepsilon_{it}^b, \end{aligned} \tag{SO}$$

which is a collection of functional relations with stochastic shocks, decomposed into observable part $\delta' W$ and unobservable part ε. The terms ε_{it}^y and ε_{it}^b are the centered stochastic shocks that obey the orthogonality restrictions posed below.

The policies can be modeled via a linear form as well,

$$P_{it}(\iota) := \eta' \iota + \delta_P' W_{it} + \varepsilon_{it}^p, \tag{P}$$

although linearity is not critical.[15]

[15] Under some additional independence conditions, this can be replaced by an arbitrary non-additive function $P_{it}(\iota) = p(\iota, W_{it}, \varepsilon_{it}^p)$, such that the unconfoundedness condition stated in the next footnote holds.

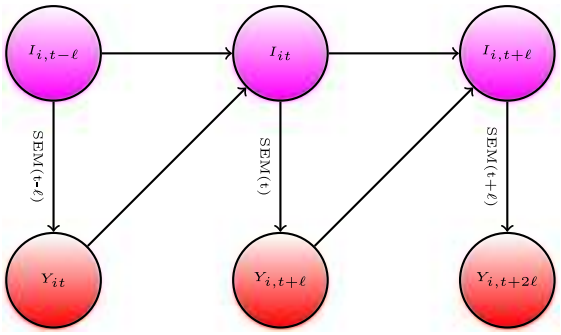

Fig. 5. Diagram for Information Dynamics in SEM.

The exogeneity restrictions on the stochastic shocks are as follows:

$$\begin{aligned} \varepsilon^{y}_{it} &\perp (\varepsilon^{b}_{it}, \varepsilon^{p}_{it}, W_{it}, I_{it}), \\ \varepsilon^{b}_{it} &\perp (\varepsilon^{p}_{it}, W_{it}, I_{it}), \\ \varepsilon^{p}_{it} &\perp (W_{it}, I_{it}), \end{aligned} \tag{E}$$

where we say that $V \perp U$ if $EVU = 0$.[16] This is a standard way of representing restrictions on errors in structural equation modeling in econometrics.[17]

The observed variables are generated by setting $\iota = I_{it}$ and propagating the system from the last equation to the first:

$$\begin{aligned} Y_{i,t+\ell} &:= Y_{i,t+\ell}(B_{it}, P_{it}, I_{it}), \\ B_{it} &:= B_{it}(P_{it}, I_{it}), \\ P_{it} &:= P_{it}(I_{it}). \end{aligned} \tag{O}$$

The specification of the model above grasps one-period responses. The dynamics over multiple periods will be induced by the evolution of information variables, which include time, lagged and integrated values of outcome[18]:

$$I_{it} := I_t(Y_{it}, I_{i,t-\ell}) := \left(g(t), Y_{it}, \sum_{m=0}^{\lfloor t/\ell \rfloor} Y_{i,t-\ell m}\right)' \tag{I}$$

for each $t \in \{0, 1, \ldots, T\}$, where g is deterministic function of time, e.g., month indicators, assuming that the log of new cases at time $t \leq 0$ is zero, for notational convenience.[19] In this structure, people respond to both global information, captured by a function of time such as month dummies, and local information sources, captured by the local growth rate and the total number of cases. The local information also captures the persistence of the growth rate process. We model the reaction of people's behavior via the term $\gamma' I_t$ in the behavior equation. The lagged values of behavior variable may be also included in the information set, but we postpone this discussion after the main empirical results are presented.

With any structure of this form, realized outcomes may become new information for future periods, inducing a dynamical system over multiple periods. We show the resulting dynamical system in a diagram of Fig. 5. Specification of this system is useful for studying delayed effects of policies and behaviors and in considering the counterfactual policy analysis.

Next we combine the above parts together with an appropriate initialization to give a formal definition of the model we use.

> Structural Equations Model (SEM). Let $i \in \{1, \ldots, N\}$ denote the observational unit, t be the time periods, and ℓ be the time delay. (1) For each i and $t \leq -\ell$, the confounder, information, behavior, and policy variables

[16] An alternative useful starting point is to impose the Rosenbaum–Rubin type unconfoundedness condition:

$$Y_{i,t+\ell}(\cdot,\cdot,\cdot) \perp\!\!\!\perp (P_{it}, B_{it}, I_{it}) \mid W_{it}, \;\; B_{it}(\cdot,\cdot) \perp\!\!\!\perp (P_{it}, I_{it}) \mid W_{it}, \;\; P_{it}(\cdot) \perp\!\!\!\perp I_{it} \mid W_{it},$$

which imply, with treating stochastic errors as independent additive components, the orthogonal conditions stated above. The same unconfoundedness restrictions can be formulated using formal causal DAGs, and also imply orthogonality restrictions stated above, once stochastic errors are modeled as independent additive components.

[17] The structural equations of this form are connected to triangular structural equation models, appearing in microeconometrics and macroeconometrics (SVARs), going back to the work of Strotz and Wold (1960).

[18] Our empirical analysis also considers a specification in which information variables include lagged national cases/deaths as well as lagged behavior variables.

[19] The general formula for $I_{i,t-1}$ is $S_{i,t,\ell} + \sum_{m=1}^{\lfloor t/\ell \rfloor} Y_{i,t-\ell m}$, where $S_{i,t,\ell}$ is the initial condition, the log of new cases at time $-t \mod \ell$.

$W_{it}, I_{it}, B_{it}, P_{it}$ are determined outside of the model, and the outcome variable $Y_{i,t+\ell}$ is determined by factors outside of the model for $t \leq 0$. (2) For each i and $t \geq -\ell$, confounders W_{it} are determined by factors outside of the model, and information variables I_{it} are determined by (I); policy variables P_{it} are determined by setting $\iota = I_{it}$ in (P) with a realized stochastic shock ε^p_{it} that obeys the exogeneity condition (E); behavior variables B_{it} are determined by setting $\iota = I_{it}$ and $p = P_{it}$ in (SO) with a shock ε^b_{it} that obeys (E); finally, the outcome $Y_{i,t+\ell}$ is realized by setting $\iota = I_{it}$, $p = P_{it}$, and $b = B_{it}$ in (SO) with a shock ε^y_{it} that obeys (E).

2.2. Main testable implication, identification, parameter estimation

The system above together with orthogonality restrictions (E) implies the following collection of projection equations for realized variables:

$$Y_{i,t+\ell} = \alpha' B_{it} + \pi' P_{it} + \mu' I_{it} + \delta_Y' W_{it} + \varepsilon^y_{it}, \qquad \varepsilon^y_{it} \perp B_{it}, P_{it}, I_{it}, W_{it} \qquad \text{(BPI}\to\text{Y)}$$

$$B_{it} = \beta' P_{it} + \gamma' I_{it} + \delta_B' W_{it} + \varepsilon^b_{it}, \qquad \varepsilon^b_{it} \perp P_{it}, I_{it}, W_{it} \qquad \text{(PI}\to\text{B)}$$

$$P_{it} = \eta' I_{it} + \delta_P' W_{it} + \varepsilon^p_{it}, \qquad \varepsilon^p_{it} \perp I_{it}, W_{it} \qquad \text{(I}\to\text{P)}$$

$$Y_{i,t+\ell} = (\alpha'\beta' + \pi')P_{it} + (\alpha'\gamma' + \mu')I_{it} + \bar{\delta}' W_{it} + \bar{\varepsilon}_{it}, \qquad \bar{\varepsilon}_{it} \perp P_{it}, I_{it}, W_{it}. \qquad \text{(PI}\to\text{Y)}$$

Therefore the projection equation:

$$Y_{i,t+\ell} = \mathsf{a}' P_{it} + \mathsf{b}' I_{it} + \tilde{\delta}' W_{it} + \bar{\varepsilon}_{it}, \quad \bar{\varepsilon}_{it} \perp P_{it}, I_{it}, W_{it}. \qquad \text{(Y}\sim\text{PI)}$$

should obey:

$$\mathsf{a}' = (\alpha'\beta' + \pi') \text{ and } \mathsf{b}' = (\alpha'\gamma' + \mu'). \qquad \text{(TR)}$$

Without any exclusion restrictions, this equality is just a decomposition of total effects into direct and indirect components and is not a testable restriction. However, in our case we rely on the SIR model with testing to motivate the presence of change in testing rate as a confounder in the outcome equations but not in the behavior equation (therefore, a component of δ_B and δ_P is set to 0), implying that (TR) does not necessarily hold and is testable. Furthermore, we estimate (PI→B) on the data set that has many more observations than the data set used to estimate the outcome equations, implying that (TR) is again testable. Later we shall also try to utilize the contextual knowledge that mask mandates only affect the outcome directly and not by changing mobility (i.e., $\beta = 0$ for mask policy), implying again that (TR) is testable. If not rejected by the data, (TR) can be used to sharpen the estimate of the causal effect of mask policies on the outcomes.

Validation of the model by (TR) allows us to check exclusion restrictions brought by contextual knowledge and check stability of the model by using different data subsets. However, passing the (TR) does not guarantee that the model is necessarily valid for recovering causal effects. The only fundamental way to truly validate a causal model for observational data is through a controlled experiment, which is impossible to carry out in our setting.

The parameters of the SEM are identified by the projection equation set above, provided the latter are identified by sufficient joint variation of these variables across states and time. We can develop this point formally as follows. Consider the previous system of equations, after partialling out the confounders:

$$\begin{aligned}
\tilde{Y}_{i,t+\ell} &= \alpha' \tilde{B}_{it} + \pi' \tilde{P}_{it} + \mu' \tilde{I}_{it} + \varepsilon^y_{it}, & \varepsilon^y_{it} &\perp \tilde{B}_{it}, \tilde{P}_{it}, \tilde{I}_{it}, \\
\tilde{B}_{it} &= \beta' \tilde{P}_{it} + \gamma' \tilde{I}_{it} + \varepsilon^b_{it}, & \varepsilon^b_{it} &\perp \tilde{P}_{it}, \tilde{I}_{it}, \\
\tilde{P}_{it} &= \eta' \tilde{I}_{it} + \varepsilon^p_{it}, & \varepsilon^p_{it} &\perp \tilde{I}_{it} \\
\tilde{Y}_{i,t+\ell} &= \mathsf{a}' \tilde{P}_{it} + \mathsf{b}' \tilde{I}_{it} + \bar{\varepsilon}^y_{it}, & \bar{\varepsilon}^y_{it} &\perp \tilde{P}_{it}, \tilde{I}_{it},
\end{aligned} \qquad (1)$$

where $\tilde{V}_{it} = V_{it} - W_{it}' \mathrm{E}[W_{it} W_{it}']^{-} \mathrm{E}[W_{it} V_{it}]$ denotes the residual after removing the orthogonal projection of V_{it} on W_{it}. The residualization is a linear operator, implying that (1) follows immediately from the above. The parameters of (1) are identified as projection coefficients in these equations, provided that residualized vectors appearing in each of the equations have non-singular variance, that is

$$\mathrm{Var}(\tilde{P}_{it}', \tilde{B}_{it}', \tilde{I}_{it}') > 0, \ \mathrm{Var}(\tilde{P}_{it}', \tilde{I}_{it}') > 0, \quad \text{and } \mathrm{Var}(\tilde{I}_{it}') > 0. \qquad (2)$$

Our main estimation method is the standard correlated random effects estimator, where the random effects are parameterized as functions of observable characteristic, W_{it}, which include both state-level and time random effects. The state-level random effects are modeled as a function of state level characteristics, and the time random effects are modeled by including month dummies and their interactions with state level characteristics (in the sensitivity analysis, we also add weekly dummies). The stochastic shocks $\{\varepsilon_{it}\}_{t=1}^T$ are treated as independent across states i and can be arbitrarily dependent across time t within a state.

Another modeling approach is the fixed effects panel data model, where W_{it} includes latent (unobserved) state level confonders W_i and time level effects W_t, which must be estimated from the data. This approach is much more demanding

of the data and relies on long time and cross-sectional histories to estimate W_i and W_t, resulting in amplification of uncertainty. In addition, when histories are relatively short, large biases emerge and they need to be removed using debiasing methods, see e.g., Chen et al. (2019) for overview. We present the results on debiased fixed effect estimation with weekly dummies as parts of our sensitivity analysis. Our sensitivity analysis also considers a debiased machine learning approach using Random Forest in which observed confounders enter the model nonlinearly.

With exclusion restrictions there are multiple approaches to estimation, for example, via generalized method of moments. We shall take a more pragmatic approach where we estimate the parameters of equations separately and then compute

$$\frac{1}{2}\hat{a}' + \frac{1}{2}(\hat{\alpha}'\hat{\beta}' + \hat{\pi}') \text{ and } \frac{1}{2}\hat{b}' + \frac{1}{2}(\hat{\alpha}'\hat{\gamma}' + \hat{\mu}'),$$

as the estimator of the total policy effect. Under standard regularity conditions, these estimators concentrate around their population analogues

$$\frac{1}{2}a' + \frac{1}{2}(\alpha'\beta' + \pi') \text{ and } \frac{1}{2}b' + \frac{1}{2}(\alpha'\gamma' + \mu'),$$

with approximate deviations controlled by the normal laws, with standard deviations that can be approximated by the bootstrap resampling of observational units i. Under correct specification the target quantities reduce to

$$\alpha'\beta' + \pi' \text{ and } \alpha'\gamma' + \mu',$$

respectively.[20]

2.3. Counterfactual policy analysis

We also consider simple counterfactual exercises, where we examine the effects of setting a sequence of counterfactual policies for each state:

$$\{P_{it}^\star\}_{t=1}^T, \quad i = 1, \ldots, N. \tag{CF-P}$$

We assume that the SEM remains invariant, except for the policy equation.[21] The assumption of invariance captures the idea that counterfactual policy interventions would not change the structural functions within the period of the study. The assumption is strong but is necessary to conduct counterfactual experiments, e.g. Sims (1972) and Strotz and Wold (1960). To make the assumption more plausible we limited our study to the early pandemic period.[22]

Given the policies, we generate the counterfactual outcomes, behavior, and information by propagating the dynamic equations:

$$\begin{aligned} Y_{i,t+\ell}^\star &:= Y_{i,t+\ell}(B_{it}^\star, P_{it}^\star, I_{it}^\star), \\ B_{it}^\star &:= B_{it}(P_{it}^\star, I_{it}^\star), \\ I_{it}^\star &:= I_t(Y_{it}^\star, I_{i,t-\ell}^\star), \end{aligned} \tag{CF-SEM}$$

with the same initialization as the factual system up to $t \leq 0$. In stating this counterfactual system of equations, we assume that structural outcome equations (SO) and information equations (I) remain invariant and so do the stochastic shocks, decomposed into observable and unobservable parts. Formally, we record this assumption and above discussion as follows.

> Counterfactual Structural Equations Model (CF-SEM). Let $i \in \{1, \ldots, N\}$ be the observational unit, t be time periods, and ℓ be the time delay. (1) For each i and $t \leq 0$, the confounder, information, behavior, policy, and outcome variables are determined as previously stated in SEM: $W_{it}^\star = W_{it}$, $I_{it}^\star = I_{it}$, $B_{it}^\star = B_{it}$, $P_{it}^\star = P_{it}$, $Y_{it}^\star = Y_{it}$. (2) For each i and $t \geq 0$, confounders $W_{it}^\star = W_{it}$ are determined as in SEM, and information variables $I_{it}^\star$ are determined by (I); policy variables $P_{it}^\star$ are set in (CF-P); behavior variables $B_{it}^\star$ are determined by setting $\iota = I_{it}^\star$ and $p = P_{it}^\star$ in (SO) with the same stochastic shock ε_{it}^b in (SO); the counterfactual outcome $Y_{i,t+\ell}^\star$ is realized by setting $\iota = I_{it}^\star$, $p = P_{it}^\star$, and $b = B_{it}^\star$ in (SO) with the same stochastic shock ε_{it}^y in (SO).

Figs. 6 and 7 present the causal path diagram for CF-SEM as well as the dynamics of counterfactual information in CF-SEM.

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[20] This construction is not as efficient as generalized method of moments but has a nicer interpretation under possible misspecification of the model: we are combining predictions from two models, one motivated via the causal path, reflecting contextual knowledge, and another from a "reduced form" model not exploiting the path. The combined estimator can improve on precision of either estimator.

[21] It is possible to consider counterfactual exercises in which policy responds to information through the policy equation if we are interested in endogenous policy responses to information. Counterfactual experiments with endogenous government policy would be important, for example, to understand the issues related to the lagged response of government policies to higher infection rates due to incomplete information.

[22] Furthermore, we conducted several stability checks, for example, checking if the coefficients on mask policies remain stable (reported in the previous version) and also looking at more recent data during reopening, beyond early pandemic, to examine the stability of the model.

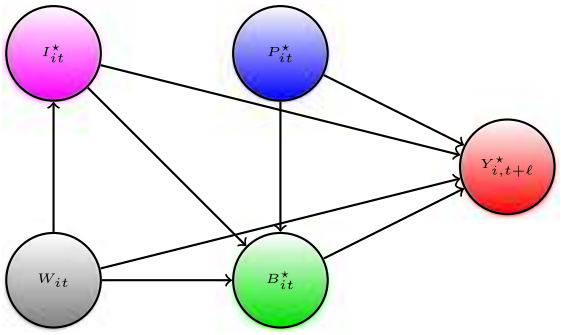

Fig. 6. Causal path diagram for CF-SEM.

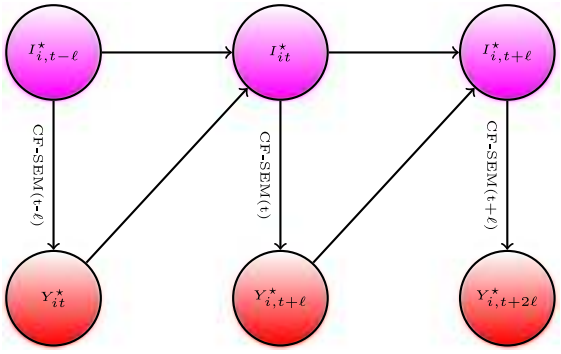

Fig. 7. A Diagram for Counterfactual Information Dynamics in CF-SEM.

The counterfactual outcome $Y^\star_{i,t+\ell}$ and factual outcome $Y_{i,t+\ell}$ are given by:

$$Y^\star_{i,t+\ell} = (\alpha'\beta' + \pi')P^\star_{it} + (\alpha'\gamma' + \mu')I^\star_{it} + \bar{\delta}'W_{it} + \bar{\varepsilon}^y_{it},$$

$$Y_{i,t+\ell} = (\alpha'\beta' + \pi')P_{it} + (\alpha'\gamma' + \mu')I_{it} + \bar{\delta}'W_{it} + \bar{\varepsilon}^y_{it}.$$

In generating these predictions, we explore the assumption of invariance stated above. We can write the counterfactual contrast into the sum of three components:

$$\underbrace{Y^\star_{i,t+\ell} - Y_{i,t+\ell}}_{\text{CF Change}} = \underbrace{\alpha'\beta'\left(P^\star_{it} - P_{it}\right)}_{\text{CF Policy Effect via Behavior}} + \underbrace{\pi'\left(P^\star_{it} - P_{it}\right)}_{\text{CF Direct Effect}}$$

$$+ \underbrace{\alpha'\gamma'\left(I^\star_{it} - I_{it}\right) + \mu'\left(I^\star_{it} - I_{it}\right)}_{\text{CF Dynamic Effect}}$$

$$=: \text{PEB}^\star_{it} + \text{PED}^\star_{it} + \text{DynE}^\star_{it}, \tag{3}$$

which describe the immediate indirect effect of the policy via behavior, the direct effect of the policy, and the dynamic effect of the policy. By recursive substitutions the dynamic effect can be further decomposed into a weighted sum of delayed policy effects via behavior and a weighted sum of delayed policy effects via direct impact.

All counterfactual quantities and contrasts can be computed from the expressions given above. For examples, given $\Delta C_{i0} > 0$, new confirmed cases are linked to growth rates via relation (taking t divisible by ℓ for simplicity):

$$\frac{\Delta C^\star_{it}}{\Delta C_{i0}} = \exp\left(\sum_{m=1}^{t/\ell} Y^\star_{i,m\ell}\right) \text{ and } \frac{\Delta C_{it}}{\Delta C_{i0}} = \exp\left(\sum_{m=1}^{t/\ell} Y_{i,m\ell}\right).$$

The cumulative cases can be constructed by summing over the new cases. Various contrasts are then calculated from these quantities. For example, the relative contrast of counterfactual new confirmed cases to the factual confirmed cases

is given by:

$$\frac{\Delta C_{it}^{\star}}{\Delta C_{it}} = \exp\left(\sum_{m=1}^{t/\ell}(Y_{i,m\ell}^{\star} - Y_{i,m\ell})\right).$$

We refer to the appendix for further details. Similar calculations apply for fatalities. Note that our analysis is conditional on the factual history and structural stochastic shocks.[23]

The estimated counterfactuals are smooth functionals of the underlying parameter estimates. Therefore, we construct the confidence intervals for counterfactual quantities and contrasts by bootstrapping the parameter estimates. We refer to the appendix for further details.

2.4. Outcome and key confounders via SIRD model

We next provide details of our key measurement equations, defining the outcomes and key confounders. We motivate the structural outcome equations via the fundamental epidemiological model for the spread of infectious decease called the Susceptible–Infected–Recovered–Dead (SIRD) model with testing.

Letting C_{it} denote the cumulative number of confirmed cases in state i at time t, our outcome

$$Y_{it} = \Delta \log(\Delta C_{it}) := \log(\Delta C_{it}) - \log(\Delta C_{i,t-7}) \tag{4}$$

approximates the weekly growth rate in new cases from $t-7$ to t. Here Δ denotes the differencing operator over 7 days from t to $t-7$, so that $\Delta C_{it} := C_{it} - C_{i,t-7}$ is the number of new confirmed cases in the past 7 days.

We chose this metric as this is the key metric for policy makers deciding when to relax Covid mitigation policies. The U.S. government's guidelines for state reopening recommend that states display a "downward trajectory of documented cases within a 14-day period" (The White House, 2020). A negative value of Y_{it} is an indication of meeting this criteria for reopening. By focusing on weekly cases rather than daily cases, we smooth idiosyncratic daily fluctuations as well as periodic fluctuations associated with days of the week.

Our measurement equation for estimating Eqs. (BPI→Y) and (PI→Y) will take the form:

$$\Delta \log(\Delta C_{it}) = X_{i,t-14}'\theta - \gamma + \delta_T \Delta \log(T_{it}) + \epsilon_{it}, \tag{M-C}$$

where i is state, t is day, C_{it} is cumulative confirmed cases, T_{it} is the number of tests over 7 days, Δ is a 7-days differencing operator, and ϵ_{it} is an unobserved error term. $X_{i,t-14}$ collects other behavioral, policy, and confounding variables, depending on whether we estimate (BPI→Y) or (PI→Y), where the lag of 14 days captures the time lag between infection and confirmed case (see Appendix A.6). Here

$$\Delta \log(T_{it}) := \log(T_{it}) - \log(T_{i,t-7})$$

is the key confounding variable, derived from considering the SIRD model below. We are treating the change in testing rate as exogenous.[24] We describe other confounders in the empirical section.

Our main measurement equation (M-C) is motivated by a variant of SIRD model, where we add confirmed cases and infection detection via testing. Let S, $\mathcal{I}$, R, and D denote the number of susceptible, infected, recovered, and deceased individuals in a given state. Each of these variables are a function of time. We model them as evolving as

$$\dot{S}(t) = -\frac{S(t)}{N}\beta(t)\mathcal{I}(t) \tag{5}$$

$$\dot{\mathcal{I}}(t) = \frac{S(t)}{N}\beta(t)\mathcal{I}(t) - \gamma\mathcal{I}(t) \tag{6}$$

$$\dot{R}(t) = (1-\kappa)\gamma\mathcal{I}(t) \tag{7}$$

$$\dot{D}(t) = \kappa\gamma\mathcal{I}(t) \tag{8}$$

where N is the population, $\beta(t)$ is the rate of infection spread, γ is the rate of recovery or death, and κ is the probability of death conditional on infection.

Confirmed cases, $C(t)$, evolve as

$$\dot{C}(t) = \tau(t)\mathcal{I}(t), \tag{9}$$

where $\tau(t)$ is the rate that infections are detected.

[23] For unconditional counterfactual, we need to make assumptions about the evolution of stochastic shocks appearing in Y_{it}. See, e.g., previous versions of our paper in ArXiv, where unconditional counterfactuals were calculated by assuming stochastic shocks are i.i.d. and resampling them from the empirical distribution. The differences between conditional and unconditional contrasts were small in our empirical analysis.

[24] To check sensitivity to this assumption we performed robustness checks, where we used the further lag of $\Delta \log(T_{it})$ as a proxy for exogenous change in the testing rate, and we also used that as an instrument for $\Delta \log(T_{it})$; this did not affect the results on policy effects, although the instrument was not sufficiently strong.

Our goal is to examine how the rate of infection $\beta(t)$ varies with observed policies and measures of social distancing behavior. A key challenge is that we only observed $C(t)$ and $D(t)$, but not $\mathcal{I}(t)$. The unobserved $\mathcal{I}(t)$ can be eliminated by differentiating (9) and using (6) as

$$\frac{\ddot{C}(t)}{\dot{C}(t)} = \frac{S(t)}{N}\beta(t) - \gamma + \frac{\dot{\tau}(t)}{\tau(t)}. \tag{10}$$

We consider a discrete-time analogue of Eq. (10) to motivate our empirical specification by relating the detection rate $\tau(t)$ to the number of tests T_{it} while specifying $\frac{S(t)}{N}\beta(t)$ as a linear function of variables $X_{i,t-14}$. This results in

$$\underbrace{\Delta \log(\Delta C_{it})}_{\frac{\ddot{C}(t)}{\dot{C}(t)}} = \underbrace{X'_{i,t-14}\theta + \epsilon_{it}}_{\frac{S(t)}{N}\beta(t)-\gamma} + \underbrace{\delta_T \Delta \log(T)_{it}}_{\frac{\dot{\tau}(t)}{\tau(t)}}$$

which is equation (M-C), where $X_{i,t-14}$ captures a vector of variables related to $\beta(t)$.

Structural Interpretation. Early in the pandemic, when the number of susceptibles is approximately the same as the entire population, i.e. $S_{it}/N_{it} \approx 1$, the component $X'_{i,t-14}\theta$ is the projection of infection rate $\beta_i(t)$ on $X_{i,t-14}$ (policy, behavioral, information, and confounders other than testing rate), provided the stochastic component ϵ_{it} is orthogonal to $X_{i,t-14}$ and the testing variables:

$$\beta_i(t)S_{it}/N_{it} - \gamma = X'_{i,t-14}\theta + \epsilon_{it}, \quad \epsilon_{it} \perp X_{i,t-14}.$$

The specification for growth rate in deaths as the outcome is motivated by SIRD as follows. By differentiating (8) and (9) with respect to t and using (10), we obtain

$$\frac{\ddot{D}(t)}{\dot{D}(t)} = \frac{\ddot{C}(t)}{\dot{C}(t)} - \frac{\dot{\tau}(t)}{\tau(t)} = \frac{S(t)}{N}\beta(t) - \gamma. \tag{11}$$

Our measurement equation for the growth rate of deaths is based on Eq. (11) but accounts for a 21 day lag between infection and death as

$$\Delta \log(\Delta D_{it}) = X'_{i,t-21}\theta + \epsilon_{it}, \tag{M-D}$$

where

$$\Delta \log(\Delta D_{it}) := \log(\Delta D_{it}) - \log(\Delta D_{i,t-7}) \tag{12}$$

approximates the weekly growth rate in deaths from $t-7$ to t in state i.

3. Empirical analysis

3.1. Data

All code is available at https://github.com/ubcecon/covid-impact. Our baseline measures for daily Covid-19 cases and deaths are from The New York Times (NYT). When there are missing values in NYT, we use reported cases and deaths from JHU CSSE, and then the Covid Tracking Project. The number of tests for each state is from Covid Tracking Project. As shown in the lower right panel of Fig. A.17 in the appendix, there was a rapid increase in testing in the second half of March and then the number of tests increased very slowly in each state in April.

We use the database on US state policies created by Raifman et al. (2020). In our analysis, we focus on 6 policies: stay-at-home, closed nonessential businesses, closed K-12 schools, closed restaurants except takeout, closed movie theaters, and face mask mandates for employees in public facing businesses. We believe that the first four of these policies are the most widespread and important. Closed movie theaters is included because it captures common bans on gatherings of more than a handful of people. We also include mandatory face mask use by employees because its effectiveness on slowing down Covid-19 spread is a controversial policy issue (Howard et al., 2020; Greenhalgh et al., 2020; Zhang et al., 2020b). Table 1 provides summary statistics, where N is the number of states that have ever implemented the policy. We also obtain information on state-level covariates mostly from Raifman et al. (2020), which include population size, total area, unemployment rate, poverty rate, a percentage of people who are subject to illness, and state governor's party affiliations. These confounders are motivated by Wheaton and Thompson (2020) who find that case growth is associated with residential density and per capita income.

We obtain social distancing behavior measures from "Google COVID-19 Community Mobility Reports" (Google LLC, 2020). The dataset provides six measures of "mobility trends" that report a percentage change in visits and length of stay at different places relative to a baseline computed by their median values of the same day of the week from January 3 to

Table 1
State policies.

	N	Min	Median	Max
Date closed K 12 schools	51	2020-03–13	2020-03–17	2020-04-03
Stay at home shelter in place	42	2020-03–19	2020-03–28	2020-04-07
Closed movie theaters	49	2020-03–16	2020-03–21	2020-04-06
Closed restaurants except take out	48	2020-03–15	2020-03–17	2020-04-03
Closed non essential businesses	43	2020-03–19	2020-03–25	2020-04-06
Mandate face mask use by employees	44	2020-04–03	2020-05–01	2020-08-03

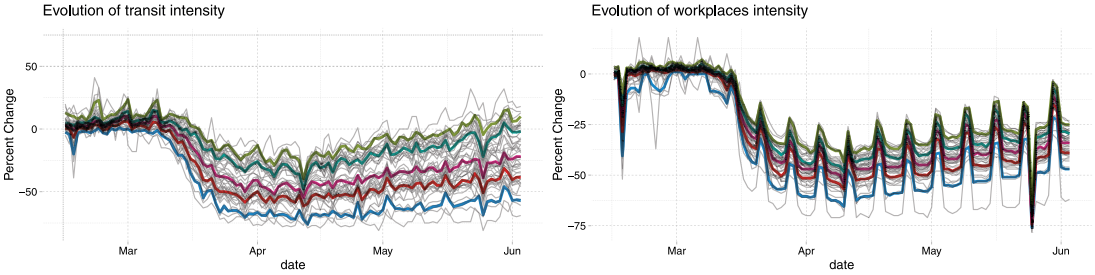

Fig. 8. The Evolution of Google Mobility Measures: Transit stations and Workplaces. This figure shows the evolution of "Transit stations" and "Workplaces" of Google Mobility Reports. Thin gray lines are the value in each state and date. Thicker colored lines are quantiles of the variables conditional on date. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

February 6, 2020. Our analysis focuses on the following four measures: "Grocery & pharmacy", "Transit stations", "Retail & recreation", and "Workplaces".[25]

Fig. 8 shows the evolution of "Transit stations" and "Workplaces", where thin lines are the value in each state and date while thicker colored lines are quantiles conditional on date. The figures illustrate a sharp decline in people's movements starting from mid-March as well as differences in their evolutions across states. They also reveal periodic fluctuations associated with days of the week, which motivates our use of weekly measures.

In our empirical analysis, we use weekly measures for cases, deaths, and tests by summing up their daily measures from day t to $t-6$. We focus on weekly cases and deaths because daily new cases and deaths are affected by the timing of reporting and testing and are quite volatile as shown in the upper right panel of Fig. A.17 in the appendix. Aggregating to weekly new cases/deaths/tests smooths out idiosyncratic daily noises as well as periodic fluctuations associated with days of the week. We also construct weekly policy and behavior variables by taking 7 day moving averages from day $t-14$ to $t-21$ for case growth, where the delay reflects the time lag between infection and case confirmation. The four weekly behavior variables are referred to "Transit Intensity", "Workplace Intensity", "Retail Intensity", and "Grocery Intensity". Consequently, our empirical analysis uses 7 day moving averages of all variables recorded at daily frequencies. Our sample period is from March 7, 2020 to June 3, 2020.

Table 2 reports that weekly policy and behavior variables are highly correlated with each other, except for the"masks for employees" policy. High correlations may cause multicolinearity problems and could limit our ability to separately identify the effect of each policy or behavior variable on case growth. For this reason, we define the "business closure policies" variable by the average of closed movie theaters, closed restaurants, and closed non-essential businesses variables and consider a specification that includes business closure policies in place of these three policy variables separately.

Fig. 9 shows the portion of states that have each policy in place at each date. For most policies, there is considerable variation across states in the time in which the policies are active. The one exception is K-12 school closures. About 80% of states closed schools within a day or two of March 15th, and all states closed schools by early April. This makes the effect of school closings difficult to separate from aggregate time series variation.

3.2. The effect of policies and information on behavior

We first examine how policies and information affect social distancing behaviors by estimating a version of (PI→B):

$$B_{it}^{j} = (\beta^{j})' P_{it} + (\gamma^{j})' I_{it} + (\delta_{B}^{j})' W_{it} + \varepsilon_{it}^{bj},$$

where B_{it}^{j} represents behavior variable j in state i at time t. P_{it} collects the Covid related policies in state i at t. Confounders, W_{it}, include state-level covariates, month indicators, and their interactions. I_{it} is a set of information variables that affect

[25] The other two measures are "Residential" and "Parks". We drop "Residential" because it is highly correlated with "Workplaces" and "Retail & recreation" at correlation coefficients of −0.98 and −0.97, respectively. We also drop "Parks" because it does not have clear implication on the spread of Covid-19.

Table 2
Correlations among policies and behavior.

	workplaces	retail	grocery	transit	masks for employees	closed K-12 schools	stay at home	closed movie theaters	closed restaurants	closed non-essent bus	business closure policies
workplaces	1.00										
retail	0.93	1.00									
grocery	0.75	0.83	1.00								
transit	0.89	0.92	0.83	1.00							
masks for employees	−0.32	−0.17	−0.15	−0.29	1.00						
closed K-12 schools	−0.91	−0.79	−0.55	−0.72	0.43	1.00					
stay at home	−0.69	−0.69	−0.70	−0.71	0.28	0.62	1.00				
closed movie theaters	−0.81	−0.76	−0.64	−0.71	0.34	0.82	0.72	1.00			
closed restaurants	−0.77	−0.82	−0.68	−0.76	0.21	0.74	0.72	0.82	1.00		
closed non-essent bus	−0.65	−0.68	−0.68	−0.64	0.08	0.56	0.76	0.68	0.71	1.00	
business closure policies	−0.84	−0.84	−0.75	−0.79	0.24	0.78	0.81	0.92	0.93	0.87	1.00

Each off-diagonal entry reports a correlation coefficient of a pair of policy and behavior variables. "business closure policies" is defined by the average of closured movie theaters, closured restaurants, and closured non-essential businesses.

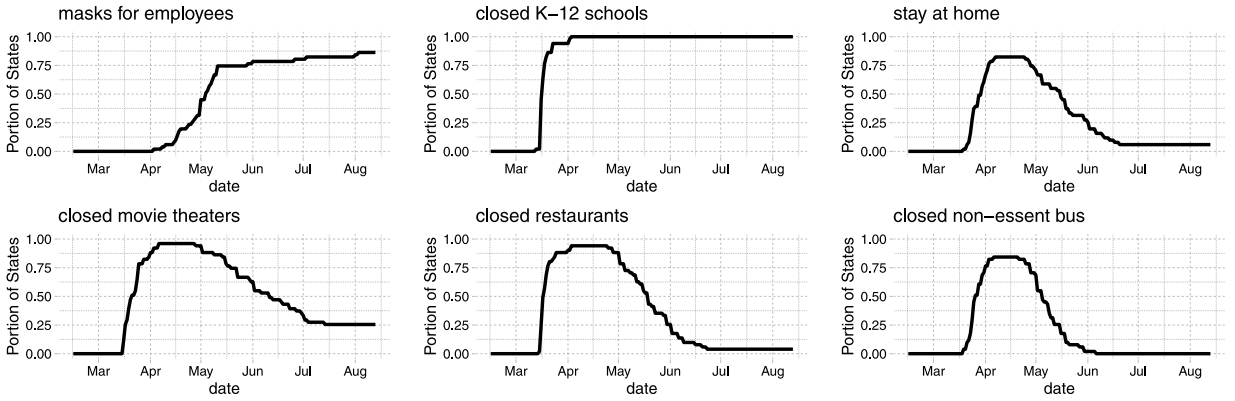

Fig. 9. Portion of states with each policy.

people's behaviors at t. As information, we include each state's growth of cases (in panel (a)) or deaths (in panel (b)), and log cases or deaths. Additionally, in columns (5)–(8) of Table 3, we include national growth and log of cases or deaths.

Table 3 reports the estimates with standard errors clustered at the state level. Across different specifications, our results imply that policies have large effects on behavior. Comparing columns (1)–(4) with columns (5)–(8), the magnitude of policy effects are sensitive to whether national cases or deaths are included as information. The coefficient on school closures is particularly sensitive to the inclusion of national information variables. As shown in Fig. 9, there is little variation across states in the timing of school closures. Consequently, it is difficult to separate the effect of school closures from a behavioral response to the national trend in cases and deaths.

The other policy coefficients are less sensitive to the inclusion of national case/death variables. After school closures, business closure policies have the next largest effect followed by stay-at-home orders. The effect of masks for employees is small.[26]

The row "$\sum_j \text{Policy}_j$" reports the sum of the estimated effect of all policies, which is substantial and can account for a large fraction of the observed declines in behavior variables. For example, in Fig. 8, transit intensity for a median state was approximately -50% at its lowest point in early April. The estimated policy coefficients in columns imply that imposing all policies would lead to roughly 75% (in column 4) or roughly 35% (in column 8) of the observed decline. The large impact of policies on transit intensity suggests that the policies may have reduced the Covid-19 infection by reducing people's use of public transportation.[27]

[26] Similar to our finding, Kovacs et al. (2020) find no evidence that introduction of compulsory face mask policies affect community mobility in Germany.

[27] Analyzing the New York City's subway ridership, Harris (2020) finds a strong link between public transit and spread of infection.

Table 3
The effect of policies and information on behavior (PI→B).

(a) Cases as Information

	Dependent variable:							
	workplaces (1)	retail (2)	grocery (3)	transit (4)	workplaces (5)	retail (6)	grocery (7)	transit (8)
masks for employees	0.023*	0.033*	0.012	0.015	0.005	0.0005	0.003	−0.010
	(0.012)	(0.020)	(0.012)	(0.025)	(0.008)	(0.015)	(0.011)	(0.023)
closed K-12 schools	−0.196***	−0.253***	−0.143***	−0.243***	−0.044***	−0.025	−0.069**	−0.047
	(0.030)	(0.048)	(0.027)	(0.050)	(0.013)	(0.018)	(0.027)	(0.041)
stay at home	−0.028**	−0.024	−0.068***	−0.062**	−0.034***	−0.047***	−0.071***	−0.074***
	(0.013)	(0.017)	(0.015)	(0.028)	(0.011)	(0.013)	(0.015)	(0.028)
business closure policies	−0.081***	−0.136***	−0.088***	−0.080**	−0.049***	−0.094***	−0.073***	−0.042
	(0.017)	(0.028)	(0.017)	(0.038)	(0.012)	(0.020)	(0.018)	(0.036)
$\Delta \log \Delta C_{it}$	0.015***	−0.002	0.016***	0.014***	0.017***	0.014***	0.018***	0.020***
	(0.003)	(0.005)	(0.004)	(0.005)	(0.002)	(0.004)	(0.004)	(0.005)
$\log \Delta C_{it}$	−0.024***	−0.022***	−0.0002	−0.018*	−0.005	−0.001	0.009	0.004
	(0.005)	(0.008)	(0.005)	(0.010)	(0.004)	(0.007)	(0.006)	(0.011)
$\Delta \log \Delta C_{it}$.national					−0.033***	−0.086***	−0.018**	−0.053***
					(0.005)	(0.008)	(0.008)	(0.012)
$\log \Delta C_{it}$.national					−0.072***	−0.103***	−0.035***	−0.091***
					(0.004)	(0.008)	(0.008)	(0.012)
state variables	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Month ×state variables	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
$\sum_j \text{Policy}_j$	−0.282***	−0.380***	−0.287***	−0.371***	−0.122***	−0.166***	−0.211***	−0.172***
	(0.041)	(0.066)	(0.040)	(0.078)	(0.022)	(0.035)	(0.037)	(0.060)
Observations	3,825	3,825	3,825	3,825	3,825	3,825	3,825	3,825
R^2	0.913	0.829	0.749	0.818	0.953	0.906	0.765	0.856
Adjusted R^2	0.912	0.829	0.748	0.817	0.952	0.905	0.764	0.855

(b) Deaths as Information

	Dependent variable:							
	workplaces (1)	retail (2)	grocery (3)	transit (4)	workplaces (5)	retail (6)	grocery (7)	transit (8)
masks for employees	0.018	0.027	0.006	0.006	0.007	0.012	0.002	−0.005
	(0.011)	(0.017)	(0.014)	(0.026)	(0.009)	(0.016)	(0.012)	(0.025)
closed K-12 schools	−0.226***	−0.261***	−0.114***	−0.240***	−0.045***	−0.033*	−0.024	−0.050
	(0.024)	(0.033)	(0.018)	(0.035)	(0.014)	(0.019)	(0.020)	(0.039)
stay at home	−0.031**	−0.035**	−0.082***	−0.072**	−0.024*	−0.032**	−0.073***	−0.066**
	(0.012)	(0.017)	(0.016)	(0.031)	(0.012)	(0.015)	(0.017)	(0.032)
business closure policies	−0.101***	−0.156***	−0.101***	−0.111***	−0.044***	−0.091***	−0.067***	−0.054
	(0.022)	(0.033)	(0.020)	(0.041)	(0.012)	(0.021)	(0.020)	(0.039)
$\Delta \log \Delta D_{it}$	−0.012***	−0.031***	−0.001	−0.021***	−0.003	−0.012***	−0.002	−0.009*
	(0.005)	(0.006)	(0.004)	(0.006)	(0.002)	(0.004)	(0.004)	(0.005)
$\log \Delta D_{it}$	−0.013***	−0.001	−0.005	−0.006	−0.007	0.003	0.002	−0.0003
	(0.004)	(0.006)	(0.005)	(0.009)	(0.004)	(0.007)	(0.005)	(0.010)
$\Delta \log \Delta D_{it}$.national					−0.058***	−0.095***	−0.008	−0.067***
					(0.005)	(0.008)	(0.006)	(0.010)
$\log \Delta D_{it}$.national					−0.056***	−0.065***	−0.033***	−0.057***
					(0.004)	(0.007)	(0.006)	(0.010)
state variables	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Month ×state variables	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
$\sum_j \text{Policy}_j$	−0.340***	−0.425***	−0.292***	−0.417***	−0.105***	−0.144***	−0.162***	−0.176***
	(0.026)	(0.036)	(0.033)	(0.060)	(0.024)	(0.039)	(0.034)	(0.068)
Observations	3,468	3,468	3,468	3,468	3,468	3,468	3,468	3,468
R^2	0.908	0.836	0.760	0.826	0.953	0.899	0.783	0.856
Adjusted R^2	0.907	0.835	0.759	0.825	0.953	0.898	0.782	0.855

Note: *p<0.1; **p<0.05; ***p<0.01.
Dependent variables are "Transit Intensity," "Workplace Intensity," "Retail Intensity," and "Grocery Intensity" defined as 7 days moving averages of corresponding daily measures obtained from Google Mobility Reports. All specifications include state-level characteristics (population, area, unemployment rate, poverty rate, a percentage of people subject to illness, and governor's party) as well as their interactions with the log of days since Jan 15, 2020. The row "$\sum_j \text{Policy}_j$" reports the sum of four policy coefficients. Standard errors are clustered at the state level.

In Table 3(b), estimated coefficients of deaths and death growth are generally negative. This suggests that the higher number of deaths reduces social interactions measured by Google Mobility Reports perhaps because people are increasingly aware of prevalence of Covid-19 (Maloney and Taskin, 2020). The coefficients on log cases and case growth

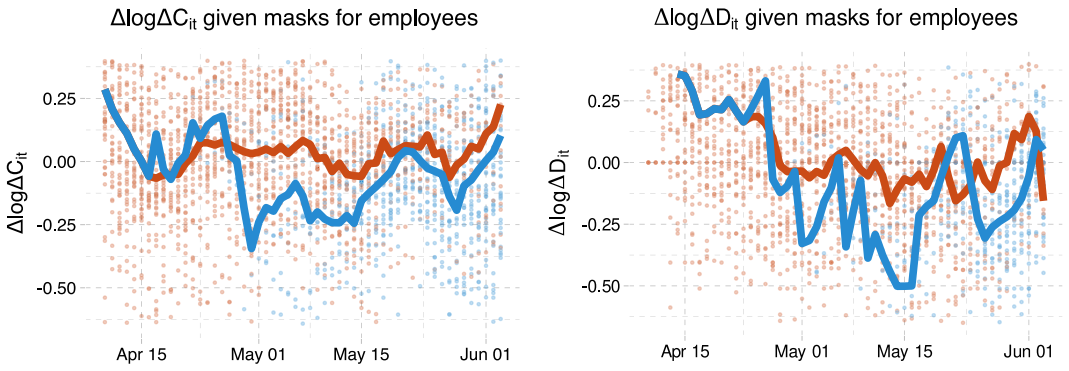

Fig. 10. Case and death growth conditional on mask mandates. In these figures, red points are the case or death growth rate in states without a mask mandate. Blue points are states with a mask mandate 14 (21 for deaths) days prior. The red line is the average across states without a mask mandate 14 (21 for deaths) days earlier. The blue line is the average across states with a mask mandate 14 (21 for deaths) earlier. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

in Table 3(a) are more mixed.[28] In columns (5)–(8) of both panels, we see that national case/death variables have large, negative coefficients. This suggests that behavior responded to national conditions although it is also likely that national case/death variables capture unobserved aggregate time effects beyond information which are not fully controlled by month dummies (e.g., latent policy variables and time-varying confounders that are common across states).

3.3. The direct effect of policies and behavior on case and death growth

We now analyze how behavior and policies together influence case and death growth rates. We begin with some simple graphical evidence of the effect of policies on case and death growth. Fig. 10 shows average case and death growth conditional on date and whether masks are mandatory for employees.[29] The left panel of the figure shows that states with a mask mandate consistently have 0–0.2 lower case growth than states without. The right panel also illustrates that states with a mask mandate tend to have lower average death growth than states without a mask mandate.

Similar plots are shown for other policies in Figs. A.20 and A.21 in the appendix. The figures for stay-at-home orders and closure of nonessential businesses are qualitatively similar to that for masks. States with these two policies appear to have about 0.1 percentage point lower case growth than states without. The effects of school closures, movie theater closures, and restaurant closures are not clearly visible in these figures. These figures are merely suggestive; the patterns observed in them may be driven by confounders.

We more formally analyze the effect of policies by estimating regressions. We first look at the direct effect of policies on case and death growth conditional on behavior by estimating equation (BPI→Y):

$$Y_{i,t+\ell} = \alpha' B_{it} + \pi' P_{it} + \mu' I_{it} + \delta_Y' W_{it} + \varepsilon_{it}^{y}, \tag{13}$$

where the outcome variable, $Y_{i,t+\ell}$, is either case growth or death growth.

For case growth as the outcome, we choose a lag length of $\ell = 14$ days for behavior, policy, and information variables to reflect the delay between infection and confirmation of case.[30] $B_{it} = (B_{it}^1, \ldots, B_{it}^4)'$ is a vector of four behavior variables in state i. P_{it} includes the Covid-related policies in state i that directly affect the spread of Covid-19 after controlling for behavior variables (e.g., masks for employees). We include information variables, I_{it}, that include the past cases and case growths because the past cases may be correlated with (latent) government policies or people's behaviors that are not fully captured by our observed policy and behavior variables. We also consider a specification that includes the past cases and case growth at the national level as additional information variables. W_{it} is a set of confounders that includes month dummies, state-level covariates, and the interaction terms between month dummies and state-level covariates.[31] For case growth, W_{it} also includes the test rate growth $\Delta \log(T)_{it}$ to capture the effect of changing test rates on confirmed cases. Eq. (13) corresponds to (M-C) derived from the SIR model.

[28] Rewrite a regression specification after omitting other variables as $B_{it} = \gamma_1 \Delta \log \Delta C_{it} + \gamma_2 \log \Delta C_{it} = (\gamma_1 + \gamma_2) \log \Delta C_{it} - \gamma_1 \log \Delta C_{i,t-7}$. In columns (1)–(4) of Table 3(a), the estimated values of both $(\gamma_1 + \gamma_2)$ and $-\gamma_1$ are negative except for grocery. This suggests that a higher *level* of confirmed cases reduces people's mobility in workplaces, retails, and transit. For grocery, the positive estimated coefficient of $(\gamma_1 + \gamma_2)$ may reflect stock-piling behavior in early pandemic periods.

[29] We take 14 and 21 day lags of mask policies for case and death growths, respectively, to identify the states with a mask mandate because policies affect cases and deaths with time lags. See our discussion in Appendix A.6.

[30] As we review in Appendix A.6, a lag length of 14 days between exposure and case reporting, as well as a lag length of 21 days between exposure and deaths, is broadly consistent with currently available evidence. Section 4 provides a sensitivity analysis under different timing assumptions.

[31] Month dummies also represent the latent information that is not fully captured by the past cases and growths.

Table 4
The direct effect of behavior and policies on case and death growth (BPI→Y).

	Dependent variable:			
	$\Delta \log \Delta C_{it}$			
	(1)	(2)	(3)	(4)
lag(masks for employees, 14)	−0.090***	−0.091***	−0.100***	−0.100***
	(0.031)	(0.032)	(0.029)	(0.030)
lag(closed K-12 schools, 14)	−0.074	−0.083	0.043	0.031
	(0.080)	(0.090)	(0.096)	(0.103)
lag(stay at home, 14)	−0.063	−0.058	−0.079	−0.071
	(0.050)	(0.048)	(0.052)	(0.050)
lag(business closure policies, 14)	0.051		0.045	
	(0.062)		(0.060)	
lag(closed movie theaters, 14)		0.032		0.045
		(0.050)		(0.049)
lag(closed restaurants, 14)		0.023		0.022
		(0.044)		(0.043)
lag(closed non-essent bus, 14)		−0.001		−0.016
		(0.040)		(0.040)
lag(workplaces, 14)	1.055*	1.042*	0.391	0.355
	(0.543)	(0.556)	(0.610)	(0.618)
lag(retail, 14)	0.594*	0.611**	0.316	0.342
	(0.303)	(0.309)	(0.316)	(0.317)
lag(grocery, 14)	−0.471*	−0.478*	−0.259	−0.266
	(0.284)	(0.288)	(0.282)	(0.284)
lag(transit, 14)	0.347	0.339	0.355	0.339
	(0.258)	(0.268)	(0.247)	(0.253)
lag($\Delta \log \Delta C_{it}$, 14)	0.015	0.015	0.024	0.024
	(0.026)	(0.025)	(0.028)	(0.028)
lag($\log \Delta C_{it}$, 14)	−0.105***	−0.105***	−0.088***	−0.087***
	(0.019)	(0.019)	(0.021)	(0.021)
lag($\Delta \log \Delta C_{it}$.national, 14)			−0.095**	−0.095**
			(0.042)	(0.043)
lag($\log \Delta C_{it}$.national, 14)			−0.177***	−0.180***
			(0.049)	(0.050)
$\Delta \log T_{it}$	0.152***	0.153***	0.155***	0.156***
	(0.043)	(0.043)	(0.042)	(0.041)
state variables	Yes	Yes	Yes	Yes
Month ×state variables	Yes	Yes	Yes	Yes
$\sum_j \text{Policy}_j$	−0.176	−0.178	−0.091	−0.090
	(0.128)	(0.133)	(0.153)	(0.158)
$\sum_k w_k \text{Behavior}_k$	−0.804***	−0.801***	−0.425***	−0.413***
	(0.140)	(0.140)	(0.157)	(0.160)
Observations	3,825	3,825	3,825	3,825
R^2	0.761	0.761	0.766	0.766
Adjusted R^2	0.759	0.759	0.763	0.764

	Dependent variable:			
	$\Delta \log \Delta D_{it}$			
	(1)	(2)	(3)	(4)
lag(masks for employees, 21)	−0.146***	−0.150***	−0.147***	−0.150***
	(0.050)	(0.050)	(0.049)	(0.049)
lag(closed K-12 schools, 21)	−0.232**	−0.250**	−0.178*	−0.198**
	(0.102)	(0.098)	(0.103)	(0.100)
lag(stay at home, 21)	−0.066	−0.050	−0.065	−0.050
	(0.067)	(0.065)	(0.067)	(0.064)
lag(business closure policies, 21)	0.098		0.107	
	(0.087)		(0.092)	
lag(closed movie theaters, 21)		0.006		0.021
		(0.090)		(0.088)
lag(closed restaurants, 21)		0.087		0.083
		(0.072)		(0.070)
lag(closed non-essent bus, 21)		−0.001		−0.001
		(0.058)		(0.059)
lag(workplaces, 21)	1.297**	1.279**	0.896	0.889
	(0.515)	(0.510)	(0.554)	(0.558)
lag(retail, 21)	0.572	0.598	0.523	0.546
	(0.441)	(0.460)	(0.438)	(0.455)
lag(grocery, 21)	−0.935**	−0.966**	−0.887**	−0.912**
	(0.388)	(0.397)	(0.368)	(0.377)

(*continued on next page*)

Table 4 (*continued*).

	Dependent variable:			
	$\Delta \log \Delta D_{it}$			
	(1)	(2)	(3)	(4)
lag(transit, 21)	0.348	0.368	0.384	0.396
	(0.284)	(0.273)	(0.283)	(0.272)
lag($\Delta \log \Delta D_{it}$, 21)	0.016	0.015	0.016	0.015
	(0.035)	(0.035)	(0.037)	(0.037)
lag($\log \Delta D_{it}$, 21)	−0.055**	−0.052**	−0.053**	−0.050**
	(0.024)	(0.025)	(0.024)	(0.024)
lag($\Delta \log \Delta D_{it}$.national, 21)			−0.034	−0.036
			(0.044)	(0.046)
lag($\log \Delta D_{it}$.national, 21)			−0.047	−0.046
			(0.039)	(0.038)
state variables	Yes	Yes	Yes	Yes
Month ×state variables	Yes	Yes	Yes	Yes
$\sum_j \text{Policy}_j$	−0.346**	−0.358**	−0.283*	−0.296*
	(0.162)	(0.164)	(0.172)	(0.175)
$\sum_k w_k \text{Behavior}_k$	−0.837***	−0.845***	−0.661***	−0.670***
	(0.164)	(0.170)	(0.176)	(0.179)
Observations	3,468	3,468	3,468	3,468
R^2	0.518	0.518	0.518	0.519
Adjusted R^2	0.512	0.512	0.513	0.513

Note: *p<0.1; **p<0.05; ***p<0.01.
Dependent variable is the weekly growth rate of confirmed cases (in the upper panel) or deaths (in the lower panel) as defined in Eq. (4). The covariates include lagged policy and behavior variables, which are constructed as 7 day moving averages between t to $t-7$ of corresponding daily measures. The row "$\sum_j \text{Policies}_j$" reports the sum of all policy coefficients. The row "$\sum_k w_k \text{Behavior}_k$" reports the sum of four coefficients of behavior variables weighted by the average of each behavioral variable from April 1st-10th. "business closure policies" is defined by the average of closured movie theaters, closured restaurants, and closured non-essential businesses. Standard errors are clustered at the state level.

For death growth as the outcome, we take a lag length of $\ell = 21$ days. The information variables I_{it} include past deaths and death growth rates; W_{it} is the same as that of the case growth equation except that the growth rate of test rates is excluded from W_{it} as implied by Eq. (M-D).

Table 4 shows the results of estimating (13) for case and death growth rates.

Column (1) represents our baseline specification while column (2) replaces business closure policies with closed movie theaters, closed restaurants, and closed non-essential businesses. Columns (3) and (4) include past cases/deaths and growth rates at national level as additional regressors.

The estimates indicate that mandatory face masks for employees reduce the growth rate of infections and deaths by 9–15 percent, while holding behavior constant. This suggests that requiring masks for employees in public-facing businesses may be an effective preventive measure.[32] The estimated effect of masks on death growth is larger than the effect on case growth, but this difference between the two estimated effects is not statistically significant.

Closing schools has a large and statistically significant coefficient in the death growth regressions. As discussed above, however, there is little cross-state variation in the timing of school closures, making estimates of its effect less reliable.

Neither the effect of stay-at-home orders nor that of business closure policies is estimated significantly different from zero, suggesting that these lockdown policies may have little direct effect on case or death growth when behavior is held constant.

The row "$\sum_k w_k \text{Behavior}_k$" reports the sum of estimated coefficients weighted by the average of the behavioral variables from April 1st-10th. The estimates of −0.80 and −0.84 for "$\sum_k w_k \text{Behavior}_k$" in column (1) imply that a reduction in mobility measures relative to the baseline in January and February have induced a decrease in case and death growth rates by 80 and 84 percent, respectively, suggesting an importance of social distancing for reducing the spread of Covid-19. When including national cases and deaths in information, as shown in columns (3) and (4), the estimated aggregate impact of behavior is substantially smaller but remains large and statistically significant.

A useful practical implication of these results is that Google Mobility Reports and similar data might be useful as a leading indicator of potential case or death growth. This should be done with caution, however, because other changes in the environment might alter the relationship between behavior and infections. Preventative measures, including mandatory face masks, and changes in habit that are not captured in our data might alter the future relationship between Google Mobility Reports and case/death growth.

[32] Note that we are *not* evaluating the effect of *universal* mask-wearing for the public but that of mask-wearing for employees. The effect of *universal* mask-wearing for the public could be larger if people comply with such a policy measure. Tian et al. (2020) considered a model in which mask wearing reduces the reproduction number by a factor $(1 - e \cdot pm)^2$, where e is the efficacy of trapping viral particles inside the mask and pm is the percentage of mask-wearing population. Given an estimate of $R_0 = 2.4$, Howard et al. (2020) argue that 50% mask usage and a 50% mask efficacy level would reduce the reproduction number from 2.4 to 1.35, an order of magnitude impact.

Table 5
The total effect of policies on case and death growth (PI→Y).

	Dependent variable:			
	$\Delta \log \Delta C_{it}$			
	(1)	(2)	(3)	(4)
lag(masks for employees, 14)	−0.083**	−0.081**	−0.103***	−0.102***
	(0.038)	(0.040)	(0.033)	(0.035)
lag(closed K-12 schools, 14)	−0.226**	−0.236**	0.029	0.017
	(0.089)	(0.097)	(0.102)	(0.107)
lag(stay at home, 14)	−0.127**	−0.121**	−0.115**	−0.103**
	(0.057)	(0.054)	(0.054)	(0.052)
lag(business closure policies, 14)	−0.076		−0.001	
	(0.068)		(0.061)	
lag(closed movie theaters, 14)		0.027		0.062
		(0.051)		(0.046)
lag(closed restaurants, 14)		−0.041		−0.011
		(0.049)		(0.045)
lag(closed non-essent bus, 14)		−0.051		−0.038
		(0.050)		(0.043)
lag($\Delta \log \Delta C_{it}$, 14)	0.040	0.041*	0.036	0.035
	(0.024)	(0.025)	(0.028)	(0.028)
lag($\log \Delta C_{it}$, 14)	−0.137***	−0.137***	−0.091***	−0.090***
	(0.022)	(0.022)	(0.026)	(0.026)
lag($\Delta \log \Delta C_{it}$.national, 14)			−0.128***	−0.123***
			(0.039)	(0.041)
lag($\log \Delta C_{it}$.national, 14)			−0.243***	−0.245***
			(0.045)	(0.045)
$\Delta \log T_{it}$	0.156***	0.157***	0.158***	0.160***
	(0.044)	(0.044)	(0.042)	(0.041)
state variables	Yes	Yes	Yes	Yes
Month ×state variables	Yes	Yes	Yes	Yes
$\sum_j \text{Policy}_j$	−0.512***	−0.504***	−0.190	−0.175
	(0.150)	(0.154)	(0.156)	(0.159)
Observations	3,825	3,825	3,825	3,825
R^2	0.749	0.750	0.763	0.763
Adjusted R^2	0.747	0.747	0.760	0.761
	Dependent variable:			
	$\Delta \log \Delta D_{it}$			
	(1)	(2)	(3)	(4)
lag(masks for employees, 21)	−0.134***	−0.133**	−0.156***	−0.155***
	(0.051)	(0.053)	(0.050)	(0.052)
lag(closed K-12 schools, 21)	−0.610***	−0.621***	−0.234**	−0.248**
	(0.115)	(0.121)	(0.111)	(0.109)
lag(stay at home, 21)	−0.082	−0.075	−0.068	−0.057
	(0.066)	(0.064)	(0.066)	(0.062)
lag(business closure policies, 21)	−0.059		0.059	
	(0.086)		(0.086)	
lag(closed movie theaters, 21)		−0.006		0.050
		(0.089)		(0.082)
lag(closed restaurants, 21)		−0.012		0.030
		(0.061)		(0.055)
lag(closed non-essent bus, 21)		−0.040		−0.016
		(0.066)		(0.063)
lag($\Delta \log \Delta D_{it}$, 21)	−0.001	−0.001	0.017	0.016
	(0.033)	(0.033)	(0.036)	(0.037)
lag($\log \Delta D_{it}$, 21)	−0.078***	−0.078***	−0.064**	−0.063**
	(0.026)	(0.027)	(0.027)	(0.027)
lag($\Delta \log \Delta D_{it}$.national, 21)			−0.147***	−0.148**
			(0.056)	(0.057)
lag($\log \Delta D_{it}$.national, 21)			−0.116***	−0.117***
			(0.032)	(0.032)
state variables	Yes	Yes	Yes	Yes
Month ×state variables	Yes	Yes	Yes	Yes

(*continued on next page*)

The negative coefficients of the log of past cases or deaths in Table 4 is consistent with a hypothesis that higher reported cases and deaths change people's behavior to reduce transmission risks. Such behavioral changes in response to

Table 5 (*continued*).

	Dependent variable:			
	$\Delta \log \Delta D_{it}$			
	(1)	(2)	(3)	(4)
$\sum_j \text{Policy}_j$	−0.885***	−0.887***	−0.399**	−0.396**
	(0.159)	(0.166)	(0.183)	(0.188)
Observations	3,468	3,468	3,468	3,468
R^2	0.502	0.502	0.512	0.512
Adjusted R^2	0.497	0.497	0.507	0.507

Note: *p<0.1; **p<0.05; ***p<0.01.
Dependent variable is the weekly growth rate of confirmed cases (in the upper panel) or deaths (in the lower panel) as defined in Eq. (4). The covariates include lagged policy variables, which are constructed as 7 day moving averages between t to $t-7$ of corresponding daily measures. The row "$\sum_j \text{Policies}_j$" reports the sum of all policy coefficients. "business closure policies" is defined by the average of closed movie theaters, closed restaurants, and closed non-essential businesses. Standard errors are clustered at the state level.

Table 6
Direct and indirect policy effects without national case/death variables.

Cases						
	Direct	Indirect	Total	PI→Y Coef.	Average	Difference
masks for employees	−0.090***	0.043	−0.047	−0.083**	−0.065	0.036**
	(0.031)	(0.028)	(0.043)	(0.038)	(0.040)	(0.015)
closed K-12 schools	−0.074	−0.374***	−0.448***	−0.226***	−0.337***	−0.223***
	(0.080)	(0.095)	(0.116)	(0.086)	(0.098)	(0.055)
stay at home	−0.063	−0.034	−0.096*	−0.127**	−0.112**	0.031**
	(0.049)	(0.029)	(0.055)	(0.058)	(0.056)	(0.015)
business closure policies	0.051	−0.153***	−0.101	−0.076	−0.089	−0.025
	(0.062)	(0.045)	(0.068)	(0.067)	(0.067)	(0.021)
$\sum_j \text{Policy}_j$	−0.176	−0.517***	−0.693***	−0.512***	−0.603***	−0.181***
	(0.129)	(0.145)	(0.182)	(0.147)	(0.162)	(0.061)
$\Delta \log \Delta C_{it}$	0.015	0.012	0.027	0.040	0.033	−0.013**
	(0.026)	(0.009)	(0.025)	(0.025)	(0.025)	(0.007)
$\log \Delta C_{it}$	−0.105***	−0.045***	−0.150***	−0.137***	−0.144***	−0.013*
	(0.018)	(0.015)	(0.025)	(0.021)	(0.023)	(0.008)
Deaths						
	Direct	Indirect	Total	PI→Y Coef.	Average	Difference
masks for employees	−0.146***	0.035***	−0.111**	−0.134***	−0.122**	0.022
	(0.049)	(0.000)	(0.049)	(0.051)	(0.049)	(0.021)
closed K-12 schools	−0.232**	−0.420***	−0.653***	−0.610***	−0.632***	−0.042*
	(0.095)	(0.084)	(0.111)	(0.109)	(0.109)	(0.023)
stay at home	−0.066	−0.008	−0.073	−0.082	−0.078	0.008
	(0.068)	(0.031)	(0.067)	(0.067)	(0.067)	(0.016)
business closure policies	0.098***	−0.163**	−0.065	−0.059	−0.062	−0.006
	(0.000)	(0.065)	(0.065)	(0.086)	(0.061)	(0.089)
$\sum_j \text{Policy}_j$	−0.346***	−0.557***	−0.902***	−0.885***	−0.894***	−0.018
	(0.122)	(0.137)	(0.156)	(0.157)	(0.147)	(0.106)
$\Delta \log \Delta D_{it}$	0.016	−0.040***	−0.024	−0.001	−0.012	−0.023***
	(0.034)	(0.011)	(0.030)	(0.032)	(0.031)	(0.005)
$\log \Delta D_{it}$	−0.055**	−0.015	−0.070**	−0.078***	−0.074***	0.009
	(0.024)	(0.009)	(0.028)	(0.026)	(0.027)	(0.005)

Direct effects capture the effect of policy on case growth holding behavior, information, and confounders constant. Direct effects are given by π in Eq. (BPI→Y). Indirect effects capture how policy changes behavior and behavior shift case growth. They are given by α from (BPI→Y) times β from (PI→B). The total effect is $\pi + \beta\alpha$. Column "PI→Y Coefficients" shows the coefficient estimates from (PI→Y). Columns "Difference" are the differences between the estimates from (PI→Y) and the combination of (BPI→Y) and (PI→B) while column "Average" are their averages. Standard errors are computed by bootstrap and clustered on state.

new information are partly captured by Google mobility measures, but the negative estimated coefficient of past cases or deaths imply that other latent behavioral changes that are not fully captured by Google mobility measures (e.g., frequent hand-washing, wearing masks, and keeping 6ft/2m distancing) are also important for reducing future cases and deaths.

If policies are enacted and behavior changes, then future cases/deaths and information will change, which will induce further behavior changes. However, since the model includes lags of cases/deaths as well as their growth rates, computing a long-run effect is not completely straightforward. We investigate dynamic effects that incorporate feedback through information in Section 5.

Table 7
Direct and Indirect Policy Effects without national case/death variables, **restrictions imposed**.

Cases						
	Direct	Indirect	Total	PI→Y Coef.	Average	Difference
masks for employees	−0.096***	0.000	−0.096***	−0.083**	−0.089***	−0.013
	(0.030)	(0.000)	(0.030)	(0.039)	(0.032)	(0.025)
closed K-12 schools	−0.073	−0.364***	−0.436***	−0.226**	−0.331***	−0.210***
	(0.078)	(0.094)	(0.119)	(0.092)	(0.102)	(0.056)
stay at home	−0.053	−0.032	−0.085	−0.127**	−0.106*	0.042**
	(0.052)	(0.028)	(0.058)	(0.057)	(0.057)	(0.020)
business closure policies	0.000	−0.157***	−0.157***	−0.076	−0.117**	−0.081
	(0.000)	(0.042)	(0.042)	(0.066)	(0.048)	(0.054)
$\sum_j \text{Policy}_j$	−0.221**	−0.553***	−0.774***	−0.512***	−0.643***	−0.262***
	(0.108)	(0.124)	(0.166)	(0.151)	(0.156)	(0.061)
$\Delta \log \Delta C_{it}$	0.013	0.009	0.021	0.040*	0.031	−0.019***
	(0.026)	(0.009)	(0.024)	(0.024)	(0.024)	(0.007)
$\log \Delta C_{it}$	−0.104***	−0.042***	−0.147***	−0.137***	−0.142***	−0.010
	(0.017)	(0.015)	(0.024)	(0.021)	(0.023)	(0.007)
Deaths						
	Direct	Indirect	Total	PI→Y Coef.	Average	Difference
masks for employees	−0.152***	0.000	−0.152***	−0.134***	−0.143***	−0.019
	(0.048)	(0.000)	(0.048)	(0.051)	(0.049)	(0.020)
closed K-12 schools	−0.228**	−0.391***	−0.619***	−0.610***	−0.615***	−0.009
	(0.101)	(0.079)	(0.117)	(0.112)	(0.114)	(0.031)
stay at home	−0.047	−0.006	−0.054	−0.082	−0.068	0.028
	(0.063)	(0.031)	(0.063)	(0.067)	(0.064)	(0.023)
business closure policies	0.000	−0.154***	−0.154***	−0.059	−0.106*	−0.095
	(0.000)	(0.059)	(0.059)	(0.084)	(0.061)	(0.078)
$\sum_j \text{Policy}_j$	−0.427***	−0.551***	−0.978***	−0.885***	−0.931***	−0.093
	(0.123)	(0.124)	(0.149)	(0.158)	(0.150)	(0.060)
$\Delta \log \Delta D_{it}$	0.014	−0.040***	−0.025	−0.001	−0.013	−0.025***
	(0.035)	(0.010)	(0.032)	(0.033)	(0.032)	(0.005)
$\log \Delta D_{it}$	−0.052**	−0.012	−0.064**	−0.078***	−0.071***	0.014**
	(0.023)	(0.010)	(0.026)	(0.026)	(0.026)	(0.007)

Direct effects capture the effect of policy on case growth holding behavior, information, and confounders constant. Direct effects are given by π in Eq. (BPI→Y). Indirect effects capture how policy changes behavior and behavior shift case growth. They are given by α from (BPI→Y) times β from (PI→B). The total effect is $\pi + \beta\alpha$. Column "PI→Y Coefficients" shows the coefficient estimates from (PI→Y). Columns "Difference" are the differences between the estimates from (PI→Y) and the combination of (BPI→Y) and (PI→B) while column "Average" are their averages. Standard errors are computed by bootstrap and clustered on state.

3.4. The total effect of policies on case growth

In this section, we focus our analysis on policy effects when we hold information constant. The estimated effect of policy on behavior in Table 3 and those of policies and behavior on case/death growth in Table 4 can be combined to calculate the total effect of policy as well as its decomposition into direct and indirect effects.

The first three columns of Table 6 show the direct (holding behavior constant) and indirect (through behavior changes) effects of policy under a specification that excludes national information variables. These are computed from the specification with national cases or deaths included as information (columns (1)–(4) of Table 3 and column (1) of Table 4). The estimates imply that all policies combined would reduce the growth rate of cases and deaths by 0.69 and 0.90, respectively, out of which more than one-half to two-third is attributable to the indirect effect through their impact on behavior. The estimate also indicates that the effect of mandatory masks for employees is mostly direct.

We can also examine the total effect of policies and information on case or death growth, by estimating (PI→Y). The coefficients on policy in this regression combine both the direct and indirect effects.

Table 5 shows the full set of coefficient estimates for (PI→Y). The results are broadly consistent with what we found above. As in Table 3, the effect of school closures is sensitive to the inclusion of national information variables. Also as above, mask mandates have a significant negative effect on growth rates.

Similarly to Table 6, the first three columns of Table 7 report the estimated direct and indirect effects of policy but impose that masks for employees only affect cases/deaths directly without affecting behavior and that business closure policies only affect cases/deaths indirectly through their effects on behavior.[33] The estimated total effect of masks for employees in the third column of Table 7 is higher than that of Table 6. Similarly, the total effect of business closure policies is estimated to be larger in Table 7 than in Table 6.

[33] These are computed from estimating the specification in columns (1)–(4) of Table 3 and column (1) of Table 4 but imposing that the coefficient of masks for employees is zero in (BPI→Y) and that the coefficient of business closure policies is zero in (PI→B).

Table 8
Direct and indirect policy effects with national case/death variables.

Cases						
	Direct	Indirect	Total	PI→Y Coef.	Average	Difference
masks for employees	−0.100***	−0.002	−0.102***	−0.103***	−0.103***	0.001
	(0.028)	(0.018)	(0.035)	(0.032)	(0.033)	(0.011)
closed K-12 schools	0.043	−0.024	0.019	0.029	0.024	−0.011
	(0.092)	(0.036)	(0.101)	(0.099)	(0.100)	(0.015)
stay at home	−0.079	−0.036*	−0.115**	−0.115**	−0.115**	0.000
	(0.051)	(0.019)	(0.052)	(0.054)	(0.053)	(0.011)
business closure policies	0.045	−0.045*	0.000	−0.001	−0.000	0.001
	(0.057)	(0.026)	(0.059)	(0.057)	(0.058)	(0.012)
$\sum_j \text{Policy}_j$	−0.091	−0.107*	−0.198	−0.190	−0.194	−0.008
	(0.151)	(0.061)	(0.159)	(0.154)	(0.156)	(0.022)
$\Delta \log \Delta C_{it}$	0.024	0.014*	0.038	0.036	0.037	0.002
	(0.028)	(0.007)	(0.027)	(0.028)	(0.027)	(0.004)
$\log \Delta C_{it}$	−0.088***	−0.003	−0.091***	−0.091***	−0.091***	−0.000
	(0.020)	(0.010)	(0.026)	(0.025)	(0.025)	(0.005)
$\Delta \log \Delta C_{it}$.national	−0.095**	−0.054***	−0.149***	−0.128***	−0.138***	−0.022
	(0.040)	(0.016)	(0.040)	(0.037)	(0.038)	(0.013)
$\log \Delta C_{it}$.national	−0.177***	−0.084***	−0.261***	−0.243***	−0.252***	−0.018*
	(0.048)	(0.023)	(0.044)	(0.044)	(0.043)	(0.010)
Deaths						
	Direct	Indirect	Total	PI→Y Coef.	Average	Difference
masks for employees	−0.147***	0.009***	−0.138***	−0.156***	−0.147***	0.018
	(0.050)	(0.000)	(0.050)	(0.052)	(0.050)	(0.017)
closed K-12 schools	−0.178*	−0.055	−0.234**	−0.234**	−0.234**	0.000
	(0.100)	(0.038)	(0.112)	(0.108)	(0.110)	(0.019)
stay at home	−0.065	0.001	−0.063	−0.068	−0.066	0.005
	(0.067)	(0.029)	(0.066)	(0.067)	(0.066)	(0.015)
business closure policies	0.107***	−0.048	0.059	0.059	0.059	−0.001
	(0.000)	(0.036)	(0.036)	(0.082)	(0.044)	(0.091)
$\sum_j \text{Policy}_j$	−0.283**	−0.094	−0.377**	−0.399**	−0.388**	0.023
	(0.130)	(0.069)	(0.151)	(0.186)	(0.163)	(0.092)
$\Delta \log \Delta D_{it}$	0.016	−0.010**	0.006	0.017	0.012	−0.010***
	(0.037)	(0.005)	(0.036)	(0.036)	(0.036)	(0.004)
$\log \Delta D_{it}$	−0.053**	−0.006	−0.059**	−0.064**	−0.062**	0.005
	(0.023)	(0.009)	(0.026)	(0.026)	(0.026)	(0.005)
$\Delta \log \Delta D_{it}$.national	−0.034	−0.120***	−0.154***	−0.147***	−0.151***	−0.007
	(0.043)	(0.022)	(0.048)	(0.054)	(0.051)	(0.013)
$\log \Delta D_{it}$.national	−0.047	−0.077**	−0.124***	−0.116***	−0.120***	−0.008
	(0.038)	(0.030)	(0.035)	(0.032)	(0.033)	(0.013)

Direct effects capture the effect of policy on case growth holding behavior, information, and confounders constant. Direct effects are given by π in Eq. (BPI→Y). Indirect effects capture how policy changes behavior and behavior shift case growth. They are given by α from (BPI→Y) times β from (PI→B). The total effect is $\pi + \beta\alpha$. Column "PI→Y Coefficients" shows the coefficient estimates from (PI→Y). Columns "Difference" are the differences between the estimates from (PI→Y) and the combination of (BPI→Y) and (PI→B) while column "Average" are their averages. Standard errors are computed by bootstrap and clustered on state.

Column "Difference" in Tables 6 and 7 show the difference between the estimate of (PI→Y) in column "PI→Y Coefficient" and the implied estimate from (BPI→Y)-(PI→B) in column "Total". Differences are generally small except for the coefficient of closed K-12 schools and the sum of all policies in Table 6. The large differences in school closures may be due to the difficulty in identifying the effect of school closures given a lack of cross-sectional variation. Imposing the coefficients of masks for employees and business closure policies to be zero in (BPI→Y) and (PI→B), respectively, does not increase differences between "Total" and "PI→Y Coefficient" as reported in the last column of Table 7.

Tables 8 and 9 present the results for a specification that includes national information variables, where the estimates on masks for employees are similar to those in Tables 6 and 7. Column "Difference" of Table 9 indicates that the restrictions of zero coefficients for masks for employees in (BPI→Y) and for business closure policies in (PI→B) are not statistically rejected.

Column "Average" of Tables 6 and 8 reports the average of "Total" and "PI→Y Coefficient" columns. The average is an appealing and simple way to combine the two estimates of the total effect: one relying on the causal structure and another inferred from a direct estimation of equation (PI → Y). We shall be using the average estimate in generating the counterfactuals in the next section. Turning to the results, the estimates of Tables 6 and 8 imply that all policies combined would reduce $\Delta \log \Delta D$ by 0.93 and 0.39, respectively. For comparison, the median of $\Delta \log \Delta D_{it}$ reached its peak in mid-March of about 1.3 (see Fig. A.18 in the appendix). Since then it has declined to near 0. Therefore, −0.93 and −0.39 imply that policy changes can account for roughly one-third to two-third of the observed decrease in death growth. The remainder of the decline is likely due to changes in behavior from information.

Table 9
Direct and Indirect Policy Effects with national case/death variables, **restrictions imposed**.

Cases						
	Direct	Indirect	Total	PI→Y Coef.	Average	Difference
masks for employees	−0.105***	0.000	−0.105***	−0.103***	−0.104***	−0.001
	(0.027)	(0.000)	(0.027)	(0.031)	(0.028)	(0.016)
closed K-12 schools	0.045	−0.022	0.023	0.029	0.026	−0.007
	(0.092)	(0.034)	(0.101)	(0.099)	(0.100)	(0.015)
stay at home	−0.071	−0.033*	−0.104*	−0.115**	−0.110**	0.011
	(0.052)	(0.019)	(0.056)	(0.052)	(0.053)	(0.017)
business closure policies	0.000	−0.038	−0.038	−0.001	−0.019	−0.038
	(0.000)	(0.024)	(0.024)	(0.061)	(0.038)	(0.054)
$\sum_j \text{Policy}_j$	−0.131	−0.094*	−0.225*	−0.190	−0.207	−0.035
	(0.123)	(0.049)	(0.134)	(0.155)	(0.143)	(0.047)
$\Delta \log \Delta C_{it}$	0.023	0.013**	0.036	0.036	0.036	0.000
	(0.028)	(0.007)	(0.027)	(0.027)	(0.027)	(0.004)
$\log \Delta C_{it}$	−0.087***	−0.003	−0.090***	−0.091***	−0.091***	0.000
	(0.021)	(0.011)	(0.027)	(0.025)	(0.026)	(0.005)
$\Delta \log \Delta C_{it}$.national	−0.098**	−0.050***	−0.147***	−0.128***	−0.137***	−0.020
	(0.040)	(0.016)	(0.040)	(0.037)	(0.038)	(0.014)
$\log \Delta C_{it}$.national	−0.178***	−0.078***	−0.256***	−0.243***	−0.249***	−0.013
	(0.048)	(0.024)	(0.042)	(0.044)	(0.043)	(0.011)
Deaths						
	Direct	Indirect	Total	PI→Y Coef.	Average	Difference
masks for employees	−0.154***	0.000	−0.154***	−0.156***	−0.155***	0.002
	(0.046)	(0.000)	(0.046)	(0.048)	(0.047)	(0.018)
closed K-12 schools	−0.177*	−0.051	−0.227**	−0.234**	−0.231**	0.006
	(0.102)	(0.036)	(0.113)	(0.109)	(0.111)	(0.025)
stay at home	−0.046	0.004	−0.043	−0.068	−0.055	0.026
	(0.063)	(0.027)	(0.062)	(0.065)	(0.063)	(0.020)
business closure policies	0.000	−0.040	−0.040	0.059	0.009	−0.099
	(0.000)	(0.032)	(0.032)	(0.084)	(0.048)	(0.084)
$\sum_j \text{Policy}_j$	−0.377***	−0.087	−0.464***	−0.399**	−0.432***	−0.065
	(0.124)	(0.063)	(0.144)	(0.178)	(0.157)	(0.074)
$\Delta \log \Delta D_{it}$	0.015	−0.010**	0.006	0.017	0.011	−0.011***
	(0.037)	(0.005)	(0.036)	(0.036)	(0.036)	(0.004)
$\log \Delta D_{it}$	−0.050**	−0.006	−0.056**	−0.064**	−0.060**	0.008
	(0.023)	(0.008)	(0.026)	(0.026)	(0.026)	(0.006)
$\Delta \log \Delta D_{it}$.national	−0.039	−0.112***	−0.151***	−0.147***	−0.149***	−0.004
	(0.044)	(0.020)	(0.048)	(0.054)	(0.051)	(0.013)
$\log \Delta D_{it}$.national	−0.043	−0.070**	−0.113***	−0.116***	−0.114***	0.002
	(0.036)	(0.029)	(0.030)	(0.031)	(0.030)	(0.013)

Direct effects capture the effect of policy on case growth holding behavior, information, and confounders constant. Direct effects are given by π in Eq. (BPI→Y). Indirect effects capture how policy changes behavior and behavior shift case growth. They are given by α from (BPI→Y) times β from (PI→B). The total effect is $\pi + \beta\alpha$. Column "PI→Y Coefficients" shows the coefficient estimates from (PI→Y). Columns "Difference" are the differences between the estimates from (PI→Y) and the combination of (BPI→Y) and (PI→B) while column "Average" are their averages. Standard errors are computed by bootstrap and clustered on state.

4. Sensitivity analysis

4.1. Specifications, timings, and flexible controls via machine learning

In this section, we provide sensitivity analysis by estimating (PI→Y) with alternative specifications and methods. Fig. 11 shows the 90% confidence intervals of coefficients of (A) masks for employees, (B) closed K-12 school, (C) stay-at-home, and (D) the average variable of closed movie theaters, closed restaurants, and closed non-essential businesses for the following specifications and estimation methods:

(1) Baseline specification in columns (1) and (3) of Table 5.
(2) Exclude the state of New York from the sample because it may be viewed as an outlier in the early pandemic period.
(3) Add the percentage of people who wear masks to protect themselves in March and April as a confounder for unobserved personal risk-aversion and initial attitude toward mask wearing.[34]

[34] The survey is conducted online by YouGov and is based on the interviews of 89,347 US adults aged 18 and over between March 26–April 29, 2020. The survey question is "Which, if any, of the following measures have you taken in the past 2 weeks to protect yourself from the Coronavirus (COVID-19)?".

(4) Add the log of Trump's vote share in the 2016 presidential election as a confounder for unobserved private behavioral response.
(5) Add past behavior variables as information used to set policies. Under this specification, our causal interpretation is valid when policy variables are sufficiently random conditional on past behavior variables.
(6) Include all additional controls in (3)–(5) with the sample that excludes New York as in (2).
(7) Add weekly dummies to the baseline specification.
(8) Baseline specification estimated by instrumenting $\Delta \log T_{it}$ with one week lagged logarithm value of the number of tests per 1000 people.
(9) Estimated by Double Machine Learning (DML) (e.g., Chernozhukov et al., 2018) with Lasso to reduce dimensionality while including all additional controls in (3)–(5).
(10) Estimated by DML with Random Forest to reduce dimensionality and capture some nonlinearities while including all additional controls in (3)–(5).

In Fig. 11, "red", "green", "blue", and "purple" indicate the regression models for case growth without national information variables, case growth with national information variables, death growth without national information variables, and death growth with national information variables, respectively. The left panel of "(i) baseline timing" assume that the times from exposure to case confirmation and death reporting are 14 and 21 days, respectively, while they are 7 and 24 days, respectively, in the right panel of "(ii) alternative timing".[35]

Panel (A) of Fig. 11 illustrates that the estimated coefficients of mask mandates are negative and significant in most specifications, methods, and timing assumptions, confirming the importance of mask policy on reducing case and death growths.

In Panel (B) of Fig. 11, many estimates of closures of K-12 schools suggest that the effect of school closures is large. The visual evidence on growth rates for states with and without school closures in Fig. 12 also suggests that there may be a potentially large effect, though the history is very short. This evidence is consistent with the emerging evidence of prevalence of Covid-19 among children (Lee et al., 2020b; Szablewski et al., 2020). Davies et al. (2020) find that although children's transmission and susceptibility rates are half that of ages 20–30, children's contact rates are much higher. This type of evidence, as well as, evidence that children carry viral loads similar to older people (Jones et al., 2020), led Germany to make the early decision of closing schools.

Our estimates of school closures substantially vary across specifications, however. In particular, the estimated effects of school closures on case/death growth become notably smaller once national cases/deaths or weekly dummies are controlled for. In the US state-level data, there is little variation across states in the timing of school closures. Consequently, its estimate is particularly sensitive to an inclusion of some aggregate variables such as national cases or weekly dummies. Given this sensitivity, there still exists a lot of uncertainty as to the magnitude of the effect of school closures. Any analyses of re-opening plans need to be aware of this uncertainty. An important research question is how to resolve this uncertainty using additional data sources.

Panel (C) of Fig. 11 indicates that the estimated coefficients of stay-at-home orders are generally negative and often significant, providing evidence that stay-at-home orders reduce the spread of COVID-19, although the estimates are sometimes sensitive to timing assumptions. Panel (D) shows that the estimated coefficients of business closure policies substantially vary across specifications, providing a mixed evidence for the effect of closures of businesses on case/death growth.

4.2. Fixed effects specification

Table 10 presents the results of estimating (PI→Y) with state fixed effects and weekly dummies. Because fixed effects estimator could be substantially biased when the time dimension is relatively short, we report not only the standard fixed effects estimator in columns (1) and (3) but also the debiased fixed effects estimator (e.g., Chen et al., 2019) in columns (2) and (4), where the state-level clustered bootstrap standard errors are reported in all columns.

The estimated coefficients of masks for employees largely confirm our finding that mandatory mask policies reduce the case and death growths. The estimated coefficients of stay-at-home orders and business closures are negative in columns (1) and (2) but their magnitudes as well as statistical significance are somewhat sensitive to whether bias corrections are applied or not.

The results in Table 10 should be interpreted with caution. The fixed effects approach may not be preferred to random effects approach here because the former relies on long time and cross-sectional histories but, in our data, the effective time-dimension is short and the number of states is not large. Furthermore, the fixed effects approach could suffer more from measurement errors, which could be a concern for our behavior and policy variables.

[35] This alternative timing assumption is motivated by the lower bound estimate of median times from exposure to case confirmation or death reporting in Table 2 of https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html, which are based on data received by CDC through June 29, 2020. We thank C. Jessica E. Metcalf for recommending us to do a sensitivity analysis on the timing assumption while suggesting this reference to us.

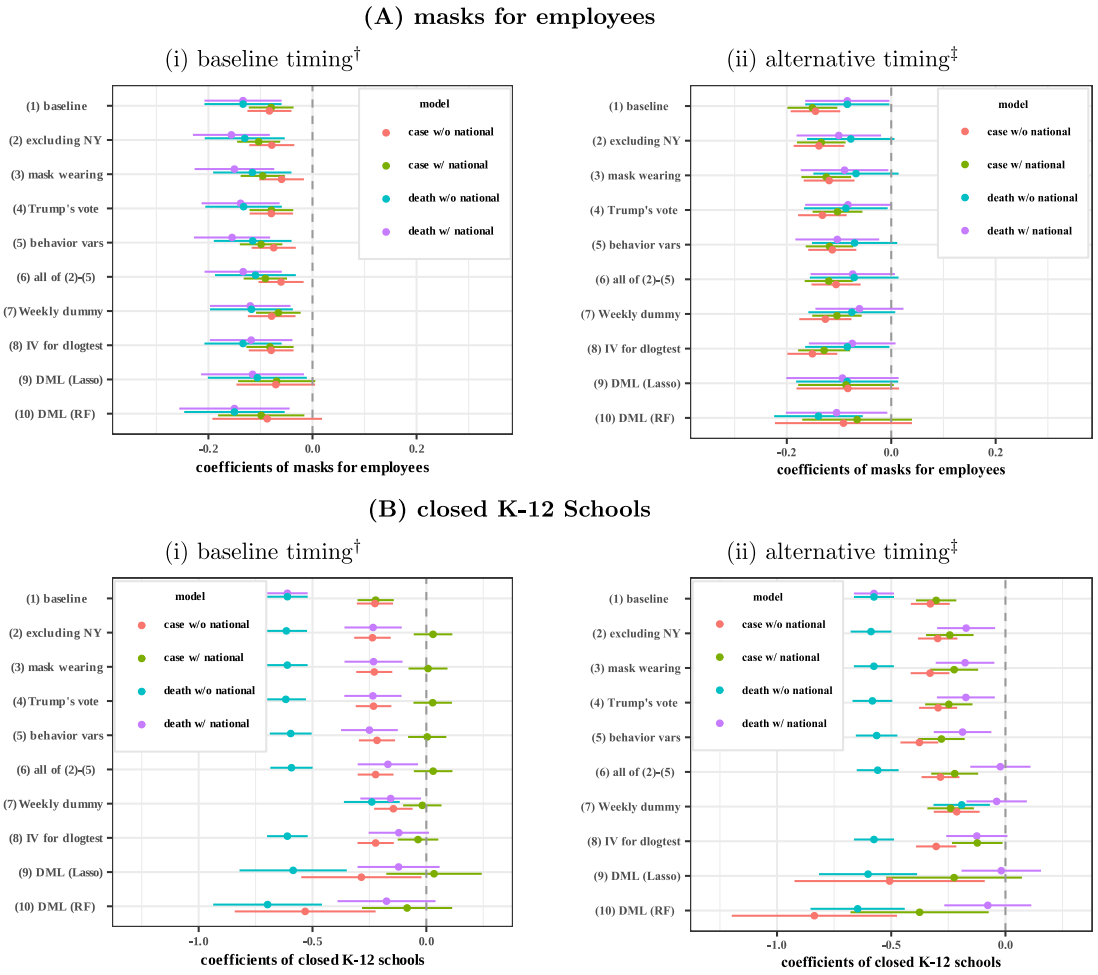

Fig. 11. Estimated Coefficients for Policy Variables: Sensitivity Analysis. †The times from exposure to case confirmation and death reporting are assumed to be 14 and 21 days, respectively. ‡The times from exposure to case confirmation and death reporting are assumed to be 7 and 24 days, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

5. Empirical evaluation of counterfactual policies

We now turn our focus to dynamic feedback effects. Policy and behavior changes that reduce case and death growth today can lead to a more optimistic, riskier behavior in the future, attenuating longer run effects. We perform the main counterfactual experiments using the average of two estimated coefficients as reported in column "Average" of Table 7 under a specification that excludes the number of past national cases and deaths from information variables and constrains masks to have only direct effects and business policies only indirect effects.[36] Details of the counterfactual computations are in Appendix B.4.

5.1. Business mask mandate

We first consider the impact of a nationwide mask mandate for employees beginning on March 14th. As discussed earlier, we find that mask mandates reduce case and death growth even when holding behavior constant. In other words, mask mandates may reduce infections with relatively little economic disruption. This makes mask mandates a particularly attractive policy instrument. In this section we examine what would have happened to the number of cases if all states had imposed a mask mandate on March 14th.[37]

[36] Results (not shown) using the unconstrained estimates in Table 6 are very similar.

[37] We feel this is a plausible counterfactual policy. Many states began implement business restrictions and school closures in mid March. In a paper made publicly available on April 1st, Abaluck et al. (2020) argued for mask usage based on comparisons between countries with and without pre-existing norms of widespread mask usage.

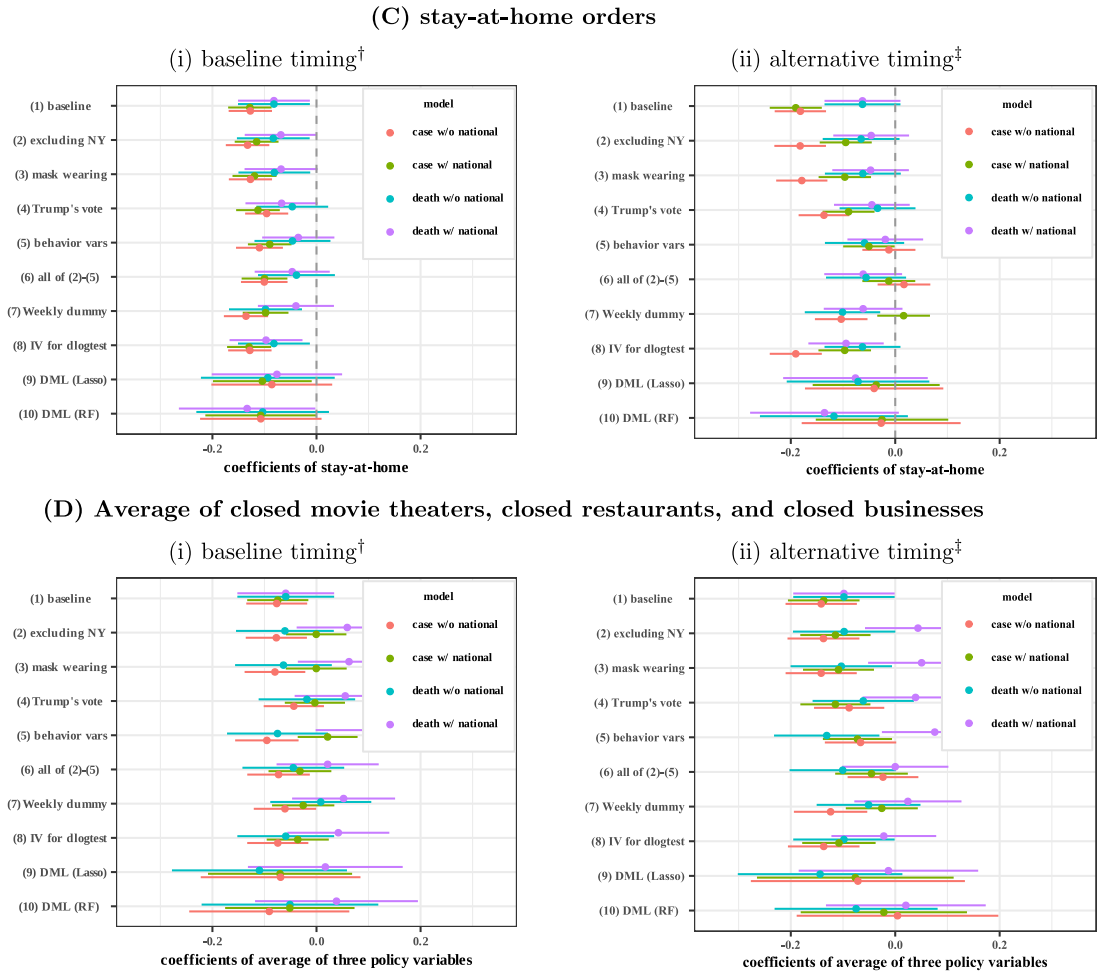

Fig. 11. (*continued*).

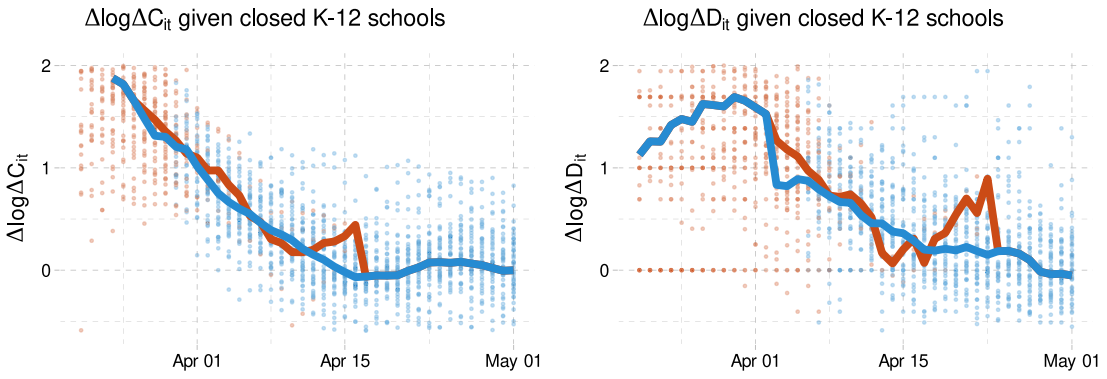

Fig. 12. Case and death growth conditional on school closures. In these figures, red points are the case or death growth rate in states without each policy 14 (or 21 for deaths) days earlier. Blue points are states with each policy 14 (or 21 for deaths) days earlier. The red line is the average across states without each policy. The blue line is the average across states with each policy. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

For illustrative purpose, we begin by focusing on Washington State. The left column of Fig. 13 shows the change in growth rate from mandating masks on March 14th. The shaded region is a 90% pointwise confidence interval. As shown, mandating masks on March 14th lowers the growth of cases or deaths 14 or 21 days later by 0.07 or 0.14. This effect then gradually declines due to information feedback. Mandatory masks reduce past cases or deaths, which leads to less

Table 10
Fixed effects specification: the total effect of policies on case and death growth (PI→Y).

	Dependent variable:			
	$\Delta \log \Delta C_{it}$			
	(1)	(2)	(3)	(4)
lag(masks for employees, 14)	−0.103**	−0.271***	−0.097**	−0.255***
	(0.044)	(0.075)	(0.044)	(0.071)
lag(closed K-12 schools, 14)	−0.023	0.085	−0.050	0.042
	(0.060)	(0.098)	(0.066)	(0.094)
lag(stay at home, 14)	−0.123**	−0.088	−0.099**	−0.055
	(0.051)	(0.068)	(0.049)	(0.075)
lag(business closure policies, 14)	−0.080	−0.162*		
	(0.076)	(0.086)		
lag(closed movie theaters, 14)			0.049	0.077
			(0.068)	(0.084)
lag(closed restaurants, 14)			−0.031	−0.068
			(0.053)	(0.065)
lag(closed non-essent bus, 14)			−0.099**	−0.166***
			(0.047)	(0.063)
lag($\Delta \log \Delta C_{it}$, 14)	0.063**	0.079***	0.061**	0.076***
	(0.029)	(0.026)	(0.029)	(0.028)
lag($\log \Delta C_{it}$, 14)	−0.216***	−0.185***	−0.214***	−0.181***
	(0.020)	(0.032)	(0.021)	(0.033)
$\Delta \log T_{it}$	0.116***	0.116***	0.118***	0.147***
	(0.042)	(0.042)	(0.042)	(0.047)
Observations	3,825	3,825	3,825	3,825
R^2	0.782	0.782	0.782	0.782
Adjusted R^2	0.778	0.778	0.778	0.778
	Dependent variable:			
	$\Delta \log \Delta D_{it}$			
	(1)	(2)	(3)	(4)
lag(masks for employees, 21)	−0.136***	−0.144*	−0.129***	−0.109
	(0.047)	(0.074)	(0.047)	(0.075)
lag(closed K-12 schools, 21)	−0.115	−0.007	−0.161	−0.026
	(0.108)	(0.091)	(0.123)	(0.103)
lag(stay at home, 21)	−0.047	−0.097	−0.010	−0.151
	(0.077)	(0.099)	(0.072)	(0.112)
lag(business closure policies, 21)	−0.081	−0.166		
	(0.099)	(0.137)		
lag(closed movie theaters, 21)			0.041	−0.035
			(0.099)	(0.128)
lag(closed restaurants, 21)			0.015	−0.029
			(0.086)	(0.097)
lag(closed non-essent bus, 21)			−0.143**	−0.024
			(0.067)	(0.084)
lag($\Delta \log \Delta D_{it}$, 21)	0.009	0.083*	0.006	0.084
	(0.031)	(0.045)	(0.032)	(0.055)
lag($\log \Delta D_{it}$, 21)	−0.113***	−0.113***	−0.108***	−0.232***
	(0.018)	(0.018)	(0.018)	(0.040)
Observations	3468	3468	3468	3468
R^2	0.536	0.536	0.537	0.537
Adjusted R^2	0.527	0.527	0.528	0.528

Note: *p<0.1; **p<0.05; ***p<0.01.
All specifications include weekly dummies and state fixed effects. Dependent variable is the weekly growth rate of confirmed cases (in the upper panel) or deaths (in the lower panel) as defined in Eq. (4). Columns (1) and (3) report the standard fixed effects estimator while Columns (2) and (4) report the fixed effects estimator with bias corrections. Standard errors are computed by multiplier bootstrap clustered at the state level.

cautious behavior, attenuating the impact of the policy. The reversal of the decrease in growth in late May is due to our comparison of a mask mandate on March 14th with Washington's actual mask mandate in early May. By late May, the counterfactual mask effect has decayed through information feedback, and we are comparing it to the undecayed impact of Washington's actual, later mask mandate.

The middle column of Fig. 13 shows how the changes in case and death growth translate into changes in daily cases and deaths. The estimates imply that mandating masks on March 14th would have led to about 70 fewer cases and 5 fewer deaths per day throughout April and May. Cumulatively, this implies 19% [9, 29]% fewer cases and 26% [14, 37]% fewer deaths in Washington by the start of June.

The results for other states are similar to those for Washington. Fig. 14 shows the national effect of mask mandate on March 14th. The top panel shows the effect on cases and the bottom panel shows the effect on deaths. The left column

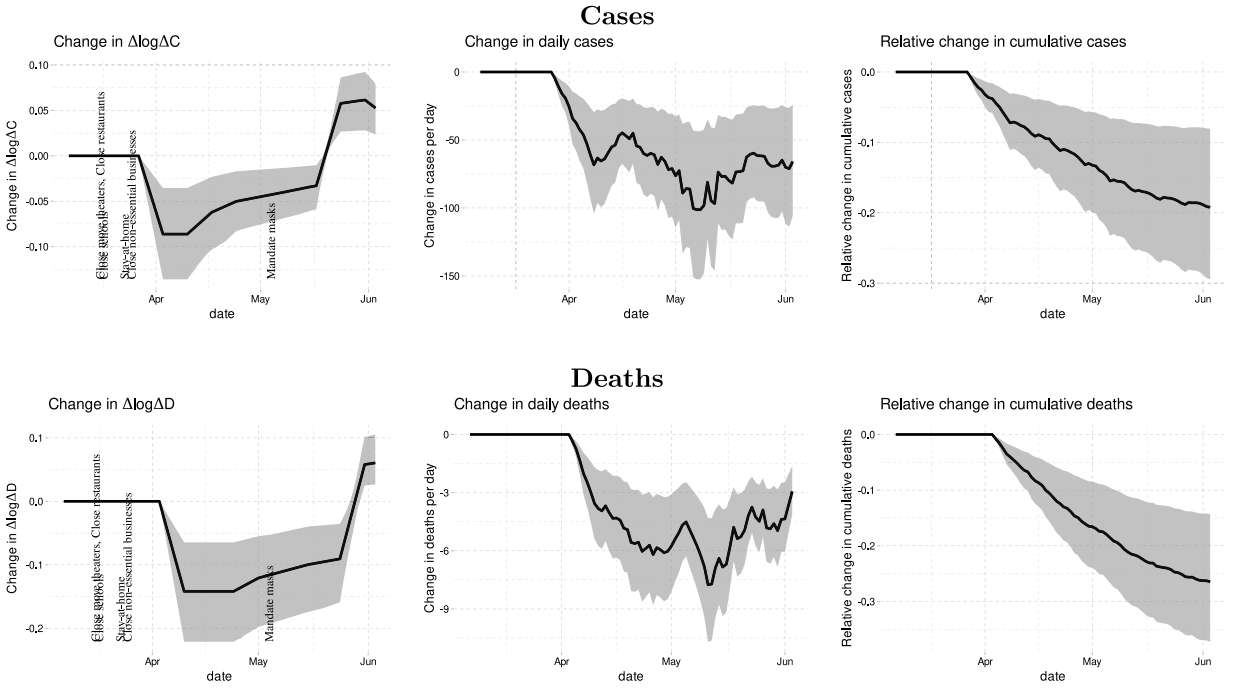

Fig. 13. Effect of mandating masks on March 14th in Washington State. The vertical text denotes the dates that Washington imposed each policy. To compute the estimated and counterfactual paths we use the average of two estimated coefficients as reported in column "Average" of Table 7. We set initial $\Delta \log \Delta C$ and $\log \Delta C$ to their values first observed in the state we are simulating. We hold all other regressors at their observed values. The shaded region is a point-wise 90% confidence interval. See Appendix B.4 for more details.

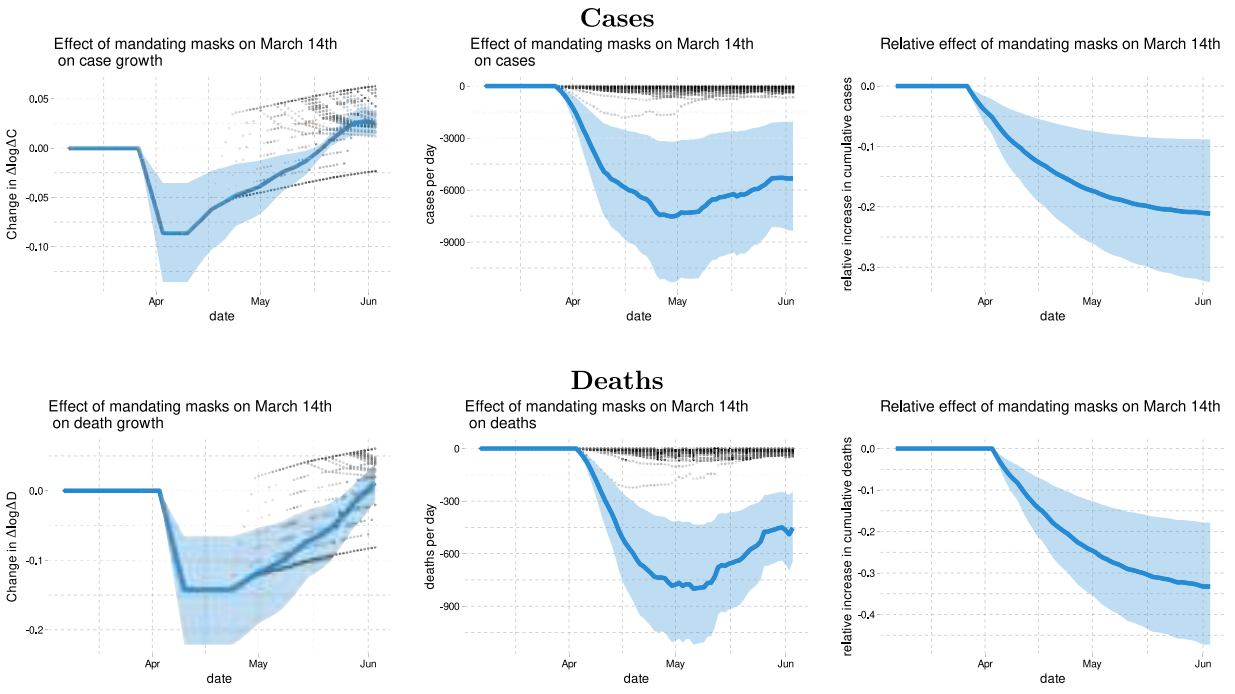

Fig. 14. Effect of nationally mandating masks for employees on March 14th in the US. In the left column, the dots are the average change in growth in each state. The blue line is the average across states of the change in growth. The shaded region is a point-wise 90% confidence interval for the national average change in growth. The middle column shows the total national change in daily cases and deaths. Black dots are the changes in each state. The right column shows the change in cumulative cases or deaths relative to the baseline of actual policies.

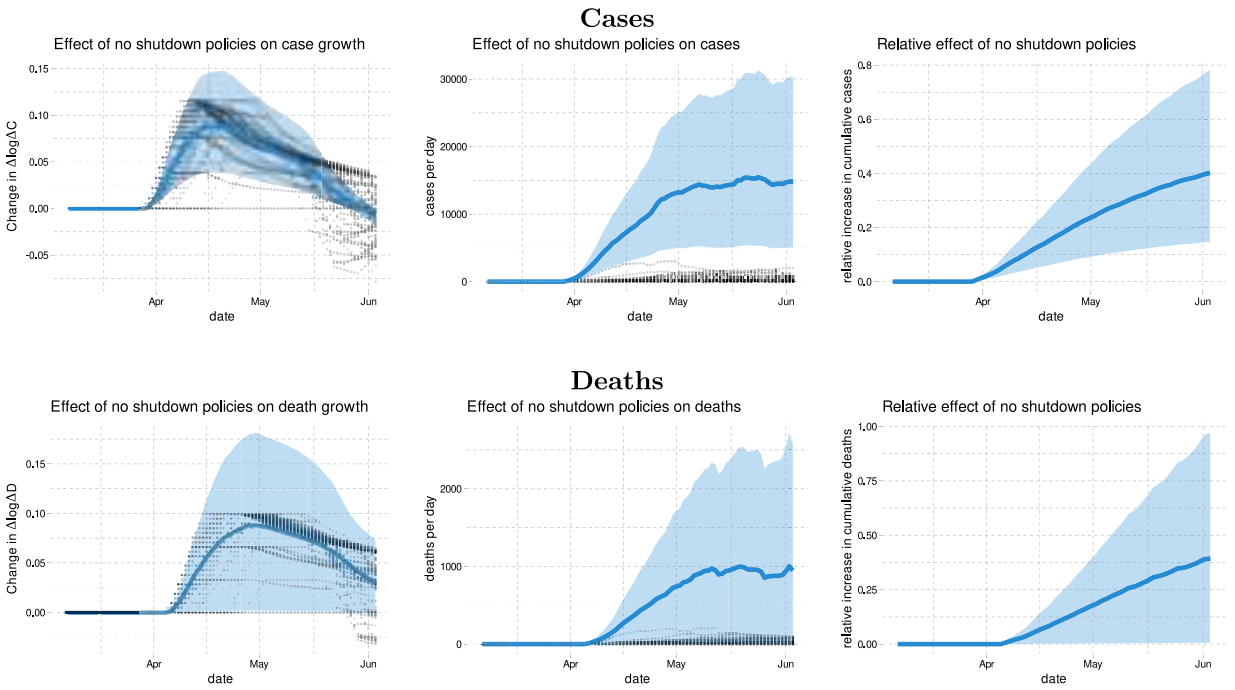

Fig. 15. Effect of having no business closure policies in the US. In the left column, the dots are the average change in growth in each state. The blue line is the average across states of the change in growth. The shaded region is a point-wise 90% confidence interval for the national average change in growth. The middle column shows the total national change in daily cases and deaths. Black dots are the changes in each state. The right column shows the change in cumulative cases or deaths relative to the baseline of actual policies.

shows the change in growth rates. Dots are the average change in growth rate in each state (i.e. the dots are identical to the solid line in the left panel of Fig. 13, except for each state instead of just Washington). The solid blue line is the national average change in growth rate. The shaded region is a 90% pointwise confidence band for the national average change in growth rate.

The middle column shows the changes in cases and deaths per day. Dots are the expected change in each state. The thick line is the national total change in daily cases or deaths. The shaded region is a pointwise 90% confidence band for the national total change. The estimates that a mask mandate in mid March would have decreased cases and deaths by about 6000 and 600 respectively throughout April and May.

The right column of Fig. 14 shows how these daily changes compare to the total cumulative cases and deaths. The right column shows the national relative change in cumulative cases or deaths. The point estimates indicate that mandating masks on March 14th could have led to 21% fewer cumulative cases and 34% fewer deaths by the end of May with their 90 percent intervals given by $[9, 32]$% and $[19, 47]$%, respectively. The result roughly translates into 19 to 47 thousand saved lives.

5.2. Business closure policies

Business closures are particularly controversial. We now examine a counterfactual where there are no business closure policies (no restaurant, movie theater, or non-essential business closure). Fig. 15 shows the national effect of never restricting businesses on cases and deaths. The point estimates imply that, without business closures, cases and deaths would be about 40% higher at the end of May. The confidence intervals are wide. A 90 percent confidence interval for the increase in cases at the end of May is $[17, 78]$%. The confidence interval for deaths is even wider, $[1, 97]$%.

5.3. Stay-at-home orders

We next examine a counterfactual where stay-at-home orders had been never issued. Fig. 16 shows the national effect of no stay-at-home orders. On average, without stay-at-home orders, case growth rate would have been nearly 0.075 higher in late April. This translates to 37% $[6, 63]$% more cases per week by the start of June. The estimated effect for deaths is a bit smaller, with no increase included in a 90 percent confidence interval, $[-7, 50]$%.

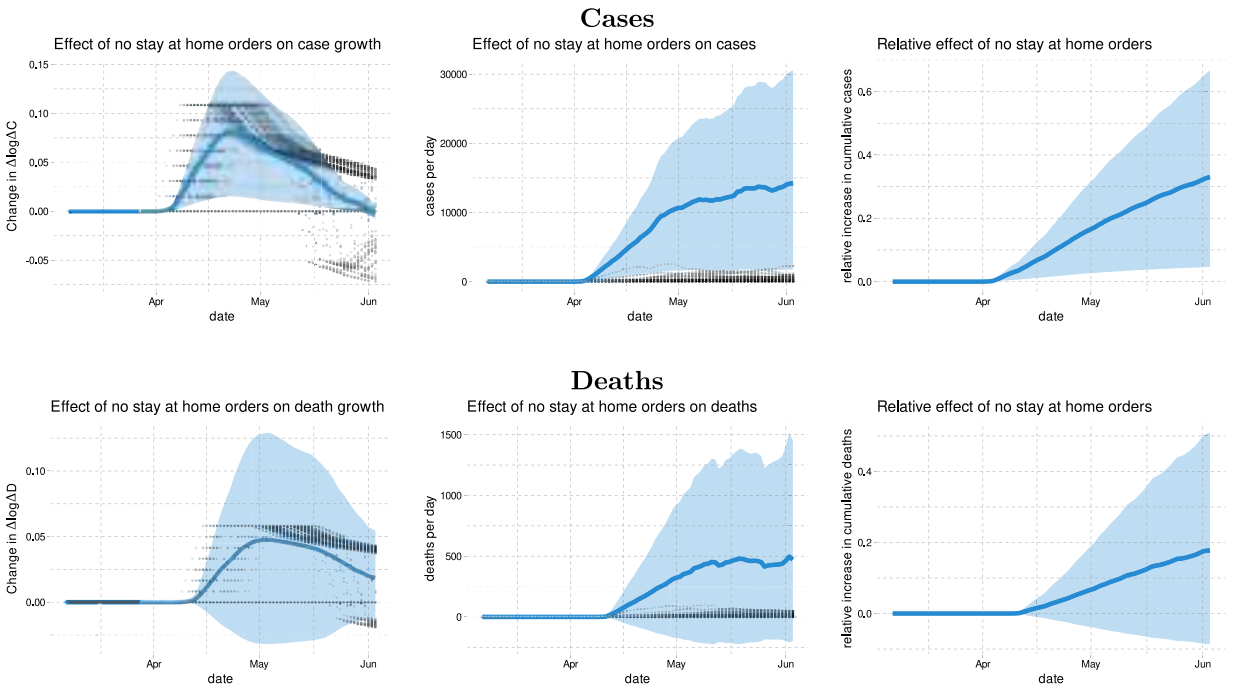

Fig. 16. Effect of having no stay-at-home orders in the US. In the left column, the dots are the average change in growth in each state. The blue line is the average across states of the change in growth. The shaded region is a point-wise 90% confidence interval for the national average change in growth. The middle column shows the total national change in daily cases and deaths. Black dots are the changes in each state. The right column shows the change in cumulative cases or deaths relative to the baseline of actual policies.

6. Conclusion

This paper assesses the effects of policies on the spread of Covid-19 in the US using state-level data on cases, tests, policies, and social distancing behavior measures from Google Mobility Reports. Our findings are summarized as follows.

First, our empirical analysis robustly indicates that mandating face masks has reduced the spread of Covid-19 without affecting people's social distancing behavior measured by Google Mobility Reports. Our counterfactual experiment suggests that if all states had adopted mandatory face mask policies on March 14th of 2020, then the cumulative number of deaths by the end of May would have been smaller by as much as 19 to 47%, which roughly translates into 19 to 47 thousand saved lives.

Second, our baseline counterfactual analysis suggests that keeping all businesses open would have led to 17 to 78% more cases while not implementing stay-at-home orders would have increased cases by 6 to 63% by the end of May although we should interpret these numbers with some caution given that the estimated effect of business closures and stay-at-home orders vary across specifications in our sensitivity analysis.

Third, we find considerable uncertainty over the impact of school closures on case or death growth because it is difficult to identify the effect of school closures from the US state-level data due to the lack of variation in the timing of school closures across states.

Fourth, our analysis shows that people voluntarily reduce their visits to workplace, retail stores, grocery stores, and people limit their use of public transit when they receive information on a higher number of new cases and deaths. This suggests that individuals make decisions to voluntarily limit their contact with others in response to greater transmission risks, leading to an important feedback mechanism that affects future cases and deaths. Model simulations that ignore this voluntary behavioral response to information on transmission risks would over-predict the future number of cases and deaths.

Beyond these findings, our paper presents a useful conceptual framework to investigate the relative roles of policies and information on determining the spread of Covid-19 through their impact on people's behavior. Our causal model allows us to explicitly define counterfactual scenarios to properly evaluate the effect of alternative policies on the spread of Covid-19. More broadly, our causal framework can be useful for quantitatively analyzing not only health outcomes but also various economic outcomes (Bartik et al., 2020; Chetty et al., 2020).

Table A.11
Correlation of cumulative cases.

	NYT	JHU	CTP
NYT	1.00000	0.99985	0.99970
JHU	0.99985	1.00000	0.99985
CTP	0.99970	0.99985	1.00000

Table A.12
Portion of cumulative cases that are equal between data sets.

	1	2	3
NYT	1.00	0.38	0.32
JHU	0.38	1.00	0.51
CTP	0.32	0.51	1.00

Table A.13
Correlation and variance of log daily new cases.

	NYT	JHU	CTP
NYT	1.00	0.93	0.86
JHU	0.93	1.00	0.82
CTP	0.86	0.82	1.00
Variance	5.05	5.81	6.11

Table A.14
Correlation and variance of log weekly new cases.

	NYT	JHU	CTP
NYT	1.00	1.00	0.98
JHU	1.00	1.00	0.98
CTP	0.98	0.98	1.00
Variance	3.68	3.76	3.47

Acknowledgments

We are grateful to Daron Acemoglu, V.V. Chari, Raj Chetty, Christian Hansen, Glenn Ellison, Ivan Fernandez-Val, David Green, Ido Rosen, Konstantin Sonin, James Stock, Elie Tamer, and Ivan Werning for helpful comments. We also thank Chiyoung Ahn, Joshua Catalano, Jason Chau, Samuel Gyetvay, Sev Chenyu Hou, Jordan Hutchings, and Dongxiao Zhang for excellent research assistance. We are especially grateful to C. Jessica E. Metcalf and an anonymous referee for detailed and insightful comments, which considerably improved the paper. All mistakes are our own.

Appendix A. Data construction

A.1. Measuring ΔC and $\Delta \log \Delta C$

We have three data sets with information on daily cumulative confirmed cases in each state. As shown in Table A.11, these cumulative case numbers are very highly correlated. However, Table A.12 shows that the numbers are different more often than not.

The upper left panel of Fig. A.17 shows the evolution of new cases in the NYT data, where daily changes in cumulative cases exhibit some excessive volatility. This is likely due to delays and bunching in testing and reporting of results. Table A.13 shows the variance of log new cases in each data set, as well as their correlations. As shown, the correlations are approximately 0.9. The NYT new case numbers have the lowest variance.[38] In our subsequent results, we will primarily use the case numbers from The New York Times.

For most of our results, we focus on new cases in a week instead of in a day. We do this for two reasons as discussed in the main text. First, a decline in new cases over two weeks has become a key metric for decision makers. Secondly, aggregating to weekly new cases smooths out the noise associated with the timing of reporting and testing.

Table A.14 reports the correlation and variance of weekly log new cases across the three data sets. The upper right panel of Fig. A.17 shows the evolution of weekly new cases in each state over time from the NYT data. The upper panel of Fig. A.18 shows the evolution of the weekly growth rate of new cases in each state over time.

[38] This comparison is somewhat sensitive to how you handle negative and zero cases when taking logs. Here, we replaced log(0) with −1. In our main results, we work with weekly new cases, which are very rarely zero.

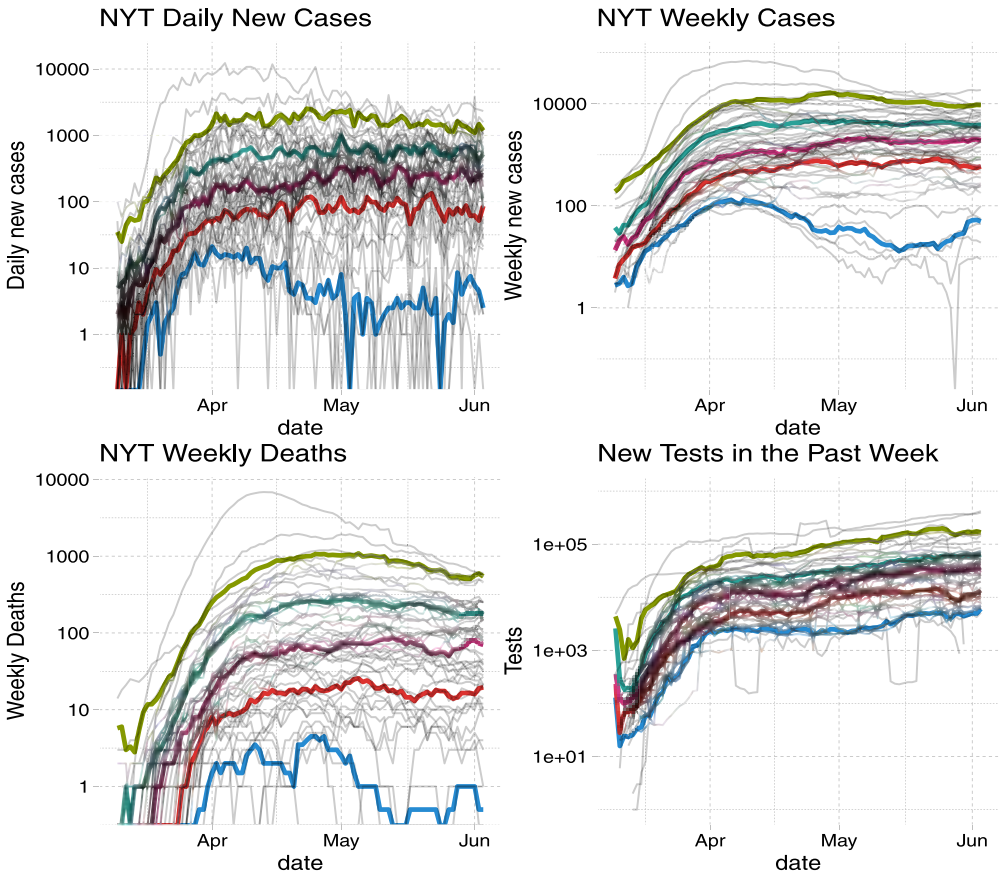

Fig. A.17. Daily Cases, Weekly Cases, Weekly Deaths from NYT Data, and Weekly Tests from JHU. Thin gray lines are the log of cases, death, and tests in each state and date. Thicker colored lines are their quantiles conditional on date. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table A.15
Correlation and variance of weekly deaths.

	NYT	JHU	CTP
NYT	1.00	0.98	0.97
JHU	0.98	1.00	0.98
CTP	0.97	0.98	1.00
Variance	172292.15	174310.07	126952.94

A.2. Deaths

Table A.15 reports the correlation and variance of weekly deaths in the three data sets. The lower left panel of Fig. A.17 shows the evolution of weekly deaths in each state from the NYT data. As with cases, we use death data from The New York Times in our main results. The lower panel of Fig. A.18 shows the evolution of the weekly growth rate of new deaths in each state over time.

A.3. Tests

Our test data comes from The Covid Tracking Project. The lower right panel of Fig. A.17 shows the evolution of the weekly number of tests over time.

A.4. Social distancing measures

In measuring social distancing, we focus on Google Mobility Reports. This data has international coverage and is publicly available. Fig. A.19 shows the evolution of the four Google Mobility Reports variables that we use in our analysis.

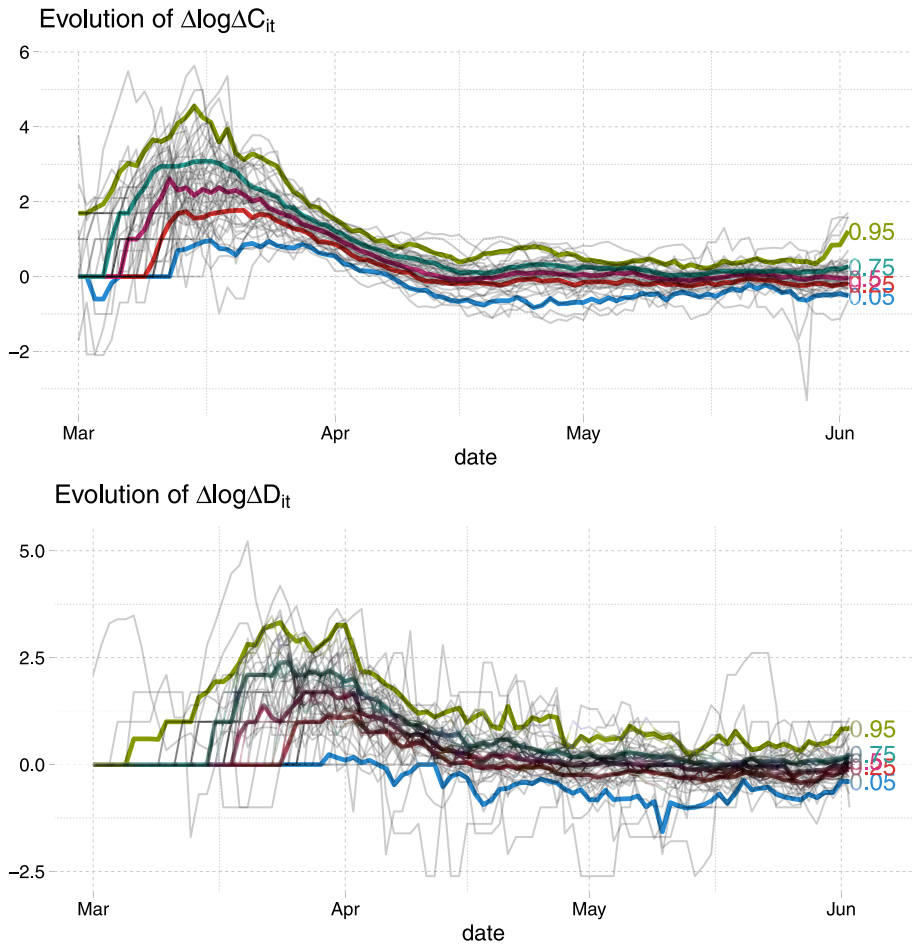

Fig. A.18. Case and death growth. Thin gray lines are case or death growth in each state and date. Thicker colored lines are quantiles of case or death growth conditional on date. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

A.5. Policy variables

We use the database on US state policies created by Raifman et al. (2020). As discussed in the main text, our analysis focuses on six policies. For stay-at-home orders, closed nonessential businesses, closed K-12 schools, closed restaurants except takeout, and closed movie theaters, we double-checked any state for which Raifman et al. (2020) does not record a date. We filled in a few missing dates. Our modified data is available here. Our modifications fill in 1 value for school closures, 2 for stay-at-home orders, 3 for movie theater closure, and 4 for non-essential business closures. Table A.16 displays all 25 dated policy variables in Raifman et al. (2020)'s database with our modifications described above.

Figs. A.20–A.21 show the average case and death growth conditional on date and whether each of six policies is implemented or not.

A.6. Timing

There is a delay between infection and when a person is tested and appears in our case data. MIDAS (2020) maintain a list of estimates of the duration of various stages of Covid-19 infections. The incubation period, the time from infection to symptom onset, is widely believed to be 5 days. For example, using data from Wuhan, Li et al. (2020) estimate a mean incubation period of 5.2 days. Siordia (2020) reviews the literature and concludes the mean incubation period is 3–9 days.

Estimates of the time between symptom onset and case reporting or death are less common. Using Italian data, Cereda et al. (2020) estimate an average of 7.3 days between symptom onset and reporting. Zhang et al. (2020a) find an average of 7.4 days using Chinese data from December to early February, but they find this period declined from 8.9 days in

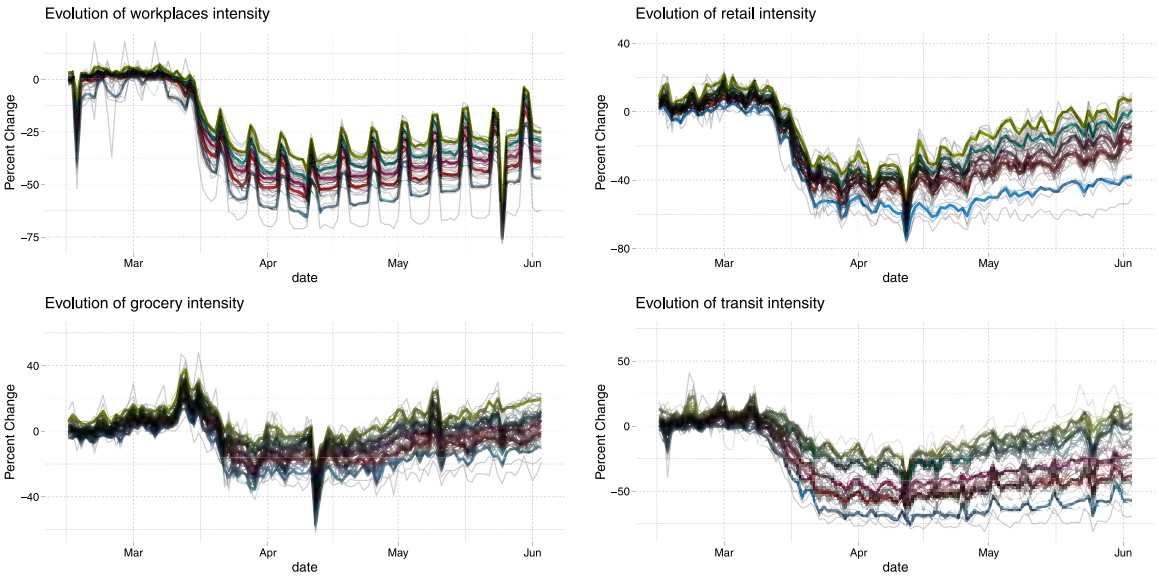

Fig. A.19. Evolution of Google Mobility Reports. This figure shows the evolution of Google Mobility Reports over time. Thin gray lines are the value of the variables in each state and date. Thicker colored lines are quantiles of the variables conditional on date. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table A.16
State Policies.

	N	Min	Median	Max
State of emergency	51	2020-02-29	2020-03-11	2020-03-16
Date closed K 12 schools	51	2020-03-13	2020-03-17	2020-04-03
Closed day cares	15	2020-03-16	2020-03-23	2020-04-06
Date banned visitors to nursing homes	30	2020-03-09	2020-03-16	2020-04-06
Closed non essential businesses	43	2020-03-19	2020-03-25	2020-04-06
Closed restaurants except take out	48	2020-03-15	2020-03-17	2020-04-03
Closed gyms	49	2020-03-16	2020-03-20	2020-04-03
Closed movie theaters	49	2020-03-16	2020-03-21	2020-04-06
Stay at home shelter in place	42	2020-03-19	2020-03-28	2020-04-07
End relax stay at home shelter in place	39	2020-04-24	2020-05-18	2020-06-19
Began to reopen businesses statewide	50	2020-04-20	2020-05-07	2020-06-05
Reopen restaurants	48	2020-04-24	2020-05-18	2020-06-22
Reopened gyms	44	2020-04-24	2020-05-18	2020-07-13
Reopened movie theaters	37	2020-04-27	2020-06-01	2020-07-13
Resumed elective medical procedures	35	2020-04-20	2020-04-30	2020-05-29
Mandate face mask use by all individuals in public spaces	35	2020-04-08	2020-06-26	2020-08-05
Mandate face mask use by employees in public facing businesses	44	2020-04-03	2020-05-01	2020-08-03
Stop Initiation of Evictions overall or due to COVID related issues	30	2020-03-16	2020-03-24	2020-05-30
Stop enforcement of evictions overall or due to COVID related issues	29	2020-03-15	2020-03-24	2020-06-08
Renter grace period or use of security deposit to pay rent	3	2020-04-10	2020-04-24	2020-05-20
Order freezing utility shut offs	34	2020-03-12	2020-03-19	2020-04-13
Froze mortgage payments	1	2020-03-21	2020-03-21	2020-03-21
Waived one week waiting period for unemployment insurance	36	2020-03-08	2020-03-18	2020-04-06

January to 5.4 days in the first week of February. Both of these papers on time from symptom onset to reporting have large confidence intervals covering approximately 1 to 20 days.

Studying publicly available data on infected persons diagnosed outside of Wuhan, Linton et al. (2020) estimate an average of 15 days from onset to death. Similarly, using publicly available reports of 140 confirmed Covid-19 cases in China, mostly outside Hubei Province, Sanche et al. (2020) estimate the time from onset to death to be 16.1 days.

Based on the above, we expect a delay of roughly two weeks between changes in behavior or policies, and changes in reported cases while a corresponding delay of roughly three weeks for deaths.

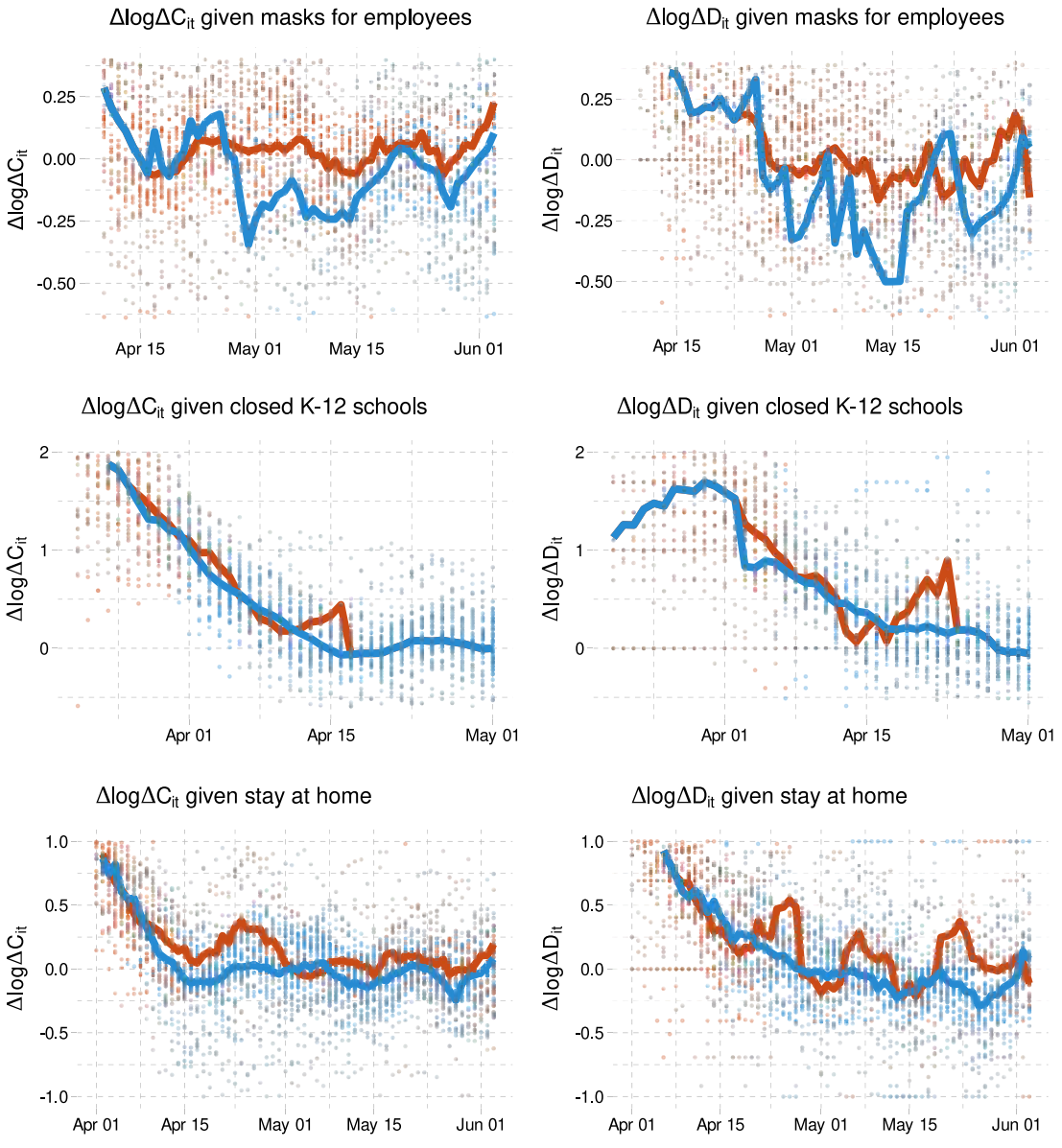

Fig. A.20. Case and death growth conditional on policies. In these figures, red points are the case or death growth rate in states without each policy 14 (or 21 for deaths) days earlier. Blue points are states with each policy 14 (or 21 for deaths) days earlier. The red line is the average across states without each policy. The blue line is the average across states with each policy. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Appendix B. Additional results

B.1. Direct and indirect policy effects with national case/death variables

Tables 8 and 9 present the estimates of direct and indirect effects of policies for the specification with past national case/death variables. The effects of school closures and the sum of policies are estimated substantially smaller in Table 8 when national case/death variables are included than in Table 6. This sensitivity reflects the difficulty in identifying the aggregate time effect—which is largely captured by national cases/deaths—given little cross-sectional variation in the timing of school closures across states. On the other hand, the estimated effects of policies other than school closures are similar between Tables 6 and 8; the effect of other policies are well-identified from cross-sectional variations.

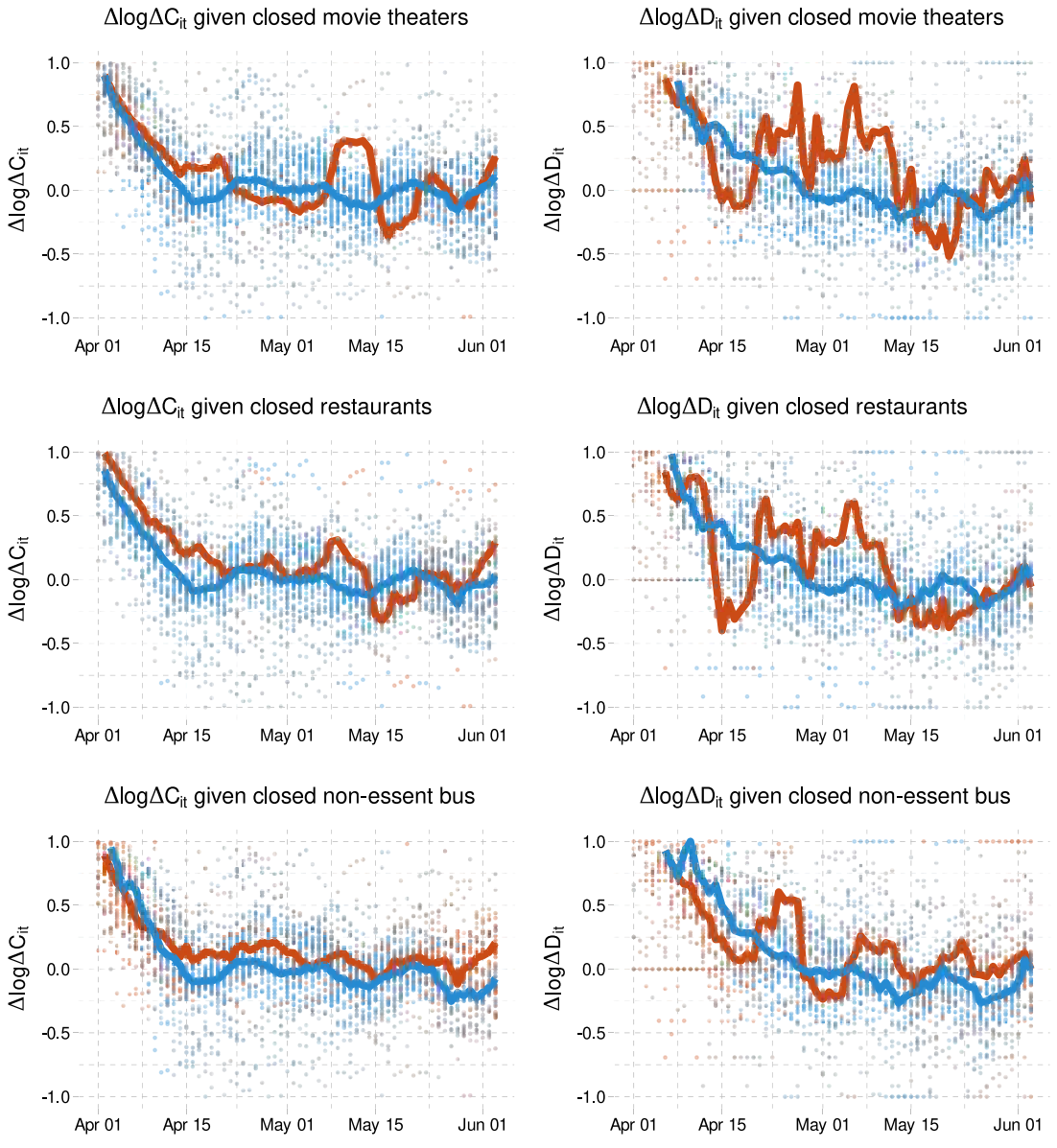

Fig. A.21. Case and death growth conditional on policies. In these figures, red points are the case or death growth rate in states without each policy 14 (or 21 for deaths) days earlier. Blue points are states with each policy 14 (or 21 for deaths) days earlier. The red line is the average across states without each policy. The blue line is the average across states with each policy. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

B.2. Double machine learning

To estimate the coefficient of the jth policy variable, P_{it}^j, using double machine learning (Chernozhukov et al., 2018), we consider a version of (PI→Y) as follows:

$$Y_{i,t+\ell} = P_{it}^j \theta_0 + \phi' X_{it} + g_0(W_{it}) + \xi_{it}, \qquad E[\xi_{it} | P_{it}^j, X_{it}, W_{it}] = 0,$$
$$P_{it}^j = \psi' X_{it} + m_0(W_{it}) + V_{it}, \qquad E[V_{it} | X_{it}, W_{it}] = 0,$$

where $X_{it} = ((P_{it}^{-j})', B_{it}', I_{it}')'$ collects policy variables except for the jth policy variables P_{it}^{-j}, behavior variables B_{it}, and information variables I_{it}. The confounding factors W_{it} affect the policy variable P_{it}^j via the function $m_0(W)$ and the outcome variable $Y_{i,t+\ell}$ via the function $g_0(W)$. We apply Lasso or Random Forests to estimate $g_0(W)$ for dimension reductions or for capturing non-linearity while the coefficients of X_{it} are estimated under linearity without imposing any dimension

reductions. We omit the details of estimation procedure here. Please see the discussion in Example 1.1 of Chernozhukov et al. (2018) for reference.

B.3. Debiased fixed effects estimator

We apply cross-over Jackknife bias correction as discussed in Chen et al. (2020) in detail. Here, we briefly describe our debiased fixed effects estimator.

Given our panel data with $N = 51$ states and $T = 75$ days for case growth equation (PI→Y), consider two subpanels as follows:

$$\mathbf{S}_1 = \{(i,t) : i \leq \lceil N/2 \rceil, t \leq \lceil T/2 \rceil\} \cup \{(i,t) : i \geq \lfloor N/2+1 \rfloor, t \geq \lfloor T/2+1 \rfloor\}$$

and

$$\mathbf{S}_2 = \{(i,t) : i \leq \lceil N/2 \rceil, t \geq \lfloor T/2+1 \rfloor\} \cup \{(i,t) : i \geq \lfloor N/2+1 \rfloor, t \leq \lceil T/2 \rceil\}$$

where $\lceil . \rceil$ and $\lfloor . \rfloor$ are the ceiling and floor functions. Each of these two subpanels includes observations for all cross-sectional units and time periods.

We form the debiased fixed effects estimator as

$$\widehat{\beta}_{BC} = 2\widehat{\beta} - \widetilde{\beta}_{\mathbf{S}_1 \cup \mathbf{S}_2},$$

where $\widehat{\beta}$ is the standard fixed effects estimator while $\widetilde{\beta}_{\mathbf{S}_1 \cup \mathbf{S}_2}$ denotes the fixed effects estimator using the data set $\mathbf{S}_1 \cup \mathbf{S}_2$ but treats the states in $\mathbf{S}_1$ differently from those in $\mathbf{S}_2$ to form the fixed effects estimator; namely, we include approximately twice more state fixed effects to compute $\widetilde{\beta}_{\mathbf{S}_1 \cup \mathbf{S}_2}$.[39] We obtain bootstrap standard errors by using multiplier bootstrap with state-level clustering.

B.4. Details for computing counterfactuals

We compute counterfactuals from the "total effect" version of the model, with behavior concentrated out.

$$Y_{i,t+\ell} = \mathsf{a}' P_{it} + \mathsf{b}' I_{it} + \tilde{\delta}' W_{it} + \bar{\varepsilon}_{it}$$

We consider a counterfactual change of P_{it} to $P^\star_{it}$, while W_{it} and $\bar{\varepsilon}_{it}$ are held constant. In response to the policy change, $Y_{i,t+\ell}$ and the part of I_{it} that contains Y_{it}, change to $Y^\star_{i,t+\ell}$ and $I^\star_{it}$. To be specific, let C_{it} denote cumulative cases in state i on day t. Our outcome is:

$$Y_{i,t+\ell} \equiv \log\left(C_{i,t+\ell} - C_{i,t+\ell-7}\right) - \log\left(C_{i,t+\ell-7} - C_{i,t+\ell-14}\right) \equiv \Delta \log \Delta C_{i,t+\ell}$$

where Δ is a 7 day difference operator. Writing the model in terms of $\Delta \log \Delta C$ we have:

$$\Delta \log \Delta C_{i,t+\ell} = \mathsf{a}' P_{it} + \mathsf{b}_D \Delta \log \Delta C_{i,t} + \mathsf{b}_L \log \Delta C_{i,t} + \tilde{\delta}' W_{it} + \bar{\varepsilon}_{it}$$

To simplify computation, we rewrite this model in terms of $\log \Delta C$:

$$\log \Delta C_{i,t+\ell} = \mathsf{a}' P_{it} + \log \Delta C_{i,t+\ell-7} + (\mathsf{b}_D + \mathsf{b}_L) \log \Delta C_{i,t} - \mathsf{b}_D \log \Delta C_{i,t-7} + \tilde{\delta}' W_{it} + \bar{\varepsilon}_{it}$$

This equation is used to iteratively compute $\log \Delta C^\star_{i,t+\ell}$ conditional on initial $\{\log \Delta C_{i,s}\}_{s=-\ell-7}^{0}$, and the entire sequence of $\{W_{i,t}, P^\star_{i,t}, \bar{\varepsilon}_{it}\}_{t=0}^{T}$.

Weekly cases instead of log weekly cases are given simply by

$$\Delta C^\star_{i,t+\ell} = \exp(\log \Delta C^\star_{i,t+\ell})$$

Cumulative cases can be recursively computed as:

$$C_{i,t} = C_{i,t-7} + \Delta C_{i,t} = C_{i,t-7} + \exp(\log \Delta C_{i,t})$$

given initial $\{C_{i,s}\}_{s=-7}^{0}$.

Note that $\log \Delta C^\star_{i,t+\ell}$ depends linearly on $\bar{\varepsilon}$, so the residuals (and our decision to condition on versus integrate them out) do not matter when considering linear constants of $\log \Delta C_{it}$ or $\Delta \log \Delta C_{it}$, or when considering relative contrasts of ΔC_{it}.

[39] Alternatively, we may form the cross-over jackknife corrected estimator as $\widehat{\beta}_{CBC} = 2\widehat{\beta} - (\widetilde{\beta}_{\mathbf{S}_1} + \widetilde{\beta}_{\mathbf{S}_2})/2$, where $\widetilde{\beta}_{\mathbf{S}_j}$ denotes the fixed effect estimator using the subpanel $\mathbf{S}_j$ for $j = 1, 2$. In our empirical analysis, these two cross-over jackknife bias corrected estimators give similar result.

Inference

Let $S(\theta, \boldsymbol{\varepsilon})$ denote some counterfactual quantity or contrast of interest, where $\theta = (\mathrm{a}, \mathrm{b}, \tilde{\delta})$ are the parameters, and $\boldsymbol{\varepsilon}$ is the vector of residuals. Examples of S that we compute include:

- Contrasts of growth rates: $S(\theta, \boldsymbol{\varepsilon}) = \Delta \log \Delta C_{it}^{\star} - \Delta \log \Delta C_{it}$
- Relative contrasts of weekly cases: $S(\theta, \boldsymbol{\varepsilon}) = \Delta C_{it}^{\star} / \Delta C_{it}$
- Relative contrasts of cumulative cases: $S(\theta, \boldsymbol{\varepsilon}) = \frac{C_{it}^{\star} - C_{it}}{C_{it}}$

The first two examples do not actually depend on $\boldsymbol{\varepsilon}$, but the third one does. Inference is by simulation. Let $\hat{\theta}$ denote our point estimates and $\hat{\boldsymbol{\varepsilon}}$ the associated residuals. We draw $\tilde{\theta}_j$ from the asymptotic distribution of $\hat{\theta}$. Let $\tilde{\varepsilon}_j$ denote the residuals associated with $\tilde{\theta}_j$. We then compute $\tilde{s}_j = S(\tilde{\theta}_j, \tilde{\varepsilon}_j)$ for $j = 1, \ldots, 200$ and plots the mean across j as a point estimate and quantiles across j for confidence intervals.

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Face Masks and GDP

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New US coronavirus cases have risen sharply in recent weeks, leading investors to worry that renewed lockdowns will again depress economic activity. But since the first infection wave in March and April, it has become clear that broad lockdowns are not the only way to lower virus transmission, and many governments have started to require the wearing of face masks in public settings. Should the United States follow suit with a national mandate? This is inherently a political decision, but we can

use our analytical tools to answer three questions that are relevant to it. First, how effective is a face mask mandate in increasing face mask usage? Second, does increased face mask usage lower virus transmission, and if so by how much? And third, how economically valuable is a face mask mandate in terms of reducing the need for broad lockdowns with their well-documented negative effects on GDP?

VIEW VIDEO: Jan Hatzius, head of Goldman Sachs Research and the firm's chief economist, explores the link between face masks and coronavirus outcomes, and the economic value of a national face mask mandate in reducing the need for broad lockdowns.

- The sharp increase in confirmed coronavirus cases in the US Sun Belt has led investors to worry about renewed broad lockdowns with large negative effects on GDP. But there are also other ways to reduce infections, including stringent bans on large gatherings and greater use of face masks.
- In particular, we argue that a national face mask mandate could partially substitute for renewed lockdowns. We start by showing that a national mandate would likely increase face mask usage

meaningfully, especially in states such as Florida and Texas where masks remain largely voluntary to date.

- We then investigate the link between face masks and coronavirus outcomes. Our analysis includes 1) a US regional panel in which we relate the growth rate of infections and fatalities to the introduction of state face mask mandates, 2) a large country-level cross section in which we relate cumulative infections and fatalities to the lag between the onset of spread and the introduction of a face mask mandate, and 3) a smaller country-level panel in which we relate the growth rate of infections and fatalities to lagged mask usage.
- We find that face masks are associated with significantly better coronavirus outcomes. Since this is true across all three of our models and the results are robust to the inclusion of a number of control variables, it seems to reflect a largely causal impact of masks rather than correlation with other factors (such as reduced mobility or avoidance of large gatherings). Our baseline estimate is that a national mandate could raise the percentage of people who wear masks by 15pp and cut the daily growth rate of confirmed cases by 1.0pp to 0.6%.
- Finally, we translate our results into GDP terms by asking how much our Effective Lockdown Index (ELI) would need to increase in order to cut infections by as much as a national mask mandate, and then converting the ELI impact into a GDP impact using the estimated cross-country relationship between the two. These calculations imply that a face mask mandate could potentially substitute for lockdowns that would otherwise subtract nearly 5% from GDP.

Face Masks and GDP [1]

New US coronavirus cases have risen sharply in recent weeks, with most of the deterioration concentrated in the "Sun Belt," including Florida, Texas, Arizona, and California. This has led investors to worry that renewed lockdowns will again depress economic activity. By our estimates, the increase in our Effective Lockdown Index (ELI)—a combination of official restrictions and actual social distancing data—subtracted 17% from US GDP between January and April, and other countries with even more aggressive restrictions saw even larger economic effects.

Since the first infection wave in March and April, however, it has become clear that broad lockdowns are not the only way to lower virus transmission significantly. For one thing, public health experts have long believed that bans on large gatherings can bring disproportionate benefits. This belief has only grown with a multitude of studies documenting the importance of "super spreader" events, such as those associated with the Shinjeonji Church in South Korea, the Austrian ski resort Ischgl, various European soccer matches, and the celebrations in New Orleans for Mardi Gras.

A more abrupt shift has occurred in the official view on face masks. As late as March 30, the World Health Organization advised that there was "no specific evidence to suggest that the wearing of masks by the mass population has any potential benefit."[2] Since

then, however, the public health community's thinking has changed dramatically and many governments have started to require the wearing of face masks.

Should the United States follow these countries and adopt a national face mask mandate? This is inherently a political decision, but we can use our analytical tools to answer three questions that are relevant to it. First, how effective is a face mask mandate in increasing face mask usage? Second, does increased face mask usage lower virus transmission, and if so by how much? And third, how economically valuable is a face mask mandate in terms of reducing the need for broad lockdowns with their well-documented negative effects on GDP?

Face Mask Mandates and Usage

At present, the United States is among the less restrictive countries with respect to face mask mandates. The federal government did issue a national "recommendation" to wear masks in public settings in April, and many state and local governments have taken more stringent measures. However, a recommendation is not a mandate and the governors of both Florida and Texas—the two most heavily affected large states—recently reiterated their opposition to a statewide mask mandate. By contrast, many European countries now have national mask mandates in place, as shown in Exhibit 1, and much of East Asia has strong social norms of mask wearing when sick and during pandemics.

Exhibit 1: The US Is Among the Less Restrictive Economies with Respect to Face Mask Mandates

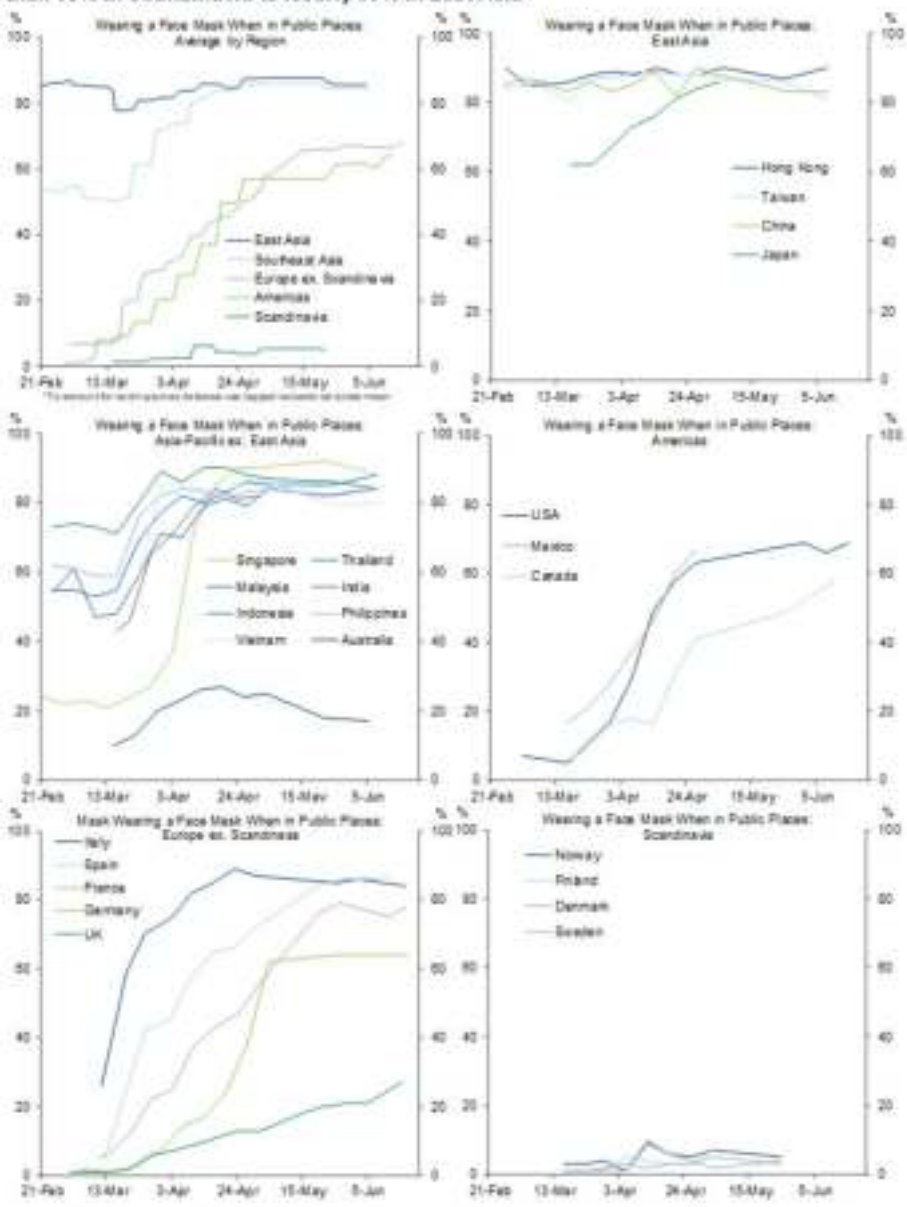
Economy	Region	Mask Policy*	Policy Details*	Date Implemented*
China	East Asia	National Norm/Universal Mask Usage		
Hong Kong	East Asia	National Norm/Universal Mask Usage		
South Korea	East Asia	National Norm/Universal Mask Usage		
Japan	East Asia	National Norm/Universal Mask Usage		
Singapore	Southeast Asia	National Mandate	Everywhere in Public	14-Apr-20
Germany	Europe	National Mandate	Public Transport & Stores	27-Apr-20
India	South Asia	National Mandate	Everywhere in Public	1-May-20
Italy	Europe	National Mandate	Public Transport & Stores	4-May-20
France	Europe	National Mandate	Public Transport & Schools & Stores	11-May-20
Mexico	Americas	National Mandate	Public Transport	20-May-20
UK	Europe	National Mandate	Public Transport	15-Jun-20
Spain	Europe	National Mandate	Public Transport & Stores	21-Jun-20
Brazil	Americas	Regional Mandate	Belo Horizonte, Federal District, Rio Grande do Sul, Rio de Janeiro, Salvador***	
Russia	Central Asia	Regional Mandate	Moscow, St. Petersburg***	
US	Americas	Regional Mandate	CA, CT, DE, DC, HI, IL, KY, ME, MD, MA, MI, NV, NJ, NM, NY, NC, PA, RI, UT, VA, WA	
Switzerland	Europe	National Recommendation	Public Transport & Stores	22-Apr-20
Canada	Americas	National Recommendation	Public Settings**	20-May-20
Australia	Oceania	None		
New Zealand	Oceania	None		
Norway	Scandinavia	None		
Sweden	Scandinavia	None		

* Based on information on MASKS4ALL Website (https://masks4all.co) and Leffler et al. (2020) study.
** Where social distancing is not possible.
*** List not exhaustive.

Source: masks4all.co, Leffler et al. 2020, Goldman Sachs Global Investment Research

What about actual mask usage? In this respect, the US scores somewhat better than one might expect, at least when looking at the national self-reported average. As shown in Exhibit 2, the share of respondents saying that they wear a face mask in public is nearly 90% in East Asia, 80% in Southern Europe, just below 70% in the US and Germany, 30% in the UK, and as low as 10% in Scandinavia. Most countries, including the US, have seen large increases in self-reported mask usage since the start of the pandemic.

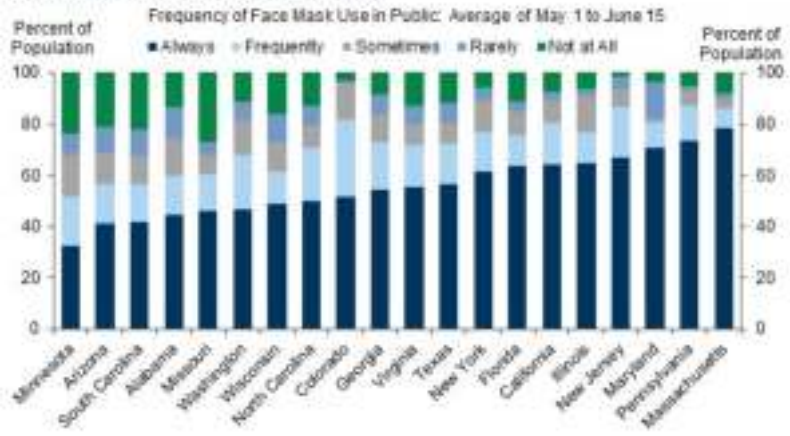
Exhibit 2: The Percentage of People Saying That They Wear a Face Mask in Public Ranges from Less than 10% in Scandinavia to Nearly 90% in East Asia



Source: YouGov, Goldman Sachs Global Investment Research

However, the national data don't tell the full story. As shown in Exhibit 3, face mask usage is highest in the Northeast, where the virus situation has improved dramatically in recent months, and generally lower in the South, where the numbers have deteriorated.[3] For example, only about 40% of respondents in Arizona say that they "always" wear face masks in public, compared with nearly 80% in Massachusetts.

Exhibit 3: The Share "Always" Wearing a Face Mask in Public Ranges from Around 40% in Minnesota and Arizona to 80% in Massachusetts



Source: YouGov, Goldman Sachs Global Investment Research

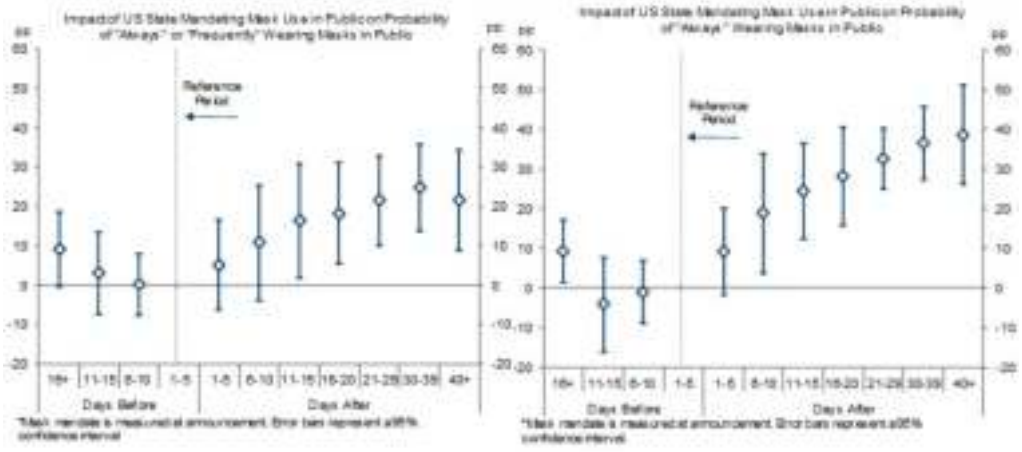
How effective would a national mask mandate be in pushing mask usage to Southern European or East Asian levels? To investigate this, we turn to a statistical event study that relates the adoption of mask mandates across US states to subsequent changes in self-reported mask usage.

We analyze the impact of face mask mandates issued by 20 US states plus DC between April 8 and June 24 in a state panel. We collect the announcement dates of mask mandates from a study in Health Affairs by Wei Lyu and George Wehby and construct statewide time series of face mask usage outside the home using YouGov Covid-19 Behaviour Tracker respondent-level data. We regress state-level mask usage on various event time dummies around the announcement and include state fixed effects and time fixed effects.[4]

Exhibit 4 shows our estimates of a large and highly significant impact of mandates on mask usage. We estimate that statewide mask mandates gradually raise the percentage of people who "always" or "frequently" wear masks by around 25pp in the 30+ days after

signing (left panel). The percent of respondents who "always" wear masks rises by nearly 40pp 30+ days after, reflecting some people switching from "frequently" and other categories to "always" (right panel).

Exhibit 4: Mask Mandates Raise the Percentage of People Who "Always" or "Frequently" Wear Masks by Around 25pp in the 30+ Days After Signing



Source: YouGov, Goldman Sachs Global Investment Research

Exhibit 4 suggests that a national mask mandate could increase US face mask usage by statistically significant and economically large amounts, especially in states such as Florida and Texas that currently don't have a comprehensive mandate and are seeing some of the worst outbreaks. Specifically, we estimate that a national mandate would increase the national average share of people who "always" or "frequently" wear masks by 15pp. This estimate is based on two assumptions. First, we assume that states that currently don't have a mandate—which account for 50% of the population—experience a 25pp rise in mask usage in line with the average response to statewide mandates. Second, we assume that states which already have a state mandate see a 5pp increase in mask usage because of increased focus on the issue.

Face Masks and Virus Outcomes

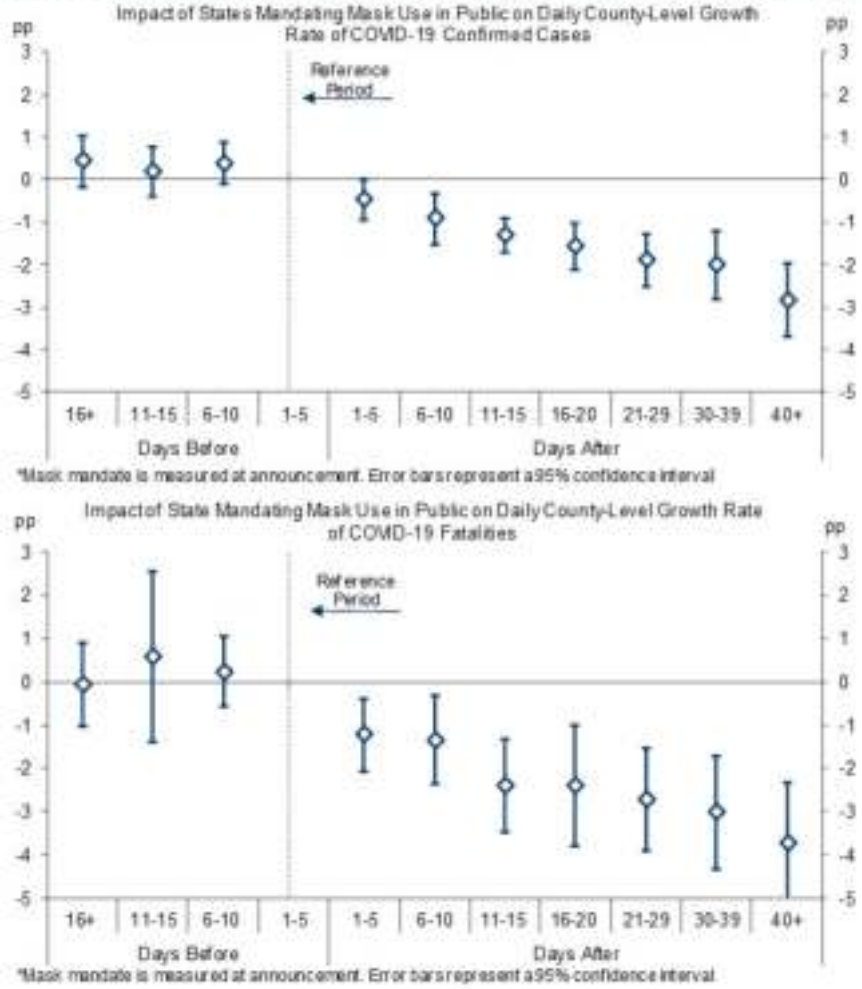
Approach 1: US County Panel

Does increased face mask usage lower virus transmission, and if so by how much? To investigate this, we turn to three statistical approaches relating face mask usage and mandates to virus spread and fatalities.

Our first approach extends our event study analysis of US state-level mandates to the impact on the growth rate of infections and fatalities. Specifically, we regress county-level growth rates of infections and fatalities on event time dummies around the announcement and control for state fixed effects, time fixed effects, and a rich set of county-level controls.[5]

As shown in Exhibit 5, we estimate that face mask mandates have large and highly statistically significant effects on health outcomes. Our estimates imply that mask mandates lower the infection growth rate by 1.3pp in the 11-15 days after announcement. Relative to the 5.4% average infection growth rate prior to announcement, the growth rate of infections is cut by 25%. We also estimate significant and somewhat larger declines in the growth rate of COVID-19 fatalities of 2.4pp in the 11-15 days after announcement and of 3.7pp in the 21-29 days after.

Exhibit 5: Mask Mandates Are Associated with Large Declines in COVID-19 Case and Fatality Growth



Source: YouGov, Goldman Sachs Global Investment Research

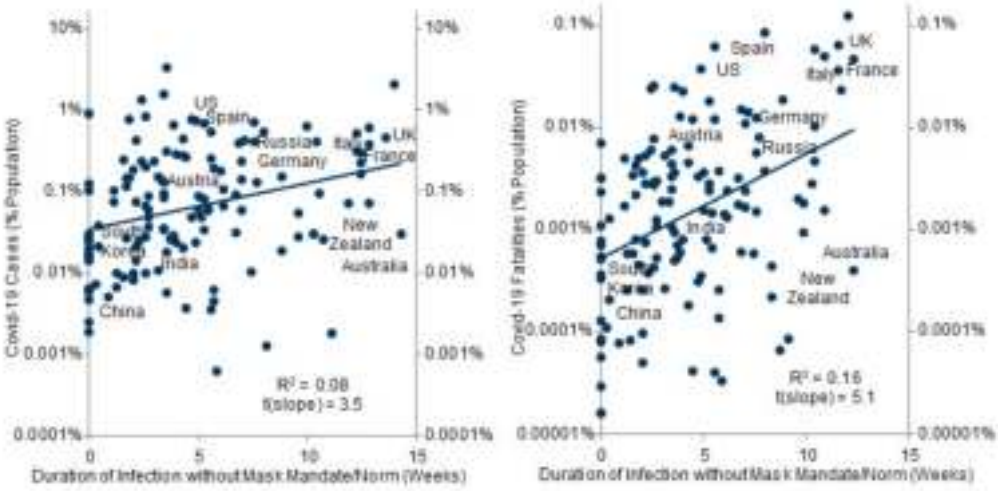
Approach 2: Large Country Cross-Section

Our second approach is a large country cross section in which we relate cumulative case counts and fatalities to the lag between the onset of spread and the introduction of a face mask mandate, building on a study by Christopher Leffler and co-authors.

Exhibit 6 presents the descriptive relationships graphically by plotting the length of the outbreak before masks were widely adopted against cumulative cases per capita (left panel) and cumulative fatalities per capita (right panel). We measure the start of the outbreak as the day of the first fatality. Both graphs show a positive and statistically significant slope,

indicating that countries which took longer to reach widespread mask usage (whether by policy or cultural norms) suffered more virus cases and fatalities. The better fit for fatalities than cases likely reflects the relatively better measurement of fatalities.

Exhibit 6: Countries Which Took Longer to Reach Widespread Mask Usage Experienced More COVID-19 Cases and Fatalities



Source: masks4all.co, Leffler et al. 2020, Goldman Sachs Global Investment Research

To formalize this finding, Exhibit 7 presents cross-sectional regression models of log cases and log fatalities for around 125 countries. In both regressions, we find statistically significant negative effects of masks on cumulative cases and fatalities after including controls such as the obesity rate, population density, age structure, and testing policy. Our numerical estimates are that cumulative cases grow 17.3% per week without a mask mandate but only 7.3% with a mask mandate, and that cumulative fatalities grow 29% per week without a mask mandate but only 16% with a mask mandate.

Exhibit 7: Mask Policies and Norms Have Lowered COVID-19 Case Counts and Fatalities

	Country Cross-Section: Impact of Mask Wearing on COVID-19*			
	Log COVID-19 Cumulative Cases per Capita		Log COVID-19 Fatalities per Capita	
	Coefficient [t-stat]	sp coefficient	Coefficient [t-stat]	sp coefficient
Intercept	-4.696*** [-18.07]	–	-4.963*** [-23.46]	–
Weeks of Infection	0.065*** [3.22]	1.173	0.109*** [4.27]	1.285
Weeks of Infection with Mask Mandate/Norm**	-0.035*** [-3.34]	0.915	-0.044*** [-3.09]	0.904
Obesity Rate (%)	0.039*** [6.53]	1.093	0.031*** [4.77]	1.074
Population Density***	0.181*** [2.73]	1.519		
Testing Policy****	0.570*** [4.48]	3.712		
% of Population Over 65			0.034*** [3.74]	1.081
Observations	121		131	
R-squared	0.48		0.48	

*Data as of 23 June.
**Calculated upto 28 days before June 23 for Fatalities and 14 days before June 23 for Cases.
***1000 people per square km of land area.
****Proportion of time testing available to anyone showing COVID-19 symptoms (based on Oxford COVID-19 Testing Policy Indicator) from 10 days before first fatality to 14 days before 23 June.

Source: World Bank, Blavatnik School of Government, Oxford, Leffler et al. 2020, MasksAll.co, Goldman Sachs Global Investment Research

Approach 3: Country Panel

Our third approach consists of a smaller country panel in which we relate the daily growth rate of infections and fatalities to lagged self-reported mask usage, plus a number of control variables. There are three main results, illustrated in Exhibit 8.

First, face masks have a large negative impact on infections and fatalities, controlling for population density and income inequality (columns 1 and 4). This negative and significant impact of face masks is robust to controlling for our Effective Lockdown Index (ELI), the share of the population that say they avoid crowded public places (columns 2 and 5), and country and time fixed effects (columns 3 and 6). Our estimates suggest that a 25pp increase in the self-reported mask usage, for instance as a result of a mask mandate, lowers the growth rate of cumulative cases by 1.9pp and the growth rate of cumulative fatalities by 0.8pp.[6]

Second, the share of respondents that avoid crowded public places also has a large and highly significant negative impact on infections and fatalities. This not

only suggests a significant role for “super spreader” events, but also strengthens our main results because it implies that the face mask result is not just driven by the correlation between face masks and other risky activities.

Third, the virus impact of mask usage is large, not just in absolute terms but also relative to the effect of economically costly shutdowns (as measured by our ELI). In fact, the coefficients on the percentage of self-reported mask usage are slightly bigger than those on the ELI, which is interesting as both variables are on a 0-100 scale.

Exhibit 8: Face Masks and Limiting Mass Gathering Lower COVID-19 Case and Fatality Growth

	International Panel: Impact of Mask Wearing on COVID-19 Spread					
	Daily Growth Rate of Confirmed Cases per Million*			Daily Growth Rate of Fatalities per Million*		
	(1)	(2)	(3)	(4)	(5)	(6)
Intercept	-12.37	4.29	8.05	-6.80	4.56	2.32
	[-3.83]***	[0.68]	[1.27]	[-3.77]***	[1.43]	[1.06]
% of Pop. Wearing Msks in Public, Lagged**	-0.11	-0.07	-0.08	-0.06	-0.03	-0.03
	[-5.2]***	[-3.21]***	[-3.63]***	[-5.05]***	[-2.06]**	[-2.19]**
GS Effective Lockdown Index, Lagged**		-0.05	-0.07		-0.04	-0.04
		[-1.59]	[-3.00]***		[-1.94]*	[-2.28]**
% of Pop Avoiding Crowded Public Places, Lagged**		-0.23	-0.15		-0.15	-0.11
		[-3.11]***	[-2.39]**		[-4.79]***	[-2.38]**
Income Inequality	0.54	0.57	1.10	0.32	0.32	0.43
	[4.96]***	[5.76]***	[2.63]***	[5.98]***	[5.71]***	[2.59]***
Population Density	0.01	0.01	0.02	0.01	0.01	0.01
	[3.83]***	[3.05]***	[2.89]***	[3.03]***	[2.31]**	[3.74]***
Time FEs	No	No	Yes	No	No	Yes
Country FEs	No	No	Yes	No	No	Yes
Num. of Countries	22	18	18	22	18	18
Observations	2086	1743	1743	1711	1491	1491
R-squared	0.19	0.43	0.69	0.11	0.29	0.51

Note: T-statistics in brackets and robust standard errors clustered by country.
* Growth rates are natural log differences*100.
** Lagged 14 days for cases per million regressions; lagged 28 days for fatalities per million regressions.

Source: JHU CSSE, YoGov, Goldman Sachs Global Investment Research.

The Impact of a Mandate on Infections

Before we translate our statistical results into a baseline estimate of the impact of face mask mandates on virus outcomes, we need to address two potential concerns about our analysis up front.

The first concern is that the correlation between face masks and virus outcomes might reflect the effect of other unobserved forms of cautious behavior that are correlated with mask mandates or usage, instead of a truly causal effect of masks. But there are some reasons to believe that this type of bias in not a big issue for our analysis. Not only do we obtain remarkably similar estimates across our three approaches, but we also control for a number of other observable forms of cautious behavior. Specifically, our cross-country results on masks include our Effective Lockdown Index among the explanatory variables, and they are largely unchanged when we include the share of respondents who say they stay home from work, don't touch objects, improve personal hygiene, avoid contact with tourists, avoid raw meat, and don't send their children to school.[7]

The second potential concern is that our main results are based on confirmed infections, which can be distorted by a lack of testing. However, it is important to note that this would, if anything, lead to an understatement of the effect assuming that increases in testing are positively correlated with increases in mask usage. Moreover, we control for testing regime indicators in our cross-sectional regression, and we obtain generally similar estimates for fatalities—which are better measured—across all three of our approaches.

So what is a reasonable baseline estimate of the impact of a US national mask mandate on the growth rate of confirmed infections? To generate such an estimate, we

apply our country panel results separately to two groups of US states, namely ones with and without a state-level mask mandate in place.

States that currently don't have a state-level mandate account for 40% of US total confirmed cases, 45% of US GDP, half of the population, and two-thirds of new infections. This group has also experienced an average daily growth rate in confirmed infections of 2.9% in the past 7 days. Based on our analysis of state-level mandates, we estimate that a national mask mandate would raise mask usage by 25pp in these states. Our country panel shows that a 25pp increase in self-reported mask usage lowers the infection growth rate by 1.9pp (or just over 60%). The national mandate could therefore lower the daily growth rate in the group of states without a mandate from 2.9% to just over 1%.

States that currently do have a mandate have experienced a lower average daily growth rate in confirmed infections of 0.8% in the past 7 days. Combined with our assumption that a national mandate would lead to a smaller increase in mask usage of 5pp through extra awareness in this group of states, our country panel suggests a 0.4pp decline in the infection growth rate to 0.4-0.5%.

Combining the estimates for these two groups of states, we estimate that a national mandate could cut the national average growth rate of infections by nearly 1.0pp to 0.6-0.7%.

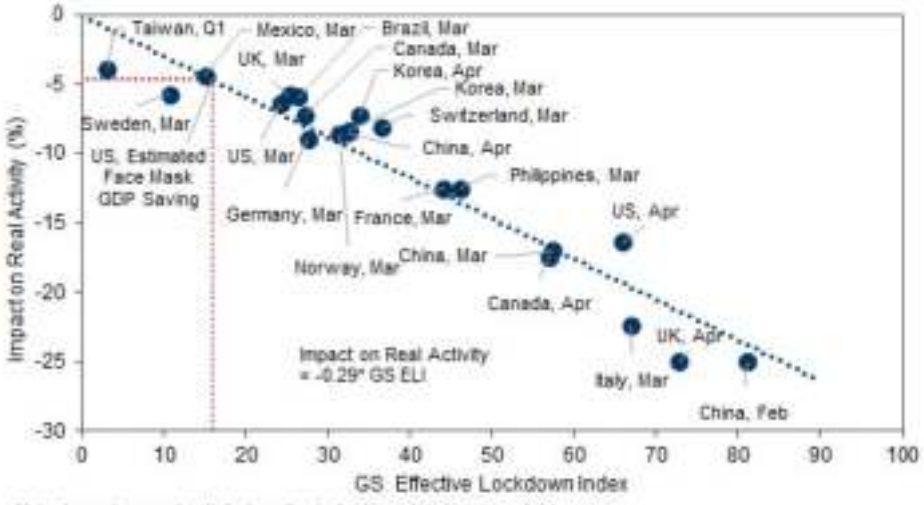
The Impact of a Mandate on GDP

If a face mask mandate meaningfully lowers coronavirus infections, it could be valuable not only from a public health perspective but also from an economic perspective because it could substitute for renewed lockdowns that would otherwise hit GDP.

How big is this potential effect? To generate an answer, we proceed in two steps. First, we use our cross-country panel analysis to ask how much our effective lockdown index (ELI) would need to increase in order to lower the daily case growth rate by 1.0pp, i.e. the estimated impact of a national face mask mandate. The answer is an increase in our ELI of 16pp.

Second, we ask how much a 16pp ELI increase would subtract from the level of GDP. As shown in Exhibit 9, the cross-country relationship implies that such an increase might reduce GDP by just under 5%.

Exhibit 9: A Close Relationship Between the ELI and GDP



Note: Impact on real activity is estimated where data is not available.

References to China are to Mainland China

Source: Goldman Sachs Global Investment Research

Thus, the upshot of our analysis is that a national face mask mandate could potentially substitute for renewed lockdowns that would otherwise subtract nearly 5% from GDP. It is important to recognize that this estimate is quite uncertain because it is based on a number of statistical relationships that are all measured with error. Despite the numerical uncertainty, however, our analysis suggests that the economic benefit from a face mask mandate and increased face mask usage could be sizable.

So will the US adopt a national face mask mandate? This is uncertain, partly because masks have become such a politically and culturally charged issue. However, even in the absence of a national mandate, state and local authorities might well broaden mandates in ways that ultimately mimic the impact of a national mandate. Either way, our analysis suggests that the economy could benefit significantly from such moves, especially when compared with the alternative of a return to broader lockdowns.

Jan Hatzius

Daan Struyven

Isabella Rosenberg

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[1] We thank Sid Bhushan and Dan Milo for valuable help with this report.

[2] See Jaqueline Howard, "WHO stands by recommendation to not wear masks if you are not sick," CNN, March 30, 2020.

[3] As an aside, note that Minnesota has the lowest self-reported rate of mask usage among larger states in the US. This is interesting because the state is home to a

large population of Scandinavian-Americans and Scandinavia has some of the lowest rates of face mask usage in the world.

[4] Our mask usage regressions are weighted by state population, focus on states with more than 4 million people (given the small samples in the respondent-level data) and use robust standard errors at the state level. Our sample starts on April 2nd when respondent-level data become available. We also control for cumulative cases per million and cumulative deaths per million.

[5] The county-level controls are population density, median house value, median household income, homeownership, pollution, maximum summer temperature, and maximum winter temperature, educational attainment, mean Body Mass Index, and the share of population over 65. We use county population weights and cluster robust standard errors at the state level. Our sample covers 2,373 counties and extends from March 31 to June 24. See Lyu and Wehby (2020).

[6] Relative to the sample average growth rates of 3.8% and 2.8%, these estimates imply that a mask mandate raising mask usage by 25pp cuts the growth rates of infections and fatalities by nearly one half and one quarter respectively.

[7] The cross-country panel and cross-county panel results are also robust to controlling for the lagged levels of fatalities and infections per capita, which helps address the concern that the mask effects pick up the impact of other forms of unobserved cautious behavior in response to the size of the outbreak.

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The introduction of a mandatory mask policy was associated with significantly reduced COVID-19 cases in a major metropolitan city

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Conflicts of interest:

BC serves on the National COVID-19 Health Research Advisory Committee that provides guidance to the Federal Government's COVID-19 response.

NS, MH, A Saeri, EG and LS provide guidance to the Victorian Government's COVID-19 response.

MH and NS receive funding from the Victorian Government for the Optimise Study and modelling work.

A Saeri and EG receive funding from the Victorian Government for the SCRUB project.

CRM serves on the National COVID-19 Health Research Advisory Committee that provides guidance to the Federal Government's COVID-19 response. She currently receives funding from the National Health and Medical Research Council and Medical Research Futures Fund, Office of Health Protection, Department of Health, Sanofi and from the Defence Intelligence Organisation.

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Summary

Background Whilst evidence of face masks' effectiveness in reducing COVID-19 cases is increasing, the impact of mandatory use across a large population has been difficult to assess. Introduction of mandatory mask use on July 22, 2020 during a resurgence of COVID-19 in Melbourne, Australia created a natural experiment to assess the impact of the policy on the epidemic growth rate as its introduction occurred in the absence of other changes to restrictions.

Methods Exponential epidemic growth or decay rates in daily COVID-19 diagnoses were estimated using a non-weighted linear regression of the natural logarithm of the daily cases against time, using a linear spline model with one knot (lspline package in R v 3.6.3). The model's two linear segments straddle the hinge day, determined from the model fit, on which the mask policy began to take effect. We used two forms of data to assess change in mask usage: population-based survey data and images of people wearing masks in public places obtained from a major media outlet. Potential confounding factors (including daily COVID-19 tests, number of COVID-19 cases among population subsets affected differentially by the mask policy – e.g. healthcare workers) were examined for their impact on the results.

Findings Introduction of a mandatory mask policy was associated with an estimated 23% reduction in the effective reproduction ratio, from 1.18 to 0.91. The hinge day in the linear spline model occurred eight days after the policy was introduced on July 23, 2020. Daily cases grew exponentially in the first log-linear segment (k = +0.042, s.e. = 0.007), and decayed exponentially in the second (k = -0.023, s.e. = 0.017). Analysis of images of people in public spaces showed mask usage rose from approximately 43% to 97%. Analysis of survey data found that on the third day before policy introduction, 44% of participants reported "often" or "always" wearing a mask; on the fourth day after, 100% reported "always" doing so. No potentially confounding factors were associated with the observed change in growth rates.

Interpretation. The mandatory mask use policy substantially increased public use of masks and was associated with a significant decline in COVID-19 transmission after introduction of the policy. The hinge date (where the shift in epidemic growth was observed) occurred eight days after policy introduction, consistent with the incubation time of COVID-19 and the time needed to test and report new cases. Although studies emphasise the importance of masks in a clinical setting, to our knowledge no previous peer reviewed publications measured the role of masks for controlling epidemics in the broader community.

Funding: Burnet Institute.

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Research in context

Evidence before this study

Multiple studies that show that face masks can reduce transmission of respiratory virus infections, with the use of facial coverings and masks to reduce transmission of COVID-19 being widely recommended and, in some cases, mandated. Most studies have occurred in laboratory or clinical settings; there is little evidence of masks' effectiveness in community settings.

Added value of this study

A policy of mandatory use of facial coverings and masks (hereafter, masks) was introduced in Melbourne, Australia during a period of exponentially increasing COVID-19 cases. The abrupt increase in mask use observed after policy introduction, coupled with strong surveillance of the population, allowed a unique assessment of the impact of a mandatory mask policy on COVID-19 cases. On day 8 following the introduction of the policy, there was a clear transition from an exponential increase to an exponential decrease in daily new cases that could not be explained by potential confounding factors. This study reinforces the strong correlation between the mandatory introduction of face masks and decreasing COVID-19 cases in a large metropolitan area.

Implications of all the available evidence

This new data, coupled with existing data on use of face masks, provides powerful evidence that introduction of the mandatory face mask policy was effective in reducing COVID-19 cases.

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Background

Australia, like many countries, experienced an initial rise in SARS-CoV-2 (COVID-19) cases peaking on March 28, 2020, followed by a relatively sharp decline in April after federal and state governments introduced strict community controls, travel bans and quarantining of all travellers arriving in Australia.[1] Throughout late June and July, Victoria, Australia's second most populous state, experienced a resurgence of COVID-19, with 13,078 cases detected between 14th June and 10th August and new daily case numbers peaking at 686 on 5th August[2], with 95% in the state capital, Melbourne. By the end of September, daily numbers had declined to fewer than 20 and are continuing to decline.[2]

The resurgence of COVID-19 in Victoria led to multiple control measures being reintroduced in urban Melbourne, a city of 4.93 million people, in July 2020. These included Stage 3 restrictions (closure of pubs, bars, entertainment venues, places of worship, restricting restaurants and cafes to takeaway only, and limiting public gatherings to two people, plus requiring people in the restricted area to stay home, with only four reasons to leave home: shopping for essentials, caregiving, exercise, and work or study that cannot be done from home) in 10 postcodes with relatively high case numbers at 11:59pm on July 1, 2020. Stage 3 was expanded on 4th July to include two additional postcodes and complete quarantine/isolation of several high-rise public housing estates considered to be at high risk; residents were required to stay inside their homes under the 'detention' directives, unless granted permission to receive medical care. On 8th July, Stage 3 restrictions were extended to include all of metropolitan Melbourne and Mitchell Shire, and Victoria's borders with other states/jurisdictions were closed (Table 1). Previous work has shown that the introduction of Stage 3 restrictions slowed but did not reverse the exponential growth in daily cases[1]; the growth rate fell from 0.140 to 0.037 per day, which translates into a fall in the R_{eff} from 1.75 to 1.16. Despite the continued growth, this reduction was estimated to have averted 9,000–37,000 new infections throughout July, compared to a scenario of continued trend in growth.[1]

Mandatory use of masks or other face coverings including face shields, scarves and bandanas (hereafter, masks) in public settings was introduced in Victoria on 22nd July, while Stage 3 restrictions were in place. This was followed by an 8pm curfew and 5km movement restrictions introduced on 2nd August, and Stage 4 restrictions (closure of childcare and non-essential businesses, including retail, and schools delivering online learning only) on 5th August (Table 1).

[Table 1 about here[2]]

There is increasing evidence of the effectiveness of masks in reducing the transmission of SARS-CoV-2 and hence COVID-19; the World Health Organization (WHO), the United States' (US) Centre for

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Disease Control and Prevention (CDC), other public health organisations and governments recommend the use of masks in specific circumstances.[3-9] Simultaneously, some reports suggest mask use in public spaces has limited impact on COVID-19 transmission.[10] To date there have been few opportunities to examine the impact of a mandatory mask use policy at a population level. The timing of the introduction of a mandatory mask use policy created a natural experiment, allowing us to compare pre- and post-intervention epidemic growth and/or decay rates to estimate the population-level impact of the policy.

In this paper, we describe our examination of whether the mandatory mask use policy was associated with a statistically significant change in the COVID-19 epidemic growth rate in metropolitan Melbourne and the Mitchell Shire.

Methods:

Analysis of COVID-19 cases 10th July to 10th August inclusive.

Daily diagnosed COVID-19 case numbers in Victoria (excluding cases in returned international travellers in hotel quarantine) were derived from the cumulative cases reported in daily updates[2] from the Victorian Department of Health and Human Services (DHHS). Due to the generation interval for SARS-CoV-2 infection and delays in testing and reporting, there is an expected delay between the introduction of restrictions and observing them in diagnosis data. Previous work found that the introduction of Stage 3 took eight days to be observed in the diagnosis data.[1] Therefore, cases for the period 10th July to 10th August[2] were used for the analysis; the impact of Stage 3 would be already apparent, but the impact of curfew (2nd August) or Stage 4 restrictions (5th August) would not have commenced. The period prior to the mandatory introduction of masks on the 11.59pm on 22 July is referred to as the *pre-mask period* and the period from the 23rd July as the *post-mask period*.

The growth or decay of the daily number of new cases was approximated using an exponential model. This means that the logarithm of the daily cases should increase or decrease linearly with time, and analysis of residuals was used to test this assumption. The growth or decay rates of the epidemic were estimated using a non-weighted linear regression to fit the natural logarithm of the daily cases against time, using a linear spline model with one knot.[11] The knot allows for a possible deflection in the line of best fit during the period of observation, dividing the model into two linear segments that are connected at a hinge day. We tested the assumption of linearity of the two linear segments by assessing whether standardised residuals were normally distributed and independent of the time. To determine the optimal knot day, we performed sensitivity analysis to determine the

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knot/hinge day that returned the linear spline model with the maximal adjusted coefficient of determination R^2 (the best-fitting model).

This analysis estimated the growth constant (k) (i.e. the slope of the ln(daily cases) vs time regression) for each segment. We calculated the doubling/halving time of the epidemic as

$t_2 = \ln(2)/k$

We also calculated the daily multiplication rate of new cases as e^k and estimated the effective reproduction ratio (R_{eff}) as the relative change in new cases over one generation interval for SARS-CoV-2 infections, using the estimate of four days based on 468 pairs of infections in Wuhan.[12] Since the measured intervals in this estimate had an approximately normal distribution, we used the following simple estimate

$$R_{eff} = e^{k*4}$$

The Survey of COVID-19 Responses to Understand Behaviour (SCRUB) project - analysis of mask use

The Survey of COVID-19 Responses to Understand Behaviour (SCRUB) project includes measures of protective behaviour adherence among Australians during the COVID-19 pandemic; it commenced in March 2020.[13] The survey targets a representative (age, gender, metro/regional) sample of 1000 Victorian residents and 700 Australian residents outside Victoria in each round.

An item measuring self-reported mask use frequency was included from wave 6 onwards. Here we include data from round 6 (data collected 20–26 July 2020) for the question "*In the past 7 days, how frequently have you taken the following actions?"* and the specific item "*Wear a face mask whenever in public" (response scale: Never, Rarely, Sometimes, Often, Always).* For this analysis, we collapsed responses into *Never, Rarely, Sometimes* vs *Often, Always*. Respondent postcode and survey completion date were used to identify responses from people living within the areas subjected to the mandatory mask policy (Melbourne metropolitan region and Mitchell Shire), which we compared across the pre-mask and post-mark periods.

Photographic observation of mask use

To triangulate self-report data from the SCRUB study, we assessed changes in mask-wearing behaviours using images from the digital archive of *The Age* (https://www.theage.com.au/), one of the two major daily Victorian newspapers. Using consecutive sampling of photos taken in public spaces in metropolitan Melbourne between July 10 and August 2, 2020 (14 days before and 14 days after mandatory mask policy introduction), we estimated the proportion of people wearing masks in public (number of people wearing masks / number of people in the image) across three time periods: period 1, 10–19 July (the period preceding mandatory mask policy announcement); period

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2, 20–22 July (period between announcing and commencing mandatory mask wearing); and period 3, 23 July to 2 August (mandatory mask wearing period). We excluded people who were potentially exempt from mask wearing under the relevant directions, such as children and people drinking or eating while in public. The proportions of individuals wearing masks in each period were compared using cross-sectional chi-square tests.

Possible confounders

Data collected to explore potential confounding effects included 1) daily cases from regional Victoria, 2) daily cases in health care workers, 3) daily COVID-19 tests, 4) the proportion of diagnosed cases assigned to a known cluster within 24 hours of testing, and 5) mobility indices for Melbourne residents. Secondary regression analyses were run to assess changes in these measures over the time period of interest.

Daily cases in regional Victoria were derived from the cumulative cases reported in daily updates.[2] Daily cases in health care workers, which were classified as acquired in health care and aged care facilities, were obtained from the Victorian DHHS web site.[14] Daily COVID-19 tests and the proportion of diagnosed cases assigned to known clusters within 24 hours of testing were obtained from the Australian Broadcasting Corporation's coronavirus summary.[15]

Mask use in residents of regional Victoria (other than Mitchell Shire) and in health care workers in health care and aged care facilities may not have changed as a result of the mandatory mask use policy in Melbourne. To test for the impact of these potential confounders, as well as any impact of variations in testing rates, we undertook secondary regression analyses using dependent variables of log(total daily cases less regional cases), log(total daily cases less HCW cases) and log(ratio of total daily cases to number of daily tests).

Mobility indices for Melbourne were obtained from CityMapper.[16] The Citymapper Mobility Index is calculated by comparing trips planned in the Citymapper app to a recent typical usage period. Typical usage period is defined as four weeks between January 6 and February 2, 2020. A day is defined as midnight to midnight UTC, thus for certain cities may not correspond with calendar days.

Results:

Impact of masks on total cases

There were 11,714 cases reported between July10 and August 10 inclusive, with daily cases increasing from 143 cases on July 10 to a peak of 686 cases on August 5, before declining to 310 cases on August 10.

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The sensitivity analysis indicated that the best fit for the linear spline model included a hinge day on July 31, eight days after the introduction of mandatory mask usage (Table S1). Using this as the hinge day, the first log-transformed linear segment, representing the pre-mask period, demonstrated significant exponential growth in daily cases (k = +0.042, standard error [s.e.] = 0.007; p<.001). This growth equated to a projected doubling of cases every 16.5 days. The second log-transformed linear segment, representing the post-mask period, demonstrated exponential decay in daily cases (k = -0.023, s.e. = 0.017; p=0.190). This decay equated to a projected halving of cases every 30 days. The difference in exponential growth/decay rates between the pre- and post-masks periods was statistically significant (Δk=-0.065, s.e. = 0.022; p=0.006) (Figure 1; Table 2). Based on a four-day generation interval, these growth rates correspond to a 23% reduction in the R_{eff} from 1.18 in the pre-mask period to 0.91 in the post-mask period.

[Figure 1 about here]

On testing our model for goodness-of-fit, the distribution of residual values of the log transformed cases was indistinguishable from a normal distribution and showed no variation with day. Thus, the data was an excellent fit to an exponential increase in the Stage 3 period followed by an exponential decrease after masks became mandatory.

[Table 2 about here]

SCRUB Study – self reported mask use

Analysis of data from Wave 6 of the SCRUB study found 44% of participants interviewed in Melbourne and Mitchell Shire on the third day before the mask policy was introduced (July 20, 2020) reported they "often" or "always" wore a mask, and 100% of those interviewed on the fourth day afterwards (July 26) reported "always" wearing a mask. The survey found that 56% of participants reported "often" or "always" wearing a mask over 20–22 July, and 71% over 23–26 July (χ^2(1, N=808) = 8.73, p=0.002) (Figure 2). This change in mask usage was not observed in SCRUB data collected from participants from other Australian states.

[Figure 2 about here]

Photographic observation of mask use

We analysed 44 published photographic images taken between July 10 and August 2, 2020. They included a range of public locations, including streetscapes, markets, train stations and supermarkets, and included 304 unique individuals (after excluding those potentially exempt from

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mask use, as described in Methods). Nineteen photos taken in period 1 (prior to mandatory mask policy announcement) contained 101 unique individuals, of whom 43 (43%) were wearing masks. Seven photos taken in period 2 (following mandatory mask policy announcement but prior to policy introduction) contained 47 unique individuals, of whom 35 (74%) were wearing masks. Eighteen photos taken in period 3 (mandatory mask wearing period) contained 156 unique individuals, of whom 153 (98%) were wearing masks. The proportion of individuals wearing masks significantly increased from period 1 to period 2 ($\chi^2(1) = 13.09$, $p<0.001$) and again from period 2 to period 3 ($\chi^2(1) = 29.42$, $p<0.001$).

Investigation of confounding variables

The proportion of non-metropolitan daily cases remained low (approximately 5%) across the period of interest (July 10 – August 10, 2020) and paralleled total Victorian cases. Subtracting rural cases from the total cases made no significant difference to the calculated pre- and post-growth constants of the metropolitan cases (Table 3). There was a significant change in the rural growth rates coincidental with the introduction of masks in the metropolitan region.

[Table 3 about here]

The proportion of daily cases in health care workers classified as acquired in health care and aged care facilities increased steadily, but there was no significant change in the case growth rates across the pre- and post-mask periods (Table 3). Subtracting these cases from total cases again made little difference to the estimated pre- and post-mask growth rates (Table 3).

There was a significant decrease in the number of tests per day performed over the study period, with approximately 33% fewer tests on the last day, August 10, than the first, July 10 (linear regression: intercept 29,496; slope -310; p=0.026). In addition, the pre- and post-mask period growth constants for the exponential increase and decrease in positive test ratio were higher than the corresponding growth rates for cases. However, the difference in the growth rates for pre- and post-mask were similar for cases and for the positive test ratio (Table 3). The proportion of cases that were assigned to known clusters within 24 hours was approximately constant throughout the analysis period.

The mobility data showed no significant change: 14.0% mobility pre-mask and 13.1% post-mask (p=0.09) relative to mobility in February 2020, prior to the onset of the Australian COVID-19 epidemic (Figure 1).

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Discussion:

We assessed growth rates in daily COVID-19 diagnoses in Victoria, Australia before and after the introduction of a mandatory mask policy in Melbourne and Mitchell Shire (where 95% of Victoria's diagnosed cases occurred), and estimated a 23% reduction in R_{eff} from 1.18 in the pre-mask period to 0.91 in the post-mask period. The policy was associated in a change from an exponential increase in the epidemic with a doubling time of 16.5 days, to an exponential decrease with a halving time of 30 days.

Sensitivity analysis identified a hinge day that marked the transition in the growth curves, eight days after the introduction of the mandatory mask policy. This is consistent with the delay observed in an earlier study following the introduction of stringent physical distancing, the Stage 3 restrictions (Table 1).[1] This also fits the observed generation interval for COVID-19 infections[12] combined with the estimated delays in undertaking and reporting testing.

A unique feature of this study is that it observed a rapid and substantial increase in the use of masks within the population after July 23, 2020, as demonstrated in both self-report data and photographic data, that preceded a significant change in the growth rate of the epidemic. The rapid transition in the adoption of mask usage, based on photographic evidence, was striking: from 43% before the announcement of the upcoming mandatory mask policy, to an average of 74% in a three-day transition period between announcement and policy introduction, to near-complete compliance (98%) after policy implementation. The photographic data was complemented by self-report survey data that showed consistent rapid change, from just over 40% of participants reporting always or often wearing a mask on July 20, to 100% always wearing a mask on 26 July (Figure 2).

Our work has several limitations. We measured the overall impact of the introduction of mandatory mask use on daily cases. Care should be taken in ascribing causality; we did not assess the direct effectiveness of masks in preventing COVID-19 transmission. We cannot determine whether masks had a direct effect or whether near-universal adoption of masks reminded wearers to engage in other behaviours recommended to reduce COVID-19 transmission, including regular hand hygiene and physical distancing. Interestingly, introduction of masks in the metropolitan area coincided with a decrease in the growth rate in rural areas, where masks were not introduced, which is consistent with an indirect effect, a decrease in seeding of rural areas from the metropolitan area, or both. Participants in the Scrub Study were meant to report their mask use in the previous seven days, the rapid change in behaviour over 20–26 July suggests participants interpreted this question as referring to their mask use on the day they responded to the survey.

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Other factors may have contributed to the decline in COVID-19 transmission at the time the mandatory mask policy was introduced. Melburnians may have reduced their overall movement in response to other official messages or how they interacted with each other, such as whether people physically distanced from each other. Examination of mobility data across the relevant time period suggests mobility was stable[16], although unpublished behavioural data collected through July suggests people were less likely to interact with other people as the month wore on, and when they did, kept physically distanced (*pers comm., J McCaw, Doherty Institute*). It is difficult to know whether this change in interaction and physical distancing would increase or decrease the effect we observed. The decrease in interactions/contact may also have affected case numbers but the decline in interactions was steady over time, so cannot account for the hinge effect we observed. Moreover, reduced interaction could mean that the mask policy was more effective than measured, because masks were still effective despite potentially fewer episodes of risky contact. Changes to the time needed for contact tracing may have influenced the result; if the time taken from identifying a case to contacting and isolating all their contacts fell substantially during the period in question, it may have created its own reduction in transmission. However unpublished data from the Victorian DHHS suggests the time taken to perform contact tracing was relatively stable across the period of interest (*pers comm., B Sutton, DHHS Victoria*).

To make the analysis as robust as possible, we did not exclude health care workers classified as having acquired COVID-19 in health care and aged care facilities from the analysis, despite increasing numbers of cases in this group over the study period, reflecting the high occupational risk of infection in these settings. However, subtracting cases of health care workers from the Melbourne totals made little difference to the overall growth constants. Health care workers were wearing extensive personal protective equipment (PPE), including masks, in their work environment before mandatory mask policy implementation, and there is no reason to believe that mask usage changed in the health care setting during the study period; this supports the case that the changes observed in the general population are due to increased mask wearing.

We did not have access to daily case numbers for residents of aged care facilities over the whole of the analysis period, but the available data suggests that the cases in this group were growing rapidly during this time. Again, staff in aged care facilities were using PPE, including masks, extensively prior to masks becoming mandatory in the general community. This would suggest that the introduction of the mandatory mask policy would have less of an impact in this setting, given masks were already in use, hence leading to an underestimate of the overall impact of masks. Availability of more detailed case numbers over the whole Stage 3 and Stage 3+ masks period would allow this possibility to be tested rigorously. In addition, our analysis did not take account of transmission of COVID-19 in

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settings where mask use was not required, such as households or some workplaces. Given very high transmission within households[17], again, this would lead to an underestimation of the impact of the widespread use of masks.

Whilst acknowledging these limitations, we believe our results make an important contribution to the current literature on the population impact of masks in reducing COVID-19 transmission, as well as public dialogue concerning the appropriateness of mandatory mask policies. Despite WHO, CDC and others recommending the use of masks in specific settings[3,18-20] there is minimal data from community settings supporting mask use. An observational study in Beijing directly assessed the impact of mask use on SARS-CoV-2 transmission, measuring the reduction of secondary transmission in households due to face mask use. Masks were found to be 79% effective in preventing transmission if used by all household members prior to symptoms occurring.[21,22] A non-peer-reviewed report on the impact of mask mandates and other non-pharmaceutical interventions on COVID-19 cases found the introduction of a mask mandate in Ontario was associated with an average reduction of 25–31% in the weekly number of newly diagnosed COVID-19 cases.[7]

A German study used a synthetic control method to build a counterfactual to analyse the effect of face masks on the spread of COVID-19.[8] The authors compared the city of Jena and six regions in Germany that adopted a face mask policy in early to mid-April 2020, before their respective state mandates. The authors found that masks reduced the cumulative number of registered COVID-19 cases per region by between 2.3% and 13% over the 10 days after they became mandatory. They concluded that face masks reduced the average daily growth rate of reported infections by around 40%. A recent US report focusing on Arizona suggests the number of COVID-19 cases stabilised after the sustained implementation and enforcement of state-wide and local mitigation measures. There was an initial decrease in cases approximately two weeks after the implementation and enforcement of mask mandates and enhanced sanitation practices, followed by a further decrease in cases after the imposition of state-wide restrictions and the closure of certain services and businesses, but the effect of masks alone in this study is more difficult to separate compared to our study.[5]

A systematic review and meta-analysis examined how physical distancing, face masks and eye protection affect the spread of COVID-19, SARS, and MERS in both community and healthcare settings.[4] This work included 172 observational studies across 16 countries but did not identify any published randomised controlled trials on the effectiveness of masks. The review found that mask use (including respirator use) could result in an 85% risk protection overall, with surgical masks and well-designed cloth masks giving 67% protection. However, it should be noted that many of these studies were in health care settings; only three were from other settings and all three assessed SARS

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infection. Also, only six studies included data on COVID-19. These differences may account for the lower impact of mask wearing observed in our study.

Variation in the type and quality of masks may affect their overall effectiveness. A 12-16-layered cloth mask can protect as well as a surgical mask, but a single layered cloth mask may offer little or no protection.[4] Moreover, more recent work suggests the poor performance of some cloth masks was due to inadequate washing (masks washed daily in 60°C water and soap were protective).[23] The rapid imposition of the mask mandate in Melbourne and Mitchell Shire may have forced many people to resort to low-quality face coverings, such as scarves or bandanas, thereby reducing the effectiveness of the policy across the population.

Mask use in the community can protect by preventing outward transmission from infected people (source control) or protecting well people.[24] Normal breathing and speaking generate substantial aerosols[25], and masks can block coronaviruses being exhaled in tidal breathing.[26] The high rate of asymptomatic transmission of SARS-CoV-2 is an important rationale for community masking.[27] In the US, universal masking in a hairdressing salon prevented transmission from two infected stylists to their clients[28], providing some additional evidence for community mask use. Further, the use of masks may reduce the exposure dose of SARS-CoV-2 and result in less severe infection.[4]

Our results suggest the policy of mandatory face masks use was effective in reducing COVID-19 transmission in a community setting with restrictions already in place, accelerating the reduction of SARS-CoV-2 transmission. For the reasons outlined previously, we have probably underestimated the impact of masks in the community more broadly. Our work also indicates a high level of compliance with the Victorian Government's policy, and the rapid increase in mask use following a mandate. Face masks, whilst somewhat inconvenient for the individual user, are less likely to have unintended negative impacts on the broader community than policies restricting movement, social engagement and the operations of business, schools and childcare. During the pandemic, until an effective vaccine is widely available, the risk of recurrent local epidemics is real[29], and all available non-pharmaceutical interventions need to be used to mitigate that risk.

This is the first-time a mandatory mask policy has been shown to have an impact in a 'real-world' community setting in Australia, and is one of few examples anywhere in the world that has been able to capture the impact of such a policy. In the absence of randomised controlled trial data on the efficacy of masks to prevent COVID-19 transmission in community settings, outcomes of natural experiments such as that which occurred in Victoria are important to help guide public health policy.[30] Our work supports the use of face masks, and they should be considered in other settings in Australia and globally to reduce community transmission of SARS-CoV-2.

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Table 1: Directions issued by Victoria's Chief Health Officer in Melbourne and Mitchell Shire in July and August 2020[2]

Date:	Directions
July 8 at 11:59pm	Stage 3 restrictions introduced to all of metropolitan Melbourne and the adjoining Mitchell Shire
July 20 at 11:59pm	Government announces that the mandatory use of masks or face coverings will be introduced in public settings for metropolitan Melbourne and Mitchell Shire on the July 22 at 11.59 pm
July 22 at 11:59pm	Mandatory use of masks or face coverings in public settings for metropolitan Melbourne and Mitchell Shire
August 2	8 pm curfews and 5 km restrictions on movement for metropolitan Melbourne (excluding Mitchell Shire)
August 5 at 11:59pm	Stage 4 restrictions for metropolitan Melbourne (excluding Mitchell Shire)

Table 2: Coefficients from the linear spline model with a knot on 31st July

	Estimate	Std. Error	t value	Pr(>|t|)
Intercept	5.301	0.096	55.378	0.000
Slope estimate, pre-mask	0.042	0.007	5.858	0.000
Slope estimate, with masks	-0.023	0.017	-1.342	0.190
Change in slope, introduction of mandatory masks	-0.065	0.022	-2.953	0.006

Residual standard error: 0.239 on 29 degrees of freedom; Multiple R-squared: 0.582 Adjusted R-squared: 0.554; F-statistic: 20.21 on 2 and 29 DF, p-value: < 0.001

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Table 3. Secondary regression analyses

	Estimate	Std. Error	t value	Pr(>|t|)
Daily cases less Rural cases				
Intercept	5.330	0.099	53.669	0.000
Slope estimate, pre-mask	0.039	0.007	5.309	0.000
Slope estimate, post-masks	-0.023	0.022	-1.294	0.206
Change in slope, introduction of mandatory masks	**-0.063**	**0.0293**	**-2.601**	**0.015**
Daily cases less HCW cases				
Intercept	5.249	0.113	46.537	0.000
Slope estimate, pre-mask	0.036	0.008	4.242	0.000
Slope estimate, post-masks	-0.024	0.017	-1.184	0.246
Change in slope, introduction of mandatory masks	**-0.060**	**0.0274**	**-2.190**	**0.037**
Daily positive test ratio				
Intercept	-4.971	0.118	-41.908	0.000
Slope estimate, pre-mask	0.0534	0.009	5.975	0.000
Slope estimate, post-masks	-0.0016	0.0215	-0.0747	0.941
Change in slope, introduction of mandatory masks	**-0.055**	**0.0347**	**-1.586**	**0.124**
Daily rural cases				
Intercept	0.946	0.262	3.609	0.001
Slope estimate, pre-mask	0.117	0.020	5.930	0.000
Slope estimate, post-masks	-0.015	0.047	-0.311	0.758
Change in slope, introduction of mandatory masks	**-0.132**	**0.0637**	**-2.069**	**0.0475**
Daily HCW cases				
Intercept	2.409	0.111	21.633	0.000
Slope estimate, pre-mask	0.117	0.020	5.930	0.000
Slope estimate, post-masks	0.092	0.008	10.961	0.000
Change in slope, introduction of mandatory masks	**-0.025**	**0.027**	**-0.932**	**0.359**

Table S1. Sensitivity analysis for hinge day in the linear spline model. Estimate for the change in slope parameter for models that assume different transition dates

Day mask impact observed	**Estimate**	**Std. Error**	**t value**	**Pr(>|t|)**	**Adjusted R^2 for overall model**
30-Jul	-0.060	0.021	-2.863	0.014	0.547
31-Jul (best fitting model)	*-0.065*	*0.022*	*-2.953*	*0.006*	*0.554*
1-Aug	-0.070	0.024	-2.9629	0.007	0.552

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Figure 1: COVID-19 cases detected per day in Victoria. Observed daily cases (dots) and fitted linear spline model with a hinge day on 31st July, with shading representing upper and lower 95% confidence interval of the fitted curves. Red: analysis period for pre-masks; Blue: analysis period for post-masks.

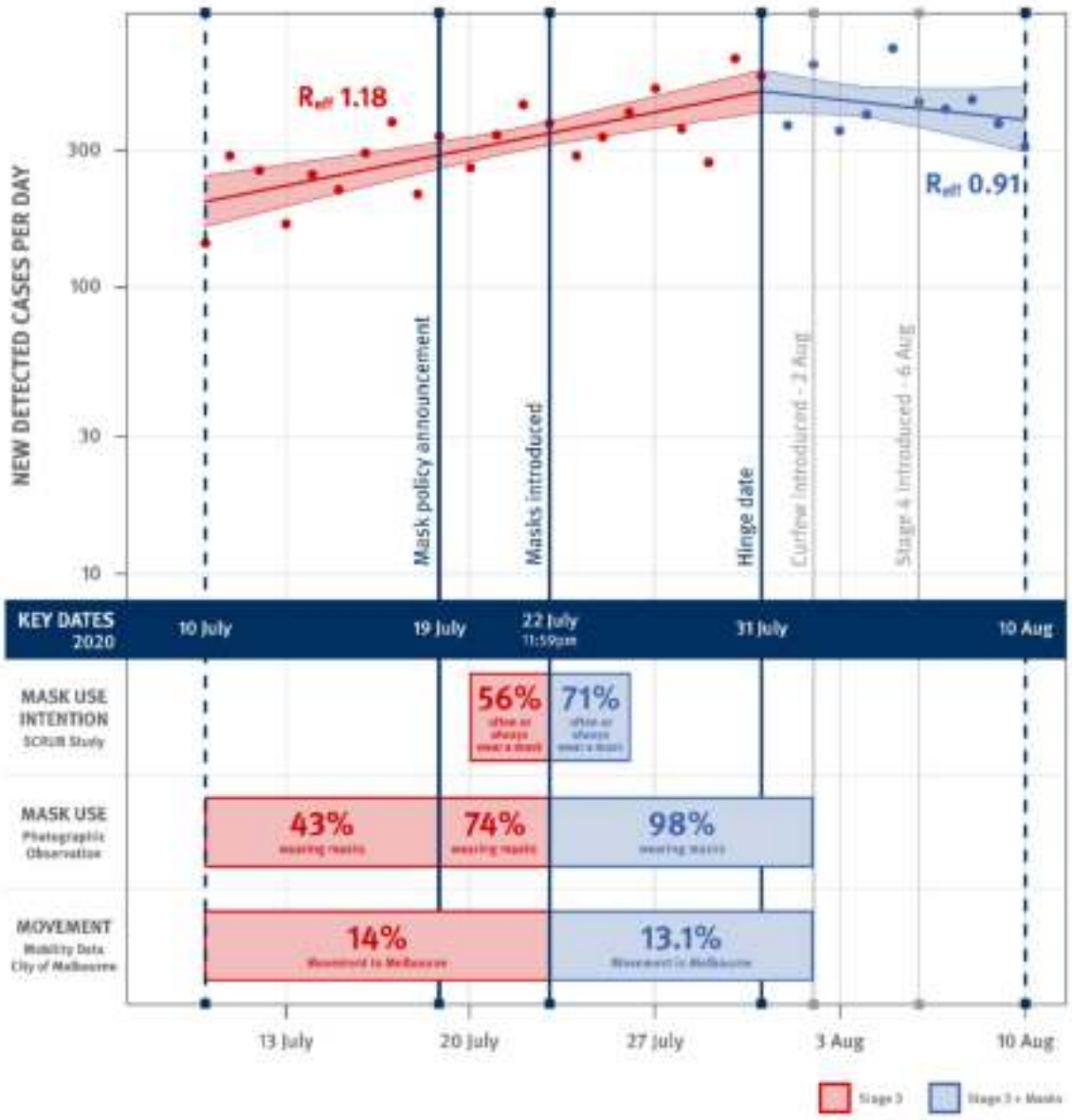

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Figure 2: results from the SCRUB survey. Left: for Wave 6 respondents (20-26 July) in Victorian Stage 4 restriction areas, reported frequency of mask use in the past 7 days. Numbers on top of bars represent total respondents. Right: the percentage of wave 6 respondents who reported always of often wearing a mask over time, Victorian Stage 4 restriction areas and compared to major cities in other states.

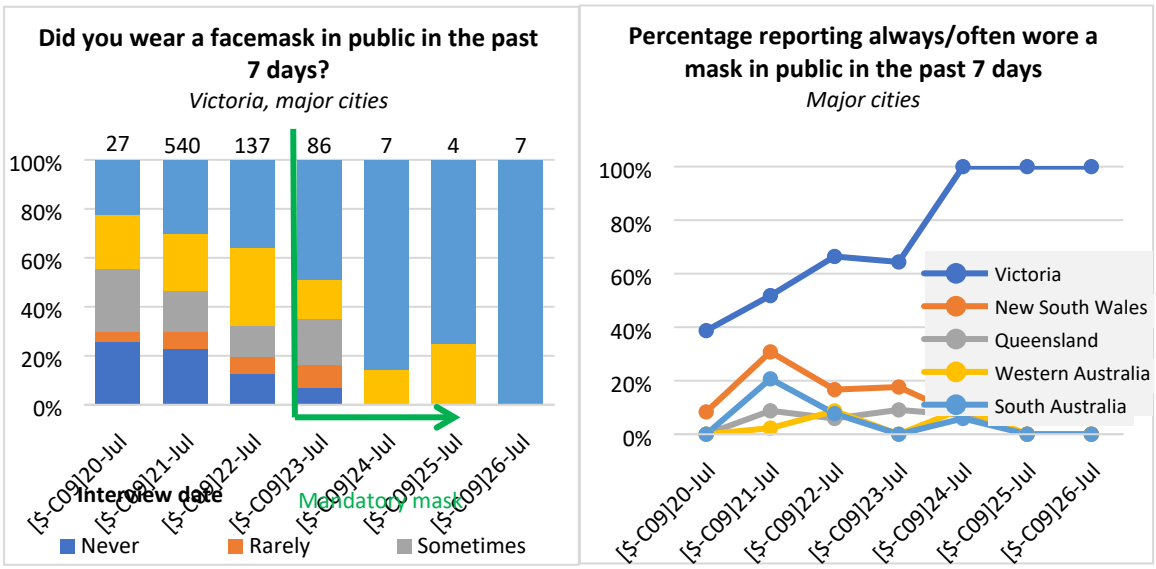

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Figure 1: COVID-19 cases detected per day in Victoria. Observed daily cases (dots) and fitted linear spline model with a hinge day on 31st July, with shading representing upper and lower 95% confidence interval of the fitted curves. Red: analysis period for pre-masks; Blue: analysis period for post-masks.

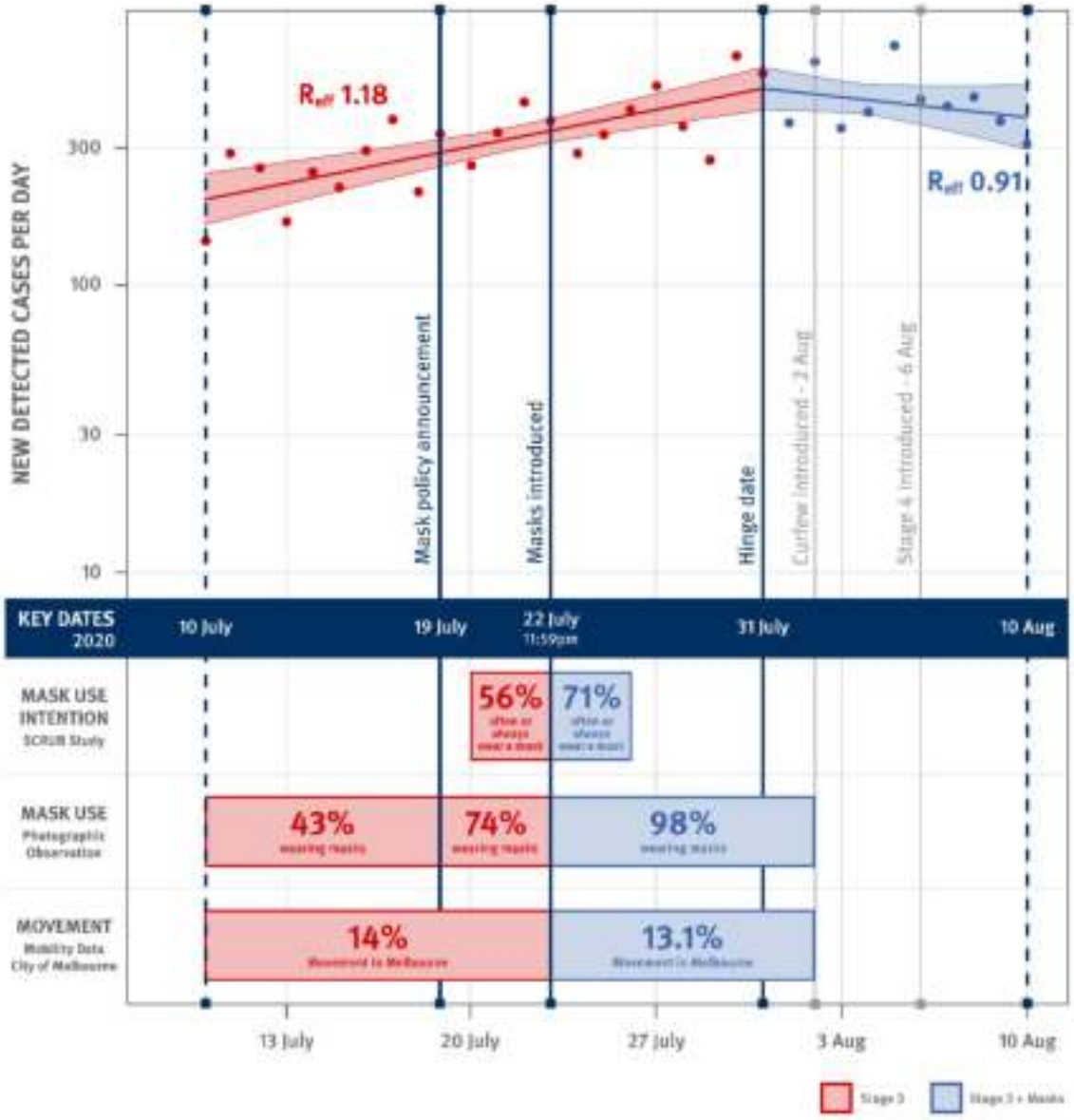

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Figure 2: results from the SCRUB survey. Left: for Wave 6 respondents (20-26 July) in Victorian Stage 4 restriction areas, reported frequency of mask use in the past 7 days. Numbers on top of bars represent total respondents. Right: the percentage of wave 6 respondents who reported always of often wearing a mask over time, Victorian Stage 4 restriction areas and compared to major cities in other states.

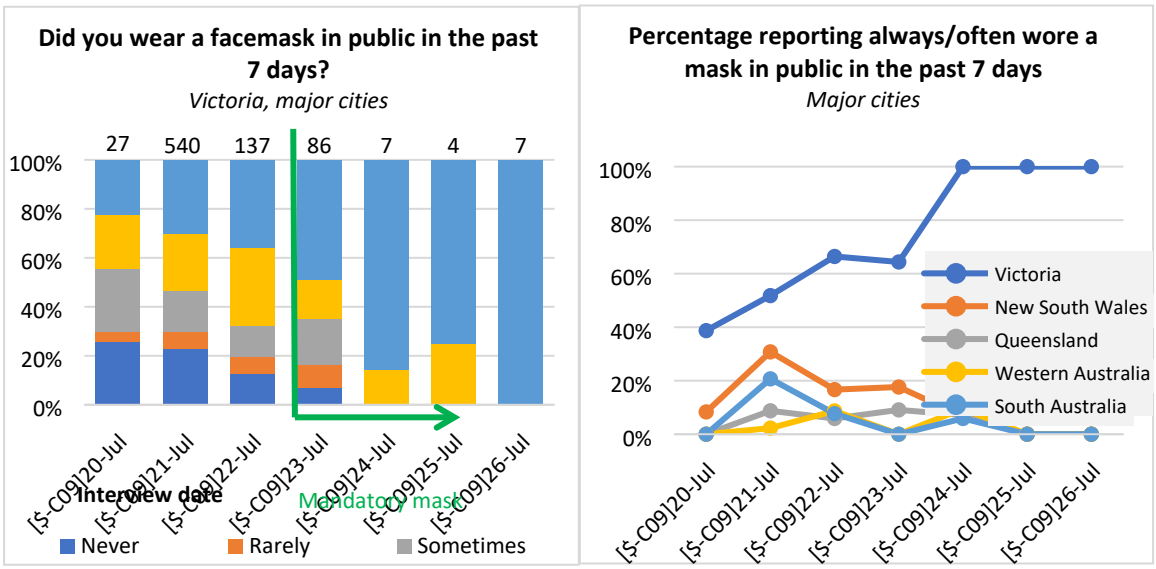

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Table 1: Directions issued by Victoria's Chief Health Officer in Melbourne and Mitchell Shire in July and August 2020[2]

Date:	Directions
July 8 at 11:59pm	Stage 3 restrictions introduced to all of metropolitan Melbourne and the adjoining Mitchell Shire
July 20 at 11:59pm	Government announces that the mandatory use of masks or face coverings will be introduced in public settings for metropolitan Melbourne and Mitchell Shire on the July 22 at 11.59 pm
July 22 at 11:59pm	Mandatory use of masks or face coverings in public settings for metropolitan Melbourne and Mitchell Shire
August 2	8 pm curfews and 5 km restrictions on movement for metropolitan Melbourne (excluding Mitchell Shire)
August 5 at 11:59pm	Stage 4 restrictions for metropolitan Melbourne (excluding Mitchell Shire)

Table 2: Coefficients from the linear spline model with a knot on 31st July

	Estimate	Std. Error	t value	Pr(>|t|)
Intercept	5.301	0.096	55.378	0.000
Slope estimate, pre-mask	0.042	0.007	5.858	0.000
Slope estimate, with masks	-0.023	0.017	-1.342	0.190
Change in slope, introduction of mandatory masks	-0.065	0.022	-2.953	0.006

Residual standard error: 0.239 on 29 degrees of freedom; Multiple R-squared: 0.582 Adjusted R-squared: 0.554; F-statistic: 20.21 on 2 and 29 DF, p-value: < 0.001

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Table 3. Secondary regression analyses

	Estimate	Std. Error	t value	Pr(>|t|)
Daily cases less Rural cases				
Intercept	5.330	0.099	53.669	0.000
Slope estimate, pre-mask	0.039	0.007	5.309	0.000
Slope estimate, post-masks	-0.023	0.022	-1.294	0.206
Change in slope, introduction of mandatory masks	**-0.063**	**0.0293**	**-2.601**	**0.015**
Daily cases less HCW cases				
Intercept	5.249	0.113	46.537	0.000
Slope estimate, pre-mask	0.036	0.008	4.242	0.000
Slope estimate, post-masks	-0.024	0.017	-1.184	0.246
Change in slope, introduction of mandatory masks	**-0.060**	**0.0274**	**-2.190**	**0.037**
Daily positive test ratio				
Intercept	-4.971	0.118	-41.908	0.000
Slope estimate, pre-mask	0.0534	0.009	5.975	0.000
Slope estimate, post-masks	-0.0016	0.0215	-0.0747	0.941
Change in slope, introduction of mandatory masks	**-0.055**	**0.0347**	**-1.586**	**0.124**
Daily rural cases				
Intercept	0.946	0.262	3.609	0.001
Slope estimate, pre-mask	0.117	0.020	5.930	0.000
Slope estimate, post-masks	-0.015	0.047	-0.311	0.758
Change in slope, introduction of mandatory masks	**-0.132**	**0.0637**	**-2.069**	**0.0475**
Daily HCW cases				
Intercept	2.409	0.111	21.633	0.000
Slope estimate, pre-mask	0.117	0.020	5.930	0.000
Slope estimate, post-masks	0.092	0.008	10.961	0.000
Change in slope, introduction of mandatory masks	**-0.025**	**0.027**	**-0.932**	**0.359**

Table S1. Sensitivity analysis for hinge day in the linear spline model. Estimate for the change in slope parameter for models that assume different transition dates

Day mask impact observed	**Estimate**	**Std. Error**	**t value**	**Pr(>|t|)**	**Adjusted R^2 for overall model**
30-Jul	-0.060	0.021	-2.863	0.014	0.547
31-Jul (best fitting model)	*-0.065*	*0.022*	*-2.953*	*0.006*	*0.554*
1-Aug	-0.070	0.024	-2.9629	0.007	0.552

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ECOLOGIC STUDIES IN EPIDEMIOLOGY: Concepts, Principles, and Methods

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KEY WORDS: epidemiologic methods, study design, sources of bias, causal inference, aggregate studies

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ABSTRACT

An ecologic study focuses on the comparison of groups, rather than individuals; thus, individual-level data are missing on the joint distribution of variables within groups. Variables in an ecologic analysis may be aggregate measures, environmental measures, or global measures. The purpose of an ecologic analysis may be to make biologic inferences about effects on individual risks or to make ecologic inferences about effects on group rates. Ecologic study designs may be classified on two dimensions: (*a*) whether the primary group is measured (exploratory vs analytic study); and (*b*) whether subjects are grouped by place (multiple-group study), by time (time-trend study), or by place and time (mixed study). Despite several practical advantages of ecologic studies, there are many methodologic problems that severely limit causal inference, including ecologic and cross-level bias, problems of confounder control, within-group misclassification, lack of adequate data, temporal ambiguity, collinearity, and migration across groups.

INTRODUCTION

An ecologic or aggregate study focuses on the comparison of groups, rather than individuals. The underlying reason for this focus is that individual-level data are missing on the joint distribution of at least two and perhaps all

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variables within each group; in this sense, an ecologic study is an incomplete design (35). Ecologic studies have been conducted by social scientists for more than a century (14a) and have been used extensively by epidemiologists in many research areas. Nevertheless, the distinction between individual-level and group-level (ecologic) studies and the inferential implications are far more complicated and subtle than they first appear. Before 1980, ecologic studies were usually presented in the first part of epidemiology textbooks as simple descriptive analyses in which disease rates are stratified by place and/or time to generate or test hypotheses; little attention was given to statistical methods or inference (e.g. 41). The purpose of this review is to provide a methodologic overview of ecologic studies that emphasizes study design and causal inference. Although ecologic studies are easily and inexpensively conducted, the results are often difficult to interpret.

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CONCEPTS AND RATIONALE

Before discussing the design and interpretation of ecologic studies, we must first define the concepts of ecologic measurement, analysis, and inference.

Levels of Measurement

The sources of data used in epidemiologic studies typically involve direct observations of individuals (e.g. age and sex), sometimes subindividual parts (e.g. intraocular pressure of each eye), and occasionally groups or regions (e.g. air pollution and social disorganization). These direct observations are then organized to measure specific variables in the study population: Individual-level variables are properties of individuals, and ecologic variables are properties of groups. To be more specific, ecologic measures may be classified into three types:

1. *Aggregate measures* are summaries (e.g. means or proportions) of observations derived from individuals in each group (e.g. the proportion of smokers or median family income).
2. *Environmental measures* are physical characteristics of the place in which members of each group live or work (e.g. air-pollution level or hours of sunlight). Note that each environmental measure has an analogue at the individual level, and these individual exposures, or doses, usually vary among members of each group, though they may remain unmeasured.
3. *Global measures* are attributes of groups or places for which there is no distinct analogue at the individual level, unlike aggregate and environmental measures (e.g. population density, level of social disorganization, or the existence of a specific law).

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Levels of Analysis

The unit of analysis is the common level for which the data on all variables are reduced and analyzed. In an *individual-level analysis*, a value for each variable is assigned to every subject in the study. It is possible, even common in environmental epidemiology, for one or more variables to be ecologic measures. For example, the average pollution level of each county might be assigned to every resident of that county.

In a *completely ecologic analysis*, all variables (exposure, disease, and covariates) are ecologic measures, so the unit of analysis is the group (e.g. region, worksite, school, demographic stratum, or time interval). Thus, within each group, we do not know the joint distribution of any combination of variables at the individual level (e.g. the frequencies of exposed cases, unexposed cases, exposed noncases, and unexposed noncases); all we know is the marginal distribution of each variable (e.g. the proportion exposed and the disease rate—the T frequencies in Figure 1).

In a *partially ecologic analysis* of three or more variables, we have additional information on certain joint distributions (the M and/or N frequencies in Figure 1 and/or rarely the L frequencies); but we still do not know the full joint distribution of all variables within each group (i.e. the ? cells in Figure 1 are missing). For example, in an ecologic study of cancer incidence by county, the joint distribution of age (a covariate) and disease status within each county (the M frequencies in Figure 1) might be obtained from the census and a population tumor registry.

Multilevel analysis is a special type of modeling technique that combines analyses conducted at two or more levels (6, 71, 72). For example, an individual-level analysis might be conducted in each group, followed by an ecologic analysis of all groups using the results from the individual-level analyses. This approach is described in a later section.

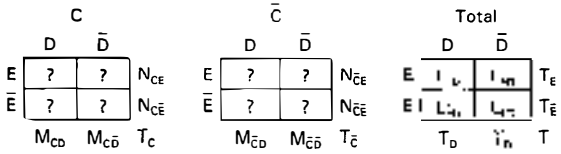

Figure 1 Joint distribution of exposure status (E vs $\bar{E}$), disease status (D vs $\bar{D}$), and covariate status (C vs $\bar{C}$) in each group of a simple ecologic analysis: T frequencies are the only data available in a completely ecologic analysis of all three variables; M frequencies require additional data on the joint distribution of C and D within each group; N frequencies require additional data on the joint distribution of E and C within each group; L frequencies require additional data on the joint distribution of E and D within each group (rarely available); and ? cells are missing in an ecologic analysis.

Levels of Inference

The underlying goal of a given epidemiologic study or analysis may be to make *biologic* (or *biobehavioral*) *inferences* about effects on individual *risks* or to make *ecologic inferences* about effects on group *rates* (45). The target level of causal inference, however, does not always match the level of analysis. For example, the purpose of an ecologic analysis may be to make a biologic inference about the effect of a specific exposure on disease risk. As we see later in this review, such *cross-level inferences* are particularly vulnerable to bias.

If the objective of a study is to estimate the *biologic effect* of wearing a motorcycle helmet on the risk of motorcycle-related mortality among motorcycle riders, the target level of causal inference is biologic. On the other hand, if the objective is to estimate the *ecologic effect* of helmet-use laws on the motorcycle-related mortality rate of riders in different states, the target level of causal inference is ecologic. Note that the magnitude of this ecologic effect depends not only on the biologic effect of helmet use but also on the degree and pattern of compliance with the law in each state. Furthermore, the validity of the ecologic-effect estimate depends on our ability to control for differences among states in the joint distribution of confounders, including individual-level variables such as age and amount of motorcycle riding.

We might also be interested in estimating the *contextual effect* of an ecologic exposure on individual risk, which is also a form of biologic inference (5, 64). If the ecologic exposure is an aggregate measure, we would generally want to separate its effect from the effect of its individual-level analogue. For example, we might estimate the contextual effect of living in a poor area on the risk of disease, controlling for individual poverty level (33). Similarly, in evaluating motorcycle-helmet laws in the U.S., we might want to estimate the contextual effect of living in a state that mandates helmet use on the risk of motorcycle-related mortality in riders, controlling for individual helmet use. Contextual effects are also relevant in infectious-disease epidemiology, where the risk of disease depends on the prevalence of the disease in others with whom the individual has contact (37, 65).

Rationale for Ecologic Studies

There are several reasons for the widespread use of ecologic studies in epidemiology, despite frequent cautions about their methodologic limitations:

1. *Low cost and convenience* Ecologic studies are inexpensive and take little time because various secondary data sources, each involving different information needed for the analysis, can easily be linked at the aggregate level. For example, data obtained from population registries, vital records,

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large surveys, and the census are often linked at the state, county, or census-tract level.

2. *Measurement limitations of individual-level studies* In environmental epidemiology and other research areas, we often cannot accurately measure relevant exposures or doses at the individual level for large numbers of subjects—at least not with available time and resources. Thus, the only practical way to measure the exposure may be ecologically (45, 46). This advantage is especially true when investigating apparent clusters of disease in small areas (66). Sometimes individual-level exposures, such as dietary factors, cannot be measured accurately because of substantial within-person variability; yet ecologic measures might accurately reflect group averages (31).
3. *Design limitations of individual-level studies* Individual-level studies may not be practical for estimating exposure effects if the exposure varies little within the study area. However, ecologic studies covering a much wider area might be able to achieve substantial variation in mean exposure across groups (e.g. 50).
4. *Interest in ecologic effects* As noted above, the stated purpose of a study may be to assess an ecologic effect, i.e. the target level of inference may be ecologic rather than biologic. Ecologic effects are particularly relevant when evaluating the impacts of population interventions such as new programs, policies, or legislation.
5. *Simplicity of analysis and presentation* In large, complex studies conducted at the individual level, it may be conceptually and statistically simpler to perform ecologic analyses and to present ecologic results than to do individual-level analyses. For example, data from large, periodic surveys, such as the National Health Interview Survey, are often analyzed ecologically by treating some combination of year, region, and demographic group as the unit of analysis.

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STUDY DESIGNS

In an ecologic study design, the planned unit of analysis is the group. Ecologic designs may be classified on two dimensions: the method of exposure measurement and the method of grouping (35, 45). Regarding the first dimension, an ecologic design is called *exploratory* if the primary exposure of potential interest is not measured, and *analytic* if the primary exposure variable is measured and included in the analysis. In practice, this dimension is a continuum, since most ecologic studies are not conducted to test a single hypothesis. Regarding the second dimension, the groups of an ecologic study may be identified by place (multiple-group design), by time (time-trend design), or by a combination of place and time (mixed design).

Multiple-Group Study

EXPLORATORY In this type of exploratory study, we compare the rate of disease among many regions during the same period. The purpose is to search for spatial patterns that might suggest an environmental etiology or more specific etiologic hypotheses. For example, the National Cancer Institute (NCI) mapped the age-adjusted cancer mortality rates in the U.S. by county for the period 1950–69 (42). For oral cancers, they found a striking difference in geographic patterns by sex: Among men, the mortality rates were greatest in the urban Northeast, but among women, the rates were greatest in the Southeast. These findings led to the hypothesis that snuff dipping, which is common among rural southern women, is a risk factor for oral cancers (2). The results of a subsequent case-control study supported this hypothesis (70).

Exploratory ecologic studies may also involve the comparison of rates between migrants and their offspring and residents of their countries of emigration and immigration (31, 41). If the rates differ appreciably between the countries of emigration and immigration, migrant studies often yield results suggesting the influence of certain types of risk factors for the disease under study. For example, if US immigrants from Japan have rates of a disease similar to US whites but much lower than Japanese residents, the difference may be due to environmental or behavioral risk factors operating during adulthood. However, the interpretation of results from these studies is often limited by differences between countries in the classification and detection of disease or cause of death.

In mapping studies, such as the NCI investigation, a simple comparison of rates across regions is often complicated by two statistical problems. First, regions with smaller numbers of observed cases show greater variability in the estimated rate; thus the most extreme rates tend to be observed for those regions with the fewest cases. Second, nearby regions tend to have more similar rates than do distant regions (i.e. autocorrelation) because unmeasured risk factors tend to cluster in space. Statistical methods for dealing with both problems have been developed by fitting the data to an autoregressive spatial model and using empirical Bayes techniques to estimate the smoothed rate for each region (9, 44, 47). The degree of spatial autocorrelation or clustering can be measured to reflect environmental effects on the rate of disease (68, 69). The empirical Bayes approach can also be applied to data from analytic multiple-group studies (described below) by including covariates in the model (e.g. 8, 12).

ANALYTIC In this type of study, we assess the ecologic association between the average exposure level or prevalence and the rate of disease among many groups. This is the most common ecologic design; typically, the unit of analysis is a geopolitical region. For example, Hatch & Susser (29) examined the

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association between background gamma radiation and the incidence of childhood cancers between 1975 and 1985 in the region surrounding a nuclear power plant. Average radiation levels for each of 69 tracts in the region were estimated from a 1976 aerial survey. The authors found positive associations between radiation level and the incidence of leukemia (an expected finding) as well as solid tumors (an unexpected finding).

Data analysis in this type of multiple-group study usually involves fitting the data to a mathematical model. For example, Prentice & Sheppard (51) proposed a linear relative rate model using iteratively reweighted least-squares procedures to estimate the model parameters. Prentice & Thomas (52) also considered an exponential relative rate model, which, they argue, may be more parsimonious than the linear-form model for specifying covariates. These methods can be applied to data aggregated by place and/or time (to be discussed below). Use of ecologic modeling to estimate exposure effects is described in the next section.

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Time-Trend Study

EXPLORATORY An exploratory time-trend or time-series study involves a comparison of the disease rates over time in one geographically defined population. In addition to providing graphical displays of temporal trends, time-series data can also be used to forecast future rates and trends. This latter application, which is more common in the social sciences than in epidemiology, usually involves fitting the outcome data to autoregressive integrated moving average (ARIMA) models (30, 48). The method of ARIMA modeling can also be extended to evaluate the impact of a population intervention (43), to estimate associations betweens two or more time-series variables (7, 48), and to estimate associations in a mixed ecologic design (60; see below).

A special type of exploratory time-trend analysis often used by epidemiologists is age-period-cohort (or cohort) analysis. Through graphical displays or formal modeling techniques, the objective of this approach is to estimate the separate effects of three time-dependent variables on the rate of disease: age, period (calendar time), and birth cohort (year of birth) (32, 35). Because of the linear dependency of these three variables, there is an inherent statistical limitation (identification problem) with the interpretation of age-period-cohort results. The problem is that each data set has alternative explanations with respect to the combination of age, period, and cohort effects; there is no unique set of effect parameters when all three variables are considered simultaneously. The only way to decide which interpretation should be accepted is to consider the findings in light of prior knowledge and, possibly, to constrain the model by ignoring one effect.

Lee et al (40) conducted an age-period-cohort analysis of melanoma mortality among white males in the U.S. between 1951 and 1975. They concluded

that the apparent increase in the melanoma mortality rate was due primarily to a cohort effect. That is, persons born in more recent years experienced throughout their lives a higher rate than did persons born earlier. In a subsequent paper, Lee (39) speculated that this cohort effect might reflect increases in sunlight exposure or sunburning during youth.

ANALYTIC In this type of time-trend study, we assess the ecologic association between change in average exposure level or prevalence and change in disease rate in one geographically defined population. As with exploratory designs, this type of assessment can be done by simple graphical displays or by time-series regression modeling (e.g. 48). With either approach, however, the interpretation of findings is often complicated by two problems. First, changes in disease classification and diagnostic criteria can produce very misleading results. Second, the latency of the disease with respect to the primary exposure may be long, variable across cases, or simply unknown. Thus, employing an arbitrary lag between observations—or an empirically defined lag that maximizes the estimated association between the two trends—can also produce misleading results (28).

Darby & Doll (13) examined the associations between average annual absorbed dose of radiation fallout from weapons testing and the incidence rate of childhood leukemia in three European countries between 1945 and 1985. Although the leukemia rate varied over time in each country, they found no convincing evidence that these changes were attributable to changes in fallout radiation.

Mixed Study

EXPLORATORY The mixed ecologic design combines the basic features of the multiple-group study and the time-trend study. Time-series (ARIMA) modeling or age-period-cohort analysis can be used to describe or predict trends in the disease rate for multiple populations. For example, to test Lee's (39) hypothesis that changes in sunlight exposure during youth can explain the observed increase in melanoma mortality in the U.S., we might conduct an age-period-cohort analysis, stratifying on region according to approximate sunlight exposure (without measuring the exposure). Assuming the amount of sunlight in the regions has not changed differentially over the study period, we might expect the cohort effect described above to be stronger for sunnier regions.

ANALYTIC In this type of mixed ecologic design, we assess the association between change in average exposure level or prevalence and change in disease rate among many groups. Thus the interpretation of estimated effects is en-

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hanced because two types of comparisons are made simultaneously: change over time within groups and differences among groups. For example, Crawford et al (11) evaluated the hypothesis that hard drinking water (i.e. water with a high concentration of calcium and magnesium) is a protective risk factor for cardiovascular disease (CVD) mortality. They compared the absolute change in CVD mortality rate between 1948 and 1964 in 83 British towns, by water-hardness change, age, and sex. In all sex-age groups, especially for men, the authors found an inverse association between water-hardness change and CVD mortality. In middle-aged men, for example, the increase in CVD mortality was less in towns that made their water harder than in towns that made their water softer.

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EFFECT ESTIMATION

A major quantitative objective of most epidemiologic studies is to estimate the effect of one or more exposures on disease occurrence in a well-defined population at risk. A measure of effect in this context is not just any measure of association, such as a correlation coefficient; rather, it reflects a particular causal parameter, i.e. a counterfactual contrast in disease occurrence (21, 24, 27, 46, 58). In studies conducted at the individual level, effects are usually estimated by comparing the rate or risk of disease, in the form of a ratio or difference, for exposed and unexposed populations. In multiple-group ecologic studies, however, we cannot estimate effects directly in this way because of the missing information on the joint distribution within groups. Instead, we regress the group-specific disease rates (Y) on the group-specific exposure prevalences (X). For example, fitting the data to a linear model produces the following prediction equation: $\hat{Y} = B_0 + B_1X$, where B_0 and B_1 are the estimated intercept and slope, using ordinary least-squares methods. The estimated biologic effect of the exposure (at the individual level) can be derived from the regression results (1, 19). The predicted disease rate ($\hat{Y}$) in a group that is entirely exposed is $B_0 + B_1(1) = B_0 + B_1$, and the predicted rate in a group that is entirely unexposed is $B_0 + B_1(0) = B_0$. Therefore, the estimated rate difference is B_1 and the estimated rate ratio is $1 + B_1/B_0$. Note that this ecologic method of effect estimation requires rate predictions be extrapolated to both extreme values of the exposure variable (i.e. $X = 0$ and 1), which are likely to lie well beyond the observed range of the data. It is not surprising, therefore, that different model forms (e.g. log-linear vs linear) can lead to very different estimates of effect (22). Fitting a linear model, in fact, may lead to negative, and thus meaningless, estimates of the rate ratio.

As an illustration of rate-ratio estimation in an ecologic study, consider Durkheim's (16) examination of religion and suicide in four groups of Prussian provinces between 1883 and 1890 (see Figure 2). The groups were formed by

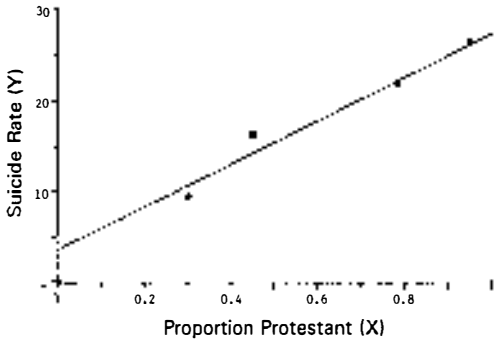

Figure 2 Suicide rate (Y, per 10^5/year) by proportion Protestant (X) for four groups of Prussian provinces, 1883–90. The four observed points (X, Y) are (0.30, 9.56), (0.45, 16.36), (0.785, 22.00), and (0.95, 26.46); the fitted line is based on unweighted least-squares regression [Source: Adapted from Durkheim (16)].

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ranking 13 provinces according to the proportion (X) of the population that was Protestant. Using ordinary least-squares linear regression, we estimate the suicide rate ($\hat{Y}$, per 10^5/year) in each group to be $3.66 + 24.0(X)$. Therefore, the estimated rate ratio, comparing Protestants with other religions, is $1 + (24.0/3.66) = 7.6$. Note in Figure 2 that the fit of the linear model is excellent ($R^2 = 0.97$).

There are two methods used to control for confounders in multiple-group ecologic analyses. The first is to treat ecologic measures of the confounders as covariates ($\mathbf{Z}$) in the model, e.g. percent male and percent white in each group. If the individual-level effects of the exposure and covariates are additive (i.e. if the disease rates follow a linear model), then the ecologic regression of Y on X and $\mathbf{Z}$ will also be linear with the same coefficients (22, 38). That is, the estimated coefficient for the exposure variable can be interpreted as the rate difference adjusted for other covariates, analogously to the crude estimate discussed above.

The second method used to control for confounders in ecologic analyses is rate standardization for these confounders (57), followed by regression of the standardized rates as the outcome variable. Note that this method requires additional data on the joint distribution of the covariate and disease within each group (i.e. the M frequencies in Figure 1). Nevertheless, it cannot be expected to reduce bias unless all predictors in the model (X and $\mathbf{Z}$) are mutually standardized for the same confounders (22, 25, 56). Standardization of the exposure prevalences, for example, requires data on the joint distribution of the covariate and exposure within groups (i.e. the N frequencies in Figure 1); however, this information is not often available in ecologic studies.

As in individual-level analyses, product terms (e.g. XZ) are often used in ecologic analyses to model interaction effects, i.e. to assess effect modification. In ecologic analyses, however, the product of X and Z (both group averages) is not, in general, equal to the average product of the exposure (x) and covariate (z) at the individual level within groups. Assuming a linear model, XZ will be equal to the mean xz in each group only if x and z are uncorrelated within groups (22). Thus, as pointed out in the next section, interaction (nonadditive) effects at the individual level complicate the interpretation of ecologic results.

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METHODOLOGIC PROBLEMS

Despite the many practical advantages of ecologic studies mentioned previously, there are several methodologic problems that may severely limit causal inference, especially biologic inference.

Ecologic Bias

The major limitation of ecologic analysis for making causal inferences is ecologic bias, which is the failure of expected ecologic effect estimates to reflect the biologic effect at the individual level (18, 19, 25, 45, 54). In addition to the usual sources of bias that threaten individual-level analyses (35, 57), the underlying problem of ecologic analyses for estimating biologic effects is heterogeneity of exposure level and/or covariate levels within groups; as noted earlier, this heterogeneity is not fully captured with ecologic data because of missing information on joint distributions (see Figure 1). Robinson (55) was the first to describe mathematically how ecologic associations could differ from the corresponding associations at the individual level within groups of the same population. He expressed this relationship in terms of correlation coefficients; this relationship was later extended by Duncan et al (15) to regression coefficients in a linear model. The phenomenon became widely known as the *ecologic(al) fallacy* (61), and the magnitude of the ecologic bias may be severe in practice (10, 17, 54, 62, 63).

As an illustration of ecologic bias, consider again Durkheim's data on religion and suicide (Figure 2). The estimated rate ratio of 7.6 in the ecologic analysis may not mean that the suicide rate was nearly eight times greater in Protestants than in non-Protestants. Rather, since none of the regions were entirely Protestant or non-Protestant, it may have been non-Protestants (primarily Catholics) who were committing suicide in predominantly Protestant provinces. It is certainly plausible that members of a religious minority might have been more likely to take their own lives than were members of the majority. The implication of this alternative explanation is that living in a predominantly Protestant area has a contextual effect on suicide risk among

non-Protestants, i.e. there is an interaction effect at the individual level between religion and religious composition of one's area of residence.

Interestingly, Durkheim (16) compared the suicide rates (at the individual level) for Protestants, Catholics, and Jews living in Prussia. From his data, we find that the rate was about twice as high in Protestants as in other religious groups. Thus, there appears to be substantial ecologic bias (i.e. comparing rate-ratio estimates of about 2 vs 8). Durkheim, however, failed to notice this quantitative difference because he did not actually estimate the magnitude of the effect in either analysis.

Greenland & Morgenstern (25) showed that ecologic bias can arise from three sources when using simple linear regression to estimate the crude exposure effect: The first may operate in any type of study; the latter two are unique to ecologic studies (i.e. *cross-level bias*), but are defined in terms of individual-level associations.

1. *Within-group bias* The exposure effect within groups may be biased by confounding, selection methods, or misclassification (35, 57). Thus, for example, if there is positive net bias in every group, we would expect the ecologic estimate to be biased as well.
2. *Confounding by group* Ecologic bias may result if the background rate of disease in the unexposed population varies across groups, specifically if there is a nonzero ecologic (linear) correlation between mean exposure level and the background rate.
3. *Effect modification by group* Ecologic bias may also result if the rate difference for the exposure effect at the individual level varies across groups.

Confounding and effect modification by group (the sources of cross-level bias) can arise in three ways: (*a*) Extraneous risk factors (confounders or modifiers) are differentially distributed across groups; (*b*) the ecologic exposure variable has an effect on risk separate from the effect of its corresponding individual-level analogue, e.g. living in a predominantly Protestant area vs being Protestant (in the suicide example); or (*c*) disease risk depends on the prevalence of that disease in other members of the group, which is true of many infectious diseases (37).

Unfortunately, those conditions that produce ecologic bias cannot be observed in ecologic data. Furthermore, the fit of the ecologic regression model, in general, gives no indication of the presence, direction, or magnitude of ecologic bias. Thus, a model with excellent fit may yield substantial bias (e.g. Figure 2), and one model with a better fit than another model may yield more bias.

A potential strategy for reducing ecologic bias is to use smaller units in an ecologic study (e.g. counties instead of states) in order to make the groups

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more homogeneous with respect to the exposure. On the other hand, this strategy might not be feasible because of the lack of available data aggregated at the same level, and it might lead to two other problems: greater migration between groups (see below) and less precise estimation of disease rates (45, 67).

Problems of Confounder Control

As already indicated, covariates are included in ecologic analyses to control for confounding, but the conditions for a covariate being a confounder are different at the ecologic and individual levels (25, 26). At the individual level, a risk factor must be associated with the exposure to be a confounder. In a multiple-group ecologic study, in contrast, a risk factor may produce ecologic bias (i.e. it may be an ecologic confounder) even if it is unassociated with the exposure in every group, especially if the risk factor is ecologically associated with the exposure across groups (22, 25). Conversely, a risk factor that is a confounder within groups may not produce ecologic bias if it is ecologically unassociated with the exposure across groups.

Control for confounders is more problematic in ecologic analyses than in individual-level analyses (22, 25, 26). Even when all variables are accurately measured for all groups, adjustment for extraneous risk factors may not reduce the ecologic bias produced by these risk factors. In fact, it is possible for such ecologic adjustment to increase bias. It follows from the principles presented in the previous section (25) that there will be no ecologic bias in a multiple-linear-regression analysis if the following conditions are met:

1. There is no residual within-group bias in exposure effect in any group because of confounding by unmeasured risk factors, selection methods, or misclassification.
2. There is no ecologic correlation between the mean value of each predictor and the background rate of disease in the joint reference (unexposed) level of all predictors.
3. The rate difference for each predictor is uniform across levels of the other predictors within groups (i.e. the effects are additive), and each rate difference is uniform across groups (i.e. group does not modify the effect of each predictor at the individual level).

These conditions are sufficient, but not necessary, for the ecologic estimate to be unbiased, i.e. there might be little or no bias even if none of these conditions are met. On the other hand, minor deviations from these conditions can produce substantial ecologic bias (22). Since the sufficient conditions for no ecologic bias cannot be checked with ecologic data alone, the unpredictable and potentially severe nature of such bias makes biologic inference from ecologic analyses particularly problematic. Prentice & Sheppard (51) have

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suggested that ecologic data be supplemented with individual-level data from each group (or a representative sample) to enhance biologic inference.

Lack of additivity at the individual level (see #3 above) is common in epidemiology, but unmeasured modifiers do not bias results at the individual level if they are unrelated to the exposure (21). Furthermore, interactions may be handled readily at the individual level by including product terms as predictors in the model (e.g. xz). In ecologic analyses, however, lack of additivity within groups is a source of ecologic bias, and this bias cannot be eliminated or reduced by the inclusion of product terms (e.g. XZ) unless the effects are exactly multiplicative and the two variables are uncorrelated within groups (53).

Another source of ecologic bias is misspecification of confounders (26). Although this problem can also arise in individual-level analyses, it is more difficult to avoid in ecologic analyses because the relevant confounder may be the distribution of covariate histories for all individuals within each group. In ecologic studies, therefore, adjustment for covariates derived from available data (e.g. proportion of current smokers) may be inadequate to control confounding. It is preferable, whenever possible, to control for more than a single summary measure of the covariate distribution (e.g. the proportions of the group in each of several smoking categories). In addition, since it is usually necessary to control for several confounders (among which the effects may not be linear and additive), the best approach for reducing ecologic bias is to include covariates for categories of their joint distribution within regions. For example, to control ecologically for race and sex, the investigator might adjust for the proportions of white women, nonwhite men, and nonwhite women (treating white men as the referent), rather than the conventional approach of adjusting for the proportions of men (or women) and whites (or nonwhites).

Within-Group Misclassification

The principles of misclassification bias with which epidemiologists are familiar when interpreting the results of analyses conducted at the individual level do not apply to ecologic analyses. At the individual level, for example, nondifferential misclassification of exposure nearly always leads to bias toward the null. In multiple-group ecologic studies, however, this principle does not hold when the exposure variable is an aggregate measure. Brenner et al (4) have shown that nondifferential misclassification of a binary exposure within groups usually leads to bias away from the null and that the bias may be severe. Greenland & Brenner (23) have provided a simple method to correct for nondifferential misclassification of exposure or disease in ecologic analyses, based on estimates of sensitivity and specificity.

In studies conducted at the individual level, misclassification of a covariate, if nondifferential with respect to both exposure and disease, will usually reduce

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our ability to control for that confounder (20, 59). That is, adjustment will not completely eliminate the bias due to the confounder. In ecologic studies, however, nondifferential misclassification of a binary confounder within groups does not affect our ability to control for that confounder, provided there is no cross-level bias (3).

If all but one variable (e.g. the exposure or a covariate) in a given analysis is measured at the individual level, this partially ecologic analysis may also be regarded as nonecologic with the ecologic variable misclassified. Thus, the resulting bias may be understood in terms of misclassification bias operating at the individual level.

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Other Problems

LACK OF ADEQUATE DATA Certain types of data, such as medical histories, may not be available in aggregate form; or available data may be too crude, incomplete, or unreliable, such as sales data for measuring behaviors (45, 67). In addition, secondary sources of data from different administrative areas or from different periods may not be comparable. For example, disease rates may vary across countries because of differences in disease classification or case detection. Furthermore, since many ecologic analyses are based on mortality rather than incidence data, causal inference is further limited (35).

TEMPORAL AMBIGUITY In a well-designed cohort study of disease incidence, we can usually be confident that disease occurrence did not precede the exposure. In ecologic studies, however, use of incidence data provides no such assurance against this temporal ambiguity (45). The problem is most troublesome when the disease can influence exposure status in individuals or when the disease rate can influence the mean exposure in groups (through the impact of population interventions designed to change exposure levels in areas with high disease rates).

The problem of temporal ambiguity in ecologic studies (especially time-trend studies) is further complicated by an unknown or variable latent period between exposure and disease occurrence (28, 67). The investigator can only attempt to deal with this problem in the analysis by examining associations for which there is a specified lag between observations of average exposure and disease rate. Unfortunately, there may be little prior information about latency on which to base the lag, or appropriate data may not be available to accommodate the desired lag.

COLLINEARITY Another problem with ecologic analyses is that certain predictors, such as sociodemographic and environmental factors, tend to be more highly correlated with each other than they are at the individual level (10, 62).

The implication of such collinearities is that it is very difficult to separate the effects of these variables statistically; analyses yield model coefficients with very large variances, so effect estimates may be severely distorted. In general, collinearity is most problematic in multiple-group ecologic analyses involving a small number of large, heterogeneous regions (15, 64).

MIGRATION ACROSS GROUPS Migration of individuals into or out of the source population can produce selection bias in a study conducted at the individual level because migrants and nonmigrants may differ on both exposure prevalence and disease risk. Although it is clear that migration can also cause ecologic bias (36, 49), little is known about the magnitude of this bias or how it can be reduced in ecologic studies (46).

CONTEXTUAL AND MULTILEVEL ANALYSES

Knowing the severe methodologic limitations of ecologic analysis for making biologic inferences, many epidemiologists who report ecologic results argue that there can be no cross-level bias because their primary objective is to estimate an ecologic effect. For example, we might want to estimate the ecologic effect (effectiveness) of state laws requiring smoke detectors by comparing the fire-related mortality rate in those states with the law vs other states without the law (45). Although this is a reasonable objective, the interpretation of observed ecologic effects is complicated by two issues:

First, biologic inference may be implicit to the objectives of an ecologic study unless the underlying biologic and contextual effects are already known from previous research. Can smoke detectors placed appropriately in homes reduce the risk of fire-related mortality in those homes by providing an early warning of smoke? Does living in an area where most homes are properly equipped with smoke detectors reduce the risk of fire-related mortality in homes with and without smoke detectors? The first question refers to a possible biologic (biobehavioral) effect; the second question refers to a possible contextual effect. Even if these effects exist, the ecologic effect of smoke-detector laws also depends on other factors, e.g. the level of enforcement, the quality of smoke-detector design and construction, the cost and availability of smoke detectors, and their proper placement, installation, operation, and maintenance. In an ecologic study without additional information, the ecologic effect is completely confounded with biologic and contextual effects.

The second complicating issue in interpreting observed ecologic effects is the need to control for confounders measured at the individual level. Even if the exposure is a global measure, such as a law, groups are seldom completely homogeneous or comparable with respect to confounders. To make a valid comparison between states with and without smoke-detector laws, for example,

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we would need to control for differences among states in the joint distribution of extraneous risk factors, such as socioeconomic status of residents, firefighter availability and access, building design, and construction (see also *Problems of Confounder Control*).

Perhaps the best solution to these problems is to incorporate both individual-level and ecologic measures in the same analysis. This approach might include different measures of the same factor; e.g. each subject would be characterized by his/her own exposure level as well as the average exposure level for all members of the group to which s/he belongs (aggregate measure). Not only would this approach help to clarify the sources and magnitude of ecologic and cross-level bias, but it would also allow us to separate biologic, contextual, and ecologic effects. It is especially appropriate in social epidemiology, infectious-disease epidemiology, and the evaluation of population interventions.

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There are two statistical methods for including both individual-level and ecologic measures in the same analysis. The first method, often called *contextual analysis* in the social sciences, is a simple extension of conventional modeling such as multiple linear regression or logistic regression (5, 34). The model, which is fit to the data at the individual level, includes both individual-level and ecologic predictors. For example, suppose we wanted to estimate the effect of "herd immunity" on the risk of an infectious disease. The risk (y) of disease might be modeled as a function of the following linear component: $b_0 + b_1x + b_2\bar{x} + b_3x\bar{x}$, where x is the individual's immunity status and $\bar{x}$ is the prevalence of immunity in the group to which that individual belongs (65). Therefore, b_2 represents the contextual effect of herd immunity, and b_3 represents the interaction effect, which allows the herd-immunity effect to depend on the individual's immune status. The interaction term is needed in this application, since we would expect no herd-immunity effect among immune individuals. Note, however, that the interpretation of the interaction effect depends on the form of the model (35, 57).

An important limitation of contextual analysis is that observations for individuals within groups are not likely to be independent, which is a basic assumption of conventional modeling. If there are contextual effects, then the outcomes for individuals in the same group are more likely to resemble each other than are the outcomes for individuals in different groups. To handle this problem of within-group clustering, we treat the sampling of individuals from groups as random effects; this approach is called *multilevel modeling, hierarchical regression,* or *random-effects modeling* (6, 71, 72).

Multilevel modeling is a powerful technique with many applications; it can be used to estimate contextual and ecologic effects and to derive improved (empirical Bayes) estimates of biologic effects. At the first level of analysis, we might predict individual risk or health status within each group as a function

of several individual-level variables. At the second (ecologic) level, we predict the estimated regression parameters (e.g. the intercept and slopes) from the first level as a function of several ecologic variables. For example, Humphreys & Carr-Hill (33) used multilevel modeling to estimate the contextual effect of living in a poor area on several health outcomes, controlling for the individual's income and other covariates. In a conventional ecologic analysis, the effects of living in a poor area and income would be confounded, and ecologic estimates of effect would be susceptible to cross-level bias.

CONCLUSIONS

Several practical advantages make ecologic studies especially appealing for undertaking various types of epidemiologic research. Despite these advantages, however, ecologic analysis poses major problems of interpretation when making ecologic inferences and especially when making biologic inferences (due to ecologic bias, etc). From a methodologic perspective, it is best to have individual-level data on as many relevant nonglobal measures as possible. Just because the exposure variable is measured ecologically, for example, does not mean that other variables should be as well.

Even when the stated purpose of the study is to estimate an ecologic effect, biologic inference is usually implicit in epidemiology. Thus, to address the underlying research questions, we typically would want to estimate and/or control for biologic and contextual effects, preferably using multilevel analysis. In contemporary epidemiology, the "ecologic fallacy" reflects the failure of the investigator to recognize the need for biologic inference and thus for individual-level data.

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THE ECOLOGICAL FALLACY

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The purpose of this paper is to emphasize for epidemiologists the possibility of serious errors resulting from inferences based on ecological analyses. Variables that describe groups of individuals, rather than the individuals themselves, are termed "ecological" and are often used when the analysis of individuals' data is not possible (1). Ecological analyses may be preferred when 1) variables are more conveniently defined or measured on groups because the analysis on individuals would require excessive time or extensive data gathering; 2) ecological analyses permit study of a wider range of values for the independent variable, as in international studies of diet; 3) the precision of aggregate measures like alcohol consumption is likely to be higher for groups than for individuals; and 4) population responses such as smoking quit rates may be of primary interest. Frequently, more than one reason applies. For example, some of the evidence favoring environmental and dietary causes of cancer comes from the comparison of incidence or mortality rates with average levels of risk factors measured on culturally or geographically defined groups of individuals. The first three reasons are relevant to this type of study.

We assume in this paper that measurements on individuals are not available, as in the diet and cancer example, since when this information is known, it might be used in place of, or to correct for biases in, the ecological analysis. Serious errors can result when an investigator makes the seemingly natural assumption that the inferences from an ecological analysis must pertain either to the individuals within the groups or to individuals across groups. A frequently cited early example of an ecological inference was Durkheim's study of the correlation between suicide rates and religious denominations in Prussia (2) in which the suicide rate was observed to be correlated with the number of Protestants. However, it could as well have been the Catholics who were committing suicide in largely Protestant provinces. The potential falsity of ecological inferences, at least in the case of simple correlations, was pointed out by Robinson (3), who gave it the name "ecological fallacy" and provided the mathematical relation, without proof, between the ecological correlation and the individual correlation across all groups. Duncan et al. (4) have extended the equations to include simple linear regression coefficients. The dangers of inferences about individuals from ecological studies have been emphasized by some investigators (5–7), while others (8–11) have sought to minimize the concern over the possible biases in ecological analyses, proposing alternatives or delineating circumstances in which ecological inferences are justified (e.g., certain linear regression models when data on individuals are available). Firebaugh (11) gives a particularly thorough discussion and list of references related to this aspect of the problem.

Although there has been a persistent interest in the problems associated with ecological analyses in the social science literature, the impression seems to remain, even among seasoned epidemiologists, that ecological analyses may not have large biases,

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at least in certain cases. Such impressions result, in part, from the nonintuitive sound of serious disparity between group level and individual level statistics. Our goal is to provide convincing evidence, intuitively, mathematically, and empirically, of the possibility of important bias in ecological analyses and to clarify some recent work on this topic. We present a hypothetical example of the ecological fallacy and a simple derivation of the relation between the individual correlation and the ecological correlation. We extend this derivation to outline the relation between the individual regression slope and the ecological regression slope. In addition, theoretical observations are supported by an ecological analysis of correlations and regression coefficients for a set of real data, using variables often encountered in epidemiologic practice.

Hypothetical example

The ecological fallacy is illustrated in a simple case by considering the hypothetical data in table 1. Although these data are contrived, they are useful since the relevant correlations are evident by inspection or simple calculation. Here, N individuals are classified into r groups of equal size $n_i = k$. A variable, X, is assigned to each individual and has the values of the consecutive integers from $k(i-1)+1$ to ki in the ith group. Within each group, the values of a second variable, Y, are chosen to be the descending consecutive integers from ki to $k(i-1)+1$ in the ith group (i.e., the reverse order of the X's). These data have the following characteristics. The overall means of X and Y, $\bar{X}$ and $\bar{Y}$, are equal, as are the within-group means, $\bar{X}_i$ and $\bar{Y}_i$. Similarly, the overall variances are equal, as are the within-group variances. The within-group correlation coefficient, ρ_i, equals -1 for all i, but since the group means for X and Y are identical, the between-group or ecological correlation, ρ_e, equals 1. It is easily shown (see Appendix 1), however, that for these data, the overall correlation between X and Y, ignoring groups, is

$$\rho = \frac{N^2 + 1 - 2k^2}{N^2 - 1}.$$

Thus, $\rho = \rho_i$ only when $k = N$ (i.e., a single group), and $\rho = \rho_e$ when $k = 1$ or as $N \to \infty$ and $k \ll \infty$. In instances like this, however, in which there is an appreciable group effect (i.e., the expected value of Y given X, $E(Y \mid X)$, is not the same in all groups), the correlation of interest is neither ρ nor ρ_e but the average within-group correlation, ρ_a, (defined later), which in the present example equals -1 since all ρ_i are the same. For this example, the value of ρ always exceeds 0.5, 0.92, and 0.98, respectively, for two, five, and 10 groups, whatever the number of subjects in each group. Furthermore, since the overall and within-group variances for X and Y are equal, the linear model

$$Y = \alpha + \beta X$$

and its ecological counterpart

$$\bar{Y}_i = \alpha_e + \beta_e \bar{X}_i$$

would give estimates $\hat{\beta} = \rho$ and $\hat{\beta}_e = \rho_e$. This simple example demonstrates maximal disparity between the ecological correlation or the ecological regression slope, and the corresponding overall or within-group estimates.

TABLE 1

Hypothetical data illustrating the ecological fallacy

X	Y	Group
1	k	1
2	$k-1$	1
3	$k-2$	1
.	.	.
.	.	.
.	.	.
k	1	1
$k+1$	$2k$	2
$k+2$	$2k-1$	2
$k+3$	$2k-2$	2
.	.	.
.	.	.
.	.	.
N	$N-k+1$	N/k

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Derivation of general relations

To understand the source of the ecological fallacy in the general case, consider N individuals classified into r groups of size n_i, where $i = 1, 2, \ldots, r$, and a single covariate, X, linearly related to a response Y for each individual. The relation between ecological analyses and other analyses based on individuals can be seen by appropriate partitions of the total sums of squares and cross-products. Define

$$X_{\cdot\cdot} = \sum_{i=1}^{r} \sum_{j=1}^{n_i} X_{ij} = N\bar{X}_{\cdot},$$

and an analogous definition for Y. For notational convenience, sums of squares and cross-products are denoted by T (total), W (within groups), or E (ecological or between groups), with subscripts indicating the variables involved. Thus, in the usual analysis of covariance (12) (table 2), T_{xx} is the total sum of squares of X, W_{xy} is the within-groups sum of cross-products of X and Y, and E_{yy} is the between-groups sum of squares of Y. The total sum of cross-products about the mean across all individuals may be partitioned into within-group and between-group components as follows:

$$T_{xy} = \sum_{i=1}^{r} \sum_{j=1}^{n_i} (X_{ij} - \bar{X}_{\cdot})(Y_{ij} - \bar{Y}_{\cdot}) = W_{xy} + E_{xy},$$

where

$$W_{xy} = \sum_{i=1}^{r} \sum_{j=1}^{n_i} (X_{ij} - \bar{X}_{i})(Y_{ij} - \bar{Y}_{i}),$$

and

$$E_{xy} = \sum_{i=1}^{r} n_i(\bar{X}_{i} - \bar{X}_{\cdot})(\bar{Y}_{i} - \bar{Y}_{\cdot}).$$

The corresponding formulas for the sum of squares of X (or Y) are obtained by replacing Y with X (or X with Y) in these equations. The between-group or ecological sums of squares and cross-products are weighted by the number of individuals in each group. The correlation coefficient between X and Y, ignoring groups, is

$$\rho = \frac{T_{xy}}{\{T_{xx}T_{yy}\}^{1/2}} = \frac{E_{xy}}{\{T_{xx}T_{yy}\}^{1/2}} + \frac{W_{xy}}{\{T_{xx}T_{yy}\}^{1/2}}. \quad (1)$$

Rewriting equation 1 as

$$\rho = \frac{\{E_{xx}E_{yy}\}^{1/2}}{\{T_{xx}T_{yy}\}^{1/2}} \cdot \frac{E_{xy}}{\{E_{xx}E_{yy}\}^{1/2}} + \frac{\{W_{xx}W_{yy}\}^{1/2}}{\{T_{xx}T_{yy}\}^{1/2}} \cdot \frac{W_{xy}}{\{W_{xx}W_{yy}\}^{1/2}}, \quad (2)$$

we may now define the *ecological correlation*

$$\rho_e = \frac{E_{xy}}{\{E_{xx}E_{yy}\}^{1/2}},$$

and the *average within-group correlation*

$$\rho_w = \frac{W_{xy}}{\{W_{xx}W_{yy}\}^{1/2}};$$

so that

$$\rho = \left\{\frac{E_{xx}E_{yy}}{T_{xx}T_{yy}}\right\}^{1/2} \rho_e + \left\{\frac{W_{xx}W_{yy}}{T_{xx}T_{yy}}\right\}^{1/2} \rho_w. \quad (3)$$

Note that ρ_w is not influenced by group effects. Some additional definitions will show that this last result is equivalent to that given originally by Robinson (3). Details are given in Appendix 2.

In an analogous fashion, we may define

TABLE 2

A general analysis of covariance

Source	df	Sum of squares and products		
		Σx^2	Σxy	Σy^2
Between groups	$r - 1$	E_{xx}	E_{xy}	E_{yy}
Within groups	$\Sigma n_i - r$	W_{xx}	W_{xy}	W_{yy}
Total	$\Sigma n_i - 1$	T_{xx}	T_{xy}	T_{yy}

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the regression coefficients

$$\beta = \frac{T_{xy}}{T_{xx}},$$

$$\beta_e = \frac{E_{xy}}{E_{xx}},$$

and

$$\beta_w = \frac{W_{xy}}{W_{xx}},$$

and show that

$$\beta = \frac{E_{xx}}{T_{xx}}\beta_e + \frac{W_{xx}}{T_{xx}}\beta_w, \qquad (4)$$

where β, β_e, and β_w are the overall regression slope, *ecological regression* slope, and the *average within-group regression* slope, respectively. This can be written

$$\beta_e = \frac{T_{xx}}{E_{xx}}\beta - \left\{\frac{T_{xx}}{E_{xx}} - 1\right\}\beta_w$$

$$= \beta_w + \frac{T_{xx}}{E_{xx}}(\beta - \beta_w), \qquad (5)$$

with the first equality being the relation given by Duncan et al. (4).

Analysis of General Relations

In the absence of group effects, the regression coefficient of interest is β_e, whereas when group effects are present, β_w is a more appropriate description of the data. In fact, when group effects are absent, $\beta = \beta_w$, so that β_w is always the regression coefficient of interest. The ecological fallacy consists of incorrectly assuming that, when group effects are present, $\beta_e = \beta_w$.

We can see immediately from equation 4 that the coefficients of β_e and β_w sum to 1, so that β is always a weighted average of the ecological and within-group regression slopes. The consequence of this is that β either lies between β_e and β_w (although the order of β_e and β_w cannot be predicted) or, when there are no group effects, $\beta = \beta_e = \beta_w$. More generally, however, there are group effects so that β and β_w are unequal, and thus β_e and β_w are also unequal. For regression coefficients, the notion of separating "cross-level" bias into aggregation bias (the difference between β and β_e) and specification bias (the difference between β and β_w) (1) is not meaningful since both biases either occur together or not at all, as implied by Firebaugh (11). In fact, it may easily be shown that

$$\beta_e - \beta = \frac{W_{xx}}{E_{xx}}(\beta - \beta_w),$$

further emphasizing that aggregation bias and specification bias do not occur separately.

The results for correlation coefficients are similar. The multipliers of ρ_t and ρ_w in equation 3 do not, however, sum to 1, so that ρ is not always constrained as β was. For correlations, the ecological fallacy consists of incorrectly assuming that ρ_e estimates either ρ or ρ_w.

The point has been correctly made (1, 10, 11) that ecological correlations are likely to be poorer estimates of their individual counterparts than ecological regression slopes. This is because correlations depend on the relative dispersions of X and Y and thus are determined by the design of the experiment. Note that

$$\rho_w = \beta_w\left\{\frac{W_{xx}}{W_{yy}}\right\}^{1/2} \text{ and } \rho_e = \beta_e\left\{\frac{E_{xx}}{E_{yy}}\right\}^{1/2}.$$

Selecting groups specifically because they differ in $\bar{X}_i$ will tend to increase the variance of $\bar{X}_i$ compared with the variance of $\bar{Y}_i$, and therefore increase the ecological correlation. In the absence of group effects in regression ($\beta = \beta_e = \beta_w$), the correlations can nevertheless differ, and the relation of ρ_e and ρ_w will depend on how the groups are chosen. Although demonstrating that $\rho_e \neq 0$ can be useful, its actual value seems quite arbitrary. If the goal is to make statements about Y on the basis of X, then in this situation, β_e is a more useful quantity than ρ_e.

It has been stated by some writers (see for example Stavraky (13) and Kleinbaum et al. (14)) that ecological associations are frequently an overestimate of the magni

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tude of the underlying individual effects. While this is always possible, we can find no justification for assuming that it is more likely than the alternative. As noted above, in the absence of group effects, the selection of groups will affect ρ_w (and may well tend to increase correlations). When group effects do, however, exist (which is quite likely in epidemiologic studies), the bias can be in either direction.

The concept of group effects in regression can be expressed in other ways. As stated above, by group effects we mean that $E(Y \mid X)$ is not the same in all groups or, equivalently, that $\beta \neq \beta_a \neq \beta_w$ (i.e., there is cross-level bias). Thus, group membership is related to some confounding factor(s) which affects the observed relation between X and Y. Firebaugh (11) addresses this situation by considering a regression of the form $Y = \alpha + \beta X + \gamma \bar{X}_i$; the presence of group effects implies that $\gamma \neq 0$. Without data on individuals, this situation cannot be detected, yet it is quite likely to exist in epidemiologic studies. Of course, if an investigator is aware of potential confounding variables measured on the groups, these can be included in the ecological regression to decrease the bias (10). The issue to consider is how likely are the groups to differ by other (unmeasured) variables.

A confounder can exist on two levels. A variable could be confounding only on the group level, and thus affect both β (the overall slope for X) and β_e (the ecological slope for X), but not β_w. For example, the variable could be a characteristic of the whole group rather than the individual (e.g., geographic latitude) or the variable could be independent of X within groups, but correlated with X across groups. If such a variable were known, it could be properly incorporated in an ecological regression. The problem is that variables such as this could well exist but not be identified. If individual level data on X and Y were available, individual level regression adjusted for group effect would permit unbiased estimation of the desired effect of X on Y.

Alternatively, a variable could be confounding on both the individual and group levels (e.g., age confounding the effect of diet). In this situation, information on the confounder would have to be incorporated into the regression whether at the individual level or the ecological level.

In theory, there is a third alternative in which a variable is confounding on the individual level but is not confounding in linear regression at the group level (because the variable is uncorrelated with group membership). For example, in an investigation of the relation of diet to the risk of colon cancer, sex is a possible confounding factor, but it is conceivable that all groups have essentially the same sex ratio. In this situation, ecological regression might be preferable to unadjusted individual level regression.

EMPIRICAL STUDY OF ECOLOGICAL CORRELATIONS

We now consider an ecological analysis of data from the Second National Health and Nutrition Examination Survey (NHANES II) in which we can compare individual level and grouped estimates. This study, conducted by the National Center for Health Statistics between 1976 and 1980, was intended to assess the health and nutritional status of the general civilian noninstitutionalized population of the United States (15). Initially, a nationwide probability sample of approximately 28,000 persons was taken with oversampling in those groups thought to be at high risk of malnutrition (low income, preschool children, and the elderly). A 24-hour dietary recall questionnaire was given to a subset of 13,820 adults. From these records, we selected 11 variables for analysis describing or derived from health history, food frequency, and anthropometry (16). Measurements were on continuous scales for dietary measures, height, weight, age, and body mass index (weight in kilograms divided by the square of height in meters), ordered categories for income and education, and binary categories for sex and race (table 3). These variables were selected not because

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TABLE 3

Coding scheme for binary and ordered category variables

Variable	Code
Sex	
Male	1
Female	2
Race	
White	1
Other	2
Education	
None	0
1*	1
2	2
3	3
4	4
5	5
6	6
7	7
8	8
9	9
10	10
11	11
12	12
1†	13
2	14
3	15
4	16
>5	17
Income‡	
<1	11
1–2	12
2–3	13
3–4	14
4–5	15
5–6	16
6–7	17
7–9	18
10–15	19
15–20	20
20–25	21
>25	22

* Grade.
† Year of college.
‡ ×1,000.

of pathologic behavior but, because they represent the type of measurements likely to appear in ecological analyses conducted by epidemiologists. Three levels of aggregation were studied. Because individuals were originally selected for the NHANES II study through one of 64 primary sampling units consisting of counties or county aggregates, the primary sampling unit made a convenient grouping variable and was the lowest level of aggregation used. Individuals also represented 34 different states which were used as a second level of aggregation. Finally, states were classified into one of six regions (northeast, north central, etc.) for the highest level of aggregation. Primary sampling units contained an average of 216 people with extremes of 130 and 343. Aggregation into states resulted in an average group size of 4,086 with extremes of 132 and 1,250. The six region sizes were 3,078, 2,869, 3,395, 2,333, 763, and 1,382 (mean = 2,303).

Table 4 shows a partition of sums of squares and cross-products for the variables income and education (highest grade attained). The between-group sums of squares are weighted by the number of individuals in each area. These quantities are presented here because of their relevance to the derivation of equations 3 and 4 and could be used to calculate the necessary statistics. In practice, however, it is easier to calculate the ecological correlation coefficients and regression parameters directly from suitable statistical software packages without using the intermediate sums of squares. The quantity ρ_e is a weighted correlation of $\bar{X}_i$ and $\bar{Y}_i$ with weights equal to the number of individuals in each group. Similarly, β_e can be calculated as the weighted regression of $\bar{Y}_i$ on $\bar{X}_i$ with weights equal to the number of individuals in each group. The quantity ρ_w may be conveniently calculated from the within-group sums of squares. These same quantities may be used to calculate β_w. Alternatively, β_w can be calculated as the weighted average of within-group regression slopes; the weights for β_w are the within-group sums of squares about the mean for the independent variable X. Alternatively, in a linear analysis of covariance model that fits a separate intercept for each group, the common slope is β_w.

The behavior of ecological correlations in the NHANES II data can be seen by examining the results in table 5. Significance levels for these estimated correlation coef-

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TABLE 4

Analyses of covariance for the NHANES data (x = income, y = education)

Source	df	Σx^2	Σxy	Σy^2
Between primary sampling units	63	7,761	5,469	10,608
Individuals within primary sampling units	13,756	92,523	30,769	147,069
Between states	39	5,675	4,044	8,130
Individuals within states	13,780	94,609	31,893	146,148
Between regions	5	2,834	3,567	4,805
Individuals within regions	13,814	97,550	32,870	149,373
Total	17,819	100,384	36,237	154,178

ficients were calculated by comparing $(N - 2)^{1/2}\,\hat{\rho}/(1 - \hat{\rho}^2)^{1/2}$ with the t distribution with $N - 2$ df (17), where N is the number of observations on which the correlation is based. It is apparent that correlations among group averages not only inadequately estimate both the correlation among individuals and the average within-group correlation but also show no discernible qualitative consistency to this effect. The ecological correlations may under- or overestimate the correlation among individuals, with equally unpredictable significance levels. The average within-area correlations in table 5 are, however, essentially identical to the overall correlation that ignores groups, indicating that for these data, most of the total variation is due to within-group variation.

Of the 13 variable pairs examined in table 5, four show increasing positive or negative correlation as the level of aggregation increases, three show the reverse pattern, and six are mixed. The levels of statistical significance for testing the hypothesis that the correlation is zero (not shown) may either increase or decrease with higher aggregation. It is not surprising that aggregation fails to preserve the statistical significance of some overall correlations (e.g., race-income) because of reduced degrees of freedom at higher levels of aggregation, but it is worrisome that nonsignificant individual level statistics can produce significant ecological estimates (e.g., height-body mass index).

The behavior of ecological regression coefficients in the NHANES II data can be seen by examining table 6. Approximate 95 per cent confidence limits were calculated as $\pm\, t_{0.975}\,(N - 2\ \text{df})$ times the estimated standard error of each regression coefficient. These confidence bounds are useful for testing the hypothesis that a coefficient differs from zero, but they are not as useful for testing the equality of coefficients across levels of grouping because the covariance of two coefficients is not zero. Here again, there appears to be no constant pattern to the relation among the β's, except that β lies between β_c and β_w as required by expression 4. The order of β_c and β_w is, however, not consistent: The ecological regression coefficients may fluctuate (weight-body mass index), increase (income-education), or decrease (protein-fat) with respect to the overall regression. As for the correlation coefficients, nonsignificant individual level effects may produce significant ecological regressions (height-body mass index) and, conversely, significant individual level effects may produce nonsignificant ecological regressions (race-income). This correspondence between the regression and correlation occurs because the significance of the coefficients is assessed using equivalent tests. We note the relative consistency of the dietary ecological regressions in table 6, except at the regional level for two of them, but can offer no theoretical explanation for the observed behavior. For most variables in table 6, β_w

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TABLE 5

Selected Pearson correlation coefficients for NHANES data

Variable pair	Individual ($N = 13,821$)	Primary sampling unit ($N = 64$)		State ($N = 34$)		Region ($N = 6$)	
	ρ	ρ_x	ρ_w	ρ_y	ρ_w	ρ_x	ρ_w
Height-weight	0.602	0.260	0.604	0.272*	0.584	0.442*	0.502
Weight-body mass index	0.836	0.789	0.836	0.792	0.855	0.930*	0.855
Height-body mass index	−0.007*	−0.356	−0.003*	−0.361	−0.001*	−0.610*	−0.006*
Age-body mass index	0.230	0.523	0.226	0.637	0.325	0.963	0.328
Calories-protein	0.851	0.892	0.851	0.797	0.851	0.516*	0.821
Calories-fat	0.899	0.898	0.896	0.867	0.859	0.296*	0.859
Protein-fat	0.785	0.711	0.787	0.658	0.787	−0.140*	0.787
Income-education	0.291	0.603	0.287	0.689	0.270	0.992	0.271
Race-income	−0.179	−0.078*	−0.200	−0.040*	−0.184	−0.658*	−0.189
Race-education	−0.131	−0.054*	−0.147	0.015*	−0.146	−0.596*	−0.121
Race-weight	0.003*	−0.239*	0.014*	−0.349	0.013*	0.168*	0.002*
Sex-weight	−0.314	−0.008*	0.315	−0.618*	−0.316	0.025*	−0.314
Sex-height	−0.686	0.377	−0.698	−0.426	−0.685	−0.855*	−0.686

* $p > 0.05$ (nonsignificant).

is close to β, indicating that most of T_{xx} is due to W_{xx}. Even when β_w is close to β, the ratio T_{xx}/E_{xx} can be large, making β_x and β_w different (equation 5).

Examination of the confidence bounds reveals that, in some cases such as height-weight and income-education, the values of β_x are not consistent with the values of β_w. In other words, the disparity between the ecological and individual regression estimates is not due solely to the larger variability of the former but is due, presumably, to a confounding factor. For the protein-fat pair, the ecological regression on regions not only is inconsistent with the individual coefficient but also has the wrong algebraic sign. We note the particularly wide confidence limits for ecological regression coefficients when the independent variable is the binary variable sex. This occurs because the sex ratio differs little across groups, suggesting that in such a situation ecological regression is particularly unwise.

Finally, the results for regressions reversing the role of the dependent and independent variables may be deduced from tables 5 and 6 since the correlation coefficient is the geometric mean of the regression coefficient for Y on X and that for X on Y. The significance levels for the two regressions are the same.

Discussion

This paper shows that the relation between β_x and the individual level measurements is not qualitatively constant but depends on the effects of grouping. The case $\beta = \beta_x = \beta_w$ could arise only when the grouping has no effect on the regression. The emphasis here is, however, on observational studies in which individual level data are unavailable, and hence the assumption of no group effects cannot be verified.

In the case of linearly related variables, the ecological fallacy can be understood as the incorrect equating of between-group ratios of the sums of squares and cross-products with the relations between the totals (or within groups). When data are

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TABLE 6

Selected regression coefficients for NHANES data

Independent variable	Dependent variable	Individual ($N = 18,820$) (β)	Primary sampling unit ($N = 34$)		Stratum ($N = 34$)		Household ($N = 6$)	
		β_c	β_c		β_b	β_c	β_b	β_c
Height	Weight	0.423*	0.394	0.827	0.346	0.886	0.313	0.832
		(0.397, 0.446)†	(0.095, 0.672)	(0.803, 0.851)	(−0.094, 0.784)	(0.802, 0.969)	(−0.378, 1.216)	(0.709, 0.946)
Weight	Body mass index	0.273	0.893	0.271	0.810	0.871	0.185	0.273
		(0.259, 0.274)	(0.291, 0.866)	(0.269, 0.274)	(0.234, 0.387)	(0.269, 0.274)	(−0.344, 0.713)	(0.938, 0.274)
Height	Body mass index	−0.004	0.185	−0.001	0.163	0.002	−0.183	−0.008
		(−0.012, 0.005)	(−0.271, −0.654)	(−0.010, 0.007)	(−0.038, −0.012)	(−0.011, 0.007)	(−0.538, 0.161)	(−0.012, 0.005)
Age	Body mass index	0.084	0.093	0.084	0.106	0.083	0.105	0.084
		(0.080, 0.088)	(0.054, 0.128)	(0.080, 0.088)	(0.050, 0.159)	(0.079, 0.087)	(0.018, 0.200)	(0.079, 0.088)
Calories	Protein	0.036	0.039	0.036	0.043	0.032	0.031	0.036
		(0.036, 0.037)	(0.032, 0.046)	(0.036, 0.037)	(0.031, 0.055)	(0.036, 0.037)	(−0.044, 0.112)	(0.036, 0.037)
Calories	Fat	0.014	0.017	0.014	0.013	0.014	0.007	0.014
		(0.014, 0.015)	(0.001, 0.032)	(0.013, 0.015)	(0.004, 0.023)	(0.014, 0.015)	(−0.009, 0.023)	(0.014, 0.015)
Protein	Fat	0.088	0.775	0.257	0.620	0.885	−0.072	0.258
		(0.074, 0.097)	(0.581, 0.971)	(0.076, 0.260)	(0.304, 0.935)	(0.257, 0.900)	(−0.786, 0.637)	(0.076, 0.260)
Income	Education	0.803	0.705	0.333	0.801	0.335	1.354	0.330
		(0.541, 0.861)	(0.468, 0.942)	(0.312, 11.858)	(0.479, 1.121)	(0.316, 0.866)	(1.121, 1.587)	(0.313, 0.864)
Race	Income	−1.400	−0.046	−1.714	−0.822	−1.594	−0.788	−1.321
		(−1.532, −1.274)	(−1.508, 0.815)	(−1.851, −1.578)	(−2.021, 1.016)	(−1.628, −1.139)	(−2.363, 0.001)	(−1.448, −1.193)
Race	Education	−1.277	−0.293	−1.567	11.891	−1.494	−0.380	−1.167
		(−1.136, −1.146)	(−1.561, 1.065)	(11.744, −1.850)	(−2.687, 2.269)	(−1.668, −1.320)	(−24.867, 7.358)	(−1.327, −1.017)
Race	Weight	0.121	−1.943	0.727	−3.129	0.896	0.989	0.116
		(−0.636, 0.879)	(−4.006, 0.121)	(−0.155, 1.608)	(−6.165, −0.093)	(−0.398, 1.470)	(−10.243, 11.810)	(−0.678, 0.910)
Sex	Weight	−10.048	3.877	−10.266	−0.013	−10.080	1.271	−10.044
		(−10.548, −9.547)	(−15.088, 7.834)	(−10.672, 9.680)	(−10.983, 10.957)	(−10.565, −9.554)	(−20.815, 23.358)	(−10.559, −9.528)
Sex	Height	−12.417	−13.841	−12.432	−17.613	−12.405	−32.829	−12.413
		(−12.883, −12.186)	(−22.538, −5.249)	(−12.668, −12.191)	(−30.928, −4.108)	(−12.638, −12.167)	(−122.986, 62.126)	(−12.884, −12.161)

* Regression coefficient.
† 95 per cent confidence limits. In some instances the limits are asymmetric because of rounding error.

available on individuals and the groups to which they were assigned, the ecological analysis is seen to be a part of the usual analysis of covariance. Ecological analyses are, however, incomplete analyses of covariance since, if the information on individuals were available, it could be used to avoid these problems, although covariance adjustment on unplanned experimental data has its own difficulties (18). We believe that the investigator is never justified in interpreting the results of ecological analyses in terms of the individuals who give rise to the data. This may seem to many readers to be an overstatement; however, our theoretical and empirical analyses offer no consistent guidelines for the interpretation of ecological correlations or regressions when data on individuals are unavailable.

We note that the literature on ecological analysis, as well as our derivation above, generally neglects the possibility of interactions. If, after adjustment for confounding, the regression coefficient for X is found to differ significantly according to some other variable, that variable and X are said to have an interaction (on the scale of measurement being used). In such a situation, one may well be interested in more than the overall slope (whether individual level or ecological) or the average within-group slope. For example, if the effect of X on Y were significantly different for males compared with females, then in addition to the coefficient for X, the interaction term would also be important. This could only be determined if sex were included in the regression. While in theory this could be done for both individual level and ecological regression, in the latter situation the groups would have to have different sex ratios as well as different values of X in order to fit the full regression.

Ecological analyses become flawed in exactly the same circumstances that individual level analyses do, i.e., in the presence of confounding. The consequences of confounding bias in the ecological analysis are more severe, however. With respect to inferences about individuals, the proper role of ecological analyses is to generate new hypotheses which must then be tested using more appropriate experimental or observational methods. To interpret ecological analyses sensibly, the investigator should use outside information to judge the likelihood of serious errors. Additionally, inferences should be confined to the level of observation (or experimentation). These conclusions apply both to simple correlation coefficients and to linear regression slopes. While we are unaware of theory for nonlinear response models, it seems likely that similar problems might arise, and the same caution should be used.

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Appendix 1

Theorem: For the data in table 1,

$$\rho = \frac{N^2 + 1 - 2k^2}{N^2 - 1}. \tag{A.1}$$

Proof: By definition, the overall correlation coefficient is

$$\rho = \frac{\sum\sum X_i Y_i - N\bar{X}\bar{Y}}{[(\sum\sum X_i^2 - N\bar{X}^2)(\sum\sum Y_i^2 - N\bar{Y}^2)]^{1/2}}.$$

Since $\sum\sum X_i^2 = \sum\sum Y_i^2$ and $\bar{X} = \bar{Y}$,

$$\rho = \frac{\sum\sum X_i Y_i - N\bar{X}^2}{\sum\sum X_i^2 - N\bar{X}^2}. \tag{A.2}$$

We begin by calculating

$$\sum\sum X_i Y_i = \sum_{i=1}^{N/k}\sum_{j=1}^{k}(ik - (i-1)k + j)(ik + 1 - j).$$

Expanding the product and using the relations

$$\sum_{i=1}^{n} i = \frac{n(n+1)}{2}$$

and

$$\sum_{i=1}^{n} i^2 = \frac{n(n+1)(2n+1)}{6},$$

yields

$$\sum\sum X_i Y_i = \frac{2N^3 + 3N^2 - k^2 N + 2N}{6}. \tag{A.3}$$

Similarly,

$$N\bar{X}^2 = \frac{N^3 - 2N^2 + N}{4}. \tag{A.4}$$

and

$$\sum\sum X_i^2 = \frac{2N^3 + 3N^2 + N}{6}. \tag{A.5}$$

Substituting expressions A.3–A.5 into A.2 yields equation A.1.

Appendix 2

To show that equation 3 is Robinson's result (3), define

$$a_W = \frac{E_W}{T_W}.$$

and

$$a_* = \frac{E_*}{T_*}.$$

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These quantities, termed the correlation ratios, measure the degree of clustering in X and Y among areas (3, p. 356). We can write equation 3 in terms of η_x^2 and η_y^2 by noting

$$(1 - \eta_y^2) = \frac{T_{yy} - B_{yy}}{T_{yy}} = \frac{W_{yy}}{T_{yy}},$$

and

$$(1 - \eta_x^2) = \frac{W_{xx}}{T_{xx}}.$$

Therefore, equation 3 becomes

$$\rho = \eta_x \eta_y \rho_b + (1 - \eta_x^2)^{1/2} (1 - \eta_y^2)^{1/2} \rho_w. \tag{B.1}$$

Solving equation B.1 for ρ_b yields

$$\rho_b = (1/\eta_x \eta_y)\, \rho - \left[\frac{(1 - \eta_x^2)^{1/2} (1 - \eta_y^2)^{1/2}}{\eta_x \eta_y}\right] \rho_w, \tag{B.2}$$

which is the relation given by Robinson (3) without proof.

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Robust parameter extraction for decision support using multimodal intensive care data

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Digital information flow within the intensive care unit (ICU) continues to grow, with advances in technology and computational biology. Recent developments in the integration and archiving of these data have resulted in new opportunities for data analysis and clinical feedback. New problems associated with ICU databases have also arisen. ICU data are high-dimensional, often sparse, asynchronous and irregularly sampled, as well as being non-stationary, noisy and subject to frequent exogenous perturbations by clinical staff. Relationships between different physiological parameters are usually nonlinear (except within restricted ranges), and the equipment used to measure the observables is often inherently error-prone and biased. The prior probabilities associated with an individual's genetics, pre-existing conditions, lifestyle and ongoing medical treatment all affect prediction and classification accuracy. In this paper, we describe some of the key problems and associated methods that hold promise for robust parameter extraction and data fusion for use in clinical decision support in the ICU.

Keywords: clinical errors; data fusion; decision support; intensive care unit; noise; signal quality

1. Introduction

Intensive care provides one of the most challenging locales for both clinicians and engineers who try to support clinical activities. Intensive care unit (ICU) patients are often the sickest, frequently having several pathophysiological problems that must be managed simultaneously to avoid death or severe morbidity. Both physiological state and external interventions change frequently, demanding rapid analysis and quick, high-stakes decisions.

Advances in the development of technology, computational signal processing and biological modelling have led to a growing interest in the archiving and use of extensive hospital–medical databases. Although current clinical practice is centred on human expert assessment of the correlations between parameter values and symptoms, there is a growing awareness within medical communities that the enormous quantity and variety of data available cannot be effectively assimilated and processed without automated or semi-automated assistance.

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Automated systems have been in place in the ICU and the operating theatre (OR) for several decades, including automated arrhythmia analysis of the bedside electrocardiogram (ECG) and low (or high) oxygen saturation warnings from the photoplethysmograph (PPG). However, each device acts in an isolated fashion with no reference to related signals or an individual's prior medical information, such as genetics or medical history. Some patient-specific data are used in an ad hoc manner, such as body weight (for the adjustment of drug rates), allergies (to restrict medications) and age (for arrhythmia alarm thresholds). However, automated use of such information is rare.

In this paper, we outline a long-term approach to develop systematic bases for extracting information in order to provide assistance to clinicians faced with the enormous challenges of providing high-quality ICU care. We are currently collecting large datasets of actual patient experiences in the ICU, developing methods to analyse and abstract those data, retrieval systems to allow selection of events of interest, creating models that relate such data to patients' clinical conditions and pathophysiological status, and building both physiological and statistical models to enable sophisticated decision support systems that base alarms on an integrated view of the patient and that can assess or even suggest alternative courses of action. Although we frame these ideas within a wider context, here, we focus principally on the problems we have encountered and the solutions we have developed for collecting ICU patient data and extracting information that is useful for decision support.

We have instituted a large-scale systematic collection of data about ICU patients (Saeed *et al.* 2002) to provide a baseline understanding of what currently happens in the ICU and to allow us to learn to model patients' conditions and their responses to various interventions. These data derive from a heterogeneous set of sources, including bedside monitoring equipment; clinical observations by doctors and nurses; laboratory measurements; records of both continuous and discrete drug administration; reports from physical examinations, referring physicians, radiologists, pathologists and other specialists; and records of past conditions, treatments and outcomes, as normally recorded in discharge summaries. Each of these sources of data carries its own set of technical problems, ranging from mundane issues of data standardization to difficulties in assessing the quality of recorded data and dealing with missing data. To date, we have collected data on approximately 30 000 patients from four different ICUs at a large tertiary-care teaching hospital. Approximately 10 per cent of those records include high-frequency physiological signals recorded from the bedside monitors, including multichannel ECG, invasive arterial blood pressure (ABP) and PPG. Associated derived parameters, such as heart rate, systolic/diastolic blood pressure and oxygen saturation, are also available.

In the following sections, we describe issues we have encountered in

(i) the collection, measurement, transmission, transcription and storage of these data,
(ii) abstraction and robust parameter extraction from often noisy and incomplete data, and
(iii) extraction of clinically relevant concepts from unstructured text, which is the form in which many notes and reports are stored.

2. Errors in collection, measurement, transmission, transcription and storage of data

The first problem faced in gathering ICU data is the necessity of collecting the data from a variety of sources: instruments that acquire and digitize continuous signals; devices such as respirators and intravenous drug delivery systems that must be interrogated to record their settings; laboratory results that may have been automatically or manually transcribed into clinical information systems; and medical histories, admitting notes, progress notes, problem lists and discharge summaries that must be obtained from online or paper medical records. These diverse data streams must be synchronized in order to make sense of their inter-relationships. Even establishing basic causal relationships among data elements (did the patient's symptoms prompt a change in medication, or did the medication change cause the symptoms?) can be problematic when time is recorded by independent and unsynchronized clocks. At an even more basic level, it is necessary to match each recorded data stream with the correct patient among all those currently in the hospital, a problem that should be trivially easy to solve but is often complicated by instruments with poorly designed set-up procedures that are not always completed in the context of urgent care, human transcription errors (Hug & Clifford 2007; Vawdrey *et al.* 2007) and policies intended to protect patient privacy. The use of proprietary formats and protocols for medical data storage and communications is slowly giving way to open formats (e.g. EDF, WFDB, XML; Clifford *et al.* 2008) and protocols (such as HL7 and the IEEE medical information bus standard P1073; Alsafadi *et al.* 1994), which will reduce transcription errors. However, the processes of capturing and digesting these data into a consistent format remain complex.

Having solved all of these problems by whatever means necessary, it may be possible to assemble an electronic medical record containing most of the information upon which medical decisions are founded. Just as traditional medical records may contain errors from a variety of sources, so may their electronic equivalents. Measurement errors may stem from incorrect calibration, improperly located or malfunctioning transducers, artefact, environmental noise, or from errors in transmission, transcription, storage or retrieval (Clifford & Oefinger 2006). Some of these errors can be minimized by use of good biomedical, computer and human engineering practices, for example by stabilizing sensors to limit motion-related artefact; minimizing the area of low-voltage sensing circuits and using shielded cables to avoid signal contamination by induced currents; using error detecting and correcting codes when transmitting and storing packets of digital data; employing data communication protocols that incorporate handshaking, retransmission and redundancy to avoid data loss; redesigning workflow to capture data automatically, to avoid manual transcription of data where possible, and to verify data that must be transcribed at the time of transcription; and regular reviews of data collection practices to identify and address deficiencies.

Conscientious use of best practices can reduce but not eliminate measurement errors. The effects of those errors that remain upon subsequent analysis of the record can be minimized by searching for logical inconsistencies (such as when the systolic blood pressure is lower than the mean or diastolic blood pressure), or by

comparing multiple redundant measures of the same physiological parameters. For example, heart rate may be derived from the ECG, an invasive ABP line and the PPG. These issues are explored further in §3*d*, after discussing problems and solutions related to noise reduction, signal quality, artefacts and missing data.

3. Abstraction and robust parameter extraction

In order to provide information for medical experts (or automated decision support systems) to make choices concerning patient care, the wealth of available data must be reduced to a set of distinct concepts and features. Although many parameters are derived from patient data 'on the fly' and recorded for later review, trust metrics or signal quality measures associated with these parameters are rarely stored. Therefore, it is difficult to ascertain the credibility of a given parameter unless the original data from which the parameter was derived are available, either to visually verify the data or in order to derive independent quality metrics.

Noise reduction algorithms often introduce misleading distortions in medical time-series data and, therefore, they should be applied only when the data are determined to be too noisy for a feature extraction algorithm to be applied accurately. However, it is often necessary to extract features and compare them with a population norm, or a patient's history, in order to determine whether significant amounts of noise are present. A method for simultaneously (or recursively) extracting features and estimating noise levels is, therefore, appropriate.

In this section, we describe a generic approach to noise reduction and signal quality analysis, together with a data fusion framework that provides for a robust estimate of extracted physiological parameters that evolve over time.

(*a*) *Noise reduction*

After appropriate formatting, storage and initial coding of data, perhaps the most important stage in data processing is the application of signal processing algorithms to deal with the noisy and transient nature of physiological signals. Even when the data are continuously available and the sampling rate is high enough, data can still be masked by periods of intense noise due to movement artefact. Strategies for detecting and (where possible) removing noise in physiological data depend on the nature of both the noise and the data source and typically include infinite impulse response filters, finite impulse response filters, principal component analysis (PCA; Moody & Mark 1989), independent component analysis (ICA; McSharry & Clifford 2004; He *et al.* 2006) and wavelets (Addison 2005). Much of the data recorded in the ICU are nonlinear or non-stationary, however, and the mixing between the noise and the signal is also non-stationary. Therefore, techniques such as ICA cannot work reliably unless calculated over small, quasi-stationary segments of data and frequently updated. Furthermore, the noise and the signal are not independent, such as when heart rate increases due to activity are associated with increasing frequency of artefact (Clifford *et al.* 2002) and methods to separate them, which assume independence (such as PCA and ICA), only work when the coupling between the signal and the noise is weak. It should be noted that PCA-based techniques have proved

extremely effective for filtering on a beat-by-beat basis, particularly in applications such as QT analysis (Okin *et al.* 2002), ST analysis (Moody & Jager 2003; Jager *et al.* 2004), QRS subtraction and QRS classification (Moody & Mark 1989).

Takla *et al.* (2006) provided a thorough review of the types of contamination of signals in the OR and methods that have been proposed to deal with the noise. Although much of this information is pertinent to monitoring in general, the ICU is more problematic than the OR, since the latter is more highly controlled, with a higher staff-to-patient ratio. ICU data are often only available on an infrequent basis (relative to the underlying dynamics), and removal of noise becomes problematic. The best method to deal with noise is often simply the use of a median filter to reject outliers (Mäkivirta *et al.* 1991). For example, heart rate and blood pressure averages recorded by nursing staff every hour sometimes exhibit artefacts that are significantly different from the underlying waveform data (Hug & Clifford 2007). Although a median filter is able to reduce the average magnitude of the error in this scenario, this is only because patients tend to be stable and exhibit the same physiological parameter values from hour to hour. However, there is no guarantee that the *outlier* is not a real event. In fact, it is the rare outliers that are often of interest in biomedical time-series data, since they indicate that the aim of managed stability for a patient may be unsuccessful and that changes in treatment are required.

To allow for the non-stationary nature of ICU data, an adaptive filter is often more appropriate, where the transfer function changes in response to each new data sample or feature (Takla *et al.* 2006). Adaptive filters are generally either ad hoc (Martinez *et al.* 1997; Husoy *et al.* 2002) or model-based (Clifford *et al.* 2005; Clifford 2006; Sameni *et al.* 2007). Although model-based filters provide a much more effective suppression of noise, they tend to be more computationally intensive, and their effectiveness is dependent on the accuracy and applicability of the model employed. In Sameni *et al.* (2007), the authors recently proposed an adaptation of a model-based filtering approach to the ECG, which is particularly suitable to a real-time implementation. By using an unscented Kalman filter, a nonlinear version of the Kalman filter (KF), they leveraged the beat-to-beat dynamics (and similarities) to allow a computationally efficient Bayesian approach to ECG model parameter estimation. Although Sameni *et al.* demonstrated that the technique outperforms the best of previously described ECG filters on normal sinus rhythm ECGs, performance on arrhythmic data is unclear. In all likelihood, unless a pre-classification algorithm is employed, the model will have to be refitted to the data for moderate changes in morphology, and classified as abnormal or artefactual. It is also worth noting that, since the model is based upon a superposition of Gaussians, it is easily adapted to filtering and classification of other cardiovascular signals such as the blood pressure (Clifford & McSharry 2004; Clifford *et al.* 2005).

(*b*) *Artefacts and missing data*

Most filtering techniques are also sensitive to artefacts and missing data. In particular, even when signals have been sampled above the Nyquist limit, intervals of missing data may be frequent, due to disconnections, sensor errors, equipment

changes, intrusive diagnostics and request-based data (such as blood tests). Sometimes noise and artefact can be so high that it is best just to discard the section of data, effectively making an evenly sampled signal irregularly sampled.

Often the sampling frequency is inherently uneven, particularly in the case of diagnostic data, which are ordered when an event or combination of observations indicate that a particular test is required. Missing data and irregular sampling are highly related concepts, although the former implies that useful data may exist between each sample point and may carry further information about the state of the patient (such as a significant change in a given variable). Some form of interpolation may, therefore, be useful in estimating the unobserved information. However, it may not be appropriate to guess the values of missing or hidden data, since any slight error might lead to an erroneous decision; there are cases when an estimate is useful. Furthermore, reporting the bounds of error in an estimate allows a clinician to make safe harbour decisions.

For single-parameter time series, little more than a sample-and-hold approach (with a time-out) is generally used to fill in the missing data. This is generally a good approach for frequently sampled data from ICU patients who are usually managed for stability, and thus exhibit infrequent large changes in the value of a physiological parameter. However, the situations that are often more interesting and informative are the infrequent changes and resampling schemes are often used (such as sample-and-hold, linear or cubic spline interpolation). However, these approaches introduce spurious low- and high-frequency noise and can be extremely sensitive to the number of missing data points or to the irregularity of the missing data (Clifford *et al.* 2005).

Other more complex methods for filling in missing data involve using the statistical and/or dynamic nature of the data (rather than just neighbouring gradients) to form estimates of the intervening sample values such as min–max interpolation (Fessler & Sutton 2003), autoregressive modelling (Rajan *et al.* 1997; Cassidy & Penny 2002) and KF methods (Chin 2001; Yarita *et al.* 2007). Sometimes, however, it is more appropriate to use methods specifically designed to be used with missing data (or irregularly sampled signals). For spectral estimation, the Lomb–Scargle periodogram (LSP; Lomb 1976; Scargle 1982) is a particularly robust method for extracting frequency estimates of unevenly sampled data, and has been shown to be particularly suited to spectral quantification of heart rate variability (Moody 1993; Laguna *et al.* 1998). The LSP does not require the interpolation of any data, as it performs a least-squares fit of sinusoids at each frequency to form an estimate of the power spectral density. The LSP has been shown to be relatively insensitive to the density of missing data and removed artefact with relatively insignificant changes for up to 20 per cent missing data (Clifford *et al.* 2005).

When multiple sources of related information are available, it is possible to exploit the covariance of the data, such as when using PCA or imputation. However, such techniques again assume stationarity of the dynamics of the data (unless incremental updates are calculated on a frequent basis), and they require that the missing data be missing at random or that an accurate model of how the missing data are distributed be known. Furthermore, these techniques are sensitive to outliers and non-removed errors. Since no accurate model exists of how missing or noisy data are distributed, the interpolation of missing ICU data is extremely difficult (Abdala & Saeed 2004). (In general, data are missing because

they are perceived to be irrelevant for the current clinical problems, or because exogenous interventions or endogenous activity has rendered the data useless. Neither of these circumstances is random, or amenable to simple models.)

It should be noted that the frequency at which a parameter needs to be sampled depends on both the parameter type and the question we are asking about the patient. For example, although blood pressure can exhibit large changes over a period of a few seconds (e.g. during a head-up tilt), if we are looking for evidence of haemorrhage, we may not need to sample more frequently than once every 5 or 10 min to capture the dynamics of the situation. The required sampling frequency is also related to the intrinsic dynamics of the parameter, so that heart rhythm, which can change over a few beats, is sampled rapidly (at 100 Hz or more), whereas blood creatinine (abnormal levels of which indicate renal insufficiency) may change only over hours. Consequently, creatinine values are sampled much less frequently and can be reliably interpolated over several minutes, whereas heart rate estimates cannot. The effective Nyquist frequency for a particular parameter also depends on an individual's physiology and medical condition, and so it is difficult to be sure whether parameters are being undersampled. However, clinical teams tend to sample parameters more frequently when they believe a patient may be unstable with a rapidly changing (usually degenerating) physiological condition. Therefore, the clinical team often notices signs or symptoms indicative of rapid changes and adjusts the sampling rate so that loss of important information does not occur.

(*c*) *Signal quality analysis*

Since robust methods for dealing with missing data are not always available, it is sometimes more appropriate to define a signal quality measure for a given data stream, and simply ignore the segments of data that have a signal quality below a given value. However, metrics for signal quality are both signal and application specific. For example, noise above 20 Hz, which does not distort ABP estimates, can disturb ECG peak detection algorithms and cause heart rate variability algorithms to report incorrect values, while leaving heart rate estimation algorithms unaffected. Low-frequency noise (below 1 Hz), which only disturbs subtle features in the ECG such as the QT interval or ST segment, can cause significant errors in the estimate of the blood pressure. A general treatment of signal quality measures is therefore not possible. However, signal quality indices (SQIs) can generally be constructed by thresholding on known physiological limits such as the maximum field strength for the ECG, the maximum rate of change of the blood pressure or the distribution of energy in the frequency domain. However, it is the relationship between physiological parameters that provides the greatest opportunity to construct SQIs. For example, if heart beats are detected in several ECG and/or pulsatile waveforms within an expected period of time, all signals can be considered to be of reasonable quality.

SQIs are generally calculated by bedside monitoring equipment but are rarely used by clinical teams or automated alert systems, since there is often an assumption that the monitor will provide either no information or a *best guess* of a parameter in the absence of good quality data. However, as we have already discussed, it is very difficult to make an accurate or useful guess of a missing parameter in non-stationary data, such as that found in the ICU, and

a sample-and-hold approach is often used. Although this can be useful to a human attempting to observe the current state of the patient, this is an inappropriate solution for passing data to an automated or semi-automated algorithm.

With current trends towards semi-automated analysis, it is important that SQIs are available for each datum and, if possible, be calibrated to provide a known error for a given value of the SQI. In this way, another algorithm can make informed choices concerning the validity of the datum for a given application, and derived estimates can be provided with accurate error bounds. In Li *et al.* (2008), we calibrated a set of ECG signal quality metrics (based upon statistical, temporal, spectral and cross-spectral features of the ECG), so that a given value of an SQI metric was equated to known error in heart rate. A similar approach was also taken to ABP, and hence error bounds in derived estimates that rely on heart rate and blood pressure (such as the cardiac output) can easily be estimated from the standard compound error formula. Generally, data in the ICU are processed in isolation from other parameters and signal quality labels are therefore rarely constructed with reference to other signals. In our approach to SQI derivation, we have concentrated on the relationships between signals, such as the transit time between the ECG and the ABP (Zong *et al.* 2004) and the inter-ECG lead relationships (Li *et al.* 2008). By comparing related signals and thresholding these relationships on known physiological limits, it is possible to determine whether the data are logically consistent. Since it is rare that a sequence of extracted features will randomly manifest in a physiologically plausible manner, internal consistency between signals can indicate high signal quality on the contributing leads.

Frequently measured parameters (such as heart rate and blood pressure) are amenable to SQI analysis because there is usually an underlying rapidly sampled waveform from which the metrics can be derived. When the sampling rate of the data available drops to around 1 Hz or below, signal quality measures become problematic, since it is almost impossible to differentiate between a real physiological change and an artefact.

Errors in less frequently sampled clinical data (such as blood tests) are more difficult to determine for two reasons. First, the sampling rate is low compared with how rapidly a variable can change. (It should also be noted that there is often a considerable delay between the biological samples being sent for testing and the received results, and so an accurate knowledge of the time of the original sampling must be known.) Second, the relationship of a blood test to other signals is extremely complex, and testing the 'truth' of a measurement would require an extremely complex and accurate model of an individual's physiology. The general approach is that a clinician makes a hypothesis concerning the outcome of the test, based upon current monitored data and a medical history. If the prediction turns out to be accurate, then the belief in the result is high. Otherwise, a test may be reordered, particularly if subsequent data indicate that the test results are contradictory. This type of modelling is extremely complex and the reader is referred to Long (2001) for more details.

(*d*) *Robust data fusion*

Exploitation of the covariance structure of the data is one method of data fusion, since a non-diagonal covariance matrix implies redundancy in the individual data streams. However, weighting different data streams can be

difficult when the measurement units are different and the distributions of the data are different (and non-Gaussian). For instance, what blood pressure change (measured in mm Hg) is equivalent to a 5 per cent drop in oxygen saturation? Townsend and Tarassenko (Nairac *et al.* 1997; Tarassenko *et al.* 2001, 2002*b*) approached this problem by using a large ICU database to renormalize five clinical parameters (heart rate, blood pressure, respiration rate, oxygen saturation and temperature) to zero-mean unit variance. Large statistical deviations in this five-dimensional space equate to abnormality that has been shown to be predictive of future interventions (Tarassenko *et al.* 2006).

When the data to be fused pertain to the same parameter, the data fusion is technically more straightforward, although it requires a method for arbitrating between conflicting estimates. In a recent work, we have extended the work of Tarassenko and Townsend (Tarassenko *et al.* 2002*a*, 2003) to fuse multiple observations of different physiological signals (such as heart rate and blood pressure) from multiple sources, recorded at arbitrary times, within a KF framework (Li *et al.* 2008).

The KF is an optimal state estimation method for a stochastic signal that estimates the state of a discrete-time controlled process, x, with observable measurement data z. The KF uses the *a posteriori* state estimate $\hat{x}_k^-$, a state transition matrix $\boldsymbol{H}$ and the *Kalman gain* $\boldsymbol{K}_k$ to recursively predict the *a priori* kth state estimate, such that

$$\hat{x}_k = \hat{x}_k^- + \boldsymbol{K}_k(z_k - \boldsymbol{H}\hat{x}_k^-). \tag{3.1}$$

The Kalman gain is given by $\boldsymbol{K}_k = \boldsymbol{P}_k^- \boldsymbol{H}^{\mathrm{T}}(\boldsymbol{H}\boldsymbol{P}_k^- \boldsymbol{H}^{\mathrm{T}} + \boldsymbol{R})^{-1}$, where $\boldsymbol{P}_k^-$ is the error covariance of the *a priori* estimate and $\boldsymbol{R}$ is the state noise covariance. The above estimate minimizes the measurement innovation η (or residual, sometimes denoted r) given by $\eta_k = z_k - \boldsymbol{H}\hat{x}_k^-$ (the error between the prediction and the observation).

Note that $\boldsymbol{K}$ is inversely proportional to $\boldsymbol{R}$, the measurement noise covariance, and represents how rapidly the KF will adapt to new observations. In a recent paper (Li *et al.* 2008), we have proposed a modification to $\boldsymbol{R}$ by a multiplicative factor, such that $\boldsymbol{R} \rightarrow \gamma \boldsymbol{R}$, where

$$\gamma = \mathrm{e}^{(s^{-1}-1)}, \tag{3.2}$$

and s is a signal quality threshold raging between 0 (poor signal) and 1 (excellent signal quality) inclusively. This modification has the effect of forcing a KF tracking algorithm to trust any given observation when the SQI, s, is high (since as $s \rightarrow 1$, $\gamma \rightarrow 1$). When the SQI, s, is low, γ tends to infinity and the resultant large increase in $\boldsymbol{R}$ results in a low Kalman gain. Therefore, the KF no longer trusts the current observation to make a prediction, and relies on previous observations instead. This approach turns out to provide a low error, unbiased estimator for cardiovascular time series of heart rate and blood pressure, even in extremely high noise scenarios since noisy segments of data are automatically rejected.

This KF approach also provides a robust framework for fusing multiple observations of the same parameter from different sensors. Tarassenko and Townsend (Tarassenko *et al.* 2002*a*, 2003) proposed weighting each observation, x_k, of a physiological parameter by the inverse of the normalized innovation, η, for each channel. In the two-channel scenario ($k=1, 2$), the weighted estimate of

a parameter becomes

$$x = \left(\frac{\eta_2^2}{\eta_1^2 + \eta_2^2}\right) x_1 + \left(\frac{\eta_1^2}{\eta_1^2 + \eta_2^2}\right) x_2. \tag{3.3}$$

In their application, x was separately given as a scalar heart rate or respiration rate. Furthermore, $\boldsymbol{H}$ was assumed to be unity and so the current state is approximately the same as the last state ($x_k \approx x_{k-1}$). For beat-to-beat or breath-to-breath updates, this can be considered approximately true.

Although equation (3.3) weights observations with low innovations more heavily, the higher innovation can sometimes be associated with the more accurate estimate. Therefore, we added a scaling function to the innovation, such that $\eta^2 \rightarrow \eta^2 s^{-2}$, for each channel and low-quality estimates are 'unweighted'. For N-channels, this becomes

$$x = \sum_{k=1}^{N} \left(\frac{\prod_{i=1, i\neq k}^{N} \left(\frac{\eta_i}{\lambda_i s_i}\right)^2}{\sum_{i=1}^{N} \left(\prod_{j=1, j\neq i}^{N} \left(\frac{\eta_j}{\lambda_i s_j}\right)^2 \right) x_k} \right) \quad (k = 1, 2, \ldots, N), \tag{3.4}$$

where the $0 \leq \lambda \leq 1$ are *trust* factors for each of the channels of data. This formulation is particularly useful for the ICU data where multiple estimates of the same physiological parameter can be derived. For example, one might use the PPG, or pulmonary arterial pressure, as well as the ABP and ECG to determine physiological parameters such as HR, ABP or cardiac output.

The trust factor λ can be useful when two measurements of the same variable come from devices that are known to have independent and different error profiles, such as the invasive and non-invasive cuff measurement of blood pressure. In this case, the λ for the invasive arterial line could be set to 0.9 (to reflect a 10% error) and the λ for the sphygmomanometer cuff measurement could be set to 0.8 (to reflect an inherent 20% error in the reading).

This approach can also be thought of as a robust weighted interpolation scheme, with a sampling frequency of the combined set of observations. That is, the KF is updated at every observation, and every channel of data provides an estimate of the physiological parameter at a different time point. Therefore, the resultant time series has a sample point at each observation that is fit to a weighted sum of previous and current measurements.

The signal quality-modified KF approach described above involves a scalar observation model with the simplest dynamical approach (assuming that the next observation will be approx. equal to the last observation). Extensions that employ models of the dynamic evolution of the cardiovascular system, or vector KF formulations that employ models of how each signal is related to each of the other recorded signals, are likely to improve this method of tracking and noise rejection approach.

For example, Pueyo *et al.* (2008) used a KF to fuse information from the QT and RR intervals to dynamically characterize beat-to-beat adaptation of the repolarization period to changes in heart rate. Our group has also made significant progress in building both statistical (Roberts *et al.* 2006) and explicit cardiovascular models (Parlikar *et al.* 2006, 2007) for the ICU data. In particular,

cycle-averaged models of blood pressure changes have proved accurate for modelling changes in the blood pressure and estimating cardiac output (Parlikar *et al.* 2007).

However, considerable barriers remain, including modelling non-stationarities in the parameters and dealing with the underlying noise. Without good methods for rejecting (or unweighting) noise, no system of modelling, data fusion or missing information estimation is likely to work reliably. Signal quality measures should therefore be evaluated on large databases, and then calculated and stored for all possible signals in the ICU.

(*e*) *False alarms in the ICU*

One example of where we have applied the concepts of signal quality and data fusion is in the arena of false alarm (FA) suppression in the ICU. FAs in the ICU can lead to a disruption of care, impacting both the patient and the clinical staff. The resultant excessive noise pollution, desensitization to warnings and slowing of response times (Chambrin 2001) can lead to missed alarms, decreased quality of care (Donchin & Jacob 2002; Imhoff & Kuhls 2006), sleep problems (Meyer *et al.* 1994; Parthasarathy & Tobin 2004), stress for both patients and staff (Baker 1992; Novaes *et al.* 1997), depressed immune systems and longer patient stays (Hagerman *et al.* 2005).

Tsien & Fackler (1997) conducted a prospective, observational study in a multidisciplinary ICU to record the occurrence rate, cause and appropriateness of all alarms from tracked monitors. After 298 monitored hours, 86 per cent of a total of 2942 alarms were found to be false-positive alarms, while an additional 6 per cent were classified as clinically irrelevant true alarms (TAs). Only 8 per cent of all alarms tracked during the study period were determined to be TAs with a clinical significance associated with them.

Recently, Zhang *et al.* (2007) designed a system to simultaneously collect physiological data and clinical annotations at the ICU bedside, and to develop alarm algorithms in real time based on patient-specific data collected while using the system. After deployment of a prototype in a paediatric ICU equipped with a newer generation bedside monitoring system, a dataset of 196 hours of vital sign measurements at 1 Hz together with associated alarms was collected. Approximately 89 per cent of the recorded alarms were found to be clinically relevant true positives, 6 per cent were true positives without clinical relevance and 5 per cent were false positives (Zhang *et al.* 2007). Real-time machine learning showed improved performance over time and generated alarm algorithms that outperformed the previous generation of bedside monitors and came close in performance to the latest generation of bedside monitor alarm algorithms (Zhang 2007). Interestingly, this work shows that an algorithm trained only on data from a specific patient can approach the level of performance of commercial algorithms that are trained on much larger datasets (Zhang & Szolovits 2008).

Our recent analysis concerned the suppression of false life-threatening arrhythmia alarms issued by the bedside ECG monitor. Using two independent reviewers, we annotated 5386 alarms from a total of 447 adult patient records spanning 41 301 hours of simultaneously acquired ECG and ABP. A third reviewer then checked each alarm to adjudicate discrepancies and check the

overall quality of the alarms. The critical arrhythmia alarm types were selected to be (i) asystole, (ii) extreme bradycardia, (iii) extreme tachycardia, (iv) ventricular tachycardia (VTach), and (v) ventricular fibrillation. Annotation revealed the FA rates of these five alarm types to be 90.7, 29.3, 23.1, 46.6 and 79.6 per cent, respectively, with an average FA rate of 42.7 per cent. An algorithm to suppress these FAs was then developed, which used a signal quality measure, s_N, derived from the ABP waveform to decide on the truth of the ECG arrhythmia alarm. (In this application, s_N was actually a signal 'normality' index (Sun *et al.* 2006). Signal normality equates to a high signal quality and no features indicative of a non-sinus rhythm.) At each ECG alarm point, a reference was made back to a 20 s synchronous segment of the ABP waveform, and if s_N was higher than a given threshold, the blood pressure was considered to be commensurate with a sinus rhythm, and the ECG alarm was suppressed if the ABP-derived heart rate was too slow (or fast). The threshold, s_N, was expected to differ for each alarm type since abnormalities in the ECG will differ depending on rhythm and heart rate. Therefore, the annotated alarms were divided into two sets: a training set and a testing set. Each s_N was then optimized (together with other alarm-specific thresholds, such as the number of beats from which to calculate the heart rate), to determine the highest FA reduction rate, with the lowest TA suppression rate.

This approach provided an overall FA reduction rate for the five alarm categories above of (i) 93.5 per cent, (ii) 81.0 per cent, (iii) 63.7 per cent, (iv) 33.0 per cent, and (v) 58.2 per cent, with an overall suppression rate of 59.7 per cent. This equates to an equivalent FA rate of (i) 5.5 per cent, (ii) 5.5 per cent, (iii) 8.4 per cent, (iv) 30.8 per cent, and (v) 33.1 per cent, with an overall FA rate of 17.2 per cent. However, it should be noted that invasive arterial lines are not available for all patients in the ICU (only approx. two-thirds of the population), and so to provide this level of FA suppression for all life-threatening alarms would require an extension of the algorithm to use the oxygen saturation waveform. TA suppression rates were all zero except for VTach, indicating that VTach does not always manifest as an abnormal ABP waveform, and referencing back to the ECG is required. A full description of the method and results can be found in Clifford *et al.* (2006) and Aboukhalil *et al.* (2008).

Significant work still remains in the arena of FA reduction, particularly with respect to lower priority alarms, which, although less important, still add significantly to the problem of FA pollution in the ICU. In fact, non-critical alarms constitute over 90 per cent of the alarms in the ICU. Furthermore, these alarms are not split into groups relating to clinically insignificant, clinically relevant and immediately actionable. The data and annotated alarms, a subset of the MIMIC II database, have therefore been made publicly available via PhysioNet (Goldberger *et al.* 2000; LCP 2008) in the hope that public collaboration will rapidly improve this situation.

4. Coding of clinically relevant events and concepts

Once parameters have been robustly extracted, they must be provided with a useful label. In the case of standard cardiovascular parameters, the label is self-evident (heart rate, blood pressure, cardiac output, etc.). However, combinations

of parameters can provide a richer picture of the state or class of a patient. For example, a series of desaturations during the night followed by cessations in breathing are indicative of apnoea. The prior probability of placing the patient into a given class can be extremely important and a rich database of ICU data also provides the opportunity to extract information for such prior probabilities from alternative sources.

(*a*) *Medical lexicons for annotating ICU data*

The objective (or semi-objective) classification of ICU data requires a standardized lexicon or system of labelling. Although such systems exist for some signals (such as the ECG), many labels rely on subjective observations with high interobserver variability. Furthermore, for many medical diagnoses, there are no agreed definitions, and the divisions between categories are fuzzy. For example, more than 30 different definitions of acute renal failure have been used in the literature (Bellomo *et al.* 2004). However, with multiple experts and a well-defined set of criteria, the labelling of a given event or condition reaches agreement levels of 95 per cent (Douglass *et al.* 2004; Neamatullah *et al.* 2008). Labelling of ICU data can occur manually, automatically or in a semi-automated fashion, but in each case, a standard lexicon is required. There are several standard lexicons for labelling ICU data, depending on the category of data. These include Logical Observation Identifiers, Names and Codes (LOINC; for laboratory and other diagnostic results), the Systematized Nomenclature of Medicine–Clinical Terms (SNOMED-CT; for diseases, findings, procedures, micro-organisms, pharmaceuticals, etc.), Medical Subject Headings (the National Library of Medicine's controlled vocabulary thesaurus of naming descriptors organized in a hierarchical structure) and the International Classification of Diseases (Chen *et al.* 2007).

The Unified Medical Language System (UMLS) acts as an umbrella lexicon for many of these subsystems (although with some enhanced features; Zhang *et al.* 2005). The UMLS is very large and complex, however; it poses significant comprehension problems for users and database maintenance personnel (Gu *et al.* 2000). Furthermore, the UMLS contains omissions of concepts, errors of semantic type classification and concept ambiguities. In particular, there is no one-to-one mapping between sub-lexicons and often multiple UMLS terms are required to describe a particular event or procedure.

We have therefore developed open-source Java software for using a subset of the UMLS to construct descriptors of events in the ICU data (Shu *et al.* 2004). The UMLS descriptors associated with a given event generally consist of an event code (such as 'C0340535, acute massive pulmonary embolism') or a *state* code (such as 'C0018802, congestive heart failure'). The codes are often associated with a qualifier (such as 'C0184511, improved', 'C0205360, stable' or 'C0332271, worsening'). Although many of these codes are predefined in drop-down lists to enable rapid and accurate coding, some events necessarily require a new code. In this case, a free text string can be entered by the clinician to see a range of possible codes to select from. We found that spell checking, general abbreviation dictionaries and personalized abbreviation dictionaries were necessary to enable clinicians to find relevant codes in a timely manner.

(b) *Extracting clinical data from text*

Much of the data about patients that are not directly measured by computerized instruments is available only in the form of unstructured natural language statements by clinicians. These data can be typed directly by a clinician or transcribed from dictation or handwritten notes. Unfortunately, manual data entry practices and conversion of data into electronic medical records are prone to error. One study (Dean *et al.* 1995) showed that the most common types of data errors in 1995 were omitted and incorrect doses (in UK hospitals) and incorrect and unordered doses (in US hospitals). More recently, Lisby *et al.* (2005) showed that errors in medication ordering and transcription can be frequent and lead to potentially adverse events. However, the most common types of error throughout the medication process were found to be lack of convenient input modalities (forms or entry terminals), unordered drugs, omission of drugs/dosage levels and lack of identity control.

However, inaccurate transcription and data entry is not confined to medications. Recently, we compared manual acceptance of measurements of heart rate and blood pressure from bedside monitors, with measurements gated by robust automatic measures of signal quality (Hug & Clifford 2007). Results showed that the clinically verified BP values exhibit a small but significant bias towards overestimation. In particular, we demonstrated that hypotensive events are often missed by the action of human recording. Other studies (Nelson *et al.* 2005; Vawdrey *et al.* 2007) have also demonstrated the inherent errors in human recording of physiological signals.

Regardless of the method of transcription, the notes must be interpreted by fairly sophisticated algorithms in order to turn them into a structured form that is suitable for searching, modelling and further analysis. We have found that the notes taken by clinicians during the delivery of care are often most difficult to analyse, even when they are typed rather than handwritten. Perhaps owing to the pressing need for speed, these are often poorly organized, full of non-standard abbreviations and typographic errors, and thus pose the greatest challenges to automated processing. By contrast, more formal notes such as discharge summaries, which summarize a patient's hospital stay, are often more carefully written, consciously trying to inform readers other than the writer, and are thus easier to analyse.

We have developed a computer program to extract diseases and procedures attributed to patients in discharge summaries as an aid to semi-automated annotation of our large case collection. The program maps phrases from the text to the approximately 6 million terms that represent approximately 1.5 million concepts listed in the UMLS, and then maps these to the approximately 1 million listed SNOMED-CT concepts. (In practice, of course, very few of these actually appear in clinical texts.) As reported in Long (2007), this program was able to find 93 per cent of the 1326 clinically significant concepts that had been identified in 96 discharge summaries through a manual review by one to three clinicians. However, the program achieves this high level of recall by allowing many irrelevant and misclassified concepts (almost three times as many as the relevant concepts that it finds). Because the purpose of this program was to help annotators find all the relevant concepts, and it is much easier in annotation to reject an unneeded concept than to code a concept de novo, this bias is

acceptable for our application. Nevertheless, we would prefer to have an automated annotation tool that finds almost all the needed concepts but few spurious ones.

If we could build a program that 'understands' natural language, then it would be relatively easy to pick out the concepts we want to recognize. However, the problem of understanding text is thought to be *artificial intelligence complete*—it would require a program with true human-level intelligence. Of course, we are not anywhere near that in our technical abilities. Therefore, researchers have taken a range of approaches to the extraction problem. At one extreme are systems that use the best available computational linguistics methods to assign likely parts of speech and semantic categories to individual words, to parse the linguistic structure of the phrases, clauses, sentences and paragraphs that express information, and thus to do a deep analysis of the text. Our program takes a more minimalist approach, dividing the text using punctuation, conjunctions, numbers and a few verbs into phrases. Within these, it looks for the maximum length sub-phrase that matches a UMLS concept, without regard to the surrounding text. We have demonstrated that this approach works well when sensitivity is the overriding concern. It needs further enhancement when elimination of irrelevant concepts is important (e.g. when a disease name is mentioned in a note, but is not associated with the patient).

5. Summary

Over the last 5 years, we have encountered significant barriers to the analysis of data in the ICU. These include inaccuracies in time stamps, the sparseness or incompleteness of information (such as when databases are not fully integrated, or events are not recorded), non-specific labelling (such as when free text is used instead of a standard medical lexicon), contradictory information (such as when two monitors disagree about a measurement) and simply incorrect information (such as FAs). To some extent, we have addressed many of these issues using data fusion techniques, model construction and automated coding. However, the issues described in this paper still present significant barriers to the use of ICU data for decision support, particularly with respect to the sparseness of the data and the non-specific labelling of clinical information in free text. Despite this, current trends in hospital information systems provide for an optimistic horizon, as increasing volumes of more frequent data are being captured automatically from monitors (together with event codes and signal quality indicators). Hospital information systems are also moving towards using universal lexicons. Furthermore, current trends towards open data storage formats and interchange protocols mean that open source tools we have developed are likely to be generally useful on a wide variety of data.

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Special Article

The Quality of Modern Cross-Sectional Ecologic Studies: A Bibliometric Review

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The ecologic study design is routinely used by epidemiologists in spite of its limitations. It is presently unknown how well the challenges of the design are dealt with in epidemiologic research. The purpose of this bibliometric review was to critically evaluate the characteristics, statistical methods, and reporting of results of modern cross-sectional ecologic papers. A search through 6 major epidemiology journals identified all cross-sectional ecologic studies published since January 1, 2000. A total of 125 articles met the inclusion requirements and were assessed via common evaluative criteria. It was found that a considerable number of cross-sectional ecologic studies use unreliable methods or contain statistical oversights; most investigators who adjusted their outcomes for age or sex did so improperly (64%), statistical validity was a potential issue for 20% of regression models, and simple linear regression was the most common analytic approach (31%). Many authors omitted important information when discussing the ecologic nature of their study (31%), the choice of study design (58%), and the susceptibility of their research to the ecological fallacy (49%). These results suggest that there is a need for an international set of guidelines that standardizes reporting on ecologic studies. Additionally, greater attention should be given to the relevant biostatistical literature.

cross-sectional studies; ecological models; epidemiologic methods; research design; review

The ecologic study design is one of the oldest in epidemiology. Its susceptibility to bias has been well known since Robinson (1) popularized the concept of the ''ecological fallacy'' in 1950, although the potential incongruence between group and individual associations was studied by Thorndike (2) as far back as 1939. Since then, there has been significant progress in discovering the many avenues by which ecologic bias may manifest. It is now well documented that the relations between individual- and group-level inferences are often complex, and sometimes even counterintuitive. In spite of this wealth of knowledge, the ecologic design and its fallacy often remain misunderstood (3).

Limitations of the ecologic design have not prevented its use. This is especially true in community health research, where investigators are often interested in both individual-level and ecologic associations with the study outcome. The appeal of ecologic studies reflects interest in collecting information beyond the level of individuals by incorporating aggregate variables as well as those without individual-level analogs. Additionally, ecologic studies do not require information on individuals within groups, making such studies easier to conduct and less expensive. In recent articles, authors have defended the ecologic design and nonindividualistic perspectives in general (4–6), arguing that ecologic analyses need not always be relegated to the role of a poor approximation of other designs, since legitimate insights may exist at the group level. Shifts in the conception of causality and the means by which it exerts itself have also helped in asserting the value of ecologic studies. For these reasons and others, ecologic studies continue to be performed in epidemiology.

Given that ecologic analyses are often misunderstood yet continue to be used, it is important to assess the quality of the literature. Insofar as we are aware, there have been no reviews of ecologic studies. Our objective in this bibliometric review was to address this need by evaluating how well modern ecologic studies are designed, analyzed, and reported in epidemiology. Emphasis was placed on statistical methods and the clarity of reporting. All articles were collected from 6 major epidemiology journals, with attention restricted to cross-sectional etiologic studies. A total of 125 articles published between the years 2000 and 2009 met the inclusion

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requirements and were analyzed according to common evaluative criteria.

MATERIALS AND METHODS

Journal selection

Articles published in 6 high-impact epidemiology journals were selected to collectively represent the discipline. The following journals were chosen: the *American Journal of Epidemiology*, the *Annals of Epidemiology*, *Epidemiology*, the *International Journal of Epidemiology*, the *Journal of Clinical Epidemiology*, and the *Journal of Epidemiology and Community Health*. Although many epidemiologic articles are published outside of pure epidemiology journals, it was nevertheless felt that these 6 would provide a useful core sample for the purposes of the review. Articles published between 2000 and 2009 were included, reflecting our interest in recent applications of ecologic studies.

Search method

Articles were found by reading through each issue of the selected journals for the time period January 1, 2000, through December 31, 2009. An alternative approach would have been to conduct computer searches of databases such as MEDLINE with the use of strategic keywords or Medical Subject Headings. While this may be an adequate means of obtaining data on many types of studies, the ecologic design is so varied in its applications that some researchers may use it unknowingly or without including the kinds of keywords that would be found by search engines or database categorization. Thus, a manual search was performed.

Inclusion and exclusion criteria

The focus of this review was on etiologic cross-sectional studies. Therefore, each study had to employ a cross-sectional design. Ecologic studies using temporal, spatiotemporal, or case-control designs were excluded from the review. For example, Loomis et al. (7) analyzed workplaces to determine risk characteristics for homicide. Workplaces were selected on the basis of whether or not a homicide had taken place there, which made the study design case-control, not cross-sectional.

Additionally, investigators in each study needed to present original research of an etiologic nature. Consequently, spatial descriptive studies or articles that discussed ecologic methodology were excluded. An article did not need to be entirely ecologic to be included in the review, as long as the study's ecologic aspects met the inclusion criteria. Thus, articles with multilevel or individual-level components in addition to ecologic analyses were included as well.

Evaluation criteria

Each article was evaluated according to 3 broad themes: study design, statistical methodology and practices, and quality of reporting.

Study design and focus. We attempted to obtain an impression of the scope of each study, its nontechnical methods, and its focus. Aspects of study design which were analyzed included sample size, given by the number of ecologic units; the level of aggregation at which the units existed, grouped from smallest to largest as census tracts or neighborhoods, municipalities, municipal areas or counties, states or provinces, and nations; whether the inferences were made at the group level or the individual level; and whether the ecologic units were explicitly chosen to suit the hypothesis or were seemingly motivated by convenience or necessity. This last criterion was deemed relevant because many ecologic analyses may be limited by the availability of preexisting aggregate data.

We also recorded the primary outcome for each study according to a set of broad classifications. Whenever possible, outcomes were given one of the following categorizations, which were motivated by the literature itself: cancer, cardiovascular disease, respiratory disease, chronic disease, infectious disease, mortality, suicide or self-harm, and criminal activity. Often, a given study had more than one outcome and thus more than one classification. In this case, all outcomes were recorded.

Statistical methodology. Four aspects of statistical methodology were evaluated: analytic methods, the number of ecologic units relative to the number of regression coefficients modeled, whether any consideration was given to spatial dependence, and methods used to account for confounders. Whenever possible, analytic methods used were grouped by topic. The notation of statistical methodology was intended to provide a measure of the analytical sophistication, diversity, and propriety of current ecologic studies. It was especially important to note the prevalence of simple methods such as ordinary least squares regression and Pearson correlation, since these have well-known limitations in ecologic settings (8, 9).

The statistical validity of each regression model was also observed. Simulation studies have indicated that the validity of statistical inferences is probably compromised when the ratio of covariates to observations or events exceeds a certain threshold (10). The most common recommendation is to have a minimum of 10 observations per covariate, though this may be too conservative for some models (11). Therefore, for each regression analysis, we recorded whether there were fewer than 10 ecologic units per covariate, 10–20 units per covariate, or more than 20 units per covariate. This criterion was developed in the context of individual-level analyses for independent outcomes. It probably only holds approximately for ecologic studies, as event rates and cluster size are likely to play a role in the validity of statistical inferences.

Spatial autocorrelation is a potential concern for many ecologic studies, since units are often aggregated over spatial regions such as contiguous census tracts. The concern is that the omission of spatial effects may cause a loss of information that could otherwise improve parameter estimation, as indicated by recent simulation studies (12, 13). Indeed, explicitly modeling spatial variability may help account for bias when the spatial variation of the covariate is similar to that of disease risk and location itself acts as a confounder (14). However, it is sometimes difficult to know which approaches are based on reasonable assumptions for a given situation, since assumptions are often untestable (15). Nonetheless, we recorded the number of studies accounting for spatial effects

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to report the habits of researchers and the sophistication of the literature.

The final methodological criterion investigated the use of covariate adjustment. Although more complex, confounding may still occur at the ecologic level, and under certain conditions it can be accounted for by the inclusion of covariates. Similarly, we sought to determine whether the covariates were themselves properly adjusted when regressed upon adjusted outcomes; Rosenbaum and Rubin (16) point out that aggregate studies commonly regress age- or sex-standardized outcomes on unstandardized predictors, which may lead to bias. They recommend that regression analyses with group-level data incorporate either adjusted covariates or crude covariates along with moments of the population distribution for the confounder (such as mean age). We report how often this is done in practice.

Quality of reporting. The complexities of the ecologic design are such that in every ecologic study, investigators should justify their choice of study design and present their results in a transparent fashion. Each article should be written so that even readers unfamiliar with the ecological fallacy are mindful of its potential. To this end, we searched each paper to see whether the authors mentioned one of the keywords ''ecologic,'' ''ecological,'' or ''aggregate'' in their article, excluding references. This was intended to estimate the proportion of authors who clearly informed the reader of the study design. We also looked to see whether the authors explicitly justified an ecologic analysis. A justification allows readers to be informed of the rationale for the choice of design and to decide for themselves whether an ecologic analysis was truly warranted. It was not deemed essential for the justification to mention any of the above keywords as long as the authors presented a clear explanation.

We also recorded whether the authors sufficiently cautioned readers, in interpreting their results, against making heedless individual-level inferences, preferably with the use of terms such as ''ecological fallacy'' or ''cross-level bias.'' The statement did not need to be elaborate. It merely needed to point out that the results were not necessarily applicable to different levels of aggregation.

None of the above criteria for reporting are present in the STROBE guidelines for the reporting of observational studies in epidemiology (17), which presently omit ecologic studies.

RESULTS

Our search yielded a total of 125 cross-sectional ecologic papers. Table 1 shows their distribution by journal and year of publication. From Table 1, it can be seen that the number of published cross-sectional studies has remained relatively stable over the past decade.

Study design and focus

The most common area of focus was cancer, which comprised 16% of all primary outcomes. Other research areas such as mortality, chronic disease, and cardiovascular disease followed behind, representing 14%, 13%, and 10% of total analyses, respectively. Infectious and respiratory diseases

Table 1. Numbers of Cross-Sectional Ecologic Studies Included in a Bibliometric Review, by Journal and Period, 2000–2010

Journal	2000–2002	2003–2005	2006–2009	Total
American Journal of Epidemiology	4	3	5	12
Annals of Epidemiology	2	4	6	12
Epidemiology	5	0	7	12
International Journal of Epidemiology	12	9	7	28
Journal of Clinical Epidemiology	1	1	2	4
Journal of Epidemiology and Community Health	14	20	23	57
Total	38	37	50	125

Table 2. Results for Study Design and Focus Criteria in a Bibliometric Review of Ecologic Studies, 2000–2010

Evaluation Criterion	Observed Frequency (n = 125)	
	No.	%
Sample size		
Median	70	
Maximum	~200,000	
Minimum	8	
Level of data aggregation		
Census tract or neighborhood	48	38
City or town	11	9
County	22	18
Province or state	15	12
Nation or nation-cluster	25	20
Other	4	3
Level of inference		
Individual	43	34
Ecologic	34	27
Unclear	48	38
Prespecification of ecologic units (yes)	22	18
Classification of primary outcome(s)[a]		
Violent crime	8	6
Suicide and self-harm	9	7
Respiratory disease	10	8
Infectious disease	11	9
Cardiovascular disease	13	10
Chronic disease	16	13
Mortality	18	14
Cancer	20	16
Other	26	21

[a] Total exceeds 125 because categories were not mutually exclusive.

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Table 3. Results for Statistical Methodology Criteria in a Bibliometric Review of Ecologic Studies, 2000–2010

Evaluation Criterion	Observed Frequency (n = 125)	
	No.	%
Analytic methodology[a]		
Ordinary least squares regression	47	31
Poisson regression	20	13
Weighted linear regression	18	12
Nonparametric methods	12	8
Pearson or Spearman correlations	12	8
Bayesian models	12	8
Logistic regression	7	5
Negative binomial regression	7	5
Other	18	12
Validity of regression[a]		
<10 units per covariate	27	20
10–20 units per covariate	48	36
>20 units per covariate	43	32
Not applicable	11	8
Unclear	5	4
Use of covariates (yes)	92	74
Spatial analysis (yes)	26	21
Did not properly adjust for covariates (n = 36)	23	64

[a] Total exceeds 125 because categories were not mutually exclusive.

Table 4. Results for Quality-of-Reporting Criteria in a Bibliometric Review of Ecologic Studies, 2000–2010

Evaluation Criterion	Observed Frequency (n = 125)	
	No.	%
Statement of study design (yes)	86	69
Justification of study design (yes)	52	42
Discussion of cross-level bias		
Yes	55	44
Not applicable	9	7

comprised 9% and 8% of all outcomes, respectively; suicide and self-harm accounted for another 7%; and criminal activity such as homicide accounted for 6% (Table 2). Twenty-six analyses did not fall into one of the above broad subclassifications, with outcomes ranging from pollution exposure to regional disparity.

It appears that much cross-sectional research potentially has its data dictated by either the convenience or the necessity of using preexisting information. We suspect that this is the case after observing that only in 22 studies (18%) did authors implicitly or explicitly justify their choice of ecologic units. In a few cases, the units of aggregation were constructed specifically for the study.

Potentially, investigators in many other studies simply used what was available. With regard to level of aggregation, many studies utilized small areas. Ecologic units aggregated approximately at the level of census tracts were by far the most numerous, being the observational units for 48 studies (38%). Large international studies were the second most prevalent, being the focus of 25 studies (20%). All other levels of aggregation were present as follows: towns and cities, 9%; counties (which include not only cities but their contiguous areas as well), 18%; and states or provinces, 12%. Four studies could not have their ecologic units classified as above, either because the units were disparate areas specifically constructed for the study or because they were nonspatial.

Many investigators intended their inferences to be applied at the individual level. Of the 125 articles in the review, 43 (34%) clearly had conclusions or hypotheses concerned with individual-level risks and outcomes. In 34 studies, authors unambiguously tailored their discussions to group-level inferences (27%). However, this should be taken lightly, since a lack of clarity on the part of 48 studies (38%) prevented us from confidently determining their intended levels of inference. The vast majority of outcomes were aggregate in nature (97%), meaning they had individual-level analogs which could apply to units within groups. Nonaggregate outcomes included measures such as regional socioeconomic inequality and governmental health-care expenditures.

Sample sizes ranged from very small to extremely large. The minimum sample size was 8 ecologic units, and the maximum was approximately 200,000. The median sample size was 70. Fifty-four percent of studies relied on fewer than 100 observations.

Quality of statistical methods and practices

The literature is highly diverse in its methodological complexity. Nevertheless, there were notable preferences. The most common approach was to use either ordinary least squares regression or Poisson regression, methods that were employed in 47 and 20 analyses, respectively (Table 3). Weighted linear regression was the third most common approach, being used in 18 analyses. Nonparametric approaches and simple Pearson or Spearman correlations each accounted for 12 analyses. The more complex approaches of Bayesian analytic methods, logistic regression, and negative binomial regression appeared in 12, 7, and 7 articles, respectively. An additional 18 analyses did not fall into any of these categories, employing disparate techniques such as sophisticated geospatial methods, spatial autoregressive models, and simple calculations of standardized mortality ratios. Note that these counts do not refer to the number of studies but rather to the number of analyses, since investigators may have used more than 1 method. In terms of covariate adjustment, 92 studies obtained adjusted results, either by stratifying the analyses or using additional covariates in the models. Unfortunately, in 23 of 36 papers, the investigators failed to adjust covariates for age or sex when the outcomes had been standardized for these potential confounders. Thus, it would appear that in over half of all studies using standardized outcomes, investigators were at risk of publishing biased inferences.

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There was mixed performance with regard to the statistical validity of regression models. Although we were unable to determine the ratio of ecologic units to predictor variables for 5 studies, we found that of the 109 studies with regression models, 27 had fewer than 10 units per covariate. Forty-eight analyses had 10–20 units per covariate, and 43 regression analyses had more than 20.

One-fifth of all studies included some investigation of spatial effects. Techniques such as spatially autocorrelated regression models and spatial scan statistics appeared to be the most common. Some of these techniques merely detect and describe spatial clustering, while others seek to incorporate spatial data into effect measure estimation.

Quality of reporting

Of the papers reviewed, authors in 86 (69%) clearly specified their study design by mentioning ''ecologic,'' ''ecological,'' or ''aggregate'' at some point in the main body of their work in a clear and relevant fashion (Table 4). Only 52 studies (42%) adequately and explicitly justified an ecologic analysis, while the other articles did not provide any rationale whatsoever as to why the design was either necessary or desirable. Perhaps most significantly, we discovered that in the majority of the reviewed studies, investigators did not sufficiently inform the reader about the possibility of cross-level bias; in 55 articles (44%), authors tempered their results in some fashion, whereas in 61 (49%) they did not. For 9 articles this criterion did not apply, either because the ecologic investigations appeared alongside multilevel analyses or because the predictors were entirely group-level in nature, thereby precluding individual-level interpretations.

DISCUSSION

Ecologic research in epidemiology is extremely diverse in its applications and sophistication. However, it appears that a combination of methodological limitations, apparent dependence on preexisting data, and insufficient reporting has compromised the quality and clarity of some articles.

Broadly speaking, the distribution of the reviewed studies could best be described as bimodal. Many investigators performed elementary analyses coupled with unclear, insufficient reporting. At the same time, a significant number of studies employed analyses appropriately suited to the study design and presented the results in a model fashion. In between these extremes, many studies were adequate with respect to 1 or 2 of the 3 fundamentals, only to perform unsatisfactorily in another.

In terms of statistical methodology, researchers must better heed many of the important technical results published in the biostatistical and epidemiologic literature. More attention needs to be paid to proper covariate adjustment and the validity of regression models. It is also apparent that linear regression and simple correlation coefficients have become the default techniques for many ecologic studies. Given their documented susceptibility to ecologic bias, this may indicate that some technical details of group-level analysis remain unknown or misunderstood. While the validity of these approaches must be decided on a case-by-case basis, the fact that over half of analyses rely on them suggests that ecologic researchers depend too often on techniques of uncertain reliability.

The area of greatest concern in this review was the quality of reporting. The results showed a lack of important information when it came to stating the origins of the data, the intended level of inference, the nature of the study design, and the study's limitations. The sensitive and diverse nature of ecologic analyses makes it essential that readers from all backgrounds be sufficiently informed. Too often, authors seemingly assumed that their choice of study design was self-evident, did not require justification, and provided unambiguous results.

For the selection of ecologic groups, the ideal is that in every study investigators choose their units according to the specific causal constructs of their research. However, as Morgenstern (18) stated, ecologic studies are often made possible by preexisting data. Since few investigators made their selection criteria known, there is often reason to wonder how or why the data were chosen. The high prevalence of studies conducted at the census tract and national levels may be a result of the fact that easily available information tends to exist at these scales of aggregation. In future papers, researchers should state why their particular units and levels of aggregation were suitable for the hypothesis at hand.

In accordance with recommendations made by von Elm et al. (17), we submit that there is presently a need for a set of guidelines to standardize the reporting of results from ecologic studies. Many of the concerns we identified could be attenuated or prevented altogether if such a document were published. Providing a set of guidelines that not only lists detailed criteria but also explains their importance and the potential consequences of their neglect may emphasize their relevance to the research community. From the results of this review, it is clear that the cross-sectional ecologic design continues to be an important approach relied upon by epidemiologists and public health researchers, and therefore it would be worthwhile to augment the STROBE document (17) with recommendations for the reporting of ecologic findings.

In Appendix Table 1, we list 9 items that could serve as a useful beginning for updating the STROBE document. For ease of reference, the table has the same headings, titles, and numberings as the STROBE document itself (17). Ideally, future discussions on this topic by others in the epidemiology community would provide further critiques of and refinements to this list.

Difficulties in correctly designing, analyzing, and reporting results are not unique to ecologic studies. Analogous methodological errors have been reported for both observational studies (19) and randomized trials (20). There may be some reason for optimism, since Hopewell et al. (20) did find some improvement in the reporting of randomized trials following release of the CONSORT statement (21). This provides further motivation for developing reporting guidelines for ecologic studies.

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(Appendix follows)

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Appendix Table 1. Suggested Additions to the STROBE Document for Ecologic Reporting[a]

STROBE Section	Recommendation Addition(s)
Title and abstract	Indicate the study's design with a commonly used term in the title or abstract.
	Ecologic study—Use one of the following terms in your description: "ecological," "ecologic," or "aggregate."
Introduction	
Objectives	State specific objectives, including any prespecified hypotheses.
	Ecologic study—Specify the level(s) of inference to which your investigation is intended to apply.
Methods	
Study design	Present key elements of the study design early on in the paper.
	Ecologic study—Provide a rationale or justification for the design, taking your study objectives into account.
Participants	Ecologic study—Give the eligibility criteria for the ecologic units, as well as their sources and any sampling methods used. Provide a rationale for their selection. If the units were aggregated for the study, explain how this was done and the criteria by which they were constructed.
Discussion	
Limitations	Discuss limitations of the study, taking into account sources of potential bias or imprecision.
	Ecologic study—Provide a discussion that either informs the reader of the potential for cross-level bias or explains why it is not a possibility for your results and inferences.

Abbreviation: STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.
[a] Patterned after the STROBE statement (17).

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BMJ Global Health

Reduction of secondary transmission of SARS-CoV-2 in households by face mask use, disinfection and social distancing: a cohort study in Beijing, China

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ABSTRACT

Introduction Transmission of COVID-19 within families and close contacts accounts for the majority of epidemic growth. Community mask wearing, hand washing and social distancing are thought to be effective but there is little evidence to inform or support community members on COVID-19 risk reduction within families.

Methods A retrospective cohort study of 335 people in 124 families and with at least one laboratory confirmed COVID-19 case was conducted from 28 February to 27 March 2020, in Beijing, China. The outcome of interest was secondary transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) within the family. Characteristics and practices of primary cases, of well family contacts and household hygiene practices were analysed as predictors of secondary transmission.

Results The secondary attack rate in families was 23.0% (77/335). Face mask use by the primary case and family contacts before the primary case developed symptoms was 79% effective in reducing transmission (OR=0.21, 95% CI 0.06 to 0.79). Daily use of chlorine or ethanol based disinfectant in households was 77% effective (OR=0.23, 95% CI 0.07 to 0.84). Wearing a mask after illness onset of the primary case was not significantly protective. The risk of household transmission was 18 times higher with frequent daily close contact with the primary case (OR=18.26, 95% CI 3.93 to 84.79), and four times higher if the primary case had diarrhoea (OR=4.10, 95% CI 1.08 to 15.60). Household crowding was not significant.

Conclusion The study confirms the highest risk of transmission prior to symptom onset, and provides the first evidence of the effectiveness of mask use, disinfection and social distancing in preventing COVID-19. We also found evidence of faecal transmission. This can inform guidelines for community prevention in settings of intense COVID-19 epidemics.

Summary box

What is already known?

- Mitigation of the COVID-19 pandemic depends solely on non-pharmaceutical interventions until drugs or vaccines are available. Transmission of COVID-19 within families and close contacts accounts for the majority of epidemic growth. Community mask wearing, hand washing and social distancing are thought to be effective but the evidence is not clear.

What are the new findings?

- The overall secondary attack rate in households was 23.0%. Face masks were 79% effective and disinfection was 77% effective in preventing transmission, while close frequent contact in the household increased the risk of transmission 18 times, and diarrhoea in the index patient increased the risk by four times. The results demonstrate the importance of the pre-symptomatic infectiousness of COVID-19 patients and shows that wearing masks after illness onset does not protect.

What do the new findings imply?

- The findings inform universal face mask use and social distancing, not just in public spaces, but inside the household with members at risk of getting infected. This further supports universal face mask use, and also provides guidance on risk reduction for families living with someone in quarantine or isolation, and families of health workers, who may face ongoing risk.

INTRODUCTION

In the absence of a vaccine for COVID-19, non-pharmaceutical interventions (NPIs) are the only available disease control measures. We have shown that population level NPIs, including travel bans and the national emergency response, were effective in flattening

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the COVID-19 epidemic curve in China.[1] However, the effect of other NPIs, such as mask use and hygiene practices, have not been well studied in the COVID-19 pandemic.

In the USA, the use of face masks in the community has been recommended.[2] It is thought that universal face mask use (UFMU) may reduce outward transmission from asymptomatically infected people and protect well people from becoming infected. However, the World Health Organization and Public Health England recommend against UFMU on the grounds that there is little evidence from randomised controlled trials to support this. Some experts suggest that in a pandemic, the precautionary principle should be used and UFMU encouraged as it is unlikely to cause harm and may result in public health gain.[3 4] In countries where personal protective equipment is scarce, people are making their own masks.

In China, over 70% of human-to-human transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred in families.[5 6] However, data to inform COVID-19 risk reduction in households are unavailable. Given epidemic growth is dominated by household transmission,[5 6] studying the use of NPIs, such as face masks, social distancing and disinfection in the household setting, may inform community epidemic control and prevent transmission of COVID-19 in households.

METHODS

Study population and design

We conducted a retrospective cohort study involving families of laboratory confirmed COVID-19 cases in Beijing, China. We defined family members as those who had lived with primary cases in a house for 4 days before and for more than 24 hours after the primary cases developed illness related to COVID-19. As of 21 February 2020, all laboratory confirmed COVID-19 cases reported in Beijing were enrolled in our study and followed-up. The outcome of interest was secondary transmission in the household. Families with secondary transmission were defined as those where some or all of the family members become infected within one incubation period (2 weeks) of symptom onset of the primary case.

To analyse the predictors of household transmission, we compared families with and without secondary transmission for various measured risk factors, preventive interventions and exposures.

Definition of confirmed case

According to national prevention and control guideline (fifth edition),[7] confirmed cases were those who met the clinical, epidemiological and laboratory testing criteria for COVID-19 simultaneously.

1. Clinical criteria included: (a) fever and/or one or more respiratory symptoms; (b) radiological evidence of pneumonia; (c) white blood cell count normal or decreased, and lymphocyte count decreased at the early stage of illness.
2. Epidemiological criteria included: (a) visits to/living in Wuhan or cities around Wuhan or other communities which had already reported COVID-19 cases in the 14 days prior to the onset of symptoms; (b) having contact with a person known to have infection with SARS-CoV-2 in the 14 days prior to onset of symptoms; (c) having contact with a person who had fever or respiratory symptoms and came from Wuhan or adjacent cities or other communities which had already reported COVID-19 cases in the 14 days prior to onset of symptoms; (d) being one of the cluster cases.

Suspected cases met one of the epidemiological criteria and any two of the clinical criteria, or met all of the clinical criteria. Confirmed cases were those suspected cases who met one of the following criteria: (a) respiratory or blood specimen tested positive for SARS-CoV-2 by real time reverse transcriptase-polymerase chain reaction; (b) virus in respiratory or blood specimen was highly homologous with known SARS-CoV-2 through gene sequencing.

Data collection

A three part structured questionnaire was developed. The first part included demographic and clinical information of the primary case. The second part was mainly focused on the primary case's knowledge about and attitudes toward COVID-19, and their self-reported practices (mask wearing, social distancing, living arrangements) and activities in the home. The third part was about self-reported behaviours of all family members, as well as the family's accommodation and household hygiene practices from 4 days before the illness onset to the day the primary case was isolated, including room ventilation, room cleaning and disinfection. Close contact was defined as being within 1 m or 3 feet of the primary case, such as eating around a table or sitting together watching TV. The frequency of contact, disinfection and ventilation was measured.

After diagnosis, the primary case was hospitalised as per standard practice in Beijing. Eligible primary cases and their family members were interviewed between 28 February and 8 March. Data on the primary case were extracted from epidemiological investigating reports from Beijing Centre for Disease Prevention and Control and supplemented by interview.

The clinical severity of the COVID-19 case was categorised as mild, severe or critical. Mild disease included non-pneumonia and mild pneumonia cases. Severe disease was characterised by dyspnoea, respiratory frequency ≥30/min, blood oxygen saturation ≤93%, PaO2/FiO2 ratio <300 and/or lung infiltrates >50% within 24–48 hours. Critical cases were those who exhibited respiratory failure, septic shock and/or multiple organ dysfunction/failure.[8]

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Statistical analysis

Risk factors for secondary transmission were analysed by characteristics of the primary case, characteristics of well family members and household hygiene practices. Categorical variables are presented as counts and percentages, and continuous variables as medians (IQR). The χ^2 test and Fisher exact test were applied to compare difference between groups when necessary. A composite COVID-19 knowledge score and hand hygiene score were created with multiple sub-questions. A multivariable logistic regression model was used to identify risk factors associated with SARS-CoV-2 household transmission. Univariable analysis was first performed with all measures and only those variables significant at $p<0.1$ could be selected in the following multivariable logistic regression analysis. Backward elimination was performed to establish a final model retaining those with $p<0.05$ in the model. Statistical analyses were performed using SAS software (V.9.4).

Ethics statement

As our study was embedded within the COVID-19 prevention and control practice within public health units, and the telephone interview was a supplementary survey of the epidemiological field investigation, ethics approval was not required. We obtained subjects' verbal informed consent before the start of the interviews.

Patient and public involvement

No patients or the public were involved in the study design, setting the research questions, interpretation or writing up of results, or reporting of the research.

RESULTS

As of 21 February 2020, 399 confirmed COVID-19 cases in 181 families were reported in Beijing. Four family clusters were excluded because we were unable to determine whether there was secondary transmission or co-exposure, leaving 177 families. After reviewing information in the epidemiological investigation reports and survey calls, 40 families were excluded as they did not meet the study inclusion criteria. A further 13 families declined to be interviewed and were also excluded, leaving 124 families for study (figure 1).

Over the 2 weeks of follow-up from onset of the primary case, secondary transmission occurred in 41/124 families (77 secondary cases), and 83/124 families had no secondary transmission. The overall secondary attack rate in families was 23.0% (77/335). In the secondary transmission group, 41 primary cases caused 77 secondary cases, with a median secondary case number in families of 2 (IQR 1–2). In the secondary transmission group, the secondary attack rate in children <18 years of age was 36.1% (13/36), compared with 69.6% (64/92) in adults, and the difference between these two age groups was significant (χ^2=12.08, $p<0.001$). The median age of the 13 secondary child cases was 3 years (IQR 2–6), 12/13 were

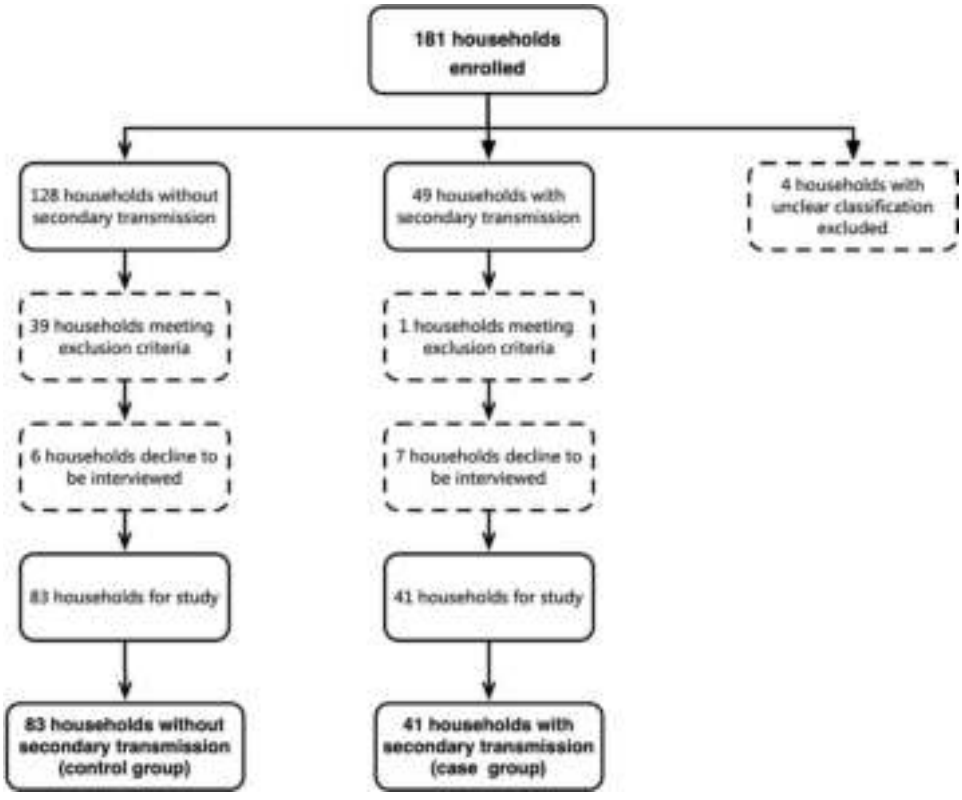

Figure 1 Selection and inclusion of interviewing subjects. Summary of household enrolment, and inclusion and interview response in the analysis of SARS-CoV-2 household transmission in Beijing, China.

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Table 1 Characteristics of primary cases of COVID-19: univariable analysis

Primary cases	Total (n (%)) (n=124)	Families without transmission (n (%)) (n=83)	Families with transmission (n (%)) (n=41)	P value	Unadjusted OR (95% CI)
Age (years) (median (IQR))	45.0 (35.7–60.0)	42.0 (34.0–57.5)	52.0 (39.3–61.0)	–	–
<18	0	0	0	–	–
18–59	92 (74.2)	63 (75.9)	29 (70.7)	–	Ref
≥60	32 (25.8)	20 (24.1)	12 (29.3)	0.54	1.30 (0.56 to 3.02)
Sex	–	–	–	–	–
Men	61 (49.2)	40 (48.2)	21 (51.2)	–	Ref
Women	63 (50.8)	43 (51.8)	20 (48.8)	0.75	0.89 (0.42 to 1.87)
Education level	–	–	–	–	–
High school or lower	26 (21.0)	18 (21.7)	8 (19.5)	–	Ref
Bachelor degree	69 (55.6)	47 (56.6)	22 (53.7)	0.53	0.75 (0.30 to 1.86)
Graduate degree	29 (23.4)	18 (21.7)	11 (26.8)	0.65	0.77 (0.25 to 2.38)
Clinical severity	–	–	–	–	–
Mild	96 (77.4)	63 (75.9)	33 (80.4)	–	Ref
Severe	20 (16.1)	16 (19.3)	4 (9.8)	0.22	0.48 (0.15 to 1.54)
Critical	8 (6.5)	4 (4.8)	4 (9.8)	0.38	1.91 (0.45 to 8.13)
Fever (≥37.3℃)	–	–	–	–	–
No	18 (14.5)	9 (10.8)	9 (22.0)	–	Ref
Yes	106 (85.5)	74 (89.2)	32 (78.0)	0.11	0.43 (0.16 to 1.19)
Cough*	–	–	–	–	–
No	66 (53.2)	45 (54.2)	21 (51.2)	–	Ref
Yes	58 (46.8)	38 (45.8)	20 (48.8)	0.75	1.13 (0.53 to 2.39)
Diarrhoea†	–	–	–	–	–
No	109 (87.9)	76 (91.6)	33 (80.5)	–	Ref
Yes	15 (12.1)	7 (8.4)	8 (19.5)	0.08	2.63 (0.88 to 7.85)
Comorbidity	–	–	–	–	–
No	103 (83.1)	72 (86.7)	31 (75.6)	–	Ref
Yes	21 (16.9)	11 (13.3)	10 (24.4)	0.13	2.11 (0.81 to 5.48)
Time interval from illness onset to first hospital visit (days) (median (IQR))‡	3.0 (1.0–7.0)	3.0 (1.0–7.0)	4.0 (2.0–7.0)	–	–
≤2	47 (37.9)	35 (42.2)	12 (29.3)	–	Ref
>2	77 (62.1)	48 (57.8)	29 (70.7)	0.17	1.76 (0.79 to 3.93)
Time interval from illness onset to medical isolation (days) (median (IQR))	5.0 (2.0–7.0)	5.0 (2.0–7.0)	5.0 (3.0–9.0)	–	–
≤2	32 (25.8)	26 (31.3)	6 (14.6)	–	Ref
>2	92 (74.2)	57 (68.7)	35 (85.4)	**0.05**	2.66 (1.00 to 7.12)
Time interval from illness onset to laboratory confirmation (days) (median (IQR))	7.0 (4.7–10.2)	7.0 (4.4–9.9)	8.0 (5.6–12.9)	–	–
≤3	16 (12.9)	13 (15.7)	3 (7.3)	–	Ref
>3	108 (87.1)	70 (84.3)	38 (92.7)	0.20	2.35 (0.63 to 8.77)
Knowledge score on COVID-19 before illness onset (14 in total) (median (IQR))§	5 (0–9)	5 (0–9)	5 (0–10)	–	–
≥10	31 (25.0)	18 (21.7)	13 (31.7)	–	Ref
3–9	45 (36.3)	32 (38.6)	13 (31.7)	0.24	0.56 (0.22 to 1.47)
≤2	48 (38.7)	33 (39.7)	15 (36.6)	0.33	0.63 (0.25 to 1.61)
Self-awareness of being infected with SARS-CoV-2 when developed illness	–	–	–	–	–
Likely	45 (36.3)	35 (42.2)	10 (24.4)	–	Ref

Continued

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Table 1 Continued

Primary cases	Total (n (%)) (n=124)	Families without transmission (n (%)) (n=83)	Families with transmission (n (%)) (n=41)	P value	Unadjusted OR (95% CI)
Unlikely	79 (63.7)	48 (57.8)	31 (75.6)	0.06	2.26 (0.98 to 5.21)
Knowledge of their own infectiousness after illness onset	–	–	–	–	–
Likely	84 (67.7)	62 (74.7)	22 (53.7)	–	Ref
Unlikely	40 (32.3)	21 (25.3)	19 (46.3)	0.02	2.55 (1.16 to 5.61)
Wear mask at home after illness onset¶	–	–	–	–	–
Never	41 (33.1)	24 (28.9)	17 (41.5)	–	Ref
Sometimes	37 (29.8)	21 (25.3)	16 (39.0)	0.76	1.15 (0.46 to 2.87)
All the time	46 (37.1)	38 (45.8)	8 (19.5)	0.02	0.30 (0.11 to 0.82)
Self-isolated after illness onset	–	–	–	–	–
Yes	79 (63.7)	58 (69.9)	21 (51.2)	–	Ref
No	45 (36.3)	25 (30.1)	20 (48.8)	0.05	2.17 (1.00 to 4.70)
Eat separately at home after illness onset	–	–	–	–	–
Yes	70 (56.5)	54 (65.1)	16 (39.0)	–	Ref
No	54 (43.5)	29 (34.9)	25 (61.0)	0.008	2.86 (1.32 to 6.19)
Eat with separate tableware	–	–	–	–	–
Yes	81 (65.3)	58 (69.9)	23 (56.1)	–	Ref
No	43 (34.7)	25 (30.1)	18 (43.9)	0.14	1.78 (0.82 to 3.88)
Score on hand hygiene (8 in total) (with 11 missing values) (median (IQR))	8 (7–8)	8 (7–8)	7 (6–8)	–	–
≥6	103 (91.2)	68 (93.2)	35 (87.5)	–	Ref
4–5	7 (6.2)	4 (5.5)	3 (7.5)	0.63	1.46 (0.31 to 6.88)
≤3	3 (2.6)	1 (1.3)	2 (5.0)	0.28	3.88 (0.34 to 44.29)

*Primary case ever had the symptom of cough when living with others at home.
†Primary case ever had the symptom of diarrhoea (change of character of stool) when living with others at home.
‡Date on which cases self-reported the appearance of either fever (≥37.3℃) or any respiratory symptom during epidemiological investigation. Date of hospital visit was the earliest date that cases sought medical service for COVID-19 related illness.
§A composite variable involving the primary case's knowledge on the infectivity of SARS-CoV-2, contagious population, transmission route, susceptible population, incubation period, common symptoms and preventive measures.
¶Refers to the primary case or family members wearing a face mask at home, regardless of whether it was a N95 mask, disposable surgical mask or a common mask, including cloth mask. Wearing masks all the time means the primary case wears a mask all the time except when having dinner or sleeping at home.
**A composite variable involving the primary case's hand washing practice, including using running water, washing frequency, using sanitiser and under what conditions.

mild and 1/13 was asymptomatic. Of 64 secondary adult cases, 82.8% (53/64) were mild, 10.9% (7/64) were severe, 1.6% (1/64) was critical and 4.7% (3/64) were asymptomatic. No statistically significant difference was observed in clinical severity between 41 index adult cases (table 1) and 64 secondary adult cases for the secondary transmission group (p=0.18).

The univariable analysis for association with secondary transmission of SARS-CoV-2 within families is shown in tables 1–3. Significant associations were:

1. Characteristics, behaviours and knowledge of the primary case: having diarrhoea, interval from illness onset to medical isolation >2 days, self-awareness of being infected with SARS-CoV-2 when the primary case developed the illness, lack of knowledge of their own infectiousness, mask wearing in the home after illness onset, failing to self-isolate and not eating separately were associated with transmission (table 1).
2. Behaviours of family members: having daily close contact with the primary case at home, and number of family members wearing a mask in the home before and after the primary case's illness onset date were associated with transmission (table 2).
3. Household practices: frequency of using chlorine or ethanol based disinfectant for household cleaning and household ventilation duration were protective (table 3).

In multivariable logistic regression model, four factors remained significantly associated with secondary transmission. The primary case having diarrhoea in the home and daily close contact with the primary case in the home increased the risk. Transmission was significantly reduced

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Table 2 Characteristics of well family members: univariable analysis

Family members	Total (n (%)) (n=121)	Families without transmission (n (%)) (n=81)	Families with transmission (n (%)) (n=40)	P value	Unadjusted OR (95% CI)
Family size (median (IQR))	4 (3–5)	3 (3–5)	4 (3–6)	–	–
≤3	56 (46.3)	41 (50.6)	15 (37.5)	–	Ref
>3	65 (53.7)	40 (49.4)	25 (62.5)	0.18	1.71 (0.79 to 3.71)
Close contact with primary cases at home (within 1 m or 3 feet) (No of times)*	–	–	–	–	–
0	41 (33.9)	36 (44.4)	5 (12.5)	–	Ref
1–3	61 (50.4)	38 (46.9)	23 (57.5)	**0.005**	4.55 (1.57 to 13.20)
≥4	19 (15.7)	7 (8.7)	12 (30.0)	**<0.001**	12.34 (3.30 to 46.23)
No of family members wearing mask at home before primary case's illness onset date (median (IQR))†	0 (0–1)	0 (0–2)	0 (0–0)	–	–
None	90 (74.4)	54 (66.7)	36 (90.0)	–	Ref
One or more	31 (25.6)	27 (33.3)	4 (10.0)	**0.009**	0.22 (0.07 to 0.69)
No of family members wearing mask at home after primary case's illness onset date (median (IQR))‡	1 (0–3)	2 (0–3)	0 (0–3)	–	–
None	47 (38.8)	26 (32.1)	21 (52.5)	–	Ref
Some	38 (31.4)	24 (29.6)	14 (35.0)	0.47	0.72 (0.30 to 1.73)
All	36 (29.8)	31 (38.3)	5 (12.5)	**0.004**	0.20 (0.07 to 0.60)

*Family members stay with the primary case at a short distance (within 1 m or 3 feet) for more than 10 min at a time. For example, they have dinner with the primary case around a table or watch TV sitting near.
†Before the primary case developed the illness, the primary case or his/her family contacts wear masks all the time at home.
‡When the primary case developed the illness, the primary case's family contacts wear masks all the time living with the primary case at home.

by frequent use of chlorine or ethanol based disinfectant in households and family members (including the primary case) wearing a mask at home before the primary case developed the illness (table 4).

DISCUSSION

This study confirms that the highest risk of household transmission is prior to symptom onset, but that precautionary NPIs, such as mask use, disinfection and social distancing in households can prevent COVID-19 transmission during the pandemic. This study is the first to confirm the effectiveness of mask use prior to symptom onset by family members, daily household disinfection and social distancing in the home. This could inform precautionary guidelines for families to reduce intrafamilial transmission in areas where there is high community transmission or other risk factors for COVID-19. Household transmission is a major driver of epidemic growth.[5 6] Further, in countries where health system capacity is exhausted, many people with infection are required to self-isolate at home, where their household contacts will be at risk of infection. In our study, the median family size of the 124 families was 4 (range 2–9), usually with children, parents and grandparents, which is similar to the social structure of most Chinese families.[9] Therefore, the risk of SARS-CoV-2 household transmission is high if a primary case was introduced and no measure was adopted. We showed that NPIs are effective at preventing transmission, even in homes that are crowded and small. UFMU is a low risk intervention with potential public health benefits.[3 4] The results suggest that community face mask use is likely to be the most effective inside the household during severe epidemics.

Almost a quarter of family members became infected, and the findings suggest that the risk was highest either before symptom onset or early in the clinical illness, as most primary cases were hospitalised after diagnosis, and interventions were not effective if applied after symptom onset. In the univariate analysis, wearing a mask after illness onset was significant, but in multivariate analysis, only wearing it before symptom onset was effective. Viral load is highest in the 2 days before symptom onset and on the first day of symptoms, and up to 44% of transmission is during the pre-symptomatic period in settings with substantial household clustering.[10 11] This supports UFMU, probably by reducing onward transmission from people in the pre-symptomatic phase of the illness[12 13] as well as protecting well mask users. Randomised clinical trials of face masks in the household have confirmed protection against other respiratory viruses if compliant, if used within 36 hours of the primary case symptom onset, and alone or in combination with hand hygiene.[14 15] This study now provides specific evidence for UFMU in settings of high epidemic growth to protect against COVID-19. In our study, 91.2% (103/113) of primary cases had a high score on hand hygiene, but it was not effective, confirming the results of previous randomised clinical trials which showed hand

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Table 3 Characteristics of the residence and household practices: univariable analysis between two family groups

Residence and household practices	Total (n (%)) (n=121)	Families without transmission (n (%)) (n=81)	Families with transmission (n (%)) (n=40)	P value	Unadjusted OR (95% CI)
Residential area per capita (m^2) (median (IQR))	25.0 (17.3–35.0)	28.0 (18.0–35.8)	20.0 (16.9–31.8)	–	–
≤20	50 (41.3)	30 (37.1)	20 (50.0)	–	Ref
20–40	49 (40.5)	36 (44.4)	13 (32.5)	0.16	0.54 (0.23 to 1.27)
≥40	22 (18.2)	15 (18.5)	7 (17.5)	0.51	0.70 (0.24 to 2.02)
No of bedrooms per person (median (IQR))	0.7 (0.5–1.0)	0.7 (0.5–1.0)	0.7 (0.5–1.0)	–	–
≥1	39 (32.2)	28 (34.6)	11 (27.5)	–	Ref
<1	82 (67.8)	53 (65.4)	29 (72.5)	0.49	1.34 (0.59 to 3.08)
No of washrooms (median (IQR))	1 (1–2)	1 (1–2)	1 (1–2)	–	–
2 or more	34 (28.1)	23 (28.4)	11 (27.5)	–	Ref
1	87 (71.9)	58 (71.6)	29 (72.5)	0.87	1.07 (0.46 to 2.49)
Frequency of room cleaning (wet type)	–	–	–		–
Once in 1–2 days	83 (68.6)	59 (72.8)	24 (60.0)	–	Ref
Once in >2 days	38 (31.4)	22 (27.2)	16 (40.0)	0.11	1.90 (0.86 to 4.19)
Frequency of chlorine or ethanol based disinfectant use for house cleaning*	–	–	–	–	–
Once in 2 or more days	86 (71.1)	50 (61.7)	36 (90.0)	–	Ref
Once a day or more	35 (28.9)	31 (38.3)	4 (10.0)	0.003	0.18 (0.06 to 0.55)
Ventilation duration per day (hours) (median (IQR))†	2.0 (1.0–6.0)	3.0 (1.5–8.0)	1.8 (1.0–4.0)	–	–
>1	85 (70.2)	62 (76.5)	23 (57.5)	–	Ref
≤1	36 (29.8)	19 (23.5)	17 (42.5)	0.02	2.55 (1.14 to 5.70)

*When cleaning the house, disinfectant which contains chlorine or ethanol is used to disinfect the floor, door and window handles, indoor air, tables and toilets.
†Ventilation means the practice of opening the window to allow convection of indoor air.

Table 4 Risk factors for SARS-CoV-2 household transmission: multivariable analysis

Risk factor	Adjusted OR	95% CI	P value
Primary case has diarrhoea	–	–	–
No	–	–	Ref
Yes	4.10	(1.08 to 15.60)	0.04
Close contact at home with primary cases (within 1 m or 3 feet) (times)	–	–	–
0	–	–	Ref
1–3	3.30	(1.05 to 10.40)	0.04
≥4	18.26	(3.93 to 84.79)	<0.001
No of family members (including primary case) wearing a mask at home before the primary case's illness onset date	–	–	–
None	–	–	Ref
1 or more	0.21	(0.06 to 0.79)	0.02
Frequency of chlorine or ethanol based disinfectant use for house cleaning	–	–	–
Once in 2 or more days	–	–	Ref
Once a day or more	0.23	(0.07 to 0.84)	0.03

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hygiene alone did not protect against respiratory transmissible viruses, but masks combined with hand hygiene did have effect.[16]

As the compliance of UFMU would be poor in the home, there was difficulty and also no necessity for everyone to wear masks at home. We recommended that those families with members who were at risk of getting infected with SARS-CoV-2 (such as ever having contact with a COVID-19 patient, medical workers caring for a COVID-19 patient or having a history of travelling to high risk areas) should apply UFMU to reduce the risk of household transmission.

This study showed that social distancing within the home is effective and having close contact (within 1 m or 3 feet, such as eating around a table or sitting together watching TV) is a risk factor for transmission. The study also provides evidence of effectiveness of chlorine or ethanol based household disinfection in areas with high community transmission, or where one family member is a health worker, or where there is a risk of COVID-19, such as during home quarantine, consistent with advice provided by local health authorities or organisations.[17] Diarrhoea as a symptom in the primary case is also a risk factor for SARS-CoV-2 transmission within families, which highlights the importance of disinfection of the bathroom and toilet, as well as closing the toilet lid when flushing to prevent aerosolisation of the virus.

Our study has limitations. Telephone interview has inherent limitations, including recall bias. It would take about 20 min to complete an interview, and 95% (118/124) of interviews were rated as informative by the interviewers. The evaluation results of mask wearing were reliable, but we did not collect data on the concentration of disinfectant used by families. The strengths of the study were that we had complete follow-up data and were able to accurately ascertain the incidence of secondary transmission in the cohort.

CONCLUSIONS

Household transmission in the pre-symptomatic or early symptomatic period of COVID-19 is a driver of epidemic growth and any measure aimed at reducing this can flatten the curve. This study reinforces the high risk of transmission in households but importantly shows that UFMU and hygiene measures can significantly reduce the risk of household transmission of COVID-19, independent of household size or crowding. This is the first study to show the effectiveness of precautionary mask use, social distancing and regular disinfection in the household, and can inform guidelines for prevention of household transmission. The results may also be informative for families of high risk groups, such as health workers, quarantined individuals or situations where cases of COVID-19 have to be managed at home.

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Case-Control Study of Use of Personal Protective Measures and Risk for SARS Coronavirus 2 Infection, Thailand

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We evaluated effectiveness of personal protective measures against severe acute respiratory disease coronavirus 2 (SARS-CoV-2) infection. Our case-control study included 211 cases of coronavirus disease (COVID-19) and 839 controls in Thailand. Cases were defined as asymptomatic contacts of COVID-19 patients who later tested positive for SARS-CoV-2; controls were asymptomatic contacts who never tested positive. Wearing masks all the time during contact was independently associated with lower risk for SARS-CoV-2 infection compared with not wearing masks; wearing a mask sometimes during contact did not lower infection risk. We found the type of mask worn was not independently associated with infection and that contacts who always wore masks were more likely to practice social distancing. Maintaining ≥1 m distance from a person with COVID-19, having close contact for ≤15 minutes, and frequent handwashing were independently associated with lower risk for infection. Our findings support consistent wearing of masks, handwashing, and social distancing to protect against COVID-19.

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Evaluation of the effectiveness of mask-wearing to protect healthy persons in the general public from infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease (COVID-19), is urgently needed (*1*,*2*). On February 27, 2020, during the early stages of the COVID-19 outbreak, the World Health Organization (WHO) announced that wearing a mask of any type was not recommended for asymptomatic persons (*3*). The rationale at that time was to avoid unnecessary cost, procurement burden, and a false sense of security (*3*). Several systematic reviews found no conclusive evidence to support widespread use of masks in public settings to protect against respiratory infectious diseases, such as influenza and severe acute respiratory syndrome (SARS) (*4*–*6*). However, China, South Korea, Japan, Thailand, and other countries in Asia have recommended the use of face masks among the general public since early in the COVID-19 pandemic (*7*). Evidence suggests that persons with COVID-19 can have a presymptomatic period, during which they can be contagious and transmit SARS-CoV-2 to others before symptoms develop (*8*). These findings led to a change in recommendations from the US Centers for Disease Control and Prevention on April 4, 2020, that advised all persons wear a cloth face covering when in public (*9*). On April 6 and June 5, 2020, WHO updated its advice on the use of masks for the general public and encouraged countries that issue the recommendations to conduct research on this topic (*8*).

Thailand has been implementing multiple measures against transmission of SARS-CoV-2 since the beginning of the outbreak (*10*,*11*). The country established thermal screening at airports on January 3, 2020, and detected an early case of COVID-19 outside China in a traveler from Wuhan, China, arriving at Bangkok Suvarnabhumi airport on January 8, 2020 (*10*). Thailand uses Surveillance and Rapid Response Teams (SRRTs), together with village health volunteers, to conduct contact tracing, educate the public about COVID-19, and monitor close contacts of persons with COVID-19 in quarantine (*11*). SRRTs are epidemiologic teams trained to conduct surveillance, investigations, and initial control of communicable diseases, such as SARS and influenza (*12*,*13*). More than 1,000 district-, provincial-, and regional-level SRRTs are working on COVID-19 contact tracing in Thailand.

By February 2020, public pressure to wear masks in Thailand was high. However, medical masks became difficult for the public to procure, and the government categorized medical masks as price-controlled goods. When the Ministry of Public Health (MoPH) designated COVID-19 a dangerous communicable disease, according to the Communicable Disease Act of 2015, government officials were empowered to quarantine case-contacts and close venues (*14*,*15*). On March 3, MoPH recommended public use of cloth face masks (*16*). On March 18, schools, universities, bars, nightclubs, and entertainment venues were closed (*17*). On March 26, when the country was reporting ≈100–150 new COVID-19 cases per day, the government declared a national state of emergency, prohibited public gatherings, and enforced wearing of face masks by all persons on public transport (*18*). On April 21, MoPH announced 19 new PCR-confirmed COVID-19 cases, bringing the total number of cases to 2,811 (*18*). Given the lack of evidence, we sought to evaluate the effectiveness of mask-wearing, handwashing, social distancing, and other personal protective measures against SARS-CoV-2 infection in public in Thailand.

Methods

Study Design

We conducted a retrospective case-control study by drawing persons with COVID-19 cases and noninfected controls from a cohort of contact tracing records of the central SRRT team at the Department of Disease Control (DDC), MoPH, Thailand. We included contact investigations of 3 large COVID-19 clusters in nightclubs, boxing stadiums, and a state enterprise office in Thailand.

Contacts were defined by DDC as persons who had activities with or were in the same location as a person with confirmed COVID-19 (*19*,*20*). The main aim of contact tracing was to identify and evaluate contacts, perform reverse transcription PCR (RT-PCR) diagnostic tests, and quarantine high-risk contacts, as defined by the MoPH (Appendix, https://wwwnc.cdc.gov/EID/article/26/11/20-3003-App1.pdf). RT-PCR was performed at laboratories certified for COVID-19 testing by the National Institute of Health of Thailand (*19*,*20*). Data on risk factors associated with SARS-CoV-2 infection, such as type of contact and use of mask, were recorded during contact investigations, but data sometimes were incomplete.

The central SRRT performed contact investigations for clusters of ≥5 PCR-confirmed COVID-19 cases from the same location within a 1-week period (*19*,*20*). We used these data to identify contacts who were asymptomatic during March 1–31, 2020. We used all available contact tracing records of the central SRRT in the study.

We telephoned contacts during April 30–May 27, 2020, and asked details about their contact with a COVID-19 index patient, such as dates, locations, duration, and distance of contact. We asked whether contacts wore a mask during the contact with the index patient, the type of mask, and the frequency of wearing a mask, which we defined as compliance with mask-wearing. We asked whether and how frequently contacts washed their hands while with the index patient. We asked whether contacts performed social distancing and whether they had physical contact with the COVID-19 index patient. If they did not know, or could not remember, contact with the index patient, we asked whether they had contact with other persons at the location. We asked whether the contact shared a cup or a cigarette with other persons in the place they had contact or had highest risk for contact with the index patient and whether the COVID-19 index patient, if known to the respondent, had worn a mask (Appendix, Additional Methods). We also asked, and verified by using DDC records, whether and when the contacts had symptoms and when COVID-19 was diagnosed.

For our study, we defined cases as asymptomatic contacts who later tested positive for SARS-CoV-2, on the basis of RT-PCR results available by April 21, 2020. We defined controls as asymptomatic contacts who did not have positive test results for SARS-CoV-2 by April 21, including those who tested negative and those who were not tested. We defined asymptomatic contacts as persons who had contact with or were in

the same location as a symptomatic COVID-19 patient and had no symptoms of COVID-19 on the first day of contact. We defined index patients as persons identified from contact tracing data as the potential source of SARS-CoV-2 infection; cases (as defined above) also could be index patients. We defined primary index patients as persons whose probable sources of infection were before the study period, March 1–31; for whom we were not able to identify the source of infection; or whose probable sources of infection were outside the contact tracing data included in the study. We defined high-risk exposure as that which occurred when persons lived in the same household as a COVID-19 patient; had a direct physical contact with a COVID-19 patient; were ≤1 m from a COVID-19 patient for >15 minutes; or were in the same closed environment, such as a room, nightclub, stadium, or vehicle, ≤1 m from a COVID-19 patient for >15 minutes.

We used 21 days after March 31 as a cutoff date based on evidence that most persons with COVID-19 likely would develop symptoms within 14 days (*21*) and that it could take ≤7 additional days for symptomatic persons under contact investigation to go to a healthcare facility and be tested for COVID-19. Our study follows the STROBE guidelines (*22*).

Statistical Analysis

To include only initially asymptomatic contacts in the study, we excluded persons who reported having symptoms of COVID-19 at the time of initial contact with an index patient. Because our study focused on the risk for infection in the community, we excluded contacts whose contact locations were healthcare facilities. We also excluded primary index patients if they were the first to have symptoms at the contact investigation location, had symptoms since the first day of visiting the location, or were the origin of infection based on the contact investigation.

We estimated secondary attack rates by using the percentage of new cases among asymptomatic contacts with high-risk exposure to enable comparison with other studies. We estimated odds ratios (ORs) and 95% CIs for associations between developing COVID-19 and factors evaluated. We used logistic regression with random effects for location and for index patients nested in the same location. If an asymptomatic contact had contact with ≥1 symptomatic COVID-19 index patient, the interviewer identified the index patient as the symptomatic COVID-19 patient with the closest contact. The percentage of missing values for the variable indicating whether the index patients wore a mask was 27%; thus, we did not include this variable in our analyses. For other variables, we assumed that missing values were missing at random and used imputation by chained equations (*23*,*24*). We created 10 imputed datasets and the imputation model included the case-control indicator and variables used in the multivariable models, including sex, age group, contact place, shortest distance of contact, duration of contact at ≤1 m, sharing dishes or cups, sharing cigarettes, handwashing, mask-wearing, and compliance with mask-wearing. We developed the final multilevel mixed-effect logistic regression models on the basis of previous knowledge and a purposeful selection method (*25*; Appendix, Additional Analyses). Because of collinearity between mask use and mask type, we conducted a separate analysis including mask type in the multilevel mixed-effects logistic regression model for SARS-CoV-2 infection. We also tested a predefined interaction between mask type and compliance with mask-wearing (Appendix, Additional Analyses).

To clarify patterns of behavior and factors related to compliance with mask-wearing, we used multinomial logistic regression models and the imputed dataset to estimated OR and 95% CI for associations between 3 mask-wearing compliance categories, never, sometimes, or all the time; and for other practices, including handwashing and social distancing during the contact period. We used logistic regression to estimate p values for pairwise comparisons.

To estimate the proportional reduction in cases that would occur if exposure to risk factors was reduced, we estimated the population attributable fraction by using the imputed dataset and a direct method based on logistic regression, as described previously (*26*,*27*; Appendix, Additional Analyses). We performed all analyses by using Stata version 14.2 (StataCorp, https://www.stata.com) and R version 4.0.0 (R Foundation for Statistical Computing, https://www.r-project.org).

Results

Characteristics of the Cohort Data

The contact tracing records of the central SRRT included 1,716 persons who had contact with or were in the same location as a person with diagnosed COVID-19 in an investigation of 3 large clusters (Figure 1). Overall, 18 primary index patients were identified: 11 from the nightclub cluster, 5 from the boxing stadiums cluster, and 2 from the state enterprise office cluster. Timelines of primary index patients from the 3 clusters varied (Appendix Figures

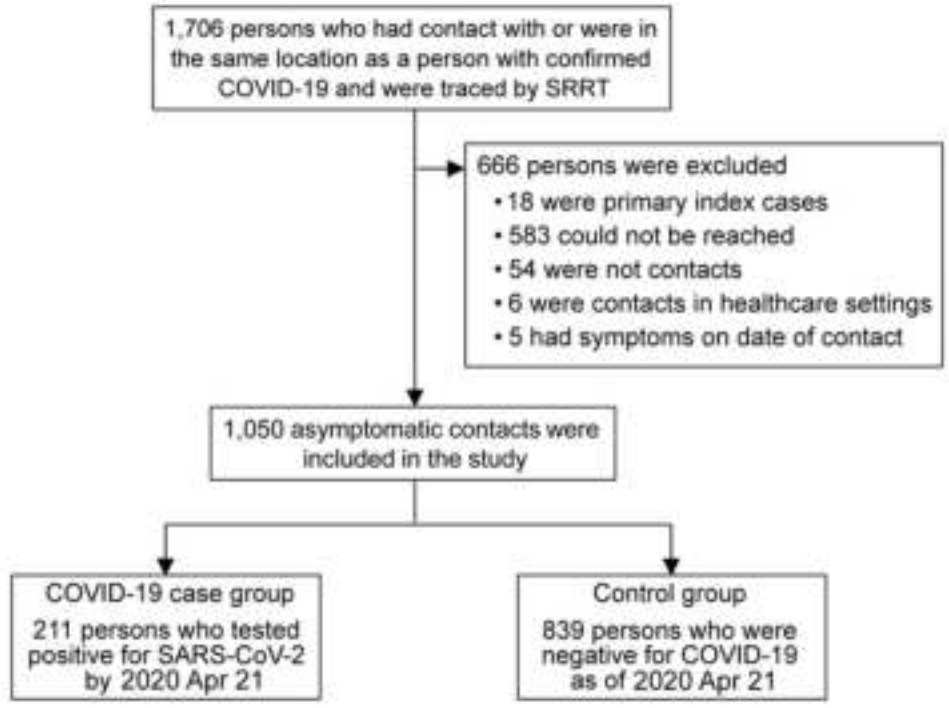

Figure 1. Flow diagram in case-control study of severe acute respiratory syndrome coronavirus 2 infections and contacts, Thailand, March–April 2020. COVID-19, coronavirus disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SRRT, Surveillance and Rapid Response Team of Ministry of Public Health.

1–3); we excluded the 18 primary index patients from our analyses.

Characteristics of Cases and Controls

After interviewing each contact by phone and applying the exclusion criteria (Figure 1), our analysis included 1,050 asymptomatic persons who had contact with or were in the same location as a symptomatic COVID-19 index patient during March 1–31, 2020. The median age of persons included was 38 years (IQR 28–51 years); 55% were male, and 45% were female (Table 1). Most (61%; n = 645) asymptomatic contacts included in the study were associated with the boxing stadiums cluster, 36% (n = 374) were related to the nightclub cluster, and 3% (n = 31) were related to the state enterprise office cluster. Overall, 890 (84.8%) contacts were considered to have high-risk exposure.

Among 1,050 asymptomatic contacts included in our analysis, 211 (20.1%) tested positive for SARS-CoV-2 by April 21, 2020, and were classified as cases; 839 (79.9%) never tested positive and were controls. Of the 211 cases, 195 (92.4%) had high-risk exposures and 150 (71.1%) had symptoms before COVID-19 diagnosis by RT-PCR (Appendix). The last date that a COVID-19 case was detected was April 9, 2020. Among the 839 controls, 695 (82.8%) had high-risk exposures and 719 (85.7%) were tested by PCR at least once.

Among asymptomatic contacts included in the study, 228 had contact with a COVID-19 index patient at nightclubs, 144 at boxing stadiums, and 20 at the state enterprise office (Figure 2). The others had contacts with a COVID-19 index patient at workplaces (n = 277), households (n = 230), and other places (n = 151). Among 890 asymptomatic contacts with high-risk exposures included in the study, the secondary attack rate from boxing stadiums was 86% (111/129), the secondary attack rate for nightclubs was 18.2% (34/187), the household secondary attack rate was 16.5% (38/230), the workplace secondary attack rate was 4.9% (10/205), and the secondary attack rate at other places was 1.4% (2/139).

Bivariate Analyses

Our analysis showed risk for SARS-CoV-2 infection was negatively associated with personal protective measures (Table 1). Crude odds ratio (OR) for infection was 0.08 (95% CI 0.02–0.31) for those maintaining a distance of ≥1 m from a COVID-19 patient; 0.13 (95% CI 0.04–0.46) for those whose duration of contact was ≤15 minutes; 0.41 (95% CI 0.18–0.91) for those who performed handwashing sometimes; 0.19 (95% CI 0.08–0.46) for those who washed hands often; and 0.16 (95% CI 0.07–0.36) for those wearing a mask all the time during contact with a COVID-19 patient. We noted a higher risk for SARS-CoV-2 infection among persons sharing dishes or cups (OR 2.71; 95% CI 1.48–4.94) and sharing cigarettes (OR 6.12; 95% CI 2.12–17.72) with other persons in general, not necessarily including a COVID-19 patient. In the bivariate model, type of mask was associated with risk for infection (p = 0.003).

Multivariable Analyses

We found a negative association between risk for SARS-CoV-2 infection and maintaining a distance of ≥1 m from a COVID-19 patient (adjusted odds ratio [aOR] 0.15; 95% CI 0.04–0.63); duration of contact ≤15 minutes (aOR 0.24; 95% CI 0.07–0.90); handwashing often (aOR 0.33; 95% CI 0.13–0.87); and wearing a mask all the time during contact with a COVID-19 patient (aOR 0.23; 95% CI 0.09–0.60) (Table 1). Wearing masks sometimes during contact with a COVID-19 patient was not statistically significantly associated with lower risk for infection (aOR 0.87; 95% CI 0.41–1.84). Sharing cigarettes with other persons was associated with higher risk for infection (aOR 3.47; 95% CI 1.09–11.02).

Compliance with mask-wearing during contact with a COVID-19 patient was strongly associated

Table 1. Factors associated with coronavirus disease among persons followed through contract tracing, Thailand, March–April 2020*

Factors	COVID-19 cases, no. (%), N = 211†	Controls, no. (%), N = 839†	Crude odds ratio (95% CI)‡	p value	Adjusted odds ratio (95% CI)‡	p value
Sex	n = 211	n = 838				
F	65 (30.8)	404 (48.2)	Referent	0.52	Referent	0.37
M	146 (69.2)	434 (51.8)	0.83 (0.47–1.46)		0.76 (0.41–1.41)	
Age group, y	n =211	n = 829				
≤15	6 (2.8)	49 (5.9)	0.65 (0.17–2.48)	0.29	0.57 (0.15–2.21)	0.21
>15–40	94 (44.5)	435 (52.5)	Referent		Referent	
>40–65	98 (46.4)	302 (36.4)	1.65 (0.91–2.97)		1.77 (0.94–3.32)	
>65	13 (6.2)	43 (5.0)	1.29 (0.33–5.07)		0.97 (0.22–4.24)	
Contact place§	n = 211	n = 839				
Nightclub	35 (16.6)	193 (23.0)	NA	NA	NA	NA
Boxing stadium	125 (59.2)	19 (2.3)				
Workplace	11 (5.2)	286 (34.0)				
Household	38 (18.0)	192 (22.9)				
Others	2 (0.9)	149 (17.8)				
Shortest distance of contact	n = 197	n = 809				
Physical contact	132 (67.0)	292 (36.1)	Referent	0.001	Referent	0.02
≤1 m without physical contact	61 (30.9)	335 (41.4)	0.76 (0.43–1.35)		1.09 (0.58–2.07)	
>1 m	4 (2.0)	182 (22.5)	0.08 (0.02–0.31)		0.15 (0.04–0.63)	
Duration of contact within 1 m	n = 199	n = 801				
>60 min	180 (90.4)	487 (60.8)	Referent	0.003	Referent	0.09
>15–60 min	14 (7.0)	162 (20.2)	0.53 (0.24–1.17)		0.67 (0.29–1.55)	
≤15 min	5 (2.5)	152 (19.0)	0.13 (0.04–0.46)		0.24 (0.07–0.90)	
Sharing dishes or cups¶	n = 210	n = 837				
N	125 (59.5)	576 (68.8)	Referent	0.001	Referent	0.39
Y	85 (40.5)	261 (31.2)	2.71 (1.48–4.94)		1.33 (0.70–2.54)	
Sharing cigarettes#	n = 209	n = 836				
N	196 (93.8)	824 (98.6)	Referent	0.001	Referent	0.03
Y	13 (6.2)	12 (1.4)	6.12 (2.12–17.72)		3.47 (1.09–11.02)	
Handwashing**	n = 210	n = 826				
None	44 (20.9)	121 (14.6)	Referent	<0.001	Referent	0.045
Sometimes	114 (54.3)	333 (40.3)	0.41 (0.18–0.91)		0.34 (0.14–0.81)	
Often	52 (24.8)	372 (45.0)	0.19 (0.08–0.46)		0.33 (0.13–0.87)	
Type of mask††	n = 211	n = 834				
None	102 (48.3)	500 (60.0)	Referent	0.003	–	–
Nonmedical masks only	25 (11.8)	77 (9.2)	0.78 (0.32–1.90)			
Nonmedical and medical	12 (5.7)	48 (5.8)	0.46 (0.13–1.64)			
Medical mask only	72 (34.1)	209 (25.0)	0.25 (0.12–0.53)			
Compliance with mask-wearing††	n = 210	n = 823				
Not wearing a mask	102 (48.6)	500 (60.7)	Referent	<0.001	Referent	0.006
Wearing a mask sometimes	79 (37.6)	125 (15.2)	0.75 (0.37–1.52)		0.87 (0.41–1.84)	
Always wearing a mask	29 (13.8)	198 (24.1)	0.16 (0.07–0.36)		0.23 (0.09–0.60)	

*NA, not applicable; COVID-19, coronavirus disease.
†Data not available for all cases and controls for all factors.
‡Crude and adjusted odds ratios were estimated using logistic regression with random effects for location and for index patient nested within the same location.
§The state enterprise office was included as a workplace. Others included restaurants, markets, malls, religious places, and households of index patients or other persons in persons not living in that household. Location was included in the model as a random effect variable.
¶Sharing multiserving dishes and using communal serving utensils to portion food individually was not categorized as sharing dishes.
#Included sharing electronic cigarettes and any vaping devices.
**Included washing with soap and water, and by using alcohol-based solutions.
††Wearing masks incorrectly, such as not covering both nose and mouth, was considered the same as not wearing a mask for analyses. Crude odds ratios of wearing mask and of each factor evaluated were estimated using logistic regression with random effects for location and for index patient nested within the same location to take into account clustering; therefore, the crude odds ratios are not equal to dividing of the odds in the case group by the odds in the control group.

with lower risk for infection in the multivariable model. Because of collinearity with mask-wearing compliance, we did not include mask type in the final model. We included mask type in a separate multivariable model and found type of mask was not independently associated with infection (p = 0.54) (Appendix Table 1). We found no evidence of effect modification between mask type and mask-wearing compliance.

Association Between Mask-Wearing Compliance and Other Social Distancing Practices

Because mask-wearing throughout the contact period was negatively associated with COVID-19, we

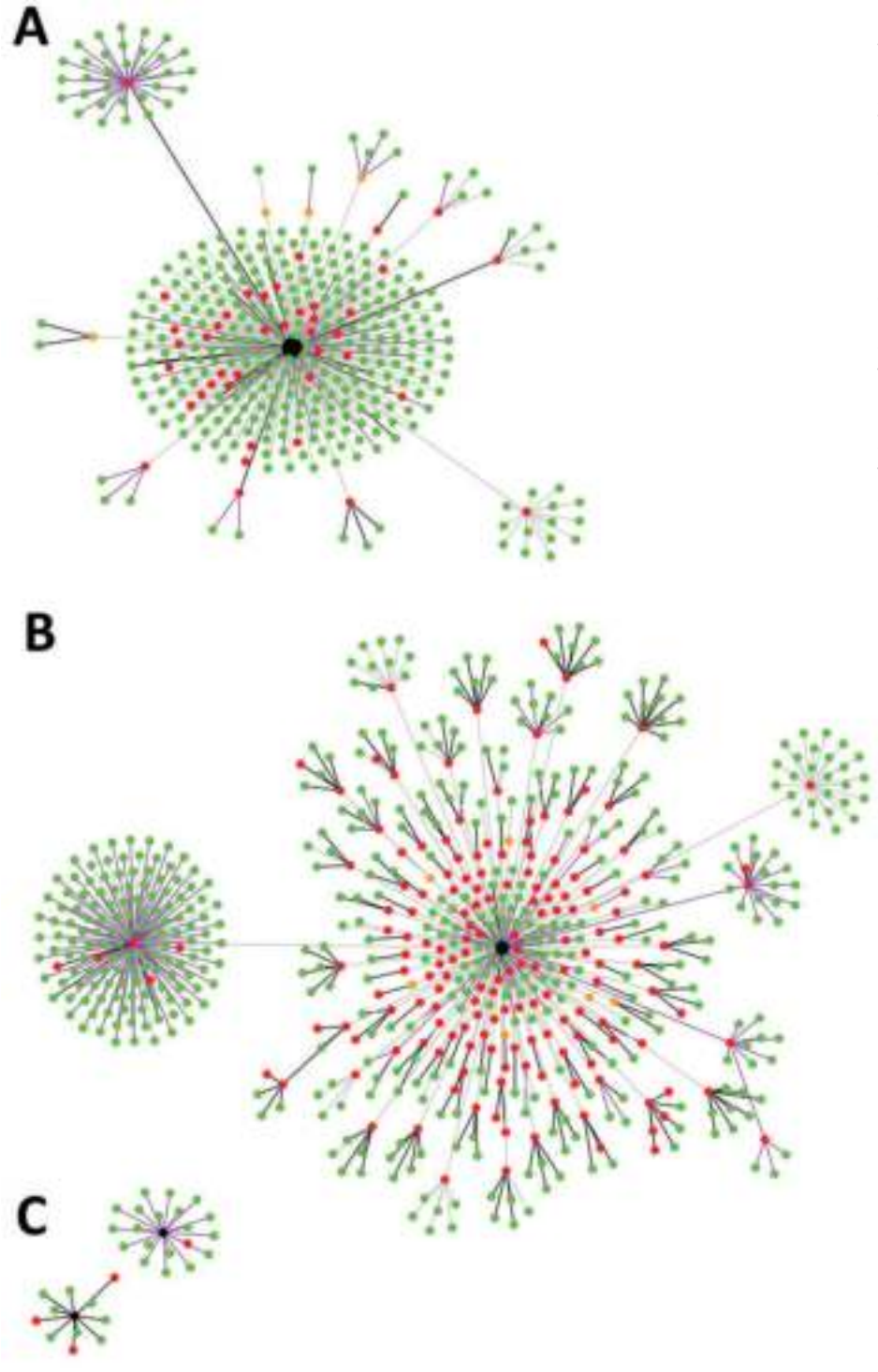

Figure 2. Development and transmission of severe acute respiratory syndrome coronavirus 2 among asymptomatic contacts, Thailand, March–April 2020. Clusters indicate coronavirus disease (COVID-19) contacts from nightclubs (A); boxing stadiums (B), and the state enterprise office (C). Black nodes represent primary index patients, red dots cases (contacts of primary index patients who had COVID-19), green dots noninfected controls, and orange dots patients with confirmed COVID-19 who could not be contacted by the study team. Black lines represent household contacts, purple lines contacts at workplaces, and gray lines contacts at other locations.

further explored characteristics of participants to ascertain whether wearing a mask produced a potential false sense of security. We found that during the contact period, 25% of persons who wore masks all the time reported maintaining ≥1 m distance from contacts compared with 18% of persons who did not wear a mask (pairwise p = 0.03). In addition, persons who wore masks all the time were more likely to report duration of contact ≤15 minutes (26% vs. 13% for those who did not wear a mask; pairwise p<0.001) and washing hands often (79% vs. 26% for those who did not wear a mask; pairwise p<0.001) (Table 2). We found that 43% of persons who wore masks sometimes were likely to wash their hands often compared with those who did not wear masks (26%; pairwise p<0.001), but they were more likely to have physical contact (50% vs. 42%; pairwise p = 0.03) and report duration of contact >60 minutes (75% vs. 67%; pairwise p = 0.04) compared with those who did not wear masks.

Discussion

Our findings provide evidence that mask-wearing, handwashing, and social distancing are independently associated with lower risk for SARS-CoV-2 infection in the general public in community settings in Thailand. We observed that wearing masks throughout the period of exposure to someone infected with SARS-CoV-2 was associated with lower risk for infection, but wearing masks only sometimes during the period was not. This evidence supports recommendations to wear masks consistently and correctly at all times in public (*2*,*7*–*9*).

The effectiveness of mask-wearing we observed is consistent with previous studies, including a randomized-controlled trial showing that consistent face

Table 2. Factors associated with compliance of mask wearing among coronavirus disease cases and controls, Thailand, March–April 2020*

Factors	Not wearing masks, no. (%), n = 602	Sometimes wearing masks, no. (%), n = 204	Always wearing masks, no. (%), n = 227	p value†
Sex	n = 601	n = 204	n = 227	
F	277 (46.1)	75 (36.8)	112 (49.3)	0.03
M	324 (53.9)	129 (63.2)	115 (50.7)	
Age group, y	n = 594	n = 204	n = 225	
≤15	45 (7.6)	5/204 (2%)	3/225 (1%)	<0.001
>15–40	269 (45.3)	117/204 (57%)	132/225 (59%)	
>40–65	236 (39.7)	76/204 (37%)	84/225 (37%)	
>65	44 (7.4)	6/204 (3%)	6/225 (3%)	
Contact places‡	n = 602	n = 204	n = 227	
Nightclub	84 (14.0)	51 (25.0)	91 (40.1)	<0.001
Boxing stadium	48 (8.0)	66 (32.4)	29 (12.8)	
Workplace	178 (29.6)	46 (22.5)	64 (28.2)	
Household	167 (27.7)	27 (13.2)	33 (14.5)	
Others	125 (20.7)	14 (6.9)	10 (4.4)	
Shortest distance of contact	n = 588	n = 191	n = 212	
Physical contact	246 (41.8)	96 (50.3)	76 (35.8)	0.005
≤1 m without physical contact	238 (40.5)	70 (36.6)	83 (39.1)	
>1 m	104 (17.7)	25 (13.1)	53 (25.0)	
Duration of contact within 1 m	n = 590	n = 190	n = 205	
>60 min	396 (67.1)	143 (75.3)	121 (59.0)	<0.001
>15–60 min	120 (20.3)	23 (12.1)	30 (14.6)	
≤15 min	74 (12.5)	24 (12.6)	54 (26.3)	
Sharing dishes or cups§	n = 601	n = 203	n = 226	
N	361 (60.1)	130 (64.0)	200 (88.5)	<0.001
Y	240 (39.9)	73 (36.0)	26 (11.5)	
Sharing cigarettes¶	n = 600	n = 202	n = 226	
N	586 (97.7)	194 (96.0)	223 (98.7)	0.29
Y	14 (2.3)	8 (4.0)	3 (1.3)	
Handwashing#	n = 594	n = 203	n = 224	
None	142 (23.9)	16 (7.9)	6 (2.7)	<0.001
Sometimes	298 (50.2)	99 (48.8)	42 (18.8)	
Often	154 (25.9)	88 (43.3)	176 (78.6)	

*Data not available for all cases and controls for all factors. Wearing masks incorrectly, such as not covering both nose and mouth, was considered the same as not wearing a mask for analyses.
†p values were estimated by using univariable multinomial logistic regression models. Missing values were imputed using the imputation model.
‡The state enterprise office was included as a workplace. Others included restaurants, markets, malls, religious places, and households of index patients or other persons but not living together (e.g., persons not living in that household).
§Sharing multiserving dishes and using communal serving utensils to portion food individually was not categorized as sharing dishes.
¶Included sharing electronic cigarettes and any vaping devices.
#Included washing with soap and water, and by using alcohol-based solutions.

mask use reduced risk for influenza-like illness (*28*), 2 case-control studies that found that mask-wearing was associated with lower risk for SARS infection (*29*,*30*), and a retrospective cohort study that found that mask-wearing by index patients or family members at home was associated with lower risk for SARS-CoV-2 infection (*31*). Previous studies found use of surgical masks or similar 12–16-layer cotton reusable masks demonstrated protection against coronavirus infection in the community (*32*), but we did not observe a difference between wearing nonmedical and medical masks in the general population. Our results suggest that wearing nonmedical masks in public can potentially reduce transmission of SARS-CoV-2. Another study found perception of risk of developing COVID-19 can increase a person's likelihood of wearing a medical mask in nonmedical settings (T.D. Huynh, unpub. data, https://www.medrxiv.org/content/10.1101/2020.03.26.20044388v1). However, given supply shortages, medical masks should be reserved for use by healthcare workers.

We found a negative association between risk for SARS-CoV-2 infection and social distancing, consistent with previous studies that found that ≥1 m physical distancing was associated with a large protective effect and distances of >2 m could be more effective (*32*). Our findings on effectiveness of hand hygiene also were consistent with reports in previous studies (*33*).

In this study, secondary attack rates at different venues varied widely. The household secondary attack rate in our study (16.5%) is comparable with ranges reported previously (11%–23%) (*34*,*35*), and relatively high compared with workplaces (4.9%) and other settings (1.4%). Although quarantine measures can be challenging and sometimes impractical, household members should immediately separate a person who develops symptoms of COVID-19; the sick person should stay in a specific room; use a separate bathroom, if possible; and not share dishes, cups, and other utensils (*36*). All household members should wear masks, frequently wash their hands, and perform social distancing to the extent possible (*37*).

The high number of COVID-19 cases associated with nightclub exposures in Bangkok is comparable to a COVID-19 outbreak associated with the Itaewon nightclub cluster in Seoul, South Korea, during May 2020 (*38*), in which persons visited several nightclubs in the same area during a short period of time. The secondary attack rate in boxing stadiums was high (86%) but similar to a cluster of COVID-19 cases associated with a football match in Italy during February 2020 (*39*). The secondary attack rate of COVID-19 at a choir practice in the United States was reported to be 53.3%–86.7% (*40*). Secondary attack rates in public gathering places with high densities of persons shouting and cheering, such as football and boxing stadiums, are still uncertain but appear to be high.

Clear and consistent public messaging from policy makers likely can prevent a false sense of security and promote compliance with social distancing in Thailand. We found that those who wore masks throughout the time they were exposed to a COVID-19 patient also were more likely to wash their hands and perform social distancing. Traditional and social media outlets can support public health responses by working with governments to provide consistent, simple, and clear messages (*41*). In Thailand, daily briefings from the Centre for COVID-19 Situation Administration provided clear, consistent messages on social distancing, how to put on a mask, and how to wash hands, which might have improved public confidence with the recommendations. Consistent public messages on how to wear masks correctly also are needed, particularly for those who wear masks sometimes or incorrectly, such as not covering both nose and mouth. We found that persons who only intermittently wore masks during exposure also did not practice social distancing adequately.

Our study has several limitations. First, because our findings were based on contacts related to 3 major COVID-19 clusters in Thailand during March 2020, they might not be generalizable to all settings. Second, estimated ORs were conditioned on reported contact with index patients; our study did not evaluate or consider the probability of having contact with other infected persons in the community, which could have occurred. Third, because only 89% of controls were tested, those not tested could have been infected; therefore, cases might have been missed in persons with mild or no symptoms or who did not report symptoms or seek care or testing. Nonetheless, we believe that misclassification likely was minimal because those who were not tested with RT-PCR were low-risk contacts; the small number likely would not change our main findings and recommendations on personal protective measures. Fourth, identifying every potential contact can be nearly impossible because some persons might have had contact with >1 COVID-19 patient. Hence, our estimated secondary attack rates among contacts with high-risk exposure could be overestimated or underestimated. Fifth, population attributable fraction is based on several assumptions, including causality, and should be interpreted with caution (*42*,*43*). Finally, findings were subject to

common biases of retrospective case-control studies, including memory bias, observer bias, and information bias (*44*). To reduce potential biases, we used structured interviews in which each participant was asked the same set of defined questions.

As many countries begin to relax social distancing measures, our findings provide evidence supporting consistent mask-wearing, handwashing, and adhering to social distancing recommendations to reduce SARS-CoV-2 transmission in public gatherings. Wearing nonmedical masks in public could help slow the spread of COVID-19. Complying with all measures could be highly effective; however, in places with a high population density, additional measures might be required.

Clear and consistent public messaging on personal protective recommendations is essential, particularly for targeting those who wear masks intermittently or incorrectly. Our data showed that no single protective measure was associated with complete protection from COVID-19. All measures, including mask-wearing, handwashing, and social distancing, can increase protection against COVID-19 in public settings.

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SARS Transmission, Risk Factors, and Prevention in Hong Kong

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We analyzed information obtained from 1,192 patients with probable severe acute respiratory syndrome (SARS) reported in Hong Kong. Among them, 26.6% were hospital workers, 16.1% were members of the same household as SARS patients and had probable secondary infections, 14.3% were Amoy Gardens residents, 4.9% were inpatients, and 9.9% were contacts of SARS patients who were not family members. The remaining 347 case-patients (29.1%) had undefined sources of infection. Excluding those ≤16 years of age, 330 patients with cases from "undefined" sources were used in a 1:2 matched case-control study. Multivariate analysis of this case-control study showed that having visited mainland China, hospitals, or the Amoy Gardens were risk factors (odds ratio [OR] 1.95 to 7.63). In addition, frequent mask use in public venues, frequent hand washing, and disinfecting the living quarters were significant protective factors (OR 0.36 to 0.58). In Hong Kong, therefore, community-acquired infection did not make up most transmissions, and public health measures have contributed substantially to the control of the SARS epidemic.

As of June 11, 2003, a total of 1,755 probable SARS cases were reported in Hong Kong (1). Some of the sources of SARS transmission are unknown. For instance, the first major SARS outbreak occurred in the Prince of Wales Hospital in March 2003, and 138 probable cases were reported from March 11 to March 25, 2003 (2). Another major outbreak occurred in the Amoy Gardens housing estate on approximately March 26, 2003, and a total of 321 residents were affected (3). A total of 381 hospital workers were affected as of May 29, 2003 (4). Other sources of infection are possible. Some inpatients were cross-infected by SARS case-patients, who were hospitalized for reasons other than SARS; others may have contracted the disease through known contacts with other SARS patients. The rest of the community-acquired case-patients contracted the diseases through less defined sources. The distributions of the "known" and "undefined" sources of infection have not been reported. Such an initiative would help assess the infectivity and modes of transmission of the virus in the community setting.

Also, reports that public health measures, such as wearing masks, frequent hand washing, avoidance of crowded places, disinfection of the living quarters had been practiced by most of the Hong Kong population during the SARS outbreak (>90%) (5). The efficacy of widespread use of masks was controversial (6), and evaluating the efficacy of such measures in controlling the epidemic is important.

Our study had two objectives. First, we sought to delineate the distribution of different sources of transmission of the SARS cases in Hong Kong. The number of cases with known and undefined sources was determined. Patients with known sources included those who were hospital workers, those who lived in the Amoy Gardens Estate, those who were probable secondary cases within a household (i.e., those with another household member who had SARS with an earlier date of onset), those who were inpatients and were cross-infected by other inpatients, and those persons who had contact with another SARS patient (who was not one of their household members) before the onset of fever. For the remaining cases, the virus was contracted through undefined sources.

The second objective was to identify the undefined source group. A number of hypotheses were tested to identify relevant risk and protective factors associated with contracting the disease. Risk factors were related to visiting places of potentially high risk and meeting at-risk people. Preventive factors were related to public health measures for prevention.

Methods

The study population comprised all probable SARS patients whose cases were reported to the Department of Health on or before May 16, 2003 (n = 1,690). The SARS case definition criteria, used by Hong Kong Hospital Authority, is as follows: radiographic evidence of infiltrates consistent with pneumonia and current temperature >38°C or a history of such at any time in the preceding 2 days, and

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at least two of the following: history of chills in the past 2 days, new or increased cough, breathing difficulty, general malaise or myalgia, typical signs of consolidation, and known exposure. These criteria for cases are equivalent to those in the World Health Organization's case definition for probable SARS cases (7).

Data Collection

Telephone numbers, as well as some demographic and clinical background information, for all probable SARS case-patients in Hong Kong (identified on or before May 16, 2003 [n = 1,690]) were obtained from the Department of Health. A team of trained interviewers called all these numbers, briefed the person answering the phone about the nature of the study, and invited their household to join the study. Informed consent was obtained directly from the respondents. The number of SARS patients in the household was ascertained, and the interviewer identified the index patient, the person who had the earliest date of onset of fever if the household had more than one SARS patient. The rest of the SARS patients, those with later onset of illness, were considered as having probable secondary or tertiary cases. When a household had had two or more SARS patients with the same fever onset date (11 households), both were treated as index patients rather than as having probable secondary cases. The information obtained was cross-checked with that obtained from the SARS registry. Ethics approval was obtained from the Ethics Committee of the Chinese University of Hong Kong.

The study was conducted from April 4, 2003, through June 10, 2003. Of the 1,690 probable SARS case-patients reported in Hong Kong as of May 16, a total of 1,214 (72%) SARS case-patients from 996 households were covered by our study. Of the remaining 476 case-patients not covered by this study, 140 case-patients (8.2%) did not have a correct telephone number, 163 (9.6%) could not be contacted after at least five attempts, 163 (9.6%) declined to participate, and 10 (0.6%) were either not in Hong Kong or could not communicate in Chinese or English.

Study Design

The study is part of a project that also includes an investigation of the secondary attack rate of household members. For the first part of this study, the index case-patients were asked whether they were hospital workers, inpatients before contracting SARS, or residents of the Amoy Gardens. The other respondents were asked whether onset of fever occurred within 10 days of contact with a SARS patient. These four types of SARS cases were classified into the known sources group. The rest of the index case-patients were classified into the undefined source group. In the second part of the study, a 1:2 matched case-control study was conducted for the undefined source group to identify risk and preventive factors associated with SARS transmission in the community setting.

Adults ≥16 years of age were included in the case-control study (17 case-patients were removed from the analysis). Potential geographically related risk factors studied included whether the case-patient had visited (but not lived in) Amoy Gardens, Prince of Wales Hospital, other hospitals or clinics, or crowded places within 10 days before onset of fever. Other risk factors were related to contact with other groups of people during the same reference period, including medical personnel, hospital visitors, and persons with influenzalike symptoms (who were not SARS case-patients). A number of protective factors were related to relevant public health measures, including the frequency of using a face mask in public venues, the frequency of washing hands each day, and disinfection of living quarters thoroughly during the same period. The same questions were asked to the control group, which was recruited by a random telephone survey. Members of the control group were matched for age and sex with the case-patient.

The reference period was the same as that of the matched case-patient. Random telephone numbers were selected from up-to-date local telephone directories. Interviews were conducted in the evening to avoid overrepresenting those who were not working during the daytime. At least three calls were made before an unanswered call was considered as a noncontact. Informed consent was obtained before the interviews were conducted. Almost all case-patients were interviewed within 14 to 28 days after their onset of fever, and the control group was interviewed accordingly. When a participant was unable to answer the questionnaire, a proxy, who was most familiar with the family situation, was interviewed.

Data Analyses

For the case-control study, odds ratios (OR) were first examined by using univariate logistic regression models. The significant univariate variables were then entered as input for the multivariate forward conditional logistic regression analysis; p values <0.05 were statistically significant. SPSS for Windows Release 11.0.1 (SPSS Inc., Chicago, IL) was used to analyze the data.

Results

Cases with Known Sources of Transmission

Of the 1,214 probable SARS cases covered by this study, 22 questionnaires (1.8%) were incomplete and did not allow us to classify the respondents into groups according to source of transmission. The rest (n = 1,192) were analyzed. A total of 192 (16.1%) had probable cases of secondary or tertiary household transmission (Table 1) (i.e.,

Table 1. Distribution of 1,214 severe acute respiratory syndrome cases covered by the study[a]

	n	%[b]
Known sources	727	61.0
Probable secondary/tertiary household infection	192[d]	16.1
Hospital care workers	317[d]	26.6
Amoy Gardens residents	170[d]	14.3
Inpatients	58[d]	4.9
Unknown sources		
Contacted SARS patient(s) within 14 days before onset of fever [c]	118	9.9
Undefined sources	347	29.1
Visited Amoy Gardens	54[d]	4.5
Visited PWH [e]	12[d]	1.0
Visited other hospitals or clinics	142[d]	11.9
Visited an affected country	45[d]	3.8
None of the above	124	10.4

[a]Incomplete information for 22 cases; complete information for 1,192 cases.
[b]Calculated based on complete data.
[c]These patients did not belong to the categories listed under known sources.
[d]These categories are not mutually excluded, i.e., a respondent may be exposed to more than one category.
[e]PWH, Prince of Wales Hospital.

another household member had SARS but fever onset occurred earlier). All the names were verified as being reported to the SARS registry. Another 317 of 1,192 (26.6%) cases were hospital workers; 170 (14.3%) lived in the Amoy Gardens; 58 (4.9%) were inpatients who had been hospitalized for diseases other than SARS and kept on wards with SARS patients. Most infected inpatients were long-term chronic patients and had been hospitalized for >2 weeks before having SARS symptoms. These patients were likely to have been cross-infected. A total of 727 case-patients belonged in one of the four categories (61% of 1,192 cases). Another 118 (9.9%) had come into contact with a SARS patient within a 10-day period before onset of fever. For 347 (29.1%) participants, the source was undefined; these participants were included in the case-control analysis. After excluding 17 case-patients ≤16 years of age, 330 participants were included in the case-control study.

Univariate Case-Control Analysis

Of the 330 patients with an undefined source of infection, 48% were men and 52% were women. The mean age of the patient group was 47.1 years for both the male and female case-patients (standard deviation [SD] 18.8 and 19.9, respectively, $p > 0.05$, *t* test). The percentage of participants in the undefined source group in the three periods of the epidemic (before March 25, 2003, from March 26 through April 10, and after April 10) were 24.2%, 36.1%, and 43.5%, respectively.

Members of the patient group were more likely than the control group to have visited mainland China (12.7% vs. 6.5%, $p < 0.005$). One patient had visited Taiwan, another patient had visited Singapore, two controls had visited Taiwan, and none of the controls had visited Singapore (Singapore and Taiwan were listed as affected areas during the study period). Similarly, patients were also more likely than controls to have visited the Amoy Gardens (15% vs. 2%, OR = 9.10, $p < 0.005$) (keeping in mind that those who lived in the Amoy Gardens had already been removed from the analysis); patients were more likely than the controls to have visited the Prince of Wales Hospital (3.6% vs. 0.5%, OR = 8.27, $p < 0.005$) or other hospitals or clinics (40.7% vs. 17.0%, OR = 3.36, $p < 0.005$) (Table 2). A total of 212 cases of the undefined source group had visited at least one of the above-mentioned categories of places. Frequency of visiting crowded places was, however, not significant in the univariate analysis (21.91% vs. 20.8%, OR = 1.07, $p > 0.05$).

Members of the case-patient and control groups were not statistically different in the percentage of having come into contact with someone with influenzalike symptoms (those having made contacts with SARS patients were already removed, 9.0% vs. 6.4%, OR = 1.42, $p > 0.05$). The two groups were also not different in the likelihood of having social contact with someone who had visited a hospital (8.2% vs. 5.2%, OR = 1.66, $p > 0.05$) or having social contact with medical personnel (7.6% vs. 8.6%, OR = 0.87, $p > 0.05$). Also patients were not more likely to have a known SARS patient living in the same housing estate, after Amoy Gardens patients had already been removed from the analysis (such data were made available to the public by the government after April 12, 2003) (8).

Furthermore, matching for the reference period, members of the case group were less likely than members of the control group to have frequently worn a face mask in public venues (27.9% vs. 58.7%, OR = 0.36, $p < 0.005$), to have been washed their hands >10 times a day (18.4% vs. 33.7% OR = 0.44, $p < 0.005$), and to have disinfected their living quarters thoroughly (46.6% vs. 74.5%, OR = 0.30, $p < 0.005$).

Multivariate Analysis

When all the variables that were significant in the univariate analysis were used as input for the multivariate stepwise conditional logistic regression analysis, the results show that among the 330 patients with undefined sources, the following were significant risk factors: having visited mainland China (OR = 1.95, $p = 0.020$, Table 2), having visited the Amoy Gardens (OR = 7.63, $p < 0.001$), having visited the Prince of Wales Hospital (OR = 7.07, $p = 0.009$), and having visited other hospitals or clinics (OR = 3.70, $p < 0.001$) during the reference period. On the other hand, using a mask frequently in public places (OR = 0.27, $p < 0.001$), washing one's hands >10 times a day (OR = 0.58, $p = 0.008$), and disinfecting the living quarters thor-

Table 2. Preventive measures and risk factors reported by cases and controls

Factors	Case[b]	Control[c]	Matched univariate OR (95% CI)	Matched multivariate OR (95% CI)	p value[d]
% visited mainland China (reference=no)	12.7	6.5	2.09 (1.33 to 3.27)[e]	1.95 (1.11 to 3.42)	0.020
% visited PWH (reference=no)	3.6	0.5	8.27 (2.32 to 29.49)[e]	7.07 (1.62 to 30.75)	0.009
% visited other hospitals/clinics (reference=no)	40.7	17.0	3.36 (2.49 to 4.54)	3.70 (2.54 to 5.39)	<0.001
% visited Amoy Gardens (reference=no)	15.5	2.0	9.10 (4.87 to 17.00)[e]	7.63 (3.77 to 15.43)	<0.001
% visited crowded places frequently (reference=occasionally/seldom/no)	21.9	20.8	1.07 (0.76 to 1.50) NS	-	-
% contacted someone with fever or influenza (reference=no)	9.0	6.4	1.42 (0.87 to 2.32) NS	-	-
% social contact with someone who visited a patient in a hospital (reference=no)	8.2	5.2	1.66 (0.96 to 2.85) NS	-	-
% social contact with medical personnel (reference=no)	7.6	8.6	0.87 (0.52 to 1.44) NS	-	-
% had a SARS case in the housing estate (reference=no)	6.6	8.5	0.76 (0.44 to 1.31) NS	-	-
% disinfected the living quarters thoroughly (reference=no)	46.6	74.5	0.30 (0.23 to 0.39)[e]	0.41 (0.29 to 0.58)	<0.001
Wore a mask in public places frequently (reference=occasionally /seldom/no)	27.9	58.7	0.27 (0.20 to 0.37)[e]	0.36 (0.25 to 0.52)	<0.001
Washed hands 11 or more times per day (reference=1–10 times/day)	18.4	33.7	0.44 (0.31 to 0.63)[e]	0.58 (0.38 to 0.87)	0.008

[a]N.S., not significant; OR, odds ratio; CI, confidence interval; PWH, Prince of Wales Hospital; -, not used by the multivariate analyses. The reference time period was the 10 days before the date of the patient's onset of fever.
[b]n = 330.
[c]n = 660.
[d]p values for multivariate OR.
[e]$p < 0.005$.

oughly (OR = 0.41, $p < 0.001$) during the reference period were significant protective factors (Table 2).

Undefined Cases

After removing those case-patients who may have contracted SARS after visiting the Amoy Gardens, the Prince of Wales Hospital, other hospitals, or an affected country, including mainland China, Singapore, and Taiwan (212 cases of the 330 cases), 118 cases remained undefined. They were likely to be community-acquired cases of unknown sources of transmission. When univariate and multivariate conditional logistic regression analyses were repeated for the 118 cases with undefined sources (after 212 patients who had visited some particular places that were associated with risk for transmission were removed from the analysis) and their controls (n = 236), similar results were obtained. The three public health variables—frequently wearing a mask in public places (adjusted OR = 0.36, $p < 0.001$), washing hands >10 times a day (adjusted OR = 0.44, $p = 0.008$), and disinfecting the living quarters thoroughly (adjusted OR = 0.36, $p < 0.001$)—remained significant protective factors. Again, similar to the results of the previous analysis applied to the 330 cases, the other five variables (visiting crowded places, having contact with someone with influenzalike symptoms, having social contact with hospital visitors, having social contact with medical workers, and living with in the same housing estate as other SARS case-patients) were not significant risk factors.

Discussion

Of the 1,192 participants in this study, approximately 16.1% had probable secondary or tertiary transmission occurring within the household, 26.6% were hospital workers with nosocomial infections, 14.3% were Amoy Gardens patients, and 4.9% were cross-infected inpatients. In 9.9%, SARS might have been contracted when the participant came in contact with a SARS patient who was a nonhousehold member, which may have occurred in a hospital or community setting. SARS may have developed in 18.7% after they visited Amoy Gardens, hospitals or clinics, or affected countries. This computation leaves 9.9% as community-acquired cases of an unknown source.

The percentage of patients related to Amoy Gardens (someone who lived there or visited there) is 18.8% (224/1,192). The percentage of patients with a hospital connection (hospital workers, inpatients, and visitors) is 44% (525/1,192). The proportion of unknown community-acquired SARS infection among all SARS cases in this study was considerably lower than the proportion of nosocomial infection, which suggests that preventing hospital outbreaks is essential.

Of the 330 undefined transmissions, 44.2% of the transmissions occurred through hospital visitors. Another study on household transmission also indicated that hospital visits were a significant risk factor for predicting household secondary infection (9). Therefore, the severity of future outbreaks, if any, would depend on the ability of the hos-

pital system to control hospital cross-infection and infection of visitors.

Visits to mainland China were associated with SARS transmission, even after adjusting for other variables. Cross-border transmission played a role in the epidemic; although the absolute percentage is not high among the 1,192 case-patients (3.6% or 43/1,192), it is substantially larger among the undefined source group (12.4%). With a case-control design, we could not establish whether this 14.4% was associated with an inflated risk. Cross-border communication and prevention, such as those set in place (temperature screening and health declaration), need to be enforced strictly and consistently. Almost 70% of the 43 participants who visited mainland China had fever onset on or before April 1 (i.e., the early phase of the epidemic) (5). None of them had onset after May 3, which is understandable as visiting mainland China was perceived as a high risk by the general public in the late phase of the epidemic (5).

The variables related to social contacts (with medical personnel or hospital visitors, with persons with influenza-like symptoms, and with persons living in a housing estate with a reported SARS patient) were not significant. These findings should be interpreted with caution. On one hand, these case-patients should not be stigmatized. On the other, the results may have been confounded because all SARS cases contracted this way were excluded from the analysis. However, confirming that these variables could not account for transmission of the undefined source cases can be useful.

Evidence does not indicate that frequent visits to crowded places were associated with a higher likelihood of community-acquired infection. This finding may remove panic that arose during the epidemic, and daily life need not change as much as it had. Hong Kong is a densely populated city, and it had a large number of SARS cases. The number of community-acquired cases in less populated cities should be much lower than that of Hong Kong. This finding should be interpreted with care as >90% of the general public wore face masks in public places, and >85% avoided visits to public places during the epidemic in Hong Kong (5). Although visiting the Amoy Gardens was a risk factor, Amoy Gardens might be the only place where such a large-scale SARS outbreak was attributable to contamination of the environment.

We now have some empirical evidence to suggest that wearing a face-mask frequently in public places, frequent handwashing, and disinfecting one's living quarter were effective public health measures to reduce the risk for transmission (adjusted OR 0.58 to 0.36). The effectiveness of mask use was controversial (6). In another study, the prevalence of these three public health preventive public health measures increased significantly from March 21, 2003, to April 1, 2003, (i.e., wearing masks 11.5%–84.3%; frequent hand washing 61.5%–95.1%; home disinfection 36.4%–80%) (5). These practices played an essential role in limiting the spread of the virus in the community in Hong Kong.

That disinfecting the living quarter is a strong protective factor has a particular relevance. The reason behind the significance is not completely clear. During the epidemic, the Hong Kong government released frequent announcements of public interest to promote home disinfection using 1:99 bleach water solutions. Most respondents who disinfected their living quarters were probably following the government's suggestion. Keeping in mind that probable secondary cases had already been removed from the analysis, such protective effect is not referring to the effects that disinfecting the quarter reduced the chance of secondary infection. Environmental contamination (suspected to be related to the sewage system) was reported in the Amoy Gardens, and similar environmental contamination probably did not occur in other places. Such contamination-related infections might be on a small scale and not been noticed. In such circumstances, home disinfection might reduce the risk for transmission. The finding suggests that, in addition to the droplet theory, the fomites theory could not be dismissed.

Our study has a few limitations as well as strengths. First, approximately 72% of all SARS case-patients were included in the study (excluding patients whose contact numbers were incorrect or not available; approximately 78% of those with a valid contact telephone number were included, and the refusal rate was about 10%). The sample size was reasonably large. Second, data were collected retrospectively. Most of the data were, however, collected from the participants within 1 month after onset of fever. Since contracting the disease is a major life event for the patient and family, they should be able to recall whether such factual and benchmark behaviors had been practiced.

The study also has strength of matching for age, sex, and reference time of the behaviors in question, so that both the case and control in a pair were referring to relevant behaviors that occurred within the same 10-day period before the date of onset of fever of the patient. Third, some questions, such as those about disinfection of households or visiting crowed places were nonspecific (the questions asked were "Whether your living quarter had been disinfected thoroughly" and "Whether you had visited crowded places"). Different participants might have defined the terms differently. Further, a number of patients were unable to answer the questions, and a household member who was "most familiar with the household situation" was invited to serve as a proxy. The responses obtained from these informants were compared to those obtained from the patients themselves, and no statistical

significance was obtained (p 0.199 to 0.854) to all variables, except for the variable about visiting the Amoy Gardens ($p < 0.05$).

One particular strength of the study in its evaluation of the three public health measures is that transmissions due to various known sources of infection had been removed as much as possible. In conclusion, the study shows that public health measures may have contributed substantially to the control of SARS epidemic in Hong Kong.

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Dr. Lau is the director of the Center for Epidemiology and Biostatistics of the School of Public Health of the Chinese University of Hong Kong. His research interests include community research on behavioral aspects of infectious disease, such as HIV prevention studies.

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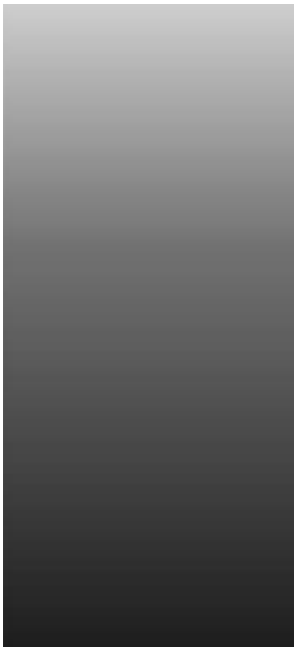

Risk Factors for SARS among Persons without Known Contact with SARS Patients, Beijing, China

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Most cases of severe acute respiratory syndrome (SARS) have occurred in close contacts of SARS patients. However, in Beijing, a large proportion of SARS cases occurred in persons without such contact. We conducted a case-control study in Beijing that compared exposures of 94 unlinked, probable SARS patients with those of 281 community-based controls matched for age group and sex. Case-patients were more likely than controls to have chronic medical conditions or to have visited fever clinics (clinics at which possible SARS patients were separated from other patients), eaten outside the home, or taken taxis frequently. The use of masks was strongly protective. Among 31 case-patients for whom convalescent-phase (>21 days) sera were available, 26% had immunoglobulin G to SARS-associated coronavirus. Our finding that clinical SARS was associated with visits to fever clinics supports Beijing's strategy of closing clinics with poor infection-control measures. Our finding that mask use lowered the risk for disease supports the community's use of this strategy.

Severe acute respiratory syndrome (SARS) is a new disease caused by a previously unrecognized coronavirus (1,2). Investigations of SARS outbreaks in several countries suggest that the primary mode of transmission is close contact with a symptomatic patient. Indeed, most cases of SARS have occurred among persons who cared for or lived with someone with the disease, and this fact is reflected in the SARS case definition developed by the World Health Organization and in definitions developed by individual countries (3–7).

The SARS epidemic in Beijing, during which a total of 2,521 probable cases were reported from March through June 2003, was notable for its magnitude (8). Another distinguishing feature was the relatively high proportion of probable case-patients with no reported close contact with other SARS patients. Although the outbreaks in Hong Kong and Toronto were also large, most case-patients had healthcare-related or household links to other SARS patients (4,9). Beijing's epidemic began with importations of SARS-associated coronavirus (SARS-CoV) in travelers returning from Guangdong Province and Hong Kong (8), and the first phase of the epidemic involved hospitalized patients, family members, and healthcare workers exposed to these travelers. During this period (March 8–April 3, 2003), almost all (96%) probable SARS patients reported close contact with a known SARS patient. However, during the peak of the epidemic (April 4–May 4), the percentage of probable SARS patients who reported no contact with another SARS patient and who were not healthcare workers rose to 42%; as the number of cases fell during the last part of the epidemic (May 5–June), this percentage increased to 65%. The reasons for these apparently unlinked SARS cases were unknown. Possible explanations included acquisition of disease from unrecognized sources in the community or healthcare setting, incomplete collection or recording of contact histories, and clinical illness that met the SARS case definition but was caused by etiologic agents other than SARS-CoV.

To evaluate these hypotheses, we conducted a matched case-control study during the Beijing outbreak among a sample of SARS patients who had no reported contact with other SARS patients.

Methods

Definitions

Probable Cases

Probable and suspected SARS cases were defined according to the China Ministry of Health's definitions,

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which included clinical and epidemiologic components. The epidemiologic criteria changed during the course of the outbreak. Before April 3, 2003, only patients who had close contact with a known SARS patient or who had infected other persons could be diagnosed with SARS. From April 4 to May 3, the epidemiologic criteria were expanded to include persons with a history of visiting or residing in cities or areas where local transmission of SARS was occurring or with a history of contact with an outbreak or a healthcare facility. After May 3, Beijing was regarded as having local transmission of SARS, and visiting or residing in Beijing was considered sufficient to meet the epidemiologic criteria of the case definition. Laboratory testing for SARS-CoV was not part of the case definition.

Close Contacts

Close contacts of SARS patients were defined as persons who shared meals, utensils, a residence, a hospital room, or a transportation vehicle with a suspected SARS patient or as persons who visited such a patient in a period beginning up to 14 days before the patient's onset of symptoms. In addition, persons with potential contact with the bodily secretions of a SARS patient during the patient's treatment or care were considered close contacts.

Study Design

A matched case-control study design was used. Case-patients and controls were matched by sex and age group (≤17, 18–25, 26–45, 46–64, and ≥65 years). The goal was to enroll 100 case-patients matched with three controls each, which, if one assumes an α of 0.05 and 80% power, would allow detection of an odds ratio of >2.3 for exposures observed in 15% of controls. For the analysis, we excluded all controls <14 years of age because of potential biases in comparing them with matched case-patients aged 14–17 years. In addition, case-patients who were reclassified as healthcare workers after interview were excluded along with their matched controls.

Case-patients were eligible for the study if they met the probable case definition and reported no close contact with any known probable or suspected SARS patients. Only patients whose hospitalization occurred after April 28, 2003, were included in the study. A list of patients admitted to the 16 designated SARS hospitals in Beijing was obtained periodically, and we called patients at the hospital ward or their homes (after discharge) to invite them to participate. The latest date of hospitalization included in our study was June 9, 2003. Case interviews were completed June 3–16.

We selected controls by sequential digit dialing, using the case-patient's home telephone number as the index number. The last digit was added to or subtracted from by one digit in an alternating sequence until three controls matched by sex and age group were enrolled. Telephone prefixes are geographically clustered in Beijing, so this strategy was intended to provide neighborhood matching. Only one control was selected for each number dialed. Control interviews were completed by July 4.

Data Collection

Data from case-patients were collected in person or by telephone, by using a standardized questionnaire. Information was collected on potential risk factors for, or exposures to, SARS-CoV infection (such as having a chronic disease or visiting a healthcare facility), personal hygiene (such as washing hands), and the use of masks. The period of inquiry was the 2 weeks before the patient's onset of symptoms. For case-patients who reported visiting hospitals during the period of interest, a supplemental questionnaire was developed to collect detailed information on reasons for the visits and the hospitals and departments visited. Controls were interviewed by telephone and were queried about a reference period corresponding to the same 2-week period as the matched case.

Trained staff from the Beijing Center for Disease Prevention and Control interviewed all case-patients and approximately half of the controls. To accelerate enrollment, we used a commercial contractor to interview the remaining controls; the contractor received interviewer training by study staff before beginning the interviews. For quality control purposes, 10% of the contractor-interviewed controls were interviewed twice.

Laboratory Tests

Case-patients were asked to come to Beijing Center for Disease Prevention and Control so that a 5-mL blood specimen could be obtained. Blood samples were centrifuged, and serum samples were refrigerated at 4°C. Sera were tested at the Beijing Center for Disease Prevention and Control for immunoglobulin (Ig) G antibody to SARS-CoV, by using an enzyme-linked immunosorbent assay kit (Beijing Huada GBI Biotechnology Co. Ltd., Beijing). All serum samples were obtained ≥21 days after illness onset, and 80% of them were obtained 76–106 days after onset of symptoms.

Statistical Analyses

Matched univariate and multivariate analyses were conducted by conditional logistic regression. The PHREG procedure in SAS version 8 (SAS, Cary, NC) was used, with case status as the dependent variable. Factors associated with p values of <0.15 on univariate analysis were included in multivariable models. Collinearity and pairwise interactions were evaluated for all variables in the final model.

Results

A total of 373 patients were called from the master list until 100 were interviewed. Among patients who could be reached, the refusal rate was approximately 50%. The most frequent reasons for refusal were "tired of being interviewed" and being reluctant to disclose any personal information for fear of stigma and discrimination. Patients who agreed to participate in the study were similar in terms of age, sex, and temperature (on clinic presentation) to all probable SARS case-patients without a history of contact with another SARS patient (n = 1,091). Seven controls were excluded because they were <14 years of age, which resulted in the elimination of two matched sets. Four matched sets were also excluded because the case-patient was subsequently reclassified as a healthcare worker. A total of 94 case-patients and 281 matched controls were included in the final analyses.

Male patients accounted for 50% of case-patients. The median age was 29 years (range 14–84) for case-patients and 31 years (range 14–82) for controls. In univariate analyses, several health-related risk factors were significantly associated with an increased risk for clinically diagnosed SARS, including having visited any fever clinic (clinics established to separate patients who might have SARS from other persons being evaluated in emergency rooms or outpatient clinics) or any hospital or having a preexisting chronic disease, such as diabetes (Table 1). Eating out more than once a week and using several types of transportation, including taking a taxi or bus at least once a week, were associated with SARS (Table 1). Having visited a farmer's market, wearing a mask when going out, and washing hands when returning home were protective factors. Factors that were not associated with SARS included visiting a school or university, participating in large social gatherings outside the home, having mice or cockroaches in the home, and having stayed home from work or school. No case-patients or controls reported having traveled to SARS-affected areas, such as Guangdong, Hong Kong, or Toronto.

Factors associated with SARS in multivariable analysis are presented in Table 2. After other factors were controlled for, visiting a fever clinic and having a chronic medical condition remained significantly associated with a risk for SARS. After other variables were adjusted for, having visited a hospital was not associated with acquiring SARS. Other factors associated with an increased risk for SARS were eating outside the home and taking taxis more than once a week. Always wearing a mask when going out was associated with a 70% reduction in risk compared with never wearing a mask. Wearing a mask intermittently was associated with a smaller yet significant reduction in risk. Going to the farmer's market and owning a pet were both protective factors.

As of August 28, 2003, a total of 31 blood specimens had been tested for IgG to SARS-CoV, and 8 (26%) were positive. Of the eight seropositive case-patients, three had not visited a hospital or fever clinic in the 2 weeks before becoming ill.

Discussion

SARS-CoV transmission is now understood to involve close contact of symptomatic patients with others. Surveillance and case management in most parts of the world have focused on patients with clinically compatible illness who had had exposure to another SARS patient or had traveled to an affected area. Once SARS was recognized as widespread in Beijing hospitals, respiratory illness in any Beijing resident raised suspicion of SARS, and health authorities urged a low threshold for consideration of SARS to institute patient isolation, case reporting, and contact tracing. In the Beijing outbreak, the large number of patients who were diagnosed with probable SARS without a contact history led to concerns that overdiagnosis was occurring or, alternatively, that unrecognized sources of transmission existed in the community. Our study suggests that both factors were involved.

Thirty percent of case-patients in this study had a history of visiting a hospital in the 2 weeks before onset of SARS. By univariate analysis, persons with SARS were more than three times as likely as age- and sex-matched controls to have visited hospitals. After other factors, including the presence of chronic medical conditions, were controlled for, visiting a hospital was not independently associated with a higher risk for clinical SARS. The frequency of a history of hospital exposure among our case-patients was consistent with the epidemiology of SARS observed in other major outbreaks, where hospitals served as important amplifiers of transmission. Instituting effective infection-control measures in healthcare settings is the most critical step in controlling the spread of SARS.

Fever clinics were established in Beijing for triage of patients who might have SARS to separate them from other persons being evaluated in emergency rooms or outpatient clinics. Our study found that visiting a fever clinic was a very strong risk factor for SARS. Through a follow-up questionnaire administered to patients who reported having visited hospitals or clinics, we attempted to ensure that the reported visits were for reasons other than the first symptoms of the SARS illness. Our finding that visiting fever clinics increased the risk for probable SARS infection confirms the suspicions of public health authorities that, early in the epidemic response, some fever clinics had not implemented appropriate isolation and triage procedures and supports the public health decision to close dozens of problematic fever clinics and enhance infection-control measures at the 66 clinics that remained open.

Table 1. Selected potential risk and protective factors among cases and matched controls during the 2 weeks before the case-patient's onset of SARS-related symptoms, Beijing, 2003[a]

Potential risk or protective factor for SARS	% of cases with factor N=94	% of controls with factor N = 281	Matched OR (95% CI)[b]	p value
Healthcare related				
Visited any hospital	30	10	3.6 (2.0 to 6.5)	<0.001
Visited any fever clinic[c]	15	1	13.4 (3.8 to 46.7)	<0.001
Having any chronic disease[d]	19	7	4.1 (1.8 to 9.3)	<0.001
Community related				
Visited any school or college	14	16	0.8 (0.4 to 1.6)	0.52
Visited any quarantine site	2	2	1.2 (0.2 to 6.2)	0.83
Attended any social gathering[e]	7	10	0.8 (0.3 to 1.8)	0.52
Visited any movie theater, concert hall, or indoor gym	2	4	0.6 (0.1 to 2.8)	0.48
Visited any farmer's market	23	37	0.5 (0.3 to 0.9)	0.01
Eating out				
Never	62	70	Reference	
Once a week	14	15	1.2 (0.6 to 2.4)	0.67
More than once a week	24	15	2.3 (1.2 to 4.5)	0.01
Riding a bus				
Never	62	73	Reference	
Once a week	13	7	2.3 (1.0 to 5.2)	0.04
More than once a week	25	19	1.7 (0.9 to 3.1)	0.08
Taking a taxi				
Never	80	79	Reference	
Once a week	7	16	0.4 (0.2 to 1.0)	0.05
More than once a week	13	4	3.2 (1.3 to 8.0)	0.01
Taking the subway				
Never	88	91	Reference	
Once a week	1	4	0.3 (0.0 to 2.3)	0.25
More than once a week	11	5	2.5 (1.0 to 6.6)	0.06
Home related				
Did not go to work/attend school	39	40	1.0 (0.6 to 1.6)	0.90
Had a pet	12[f]	20	0.5 (0.2 to 1.1)	0.08
Home infested by rats or mice	10	6	1.6 (0.7 to 3.9)	0.28
Home infested by cockroaches	16	15	1.1 (0.6 to 2.0)	0.87
Behavior related				
Wore a mask when going out				
Never	46	27	Reference	
Sometimes	27	30	0.5 (0.2 to 0.9)	0.02
Always	27	43	0.3 (0.2 to 0.6)	<0.001
Always washed hands before eating	83	89	0.6 (0.3 to 1.1)	0.11
Always washed hands after using restrooms	88	93	0.5 (0.2 to 1.2)	0.10
Always washed hands after returning home	78	90	0.3 (0.2 to 0.7)	0.003

[a]OR, odds ratio; CI, confidence interval; SARS, severe acute respiratory syndrome.
[b]Determined by use of conditional logistic regression. Exposures refer to the 2 weeks before symptom onset for cases and the same 2-week period for matched controls.
[c]Fever clinics were established for triage of patients who might have SARS to separate them from other persons being evaluated in emergency rooms or outpatient clinics.
[d]Includes diabetes, cancer, immunosuppressive treatment, and other.
[e]A gathering of ≥10 persons for a party or other social event.
[f]Pets reported by case-patients included dogs (3 cases), cats (3 cases), fish (1 case), and pigeons (1 case).

In this investigation, persons with chronic medical conditions also had a significantly higher risk of clinical SARS developing. A disproportionate occurrence of the disease in persons who are elderly or who have a chronic disease was noted in other SARS outbreaks, but whether these factors were just markers for persons likely to have nosocomial exposure to other SARS patients was unclear. Our study found that the SARS risk associated with chronic disease was independent of recent exposure to healthcare facilities and suggests that, as is the case for other types of pneumonia (10,11), persons with chronic medical conditions are more vulnerable to clinically defined SARS. We had insufficient numbers of laboratory-confirmed cases to verify that this finding was specific for SARS-CoV infection.

Because a considerable proportion of SARS cases were reported in persons without a history of contact with another SARS patient and without exposure to healthcare facilities, we sought to identify unrecognized sources of community transmission that might help target control strategies and clarify whether widespread community transmission was indeed occurring. We found that certain

Table 2. Factors significantly associated with acquisition of clinically diagnosed SARS in multivariate analysis[a]

Potential risk or protective factor for SARS	Matched OR (95% CI)[a]	p value
Healthcare related		
Visited any fever clinic[b]	12.7 (3.1 to 52.0)	<0.001
Having any chronic disease	4.8 (1.7 to 13.2)	0.002
Visited any farmer's market	0.4 (0.2 to 0.8)	0.01
Eating out		
Never	Reference	
Once a week	1.6 (0.7 to 3.8)	0.3
More than once a week	3.1 (1.2 to 7.7)	0.02
Taking a taxi		
Never	Reference	
Once a week	0.2 (0.1 to 0.8)	0.02
More than once a week	3.0 (0.9 to 10.3)	0.07
Had a pet	0.4 (0.2 to 0.9)	0.03
Wore a mask when going out		
Never	Reference	
Sometimes	0.4 (0.2 to 0.9)	0.03
Always	0.3 (0.1 to 0.6)	0.002

[a]OR, odds ratio; CI, confidence interval; SARS, severe acute respiratory syndrome.
[b]Fever clinics were established for triage of patients who might have SARS to separate them from other persons being evaluated in emergency rooms or outpatient clinics.

community exposures were significantly more common among case-patients than controls, including eating out or taking taxis frequently. By univariate analysis, use of other common transport (e.g., buses, subways) was also associated with a risk for SARS. At least one well-publicized case of SARS in Beijing occurred in a taxi driver (12), but an increased risk among passengers had not previously been documented. Our findings regarding use of transportation bordered on statistical significance and will require validation by other studies.

We also used this investigation to quantify the impact of behaviors (i.e., mask wearing, handwashing) that were promoted to reduce the risk for SARS. Wearing masks outside the home in a reference period corresponding to the 2 weeks before symptom onset for cases was significantly protective against clinical SARS. Supporting the validity of this finding, there was a dose-response effect: by multivariable analysis, persons who always wore masks had a 70% lower risk of being diagnosed with clinical SARS compared with those who never wore masks, and persons with intermittent mask use had a 60% lower risk. Many persons who wore masks in the community did not use N-95 or similar highly efficient filtration devices, which have been recommended for use in the hospital setting. We sought details on the type of masks used but were unable to evaluate the protective efficacy for different mask types. We also were not able to differentiate protective efficacy for SARS-CoV versus efficacy against other pneumonia causes that met the clinical case definition.

Handwashing has been recommended to prevent SARS and other respiratory and diarrheal infections in which contact is an important mode of transmission. We found that consistently washing hands upon returning home was associated with a reduced risk for clinical SARS by univariate but not multivariate analysis. However, self-reported handwashing practices may be particularly prone to misclassification because respondents might provide the answer they believe is expected of them.

We also explored the role of domestic animals in relation to SARS infection among persons without contact with another SARS patient. An animal source for the origin of SARS-CoV in humans is suspected (13), and, using polymerase chain reaction, investigators identified SARS-CoV in household pets and cockroaches at the Amoy Gardens apartments in Hong Kong (14). Thus, we wondered whether certain household pets or rodents might be perpetuating disease-transmission cycles. One investigator recently hypothesized that a rodent vector may have amplified transmission of SARS at Amoy Gardens (15). In addition, rumors circulating during the Beijing SARS outbreak led to some calls for banning household pets or restricting them from common areas. We sought evidence to address this community fear and found that household rodents and cockroaches were not associated with a risk for clinical SARS. We also found that persons with pets had a significantly lower risk for clinical SARS. This finding might have occurred by chance or may be confounded by another factor more directly related to pneumonia. However, controls with pets might possibly have had exposure to other animal coronaviruses that provided cross-reacting antibody to the SARS-CoV. Of note, other investigators found IgG to SARS-CoV was common among animal traders in Guangdong (16), yet disease did not occur in this population, a finding consistent with the hypothesis that cross-reacting antibodies to a closely related virus may have protected these workers.

Another unexpected finding was that visiting a farmer's market was associated with a reduced risk for clinical SARS. Nevertheless, concern that farmers represented travelers from other provinces and that markets were crowded settings prompted us to ask about this exposure as a possible risk factor. Accounting for an association with lower risk is challenging. As with ownership of pets, this finding may relate to unmeasured lifestyle factors more directly related to pneumonia risk.

Among authorities in Beijing, a leading hypothesis for the occurrence of clinical SARS among patients without known contact with another SARS patient was that overdiagnosis was occurring. We sought to determine the proportion of case-patients in this study who could be confirmed by convalescent-phase serologic tests to be infected with SARS-CoV; however, we obtained serum samples

from an insufficient number of case-patients to analyze risk factors for laboratory-confirmed cases. Serologic testing for SARS may not be 100% sensitive, and the Huada test kit has had limited validation thus far. Nevertheless, a substantial portion of case-patients without contact with other SARS patients likely had pneumonia caused by pathogens other than SARS-CoV.

Certain limitations to this study should be mentioned. First, the study was conducted late in the Beijing epidemic, after patients had been hospitalized for several weeks, and the low participation rate might be attributable to patients having already been interviewed multiple times. Furthermore, recall bias might have influenced some of the factors we explored. Telephone-based public health studies were relatively new to Beijing, and the representativeness of our control population is not known. Because the rate of study participation by case-patients was not high, those who agreed to participate may have self-selected for unknown reasons that could have biased our findings. For instance, several patients responding to the open-ended comment section mentioned that they were certain their illness was "not SARS." Relatively few patients agreed to convalescent-phase serologic testing, and those who did agree may have been more skeptical about the cause of their pneumonia than were others, which may have skewed the sample for which we have serologic results.

In conclusion, we identified several explanations for the occurrence of clinically defined SARS in persons without contact with another SARS patient during Beijing's 2003 SARS epidemic. The nonspecific clinical definition for SARS led to reporting of many cases that were not confirmed to be caused by SARS-CoV. This apparent overdiagnosis probably helped ensure rapid control of the outbreak by introducing a wide net for contact tracing and patient isolation. Increased risk for clinically defined SARS was associated with attending fever clinics, having a chronic disease, and having certain community exposures. Consistent mask use lowered the risk for disease, thus providing some justification for the use of a strategy that was very popular in the general community. Our finding that pet owners had a lower risk for clinical SARS can help dispel fears that domestic pets were causing disease transmission in Beijing. Improved laboratory diagnostic tests (i.e., tests with high sensitivity early in the illness and with rapid turnaround) may eventually allow for more specific case reporting and management. Although human-to-human transmission of SARS has apparently been interrupted as of this writing, the factors associated with clinically defined SARS in this study may help target future efforts to control other respiratory infections, including pandemic influenza, and will provide valuable evidence for the control of SARS should the disease return.

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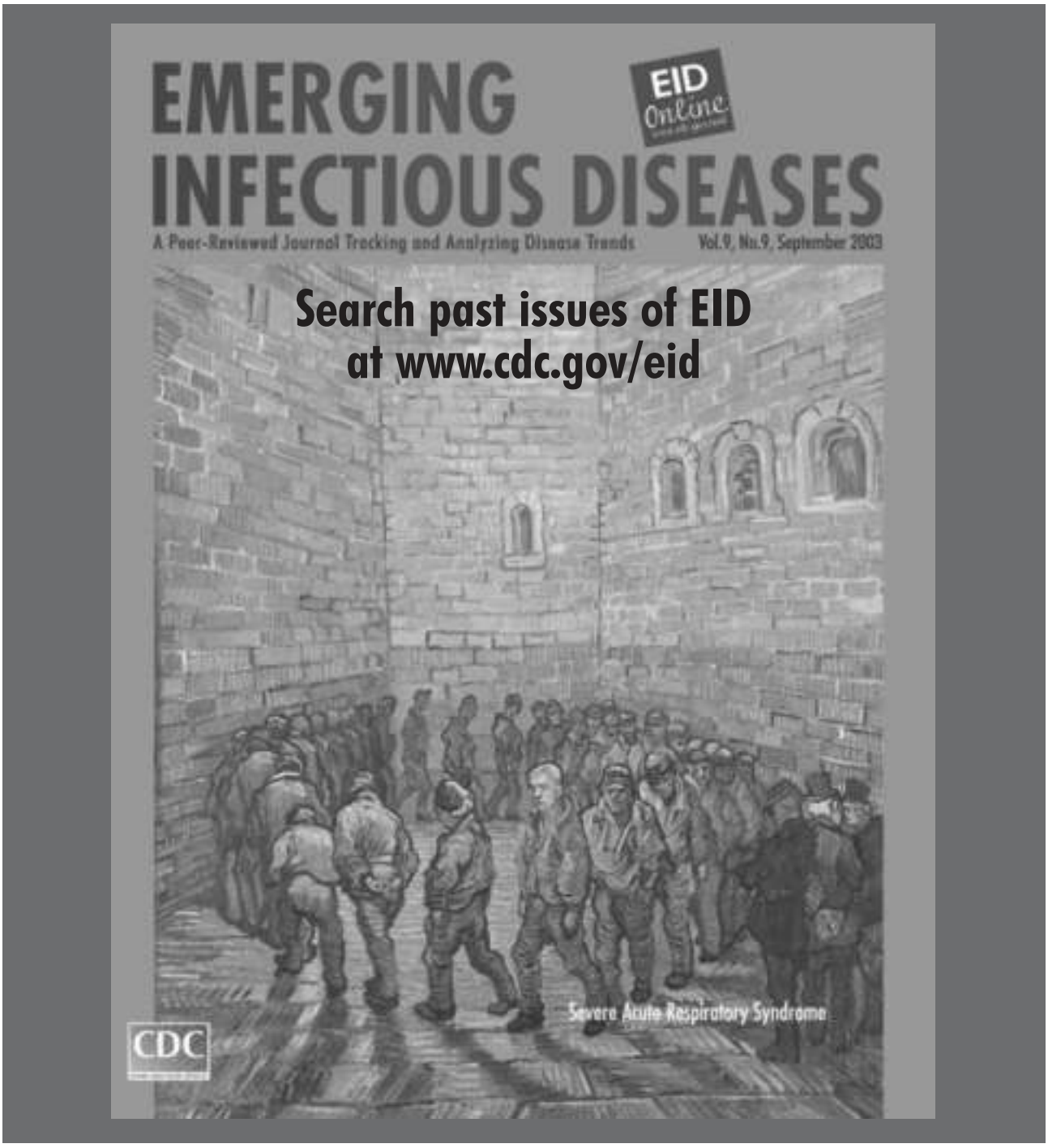

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Potential transmission of SARS-CoV-2 on a flight from Singapore to Hangzhou, China: An epidemiological investigation

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ABSTRACT

Background: Between January 24, 2020 and February 15, 2020, an outbreak of COVID-19 occurred among 335 passengers on a flight from Singapore to Hangzhou in China. This study aimed to investigate the source of the outbreak and assess the risk of transmission of COVID-19 during the flight.
Method: Using a standardized questionnaire, we collected information on the travelers' demographic characteristics and illness before, during, and after the flight. We also collected data on factors potentially associated with COVID-19 transmission during the flight.
Results: A total of 16 COVID-19 patients were diagnosed among all passengers; the overall attack rate was 4.8%. The attack rate among passengers who had departed from Wuhan was significantly higher than that among those who had departed from other places. One passenger without an epidemiological history of exposure before boarding developed COVID-19. During the flight, he was seated near four infected passengers from Wuhan for approximately an hour and did not wear his facemask correctly during the flight.
Conclusions: COVID-19 transmission may have occurred during the flight. However, the majority of the cases in the flight-associated outbreak could not be attributed to transmission on the flight but were associated with exposure to the virus in Wuhan or to infected members in a single tour group.

1. Introduction

In December 2019, a cluster of acute respiratory illness, now known as coronavirus disease 2019 (COVID-19), occurred in Wuhan, Hubei Province in China [1,2]. By March 22, 2020, a total of 81,093 COVID-19 cases had been confirmed in China, of which 50,005 cases were from Wuhan City [3]. The condition rapidly spread globally, and on March 11, 2020 the World Health Organization declared a COVID-19 pandemic [4]. Epidemiological investigation has shown that COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can be transmitted from human to human. The two primary transmission routes of SARS-CoV-2 are by contact (direct and indirect contact) or droplets, but the possibility of air-borne infection could not be totally excluded [5,6].

Air travel for leisure and business purposes has risen markedly in recent years due to economic growth and increased globalization [7,8]. Although infrequently reported and difficult to assess accurately, respiratory agents may be easily transmitted to passengers during air travel owing to limited ventilation, high occupant density and a long exposure time [9,10]. Multiple outbreaks of respiratory diseases, such as severe acute respiratory syndrome (SARS), measles, tuberculosis, and influenza, associated with air travel have been reported [11–14]. Recent studies suggest that SARS-CoV-2 may be more transmissible than severe acute respiratory syndrome (SARS) coronavirus and Middle East respiratory syndrome (MERS) coronavirus [15]. However, there have not yet been any reports of probable transmission of SARS-CoV-2 during air

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travel.

On January 24, 2020, a flight originating from Singapore, and bound for Hangzhou, in China, was strictly managed after landing because approximately 100 passengers aboard the flight had visited Wuhan. Following a quarantine inspection in the airport, several passengers had already developed fever or upper respiratory infection symptoms. They were confirmed to have SARS-CoV-2 infections on the early morning of January 25. As in closed/semiclosed settings, on flight transmission of COVID-19 is facilitated by direct person-to person contact or contact with contaminated surfaces. Consequently, all passengers were required to spend at least 14 days under medical observation. By the end of the medical observation period on February 8, 2020, a total of 16 passengers had been confirmed with SARS-CoV-2 infection.

Here we describe the investigation of the outbreak of COVID-19 among passengers on this flight. The objectives of the investigation were to identify possible sources of exposure, and to evaluate whether transmission occurred during the flight. Because there are no published reports of transmission of SARS-CoV-2 during air travel, our investigation provides preliminary evidence of the risk of SARS-CoV-2 transmission on aircraft.

2. Methods

2.1. Flight

The flight left from Singapore Changi Airport on 24 January 2020, and landed at Hangzhou Xiaoshan Airport in China a few hours later. The aircraft was a Boeing 787-9. The total seat occupancy on the flight was 89% (335/375). The aircraft was equipped with air handling systems.

The boarding time of the flight was 16:30 local time, and the time of departure and landing were 16:50 and 21:40, respectively. A total of 346 people took the flight, of whom 335 were passengers and 11 were crew members. All crew members were Singaporean. Based on the departure records, we divided the passengers into two groups: Group A comprised those who departed from Wuhan to Singapore on 19 January 2020; and Group B comprised those who did not depart from Wuhan and did not have a history of travel to Wuhan.

2.2. Epidemiological investigations

All passengers were interviewed face-to-face or by telephone using a standardized questionnaire. We collected information on traveler demographics, health conditions, and symptoms (including fever, dry cough, shivering, expectoration and headaches) before, during, and after the flight, mask-wearing status, seat location, and activity during the flight. All passengers were required to take their temperature before deplaning.

2.3. Case definition

Infected passengers were categorized as symptomatic and asymptomatic. According to the national guidelines, a confirmed case of symptomatic COVID-19 was defined as a passenger who had a SARS-CoV-2 infection confirmed by real-time reverse-transcription polymerase chain reaction (RT-PCR) testing of a throat swab sample, and had symptoms of typical upper respiratory tract infection (such as runny nose, sore throat and dry cough) [16]. Asymptomatic cases were diagnosed based on positive RT-PCR test results but without any COVID-19 symptoms. The date of the positive RT-PCR test result was used as the onset date for asymptomatic cases, which was in line with a national study [17].

2.4. Laboratory testing

Consistent with a previous national study, all samples were tested for SARS-CoV-2 by use of RT-PCR with the Chinese Centers for Disease Control and Prevention recommended kit in accordance with the protocol established by the World Health Organization [18]. The RT-PCR was conducted at the Zhejiang Provincial Center for Disease Control and Prevention.

2.5. Medical isolation and observation

Since there were a large number of passengers originating from Wuhan and two passengers presented with a fever and upper respiratory infection symptoms, all passengers were regarded as close contacts and required to follow medical isolation and observation protocols for at least 14 days after deplaning on January 24. On arrival of the flight in Hangzhou, after preliminary investigation, passengers in Group A were accommodated in Hotel A near the Hangzhou Xiaoshan international airport; and passengers in Group B were transferred to Hotel B in the center of Hangzhou City; passengers (regardless of their group) who already had symptoms after preliminary investigation were sent to the infectious hospital designated for treatment of COVID-19 in Hangzhou. Except for children staying with a parent, the other passengers lived singly for medical isolation and observation in Hotel A or Hotel B. During the medical isolation and observation period, all passengers were required to take their temperature twice daily and report their health condition if they developed symptoms of an upper respiratory tract infection. If passengers isolated in Hotel A or Hotel B developed illness, they were to be transferred to the designated hospital immediately.

All crew members were isolated in Hotel B. They returned to Singapore on January 26, 2020. According to a message from the diplomatic department of Zhejiang Province, none of these crew members were infected with SARS-CoV-2.

2.6. Ethical considerations

According to the law on public health response in China, formal ethical review and approval of this outbreak investigation was not required.

2.7. Statistical analysis

A descriptive analysis was performed using R (Version 3.6.2) statistical software. Categorical variables were presented as frequencies and percentages. Because our study focused on passengers, crew members were excluded when we calculated the attack rate or performed the analysis of risk infection. Characteristics associated with the risk of infection were compared and tested for statistical significance using the chi-square or Fisher's exact tests.

3. Results

A total of 16 infected passengers, including 10 symptomatic passengers and 6 asymptomatic passengers, were diagnosed between 24 January and 15 February 2020. The overall attack rate among the passengers was 4.8% (16/335).

3.1. Temporal distribution

All infected passengers left for Singapore on January 19, 2020 (Fig. 1). Of the 10 symptomatic passengers, 2 (Cases 1 and 7) had developed symptoms before boarding and one (Case 2) developed symptoms on 24 January after the flight had landed in Hangzhou (Table 1). During the medical isolation and observation period, two passengers (Cases 5 and 6) developed symptoms on January 26 and 27 respectively. Six asymptomatic cases (Case 3 and Cases 11–15) were diagnosed on January 26 when all passengers were sampled and tested for the first time. On February 2, one week after the landing of flight, another two passengers (Cases 10 and 16) developed fever. On 6

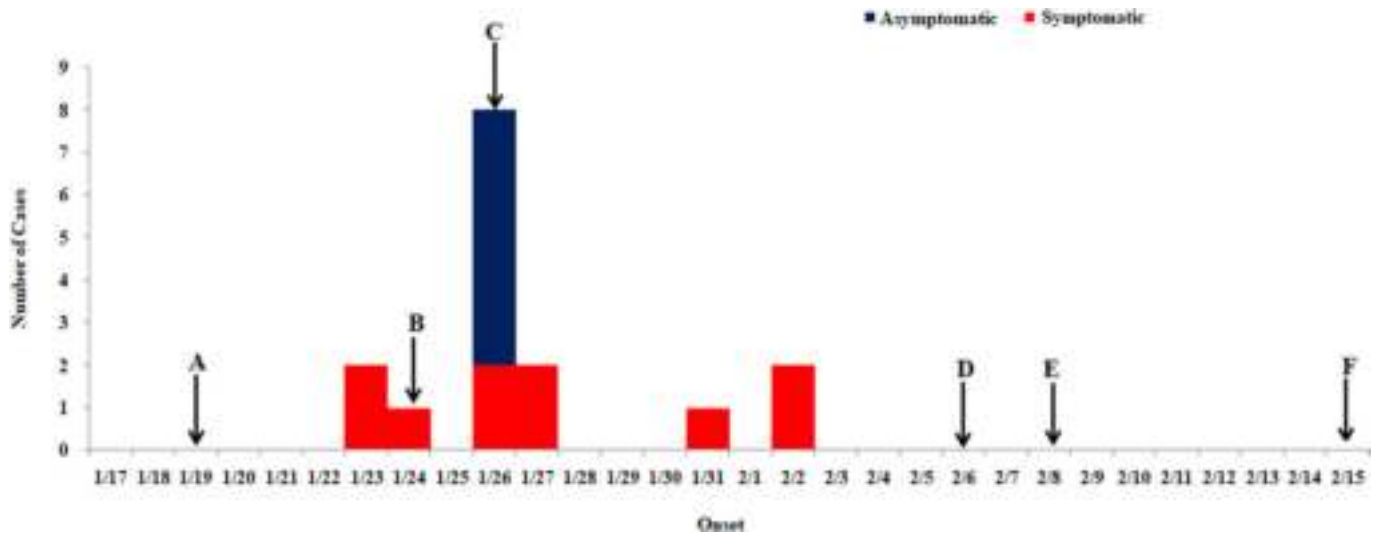

Fig. 1. Epidemic curve indicating the date of onset of COVID-19 cases among passengers on the flight, January to February 2020. (A): The case passengers flew from China to Singapore on 19 January (One passenger departed from Hangzhou; and the remaining 15 case passengers departed from Wuhan.). **(B):** The flight departed from Singapore to Hangzhou on 24 January and the passengers were placed in medical isolation and under observation on arrival in Hangzhou. **(C):** All passengers had samples collected for testing on 26 January. **(D):** All passengers had a second set of samples collected on 6 February. **(E)**: The passengers from places other than Wuhan ended their medical isolation on 8 February. **(F):** Those who departed from Wuhan ended their medical isolation one week later on 15 February.

Table 1
Summary of the details of individual cases in a flight-associated outbreak of SARS-CoV-2 infection in January–February 2020.

Case	Age (years)	Sex	Type[a]	Onset[b]	Residential city	Tour Group	Departure	Seat	Relationship
1	26	F	Symptomatic	January 23	Wuhan	A	Wuhan	11D	Leader of Tour Group A
2	45	M	Symptomatic	January 24	Wuhan	A	Wuhan	12D	Husband of Case 3
3	44	F	Asymptomatic	January 26	Wuhan	A	Wuhan	12E	Wife of Case 2
4	29	F	Symptomatic	January 26	Wuhan	A	Wuhan	12A	Daughter of Case 6; niece of Case 5
5	52	F	Symptomatic	January 27	Wuhan	A	Wuhan	44A	Aunt of Case 4; older sister of Case 6
6	45	F	Symptomatic	January 26	Wuhan	A	Wuhan	18A	Mother of Case 4; younger sister of Case 5
7	33	F	Symptomatic	January 23	Wuhan	A	Wuhan	31K	Wife of Case 8
8	36	M	Symptomatic	January 27	Wuhan	A	Wuhan	31J	Husband of Case 7
9	33	F	Symptomatic	January 31	Qinghuang Dao	A	Wuhan	11H	Wife of Case 10
10	32	M	Symptomatic	February 2	Qinghuang Dao	A	Wuhan	11J	Husband of Case 9
11	43	F	Asymptomatic	January 26	Wuhan	A	Wuhan	30D	None
12	44	M	Asymptomatic	January 26	Wuhan	A	Wuhan	30E	None
13	26	F	Asymptomatic	January 26	Wuhan	B	Wuhan	6H	None
14	28	M	Asymptomatic	January 26	Wuhan	C	Wuhan	16E	None
15	27	F	Asymptomatic	January 26	Wuhan	C	Wuhan	16F	None
16	44	M	Symptomatic	February 2	Hangzhou	D	Hangzhou	29B	None

F, female; M, male.
[a] Asymptomatic patients tested positive for SARS-CoV-2 using RT-PCR but did not have symptoms of COVID-19; Symptomatic cases tested positive for SARS-CoV-2 on RT-PCR and had symptoms of COVID-19 such as fever and dry cough.
[b] In the asymptomatic patients, the diagnosis date was used as the onset date.

February, we sampled and tested all passengers for the second time. However, no additional new cases were discovered during the second screening of all passengers. Moreover, no further cases were reported after 2 February. Passengers who had not departed from Wuhan ended their medical isolation and observation on February 8, and later, passengers who had departed from Wuhan ended their medical isolation and observation one week later, on 15 February (Fig. 1).

3.2. Seating

Fig. 2 shows seating locations on the airplane for all passengers. Two seating areas had a relatively high concentration of cases: six of the case passengers sat in Rows 11 and 12 and five case passengers sat in Rows 29 to 31. The remaining case passengers were scattered in the Row 6, Row 16, Row 18 and Row 44 (Fig. 2).

Case 16 originally sat in Seat 29B. There were no infected passengers in the first three rows close to Seat 29B; only one passenger who had departed from Wuhan was sitting in the aforementioned location. There was a wide aisle behind Seat 29B, where the toilet was located. However, during flight, Case 16 moved to Seat 30F and sat there for an hour. In the seats around Seat 30F, there were four infected passengers, with Case 11 and Case 12 sitting on the left side of him, and Case 7 and Case 8 sitting behind him on the right (Fig. 2).

3.3. Characteristics of the case passengers

Among the 16 cases, the median age was 37 years (range: 26–52 years). Six cases were female. The 16 cases belonged to four tour groups, with 12 cases in Tour Group A (TGA); one case in Tour Group B (TGB); two cases in Tour Group C (TGC); and one case in tour group D (TGD). Some cases were among passengers who were in a relationship with another case, e.g. Cases 2 and 3 were a couple (Table 1).

There were 15 tour members in TGA, of whom 12 were confirmed SARS-CoV-2 infection, an attack rate of 80%. All the cases in TGA, TGB

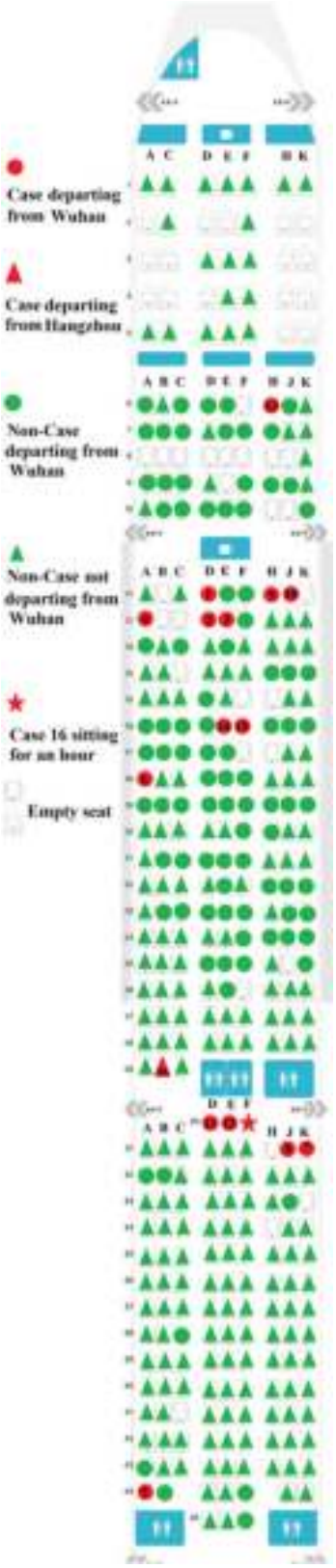

Fig. 2. Aircraft configuration and the location of the seats where the 16 case passengers sat during the flight. The numbers in the red background correspond to the Case number shown in Table 1. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

and TGC departed from Wuhan. In contrast, Case 16, who was a member of TGD, lived in Hangzhou, and departed from Hangzhou. The detailed information of all cases is listed in Table 1.

Table 2 summarizes the attack rates according to city of departure, age, and sex. The attack rate of passengers who departed from Wuhan was 13.8%, compared to 0.4% in passengers who did not depart from Wuhan ($p < 0.001$). The attack rate did not differ significantly by sex but was significantly higher among passengers aged 20–29 years, and 40–59 years, than in those aged<20 years and ≥60 years.

3.4. Exposure

According to the travel schedule, although TGA, TGB, and TGC all traveled to Singapore, there was no contact between the different groups before boarding the returning flight. All cases wore masks most of time and none of the cases visited a hospital or had contact with suspected or confirmed COVID-19 case during their travel.

Case 16 departed from Hangzhou to Singapore on 19 January 2020. None of the travelers in his tour group had visited Wuhan. Case 16 reported that he had not visited a hospital and had no contact with individuals suspected of having or confirmed with having COVID-19 before boarding the plane. Moreover, he stated he wore a mask while traveling in Singapore.

During air travel, all 16 case passengers wore masks. However, they removed their masks when they ate dinner or drank water provided during the flight. During the flight, Case 16 sat in Seat 30F for about an hour and talked to his wife and son in Seats 31E and 31F, respectively. While he talked, he reported that he did not wear his mask tightly, and his nose was outside of mask.

4. Discussion

We have described an outbreak of COVID-19 that affected 16 passengers who traveled on the same flight. The primary objective of our investigation was to determine possible sources of the outbreak and whether the transmission was occurred in the aircraft. We identified only one case (Case 16) who appears to have become infected during flight. The sources of infection in the remaining 15 passengers were complex and the passengers could have acquired their infections in Wuhan before their tour, or during the group tour before boarding.

Two cases (Cases 1 and 7) were infected before taking the flight because they were symptomatic before taking the flight. Previous research had suggested the SARS-CoV-2 is transmissible during the incubation period [19]. The high attack rate among the members of TGA indicates that SARS-CoV-2 infections occurred within TGA, which was the result of close exposure during their tour. Moreover, although TGA members drop off the mask during meals on the flight, they had donned a mask in most of other time. Considering that the median incubation period was 4 days (interquartile range: 2–7 days) [18], we hypothesize that the remaining 10 cases in TGA were probably infected before taking

Table 2
Attack rate according to characteristics of passengers involved in a flight-associated outbreak of COVID-19 in January–February 2020.

Characteristics	Total N = 335	Number of cases N = 16	Attack rate (%)	*P*
Departure city				<0.001
Wuhan	109	15	13.76	
Not Wuhan	226	1	0.44	
Sex				0.565
Male	149	6	4.03	
Female	186	10	5.38	
Age (years)				0.010
<20	69	0	0.00	
20–39	182	9	4.95	
40–59	71	7	9.86	
≥60	13	0	0.00	

the flight, rather than of during the flight. However, it was not possible to determine whether they had become infected in Wuhan, or during travel.

Case 13 in TGB and Cases 14 and 15 in TGC were asymptomatic and were diagnosed in the January 26 when we collected samples from passengers and tested them for the first time. Although they had left Wuhan on January 19, 2020, other studies have shown that transmission of SARS-CoV-2 in Wuhan on that day became widespread prior to their departure [17,20]. They also wore masks during air travel. Therefore, we believe they are most likely to have been infected in Wuhan, and not during flight.

With regard to Case 16, he did not have a history of exposure to Wuhan, or any suspected or confirmed cases of COVID-19 before boarding the flight in Singapore, and he wore a mask while traveling in Singapore. After boarding, he moved from seat 29B to 30F which was in the close proximity to the seats of Cases 7, 8, 11, and 12. Moreover, he talked to his wife (31E) and son (31F) with his mask loosened. After landing, he was immediately isolated and could not have any other source of exposure. The time from the flight landing to the onset of his symptoms fell within the accepted 1-to-14-day COVID-19 incubation period [16]. Therefore, he probably acquired SARS-CoV-2 infection during the flight. Our investigation further corroborated the probable transmission of SARS-CoV-2 on the flight recently reported by Eldin et al. [21].

Previous studies suggest that the basic reproductive number of COVID-19 ranges between 1.5 and 6.5. COVID-19 seems to be more transmissible than SARS and MERS [15]. However, in the present flight outbreak of COVID-19, the relative low number of the secondary cases that occurred due to transmission during the flight may be attributed to the wearing of masks, which have been shown to be effective in blocking the transmission of respiratory diseases at mass gatherings [22]. The low rate of transmission during the flight may also be attributed to the design of and equipment in the aircraft. The air recirculation system, with the highly efficient particulate filter equipment and laminar nature of airflow, may have effectively prevented or restricted the transmission of the virus [7,9]. In addition, after landing, all passengers were sent to designated places for medical isolation and observation. The strict management of all passengers further contributed to avoiding a larger travel-associated outbreak of COVID-19.

The atypical symptom onset of COVID-19 and the transmissibility of SARS-CoV-2 during incubation period make the prevention of SARS-CoV-2 transmission on aircraft challenging. Passengers are in close contact with one another in a confined space for hours during air travel. Numerous high-contact surfaces, such as armrests, tray tables, and seat controls, may serve as potential SARS-CoV-2 fomites [23]. Given these potential risks and those demonstrated by our investigation, development of appropriate prevention and control measures must take this into consideration. We suggest the key stakeholders should standardize aircraft disinfection protocols, train cabin crew for public health emergencies, implement technological solutions to reduce passenger contact with potentially contaminated surfaces, educate the general public to wear their masks closely and to wash their hands frequently. Fast reliable testing methods for detection of SARS-CoV-2 also need to be developed, to enable early diagnosis and to prevent infected passengers from boarding.

Our investigation had several limitations. Firstly, we collected exposure information by interview and telephone, and recall bias cannot be excluded. Moreover, we were unable to get a detailed and accurate trajectory of each case before boarding. Therefore, we cannot rule out the possibility that inapparent transmission between Case 16 and the other cases occurred in the shops, toilets, or airport lounge before boarding. Secondly, we did not perform virus isolation and genome sequencing of the virus, which could have provided evidence of whether viral transmission occurred during the flight. Thirdly, we did not perform surface swabs or take air samples in the aircraft cabin, and so do not have direct evidence of transmission occurring during the flight.

In conclusion, a flight-related outbreak of COVID-19 was investigated. The temporal, spatial, and exposure evidence suggests that SARS-CoV-2 transmission may have occurred during the flight. However, the majority of 16 cases in the outbreak were not attributed to transmission on the flight. Exposure to the virus in Wuhan or by infected members within the same tour group account for most cases in the outbreak. Our investigation suggests that it is important to take measures such as wearing a mask, temperature screening, and quarantine of close contacts to reduce the transmission of SARS-CoV-2 before, during, and after flights.

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Declaration of competing interest

For all authors none were declared.

CRediT authorship contribution statement

Junfang Chen: Writing - original draft, Investigation. **Hanqing He:** Writing - original draft, Investigation, Writing - original draft, Writing - review & editing. **Wei Cheng:** Writing - original draft, Writing - review & editing. **Yan Liu:** Writing - original draft, Investigation. **Zhou Sun:** Investigation, Writing - original draft, Writing - review & editing. **Chengliang Chai:** Writing - original draft, Investigation. **Qingxin Kong:** Writing - original draft, Investigation. **Wanwan Sun:** Writing - original draft. **Jiaqi Zhang:** Writing - original draft. **Song Guo:** Writing - original draft. **Xuguang Shi:** Writing - original draft. **Jinna Wang:** Writing - original draft. **Enfu Chen:** Writing - original draft. **Zhiping Chen:** Investigation, Writing - original draft.

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Lack of COVID-19 transmission on an international flight

In response to the *CMAJ* news article, "Communication, transparency key as Canada faces new coronavirus threat,"[1] we would like to share the public health response to the first Canadian cases of coronavirus disease 2019 (COVID-19). Case details have been published.[2] The patients travelled from Wuhan to Guangzhou, then Guangzhou to Toronto, Canada, arriving on Jan. 22, 2020. The index patient was symptomatic with dry cough during the flight. His wife developed cough on Jan. 23. Both sets of throat and nasopharyngeal swabs collected were positive for COVID-19.

There were approximately 350 passengers on board the airplane. The public was notified through the media that the index case was symptomatic during the 15-hour flight. Close contacts included 25 individuals sitting within 2 m of the index case during the flight, flight crew members, and 1 close contact on arrival in Toronto. Close contacts received active daily contact monitoring by local public health officials for 14 days from the flight's arrival in Toronto. Passengers and crew members who were not from Ontario were referred to their home jurisdictions for follow-up. On Jan. 29, 1 close contact developed symptoms of cough; however, nasopharyngeal and throat swabs were negative for COVID-19. Non-close-contact passengers were advised to self-monitor and contact public health if they became symptomatic; 5 of these passengers became symptomatic, were tested and found by nasopharyngeal and throat swabs to be negative for COVID-19.

The United States Centers for Disease Control and Prevention recommend contact tracing 2 rows in front and behind symptomatic cases with respiratory infections owing to an elevated risk within close contact.[3] However, for both severe acute respiratory syndrome–associated coronavirus (SARS-CoV) and influenza, approximately 50% of airplane transmission occurred beyond these rows.[4]

Studies of airplane transmission are commonly biased by contacts sharing exposure risks before boarding the aircraft.[5] In our investigation, transmission may have been mitigated by mild symptoms and masking during the flight. However, the lack of secondary cases after prolonged air travel exposure supports droplet transmission, not airborne, as the likely route of spread of the COVID-19.

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Absence of Apparent Transmission of SARS-CoV-2 from Two Stylists After Exposure at a Hair Salon with a Universal Face Covering Policy — Springfield, Missouri, May 2020

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On July 14, 2020, this report was posted as an MMWR *Early Release on the* MMWR *website (https://www.cdc.gov/mmwr).*

On May 12, 2020 (day 0), a hair stylist at salon A in Springfield, Missouri (stylist A), developed respiratory symptoms and continued working with clients until day 8, when the stylist received a positive test result for SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19). A second hair stylist (stylist B), who had been exposed to stylist A, developed respiratory symptoms on May 15, 2020 (day 3), and worked with clients at salon A until day 8 before seeking testing for SARS-CoV-2, which returned a positive result on day 10. A total of 139 clients were directly serviced by stylists A and B from the time they developed symptoms until they took leave from work. Stylists A and B and the 139 clients followed the City of Springfield ordinance* and salon A policy recommending the use of face coverings (i.e., surgical masks, N95 respirators,† or cloth face coverings) for both stylists and clients during their interactions. Other stylists at salon A who worked closely with stylists A and B were identified, quarantined, and monitored daily for 14 days after their last exposure to stylists A or B. None of these stylists reported COVID-19 symptoms. After stylist B received a positive test result on day 10, salon A closed for 3 days to disinfect frequently touched and contaminated areas. After public health contact tracings and 2 weeks of follow-up, no COVID-19 symptoms were identified among the 139 exposed clients or their secondary contacts. The citywide ordinance and company policy might have played a role in preventing spread of SARS-CoV-2 during these exposures. These findings support the role of source control in preventing transmission and can inform the development of public health policy during the COVID-19 pandemic. As stay-at-home orders are lifted, professional and social interactions in the community will present more opportunities for spread of SARS-CoV-2. Broader implementation of masking policies could mitigate the spread of infection in the general population.

Stylist A worked from day 0 to day 8 with COVID-19 symptoms before receiving a diagnosis of COVID-19 by polymerase chain reaction (PCR) testing. Although self-isolation was recommended after testing on day 6, stylist A continued to work until the test returned a positive result, at which time stylist A was excluded from work by salon A. On day 3, after working with stylist A, stylist B developed respiratory symptoms. During Stylist A's symptomatic period, the two stylists interacted while neither was masked during intervals between clients. Stylist B worked from day 3 to day 8 while symptomatic before self-isolating and seeking PCR testing, which returned a positive result for SARS-CoV-2 on day 10. Stylist A worked with clients for 8 days while symptomatic, as did stylist B for 5 days. During all interactions with clients at salon A, stylist A wore a double-layered cotton face covering, and stylist B wore a double-layered cotton face covering or a surgical mask.

The Greene County Health Department (Missouri) conducted contact tracing for all 139 exposed clients back to the dates that stylists A and B first developed symptoms. The 139 clients were monitored after their last exposure at salon A. Clients were asked to self-quarantine for 14 days and were called or sent daily text messages to inquire about any symptoms; none reported signs or symptoms of COVID-19. Testing was offered to all clients 5 days after exposure, or as soon as possible for those exposed >5 days before contact tracing began. Overall, 67 (48.2%) clients volunteered to be tested, and 72 (51.8%) refused; all 67 nasopharyngeal swab specimens tested negative for SARS-CoV-2 by PCR. Telephone interviews were attempted 1 month after initial contact tracings to collect supplementary information. Among the 139 exposed clients, the Greene County Health Department interviewed 104 (74.8%) persons.

Among the 139 clients, the mean age was 52 years (range = 21–93 years); 79 clients (56.8%) were male (Table 1). Salon appointments ranged from 15 to 45 minutes in length (median = 15 minutes; mean = 19.5 minutes). Among the 104 interviewed clients, 102 (98.1%) reported wearing face coverings for their entire appointment, and two (1.9%) reported wearing face coverings part of the time (Table 2). Types of face covering used by clients varied; 49 (47.1%) wore cloth face coverings, 48 (46.1%) wore surgical masks, five (4.8%) wore N95 respirators, and two (1.9%) did not know what kind of face covering they wore. Overall, 101 (97.1%) interviewed clients reported that their stylist wore a face covering for the entire appointment; three did not know. When asked about the type of face coverings worn by the stylists, 64 (61.5%) reported that their stylist wore a cloth face covering (39; 37.5%) or surgical mask

* Springfield, Missouri, city ordinance went into effect May 6, 2020, restricted seating in waiting areas to 25% of normal capacity and recommended social distancing and use of face coverings for employees and clients when social distancing was not or could not be followed. https://www.springfieldmo.gov/5140/Masks-and-Face-Coverings.

† Particulate-filtering facepiece respirators that filter ≥95% of airborne particles (https://www.cdc.gov/niosh/npptl/topics/respirators/disp_part/n95list1.html).

Summary

What is already known about this topic?

Consistent and correct use of cloth face coverings is recommended to reduce the spread of SARS-CoV-2.

What is added by this report?

Among 139 clients exposed to two symptomatic hair stylists with confirmed COVID-19 while both the stylists and the clients wore face masks, no symptomatic secondary cases were reported; among 67 clients tested for SARS-CoV-2, all test results were negative. Adherence to the community's and company's face-covering policy likely mitigated spread of SARS-CoV-2.

What are the implications for public health practice?

As stay-at-home orders are lifted, professional and social interactions in the community will present more opportunities for spread of SARS-CoV-2. Broader implementation of face covering policies could mitigate the spread of infection in the general population.

(25; 24.0%); 40 (38.5%) clients did not know or remember the type of face covering worn by stylists. When asked whether they had experienced respiratory symptoms in the 90 days preceding their appointment, 87 (83.7%) clients reported that they had not. Of those who did report previous symptoms, none reported testing for or diagnosis of COVID-19.

Six close contacts of stylists A and B outside of salon A were identified: four of stylist A and two of stylist B. All four of stylist A's contacts later developed symptoms and had positive PCR test results for SARS-CoV-2. These contacts were stylist A's cohabitating husband and her daughter, son-in-law, and their roommate, all of whom lived together in another household. None of stylist B's contacts became symptomatic.

Discussion

SARS-CoV-2 is spread mainly between persons in close proximity to one another (i.e., within 6 feet), and the more closely a person interacts with an infected person and the longer the interaction, the higher the risk for transmission (*1*). At salon A in Springfield, Missouri, two stylists with COVID-19 symptoms worked closely with 139 clients before receiving diagnoses of COVID-19, and none of their clients developed COVID-19 symptoms. Both stylists A and B, and 98% of the interviewed clients followed posted company policy and the Springfield city ordinance requiring face coverings by employees and clients in businesses providing personal care services. The citywide ordinance reduced maximum building waiting area seating to 25% of normal capacity and recommended the use of face coverings at indoor and outdoor public places where physical distancing was not possible. Both company and city policies were likely important factors in preventing the spread of SARS-CoV-2 during these interactions between clients and stylists. These results support the use of face coverings in places open to the public, especially when social distancing is not possible, to reduce spread of SARS-CoV-2.

TABLE 1. Characteristics* of clients (N = 139) who visited hair salon A and were exposed to stylists A and B with COVID-19 —Springfield, Missouri, May 2020

Characteristic	Value
Demographic characteristic	
Male, no. (%)	79 (56.8)
Age, yrs. mean (range)	52 (21–93)
Encounter information	
Appointment date range	May 12–20 (days 0–8†)
Exposure to stylist A, no. (%)	84 (60.4)
Exposure to stylist B, no. (%)	55 (39.6)
Appointment duration, mins, median (range)	15 (15–45)
Client testing	
Clients tested, no. (%)	67 (48.2)
Negative tests, no. (%)§	67 (100)

Abbreviation: COVID-19 = coronavirus disease 2019.
* All interviews were conducted via telephone by the Greene County Health Department.
† After onset of symptoms in stylist A.
§ Among those tested.

Although SARS-CoV-2 is spread largely through respiratory droplets when an ill person coughs or sneezes (*1*), data suggest that viral shedding starts during the 2-to-3-day period before symptom onset, when viral loads are at their highest (*2*). Although the rate of transmission of SARS-CoV-2 from presymptomatic patients (those who have not yet developed symptoms) and asymptomatic persons (those who do not develop symptoms) is unclear, these persons likely contribute to the spread of SARS-CoV-2 (*3*). With the potential for presymptomatic and asymptomatic transmission, widespread adoption of policies requiring face coverings in public settings should be considered to reduce the impact and magnitude of additional waves of COVID-19.

Previous studies show that both surgical masks and homemade cloth face coverings can reduce the aerosolization of virus into the air and onto surfaces (*4*,*5*). Although no studies have examined SARS-CoV-2 transmission directly, data from previous epidemics (*6*,*7*) support the use of universal face coverings as a policy to reduce the spread of SARS-CoV-2, as does observational data for COVID-19 in an analysis of 194 countries that found a negative association between duration of a face mask or respirator policy and per-capita coronavirus-related mortality; in countries that did not recommend face masks and respirators, the per-capita coronavirus-related mortality increased each week by 54.3% after the index case, compared with 8.0% in those countries with masking policies (CT Leffler, Virginia Commonwealth University, unpublished data, 2020).§ Similar outcomes have been observed for other respiratory virus outbreaks, including the 2002–04 outbreak of Severe Acute Respiratory Syndrome

§ https://doi.org/10.1101/2020.05.22.20109231.

TABLE 2. Hair salon clients' (N = 104) responses to interview questions* about their interactions with two stylists with COVID-19 during salon appointments — Springfield, Missouri, May 12–20, 2020

Interview question	Response	No. (%)
Did you wear a face covering?	Yes, for the entire appointment	102 (98.1)
	Yes, for part of the appointment	2 (1.9)
	No, not at all	0 (—)
	Did not know	0 (—)
What type of face covering did you wear?	Cloth face covering	49 (47.1)
	Surgical mask	48 (46.1)
	N95 respirator†	5 (4.8)
	Did not know	2 (1.9)
	Did not answer question	0 (—)
Did the stylist wear a face covering?	Yes, for the entire appointment	101 (97.1)
	Yes, for part of the appointment	0 (—)
	No, not at all	0 (—)
	Did not know	3 (2.9)
What type of face covering did the stylist wear?	Cloth face covering	39 (37.5)
	Surgical mask	25 (24.0)
	N95 respirator	0 (—)
	Did not know	35 (33.7)
	Did not answer question	5 (4.8)
Did you have a respiratory illness in the past 90 days?	Yes	7 (6.7)
	No	87 (83.7)
	Did not know	1 (1.0)
	Did not answer the question	9 (8.7)

Abbreviation: COVID-19 = coronavirus disease 2019.
* All interviews were conducted via telephone by the Greene County Health Department.
† Particulate-filtering facepiece respirators that filter ≥95% of airborne particles (https://www.cdc.gov/niosh/npptl/topics/respirators/disp_part/n95list1.html).

(SARS) (*6*) and the 2007–08 influenza season (*7*). A systematic review on the efficacy of face coverings against respiratory viruses analyzed 19 randomized trials and concluded that use of face masks and respirators appeared to be protective in both health care and community settings (*8*).

The findings in this report are subject to at least four limitations. First, whereas the health department monitored all exposed clients for signs and symptoms of COVID-19, and no clients developed symptoms, only a subset was tested; thus, asymptomatic clients could have been missed. Similarly, with a viral incubation period of 2–14 days, any COVID-19 PCR tests obtained from clients too early in their course of infection could return false-negative results. To help mitigate this possibility, all exposed clients were offered testing on day 5 and were contacted daily to monitor for symptoms until day 14. Second, although the health department obtained supplementary data, no information was collected regarding underlying medical conditions or use of other personal protective measures, such as gloves and hand hygiene, which could have influenced risk for infection. Third, viral shedding is at its highest during the 2 to 3 days before symptom onset; any clients who interacted with the stylists before they became symptomatic were not recruited for contact tracing. Finally, the mode of interaction between stylist and client might have limited the potential for exposure to the virus. Services at salon A were limited to haircuts, facial hair trimmings, and perms. Most stylists cut hair while clients are facing away from them, which might have also limited transmission.

The results of this study can be used to inform public health policy during the COVID-19 pandemic. A policy mandating the use of face coverings was likely a contributing factor in preventing transmission of SARS-CoV-2 during the close-contact interactions between stylists and clients in salon A. Consistent and correct use of face coverings, when appropriate, is an important tool for minimizing spread of SARS-CoV-2 from presymptomatic, asymptomatic, and symptomatic persons. CDC recommends workplace policies regarding use of face coverings for employees and clients in addition to daily monitoring of signs and symptoms of employees, procedures for screening employees who arrive with or develop symptoms at work, and posted messages to inform and educate employees and clients (https://www.cdc.gov/coronavirus/2019-ncov/community/organizations/businesses-employers.html).

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Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis

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Summary

Background Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19 and is spread person-to-person through close contact. We aimed to investigate the effects of physical distance, face masks, and eye protection on virus transmission in health-care and non-health-care (eg, community) settings.

Methods We did a systematic review and meta-analysis to investigate the optimum distance for avoiding person-to-person virus transmission and to assess the use of face masks and eye protection to prevent transmission of viruses. We obtained data for SARS-CoV-2 and the betacoronaviruses that cause severe acute respiratory syndrome, and Middle East respiratory syndrome from 21 standard WHO-specific and COVID-19-specific sources. We searched these data sources from database inception to May 3, 2020, with no restriction by language, for comparative studies and for contextual factors of acceptability, feasibility, resource use, and equity. We screened records, extracted data, and assessed risk of bias in duplicate. We did frequentist and Bayesian meta-analyses and random-effects meta-regressions. We rated the certainty of evidence according to Cochrane methods and the GRADE approach. This study is registered with PROSPERO, CRD42020177047.

Findings Our search identified 172 observational studies across 16 countries and six continents, with no randomised controlled trials and 44 relevant comparative studies in health-care and non-health-care settings (n=25 697 patients). Transmission of viruses was lower with physical distancing of 1 m or more, compared with a distance of less than 1 m (n=10 736, pooled adjusted odds ratio [aOR] 0·18, 95% CI 0·09 to 0·38; risk difference [RD] –10·2%, 95% CI –11·5 to –7·5; moderate certainty); protection was increased as distance was lengthened (change in relative risk [RR] 2·02 per m; $p_{interaction}$=0·041; moderate certainty). Face mask use could result in a large reduction in risk of infection (n=2647; aOR 0·15, 95% CI 0·07 to 0·34, RD –14·3%, –15·9 to –10·7; low certainty), with stronger associations with N95 or similar respirators compared with disposable surgical masks or similar (eg, reusable 12–16-layer cotton masks; $p_{interaction}$=0·090; posterior probability >95%, low certainty). Eye protection also was associated with less infection (n=3713; aOR 0·22, 95% CI 0·12 to 0·39, RD –10·6%, 95% CI –12·5 to –7·7; low certainty). Unadjusted studies and subgroup and sensitivity analyses showed similar findings.

Interpretation The findings of this systematic review and meta-analysis support physical distancing of 1 m or more and provide quantitative estimates for models and contact tracing to inform policy. Optimum use of face masks, respirators, and eye protection in public and health-care settings should be informed by these findings and contextual factors. Robust randomised trials are needed to better inform the evidence for these interventions, but this systematic appraisal of currently best available evidence might inform interim guidance.

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See Online for appendix

Introduction

As of May 28, 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 5·85 million individuals worldwide and caused more than 359 000 deaths.[1] Emergency lockdowns have been initiated in countries across the globe, and the effect on health, wellbeing, business, and other aspects of daily life are felt throughout societies and by individuals. With no effective pharmacological interventions or vaccine available in the imminent future, reducing the rate of infection (ie, flattening the curve) is a priority, and prevention of infection is the best approach to achieve this aim.

SARS-CoV-2 spreads person-to-person through close contact and causes COVID-19. It has not been solved if

Research in context

Evidence before this study

We searched 21 databases and resources from inception to May 3, 2020, with no restriction by language, for studies of any design evaluating physical distancing, face masks, and eye protection to prevent transmission of the viruses that cause COVID-19 and related diseases (eg, severe acute respiratory syndrome [SARS] and Middle East respiratory syndrome [MERS]) between infected individuals and people close to them (eg, household members, caregivers, and health-care workers). Previous related meta-analyses have focused on randomised trials and reported imprecise data for common respiratory viruses such as seasonal influenza, rather than the pandemic and epidemic betacoronaviruses causative of COVID-19 (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), SARS (SARS-CoV), or MERS (MERS-CoV). Other meta-analyses have focused on interventions in the health-care setting and have not included non-health-care (eg, community) settings. Our search did not retrieve any systematic review of information on physical distancing, face masks, or eye protection to prevent transmission of SARS-CoV-2, SARS-CoV, and MERS-CoV.

Added value of this study

We did a systematic review of 172 observational studies in health-care and non-health-care settings across 16 countries and six continents; 44 comparative studies were included in a meta-analysis, including 25 697 patients with COVID-19, SARS, or MERS. Our findings are, to the best of our knowledge, the first to rapidly synthesise all direct information on COVID-19 and, therefore, provide the best available evidence to inform optimum use of three common and simple interventions to help reduce the rate of infection and inform non-pharmaceutical interventions, including pandemic mitigation in non-health-care settings. Physical distancing of 1 m or more was associated with a much lower risk of infection, as was use of face masks (including N95 respirators or similar and surgical or similar masks [eg, 12–16-layer cotton or gauze masks]) and eye protection (eg, goggles or face shields). Added benefits are likely with even larger physical distances (eg, 2 m or more based on modelling) and might be present with N95 or similar respirators versus medical masks or similar. Across 24 studies in health-care and non-health-care settings of contextual factors to consider when formulating recommendations, most stakeholders found these personal protection strategies acceptable, feasible, and reassuring but noted harms and contextual challenges, including frequent discomfort and facial skin breakdown, high resource use linked with the potential to decrease equity, increased difficulty communicating clearly, and perceived reduced empathy of care providers by those they were caring for.

Implications of all the available evidence

In view of inconsistent guidelines by various organisations based on limited information, our findings provide some clarification and have implications for multiple stakeholders. The risk for infection is highly dependent on distance to the individual infected and the type of face mask and eye protection worn. From a policy and public health perspective, current policies of at least 1 m physical distancing seem to be strongly associated with a large protective effect, and distances of 2 m could be more effective. These data could also facilitate harmonisation of the definition of exposed (eg, within 2 m), which has implications for contact tracing. The quantitative estimates provided here should inform disease-modelling studies, which are important for planning pandemic response efforts. Policy makers around the world should strive to promptly and adequately address equity implications for groups with currently limited access to face masks and eye protection. For health-care workers and administrators, our findings suggest that N95 respirators might be more strongly associated with protection from viral transmission than surgical masks. Both N95 and surgical masks have a stronger association with protection compared with single-layer masks. Eye protection might also add substantial protection. For the general public, evidence shows that physical distancing of more than 1 m is highly effective and that face masks are associated with protection, even in non-health-care settings, with either disposable surgical masks or reusable 12–16-layer cotton ones, although much of this evidence was on mask use within households and among contacts of cases. Eye protection is typically underconsidered and can be effective in community settings. However, no intervention, even when properly used, was associated with complete protection from infection. Other basic measures (eg, hand hygiene) are still needed in addition to physical distancing and use of face masks and eye protection.

SARS-CoV-2 might spread through aerosols from respiratory droplets; so far, air sampling has found virus RNA in some studies[2–4] but not in others.[5–8] However, finding RNA virus is not necessarily indicative of replication-competent and infection-competent (viable) virus that could be transmissible. The distance from a patient that the virus is infective, and the optimum person-to-person physical distance, is uncertain. For the currently foreseeable future (ie, until a safe and effective vaccine or treatment becomes available), COVID-19 prevention will continue to rely on non-pharmaceutical interventions, including pandemic mitigation in community settings.[9] Thus, quantitative assessment of physical distancing is relevant to inform safe interaction and care of patients with SARS-CoV-2 in both health-care and non-health-care settings. The definition of close contact or potentially exposed helps to risk stratify, contact trace, and develop guidance documents, but these definitions differ around the globe.

To contain widespread infection and to reduce morbidity and mortality among health-care workers and others in contact with potentially infected people, jurisdictions have issued conflicting advice about physical or social distancing. Use of face masks with or

without eye protection to achieve additional protection is debated in the mainstream media and by public health authorities, in particular the use of face masks for the general population;[10] moreover, optimum use of face masks in health-care settings, which have been used for decades for infection prevention, is facing challenges amid personal protective equipment (PPE) shortages.[11]

Any recommendations about social or physical distancing, and the use of face masks, should be based on the best available evidence. Evidence has been reviewed for other respiratory viral infections, mainly seasonal influenza,[12,13] but no comprehensive review is available of information on SARS-CoV-2 or related betacoronaviruses that have caused epidemics, such as severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS). We, therefore, systematically reviewed the effect of physical distance, face masks, and eye protection on transmission of SARS-CoV-2, SARS-CoV, and MERS-CoV.

Methods

Search strategy and selection criteria

To inform WHO guidance documents, on March 25, 2020, we did a rapid systematic review.[14] We created a large international collaborative and we used Cochrane methods[15] and the GRADE approach.[16] We prospectively submitted the systematic review protocol for registration on PROSPERO (CRD42020177047; appendix pp 23–29). We have followed PRISMA[17] and MOOSE[18] reporting guidelines (appendix pp 30–33).

From database inception to May 3, 2020, we searched for studies of any design and in any setting that included patients with WHO-defined confirmed or probable COVID-19, SARS, or MERS, and people in close contact with them, comparing distances between people and COVID-19 infected patients of 1 m or larger with smaller distances, with or without a face mask on the patient, or with or without a face mask, eye protection, or both on the exposed individual. The aim of our systematic review was for quantitative assessment to ascertain the physical distance associated with reduced risk of acquiring infection when caring for an individual infected with SARS-CoV-2, SARS-CoV, or MERS-CoV. Our definition of face masks included surgical masks and N95 respirators, among others; eye protection included visors, faceshields, and goggles, among others.

We searched (up to March 26, 2020) MEDLINE (using the Ovid platform), PubMed, Embase, CINAHL (using the Ovid platform), the Cochrane Library, COVID-19 Open Research Dataset Challenge, COVID-19 Research Database (WHO), Epistemonikos (for relevant systematic reviews addressing MERS and SARS, and its COVID-19 Living Overview of the Evidence platform), EPPI Centre living systematic map of the evidence, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, relevant documents on the websites of governmental and other relevant organisations, reference lists of included papers, and relevant systematic reviews.[19,20] We handsearched (up to May 3, 2020) preprint servers (bioRxiv, medRxiv, and Social Science Research Network First Look) and coronavirus resource centres of *The Lancet*, *JAMA*, and *N Engl J Med* (appendix pp 3–5). We did not limit our search by language. We initially could not obtain three full texts for evaluation, but we obtained them through interlibrary loan or contacting a study author. We did not restrict our search to any quantitative cutoff for distance.

Data collection

We screened titles and abstracts, reviewed full texts, extracted data, and assessed risk of bias by two authors and independently, using standardised prepiloted forms (Covidence; Veritas Health Innovation, Melbourne, VIC, Australia), and we cross-checked screening results using artificial intelligence (Evidence Prime, Hamilton, ON, Canada). We resolved disagreements by consensus. We extracted data for study identifier, study design, setting, population characteristics, intervention and comparator characteristics, quantitative outcomes, source of funding

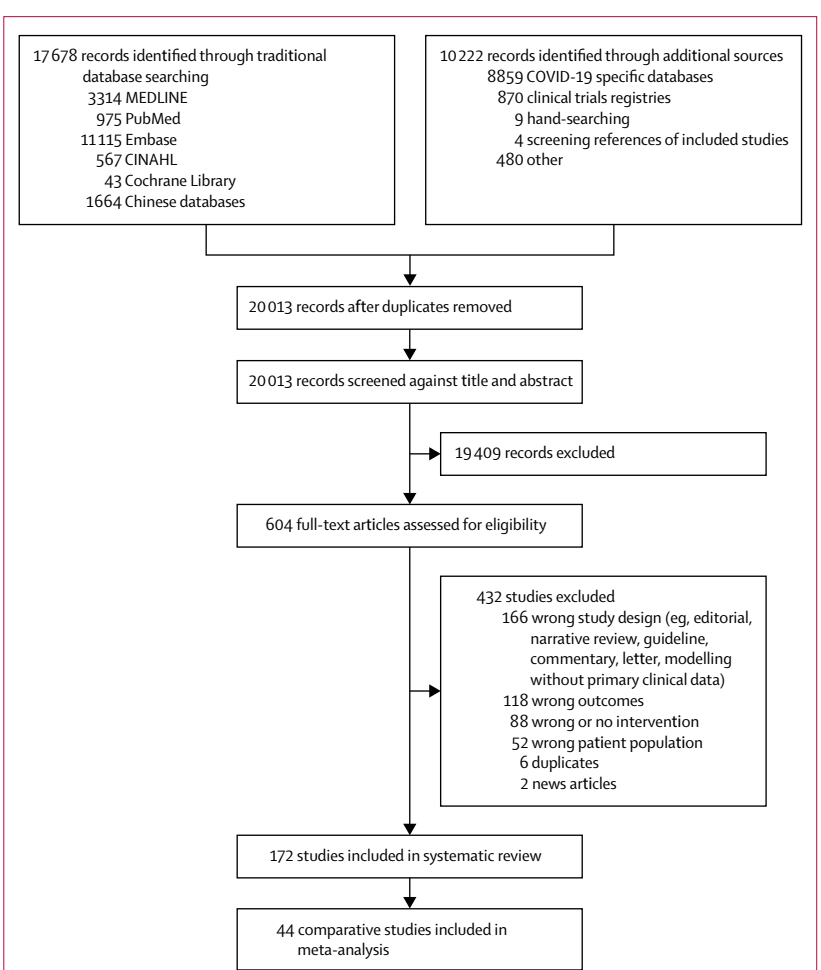


Figure 1: **Study selection**

	Population size (n)	Country	Setting	Disease caused by virus	Case definition (WHO)	Adjusted estimates	Risk of bias*
Alraddadi et al (2016)[34]	283	Saudi Arabia	Health care	MERS	Confirmed	Yes	********
Arwady et al (2016)[35]	79	Saudi Arabia	Non-health care (household and family contacts)	MERS	Confirmed	No	******
Bai et al (2020)[36]	118	China	Health care	COVID-19	Confirmed	No	*****
Burke et al (2020)[37]	338	USA	Health care and non-health care (including household and community)	COVID-19	Confirmed	No	****
Caputo et al (2006)[38]	33	Canada	Health care	SARS	Confirmed	No	*****
Chen et al (2009)[39]	758	China	Health care	SARS	Confirmed	Yes	*******
Cheng et al (2020)[40]	226	China	Non-health care (household and family contacts)	COVID-19	Confirmed	No	******
Ha et al (2004)[42]	117	Vietnam	Health care	SARS	Confirmed	No	**
Hall et al (2014)[43]	48	Saudi Arabia	Health care	MERS	Confirmed	No	***
Heinzerling et al (2020)[44]	37	USA	Health care	COVID-19	Confirmed	No	****
Ho et al (2004)[45]	372	Taiwan	Health care	SARS	Confirmed	No	********
Ki et al (2019)[47]	446	South Korea	Health care	MERS	Confirmed	No	******
Kim et al (2016)[48]	9	South Korea	Health care	MERS	Confirmed	No	*****
Kim et al (2016)[49]	1169	South Korea	Health care	MERS	Confirmed	No	******
Lau et al (2004)[50]	2270	China	Non-health care (households)	SARS	Probable	Yes	******
Liu et al (2009)[51]	477	China	Health care	SARS	Confirmed	Yes	*****
Liu et al (2020)[52]	20	China	Non-health care (close contacts)	COVID-19	Confirmed	No	*******
Loeb et al (2004)[53]	43	Canada	Health care	SARS	Confirmed	No	**
Ma et al (2004)[54]	426	China	Health care	SARS	Confirmed	Yes	*********
Nishiura et al (2005)[55]	115	Vietnam	Health care	SARS	Confirmed	Yes	********
Nishiyama et al (2008)[56]	146	Vietnam	Health care	SARS	Confirmed	Yes	******
Olsen et al (2003)[57]	304	China	Non-health care (airplane)	SARS	Confirmed	No	******
Park et al (2004)[58]	110	USA	Health care	SARS	Confirmed	No	**********
Park et al (2016)[59]	80	South Korea	Health care	MERS	Confirmed and probable	No	***
Peck et al (2004)[60]	26	USA	Health care	SARS	Confirmed	No	*********
Pei et al (2006)[61]	443	China	Health care	SARS	Confirmed	No	********
Rea et al (2007)[62]	8662	Canada	Non-health care (community contacts)	SARS	Probable	No	****
Reuss et al (2014)[63]	81	Germany	Health care	MERS	Confirmed	No	*****
Reynolds et al (2006)[64]	153	Vietnam	Health care	SARS	Confirmed	No	***
Ryu et al (2019)[65]	34	South Korea	Health care	MERS	Confirmed	No	******
Scales et al (2003)[66]	69	Canada	Health care	SARS	Probable	No	**
Seto et al (2003)[67]	254	China	Health care	SARS	Confirmed	Yes	********
Teleman et al (2004)[68]	86	Singapore	Health care	SARS	Confirmed	Yes	********
Tuan et al (2007)[69]	212	Vietnam	Non-health care (household and community contacts)	SARS	Confirmed	Yes	******
Van Kerkhove et al (2019)[46]	828	Saudi Arabia	Non-health care (dormitory)	MERS	Confirmed	Yes	********
Wang et al (2020)[41]	493	China	Health care	COVID-19	Confirmed	Yes	****

(Table 1 continues on next page)

	n	Country	Setting	Disease caused by virus	Case definition (WHO)	Adjusted estimates	Risk of bias*
(Continued from previous page)							
Wang et al (2020)[70]	5442	China	Health care	COVID-19	Confirmed	No	*****
Wiboonchutikul et al (2016)[71]	38	Thailand	Health care	MERS	Confirmed	No	*****
Wilder-Smith et al (2005)[72]	80	Singapore	Health care	SARS	Confirmed	No	********
Wong et al (2004)[73]	66	China	Health care	SARS	Confirmed	No	*****
Wu et al (2004)[74]	375	China	Non-health care (community)	SARS	Confirmed	Yes	********
Yin et al (2004)[75]	257	China	Health care	SARS	Confirmed	Yes	******
Yu et al (2005)[76]	74	China	Health care	SARS	Confirmed	No	*******
Yu et al (2007)[77]	124 wards	China	Health care	SARS	Confirmed	Yes	*******

Across studies, mean age was 30–60 years. SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome. *The Newcastle-Ottawa Scale was used for the risk of bias assessment, with more stars equalling lower risk.

Table 1: **Characteristics of included comparative studies**

and reported conflicts of interests, ethics approval, study limitations, and other important comments.

Outcomes

Outcomes of interest were risk of transmission (ie, WHO-defined confirmed or probable COVID-19, SARS, or MERS) to people in health-care or non-health-care settings by those infected; hospitalisation; intensive care unit admission; death; time to recovery; adverse effects of interventions; and contextual factors such as acceptability, feasibility, effect on equity, and resource considerations related to the interventions of interest. However, data were only available to analyse intervention effects for transmission and contextual factors. Consistent with WHO, studies generally defined confirmed cases with laboratory confirmation (with or without symptoms) and probable cases with clinical evidence of the respective infection (ie, suspected to be infected) but for whom confirmatory testing either had not yet been done for any reason or was inconclusive.

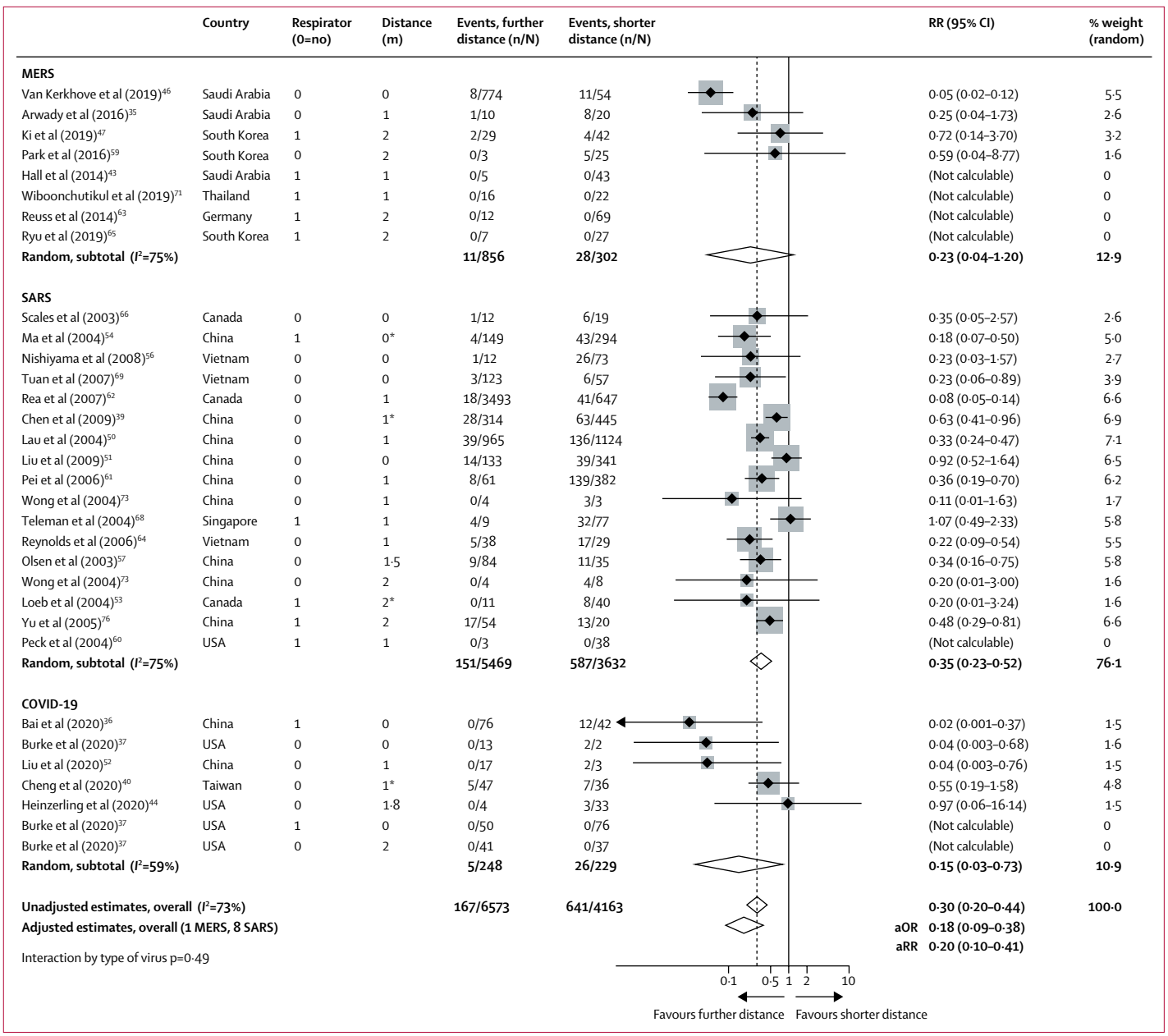
Data analysis

Our search did not identify any randomised trials of COVID-19, SARS, or MERS. We did a meta-analysis of associations by pooling risk ratios (RRs) or adjusted odds ratios (aORs) depending on availability of these data from observational studies, using DerSimonian and Laird random-effects models. We adjusted for variables including age, sex, and severity of source case; these variables were not the same across studies. Because between-study heterogeneity can be misleadingly large when quantified by I^2 during meta-analysis of observational studies,[21,22] we used GRADE guidance to assess between-study heterogeneity.[21] Throughout, we present RRs as unadjusted estimates and aORs as adjusted estimates.

We used the Newcastle-Ottawa scale to rate risk of bias for comparative non-randomised studies corresponding to every study's design (cohort or case-control).[23,24] We planned to use the Cochrane Risk of Bias tool 2.0 for randomised trials,[25] but our search did not identify any eligible randomised trials. We synthesised data in both narrative and tabular formats. We graded the certainty of evidence using the GRADE approach. We used the GRADEpro app to rate evidence and present it in GRADE evidence profiles and summary of findings tables[26,27] using standardised terms.[28,29]

For more on the **GRADEpro app** see https://www.gradepro.org

We analysed data for subgroup effects by virus type, intervention (different distances or face mask types), and setting (health care *vs* non-health care). Among the studies assessing physical distancing measures to prevent viral transmission, the intervention varied (eg, direct physical contact [0 m], 1 m, or 2 m). We, therefore, analysed the effect of distance on the size of the associations by random-effects univariate meta-regressions, using restricted maximum likelihood, and we present mean effects and 95% CIs. We calculated tests for interaction using a minimum of 10 000 Monte Carlo random permutations to avoid spurious findings.[30] We formally assessed the credibility of potential effect-modifiers using GRADE guidance.[21] We did two sensitivity analyses to test the robustness of our findings. First, we used Bayesian meta-analyses to reinterpret the included studies considering priors derived from the effect point estimate and variance from a meta-analysis of ten randomised trials evaluating face mask use versus no face mask use to prevent influenza-like illness in health-care workers.[31] Second, we used Bayesian meta-analyses to reinterpret the efficacy of N95 respirators versus medical masks on preventing influenza-like illness after seasonal viral (mostly influenza) infection.[13] For these sensitivity analyses, we used hybrid Metropolis-Hastings and Gibbs sampling, a 10 000 sample burn-in, 40 000 Markov chain Monte Carlo samples, and we tested non-informative and sceptical priors (eg, four time variance)[32,33] to inform



	Country	Respirator (0=no)	Distance (m)	Events, further distance (n/N)	Events, shorter distance (n/N)	RR (95% CI)	% weight (random)
MERS							
Van Kerkhove et al (2019)[46]	Saudi Arabia	0	0	8/774	11/54	0·05 (0·02–0·12)	5·5
Arwady et al (2016)[35]	Saudi Arabia	0	1	1/10	8/20	0·25 (0·04–1·73)	2·6
Ki et al (2019)[47]	South Korea	1	2	2/29	4/42	0·72 (0·14–3·70)	3·2
Park et al (2016)[59]	South Korea	0	2	0/3	5/25	0·59 (0·04–8·77)	1·6
Hall et al (2014)[43]	Saudi Arabia	1	1	0/5	0/43	(Not calculable)	0
Wiboonchutikul et al (2019)[71]	Thailand	1	1	0/16	0/22	(Not calculable)	0
Reuss et al (2014)[63]	Germany	1	2	0/12	0/69	(Not calculable)	0
Ryu et al (2019)[65]	South Korea	1	2	0/7	0/27	(Not calculable)	0
Random, subtotal (I^2=75%)				**11/856**	**28/302**	**0·23 (0·04–1·20)**	**12·9**
SARS							
Scales et al (2003)[66]	Canada	0	0	1/12	6/19	0·35 (0·05–2·57)	2·6
Ma et al (2004)[54]	China	1	0*	4/149	43/294	0·18 (0·07–0·50)	5·0
Nishiyama et al (2008)[56]	Vietnam	0	0	1/12	26/73	0·23 (0·03–1·57)	2·7
Tuan et al (2007)[69]	Vietnam	0	0	3/123	6/57	0·23 (0·06–0·89)	3·9
Rea et al (2007)[62]	Canada	0	1	18/3493	41/647	0·08 (0·05–0·14)	6·6
Chen et al (2009)[39]	China	0	1*	28/314	63/445	0·63 (0·41–0·96)	6·9
Lau et al (2004)[50]	China	0	1	39/965	136/1124	0·33 (0·24–0·47)	7·1
Liu et al (2009)[51]	China	0	0	14/133	39/341	0·92 (0·52–1·64)	6·5
Pei et al (2006)[61]	China	0	1	8/61	139/382	0·36 (0·19–0·70)	6·2
Wong et al (2004)[73]	China	0	1	0/4	3/3	0·11 (0·01–1·63)	1·7
Teleman et al (2004)[68]	Singapore	1	1	4/9	32/77	1·07 (0·49–2·33)	5·8
Reynolds et al (2006)[64]	Vietnam	0	1	5/38	17/29	0·22 (0·09–0·54)	5·5
Olsen et al (2003)[57]	China	0	1·5	9/84	11/35	0·34 (0·16–0·75)	5·8
Wong et al (2004)[73]	China	0	2	0/4	4/8	0·20 (0·01–3·00)	1·6
Loeb et al (2004)[53]	Canada	1	2*	0/11	8/40	0·20 (0·01–3·24)	1·6
Yu et al (2005)[76]	China	1	2	17/54	13/20	0·48 (0·29–0·81)	6·6
Peck et al (2004)[60]	USA	1	1	0/3	0/38	(Not calculable)	0
Random, subtotal (I^2=75%)				**151/5469**	**587/3632**	**0·35 (0·23–0·52)**	**76·1**
COVID-19							
Bai et al (2020)[36]	China	1	0	0/76	12/42	0·02 (0·001–0·37)	1·5
Burke et al (2020)[37]	USA	0	0	0/13	2/2	0·04 (0·003–0·68)	1·6
Liu et al (2020)[52]	China	0	1	0/17	2/3	0·04 (0·003–0·76)	1·5
Cheng et al (2020)[40]	Taiwan	0	1*	5/47	7/36	0·55 (0·19–1·58)	4·8
Heinzerling et al (2020)[44]	USA	0	1·8	0/4	3/33	0·97 (0·06–16·14)	1·5
Burke et al (2020)[37]	USA	1	0	0/50	0/76	(Not calculable)	0
Burke et al (2020)[37]	USA	0	2	0/41	0/37	(Not calculable)	0
Random, subtotal (I^2=59%)				**5/248**	**26/229**	**0·15 (0·03–0·73)**	**10·9**
Unadjusted estimates, overall (I^2=73%)				**167/6573**	**641/4163**	**0·30 (0·20–0·44)**	**100·0**
Adjusted estimates, overall (1 MERS, 8 SARS)						**aOR 0·18 (0·09–0·38)**	
						aRR 0·20 (0·10–0·41)	
Interaction by type of virus p=0·49							

Figure 2: **Forest plot showing the association of COVID-19, SARS, or MERS exposure proximity with infection**
SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome. RR=relative risk. aOR=adjusted odds ratio. aRR=adjusted relative risk. *Estimated values; sensitivity analyses excluding these values did not meaningfully alter findings.

mean estimates of effect, 95% credibility intervals (CrIs), and posterior distributions. We used non-informative hyperpriors to estimate statistical heterogeneity. Model convergence was confirmed in all cases with good mixing in visual inspection of trace plots, autocorrelation plots, histograms, and kernel density estimates in all scenarios. Parameters were blocked, leading to acceptance of approximately 50% and efficiency greater than 1% in all cases (typically about 40%). We did analyses using Stata version 14.3.

Role of the funding source

The funder contributed to defining the scope of the review but otherwise had no role in study design and data collection. Data were interpreted and the report drafted and submitted without funder input, but according to contractual agreement, the funder provided review at the time of final publication. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

	Studies and participants	Relative effect (95% CI)	Anticipated absolute effect (95% CI), eg, chance of viral infection or transmission		Difference (95% CI)	Certainty*	What happens (standardised GRADE terminology)[29]
			Comparison group	Intervention group			
Physical distance ≥1 m *vs* <1 m	Nine adjusted studies (n=7782); 29 unadjusted studies (n=10 736)	aOR 0·18 (0·09 to 0·38); unadjusted RR 0·30 (95% CI 0·20 to 0·44)	Shorter distance, 12·8%	Further distance, 2·6% (1·3 to 5·3)	−10·2% (−11·5 to −7·5)	Moderate†	A physical distance of more than 1 m probably results in a large reduction in virus infection; for every 1 m further away in distancing, the relative effect might increase 2·02 times
Face mask *vs* no face mask	Ten adjusted studies (n=2647); 29 unadjusted studies (n=10 170)	aOR 0·15 (0·07 to 0·34); unadjusted RR 0·34 (95% CI 0·26 to 0·45)	No face mask, 17·4%	Face mask, 3·1% (1·5 to 6·7)	−14·3% (−15·9 to −10·7)	Low‡	Medical or surgical face masks might result in a large reduction in virus infection; N95 respirators might be associated with a larger reduction in risk compared with surgical or similar masks§
Eye protection (faceshield, goggles) *vs* no eye protection	13 unadjusted studies (n=3713)	Unadjusted RR 0·34 (0·22 to 0·52)¶	No eye protection, 16·0%	Eye protection, 5·5% (3·6 to 8·5)	−10·6% (−12·5 to −7·7)	Low‖	Eye protection might result in a large reduction in virus infection

Table based on GRADE approach.[26–29] Population comprised people possibly exposed to individuals infected with SARS-CoV-2, SARS-CoV, or MERS-CoV. Setting was any health-care or non-health-care setting. Outcomes were infection (laboratory-confirmed or probable) and contextual factors. Risk (95% CI) in intervention group is based on assumed risk in comparison group and relative effect (95% CI) of the intervention. All studies were non-randomised and evaluated using the Newcastle-Ottawa Scale; some studies had a higher risk of bias than did others but no important difference was noted in sensitivity analyses excluding studies at higher risk of bias; we did not further rate down for risk of bias. Although there was a high I^2 value (which can be exaggerated in non-randomised studies)[21] and no overlapping CIs, point estimates generally exceeded the thresholds for large effects and we did not rate down for inconsistency. We did not rate down for indirectness for the association between distance and infection because SARS-CoV-2, SARS-CoV, and MERS-CoV all belong to the same family and have each caused epidemics with sufficient similarity; there was also no convincing statistical evidence of effect-modification across viruses; some studies also used bundled interventions but the studies include only those that provide adjusted estimates. aOR=adjusted odds ratio. RR=relative risk. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. SARS-CoV=severe acute respiratory syndrome coronavirus. MERS-CoV=Middle East respiratory syndrome coronavirus. *GRADE category of evidence; high certainty (we are very confident that the true effect lies close to that of the estimate of the effect); moderate certainty (we are moderately confident in the effect estimate; the true effect is probably close to the estimate, but it is possibly substantially different); low certainty (our confidence in the effect estimate is limited; the true effect could be substantially different from the estimate of the effect); very low certainty (we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect). †The effect is very large considering the thresholds set by GRADE, particularly at plausible levels of baseline risk, which also mitigated concerns about risk of bias; data also suggest a dose–response gradient, with associations increasing from smaller distances to 2 m and beyond, by meta-regression; we did not rate up for this domain alone but it further supports the decision to rate up in combination with the large effects. ‡The effect was very large, and the certainty of evidence could be rated up, but we made a conservative decision not to because of some inconsistency and risk of bias; hence, although the effect is qualitatively highly certain, the precise quantitative effect is low certainty. §In a subgroup analysis comparing N95 respirators with surgical or similar masks (eg, 12–16-layer cotton), the association was more pronounced in the N95 group (aOR 0·04, 95% CI 0·004–0·30) compared with other masks (0·33, 0·17–0·61; $p_{interaction}$=0·090); there was also support for effect-modification by formal analysis of subgroup credibility. ¶Two studies[54,75] provided adjusted estimates with n=295 in the eye protection group and n=406 in the group not wearing eye protection; results were similar to the unadjusted estimate (aOR 0·22, 95% CI 0·12–0·39). ||The effect is large considering the thresholds set by GRADE assuming that ORs translate into similar magnitudes of RR estimates; this mitigates concerns about risk of bias, but we conservatively decided not to rate up for large or very large effects.

Table 2: **GRADE summary of findings**

Results

We identified 172 studies for our systematic review from 16 countries across six continents (figure 1; appendix pp 6–14, 41–47). Studies were all observational in nature; no randomised trials were identified of any interventions that directly addressed the included study populations. Of the 172 studies, 66 focused on how far a virus can travel by comparing the association of different distances on virus transmission to people (appendix pp 42–44). Of these 66 studies, five were mechanistic, assessing viral RNA, virions, or both cultured from the environment of an infected patient (appendix p 45).

44 studies were comparative[34–77] and fulfilled criteria for our meta-analysis (n=25 697; figure 1; table 1). We used these studies rather than case series and qualitative studies (appendix pp 41–47) to inform estimates of effect. 30 studies[34,37,41–45,47–51,53–56,58–61,64–70,72,74,75] focused on the association between use of various types of face masks and respirators by health-care workers, patients, or both with virus transmission. 13 studies[34,37–39,47,49,51,54,58,60,61,65,75] addressed the association of eye protection with virus transmission.

Some direct evidence was available for COVID-19 (64 studies, of which seven were comparative in design),[36,37,40,41,44,52,70] but most studies reported on SARS (n=55) or MERS (n=25; appendix pp 6–12). Of the 44 comparative studies, 40 included WHO-defined confirmed cases, one included both confirmed and probable cases, and the remaining three studies included probable cases. There was no effect-modification by case-definition (distance $p_{interaction}$=0·41; mask $p_{interaction}$=0·46; all cases for eye protection were confirmed). Most studies reported on bundled interventions, including different components of PPE and distancing, which was usually addressed by statistical adjustment. The included studies all occurred during recurrent or novel outbreak settings of COVID-19, SARS, or MERS.

Risk of bias was generally low-to-moderate after considering the observational designs (table 1), but both within studies and across studies the overall findings were similar between adjusted and unadjusted estimates. We did not detect strong evidence of publication bias in the body of evidence for any intervention (appendix pp 15–18). As we did not use case series data to inform estimates of effect of each intervention, we did not systematically rate risk of bias of these data. Therefore, we report further only those studies with comparative data.

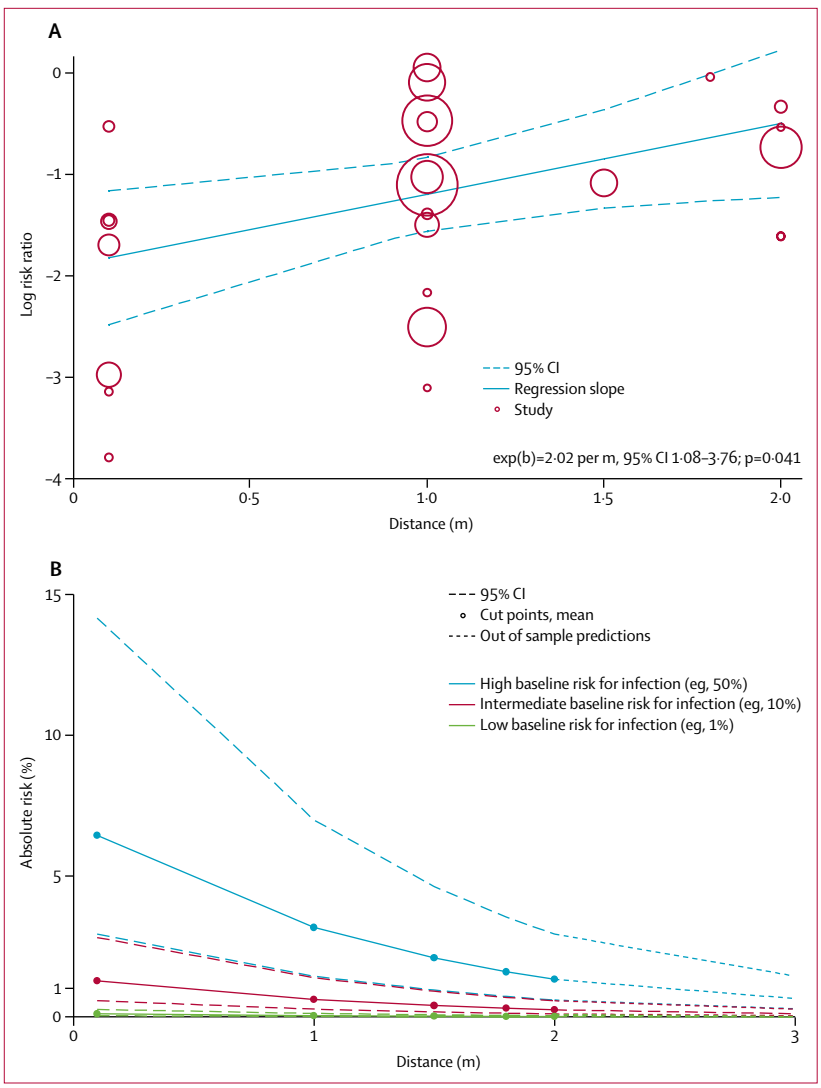


Figure 3: **Change in relative risk with increasing distance and absolute risk with increasing distance**
Meta-regression of change in relative risk with increasing distance from an infected individual (A). Absolute risk of transmission from an individual infected with SARS-CoV-2, SARS-CoV, or MERS-CoV with varying baseline risk and increasing distance (B). SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. SARS-CoV=severe acute respiratory syndrome coronavirus. MERS-CoV=Middle East respiratory syndrome coronavirus.

Across 29 unadjusted and nine adjusted studies,[35–37,39,40,43,44,46,47,50–54,56,57,59–66,68,69,71,73,76] a strong association was found of proximity of the exposed individual with the risk of infection (unadjusted n=10 736, RR 0·30, 95% CI 0·20 to 0·44; adjusted n=7782, aOR 0·18, 95% CI 0·09 to 0·38; absolute risk [AR] 12·8% with shorter distance *vs* 2·6% with further distance, risk difference [RD] –10·2%, 95% CI –11·5 to –7·5; moderate certainty; figure 2; table 2; appendix p 16). Although there were six studies on COVID-19, the association was seen irrespective of causative virus ($p_{interaction}$=0·49), health-care setting versus non-health-care setting ($p_{interaction}$=0·14), and by type of face mask ($p_{interaction}$=0·95; appendix pp 17, 19). However, different studies used different distances for the intervention. By meta-regression, the strength of association was larger with increasing distance (2·02 change in RR per m, 95% CI 1·08 to 3·76; $p_{interaction}$=0·041; moderate credibility subgroup effect; figure 3A; table 2). AR values with increasing distance given different degrees of baseline risk are shown in figure 3B, with potential values at 3 m also shown.

Across 29 unadjusted studies and ten adjusted studies,[34,37,41–45,47–51,53–56,58–61,64–70,72,74,75] the use of both N95 or similar respirators or face masks (eg, disposable surgical masks or similar reusable 12–16-layer cotton masks) by those exposed to infected individuals was associated with a large reduction in risk of infection (unadjusted n=10 170, RR 0·34, 95% CI 0·26 to 0·45; adjusted studies n=2647, aOR 0·15, 95% CI 0·07 to 0·34; AR 3·1% with face mask *vs* 17·4% with no face mask, RD –14·3%, 95% CI –15·9 to –10·7; low certainty; figure 4; table 2; appendix pp 16, 18) with stronger associations in health-care settings (RR 0·30, 95% CI 0·22 to 0·41) compared with non-health-care settings (RR 0·56, 95% CI 0·40 to 0·79; $p_{interaction}$=0·049; low-to-moderate credibility for subgroup effect; figure 4; appendix p 19). When differential N95 or similar respirator use, which was more frequent in health-care settings than in non-health-care settings, was adjusted for the possibility that face masks were less effective in non-health-care settings, the subgroup effect was slightly less credible ($p_{interaction}$=0·11, adjusted for differential respirator use; figure 4). Indeed, the association with protection from infection was more pronounced with N95 or similar respirators (aOR 0·04, 95% CI 0·004 to 0·30) compared with other masks (aOR 0·33, 95% CI 0·17 to 0·61; $p_{interaction}$=0·090; moderate credibility subgroup effect; figure 5). The interaction was also seen when additionally adjusting for three studies that clearly reported aerosol-generating procedures ($p_{interaction}$=0·048; figure 5). Supportive evidence for this interaction was also seen in within-study comparisons (eg, N95 had a stronger protective association compared with surgical masks or 12–16-layer cotton masks); both N95 and surgical masks also had a stronger association with protection versus single-layer masks.[38,39,51,53,54,61,66,67,75]

We did a sensitivity analysis to test the robustness of our findings and to integrate all available information on face mask treatment effects for protection from COVID-19. We reconsidered our findings using random-effects Bayesian meta-analysis. Although non-informative priors showed similar results to frequentist approaches (aOR 0·16, 95% CrI 0·04–0·40), even using informative priors from the most recent meta-analysis on the effectiveness of masks versus no masks to prevent influenza-like illness (RR 0·93, 95% CI 0·83–1·05)[31] yielded a significant association with protection from COVID-19 (aOR 0·40, 95% CrI 0·16–0·97; posterior probability for RR <1, 98%). Minimally informing (25% influence with or without four-fold smaller mean effect size) the most recent and rigorous meta-analysis of the effectiveness of N95

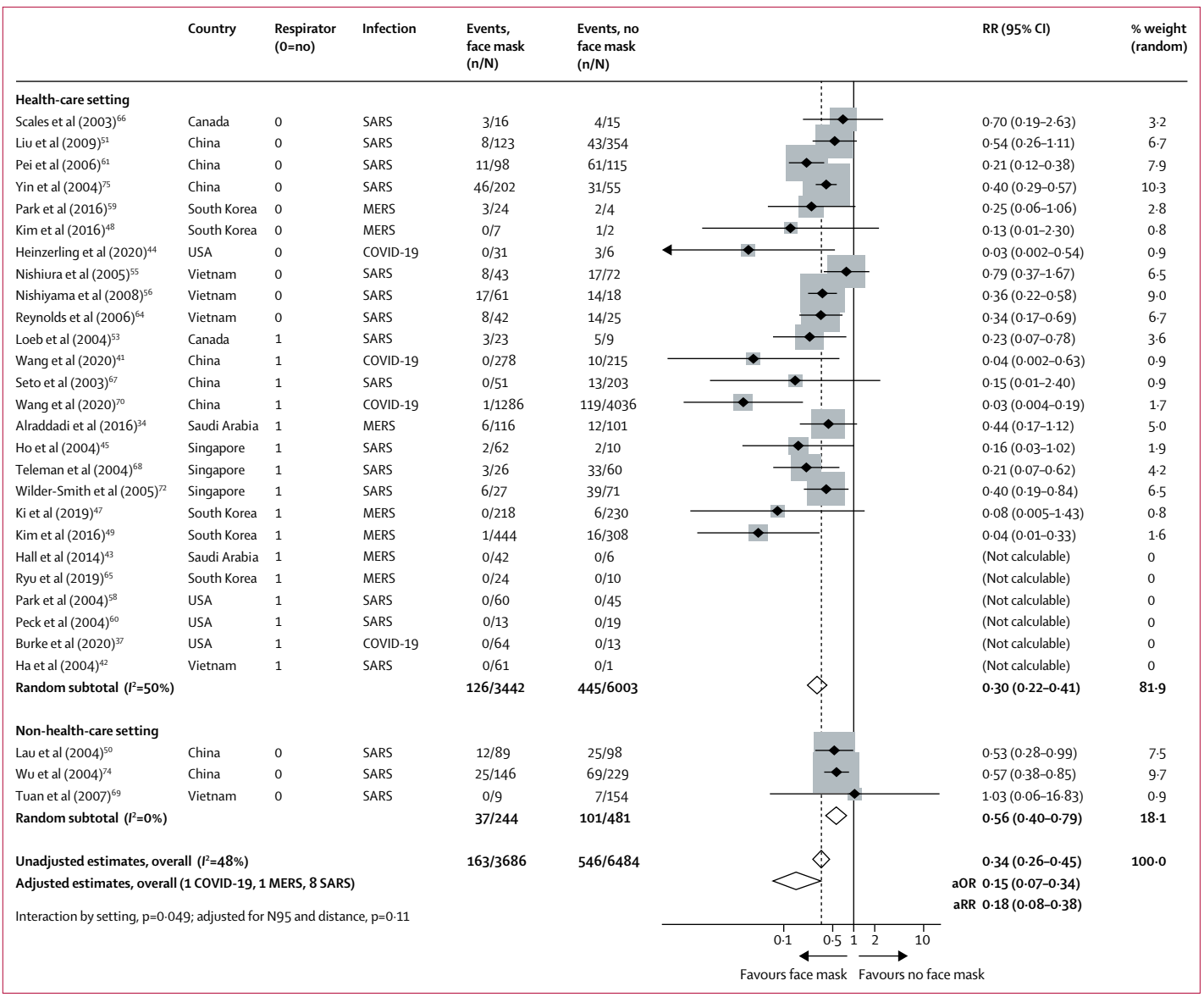


Figure 4: **Forest plot showing unadjusted estimates for the association of face mask use with viral infection causing COVID-19, SARS, or MERS**
SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome. RR=relative risk. aOR=adjusted odds ratio. aRR=adjusted relative risk.

respirators versus medical masks in randomised trials (OR 0·76, 95% CI 0·54–1·06)[13] with the effect-modification seen in this meta-analysis on COVID-19 (ratio of aORs 0·14, 95% CI 0·02–1·05) continued to support a stronger association of protection from COVID-19, SARS, or MERS with N95 or similar respirators versus other face masks (posterior probability for RR <1, 100% and 95%, respectively).

In 13 unadjusted studies and two adjusted studies,[34,37-39,47,49,51,54,58,60,61,65,75] eye protection was associated with lower risk of infection (unadjusted n=3713, RR 0·34, 95% CI 0·22 to 0·52; AR 5·5% with eye protection *vs* 16·0% with no eye protection, RD –10·6%, 95% CI –12·5 to –7·7; adjusted n=701, aOR 0·22, 95% CI 0·12 to 0·39; low certainty; figure 6; table 2; appendix pp 16–17).

Across 24 studies in health-care and non-health-care settings during the current pandemic of COVID-19, previous epidemics of SARS and MERS, or in general use, looking at contextual factors to consider in recommendations, most stakeholders found physical distancing and use of face masks and eye protection acceptable, feasible, and reassuring (appendix pp 20–22). However, challenges included frequent discomfort, high resource use linked with potentially decreased equity, less clear communication, and perceived reduced empathy of care providers by those they were caring for.

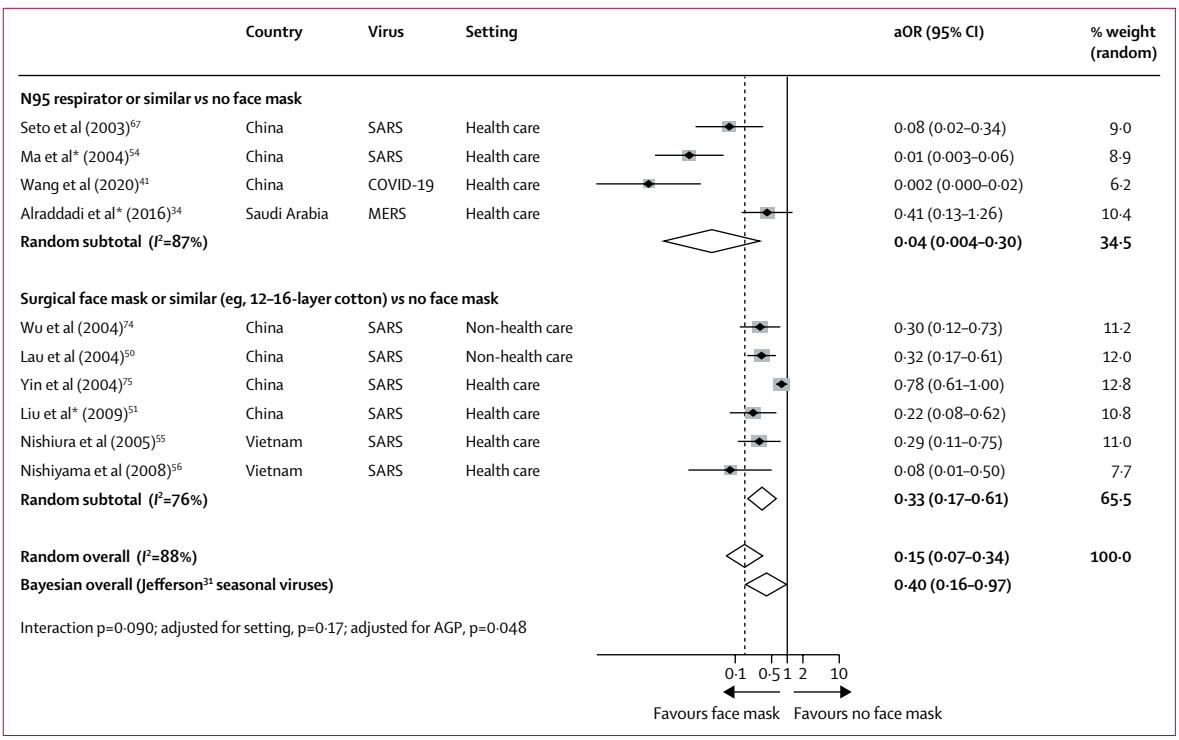


Figure 5: **Forest plot showing adjusted estimates for the association of face mask use with viral infection causing COVID-19, SARS, or MERS**
SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome. RR=relative risk. aOR=adjusted odds ratio. AGP=aerosol-generating procedures. *Studies clearly reporting AGP.

Discussion

The findings of this systematic review of 172 studies (44 comparative studies; n=25 697 patients) on COVID-19, SARS, and MERS provide the best available evidence that current policies of at least 1 m physical distancing are associated with a large reduction in infection, and distances of 2 m might be more effective. These data also suggest that wearing face masks protects people (both health-care workers and the general public) against infection by these coronaviruses, and that eye protection could confer additional benefit. However, none of these interventions afforded complete protection from infection, and their optimum role might need risk assessment and several contextual considerations. No randomised trials were identified for these interventions in COVID-19, SARS, or MERS.

Previous reviews are limited in that they either have not provided any evidence from COVID-19 or did not use direct evidence from other related emerging epidemic betacoronaviruses (eg, SARS and MERS) to inform the effects of interventions to curtail the current COVID-19 pandemic.[13,19,31,78] Previous data from randomised trials are mainly for common respiratory viruses such as seasonal influenza, with a systematic review concluding low certainty of evidence for extrapolating these findings to COVID-19.[13] Further, previous syntheses of available randomised controlled trials have not accounted for cluster effects in analyses, leading to substantial imprecision in treatment effect estimates. In between-study and within-study comparisons, we noted a larger effect of N95 or similar respirators compared with other masks. This finding is inconsistent with conclusions of a review of four randomised trials,[13] in which low certainty of evidence for no larger effect was suggested. However, in that review, the CIs were wide so a meaningful protective effect could not be excluded. We harmonised these findings with Bayesian approaches, using indirect data from randomised trials to inform posterior estimates. Despite this step, our findings continued to support the ideas not only that masks in general are associated with a large reduction in risk of infection from SARS-CoV-2, SARS-CoV, and MERS-CoV but also that N95 or similar respirators might be associated with a larger degree of protection from viral infection than disposable medical masks or reusable multilayer (12–16-layer) cotton masks. Nevertheless, in view of the limitations of these data, we did not rate the certainty of effect as high.[21] Our findings accord with those of a cluster randomised trial showing a potential benefit of continuous N95 respirator use over medical masks against seasonal viral infections.[79] Further high-quality research, including randomised trials of the optimum physical distance and the effectiveness of different types of masks in the general population and for health-care workers' protection, is urgently needed. Two trials are registered to better inform the optimum use of face masks for COVID-19 (NCT04296643 [n=576] and

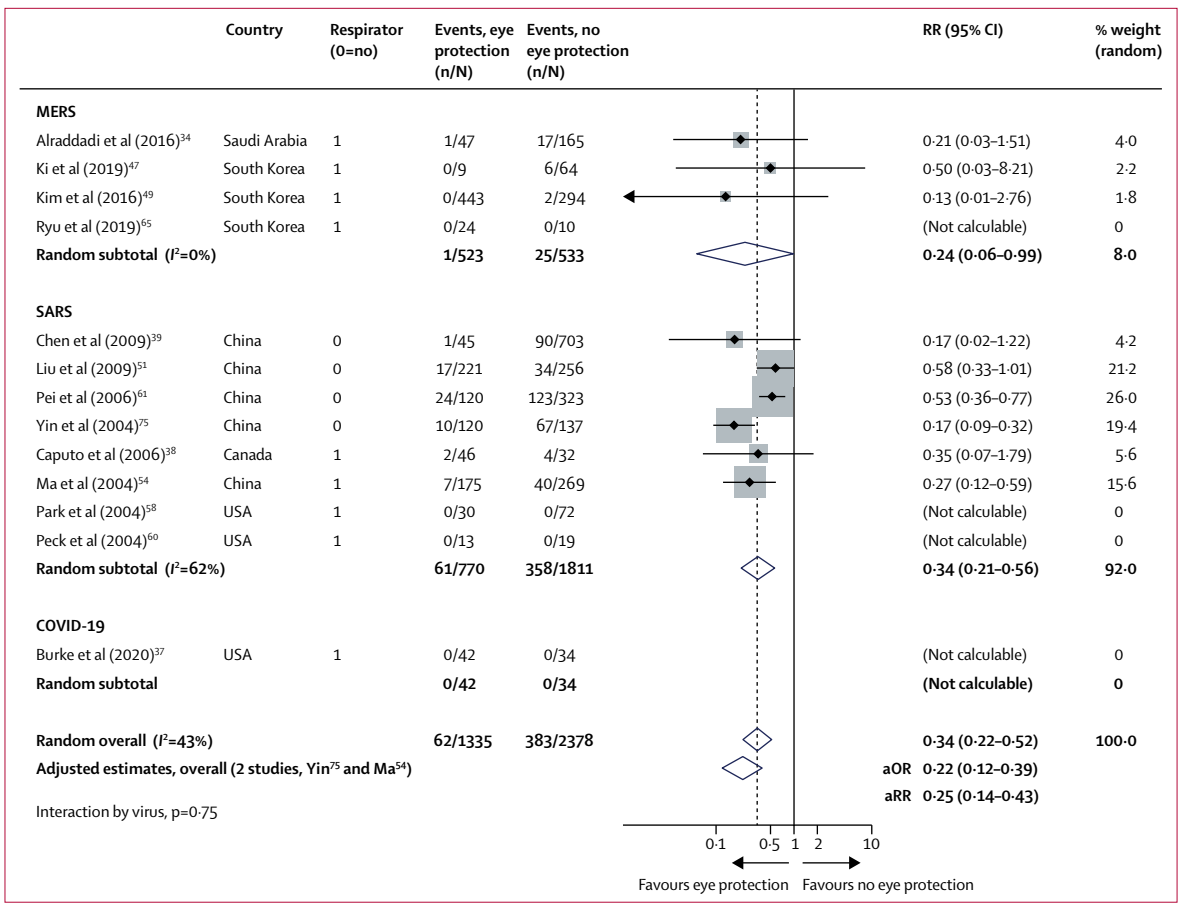


Figure 6: **Forest plot showing the association of eye protection with risk of COVID-19, SARS, or MERS transmission**
Forest plot shows unadjusted estimates. SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome. RR=relative risk. aOR=adjusted odds ratio. aRR=adjusted relative risk.

NCT04337541 [n=6000]). Until such data are available, our findings represent the current best estimates to inform face mask use to reduce infection from COVID-19. We recognise that there are strong, perhaps opposing, sentiments about policy making during outbreaks. In one viewpoint, the 2007 SARS Commission report stated:

> "…recognize, as an aspect of health worker safety, the precautionary principle that reasonable action to reduce risk, such as the use of a fitted N95 respirator, need not await scientific certainty".[80]

> "…if we do not learn from SARS and we do not make the government fix the problems that remain, we will pay a terrible price in the next pandemic".[81]

A counter viewpoint is that the scientific uncertainty and contextual considerations require a more nuanced approach. Although challenging, policy makers must carefully consider these two viewpoints along with our findings.

We found evidence of moderate certainty that current policies of at least 1 m physical distancing are probably associated with a large reduction in infection, and that distances of 2 m might be more effective, as implemented in some countries. We also provide estimates for 3 m. The main benefit of physical distancing measures is to prevent onward transmission and, thereby, reduce the adverse outcomes of SARS-CoV-2 infection. Hence, the results of our current review support the implementation of a policy of physical distancing of at least 1 m and, if feasible, 2 m or more. Our findings also provide robust estimates to inform models and contact tracing used to plan and strategise for pandemic response efforts at multiple levels.

The use of face masks was protective for both health-care workers and people in the community exposed to infection, with both the frequentist and Bayesian analyses lending support to face mask use irrespective of setting. Our unadjusted analyses might, at first impression, suggest use of face masks in the community setting to be less effective than in the health-care setting, but after accounting for differential N95 respirator use between health-care and non-health-care settings, we did not detect any striking differences in effectiveness of

face mask use between settings. The credibility of effect-modification across settings was, therefore, low. Wearing face masks was also acceptable and feasible. Policy makers at all levels should, therefore, strive to address equity implications for groups with currently limited access to face masks and eye protection. One concern is that face mask use en masse could divert supplies from people at highest risk for infection.[10] Health-care workers are increasingly being asked to ration and reuse PPE,[82,83] leading to calls for government-directed repurposing of manufacturing capacity to overcome mask shortages[84] and finding solutions for mask use by the general public.[84] In this respect, some of the masks studied in our review were reusable 12–16-layer cotton or gauze masks.[51,54,61,75] At the moment, although there is consensus that SARS-CoV-2 mainly spreads through large droplets and contact, debate continues about the role of aerosol,[2–8,85,86] but our meta-analysis provides evidence (albeit of low certainty) that respirators might have a stronger protective effect than surgical masks. Biological plausibility would be supported by data for aerosolised SARS-CoV-2[5–8] and preclinical data showing seasonal coronavirus RNA detection in fine aerosols during tidal breathing,[87] albeit, RNA detection does not necessarily imply replication and infection-competent virus. Nevertheless, our findings suggest it plausible that even in the absence of aerosolisation, respirators might be simply more effective than masks at preventing infection. At present, there is no data to support viable virus in the air outside of aerosol generating procedures from available hospital studies. Other factors such as super-spreading events, the subtype of health-care setting (eg, emergency room, intensive care unit, medical wards, dialysis centre), if aerosolising procedures are done, and environmental factors such as ventilation, might all affect the degree of protection afforded by personal protection strategies, but we did not identify robust data to inform these aspects.

Strengths of our review include adherence to full systematic review methods, which included artificial intelligence-supported dual screening of titles and abstracts, full-text evaluation, assessment of risk of bias, and no limitation by language. We included patients infected with SARS-CoV-2, SARS-CoV, or MERS-CoV and searched relevant data up to May 3, 2020. We followed the GRADE approach[16] to rate the certainty of evidence. Finally, we identified and appraise a large body of published work from China, from which much evidence emerged before the pandemic spread to other global regions.

The primary limitation of our study is that all studies were non-randomised, not always fully adjusted, and might suffer from recall and measurement bias (eg, direct contact in some studies might not be measuring near distance). However, unadjusted, adjusted, frequentist, and Bayesian meta-analyses all supported the main findings, and large or very large effects were recorded. Nevertheless, we are cautious not to be overly certain in the precise quantitative estimates of effects, although the qualitative effect and direction is probably of high certainty. Many studies did not provide information on precise distances, and direct contact was equated to 0 m distance; none of the eligible studies quantitatively evaluated whether distances of more than 2 m were more effective, although our meta-regression provides potential predictions for estimates of risk. Few studies assessed the effect of interventions in non-health-care settings, and they primarily evaluated mask use in households or contacts of cases, although beneficial associations were seen across settings. Furthermore, most evidence was from studies that reported on SARS and MERS (n=6674 patients with COVID-19, of 25 697 total), but data from these previous epidemics provide the most direct information for COVID-19 currently. We did not specifically assess the effect of duration of exposure on risk for transmission, although whether or not this variable was judged a risk factor considerably varied across studies, from any duration to a minimum of 1 h. Because of inconsistent reporting, information is limited about whether aerosol-generating procedures were in place in studies using respirators, and whether masks worn by infected patients might alter the effectiveness of each intervention, although the stronger association with N95 or similar respirators over other masks persisted when adjusting for studies reporting aerosol-generating medical procedures. These factors might account for some of the residual statistical heterogeneity seen for some outcomes, albeit I^2 is commonly inflated in meta-analyses of observational data,[21,22] and nevertheless the effects seen were large and probably clinically important in all adjusted studies.

Our comprehensive systematic review provides the best available information on three simple and common interventions to combat the immediate threat of COVID-19, while new evidence on pharmacological treatments, vaccines, and other personal protective strategies is being generated. Physical distancing of at least 1 m is strongly associated with protection, but distances of up to 2 m might be more effective. Although direct evidence is limited, the optimum use of face masks, in particular N95 or similar respirators in health-care settings and 12–16-layer cotton or surgical masks in the community, could depend on contextual factors; action is needed at all levels to address the paucity of better evidence. Eye protection might provide additional benefits. Globally collaborative and well conducted studies, including randomised trials, of different personal protective strategies are needed regardless of the challenges, but this systematic appraisal of currently best available evidence could be considered to inform interim guidance.

Contributors

DKC, EAA, SD, KS, SY, and HJS designed the study. SY, SD, KS, and HJS coordinated the study. SY and LH designed and ran the literature search. All authors acquired data, screened records, extracted data, and assessed risk of bias. DKC did statistical analyses. DKC and HJS wrote the report. All authors provided critical conceptual input, analysed and interpreted data, and critically revised the report.

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Declaration of interests
ML is an investigator of an ongoing clinical trial on medical masks versus N95 respirators for COVID-19 (NCT04296643). All other authors declare no competing interests.

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The Polymerase Chain Reaction

History Methods, and Applications

Nancy Smyth Templeton, Ph.D.

The polymerase chain reaction (PCR) uses in vitro enzymatic synthesis to amplify specific DNA sequences. PCR amplification can produce approximately 100 billion copies of one molecule of DNA in a few hours. PCR has revolutionized research in the biological sciences and medicine, and has influenced criminology and law. Several major scientific discoveries, including purification of DNA polymerase and elucidation of the mechanism of DNA replication, were essential for development of the present PCR technology. An overview of these discoveries and early work on in vitro DNA synthesis are presented. Basic PCR methodology, instrumentation, advanced PCR techniques, and applications are also discussed in this review. Several new amplification systems are mentioned. PCR is an extremely important and simple technology for research and diagnostic analyses of DNA and RNA. PCR technology and other amplification procedures will continue to produce novel applications in basic research and clinical medicine.

Key Words: DNA polymerase—Amplification—DNA synthesis—Denaturation—Annealing—Primer extension.

Diagn Mol Pathol 1(1): 58–72, 1992.

The polymerase chain reaction (PCR) is defined as the in vitro enzymatic synthesis and amplification of specific DNA sequences (6). Several reviews and books have been written recently on the subject (5,6,8,10,13,23,27,31). PCR amplification can produce approximately 100 billion copies of one molecule of DNA in a few hours (23,24,29). Twenty cycles of PCR produce about a millionfold (2^{20}) amplification (6,23). Typically, PCR reactions begin using picogram quantities of template DNA which go through 30–40 cycles of amplification.

The present PCR technology is the end result of a series of major discoveries in basic science research, beginning with the discovery of the first DNA polymerase by Arthur Kornberg around 1955. DNA polymerase, the enzyme responsible for the synthesis of DNA, was purified in 1958. During the years 1955–70, scientists described the thermodynamics of DNA annealing and primer extension in the 5′ to 3′ direction. The idea of amplified synthesis of DNA was first described in a 1971 paper (17) based on the work of Dr. Har Gobind Khorana's group, which was studying synthesis of the gene that encodes the major Ala-tRNA from yeast. The final paragraph of this paper presents the theory of PCR in complete detail. At that time, the in vitro synthesis of DNA was called "DNA repair replication."

The first PCR experiment was performed by Dr. Kjell Kleppe, a postdoctoral fellow in Dr. Khorana's laboratory. This experiment was a reaction involving two cycles of amplification of a 30-nucleotide-long duplex DNA, using primers nine and 10 nucleotides long. Dr. Kleppe described his experiment publicly at the 1969 Gordon Conference on Nucleic Acids; his data are shown in Fig. 1 [Dr. Ruth Kleppe, personal communication on behalf of Dr. Kjell Kleppe (deceased 1988); previously unpublished data]. "The upper curve . . . shows the incorporation of dCTP-^{14}C into duplex II which was

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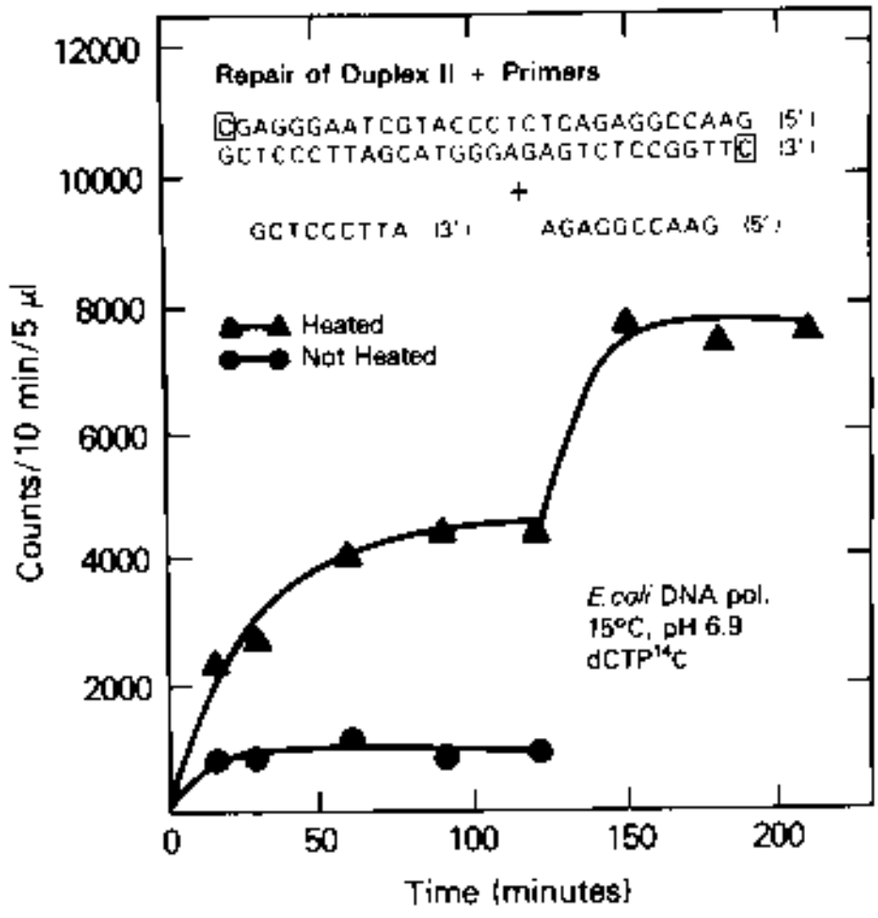

FIG. 1. Replication of duplex II by repair process. This figure represents the first PCR experiment performed by Dr. Kjell Kleppe in 1969.

heated at zero time in the presence of the primers, a deca- and a nona-nucleotide. The heating period was two minutes at 100°C, then the mixture was chilled and DNA polymerase and triphosphates added. After approximately two hours the incorporation levels off. If the mixture is heated again and new DNA polymerase added, more dCTP is incorporated and a new plateau is reached after approximately 1 hour. The theoretical amount of counts for one round of "repair" replication is approximately 7000 counts. The bottom curve represents the incorporation into duplex + the two primer pieces; the mixture in this case, has not been heated, and the incorporation is due to the two terminal C residues missing in this duplex. Several other control experiments, not shown confirm the above results. One must, therefore, conclude that the incorporation observed is due to repair processes of the new duplexes formed upon heating and chilling. The above results suggest that replication by this method might be feasible, but considerably more work is needed to perfect the method" (Dr. Ruth Kleppe, personal communication regarding the lecture presented by Dr. Kjell Kleppe at the Gordon Research Conference on Nucleic Acids on June 18, 1969).

Between 1970 and 1972, three rounds of amplification of four relatively short DNA duplexes were also achieved by Dr. Ian J. Molineux in Dr. Khorana's laboratory (26). Because the Klenow fragment was not available at that time, these experiments were all carried out using the intact DNA polymerase I molecule to synthesize DNA in vitro. To avoid degradation of the product DNA during synthesis, it was necessary to work at a pH far removed from the optimum for the enzyme. In turn, this made the reactions very slow. Incubations usually required 1–2 h at 15°C, and large amounts of the enzyme were required to sustain acceptable rates of synthesis.

In addition, it was technically impossible to perform many rounds of DNA amplification. DNA primers were extremely laborious and expensive to produce, and the millionfold excess of primers routinely used in modern PCR could not be made. In the late 1960s, it would take a trained postdoctoral organic chemist in Dr. Khorana's laboratory 6 months of full-time work to synthesize relatively small quantities of just two decanucleotides. The two icosanucleotides originally planned to be part of the synthetic yeast Ala-tRNA gene each took a postdoctoral fellow 2 years to synthesize. The successful synthesis of a defined sequence oligonucleotide usually led to a substantial publication in, for example, the *Journal of Molecular Biology* (see the complete issue of *J Mol Biol* 1972;72:209–474). It is

therefore not surprising that these valuable compounds were kept locked in the freezer. Two of the chemists and Dr. Khorana kept the only keys, and the biochemistry postdoctoral fellows in the laboratory had to fully justify any proposed use of oligonucleotides before they would be given out.

There were other hardships in performing PCR reactions in these early days of molecular biology. Template DNAs had to be made from the synthetic oligonucleotides, and the Khorana laboratory was instrumental in establishing the conditions for the use of DNA ligase on short DNA molecules. [γ-^{32}P]ATP (to monitor the progress of ligase reactions) and often [α-^{32}P]dNTPs (to follow kinetics of DNA polymerase reactions) were also chemically synthesized by the postdoctoral fellows in the Khorana laboratory. Because DNA polymerase was not commercially available, it was routinely purified. The Klenow fragment had only just been discovered; in 1971, it was actually still being characterized by Dr. Hans Klenow himself, while a visiting professor in the laboratory. Similarly, polynucleotide kinase and DNA ligase were not commercially available and had to be purified from T4-infected cells. These cells (and the phage to infect them!) had themselves to be grown in large quantities, often in 100-l or larger fermentors. All the foregoing was an integral part of the research projects using synthetic DNA. Indeed Dr. Molineux estimates that he spent the majority of his time in preparing and characterizing substrates and reagents, rather than doing PCR (repair replication reactions) or analyzing their products. Product analysis was also laborious; the technologies of gel electrophoresis of DNA molecules and DNA sequencing had not been developed. DNAs were usually purified using chromatography on meter-long (or greater) Sephadex columns and "sequenced" by a combination of nucleoside:nucleotide ratios and digestion to 5′ or 3′ mononucleotides, followed by paper chromatography and scintillation counting of the separated compounds.

Large-scale automation of DNA amplification was not pursued by the Khorana laboratory for several reasons (Drs. H.G. Khorana and I.J. Molineux, personal communications). Primarily, they believed that the goal of in vitro DNA synthesis had been achieved and therefore became interested in producing new discoveries in other areas. Furthermore, high temperature–stable DNA polymerases, which also transformed PCR from a method of last resort to one of first choice (6), were unknown; thus was automation precluded. In addition, DNA cloning, which had just begun, became the preferred method for producing large amounts of DNA. Finally, perhaps because it was so difficult to synthesize large amounts of primers, no one thought that the specific amplification of genomic DNA was feasible. Both Drs. Khorana and Molineux have stated that they would make the same choices again even with our current knowledge of PCR (personal communications); they preferred to leave the development of PCR technology in the hands of industry. Furthermore, Dr. Molineux does not think that it is ethical to patent a scientific discovery that is funded by government grants unless licenses are readily available and the discovery benefits only nonprofit organizations. He believes that his discoveries belong in the public domain.

Modern PCR technology was initially developed by Dr. Kary B. Mullis, a research scientist at the Perkin–Elmer Cetus Corporation in April 1983 (23). He was unfamiliar with the previous work of Drs. Khorana, Kleppe, and Molineux; despite a thorough search of the literature, he did not come across their publications on DNA repair replication (23). In 1985, Dr. Mullis first described the PCR technique at the American Society of Human Genetics meeting; the first publications utilizing PCR appeared in the same year (13). Since that time, over 1,000 research articles and reports including PCR data have been published. In 1988, only the subject of high-temperature superconductors was cited more frequently than PCR (8). In 1989, *Science* named DNA polymerase the Molecule of the Year because of its application to the PCR technique, and PCR was proclaimed the major scientific development of the year (10). Others have claimed that PCR represents one of the greatest technical advances of the last decade (5) and predicted that it will alter the course of scientific history. However, other methods of amplification have also been developed.

PCR will probably replace many conventional gene cloning techniques for the amplification of DNA for sequencing. In addition, PCR has had and will continue to have a major impact on the biological sciences, medicine, criminology, and law (31). Furthermore, PCR is a simple technique. In the words of Dr. Henry Erlich, a senior investigator at the Perkin–Elmer Cetus Corporation, "PCR allows people to practice molecular biology without a license" (6). Therefore, as Dr. Petr Karlovsky has warned us, intelligent application and critical utilization of PCR must be maintained (16). PCR has allowed us to address certain important questions that were out of our reach prior to the development of this technology.

METHODS AND INSTRUMENTATION

PCR resembles the in vivo process of DNA replication. It begins with one molecule of double-stranded DNA to be amplified, called "target," or "template," DNA. The target DNA is flanked by two primers. After one cycle, two molecules of identical double-stranded target DNA are produced (Fig. 2). Therefore, the number of DNA molecules doubles after each cycle. There is a geometrical increase in the number of DNA molecules produced after each cycle. After 30 cycles, over one billion (a 2^{30} amplification) copies of target DNA are produced.

Several basic goals have been achieved with PCR. A single molecule of DNA can be amplified to yield a 10^7–10^{11}-fold amplification. Approximately 2–3 μg DNA can be produced by one 100 μl PCR reaction mix. Target DNA up to 10 kilobases (kb) have been amplified, and protocols are being designed to amplify DNA up to 18 kb in length. Because it works successfully more often, most investigators find that target DNA about 4 kb and shorter are optimal for PCR amplification. It is difficult to amplify target DNAs greater than 4 kb in length. PCR can also detect one copy of DNA in 10^6 genomes. More specifically, if a gene is represented once in the genome, detection by PCR can be achieved using as few as 1 million cells.

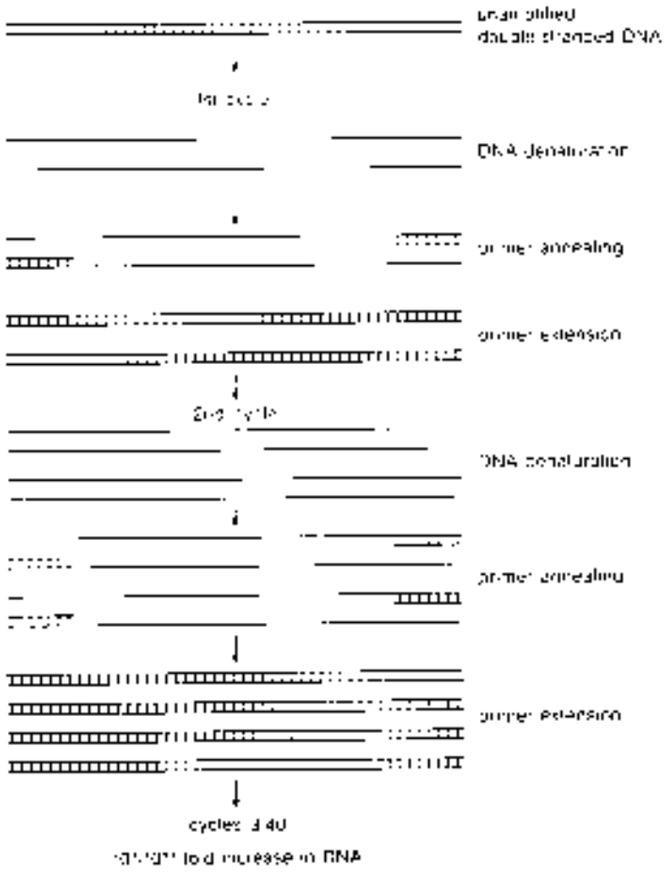

FIG. 2. Polymerase chain reaction.

PCR consists of several cycles in which three steps are repeated in the same order for each cycle. These steps are denaturation, annealing of oligonucleotide primers, and primer extension (Fig. 2). The first step is to heat the double-stranded DNA at 94°C in order to denature it into single-stranded DNA. The DNA remains single-stranded until the temperature is lowered for the next step of primer annealing. Single-stranded target DNA can then anneal to single-stranded DNA primers.

Two primers, generally 15–30 base pairs (bp) in length, are made that are complementary to each strand of the target DNA. Usually, this requires that the sequence of the ends of target DNA be known; however, exceptions to this requirement will be discussed. These primers are typically not complementary to each other. It is better to avoid using AT- and GC-rich primers, if possible, and to avoid primers containing internal secondary structure. The primers are hybridized to opposite DNA strands and bind at the 3′ ends of the complementary DNAs in the 5′ → 3′ orientation (Fig. 3). Thus, extension by DNA polymerase can proceed in the 5′ → 3′ direction, and the DNA strand is synthesized by the addition of deoxynucleoside triphosphates. The primers are added to the PCR reaction in huge excess in order to favor the binding of the primers to the target DNA and not the reassociation of the complementary target DNA strands.

The temperature used for annealing is in the range of 37–55°C. The lower temperature of annealing is used for amplifications in which high specificity or stringency is not required. For example, if the objective is to amplify genomic DNA to find new members of a gene family or DNA sequences that have partial homology to the target DNA, then a lower temperature should be used for hybridization. Also, if the complementarity between the primers and the target DNA is not 100% certain, a lower temperature for hybridization is used. A higher temperature is used for annealing in amplifi-

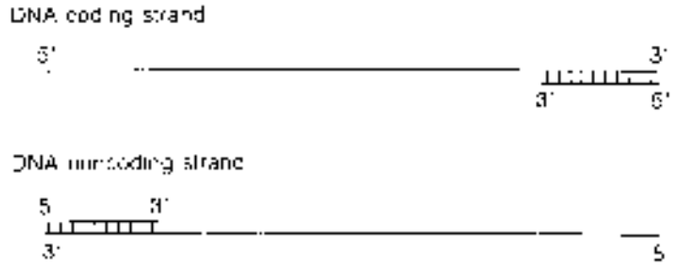

FIG. 3. Primer complementarity with denatured DNA.

cations requiring greater specificity or stringency. For instance, if the goal is to amplify one specific target DNA from genomic DNA, then a higher annealing temperature will produce fewer DNA fragments that are not of interest. It may take some trial and error to find the most appropriate temperature to use for a given experiment.

PCR specificity is also affected by factors other than the annealing temperature. The concentrations of deoxynucleoside triphosphates, primers, magnesium, and DNA polymerase can be varied. The times used for denaturation, annealing, and extension can be changed to allow a given specificity. The number, location, nature, and context of mismatches between the target DNA and primers will also influence PCR specificity.

After the primers are annealed to the target DNA, the appropriate DNA deoxynucleoside triphosphates are incorporated by the DNA polymerase starting at the 3' end of the primer and proceeding in the 5' → 3' direction. The extension continues until the entire target DNA has been replicated.

There are many types of DNA polymerases. The first PCR experiments performed by Perkin–Elmer Cetus used the Klenow fragment, the large fragment of DNA polymerase I, from *Escherichia coli* for primer extension at 37°C. This approach had several drawbacks because the Klenow fragment is not stable at high temperatures; therefore, it needs to be added after the denaturation step of every cycle. This enzyme is also less specific and yields high backgrounds. In addition, the Klenow fragment could amplify target DNAs no greater than a few hundred base pairs.

A breakthrough occurred upon the discovery that *Taq* DNA polymerase could be used in PCR (28). This polymerase is thermostable; it was first found in *Thermus aquaticus* (2), which live in the boiling geysers of Yellowstone National Park. *Taq* DNA polymerase was isolated and purified by several research laboratories (15,18,28). The PCR extension step is done at 72°C with *Taq* DNA polymerase, and this enzyme remains active at 72°C after repeated exposure to 94°C during the denaturation step. This polymerase is more specific, produces less background in PCR, and can amplify targets up to 10 kb. Presently, there are at least nine commercially available thermostable DNA polymerases that have been isolated from *Thermus flavis*, *Thermococcus litoralis*, and *Thermus aquaticus* (27). The use of thermostable DNA polymerases has allowed for the automation of PCR, thus making the PCR technique highly desirable.

As usually purified, *Taq* DNA polymerase does not appear to have an editing (proofreading) function to correct mistakes in the addition of deoxynucleoside triphosphates during extension. Editing removes any incorrect deoxynucleoside triphosphates that have been added by the polymerase. The estimated error rate for the *Taq* polymerase is less than one in 75,000 nucleotides polymerized, which is not a problem for most amplifications (6). For experiments requiring lower error rates, the T4 or T7 DNA polymerases can be used. However, these enzymes are not thermostable. It would be useful if thermostable enzymes that produce less error during DNA polymerization were available.

The most convenient method of performing PCR is to use a commercially distributed automated thermal cycler. Presently, there are 24 different types of thermal cyclers produced by 14 different corporations (27). The typical thermal cycler is a software-controlled heating/cooling system in which temperature and time are regulated. There is one heating/cooling block that holds 48–96 0.5 ml eppendorf tubes; this block is cycled through the various temperatures. The cycler is able to make the temperature changes very rapidly.

Some commercially available automated PCR machines use robotic work stations in which the samples are moved among three different temperature blocks, each set at a different temperature. These devices have several disadvantages and require a large bench space in the laboratory. Some laboratories have created their own homemade PCR machines, including a low-cost air-driven cycling oven (13), modification of a histokinette (13), a teacup/beaker device (13), and a do-it-yourself robotics work station (14). The cheapest, most labor intensive method is to set up three temperature blocks, each at a different temperature, and move the sample tubes manually using a timer to signal the end of each step. It is worth trying this method once in order to have a true appreciation of automated PCR.

Some laboratories use multi-channel automated liquid handlers for automation of pipetting in the preparation of PCR samples. Many investigators find that preparation and use of a master mix that includes all the reagents necessary for PCR, including the *Taq* DNA polymerase, is efficient and reduces pipetting errors. The master mix is added to the sample tubes containing the DNA to be amplified and the primers. Large numbers of samples can be prepared by this method, so that a sophisticated automated liquid handler is not necessary.

Because PCR is so sensitive, it is easy to amplify unwanted contaminants. In order to reduce contamination of PCR samples, many laboratories utilize positive displacement or motorized pipettors.

These pipettors allow for slow and even uptake of solutions, thereby decreasing the risk of DNA solutions becoming aerosolized during suction and contaminating the pipettors. However, many investigators are able to use the standard pipettors carefully with no contamination. It is best to set aside a set of pipettors that are used only for PCR. Contamination of PCR samples can also be avoided by aliquoting reagents that are used for PCR and including amplification of highly characterized positive and negative controls in all experiments.

The typical PCR sample contains 1 ng–1 μg of DNA to be amplified, 1.0 μM of each primer, 200 μM of each dNTP (dATP, dCTP, dTTP, dGTP), 10 μl of ×10 reaction buffer (500 mM KCl, 100 mM Tris-HCl pH 8.3, 15 mM $MgCl_2$, 0.1% gelatin), 2.5 units *Taq* polymerase, and double-distilled water to give a final volume of 100 μl. On top of the sample, 100 μl of high quality mineral oil is layered in order to prevent evaporation. A typical cycle will perform denaturation for 1.0–1.5 min, primer annealing for 1.5–2.0 min, and primer extension for 3.0 min. A total of 25–45 cycles are usually done. If RNA instead of DNA is used in the initial PCR sample, then it is necessary to produce the first strand cDNA with reverse transcriptase before starting PCR. A new thermostable DNA polymerase, rTth DNA polymerase (Cetus), functions as a reverse transcriptase and a DNA polymerase. This allows production of the first strand cDNA and cDNA amplification in the same tube with the same enzyme.

PCR conditions can be optimized for certain DNAs. Some DNAs require different conditions that are determined by trial and error. For instance, the concentration of $MgCl_2$ in the reaction buffer can be varied from 1.5 to 4.0 mM, the primer extension time can be shortened to 1.0–2.0 min, the amount of *Taq* polymerase used can be decreased, and the temperature for annealing of the primers can be increased. If too little $MgCl_2$ is used in the reaction buffer, no PCR product will be produced. Too much $MgCl_2$ will produce nonspecific DNA fragments during PCR. A new thermostable DNA polymerase, AmpliTaq DNA polymerase Stoffel fragment (Cetus), is available that minimizes optimization experiments for PCR. It is useful to amplify a control DNA utilizing control primers that produce a single DNA fragment of known size in order to determine if the PCR experiment has been successful (at least for the control DNA). Most PCR kits sold commercially include these control reagents along with all the necessary reagents needed for PCR. There are at least 21 different commercial PCR kits produced by six different corporations (27).

Another popular method called "fast," or "turbo," PCR has been used successfully by several investigators to amplify target genomic DNA that seems difficult to amplify or to increase the yield of amplification product. This procedure involves significantly decreasing the duration of all the steps in the cycle: Denaturation time is 15 sec (30 sec for cycle 1), primer annealing time is 15 sec, and primer extension time is 1.0 min. The total number of cycles of PCR performed is 60. Because the times for each step are decreased, the *Taq* polymerase can catalyze replication effectively throughout all 60 cycles. Under typical PCR conditions, with longer times for each step, there is no detectable increase in amplified DNA after cycle 40. Target DNA of up to 3.0 kb can be efficiently amplified by the fast PCR procedure.

After the last PCR cycle, the samples are placed at 4°C or the thermal cycler can be programmed to end with a 4°C cycle of indefinite length. The samples are analyzed to determine the products that were produced and to verify that the PCR was successful. This is done by removing 5.0 μl of the total 100 μl PCR sample by placing the pipette tip on the pipettor under the mineral oil layer and suctioning. The sample aliquots may be electrophoresed on agarose or polyacrylamide gels and stained with ethidium bromide. In order to distinguish short DNA fragments 20–250 bp in length, it is best to use a 2.5–3.0% agarose gel, a 20% polyacrylamide gel, or a 3.0% NuSieve/1.0% agarose gel for electrophoresis. If the results of gel electrophoresis are not clear or if the goal of PCR is to identify fragments of an unknown length, it may be necessary to perform a Southern blot analysis on the gel using the target DNA or target DNA oligonucleotides as probes.

In order to "clean up" PCR samples for use in other experiments, the following method is generally used if the PCR produced only one DNA fragment of expected size. The PCR sample is placed on dry ice for 5 min so that the sample is frozen and the mineral oil on top is not frozen. The oil is then removed; the sample is phenol-extracted, chloroform-extracted, precipitated in 100% ethanol, washed in 70% ethanol, dried, and resuspended in the appropriate volume of TE buffer. Other commercially available methods of purification include column chromatography or centrifugation. Alternatively, it is possible to perform certain procedures, such as restriction enzyme digestions, without cleaning up the PCR sample. In this case it is necessary to determine whether the components of the PCR reaction are or can be adjusted to be compatible with the conditions required for adequate activity of the restriction enzyme.

If more than one PCR fragment was produced, it is necessary to first separate the fragments on a polyacrylamide or a low-melting temperature agarose gel. The DNA fragments of interest are cut from the gel and purified. Some procedures, such as DNA ligations, can be performed on DNA fragments while they are embedded in certain gel matrices. Other protocols require that the DNA be eluted from the gel first and purified.

In order to produce PCR fragments for use in subcloning, restriction enzyme recognition sites are added at the 5' ends of the primers (Fig. 4). This methodology is possible because PCR is successful in the presence of a few nucleotides at the 5' end of the primers that are not complementary to the target DNA. The primer typically has 15–30 nucleotides that are complementary to the target DNA, preceded by 4–8 nucleotides at the 5' end to produce the restriction enzyme recognition site of choice; it also has 2–4 nucleotides at the outermost 5' end to allow for more efficient digestion by the restriction enzyme of choice at the recognition site (Fig. 4). Addition of extra nucleotides at the 5' ends of the primers does not interfere with PCR efficiency. In fact, *Taq* DNA polymerase adds extra nucleotides at the ends of template DNA during DNA synthesis. In order to produce a PCR fragment for directional ("forced") cloning, each primer is designed to have a different restriction enzyme recognition site. Both sites should have compatible ends with the sites found in the polylinker of the cloning vector. Thus, the investigator

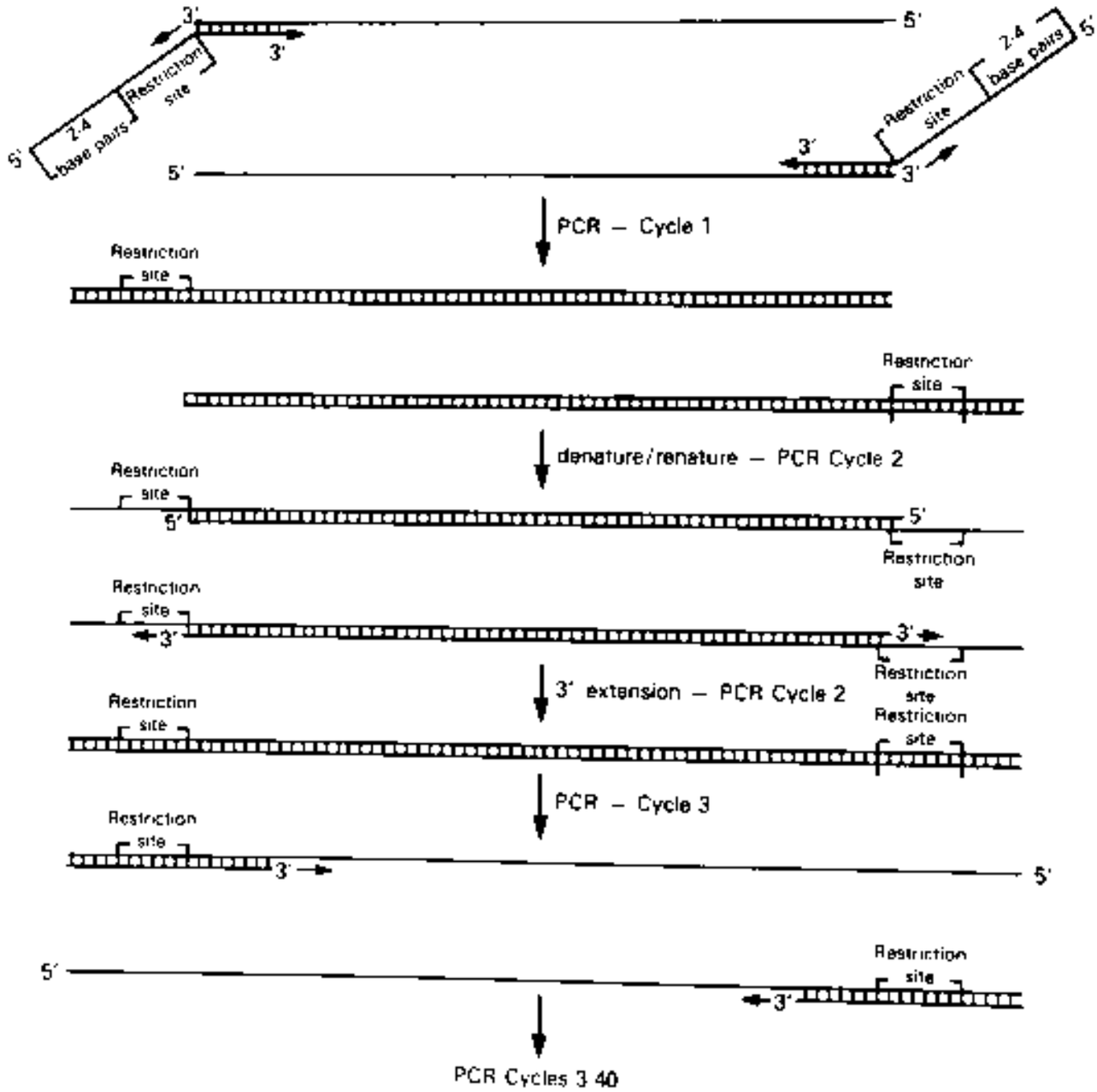

FIG. 4. Addition of restriction enzyme recognition sites in PCR.

can choose the orientation of the PCR fragment within the cloning vector. In addition to designing restriction enzyme recognition sites, this methodology can be used to introduce site-directed point mutations into amplified products of the target DNA by placing point mutations into the primers.

Inverse PCR allows amplification of DNA regions of unknown sequence that flank DNA of known sequence (Fig. 5). First the DNA is cut with restriction enzymes within the regions of unknown sequence so that the two DNA ends are compatible. Then the DNA is circularized by ligation. Primers are made to the known DNA sequence adjacent to the unknown DNA sequence, so that amplification occurs over the unknown sequence region. This method requires restriction enzyme recognition site information in the areas of unknown sequence. Therefore, restriction mapping must be done prior to PCR, and sites chosen for restriction enzymes must not cut within the vector or the region of known sequence. The optimal length for the target DNA is <4 kb. Inverse PCR is used for gene walking, identifying and amplifying transposable elements, for sequencing DNA flanking viral integration sites, and for analyzing genetic regulatory elements located outside or adjacent to genes of known sequence.

Anchor PCR allows amplification of DNA and RNA sequences that have variable termini and RNA whose 5' sequence is not known (7,20,25). Figure 6 demonstrates this technique starting with an mRNA with an unknown 5' sequence. The mRNA is transcribed into cDNA using reverse transcriptase. A poly (dG) tail is added at the 3' end of the cDNA using deoxynucleotidyl transferase. An anchor primer, a poly (dC) tail that could also contain a convenient restriction enzyme recognition site at the 5' end (for use in subsequent subcloning), and a specific primer are hybridized to the "tailed" cDNA. A typical PCR can then be performed to amplify this cDNA. Anchor PCR is significant because a cDNA, with unknown 5' sequence, could not be amplified by inverse PCR without subcloning into a vector first. Therefore, anchor PCR eliminates the requirement for subcloning.

Several methods are now used to sequence DNA fragments directly after PCR. These procedures include Sanger sequencing of single-stranded DNA fragments produced by asymmetric PCR (3,11,21), directly sequencing double-stranded PCR products (1,3) by the Sanger method, direct Sanger sequencing of single-stranded DNA produced by PCR using biotinylated primers (3,22), Maxam-Gilbert direct sequencing of PCR-amplified DNA (3,30), and

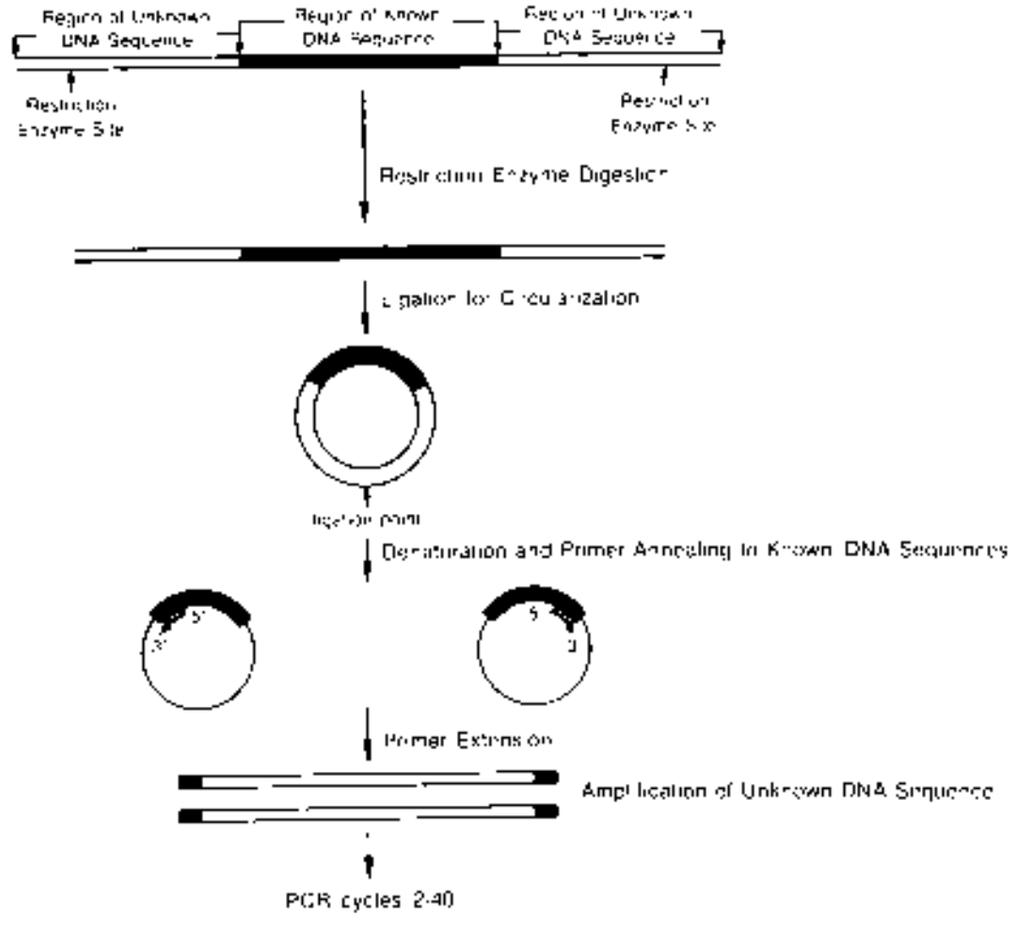

FIG. 5. Inverse PCR.

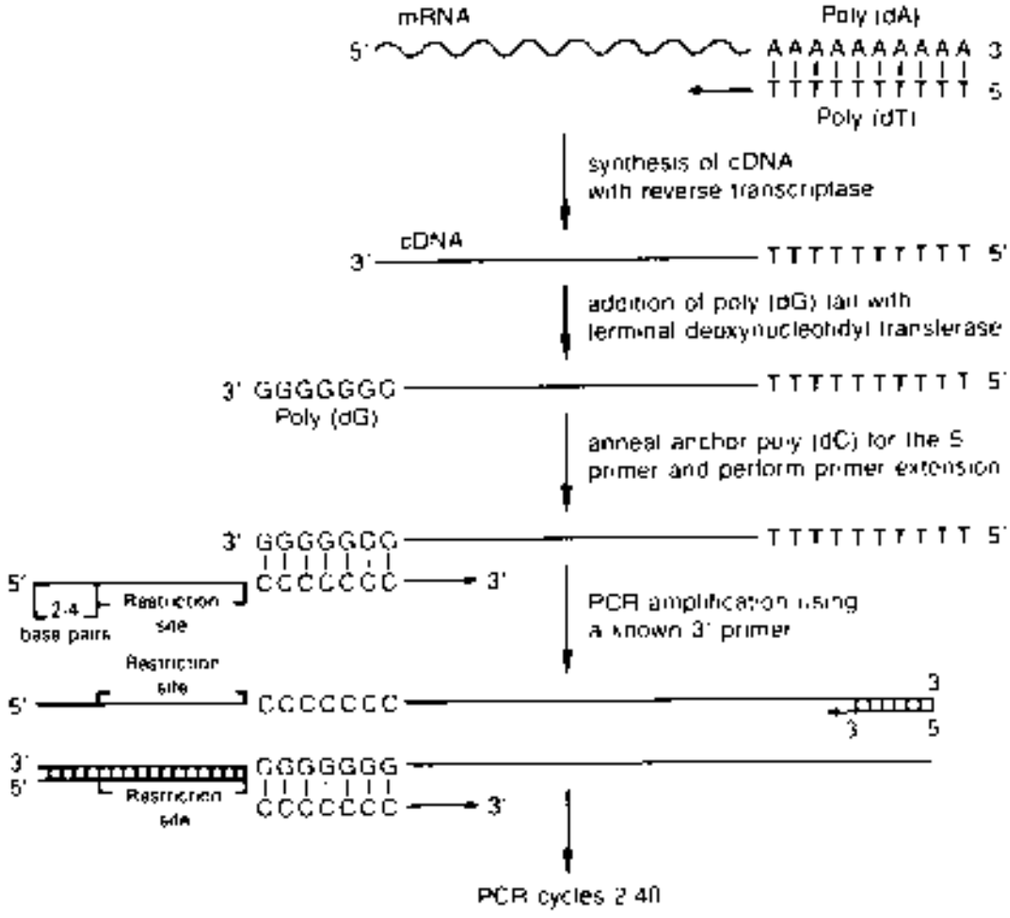

FIG. 6. Anchor PCR.

Sanger sequencing of single-stranded DNA generated by λ exonuclease digestion of double-stranded DNA products (3).

Because sequencing of PCR fragments is easier to do using single-stranded DNA, the basic strategy for direct sequencing of PCR products is to isolate or produce one DNA strand. Asymmetric PCR produces mainly single-stranded DNA fragments because the PCR samples contain primers in different molar concentrations (Fig. 7). Asymmetric primer ratios in the range of 50:1 to 100:1 are typically used. Double-stranded DNA is produced exponentially until cycles 10 to 15. The primer in lower concentration becomes depleted; therefore, the DNA strand that is primed with this primer is no longer produced. Only the DNA strand primed with the primer in greater concentration is produced linearly throughout the remaining cycles. Thus, 10–20 times more single-stranded than double-stranded DNA is produced during the amplification procedure.

Another way of isolating one DNA strand from the other is to purify one strand. This method makes use of biotinylated primers in PCR. By labelling the 5' end of one PCR primer with biotin-NSH (3,22), the target DNA strand synthesized from this primer contains biotin at its 5' end. The two PCR fragments produced are separated by purifying the heat-denatured sample on a streptavidin agarose column (22) or on magnetic/streptavidin beads (12) after PCR is completed. The biotinylated DNA strand will be bound to either the column or to the beads, respectively and the biotinylated DNA can be eluted. Sequencing can be performed on the biotinylated DNA while it is attached to the magnetic beads. This technique works extremely well. Good sequence data have also been produced on an

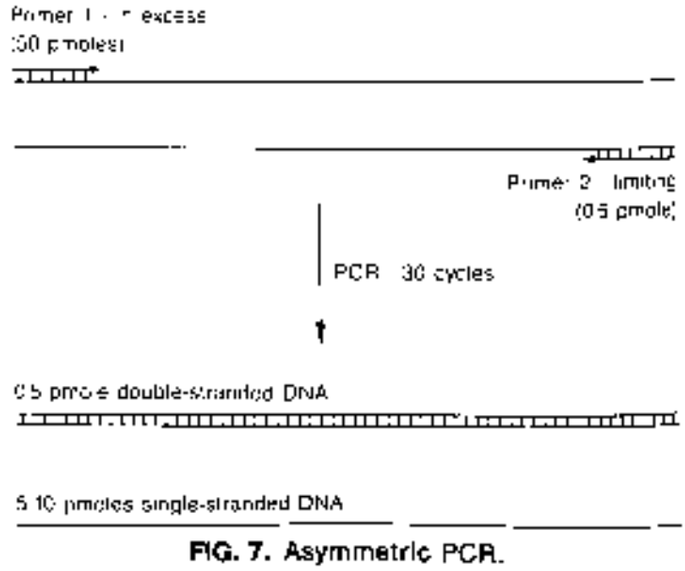

FIG. 7. Asymmetric PCR.

automated fluorescence DNA sequencer. The non biotinylated DNA strand can also be recovered and sequenced.

Internal site-specific mutagenesis can be produced by introducing point mutations into primers for PCR fragments that overlap in sequence (Fig. 8). A point mutation is introduced into the 3′ primer for the 5′ upstream DNA fragment. The same point mutation is placed into the 5′ primer for the 3′ downstream DNA fragment. The first PCR amplification is performed on the overlapping DNAs separately through about 40 cycles. The amplification products from both PCRs are combined, the primers are removed, and the DNA strands are denatured and renatured. A population of DNAs will anneal so that they will join only at the short region of overlap. Primer extension can then be performed in the 5′ → 3′ direction on the DNAs that overlap in a manner producing exposed 3′ ends. The extended DNA is denatured and renatured in the presence of primers from the outermost ends of the original overlapping DNA fragments, so that only the fully extended overlapping DNA will be amplified in the second PCR for about 40 cycles. The PCR product produced after the second PCR contains the internal site-directed mutation.

Internal insertions, internal deletions, and sequence recombination can be produced by PCR in a method similar to that described for introducing internal site-specific mutagenesis. For internal insertions, the insertion is placed into the 3′ primer for the 5′ upstream overlapping DNA fragment (Fig. 9). The same insertion is placed into the 5′ primer for the 3′ downstream overlapping DNA fragment. The first and second PCR amplifications are carried out as described for producing internal site-directed

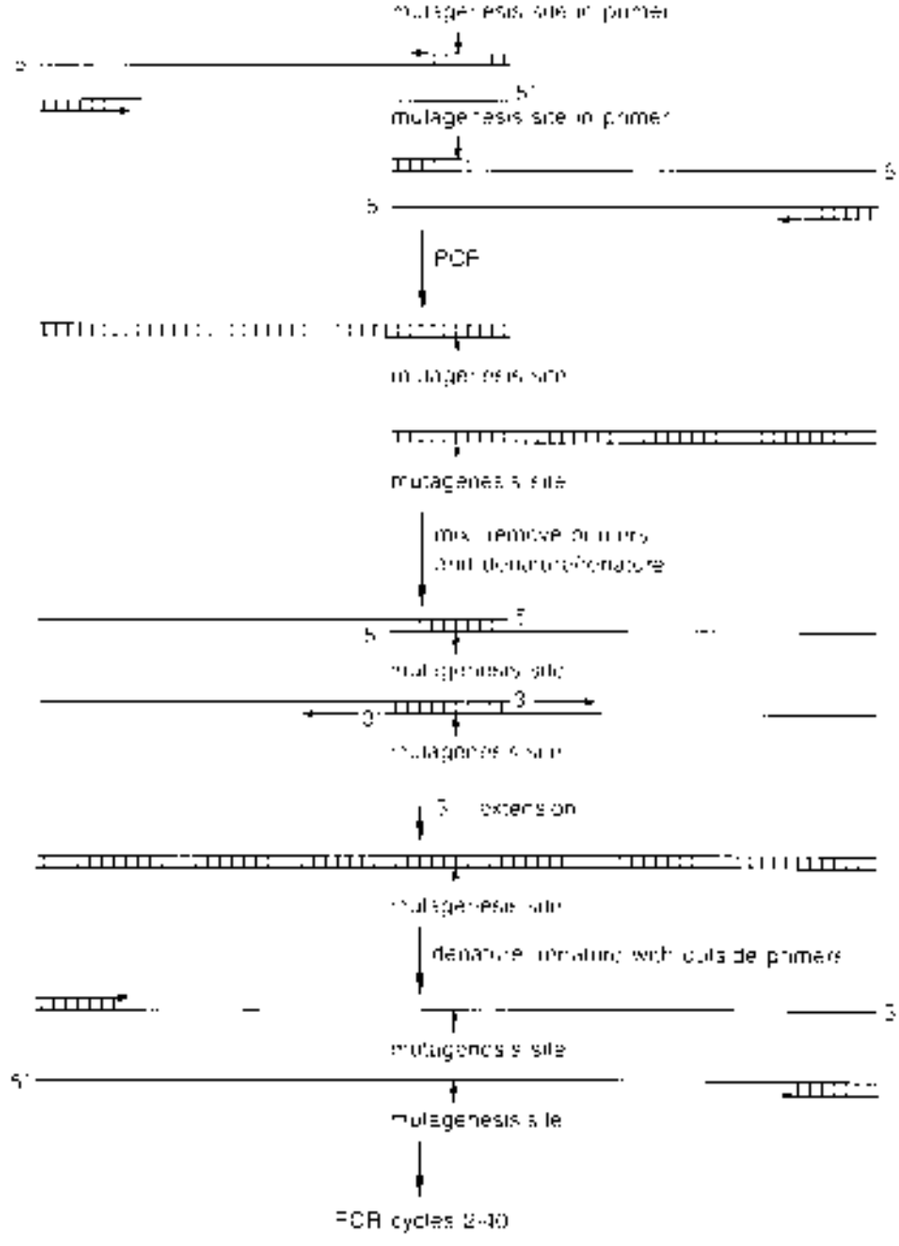

FIG. 8. Internal site-specific mutagenesis by PCR.

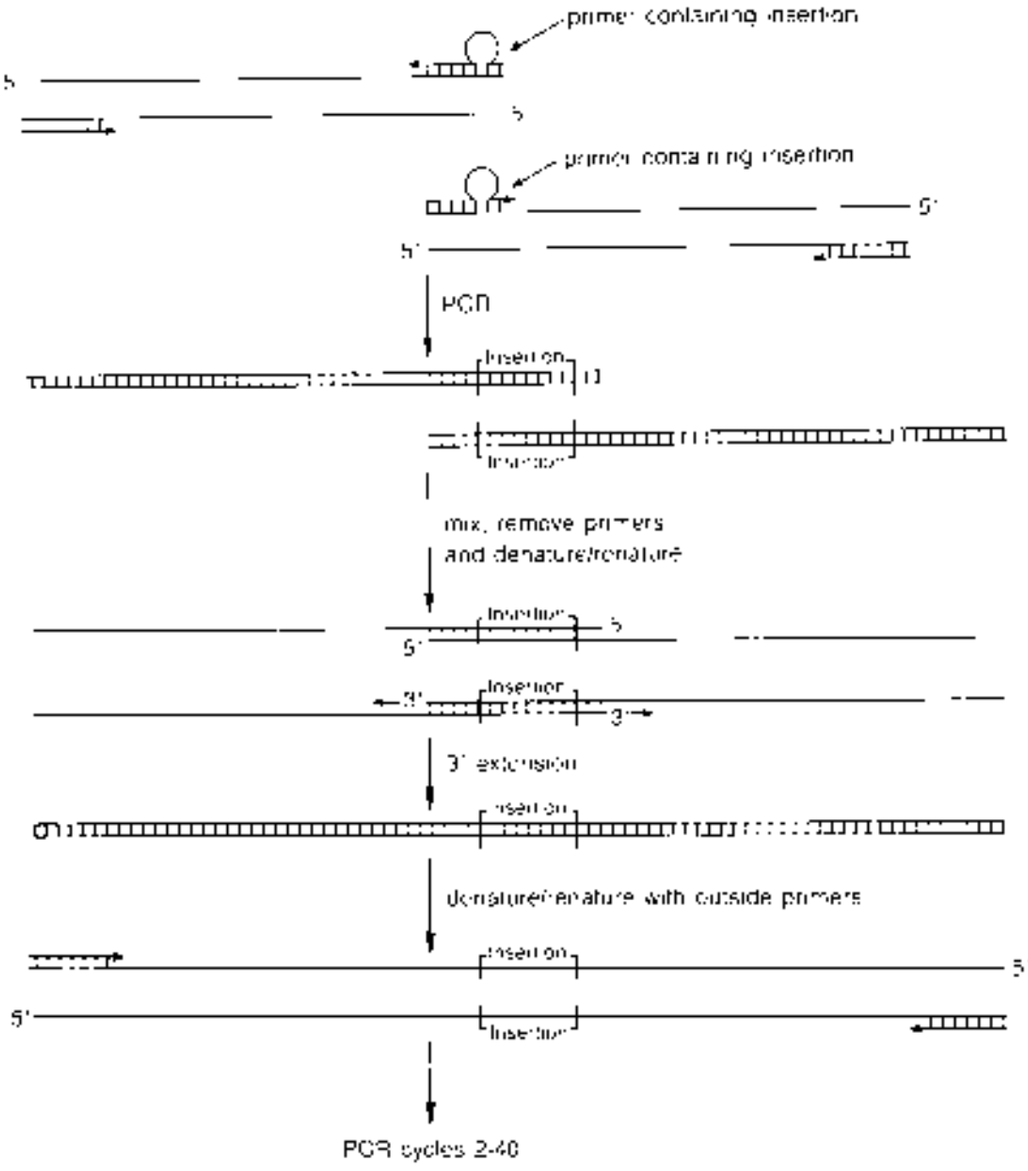

FIG. 9. Internal insertion by PCR.

mutagenesis. The PCR product produced after the second PCR contains the internal insertion of interest. The method is similar for introducing internal deletions by PCR (Fig. 10). The only difference is that a deletion is made in the 3′ primer for the 5′ upstream overlapping DNA fragment. A similar deletion is made in the 5′ primer for the 3′ downstream overlapping DNA fragment. The first and second PCR amplifications are performed as described for producing internal site-directed mutagenesis. The PCR product created after the second PCR contains the desired internal deletion.

Sequence recombination by PCR is a method that joins two unrelated DNA fragments (Fig. 11). This is done by placing a short sequence complementary to the 5′ end of DNA 2 onto the 3′ primer for DNA 1. Also, a short sequence complementary to the 3′ end of DNA 1 is placed onto the 5′ primer for DNA 2. This procedure creates a region of complementarity between DNAs 1 and 2. The first and second PCR amplifications are performed as described for producing internal site-directed mutagenesis. The PCR product produced after the second PCR is a fusion of DNAs 1 and 2.

Other systems for amplification besides PCR are presently available (see 4,9,19,27 for more detailed information). These systems include the ligation amplification reaction (LAR), Qβ replicase amplification, nucleic acid sequence-based amplification (NASBA), the transcription-based amplification system (TAS), and the self-sustained sequence replication system (3SR). LAR amplifies DNA sequences by ligation using bacteriophage T4 DNA ligase; a related method, LAS (ligase-based amplification system), uses *Escherichia coli* DNA ligase. In these two methods, primers that hybridize to adjacent regions of DNA of known sequence are brought together through ligation. These methods, which amplify target DNA no longer than about 50 bp, are used to distinguish normal alleles of genes

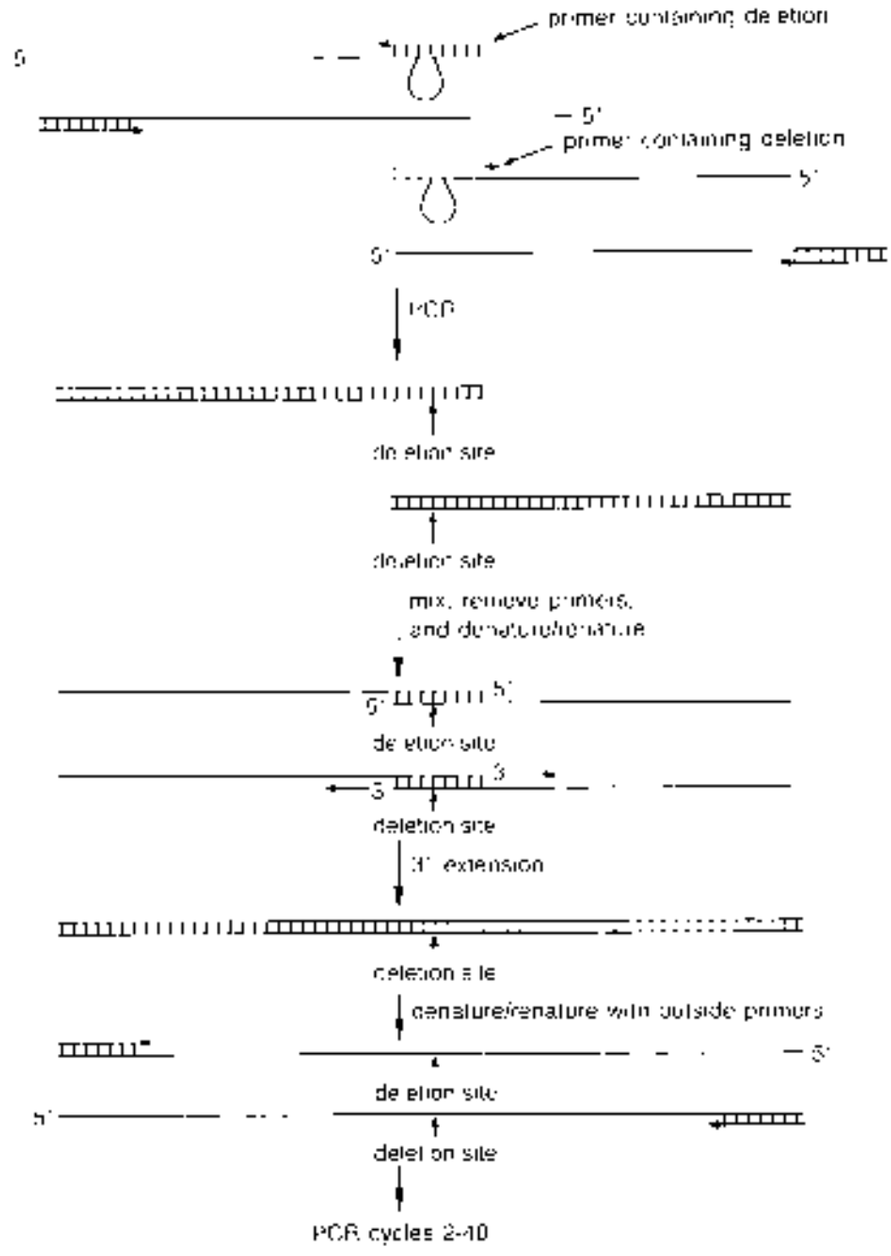

FIG. 10. Internal deletion by PCR.

from alleles containing point mutations. Primers that do not complement the target DNA exactly cannot be ligated. The advantages of ligase-based amplification are speed, reliability, and consistency. Also, there is no requirement for characterization of the amplified product, because evidence that the ligation occurred is proof that the sequence of interest is present.

Qβ replicase amplifies the signal of an RNA probe and is useful in determining the presence of a certain DNA or RNA. Qβ replicase is an RNA polymerase isolated from the RNA bacteriophage Qβ. This polymerase can also copy an RNA named midivariant (MDV-1) which is found in *Plasmodium falciparum*, a protozoan parasite. The probe of interest is first subcloned into MDV-1; therefore, the MDV-1 RNA and the probe are amplified in the presence of an activated Qβ replicase. Some advantages of this system are that (a) all steps of the reaction are performed at 37°C and no thermal cycling is required; (b) amplification is so great (10^9-fold in 30 min) that products can be detected colorimetrically; and (c) the amount of RNA produced within a given period of time can be used to determine the initial number of target sequences. Disadvantages of this amplification system are that Qβ replicase is extremely unstable, produces many errors during replication, and produces many false positives.

There are several systems that use RNA transcription to produce more amplified product. These systems are more efficient than PCR because transcription produces hundreds of copies of the RNA target from one cDNA. NASBA amplifies DNA and RNA without changing temperature and cycles DNA and RNA synthesis evenly. This system uses T7 RNA polymerase, RNase H, and AMV reverse

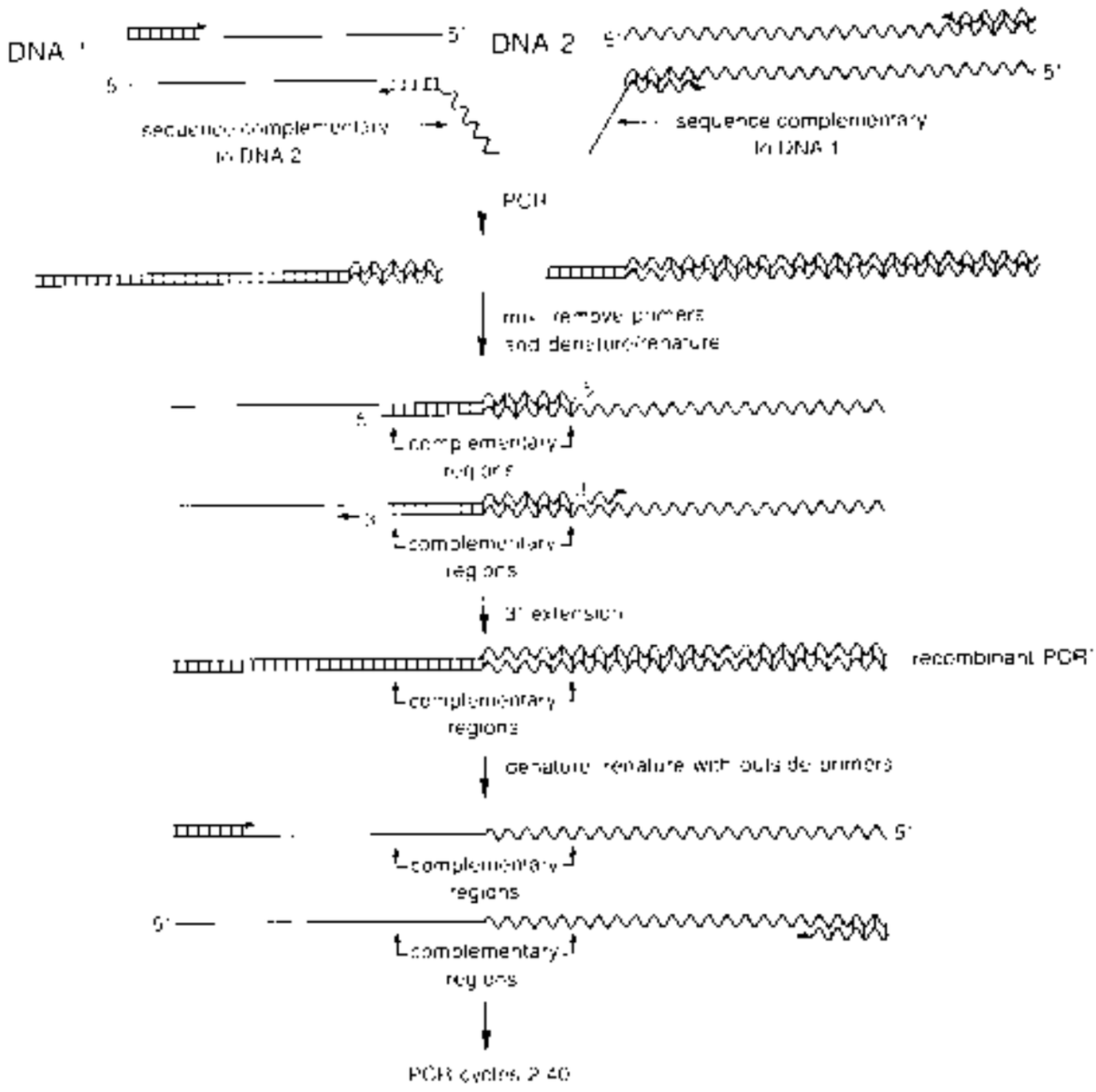

FIG. 11. Sequence recombination by PCR.

transcriptase to produce amplification in a series of many steps (4). The reaction is performed at 42°C for 1–2 h and produces about a 10^9-fold amplification. The amplification products are analyzed on an agarose gel, a slot blot, or a dot blot. As few as 10 molecules in a mix of 10^{10} molecules can be detected (19). TAS amplifies DNA or RNA targets by RNA transcription using T7, T3, or SP6 RNA polymerase (13,27). cDNA synthesis and RNA transcription occur at each cycle. Complementary strands for both RNA and cDNA are produced by the reverse transcriptase when it is added after the RNA-DNA hybrid is denatured. An advantage of this system is that RNA produced after amplification can be directly sequenced. 3SR is an amplification system similar to TAS except that the RNA-DNA hybrids are separated by RNase H and not by heat denaturation (9,27). Thus, all steps can be done at one temperature, and a thermal cycler is not required.

PCR APPLICATIONS

One of the most significant applications of PCR technology is the identification and analysis of mutations in eukaryotic DNA (21). DNA deletions and insertions can be detected by a change in size of the PCR product. Failure to produce any PCR fragment indicates that the primer is found in an area of deletion. Mutations can be identified by hybridizing PCR-generated DNA fragments to radioactively labelled RNA probes and digesting the DNA-RNA complex with RNase A. Digestion will occur if the complex contains any mismatches. Localization of mutations has also been achieved by examining

PCR products using denaturing gradient gel electrophoresis (DGGE). DGGE separates about 50% of DNA strands <1,000 bp in length that have single base changes (6). This technique separates DNA strands by electrophoresis through a polyacrylamide gel containing a linear gradient of DNA denaturants. The DNA strands migrate differently because they have slightly different melting properties. In addition, differences in a single DNA base can be detected by competitive nucleotide priming. In this procedure, two different primers that differ in one DNA base are used in PCR to prime one DNA strand. Thus, there are three primers used in the entire PCR sample. One of the two similar primers is radioactively labelled, allowing the amount of PCR products yielded by each primer to be determined. The sequence of the amplified target DNA is that of the primer that produced the greatest amplification.

Over 23 different human gene mutations and allele-linked disorders have been diagnosed using PCR (5). Some of these diagnoses have been performed prenatally or on embryos before they are implanted for in vitro fertilization. In addition, detection of amplified oncogenes has been achieved by differential PCR. In this procedure, the oncogene of interest and a single-copy reference gene are coamplified in the same PCR tube. Gene amplification is determined by comparing the intensity of the oncogene PCR product with that of the amplified reference single-copy gene. This method can detect even twofold differences and has been used to study gene amplifications of the *neu* oncogene and the epidermal growth factor (EGF) gene.

PCR has been used to identify over 22 different pathogenic organisms in clinical samples (5,13). A dispute in the field of AIDS research was settled by a critical PCR experiment. Some investigators questioned HIV-1 as the cause of AIDS because this virus could not be detected in late-stage AIDS patients. PCR was performed on CD4+ T cells from the circulatory systems of late-stage AIDS patients. The result of this experiment demonstrated that these cells contain large amounts of HIV-1.

PCR has been used for identification of biological and forensic samples (5,13); however, extreme care must be taken to eliminate DNA contaminants that may be erroneously amplified. DNA has been amplified from a single hair, one sperm, semen stains, blood, blood stains, saliva, buccal epithelial cells, and paraffin-embedded tissues. DNA fingerprint analysis can be performed on the PCR-amplified DNA in order to identify a specific individual. These analyses have been able to identify criminals involved in murder, sexual assault, etc., and have been used to settle paternity cases. PCR has been used in HLA analysis and tissue-typing for organ transplantation. DNA from certain organelles, such as the mitochondria, has been amplified by PCR for further analysis. Advances in the identification and screening of transgenic mice have also been possible with PCR technology. PCR-amplified DNA has been used in studies of gene polymorphisms; these studies have made major contributions to the field of evolution. DNA has been amplified from ancient archeological specimens, including Egyptian mummies, bone, teeth, 7,000-year-old brain tissue, etc.

PCR has had a major impact on developmental biology research (5,13). DNA from certain organisms that do not grow rapidly, such as some fungi, can now be amplified by PCR and analyzed. PCR has contributed to the analyses of expression of growth factors in small quantities of macrophages during wound healing; gene expression during embryogenesis; examination of site-directed homologous recombination of genes in embryonic cells; detection of nucleotide changes resulting from RNA processing events; quantitation of gene expression in specific organs, such as dystrophin gene expression in muscle; and studies of gene rearrangements that occur during development, such as the V-J region rearrangements in the T-cell receptor α-chain.

In conclusion, PCR is an extremely important yet simple technology for research and diagnostic analyses of DNA and RNA. It will be exciting to witness the new applications that arise in the future from this technology or other amplification procedures. The major advantages of PCR are the ability to utilize minute samples to produce a high yield of amplified target DNA, the specificity of the reaction, the flexibility of the method, and the simplicity and speed of the automated procedure. □

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Polymerase chain reaction: A landmark in the history of gene technology

Joe G. N. Garcia, MD; Shwu-Fan Ma, PhD

Definitions

The polymerase chain reaction, known worldwide by the abbreviation PCR, was defined by Kary B. Mullis, the 1993 Nobel laureate, not only as a specific technique or cluster of techniques but also as a concept. Mullis invented the PCR technique in 1985 while working as a chemist at the Cetus Corporation, a biotechnology firm in Emeryville, California. Basically, PCR uses a naturally occurring nuclease enzyme, polymerase, to catalyze the regeneration of DNA with a chain reaction, consisting of three steps (Fig. 1) that are repeated over and over to exponentially amplify the target DNA (1).

History of Development

The Klenow fragment of *Escherichia coli* DNA polymerase I was first used to catalyze the formation and amplification of DNA in 1983 (2). When PCR was conducted manually, the process was time consuming and labor intensive because the heat denaturation step, which is required for the separation of the newly synthesized strands of DNA, also denatured the polymerase. Therefore, fresh enzyme had to be added to the reaction mixture after the completion of each cycle. Fortunately, nature helped to overcome this disadvantage when a thermostable and heat-resistant DNA polymerase derived from *Thermus aquaticus* was purified (*Taq* DNA polymerase) (3–5). Using this heat-resistant polymerase, the amplification reaction could run through heat cycles without interruption. Cetus scientists and others automated the PCR process and developed the first thermocycling machine, "Mr. Cycle," in 1992. Employment of *Taq* DNA polymerase significantly improved the specificity and sensitivity of the reaction and increased yield and length of products. Novel technologies that significantly shorten the chain reaction time have also propelled the efficiency of PCR to a new level. Thus, PCR has allowed genetic material that was once scarce to be extremely abundant for analysis.

How Does PCR Work?

PCR requires placement of a small amount of a gene or segment of DNA (template) and an excessive amount of the DNA building blocks (i.e., the deoxynucleotides, deoxyadenosine triphosphate, deoxycytidine triphosphate, deoxyguanosine triphosphate, deoxythymidine triphosphate) into a PCR tube. A pair (sense and antisense) of synthesized short DNA segments (primers) that flank the sequence of the template are then added. These "primers" anneal to the right portion (complementary sequence) of the template and serve as starting points for the DNA polymerase to begin template copying. On addition of DNA polymerase to this mixture, DNA polymerase builds new complementary DNA (cDNA) strands dictated by the sequence of the target gene located between the two primers. The PCR tube is then heated, and the DNA's double helix separates into two strands (denaturation). The DNA sequence of each strand of the helix is thus exposed, and as the temperature is lowered, the primers again automatically bind to their complementary portions of the DNA sample (annealing). At the same time, the DNA polymerase links the loose deoxynucleotides to the primer and to each of the separated DNA strands in the appropriate sequence (extension). The three steps of denaturation, annealing, and extension are repeated 30–40 cycles, resulting in the exponential accumulation of the specific target fragment, approximately 2^n, where n is the number of cycles (6–7) (Fig. 1).

The concept and technology of reverse transcriptase (RT)-PCR and real-time PCR are similar to PCR with some modification. In RT-PCR, RNA and not DNA is used as the template and the RT is needed to transcribe RNA to cDNA before the initiation of PCR. Both PCR and RT-PCR can be used to quantitate the concentration of a particular target by amplifying the target sequence and a reference sequence, commonly referred to as a housekeeping gene, to a more readily detectable quantity. By comparing the amount of amplified product (amplicon) generated by the reference and the target sequences, one can estimate the relative amounts of the target sequence produced in a particular situation. However, this assay measures end-products without precisely knowing the saturation phase, thus rendering this approach less accurate (8). Quantification is more accurate if, during the exponential phase of the chain reaction, the reference and target sequence are present in approximately equal concentrations and both sequences amplify with equal efficiency (9).

The technique of real-time PCR employs similar concepts to quantify the amount of the target sequence throughout all cycles but uses a template-specific fluorescent reporter. This reporter increases the sensitivity of detection of the PCR product and is thus more accurate and reproducible (10). The fluorescence signal increases in direct proportion to the amount of PCR product in a reaction during each cycle (i.e., in real time) as opposed to at the end point detection (Fig. 2). By recording the amount of fluorescence emission at each cycle, it is possible to monitor the PCR reaction during the exponential phase, where the first significant increase in the amount of PCR product correlates with the initial amount of target template. The higher the starting copy number of the DNA target, the sooner a significant increase

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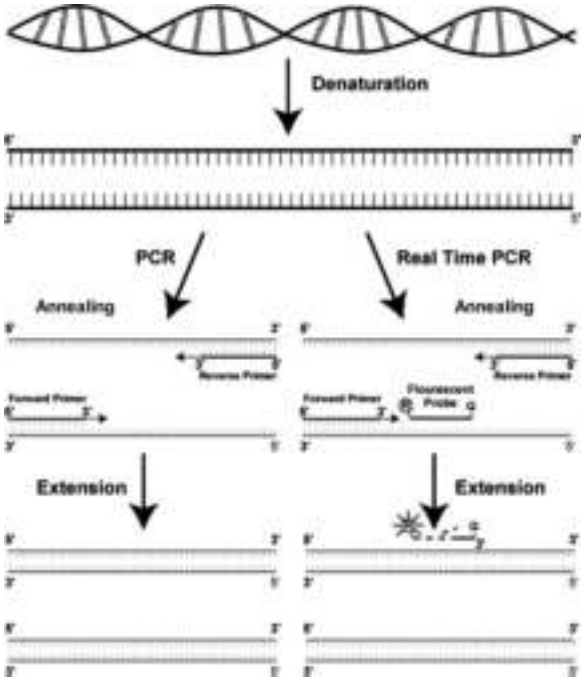

Figure 1. Three steps in polymerase chain reaction (*PCR*) and real-time PCR. Step 1, Denaturation: Template DNA mixture is heated to 90–95°C, allowing the DNA double strand to denature and separate into two single strands. Step 2, Annealing: Template DNA mixture is cooled to 50–60°C to allow primers (for PCR) and primers plus the TaqMan probe, which consists of an oligonucleotide with a 5'-reporter dye (R) and a downstream, 3'-quencher dye (Q) (for real-time PCR), to anneal to the single-stranded DNA. Step 3, Extension: The temperature is raised to 72°C to allow *Taq* polymerase to add deoxynucleotides to the target DNA (for PCR) and complete the amplification. For real-time PCR, the TaqMan probe containing a reporter dye at the 5' end and a quencher dye at the 3' end is separated on cleavage by DNA polymerase, resulting in increased fluorescence of the reporter as well as the newly amplified target DNA. These three steps are repeated 30–40 times to replicate 2^n copies of DNA region of interest where n = cycle number.

in fluorescence indicates the detection of PCR product accumulation. Similar to the RT-PCR, RNA can also be used as target source and termed real-time RT-PCR. In comparison to conventional RT-PCR, real-time RT-PCR offers a much wider dynamic range of ratios of target and reference (up to 10^7-fold) with equal sensitivity and specificity compared with conventional RT-PCR (1000-fold).

Why It Is Important

Why has PCR become a landmark for gene technology? Nobel laureate Mullis said, "The thing that was the 'Aha!', the 'Eureka!' thing about PCR, wasn't just putting those [things] together. . .the remarkable part is that you will pull out a little piece of DNA from its context, and that's what you will get amplified and that is the genius thing." Based on this key point, PCR has been used in examining nucleotide sequence variations to localize the genetic alterations and chromosomal rearrangements (11) underlying hereditary diseases, for high-efficiency cloning of genomic sequences (12), for direct sequencing of mitochondrial (3) and genomic DNAs in the Human Genome Organization (HUGO) project (13), and for detecting viral pathogens and HIV infections (14). Obviously, in crime investigation, PCR provides decisive information since it is now possible to analyze the DNA in a single drop of blood or in a hair found at the scene of a crime (15). Thanks to PCR, it became possible to mass-produce DNA from fossil remains. Researchers have succeeded in amplifying genetic material from insects that have been extinct for >20 million years by applying the PCR method to DNA extracted from amber. This prospect has inspired authors of science fiction such as *Jurassic Park* by Michael Crichton.

How It Is Presented

Agarose gel electrophoresis is the universal way of separating and analyzing the PCR products (Fig. 2). With the addition of ethidium bromide, which binds strongly to DNA by intercalating between the bases, the amplicon (~20 ng or 10–20 μL of post-PCR mixture) can be visualized by fluorescence, since ethidium bromide converts invisible ultraviolet light to the visible orange light spectrum. Visualization of the PCR products allows immediate evaluation and conclusion regarding whether the resulting product is the correct size and whether other products were amplified as well. Most agarose gels are made between 0.7% and 2% to separate two groups of amplicons based on size (5–10 kb and 0.2–1 kb) with 1% gels usually used for general purpose (16).

Its Importance in Critical Illness

Real-time PCR/RT-PCR protocols have been widely applied to facilitate the diagnosis in critical illness. Prucha et al. (17) hypothesized that gene expression profiling is applicable to sepsis diagnosis and used a microarray approach to identify 50 randomly chosen transcripts that were significantly differentially expressed in sepsis patients. Followed by PCR validation, they observed a striking correlation between the conventional diagnostic classification and the microarray approach, regardless of the heterogeneity of the patients. In addition to a global microarray approach, PCR was also applied to single gene validation. To study the expression levels of nitric oxide synthase and heme oxygenase, Reade et al. (18) isolated mesenteric arterial smooth muscle and peripheral blood mononuclear cell RNA from patients with early septic shock and from control individuals. Based on real-time RT-PCR data, they reported that messenger RNA for inducible and endothelial nitric oxide synthase was reduced in both arterial smooth muscle and peripheral blood mononuclear cells from septic patients. In contrast, inducible heme oxygenase messenger RNA was increased in sepsis in both cell types. Similarly, Kalkoff et al. (19) used real-time RT-PCR to quantify the pattern of inflammatory mediator messenger RNA expression in circulating leukocytes from adult patients diagnosed with severe sepsis and found distinct gene expression patterns, concluding that real-time RT-PCR is a useful tool to monitor the immune response in septic patients. Our group (20) recently identified a novel biomarker, pre-B-cell colony-enhancing factor, asso-

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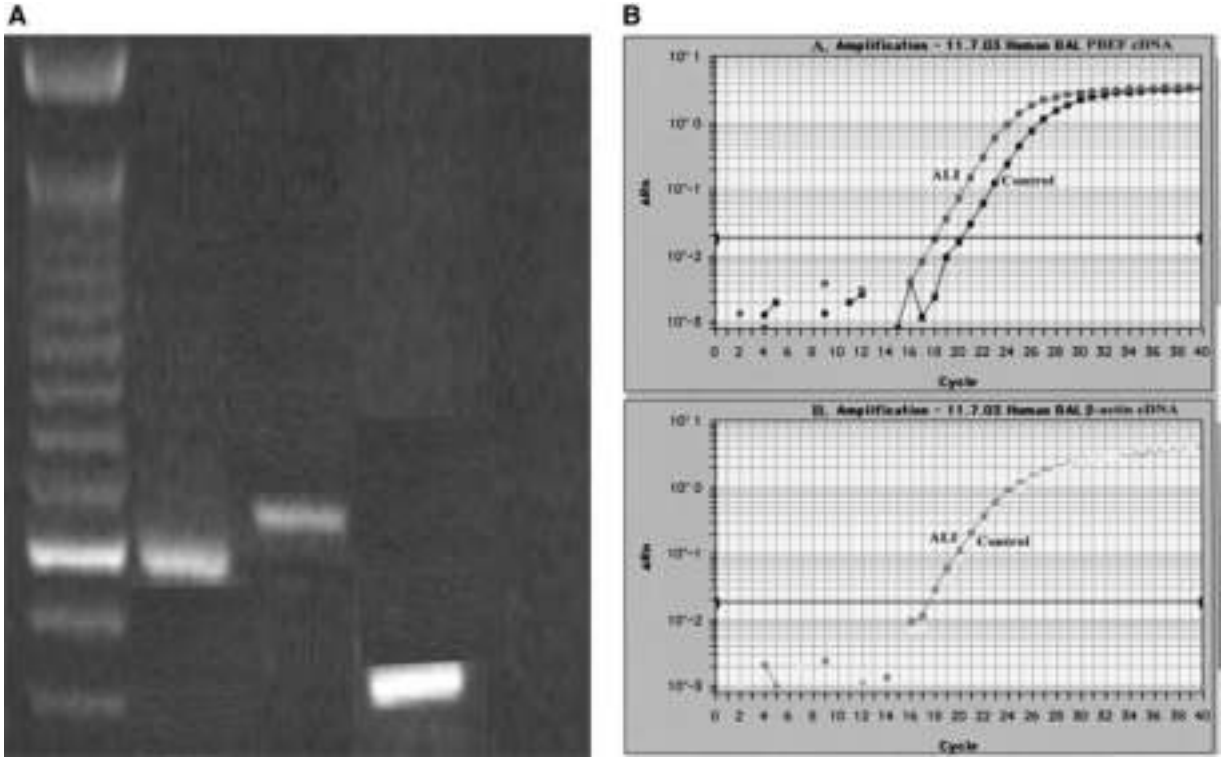

Figure 2. Visualization of polymerase chain reaction (*PCR*) and real-time PCR products. *A*, agarose gel (1%) electrophoresis of PCR products. *Lane 1*, 100 base-pair ladder. *Lanes 2–4*, PCR products of template DNA of interest. *Lane 5*, negative control. *B*, real-time PCR amplification plots comparing gene of interest in patients with acute lung injury (*ALI*) and control subjects. Actin was used as a housekeeping gene control. Accumulation of PCR products is detected by monitoring the increase in fluorescence of the reporter dye and is a direct consequence of target amplification during PCR. Since the variable C_T (threshold cycle) is defined as the cycle number at which the fluorescence emission exceeds the fixed threshold (baseline), the higher the initial amount of template, the sooner accumulated product is detected in the real-time PCR process, and the lower the C_T value. ΔRn, the difference between the normalized reporter signal and baseline signal; BAL, bronchoalveolar lavage; *PBEF*, pre-B-cell colony-enhancing factor; *cDNA*, complementary DNA.

ciated with lung pathophysiology. Real-time RT-PCR validates the significant increase of pre-B-cell colony-enhancing factor in both bronchoalveolar lavage fluid and serum of acute lung injury models and in cytokine- or cyclic stretch-activated lung microvascular endothelium. Pre-B-cell colony-enhancing factor single-nucleotide polymorphisms in a well-characterized sample of white patients with sepsis-associated acute lung injury, patients with severe sepsis, and healthy subjects detected by PCR further support the association between these single-nucleotide polymorphisms and susceptibility to acute lung injury.

Tips and Caveats

Since PCR amplifies a target DNA sequence from only a few molecules to >10 million copies, samples should be extremely well guarded from contamination with other DNA or previously amplified products (amplicons) that may reside in the laboratory environment. It is therefore recommended to always run both a negative control to verify that no contaminants are present in any of the reagent stocks and a positive control to verify that the PCR amplification reaction was successful for every round of amplification performed. The standard PCR protocol can only be followed as a guideline, and the optimal condition for each component or condition must be determined empirically.

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WHO Information Notice for IVD Users 2020/05

Nucleic acid testing (NAT) technologies that use polymerase chain reaction (PCR) for detection of SARS-CoV-2

20 January 2021 | Medical product alert | Geneva | Reading time: 1 min (370 words)

Français Español

Related

Product type: Nucleic acid testing (NAT) technologies that use polymerase chain reaction (PCR) for detection of SARS-CoV-2

Date: 13 January 2021

WHO-identifier: 2020/5, version 2

Target audience: laboratory professionals and users of IVDs.

Purpose of this notice: clarify information previously provided by WHO. This notice supersedes WHO Information Notice for In Vitro Diagnostic Medical Device (IVD) Users 2020/05 version 1, issued 14 December 2020.

Description of the problem: WHO requests users to follow the instructions for use (IFU) when interpreting results for specimens tested using PCR methodology.

Users of IVDs must read and follow the IFU carefully to determine if manual adjustment of the PCR positivity threshold is recommended by the manufacturer.

WHO guidance Diagnostic testing for SARS-CoV-2 states that careful interpretation of weak positive results is needed (*1*). The cycle threshold (Ct) needed to detect virus is inversely proportional to the patient's viral load. Where test results do not correspond with the clinical presentation, a new specimen should be taken and retested using the same or different NAT technology.

WHO reminds IVD users that disease prevalence alters the predictive value of test results; as disease prevalence decreases, the risk of false positive increases (*2*). This means that the probability that a person who has a positive result (SARS-CoV-2 detected) is truly infected with SARS-CoV-2 decreases as prevalence decreases, irrespective of the claimed specificity.

Most PCR assays are indicated as an aid for diagnosis, therefore, health care providers must consider any result in combination with timing of sampling, specimen type, assay specifics, clinical observations, patient history, confirmed status of any contacts, and epidemiological information.

Actions to be taken by IVD users:

1. Please read carefully the IFU in its entirety.
2. Contact your local representative if there is any aspect of the IFU that is unclear to you.
3. Check the IFU for each incoming consignment to detect any changes to the IFU.
4. Provide the Ct value in the report to the requesting health care provider.

Contact person for further information:

Anita SANDS, Regulation and Prequalification, World Health Organization, e-mail: rapidalert@who.int

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A Viral Fragmentation Signature for SARS-CoV-2 in Clinical Samples Correlating with Contagiousness

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Abstract

The viral load of SARS-CoV-2 in clinical samples as measured by the primary diagnostic tool of RT-PCR is an imperfect readout for infection potential as most targeted assays designed for sensitivity, indiscriminately detect short and long RNA fragments, although infectivity is embodied only in the whole virus and its intact genome. Here, we used next-generation sequencing (NGS) to characterize 155 clinical samples and show sensitive and quantitative detection of viral RNA which confirmed subgenomic RNA in 57.6% of samples and provided a novel method to determine relative integrity of viral RNA in samples. The relative abundance of long fragments quantified as a viral fragmentation score was positively associated with viral load and inversely related to time from disease onset. An empirically determined score cut-off for presence of substantially fragmented RNA was able to identify 100% of samples collected after 8 days of illness with poor infection potential in line with current clinical understanding of infectiousness of SARS-CoV-2. The quantification of longer fragments in addition to existing short targets in an NGS or RT-PCR-based assay could provide a valuable readout of infection potential simultaneous to the detection of any fragments of SARS-CoV-2 RNA in test samples.

Introduction

In March 2020, the World Health Organization (WHO) declared a pandemic of the coronavirus disease 2019 (COVID-19), an infection caused by severe acute respiratory

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syndrome coronavirus 2 (SARS-CoV-2)[1]. By end of 2020, 82 million infections have been reported worldwide with 1.79 million deaths (https://coronavirus.jhu.edu). Diagnostic tools for detection of present and past infection of SARS-CoV-2 have been crucial for the management of this public health emergency, and include an array of molecular tests and immunoassays[2]. Direct detection of nucleic acids via reverse-transcription-polymerase chain reaction (RT-PCR) is the most widely deployed modality. Next-generation sequencing (NGS) is a related molecular method, and is characterized by the ability to identify polymorphisms and to define interrelatedness of virus strains[3,4], facilitated by the whole-genome interrogation of the virus.

Sensitive methods for detecting SARS-CoV-2 have been paramount in the identification and isolation of infected individuals and their close contacts, reducing viral transmission. Releasing infected persons prematurely from isolation carries the risk of fuelling transmission, while prolonging isolation unnecessarily can adversely affect resource allocation and cause undue disruptions[5]. While RT-PCR assays are widely regarded as the most sensitive of diagnostic methods, the inability to distinguish intact viral RNA – packaged in virions and able to cause onward transmission – from products of degradation of viral RNA ineffectual at further infection, has led to considerable debate on the dichotomous interpretation of RT-PCR results as positive/negative, and the in-depth analysis of the period of infectiousness[6,7]. Positive detection of virus RNA does not prove presence of infectious virus, as persistent detection of viral RNA in samples has been reported up to 35 days from symptom onset[8–12], and after resolution of clinical symptoms of both mild and severe disease[13–16]. As large-scale vaccination is deployed across countries[17–19], the uncertain impact of vaccination on potential contagiousness[20,21], further highlights the need for means to quantify contagiousness accurately.

The isolation of whole virions in cultured cells, in contrast to RNA fragments provides evidence of the isolate's replicative potential and more closely reflects the true infection potential[6]. Duration of live virus detection is much shorter than viral shedding and no live virus has been isolated in samples taken more than 8 days since symptom onset in immunocompetent patients [8,11,22]. In accordance with this, in a hamster model, transmissibility of SARS-CoV-2 correlated with detection of infectious virus by culture, but not by RT-PCR-positivity alone, and the communicable period was less than 6 days for inoculated donor animals[23]. Viral load dynamics also differ between upper respiratory tract samples, where highest viral loads were reported at the time of symptom onset or soon after at 3-5 days of illness followed by consistent decline, and in lower respiratory tract samples where peak viral load is in the second week of illness[7]. It is at present unclear if this dynamic is related to dynamic infection potential of transmitted material from each site.

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Detection of subgenomic RNA (sgRNA) has been used as a proof of viral replication, which can only happen in infected cells, and declines over days 10-11 from infection[8]. sgRNA does not get packaged into virions therefore detection of sgRNA is indicative of actively infected cells in a sample, and complements the detection of infectious viral RNA packaged into virions. SgRNA have been detected in cultured cells and in limited clinical samples most commonly by NGS and by RT-PCR for specific sgRNA fusion products, but are not routinely studied [8,24,25].

Prompted by the limitations of the most commonly used diagnostic device for SARS-CoV-2 for informing contagiousness, and by the urgent need to address this crucial parameter, in this study we employed whole-genome NGS with molecular barcoding and sequencing error-correction to characterize clinical samples collected from a cohort of migrant workers in Singapore. As a comprehensive tool with full genome targeting, NGS can inform presence of any SARS-CoV-2 RNA, the presence of sequence variants and sgRNA, and as we show for the first time, this method can also characterize the lengths of fragments of RNA in a sample. We go on to show that fragment lengths, characterized as a viral fragmentation score, are related to intactness of viral RNA, which is a prerequisite for infectiousness in the form of whole virus, and is correlated in with other clinical parameters of potential infectiousness such as viral load, sgRNA and duration of illness.

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Materials and Methods

Sample collection

Samples used in this study were collected as part of a previous study conducted in a large cohort of migrant workers in Singapore, and evaluated and approved by the Director of Medical Services, Ministry of Health, under Singapore's Infectious Disease Act[26]. A total of 155 samples, corresponding to 48 individuals were analyzed by NGS. The samples included 37 nasopharyngeal (NP) swabs collected in 3 mL of viral transport medium, 60 self-nasal swabs, and 58 oropharyngeal saliva samples collected in 2 mL of viral RNA stabilization fluid (SAFER™ VTM, Lucence, Singapore). The majority of the cases (35 of 48, 72.9%) were symptomatic at the time of first sample collection, one case was presymptomatic at time of first sampling, and 12 cases (25%) were asymptomatic through the study. For asymptomatic cases, the day of the first diagnostic test was used to determine days since diagnosis. For 17 cases (35.4%), only a single sample was available for sequencing, and for the remaining 31 (64.5%) of cases, between 2 and 9 samples were studied. For 5 cases (10.41%), samples from different sites (NP, nasal swab or saliva) were available but from the same timepoint (not longitudinal). All samples had previously been characterized for presence of SARS-CoV-2 using an RT-PCR assay using primers and probes sequences from the CDC 2019-nCoV Real-Time RT-PCR Diagnostic Panel[26,27], henceforth referred to as CDC RT-PCR assay. Samples were selected for NGS based on SARS-CoV-2 positivity at at least one of 2 or 3 timepoints of sample collection and relatively high viral loads as estimated by the RT-PCR assay. Archived extracted RNA from anonymized samples were used for this study.

Sample processing

Viral nucleic acid is extracted from the specimens (200 or 400 µl) using Viral Nucleic Acid Extraction Kit II (Geneaid Biotech Ltd., Taiwan) or QIAsymphony DSP Virus/Pathogen Kit (QIAGEN). For each sample, aliquots of extracted nucleic acid (RNA) was screened for presence of SARS-CoV-2 RNA using real-time reverse transcription-polymerase chain reaction (RT-PCR) targeting the N1 and N2 markers as specified by Centers for Disease Control and Prevention (CDC), and also processed for library preparation for NGS. Samples were processed in a College of American Pathologists (CAP) accredited and a Clinical Laboratory Improvement Amendments (CLIA) licensed laboratory (Lucence).

Analytical validation of SARS-CoV-2 NGS method

Lower limit of detection (sensitivity) of the NGS method was determined using synthetic SARS-CoV-2 RNA spiked into pooled clinical matrix that tested negative for the virus by a RT-PCR method. For the analytical validation of NGS, synthetic SARS-CoV-2 RNA

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genomes (Twist Bioscience, San Francisco, USA) of known concentrations were spiked in to pooled negative clinical matrix (nasopharyngeal swab specimens) at known copy numbers prior to RNA extraction. The synthetic controls corresponded to these GenBank IDs of various published SARS-CoV-2 genome isolates. MT007544.1 (SKU: 102019), MN908947.3 (SKU: 102024), LC528232.1 (SKU: 102860), MT106054.1 (SKU: 102862), MT188340.1 (SKU: 102917), MT118835.1 (SKU: 102918). The threshold for detection of SARS-CoV-2 was determined by comparing the genome coverage (%) resulting from confirmed negative samples (by RT-PCR), and no-template controls and that resulting from known positive samples (by RT-PCR).

Design of multiplex PCR panel for SARS-CoV-2 genome

A multiplex amplicon-based next generation sequencing (NGS) platform was developed to sequence the entire SARS-CoV-2 genome. Primers for 327 amplicons were designed to span the entire SARS-CoV-2 genome in tiled configuration, and alternately assigned to two separate primer pools (Pool 1 and Pool 2) to allow amplification of the whole genome while minimizing formation of short overlapping amplicons. Five primer pairs designed to target five different human housekeeping genes (*TBP*, *MYC*, *LRP1*, *ITGB7*, and *HMBS*) are used as control in both pools. Each forward primer additionally includes on the 5' end, a random 10 nucleotide sequence to serve as molecular barcode. Each designed primer was checked against published SARS CoV-2 genomes as of April 15 2020, and base degeneracy was incorporated when required to achieve coverage of >99% of Asian, USA, Europe and Chinese genomes published.

Preparation of library for NGS of SARS-CoV-2

Based on the CDC RT-PCR results, extracted nucleic acid were diluted 10-fold for samples with cycle threshold (Ct) ≤20 or undiluted for samples with Ct>20, followed by reverse transcription using High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, USA) to generate complementary DNA (cDNA). A synthetic spike-in RNA control was added to the sample just before cDNA synthesis. The RNA control comprises a nucleotide sequence which is not found in a genome or a transcriptome of the virus, and is further not found in a genome or a transcriptome of a human, and is further not found in a genome or a transcriptome of a microorganism. Each cDNA was split into two reactions for target capture and enrichment of Pool 1 and Pool 2 using Platinum SuperFi II DNA Polymerase (Invitrogen, USA) under the following thermocycling conditions: Denaturation at 98^0C for 30s, followed by 5 to 15 cycles (5 cycles for samples with Ct <15, 10 cycles for samples with Ct 15-30, 15 cycles for samples with Ct >30) of 98^0C for 1 min, 60^0C for 1 min, and 72^0C for 1 min, with final extension at 72^0C for 5 min. At the end of the reaction, excess primers were removed

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by purification two times with 1.5x AMPure XP beads (Beckman Coulter,USA). Purified products were subjected to a final PCR to amplify targets and to complete the library with indexed sequencing adaptors for sequencing on the Illumina platform. Briefly, purified product was amplified with indexed P5 adapter sequence and indexed P7 adapter sequence using KAPA HiFi HotStart ReadyMix under the following thermocycling conditions: Denaturation at 98^0C for 45 s, followed by 18 cycles of 98^0C for 15 s, 60^0C for 30 s, and 72^0C for 30 s, with a final extension at 72^0C for 1 min. The amplified library was purified twice with 0.7x AMPure XP beads to remove non-specific products. The quality and quantity of the sequencing library is assessed using the 4200 Tapestation system (Agilent Technologies, USA) and KAPA Library Quantification Kit for Illumina® Platforms (Kapa Biosystems Inc., USA) respectively. Paired-end sequencing (2x151bp) of the final dual-indexed libraries is performed on the Illumina platform as per manufacturer's instructions.

Primary sequencing data analysis

FASTQ files were processed using a custom pipeline. First, expected amplicons were identified and labeled in the FASTQ files based on the expected primer sequences in Read 1 and paired Read 2. Primer sequences and upstream molecular barcode sequences were trimmed using cutadapt, primer trimmed sequences were mapped to the reference genome SARS-CoV-2 reference genome (NCBI Reference Sequence: NC_045512.2) using bwa-mem. Molecular tag (or barcode) sequences were included in the trimmed "primer" sequences of read 1, and can be extracted given the unique structure of primer sequences in read 1. Barcode sequences were clustered based on sequence and amplicon identity, and consensus calling was done for each molecular tag (or barcode) cluster, by first performing global alignment among all associated reads using MAFFT. The consensus base in each aligned position was called by determining the majority representative base type, the percentage of which should be no less than an automatically determined threshold. The threshold is a function of the total number of reads for that barcode sequence. If no representative base could be called, the position was assigned N (as opposed to one of A, C, T, G). An overall quality score, of either 90^{th} percentile of all the quality values from the representative base type in that position (if a consensus base is found), or 10^{th} percentile of all quality values in that position (if no consensus bases is found) is assigned. The consensus reads are then written to a new FASTQ file.

Variant calling, subgenomic RNA analysis and phylogenetic analysis

First, consensus FASTQ files from two pool 1 and pool 2 were merged to create a single FASTQ file. Consensus FASTQ reads are mapped to the SARS-CoV-2 reference genome (NCBI Reference Sequence: NC_045512.2) using bwa-mem[28]. Samtools[29] was used to

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calculate depth per base and coverage metrics. Variant calling was performed on consensus BAM files using snippy and freebayes. For variants to be called, a minimum of 10x coverage is required. With molecular barcoding, the sequencing is error-free and can enable detection of quasispecies and increase confidence of variant calls due to the high quality of sequencing data.

Detection of subgenomic RNA (sgRNA) was done by analysis of split reads supported by multiple consensus reads. Chimeric reads in which non-contiguous regions of the genome are captured within a read are identified as split reads and have 1) unexpected combination of primers which resulted in the amplicon, 2) presence of junction sites at which fusion occurs and 3) presence of a junction core sequence for coronaviruses which is exemplified by the sequence – CTAAACGAAC – within the read[30,31]. The detection of canonical sgRNA was defined by the presence of the 5' end leader sequence of the genome and downstream ORFs on the 3'end of the genome. Due to the design of the primers and full coverage inherent in the primer panel design, all canonical sgRNA can be detected. The frequency of each sgRNA was calculated as the number of split reads supporting sgRNA/number all reads supporting the location spanning the junction 3' to the junction. For comparison across samples and across different species of sgRNA, the sgRNA split read count was normalized to the mean depth of coverage for the sample. For comparing total sgRNA, the sum of all sgRNA read counts was normalized to the mean depth of coverage for the sample.

FASTA file of the assembled genome are used to construct phylogenetic trees. The phylogenetic tree building process and parameters follows the NextStrain team's repository at https://github.com/nextstrain/ncov[32].

Insert length analysis and calculation of viral fragmentation score

For each positive sample with sequencing data, SAMtools was used to capture insert sizes from alignment files with the following specifications: samtools view -f65 -F2048 SampleXYZ_consensus.bam | cut -f 1,4,9 > SampleXYZ_f65F2048.txt where f65 = filter in read paired, first in pair (Reads which are paired and insert sizes for first read in read pair and second in read in read pair will have same same insert size with "negative" length); F2048 = filter out reads with supplementary alignment (removes most subgenomic RNA reads which have part of reads with supplementary alignment and removes chimeric reads. Finally inserts of size 70 to 1000 are retained to get representation of expected insert sizes as no insert is expected to be shorter than 72 bp (design of inserts) and remove extremely long inserts.

Binning of inserts was done based on the expected and observed insert sizes into 0-150 bp (short) and 151-350 bp (long) ranges. Short and long insert counts were determined for each

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sample, representing short and long viral fragments, respectively. The viral fragmentation score is then derived as (number of fragments of size 151-350bp)/(number of fragments of size 0-150bp).

Multiplex RT-PCR assay for simultaneous detection of fragments of different lengths

A multiplex three-target RT-PCR assay was designed for the simultaneous detection of two short targets of 70 bp each in the N gene region (in two separate detection channels), and one long amplicon of 240 bp in the S gene of the SARS-CoV-2 genome. An internal housekeeping control target was included as fourth target in the multiplex reaction. Briefly, extracted RNA (5 µl) was mixed with the primers/probes for the multiplexed targets with Luna® Universal Probe One-Step RT-qPCR Kit (New England Biolabs, USA) and RT-PCR was performed using recommended protocol for the Luna master mix on a BioRad CFX96. Cycle threshold (Ct) values for each target were collected from respective channels and compared.

Statistical Methods

All datapoints are described individually with median and interquartile ranges, where appropriate. For comparison between groups, the Mann-Whitney unpaired t-test was used. Regression analysis and curve fitting was done using Prism 8.0.1.

Results

Detection of SARS-CoV-2 in clinical samples by whole-genome sequencing

Whole-genome sequencing was performed on RNA extracted from 155 samples corresponding to 48 individuals in this study. The samples included 37 nasopharyngeal swabs, 60 self-nasal swabs, and 58 saliva samples. An amplicon-based next-generation sequencing (NGS) panel covering the whole SARS-CoV-2 genome except the first 25 bases and 30 bases upstream of the final polyA tail was used. All samples had been previously characterized by the CDC RT-PCR assay, of which 11 (7.09%) of 155 samples were negative for SARS-CoV-2 and were included in the study to demonstrate the specificity of detection of SARS-CoV-2 by sequencing. The negative samples were from 6 cases which had at least one other matched positive sample from the same or different timepoint. Due to the high rate of positivity (92.9%) among the samples in this study, a set of 25 unrelated samples from the community confirmed to be negative by the same RT-PCR assay were also subjected to sequencing to establish a true threshold for calling positive based on the percentage of genome coverage obtained from sequencing. Additionally, 24 no-template

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controls (NTC) were included to demonstrate the specific detection of SARS-CoV-2 in samples, unaffected by background rates of formation of non-specific products from highly multiplexed amplicon-based sequencing. The cut-off of 1.8% genome coverage correctly classified 100% of positive cases, while 2 samples called negative by RT-PCR were just above the cut-off at 2% and 3% genome coverage, respectively (Fig. 1A.) No false positives were seen among the community negative and NTC samples. The genome coverage percentage for positive samples was closely related to the sample's cycle threshold (Ct) value from RT-PCR assay (Fig. 1B). A large proportion of samples (62 of 144, 43.1%) had >99% genome coverage which corresponded to a median Ct value of 23.61 (inter-quartile range, IQR: 18.37-26.26). Average depth of coverage was slightly higher in saliva samples compared to upper respiratory tract (URT) samples (nasopharyngeal and nasal swabs) ($p = 0.0281$) (Fig. 1C), but dependent mainly on the viral load in the sample represented by the Ct value (Fig. 1D). Limit of detection studies with synthetic SARS-CoV-2 reference genomes for sequencing-based detection of SARS-CoV-2 was determined to be 50 copies/ml (Fig. S1) and expected detection of variants from synthetic reference genome was also validated using this method (Fig. S2).

Variant analysis and phylogenetic classification

Comparative variant analysis on the SARS-CoV-2 genomes assembled from sequencing data was done for samples with >95% genome coverage (69 of 144, 47.9%) using the Wuhan/Hu-1/2019 genome as reference. Comparing samples originating from a single individual, samples from multiple timepoints, and those from differing sampling sites (upper respiratory tract or saliva), variants confidently detected (supported by >20x depth of coverage) were completely identical (Fig. 2A). This is contrast to a study in which throat swab and sputum from a patient sampled on the same day showed the presence of a unique variant in the throat swab, suggestive of independent replication in the two tissue sites[8]. Among the variants identified, a stop codon in ORF8 gene c.175G>T p.Glu59* - 28068G>T was observed in 6 samples coming from one individual, and 2 samples and one sample from two other individuals, respectively. Premature stop mutations in ORF8 have been reported among SARS-CoV-2 sequences in GenBank and GISAID initiative[33].

As the identity of variants among multiple samples from the same case were conserved, a single representative sequence from each case was used for the phylogenetic tree construction. A total of 28 cases (58.3%) were analyzed, as they had at least one sample satisfying the >92% genome coverage lacking stretches of N's required for phylogenetic analysis[34]. All sequences were identical or highly similar to sequences reported in previous analyses of SARS-CoV-2 cases in Singapore, and belonged to Clade O by GISAID

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nomenclature[35], and lineage B.6 by PANGOLIN system of nomenclature[36] and with respect to each other the 28 cases fit into 3 main clusters (Fig. 2B). One Case-28 which formed a single-case branch, harboured three unique variants M c.120C>T p.Ala40Ala - 26642C>T and ORF3a c.377G>A p.Arg126Lys - 25769G>A and orf1a c.6267G>T p.Glu2089Asp - 6532G>T in four different samples collected for this case.

Frequent detection of subgenomic RNA in clinical samples

The panel of primers for whole-genome sequencing of SARS-CoV-2 was specifically designed to also capture subgenomic RNA (sgRNA) sequences involving the fusion of the 5' leader sequence (first 72 nt of the genome) of the SARS-CoV-2 genome with the 5' end of each mRNA coding sequence, called the "body". The tiled design of primer pairs and inclusion of the primer targeting the 5' leader in both primer pools allows the capture of sequences corresponding to canonical sgRNA containing a consensus core sequence[24]. The relative abundance of each sgRNA was normalized by the mean genome depth of coverage of a sample to make comparisons across samples and sgRNA species. Among individuals with symptoms, sgRNA was found be relatively more abundant when found in URT (NP and nasopharyngeal) samples relative to saliva samples (unmatched) and was mostly detectable between -1 to 7 days since symptom onset (Fig. 3A). In both URT samples and saliva, the three most abundant sgRNA species were N, M genes and ORF3a. ORF10 was detected in only one of 68 evaluable positive URT samples, and was not detected in any of 59 positive saliva samples from symptomatic cases. This is in accordance with previous findings which found almost no subgenomic reads corresponding to ORF10[24,25,31]. Presence of sgRNA is considered an indicator of active viral replication[8,11] with more frequent detection in samples collected <8 days after symptom onset[11] and has been reported to persist up to 22 days[37] after onset of clinical symptoms Among samples in the present study, the persistence of sgRNA detection was observed in samples from 8-12 days since symptom onset and up to day 13 in saliva (Fig. 3A). Samples from asymptomatic cases also had prevalent sgRNA detection in URT samples 0-3 days since diagnosis (Fig. 3B). In contrast to URT samples, in saliva from asymptomatic cases, sgRNA could be detected in up to 5-6 days since diagnosis. No sgRNA was detected at 8 days since diagnosis. Individually assessed, detection rate of sgRNA progressively decreased over time (Fig. S3). Across all types of samples and cases, when detected, the relative total amount of sgRNA (sum of individual sgRNA) did not appear to be related to the viral load of samples as measured by the Ct values (Fig. 3C). However, for samples with Ct ≥28.67 (n = 80), 61 (76.25%) had no sgRNA expression while 100% of samples with Ct <28.67 (n = 64), had some sgRNA expression, for an overall sgRNA detection rate of 57.6% in all samples (Fig.

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3C). These results suggest that sgRNA is frequently detected in multiple samples types containing a minimal viral load related to Ct value in both symptomatic and asymptomatic cases. However, there is no relation between the abundance of sgRNA and Ct; following an approximate dichotomy of detection around Ct 28.7.

SARS-CoV-2 RNA fragments of differing lengths are captured by NGS

We observed that one of the consequences of tiling multiple primer pairs (in subsequence) to capture the entire known target template of SARS-CoV-2 in a highly multiplexed PCR-based NGS method, was the capture of longer inserts in addition to the inserts expected to be formed from amplicons of length 130-178 bp for which primer pairs were originally designed (Fig. S4A). The origin of the longer inserts was the formation of amplicons between a given forward primer and a reverse primer that is 1-, 2-, 3-, 4- and so on-displaced in the subsequence of primer pairs in the pool of primers (Fig. S4B). We reasoned that the more degraded the viral RNA template, the more the capture of short inserts (representing short fragments) would be favoured, due to the unavailability of intact RNA template for longer amplicons to form (Fig. S4C). Analysis of the sequencing data for the distribution of insert lengths per sample, showed that 2 to 3 distinct ranges of insert lengths could be captured per sample, and the number of sequencing reads supporting inserts in each insert length group could vary substantially between samples (Fig. 4A). Based on the dominance of inserts of lengths either 70-150 bp or 220-350 bp in sequencing data (and not other longer insert length groups), we chose these two insert length groups for further study and refer to them as “short” and “long” fragments, respectively. The cumulative number of short and long fragments (all reads mapping to SARS-CoV-2 from all potential primer combinations across the targeted genome) for samples were determined. It is noted that the sizes of the amplicons for N1 and N2 targets from the CDC RT-PCR assay initially used to characterize the samples are 72 bp and 67 bp, allowing sensitive detection of even very small fragments of virus RNA. It follows that such an RT-PCR assay would not be able to distinguish between long and short fragments that may exist in a given sample, but would give a cumulative read-out comprising all fragments. In 144 samples positive for SARS-CoV-2 by the CDC RT-PCR assay, the sequencing read counts for long and short fragments were each correlated with Ct value as expected, diminishing as the Ct value increased or presumed viral load decreased. However, the longer fragments had a steeper change in abundance relative to Ct value, become disproportionately fewer relative to short fragments in samples with low viral load reflected by later Ct values (Fig. 4B). We hypothesize, given a mass of viral RNA (a mix of intact and degraded RNA), measurable as a Ct value by an assay like the CDC RT-PCR assay with very short amplicons, that at later Ct values, previously long fragments have been converted to short fragments due to degradation of viral RNA, and contribute in turn to the

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observed read counts for short fragments which continue to maintain a relatively higher count from this contribution. Consequently, degradation of viral RNA more rapidly leads to the diminishing read counts for long fragments observed at late Ct values. This suggests that counting long fragments or the relative distribution of long to short fragments would provide a more accurate read-out for presence, if any, of intact viral RNA in samples.

We devised a viral fragmentation score, VFS (long to short fragment count ratio) to capture this variability in distribution of fragment lengths. VFS showed a moderate correlation with Ct (R^2 = 0.65 in NP and nasal swabs, and R^2 = 0.74 in saliva), suggesting relative abundances of long and short fragments within a sample are not captured fully by its Ct value, despite detection of long fragments diminishing with increasing Ct values (Fig. 4C). For 5 samples sequencing libraries were repeated from RNA extracts and VFS were shown to be within reproducible range for the same sample (Table S1). To rule out a fully Ct value-dependent behaviour of VFS, we made use of intact synthetic SARS-CoV-2 RNA genomes and prepared sequencing libraries from serial dilutions of synthetic RNA spiked in to negative clinical matrix and extracted via routine procedures. Synthetic RNA mimics SARS-CoV-2 genome but is composed of 6 fragments of 5000 bp each representing the genome, which we take as a relatively intact starting material. For the amounts of synthetic RNA spiked in- 250000, 25000, 2500 and 500 copies/ml - the Ct values measured by the same CDC RT-PCR assay were on average 24.4, 27.97, 31.73 and 33.45, respectively. Since the RNA in the serial dilutions are similarly intact, being derived from the same stock of synthetic RNA, the increase in Ct values are attributable only to the total copy numbers of RNA detectable by the RT-PCR assay. However, the VFS for the serial dilutions of synthetic RNA, do not show the same degree of decrease as the trend for increasing Ct values and ranged with a median: 0.384 (IQR: 0.289-0.449) across all 4 serial dilutions (Fig. 4C, Fig. S5). This experiment shows that factors besides total viral RNA amount measured by a Ct value (with short PCR amplicons) determine the VFS, which depends on the presence of long fragments, more of which is likely to be present in a sample with more intact. This is supported by the wide variation in VFS that was observed in clinical samples, which was higher in saliva relative to URT samples (p = 0.0035) and ranged from 0.0433 to 184.9 in saliva (n =58, median: 0.267, IQR: 0.113-0.68) and from 0.02073 to 14.38 in URT samples (n =81, median: 0.124, IQR: 0.074-0.246) (Fig. 4D). On the basis of VFS, on average, saliva samples in this study had less fragmented SARS-CoV-2 RNA. However, a relation with the disease time-course, symptomatic/asymptomatic status as an explanation for this observation cannot be ruled out. Importantly, what constitutes a high enough VFS score to be considered clinically relevant as infectious virus with intact RNA is not established.

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Overall, these results support the presence of a wide range of fragmentation profiles in clinical samples which is readily detectable by NGS.

Correlation of viral fragmentation scores (VFS) with clinically relevant measures of infectiousness

As our NGS method was able to quantify relative abundances of short and long fragments representing less and more intact virus, respectively, next we determined if VFS was related to other clinical correlates of infectivity. This is particularly relevant as it is well-recognised that RT-PCR positivity alone, particularly from a test designed for short targets, does not translate to viable virus with infection potential[5,6]. We have already shown that VFS is moderately correlated with Ct value (Fig. 4C), which in itself is considered a proxy for infectious potential of SARS-CoV-2 in clinical samples based on the culturability of virus isolates[8,11,12,22,38,39] although with widely differing Ct cut-offs. In multiple studies, no live virus has been culturable after eight days in non-immunocompromised patients[2,10,14]. The typical clinical profile of the symptomatic cases in our study was immunocompetent with presentation of mild to moderate respiratory symptoms. Compared directly, VFS and days since symptom onset was not strongly correlated in both URT and saliva samples over the full duration of the symptom onset (days -1 to day 14) (Fig. 5A and 5B). However, transposing a VFS derived from a sample with known integrity i.e. synthetic RNA (refer to Fig. 4C), subject to the same extraction and sequencing procedure as the clinical samples, we selected a cut-off of 0.382 to separate samples with intact RNA from those without. We noted that with this cut-off value, no URT samples (total 69) collected >8 days since symptoms (n= 36) qualified as having intact RNA (Fig. 5A, top left quadrant). In saliva samples (total 46), only 1 (5.26%) of 19 samples collected >8 days since symptoms had a VFS indicative of intact viral RNA (Fig. 5B). Of 37 URT samples collected ≤8 days, 15 (40.5%), and of 29 saliva samples collected ≤8 days, 16 (55%) had VFS greater than 0.382 suggesting intact RNA profiles. These results suggest about 50% of samples collected ≤8 days have relatively fragmented RNA, in accordance with observations made in previous studies where about 29%-42% of samples with high viral load inferred from low Ct or from ≤8 days did not recover live virus[9,11,22]. Among asymptomatic cases, 25 (96%) of 26 samples had low VFS below 0.382 cut-off, from 0 to 8 days from diagnosis, suggesting that viral RNA from most asymptomatic cases is fragmented (Fig. 5C). For one case, VFS 3.36 of saliva sample collected on the day of diagnosis was matched with URT samples (NP and nasal swabs) from the same case with VFS of 0.79 and 0.14, suggesting a less fragmented SARS-CoV-2 RNA in saliva even at same timepoint. Overall, VFS differed significantly between samples collected ≤8 days from symptoms and those after 8 days for cases with information on symptom onset (Fig. 5D, left), but it was difficult to find a time measure that trended with

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VFS for asymptomatic cases (Fig. 5D, right). For cases with multiple longitudinal samples, VFS were tracked with respect to time from symptom onset and were generally observed to be higher early between days -1 to 6 and generally decreased with time reaching levels similar to those seen asymptomatic cases through the course of the asymptomatic infection (Fig. 5E).

We observed no linear correlation between increasing VFS and total sgRNA abundance (Fig. 6A), but there was a significant difference in VFS of samples with any sgRNA compared to those with none, showing a dichotomous distribution ($p<0.0001$) (Fig. 6B). The dichotomy of distribution was related to the VFS cut-off of 0.382 determined earlier. All 33 samples with VFS ≥0.382 had some sgRNA expression, whereas 58 (54%) of 107 samples with VFS <0.382 had no sgRNA (Fig. 6A, 6B). When individual species of sgRNA were separately considered, interestingly, there was an inverse correlation with the VFS for S and N genes only, and not for other most abundant sgRNA M gene and ORF3a (Fig. 6C). No other sgRNA species showed a correlation with VFS (not shown), suggesting a specific effect of intact RNA on the abundance of S and N genes expression in clinical samples.

Finally, we demonstrate that the viral fragmentation score (VFS) can be translated into a simple multiplexed RT-PCR assay deliberately composed of a long amplicon of 240 bp and short amplicon of 70 bp to detect the long and short fragments observed in clinical samples using NGS. In a set of 20 clinical samples, a good correlation was seen between VFS from NGS and from the difference in Ct signal of short 70 bp and Ct signal of long 240 bp amplicon, here referred to as a viral fragmentation index (VFI) (Fig. 7A). For 7 samples with low VFS, 240bp amplicon was not detectable by PCR, potentially reflecting the higher sensitivity of NGS for detection due to the interrogation of the whole genome with multiple targets, but still in line with the expectation of continued detection of short 70 bp amplicon in these samples. For 13 samples with detection of both 70 and 240 bp by RT-PCR, the delta Ct (70bp-240bp) VFI was correlated with the VFS (R^2 =0.79, $p<0.0001$) (Fig. 7A, right). Over days since symptom onset, the VFI became more negative, indicating the increasingly greater abundance of short 70 bp amplicon, likely due to increasing fragmentation of viral RNA over clinical course of the disease (Fig. 7B).

Discussion

We used next-generation sequencing (NGS) to characterize clinical samples related to the spread of SARS-CoV-2 infection in a cohort of migrant workers in Singapore, collected from different tissue sites and over serial timepoints. The design of the NGS panel allowed virus

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detection, genomic variant and sgRNA analysis. Further exploiting the design of the NGS panel for whole-genome sequencing of the virus, we have shown for the first time to our knowledge that NGS can be used for the detection of differential fragment lengths of viral RNA in clinical samples, potentially related to the integrity and transmissibility or infectiousness of the virus. We present a novel measure of fragmentation of viral RNA, which could be translated to a test for transmission potential of a current infection.

We show that relative to the gold-standard RT-PCR assay, NGS is a sensitive and specific method of detection of SARS-CoV-2, with 100% detection of virus in clinical samples known to be positive by RT-PCR. Additional detection of virus fragments spanning ~3% of the virus genome in two RT-PCR negative samples, highlights that NGS may be a more sensitive diagnostic method for low levels of SARS-CoV-2. This is attributable to the targeting of the whole genome of the virus in NGS compared to RT-PCR assays targeting specific loci which may not be present among the virus fragments in a sample low levels of SARS-CoV-2. In agreement with other NGS-based detection methods[40–42], sensitivity was high with analytical limit of detection determined to be 50 copies/ml. The detection of SARS-CoV-2 was quantitative, as the genome coverage % and the mean depth of coverage of a sample which was closely related to a Ct value from an orthogonal RT-PCR assay. As this method incorporates molecular barcodes in the primer sequences, the number of consensus reads corresponding to various regions of the genome are representative of the copy number of viral RNA fragments that are present during library preparation. Other SARS-CoV-2 NGS methods do not report similar quantitative capacity[40–42]. The quantitative feature of the method allows counting of reads to correlate with other parameters as described further on. Genomic variant analysis showed complete similarity of variants in multiple samples derived from a single case, suggesting no independent replication or generation of minor variants over time course of infection, in contrast to previous reports[8,9]. Phylogenetic analyses was possible on assembled SARS-CoV-2 genomes from 28 cases and showed that all cases were infected with virus belonging to the Clade O, lineage B.6, known to be circulating in Singapore and India.

Besides the sensitive detection of virus and identification of genomic variants, the method provided novel insights into two aspects of SARS-CoV-2 infection which have become increasingly more relevant in the context of predicting the onward transmission potential of an infection. In this work, we were able to elicit information on the presence of subgenomic RNA in clinical samples as well as the relative degree of fragmentation of the viral RNA in a sample.

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Detection of sgRNA has been used as a proof of viral replication in infected cells and decline over days 10-11 from infection[8]. sgRNA detection outlasted successful virus culture and was a poor predictor of successful virus culture[14], or showed moderate agreement with virus culture, and was detected in 18 (81.8%) of 22 specimens collected <8 days after symptom onset and in 1 (9.1%) of 11 specimens collected ≥9 days after symptom onset[11]. Due to the prolonged detection of sgRNA in clinical samples including up to 22 days since start of illness, sgRNA may not be a marker of active replication but remain detectable in clinical samples due their stability[37].

In this study, abundant sgRNA was detected in clinical samples including prolonged detection in a saliva sample taken 13 days from illness onset from a symptomatic case. In samples with high viral loads, sgRNA was consistently detected, but became undetectable in ~75% of samples with low viral loads (Ct≥28.67), suggesting that both viral load and sgRNA stability account for its detection. This study, to our knowledge, is the first one to demonstrate direct sgRNA detection in samples from immunocompetent asymptomatic individuals[43] although at lower levels than symptomatic cases, in line with the non-zero but reduced transmission potential of asymptomatic carriers[44] .

It is increasingly becoming apparent that positive detection of virus RNA by RT-PCR is unrelated to presence of infectious virus, as viral RNA shedding can persist even after resolution of clinical symptoms of both mild and severe disease[8–16]. While more ill patients have generally longer detection of RNA, persistent positivity by PCR is seen in patients with mild illness as well as in asymptomatic cases[5]. A better measure of infectiousness is the culture of live virus from clinical specimens as successful virus growth is reliant on the presence of intact whole virions with complete RNA genomes. By this measure, samples taken more than 8 days since symptom onset in immunocompetent patients, do not have infectious virus as no live virus could be cultured from them[8,11,22]. In immunocompromised patients or those with severe illness, live virus could be isolated up to 14 days[12], 20 days[14] and much longer in severely immunocompromised patients[45]. Ability to culture live virus has been shown to be similar in asymptomatic and symptomatic indivduals [46–48]. Some studies have correlated viral loads measured by Ct value with ability to culture live virus[8,11,14,22,38,46], and no viral growth was reported based on a Ct value cut-off (varying between >24 and ≥35)[22,38,48]. Intriguingly, a number of studies have reported limited correlation between Ct value (or viral load) and success of virus isolation[49,50]. Samples with low Ct values (Ct<23), constituted 28.6% of samples with unsuccessful viral culture [50], and conversely, samples with low viral loads (Ct >35) could harbor viable virus[49,50].

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The observation that not all samples with high viral loads generate live virus, suggest that factors other than viral genome copies are important. The topmost factor would be viral integrity, whether for a small or large viral load. Only the full-length intact viral RNA would represent the virus fragment that is capable of infection. It is understood that the processing of sample in the laboratory (extraction, enzymatic reactions) would lead to some degree of fragmentation, and the use of primer-limited amplicons would artificially limit fragment lengths but relative to a sample with highly fragmented viral RNA, a sample with intact viral RNA would contain more long fragments relative to short fragments.

In this work we have shown for the first time that NGS data can not only provide total viral RNA abundance information, it can also characterize the viral RNA fragments by length. This was possible due to combination of consensus read counting (related to the original copy numbers of virus RNA in a sample undergoing library preparation) and the tiled configuration of the primer panel which could capture long fragments, if present. In other words, the more intact or full-length RNA that is present in a sample, the more long fragments would be captured by the method. The relative abundances of long and short fragments was converted to a viral fragmentation score (VFS), representing the relative integrity of the virus RNA in the sample and was shown to be related to the viral load measured as Ct value by an RT-PCR assay. It is important to highlight that the CDC RT-PCR assay targets particularly short amplicons of about 70 bp, which means it would accurately detect intact RNA when present, but would continue give an abundant signal even when largely fragmented RNA was present in a sample. At early Ct values (representing abundant viral load), the relative abundance of long fragments were as much as 100-185 times more than short fragments (very high viral fragmentation score) and could not have resulted simply as a result of the specific sequencing method.

To further address if the observed relative abundances were simply a function of the copy number of template subject to sequencing, irrespective of its starting length, we showed using synthetic SARS-CoV-2 RNA, that for relatively intact RNA template molecules the VFS remains constant even over 500-fold reduction in starting copy numbers. An empirically determined cut-off from synthetic RNA applied to clinical samples was able to separate all samples collected >8 days since illness onset as having predominantly fragmented RNA. This correlated very well with the failure to culture live virus from clinical samples collected after 8-9 days of illness in immunocompetent patients [8,11,22,38,47,51]. Conversely, based on the cut-off, about 50% of case with VFS <0.382 (hence lesser intact RNA) were collected ≤ 8 days from symptom onset. This fraction mirrors those observed previous studied with about 29%-42% of samples high viral inferred from low Ct or from ≤8 days did not recover live virus[9,11,22].

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Another variable to consider is the sample type. Viral load and duration of positivity tends to be greater in lower respiratory tract samples (sputum) compared to throat and nasal swabs[5,52]. Accordingly, prolonged ability to culture virus has been reported for samples from severely ill patients with mostly lower respiratory tract samples[14], compared to the success rate in upper respiratory tract samples[46]. In the present study, upper respiratory tract samples (nasopharyngeal and nasal swabs) and oropharyngeal saliva samples were compared. Oropharyngeal saliva contains secretion of the salivary glands mixed with sputum from lower respiratory tract[53], hence is more akin to lower respiratory tract samples. In line with this, we observed higher VFS (more long fragments) in saliva samples on average compared to URT samples.

One study has looked at the potential of RT-PCR assays to determine the integrity of viral RNA and suggested that strong correlation between the levels of detection of multiple amplicons spanning the intact genome is indicative of viral integrity (and demonstrated this with live virus culture)[39], as opposed to non-correlated levels. In the light of findings in this study and especially with the evidence that both high viral load samples and low viral load samples can produce unexpected live virus culture results, another direct measure of viral integrity is urgently needed.

Despite the large body of knowledge surrounding viral infectiousness, several gaps and hurdles remain. First, Ct value as a surrogate measure of infectivity is variably correlated with success of viral culture and multiple RT-PCR assays with Ct scales that are not directly comparable are in clinical use (evidenced from the dramatically different Ct cut-offs derived based on culture positivity [22,38,48]). Second, typical RT-PCR assays are designed to detect short target templates and will readily amplify small amounts of fragmented viral RNA, precluding any consideration of integrity of the viral RNA. Third, duration since symptom onset has been shown to correlate with success of viral culture, however, all measures suffer from recall bias [22,46,54]. Fourth, the viral culture test is labor intensive and requires the Biosafety Level 3, which precludes it from being established in all diagnostic laboratories, and suffers from variations in accuracy and permissiveness of cell lines. Accurate measurement of infection potential becomes particularly relevant as vaccines against SARS-CoV-2 that immunize against COVID-19 disease become available, but transmission capacity of an immunized individual remains unknown[55,56].

We emphasize that the viral fragmentation scores (VFS) determined in this study are relative and post-laboratory processing and no determination of absolute fragment lengths contained in a sample has been attempted. The viral culture assay is the closest surrogate of this measure. Further work to correlate the insert length or an RT-PCR-based measurement of

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integrity to virus culture is necessary to further these findings. There are important limitations to this study. The use of the exact cut-off of VFS to categorize samples into clinical groups may not universally apply. Nonetheless, the basic premise of the argument that more intact virus would reflect in more longer fragments in a clinical sample would universally apply. As the study's main conclusions are based on NGS, with some comparison to RT-PCR results, without evidence from virus culture studies it cannot be ruled out that some of the observed infectivity measures are correlated and result from a feature of the specific NGS method.

In conclusion, we have applied NGS to comprehensively characterize longitudinal samples collected from different sites. NGS is an enabling tool that provides sequence-related information for which it is primarily designed, and also information from size and length dimensions. Based on this, we identify fragment length differences among clinical samples which are correlated to clinical features of infectiousness of SARS-CoV-2, quantification of which could be incorporated as relevant and straightforward measure to determine infection potential.

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Competing interests

The authors declare no competing interests.

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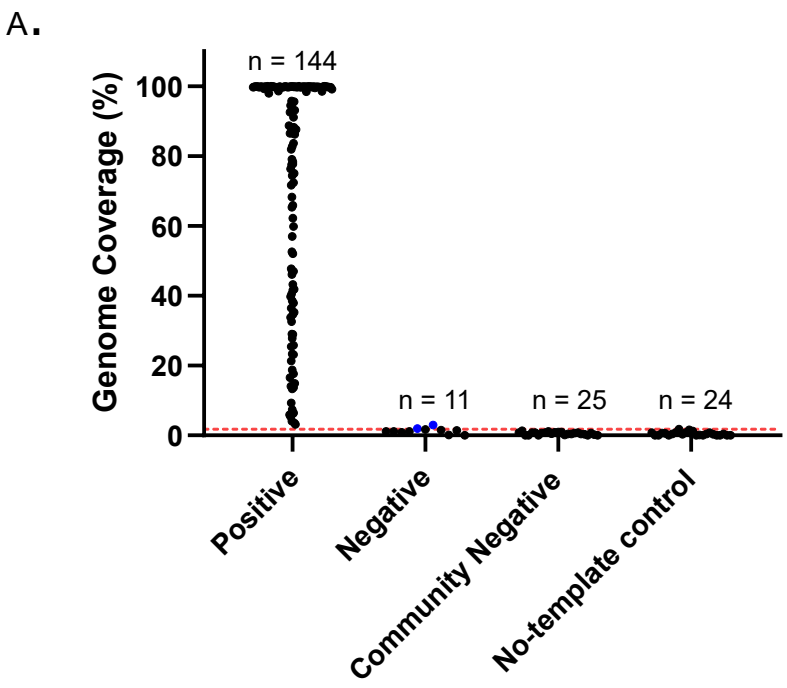

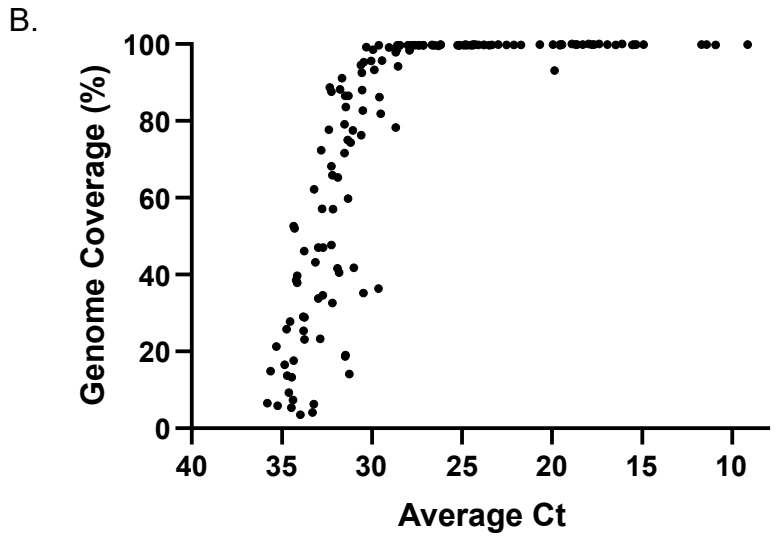

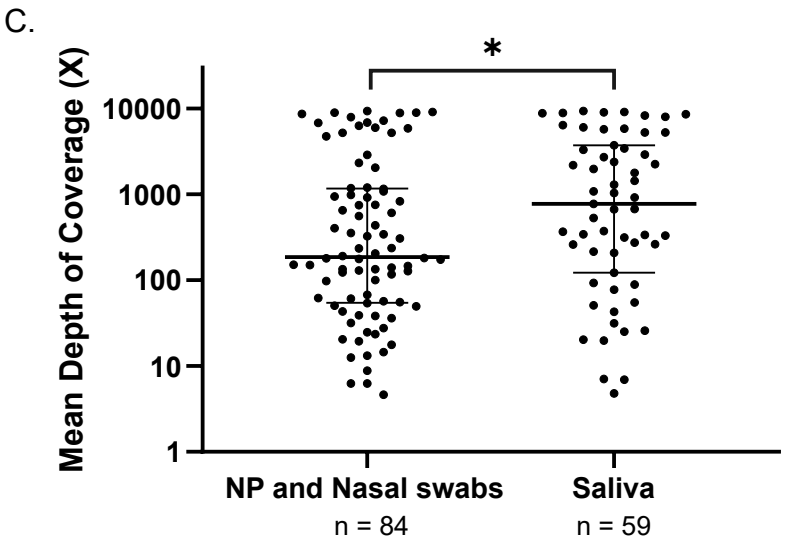

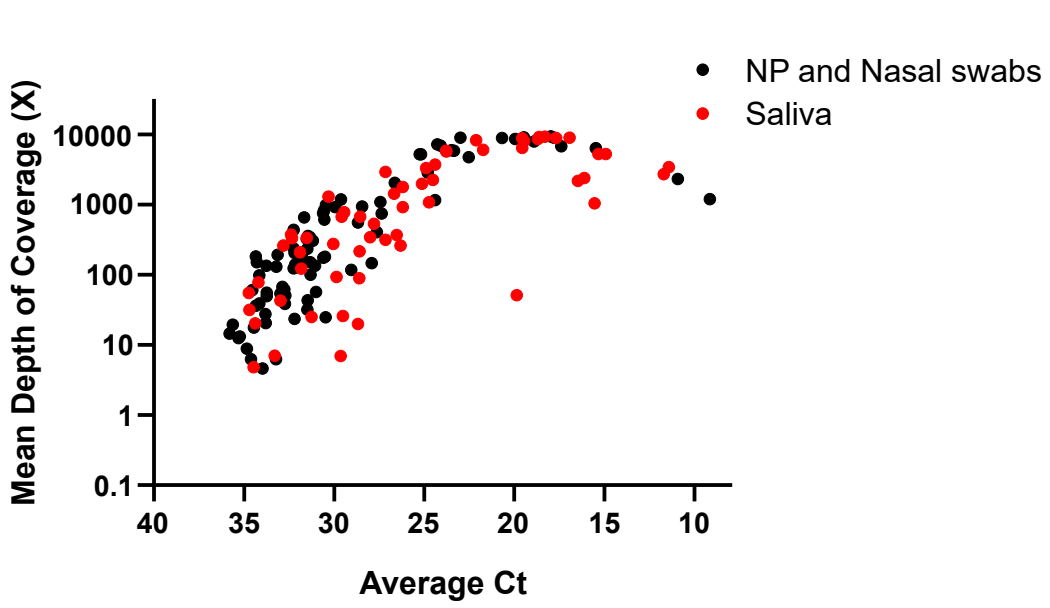

Figure 1. Next-generation sequencing (NGS) allows quantitative, sensitive and specific detection of SARS-CoV-2 in clinical samples (A) Grouped plot showing the breadth of genome coverage for samples including positive and matched negative samples from this study, confirmed negative samples from the community, which are unlikely to have any SARS-CoV-2 and no-template control (NTC) samples run parallelly with the samples over multiple batches of library preparation for sequencing. The cut-off genome coverage for positive samples was determined to be ~1.8% based on confirmed negative samples from the community (indicated by the red dotted line). Two of 11 samples negative by RT-PCR were just above the cut-off qualifying as positive for SARS-CoV-2 by sequencing. It remains possible that samples testing negative RT-PCR from the present study have very low-level positivity, which is at the limit of detection of the PCR assay. **(B)** The genome coverage (%) of SARS-CoV-2 by NGS (≥1x depth of coverage) is related to the original viral load in the clinical sample as measured by Ct value in RT-PCR. For clinical samples (n = 144) as Ct decreases, the % genome coverage reduces. **(C)** Mean depth of coverage is marginally higher in saliva samples (median: 186.7x, IQR: 54.33-1175x) relative to upper respiratory tract samples (URT) -nasopharygeal (NP) and nasal swabs (median: 776.8x, IQR: 122.5-3731x). *Mann-Whitney test, p = 0.0281. **(D)** Mean depth of coverage achieved is related to the viral load of the sample as measured by Ct value and decreases with increasing Ct value in both saliva and NP and nasal swabs.

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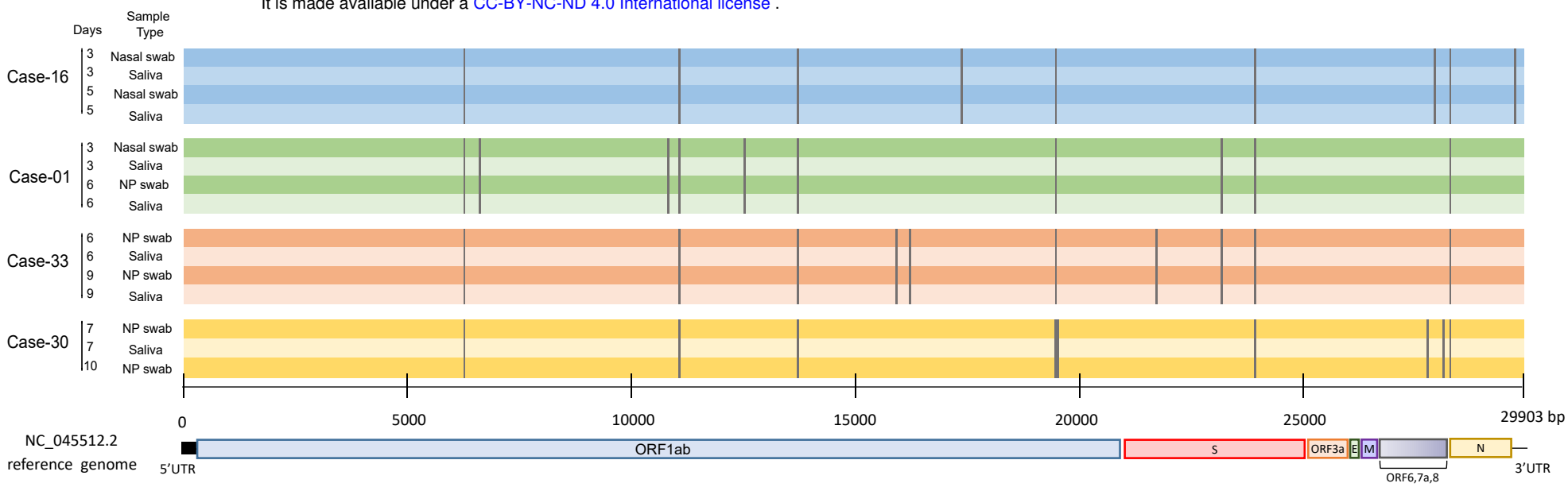
A.



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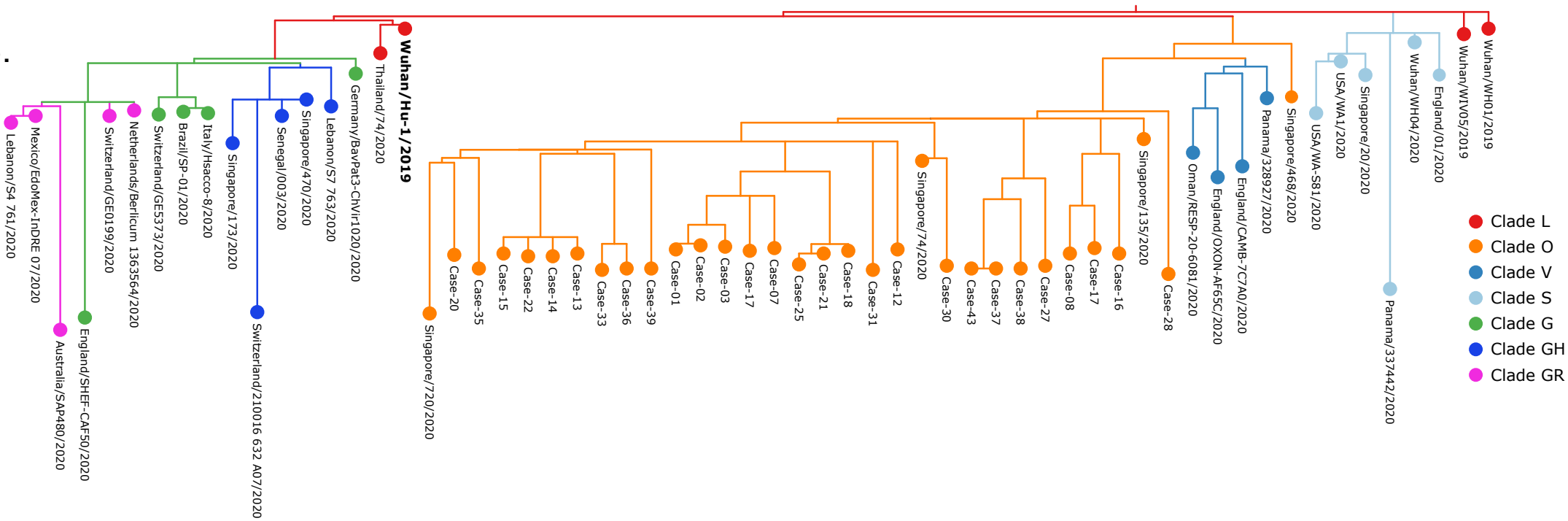

Figure 2. Genomic sequence analysis of SARS-CoV-2 in samples from multiple sites and over serial timepoints. (A) Genetic variant profiles of sequenced SARS-CoV-2 genome relative to the Wuhan/Hu-1/2019 reference from 4 representative cases with samples from multiple sites (NP or nasal swab or saliva) and over different time points since symptom onset (days). Genomic regions are depicted by shaded areas colored according to the case, and the grey lines represent the position of the detected variants. For each case with multiple samples each with >95% genome coverage (16 cases, not all depicted), identities of confidently called variants were conserved among the case's samples. **(B)** Phylogenetic tree of SARS-CoV-2 genomes from 28 cases relative to each other and to selected samples representing 7 GISAID clades (branches colored by clades). Cases from this study all belong to GISAID Clade O (orange branch) and cluster with each other and other Singapore samples. Phylogenetic reconstruction was performed using Nextstrain (https://nextstrain.org/) and GISAID (Global Initiative; https://www.gisaid.org).

Figure 3

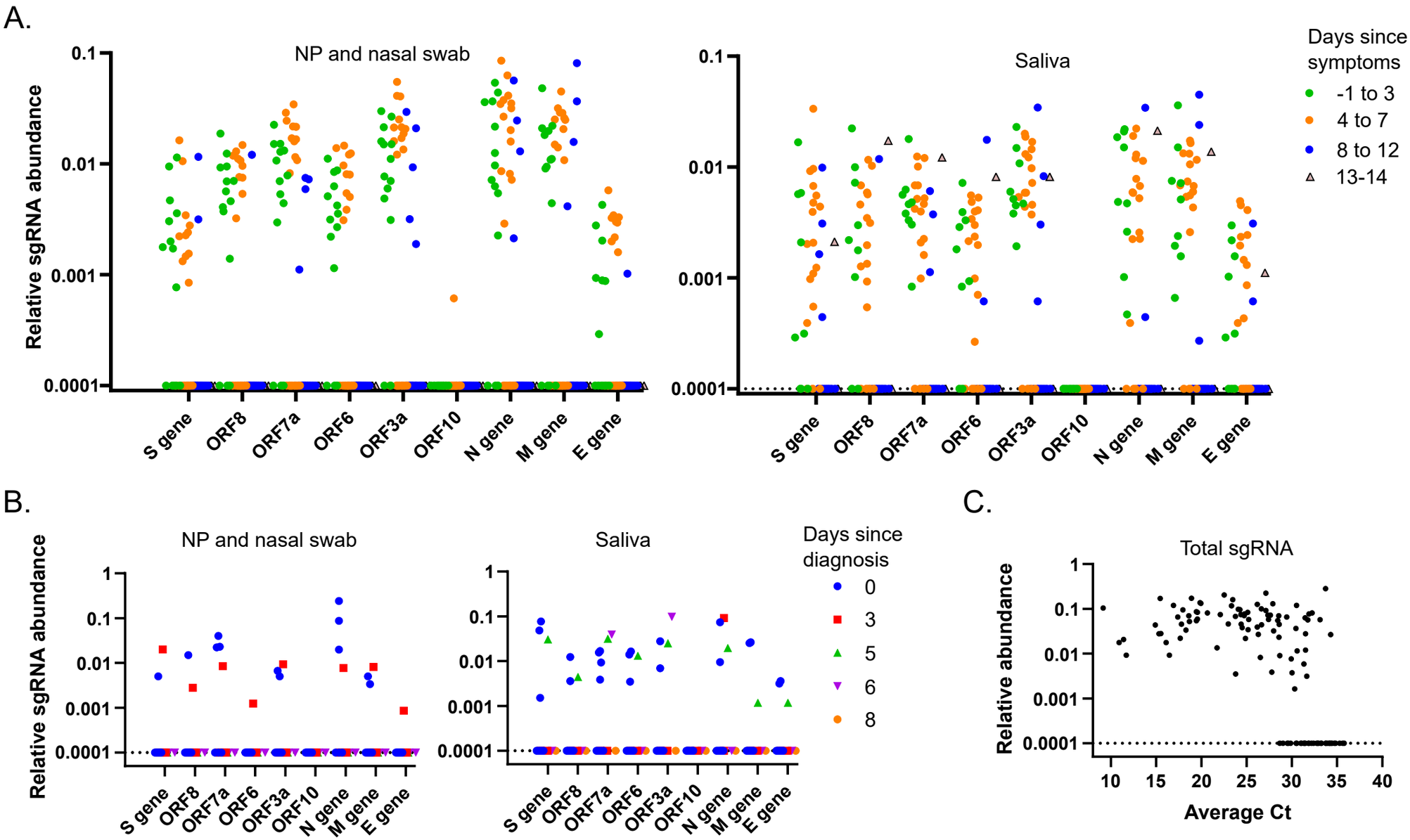

Figure 3. Detection of subgenomic RNA (sgRNA) in samples from symptomatic and asymptomatic cases over time. (A) In symptomatic cases, sgRNA species were abundantly detectable in both NP and nasal swab (URT) and saliva samples, and showed persistence up to 13 days since symptoms. Positive detection of sgRNA was largely within -1 to 7 days since symptom onset. N, M genes and ORF3a were the most abundant sgRNA in both sample types, while ORF10 was detected in only one sample. **(B)** In asymptomatic cases, sgRNA was most detectable in samples collected 0-3 days since diagnosis in both URT and saliva and was seen to persist up to 5-6 days since diagnosis in saliva. (C) Amount of total sgRNA, when detected, was not correlated with Ct value, but showed a Ct-related drop-off in detection, where 76.25% (61 of 80) samples with Ct≥28.67 did not have any sgRNA. Graph combines URT and saliva samples from symptomatic and asymptomatic cases. Zero values have been converted to 0.0001 to allow plotting on logarithmic scale and cluster on y-axes line at 0.0001.

Figure 4

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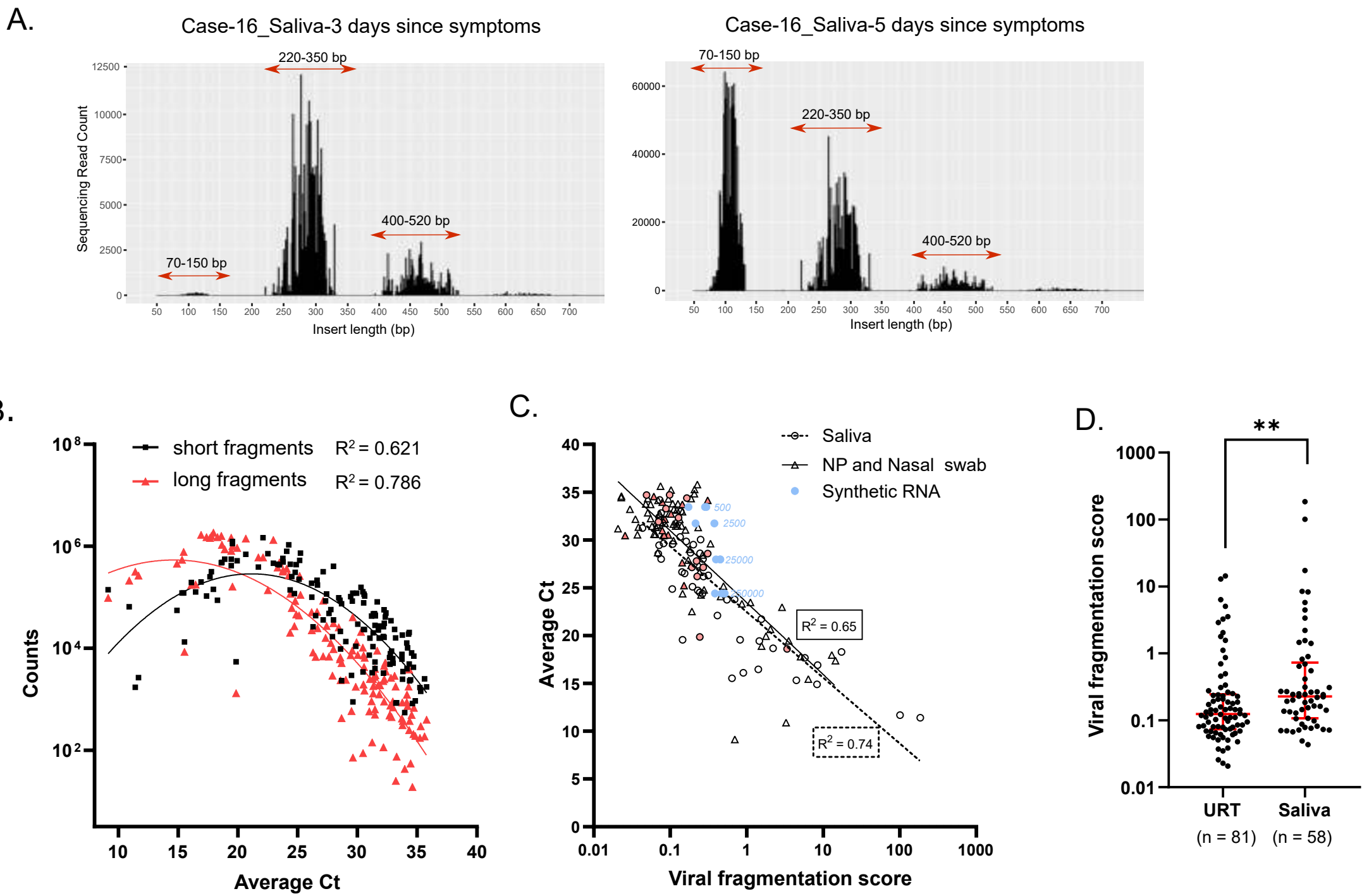

Figure 4. SARS-CoV-2 fragments of differing lengths can be detected by NGS as short or long inserts with varying relative abundances. (A) Histogram of sequencing read counts supporting insert lengths of ranges 70-150 bp, 220-350 bp, and 400-520 bp. Insert length distributions in longitudinal saliva samples from a single case are shown as examples. The relative abundance of insert lengths changes from a dominant 220-350 bp (long inserts) distribution in a sample taken 3 days from symptom onset, to a more abundant 70-150 bp (short inserts) distribution prominent in a sample taken 5 days from symptom onset. Insert lengths are representative of viral RNA fragments lengths. **(B)** Long and short fragment counts are each correlated with the Ct value of the sample measured by the CDC RT-PCR assay. Long fragments have a steeper decline in abundance, becoming differentially fewer compared to short fragments at Ct values greater than 25. URT (NP and nasal swab) and saliva samples are plotted together. **(C)** Long fragments count/short fragments count = viral fragmentation score (VFS) is moderately correlated with Ct value of a sample, in both URT and saliva samples. R2 values of correlation are shown. Pink-filled circles represent asymptomatic cases. Blue circles represent synthetic RNA samples of known integrity that generate a considerably constant VFS (median: 0.384, IQR: 0.289-0.449) across Ct values 24.4-33.45 over 500-fold serial dilution of synthetic RNA. Numbers next to blue circles are the concentrations in copies/ml of synthetic RNA. **(D)** Viral fragmentation scores are significantly higher across saliva samples compared to URT samples. Red lines represent median and interquartile ranges. **Mann-Whitney test p = 0.0035.

Figure 5

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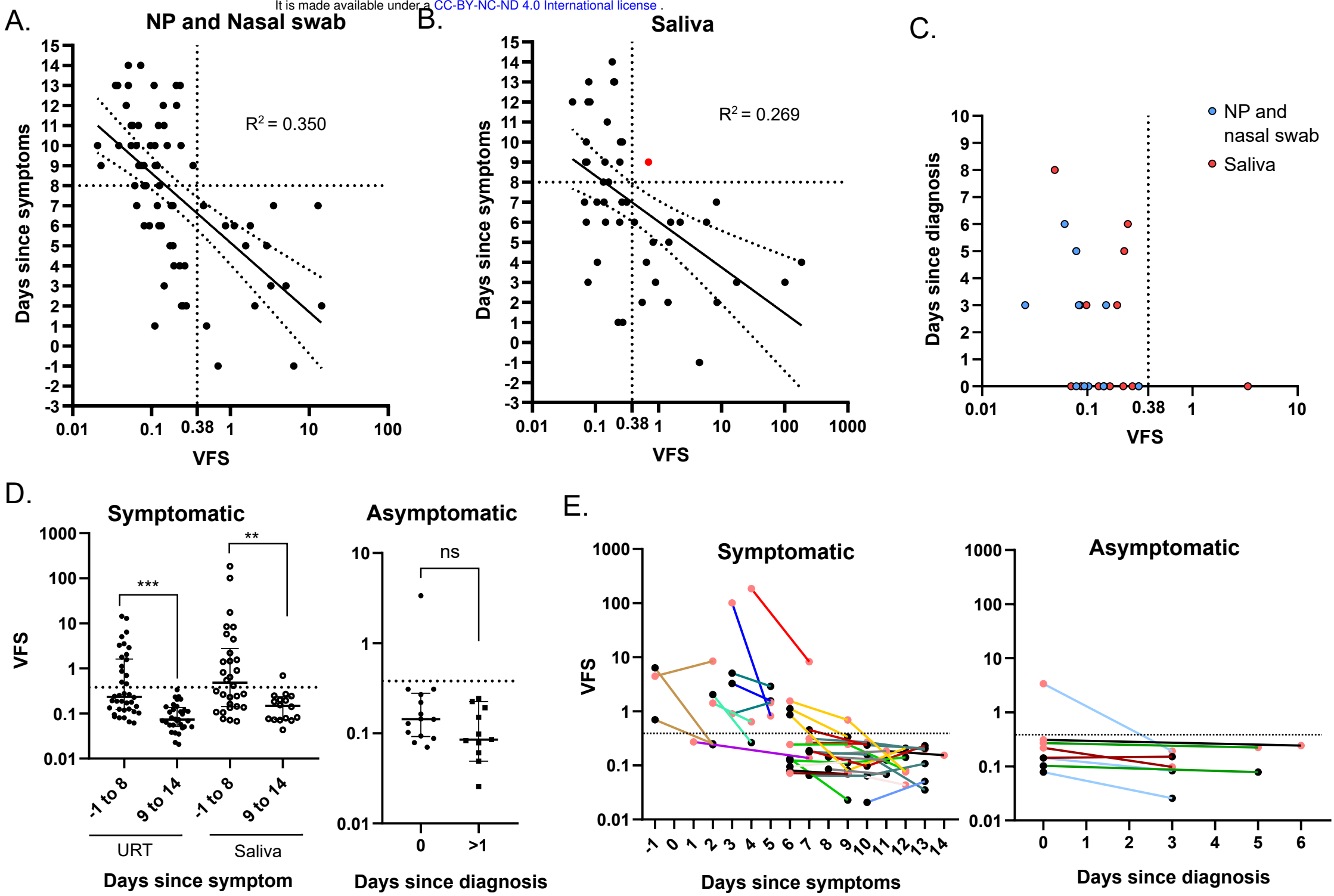

Figure 5. Viral fragmentation score is related to the clinical time-course of SARS-CoV-2 infection. In symptomatic cases, the relative amount of long fragments (viral fragmentation score, VFS) decreases with days since symptoms in both **(A)** URT and **(B)** saliva samples. With the exception of one saliva sample (red circle), beyond 8 days since symptoms, VFS does not exceed the cut-off of 0.38 (dotted line) estimated for intact RNA based on synthetic SARS-CoV-2 (upper left quadrants). For samples collected ≤8 days since symptoms onset, 15 (40.5%) of 37 URT samples and 16 (55%) of 29 saliva samples exceeded the cut-off (lower right quadrant). The fitted regression lines and 95% CI error are shown on graphs. **(C)** Most (96%) samples from asymptomatic cases had low VFS. **(D)** (Left) VFS differ significantly in URT and saliva between samples collected ≤8 days after symptoms onset and later samples.***Mann-Whitney test $p<0.0001$, **$p=0.0017$. (Right) No significant difference between VFS from samples collected on day 0 of diagnosis and later samples in asymptomatic cases (URT and saliva samples combined). Median and IQR lines are shown. **(E)** Matched longitudinal samples from 15 symptomatic cases (left) and 4 asymptomatic cases (right) and VFS. Each case is colored by a different line. Lines marked by pink ends are saliva samples while the rest are URT samples.

Figure 6

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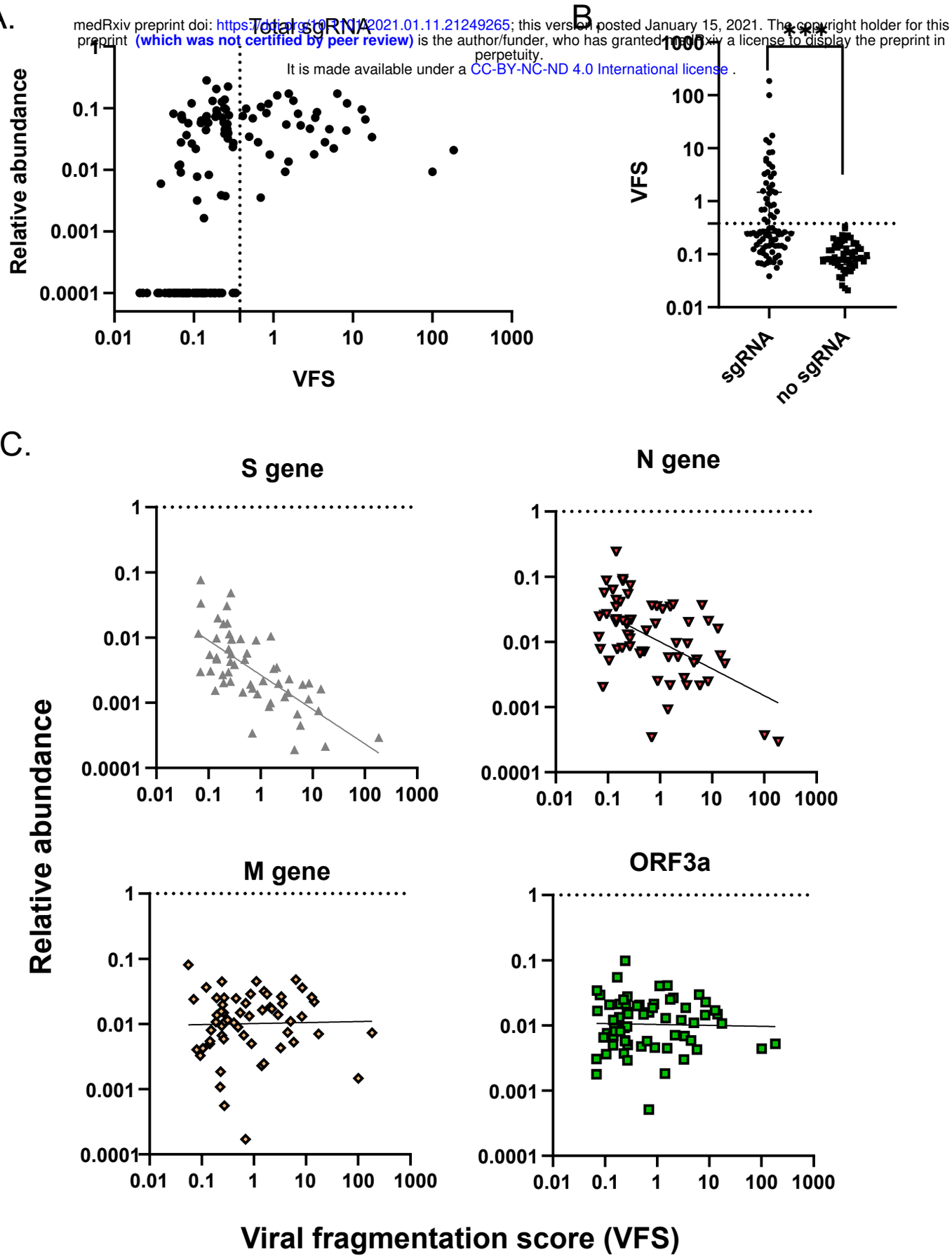

Figure 6. Profiles of subgenomic RNA (sgRNA) with relation to viral fragmentation score. (A) Across all sample types, sgRNA expression begins to tend to zero when VFS is low and a cut-off of 0.382 (dotted line) separates, 33 samples, all of which have VFS ≥0.382 and sgRNA detected, and 58 (54%) of 107 samples with VFS <0.382 having no sgRNA. **(B)** Significant difference in VFS between samples with zero or any sgRNA detected. ***Mann-Whitney test p<0.0001. Dotted line is VFS cut-off of 0.382. **(C)** S gene and N gene abundances are inversely related to the VFS, but other abundant sgRNA E gene and ORF3a are not.

Figure 7

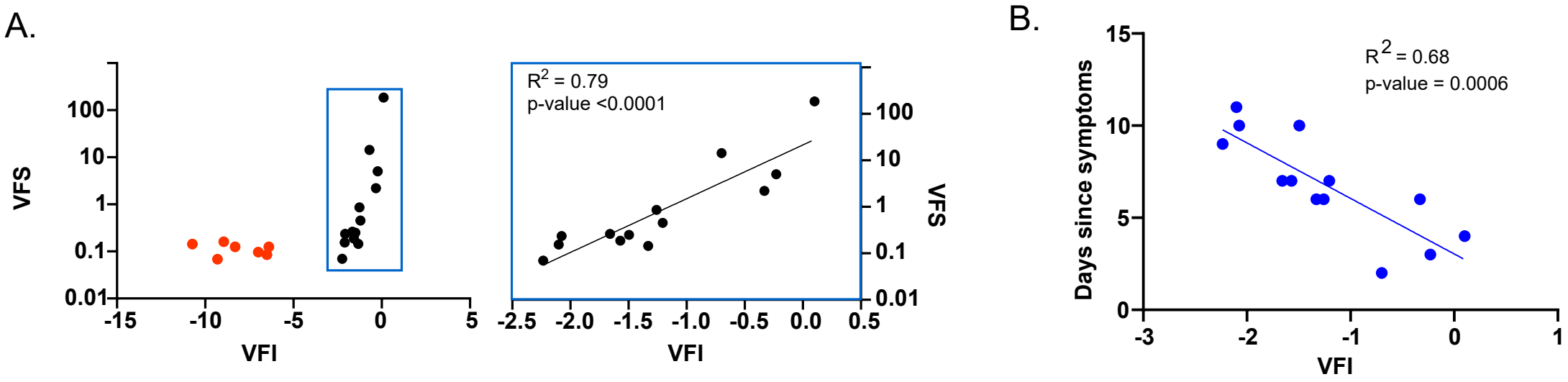

Figure 7. Viral fragmentation score can be captured in a multiplex RT-PCR assay for long (240 bp) and short (70 bp) amplicons. (A) Translation of the VFS obtained from NGS to an RT-PCR assay with calculation of difference in Ct value of short to long amplicon (Ct_70bp-Ct_240bp) for 20 clinical samples. The deltaCt value is referred to as the viral fragmentation index (VFI). (Left) Red dots are samples with no detection of 240 bp amplicon, for which Ct values are assigned to 40. (Right) Correlation of VFS and VFI for samples within blue margin is shown. **(C)** VFI from RT-PCR assay shows a correlation with days since diagnosis and for 7 samples not plotted due to non-detection of 240 bp, the days from diagnosis were ≥ 7.

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Review

The duration of infectiousness of individuals infected with SARS-CoV-2

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Contact tracing

SUMMARY

Objectives: To summarise the evidence on the duration of infectiousness of individuals in whom SARS-CoV-2 ribonucleic acid is detected.
Methods: A rapid review was undertaken in PubMed, Europe PubMed Central and EMBASE from 1 January 2020 to 26 August 2020.
Results: We identified 15 relevant studies, including 13 virus culture and 2 contact tracing studies. For 5 virus culture studies, the last day on which SARS-CoV-2 was isolated occurred within 10 days of symptom onset. For another 5 studies, SARS-CoV-2 was isolated beyond day 10 for approximately 3% of included patients. The remaining 3 virus culture studies included patients with severe or critical disease; SARS-CoV-2 was isolated up to day 32 in one study. Two studies identified immunocompromised patients from whom SARS-CoV-2 was isolated for up to 20 days. Both contact tracing studies, when close contacts were first exposed greater than 5 days after symptom onset in the index case, found no evidence of laboratory-confirmed onward transmission of SARS-CoV-2.
Conclusion: COVID-19 patients with mild-to-moderate illness are highly unlikely to be infectious beyond 10 days of symptoms. However, evidence from a limited number of studies indicates that patients with severe-to-critical illness or who are immunocompromised, may shed infectious virus for longer.
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Introduction

Severe acute respiratory syndrome coronavirus, type 2 (SARS-CoV-2) is a highly infectious virus that is responsible for tens of millions of cases of coronavirus disease 2019 (COVID-19) worldwide.[1] SARS-CoV-2 constitutes a significant public health concern due to its high basic reproduction rate (R_0 of 4–5 in the unmitigated setting), the absence of immunity in the human population, the lack of effective treatment or vaccination approaches, the high SARS-CoV-2 viral loads detectable in respiratory samples, and the occurrence of transmission early in the disease course, often pre-symptomatically, or by those asymptomatic or paucisymptomatic.[2-7] Due to the lack of effective antiviral therapy or a vaccine, the rapid diagnosis, contact tracing, and isolation of suspected COVID-19 cases are of critical importance in the control of this pandemic.[3]

Isolation is defined as separating those with symptoms of, or diagnosed with, COVID-19, from people who are not infected.[8] This is distinct from quarantine, which is defined as separating and restricting the movements of people who were exposed or potentially exposed to COVID-19, as a precautionary measure to prevent transmission should they later become infected.[8] In circumstances in which cases are confirmed, isolation should continue until a patient is no longer expected to be infectious. However, recommendations regarding the appropriate duration of isolation for those who test positive for SARS-CoV-2 ribonucleic acid (RNA) have evolved since the emergence of the virus in China in December 2019, and vary across jurisdictions, generally ranging from 7 days[9] to 14 days.[10]

SARS-CoV-2 infection is primarily diagnosed based on detecting the presence of viral RNA by molecular testing, usually by re-

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verse transcription polymerase chain reaction (RT-PCR) in a specimen from an individual's respiratory tract. However, detection of viral RNA does not necessarily mean that a person is infectious, i.e. that they are capable of transmitting the virus to another person.[3] Several factors determine viral transmission risk: these include whether a virus is still replication-competent (or viable); the amount of replicative virus; the presence of symptoms, such as a cough which can spread infectious droplets; the individual's local mucosal immune response to the virus; and the behavioural and environmental factors associated with the infected individual and their contacts.[11] Determination of the presence of viable virus may be accomplished by monitoring the ability of SARS-CoV-2 to replicate in laboratory-based cell culture. Such virus culture serves as a marker of potential viral infectivity.[12] Therefore, for the purpose of determining the infectiousness of a patient, and the duration of isolation required to minimise the risk of onward transmission, virus culture is significantly more informative than simple detection of viral RNA which could reflect non-replicative virus.[11,13–15] It is important to note that cells used to culture SARS-CoV-2 in the laboratory have been developed to be susceptible to, and enhance replication, of a wide range of viruses and therefore do not necessarily "mimic" the susceptibility of cells in a patient.[16] In addition, virus culture is usually used to identify the causative agent of an infection, and not to infer the infectivity of the individual from whom the sample was collected.[12] Therefore, the culture of SARS-CoV-2 derived from a patient's clinical sample does not necessarily prove that the patient is infectious at the time of sampling, but rather that they were potentially infectious due to the presence of viable virus. Evidence from epidemiological investigations can supplement the knowledge gained from virus culture studies by describing the transmission dynamics between index cases and their close contacts. Together, virus culture studies and epidemiological investigations (i.e., contact tracing studies) provide a more complete understanding of the duration of infectiousness.[15]

The aim of this rapid review was to summarise the evidence on the potential duration of patient infectiousness, as derived from virus culture and contact tracing studies, for those individuals in whom SARS-CoV-2 RNA is detected, and hence inform guidance on the duration of isolation.

Materials and methods

We conducted a rapid review to answer the following research question: *What is the duration of infectiousness in those in whom SARS-CoV-2 RNA is detectable?* This rapid review followed a standardised protocol,[17] in keeping with Cochrane rapid review methodology guidance.[18] We searched PubMed, Europe PubMed Central and EMBASE from 1 January 2020 to 26 August 2020. The search combined terms for COVID-19 and SARS-CoV-2 with terms for infectiousness, virus culture, and contact tracing. Reference lists of systematic reviews were also screened. No language restrictions were applied. Only articles including human subjects were included. The search strategy is provided in the supplementary material (Appendix 1).

All potentially eligible papers, including non-peer-reviewed preprints, were exported to Covidence[19] and screened for relevance. Any study that addressed the research question and met the inclusion criteria was included (Table 1). Primary research studies presenting empirical data on duration of infectiousness of SARS-CoV-2 in human populations were included. Specifically, the included studies were laboratory studies where virus culture was performed, and contact tracing studies with case-contact pairs.

For each included study, data on the study design, participant demographics and relevant outcomes were extracted. For virus culture studies, outcomes included the days post symptom onset on which virus culture was attempted, the days on which SARS-CoV-2 culture was positive, and the viral load of the original samples (where reported). Where graphical distributions were presented to model the probability of a positive culture on each day post symptom onset, data from curves were extracted using WebPlotDigitzer, version 4.3.[20] In order to present the data specifically for the time period following symptom onset (as opposed to pre-symptomatic culture positivity), and to allow for visual comparison of curves using common axes, extracted data derived from individual studies were plotted on a common chart. Plotting of data was performed using RStudio version 1.1.442.

For contact tracing studies, outcomes included the number of days post symptom onset in the infector at which infection in contacts was observed to have occurred, and the secondary attack rate. As studies were predominantly case series or case reports in design, a *de novo* tool, adapted from related tools, was used for quality appraisal.[17] Screening, data extraction, and quality appraisal were undertaken by single reviewers, however studies excluded at full-text screening stage, extracted data, and quality appraisal judgments were double-checked for accuracy by another reviewer.[18] Given the inconsistent presentation of data across the studies, and the heterogeneity of methods used to culture SARS-CoV-2, a quantitative synthesis of results could not be reliably performed. However, a narrative synthesis, including graphical representation of findings, is presented.

Results

Search results

Of 4226 studies screened after duplicate removal, 15 were included (Fig. 1).[14,21–34] In addition, unpublished data linked to 1 of the included studies[28] were also included.[35] Thirteen of these studies attempted to culture SARS-CoV-2 (Appendix 2),[14,21–23,25–33] and 2 studies conducted contact tracing of case-contact pairs (Appendix 3).[24,34] All 15 studies reported results in relation to time since symptom onset. No studies were found that reported duration of infectiousness in asymptomatic individuals (i.e. patients that never develop symptoms).

Population characteristics of included studies

Two studies each were conducted in the United States (US),[21,28] Taiwan,[24,30] the United Kingdom (UK)[31,34] and Germany;[25,33] while 1 study each was conducted in Switzerland,[29] Australia,[22] Canada,[23] Spain,[26] South Korea,[27] Hong Kong,[14] and the Netherlands.[32]

Of the 13 SARS-CoV-2 virus culture studies, 11 were case series[14,21–23,26–29,31–33] and 2 were case reports.[25,30] The contact tracing studies were both described as prospective, case-ascertained studies.[24,34] Across all 13 virus culture studies, SARS-CoV-2 culture was attempted from samples collected from at least 808 COVID-19 patients, with SARS-CoV-2 isolated in at least 206 of these patients. A total of at least 1652 samples had SARS-CoV-2 culture attempted and at least 413 of these were positive. Five studies did not clearly provide information on the number of samples and/or patients included.[22,23,26,30,33]

Twelve studies included COVID-19 patients only after onset of symptoms.[14,22,23,25–30,32–34] Three studies additionally included patients before they become symptomatic (i.e., pre-symptomatic).[21,24,31] The earliest SARS-CoV-2 virus culture attempt was 13 days before symptom onset,[31] whereas the latest SARS-CoV-2 culture attempt was 67 days after symptom onset.[14] The contact tracing study by Cheng et al. included contacts who had their first day of exposure to the index case between day 4 before and up to day 26 after symptom onset in the index case. Contacts were subsequently followed for 14 days after the last expo-

Table 1
Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion criteria
Primary studies presenting empirical data on duration of infectiousness of SARS-CoV-2 in human populations, including: Contact tracing studies involving case-contact pairs Laboratory studies where virus culture was performed.	• Animal studies • Non-primary research (e.g. editorials/opinion pieces/guidance documents/reviews) • Studies which do not report data on duration of infectiousness (e.g. no time since first positive or symptom onset reported) • Studies reporting solely on pre-symptomatic durations, incubation periods, serial intervals, or on results based on statistical modelling • Laboratory studies where virus culturing was not undertaken • Studies where virus presence was confirmed only by culturing of non-respiratory samples (e.g. blood, faecal) • Virus culture studies where the virus was only isolated for the purpose of whole genome sequencing

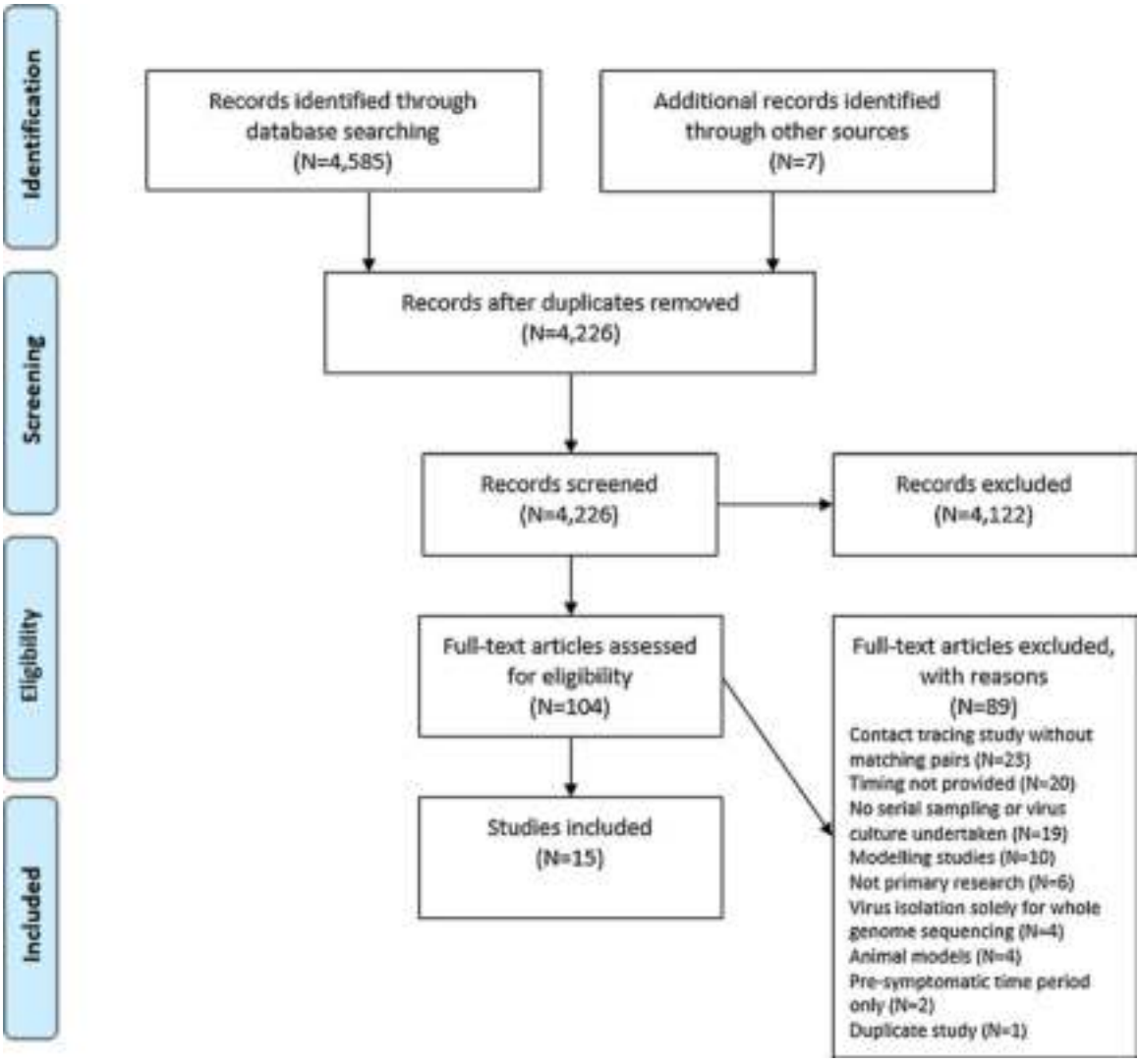

Fig. 1. PRISMA diagram indicating the flow of inclusion of studies for review.

sure to the index case.[24] The contact tracing study by Lopez Bernal et al. included household contacts who were exposed to the index case at any time between symptom onset and 14 days thereafter.[34] Follow-up of the contacts was limited to 14 days from onset of symptoms in the index case.[34]

Asymptomatic patients were included in 3 studies; however, no information was provided from these studies that could be used to inform the potential duration of infectiousness of asymptomatic patients. Results from serial sampling and attempted virus culture in asymptomatic patients were not reported,[21,31] and in 1 of the

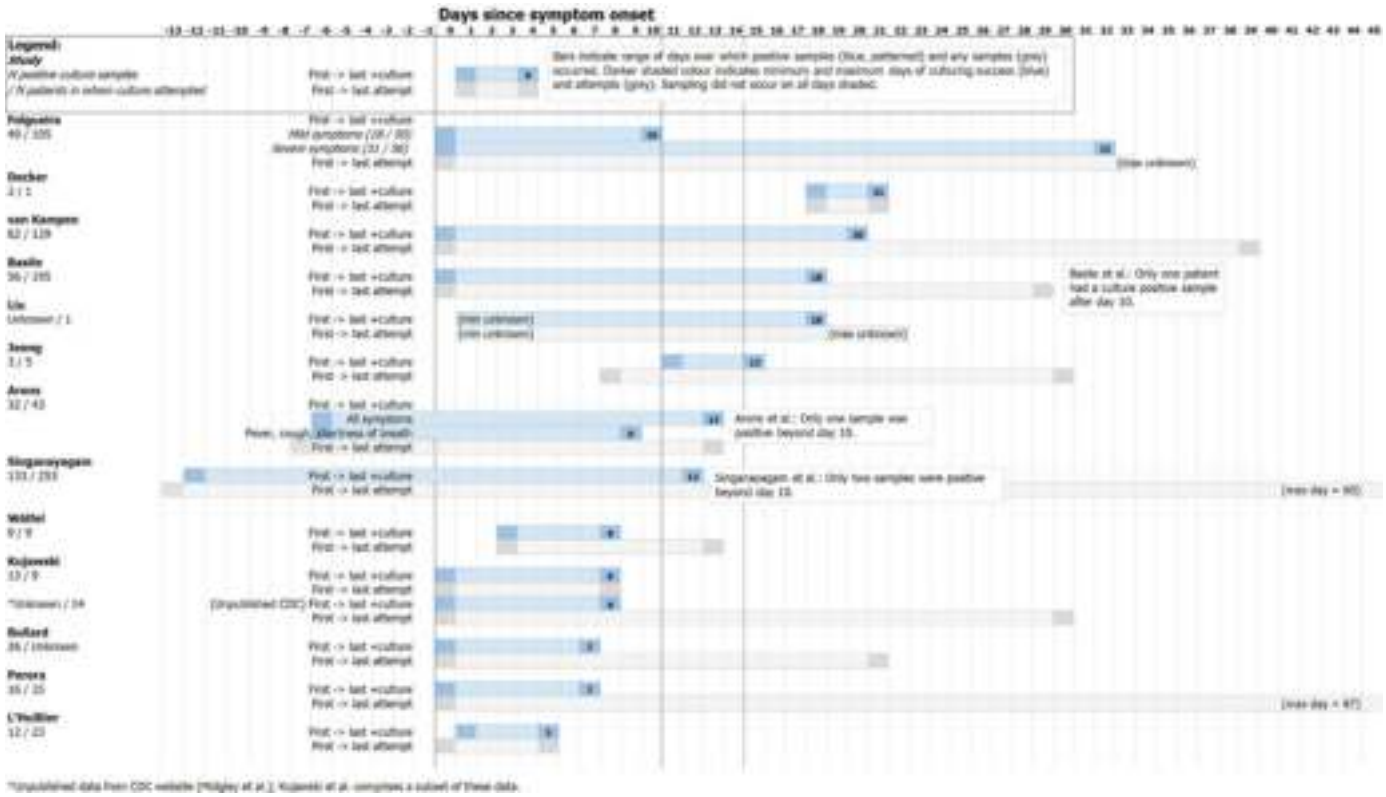

Fig. 2. Days since symptom onset at which SARS-CoV-2 virus culture was attempted (blue, patterned) and successful virus culturing (grey) took place in each study, displayed in descending order of last day of successful virus culturing.

contact tracing studies it was reported that no onward transmission occurred from the 9 asymptomatic patients included, despite 91 close contacts being identified for these patients.[24]

Virus culture study findings

Days post symptom onset on which SARS-CoV-2 could be cultured

Fig. 2 presents, for each individual study, the first and last days, post symptom onset, on which SARS-CoV-2 culture was attempted, and the first and last days on which SARS-CoV-2 culture was successful. These values are also listed in Table 2 alongside additional details of the studies.

For 5 of the 13 studies (with culture attempted in at least 76 patients), the last day on which SARS-CoV-2 could be cultured occurred within the first 10 days since onset of symptoms.[14,23,28,29,33] However, 1 of these studies, the sole study including only children, did not appear to attempt virus culture beyond day 5.[29] For the most part, the clinical severity of patients was mild-to-moderate in these 5 studies, though Perera et al. noted that 3 of the 35 patients in the study had been critically ill, while the remainder had mild disease or had been asymptomatic.[14]

In 2 studies, (with culture attempted in 296 patients) the last day on which SARS-CoV-2 culture was reported occurred between 10 and 14 days post onset of symptoms.[21,31] Singanayagam (with 133 SARS-CoV-2 culture positive samples from 253 patients) obtained only 2 culture positive samples between days 10 and 14 (1 on each of days 11 and 12). The authors also noted that more than half of the samples had been collected at least 8 days from symptom onset, and that 21% of these samples yielded SARS-CoV-2 in culture, the majority of which (25 of 27) was positive between 8 and 10 days after symptom onset. None of these late culture-positive samples included patients who were immunosuppressed or severely ill.[31] In Arons et al., 1 of 53 samples (for which the date of symptom onset was known) from 43 patients yielded SARS-CoV-2 on day 13; SARS-CoV-2 was not observed in other samples collected after day 10, though no virus culture was attempted beyond day 13.[21] There was also some uncertainty with regards to symptom onset in this study, with the longest time between the onset of typical COVID-19 symptoms (i.e., fever, cough or shortness of breath) and detection of SARS-CoV-2 culture positive recorded at 9 days, but 13 days after onset of less typical COVID-19 symptoms (i.e., chills, malaise, increased confusion, rhinorrhoea, nasal congestion, sore throat, myalgia, dizziness, headache, nausea or diarrhoea).

The remaining 6 studies, comprising 2 case reports and 4 case series (with culture attempted in 436 patients), reported successful SARS-CoV-2 culture between days 15 and 32 post symptom onset.[22,25–27,30,32] Three of the 4 case series included samples from over 100 patients.[22,26,32] Two of these studies included patients with severe disease.[26,32] Folgueira et al. ($N = 105$ patients) presented the maximum day on which SARS-CoV-2 was cultured for patients with mild symptoms (max day: 10) and severe symptoms (max day: 32).[26] Van Kampen et al. ($N = 129$ patients) reported SARS-CoV-2 culture results up until day 20. This study notably included only severely or critically ill patients, and included a large proportion of patients (23%) who were immunocompromised.[32] The third large case series, Basile et al. ($N = 195$), reported that the latest day on which a SARS-CoV-2 was cultured was day 10 for all but 1 patient (maximum day: 18).[22] The fourth case series, Jeong et al. ($N = 9$) reported positive cultures for 2 patients; the patient with SARS-CoV-2 cultured in saliva on day 15 was noted to be critically ill at the time of sampling.[27] Both of the case reports which identified SARS-CoV-2 in culture beyond day 14 were of hospitalised patients with mild disease,[25,30] although 1 of the

Table 2
Details of numbers of samples and patients for SARS-CoV-2 cultivation (positive cultures/attempted) and days on which culturing attempted and successful.

	Numbers of samples and patients (culture positive/attempted) and associated sample incubation duration			Days since symptom onset on which virus cultivation attempted		Days since symptom onset on which virus culture positive	
	N culture positive samples/ N samples where culture attempted	**N patients culture positive / N patients in whose samples culture was attempted**	**Duration (days) for which cultured cells incubated**	**First day attempted**	**Last day attempted (or further information)**	**Minimum**	**Maximum**
Studies including symptomatic period only							
Basile	56/234 (23.9%)	NR/195	5	0	29	0	18
Bullard	26/90 (28.9%)	NR	4	0	21	0	7
Decker	2/2 (100%)	1/1 (100.0%)	NR		*Only attempted on days 18 and 21.*	18	21
Folgueira	49/106 (46.2%) *Mild: 18/50* *Severe: 31/56*	NR/105 *Mild: NR/50* *Severe: NR/55*	5	1	*At least day 32*	1	10 *(mild)* 32 *(severe)*
Jeong	3/9 (33.3%) *(respiratory samples)*	2/5 (40.0%)	4	8	30	11	15
Kujawski	13/17 (76.5%) *respiratory samples)*	9/9 (100.0%)	NR	0	8	0	8
CDC unpublished (Midgley et al., Kujawski group)	*Unclear from Figure*	*Unclear*/14[†]	NR	0	30	0	8
L'Huillier	12/23 (52.2%)	12/23 (52.5%)	6	0	5	1	5
Liu	NR/NR	1/1 (100%)	NR	NR	*>18 days (exact days not reported)*	NR	18
Perera	16/68 (23.5%)	16/35 (45.7%)	6 days *(72 h followed by an additional 72 h)*	0	67	0	7
van Kampen	62/690 (9.0%)	23/129 (17.8%)	7 days	0	39	0	20
Wölfel	9/34 (26.5%) *respiratory (43 samples in total)*[*]	NR/9	6 days	3	13	3	8
Studies including pre-symptomatic and symptomatic period							
Arons	32/55 (58%)	31/43 (72.1%)	NR	−7	13	−6	13 *(where all symptoms considered)* 9 *(fever, cough, shortness of breath only)*
Singanayagam	133/324 (41%)	111/253 (44%)	Up to 14 days	−13	60	−13	12

NR: Not reported.
[*] Note that these figures are estimated from the number of markers displayed on Fig. 1d in Wölfel et al.; it is possible that the numbers are underestimated due to potential overlay of markers.
[†] CDC unpublished data by Midgley et al. includes all patients included in Kujawski et al. plus 5 additional patients.

case reports described an immunocompromised patient who had recently had a heart transplantation.[25]

Viral load and duration of infectiousness

The assays used to detect SARS-CoV-2 RNA could be regarded as semi-quantitative, using the cycle threshold (Ct) value as a surrogate marker of the SARS-CoV-2 viral load. For each study, those samples collected on the maximum day on which SARS-CoV-2 was isolated in culture are outlined in Appendix 2. Of note, lower Ct values indicate a higher viral load.

Of the 6 included studies that examined the relationship between viral load and culture of SARS-CoV-2, all 6 found an inverse correlation.[14,22,23,31–33] Singanayagam et al. ($N = 324$ samples) estimated that the probability of successfully culturing SARS-CoV-2 from samples with a Ct value greater than 35 was 8.3% (95% CI: 2.8%–18.4%).[31] Basile et al. ($N = 234$ samples) concluded that any clinical sample with a Ct value of ≥37 was not indicative of replicative (or potentially transmissible) virus.[22] Bullard et al. ($N = 90$ samples) estimated that for every 1 unit increase in Ct value, the odds of culturing SARS-CoV-2 decreased by 32%.[23] While Folgueira et al. reported culturing SARS-CoV-2 on day 32 post symptom onset in a patient with severe COVID-19, they observed a very low viral load, with a Ct value of 39.1.[26] Hence it is probable (assuming the Ct value accurately reflects the amount of virus in the patient's respiratory tract) albeit not impossible, that the patient was not highly infectious at this particular time.

Summary estimates, including probability of culturing SARS-CoV-2

Three studies presented graphical estimates of the probability of culturing SARS-CoV-2 versus the number of days since symptom onset.[31–33] These probability distributions are reproduced in Fig. 3 in an amended form (data for days 0 to 20 presented only) with overlay of curves to allow visual comparison of the probability results. Van Kampen et al.[32] and Wölfel et al.[33] both presented probit (dose-response) distributions for this outcome and estimated the day post symptom onset on which the probability of culturing SARS-CoV-2 culture fell below 5%. These results were as follows: van Kampen et al., 15.2 days (95% CI 13.4–17.2);[32] Wölfel et al., 9.8 days (95% CI 8.5–21.8).[33] Singanayagam et al.[31] presented the results of a mixed effects logistic regression analysis (to account for the clustering of samples within patients); estimates of the percentage of samples with replicative SARS-CoV-2 were presented for each of days 7 to 15 post symptom onset, and are repro-

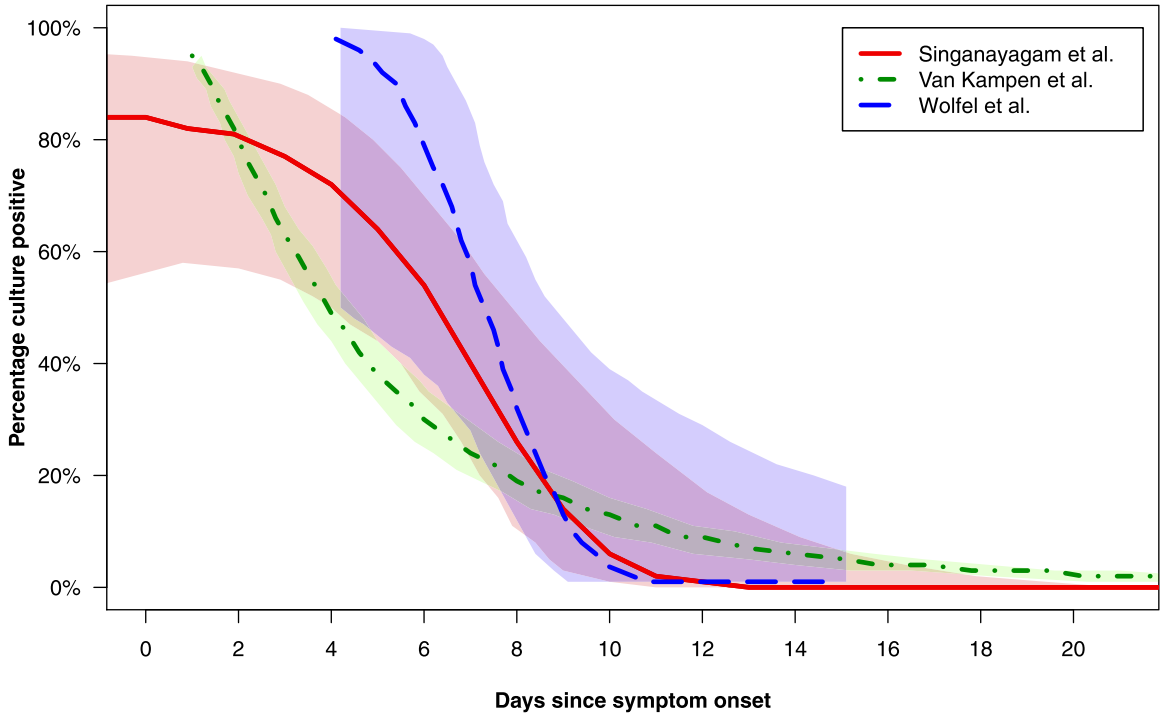

Fig. 3. Probability curves presented in 3 studies (Singanayagam et al., van Kampen et al., Wölfel et al.) which attempted to model the probability of successful virus culture versus duration of days of symptoms.[31–33] *Curves are presented with adaptation from the original presentation in the respective manuscripts in order to provide information for the first 20 days post symptom onset and to permit visual comparison of curves via overlay on a single plot. Lines (solid, dashed or dotted) depict estimated probability of positive virus culture* versus *days post symptom onset, while shaded areas depict 95% confidence intervals around these estimates.*

Table 3
Estimated percentage of samples with infectious SARS-CoV-2 for days 7–15 after symptom onset (adapted from Singanayagam et al.).

Day post symptom onset	Estimated% culture positive (95% CI)		Observed number of samples culture positive	Observed number of samples tested
7	40.1	(22.8 - 60.4)	10	14
8	25.8	(11.0 - 49.4)	9	33
9	13.7	(3.7 - 39.6)	10	34
10	6.0	(0.9 - 31.2)	6	23
11	2.2	(0.2 - 23.9)	1	6
12	0.7	(0.0 - 17.9)	1	3
13	0.2	(0.0 - 13.1)	0	4
14	0.03	(0.0 - 9.4)	0	2
15	0.006	(0.0 - 6.7)	0	2
			Total: 37	Total: 121

duced in Table 3. At 10 days post symptom onset, the probability of a sample with replicative SARS-CoV-2 was 6% (95% CI 0.9–31.2); however, these data carry a high degree of uncertainty, as shown by the wide confidence intervals.

While unpublished, Midgley et al. additionally presented a Kaplan-Meier analysis of time to a negative culture SARS-CoV-2 following illness onset.[35] This analysis represents an expanded analysis of the results reported by Kujawski et al.,[35] including a greater number of patients from the same setting ($n = 14$ versus $n = 12$ (9 of whom had samples collected for virus culture)), though the total number of samples tested is not known. Midgley et al. reported that the probability of successful SARS-CoV-2 culture fell from 50% at day 4 after illness onset, to 20% at day 8, and approached 0% after day 9.

Analysis and interpretation of virus culture study findings

Data for maximum day that SARS-CoV-2 was cultured

Several jurisdictions suggest a period of isolation for COVID-19 patients of a minimum of 10 days since the onset of symptoms.[11,15,36] As such, day 10 represents a relevant reference timepoint when considering the results of the SARS-CoV-2 culture studies included within this review.

While 8 of the 13 studies successfully cultured SARS-CoV-2 on days beyond day 10 post symptom onset, these results require contextualisation. Important aspects to consider include the number of samples and patients in whom this outcome occurred with respect to the overall number of samples and patients tested, and the patient populations included.

In total, these 8 studies included at least 337 SARS-CoV-2 culture-positive samples obtained from 732 patients.[22,25–27,30–32] In 4 of the 8 studies, only 1 patient was SARS-CoV-2 culture-positive beyond day 10,[21,22,25,30] and a further study identified only 2 samples (of 133 positive samples) yielding SARS-CoV-2 culture beyond day 10.[31] These 5 studies included at least 223 SARS-CoV-2 culture positive samples from 493 patients in whom culture was attempted (Table 2).[21,22,25,30,31] They reported a maximum of 6 patients who were SARS-CoV-2 culture-positive beyond day 10 (assuming conservatively that the 2 positive samples beyond day 10 in Singanayagam et al. arose from 2 unique patients).[31]

While these 5 studies in total reported a maximum of 6 patients from whom SARS-CoV-2 was cultured beyond day 10,[21,22,25,30,31] the total number of patients with positive samples is unknown (Table 2). However, amongst these 5 studies,

the proportion of patients from whom SARS-CoV-2 was cultured ranged from 44%[31] to 100%[25,30] (the latter representing case reports) (Table 2). Applying a worst-case scenario by adopting the lower proportion, i.e., assuming a positivity rate amongst patients of 44%, this results in an estimated minimum of 217 patients across these 5 studies. As such, 6 patients amongst 217 patients (maximum proportion of approximately 3%) are estimated to have had samples containing replicative SARS-CoV-2 in vitro beyond day 10 post symptom onset.

Within the remaining 3 studies (with culture attempted in 239 patients), wherein the latest day of successful culture exceeded day 10, it is less clear how many patients contributed to the samples resulting in this outcome.[26,27,32] Folgueira et al.[26] and Van Kampen et al.[32] noted that patients from whom SARS-CoV-2 could be isolated were severely or critically ill at the time of sampling. The remaining study, Jeong et al., included 2 patients with this outcome, 1 of whom was critically ill at the time of sampling (day 15), and the other of whom was severely ill, but recovering at the time of sampling (day 11).[27] As such, patients with severe and critical illness may represent a relevant subgroup within the data.

Probability estimate data

Two of the included studies (with culture attempted in 262 patients) which largely included patients with mild-to-moderate disease,[31,33] and additional unpublished estimates associated with 1 of the included studies,[28,35] estimated that the probability of culturing SARS-CoV-2 falls below 6% at day 10 (Fig. 3). A third study (with culture attempted in 129 patients) which modelled the probability of virus culturing versus time, suggested that the probability of a SARS-CoV-2 positive culture would fall below 5% at day 15[32] (Fig. 3). However, this latter study uniquely included only hospitalised patients with severe or critical illness.

Singanayagam et al., the virus culture study in our review with the greatest number of patients ($N = 253$ patients in whom culture was attempted), and which predominantly included patients with mild-to-moderate disease, reported numerical estimates of the probability of a sample producing a SARS-CoV-2 positive culture at each day from day 7 onwards (Table 3).[31] These data carry a high degree of uncertainty, as shown by wide confidence intervals, but showed a steep decline in the probability of culturing SARS-CoV-2 over time. For example, the estimated percentage of samples culture-positive on day 8 stood at 25.8% (95% CI 11.0–49.3) while the corresponding figure for day 10 was 6.0% (95% CI 0.9–31.2).

Contact tracing study findings

Two of the 15 included studies were contact tracing studies.[24,34] Cheng et al.[24] undertook a contact tracing study of 100 confirmed COVID-19 cases (ranging from asymptomatic to critical disease) in Taiwan. Amongst the 2761 close contacts of the 100 COVID-19 cases, there were 22 paired index-secondary cases. This study found that the overall secondary clinical attack rate was 0.7% (22 cases from 2761 contacts; 95% CI, 0.4%−1.0%). The attack rate was higher amongst the 1818 close contacts whose exposure to index cases started within 5 days of index case symptom onset (22 cases from 1818 contacts; 1.0%; 95% CI, 0.6%−1.6%) compared with those who were exposed later (0 cases from 852 contacts; 0%; 95% CI, 0%−0.4%). The 299 close contacts with exclusively pre-symptomatic exposure (up to 4 days before symptom onset in the index case) were also found to be at risk of infection (2 cases from 299 contacts; 0.7%; 95% CI, 0.2%−2.4%). The authors of this study concluded that there is a relatively short period of infectiousness of SARS-CoV-2, with higher transmissibility from 4 days before and up until 5 days after symptom onset. Based on the lack of onward transmission when close contacts were first exposed more than 5 days after symptom onset in the index case, the authors deduce that there is a lower transmission risk at the later stage of the disease.[24]

Lopez Bernal et al.[34] undertook a contact tracing study of 269 lab-confirmed COVID-19 cases in the UK, who lived with at least 1 other person. Local health protection teams contacted household contacts of these patients daily for 14 days after onset of symptoms in the index case. In total, 472 household contacts were identified. Of these 472 contacts, 65 (13.8%) had a laboratory-confirmed diagnosis of COVID-19 using RT-PCR testing, and another 96 (20.3%) had probable COVID-19 based on the onset of symptoms of fever, anosmia (i.e., loss of smell) or respiratory symptoms. The remaining 311 contacts were classified as non-cases as they did not experience any symptoms suggestive of COVID-19 within 14 days of symptom onset in the index case. The household secondary attack rate was found to be 37% (95% CI, 31%−43%) including both laboratory-confirmed and probable secondary cases.

Of the 161 laboratory-confirmed or probable secondary cases, 41 had a point source exposure (i.e., a maximum exposure window of 1 day) to an index case and data available to allow analysis of timing of exposure. Laboratory-confirmed and probable secondary cases considered together ($N = 41$) were exposed a mean of 2.37 days (standard deviation (SD) 3.36) and a median of 1 day (interquartile range (IQR) 0–4) after symptom onset in the index case; exposure ranged from 0 days to the maximum follow up of 14 days. As identification of contacts was limited to 14 days from onset of symptoms in the index case, no information was provided regarding secondary cases in household contacts outside this exposure window. Similarly, of the contacts identified in the 14-day window, follow-up was truncated at 14 days from symptom onset in the index case, so no information was provided regarding symptoms that may have arisen after this follow-up period.

Restricting to lab-confirmed secondary cases only ($N = 12$), exposure occurred a mean of 1.33 days (SD 1.61) and a median of 1 day (IQR 0–1.25) after symptom onset in the index case, ranging from 0 to 5 days. In contrast, non-cases were exposed a mean of 2.71 days (SD 2.74) and a median of 2 days (IQR 0–5) after symptom onset in the index case, ranging from 0 to 9 days. No analysis was undertaken in this study to determine whether these time differences were statistically significant.[34]

Methodological quality of included studies

There are some important methodological limitations associated with all of the included studies. All 13 SARS-CoV-2 culturing studies were retrospective in nature and were either case series[14,21–23,26–29,31–33] or case reports,[25,30] where patients do not appear to have been selected or sampled systematically. However, the contact tracing study by Cheng et al. was generally well-conducted due to its prospective nature, the systematic pairing of index cases and close contacts over time, and the follow up of contacts for 14 days after last exposure to the index case to assess for symptom onset.[24] Hence, the majority of evidence in this review comes from studies of low quality design. Importantly, it would appear that most studies did not specifically set out to identify the temporal relationship between time post symptom onset and presence of infectious virus, but rather reported culture positivity based on samples collected for other purposes.[23,26–29,31,33] Thereby, some uncertainty remains regarding the true duration of patient infectiousness, as the upper limit of outliers may not have been fully clarified. Recall bias is another issue which may have important implications on outcomes across all studies, as patients may not have been able to accurately determine when symptoms began, particularly if they were quite mild and non-specific.[37]

There are some concerns regarding the inconsistent approaches used for cell culture amongst studies, and the interpretation of

findings by the study authors. If, as noted in some studies,[14,29] a second passage of the sample is required to observe a cytopathic effect (CPE), and thereby to confirm culture positivity, this suggests a very low replicative viral load in the original sample and may reflect that the individual from whom the sample was collected is unlikely to have been infectious at the time of sampling.[38] Furthermore, given that longer periods for a CPE to develop are indicative of a lower viral replicative titre in the original sample,[16] where studies incubate the cell lines for prolonged periods, and only observe a CPE towards the end of this period, this may also lead to overestimation of the clinical significance of the findings.[31]

A *de novo* tool was also used to quality appraise case reports and case series.[39] This tool identified additional concerns regarding the limited reporting of demographic information,[22,23,30,31,33] the unclear criteria for selection of cases,[14,23,26,27,32,33] the non-consecutive inclusion of cases,[14,22,23,26,27,32,33] uncertainty regarding the appropriateness of statistical analysis[14,27,31–33] and the inconsistent use of RT-PCR testing for diagnosis.[34] Four of the studies included in this review are published as pre-prints, so have not yet been formally peer-reviewed, raising additional concerns about overall quality and the potential for results to change prior to formal publication.[22,26,32,34]

Discussion

Thirteen SARS-CoV-2 virus culture studies of various quality and size, and 2 large contact tracing studies, were included in this rapid review. The evidence to date from virus culture studies would appear to suggest that COVID-19 patients with mild-to-moderate illness are highly unlikely to be infectious beyond 10 days from symptom onset. Evidence from large contact tracing studies[24,34] appears to support this finding. However, evidence from a limited number of studies indicates that patients with severe-to-critical illness, and or those who are immunocompromised, may be infectious for a prolonged period, possibly for 20 days or more.[25,26,32] Virus culture studies suggested a steady decline in the probability of culturing SARS-CoV-2 in the first 10 days following symptom onset; the largest included study estimated the probability as falling from 40% on day 7 to 26% on day 8, 14% on day 9 and 6% by day 10. However, these results were subject to considerable uncertainty, and the clinical significance of these findings is unknown given potentially prolonged incubation of cultured cells.[31] Notably, there are important methodological limitations associated with all of the included studies. The number of studies for consideration remains few in number and sample sizes are often small; hence it is essential that the findings from these studies are interpreted in light of these caveats. Furthermore, virus culture studies determine if a sample contains replicative competent SARS-CoV-2; while a positive virus culture indicates *potential* infectiousness of the individual from whom the sample was collected, risk of transmission (i.e., clinical infectivity) is also influenced by the viral load, local immune response to SARS-CoV-2, clinical symptoms and environmental factors, and behaviour of the infected individual and their contacts.

One of the notable findings from 2 of the included studies was that patients who were found to be SARS-CoV-2 culture-positive for a prolonged period were immunosuppressed.[25,32] In particular, 1 of the case reports describes a mild clinical course of COVID-19 in a heart transplant recipient on immunosuppressant therapies (mycophenolate mofetil, ciclosporin and prednisone) from whom SARS-CoV-2 was cultured 21 days after symptom onset.[25] Although the evidence pertaining to prolonged infectiousness in immunosuppressed populations is very limited, these findings do raise important research and policy questions. Immunosuppressant therapies have been observed to delay the clearance of SARS-CoV-2 viral RNA in previous studies.[40,41] However, some of these agents are also being investigated as treatments for severe and critical COVID-19 to modulate the hyperinflammatory response (e.g., tocilizumab).[42,43] Little is known regarding the presentation and course of disease in patients who are immunocompromised; it is unknown whether all patients who are in an immunocompromised state necessarily present with severe COVID-19 disease, or how important the degree of immunosuppression is for clearance of the virus.[43] More evidence is required to understand the relationship between immunosuppression and the illness severity and duration of infectiousness of SARS-CoV-2. However, in these individuals it is very likely that any molecular investigations would indicate a significant SARS-CoV-2 viral load.

Only 1 study provided information on SARS-CoV-2 culture specifically in children.[29] However, as virus culture was only attempted once per patient, to a maximum of 5 days post symptom onset, this study provides insufficient information to inform policy decisions surrounding isolation requirements specifically for children testing positive for SARS-CoV-2 RNA. Children have generally been under-represented in COVID-19 studies to-date, although this may be a function of testing practices which initially typically prioritised those with more severe symptoms, healthcare workers and those residing in long term care settings. Given reports of milder symptoms in children, during the earlier stages of the pandemic they were less likely to be tested and diagnosed.[44] As children return to school en masse, increased testing and cases may occur in these settings, thus more data may emerge regarding the potential duration of infectiousness in this population.

The two included contact tracing studies both provide epidemiological evidence to support the findings from the virus culture studies.[24,34] Notably, there were substantial differences in the observed secondary attack rates between the 2 contact tracing studies (0.7% vs. 37%). These differences are likely to be explained by the different exposure settings at play; the study by Lopez Bernal et al. focused on transmission amongst household contacts,[34] a setting in which SARS-CoV-2 is known to be highly transmissible,[45] whereas Cheng et al. included all possible modes of transmission.[24] Differences in case or contact definitions and general approaches within the different public health systems may also explain this substantial disparity.[24,34] Despite these differences, both studies reported that when close contacts were first exposed greater than 5 days after symptom onset in the index case, there was no evidence of laboratory-confirmed onward transmission of SARS-CoV-2.

The findings from our rapid review are largely in agreement with 4 previous reviews conducted in this general area.[3,46–48] All of these reviews concluded that infectiousness generally declines 7–10 days after symptom onset, and point to uncommon outlier cases where this duration is exceeded. Another common finding across 3 of these reviews was the prolonged duration of SARS-CoV-2 RNA detection, sometimes for 2–3 months after onset of symptoms, along with cases of repeat SARS-CoV-2 RNA detection after a patient has clinically recovered.[3,46,48] Hence, patients are unlikely to be infectious for the entire duration of viral RNA detection as the presence of viral RNA may not represent transmissible or replication-competent virus.[3] Our rapid review is the first to attempt to quantify the proportion of COVID-19 patients that are potentially infectious beyond day 10 post symptom onset, and draws on more recent evidence, including both virus culture and contacting tracing studies. Hence, our rapid review adds greater clarity to this complex issue.

Evidence from our rapid review has directly informed the decision to reduce the duration of isolation in individuals who test positive for SARS-CoV-2 RNA in Ireland, from 14 to 10 days (with the additional clinical requirement of being fever-free for 5 days).[49,50] Though guidance still varies on this topic globally, several public health agencies have updated their recommendations

in recent times in light of the growing evidence of this rapid reduction in infectiousness post symptom onset, and a greater understanding of the prolonged shedding of non-transmissible SARS-CoV-2 RNA.[11,15,36,51]

The World Health Organization (WHO) currently recommends that a COVID-19 patient (regardless of symptom severity) can end isolation, without requiring re-testing, 10 days after symptom onset and at least 3 additional days without symptoms.[11] Previously, WHO recommendations published in January 2020 stated that COVID-19 patients could only be released from isolation if they were clinically recovered and received 2 negative RT-PCR results on sequential samples taken at least 24 h apart.[11] In contrast, the European Centre for Disease Prevention and Control (ECDC) issued a recommendation in April 2020, in the context of widespread community transmission, that COVID-19 patients in the community with mild or asymptomatic illness can end isolation 8 days after the onset of symptoms.[51] This recommendation is conditional on resolution of fever and clinical improvement of other symptoms for at least 3 days.[51] Previous recommendations issued by ECDC in March 2020 advised that mild cases of COVID-19 could be discharged from hospital, if clinically appropriate, with a further 14 days of isolation post-discharge.[52] The Centers for Disease Control and Prevention (CDC) in the United States (US) recommended in July 2020 that isolation can generally be discontinued (in patients with mild-to-moderate illness) 10 days after symptom onset and resolution of fever for at least 24 h (without the use of fever-reducing medications) and with improvement of other symptoms.[53] This may be contrasted with the previously recommended period of isolation of 14 days. However, the CDC also now recommends that isolation may be required for up to 20 days after symptom onset in a limited number of severe cases, and recommend that for patients who are severely immunocompromised, a test-based strategy (using RT-PCR) may be considered to discontinue isolation, in consultation with infectious diseases experts.[15] For all other patients, the CDC no longer recommend a test-based strategy to discontinue isolation.[15] The CDC also points to the lack of equivalent data from children and infants and the need for more data regarding immunocompromised individuals. As new evidence emerges for these subgroups of interest, recommendations regarding the duration of isolation in these populations may change.

It is important to note that the majority of evidence in this review is derived from studies of low quality design, where determining the duration of infectiousness may not have been the primary objective and SARS-CoV-2 culturing methods were not consistent. Furthermore, the inconsistent reporting of data precluded any meaningful quantitative synthesis. Notably, virus culture studies are inherently fraught with challenges,[54] but the requirement for biosafety level 3 (BSL-3) facilities is a particular barrier to research. Further work is required to develop standardised methods to optimise culturing of SARS-CoV-2.

Future research should ideally be prospective in design, following a large cohort of COVID-19 patients with a broad spectrum of disease and inclusive of subgroups of interest (such as children, asymptomatic and immunosuppressed patients). Patients should be regularly and systematically sampled and SARS-CoV-2 virus culturing attempted using standardised methods, until virus can no longer be successfully isolated.[47] The time between sample inoculation and the detection of viral growth should be reported for all studies, as this is a reflection of the viral load of infectious virus in the original sample. The findings of such virus culture studies should be supplemented with epidemiological evidence of onward transmission at different time points, as derived from well-conducted, large and prospective contact tracing studies. A core outcome set should be measured and reported, stratified by different subgroups, thus enabling better synthesis by systematic reviewers to better facilitate interpretation and decision-making by policy-makers.[55]

Conclusion

The evidence to date suggests that COVID-19 patients with mild-to-moderate illness are highly unlikely to be infectious beyond 10 days from symptom onset. However, evidence from a very limited number of studies indicates that patients with severe-to-critical illness or those who are immunocompromised, may shed infectious virus for longer than 10 days. Future research is required to confirm these findings and to provide information on the duration of infectiousness in subgroups such as children, and asymptomatic and immunosuppressed patients.

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Supplementary materials

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hivma hiv medicine association
OXFORD

Correlation Between 3790 Quantitative Polymerase Chain Reaction–Positives Samples and Positive Cell Cultures, Including 1941 Severe Acute Respiratory Syndrome Coronavirus 2 Isolates

To the Editor—The outbreak of the coronavirus disease 2019 (COVID-19) pandemic due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic on 12 March 2020 by the World Health Organization [1]. A major issue related to the outbreak has been to correlate viral RNA load obtained after reverse-transcription polymerase chain reaction (RT-PCR) and expressed as the cycle threshold (Ct) with contagiousness and therefore duration of eviction from contacts and discharge from specialized infectious disease wards. Several recent publications, based on more than 100 studies, have attempted to propose a cutoff Ct value and duration of eviction, with a consensus at approximately Ct >30 and at least 10 days, respectively [2–5]. However, in an article published in *Clinical Infectious Diseases*, Bullard et al reported that patients could not be contagious with Ct >25 as the virus is not detected in culture above this value [6]. This limit was then evoked in the French media during an interview with a member of the French Scientific Council Covid-19 as a possible value above which patients are no longer contagious [7].

At the beginning of the outbreak, we correlated Ct values obtained using our PCR technique based on amplification of the E gene and the results of the culture [8]. Since the beginning of the pandemic, we have performed 250 566 SARS-CoV-2 RT-PCR for 179 151 patients, of whom 13 161 (7.3%) tested positive. Up to the end of May, 3790 of these samples, reported as positive on nasopharyngeal samples, were inoculated and managed for culture as previously described [8]. Of these 3790 inoculated samples, 1941 SARS-CoV-2 isolates could be obtained after the first inoculation or up to 2 blind subcultures. The correlation between the scanner values and the positivity of the culture allows us to observe that the image obtained with 10 times more isolates than in our preliminary work (1941 vs 129) does not change significantly (Figure 1). It can be observed that at Ct = 25, up to 70% of patients remain positive in culture and that at Ct = 30 this value drops to 20%. At Ct = 35, the value we used to report a positive result for PCR, <3% of cultures are positive. Our Ct value of 35, initially based on the results

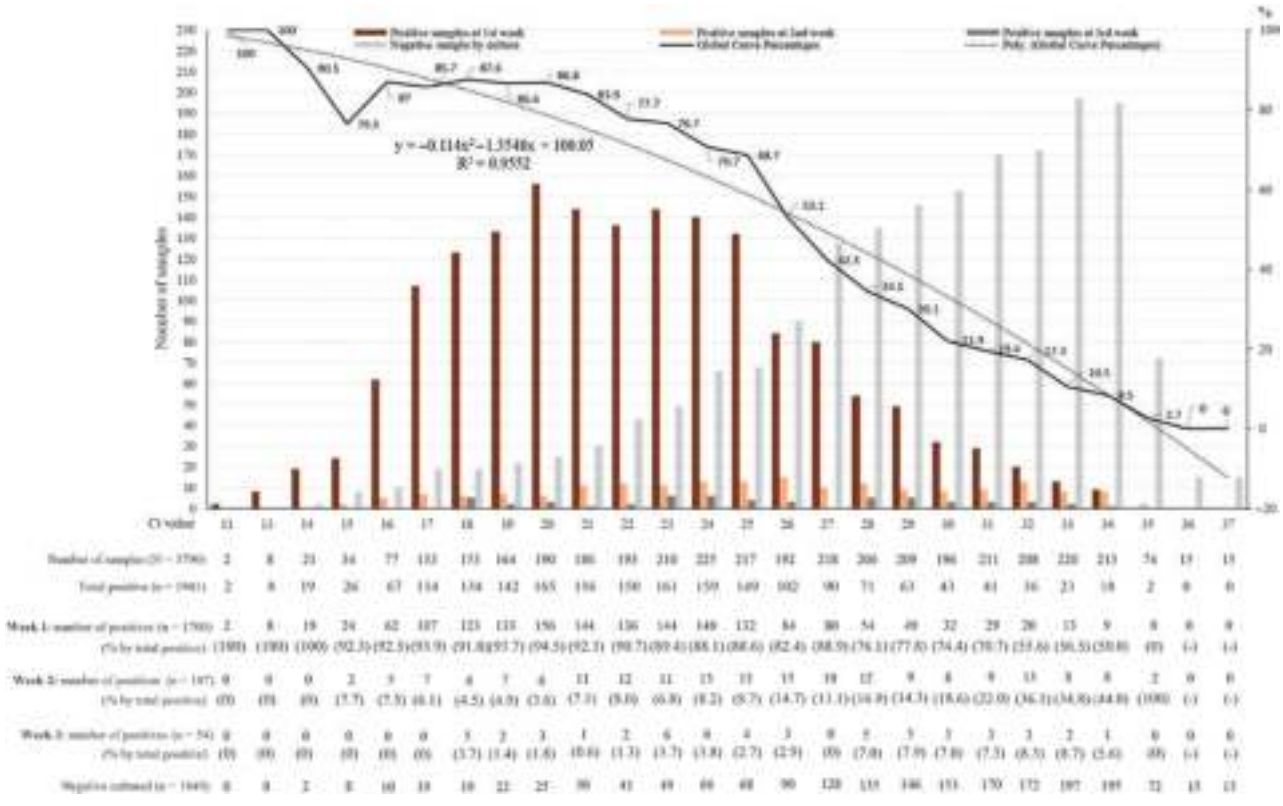

Figure 1. Percentage of positive viral cultures of severe acute respiratory syndrome coronavirus 2 polymerase chain reaction–positive nasopharyngeal samples from coronavirus disease 2019 patients, according to Ct value (plain line). The dashed curve indicates the polynomial regression curve. Abbreviations: Ct, cycle threshold; Poly., polynomial.

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obtained by RT-PCR on control negative samples in our laboratory and initial results of cultures [8], is validated by the results herein presented and is in correlation with what was proposed in Korea [9] and Taiwan [10]. We could observe that subcultures, especially the first one, allow an increasing percentage of viral isolation in samples with Ct values, confirming that these high Ct values are mostly correlated with low viral loads. From our cohort, we now need to try to understand and define the duration and frequency of live virus shedding in patients on a case-by-case basis in the rare cases when the PCR is positive beyond 10 days, often at a Ct >30. In any cases, these rare cases should not impact public health decisions.

Notes

Ethical approval. The protocol was approved by the University Hospital Institute Méditerranée Infection Ethical Committee. All patients provided informed consent in accordance with the Declaration of Helsinki.

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Rapid communication

Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020

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Severe acute respiratory syndrome coronavirus 2 viral load in the upper respiratory tract peaks around symptom onset and infectious virus persists for 10 days in mild-to-moderate coronavirus disease (n = 324 samples analysed). RT-PCR cycle threshold (Ct) values correlate strongly with cultivable virus. Probability of culturing virus declines to 8% in samples with Ct > 35 and to 6% 10 days after onset; it is similar in asymptomatic and symptomatic persons. Asymptomatic persons represent a source of transmissible virus.

Since the emergence of coronavirus disease (COVID-19) at the end of 2019, rapid tracing and isolation of confirmed cases and close contacts with restrictions on social movement have played an important role in controlling onward spread of the virus. Understanding the duration of infectiousness in persons who test positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is critical to developing evidence-based public health policies on isolation, contact tracing and return to work. Virus detection by reverse transcription-PCR (RT-PCR) from respiratory samples is widely used to diagnose and monitor SARS-CoV-2 infection and, increasingly, to infer infectivity of an individual. However, RT-PCR does not distinguish between infectious and non-infectious virus. Propagating virus from clinical samples confirms the presence of infectious virus but is not widely available, requires biosafety level 3 facilities, and the results are not timely to inform public health actions. The aim of this work was to understand how RT-PCR detection relates to cultivable virus, which can be used as a proxy for infectiousness and can inform and support decisions on infection control.

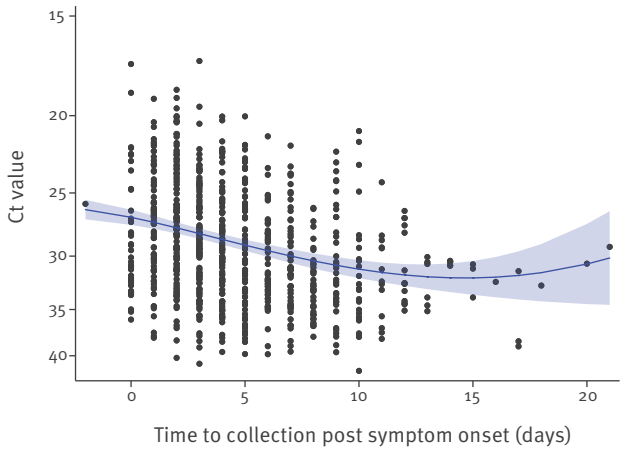
Kinetics of viral RNA detection from the respiratory tract

Upper respiratory tract (URT) samples from persons with suspected COVID-19 were tested at the national respiratory virus reference laboratory at Public Health England to support routine clinical care and surveillance activities during the COVID-19 pandemic. Samples included nose, throat, combined nose-and-throat and nasopharyngeal swabs, or nasopharyngeal aspirates; the majority were taken by clinical staff but some were self-sampled nose swabs.

In the first 3 months of the COVID-19 pandemic in the United Kingdom (UK) (late January to early April 2020), we received 754 URT samples from 425 symptomatic cases that tested positive for SARS-CoV-2 by RT-PCR targeting the RNA-dependent RNA polymerase (RdRp) gene [1] and that had a clear record of the dates of symptom onset and sample collection. These samples were collected as part of the First Few 100 surveillance study described in Boddington et al. [2]. Using RT-PCR cycle threshold (Ct) values as a semiquantitative measure of SARS-CoV-2 viral load identified that the level of SARS-CoV-2 RNA in the URT was greatest around symptom onset, steadily decreased during the first 10 days after illness onset and then plateaued (Figure 1). In the first week after symptom onset (days −2 to 7), geometric mean (GM) Ct was 28.18 (95% confidence interval (CI): 27.76–28.61). In the second week (days 8 to 14), GM Ct was 30.65 (95% CI: 29.82–31.52; $p < 0.001$ compared with week 1) and after 14 days, GM Ct was 31.60 (95% CI: 31.60–34.49; $p = 0.01$ compared with week 1). There was no significant difference in Ct values between days 8–14 and after 14 days ($p = 0.49$).

Figure 1

Detection of SARS-CoV-2 by RT-PCR targeting the RdRp gene, England, January–April 2020 (n = 754)

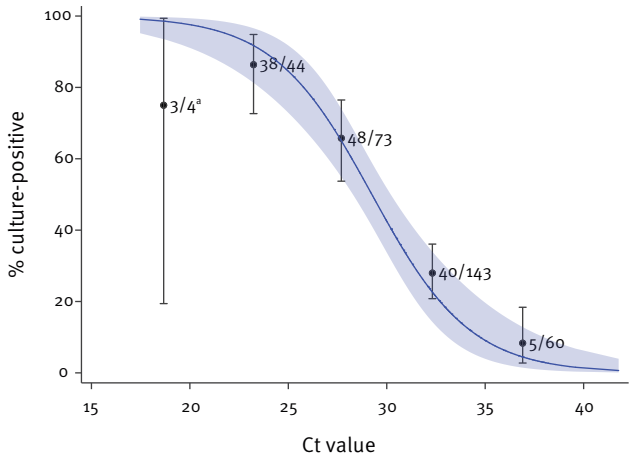


Ct: cycle threshold.

To capture the nonlinear relationship between days post symptom onset (days) and Ct value, a fractional polynomial model was used, indicating predictors days2 and days2ln(days). These were fitted in a random intercept regression model with ln(Ct value) as the outcome variable. Analysis accounted for multiple samples from the same individuals. The random intercept for individuals was not statistically significant, providing no evidence for dependencies within person, thus each individual sample was treated as being independent. The y axis was created in Stata 15.1 with reversed log scale*.

Figure 2

Relationship between RT-PCR Ct value and culture positivity in mixed effects logistic regression analysis, SARS-CoV-2, England, January–May 2020 (n = 324)



Ct: cycle threshold.

[a] Wide confidence intervals due to small sample size.

Isolation of infectious virus from respiratory samples

Virus culture was attempted from 324 URT samples (from 253 cases) that tested positive for SARS-CoV-2 by RT-PCR. Samples were obtained from a range of clinical scenarios including community and healthcare worker surveillance, symptomatic persons tested as part of the early epidemic response and samples acquired in outbreak investigations. Selection of asymptomatic cases was through swabbing of contacts or facility/family/household testing in the context of outbreak investigations; we cannot be certain of their date of exposure or start of infection. Vero E6 cells were inoculated with clinical specimens and incubated at 37°C, 5% CO_2. Cells were inspected for cytopathic effect daily up to 14 days. Presence of SARS-CoV-2 was confirmed by SARS-CoV-2 nucleoprotein staining by enzyme immunoassay on infected cells. Cultivable virus was isolated from 133 (41%) samples (from 111 cases).

Median Ct of all 324 samples was 31.15 (interquartile range (IQR): 27.50–33.86; range: 17.47–41.78). Some 233 cases (92%) were classified as non-severe (asymptomatic or mild-to-moderate) and 20 (8%) had severe illness (requiring intensive care admission and/or fatal). There was no difference in Ct values between those with asymptomatic (median Ct = 31.23; IQR: 28.21–32.97), mild-to-moderate (median Ct = 30.94; IQR: 27.08–34.57) or severe (median Ct = 32.55; IQR 28.39–33.66) illness (p = 0.79). A stratified comparison of the severe cases over time showed a similar result as described above: Ct values were lower (higher viral load) in week 1 than week 2. There were 62 samples from 61 asymptomatic cases and no difference in culture positivity rate was observed: 21 of 62 samples from asymptomatic individuals vs 112 of 262 samples from symptomatic individuals (estimated odds ratio (OR) = 0.66; 95% CI: 0.34–1.31; mixed effects logistic regression model, p = 0.23).

Relationship between Ct value and virus isolation

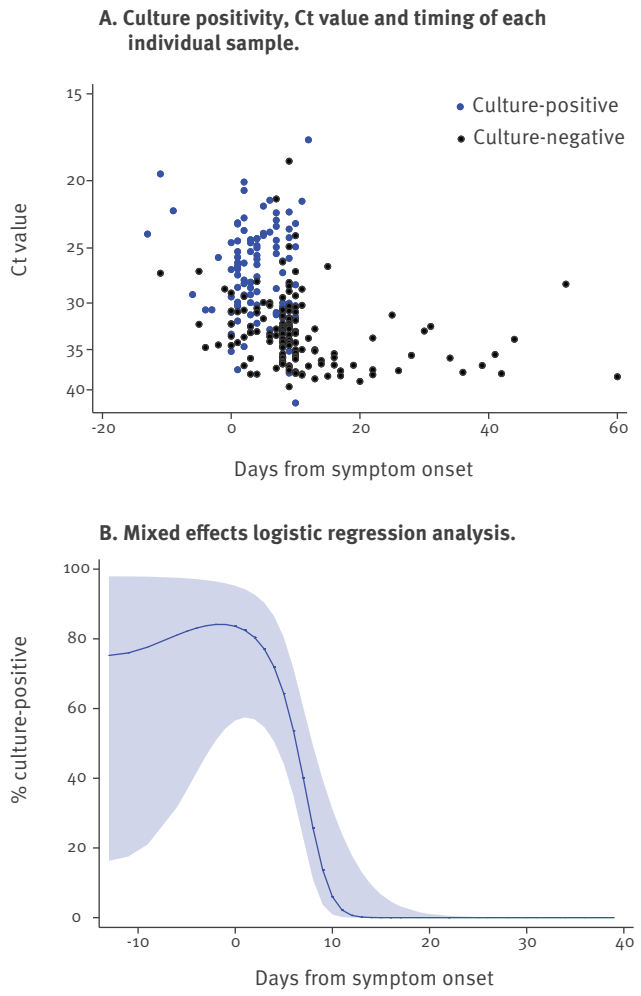
We observed a strong relationship between Ct value and ability to recover infectious virus. The estimated OR of recovering infectious virus decreased by 0.67 for each unit increase in Ct value (95% CI: 0.58–0.77) (Figure 2). Virus propagation was successful from five of 60 samples with Ct›35; all five were from symptomatic cases and none had severe illness. The estimated probability of recovery of virus from samples with Ct›35 was 8.3% (95% CI: 2.8%–18.4%).

Relationship between 'symptom to test' interval and virus isolation

There were 246 samples from 176 symptomatic cases where the date of symptom onset was known, of which 103 (42%) samples from 81 cases were culture-positive. Detection of cultivable virus peaked around the time of symptom onset (Figure 3). Median duration of virus shedding as measured by culture was 4 days (IQR: 1–8; range: –13 to 12, with symptom onset dates based on symptom recall). The culture positivity rate was significantly higher during week 1 than week 2 (74% vs 20%; p = 0.002). Ten days after symptom onset, the probability of culturing virus declined to 6.0% (95% CI: 0.9–31.2%) (Table 1). Where cases

Figure 3

Relationship between culture positivity and time between symptom onset and sample collection, SARS-CoV-2, England, January–May 2020 (n = 246)



Ct = cycle threshold. The y axis on Figure 3A was created in Stata 15.1 with reversed log scale*.

were followed up within outbreak investigations, 13 individuals who were asymptomatic at the time of sampling developed symptoms within 14 days of sampling and were classified as presymptomatic, of whom seven were culture-positive. Regression analysis indicates that presymptomatic samples were at least as likely to be culture-positive as samples taken during symptomatic phases.

More than half the samples (n = 130, 53%) tested (from 91 cases) were received more than 7 days after symptom onset and 21% of those (27 samples from 18 cases) were culture-positive; none of the 91 patients had severe illness or were immunosuppressed. Most of these late culture-positive samples (25/27) were taken between 8 and 10 days after symptom onset.

Comparison of virus detection by age group

There was no significant difference in Ct values (p = 0.12) or culture positivity (p = 0.63) from URT samples received across the different age groups, although this dataset included few children younger than 16 years. The proportion of asymptomatic cases was similar across age groups, except for 81–100 year-olds who were more likely to be asymptomatic than the other age groups (p = 0.006, cluster-adjusted logistic regression) (Table 2). There was no difference in the proportion of asymptomatic cases between males and females, with an estimated OR of 0.86 (95% CI: 0.46–1.90; p = 0.63).

Discussion

Readouts from semiquantitative RT-PCR using Ct values provide a valuable proxy for infectious virus detection and may help to inform decision-making on infection control. This study adds to the evidence base on duration of infectiousness following mild-to-moderate COVID-19, demonstrating that infectious virus can persist for a week or more after symptom onset, declining over time. At 10 days after symptom onset, in line with current guidance from the World Health Organization [3] and the UK [4] on release from isolation, probability of culturing virus declines to 6%. The findings concur with smaller studies that identified infectious virus shed for 8 or 9 days [5-9] and others demonstrating correlation between Ct value/viral load and cultivable virus [5,9-11]. Strengths include the comparatively large size of this dataset, inclusion of a large proportion (> 50%) of samples taken more than 7 days after symptom onset and that all analysis was performed in a single laboratory. Van Kampen et al. reported more prolonged detection of cultivable virus from 23 hospitalised cases, for up to 20 days after symptom onset [10]. However, their cohort included mostly lower respiratory tract samples from patients with more severe disease including nearly one in five who were immunocompromised, which is unlikely to be representative of the general population. Taken together with data presented here, the results of Van Kampen et al. indicate that more prolonged excretion of infectious virus could be associated with severe disease or an immunocompromised state.

This study identified that Ct values and the presence of infectious virus were similar in samples from asymptomatic and presymptomatic persons, compared with those who were symptomatic, and is one of the first reports of virus isolation from cases who remain completely asymptomatic. The findings suggest that asymptomatic and presymptomatic persons do represent a source of potentially transmissible virus. Extensive data on cultivable virus from asymptomatic or presymptomatic individuals are lacking, with one outbreak investigation in a care home reporting detection of cultivable virus in one asymptomatic and 17 presymptomatic cases [8]. Although we saw a higher proportion of asymptomatic cases in the age group 81–100 years, the reasons and significance of this are unclear. It may reflect sampling bias from care home outbreaks. However, it could also reflect real differences in response to infection in this age group (e.g.

Table 1

Estimated percentage of SARS-CoV-2 samples culture-positive 7–15 days after symptom onset, England, January–May 2020 (n = 121)

Day post symptom onset	Estimateda percentage culture-positive (95% CI)	N (observed number tested)	R (observed number culture-positive
7	40.1 (22.8–60.4)	14	10
8	25.8 (11.0–49.4)	33	9
9	13.7 (3.7–39.6)	34	10
10	6.0 (0.9–31.2)	23	6
11	2.2 (0.2–23.9)	6	1
12	0.7 (0.0–17.9)	3	1
13	0.2 (0.0–13.1)	4	0
14	0.03 (0.0–9.4)	2	0
15	0.006 (0.0–6.7)	2	0

CI: confidence interval.

[a] From mixed effects logistic regression model.

Table 2

Comparison of virus detection and presence of symptoms, by age group, England, January–May 2020 (n = 324)

Age group in years	Number of cases	Ct value		Virus isolation		Asymptomatic cases	
		Geometric mean	95% CI	Estimated % culture-positive	95% CI	%	95% CI
0–20	14	28.81	26.50–31.33	57.8	26.7–83.8	14.3	3.0–47.3
21–40	81	30.81	29.77–31.90	43.2	30.7–56.5	17.5	10.0–28.9
41–60	140	30.83	30.03–31.65	37.7a	27.8–48.7	13.6	8.6–20.8
61–80	40	29.87	28.42–31.38	41.3	24.4–60.5	17.5	7.8–34.6
81–100	49	29.09	27.84–30.41	32.1	18.8–49.2	40.8	27.4–55.7

CI: confidence interval; Ct: cycle threshold.

Estimated geometric mean Ct value, proportion culture-positive and proportion asymptomatic from random intercept linear, random intercept logistic regression and cluster adjusted logistic regression models.

[a] Total excluding one case because one sample was cytotoxic on cell culture.

lower response to fever, lower reporting of subjective symptoms in this age group).

Of note, recall bias may affect the interpretation of timing of virus detection in relation to symptom onset, particularly in elderly patients and those presenting with atypical symptoms. Duration and cessation of symptoms is also not well recorded. For asymptomatic cases, the time when infection was acquired is not known. A further limitation is that this dataset comprises real-world data and subjects were not sampled systematically; therefore, there may be bias in the timing of sampling related to the clinical scenario. Finally, the sensitivity of virus propagation from clinical samples is dependent on laboratory expertise, cell lines and protocols used, and may be affected by sample quality, storage and transport conditions, meaning it is difficult to directly compare data between laboratories described in other literature.

Conclusion

Based on the real-world data described here, we recommend that infection control measures for persons with mild-to-moderate COVID-19 be particularly focussed immediately after onset of symptoms and retained for 10 days. Asymptomatic and presymptomatic persons are likely to be a source of infectious virus. Detection of cultivable SARS-CoV-2 from URT samples is valuable as a proxy for infectiousness; however, as the human infectious dose remains unknown, the significance of low titres of infectious virus for human-to-human transmission remains uncertain. Correlation with observational epidemiological data analysing known infector–infectee pairs is required to fully understand the dynamics of infectiousness and viral transmissibility.

*Authors' correction

An explanatory comment was added on 18 February 2021 to the footnotes of Figures 1 and 3.

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Conflict of interest

None declared.

Authors' contributions

A. Singanayagam collated and analysed the data and wrote the first draft of the manuscript; A. Charlett performed the statistical analysis and constructed figures; M. Patel and R. Gopal designed and performed laboratory experiments; J. Ellis supervised the laboratory PCR work, J. Lopez Bernal, V. Saliba and S. Ladhani coordinated collection of clinical data. M. Zambon supervised and coordinated the samples and testing and critically revised the first version. All authors approved the final version of the manuscript.

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BRIEF REPORT

Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards

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Abstract

In a preliminary clinical study, we observed that the combination of hydroxychloroquine and azithromycin was effective against SARS-CoV-2 by shortening the duration of viral load in Covid-19 patients. It is of paramount importance to define when a treated patient can be considered as no longer contagious. Correlation between successful isolation of virus in cell culture and Ct value of quantitative RT-PCR targeting E gene suggests that patients with Ct above 33–34 using our RT-PCR system are not contagious and thus can be discharged from hospital care or strict confinement for non-hospitalized patients.

Keywords SARS-CoV2 · Covid-19 · RT-PCR · Co-culture · Viral load · Correlation

Introduction

An outbreak of an emerging disease (Covid-19) due to SARS-CoV-2 started in Wuhan, China, then rapidly spread in China, and was declared pandemic on March 12, 2020, by the WHO [1–3]. Currently, the overall case fatality rate is about 2.3% in China, which is likely an overestimate because most patients have mild symptoms and are thus not tested [4]. Because of a study showing that chloroquine and hydroxychloroquine inhibit SARS-CoV-2 in vitro, we tested hydroxychloroquine as a treatment in Covid-19 patients [5, 6]. Our results show that in treated patients, the nasopharyngeal viral load of SARS-CoV-2-infected patients was cleared in only 3 to 6 days. Our results also suggest a synergistic effect of the combination of hydroxychloroquine and azithromycin, two molecules previously demonstrated to be active in vitro against Zika and Ebola viruses [7–10] and to prevent severe respiratory tract infections when administered to patients suffering viral infection [11]. These results are of great importance because a recent paper has shown that the median duration of viral RNA detection in patients suffering from Covid-19 in China was 20 days, with the longest duration being 37 days [12]. We are now facing a massive influx of patients in need of treatment and hospitalization, ideally in infectious disease wards equipped with NSB3 modules with negative pressure. Thus, in addition to obtaining complete disappearance of virus RNA in respiratory samples, having a PCR-based indicator of loss of contagiousness is a major priority for discharge from infectious diseases ward. Based on a set of 183 samples from 155 patients, we observed a significant relationship between viral RNA load and culture positivity.

The Méditerranée Infection University Hospital Institute in Marseille is the reference center for highly infectious diseases for Southeastern France. It was the only center in this region with diagnostic tests available during the first weeks of the epidemic in France and received patients' samples from this whole area. From the day of the first positive test, on February 27 until March 12, 4384 clinical samples were tested by RT-PCR for 3466 patients. Since the beginning of this crisis and until now, on March 26, we inoculated 1049 samples and could obtain in culture 611 SARS-CoV-2 isolates. A total of 183 samples testing positive by RT-PCR, including 9 sputum samples and 174 nasopharyngeal swabs from 155 patients, were inoculated in cell cultures. SARS-CoV-2 RNA positivity in patient samples was

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assessed by real-time reverse transcription-PCR targeting the E gene, as previously described [13]. For all patients, 500 μL of nasopharyngeal swab fluid (Virocult, Elitech, France) or sputum sample were passed through 0.22-μm pore sized centrifugal filter (Merck Millipore, Darmstadt, Germany) and then were inoculated in 4 wells of 96-well culture microplates containing Vero E6 cells (ATCC CRL-1586) into Minimum Essential Medium culture medium with 4% fetal calf serum and 1% glutamine. All samples were inoculated between 4 and 10 h after sampling and kept at + 4 °C before processing. After centrifugation at 4000×*g*, microplates were incubated at 37 °C. They were observed daily for evidence of cytopathogenic effect. Two subcultures were performed weekly. Presumptive detection of virus in supernatant showing cytopathic effect was done using the SU5000 scanning electron microscope (Hitachi High-Tech Corporation, Tokyo, Japan) and then confirmed by specific RT-PCR targeting E gene. Variation of culture positivity rate was assessed statistically as the proportion of variance explained by Ct value and considered adequately fitted if the coefficient of determination (R^2 statistic) was > 50%.

Among the 183 samples inoculated in the studied period of time, 129 led to virus isolation. Of these, 124 samples had detectable cytopathic effect between 24 and 96 h. Blind subcultures allowed obtaining 5 additional isolates only. We observed a significant relationship between Ct value and culture positivity rate (Fig. 1). Samples with Ct values of 13–17 all led to positive culture. Culture positivity rate then decreased progressively according to Ct values to reach 12% at 33 Ct. No culture was obtained from samples with Ct ≥ 34. The 5 additional isolates obtained after blind subcultures had Ct between 27 and 34, thus consistent with low viable virus load.

In the present work, we observe a strong correlation between Ct value and sample infectivity in a cell culture model. On the basis of this data, we can deduce that with our system, patients with Ct values equal or above 34 do not excrete infectious viral particles. It was observed that SARS-CoV-2 was detected up to 20 days after onset of symptoms by PCR in infected patients but that the virus could not be isolated after day 8 in spite of ongoing high viral loads of approximately 10^5 RNA copies/mL of sample, using the RT-PCR system used in the present study [14]. Progressive decrease of viral load over time is observed in all studies conducted in Covid-19 patients with positive detection being observed until 17–21 days after onset of symptoms, independently of symptoms [15]. These previous observations suggested that isolation of patients after diagnosis was mandatory. However, due to prolonged shedding of RNA in respiratory samples, the criteria for ending the isolation of a patient were not clear, and there was a need to correlate viral load to cultivable viruses. Our results show that in our system of RT-PCR, we can assess that patients with Ct equal or above 34 may be discharged. In 6 patients under the current therapeutic protocol used at our institute (hydroxychloroquine and azithromycin), Ct values ≥ 34 were obtained between days 2 and 4 post-treatment [6]. There is no previous correlation demonstrated between level viral load in respiratory samples and infectivity. However, this reduction is the basis of all procedures used for the validation of disinfectants [16]. One limitation of our work is that it cannot be extrapolated to other hospital centers since they use different systems of sample transport, of RNA extraction, and of PCR with different primers and probes; i.e. it has been suggested that sensitivity of amplification based on Gene E detection

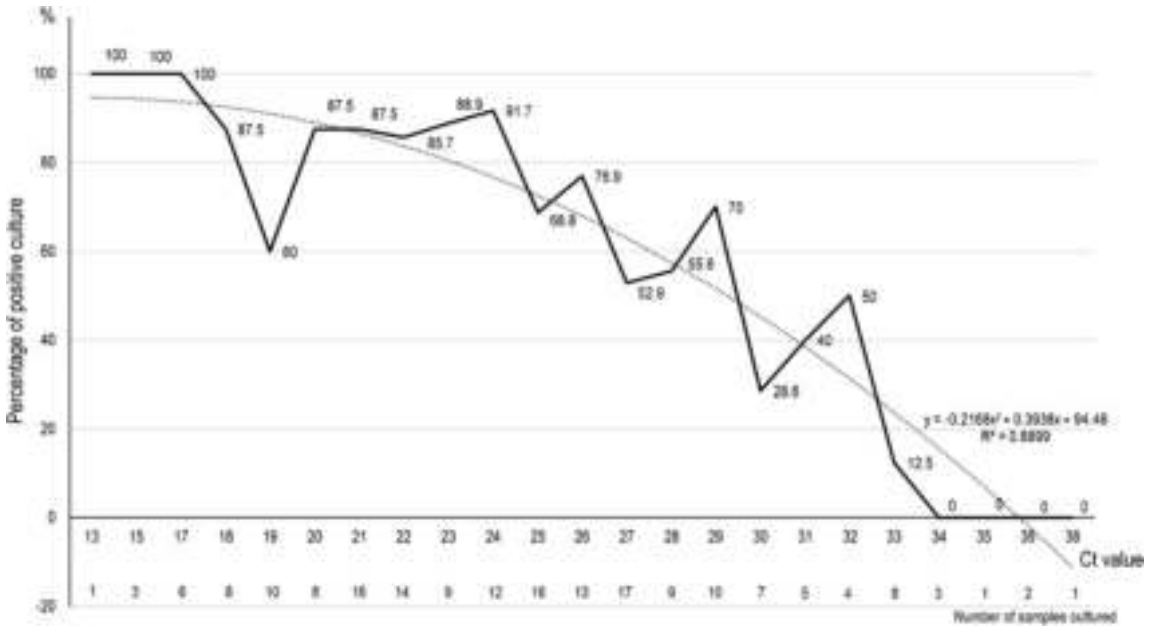

Fig. 1 Percentage of positive viral culture of SARS-CoV-2 PCR-positive nasopharyngeal samples from Covid-19 patients, according to Ct value (plain line). The dashed curve indicates the polynomial regression curve

would be less sensitive than ORF1ab or N genes. We propose that each center perform its own correlation between culture results and viral RNA load from patients' samples. Another potential limitation is that nasopharyngeal swab fluid might be less representative than sputum samples. However, from the data obtained from patients rather tested in sputum, the viral load follows the same reduction with time of evolution than upper respiratory specimens [17].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The protocol was approved by the ethical committee of the University Hospital Institute Méditerranée Infection (No. 2020-01).

Informed consent All subjects gave a written informed consent in accordance with the Declaration of Helsinki.

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Article

Assessing Viral Shedding and Infectivity of Asymptomatic or Mildly Symptomatic Patients with COVID-19 in a Later Phase

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Abstract: Background: The coronavirus disease (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a major global public health issue. SARS-CoV-2 infection is confirmed by the detection of viral RNA using reverse transcription polymerase chain reaction (RT-PCR). Prolonged viral shedding has been reported in patients with SARS-CoV-2 infection, but the presence of viral RNA does not always correlate with infectivity. Therefore, the present study aimed to confirm the presence of viable virus in asymptomatic or mildly symptomatic patients in the later phase of the disease, more than two weeks after diagnosis. Method: Asymptomatic or mildly symptomatic COVID-19 patients who had been diagnosed with the disease at least two weeks previously and admitted to a community treatment center (CTC) from 15 March to 10 April 2020 were enrolled in this study. Nasopharyngeal and salivary swab specimens were collected from each patient. Using these specimens, RT-PCR assay and viral culture were performed. Result: In total, 48 patients were enrolled in this study. There were no significant differences in baseline characteristics between the asymptomatic and mildly symptomatic patient groups. RT-PCR assay and viral culture of SARS-CoV-2 were performed using nasopharyngeal and salivary swabs. The results of RT-PCR performed using salivary swab specimens, in terms of cycle threshold (Ct) values, were similar to those of RT-PCR using nasopharyngeal swab specimens. In addition, no viable virus could be cultured from swab specimens collected from the late-phase COVID-19 patients with prolonged viral RNA shedding. Conclusions: In conclusion, our study suggests that even if viral shedding is sustained in asymptomatic or mildly symptomatic patients with later phase of COVID-19, it can be expected that the transmission risk of the virus is low. In addition, saliva can be used as a reliable specimen for the diagnosis of SARS-CoV-2 infection.

Keywords: coronavirus disease 2019; COVID-19; RT-PCR; viral culture; saliva

1. Introduction

The coronavirus disease (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a major global public health issue. At the time of writing,

the massive viral outbreak has affected 216 countries, with more than 13 million people infected and 580,000 having died [1].

In South Korea, the number of patients has increased rapidly since February 2020. For the proper management of COVID-19 patients, asymptomatic or mildly symptomatic patients were admitted to community treatment centers (CTCs), which are non-medical facilities for isolation and monitoring.

However, patients with prolonged viral RNA detection after resolution of symptoms presented difficulties in terms of their safe discharge from isolation. For efficient distribution of medical resources, the revised WHO discharge guidelines recommend that symptomatic patients should be discharged 10 days after the onset of symptoms, following at least three additional days without symptoms, and that asymptomatic patients should be discharged 10 days after testing positive for SARS-CoV-2 [2].

Diagnosis of COVID-19 is achieved using a nasopharyngeal swab. At present, real-time reverse transcription polymerase chain reaction (RT-PCR) analysis of respiratory specimens is the gold standard test for detecting SARS-CoV-2 infection [3].

Over the course of infection, viral RNA has been identified in respiratory tract specimens 1–3 days prior to the onset of symptoms. The viral load is thought to persist for up to 7–10 days after the onset of symptoms in mild cases. In more severe cases, it tends to peak up to 11 days after the onset, followed by gradual decrease over time [4]. Viral RNA has been detected in various specimens of the human body, such as the upper and lower respiratory tract, blood, pharyngeal swabs, saliva, urine, and feces [5,6].

Prolonged viral shedding has been reported from nasopharyngeal swabs up to 63 days after the onset of symptoms among adult patients [7,8]. However, viral shedding of SARS-CoV-2 does not always indicate infectivity, unless the virus is isolated and cultured from the specimens. The revised WHO release criteria do not require additional examination prior to discharge. Therefore, there is a residual risk that the disease can still spread when these criteria are adhered to. Accordingly, in late-phase COVID-19 patients with prolonged viral RNA detection, it is important to determine the risk of transmission.

In this study, we attempted to confirm the presence of viable virus by performing RT-PCR assay and culture using salivary and nasopharyngeal swabs of asymptomatic or mildly symptomatic COVID-19 patients who had been diagnosed with the disease and admitted to a CTC at least two weeks previously.

2. Methods

2.1. Patients and Study Settings

Asymptomatic or mildly symptomatic COVID-19 patients who had been admitted to the CTC between March 15 and April 10, 2020 and had been diagnosed at least two weeks previously, were enrolled in the current study. Asymptomatic or mildly symptomatic COVID-19 patients were defined as those with an early warning score of <3 for SARS-CoV-2 infection [9]. Patients referred to other hospitals due to worsening of symptoms during isolation were excluded. Written informed consent was obtained from all study participants. Nasopharyngeal and salivary swab specimens were obtained from each patient. Ethical Statement: This study was approved by the Institutional Review Board (IRB number: 4-2020-0133) of Severance Hospital (Seoul, South Korea) and informed consent was obtained.

2.2. Definitions

RT-PCR assays targeting three genes of SARS-CoV-2, the E (envelope protein), RdRP (RNA-dependent RNA polymerase), and N (nucleocapsid protein) genes, were performed using the Allplex™ 2019-nCoV Assay (Seegene Inc., Seoul, South Korea) with nasopharyngeal and salivary swab specimens. Patients with negative RT-PCR results were tested again by RT-PCR the following day; those with positive RT-PCR results were re-tested by RT-PCR after a week; and those with inconclusive RT-PCR results were re-tested by RT-PCR after three days. The inconclusive result refers to a case in

which one or more, but not all genes included in the kit show an amplification curve after the cut-off when using a follow-up sample [10].

RT-PCR assay results were expressed as the cycle threshold (Ct) value. Ct values ≥ 40 were considered negative results. Negative conversion was defined as two consecutive negative RT-PCR results at a 24 h interval.

Rebound Ct value was defined as a negative (Ct value ≥ 40) from the single RT-PCR assay and positive (Ct value < 40) from the following RT-PCR result.

2.3. Nucleic Acid Extraction and RT-PCR for SARS-CoV-2

The nasopharyngeal swab sample was placed in 2 mL of viral transport medium. Saliva samples were collected in a sterile container and both specimens were stored frozen −70 °C. Nasopharyngeal swab specimens were subjected to total nucleic acid extraction using a viral RNA mini kit (QIAGEN, Hilden, Germany). After extraction, the total nucleic acid was recovered using 60 µL of elution buffer.

For salivary swab specimens, the same amount of PBS was added, and following the vortex process, RNA was extracted using the same process as for the nasopharyngeal swab samples. Using 8 µL of RNA, RT-PCR assay targeting the three genes of SARS-CoV-2 was performed using a Seegene Kit (Allplex 2019-nCoV Assay kit, Seegene, Korea). When the upper respiratory specimens including the nasopharyngeal swab were examined using the Allplex 2019-nCoV Assay, a Positive Percent Agreement (PPA) was 100% (95% CI: 92.75~100%), and a Negative Percent Agreement (NPA) was 93.07% (95% CI: 85.76~96.93%) [11].

2.4. SARS-CoV-2 Cell Culture

SARS-CoV-2 was cultured in a biosafety level 3 facility. Vero E6 cells were used for isolating SARS-CoV-2. Vero E6 cells were cultured in Eagle's minimum essential medium (EMEM) supplemented with heat-inactivated fetal bovine serum (FBS; 10%). Both nasopharyngeal and salivary swab specimens were used for virus isolation. Vero E6 cells were seeded with 1 mL of EMEM at a density of 1.5×10^4 cells/well in culture tubes and incubated at 37 °C in a carbon dioxide incubator for 24 h until confluence for inoculation was achieved.

The next day, each nasopharyngeal and salivary swab specimen was diluted at a ratio of 1:10 and inoculated into four wells containing EMEM (2% FBS, 1% P/S). Cells in the media were fixed with 10% formaldehyde and stained with 1% crystal violet dye.

The virus-induced cytopathic effect was examined daily for up to seven days [12,13].

3. Results

The analysis was performed on asymptomatic or mildly symptomatic COVID-19 patients who had been diagnosed and admitted to a CTC at least two weeks previously. In total, 48 patients were enrolled in this study. The mean age of all patients was 32.62 ± 14.59 years, and 14 of the patients were male (29.2%). Of all the patients, 11 (22.9%) were asymptomatic.

Baseline characteristics were similar between the symptomatic and asymptomatic patient groups. There was no statistically significant difference in terms of age, sex, comorbidities, and symptoms. The most common symptoms were myalgia (32.4%), fever (29.7%), and headache (24.3%); chest pain (2.7%) and vomiting (2.7%) were uncommon (Table 1).

Nasopharyngeal and salivary swab specimens were collected from the patients approximately 30.40 ± 5.71 days after initial diagnosis. The average Ct value of patients on the day of culture was over 30 in both the symptomatic and asymptomatic groups. A total of 17 cases (35.4%) showed rebound Ct values, which included 11 cases in the symptomatic group and 6 in the asymptomatic group (Table 2).

RT-PCR assay was performed using saliva specimens to determine the effectiveness of saliva as a diagnostic tool. As shown in Table 3, in the case of Patient 8, the saliva RT-PCR result was positive, although the RT-PCR result of the nasopharyngeal swab specimen was negative. Additionally, in eight patients, the mean Ct values of the nasopharyngeal and salivary swab specimens were

33.7 and 33.96, respectively, indicating that saliva swabs can serve as a reliable tool for diagnosing SARS-CoV-2 infection.

Table 1. Comparisons of demographic and clinical characteristics of asymptomatic and symptomatic patients with COVID-19.

Variables	Total (n = 48)	Symptomatic Group (n = 37)	Asymptomatic Group (n = 11)	p Value
Age, years	32.62 ± 14.59	31.84 ± 13.74	35.27 ± 17.62	0.499
Male, yes	14 (29.2)	12 (32.4)	2 (18.2)	0.361
Smoker	5 (10.4)	5 (13.5)	0 (0.0)	0.198
Comorbidity				
Hypertension	4 (8.3)	2 (5.4)	2 (18.2)	0.178
Allergy	4 (8.3)	2 (5.4)	2 (18.2)	0.178
Malignancy	2 (4.2)	2 (5.4)	0 (0.0)	0.431
Diabetes	1 (2.1)	1 (2.7)	0 (0.0)	0.582
Asthma	1 (2.1)	1 (2.7)	0 (0.0)	0.582
Symptoms				
Myalgia	12 (25.0)	12 (32.4)	0 (0.0)	-
Fever	11 (22.9)	11 (29.7)	0 (0.0)	-
Chill	9 (18.8)	9 (24.3)	0 (0.0)	-
Headache	9 (18.3)	9 (24.3)	0 (0.0)	-
Anosmia	8 (16.7)	8 (21.6)	0 (0.0)	-
Ageusia	7 (14.6)	7 (18.9)	0 (0.0)	-
Rhinorrhea	7 (14.6)	7 (18.9)	0 (0.0)	-
Nasal stuffiness	7 (14.6)	7 (18.9)	0 (0.0)	-
Fatigue	7 (14.6)	7 (18.9)	0 (0.0)	-
Cough	6 (12.5)	6 (16.2)	0 (0.0)	-
Sputum	6 (12.5)	6 (16.2)	0 (0.0)	-
Sore throat	4 (8.3)	4 (10.8)	0 (0.0)	-
Dizziness	3 (6.3)	3 (8.1)	0 (0.0)	-
Diarrhea	3(6.3)	3 (8.1)	0 (0.0)	
Chest pain	1 (2.1)	1 (2.7)	0 (0.0)	-
Vomiting	1 (2.1)	1 (2.7)	0 (0.0)	-

COVID-19, coronavirus disease 2019; Continuous variables are shown as the mean ± standard deviation (SD) and categorical variables, as numbers (percentage).

Table 2. Virologic data of patients with COVID-19.

	Symptomatic Group (n = 37)	Asymptomatic Group (n = 11)	p Value
Period from diagnosis to culture			
Mean	30.78 ± 5.85	29.09 ± 5.26	0.394
Median	31 (20–40)	28 (21–41)	
Mean of Ct value on the day of culture			
E gene	30.55 ± 2.96	27.60 ± 0.47	-
RdRP gene	33.93 ± 3.43	31.56 ± 3.07	-
N gene	34.98 ± 2.89	33.94 ± 3.65	-
Cases with rebound of Ct value	11 (29.7)	6 (54.5)	0.131

Continuous variables are shown as the mean ± standard deviation (SD), median values (interquartile range), and categorical variables, as numbers (percentage). COVID-19, coronavirus disease 2019; Ct, cycle threshold; E, envelop protein; N, nucleocapsid protein; RdRP, RNA-dependent RNA polymerase; NPS, nasopharyngeal swab. Ct value presented in this table correspond to RT-PCR result of nasopharyngeal swabs.

Cell culture was performed using nasopharyngeal and salivary swab specimens to confirm the isolation of viable virus. Vero cells were inoculated with nasopharyngeal and salivary swab specimens and microplates were observed for the evidence of cytopathic effect. Specimens were collected from

patients at least 20 days after diagnosis, and we found no microplates showing any cytopathic effect with these specimens (Figures 1 and 2).

Table 3. Clinical characteristics and Ct value of patients with positive salivary RT-PCR result.

Items	Age	Sex	Comorbidity	Symptoms	Rebound	Ct Value	
						NPS	Saliva
Patient1	51	M	N	Y	N	36.6	31.1
Patient2	21	M	Allergy	Y	N	38.9	37.0
Patient3	23	F	N	Y	N	35.1	31.4
Patient4	25	F	N	Y	N	32.2	35.2
Patient5	31	F	N	Y	N	33.2	36.9
Patient6	54	F	N	N	N	34.5	35.1
Patient7	27	F	N	Y	N	25.4	29.3
Patient8	33	M	N	Y	Y	0.0	35.7
Average of Ct value						33.7	33.96

RT-PCR, reverse transcriptase polymerase chain reaction; Ct, cycle threshold; NPS, Nasopharyngeal swab.

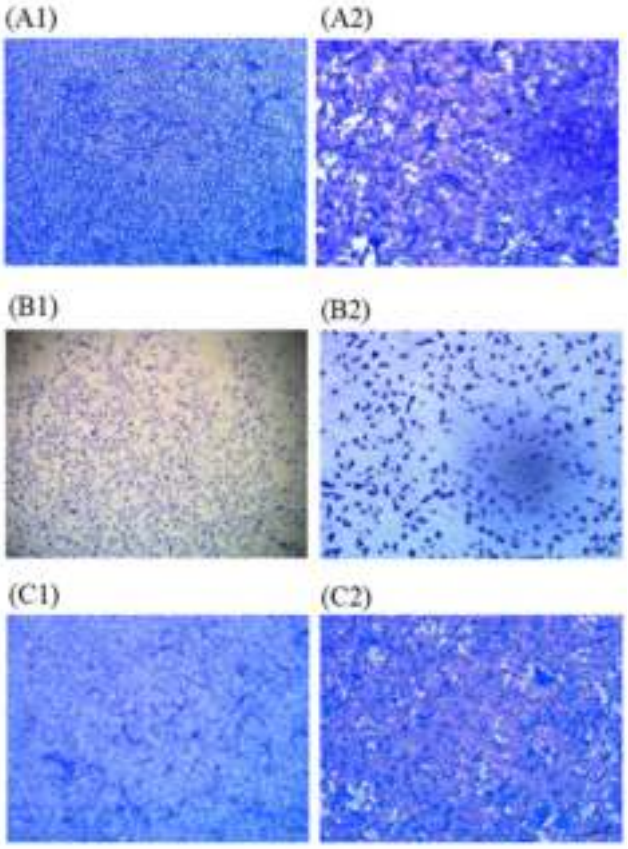

Figure 1. Microscopy image of vero monolayers. Vero cells were inoculated with nasopharyngeal swab. (A) Vero cell cultures in negative control. 40× (**A1**), 200× (**A2**) micrograph. (B) Vero cell cultures in positive control. 40× (**B1**), 200× (**B2**) micrograph. (C) Microscopy image of Vero cells inoculated with nasopharyngeal swab sample of a patient 33 days after diagnosis. No cytopathic effect was seen. 40× (**C1**), 200× (**C2**) micrograph. Virus stock used for positive control was obtained from the Centers for Disease Control and Prevention (KCDC, Seoul, Korea), the virus titer was 2.2×10^5 PFU/mL and the Ct value was 11 (KCDC03 43326).

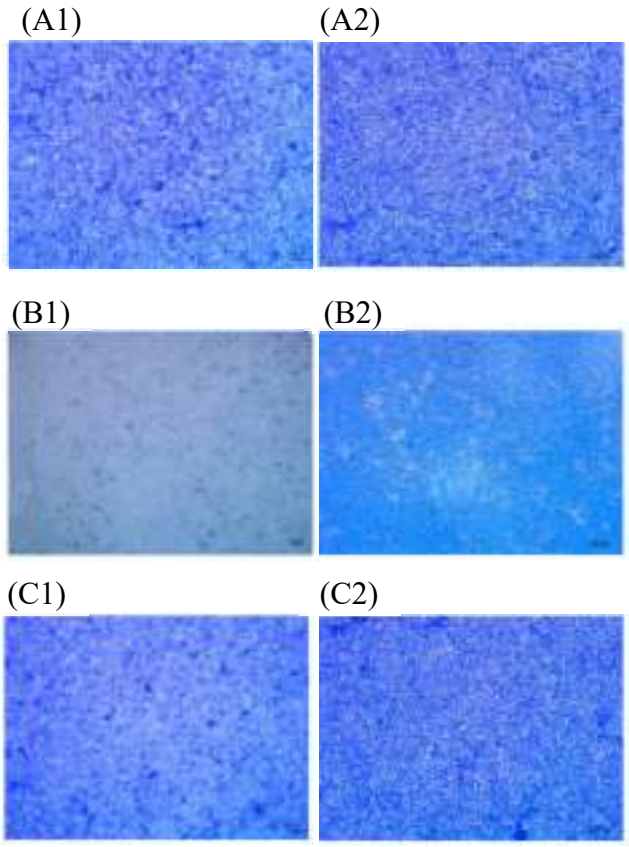

Figure 2. Microscopy image of vero monolayers. Vero cells were inoculated with salivary swab. (A) Vero cell cultures in negative control. 40× (**A1**), 100× (**A2**) micrograph. (B) Vero cell cultures in positive control. 40× (**B1**), 100× (**B2**) micrograph. (C) Microscopy image of Vero cells inoculated with salivary swab sample of a patient 33 days after diagnosis. No cytopathic effect was seen. 40× (**C1**), 100× (**C2**) micrograph. Virus stock used for positive control was obtained from the Centers for Disease Control and Prevention (KCDC), the virus titer was 2.2×10^5 PFU/mL and the Ct value was 11. (KCDC03 43326).

4. Discussion

In this study, we aimed to determine whether infectious viruses could be isolated using salivary and nasopharyngeal swab samples from patients with persistent positive RT-PCR results or rebound Ct values more than two weeks after diagnosis. SARS-CoV-2 could not be cultured from the patient specimens. Consequently, we surmised that there is no viral transmission risk in the later phase of SARS-CoV-2 infection. In addition, as indicated by the fact that the Ct values derived from salivary swab RT-PCR were similar to those of nasopharyngeal swab RT-PCR, saliva was shown to be an effective diagnostic tool for the detection of SARS-CoV-2.

SARS-CoV-2 infection is confirmed by detecting the presence of viral RNA through molecular testing, usually by RT-PCR [14]. The presence of viral RNA alone does not indicate that a patient is infectious or can transmit the virus to others. Factors affecting the transmission risk include whether the patient has symptoms, such as cough, which can spread droplets, whether a virus is infectious, and environmental factors or the behavior of the infected patient. Usually, 5 to 10 days after the initial SARS-CoV-2 infection, the patient begins to produce neutralizing antibodies. The binding of these neutralizing antibodies to the virus is expected to decrease the risk of viral transmission [4,15].

In many studies, viral shedding detected by RT-PCR from respiratory specimens has been found to persist for more than 20 days and sometimes up to 63 days after the onset of symptoms, and it appears to last beyond symptom resolution [6,8,16,17]. It has also been proven that transmission occurs in asymptomatic patients. In a study conducted by Zou et al., the viral loads of nasal and throat swabs

were similar in symptomatic and permanently asymptomatic patients [18]. In addition, in the present study, the Ct values of symptomatic and asymptomatic patients were not significantly different. This might be because in the late phase of infection the viral load is close to the detection limit, but there is evidence that viral shedding occurs in both symptomatic and asymptomatic patients after symptom improvement; however, the relationship between the detection of viral RNA and infectivity is still unclear. RT-PCR results do not necessarily indicate the possibility of viral transmission and cannot distinguish between infectious and non-infectious virus [7,15].

Viral RNA has been detected in the upper and lower respiratory tract, blood, pharyngeal swabs, saliva, urine, and feces, regardless of the severity of the disease [5,16]. The virus has also been detected in water gargled by patients diagnosed with COVID-19 [17]. We used saliva specimens for RT-PCR tests to confirm SARS-CoV-2 infection. It was confirmed that saliva showed a high concordance rate of 90% or more with the nasopharyngeal specimens in the detection of respiratory viruses including coronavirus [13,19,20].

A study by Zhou et al. indicated that angiotensin-converting enzyme II (ACE2) is likely the cell receptor for SARS-CoV-2; it was also the receptor for SARS-CoV and HCoV-NL63 [4]. According to a previous study, ACE2 is presented on the epithelial cells of oral mucosa, suggesting that the oral cavity might be at high risk of SARS-CoV-2 infection [21]. These findings suggest that ACE2-expressing cells may act as target cells and are therefore vulnerable to SARS-CoV-2 infection [22]. Since many viruses, including SARS-CoV-2, can be detected in saliva, saliva is considered a major factor in the risk of transmission of viruses that can cause respiratory infections [21]. In our study, a viral load was detected in saliva, therefore, saliva can also be expected to serve as an effective diagnostic tool.

Viral RNA tends to be detected for a longer period of time in more severe cases. According to several studies, viral RNA has been detected in respiratory tract specimens 1-3 days before the onset of symptoms. Viral load is thought to increase for up to 7–10 days after the onset of symptoms in mild cases. In more severe cases, it tends to peak up to 11 days after the onset, followed by gradual decrease over time [4,23]. Some studies have predicted that transmission risk is the highest at or around the time of symptom onset and during the first five days of disease [16].

Viral culture studies using patient specimens to confirm the presence of infectious SARS-CoV-2 are still limited. In some studies, viable viruses have been isolated from viral cultures using respiratory samples collected during the early stages of the disease or at least within eight days after the onset of symptoms [4]. According to a study investigating the relationship between the Ct value and culture positivity rate, all samples with Ct values of 13-17 led to positive culture; however, the culture positivity rate decreased as Ct values increased. Cultures could not be obtained from specimens with Ct values ≥ 34 [24]. In the present study, the mean Ct value of specimens was approximately >30, and no virus was isolated in cultures using these samples.

This study has several limitations. Firstly, the sample size of this study was small and larger studies are needed to confirm the relationship between infectivity loss and RT-PCR results. Secondly, the infectivity of individual cases and accuracy of our culture analysis may have individualized variations. Furthermore, subculture is known to improve the sensitivity of culture assays, but subculture was not performed in this study. Fourth, since serial saliva specimens were not available, serial viral load monitoring was not possible in this study. Finally, changes in the dynamics of viral shedding could have occurred due to the treatments administered to patients.

Although viral RNA can be detected in RT-PCR analyses even after the improvement of symptoms, the amount of viral RNA gradually decreases over time, eventually reducing below the level at which viable virus can be isolated. Therefore, based on the evidence that the virus is rarely detected in respiratory specimens after 10 days following the onset of symptoms, especially in mild or asymptomatic cases of SARS-CoV-2 infection, even if viral shedding is sustained in the later phase of COVID-19, it can be expected that the transmission risk of the virus is low. Accordingly, it seems safer to release patients from quarantine based on the revised WHO discharge criteria that require minimum isolation for 13 days, than to repeat RT-PCR assays. Although the transmission risk is thought to

be minimal in the later stages of COVID-19, it cannot be completely ruled out. Therefore, further investigations are warranted to understand the relationship between SARS-CoV-2 detection, viral culture, and transmission depending on the clinical course.

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ARTICLE

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Duration and key determinants of infectious virus shedding in hospitalized patients with coronavirus disease-2019 (COVID-19)

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Key questions in COVID-19 are the duration and determinants of infectious virus shedding. Here, we report that infectious virus shedding is detected by virus cultures in 23 of the 129 patients (17.8%) hospitalized with COVID-19. The median duration of shedding infectious virus is 8 days post onset of symptoms (IQR 5–11) and drops below 5% after 15.2 days post onset of symptoms (95% confidence interval (CI) 13.4–17.2). Multivariate analyses identify viral loads above 7 $\log_{10}$ RNA copies/mL (odds ratio [OR] of 14.7 (CI 3.57-58.1; $p < 0.001$) as independently associated with isolation of infectious SARS-CoV-2 from the respiratory tract. A serum neutralizing antibody titre of at least 1:20 (OR of 0.01 (CI 0.003-0.08; $p < 0.001$) is independently associated with non-infectious SARS-CoV-2. We conclude that quantitative viral RNA load assays and serological assays could be used in test-based strategies to discontinue or de-escalate infection prevention and control precautions.

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Coronavirus disease-2019 (COVID-19) is a new clinical entity caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1,2]. In particular, persons with underlying diseases, such as diabetes mellitus, hypertension, cardiovascular disease, and respiratory disease, are at increased risk for severe COVID-19, and case fatality rates increase steeply with age[3].

Understanding the kinetics of infectious virus shedding in relation to potential for transmission is crucial to guide infection prevention and control strategies[4]. Long-term shedding of viral RNA has been reported in COVID-19 patients, even after full recovery, putting serious constraints on timely discharge from the hospital or de-escalation of infection prevention and control practices[5–7]. Detection of viral RNA by reverse transcriptase-polymerase chain reaction (RT-PCR) is the gold standard for COVID-19 diagnosis and this technique is used in test-based strategies to discontinue or de-escalate infection prevention and control precautions[8–10]. However, there is no clear correlation between detection of viral RNA and detection of infectious virus using cell culture[5,11,12]. Detection of infectious virus, also called live virus or replication-competent virus, by demonstration of in vitro infectiousness on cell lines is regarded as a more informative surrogate of viral transmission than detection of viral RNA[8–10]. In a COVID-19 hamster model, the window of transmission correlated well with the detection of infectious virus using cell culture but not with viral RNA[13]. Key questions in COVID-19, like in any other infectious disease, are how long a person sheds infectious virus and what the determinants are of infectious virus shedding[5,11,12,14,15].

Two studies reported that infectious virus could not be detected in respiratory tract samples obtained more than 8 days after onset of symptoms despite continued detection of high levels of viral RNA[5,12]. For one patient, infectious virus shedding up to 18 days after onset of symptoms was reported[11]. Shedding of infectious SARS-CoV-2 has not been studied in larger groups of patients nor in patients with severe or critical COVID-19. Here, we show that patients with critical COVID-19 may shed infectious virus for longer periods of time compared to what has been reported for in patients with mild COVID-19. In addition, we show that infectious virus shedding drops to undetectable levels below a viral RNA load threshold and once serum neutralizing antibodies are present, which suggests that quantitative viral RNA load assays and serological assays could be used in test-based strategies to discontinue or de-escalate infection prevention and control precautions.

Results

We included 129 hospitalized individuals that had been diagnosed with COVID-19 by RT-PCR and for whom at least one virus culture from a respiratory tract sample was available (Table 1). Of these, 89 patients (69.0%) had been admitted to the intensive care and the remaining 40 patients (31.0%) were admitted to the medium care. Mechanical ventilation was only performed at the intensive care (81 or 91.0% of patients). Supplemental oxygen was given to 8 (9.0%) of the intensive care patients and to 35 (87.5%) medium care patients. Thirty patients were immunosuppressed (23%) of whom 19 (14.7%) were nonseverely immunocompromised and 11 (8.5%) were severely immunocompromised.

We tested 690 respiratory samples from the 129 patients for the presence of infectious virus using cell culture and determined the viral RNA load with RT-qPCR (Fig. 1). Infectious SARS-CoV-2 was isolated from 62 respiratory tract samples (9.0%) of 23 patients (17.8%). The median time of infectious virus shedding was 8 days post onset of symptoms (IQR 5–11, range 0–20) and probit analysis showed a probability of ≤5% for isolating infectious SARS-CoV-2 when the duration of symptoms was 15.2 days (95% CI 13.4–17.2) or more (Fig. 2A). The median viral load was significantly higher in culture positive samples than in culture negative samples (8.14 versus 5.88 Log_{10} RNA copies/mL, $p < 0.0001$) and the probability of isolating infectious SARS-CoV-2 was less than 5% when the viral load was below 6.63 Log_{10} RNA copies/mL (95% CI 6.24–6.91) (Fig. 2B).

For 27 patients, neutralizing antibody titers from 112 serum samples that were obtained on the same day as a respiratory tract sample were available in our diagnostic database (Table 2). The probability of isolating infectious virus was less than 5% when the neutralizing antibody titer was 1:80 or higher (Fig. 2C). In addition to these neutralizing antibody measurements, we performed RT-PCRs to detect SARS-CoV-2 subgenomic messenger RNA in the 112 corresponding respiratory tract samples. Detection of the subgenomic RNAs outlasted the detection of infectious virus (Supplementary Figs. 1 and 2), and predicted poorly if virus cultures were positive (positive predictive value of 37.5%). In addition, quantitative assessment of subgenomic RNA using cycle threshold (CT) values had no added value over measuring viral genomic RNA loads or serological response to predict infectious virus shedding (Supplementary Fig. 3).

Finally, the key parameters were compared using multivariate generalized estimating equations (Table 3). For this, timepoints for which all three data types (RT-qPCR, virus culture and serum neutralizing antibody titer) were available were included ($n = 112$). A viral load exceeding 7 Log_{10} RNA copies/mL, less than 7 days of symptoms, absence of serum neutralizing antibodies and being immunocompromised were all associated with a positive virus culture in univariate analysis. After submitting all these variables into a multivariate analysis, we found that only a viral load above 7 Log_{10} RNA copies/mL and absence of serum neutralizing antibodies were independently associated with isolation of infectious SARS-CoV-2 from the respiratory tract.

Discussion

In this study we assessed the duration and key determinants of infectious SARS-CoV-2 shedding in patients with severe and critical COVID-19. Such information is critical to design test-based and symptom-based strategies to discontinue infection prevention and control precautions. Both strategies only allow for discontinuation of infection prevention and control precautions after partial resolution of symptoms. Symptom-based strategies use as additional criterion that a certain time interval should have passed since onset of symptoms, while test-based strategies use negative SARS-CoV-2 RT-PCR results as main additional criterion.

The duration of infectious virus shedding found in this study was longer than has been reported previously[5,11,12]. Wölfel and colleagues showed for patients with mild COVID-19 that infectious virus could not be detected after more than eight days since onset of symptoms[5]. Bullard and colleagues obtained similar results, but disease severity was not reported[12]. Shedding of infectious virus up to 18 days after onset of symptoms has been reported for a single case of mild COVID-19[11]. The patients in this study had severe or critical COVID-19 and detection of infectious virus was common after eight days or more since onset of symptoms. For a single patient, infectious virus was detected up to 20 days after onset of symptoms. Higher viral loads have been reported for severe COVID-19 cases compared to mild cases, which may in part explain the longer duration of shedding found in this study[16–20]. Our findings imply that symptom-based strategies to discontinue infection prevention and control precautions should take diseases severity into account. For example, the CDC currently use a minimum disease duration of 10 days in their symptom-based strategy as the statistically estimated likelihood of recovering replication-competent virus approaches zero after ten days of symptoms[8,21]. Based on our findings, a longer disease duration could be considered for severely-ill patients.

High viral RNA loads were independently associated with shedding of infectious virus, but, upon seroconversion, shedding of

Table 1 Patient characteristics.

Characteristic	All	Intensive care	Ward	p value (ICU vs ward)
Number[a]	129	89 (69.0%)	40 (31.0%)	
Male	86 (66.7%)	65 (73.0%)	21 (52.5%)	0.04
Age (median—IQR)	65 (57–72)	66 (57–72)	63 (57–74)	0.90
Immunocompromised[b]				
Moderate	19 (14.7%)	10 (11.2%)	9 (22.5%)	0.04
Severe	11 (8.5%)	5 (5.6%)	6 (15.0%)	
Clinical parameters				
Mechanical ventilation	81 (62.8%)	81 (91.0%)	0	
Supplemental oxygen	43 (33.3%)	8 (9.0%)	35 (87.5%)	
Died	14 (10.9%)	11 (12.3%)	3 (7.5%)	
Duration of illness[c]				
Median (IQR)	18 (13–21)	18 (13–22)	15 (12–18)	0.009
Tests per patient, total (mean per person)				
Culture	690 (5.3)	601 (6.8)	89 (2.2)	
PRNT	112 (0.9)	82 (0.9)	30 (0.8)	
PCR	688 (5.3)	599 (6.7)	89 (2.2)	

[a]Disease severity classification according to NIH criteria (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/): 81/129 (62.5%) critical disease, 43/129 (33.3%) severe disease, 5/129 (3.9%) moderate disease.
[b]Immunocompromised level was scored as described previously[25]. Patients with severe immunosuppression ($n = 11$): Lung transplantation, or other solid organ transplantation and treatment for rejection within the last 3 months ($n = 3$); Underlying disease treated with daily corticosteroid dosages (based on prednisone) >30 mg for >14 days and/or immunomodulating biologicals ($n = 4$); Allogeneic hematopoietic stem cell transplantation within the last 12 months, or allogeneic hematopoietic stem cell transplantation with with graft-versus-host-disease treated with immunosuppressive drugs, or acute leukemia ($n = 4$). Patients with nonsevere immunosuppression ($n = 19$): Untreated auto-immune disease or underlying disease treated with immunosuppressive drugs (excluding treatment with daily corticosteroid dosages (based on prednisone) >30 mg for >14 days and/or treatment with immunomodulating biologicals) ($n = 10$); At least 1 year after solid organ transplantation (excluding lung transplantation) and no rejection ($n = 3$); Hematological malignancies (excluding acute leukemia and leukemia treated with induction therapy or chemotherapy resulting in neutropenia for >7 days) ($n = 4$); Other nonsevere immunodeficiencies ($n = 2$).
[c]As of April 17th 2020. PRNT = plaque-reduction neutralization titer. Respiratory tract samples for virus culture and PCR were obtained from the lower respiratory tract (sputum) on the intensive care unit (538/690 samples, 78%) and from the upper respiratory tract (swabs) on the intensive care unit as well as on the medium care unit (152/690 samples, 22%). A total of 127 out of the 690 respiratory tract samples that were submitted for virus culture (18.4%) were obtained from immunocompromised patients. For categorical variables a two-sided Chi-square test was used and for continuous variables a two-sided student's *t*-test was used. No adjustments were made for multiple comparisons.

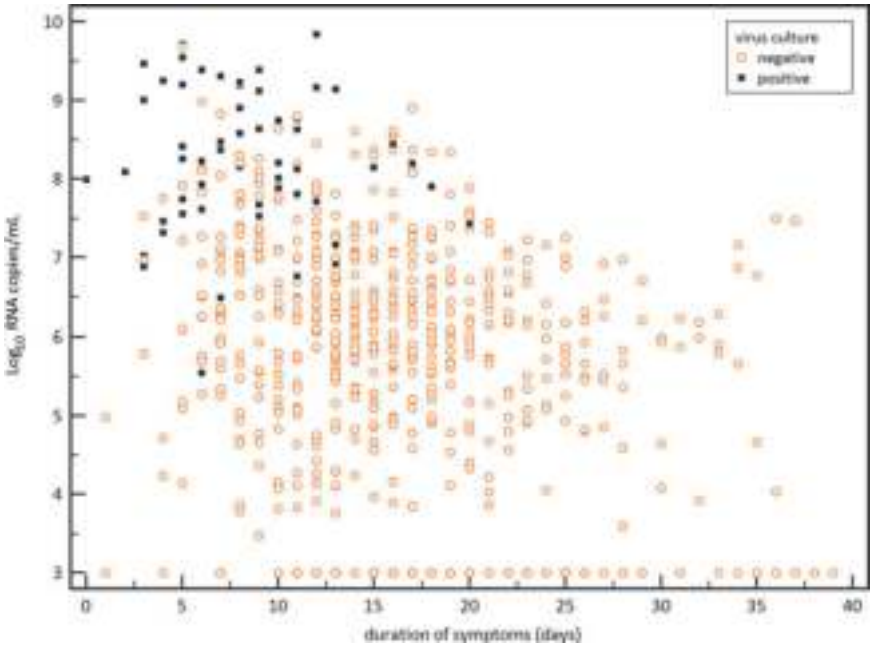

Fig. 1 Viral loads and duration of symptoms for infectious virus shedding. Viral RNA loads (Log_{10} RNA copies/mL) in the respiratory samples versus the duration of symptoms (days). Black boxes represent virus culture positive samples and open red circles represent the virus culture negative samples.

infectious virus dropped rapidly to undetectable levels. Infectious virus could not be isolated from respiratory tract samples once patients had a serum neutralizing antibody titer of at least 1:80. These results warrant the use of quantitative viral RNA load assays and serological assays in test-based strategies to discontinue or de-escalate infection prevention and control precautions. The probability of isolating infectious virus was less than 5% when viral RNA load was below 6.63 Log10 RNA copies/mL, which is strikingly similar compared to the cutoff of 6.51 Log10 RNA copies/mL reported by Wölfel et al.[5]. In addition, Bullard and colleagues used cycle threshold (ct) values as quantitative measure for viral RNA load and reported that infectious virus could not be isolated from diagnostic samples when ct values were above 24[12]. Together, these results indicate that viral RNA load cutoffs could be used in test-based strategies to discontinue infection prevention and control precautions. In addition, we report here a very strong association between neutralizing antibody response and shedding of infectious virus with an odds ratio of 0.01 for isolating infectious virus after seroconversion. Antibody responses were measured with a plaque-reduction neutralization test (PRNT)[22]. Neutralization assays, which are the gold standard in coronavirus serology, are labor-intensive and require a biosafety level 3 laboratory. We have recently cross-validated various commercial immunoassays using our PRNT50% as gold standard. Some commercial assays showed good agreement with our PRNT50%: For example, the

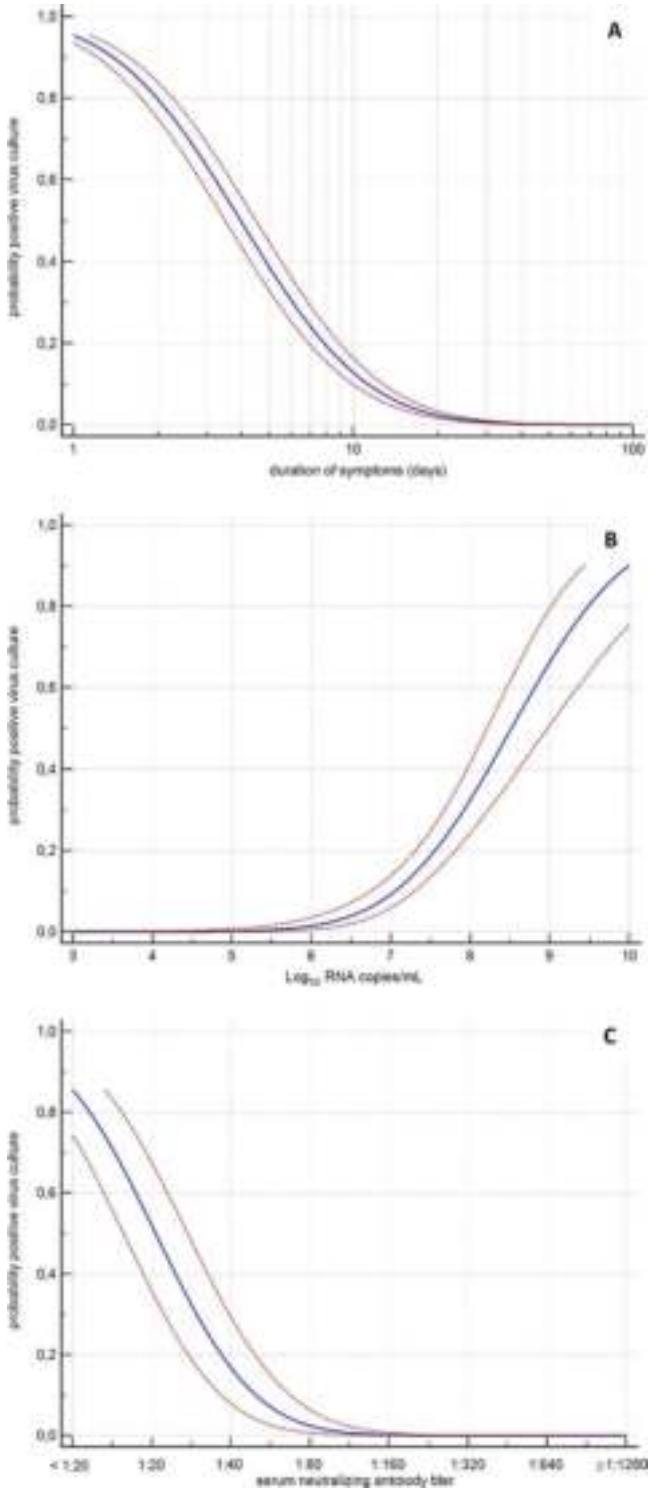

Fig. 2 Probabilities of infectious virus shedding. Probit analyses of the detection of infectious virus in respiratory samples with cell culture for duration of symptoms in days (**A**) ($n = 690$ samples), viral RNA load in Log10 copies per mL (**B**) ($n = 688$ samples), and serum neutralizing antibody titer (**C**) ($n = 112$ samples). Blue line represent the probit curve and the dotted red lines represent the 95% confidence interval. Serum neutralizing antibody titers are expressed as plaque-reduction neutralization titers 50% as described previously[27].

Table 2 Serum neutralizing antibody titers and isolation of infectious virus from the respiratory tract.

Serum neutralizing antibody titer	Total number samples	Number culture positive samples (%)	Number culture negative samples (%)
<1:20	31	27 (87%)	4 (13%)
1:20	10	4 (40%)	6 (60%)
1:40	7	2 (29%)	5 (71%)
1:80	2	0 (0%)	2 (100%)
1:160	4	0 (0%)	4 (100%)
1:320	11	0 (0%)	11 (100%)
1:640	9	0 (0%)	9 (100%)
1:1280	14	0 (0%)	14 (100%)
1:2560	16	0 (0%)	16 (100%)

Serum neutralizing antibody titers against SARS-CoV-2 were determined using a plaque-reduction neutralization assay[17]. Neutralizing antibodies (titers of 1:20 or higher) were detected in 72.3% (81/112) of the serum samples. For six patients, infectious SARS-CoV-2 was isolated from the respiratory tract despite the presence of neutralizing SARS-CoV-2 antibodies in the serum sample pairs. In four of these six patients, infectious virus was not isolated in the consecutive respiratory tract samples obtained after a virus culture positive sample (sampled from day +1, +1, +4, and +4 in respect to virus culture positive sample). For one patient, infectious virus was not isolated in the respiratory tract sample obtained one day after the virus culture positive respiratory tract sample, while the respiratory tract sample obtained 2 days after the virus culture positive respiratory tract sample was positive for infectious SARS-CoV-2. All respiratory tract samples obtained thereafter tested negative for infectious virus. For one patient, no follow-up respiratory tract samples were available.

Wantai SARS-CoV-2 Ig total ELISA has a sensitivity of 99% (95% CI 97–100%) and a specificity of 99% (95% CI 96–100%)[23]. These commercial immunoassays require less stringent biosafety measures and are amenable to high throughput use resulting in a broad application of our results to guide infection prevention strategies and discharge management for clinical cases being hospitalized.

Detection of viral subgenomic RNA correlated poorly with shedding of infectious virus. These RNAs are produced only in actively infected cells and are not packaged into virions. Subgenomic RNAs were still detected when virus cultures turned negative. This could indicate that active replication continues in severely-ill symptomatic COVID-19 patients after seroconversion and after shedding of infectious virus has stopped. Possibly, infectious virions are produced but are directly neutralized by antibodies in the respiratory tract. On the other hand, the half-life of viral subgenomic RNAs is not known in COVID-19 and these RNAs may still be detected once replication has stopped.

Our study has some limitations. Firstly, virological data were obtained from diagnostic samples only and samples were not prospectively collected at predefined timepoints. However, as many aspects of COVID-19 were still unclear, a sampling-rich diagnostic approach was applied in our institution with regular virological monitoring of confirmed COVID-19 patients. This approach resulted in a large high quality dataset from a considerable number of patients including patients with a immunocompromised status. The strikingly similar viral RNA load cutoff for a 5% probability of a positive virus culture found by us and by Wölfel et al. underpins the validity of the results[5]. Secondly, we used in vitro cell cultures as a surrogate marker for infectious virus shedding. The success of SARS-CoV-2 isolation is dependent on which cell lines is used[24]. Vero cells are currently regarded as the gold standard to detect infectious SAR-CoV-2, but the true limit of detection is unknown. Notwithstanding the above, experimental evidence from a COVID-19 hamster model showed that transmission of SARS-CoV-2 correlated well with detection of infectious SARS-CoV-2 from respiratory tract samples using in vitro Vero cell cultures while detection of viral RNA did not[13]. More data from experimental models, and epidemiological and modeling

Table 3 Univariate and multivariate analysis of key determinants for infectious virus shedding.

Variable	Positive virus culture ($n = 33$)	Negative virus culture ($n = 79$)	Univariate odds ratio (95% CI)	Multivariate odds ratio (95% CI)
Viral RNA load				
$>10^7$ RNA copies/mL	29 (87.9%)	22 (27.8%)	18.8 (5.5–64.2), $p < 0.001$	14.7 (3.7–58.1), $p < 0.001$
Duration of symptoms				
<7 days	20 (60.6%)	17 (21.5%)	5.6 (1.7–18.1), $p = 0.004$	2.1 (0.4–11.7), $p = 0.31$
Serum neutralizing antibody titer				
1:20 or higher	6 (18.2%)	75 (94.9%)	0.01 (0.003–0.05), $p < 0.001$	0.01 (0.002–0.08), $p < 0.001$
Immunocompromised				
Yes	10 (30.3%)	10 (12.7%)	3.00 (0.8–11.0), $p = 0.098$	2.0 (0.7–5.3), $p = 0.22$

Results of the univariate and multivariate generalized estimating equation analysis. The analyses were limited to the samples for which a viral RNA load and a serum neutralizing antibody titer were available from samples taken at the same day.

studies on transmission, which take viral RNA load and antibody response into account, are needed for further validation of this approach. It should be noted that, besides the infectious viral load, additional factors determine virus transmissibility. Finally, our study only included hospitalized symptomatic adults with severe or critical COVID-19 and important differences were noted in our study compared to what has been reported for in mild COVID-19. Thus, further studies are needed on the determinants and duration of infectious virus shedding in specific patient groups.

In conclusion, infection prevention and control guidelines should take into account that patients with severe or critical COVID-19 may shed infectious virus for longer periods of time compared to what has been reported for in patients with mild COVID-19. Infectious virus shedding drops to undetectable levels when viral RNA load is low and serum neutralizing antibodies are present, which warrants the use of quantitative viral RNA load assays and serological assays in test-based strategies to discontinue or de-escalate infection prevention and control precautions.

Methods

Samples and patients. Between March 8, 2020 and April 8, 2020, diagnostic respiratory samples of COVID-19 patients from the Erasmus MC that were send to our laboratory for SARS-CoV-2 PCR were also submitted for virus culture. From these patients, results from SARS-CoV-2 PCRs on diagnostic respiratory samples and results from SARS-CoV-2 neutralizing antibody measurements on serum samples were extracted from our diagnostic laboratory information management system (LabTrain version 3, bodegro, the Netherlands). The following information was extracted from the electronic patient files (HiX version 6.1, ChipSoft, the Netherlands): date of onset of symptoms, disease severity (hospitalized on ICU with mechanical ventilation, hospitalized on ICU with oxygen therapy, hospitalized to ward with oxygen therapy, hospitalized to ward without oxygen therapy), information to classify patients as immunocompetent, nonseverely immunocompromised (excluding diabetes mellitus), or severely immunocompromised as described previously[25], disease severity score according to the NIH classification (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/), and whether the patients were still alive or not as of April 17, 2020. Excel 2016 (Microsoft Corp, USA) was used as data collection software.

Sample processing and analysis. Swabs from the upper respiratory tract were collected in tubes containing 4 mL virus transport medium (Dulbecco's modified eagle's medium (DMEM, Lonza) supplemented with 40% FBS, 20 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), NaCO3, 10 µg/ml amphotericin B, 1000 U/mL penicillin, 1000 µg/mL streptomycin). Supernatant was passed through a 45-µm filter and used for PCR analysis and virus culture. For sputum samples, 6 mL sample processing medium (DMEM supplemented with 17 mM HEPES, $NaCO_3$, 1000 U/mL penicillin, 1000 µg/mL streptomycin, 12.5 µg/ml amphotericin B) was added until the final volume was 6 mL. Subsequently, samples were vortexed, centrifugated, passed through a 45-µm filter, and 1 part FBS was added to 1.5 parts supernatant. Subsequently, processed samples were used for PCR analysis and virus culture.

Real-time RT-PCR detection of SARS-CoV-2 was performed using an in-house assay[26] or using the SARS-CoV-2 test on a cobas® 6800 system (Roche Diagnostics). Subsequently, cycle threshold (ct) values were converted to Log_{10} RNA copies/mL using calibration curves based on quantified E-gene in vitro RNA transcripts[5]. SARS-CoV-2 subgenomic RNAs were detected with RT-PCR[5].

Respiratory samples were cultured on Vero cells, clone 118, using 24-wells plates with glass coverslips[27]. Cells were inoculated with 200 µL sample per well and centrifugated for 15 min at 3500 × *g*. After centrifugation, inoculum was discarded, virus culture medium (Iscove's modified Dulbecco's medium (IMDM; Lonza) supplemented with 2 mM L-glutamine (Lonza), 100 U/mL penicillin (Lonza), 100 µg/mL streptomycin (Lonza), 2.5 µg/mL amphotericin B (department of hospital pharmacy, Erasmus MC), and 1% heat-inactivated fetal bovine serum (Sigma)) was added, and samples were cultured at 37 °C and 5% CO_2 for 7 days. Each sample was cultured in triplicate: Two replicates were fixed with ice-cold acetone after 24 and 48 h, respectively irrespective if cytopathic effect (CPE) was visible. The fixed samples were further analyzed with immunofluorescence (see below). The remaining replicate was scored for CPE on a daily basis for 7 days. When CPE was visible, the sample was fixed with ice-cold acetone and further analyzed with immunofluorescence (see below). Virus cultures were regarded as negative if no CPE was visible during 7 days. For immunofluorescence read-out, the fixed cells were washed with phosphate buffer saline (PBS), and incubated for 30 min at 37 °C with 25 µL 1000-fold diluted polyclonal rabbit SARS-CoV anti-nucleoprotein antibodies (Sino Biological, catalogue number 40143-T62). After incubation, samples were washed with three times with PBS and once with deionized water. Subsequently, cells were incubated for 30 min at 37 °C with 25 µL 2000-fold diluted Alexa Fluor 488-labeled polyclonal goat anti-rabbit IgG (Invitrogen, catalogue number A-11070). Subsequently, cells were washed three times with PBS. Finally, cells were incubated for 1 min with 25 µL Evan's Blue (counterstain), washed twice with deionized water, air dried and analyzed with a fluorescence microscope.

Serum neutralizing antibodies titers against SARS-CoV-2 (German isolate; GISAID ID EPI_ISL 406862; European Virus Archive Global #026V-03883) were determined using a plaque-reduction neutralization test[22]. A plaque-reduction neutralization titer 50% (PRNT50%) of 1:20 or more was considered to be positive and a PRNT50% below 1:20 negative.

Medical ethical approval. All patient samples and data used in this study were collected in the context of routine clinical patient care. Additional analyses were performed only on surplus of patient material collected in the context of routine clinical patient care. The institutional review board of the Erasmus MC (Rotterdam, The Netherlands) approved the use of these data and samples (METC-2015-306). METC-2015-306 is a generic protocol to study viral diseases. Informed consent for COVID-19 research was waived by the privacy knowledge office of the Erasmus MC (Rotterdam, The Netherlands). Instead, patients had the right to opt-out against the use of their surplus patient material and their medical data for research. The opt-out system of the Erasmus MC was checked for all patients included in this study, and none of the patients included in this study opted-out against the use of their surplus patient material and their medical data for research.

Statistical analysis. Categorical and continuous variables were compared using the Chi-square test the student's *t*-test, respectively. Generalized estimating equations were used to identify factors that are associated with a virus culture positive respiratory tract sample. The continuous data in the generalized estimating equations were dichotomized using various cutoff values. In the main paper we present the results of the best fitting generalized estimating equations using the levels of dichotomizing that had the best fit according to the quasi-likelihood under the independence criterion (QIC)[28]. Sensitivity analysis is shown in Supplementary Table 1 and Supplementary Table 2. All variables having a p value < 0.1 in univariate analysis were submitted into a multivariate general estimating equation to account for repeated measurements obtained from the same patient during hospitalization[29]. For this analysis we used the geepack package version 1.3-1 and R version 4.0.0[29]. Probit analyses were performed with MedCalc version 19.2.3 (MedCalc Software Ltd).

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Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

All relevant data are available from the authors upon request. Source data are provided with this paper.

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Author contributions

J.J.A.v.K. conceived and designed the study, supervised the study, wrote the first draft of the manuscript. D.A.M.C.v.d.V., P.L.A.F., C.G., A.E., M.K., R.M., and C.B. contributed to the conception and design of the study. G.I.A. performed the virus cultures. C.G. and J.J.A.v.K. supervised the virus culture experiments. B.H. and M.M.L. provided intellectual input for virus culture experiments and analyses. N.O. performed the virus neutralization tests. B.L. and C.G. supervised virus neutralization tests. R.M., S.v.B., and J.C.V. supervised and interpreted the molecular analyses. D.A.M.C.v.d.V. performed the statistical analyses. P.L.A.F. and J.J.A.v.K. supervised the clinical data analyses. J.P.C.v.d.A., H.E., D.A.M.P.J.G., J.J.C., R.A.S.H., M.M.v.d.E., D.A.H., H.J.M., A.V., J.E.M.d.S., and E.C.M.v.G. were involved in COVID-19 patient care, data, and specimen collection. All authors discussed the results and implications and commented on the manuscript at all stages.

Competing interests

The authors declare no competing interests.

Additional information

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Clinical Infectious Diseases

MAJOR ARTICLE

Viral Dynamics and Immune Correlates of Coronavirus Disease 2019 (COVID-19) Severity

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Background. Key knowledge gaps remain in the understanding of viral dynamics and immune response of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection.

Methods. We evaluated these characteristics and established their association with clinical severity in a prospective observational cohort study of 100 patients with PCR-confirmed SARS-CoV-2 infection (mean age, 46 years; 56% male; 38% with comorbidities). Respiratory samples (n = 74) were collected for viral culture, serum samples for measurement of IgM/IgG levels (n = 30), and plasma samples for levels of inflammatory cytokines and chemokines (n = 81). Disease severity was correlated with results from viral culture, serologic testing, and immune markers.

Results. Fifty-seven (57%) patients developed viral pneumonia, of whom 20 (20%) required supplemental oxygen, including 12 (12%) with invasive mechanical ventilation. Viral culture from respiratory samples was positive for 19 of 74 patients (26%). No virus was isolated when the PCR cycle threshold (Ct) value was >30 or >14 days after symptom onset. Seroconversion occurred at a median (IQR) of 12.5 (9–18) days for IgM and 15.0 (12–20) days for IgG; 54/62 patients (87.1%) sampled at day 14 or later seroconverted. Severe infections were associated with earlier seroconversion and higher peak IgM and IgG levels. Levels of IP-10, HGF, IL-6, MCP-1, MIP-1α, IL-12p70, IL-18, VEGF-A, PDGF-BB, and IL-1RA significantly correlated with disease severity.

Conclusions. We found virus viability was associated with lower PCR Ct value in early illness. A stronger antibody response was associated with disease severity. The overactive proinflammatory immune signatures offer targets for host-directed immunotherapy, which should be evaluated in randomized controlled trials.

Keywords. COVID-19; cytokines; serology; viral culture; immunology.

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused great harm to health and the global economy [1, 2]. Understanding of SARS-CoV-2 pathogeneisis has advanced at an unprecedented speed, but key gaps remain and preliminary findings require validation.

Studies of patients with COVID-19 have described the inflammatory milieu in severe infections, with increased neutrophils, suppressed lymphocytes, and elevated inflammatory mediators [3, 4]. However, most studies are limited to comparing severe against nonsevere infections and lack serial data [5, 6]. A clearer definition of disease pathogenesis will support the development of risk-stratification tools and therapeutics targeting critical pathways in the inflammatory cascade.

Early seroconversion has been reported with immunoglobulin (Ig) G to the receptor binding domain (RBD) detected at day 7 [7–10]. However, evidence of correlation between antibody titers and disease severity is conflicting [8, 10–12]. There remains a need for more detailed assessment of antibody kinetics to help determine the impact of antibody-dependent enhancement in COVID-19 pathogenesis, as well as guide convalescent plasma harvesting and use of serological assays for diagnosis [13].

SARS-CoV-2 can be detected from the nasopharynx for a median of 2–3 weeks following onset of symptoms [14]. Several studies have reported that, in immunocompetent individuals, virus is typically only cultured from respiratory samples during the first week of illness when viral loads are highest [8, 15, 16]. This suggests transmission risk declines in the second

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week. This finding requires confirmation in larger cohorts as it has important implications for infection-control and isolation protocols [17].

In this multipronged study, we describe the serologic evolution, inflammatory response, and pattern of viral shedding and viability in patients with virologically confirmed COVID-19 in Singapore, and analyze the contributions these make to severe infections.

METHODS

Patient Recruitment

All individuals confirmed to have COVID-19 by SARS-CoV-2 real-time reverse transcriptase–polymerase chain reaction (RT-PCR) and admitted to any of 7 public hospitals in Singapore were eligible for inclusion in this study. RT-PCR was performed on respiratory samples, as previously described [18] (details shown in the Supplementary Methods).

Data and Specimen Collection

Clinical information was extracted from the medical record using a standardized data-collection form adapted from the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) case record form [19]. Serial blood and respiratory samples were collected during hospitalization and follow-up postdischarge (days 1, 3, 7, 14, 21, and 28 after enrollment). A stool and urine sample was also collected for SARS-CoV-2 PCR and culture on day 1.

Clinical Management

At the time of the study, all patients with COVID-19 in Singapore were admitted to airborne infection–isolation rooms regardless of disease severity. Supportive therapy, including supplemental oxygen and symptomatic treatment, was administered as required. Patients with moderate to severe hypoxia were transferred to the intensive care unit (ICU) for further management and invasive mechanical ventilation as required.

Patients were discharged from the hospital only after resolution of symptoms and when 2 consecutive nasopharyngeal swabs more than 24 hours apart were negative for SARS-CoV-2 by RT-PCR. Follow-up visits were arranged on day 28 of enrollment.

Virus Isolation

Material from nasopharyngeal swabs was collected in universal transport media and used to inoculate Vero-E6 cells (American Type Culture Collection: CRL-1586TM) for virus isolation in an Animal Biological Safety Level 3 laboratory. Urine and stool samples were collected and transported fresh for viral culture. Stools were filtered before inoculation. Cells were cultured at 37°C for 7 days or less if cytopathic effect (CPE) was observed, and 3 blind passages were performed. Cytopathic effect consisted of rounded cells and extensive cell death, usually by day 4 postinoculation. Positive isolation was confirmed by the observation of CPE and virus-specific PCR. Total RNA was extracted from all samples using the E.Z.N.A. Total RNA Kit I (Omega Bio-Tek, Inc) according to the manufacturer's instructions, and samples were analyzed by RT-PCR for the detection of SARS-CoV-2 as previously described [20].

Capture Enzyme-linked Immunosorbent Assay to Detect IgM and IgG

Serum collected during the acute and convalescent phases of infection were tested for SARS-CoV-2 receptor binding domain–specific IgM and IgG using capture enzyme-linked immunosorbent assay (ELISA) (details in the Supplementary Methods).

Multiplex Microbead-based Immunoassay

Plasma samples were collected during acute and convalescent phases and treated with a solvent/detergent based on Triton X-100 (1%) (Dow Chemical Company) for virus inactivation [21]. Immune mediator levels were measured using Cytokine/Chemokine/Growth Factor 45-Plex Human ProcartaPlex Panel 1 (ThermoFisher Scientific) (details in the Supplementary Methods). Cytokine levels were also measured in 23 healthy donor plasma samples as baseline controls.

Statistical Analysis

Patients were categorized into 3 groups for comparison: no pneumonia on chest radiographs (CXR) throughout admission, pneumonia on CXR without hypoxia, and pneumonia with hypoxia (desaturation to ≤94%) needing supplemental oxygen. Day 1 was defined as the first day of symptom onset.

Fold-changes (FCs) of antibody titers compared with negative controls were calculated. Kruskal-Wallis test followed by Dunn's multiple-comparison test was used to determine significance of antibody levels.

Unpaired *t* test was applied to ascertain significant differences in the immune mediator levels between the patients with COVID-19 and healthy controls at different time points post–illness onset. One-way analysis of variance (ANOVA) with post hoc *t* test corrected using the method of Bonferroni was used to discern the differences in immune mediator levels between the various disease-severity groups. One-way ANOVA results were corrected for multiple testing using the method of Benjamini and Hochberg.

TM4-MeV Suite (version 10.2) was used to compute hierarchical clustering and heat map on the immune mediators (details in Supplementary Methods). Biological processes and immune pathways were predicted and illustrated using the Search Tool for the Retrieval of Interacting Genes/Proteins database (STRING; version 11.0; available at: https://string-db.org). All interactions were derived from high-throughput laboratory experiments and previous knowledge in curated databases at a confidence threshold of 0.8.

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Student's *t* test or Mann-Whitney *U* test was used as appropriate for continuous variables and Fisher's exact test for categorical variables. *P* values less than .05 were considered statistically significant. Plots were generated using GraphPad Prism (version 7), MedCalc Statistical Software (version 19.2.1), or R (version 3.3.1).

Ethical Approval

Written informed consent was obtained from all participants. The study protocol at all sites was approved by the National Healthcare Group Domain Specific Review Board, study reference 2012/00917; additional study protocol at Singapore General Hospital was approved by the SingHealth Centralized Institutional Review Board, study reference 2018/3045.

RESULTS

Clinical Presentation, Treatment, and Outcome

A total of 130 patients with COVID-19 were diagnosed in Singapore from the first known case on 22 January 2020 to 6 March 2020 (Figure 1). Among the 100 (77%) enrolled in this study, viral pneumonia was diagnosed by CXR in 57, of whom 20 required supplemental oxygen for hypoxia and 12 required invasive mechanical ventilation (Table 1).

Following resolution of infection and viral shedding, 97 patients have been discharged, and after 90 days of follow-up no reinfection or recrudescence has been detected. Three patients have died. Deaths occurred 27 days or more after hospital admission, and while all were assessed by the managing clinician as related to COVID-19, they followed viral clearance and prolonged invasive mechanical ventilation.

Viral Shedding and Cultures

SARS-CoV-2 was detectable from nasopharyngeal swabs by PCR up to 48 days after symptom onset. The mean duration of viral shedding by PCR was 16.7 days (95% confidence interval [CI], 15.2–18.3 days). Cessation of viral shedding by PCR occurred in 4% by day 7, 30% by day 14, 78% by day 21, and 91% by day 28. There were no differences in the duration of viral shedding stratified by disease severity (Supplementary Figures 1 and 2).

Viral culture was attempted from 152 respiratory samples where SARS-CoV-2 was detected by PCR. These samples were collected from 74 patients and SARS-CoV-2 was isolated from 21 samples from 19 (26%) patients (Supplementary Table 1). No virus was isolated from samples where the cycle threshold (Ct) value was greater than 30, or when the sample was collected more than 14 days after symptoms onset (Figure 2, Supplementary Figures 2 and 3). There was no correlation between virus isolation by culture and infection severity, patient demographics, or symptomatology (data not shown). Viral culture was attempted from the stool of 34 patients and urine of 24 patients during acute infection; in all patients, virus was not isolated. Seven (21%) patients had virus detectable by PCR in stool.

IgM and IgG Titers Correlate With Disease Severity

Serial serum samples for ELISA were available for 30 patients. Anti–SARS-CoV-2 IgM was first detectable in 17.9% in the first week of illness, 39.3% in the second week, 35.7% in the third week, and 7.1% after the third week, and correspondingly for IgG, 7.7%, 26.9%, 50.0%, and 15.4%. The median time to seroconversion was 12.5 days (interquartile range [IQR], 9–18 days)

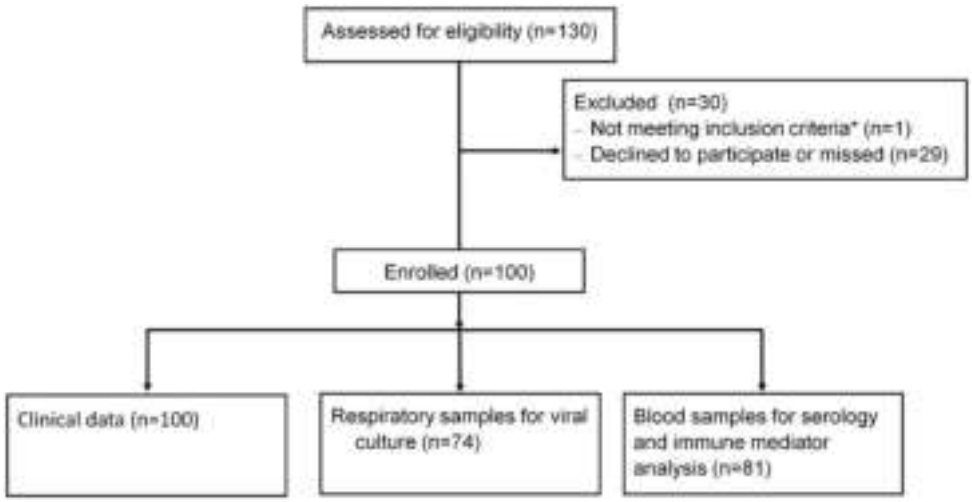

Figure 1. Flow diagram of study recruitment and follow-up in 130 patients diagnosed in Singapore as of 6 March 2020. *One excluded as diagnosis was retrospective via serology rather than PCR. The 100 patients were enrolled from the following hospitals in Singapore: National Centre for Infectious Diseases (77), National University Hospital (8), Singapore General Hospital (8), Ng Teng Fong General Hospital (3), Changi General Hospital (2), Alexandra Hospital (1), Khoo Teck Puat Hospital (1). Abbreviation: PCR, polymerase chain reaction.

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Table 1. Demographics, Presenting Symptoms, Parameters, and Laboratory Investigations Stratified by Disease Severity

	All (N = 100)	No Pneumonia (Group A) (n = 43)	Pneumonia but No Hypoxia (Group B) (n = 37)	*P* (A vs B)	Pneumonia and Hypoxia (Group C) (n = 20)	*P* (A vs C)
Demographics						
Age, years	44 (35–56)	37 (31–50)	44 (35–55)	.080	62 (49–68)	<.0001
Sex, male, n (%)	56 (56)	23 (53)	19 (51)	1.0000	6 (70)	.28
Ethnicity (Chinese), n (%)	83 (83)	33 (77)	31 (84)	.58	19 (95)	.15
Comorbidity, any, n (%)	38 (38)	12 (28)	14 (38)	.47	12 (60)	.025
Diabetes, n (%)	10 (10)	2 (5)	3 (8)	.66	5 (15)	.033
Hypertension, n (%)	19 (19)	2 (5)	8 (22)	.039	9 (45)	.0003
Charlson's score	0 (0–0)	0 (0–0)	0 (0–0)	.25	0 (0–1)	.0067
Presenting symptoms						
Duration of symptoms before admission, days	6 (2–9)	5 (2–9)	6 (4–9)	.24	7 (2.4–8)	.65
Fever, n (%)	76 (76)	26 (60)	31 (84)	.027	19 (95)	.0059
Cough, n (%)	70 (70)	29 (67)	25 (68)	1.000	16 (80)	.38
Dyspnea, n (%)	17 (17)	3 (7)	6 (16)	.76	8 (40)	.022
Sore throat and/or rhinorrhea, n (%)	47 (47)	29 (67)	17 (46)	.070	6 (30)	.0071
Diarrhea, n (%)	19 (19)	9 (21)	6 (16)	.78	4 (20)	1.000
Baseline parameters						
Temperature, °C	37.6 (37.0–38.3)	37.4 (36.9–38.0)	37.8 (37.0–38.2)	.26	38.5 (37.7–39.0)	.0045
Respiratory rate, breaths/minute	18 (17–19)	18 (17–18)	18 (17–18)	.31	20 (19–20)	.0002
Heart rate, beats/minute	89 (77–99)	85 (75–98)	86 (76–105)	.53	95 (86–104)	.017
Systolic blood pressure, mm Hg	132 (120–144)	131 (121–139)	132 (121–146)	.76	131 (112–144)	.74
Pulse oximeter oxygen saturation, %	98 (96–99)	98 (98–100)	98 (97–99)	.20	96 (95–97)	<.0001
Baseline laboratory investigations						
Hemoglobin, g/dL	13.9 (12.9–15.1)	13.9 (13.1–15.2)	14.4 (13.3–15.3)	.33	13.1 (12.3–14.2)	.033
Platelets, x 10^9/L	193 (151–259)	213 (183–263)	185 (144–259)	.14	157 (134–198)	.0017
Lymphocytes, x 10^9/L	1.1 (0.8–1.5)	1.4 (0.9–1.9)	1.1 (0.8–1.5)	.070	0.5 (0.8–1.1)	.0001
Neutrophils, x 10^9/L	3.0 (2.3–4.1)	2.6 (2.3–4.1)	3.1 (2.2–3.7)	.97	3.2 (2.4–5.1)	.32
CRP (n = 81), mg/L	11.4 (3.3–47.4)	2.8 (1.1–9.4)	11.9 (7.1–22.1)	<.0001	87.9 (64.6–153.1)	<.0001
LDH (n = 90), U/L	443 (365–595)	368 (342–416)	463 (389–585)	.0024	632 (525–871)	<.0001
Creatinine (n = 97), µmol/L	67 (54–83)	65 (53–79)	69 (52–81)	.78	76 (65–92)	.038
ALT (n = 85), U/L	34 (28–40)	23 (15–32)	27 (15–44)	.27	36 (30–56)	.0014
PCR Ct value at diagnosis	28.2 (24.3–33.3)	28.0 (21.3–34.5)	29.3 (25.4–33.9)	.35	27.0 (24.8–31.2)	.94

Values are medians (IQR) or n (%). Groups were compared using Mann-Whitney *U* test or Fisher's exact test.
Abbreviations: ALT, alanine aminotransferase; CRP, C-reactive protein; Ct, cycle threshold; IQR, interquartile range; LDH, lactate dehydrogenase; PCR, polymerase chain reaction.

for IgM and 15.0 days (IQR, 12–20 days) for IgG. The total seroconversion rate from 62 patients sampled on day 14 or later was 87.1%. Time to IgG seroconversion was significantly shorter for patients with pneumonia and hypoxia compared with less-severe infections (median, 12.5 vs 18 days; $P = .013$, Mann-Whitney). There was also a significant correlation between disease severity and peak IgM and IgG levels (Figure 3). However, IgM and IgG antibody levels were not associated with duration of viral shedding (Figure 3), baseline viral Ct values from respiratory samples, age, or comorbidities (Supplementary Figure 5).

Proinflammatory Signature of Severe COVID-19

A total of 321 plasma samples were available from 81 patients. Levels of interleukin (IL)-2, IL-18, interferon-γ (IFN-γ), tumor necrosis factor α (TNF-α), monocyte chemoattractant protein 1 (MCP-1), hepatocyte growth factor (HGF), brain-derived neurotrophic factor (BDNF), leukemia inhibitory factor (LIF), placenta growth factor-1 (PLGF-1), and beta-nerve growth factor (bNGF) were significantly elevated compared with healthy controls for their first plasma samples taken soon after admission (Figure 4A). Proinflammatory cytokines and chemokines (IL-2, IL-18, IFN-γ, and MCP-1) were elevated at the early phase of infection and were reduced to a healthy basal range at approximately 15 days post–illness onset. In contrast, the elevated levels of lung injury–associated growth factors (HGF, BDNF, LIF, PLGF-1, and bNGF) persisted throughout the infection course (Figure 4A). Stratification of patients with COVID-19 with plasma samples nearest to the onset of pneumonia and hypoxia revealed that the proinflammatory cytokines IFN-γ inducible protein (IP-10), HGF, IL-6, MCP-1, macrophage inflammatory protein-1α (MIP-1α), IL-12p70, and IL-18; growth

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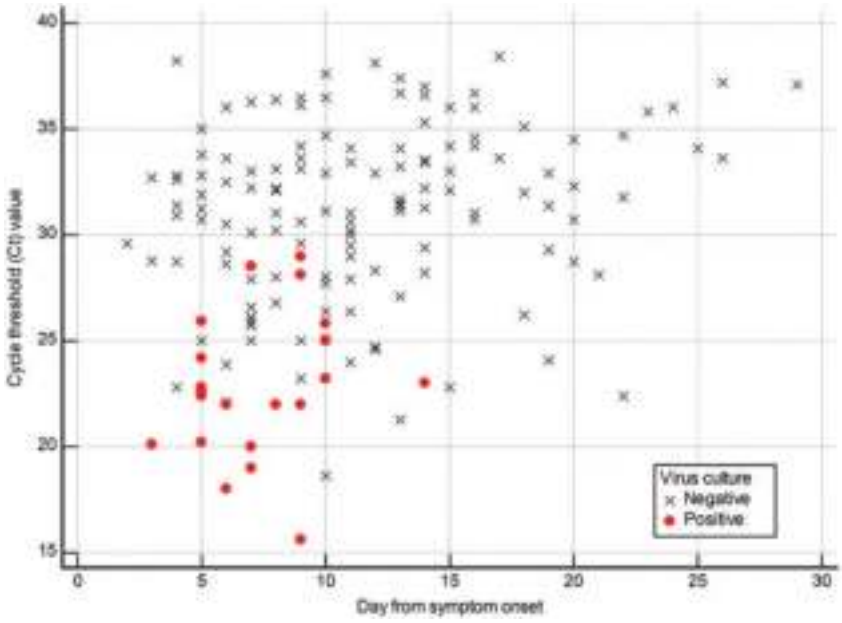

Figure 2. Scatterplot of viral culture results by day from symptom onset and PCR Ct value. Analysis includes 152 samples from 74 patients in whom virus was detectable by SARS-CoV-2 PCR. Virus was cultured from 21 (14%) samples from 19 patients. Abbreviations: PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

factors vascular endothelial growth factor A (VEGF-A) and 2 B subunits of platelet-derived growth factor (PDGF-BB); and anti-inflammatory cytokine IL-1RA were associated with severity. Levels were significantly elevated between patients with pneumonia without hypoxia and patients with hypoxia compared with patients without pneumonia, except for MCP-1, which was only significantly higher in patients with hypoxia (Figure 4B and 4C; Supplementary Tables 2 and 3).

Further network analyses showed an association between the aforementioned immune mediators and clinical parameters (pneumonia, hypoxia, and ICU admission). The intertwined relationship of the cytokines is shown in Figure 5A. In addition, Ingenuity Pathway Analysis (IPA) revealed canonical pathways associated with these immune mediators and severity, with the top 10 canonical pathways involved in inflammatory diseases and cell signalling (Figure 5B). The top canonical pathway highlights the common immune mediators between influenza and SARS-CoV-2 infection, including MCP-1, IL-1RA, IP-10, and IL-6 (Figure 5C). In addition to IPA, STRING prediction of protein–protein interactions identified IL-6 as a direct interacting partner with other severity-associated immune mediators (Figure 5D).

A longitudinal comparison of these immune mediators associated with severity in 12 ICU patients was performed to explore their role as prognostic markers for severe COVID-19 (Supplementary Figure 6). Four of these 12 patients (CT009, CT032, CT037, and CT057) recovered and were discharged at the time of study. Interestingly, HGF and VEGF-A were distinctly separated into 2 levels, with the 4 discharged patients having lower HGF and VEGF-A levels, and HGF approaching healthy baseline levels during convalescence, which further indicates that high levels of these cytokines were associated with poor prognosis in ICU patients. Similarly, these patients had lower levels of MCP-1 and IL-6 compared with other ICU patients despite having a less distinct separation. Longitudinal comparison of other immune mediators, including IP-10, IL-18, PDGF-BB, and IL-1RA, revealed decreasing levels with days post–ICU admission and approaching healthy baseline levels during the latter period after ICU admission (Supplementary Figure 6).

DISCUSSION

This study of 100 patients in the first few months of the COVID-19 pandemic in Singapore provides a detailed overview of clinical presentation, progress, and outcomes. Case detection and contact tracing in Singapore are rigorous, with the main gap possibly in missing asymptomatic cases [22]. From the cohort, 43% of patients never developed pneumonia, 37% developed pneumonia without hypoxia, and 20% developed pneumonia with hypoxia. We found no relationship between illness severity and duration of viral shedding or PCR Ct values. The central role of the immune response to SARS-CoV-2 in COVID-19 was evident from the strong correlation between disease severity and levels of IgG/IgM and inflammatory immune mediators in our cohort.

Viral shedding of SARS-CoV-2 from the respiratory tract has been observed to persist for several weeks and potentially up

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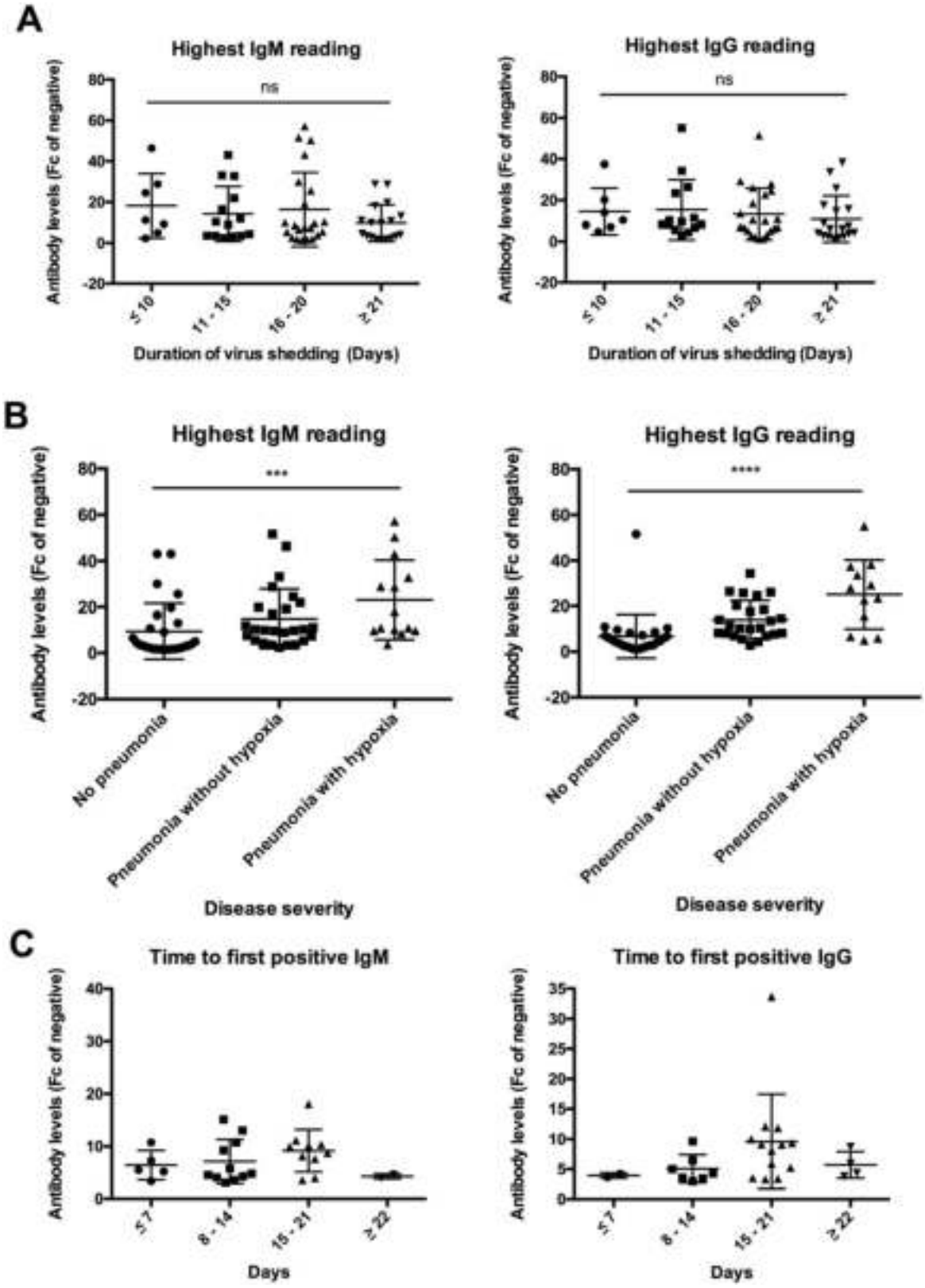

Figure 3. IgG and IgM readings stratified by (*A*) duration of viral shedding, (*B*) disease severity, and (*C*) time to first positive antibody level. Fc is calculated by dividing OD reading of a test sample by the average OD reading of negative controls. Samples with Fc >3 are considered positive. As sampling time and numbers were not uniform for all patients, we plotted the highest IgM/IgG from a single serum sample for each patient when multiple samples were available. Abbreviations: Fc, fold-change; IgG, immunoglobulin G; IgM, immunoglobulin M; ns, not significant; OD, optical density.

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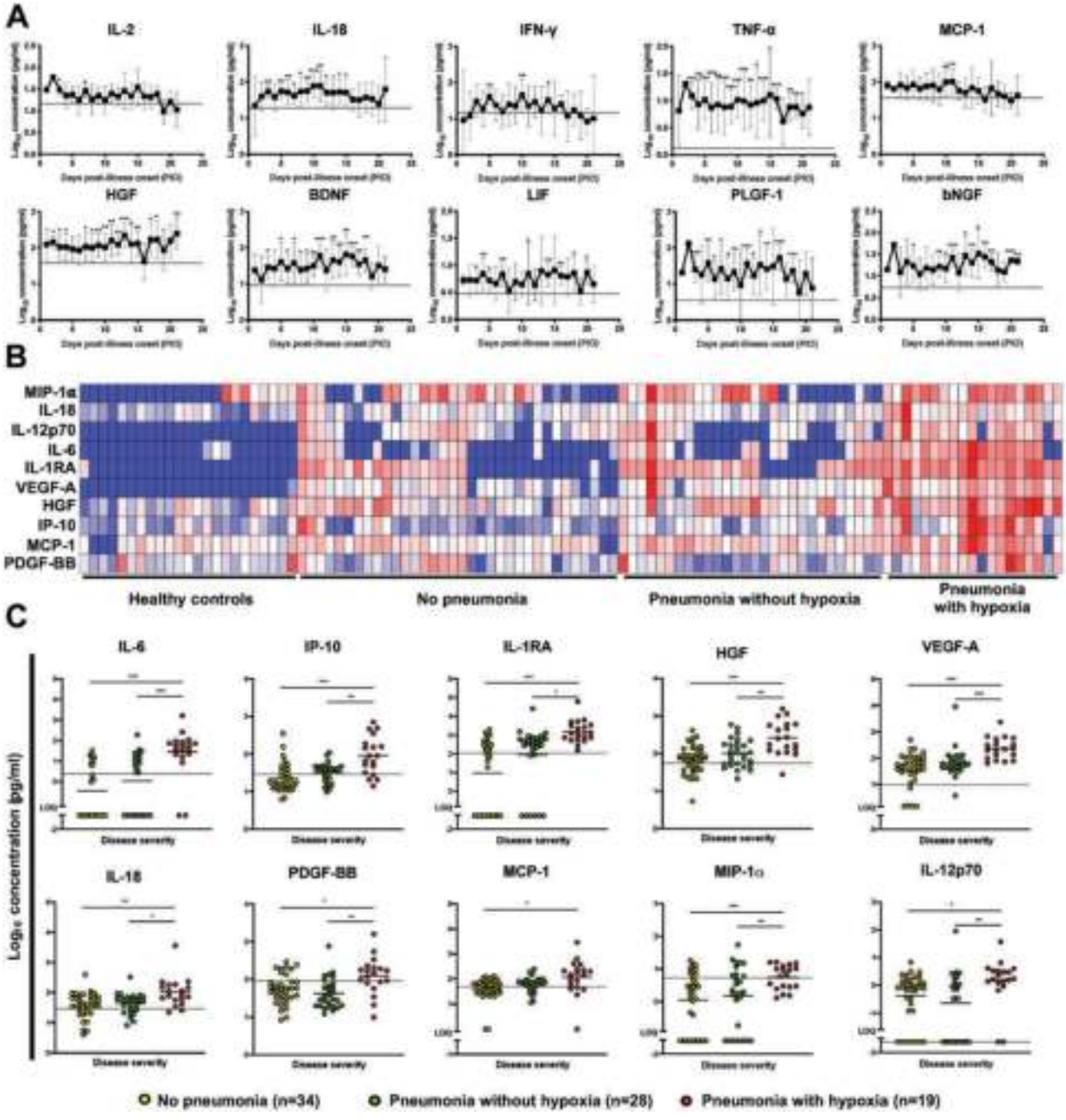

Figure 4. Immune signatures of patients with COVID-19 reveal cytokines associated with disease severity. Plasma fractions were isolated from the blood of patients with COVID-19 (n = 81) at different time points. Time points closest to event onset, including mild (no pneumonia), pneumonia without hypoxia, or pneumonia with hypoxia, were chosen to identify cytokines that were associated with disease severity. Concentrations of 45 immune mediators were quantified using a 45-plex microbead-based immunoassay. *A*, Longitudinal profile of detectable cytokines in patients with COVID-19 during the acute phase of disease. Statistical analyses were performed using unpaired *t* test against the healthy baseline (* = $P < .05$, ** = $P < .01$, *** = $P < .001$). Cytokine level for healthy controls (n = 23) is indicated by the dotted line. *B*, Heatmap of severity-associated cytokine levels in patients with different disease outcomes (healthy controls, n = 23; no pneumonia, n = 34; pneumonia without hypoxia, n = 28; pneumonia with hypoxia, n = 19). Each color represents the relative concentration of a particular analyte. Blue and red indicate low and high concentrations, respectively. *C*, Profiles of significant immune mediators are illustrated as scatterplots. One-way ANOVAs were conducted on the logarithmically transformed concentration with post hoc *t* tests corrected using the method of Bonferroni. ANOVA results were corrected for multiple testing using the method of Benjamini and Hochberg (* = $P < .05$, ** = $P < .01$, *** = $P < .001$). Cytokine level for healthy controls (n = 23) is indicated by the dotted line. Patient samples that are not detectable are assigned the value of logarithm transformation of LOQ. Abbreviations: ANOVA, analysis of variance; BDNF, brain-derived neurotrophic factor; bNGF, beta-nerve growth factor; COVID-19, coronavirus disease 2019; HGF, hepatocyte growth factor; IFN-γ, interferon-γ; IL, interleukin; IL-1RA, interleukin-1 receptor antagonist; IP-10, IFN-γ inducible protein; LIF, leukemia inhibitory factor; LOQ, limit of quantification; MCP-1, monocyte chemoattractant protein-1; PDGF-BB, 2 B subunits of platelet-derived growth factor; PLGF-1, placenta growth factor-1; TNF-α, tumor necrosis factor α; VEGF-A, vascular endothelial growth factor A.

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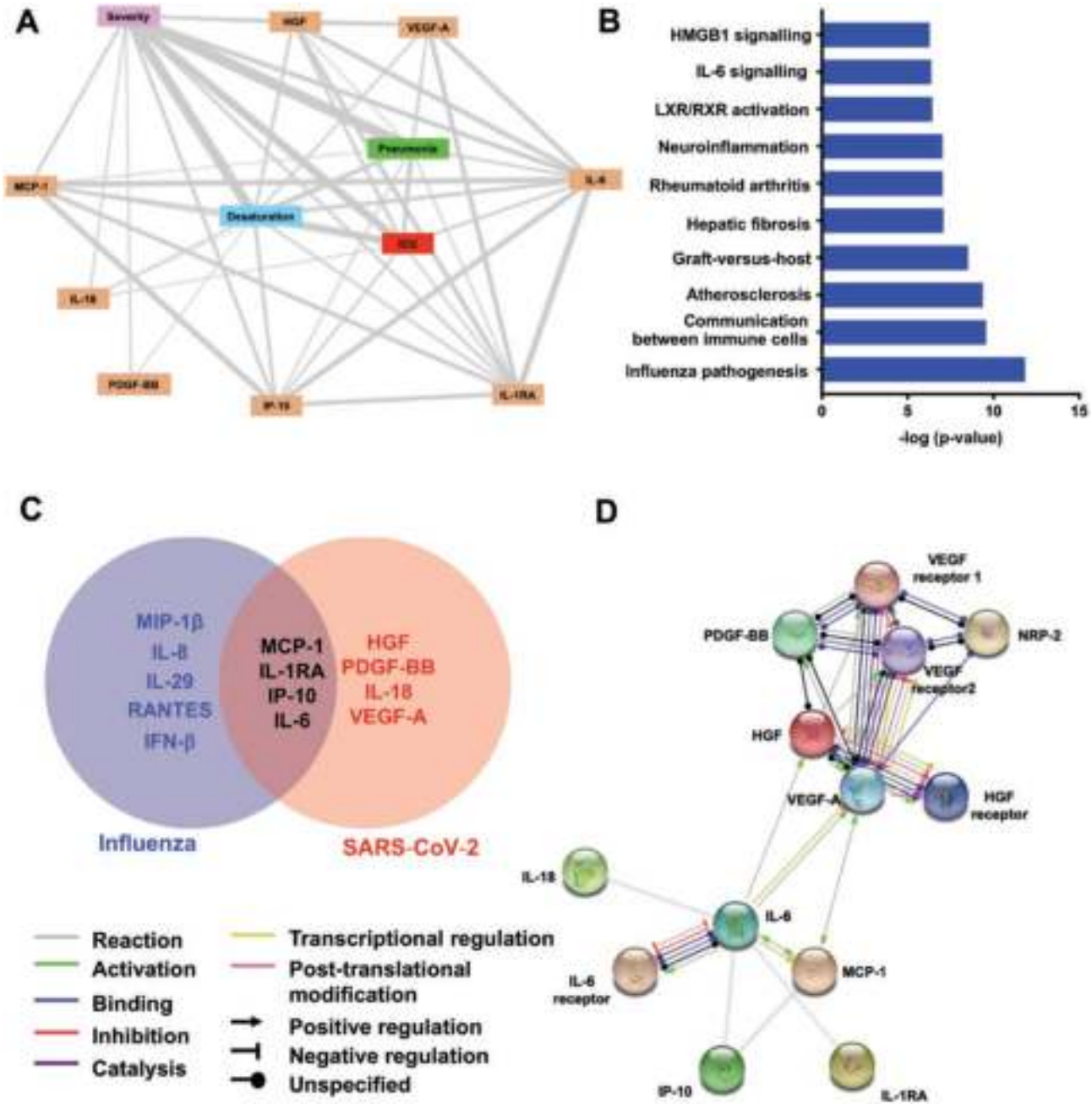

Figure 5. Network analysis of immune mediators associated with disease severity in patients with COVID-19. *A*, Interactomic analysis by IPA software. The network is displayed graphically as nodes and edges. Each node represents either severity-associated cytokine or disease condition. Thickness of edges represents the magnitude of biological relationship between connected nodes. Edges are thicker when the association between parameters is stronger. *B*, IPA analysis of the 8 significant immune mediators associated with disease severity in patients with COVID-19. The chart represents the top 10 significantly associated canonical pathways with the immune mediators. *C*, Venn diagrams show common immune mediators between influenza virus infection and SARS-CoV-2 virus infection. *D*, Interactive relationships between the immune mediators were determined by STRING analysis, with a confidence threshold of 0.8. Abbreviations: COVID-19, coronavirus disease 2019; HGF, hepatocyte growth factor; ICU, intensive care unit; IFN, interferon; IL, interleukin; IL-1RA, interleukin-1 receptor antagonist; IPA, Ingenuity Pathway Analysis; IP-10, IFN-γ inducible protein; MCP-1, monocyte chemoattractant protein-1; NRP-2, neuropilin 2; PDGF-BB, 2 B subunits of platelet-derived growth factor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; STRING, Search Tool for the Retrieval of Interacting Genes/Proteins database; VEGF-A, vascular endothelial growth factor A.

to months [18, 23–25]. Whether the virus remains infectious throughout this prolonged viral shedding is an important question to resolve. Smaller studies have found that viable virus was readily isolated from immunocompetent individuals during the first week of illness but were unable to successfully isolate viruses in culture from day 8 onward despite detectable viral loads by PCR [8, 25, 26]. However, a case report from Taiwan showed that it was possible to culture the virus up until day 18 [27],

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while positive cultures up to day 20 have been reported from a study of patients with severe infection [15]. We found that successful viral culture was associated with PCR Ct values of 30 or less. Virus was isolated up to day 14 post–symptom onset, although the majority were cultured at day 10 or earlier. Using the PCR Ct value to guide decision making on de-isolation may be an alternative to using day of illness and to provide an additional level of reassurance. However, this requires further validation.

We observed seroconversion of IgM at a median of 12.5 days and IgG at 15.0 days. Similar to a Hong Kong study of 16 patients, there were no significant differences in IgM and IgG titers by age or comorbidities [10]. We found IgM and IgG titers to be correlated with disease severity, which was similarly found in 2 Chinese studies of 173 [7] and 285 [28] patients, respectively.

We found a lower seroconversion rate of 87.1% in 62 patients from day 14 or later. A Chinese study of 173 patients reported that 94.3% of patients were IgM positive by days 15–39 and 79.8% were IgG positive by days 15–39 [7]. A Hong Kong study reported IgM positivity of 94% after day 14 and IgG positivity of 100% after day 14 in a smaller number of 16 patients [10]. The largest study from China of 285 patients reported IgM positivity of 94% by days 20–22 and IgG positivity of 100% by days 17–19 [28]. Different sample sizes and antibody assays may account for differing seroconversion rates, which merits further investigation in a large cohort over a longer period.

Serological testing is vital for determining the prevalence of infection in sero-surveys and as part of epidemiological investigations to understand transmission of clusters [29]. The timing of seroconversion may guide the timing of plasmapheresis for convalescent plasma [30, 31]. The role of antibodies in long-term immunity after infection needs further investigation.

Consistent with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), SARS-CoV-2 infection triggers a cytokine storm in a subset of patients with markedly increased levels of proinflammatory cytokines, chemokines, and growth factors [32, 33]. Notably, higher levels of IL-6, MCP-1, IP-10, IL-18, IL-1RA, PDGF-BB, HGF, VEGF-A, IL-12p70, and MIP-1α were associated with severe disease in our study. This robust induction of proinflammatory mediators indicates that innate immune cell responses and antiviral T-cell responses are responsible for SARS-CoV-2 pathogenesis in patients with COVID-19 [34]. In addition, elevation in growth factors, including HGF [35], PLGF-1 [36], and LIF [37], illuminates the repair mechanisms following acute lung injury during SARS-CoV-2 infection. Previous studies showed that ICU patients had more significant cytokine activation compared with non-ICU patients [1]. Our longitudinal cytokine profiling in ICU patients further evaluated prognostic values of specific cytokines. We observed better prognosis in critically ill patients with lower levels of acute lung injury–associated growth factors HGF and VEGF-A at the time of admission to the ICU. Our data suggest that the differences in degree of lung injury could reflect recovery rate of patients in the ICU. HGF and VEGF-A may serve as early indicators of poor prognosis and may provide guidance to make pre-emptive clinical decisions in critically ill patients.

A central role for IL-6 in lung injury has been postulated, with higher levels associated with mortality in 2 separate studies and severe immune-mediated injury in lung tissues of patients who died of COVID-19 [38, 39]. Similarly, the IL-1 pathway has been highlighted to contribute towards SARS-CoV-2 pathogenesis [40]. Importantly, our study highlighted the upregulation of IL-1 pathway mediators IL-18, MCP-1, and VEGF-A in critically ill patients, providing further evidence that dysregulation in the IL-1 pathway could contribute to the hyperinflammatory state, especially in fatal cases.

STRING analysis revealed potential protein-to-protein interactions in severe COVID-19 infection, in which IL-6 is the direct interacting partner of other cytokines associated with disease severity. Thus, several approved IL-6 receptor antagonists could be repurposed to treat severe SARS-CoV-2 infection. Given the elevated level of VEGF-A, Janus kinase (JAK) inhibitors should also be investigated as a potential therapeutic option [41, 42]. However, the serial data presented here indicate that the therapeutic window for intervention is narrow. Immune modulators will need to be active before the inflammatory cascade causing acute lung injury develops.

Our study has several limitations. Active case finding through contact tracing is likely to have identified the majority of symptomatic infections in Singapore over this time period. However, atypical or subclinical infections may have been missed. No infections were detected in children (<18 years) or residents of long-term-care facilities. Individuals were enrolled as soon as possible following admission, but while biological samples were collected serially, they were not all acquired at the same time point after symptom onset. Additionally, some laboratory data were incomplete, and clinical data such as date of symptom onset are subject to recall bias. We also did not investigate the effect of different SARS-CoV-2 lineages or mutations on study outcomes [43]. Finally, samples were processed consistently, but numerous factors determine the success of viral cultures and the correlation between culturability and infectiousness is unclear.

In conclusion, we found that virus viability was associated with lower PCR Ct values in early illness. This merits further investigation in terms of infectivity and infection control. SARS-CoV-2 IgM and IgG did not appear until days 15–21 of illness, with implications for the role of rapid diagnostic antibody assay and the timing of plasmapheresis for convalescent plasma. A stronger antibody response was associated with disease severity, suggesting a role in immune pathogenesis. Finally, the overactive proinflammatory immune signatures offer targets

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for host-directed immunotherapy, which should be evaluated in randomized controlled trials.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. B. E. Y., Y.-S. L., and D. C. L. designed the study protocol. B. E. Y., S. W. X. O., P. Y. C., S. K., L. Y. A. C., S. P., S. W. T., L. S., P. P., Y. D., P. T., and J. G. H. L. collected the data. L. F. P. N., D. E. A., W. N. C., T.-M. M., S.-W. F., Y.-H. C., C. W. T., B. L., O. R., L. C., T. B., R. T. P. L., L. R., and L.-F. W. conducted the laboratory investigations including serologic, immunologic, and viral isolation. B. E. Y. and L. W. A. conducted the data analysis. B. E. Y., S. W. X. O., L. F. P. N., W. N. C., and D. C. L. drafted the manuscript. Y.-S. L., L. R., L.-F. W., and D. C. L. provided overall supervision. B. E. Y. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript. The Singapore 2019 Novel Coronavirus Outbreak Research team: Poh Lian Lim, Brenda Sze Peng Ang, Cheng Chuan Lee, Lawrence Soon U Lee, Li Min Ling, Oon Tek Ng, Monica Chan, Kalisvar Marimuthu, Shawn Vasoo, Chen Seong Wong, Tau Hong Lee, Sapna Sadarangani, Ray Junhao Lin, Mucheli Sharavan Sadasiv, Deborah Hee Ling Ng, Chiaw Yee Choy, Glorijoy Shi En Tan, Yu Kit Tan, Stephanie Sutjipto, Pei Hua Lee, Jun Yang Tay, Tsin Wen Yeo, Bo Yan Khoo, Woo Chiao Tay, Gabrielle Ng, Yun Yuan Mah, Wilnard Tan, Partha Pratim De, Rao Pooja, Jonathan WZ Chia, Yuan Yi Constance Chen, Shehara Mendis, Boon Kiat Toh, Raymond Kok Choon Fong, Helen May Lin Oh, Jaime Mei Fong Chien, Humaira Shafi, Hau Yiang Cheong, Thean Yen Tan, Thuan Tong Tan, Ban Hock Tan, Limin Wijaya, Indumathi Venkatachalam, Ying Ying Chua, Benjamin Pei Zhi Cherng, Yvonne Fu Zi Chan, Hei Man Wong, Siew Yee Thien, Kenneth Choon Meng Goh, Shireen Yan Ling Tan, Lynette Lin Ean Oon, Kian Sing Chan, Li Lin, Douglas Su Gin Chan, Say Tat Ooi, Deepak Rama Narayana, Jyoti Somani, Jolene Ee Ling Oon, Gabriel Zherong Yan, David Michael Allen, Roland Jureen, Benedict Yan, Randy Foo, Adrian Kang, Velraj Sivalingam, Wilson How, Norman Leo Fernandez, Nicholas Kim-Wah Yeo, Rhonda Sin-Ling Chee, Siti Naqiah Amrun.

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Potential conflicts of interest. B. E. Y. reports personal fees from Roche and Sanofi, outside the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Clinical Infectious Diseases

MAJOR ARTICLE

Predicting Infectious Severe Acute Respiratory Syndrome Coronavirus 2 From Diagnostic Samples

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(See the Editorial Commentary by Binnicker on pages 2667–8.)

Background. Reverse-transcription polymerase chain reaction (RT-PCR) has become the primary method to diagnose viral diseases, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). RT-PCR detects RNA, not infectious virus; thus, its ability to determine duration of infectivity of patients is limited. Infectivity is a critical determinant in informing public health guidelines/interventions. Our goal was to determine the relationship between E gene SARS-CoV-2 RT-PCR cycle threshold (Ct) values from respiratory samples, symptom onset to test (STT), and infectivity in cell culture.

Methods. In this retrospective cross-sectional study, we took SARS-CoV-2 RT-PCR–confirmed positive samples and determined their ability to infect Vero cell lines.

Results. Ninety RT-PCR SARS-CoV-2–positive samples were incubated on Vero cells. Twenty-six samples (28.9%) demonstrated viral growth. Median tissue culture infectious dose/mL was 1780 (interquartile range, 282–8511). There was no growth in samples with a Ct > 24 or STT > 8 days. Multivariate logistic regression using positive viral culture as a binary predictor variable, STT, and Ct demonstrated an odds ratio (OR) for positive viral culture of 0.64 (95% confidence interval [CI], .49–.84; $P < .001$) for every 1-unit increase in Ct. Area under the receiver operating characteristic curve for Ct vs positive culture was OR, 0.91 (95% CI, .85–.97; $P < .001$), with 97% specificity obtained at a Ct of > 24.

Conclusions. SARS-CoV-2 Vero cell infectivity was only observed for RT-PCR Ct < 24 and STT < 8 days. Infectivity of patients with Ct > 24 and duration of symptoms > 8 days may be low. This information can inform public health policy and guide clinical, infection control, and occupational health decisions. Further studies of larger size are needed.

Keywords. SARS-CoV-2; COVID-19; RT-PCR; infectivity; public health.

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), represents a public health emergency of historic proportion. The global containment efforts have had broad societal and economic impacts. Policy decisions to relax public health measures will require a better understanding of duration of infectivity. This information will also impact infection control practices and occupational health.

To date, the diagnosis of COVID-19 has relied on the detection of SARS-CoV-2 through molecular detection. While this method is both rapid and highly sensitive, there are important limitations. Several studies describe the persistence of SARS-CoV-2 RNA within different body sites [1, 2]. It is known from other viruses that viral RNA can persist beyond infectivity [3, 4]. As a result, demonstration of in vitro infectiousness on cell lines is a more informative surrogate of viral transmission. The ability of viral culture to inform infectivity is an important aspect of diagnostics, but its use is hampered by its difficult and labor-intensive nature. This is further complicated by the need for Biosafety Level 3 facilities in the case of SARS-CoV-2. In a recent cohort study of 9 patients, no virus could be recovered beyond 7 days after symptom onset [1]. This important study is limited by the small number of patients examined and the fact that all 9 cases are linked; therefore, the data may represent a unique viral subpopulation. Here we add to the existing body of literature by presenting viral culture results on a larger cross-sectional group of patients, compared to polymerase chain reaction (PCR) data and time of symptom onset.

MATERIALS AND METHODS

SARS-CoV-2 Reverse-Transcription PCR Cycle Threshold Values and Symptom Onset to Test

All samples in this study were obtained to support routine care and surveillance of the public health response in the province of Manitoba, Canada. All suspected COVID-19 cases had

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SARS-CoV-2 reverse-transcription PCR (RT-PCR) performed on nasopharyngeal (NP) or endotracheal (ETT) samples at Cadham Provincial Laboratory (CPL), the public health laboratory.

The NP swabs and ETT specimens in viral transport media were stored at 4°C for 24–72 hours until they were tested for the presence of SARS-CoV-2 RNA using real-time RT-PCR targeting a 122-nt portion of the Sarbecovirus envelope gene (E gene) [5]. Fifty-five microliters of RNA was extracted from 200 µL of a respiratory specimen using the Ambion AM1836 RNA kit (Thermo Fisher) paired with the Kingfisher Flex instrument (Thermo Fisher). The 20 µL reactions, comprised of TaqMan Fast Virus One-step master mix and 5 µL of RNA, were cycled for 5 minutes at 50°C, 20 seconds at 95°C followed by 40 cycles of 5 seconds at 95°C and 30 seconds at 58°C on a Bio-Rad CFX96 thermal cycler. RT-PCR results were analyzed with the CFX manager software (version 3.1).

Through public health and epidemiology/surveillance and laboratory records, date of symptom onset was determined. Time from symptom onset to RT-PCR, or symptoms to test (STT), was calculated based on laboratory records. For all positive samples, the cycle threshold (Ct) was obtained. The study was performed in accordance with protocol HS23906 (H2020:211), approved by the University of Manitoba Research Ethics Board.

Median Tissue Culture Infectious Dose Assay

Samples were stored at −80°C for between 2 and 4 weeks before being processed for culture. Viral titers of patient samples were determined through median tissue culture infectious dose ($TCID_{50}$) assays inside a Biosafety Level 4 laboratory. In brief, Vero cells (ATCC: CCL-81), maintained in modified Eagle's medium (MEM) supplemented with 5% fetal bovine serum (FBS), 1% penicillin/streptomycin, 0.5 µg/mL amphotericin B, and 1% L-glutamine, were seeded into 96-well plates (Thermo Scientific, 167008) at 70% confluency. Using dilution blocks, patient samples were serially diluted 10-fold from 10^{-1} to 10^{-8} in MEM supplemented with 2% FBS, 1% penicillin/streptomycin, 0.5 µg/mL amphotericin B, and 1% L-glutamine. Dilutions were placed onto the Vero cells in triplicate and incubated at 37°C with 5% carbon dioxide for 96 hours. Following incubation of 4 days, cytopathic effect was evaluated under a microscope and recorded. $TCID_{50}$ and $TCID_{50}$/mL were calculated using the Reed and Muench method previously described [6]

Statistical Methods

Data are presented as mean ± standard deviation for normally distributed data and as median with interquartile range (IQR) for nonnormally distributed data. *P* values are reported as 2-tailed. All statistical analysis was performed with Stata version 14.2 (StataCorp, College Station, Texas). Between-group comparisons were performed using a Student *t* test or Mann-Whitney test. Normality was assessed using the Kolmogorov-Smirnov test, and logistic regression was performed with robust standard errors.

RESULTS

A total of 90 samples were analyzed. Median age of the patients sampled was 45 (IQR, 30–59) years. Almost half (49%) of our samples were from males. SARS-CoV-2 was successfully cultivated from 26 (28.9%) of the samples. The samples included in this study included those positive for SARS-CoV-2 by RT-PCR from day of symptom onset (day 0) up to 21 days after symptom onset. Within this range of samples, positive cultures were only observed up to day 8 after symptom onset (Figure 1). Median Ct count of all samples was 23 (IQR, 17–32). The median $TCID_{50}$/mL was 1780 (IQR, 282–8511). Positive culture samples had a significantly lower Ct compared with culture-negative samples (17 [IQR, 16–18] vs 27 [IQR, 22–33]; $P < .001$; Figure 2). Symptom to test time was also significantly lower in culture-positive vs culture-negative samples (3 [IQR, 2–4] days vs 7 [IQR, 4–11] days; $P < .001$; Figure 2).

Multivariate logistic regression using positive culture as a predictor variable (binary result) and STT, age, and sex as independent variables showed Ct as being significant (odds ratio [OR], 0.64 [95% confidence interval {CI}, .49–.84]; $P < .001$). This implies that for every 1-unit increase in Ct, the odds of a positive culture decreased by 32%. Increasing symptom to test time was also significantly associated with a negative culture (OR, 0.63 [95% CI, .42–.94]; $P = .025$). For every 1-day increase in STT, the odds ratio of being culture positive was decreased by 37%. Receiver operating characteristic curves constructed using Ct vs positive culture showed an area of 0.91 (95% CI, .85–.97; $P < .001$) with 97% specificity obtained at a Ct of > 24. Similarly, STT vs positive culture showed an area of 0.81 (95% CI .73–.90; $P < .001$), with 96% specificity at > 8 days. The probability of successfully cultivating SARS-CoV-2 on Vero cell culture compared to STT is demonstrated in Figure 3. The probability of

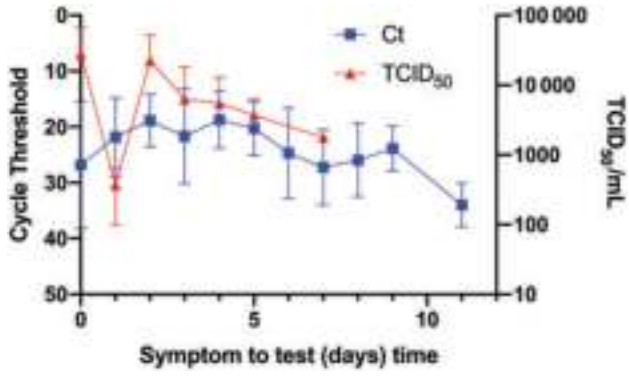

Figure 1. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral dynamics as expressed by E gene reverse-transcription polymerase chain reaction cycle threshold (Ct) value and cell culture median tissue culture infectious dose ($TCID_{50}$)/mL, over time (days).

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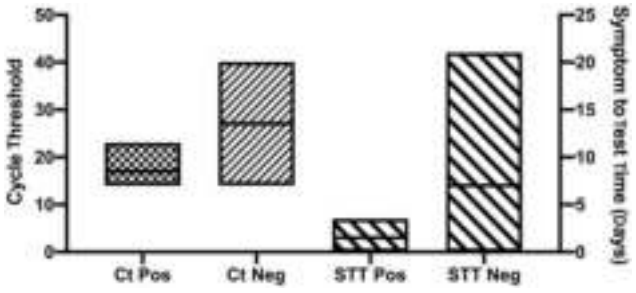

Figure 2. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) E gene reverse-transcription polymerase chain reaction cycle threshold (Ct) values and symptom to test time (STT) in samples that were culture positive or negative. Positive SARS-CoV-2 culture samples had a significantly lower Ct compared with culture-negative samples (17 [interquartile range {IQR}, 16–18] vs 27 [IQR, 22–33]; $P < .001$). STT was also significantly lower in culture-positive vs culture-negative samples (3 [IQR, 2–4] days vs 7 [IQR, 4–11] days; $P < .001$).

obtaining a positive viral culture peaked on day 3 and decreased from that point.

DISCUSSION

PCR and other nucleic amplification (NA) strategies have surpassed viral culture as the gold standard viral diagnostic, because of their wider application, higher sensitivity, rapid performance, and ability for field deployment. A major drawback to PCR and other diagnostic approaches (including other NA, serology, and antigen detection) is that they all fail to determine virus infectivity; PCR sensitivity is excellent but specificity for detecting replicative virus is poor [7]. Our study utilized a cross-sectional approach to correlate COVID-19 symptom onset to specimen collection with SARS-CoV-2 E gene RT-PCR and virus viability as determined by cell culture.

These results demonstrate that infectivity (as defined by growth in cell culture) is significantly reduced when RT-PCR Ct values are > 24. For every 1-unit increase in Ct, the odds ratio for infectivity decreased by 32%. The high specificity of Ct and STT suggests that Ct values > 24, along with duration of symptoms > 8 days, may be used in combination to determine duration of infectivity in patients. Positive cell culture results in our study were most likely between days 1 and 5. This finding is consistent with existing literature [1, 2].

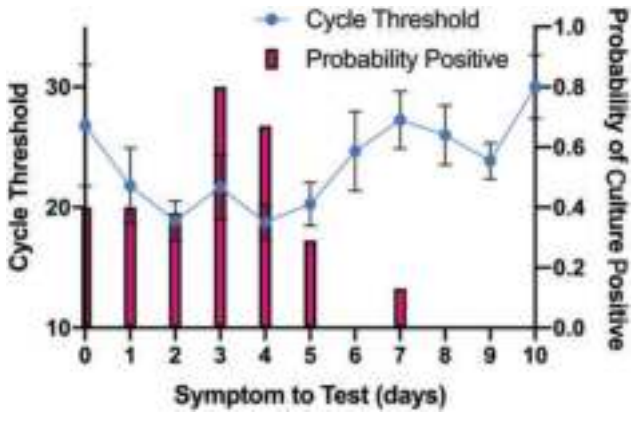

Figure 3. Comparison of symptom onset to test (days) to the probability of successful cultivation on Vero cells (Probability Positive) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) E gene reverse-transcription polymerase chain reaction cycle threshold (Ct) value.

This study is the first to report a large enough data set that demonstrates a link between in vitro viral growth, Ct value, and STT. These results have implications for clinical care, infection prevention and control, and public health. These data can be used to efficiently target case finding efforts by better defining the period of maximal transmission risk. This will be of particular importance in the maintenance phase of the response, where case finding efforts to rapidly interrupt chains of transmission will be essential. Isolation of COVID-19 cases in the community is typically recommended for at least 10 days after symptom onset. Our data supports this approach. Jurisdictions across Canada and the United States are recommending a variety of strategies to discontinue isolation of hospitalized COVID-19 cases [8–13]. Clinical criteria including 14 days from symptom onset or 72 hours symptom free (whichever is longer) are being used in some, while other jurisdictions are using 2 negative NP RT-PCR results 48 hours apart after 14 days of symptoms. Our data support the former approach since RT-PCR positivity persists significantly beyond infectivity; the alternative approach may lead to unnecessary isolation, and use of personal protective equipment and testing resources. The qualitative reporting of results of SARS-CoV-2 RT-PCR as positive or negative is sufficient for diagnosis but may be supplemented by Ct, a semiquantitative value, as well as time of symptom onset to guide infection control, public health, and occupational health decisions.

Our study has important limitations. First, our study utilized a single SARS-CoV-2 gene target (E gene). Though other gene targets may offer greater specificity, the SARS-CoV-2 E gene is more consistently used in both laboratory-developed tests and commercial assays. The testing criteria in Manitoba had sufficient pretest probability to make the likelihood of a false-positive remote. In addition, the first 71 of 90 samples were confirmed using the described protocol with the Centers for Disease Control and Prevention N1 gene target [14]. Second target confirmation was discontinued at that time based on being satisfied with testing criteria and assay sensitivity to accurately identify true COVID-19 cases. Reagent supply also played a role. Second, the recall bias of symptom onset is possible, but this likely would have been equally distributed between those who were culture positive and negative. Third, the infectivity of certain individual cases and the accuracy of our culture assay may have unique variations. Though some individuals in our cross-sectional study would be considered immunocompromised, patients with these conditions could have prolonged shedding of infective SARS-CoV-2 and may not be

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fully represented here. Few children have been diagnosed with COVID-19 in our province (median age of positive PCR, 45 [IQR, 30–59] years). With other respiratory viruses, children may have prolonged shedding. Finally, our patient numbers remain small and larger studies are needed to establish Ct criteria that reliably correlate with loss of infectivity and that utilize additional SARS-CoV-2 gene targets.

In conclusion, the SARS-CoV-2/COVID-19 pandemic represents a dynamic situation where decisions and policy must be guided by evidence. Our study showed no positive viral cultures with a Ct > 24 or STT > 8 days. The odds of a positive culture were decreased by 32% for each unit increase in Ct. These data, if confirmed, may help guide isolation, contact tracing, and testing guidelines.

Notes

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Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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Clinical Infectious Diseases

EDITORIAL COMMENTARY

Can the Severe Acute Respiratory Syndrome Coronavirus 2 Polymerase Chain Reaction Cycle Threshold Value and Time From Symptom Onset to Testing Predict Infectivity?

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(See the Major Article by Bullard et al on pages 2663–6.)

Keywords. SARS-CoV-2; PCR; cycle threshold; infectivity; COVID-19.

To curb the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a 3-pronged strategy is recommended, which consists of testing, isolating those who are infected, followed by contact tracing. To date, the vast majority of testing for SARS-CoV-2 has been performed using real-time polymerase chain reaction (PCR). This diagnostic tool is inherently sensitive, but positive results may be due to the presence of active, replicating virus or residual viral nucleic acid (ie, noninfectious virus). Despite this important limitation, real-time PCR is commonly being used as a "test of cure" following a diagnosis of coronavirus disease 2019 (COVID-19). For symptomatic patients, the US Centers for Disease Control and Prevention recommends either a symptom- or test-based strategy to guide decisions regarding the discontinuation of transmission-based precautions (ie, isolation). When following a test-based strategy, the criteria for discontinuing isolation requires negative results for SARS-CoV-2 RNA from at least 2 consecutive respiratory samples collected ≥24 hours apart [1]. Although this is a conservative approach, it has been justified during the early stages of the COVID-19 pandemic due to the lack of data on the period of infectivity of SARS-CoV-2, as well as the significant repercussions associated with discontinuing transmission-based precautions prior to confirming that an individual is no longer infectious. However, this strategy has increased the use of limited resources (eg, tests, swabs, transport media), has led to some patients testing positive for weeks following their initial diagnosis [2, 3] and, therefore, has significantly extended the period of isolation and/or quarantine for many individuals.

In this issue of *Clinical Infectious Diseases*, Bullard et al [4] assessed the correlation of the real-time PCR cycle threshold (Ct) value, as well as the time from symptom onset to testing, with growth of SARS-CoV-2 in cell culture. The study included 90 samples (nasopharyngeal swabs and endotracheal specimens in viral transport media) that were positive for SARS-CoV-2 RNA by a real-time PCR assay targeting the Sarbecovirus envelope (E) gene [5]. Among the 90 samples that were inoculated into a Vero cell culture line, a cytopathic effect consistent with SARS-CoV-2 was observed in 26 (28.9%) cases. Notably, positive cultures were not observed in samples collected from patients with >8 days of symptoms, and a PCR Ct value >24 showed a strong correlation with reduced recovery of SARS-CoV-2 in cell culture. If confirmed, these results add to our growing understanding of the period of SARS-CoV-2 infectivity and have important implications on isolation, quarantine, and return-to-work decisions. However, there are several significant limitations that should be carefully considered when interpreting the results.

First, Bullard et al tested for SARS-CoV-2 RNA using a single real-time PCR assay targeting the E gene of the virus. The data suggest that SARS-CoV-2 infectivity was reduced when the Ct value was >24, and that for every single unit increase in the Ct, the odds ratio for recovering the virus in cell culture decreased by 32%. Although real-time PCR Ct values can be used to estimate the relative concentration of target nucleic acid in clinical samples, Ct values are not interchangeable between assays. The PCR Ct value can be impacted by the assay's gene target(s) and by factors affecting the efficiency of the PCR reaction, including the nucleic acid extraction system and PCR amplification chemistry. Prior studies have demonstrated that Ct values may vary by up to 5 cycles when the same samples are tested by different assays [6, 7]. Interestingly, a recent report by La Scola et al [8] assessed the correlation of SARS-CoV-2 isolation in cell culture with real-time PCR Ct values. In this study, inoculation of 183 respiratory samples

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(nasopharyngeal swabs [n = 174], sputum [n = 9]) into a Vero E6 cell line yielded detectable cytopathic effect in 129 (70.5%) cases. As expected, culture positivity declined with increasing PCR Ct values, and SARS-CoV-2 was not isolated in culture from any sample that had a PCR Ct value ≥ 34. These data highlight that despite the same PCR gene target being used, the Ct value threshold correlating with SARS-CoV-2 culture positivity may vary significantly between tests. Therefore, Ct value criteria must be established by each healthcare institution.

A second key consideration when interpreting the results from Bullard et al is that samples were stored at −80°C for up to 4 weeks prior to being inoculated in cell culture. Although storage of clinical samples at temperatures ≤ −70°C has been shown to maintain infectivity of other human coronaviruses [9], it is important to emphasize that we do not yet fully appreciate all of the factors that may influence the recovery of SARS-CoV-2 in cell culture. Furthermore, we do not yet know what percentage of COVID-19 patients are culture positive, since the overall number of patients with confirmed disease who have had viral culture performed is exceedingly small. Due to its low sensitivity for recovery of other respiratory viruses (eg, influenza), cell culture has been discontinued in most clinical laboratories and replaced by molecular testing. Therefore, we should be hesitant to conclude that a negative viral culture equates to a lack of SARS-CoV-2 infectivity. In the study by La Scola et al [8], growth of SARS-CoV-2 in 5 cases was only accomplished following blind subculture, suggesting there was a low amount of replicating virus in these samples, which may have been missed if blind passage had not been performed. Due to these challenges, future studies incorporating viral culture should be designed to optimize the recovery of SARS-CoV-2 by inoculating cell lines as soon as possible following collection. If prolonged specimen storage is required, positive controls containing low viral titers (ie, SARS-CoV-2 whole virus spiked into representative specimen matrices) should be included and stored under the same conditions as clinical samples prior to culture. This will help control for the potential impact of prolonged storage on the recovery of SARS-CoV-2.

Despite these limitations, the study by Bullard et al provides informative data on the period of infectivity of SARS-CoV-2, and helps to confirm that PCR positivity is likely not a reliable surrogate marker for determining the infectious status of COVID-19 patients. Along with recent data emerging from South Korea [10] and Singapore [11], these results suggest that the period of SARS-CoV-2 infectivity is likely highest during the first week of illness, and subsequently declines between days 8 and 11 after onset of symptoms. Together, these data should help inform testing guidelines and isolation policies. Future studies are needed to confirm these observations, and should include a combination of testing by multiple real-time PCR assays, carefully controlled viral culture studies, and contact tracing to define which factors can be used to reliably predict the infectious status of patients with COVID-19.

Note

Potential conflicts of interest. M. J. B. reports personal fees from DiaSorin Molecular, Roche Molecular, and Abbott Molecular. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Viral cultures for COVID-19 infectious potential assessment – a systematic review

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Summary

The reliability of RT-qPCR for assessing infectious potential of Covid-19 positives is defined by testing reference and culture specimens and their relation to patient characteristics (date and severity of symptoms, medical history) and test factors (cycle threshold).

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ABSTRACT:

Objective to review the evidence from studies relating SARS-CoV-2 culture with the results of reverse transcriptase polymerase chain reaction (RT-PCR) and other variables which may influence the interpretation of the test, such as time from symptom onset

Methods We searched LitCovid, medRxiv, Google Scholar and the WHO Covid-19 database for Covid-19 to 10 September 2020. We included studies attempting to culture or observe SARS-CoV-2 in specimens with RT-PCR positivity. Studies were dual extracted and the data summarised narratively by specimen type. Where necessary we contacted corresponding authors of included papers for additional information. We assessed quality using a modified QUADAS 2 risk of bias tool.

Results We included 29 studies reporting attempts at culturing, or observing tissue infection by, SARS-CoV-2 in sputum, nasopharyngeal or oropharyngeal, urine, stool, blood and environmental specimens. The quality of the studies was moderate with lack of standardised reporting. The data suggest a relationship between the time from onset of symptom to the timing of the specimen test, cycle threshold (Ct) and symptom severity. Twelve studies reported that Ct values were significantly lower and log copies higher in specimens producing live virus culture. Two studies reported the odds of live virus culture reduced by approximately 33% for every one unit increase in Ct. Six of eight studies reported detectable RNA for longer than 14 days but infectious potential declined after day 8 even among cases with ongoing high viral loads. Four studies reported viral culture from stool specimens.

Conclusion

Complete live viruses are necessary for transmission, not the fragments identified by PCR. Prospective routine testing of reference and culture specimens and their relationship to symptoms, signs and patient co-factors should be used to define the reliability of PCR for assessing infectious potential. Those with high cycle threshold are unlikely to have infectious potential.

Keywords: Covid-19; mode of transmission, viral culture; symptom onset to test date; polymerase chain reaction; SARS-CoV-2; infectious potential.

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Introduction

Effective prevention and management of SARS-CoV-2 infections relies on our capacity to identify those who are infected or potentially infectious. In the absence of predictive clinical signs or symptoms, the major means of detection is testing using Reverse Transcriptase quantitative Polymerase Chain Reaction (RT-qPCR) [1, 2, 3]

The test amplifies genomic sequences identified in specimens, and is highly sensitive, being capable of generating observable signals from specimens containing minute amounts of matching genomic sequence. Amplification of genomic sequence is measured in cycle thresholds (Ct), each cycle being a cut off for positive detection. There may be a correlation between Ct values from respiratory specimens, symptom onset to test (STT) date and positive viral culture. Evidence suggests the lower the Ct value and the shorter the STT, the higher the infectious potential. [4] If this is so, we should be able to identify those with the highest infectious potential.

Identification of a whole virion (as opposed to fragments) and proof that the isolate is capable of replicating its progeny in culture cells is the closest we are likely to get to a gold standard. [5] RT-qPCR cannot distinguish between the shedding of live virus or of viral fragments with no infectious potential, and it cannot measure the quantity of live virus present in a person's excreta. Although viral culture is difficult, time consuming and requires specialised facilities it potentially represents the best indicator of infection and infectious potential. We, therefore, set out to review those studies attempting viral culture, regardless of specimen type tested. We investigated the probability of successful culture with time from symptom onset to test and cycle threshold. We also examined the relationship between specimen cycle threshold and infectious potential.

Methods

We searched four databases: LitCovid, medRxiv, Google Scholar and the WHO Covid-19 database, using the terms 'viral culture' or 'viral replication' and associated synonyms on 10 September 2020. For relevant articles, citation matching was undertaken and relevant results identified.

We included studies reporting attempts to culture SARS-CoV-2 and those which also estimated the potential infectivity of the isolates or observed tissue infection by SARS CoV-2 and related them to other clinical variables such as date of symptom onset to test and patient characteristics.

Isothermal methods of detection are not included in our review, as they do not provide a Ct value

One reviewer extracted data for each study and a second reviewer checked the extraction. Heterogeneity and lack of detail of some of the reported data in the included studies prevented pooling. We tabulated data and summarised it descriptively by specimen: fecal, respiratory,

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environment or mixed. Where possible, we also reported the duration of detectable RNA and the relationship of PCR cycle threshold and log 10 copies to positive viral culture.

Where necessary we contacted corresponding authors of the cited papers for additional information. We assessed quality using the QUADAS 2 risk of bias tool, simplified because the included studies were not designed as primary diagnostic accuracy studies. [6] Our methods are more fully described in our protocol (published on the 4th of July and updated on 5th of October 2020). [7]

Results

We identified 145 possible articles for inclusion and after screening, 29 full texts were read and included (see PRISMA [8] flow chart - Figure 1)**.** One unpublished study was not included as no permission was given by the authors. The included studies were published in 30 articles (see web appendix references w1-w29), four of which were in pre-print servers. The characteristics of each study are shown in Table 1. All included studies were case series of **moderate quality** (Table 2. Quality of included studies). We could not identify a protocol for any of the studies. All had been made public in 2020. We received five author responses regarding clarifying information (see Acknowledgments).

Studies using fecal specimens

Nine studies assessed viral viability from fecal specimens positive for SARS-CoV-2 based on RT-PCR result [W10, W11, W13, W17, W22, W23, W25-W27] One study reported infecting ferrets with stool supernatant; [w10] two reported visual growth in tissue [w19, w22[and four reported achieving viral replication [w13, w23, w24, w26]. In one further study, methods were unclear.[W28]

Studies using respiratory specimens

Seventeen studies reported attempting viral isolation and culture from respiratory specimens [W3, W4, W6-10, W13-16, W18, W21-23, W26, W27] One study successfully cultured 26/90 nasopharyngeal specimens: positive cultures were observed only up to day eight post-symptom onset; [w7] another study obtained cultures from 31/46 nasopharyngeal and oropharyngeal specimens. [w3] The largest study came from the La Scola group publications [w15] with positive cultures of 1,941 from 3,790 specimens. Another study of UK health care workers during a period of low viral circulation isolated SARS Cov-2 from 1/19 specimens. [w5]

Two more studies reported a clear correlation between symptoms onset, date of sampling, Ct and likelihood of viral culture. [w18, w21]

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One study [w14] of nasopharyngeal specimens from 638 patients aged <16 years reported achieving culture from 12 (52%) of the 23 who tested positive for SARS CoV-2 with a Ct of around 28. Gniazdowski [w8] assessed RNA and infectious virus detection in 161 nasopharyngeal specimens from hospitalised Covid-19 patients. Positive culture was associated with Ct values of 18.8 ± 3.4 (median 18.7); negative culture was associated with mean Ct values 27.1 ± 5.7 (median 27.5). Over 90% of the virus isolates were obtained from specimens with a Ct value below 23

Basile [w4] reported 24% culture positivity, with specimens significantly more likely to be positive from ICU. A report by the Korean Centres for Disease Control failed to grow live viruses from 108 respiratory specimens from "re-positives" i.e. people who had tested positive after previously testing negative.[w12]

Ladhani [w16] and colleagues reported a successful culture rate of 87/158 RT-PCR positive naso-pharyngeal specimens from six nursing homes in London.

Studies using environmental specimens

Two possible (the text is unclear) positive cultures were obtained from 95 environmental specimens in one study that assessed aerosol and surface transmission potential of SARS-CoV-2 [w20]. No viruses could be grown from specimens from seven areas of a large London hospital from specimens with a cut-off RT-PCR Ct > 30. [w29]

Ahn and colleagues [w1] failed to grow live virus from an unspecified number of air specimens from isolation rooms of patients with severe Covid-19, but were able to grow virus from swabs of handrails, and the external surfaces of intubation cannulae.

Mixed sources

Some studies labelled as mixed source specimens are also reported by indvidual specimen in this text.

Eight studies reported viral culture from mixed sources: 12 oropharyngeal, nine nasopharyngeal and two sputum specimens [w9], one stool specimen and an unreported number of other specimens[w10], from saliva, nasal swabs, urine, blood and stool collected from nine Covid-19 and a possible

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specimen stool culture [[w23], nine nasopharyngeal, oropharyngeal, stool, serum and urine specimens [w13], seven sputum specimens, three stool specimens and one nasopharyngeal specimen of 11 patients. [w26] . In this study all specimens had been taken within 5 days of symptom onset and there was a relationship between copy thresholds and cytopathic effect observed in infected culture cells.

Kim and colleagues reported no viral growth from an unclear number of serum, urine and stool specimens, despite these specimens being collected soon after admission [w11] . Lu and colleagues also reported no viral growth, however their specimens were from 87 cases tested "re-positive". [w17]

One study [w27] reported 21 positive cultures from from naso-pharyngeal specimens of 19 hospitalised patients in Singapore but no growth from specimens with a Ct value >30, or collected >14 days after symptoms onset. No culture was achieved from the urine or stool specimens.

Blood cultures

In one study by Andersson [w2] et al 20 RT-PCR positive serum specimens from 12 individual patients were selected at random from a Covid-19 specimen bank at 3 to 20 days following onset of symptoms. None of the 20 serum specimens produced a viral culture.

Post mortem study

One study on alveolar specimens from 68 elderly deceased reported postmortem studies on lung tissues from six cases were available for viral isolation. The evaluation showed viable SARS-CoV-2 in all six cases - in one case on day 26 from symptom onset. [w6]

Duration of RNA viral detection

Table 3 shows that nine studies report on the duration of viral RNA detection as assessed by PCR for SARS-CoV-2 RNA. [w7, w8, w10, w12, w13, w21, w24, w25, w27] All nine studies reported RNA detection for longer than 7 days. Young et al [w27] reported that SARS-CoV-2 was detectable from nasopharyngeal swabs by PCR up to 48 days after symptom onset.

Live viral culture window

The live viral culture time window was much shorter than for viral RNA identification, ranging from less than 8 days from symptom onset to test [w23] and Ct < 24 [w7]. Median duration of viral RNA identification in culture was 4 days (InterQuartile Range: 1 to 8) [w21].

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The relationship between RT-PCR results and viral culture of SARS-CoV-2

Table 4 shows that ten studies analysed the relationship between Ct values and the possibility of culturing live virus [w4, w5, w7, w8, w9 w15, w16, w21, w23, w27] and three quantified the mean log copies of detected virus and live culture [w9, w14, w18]. All reported that Ct were significantly lower and log copies were significantly higher in those with live virus culture. Five studies reported no growth in specimens based on a Ct cut-off value [w5, w7, w9, w16, w27] ranging from CT > 24 [w7] to 35 [w15].

The estimated probability of recovery of virus from specimens with Ct > 35 was 8.3% (95% CI: 2.8% to 18.4%)[w21]. All donors above the Ct threshold of 35 (n=5) producing live culture were symptomatic.

In six London nursing homes there was no correlation between Ct values and symptoms in either residents or staff, [w16] although nearly 50% of both categories were asymptomatic.

One study [w9] reported different cut-off thresholds depending on the gene fragment analysed[34]. No growth was found for the NSP 12 fragment at Ct > 31.5, whereas the value was higher for the N gene fragment (>35.2).

The odds for culturing live virus decreased by 0.64 for every one unit increase in Ct (95%CI 0.49 to 0.84, p<0.001) [w7]; another study[w21] reported similar results in line with empirical evidence of an increased Ct of 0.58 per day since symptoms started. [9]

Discussion

The studies in this review attempted, and some successfully achieved, culture of SARS-CoV-2 in the laboratory, using a range of different specimens. There is evidence of a positive relationship between lower cycle count threshold, likelihood of positive viral culture and date of symptom onset. [10] This is seen clearly in the two studies assessing the infectious potential of "re-positives", i.e. COVID-19 cases who had been discharged from hospital after testing negative repeatedly and who then tested positive again after discharge: Lu 2020 [w17] , Korean CDC [w12].

Lu and colleagues considered four hypotheses for the origin of "re-positives" [w17]. On the basis of their evidence they discarded re-infection and latency as explanations, and concluded that the most plausible explanations were either contamination of the specimen by extraneous material or

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identification in the specimen of minute and irrelevant particles of dead SARS-CoV-2 representing virus long neutralised by the immune system.

Rapid expansion in testing capability requires training protocols and precautions to avoid poor laboratory practice which may not be possible in the time pressure of a pandemic. The evidence in this review shows that those with high cycle threshold are unlikely to have infectious potential.

Interpreting the results of RT-PCR requires consideration of patient characteristics such as symptoms and their severity, contacts history, presence of pre-existing morbidities and drug history, the cycle threshold value, the number of days from symptom onset to test and the specimen donor's age.[11 12]

Several of our included studies assessed the relationship of these variables and there appears to be a time window during which RNA detection is at its highest with low cycle threshold and higher possibility of culturing a live virus, with viral load and probability of growing live virus of SARS-CoV2 peaking much sooner than that of SARS CoV-1 or MERS-CoV.[11] We propose that further work should be done on this with the aim of constructing an algorithm for integrating the results of PCR with other variables, to increase the effectiveness of detecting infectious patients.

PCR should be continuously calibrated against a reference culture in Vero E6 cells in which cytopathic effect has been observed [w6]. Confirmation of visual identification using methods, such as an immunofluorescence assay may also be needed to aid diagnosis. [13] Henderson and colleagues have called for a multicentre study of all currently manufactured SARS-CoV-2 nucleic acid amplification tests to correlate the cycle threshold values on each platform for patients who have positive and negative viral cultures. Calibration of assays could then be done to estimate virus viability from the cycle threshold with some certainty. [14]

Ascertainment of infectious potential is all the more important as there is good evidence of viral RNA persistence across a whole range of different viral diseases with little or no infectious potential in the post infectious phase of MERS,[15] measles,[16] other coronoviridae, HCV and a variety of animal RNA viruses.[17]

In one COVID-19 (former) case, viral RNA was detectable until day 78 from symptoms onset with a very high Ct [18] but no culture growth, implying a lack of infectious potential.

SARS CoV-2 methods of cell culture vary and to our knowledge have not been standardised. Methods vary depending upon the selection of the cell lines; the collection, transport, and handling of and the maintenance of viable and healthy inoculated cells. [19] We therefore urgently recommend the development of standard culture methods and external quality assessment schemes for laboratories offering testing for SARS CoV2. [20 21] If identification of viral infectious potential relies on

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visual inspection of cytopathogenic effect, then a reference culture of cells must also be developed to test recognition against infected cells. Viral culture may not be appropriate for routine daily results, but specialized laboratories should use viruses as controls, perform complete investigations when needed, and store representative clinical strains whenever possible. [22] Current evidence is too limited to establish the feasibility of generating a universal cycle threshold value as this may change with circumstances (e.g. hospital, community, cluster and symptom level), laboratory methods, so more information is urgently needed [23].

We suggest the WHO produce a protocol to standardise the use and interpretation of PCR and routine use of culture or animal model to continuously calibrate PCR testing, coordinated by designated Biosafety Level III laboratory facilities with inward directional airflow.[24] Further studies with standardised methods [25] and reporting are needed to establish the magnitude and reliability of this association.

The results of our review agree with the scoping review by Byrne and colleagues on infectious potential periods [26] and those of the living review by Cevick and colleagues[11]. The authors reviewed 79 studies on the dynamics, load and RNA detection for SARS CoV-1, MERS and SARS CoV-2 from symptoms onset. They concluded that although SARS-CoV-2 RNA identification in respiratory (up to 83 days) and stool (35 days) can be prolonged, duration of viable virus is relatively short-lived (up to a maximum of 8 days from symptoms onset). Those results are consistent with Bullard et al who found no growth in specimens with a cycle threshold greater than 24 [w7] or when symptom onset was greater than 8 days, and Wölfel et al [w23] who reported that virus could not be isolated from specimens taken after day 8 even among cases with ongoing high viral loads. The review by Rhee and colleagues reaches conclusion similar to ours.[10]

The importance of symptom onset and reported PCR threshold is shown in a study that collected test data during a prospective household transmission study. The authors found that Ct values were lowest soon after symptom onset and correlated with time elapsed since symptom onset (within 7 days after symptom onset, the median Ct value was 26.5 compared with a median of 35.0 21 days after onset). Ct values were significantly higher among those participants reporting no symptoms, and lower in those reporting upper respiratory symptoms at the time of specimen collection.[28]

The evidence is increasingly pointing to the probability of culturing live virus being related to the amount of viral RNA in the specimen and, therefore, inversely related to the cycle threshold. Thus, detection of viral RNA *per se* cannot be used to infer infectiousness. Duration of excretion may also be linked to age, male gender and possibly use of steroids and severity of illness.

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Our review is limited by the lack of standardised reporting and lack of standard testing methods amongst the included studies[20]. Ct threshold reporting was inconsistent, preventing pooling or further in-depth analysis of the data, and insufficient clinical details were reported to define the possible role of asymptomatics or pre-symptomatics in transmission. The included studies were case reports or case series with a mixture of laboratory and clinical data, and variable in reporting the relation between donor characteristics and PCR results.

We may have missed some studies or new studies as they are published and we aim to update this review with emerging evidence.

Conclusion

The evidence gathered in this review points to a relationship between the time from collection of a specimen to test, cycle threshold, and symptom severity. We recommend that a uniform international standard for reporting of comparative SARS-CoV-2 culture with index test studies be produced. Particular attention should be paid to the relationship between the results of testing, clinical conditions and the characteristics of the source patients, description of flow of specimens and testing methods. Defining cut off levels predictive of infectious potential [27]should be feasible and is necessary for diagnosing viral respiratory infections using molecular tests.

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Potential conflicts:

Tom Jefferson is a Senior Associate Tutor and Honorary Research Fellow, Centre for Evidence-Based Medicine, University of Oxford. Disclosure statement is here

TJ was in receipt of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews (2015-018). In 2014–2016, TJ was a member of three advisory boards for Boehringer Ingelheim. TJ was a member of an independent data monitoring committee for a Sanofi Pasteur clinical trial on an influenza vaccine. TJ is occasionally interviewed by market research companies about phase I or II pharmaceutical products for which he receives fees (current). TJ was a member of three advisory boards for Boehringer Ingelheim (2014-16). TJ was a member of an independent data monitoring committee for a Sanofi Pasteur clinical trial on an influenza vaccine (2015-2017). TJ is a relator in a False Claims Act lawsuit on behalf of the United States that involves sales of Tamiflu for pandemic stockpiling. If resolved in the United States' favor, he would be entitled to a percentage of the recovery. TJ is co-holder of a Laura and John Arnold Foundation grant for development of a RIAT support centre (2017-2020) and Jean Monnet Network Grant, 2017-2020 for The Jean Monnet Health Law and Policy Network. TJ is an unpaid collaborator to the project Beyond Transparency in Pharmaceutical Research and Regulation led by Dalhousie University and funded by the Canadian Institutes of Health Research (2018-2022). TJ consulted for Illumina LLC on next generation gene sequencing (2019-2020). TJ was the consultant scientific coordinator for the HTA Medical Technology programme of the Agenzia per i Serivizi Sanitari Nazionali (AGENAS) of the

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Italian MoH (2007-2019). TJ is Director Medical Affairs for BC Solutions, a market access company for medical devices in Europe. TJ is funded by NIHR UK and the World Health Organization (WHO) to update Cochrane review A122, “Physical Interventions to interrupt the spread of respiratory viruses”. TJ is funded by Oxford University to carry out a living review on the transmission epidemiology of COVID-19. Since 2020, TJ receives fees for articles published by The Spectator and other media outlets.

Elizabeth Spencer is Epidemiology and Evidence Synthesis Researcher at the Centre for Evidence-Based Medicine. Disclosure statement is here.

Jon Brassey is the Director of Trip Database Ltd, Lead for Knowledge Mobilisation at Public Health Wales (NHS) and an Associate Editor at the BMJ Evidence-Based Medicine. Jon is a shareholder in Trip Database Ltd.

Carl Heneghan is Professor of Evidence-Based Medicine, Director of the Centre for Evidence-Based Medicine and Director of Studies for the Evidence-Based Health Care Programme. Disclosure statement is here.

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Tables:

Table 1. Characteristics of included studies

Table 2. Quality of included studies

Table 3. Duration of viral detection

Table 4. Relationship of PCR Cycle threshold and Log 10 copies to Positive Viral Culture

Figures: Figure 1 PRISMA flow chart.

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Table 1 Characteristic of Included Studies

Study [ref id]	Specimens (source)	Specimens (n) [SST]	Culture methods	Culture Positive	Additional notes
Ahn 2020 [W1]	Air and surfaces of isolation room of 3 patients with severe Covid 19	48 [not reported]	Only positive samples (Ct value ≤35 for the RdRp and E genes) were cultured in Vero E6 cells 10-fold dilutions of the SARS-CoV-2 supernatants from the environmental specimens was used. The inoculated cultures were grown in a humidified 37°C incubator with 5% CO2. After 72 hours, areas of cell clearance with crystal violet staining were used to demonstrate the cytopathic effect. In the presence of cytopathic effect was observed, detection of nucleic acid of SARS-CoV-2 by rRT-PCR in the supernatant was performed to confirm a successful culture.	External surfaces of intubation cannulae and surfaces in the room of patient not intubated	No air specimens grew virus Ct values of specimens who grew virus were uniformly low below 30 except in one case.
Andersson 2020 [W2]	20 RT-PCR positive serum specimens, selected at random from a Covid-19	20 serum specimens from 12 hospitalised	Specimens VC01-20 were provided blinded for viral culture experiments. 50 µL aliquots of specimens VC1-VC20 were separately added to 2.4 x 105 Vero E6 cells in 24-well plates.	0 / 20 these serum specimens produced positive viral culture	Serum specimens.

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	specimen bank, representing specimens from 12 individual patients (four individuals were represented at two timepoints), collected at 3 to 20 days following onset of symptoms.	Covid-19 patients	Cells were propagated in DMEM supplemented with 10% FBS. Virus growth assays were done in DMEM supplemented with 1% FBS, glutamine and penicillin/streptomycin, according to published methods. In parallel, wells of the same number of cells were cultured in triplicate without virus challenge but with 50 µL control serum (VC21), or in duplicate with a stock of Victoria/01/2020 SARS-CoV-2 passage 4 (Oxford) at calculated ten-fold serial dilutions per well of 78, 7.8, 0.78 and 0.078 plaque forming units (pfu) in 50 µL of control serum (VC21). Wells were observed daily for cytopathic effects (CPE), and 50 L specimens were taken for vRNA extraction on day 3 post-challenge. On day 4, 50 L aliquots of supernatants from cells challenged with VC01-20 were “blind passaged” to fresh cells, and the remaining supernatants were harvested and stored separately at -80C for future analysis. After a further 3 days, CPE was recorded, if any, for second passage cultures.		
Arons 2020 [W3]	nasopharyngeal and oropharyngeal swabs	48 rRT-PCR–positive specimens [For asymptomatic median 4 days, Ct 23.1]	All rRT-PCR positive specimens shipped to USA CDC for viral culture using Vero-CCL-81 cells. Cells showing cytopathic effects were used for SARS-CoV-2 rRT-PCR to confirm isolation and viral growth in culture.	31 [no relation to symptoms presence. Culturable virus isolated from 6 days before to 9 days after symptom onset]	

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Basile 2020 [W4]	234 specimens, 228 (97%) from the upper respiratory tract (sputum, naso pharyngeal swabs, bronchial lavage from 195 individuals with Covid-19.	Specimens from routine laboratory tests or from patients admitted to ICU or from a physician request [mean 4.5 days, 0-18, only one day to day 18]	Probes targets for PCR included E, RdRp, N, M, and ORF1ab for specimens from ICU patients and 1 to 4 E, RdRp, N and Orf1ab for all other specimens. After stabilization at 4 degrees centigrade specimens were inoculated into Vero E6 cells and incubated at 370C in 5% CO2 for 5 days (day 0 to 4). Cultures were observed daily for cytopathic effect (CPE). CPE when it occurred took place between days 2 and 4. Day 4 was chosen for terminal sampling.	Culture positivity rate was 56 (24%) and significantly more likely positive in ICU patients compared with other inpatients or outpatients and significantly more likely positive in specimens from inpatients	The highest Ct value with a successful culture was 32 (N gene target). A Ct cut-off of ≥37 was not indicative of viable virus
Borczuk 2020 [W5]	Post mortem lung tissue from 68 elderly deaths (median age 73)	Six	When a cytopathic effect was seen, the Vero cell culture supernatant was passed to a fresh Vero cell culture tube to ensure reproducibility. SARS-CoV-2 in the supernatant was further confirmed by RT-PCR	6	No ct reported. In one case virus grew on day 26 from symptoms kick off
Brown 2020 [W6]	Combined viral throat and nose swab from each participant n=1,152	Health care workers in six UK hospitals	Specimens were sent on the same day for detection of SARS-CoV-2 RNA by RT-PCR to the PHE national reference laboratory (five hospitals) or one hospital laboratory. The PHE laboratory used an Applied Biosystems 7500 FAST system targeting a conserved region of the SARS-CoV-2 open reading frame (ORF1ab) gene. The hospital laboratory used a different CE-IVD kit, targeting 3 SARS-CoV-2 genes (RdRp, E, and N). Both PCRs had	SARS-CoV-2 virus was isolated from only one (5%) of nineteen cultured specimens. It had a Ct value of 26.2.	Symptoms in the past month were associated with threefold increased odds of testing positive (aOR 3.46, 95%CI 1.38 to 8.67; p = 0.008). 23 of 1,152 participants

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			internal controls. Viral culture of PHE laboratory positives was attempted in Vero E6 cells with virus detection confirmed by cytopathic effect up to 14 days post- inoculation.		tested positive (2.0%) with a median Ct of 35.70 (IQR:32.42 to 37.57).
Bullard 2020 [W7]	Nasopharyngeal (NP) or endotracheal (ETT) from COVID-19 patients (mean age 45 years)	90 [0 to 7 days]	NP swabs and ETT specimens in viral transport media were stored at 4°C for 24-72 hours until they were tested for the presence of SARS-CoV-2 RNA using real-time RT-PCR targeting a 122nt portion of the envelope gene (E gene). Dilutions were placed onto the Vero cells in triplicate and incubated at 37°C with 5% CO2 for 96 hours. Following incubation of 4 days, cytopathic effect was evaluated under a microscope and recorded.	26	The range of symptoms onset to negative PCT was 21 days. Within this period, positive cultures were only observed up to day 8 post symptom onset
Gniazdowski 2020 [W8]	161 probably nasopharyngeal specimens	161 cases with positive PCR [not reported]	Ct values were calculated of only one gene target per assay: the Spike (S) gene for the RealStar® SARS-CoV-2 and the nonstructural protein 101 (Nsp) 2 gene for the NeuMoDx™ SARS-CoV-2 assays. Genome sequencing was carried out. Incubation of the inoculum in VeroE6 cells cultured at 37°C was observed for 4 days for cytopathic effect and immunofluorescence used to identify viral presence	Unclear possibly 47 isolates	Positive culture was associated with Ct values of 18.8 ± 3.4. Infectious viral shedding occurred in specimens collected up to 20 days after the first positive result in symptomatics. Mean and 184 median Ct values associated with recoverable virus were 18.8 ± 3.4 and 18.17 respectively, which

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					was significantly lower than the mean and median Ct values that did not correlate with infectious virus recovery: 27.1 ± 5.7 and 27.5 respectively. PCR results should be interpreted alongside symptoms
Huang 2020 [W9]	Oropharyngeal (OP) or nasopharyngeal (NP) swabs, or sputum (SP)	60 specimens from 50 cases [3,4 days mean but see table 1 for freeze thaw cycles delays]	SARS-CoV-2 cDNA was prepared using RNA extracted from the specimens of the first patient with confirmed COVID-19. RT was performed using the MMLV Reverse transcription kit. All procedures for viral culture were conducted in a biosafety level-3 facility. Vero-E6 and MK-2 (ATCC) cells were maintained in a virus culture medium and the cells were maintained in a 37°C incubator with daily observations of the cytopathic effect.	Obtained 23 isolates from different specimen types (12 from OP, nine from NP, and two from SP).	Specimens with high copy numbers of the viral genome, indicative of higher viral load, were more likely to be culturable.
Jeong 2020 [W10]	Naso/oropharyngeal swabs, saliva, urine, and stool	5 patients	Specimens positive by qPCR were subjected to virus isolation in Vero cells. Urine and stool specimens were inoculated intranasally in ferrets and they evaluated the virus titers in nasal washes on 2, 4, 6, and 8 days post-infection (dpi). Immunofluorescence antibody assays were also done.	Naso/ oropharyngeal saliva, urine and stool Specimens were collected between days 8 to 30 of the clinical course. Viable SARS-CoV-2 was isolated from 1 naso / oropharyngeal swab. Ferrets inoculated with patient urine or stool were	Viral loads in urine, saliva, and stool specimens were almost equal to or higher than those in naso / oropharyngeal swabs. After symptom resolution, patients shed viable virus in their saliva and urine up to day 15 of illness.

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				infected. SARS-CoV-2 was isolated from the nasal washes of the 2 urine-treated ferrets and one stool-treated ferret	
Kim 2020 [W11]	Unclear. Possibly 323 serum 247 urine and 129 stool specimens	74 COVID-19 hospital patients	RT-PCR was performed on the target genes were E and RdRp. Cell culture was performed in a Level III facility by inoculum into CaCo-2 cell line after stabilisation at 4C and harvested after 5 days and the supernatant after centrifugation was re-inoculated for another 5 days and assessed with RT-PCR.	No viral growth was detected in any specimen despite a positive RT-PCR very soon after admission	
Korean CDC 2020 [W12]	Respiratory swab specimens for individuals testing positive after having previously tested positive, then negative.	108 specimens	Methods not reported	0 / 108 respiratory specimens	This report does not report the laboratory methods used.
Kujawski 2020 (for The COVID-19 Investigation Team) [W13]	Nasopharyngeal (NP), oropharyngeal (OP), stool, serum and urine specimens	12 patients had initial respiratory specimens collecte	SARS-CoV-2 real-time PCR with reverse transcription (rRT–PCR) cycle threshold (Ct) values of virus isolated from the first tissue culture passage were 12.3 to 35.7 and for one patient, virus isolated from tissue culture passage 3 had a titer of 7.75 × 106 median tissue culture infectious dose per ml; these data were likely more reflective of growth in tissue culture than patient viral load.	Viral culture was attempted on initial respiratory specimens from 9 patients and was successful in all 9, including 2 patients who not hospitalized	Viable SARS-CoV-2 was cultured at day 9 of illness (patient 10), but was not attempted on later specimens. SARS-CoV-2 rRT–PCR Ct values of virus isolated from the first tissue culture passage were 12.3 to 35.7.

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					Mean Ct values in positive specimens were 17.0 to 39.0 for NP, 22.3 to 39.7 for OP and 24.1 to 39.4 for stool. All blood and urine isolates were negative. Ct values of upper respiratory tract specimens were lower in the first week of illness than the second in most patients.
L'Huillier 2020 [W14]	Nasopharyngeal swabs in 638 patients aged less than 16 years in Geneva Hospital	23 (3.6%) tested positive for SARS CoV-2 - median age of 12 years (range 7 days to 14.9 years) [1-4]	Observation of cytopathic effect on days 2,4, and 6 of inoculum in Vero cells in two passages.	12 (52% of PCR positive)	Ct was around 28 for the children whose specimens grew viable viruses
La Scola 2020 [W15]	Naso pharyngeal swabs or sputum specimens Only Naso pharyngeal specimens from the	183 (4384 specimens from 3466 patients) [not reported]	From 1,049 specimens, 611 SARS-CoV-2 isolates were cultured. 183 specimens testing positive by RT-PCR (9 sputum specimens and 174 nasopharyngeal swabs) from 155 patients, were inoculated in cell cultures. SARS-CoV-2. RNA rtPCR targeted the E gene. Nasopharyngeal swab fluid or sputum specimen were filtered and then inoculated in Vero E6 Cells. All specimens were inoculated	Of the 183 specimens inoculated in the studied period of time, 129 led to virus isolation. Of these 124 specimens had detectable cytopathic effect	There was a significant relationship between Ct value and culture positivity rate: specimens with Ct values of 13–17 all had positive culture. Culture positivity rate decreased progressively according to Ct values to 12% at 33 Ct.

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	subsequent Jaafar et al letter.		between 4 and 10 h after sampling and kept at + 4 °C before processing. After centrifugation they were incubated at 37 °C. They were observed daily for evidence of cytopathogenic effect. Two subcultures were performed weekly and scanned by electron microscope and then confirmed by specific RT-PCR targeting E gene.	between 24 and 96 h The letter by Jaafar et al adds that 1941 SARS-Cov-2 30 isolate cultures were positive out 3 790 inoculated specimens. These could be seen after the first inoculation or up to 2 blind subcultures. At at Ct of > 34 2.6% of specimens yielded a positive culture.	No culture was obtained from specimens with Ct > 34. The 5 additional isolates obtained after blind subcultures had Ct between 27 and 34, thus consistent with low viable virus load.
Ladhani 2020 [W16]	Naso pharyngeal swabs	87 [Residents post, pre and symptomatic, 5 (6 to 3) 4 (2 to 11) 7 (10 to 4). Staff post, pre and symptomatic 7 (9 to 4) 3 (2-5) 5 (9 to _3)]	All SARS-CoV-2 positive specimens with a Ct value of <35 were incubated on Vero E6 mammalian cells and virus detection was confirmed by cytopathic effect (CPE) up to 14 days post-inoculation. Whole genome sequencing (WGS) was carried out on all RT-PCR positive specimens	87	Ct values < 35 Higher Ct values (lower virus load) specimens were associated with decreasing ability to recover infectious virus from 100% (2/2) with Ct <20.00 to 17.0% (9/53) with Ct 30.00_34.99 (x2 for trend, P<0.001)
Lu 2020 [W17]	87 cases testing “re-positive” at RT-PCR	619 hospital discharges of which tested positive after	137 swabs and 59 serum specimens from 70 “re-positive” cases to assess the immunological and virologic characteristics of the SARS-CoV-2 “re-positive” cases. From 23 January, hospital	No cultures were positive	“Re-positive” cases are unlikely to be infectious as no intact RNA single helix was detected or viral

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	137 swabs (51 nasopharyngeal, 18 throat and 68 anal)	discharge	dischargees followed a strict isolation protocol living (for example) in single dedicated hotel rooms and went home only when nucleic acid tests were negative on both respiratory tract and digestive tract specimens. Specimens (nasopharyngeal, throat and anal swabs), were collected for RT-PCR diagnosis at 7 and 14 days after discharge. Culture was carried out by inoculating Vero E6 cells with patient specimen. CPE were observed daily at 7 days with a second round of passage. RT-PCR diagnosis was carried out on RNA using three RT-PCR kits to conduct nucleic acid testing, in an attempt to avoid false negatives. Ct varied from 29 to 39 depending on gene and kit		isolated grew. Prolonged detection of viral RNA is a challenge for public health interventions targeted at isolating infectious cases. “Re-positive” discharged cases are caused by intermittent shedding of cells containing remnant RNA.
Perera 2020 [W18]	68 specimens: nasopharyngeal aspirates combined with throat swab (n=49), nasopharyngeal aspirate (n=2), nasopharyngeal swab combined with throat swab (n=3), nasopharyngeal swab (n=2), sputum (n=11) and saliva	35 patients, 32 with mild disease [1 to 67 days]	Specimens were tested for sgRNA with ≥5 log10 N gene copies per ml. The complementary DNA obtained was subjected to PCR (40 cycles). Vero E6 cells were seeded and incubated for 24 hours in a CO2 incubator. The culture medium was removed and 125 µL of the clinical specimen in virus transport medium diluted and was inoculated into 2 wells. After 2 hours incubation in a CO2 incubator at 37°C, the plates were incubated at 37°C in a CO2 incubator. A specimen (100 µL) of supernatant was specimend for a quantitative real-time RT-PCR at 0 and 72 hours post inoculation. At 72 hours, cells were scraped into	Virus was isolated from 16 specimens for 16 patients out of a total of 35 specimens	Culturable SARS CoV-2 and sub-genomic RNA (good indicator of replication) was rarely detectable beyond 8 days after onset of illness although virus RNA by RT-PCR remained for up to 70 days.

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	(n=1).		the supernatant and transferred onto fresh cells in 24-well plates and monitored for an additional 72 hours. A final quota of cells was collected for quantitative real-time RT-PCR. Cells were observed for cytopathic effect daily and harvested for testing if 25%–50% of cells showed a cytopathic effect.		
Qian 2020 [W19]	Rectal tissue obtained from a surgical procedure was available.	1 [1 to 3 days post op]	Ultrathin sections of tissue fixed in epoxy resin on formvar-coated copper grids were observed under electron microscope under 200kV. Immunohistochemical staining was used to establish expression and distribution of SARS-CoV-2 antigen.	1	No culture performed. Visualisation of virions in rectal tissue and detection of SARS-CoV-2 antigen in the rectal tissue.
Santarpia 2020 ([W20]	Windowsill and air, mean 7.3 specimens per room. The percentage of PCR positive specimens from each room was 40% -100%	13 patients [days 5 to 9 and day 18 of isolation in a quarantine unit]	Vero E6 cells were used to culture virus from environmental specimens. The cells were cultured in Dulbeccos's minimal essential medium (DMEM) supplemented with heat inactivated fetal bovine serum (10%), Penicillin/Streptomycin (10,000 IU/mL &10,000 µg/mL) and Amphotericin B (25 µg/mL).	Possibly 2 with weak cyotopathic effect	Isolates were from days 5 and 8 of occupancy of hospital/isolation rooms
Singanayagam 2020 [W21]	324 specimens: nose, throat, combined nose-and throat and nasopharyngeal swabs and aspirates	253 positive case [-10 to 60 days]	Vero E6 cells were inoculated with clinical specimens and incubated at 37 °C, 5% CO2. Cells were inspected for cytopathic effect daily up to 14 days. Presence of SARS-CoV-2 was confirmed by SARSCoV-2 nucleoprotein staining by enzyme immunoassay on infected	133 (41%) specimens (from 111 cases)	RT-PCR cycle threshold values correlate strongly with cultivable virus i.e. likelihood of infectiousness. Median Ct of all 324 specimens was 31.15. Probability of culturing virus

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			cells.		declines to 8% in specimens with Ct > 35 and to 6% 10 days after onset and was similar in asymptomatic and symptomatic persons. Asymptomatic persons represent a source of transmissible virus but there is no difference in Ct values and culturability by age group.
Wang 2020 [W22]	Bronchoalveolar fluid, sputum, feces, blood, and urine specimens from hospital in-patients with COVID-19	1,070 specimens collected from 205 patients with COVID-19	rRT-PCR targeting the open reading frame 1ab gene of SARS-CoV-2; cycle threshold values of rRT-PCR were used as indicators of the copy number of SARS-CoV-2 RNA in specimens with lower cycle threshold values corresponding to higher viral copy numbers. A cycle threshold value less than 40 was interpreted as positive for SARS-CoV-2 RNA.	Live SARS-CoV-2 was observed in the stool specimen from 2 patients who did not have diarrhea.	The details of how the specimens were cultured were not reported.
Wölfel 2020 [W23]	Saliva, nasal swabs, urine, blood and stool	9 patients [2 to 4 days]	The average virus RNA load was 6.76 × 105 copies per the whole swab until day 5, and the maximum load was 7.11 × 108 copies per swab. The last swab specimen that tested positive was taken on day 28 after the onset of symptoms.	Yes in respiratory specimens, and indicative in stool	

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Xiao F SJ 2020 [W24]	Esophageal, gastric, duodenal, and rectal tissues were obtained from 1 COVID-19 patients by endoscopy.	1 plus an unknown additional number of fecal specimens from RNA-positive patients.	Histological staining (H&E) as well as viral receptor ACE2 and viral nucleocapsid staining were performed.	1/1 RNA-positive patient. Positive staining of viral nucleocapsid protein was visualized in the cytoplasm of gastric, duodenal, and rectum glandular epithelial cell, but not in esophageal epithelium of the 1 patient providing these tissues. Additionally, positive staining of ACE2 and SARS-CoV-2 was also observed in gastrointestinal epithelium from other patients who tested positive for SARS-CoV-2 RNA in feces, results not shown.	Total specimen numbers are not reported.
Xiao F 2020 [W25]	Serial feces specimens collected from 28 hospitalised COVID-19 patients: 3 specimens from 3 RNA-positive patients were tested for possible viral culture.	3, one patient admitted day 7 post onset	Inoculation of Vero 6 cells. Cycle threshold values for the fecal specimen were 23.34 for the open reading frame 1lab gene and 20.82 for the nucleoprotein gene. A cytopathic effect was visible in Vero E cells 2 days after a second-round passage. The researchers negatively stained culture supernatant and visualized by transmission electron microscopy. Viral particles that were visible were spherical and had distinct surface spike protein projections, consistent with a previously published SARS-CoV2 image.	Infectious virus was present in faeces from two cases)	Selection of specimens is not entirely clear.

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Yao 2020 [W26]	Sputum (n=7), stool (n=3) and one nasopharyngeal specimen	11 patients admitted to hospital: 9 classified as serious or critical, 1 moderate, 1 mild symptoms [0 to 16 days]	The specimens of the 11 patients involved in this study were collected during the early phase of the Covid-19 break out in China, dates ranging from 2nd of January to the 2nd of April 2020. All except one of the patients had moderate or worse symptoms. Three patients had co-morbidities and one patient needed ICU treatment. Seven patients had sputum specimens, one nasopharyngeal and three had stool specimens The specimens were pre-processed by mixing with appropriate volume of MEM medium with 2% FBS, Amphotericin B, Penicillin G, Streptomycin and TPCK-trypsin. The supernatant was collected after centrifugation at 3000 rpm at room 434 temperature. Before infecting Vero-E6 cells, all collected supernatant was filtered using a 435 0.45 μm filter to remove cell debris etc. Vero-E6 cells were infected with 11 viral isolates and quantitatively assessed their viral load at 1, 2, 4, 8, 24, and 48 hours post-infection (PI) and their viral cytopathic effects (CPE) at 48 and 72 hours PI and examined whether the viral isolates could successfully bind to Vero-E6 243 cells as expected. Super-deep sequencing of the 11 viral isolates on the Novaseq 6000 platform was performed.	11 specimens taken up to 16 days from admission to hospital.	Cultured viruses were inoculated in Vero cells. At 8 hours post-infection there was a significant decrease in Ct value (increases in viral load) for five isolates. At 24 hours significant decreases in the Ct values for all of the viral isolates were observed. Mutations of the viruses are also reported

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Young 2020 [W27]	Naso pharyngeal swabs, stool, fresh urine	152 of 74 patients	Material from nasopharyngeal swabs was inoculated in Vero-E6 cells in a Level 3 laboratory. Urine and stool specimens were collected and transported fresh for virus culture but stools were filtered before inoculation. Cells were cultured at 37C for seven days or less if cytopathic effect (CPE) was observed by day 4 and confirmed by PCR.	21 naso pharyngeal specimens from 19 (14%) patients	No virus was isolated when the PCR cycle threshold (Ct) value was >30 or >14 days from symptom onset. Urine and stool specimens at admission did not grow virus
Zhang 2020 [W28]	Stool	Unknown [not reported]	Vero cells were used for viral isolation from stool specimens of Covid-19 patients. A 2019-nCoV strain was isolated from a stool specimen of a laboratory-confirmed COVID-19 severe pneumonia case, who experienced onset on January 16, 2020 and was specimend on February 1, 2020. The interval between sampling and onset was 15 days. The full-length genome sequence indicated that the virus had high-nucleotide similarity (99.98%) to that of the first isolated novel coronavirus isolated from Wuhan, China. In the Vero cells, viral particles with typical morphology of a coronavirus could be observed under the electron microscope.	1	We do not know what influenced successful virus culture e.g. methods optimal, or concentration of virus optimal. More information needed.
Zhou 2020 [W29]	218 surface specimens 31 air specimens	7 areas of large London hospital	RT-PCR with primers and probes for the envelope (E) gene. Duplicate PCR was carried out and specimens were considered positive if both duplicates had Ct< 40.4, or suspect if one of the two have Ct<40.4 (equivalent to one genome copy. For culture Vero E6 and Caco2 cells were used from air and environmental	No cultures were positive	The pre-defined cycle threshold cut off was too high

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			specimens using a method adapted from one previously used to culture influenza virus. On day 0 and after 5-7 days, cell supernatants were collected, and RT-qPCR to detect SARS-CoV-2 performed as described above. Specimens with at least one log increase in copy numbers for the E gene (reduced Ct values relative to the original specimens) after 5-7 days propagation in cells compared with the starting value were considered positive by viral culture.		

Key: STT = symptom onset to test date.

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Table 2. Quality of included studies

Study	Description of methods and sufficient detail to replicate	Sample sources clear	Analysis & reporting appropriate	Is bias dealt with	Applicability
Ahn 2020 [W1]	Yes	Yes	Yes	Partly	Unclear
Andersson 2020 [W2]	Yes	Yes	Yes	Partly	Yes
Arons 2020 [W3]	Yes	Yes	yes	Yes	Unclear
Basile 2020 [W4]	Yes	Yes	Yes	Unclear	unclear
Borczuk 2020 [W5]	Yes	Yes	Yes	Yes	Unclear
Brown 2020 [W6]	Yes	Yes	Yes	Unclear	Unclear
Bullard 2020 [W7]	Yes	Yes	yes	unclear	Unclear
Gniazdowski [W8]	Yes	Yes	Yes	Unclear	Unclear
Huang 2020 [W9]	yes	Yes	Yes	Unclear	Unclear
Jeong 2020 [W10]	Yes	Yes	Yes	No	Unclear
Kim 2020 [W11]	No	No	No	Unclear	Unclear
Korean CDC [W12]	No	Partly	Partly	No	Unclear
Kujawski 2020 [W13]	Yes	Yes	Yes	Unclear	Unclear

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L'Huillier 2020 [W14]	Yes	Yes	Yes	Unclear	Unclear
La Scola 2020 [W15]	Yes	Yes	Yes	Unclear	Unclear
Ladhani 2020 [W16]	Yes	Yes	Yes	Yes	Likely
Lu 2020 [W17]	Yes	Yes	Yes	Partly	Yes
Perera 2020 [W18]	Yes	Yes	Yes	Unclear	Unclear
Qian Q 2020 [W19]	Yes	Yes	Yes	Unclear	Unclear
Santarpia 2020 [W20]	Yes	Yes	Yes	Unclear	Unclear
Singanayagam [W21]	Yes	No	Yes	Unclear	Unclear
Wang W 2020 [W22]	No	Yes	Yes	No	Unclear
Wölfel 2020 [W23]	Yes	Yes	Yes	Unclear	Unclear
Xiao FSJ 2020 [W24]	No	Yes	Yes	No	Unclear
Xiao F 2020 [W25]	Yes	Yes	Yes	No	Unclear
Yoa H 2020[W26]	Yes	Yes	Yes	Unclear	Unclear
Young 2020 [W27]	Yes	Yes	Yes	Yes	Yes
Zhang 2020 [W28]	Partly	Yes	yes	No	Unclear
Zhou 2020 [W29]	Yes	Yes	Yes	Unclear	Unclear

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Table 3. Duration of **detectable SARS-CoV-2 RNA** in the included studies.

Study	**Duration of detectable SARS-CoV-2 RNA as assessed by PCR**	**Comments on the clinical course**
Bullard [w7]	Specimens included in this study included those positive for SARS-CoV-2 by RT-PCR from day of symptom onset (Day 0) up to 21 days post symptom onset.	SARS-CoV-2 Vero cell infectivity of respiratory specimens from SARS-CoV-2 positive individuals was only observed for RT-PCR Ct < 24 and symptom onset to test of < 8 days.
Gniazdowski [w8]	Patients that received repeated testing with longitudinal positive results were tested within a time frame that ranged from less than one day to more than 45 days	Four patients had infectious virus recovered from specimens collected in up to 22 days after the first positive result. Many patients who tested negative for SARS-COV-2 showed a subsequent positive result
Jeong [w10]	Five positive-PCR patients, day 8 to day 30 after symptom onset.	Viable SARS-CoV-2 was demonstrated in saliva, urine and stool specimens from COVID-19 patients up to days 11-15 of the clinical course.

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Korean CDC [w12]	On average, it took 45 days (range: 8 to 82 days) from the initial symptom onset date to testing re positive after discharge. (Based on 226 cases symptomatic at the time of initial confirmation)	This may indicate duration of viral RNA detection over a long period of time and inconsistently. These data may not be comparable with information from studies specifically observing the duration of viral RNA detection as an outcome. Time to retesting positive via PCR is reported, among this specific group of individuals who retested positive by PCR.
Kujawski (for The COVID-19 Investigation Team) [w13]	Duration of SARS-CoV-2 detection by RT-PCR was 7 to 22 days	First 12 identified patients in the US. Respiratory specimens collected between illness days 1 to 9 (median, day 4) All patients had SARS-CoV-2 RNA detected in respiratory specimens, typically for 2 to 3 weeks after illness onset. Mean duration of fever was 9 days. Two patients received a short course of corticosteroids.
Singanayagam [w21]	SARS-CoV-2 viral load identified that the level of SARS-CoV-2 RNA in the URT was greatest around symptom onset, steadily decreased during the first 10 days after illness onset and then plateaued up to day 21	Probability of culturing virus declined to 8% in specimens with Ct > 35 and to 6% 10 days after onset;
Xiao F SJ [w24]	The viral load was higher in feces than in respiratory specimens collected at multiple time points (17–28 days after symptom onset)	Isolation of virus from feces specimens collected at later time points was not successful, although results for virus RNA remained positive, indicating only RNA fragments, not infectious virus, in feces of this patient collected at later time points of disease onset.
Xiao F w25	The duration time of positive stool results ranged from 1 to 12 days.	17 (23%) patients continued to have positive results in stool after showing negative results in respiratory specimens.

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Young w27	SARS-CoV-2 RNA was detectable from nasopharyngeal swabs by PCR up to 48 days after symptom onset.	Mean duration of viral RNA detection by PCR was 16.7 days (95% CI 15.2-18.3). C Cessation of viral RNA detection by PCR occurred in 4% by day 7, 30% by day 14, 78% by day 21 and 91% by day 28. There were no differences by disease severity No virus was isolated when the PCR cycle threshold (Ct) value was >30 or >14 days after symptom onset.

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Table 4: Relationship of PCR Cycle threshold and Log ^{10} copies to Positive Viral Culture

	Specimen				Cycle Threshold			Log ^{10} copies			
Study	RT-PCR SARS-CoV-2 positive specimens (n)	Viral Culture growth (n)	No growth (n)	Gene fragment sampled on PCR Test	Positive culture Ct value	Negative culture Ct Value	No growth in specimens based on Ct	Log ^{10} copies positive culture (unless otherwise stated)	Log ^{10} copies negative culture	No growth based on log copies	ORs for Viral Culture
Basile 2020 [w4]	234	56	178	E, RdRp, N, M, and ORF1ab for ICU patients;	25.01	27.75	Ct >32 with the N gene target [3]				
Brown 2020 [w5]	23	1	22	RdRp, E, and N	26.16	35.16 ± SEM 0.63	Ct >26.2				
Bullard 2020 [w7]	90	26	64	E gene	17 [16-18]	27 [22-33]	Ct > 24				OR 0.64 (95%CI 0.49 to 0.84, p<0.001) for every one unit increase in Ct.
Gniazdowski 2020 [w8]	132	47	85	S, Nsp 2	mean 12.8 ± 3.4 median 18.17	mean 27.1 ± 5.7 median 27.5	Ct ε 23 yielded 8.5% of virus isolates				
Huang 2020	60	23	34	Nsp 12	mean 23.9 ±	mean 29.26 ±	Ct >31.47	mean 7.37 ±	mean 5.98 ±		

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[w9]					SEM 0.78	SEM 0.78		SEM 0.20	SEM 0.18		
		23	37	E	mean 22.39 ± SEM 0.75	mean 28.92 ± SEM 0.65	Ct >31.46	mean 8.21 ± SEM 0.18	mean 6.62 ± SEM 0.16		
		21	31	N	mean 27.29 ± SEM 0.77	mean 31.49 ± SEM 0.59	Ct >35.2	mean 7.87 ± SEM 0.21	mean 6.70 ± SEM 0.17		
L'Huillier 2020 [w14]	23[4]	12	11					mean 7.9×10^8 IQR $4.7\cdot10^6$ - $1.0\cdot10^9$	mean 5.4×10^7 IQR 4.2×10^3– 1.8×10^6		
La Scola 2020 (Jaafar 2020) [w15]	611 (3790)	129(1941)	482 (1849)	E			Ct ε 34 (2,6% positives)				
Ladhani 2020 [w16]	87	31	56	ORF1ab	100% cultures (2/2) with Ct <20.00 to 17.0% (9/53) with Ct 30.00-34.99	Cutoff >35					
Perera 2020 [w18]	68	16	52	N				7.5 [2]	3.8	<5.0	
Singanayagam 2020 [w21]	324	133	191	Unclear			Ct > 35 probability of no growth was 8.3% (95% CI: 2.8%–18.4%) [1]				OR 0.67 for each unit increase in Ct value (95% CI: 0.58–0.77)

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Wölfel 2020 [w23]	45	9	36	E, Subgenomic mRNA.						
Young 2020 [w27]	100	21	79	N, S, and ORF1ab	28.2 (24.3 to 33.3	>30				

1 All above CT (n=5) 35 were symptomatic

2. Of the 16 culture-positive specimens, 15 (94%) had viral RNA load >6 log10 copies/mL ($p<0.01$). All of them were collected within the first 8 days of illness

3. no CPE visualised but a decrease in Ct values between the Ct of the original clinical specimen PCR ($Ct_{specimen}$) and the terminal culture (day four) supernatant PCR ($Ct_{culture}$) of ≥3 (equivalent to a 1 log increase in virus quantity) i.e. $Ct_{specimen} - Ct_{culture} \geq 3$ = culture positive. The authors hypothesized that a $Ct_{specimen}$ minus $Ct_{culture}$ <3 was due to residual inoculated clinical specimen and not replicating virus.

4.23 SARS-CoV-2–infected children

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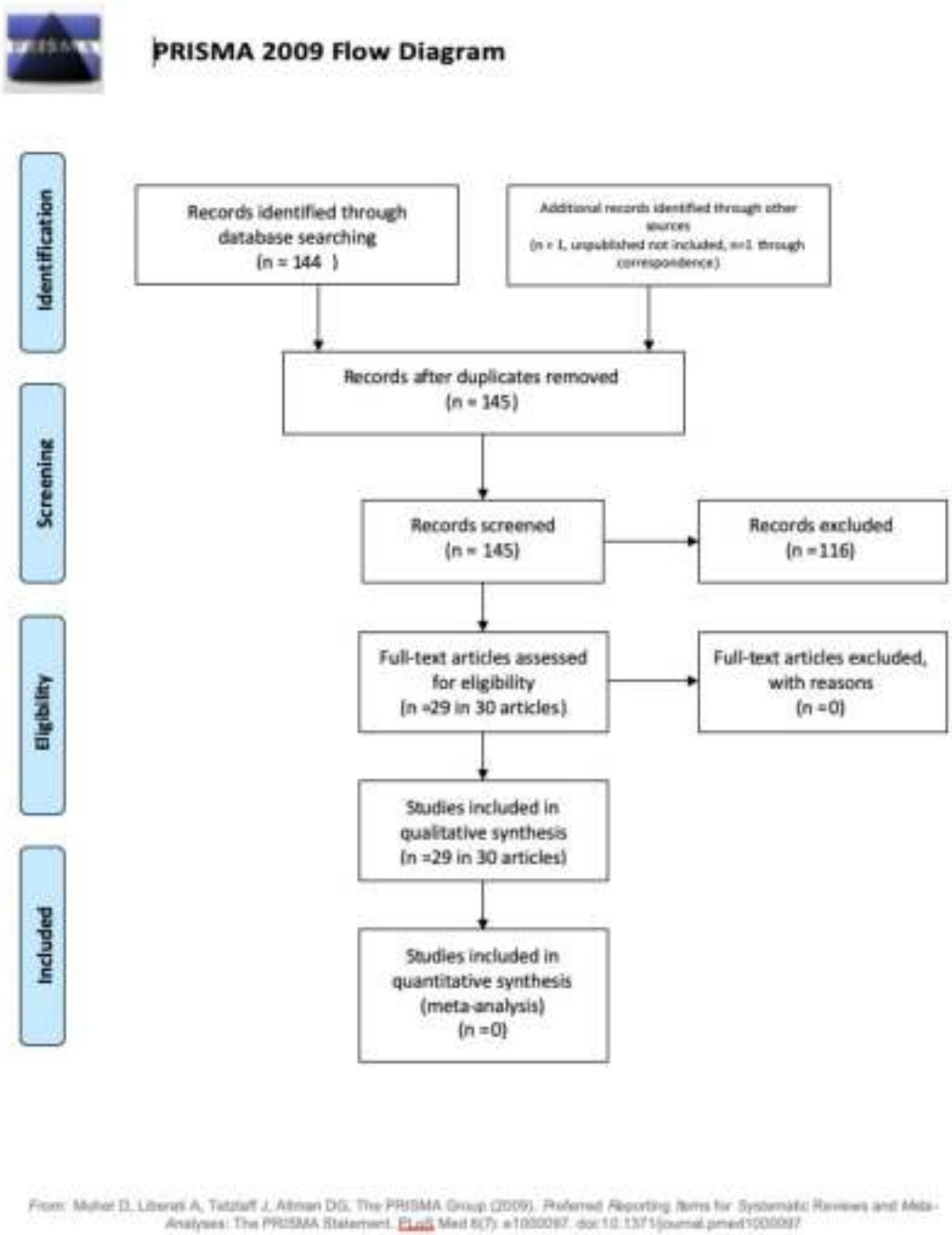
Figure 1



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Criteria for releasing COVID-19 patients from isolation

Scientific brief

17 June 2020

World Health Organization

Background

On 27 May 2020, WHO published updated interim guidance on the clinical management of COVID-19,[1,2] and provided updated recommendations on the criteria for discharging patients from isolation. The updated criteria reflect recent findings that patients whose symptoms have resolved may still test positive for the COVID-19 virus (SARS-CoV-2) by RT-PCR for many weeks. Despite this positive test result, these patients are not likely to be infectious and therefore are unlikely to be able to transmit the virus to another person.

This scientific brief provides the rationale for the changes made to the clinical management of COVID-19 guidance, based on recent scientific evidence. WHO will update these criteria as more information becomes available. For more information about clinical care of COVID-19 patients, see WHO's full guidance.[1]

Previous recommendation

Initial recommendation (published on 12 January 2020)

WHO's first technical package of guidance for the clinical management of the novel coronavirus, now known as COVID-19, was published in early January 2020, shortly after a cluster of atypical pneumonia cases was first reported in Wuhan, People's Republic of China,[3] and included recommendations on when a patient with COVID-19 is no longer considered infectious.

The initial recommendation to confirm clearance of the virus, and thus allow discharge from isolation, required a patient to be clinically recovered and to have two negative RT-PCR results on sequential samples taken at least 24 hours apart.[4] This recommendation was based on our knowledge and experience with similar coronaviruses, including those that cause SARS and MERS.[5]

Updated recommendation

New recommendation (published on 27 May 2020 as part of more comprehensive clinical care guidance[1])

Within the Clinical Management of COVID-19 interim guidance published on 27 May 2020,[1] WHO updated the criteria for discharge from isolation as part of the clinical care pathway of a COVID-19 patient. These criteria apply to all COVID-19 cases regardless of isolation location or disease severity.

Criteria for discharging patients from isolation (i.e., discontinuing transmission-based precautions) without requiring retesting[i]:

- For symptomatic patients: 10 days after symptom onset, plus at least 3 additional days without symptoms (including without fever[ii] and without respiratory symptoms)[iii]
- For asymptomatic cases[iv]: 10 days after positive test for SARS-CoV-2

For example, if a patient had symptoms for two days, then the patient could be released from isolation after 10 days + 3 = 13 days from date of symptom onset; for a patient with symptoms for 14 days, the patient can be discharged (14 days + 3 days =) 17 days after date of symptom onset; for a patient with symptoms for 30 days, the patient can be discharged (30+3=) 33 days after symptom onset).

**Countries may choose to continue to use testing as part of the release criteria. If so, the initial recommendation of two negative PCR tests at least 24 hours apart can be used.*

What is the reason for the change?

In consultations with global expert networks and Member States, WHO has received feedback that applying the initial recommendation of two negative RT-PCR tests at least 24 hours apart, in light of limited laboratory supplies, equipment, and personnel in areas with intense transmission, has been extremely difficult, especially outside hospital settings.

With widespread community transmission, these initial criteria for SARS-CoV-2 posed several challenges:

[i] Countries can choose to continue to use a laboratory testing algorithm as part of the release criteria in (a subset of) infected individuals if their risk assessment gives reason to do so.
[ii] Without the use of any antipyretics.
[iii] Some patients may experience symptoms (such as post viral cough) beyond the period of infectivity. Further research is needed. For more information about clinical care of COVID-19 patients, see our Clinical Management Guidance.[1]
[iv] An asymptomatic case is an individual who has a laboratory confirmed positive test and who has no symptoms during the complete course of infection.

- Long periods of isolation for individuals with prolonged viral RNA detection after resolution of symptoms, affecting individual well-being, society ,and access to healthcare.[13]
- Insufficient testing capacity to comply with initial discharge criteria in many parts of the world.
- Prolonged viral shedding around the limit of detection, having negative results followed by positive results, which unnecessarily challenges trust in the laboratory system.[23-28]

These challenges and newly available data on the risk of viral transmission over the course of the COVID-19 illness provided the framework for updating WHO's position on the timing of discharging recovered patients from isolation in and outside health care facilities. WHO continuously reviews scientific literature on COVID-19 through its Science Division and its COVID-19 technical teams. All aspects of clinical management of COVID-19 patients and laboratory testing strategies are discussed within WHO and with Member States and WHO's global expert networks of public health professionals, clinicians, and academics around the world. These expert networks and the Strategic and Technical Advisory Group for Infectious Hazards (STAG-IH)[7] considered the challenges and reviewed the available data in the decision process to change the initial recommendation.

The updated criteria for discharge from isolation balances risks and benefits; however, no criteria that can be practically implemented are without risk. There is a minimal residual risk that transmission could occur with these non–test-based criteria. There can be situations in which a minimal residual risk is unacceptable, for example, in individuals at high risk of transmitting the virus to vulnerable groups or those in high-risk situations or environments. In these situations, and in patients who are symptomatic for prolonged periods of time, a laboratory-based approach can still be useful.

WHO encourages the scientific community to compile additional evidence to further improve isolation discharge criteria and establish the conditions under which isolation can be abbreviated or where the possible risks of the current discharge criteria require further adaptation. Better understanding of transmission risk among individuals with different clinical presentations or comorbidities and in different settings will aid further refinement of these criteria. For situations that might still require a laboratory-based approach, we encourage the further optimization of such a laboratory algorithm. WHO encourages countries to continue testing patients, if they have the capacity to do so, for systematic data collection that will enhance understanding and better guide decisions about infection prevention and control measures, especially among patients with prolonged illness or those who are immunocompromised.

Current understanding of transmission risk

Infection with the virus causing COVID-19 (SARS-CoV-2) is confirmed by the presence of viral RNA detected by molecular testing, usually RT-PCR. Detection of viral RNA does not necessarily mean that a person is infectious and able to transmit the virus to another person. Factors that determine transmission risk include whether a virus is still replication-competent, whether the patient has symptoms, such as a cough, which can spread infectious droplets, and the behavior and environmental factors associated with the infected individual. Usually 5-10 days after infection with SARS-CoV-2, the infected individual starts to gradually produce neutralizing antibodies. Binding of these neutralizing antibodies to the virus is expected to reduce the risk of virus transmission.[10,11,29,35]

SARS-CoV-2 RNA has been detected in patients 1-3 days before symptom onset, and viral load in the upper respiratory tract peaks within the first week of infection, followed by a gradual decline over time.[10,12,15,19,21,22,36-39] In the feces and lower respiratory tract, this viral load seems to peak in the second week of illness.[19] Viral RNA has been detected in upper respiratory tract (URT) and lower respiratory tract (LRT) and feces, regardless of severity of disease.[19] There seems to be a trend in longer detection of viral RNA in more severely ill patients.[10,14,15,18,19,41-43] Studies of viral RNA detection in immunocompromised patients are limited, but one study suggested prolonged detection of viral RNA in renal transplant patients.[33] Some studies analyzed the risk of transmission related to symptom of onset, and the estimated risk of transmission was highest at or around the time of symptom onset and in the first 5 days of illness.[13,15]

The ability of the virus to replicate in cultured cells serves as a surrogate marker of infectivity but requires special laboratory capabilities and may not be as sensitive as PCR.[10,20] Animal models can aid understanding of transmission risk. In a study by Sia, et al., hamsters infected with SARS-CoV-2 were housed with healthy hamsters on either day 1 or day 6 after infection. Transmission to healthy hamsters occurred in the day 1 group, but not in those exposed 6 days after inoculation. In this model, the timing of transmission correlated with the detection of virus using cell culture, but not with detection of viral RNA in donor nasal washes.[31]

Studies using viral culture of patient samples to assess the presence of infectious SARS-CoV-2 are limited.[8-10,21,29,30,34] Viable virus has been isolated from an asymptomatic case.[9] A study of 9 COVID-19 patients with mild to moderate disease found no SARS-CoV-2 virus able to be cultured from respiratory samples after day 8 of symptom onset.[10] Three studies of patients with undisclosed or variable degree of illness showed an inability to culture virus after days 7-9 of symptom onset.[8,29,30] Patients who were RT-PCR positive on retesting after an initial negative RT-PCR on discharge from isolation were also studied, and none of these patients yielded positive viral cultures.[29] One possible outlier is a case report of a patient with mild COVID-19 who remained PCR-positive for 63 days after symptom onset. In this patient, viral cultures were positive from upper respiratory tract specimens only on the day of symptom onset, but were culture-positive from sputum samples until day 18.[22] It is unclear whether this posed a transmission risk as the patient had no respiratory symptoms. In a hospital-based study of 129 patients severely or critically ill with COVID-19, 23 patients yielded at least one positive viral culture. This study included 30 patients who were immunocompromised. The median duration of viral shedding as measured by culture was 8 days post onset, the interquartile range was 5-11, and the range was 0-20 days.[11] The probability of detecting virus in culture dropped below 5% after 15.2 days after of symptoms. In this study, patients testing positive by viral culture were still experiencing symptoms at the time of sample collection.[11] This and other studies have described the correlation between reduced infectivity with the decrease in viral loads[10,11,29,34] and a rise in neutralizing

antibodies.[10,11,29] Although viral RNA can be detected by PCR even after the resolution of symptoms, the amount of detected viral RNA is substantially reduced over time and generally below the threshold where replication competent virus can be isolated. Therefore, the combination of time after onset of symptoms and the clearance of symptoms seems to be a generally safe approach based on current data.

Conclusion

Based on evidence showing the rarity of virus that can be cultured in respiratory samples after 9 days after symptom onset, especially in patients with mild disease, usually accompanied by rising levels of neutralizing antibodies and a resolution of symptoms, it appears safe to release patients from isolation based on clinical criteria that require a minimum time in isolation of 13 days, rather than strictly on repeated PCR results. It is important to note that the clinical criteria require that patients' symptoms have been resolved for at least three days before release from isolation, with a minimum time in isolation of 13 days since symptom onset.

These modifications to the criteria for discharge from isolation (in a health facility or elsewhere) balance the understanding of infectious risk and the practicality of requiring repeated negative PCR testing, especially in settings of intense transmission or limited testing supplies. Although the risk of transmission after symptom resolution is likely to be minimal based on what is currently known, it cannot be completely ruled out. However, there is no zero-risk approach, and strict reliance on PCR confirmation of viral RNA clearance creates other risks (e.g. straining resources and limiting access to health care for new patients with acute disease). In patients with severe disease who are symptomatic for prolonged periods of time, a laboratory-based approach might also aid decision-making on the need for prolonged isolation. Such a laboratory-based approach can include measuring viral load and neutralizing antibody (or proven equivalent antibody) levels.[10,11,29] More research is needed to further validate such an approach.

WHO will update these criteria as more information becomes available. For more information about clinical care of COVID-19 patients, see WHO's full guidance.[1]

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WHO continues to monitor the situation closely for any changes that may affect this scientific brief. Should any factors change, WHO will issue a further update. Otherwise, this scientific brief will expire 2 years after the date of publication.

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COVID-19
Clinical management

Living guidance
25 January 2021

World Health Organization

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COVID-19
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This document is the update of an interim guidance originally published under the title “Clinical management of COVID-19: interim guidance, 27 May 2020".

WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance document will expire 2 years after the date of publication.

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Foreword and summary

The *Strategic preparedness and response plan* outlines the World Health Organization (WHO) strategic objectives to end the COVID-19 pandemic and assists national stakeholders with developing a structured approach to their response. The WHO's main objectives for COVID-19 are to:

1) supress transmission;
2) provide optimized care for all patients; and save lives
3) minimize the impact of the epidemic on health systems, social services and economic activity.

To achieve these objectives, the WHO *Operational considerations for case management of COVID-19 in health facility and community* describes key actions that should be taken in different scenarios: no cases; sporadic cases; clusters of cases; and community transmission, in order to enable delivery of clinical and public health services in a timely fashion.

The guidance in this document is based on the above strategic priorities, and is intended for clinicians involved in the care of patients with suspected or confirmed COVID-19. It is not meant to replace clinical judgment or specialist consultation but rather to strengthen frontline clinical management and the public health response. Considerations for special and vulnerable populations, such as paediatric patients, older people and pregnant women, are highlighted throughout the text.

In this document we refer to the **COVID-19 care pathway (Annex 1).** This describes a coordinated and multidisciplinary care pathway that a patient enters after s/he is **screened for COVID-19 and becomes a suspect COVID-19 case,** and follows the continuum of their care until release from the pathway. The objective is to ensure delivery of safe and quality care while stopping onwards viral transmission. All others enter the health system in the non-COVID-19 pathway. For the most up-to-date technical guidance related to the COVID-19 response, visit WHO Country & Technical Guidance *(1).*

Basic psychosocial support skills are at the core of any clinical intervention for COVID-19. Such skills are indispensable for all involved in the COVID-19 clinical response, whether they identify as mental health and psychosocial providers or not. Basic psychosocial skills are essential for supporting the emotional well-being of people who have COVID-19, those who have lost someone to COVID-19, or are family members and carers who are caring for someone with COVID-19 or have recovered from COVID-19.

Summary: what is this living guidance?

Clinical questions: What is the clinical management of patients with COVID-19?

Target audience: The target audience is clinicians and health care decision-makers.

Current practice: Current practice to treat COVID-19 is variable reflecting large-scale uncertainty. Numerous clinical trials are underway looking at various interventions that will inform clinical practice. Providing trustworthy guidance that is comprehensive and holistic for the optimal care of COVID-19 patients, throughout their entire illness, is necessary. The previous version of the *Clinical management of COVID-19* provided recommendations that can be applied when caring for patients during the COVID-19 care pathway. This guideline now also includes information on caring for COVID-19 patients after their acute illness.

Updates to this guidance: The panel made the following new recommendations:

- A conditional recommendation to use clinical judgment, including consideration of patients' values and preferences and local and national policy if available, to guide management decisions including admission to hospital and to the intensive care unit (ICU), rather than currently available prediction models for prognosis when caring for patients with COVID-19 of any severity assessed in a clinic or hospital (very low certainty).

- A conditional recommendation for use of pulse oximetry monitoring at home as part of a package of care, including patient and provider education and appropriate follow-up, in symptomatic patients with COVID-19 and risk factors for progression to severe disease who are not hospitalized (very low certainty).
- A conditional recommendation for the use of awake prone positioning in patients with severe COVID-19 that are hospitalized requiring supplemental oxygen or non-invasive ventilation (low certainty).
- A conditional recommendation to use thromboprophylaxis dosing of anticoagulation rather than intermediate or therapeutic dosing in patients hospitalized with COVID-19, without an established indication for higher dose of anticoagulation (very low certainty).
- A conditional recommendation for the use of existing care bundles (defined as three or more evidence-informed practices delivered together and consistently to improve care) chosen locally by hospital or ICU and adapted as necessary for local circumstances in patients with critical COVID-19 (very low certainty).
- Best practice statement: patients who have had suspected or confirmed COVID-19 (of any disease severity) who have persistent, new or changing symptoms should have access to follow-up care (see the new Chapter 24. Care of COVID-19 patients after acute illness).

For chapters without new recommendations, each responsible technical unit (member of steering committee) reviewed the chapter and provided narrative updates to reflect new literature searches. Two technical units used expert panel reviews to review and update their chapters (neurological and mental manifestations [Chapter 17] and rehabilitation [Chapter 19]).

How this guideline was created: This living guideline is an innovation from WHO, driven by the urgent need for global collaboration to provide trustworthy and evolving COVID-19 guidance informing policy and practice worldwide. An international Guideline Development Group (GDG) of content experts, clinicians, patients, ethicists and methodologists produced recommendations following standards for trustworthy guideline development using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. No conflict of interest was identified for any panel member. WHO has partnered with the non-profit MAGIC (Making GRADE the Irresistible Choice) Evidence Ecosystem Foundation for support through their publication platform that facilitates continued updating.

The latest evidence: The evidence included in this guidance update includes six rapid reviews on specific topics that can be found in Annex 3. No conflict of interest was identified for any external contributors.

Understanding the recommendations: When moving from evidence to recommendations, the panel made five conditional recommendations based primarily on low to very low certainty evidence.

- For suggested use of clinical judgment rather than available prediction models, the panel considered the evidence in favour of prognostic models in patients with COVID-19 to be of very low certainty, lack validation studies, and lack evidence of the impact of using models on decision-making and patient outcomes.
- For suggested use of pulse oximetry monitoring at home, the panel felt the potential benefits would outweigh the potential harms, especially if used in patients that were symptomatic and at risk for severe disease; but only as part of a larger package of care including education and follow-up.
- For suggested use of awake prone positioning in hospitalized patients with severe COVID-19, the panel emphasized the low certainty evidence of reduction in mortality, downgraded from higher certainty evidence for mechanically ventilated critically ill patients with acute respiratory distress syndrome (ARDS) and the limited harm with the experience thus far from different resource settings.
- For suggested use of existing care bundles, the panel emphasized the low to very low certainty evidence of reduction in mortality and possible administrative burdens for implementation; but if the hospital or ICU selected among existing care bundles and adapted them to local circumstances that would take into account contextual factors of resource considerations and increase feasibility.

For these four recommendations the panel did not expect much variation in values and preferences.

- For suggested use of thromboprophylaxis dosing rather than intermediate or therapeutic dosing, the panel emphasized the very low certainty evidence of reduction in mortality or pulmonary embolism with higher anticoagulant dosing but also an increased risk of major bleeding; the possible harm indicated by studies of therapeutic anticoagulation rather than intermediate dosing.

For this last recommendation, some panellists anticipated variability in patient values and preferences.

Update 1.4 Clinical Management of COVID-19: Living Guidance

This updated version of the *Clinical management of COVID-19* guidance includes five new recommendations and a new chapter on care for patients after acute illness with COVID-19, adding to the interim guidance published 27 May 2020. Please view section text for a summary of these new recommendations, also available within each section of the guidelines, labelled as new. Other recommendations remain unchanged although underlying content and references have been updated in this version. Concerning therapeutics for COVID-19, please see the linked WHO living guidelines also published as BMJ Rapid Recommendations, which replace the initial guidance (e.g. for corticosteroids).

As described in Methods (Chapter 2), the first interim guidance applied a simplified approach to produce rapid guidance. In this 4th updated version the GDG applied GRADE and standards for trustworthy guidelines. To reflect these two different approaches, the recommendations are therefore marked with different labels and colour codings.

This is a living guidance, so the recommendations included here will be updated, and new recommendations will be added as evidence emerges. The guideline is therefore written, disseminated and updated in MAGICapp, with a format and structure aiming to make it user friendly and easy to navigate while accommodating for dynamically updated evidence and recommendations, focusing on what is new while keeping existing recommendations within the guideline.

Abbreviations

ADL	activities of daily living
ARDS	acute respiratory distress syndrome
AWaRe	Access, Watch or Reserve (antibiotics)
BiPAP	bilevel positive airway pressure
BMI	body mass index
BP	blood pressure
bpm	beats per minute
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CRF	case record form
CT	computed tomography
DIC	disseminated intravascular coagulation
DVT	deep vein thrombosis
ECMO	extracorporeal membrane oxygenation
FiO_2	fraction of inspired oxygen
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HFNO	high-flow nasal oxygen
HIV	human immunodeficiency virus
ICU	intensive care unit
IFRC	International Federation of Red Cross and Red Crescent Societies
InFACT	International Forum for Acute Care Trialists
IPC	infection prevention and control
IQR	interquartile range
ISARIC	International Severe Acute Respiratory and emerging Infection Consortium
LRT	lower respiratory tract
LTCF	long-term care facility
MAGIC	Magic Evidence Ecosystem Foundation
MAP	mean arterial pressure
MERS-CoV	Middle East respiratory syndrome coronavirus
MHPSS	mental health and psychosocial support
MISC- C	multisystem inflammatory syndrome temporally associated with COVID-19 in children and adults
NAAT	nucleic acid amplification test
NCD	noncommunicable disease
NICU	neonatal intensive care unit
NIV	non-invasive ventilation
OI	Oxygenation Index
OSI	Oxygenation Index using SpO_2
PaO_2	partial pressure arterial oxygen
PBW	predicted body weight
PEEP	positive end-expiratory pressure
PICS	post-intensive care syndrome
PPE	personal protective equipment
PTSD	post-traumatic stress disorder
PUI	person/patient under investigation
RCT	randomized controlled trial
RDT	rapid diagnostic test
RM	recruitment manoeuvre
RT-PCR	reverse transcription polymerase chain reaction
SARS-CoV	severe acute respiratory syndrome coronavirus
SBP	systolic blood pressure
SIRS	systemic inflammatory response syndrome

SOFA	sequential organ failure assessment
SpO_2	oxygen saturation
TB	tuberculosis
UNICEF	United Nations Children's Fund
URT	upper respiratory tract
VTE	venous thromboembolism
WHO	World Health Organization

1. Background

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a newly emergent coronavirus, that was first recognized in Wuhan, Hubei province, China, in December 2019. SARS-CoV-2 is a positive-sense single-stranded RNA virus that is contagious in humans. It is the successor to SARS-CoV-1, the strain that caused the 2002–2004 SARS outbreak.

Epidemiology and virologic studies suggest that transmission mainly occurs from both symptomatic and asymptomatic people to others by close contact through respiratory droplets or by direct contact with infected persons, or by contact with contaminated objects and surfaces *(2,3,4,5,6)*, or by aerosols, i.e. in enclosed spaces indoors, crowded and inadequately ventilated spaces, where infected persons spend long periods of time with others, which may include restaurants, choir practices, fitness classes, nightclubs, offices and places of worship *(7)*, or during aerosol-generating procedures. Clinical and virologic studies that have collected repeated biological samples from confirmed patients demonstrate that shedding of SARS-CoV-2 is highest in the upper respiratory tract (URT) (nose and throat) early in the course of the disease *(8,9,10)*, within the first 3 days from onset of symptoms *(10,11,12,13)*. A study of 77 infector-infectee transmission pairs observed the highest viral load in throat swabs at the time of symptom onset, suggesting infectiousness peak on or before symptom onset with an estimated 44% (95% confidence interval, 30–57%) of onward infections happening during the pre-symptomatic phase of the index case *(14)*. The incubation period for COVID-19, which is the time between exposure to the virus (becoming infected) and symptom onset, is, on average, 5–7 days, but can be up to 14 days. During this period, also known as the “presymptomatic” period, some infected persons can be contagious, from 1–3 days before symptom onset *(12)*. It is important to recognize that presymptomatic transmission still requires the virus to be spread via infectious droplets or by direct or indirect contact with bodily fluids from an infected person. An asymptomatic case is a person infected with SARS-CoV-2 who does not develop symptoms *(15,16)*. Among symptomatic patients, the duration of infectious virus shedding has been estimated at 8 days from the onset of any symptoms *(17,18,19)*.

The proportion of persons who become infected with SARS-CoV-2 and remain asymptomatic remains to be better understood, recent meta-analysis reported an overall estimate of 31%, from seven studies with predefined screened populations, prediction interval ranging between 26–37% *(20)*. One systematic review of 79 studies found that 20% (17–25%) of people remained asymptomatic throughout the course of infection *(20)*. Another systematic review, which included 13 studies considered to be at low risk of bias, estimated that 17% of cases remain asymptomatic (14–20%) *(21)*. A further meta-analysis included 28 studies. There was wide variance between two general population studies with the proportion of asymptomatic infections at the time of testing being 20% and 75% respectively, in contacts the proportion was 8.2–50% and 59% (49–68%) of obstetric patients remained asymptomatic throughout whilst 54% (42%-65%) of nursing home residents were asymptomatic at testing of which 28% (13–50%) remained asymptomatic through follow-up *(22)*. Whole cohort testing such as in the Diamond Princess cruise ship found an asymptomatic proportion (among all infected cases) of 17.9% (95% CI: 15.5–20.2%) *(23)* and in a cohort of 356 dialysis patients, 52 (40.3%) had asymptomatic disease or disease which was not detected using RT-PCR when serological testing for antibodies were done *(24)*. In those patients that do become symptomatic, most people with COVID-19 develop only mild (40%) or moderate (40%) disease (see Table 6.3), approximately 15% develop severe disease that requires oxygen support, and 5% have critical disease with complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multiorgan failure, including acute kidney injury and cardiac injury *(25)*. Older age, smoking *(26,27)* and underlying noncommunicable diseases (NCDs), such as diabetes, hypertension, cardiac disease, chronic lung disease and cancer, have been reported as risk factors for severe disease and death, and multivariable analyses have confirmed older age, higher sequential organ failure assessment (SOFA) score and D-dimer > 1 µg/L on admission were associated with higher mortality *(28,29)* (see Table 6.3). This study also observed a median duration of viral RNA detection of 20.0 days (IQR 17–24 days) in survivors, but COVID-19 viral RNA was detectable until death in non-survivors. In a study of 20 immunocompromised haemoncology patients viral RNA was detected for up to 78 days after the onset of symptoms (IQR 24–64 days). Viable virus was detected up to 61 days after the onset of symptoms *(30)*.

COVID-19 is associated with mental and neurological manifestations, including anxiety, depression, sleep problems, headache, dizziness, impaired sense of smell or taste *(31)*, myalgias, delirium/encephalopathy, agitation, stroke, hypoxic ischaemic brain injury, seizures, coma, meningo-encephalitis and Guillain-Barré syndrome *(32,33,34,35)*. Anxiety and depression appear to be common amongst people hospitalized for COVID-19, with one hospitalized cohort from Wuhan, China, revealing over 34% of people experiencing symptoms of anxiety and 28% experiencing symptoms of depression *(36)*. Preliminary findings from retrospective cohort studies of over 60 000 COVID-19 cases in the United States of America indicate an 18.1% incidence of psychiatric diagnoses (including anxiety disorders and insomnia) in the first 2 weeks to 3 months after COVID-19 diagnosis, 5.8% of which were new diagnoses *(37)*.

In many cases, neurological manifestations have been reported even without respiratory symptoms. Over 80% of COVID-19 patients in a hospitalized United States' cohort experienced neurological symptoms during the course of their illness and these manifestations were associated with a four-fold higher risk of severe COVID-19 in this cohort *(38)*. An observational case series from France found that 65% of people with COVID-19 in ICUs showed signs of confusion (or delirium) and 69% experienced agitation *(39)*. Delirium, in particular, has been associated with increased mortality risk in the context of COVID-19 *(40)*. Moreover COVID-19 has been associated with acute cerebrovascular disease (including ischaemic and haemorrhagic stroke) with reports from multiple case series and/or cohort series from China, France, the Netherlands, the United Kingdom and the United States of America *(36,39,41,42,43)*. Case reports of Guillain-Barré syndrome and meningo-encephalitis among people with COVID-19 have also been reported *(44,45,46)*.

Clinical manifestations of COVID-19 are generally milder in children compared with adults *(47,48,49)*. Relatively few cases of infants confirmed with COVID-19 have been reported; infants also experience mild illness *(49,50)*. However, an acute presentation with a hyperinflammatory syndrome leading to multiorgan failure and shock has been reported *(51,52)*, described as multisystem inflammatory syndrome temporally associated with COVID-19 in children and adolescents. Underlying conditions with severe illness in children appear to be similar to adults. Among 655 children with laboratory-confirmed COVID-19 and complete information about underlying conditions, 23% had an underlying condition, with obesity, chronic lung disease (including asthma), cardiovascular disease and immunosuppression most commonly reported *(52)*.

The results of a living systematic review (as of 6 October 2020) show that pregnant and recently pregnant women with COVID-19 appear to be less likely to be symptomatic (0.28, 95% CI 0.13–0.62; 4 studies; 462 051 women), or manifest common symptoms such as fever, dyspnoea and myalgia, compared with non-pregnant women of reproductive age *(53)*. These findings are largely influenced by studies of pregnant women who were managed in hospitals for any reason, with limited data on women during early pregnancy or postpartum. Pregnant or recently pregnant women with severe COVID-19 are at higher risk of requiring admission to an ICU (OR=2.13, 95% CI 1.53–2.95; 7 studies, 601 108 women), invasive ventilation (OR=2.59, 95% CI 2.28–2.94; 6 studies, 601 044 women) or extra corporeal membrane oxygenation (ECMO) (OR=2.02, 95% CI 1.22–3.34; 2 studies, 461 936 women). Older maternal age, high body mass index (BMI), non-white ethnicity, pre-existing comorbidities, chronic hypertension, pre-existing diabetes, are risk factors for developing severe COVID-19. Complications related to COVID-19 did not seem to be increased in women presenting in the third trimester compared with earlier trimester of pregnancy or in multiparous compared with primiparous women, but the existing sample sizes for these comparisons are not large.

The understanding of the mid- and long-term sequelae of COVID-19 is emerging. This new condition which has been described as post-COVID syndrome or long COVID *(54)* still lacks a consensus worldwide on terminology and clinical definition. The post-intensive care syndrome (PICS) has been well described in other critically ill patients and it seems is also being observed in COVID-19 patients. However, non-hospitalized patients (or those with mild and moderate COVID-19) and children are also reporting persisting clustering of symptoms and mid- and long-term sequalae, and children. Recent data (in press at *The Lancet* by Bin Cao et al.) on the long-term consequences of COVID-19 for patients in Wuhan, warned that dysfunctions and complications could persist in some discharged patients for at least 6 months *(55)*.

2. Methods

The original version (v1.1) of this document was developed in consultation with the International Forum for Acute Care Trialists (InFACT), the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) and the Surviving Sepsis Campaign. This is the fourth edition of this document, which was originally adapted from *Clinical management of severe acute respiratory infection when Middle East respiratory syndrome coronavirus (MERS-CoV) infection is suspected* (WHO, 2019).

For the development of the third version (v1.3) of the COVID-19 clinical guidance, a formal Guideline Development Group (GDG) comprising individuals with broad expertise spanning multiple specialties and all regions was convened. Confidentiality and declarations of interest were collected and reviewed and no conflict of interest was identified (see Acknowledgements). Because of the accelerated timeline and very broad scope of the third version of the guideline, it was not feasible to undertake a formal GRADE process (PICO questions; systematic reviews; formal documentation of values and preferences and incorporation of considerations of costs, resources, and feasibility). The topics for consideration originated in the WHO interim guidance for MERS, but for COVID-19 were greatly expanded to reflect the full spectrum of illness, from screening to rehabilitation. Published evidence was synthesized under the coordination of the Science Division in rapid systematic reviews, which were pre-circulated to the GDG. The WHO Steering Committee initially drafted the recommendations about interventions based on these reviews and input from expert clinicians participating in twice-weekly clinical network teleconferences. The GDG held four virtual meetings via teleconference (total of 12 hours) to discuss all previous and new recommendations. Suggested revisions were incorporated into the guidance. Consensus was achieved for all recommendations presented in the final version. The direction and strength of recommendations are presented using symbols rather than formal GRADE terminology (strong and conditional recommendations with grading of certainty of evidence, or best practice statements).

The GREEN symbol denotes a strong recommendation or a best practice statement in favour of an intervention.

The RED symbol denotes a recommendation or a best practice statement against an intervention.

The YELLOW symbol denotes a conditional recommendation in favour of an intervention, or a recommendation where special care is required in implementation.

For this fourth version (v1.4) of the guidance, new recommendations have been developed according to standards and methods for trustworthy guidelines, making use of an innovative process to achieve efficiency in dynamic updating of recommendations. The methods are aligned with the *WHO Handbook for guideline development (56)*.

Related guidelines

This living WHO guidance for the clinical management of COVID-19 is related to the Living Guideline for therapeutics and COVID-19, also published in the BMJ and available in MAGICapp.

Timing

This guidance aims to be trustworthy and living; dynamically updated and globally disseminated once new evidence warrants a change in recommendations for COVID-19. We aim for an ambitious timeframe from trials that trigger guideline development process to WHO publication, within 1 month, while maintaining standards and methods for trustworthy guidelines (*WHO Handbook of guideline development*) *(56)*.

Stepwise approach

Here we outline the stepwise approach we take to improve efficiency and timeliness of the living, trustworthy guidance, in the development and dissemination of the recommendations. To do so, various processes occurred simultaneously.

Step 1: Evidence monitoring and mapping and triggering of evidence synthesis

Regular monitoring of evidence around key topics occurs with support from the WHO rapid review team and their network of collaborators. In September 2020, the WHO Steering Committee triggered this guidance update process, including PICO development. The trigger for producing or updating specific recommendations is based on the following:

- likelihood to change practice;
- relevance to a global audience.

Step 2: Convening the GDG

The pre-selected expert panel (see Acknowledgments) convened on four occasions. At each meeting, a review of the GRADE methodology was done, including how to make best practice statements.

The first meeting, held on 1 December 2020 reviewed the basics of GRADE methodology; including formulating PICO questions and subgroups of interests, assessment of certainty of evidence, incorporating patients' values and preferences, and prioritization of patient-important outcomes. Important questions in the clinical management of patients with COVID-19 focused on the prevention of complications by the use anticoagulation for thromboprophylaxis and the use of care bundles in ICU. The second meeting on 4 December 2020 addressed the use of pulse oximetry at home and awake prone positioning as well as further clarification around the use of care bundles in ICU. The third meeting on 11 December 2020 addressed the longer-term effects of COVID-19 and additional clarification around the use of care bundles in ICU. The fourth meeting on 11 December 2020 addressed risk factors as well as prognostic/prediction models in COVID-19 and completed recommendations for the use of care bundles in ICU.

Step 3: Evidence synthesis

The WHO Steering Committee requested the WHO methods support team to conduct rapid systematic reviews on the six PICOs. Two of the PICOs were conducted by the WHO rapid review team made up of systematic review experts, clinical experts and a librarian. The other four PICOs were addressed by collaborators, that were already engaged in conducting systematic reviews on these topics. This includes: National Institute of Health and Care Excellence (NICE, United Kingdom), the American Society of Haematology guideline/McMaster University GRADE Centre systematic review, COVIDPRECISE; and the Cochrane Library (see Acknowledgements).

Step 4: Final recommendations

The GDG panel members are responsible for the following critical activities:

- To advise on the priority questions and scope of guidance.
- To advise on the choice of important outcomes for decision-making.
- To comment on the evidence used to inform the guideline.
- To advise on the interpretation of the evidence, with explicit consideration of overall balance or risks and benefits.
- To formulate recommendations, taking into account diverse values and preferences according to GRADE.

The GRADE approach provided the framework for establishing evidence certainty and generating both the direction and strength of recommendations *(57,58)*. Good practice statements can be made in addition to, or instead of a recommendation when a large body of indirect evidence, made up of linked evidence including several indirect comparisons, strongly supports the net benefit of the recommended action, if deemed that it will be an onerous and unproductive exercise to collect the linked evidence supporting the recommendations. However, it still requires transparency and explicitness, with a clear rationale for the approach. Although a priori voting procedures were established at the outset, in case consensus was not reached, these procedures were not necessary for this recommendation which reached consensus amongst the panel.

The following key factors were used to formulate transparent and trustworthy recommendations:

- absolute benefits and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE summary of findings tables);
- quality/certainty of the evidence *(57,59)*;
- values and preferences of patients *(60)*;
- resources and other considerations (including considerations of feasibility, applicability, equity) *(60)*;
- each outcome will have an effect estimate and confidence interval, with a measure of certainty in the evidence, as presented in summary of findings tables. If such data are not available narrative summaries will be provided;

- recommendations will be rated as either conditional or strong, as defined by GRADE. If the panel members disagree regarding the evidence assessment or strength of recommendations, WHO will apply voting according to established methods.

Step 5: External and internal review
The WHO guideline was then reviewed by pre-specified external reviewers (see Acknowledgements) and then approved by the WHO Publication Review Committee.

3. The latest evidence

Based on information needs from the GDG, six rapid reviews informed development of recommendations in this update. Whereas evidence summaries are provided for each updated recommendation, details about the literature search, identified studies and references can be found in the Annex 3 of this document.

Table 3.1 Panel outcome rating from a patient perspective

Outcome	Mean	SD	Range
Death at 28 days	9.0	0.0	9-9
Need for invasive mechanical ventilation	8.4	0.8	7-9
Duration of invasive mechanical ventilation	7.7	1.0	5-9
Time to clinical improvement	7.2	1.5	4-9
Serious adverse effect leading to drug discontinuation	7.1	1.4	4-9
Time to symptom resolution	6.6	1.5	3-9
Duration of oxygen support	6.6	1.3	5-9
Duration of hospitalization	6.4	1.3	3-8
Hepatitis (increased liver enzymes)	5.3	1.8	2-9
Duration of viral shedding	4.9	2.4	2-9
Nausea/vomiting	4.5	1.7	2-9
Diarrhea	4.3	1.5	2-8

Note: 1: not important, 9: critically important.

Values and preferences
There were insufficient published data to provide the GDG with an informative systematic review of studies describing patients' experiences or values and preferences on treatment decisions for COVID-19 drug treatments. The GDG therefore relied on their own judgments of what well-informed patients would value after carefully balancing the benefits, harms and burdens of treatment and their subsequent treatment preferences. The GDG included four patient-representatives who had lived experience with COVID-19. The WHO is currently conducting a survey of patients to expand the values and preferences statements for the next version update of the guidance.

The GDG agreed that the following values and preferences would be representative of those of typical well-informed patients:

- Mortality would be the outcome most important to patients, followed by need and duration of mechanical ventilation, time to clinical improvement, and serious intervention-related adverse events.
- Most patients would be reluctant to use a medication for which the evidence left high uncertainty regarding effects on the outcomes listed above. This was particularly so when evidence suggested treatment effects, if they do exist, are small, and the possibility of important harm remains.
- In an alternative situation with larger benefits and less uncertainty regarding both benefits and harms, more patients would be inclined to choose the intervention.

The GDG acknowledged, however, that values and preferences are likely to vary. There will be patients inclined to use a treatment in which evidence has not excluded important benefit, particularly when the underlying condition is potentially fatal. On the other hand, there will be those who have a high threshold of likely benefit before they will choose the intervention. Although the GDG focused on an individual patient perspective, they also considered a population perspective in which feasibility, acceptability, equity and cost are important considerations.

4. Who the recommendations apply to

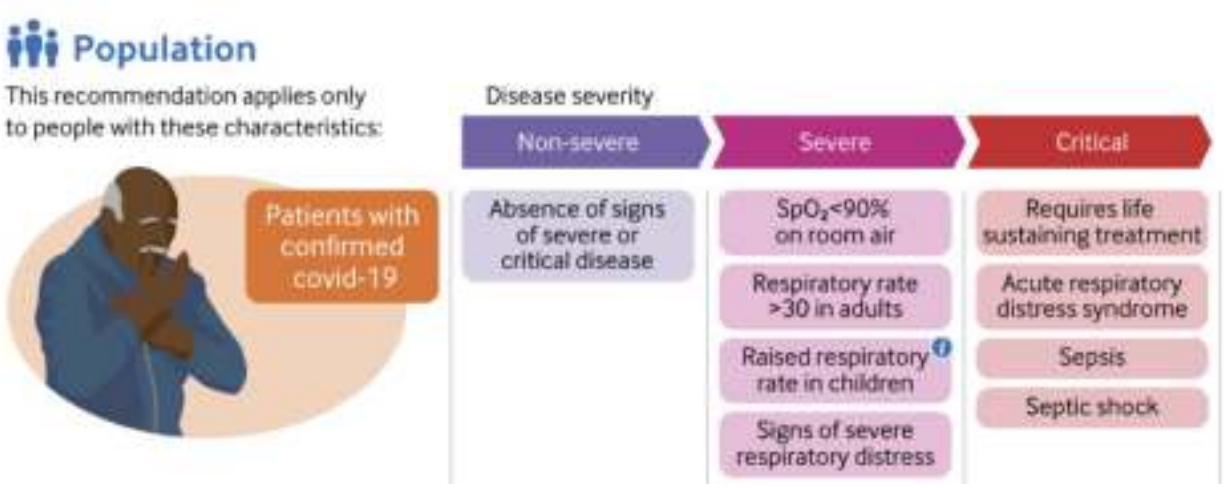
The GDG elected to use the WHO severity definitions based on clinical indicators, adapted from WHO COVID-19 disease severity categorization (see Table 6.3). These definitions avoid reliance on access to health care to define patient subgroups.

WHO Severity definitions

- Critical COVID-19: Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.
- Severe COVID-19: Defined by any of:
  - Oxygen saturation < 90% on room air.
  - Respiratory rate > 30 breaths/min in adults and children > 5 years old; ≥ 60 breaths/min in children < 2 months old; ≥ 50 in children 2–11 months old; and ≥ 40 in children 1–5 years old.
  - Signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs).
- Non-severe COVID-19: Defined as absence of any criteria for severe or critical COVID-19.

Caution: The panel noted that the oxygen saturation threshold of 90% to define severe COVID-19 was arbitrary and should be interpreted cautiously. For example, clinicians must use their judgment to determine whether a low oxygen saturation is a sign of severity or is normal for a given patient with chronic lung disease. Similarly, a saturation > 90–94% on room air is abnormal (in patient with normal lungs) and can be an early sign of severe disease, if patient is on a downward trend. Generally, if there is any doubt, the panel suggested erring on the side of considering the illness as severe.

The infographic illustrates these three disease severity groups and key characteristics to apply in practice, for a recommendation within this guideline.



Infographic co-produced by BMJ and MAGIC; designer Will Stahl-Timmins (see BMJ Rapid Recommendations).

5. COVID-19 care pathway (see Annex 1)

We recommend that COVID-19 care pathways be established at local, regional and national levels. COVID-19 care pathways are for persons with suspected or confirmed COVID-19.

Remarks:

1. A person enters the COVID-19 care pathway after s/he is *screened*, based on a standardized case definition, including assessment of symptoms, and meets criteria for a suspect case.
   - Suspect cases may be referred to as "persons or patients under investigation" (PUIs) in some contexts.
   - Probable cases are suspect cases for whom testing for SARS-CoV-2 is inconclusive or not available.
   - Confirmed cases are persons with laboratory confirmation of infection with SARS-CoV-2.
2. All persons with suspected, probable or confirmed infection with SARS-CoV-2 should be immediately isolated to contain virus transmission. Refer to Chapter on IPC considerations in cohorting suspect, probable and confirmed cases separately.
3. Considerations for co-infections (i.e. influenza, malaria, TB) and/or chronic diseases must be made within the COVID-19 care pathway. Ensuring that these other conditions can management according to national or local protocols.
4. All suspect cases should be tested to determine if they are a ***confirmed*** case. Until proven negative, all suspected cases should remain in the COVID-19 care pathway. If testing is not available, the person becomes a probable case (based on clinical suspicions) and should be cared for in the COVID-19 pathway.

Discontinue transmission-based precautions (including isolation) and release from COVID-19 care pathway as follows.

Remarks:

1. Criteria for discharging patients from isolation (i.e. discontinuing transmission-based precautions) without requiring retesting:
   - For symptomatic patients: 10 days after symptom onset, plus at least 3 additional days without symptoms (including without fever and without respiratory symptoms).
   - For asymptomatic cases: 10 days after positive test for SARS-CoV-2.
2. For example, if patient had symptoms for 2 days, then the patient could be released from isolation after 10 days + 3 = 13 days from date of symptom onset; for a patient with symptoms for 14 days, then the patient can be discharged 14 days + 3 days = 17 days from date of symptom onset; for a patient with symptoms for 30 days, the patient can be discharged 30 days + 3 days = 33 days after symptom onset.
3. Countries may choose to continue to use testing as part of the release criteria. If so, the initial recommendation of two negative PCR tests at least 24 hours apart can be used.
4. Some patients may experience symptoms beyond the period of infectivity. See Chapter 24. Care of COVID-19 patients after acute illness.
5. Please note that the clinical pathway needs to be clearly outlined by countries to follow each patient until outcome, including full recovery. Discharge criteria from clinical care need to take into account the patient's condition, disease experience and other factors.
6. Release from the COVID-19 care pathway is not the same as clinical discharge from a facility or from one ward to another. For example, some patients may still require ongoing rehabilitation, or other aspects of care, beyond release from the COVID-19 care pathway, based on clinical needs in the COVID-19 care pathway. If release from the COVID-19 care pathway coincides with clinical discharge, then several clinical considerations, such as medication reconciliation, plan for follow up with clinical provider in place, review of routine immunization status, among others, should be taken into account.
7. See scientific brief *Criteria for releasing COVID-19 patients from isolation* for more details *(13)*.

6. Screening, triage and clinical assessment: early recognition of patients with COVID-19

The primary objective of the COVID-19 global response is to slow and stop transmission, find, isolate and test every suspect case, and provide timely appropriate care of patients with COVID-19. The recommended location of care will depend on the epidemiologic scenario and be either at a designated COVID-19 health facility, community facility or, where not possible, at home. Refer to the WHO *Operational considerations for case management of COVID-19 in health facility and community (61).*

Please find new recommendation on methods for clinical decision-making in COVID-19 as the third recommendation.

We recommend screening all persons at the first point of contact with the health system in order to identify individuals that have suspected or confirmed COVID-19.

Remarks:

1. Screening can be performed in areas such as the emergency unit, outpatient department/primary care clinic, in the community by a community health worker or by telemedicine. In the context of this outbreak, this should be done at a distance (> 1 m). Use a simple set of questions based on the WHO case definition (see Table 6.1). This is best done by establishing screening protocols at all health access points and during contact tracing activities. Older people and those immunosuppressed may present with atypical symptoms such as fatigue, reduced alertness, reduced mobility, diarrhoea, loss of appetite, delirium and absence of fever *(62,63,64)*. Thus, screening questions may need to be adjusted for certain settings and guided by epidemiologic considerations.
2. Persons with symptoms (see Table 6.1) that meet the case definition for suspected COVID-19 enter into the COVID-19 care pathway and should immediately be given a medical mask and directed to a single room. If a single room is not possible, then group patients with similar clinical diagnosis and based on epidemiological risk factors, with a spatial separation (at least 1 m between patients). Suspected cases should not be cohorted together with confirmed cases (see Chapter 7 on infection prevention and control (IPC)).
3. In areas with other endemic infections that cause fever, such as malaria, dengue, tuberculosis (TB) etc., as part of screening, febrile patients should be tested as per routine protocols *(65,66,67,68,69)*, irrespective of the presence of respiratory signs and symptoms. Coinfection with COVID-19 may coexist.
4. When influenza virus is known or suspected to be circulating, ensure that is also considered as part of screening of patients with fever and influenza-like-illness; and that testing is per local routine protocols. Coinfection with COVID-19 may exist.
5. Large outbreaks have been observed in long-term care facilities (LTCFs) *(63)*. The COVID-19 care pathway should be activated for all residents of LTCFs who are contacts of a confirmed case in that LTCF, including immediate isolation, testing and treatment as needed. The priority focus in these settings should be to ensure the well-being of residents and protect health workers, and implementation of clinical management and IPC that considers the individual's condition and prognosis (such as screening visitors for COVID-19) *(70)*.

In community settings, community health workers should continue to follow usual protocols for recognition and treatment of other common illnesses and danger signs while activating the COVID-19 care pathway (including for referral as needed) for suspect cases. Refer to WHO/IFRC/UNICEF guidance on community-based health care, including outreach and campaigns, in the context of the COVID-19 pandemic *(71)*.

At a health facility, after screening and isolation, triage patients with suspected COVID-19 using a standardized triage tool (such as the WHO/IFRC Interagency Integrated Triage Tool); and evaluate the patient to determine disease severity (see Table 6.3).

- **Initiate timely care for the acutely ill using a systematic approach, as described in WHO/ICRC Basic emergency care *(72,73)*.**
- **After initial assessment, management and stabilization, refer patient to appropriate COVID-19 care destination: within the health facility (critical care unit or ward); to a different health facility; community facility; or home, according to patient medical needs and established COVID-19 care pathways.**

Remarks:

1. Patients with mild and moderate illness may not require emergency interventions or hospitalization; however, isolation is necessary for all suspect or confirmed cases to contain virus transmission. The decision to monitor a suspect case in a health facility, community facility or home should be made on a case-by-case basis. This decision will depend on the clinical presentation, requirement for supportive care, potential risk factors for severe disease (see Table 6.2), and conditions at home, including the presence of vulnerable persons in the household. In situations where TB may co-exist, specific measures may be necessary in addition to the above *(67)*.
2. Early identification of patients at risk for and with severe disease allows for rapid initiation of optimized supportive care treatments and safe, rapid referral to a designated destination in the COVID-19 care pathway (with access to oxygen and respiratory support).
3. Known risk factors for rapid deterioration, severe disease, and/or increased mortality are: older age (> 60 years) and NCDs such as cardiovascular disease, diabetes mellitus, chronic lung disease, cancer and cerebrovascular disease *(28)* (see Table 6.2). Patients with one or more of these risk factors should be monitored closely for deterioration, preferably in a health facility. As described above, the decision to monitor in a health facility, community facility or home should be made on a case-by-case basis. This decision will depend on the clinical presentation, requirement for supportive care, risk factors and conditions at home, including the presence of additional vulnerable persons in the household. Risk factors for severe disease in pregnancy include increasing maternal age, high BMI, non-white ethnicity, pre-existing comorbidities and pregnancy-specific conditions such as gestational diabetes and pre-eclampsia *(53)*.
4. Some patients develop severe pneumonia and require oxygen therapy, and a minority progress to critical disease with complications such as respiratory failure or septic shock (see Table 6.3) *(74,75)*.
5. COVID-19 confirmation needs to be made prior to determining severity; particularly in children, for whom the differential diagnosis for respiratory distress is particularly important.
6. Children with suspected or confirmed COVID-19 infection should be kept together with caregivers wherever possible (if caregivers also have suspected or confirmed COVID-19 infection), and cared for in child-friendly spaces, taking into account specific medical, nursing, nutritional, and mental health and psychosocial support needs of children.

Methods for clinical decision-making in COVID-19

Conditional recommendation for

For patients COVID-19 of any severity assessed in a clinic or hospital, we suggest clinical judgment, including consideration of patients' values and preferences and local and national policy if available, to guide management decisions including admission to hospital and to the ICU, rather than currently available prediction models for prognosis (conditional recommendation, very low certainty).

Evidence to decision

Benefits and harms Important harms

Clinical judgment and policy developed locally or nationally are typically used to make decisions regarding admission of patients with COVID-19 to hospital and to the ICU. Judgment and policy may include ethical considerations regarding allocation of resources. Over the course of the pandemic, many models have been developed for patients with COVID-19 to predict hospital admission, ICU admission, need for

mechanical ventilation, mortality, or other outcomes. All existing models are at unclear or high risk of bias using the multiple domain PROBAST assessment tool *(76)*, and there are as yet no studies of whether the use and implementation of these models improves (shared) decision-making and subsequent patient outcomes. With respect to their effects on patient outcomes, the certainty of evidence for any of these prognostic models is very low.

Certainty of the evidence — Very low

The GDG considered the evidence in favour of prognostic models in patients with COVID-19 to be of very low certainty, due to risk of bias, insufficient predictive accuracy with many models (range of C-statistics for prognosis models 0.54 to 0.99), lack of validation studies, and lack of evidence of the impact of using models on decision-making and patient outcomes. A review and assessment of existing models on their applicability and risks of bias is available (https://www.covprecise.org/living-review/). These prediction models for patient prognosis are distinct from triage models that have been developed to decide which patients are offered admission (typically to an ICU); triage models were not reviewed.

The GDG acknowledged that ongoing model development and validation, along with studies of predictive accuracy and impact on decision-making and patient outcomes of those selected models with sufficient predictive accuracy, may change the certainty of evidence in the future.

Values and preferences — Substantial variability is expected or uncertain

Applying the agreed values and preferences, the GDG inferred that the majority of well-informed physicians and patients would not want care decisions to be based on existing prognostic models, due to the very low certainty of evidence for benefit on patient outcomes. Given the lack of evidence of harm, some patients may choose to have their care informed by the use of such models.

Resources and other considerations — Important considerations

Commonly included predictors in these prognostic models include age, sex, comorbidities, vital signs (e.g. temperature, heart rate, respiratory rate, oxygen saturation, blood pressure), imaging features, lymphocyte count, and C reactive protein (https://www.covprecise.org/living-review/). Some laboratory tests and imaging modalities may not be available in resource-constrained settings, and existing models have not been validated such settings.

Justification

The GDG emphasized the very low certainty evidence supporting the use of prognostic models to enhance clinical-decision making and patient outcomes, and recognized the lack of studies and uncertain feasibility in resource-constrained settings and potential negative impact on health equity, depending on how prognostic models are used to inform clinical decisions. Accordingly, the GDG made a conditional recommendation in favour of usual practice to guide decision-making, consisting of clinical judgment, patients' values and preferences, and local and national policy, if available.

Subgroup analyses

The GDG did not find any evidence bearing on subgroup effects across patients with different levels of COVID-19 disease severity or between children and adults. In other words, the conditional recommendation is applicable across all these subgroups.

Applicability

Special populations

There is insufficient information on the performance and impact of prognostic models in pregnant women. Therefore, the GDG concluded that the recommendation applies to pregnant women.

Practical info

Existing prognostic models are reviewed in a living systematic review, available at https://www.covprecise.org/living-review/.

Uncertainties

Available prognostic models need to be validated in other populations.

Table 6.1 Symptoms associated with COVID-19

Presenting signs and symptoms of COVID-19 vary.

Most persons experience fever (83–99%), cough (59–82%), fatigue (44–70%), anorexia (40–84%), shortness of breath (31–40%), myalgias (11–35%). Other non-specific symptoms, such as sore throat, nasal congestion, headache, diarrhoea, nausea and vomiting, have also been reported *(28,77,78,79)*. Loss of smell (anosmia) or loss of taste (ageusia) preceding the onset of respiratory symptoms has also been reported *(31,80,81)*.

Additional neurological manifestations reported include dizziness, agitation, weakness, seizures, or findings suggestive of stroke including trouble with speech or vision, sensory loss, or problems with balance in standing or walking *(32,33)*.

Older people and immunosuppressed patients in particular may present with atypical symptoms such as fatigue, reduced alertness, reduced mobility, diarrhoea, loss of appetite, confusion, and absence of fever *(62,63,64)*.

Symptoms such as dyspnoea, fever, gastrointestinal (GI) symptoms or fatigue due to physiologic adaptations in pregnant women, adverse pregnancy events, or other diseases such as malaria, may overlap with symptoms of COVID-19 *(82)*.

Children might not have reported fever or cough as frequently as adults *(83)*.

Table 6.2 Risk factors associated with severe disease

Age more than 60 years (increasing with age).

Underlying noncommunicable diseases (NCDs): diabetes, hypertension, cardiac disease, chronic lung disease, cerebrovascular disease, dementia, mental disorders, chronic kidney disease, immunosuppression, obesity and cancer have been associated with higher mortality *(84,85)*.

In pregnancy, increasing maternal age, high BMI, non-white ethnicity, chronic conditions and pregnancy specific conditions such as gestational diabetes and pre-eclampsia *(53)*.

Smoking.

Table 6.3 COVID-19 disease severity

Mild disease		Symptomatic patients (Table 6.1) meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia. See the WHO website for most up-to-date case definitions *(1)*.
Moderate disease	**Pneumonia**	**Adolescent or adult** with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SpO_2 ≥ 90% on room air *(86)*. **Child** with clinical signs of non-severe pneumonia (cough or difficulty breathing + fast breathing and/or chest indrawing) and no signs of severe pneumonia. Fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40 *(87)*. While the diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications. **Caution:** The oxygen saturation threshold of 90% to define severe COVID-19 was arbitrary and should be interpreted cautiously. For example, clinicians must use their judgment to determine whether a low oxygen

		saturation is a sign of severity or is normal for a given patient with chronic lung disease. Similarly, a saturation >90–94% on room air is abnormal (in patient with normal lungs) and can be an early sign of severe disease, if patient is on a downward trend. Generally, if there is any doubt, the panel suggested erring on the side of considering the illness as severe.
Severe disease	**Severe pneumonia**	**Adolescent or adult** with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO_2 < 90% on room air *(86,88)*. **Child** with clinical signs of pneumonia (cough or difficulty in breathing) + at least one of the following: • Central cyanosis or SpO_2 < 90%; severe respiratory distress (e.g. fast breathing, grunting, very severe chest indrawing); general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions *(87)*. • Fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40 *(87)*. While the diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.
Critical disease	**Acute respiratory distress syndrome (ARDS)** *(89,90,91)*	**Onset:** within 1 week of a known clinical insult (i.e. pneumonia) or new or worsening respiratory symptoms. **Chest imaging:** (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules. **Origin of pulmonary infiltrates:** respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/oedema if no risk factor present. **Oxygenation impairment in adults** *(89,91)*: • Mild ARDS: 200 mmHg < PaO2/FiO2a ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH2O).b • Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤ 200 mmHg (with PEEP ≥ 5 cmH2O).b • Severe ARDS: PaO_2/FiO_2 ≤ 100 mmHg (with PEEP ≥ 5 cmH_2O).[b] **Oxygenation impairment in children:** note OI and OSI.[c] Use OI when available. If PaO_2 not available, wean FiO_2 to maintain SpO^2 ≤ 97% to calculate OSI or SpO_2/FiO_2 ratio: • Bilevel (NIV or CPAP) ≥ 5 cmH2O via full face mask: PaO2/FiO2 ≤ 300 mmHg or SpO2/FiO2 ≤ 264. • Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5. • Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3. • Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥ 12.3.
	Sepsis *(92,93)*	**Adults:** acute life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection. Signs of organ dysfunction include: altered mental status (delirium), difficult or fast breathing, low oxygen saturation, reduced urine output *(92)*, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate, or hyperbilirubinemia. **Children:** suspected or proven infection and ≥ 2 age-based systemic inflammatory response syndrome (SIRS) criteria,[d] of which one must be abnormal temperature or white blood cell count.
	Septic shock *(92,93)*	**Adults:** persistent hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥ 65 mmHg and serum lactate level > 2 mmol/L. **Children:** any hypotension (SBP < 5th centile or > 2 SD below normal for age) or two or three of the following: altered mental status; bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and heart rate < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or weak pulse;

		fast breathing; mottled or cool skin or petechial or purpuric rash; high lactate; reduced urine output; hyperthermia or hypothermia *(94)*.
	Acute thrombosis	Acute venous thromboembolism (i.e. pulmonary embolism), acute coronary syndrome, acute stroke.
	MIS-C	**Preliminary case definition:** children and adolescents 0–19 years of age with fever ≥ 3 days **AND** two of the following: rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet); hypotension or shock; features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP); evidence of coagulopathy (by PT, PTT, elevated D-dimers), acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain); **AND** elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin. **AND** no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. **AND e**vidence of COVID-19 **(**RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19. See scientific brief, 15 May 2020 WHO: Multisystemic inflammatory syndrome in children and adolescents temporally related to COVID-19

[a] If altitude is higher than 1000 m, then the correction factor should be calculated as follows: PaO_2/FiO_2 x barometric pressure/760.
[b] When PaO_2 is not available, $SpO_2/FiO_2 \leq 315$ suggests ARDS (including in non-ventilated patients).
[c] Oxygenation Index (OI) is an invasive measurement of the severity of hypoxaemic respiratory failure and may be used to predict outcomes in paediatric patients. It is calculated as follows: percentage of fraction of inhaled oxygen multiplied by the mean airway pressure (in mmHg), divided by the partial pressure of arterial oxygen (in mmHg). Oxygen Saturation Index (OSI) is a non-invasive measurement and has been shown to be a reliable surrogate marker of OI in children and adults with respiratory failure. OSI replaces PaO_2 with oxygen saturation as measured by pulse oximetry (SpO_2) in the OI equation.
[d] SIRS criteria: abnormal temperature (> 38.5 °C or < 36 °C); tachycardia for age or bradycardia for age if < 1 year; tachypnoea for age or need for mechanical ventilation; abnormal white blood cell count for age or > 10% bands.
Abbreviations: BP blood pressure; bpm beats per minute; CPAP continuous positive airway pressure; CT computed tomography; FiO_2 fraction of inspired oxygen; MAP mean arterial pressure; NIV non-invasive ventilation; OI Oxygenation Index; OSI Oxygenation Index using SpO_2; PaO_2 partial pressure arterial oxygen; PEEP positive end-expiratory pressure; SBP systolic blood pressure; SD standard deviation; SIRS systemic inflammatory response syndrome; SOFA sequential organ failure assessment; SpO_2 oxygen saturation.

7. Immediate implementation of appropriate infection prevention and control measures

Infection prevention and control (IPC) is a critical and integral part of clinical management of patients, health workers' safety and hospital-acquired infections. In addition to screening, triage, and rapid source control, WHO guidance emphasizes the importance of administrative, environmental and engineering controls in health care settings *(95)*. Universal masking in health facilities (wearing a mask at all times except when eating or drinking) is required for all persons (staff, patients, visitors, service providers and others) in areas of known or suspected community or cluster SARS-CoV-2 transmission *(96)*, as well as rational and appropriate use of all personal protective equipment (PPE) *(101)*.

For the most up-to-date, comprehensive WHO guidance see *Infection prevention and control during health care when coronavirus disease (COVID-19) is suspected or confirmed (95)* and *Transmission of SARS-CoV- 2: implications for infection prevention precautions*, 9 July 2020 *(102)*.

How to implement IPC measures for patients with suspected or confirmed ***(95)***

Screening and triage for early recognition of suspected COVID-19 patients and rapid implementation of source control measures. Screen all persons at first point of contact in health facility to allow for early recognition followed by their immediate isolation/separation.

Remarks:
Ask the suspected or confirmed COVID-19 patient to wear a medical mask and direct the patient to a separate, well-ventilated area, ideally an isolation room/area if available. Keep at least 1 m distance between patients. Instruct all patients to cover nose and mouth during coughing or sneezing with tissue or flexed elbow, dispose of tissues safely immediately after use in a closed bin and perform hand hygiene

after contact with respiratory secretions. In areas with COVID-19 community transmission, restrict visitors to those that are essential such as the parents of paediatric patients and caregivers and ask them to wear a mask.

Apply standard precautions for all patients.

Remarks:
Apply standard precautions according to risk assessment for all patients, at all times, when providing any diagnostic and care services. Standard precautions include but are not limited to, hand and respiratory hygiene and the appropriate use of PPE; universal masking is required for all persons in areas of known or suspected community or cluster SARS-CoV-2 transmission *(96)*. Standard precautions also include appropriate patient placement; environmental cleaning; prevention of needle-stick or sharps injury and safe waste management.

Carefully practise hand hygiene using an alcohol-based hand rub if hands are not visibly dirty or soap and water and disposable towels, before PPE use and after PPE removal, and when indicated while providing care, according to the WHO Five Moments for hand hygiene *(97)*.

If possible, use either disposable or dedicated equipment (e.g. stethoscopes, blood pressure cuffs, pulse oximeters and thermometers). If equipment needs to be shared among patients, clean and disinfect between each patient use. Ensure that health care workers avoid contaminating environmental surfaces that are not directly related to patient care (e.g. door handles and light switches) and refrain from touching their eyes, nose and mouth with potentially contaminated gloved or ungloved hands. All surfaces should be routinely cleaned and disinfected, especially high touch surfaces, those surfaces touched by patients and whenever visibly soiled or if contaminated with blood and body fluids.

Best practices for safely managing health care waste, including waste related to surgeries and obstetric care, should be followed.

Apply contact and droplet precautions for suspected or confirmed COVID-19 patients.

Remarks:
For suspected and confirmed COVID-19 patients, contact and droplet or airborne precautions should be applied depending on activity to be undertaken. Where possible, designate a team of health workers to care for patients with suspected or confirmed COVID-19 and restrict their contact with COVID-19 patients.

Place all cases in well-ventilated single rooms if feasible. When single rooms are not available or bed occupancy rate is anticipated to be 100% or more, suspected, probable or confirmed COVID-19 patients should be grouped together (cohorted) in adequately ventilated areas with bed space at least 1 m apart.

Limit patient movement within the institution and ensure that patients wear medical masks when outside of their care area (e.g. when being transported).

Health workers should use gloves, a clean, long sleeved gown, medical mask and eye protection (goggles or face shield). Remove PPE when leaving the patient care area, following instructions how to remove PPE safely *(98)*.

Apply airborne precautions when performing aerosol-generating procedures.

Remarks:
Perform procedure in adequately ventilated rooms.

When performing aerosol-generating procedures (tracheal intubation, non-invasive ventilation [CPAP and BiPAP], tracheotomy, cardiopulmonary resuscitation, manual ventilation before intubation, bronchoscopy and sputum induction induced by using nebulized hypertonic saline) or in settings where aerosol-generating procedures are performed, airborne in combination with contact precautions should be used. Use the appropriate PPE, including fit-tested particulate respirators (N95 or equivalent, or higher level of protection), gloves, long-sleeved gowns, eye protection (goggles or face shield). In areas of community transmission, in ICUs where aerosol-generating procedures are frequently performed, the health worker may choose to wear a particulate respirator throughout their shift. There is insufficient evidence to classify

high-flow nasal oxygen (HFNO) and nebulizer therapy as an aerosol-generating procedure that is associated with transmission of COVID-19; thus airborne in combination with contact precautions should be used.

Note: In situations where TB may co-exist, specific measures may be necessary in addition to the above *(67)*.

8. Laboratory diagnosis

For more details, we refer to published WHO guidance *Diagnostic testing for SARS-CoV-2* regarding specimen collection, processing and laboratory testing and the diagnostic algorithm *(99)*.

We recommend, for all suspect COVID-19 cases, at minimum the collection of respiratory specimens for nucleic acid amplification testing (NAAT), for example reverse transcription polymerase chain reaction (RT-PCR). Repetitive testing of upper respiratory tract (URT) and/or lower respiratory tract (LRT) might be needed to establish a diagnosis *(100)*. Additional samples that might aid the diagnosis of COVID-19 can be faecal specimens (if appropriately validated by the receiving laboratory). If deceased consider the collection of postmortem specimens *(99)*. In addition, testing for other respiratory viruses and bacteria should be considered when clinically indicated according to local guidelines.

SARS-CoV-2 antibody tests are not recommended for diagnosis of current infection with COVID-19.

Remarks:

1. Use appropriate PPE for specimen collection (droplet and contact precautions for URT specimens; airborne precautions for LRT specimens). See IPC guidelines for the most up-to-date guidance *(101,102)*.
2. In the first week of symptom onset relatively high viral loads are generally observed in the upper respiratory tract (URT) specimens. For the collection of URT samples, we recommend the collection of nasopharyngeal and oropharyngeal specimens. When collecting URT samples, use viral swabs (sterile Dacron or rayon, not cotton), for nasopharyngeal swabbing use a swab with a long flexible shaft designed for nasopharyngeal sampling. For instructions on appropriate URT sampling see *Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation (73)*. Unless specified differently by the receiving laboratory, transport sample in viral transport media.
3. LRT (vs URT) samples are more likely to be positive after the first week of illness. Thus if URT are negative and clinical suspicion remains, also collect specimens from the LRT when readily available (expectorated sputum, or endotracheal aspirate/bronchoalveolar lavage in ventilated patient). Clinicians may elect to collect only LRT samples when these are readily available (for example, in mechanically ventilated patients). Sputum induction should be avoided owing to increased risk of aerosol transmission. In a patient with suspected COVID-19, especially with pneumonia or severe illness, a single negative URT sample does not exclude the diagnosis, and additional URT and LRT samples are recommended *(99)*. In hospitalized patients with confirmed COVID-19, repeated URT and LRT samples can be collected, as clinically indicated, but are no longer indicated for release from COVID-19 precautions *(13)*.
4. NAAT testing is the recommended for the diagnosis of COVID-19. However in cases where NAAT is unavailable or where prolonged turnaround times preclude clinical utility, antigen testing can be included in the diagnostic algorithm under the right circumstances. For details on appropriate utilization of antigen testing see interim guidance *Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays (103)*. If antigen testing is used, assure that sample collection and testing is performed according to the instructions for use of the antigen tests, staff are appropriately trained and testing quality is embedded in a diagnostic quality system and assessed regularly.
5. If repetitive negative NAAT/RT-PCR results are obtained from a patient in whom COVID-19 is strongly suspected, a paired serum specimen could be collected. One specimen taken in the acute phase and one in the convalescent phase 2–4 weeks later. This is only useful if validated (semi) quantitative

serology assays and trained staff for the interpretations are available in the receiving laboratory. With these paired samples it can be retrospectively evaluated whether there is seroconversion or a rise in antibody titres, further supporting the suspicion that this individual indeed had recent COVID-19 despite negative NAATs.

Depending on the local epidemiology and clinical symptoms, test for other potential etiologies (e.g. influenza, malaria, dengue fever, typhoid fever) as appropriate.

Remarks:

1. Patients should also be tested for other respiratory pathogens, as recommended in local clinical management guidelines. Examples, but not excluding others as this depends on epidemiological or clinical parameters, are the viral respiratory pathogens influenza A and B (including zoonotic influenza A), respiratory syncytial virus, parainfluenza viruses, rhinoviruses, adenoviruses, enteroviruses (e.g. EVD68), human metapneumovirus and endemic human coronaviruses (i.e. HKU1, OC43, NL63, and 229E). Examples of bacterial pathogens include *Streptococcus pneumoniae, Haemophilus influenzae*, atypical respiratory pathogens (e.g. *Legionella pneumophila, Coxiella burnetii, Chlamydia psittaci or pneumoniae, Mycoplasma pneumoniae*). URT and LRT specimens are generally suitable for viral respiratory pathogens. For bacterial culture sputum or other LRT specimens are required.
2. Dual infections with other respiratory infections (viral, bacterial and fungal) have been found in COVID-19 patients *(104)*. As a result, a positive test for a non-COVID-19 pathogen does not rule out COVID-19, or vice versa. Some microbes found in respiratory culture can be either be a pathogen or be part of normal mouth/respiratory flora, thus evaluation on whether a found micro-organism is a coinfection or part of the normal flora needs to be weighted for each individual patient.
3. In malaria-endemic areas, patients with fever should be tested for the presence of malaria or other co-infections with validated rapid diagnostic tests (RDTs) or thick and thin blood films and treated as appropriate *(105)*. In endemic settings, arbovirus infection (dengue/chikungunya) should also be considered in the differential diagnosis of undifferentiated febrile illness, particularly when thrombocytopenia is present *(65)*. Coinfection with COVID-19 virus may also occur and a positive diagnostic test for dengue (e.g. dengue RDTs) does not exclude the testing for COVID-19 *(106)*. If TB is also suspected, collect sputum with specific instructions (e.g. to be done in open area outside the home and away from others) or in an open, well-ventilated space – preferably outside of the health facility *(67)*. Staff should not stand near the patient during sample collection.
4. When influenza virus is known or suspected to be circulating, test patients with severe or complicated disease and those with risk factors for severe influenza (note, this includes younger children and pregnant women up to two weeks postpartum) for influenza virus with a rapid molecular testing when results can be made available within 24 hours preferably. The longer the time lag between sampling and test results, the less the test will benefit clinical management (see policy brief) *(107)*. Empiric treatment, when indicated, should not be delayed while waiting for results (see Chapter 16. Treatment of other acute and chronic infections in patients with COVID-19).

For COVID-19 patients with severe or critical disease, also collect blood cultures, ideally prior to initiation of antimicrobial therapy *(92)*.

Remark:

If blood cultures cannot be taken timely before the administration of antimicrobial therapies, indicate the details of administered antibiotics on the laboratory request.

9. Management of mild COVID-19: symptomatic treatment

Patients with mild disease may present to an emergency unit, primary care/outpatient department, or be encountered during community outreach activities, such as home visits or by telemedicine.

Please find new recommendation on the use of pulse oximetry at home in Chapter 10 (Management of moderate COVID-19: pneumonia treatment).

We recommend that patients with suspected or confirmed mild COVID-19 be isolated to contain virus transmission according to the established COVID-19 care pathway. This can be done at a designated COVID-19 health facility, community facility or at home (self-isolation).

Remarks:

1. In areas with other endemic infections that cause fever (such as malaria, dengue, etc.), febrile patients should be tested and treated for those endemic infections per routine protocols *(65,66,69)* irrespective of the presence of respiratory signs and symptoms. Coinfection with COVID-19 may occur.
2. The decision to monitor a suspect case with mild COVID-19 in a health facility, community facility or home should be made on a case-by-case basis based on the local COVID-19 care pathway. Additionally, this decision may depend on the clinical presentation, requirement for supportive care, potential risk factors for severe disease, and conditions at home, including the presence of vulnerable persons in the household.
3. If managed at home in self-isolation, refer to WHO guidance on home care for patients with COVID-19 presenting with mild symptoms and management of their contacts *(108)*.

We recommend patients with mild COVID-19 be given symptomatic treatment such as antipyretics for fever and pain, adequate nutrition and appropriate rehydration.

Remark:
At present, there is no evidence to indicate that there are severe adverse events in patients with COVID-19 as a result of the use of non-steroidal anti-inflammatory drugs *(109)*.

Counsel patients with mild COVID-19 about signs and symptoms of complications that should prompt urgent care.

Remark:
Patients with risk factors for severe illness should be monitored closely, given the possible risk of deterioration. If they develop any worsening symptoms (such as light headedness, difficulty breathing, chest pain, dehydration, etc.), they should seek urgent care through the established COVID-19 care pathway. Caregivers of children with mild COVID-19 should monitor for signs and symptoms of clinical deterioration requiring urgent re-evaluation. These include difficulty breathing/fast or shallow breathing (for infants: grunting, inability to breastfeed), blue lips or face, chest pain or pressure, new confusion, inability to awaken/not interacting when awake, inability to drink or keep down any liquids. Consider alternative delivery platforms such as home-based, phone, telemedicine or community outreach teams to assist with monitoring *(110)*. See new recommendation in Chapter 10 on use of home pulse oximetry.

We recommend that antibiotic therapy or prophylaxis should not be used in patients with mild COVID-19.

Remark:
Widespread use of antibiotics should be discouraged, as their use may lead to higher bacterial resistance rates, which will impact the burden of disease and deaths in a population during the COVID-19 pandemic and beyond *(111,112,113)*.

10. Management of moderate COVID-19: pneumonia treatment

Patients with moderate disease may present to an emergency unit or primary care/outpatient department, or be encountered during community outreach activities, such as home visits or by telemedicine. See Table 6.3 for definition of non-severe pneumonia.

Please find new recommendation on the use of pulse oximetry at home in this chapter as the second recommendation.

We recommend that patients with suspected or confirmed moderate COVID-19 (pneumonia) be isolated to contain virus transmission. Patients with moderate illness may not require emergency interventions or hospitalization; however, isolation is necessary for all suspect or confirmed cases.

- **The location of isolation will depend on the established COVID-19 care pathway and can be done at a health facility, community facility or at home.**
- **The decision on location should be made on a case-by-case basis and will depend on the clinical presentation, requirement for supportive care, potential risk factors for severe disease, and conditions at home, including the presence of vulnerable persons in the household.**
- **For patients at high risk for deterioration (see Table 6.2), isolation in hospital is preferred.**

Remark:
In areas with other endemic infections that cause fever (such as malaria, dengue, etc.), febrile patients should be tested and treated for those endemic infections per routine protocols *(65,66,105)*, irrespective of the presence of respiratory signs and symptoms. Coinfection with COVID-19 may occur.

Conditional recommendation for

For symptomatic patients with COVID-19 and risk factors for progression to severe disease who are not hospitalized, we suggest the use of pulse oximetry monitoring at home as part of a package of care, including patient and provider education and appropriate follow-up (conditional recommendation, very low certainty evidence).

Evidence to decision

Benefits and harms — Uncertain benefits or harms

Possible theoretical benefits of home oximetry monitoring include earlier detection of and intervention for severe disease (such as more intense monitoring for deterioration or starting corticosteroid therapy), patient reassurance in case of normal values, limiting hospital strain due to prevented admission of patients who may not need acute care, and increased opportunities for patient-provider educational conversations (very low certainty).

Possible harms of home oximetry monitoring include the possibility of increased patient anxiety and stress, the possibility of increased hospital visits for patients who would otherwise not seek out hospital care, and the possibility of false reassurance with misinterpretation of the data. Low quality or inaccurate pulse oximeters, particularly with pulse oximeters not validated in different skin colours, may provide false reassurance or false alarms (very low certainty).

The GDG suggested that the possible benefits would outweigh the possible harms, and this may be most likely in specific subgroups of patients, i.e. those with symptoms and those with risk factors for severe disease. The GDG also suggested that the intervention would only have benefit in symptomatic patients with COVID-19, and that asymptomatic patients would have no benefit.

Certainty of the evidence	Very low

For key outcomes of hospitalization, mortality, mechanical ventilation, and ICU admission the panel considered the evidence to be of very low certainty.

Values and preferences	No substantial variability expected

Applying the agreed values and preferences, the GDG inferred that well-informed patients would consider the minimal possible harms associated with home oximetry monitoring to not outweigh the possible, theoretical benefits on the outcomes of hospitalization and patient satisfaction. Patient members of the panel agreed with this standard.

Resources and other considerations	Important considerations

Home oximetry monitoring is not accessible to many patients, due to lack of available equipment, lack of relevant personnel to monitor it, lack of ability to interpret the results at home, or lack of knowledge about implementation. Home pulse oximetry may be useful in certain settings, including low-resource settings, particularly when hospitals are strained and where it may be necessary to effectively monitor patients in a home-based setting. However, home oximetry monitoring will only be of value if the users are adequately informed on how to interpret the readings and have ready access to providers who can advise on the response to readings. Considerations for education and training of patients and providers, as well as adequate staffing, to implement care pathways with available access to acute care, will need to be integrated.

Justification

When moving from evidence to the conditional recommendation for the use of home pulse oximetry monitoring for patients with COVID-19, the panel emphasized the lack of evidence in either direction and the need for high-quality clinical trials examining both patient symptoms of stress, as well as other clinical outcomes listed above. The panel also emphasized contextual factors, such as resource considerations, accessibility, feasibility, and impact on health equity as important considerations. Ultimately, the panel thought that the theoretical benefit targeted to symptomatic and high-risk populations was notable only as part of a larger package of care including education and follow-up. Important caveats raised by the panel included the importance of integrating any intervention with education between providers and patients about the meaning of relevant output from the pulse oximeter and ability to act on results.

Subgroup analyses

There were insufficient data based on the presented data to perform any subgroup analyses.

Applicability

Special populations

There is no evidence for home pulse oximetry monitoring for patients with COVID-19 in special populations. Considerations for implementation and applicability centred around focusing on higher-risk populations, where benefits would be most notable. Please see Table 6.2 for information on definitions of who would be considered high risk for this implementation.

Practical info

The GDG made a conditional recommendation for the use of home pulse oximetry monitoring. This recommendation is predicated on the availability and accessibility of high-quality and reliable pulse oximeters for home use; the integration of home pulse oximetry into a health system, from a training and human resources perspective; and targeting the intervention to patients who would likely get the most benefit, namely those at high risk and those who are symptomatic. Also, no recommendation was made on the frequency or duration of pulse oximetry monitoring. *Note:* training on appropriate IPC (cleaning and disinfection) should be included.

Uncertainties

The panel encourage further research to clarify uncertainties, especially in low-resource settings. Research gaps remain as to ensuring standards of quality across pulse oximeter devices.

PICO (12.1)
Population: Patients treated at home with confirmed or suspected COVID-19 disease
Intervention: SpO_2 < 92% (Pulse oximetry use at home)
Comparator: SpO_2 ≥ 92% (Pulse oximetry use at home)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SpO_2 ≥ 92% (Pulse oximetry use at home)	 SpO_2 < 92% (Pulse oximetry use at home)	**Certainty of the evidence** (Quality of evidence)	**Plain text summary**
Hospitalization	Relative risk: 7.0 (CI 95% 3.4–14.5) Based on data from 77 patients in 1 study	**103** per 1000	**840** per 1000 Difference: **737 more per 1000** (CI 95% 453 more – 1597 more)	**Very low** Due to serious risk of bias. Due to serious imprecision[a]	SpO_2 < 92% possibly increases need for hospitalization.
ICU admission	Relative risk: 9.8 (CI 95% 2.2–44.6) Based on data from 77 patients in 1 study	per 1000	per 1000 Difference: **fewer per 1000**	**Very low** Due to serious risk of bias. Due to serious imprecision[b]	SpO_2 < 92% possibly increases need for ICU admission.
ARDS	Relative risk: 8.2 (CI 95% 1.7–38.7) Based on data from 77 patients in 1 study	per 1000	per 1000 Difference: **fewer per 1000**	**Very low** Due to serious risk of bias. Due to serious imprecision[c]	SpO_2 < 92% possibly increases the risk of ARDS.
Septic shock	Relative risk: 6.6 (CI 95% 1.3–32.9) Based on data from 77 patients in 1 study	per 1000	per 1000 Difference: **fewer per 1000**	**Very low** Due to serious risk of bias. Due to serious imprecision[d]	SpO_2 < 92% possibly increases the risk of septic shock.
Hospitalization	Based on data from patients in 2 studies	Two small single arm (no comparator group) studies that offered home monitoring to patients discharged from emergency department. 3/20 (150 per 1000) and 6/52 (115 per 1000) of patients using home SpO_2 monitors required hospitalization.		**Very low** Due to serious risk of bias. Due to serious imprecision[e]	No data re whether home SpO_2 monitoring vs no monitoring affects hospitalization rates.

[a] **Risk of bias: serious. Imprecision: serious.**
[b] **Risk of bias: serious. Imprecision: serious.**
[c] **Risk of bias: serious. Imprecision: serious.**
[d] **Risk of bias: serious. Imprecision: serious.**
[e] **Risk of bias: serious. Imprecision: serious.**

We recommend for patients with suspected or confirmed moderate COVID-19, that antibiotics should not be prescribed unless there is clinical suspicion of a bacterial infection.

Remarks:

1. Few patients with COVID-19 experience a secondary bacterial infection. A recent systematic review of patients hospitalized with COVID-19 reported only 8% were reported as experiencing bacterial/fungal co-infection during hospital admission *(104)*.
2. Consider in older people, particularly those in LTCFs, and children < 5 years of age, to provide empiric antibiotic treatment for possible pneumonia *(111,112)*. As these patients are not hospitalized, treatment with Access antibiotics (such as co-amoxicillin) is adequate, instead of broad-spectrum antibiotics (Watch and Reserve antibiotics) *(113)*.

We recommend close monitoring of patients with moderate COVID-19 for signs or symptoms of disease progression. Provision of mechanisms for close follow up in case of need of escalation of medical care should be available.

Remarks:

1. For patients being treated at home, counselling regarding signs and symptoms of complications (such as difficulty breathing, chest pain, etc.) should be provided to patients and their caregivers. If they develop any of these symptoms, they should seek urgent care through the established COVID-19 care pathway. Consider alternative delivery platforms such as home-based, phone, telemedicine or community outreach teams to assist with monitoring.
2. For hospitalized patients, regularly monitor vital signs (including pulse oximetry) and, where possible, utilize medical early warning scores (e.g. NEWS2, PEWS) that facilitate early recognition and escalation of treatment of the deteriorating patient *(114)*.

11. Management of severe COVID-19: severe pneumonia treatment

Please find new recommendation on awake prone positioning in this chapter as the fourth recommendation.

All areas where severe patients may be cared for should be equipped with pulse oximeters, functioning oxygen systems and disposable, single-use, oxygen-delivering interfaces (nasal cannula, Venturi mask and mask with reservoir bag).

Remark:
This includes areas in any part of health facilities, including emergency units, critical care units, primary care/outpatient clinics, as well as pre-hospital settings and ad hoc community facilities that may receive patients with severe COVID-19. See WHO *Oxygen sources and distribution for COVID-19 treatment centres (115)*.

We recommend immediate administration of supplemental oxygen therapy to any patient with emergency signs during resuscitation to target SpO_2 ≥ 94% and to any patient without emergency signs and hypoxaemia (i.e. stable hypoxaemic patient) to target SpO_2 > 90% or ≥ 92–95% in pregnant women.

Remarks for adults:

1. Adults with emergency signs (obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma and/or convulsions) should receive emergency airway management and oxygen therapy during resuscitation to target SpO_2 ≥ 94% *(72,116)*.
2. Once the patient is stable, target > 90% SpO_2 in non-pregnant adults and ≥ 92–95% in pregnant women.
3. Deliver oxygen flow rates using appropriate delivery devices (e.g. use nasal cannula for rates up to 5 L/min; Venturi mask for flow rates 6–10 L/min; and face mask with reservoir bag for flow rates 10–15 L/min). For more details about oxygen titration, refer to the WHO *Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation (73)*.
4. In adults, techniques such as positioning, e.g. high supported sitting, may help to optimize oxygenation, ease breathlessness and reduce energy expenditure *(117)*.
5. In adult patients with evidence of increased secretion production, secretion retention, and/or weak cough, airway clearance management may assist with secretion clearance. Techniques include gravity-assisted drainage and active cycle of breathing technique. Devices including mechanical insufflation-exsufflation and inspiratory positive pressure breathing should be avoided where possible. Implementation of techniques should be tailored to the individual patient and follow available guidelines *(117)*.

Remarks for children:

1. Children with emergency signs (obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma or convulsions) should receive emergency airway management and oxygen therapy during resuscitation to target SpO_2 ≥ 94% *(72,116,118)*.
2. Once patient is stable, the target is > 90% SpO_2 *(118)*.
3. Use of nasal prongs or nasal cannula is preferred in young children, as they may be better tolerated.

Closely monitor patients for signs of clinical deterioration, such as rapidly progressive respiratory failure and shock and respond immediately with supportive care interventions.

Remarks:

1. Patients hospitalized with COVID-19 require regular monitoring of vital signs (including pulse oximetry) and, where possible, utilization of medical early warning scores (e.g. NEWS2, PEWS) that facilitate early recognition and escalation of treatment of the deteriorating patient *(114)*.
2. Haematology and biochemistry laboratory testing and electrocardiogram and chest imaging should be performed at admission and as clinically indicated to monitor for complications, such as ARDS and acute liver injury, acute kidney injury, acute cardiac injury, disseminated intravascular coagulation (DIC) and/or shock. Application of timely, effective and safe supportive therapies is the cornerstone of therapy for patients who develop severe manifestations of COVID-19.
3. Monitor patients with COVID-19 for signs or symptoms suggestive of venous or arterial thromboembolism, such as stroke, deep venous thrombosis, pulmonary embolism or acute coronary syndrome, and proceed according to hospital protocols for diagnosis (such as laboratory tests and/or imaging) and further management.
4. After resuscitation and stabilization of the pregnant woman, fetal well-being should be monitored. The frequency of fetal heart rate observations should be individualized based on gestational age, maternal clinical status (e.g. hypoxia) and fetal conditions.

Conditional recommendation for

We suggest awake prone positioning of severely ill patients hospitalized with COVID-19 requiring supplemental oxygen (includes high-flow nasal oxygen) or non-invasive ventilation (conditional, low certainty evidence).

Evidence to decision

Benefits and harms — Uncertain benefits or harms

There have been no randomized controlled trials (RCTs) completed for awake prone positioning for patients with COVID-19 requiring supplemental oxygen or non-invasive ventilation. Observational studies of awake prone position in patients with COVID-19 suggest benefits on patient-important outcomes of mortality and the need for intubation COVID-19 (very low certainty). Evidence from RCTs of prone positioning for intubated, critically ill patients with ARDS (non-COVID-19) have demonstrated benefits in mortality. The effect on less important outcomes is uncertain.
The harms of awake prone positioning are possibly patient discomfort and pain (very low certainty). The indirect evidence on harms of prone positioning from the randomized evidence on sedated, intubated patients are pressure sores, nerve injury, and haemodynamic instability, which were not considered relevant for this less severely ill population.

Certainty of the evidence — Low

For patient-important outcomes of mortality and the need for mechanical ventilation, the panel considered the direct evidence to be of very low certainty. For the patient-important outcomes of mortality, indirect evidence from intubated, sedated patients with ARDS was downgraded for indirectness, from high to low, with key considerations including the different physiology of critical disease, data from a non-COVID-19 period, and the different sedation strategies employed.

Values and preferences — No substantial variability expected

Applying the agreed values and preferences, the GDG inferred that almost all well-informed patients would want to undergo prone positioning if awake, requiring oxygen or non-invasive respiratory support, given the lack of harm from the observational studies and panel experience. The panel did not expect there would be much variation in values and preferences between patients when it came to this intervention. Patient discomfort for prone position could limit time spent in individual circumstances.

Resources and other considerations — Important considerations

Patients who are able to follow instructions can self-prone, without assistance from health care workers. Proning patients who require assistance is associated with human resource requirements regarding training, particularly with monitoring of respiratory status. The panel felt that that this intervention should be feasible in all settings, but implementation requires dedicated training and monitoring.

Justification

When moving from evidence to the conditional recommendation for the use of awake prone positioning in severely ill hospitalized patients with COVID-19, the panel emphasized the low certainty evidence of reduction in mortality, downgraded from higher certainty evidence in critically ill patients with ARDS. It also noted the limited harm with the experience thus far with awake prone positioning across different resource settings.

Subgroup analyses

The panel commented on the need for data in specific populations, namely paediatrics, older people, and pregnant women in the first two trimesters.

Practical info

The GDG made a conditional recommendation for awake prone positioning in severely ill patients with COVID-19 requiring supplemental oxygen (including HFNO) or non-invasive ventilation.

In light of the uncertain benefits of awake prone positioning, a high level of vigilance should be maintained, and patients should be monitored closely for signs of clinical deterioration.

Monitoring of patients and training of providers in caring for patients who are awake and prone is an important part of implementation, as part of multi-faceted training for acute care management, which includes medical device training.

As for duration, some suggest regimens that target being in awake prone position for 8–12 hours/day, broken into shorter periods over the day.

Uncertainties

Further RCTs are recommended to better define benefits and harms, as well as specific populations of interest.

PICO (13.1)

Population: Patients hospitalized with severe COVID-19 infection
Intervention: Awake prone positioning + usual care
Comparator: Usual care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Usual care	Awake prone positioning + usual care	**Certainty of the evidence** (Quality of evidence)	**Plain text summary**
Mortality	Based on data from 334 patients in 17 studies	17 single arm (no comparator group) studies that enrolled a total of 334 participants. 37/334 (110 per 1000) patients positioned prone while receiving oxygen supplementation or NIV dead.		**Very low** Due to serious risk of bias. Due to very serious imprecision[a]	There are no comparative data assessing the effect of awake proning in COVID-19 patients with regards to mortality.

Intubation	Based on data from 450 patients in 25 studies	25 single arm (no comparator group) studies that enrolled a total of 450 participants. 130/450 (289 per 1000) patients positioned prone while receiving oxygen supplementation or NIV required intubation.	**Very low** Due to serious risk of bias. Due to very serious imprecision[b]	There are no comparative data assessing the effect of awake proning in COVID-19 patients with regards to intubation rates.
Adverse effect (pain or discomfort)	Based on data from 151 patients in 6 studies	6 single arm (no comparator group) studies that enrolled a total of 151 participants. 29/151 (192 per 1000) patients positioned prone while receiving oxygen supplementation or NIV reported pain or discomfort.	**Very low** Due to serious risk of bias. Due to very serious imprecision[c]	There are no comparative data assessing the effect of awake proning in COVID-19 patients with regards to adverse events.

[a] **Risk of bias: serious. Imprecision: very serious.**
[b] **Risk of bias: serious. Imprecision: very serious.**
[c] **Risk of bias: serious. Imprecision: very serious.**

Use cautious fluid management in patients with COVID-19 without tissue hypoperfusion and fluid responsiveness.

Remark:

Patients with COVID-19 should be treated cautiously with intravenous fluids; aggressive fluid resuscitation may worsen oxygenation, especially in settings where there is limited availability of mechanical ventilation *(119)*. This applies to both children and adults.

12. Management of critical COVID-19: acute respiratory distress syndrome (ARDS)

The mortality in hospitalized and critically ill patients has varied substantially in different case series throughout the pandemic. The following recommendations are aligned with current international standards for management of all cause ARDS *(92)*.

Please find new recommendation on the use of existing care bundles in Chapter 14 (Prevention of complications in hospitalized and critically ill patients with COVID-19).

The following recommendations pertain to adult and paediatric patients with mild ARDS who are treated with non-invasive or HFNO systems.

In selected patients with COVID-19 and mild ARDS, a trial of HFNO, non-invasive ventilation – continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP) may be used. Refer to Table 6.3 for definitions of mild, moderate and severe ARDS.

Remarks:

1. Patients with hypoxaemic respiratory failure and haemodynamic instability, multiorgan failure or abnormal mental status should not receive HFNO or NIV in place of other options such as invasive ventilation.
2. Patients receiving a trial of HFNO or NIV should be in a monitored setting and cared for by personnel experienced with HFNO and/or NIV and capable of performing endotracheal intubation in case the patient acutely deteriorates or does not improve after a short trial (about 1 hour). Intubation should not be delayed if the patient acutely deteriorates or does not improve after a short trial.
3. Adult HFNO systems can deliver 60 L/min of gas flow and FiO_2 up to 1.0. Paediatric circuits generally only handle up to 25 L/min, and many children will require an adult circuit to deliver adequate flow. When considering delivering HFNO or NIV outside the usual care settings, evaluating oxygen capacity is important to ensure the higher flow rates required for these devices can be maintained. See WHO *Oxygen sources and distribution for COVID-19 treatment centres (115)*.

4. Because of uncertainty around the potential for aerosolization, HFNO, NIV, including bubble CPAP, should be used with airborne precautions until further evaluation of safety can be completed. If these interventions are performed outside of private rooms in ICUs with appropriate ventilation systems installed, then cohorting of patients requiring these interventions in designated wards will facilitate the implementation of airborne precautions, ensuring all staff entering wear appropriate PPE and adequate environmental ventilation is ensured.
5. Compared with standard oxygen therapy, HFNO may reduce the need for intubation *(121)*. Patients with hypercapnia (exacerbation of obstructive lung disease, cardiogenic pulmonary oedema), haemodynamic instability, multiorgan failure or abnormal mental status should generally not receive HFNO, although emerging data suggest that HFNO may be safe in patients with mild-moderate and non-worsening hypercapnia *(121)*. Evidence-based guidelines on HFNO do not exist, and reports on HFNO in patients infected with other coronaviruses are limited *(122,123)*.
6. NIV guidelines make no recommendation on use in hypoxaemic respiratory failure (apart from cardiogenic pulmonary oedema, postoperative respiratory failure and early NIV for immunocompromised patients) or pandemic viral illness (referring to studies of SARS and pandemic influenza) *(120)*. Risks include delayed intubation, large tidal volumes, and injurious transpulmonary pressures. Limited data suggest a high failure rate in patients with other viral infections such as MERS-CoV who receive NIV *(123)*.
7. In situations where mechanical ventilation might not be available, bubble nasal CPAP may be a more readily available alternative for newborns and children with severe hypoxaemia *(124)*.

The following recommendations pertain to adult and paediatric patients with ARDS who need intubation and invasive mechanical ventilation.

We recommend prompt recognition of progressive acute hypoxaemic respiratory failure when a patient with respiratory distress is failing to respond to standard oxygen therapy and adequate preparation to provide advanced oxygen/ventilatory support.

Remark:

Patients may continue to have increased work of breathing or hypoxaemia even when oxygen is delivered via a face mask with reservoir bag (flow rates of 10–15 L/min, which is typically the minimum flow required to maintain bag inflation; FiO_2 0.60–0.95). Hypoxaemic respiratory failure in ARDS commonly results from intrapulmonary ventilation-perfusion mismatch or shunt and usually requires mechanical ventilation *(92)*.

We recommend that endotracheal intubation be performed by a trained and experienced provider using airborne precautions.

Remark:

Patients with ARDS, especially young children or those who are obese or pregnant, may desaturate quickly during intubation. Pre-oxygenation with 100% FiO_2 for 5 minutes, and use of a face mask with reservoir bag is preferred. When possible, avoid bag-valve mask ventilation to reduce exposure to aerosols. Rapid-sequence intubation is appropriate after an airway assessment that identifies no signs of difficult intubation *(125,126,127)*.

The following recommendations pertain to mechanically ventilated adult and paediatric patients with ARDS *(92,128)*.

We recommend implementation of mechanical ventilation using lower tidal volumes (4–8 mL/kg predicted body weight [PBW]) and lower inspiratory pressures (plateau pressure < 30 cmH_2O).

Remark for adults:
The implementation of mechanical ventilation using lower tidal volumes and lower inspiratory pressures is a strong recommendation from a clinical guideline for patients with ARDS *(92)*, and is also suggested for patients with sepsis-induced respiratory failure who do not meet ARDS criteria *(92)*. The initial target tidal

volume is 6 mL/kg PBW; tidal volume up to 8 mL/kg PBW is allowed if undesirable side-effects occur (e.g. dyssynchrony, pH < 7.15). Permissive hypercapnia is permitted. Ventilator protocols are available *(129)*. The use of deep sedation may be required to control respiratory drive and achieve tidal volume targets.

Remarks for children:
In children, a lower level of plateau pressure (< 28 cmH_2O) is targeted, and a lower target of pH is permitted (7.15–7.30). Tidal volumes should be adapted to disease severity: 3–6 mL/kg PBW in the case of poor respiratory system compliance, and 5–8 mL/kg PBW with better preserved compliance *(128)*.

In adult patients with severe ARDS (PaO_2/FiO_2 < 150) prone ventilation for 12–16 hours per day is recommended.

Remarks:
Application of prone ventilation is recommended for adult patients, preferably for 16 hours per day, and may be considered for paediatric patients with severe ARDS but requires sufficient human resources and expertise to be performed safely; protocols (including videos) are available *(130,131)*.
There is little evidence on prone positioning in pregnant women with ARDS; this could be considered in early pregnancy. Pregnant women in the third trimester may benefit from being placed in the lateral decubitus position.

Use a conservative fluid management strategy for ARDS patients without tissue hypoperfusion and fluid responsiveness.

Remarks for adults and children:
This has also been recommended in another international guideline *(92)*. The main effect is to shorten the duration of ventilation. A sample protocol for implementation of this recommendation is available *(132)*.

In patients with moderate or severe ARDS, a trial of higher positive end-expiratory pressure (PEEP) instead of lower PEEP is suggested and requires consideration of benefits versus risks. In COVID-19, we suggest the individualization of PEEP where during titration the patient is monitored for effects (beneficial or harmful) and driving pressure.

Remarks:
PEEP titration requires consideration of benefits (reducing atelectrauma and improving alveolar recruitment) vs risks (end-inspiratory overdistension leading to lung injury and higher pulmonary vascular resistance). Tables are available to guide PEEP titration based on the FiO_2 required to maintain SpO_2 *(133)*. In younger children, maximal PEEP pressures are 15 cmH_2O. Although high driving pressure (plateau pressure − PEEP) may more accurately predict increased mortality in ARDS compared with high tidal volume or plateau pressure *(134)*; data from RCTs of ventilation strategies that target driving pressure are not currently available.
A related intervention of recruitment manoeuvres (RMs) is delivered as episodic periods of high CPAP (30–40 cmH_2O), progressive incremental increases in PEEP with constant driving pressure, or high driving pressure; considerations of benefits vs risks are similar. Higher PEEP and RMs were both conditionally recommended in a clinical practice guideline. For PEEP, the guideline considered an individual patient data meta-analysis *(135)* of three RCTs. However, a subsequent RCT of high PEEP and prolonged high-pressure RMs showed harm, suggesting that the protocol in this RCT should be avoided *(136)*. Monitoring of patients to identify those who respond to the initial application of higher PEEP or a different RM protocol and stopping these interventions in non-responders are suggested *(137)*.

In patients with moderate-severe ARDS (PaO_2/FiO_2 < 150), neuromuscular blockade by continuous infusion should not be routinely used.

Remark:
A trial found that this strategy improved survival in adult patients with moderate-severe ARDS (PaO_2/FiO_2 < 150) without causing significant weakness *(138)*, but results of a recent larger trial found that use of neuromuscular blockade with high PEEP strategy was not associated with a survival benefit when

compared with a light sedation strategy without neuromuscular blockade *(139)*. Intermittent or continuous neuromuscular blockade may still be considered in patients with ARDS, both adults and children, in certain situations: ventilator dyssynchrony despite sedation, such that tidal volume limitation cannot be reliably achieved; or refractory hypoxaemia or hypercapnia.

Avoid disconnecting the patient from the ventilator, which results in loss of PEEP, atelectasis and increased risk of infection of health care workers.

Remarks:

Use in-line catheters for airway suctioning and clamp endotracheal tube when disconnection is required (for example, transfer to a transport ventilator).
Manual hyperinflation should be avoided and ventilator hyperinflation used instead, if indicated *(117)*.

In patients with excessive secretions, or difficulty clearing secretions, consider application of airway clearance techniques. These should be performed only if deemed medically appropriate *(117)* and appropriate IPC measures are in place.

Remarks:

Active cycle of breathing techniques and positioning techniques can be used to optimize oxygenation *(140,141)*. Techniques for airway clearance and secretion management include positioning with gravity-assisted drainage, active cycle of breathing techniques, positive expiratory pressure therapy, and assisted or stimulated cough manoeuvres *(141)*. These techniques are only indicated for patients with mucous hypersecretion and difficulties clearing secretions, and for patients with co-existing respiratory or neuromuscular comorbidities *(141)*.
All interventions inducing cough for airway clearance are potentially aerosol-generating procedures, and airborne precautions should be in place (see Chapter 7 on IPC) *(95)*; and single-patient-use disposable options are recommended (such as positive expiratory pressure device).
Consider use respiratory muscle training in patients recovering from critical illness with suspected respiratory muscle weakness *(141)*.
Especially for critically ill patients, the early involvement of the multidisciplinary rehabilitation team is paramount to improve short- and long-term outcomes. This may include physiotherapists, occupational therapists, speech and language therapists, mental health and psychosocial providers, dieticians and in complex cases, physical and rehabilitation medicine doctors. However, rehabilitation workforce composition may vary by context and availability in different parts of the world.

The following recommendations pertain to adult and paediatric patients with ARDS in whom lung protective ventilation strategy fails to achieve adequate oxygenation and ventilation.

In settings with access to expertise in ECMO, consider referral of patients who have refractory hypoxaemia (e.g. including a ratio of partial pressure of arterial oxygen [PaO_2] to the fraction of inspired oxygen [FiO_2] of < 50 mmHg for 3 hours, a PaO_2:FiO_2 of < 80 mmHg for > 6 hours) despite lung protective ventilation.

Remarks for adults:
An RCT of ECMO for adult patients with ARDS was stopped early and found no statistically significant difference in the primary outcome of 60-day mortality between ECMO and standard medical management (including prone positioning and neuromuscular blockade) *(142)*. However, ECMO was associated with a reduced risk of the composite outcome that consisted of mortality and crossover to ECMO treatment *(142)*, and a post-hoc Bayesian analysis of this RCT showed that ECMO is very likely to reduce mortality across a range of prior assumptions *(143)*. In patients with MERS, ECMO vs conventional treatment was associated with reduced mortality in a cohort study *(123)*. ECMO is a resource-intensive therapy and should be offered only in expert centres with a sufficient case volume to maintain expertise and staff volume and capacity to apply the IPC measures required *(144,145)*. In children, ECMO can also be considered in those with severe ARDS, although high-quality evidence for benefit is lacking *(128)*.

13. Management of critical COVID-19: septic shock

The mortality in hospitalized and critically ill patients has varied substantially in different case series throughout the pandemic. The following recommendations are aligned with current international standards for management of all-cause sepsis *(92)*.

Please find new recommendation on the use of existing care bundles in Chapter 14 (Prevention of complications in hospitalized and critically ill patients with COVID-19).

Recognize septic shock in adults when infection is suspected or confirmed AND vasopressors are needed to maintain mean arterial pressure (MAP) ≥ 65 mmHg AND lactate is ≥ 2 mmol/L, in the absence of hypovolaemia (see Table 6.3).

Recognize septic shock in children with any hypotension (SBP < 5th centile or > 2 SD below normal for age) or two or more of the following: altered mental status; bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and HR < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or feeble pulses; tachypnoea; mottled or cold skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia (see Table 6.3).

Remarks:

1. In the absence of a lactate measurement, use blood pressure (i.e. MAP) and clinical signs of perfusion to define shock.
2. Standard care includes early recognition and the following treatments to be done immediately, within 1 hour of recognition: antimicrobial therapy, and initiation of fluid bolus and vasopressors for hypotension *(92)*. The use of central venous and arterial catheters should be based on resource availability and individual patient needs. Detailed guidelines from the Surviving Sepsis Campaign and WHO are available for the management of septic shock in adults *(92)* and children *(87,93)*. Alternate fluid regimens are suggested when caring for adults and children in resource-limited settings *(146,147)*.

The following recommendations pertain to resuscitation strategies for adult and paediatric patients with septic shock.

In resuscitation for septic shock in adults, give 250–500 mL crystalloid fluid as rapid bolus in first 15–30 minutes.

In resuscitation for septic shock in children, give 10–20 mL/kg crystalloid fluid as a bolus in the first 30–60 minutes.

Fluid resuscitation may lead to volume overload, including respiratory failure, particularly with ARDS. If there is no response to fluid loading or signs of volume overload appear (e.g. jugular venous distension, crackles on lung auscultation, pulmonary oedema on imaging, or hepatomegaly), then reduce or discontinue fluid administration. This step is particularly important in patients with hypoxaemic respiratory failure.

Remarks:

1. Crystalloids include normal saline and Ringer's lactate.
2. Determine the need for additional fluid boluses (250–500 mL in adults; 10–20 mL/kg in children) based on clinical response and improvement of perfusion targets and reassess for signs of fluid overload after each bolus. Perfusion targets include MAP (> 65 mmHg or age-appropriate targets in children), urine output (> 0.5 mL/kg/hr in adults; 1 mL/kg/hr in children), and improvement of skin mottling and extremity perfusion, capillary refill, heart rate, level of consciousness, and lactate.
3. Consider dynamic indices of volume responsiveness to guide volume administration beyond initial resuscitation based on local resources and experience *(92)*. These indices include passive leg raises, fluid challenges with serial stroke volume measurements, or variations in systolic pressure, pulse

pressure, inferior vena cava size, or stroke volume in response to changes in intrathoracic pressure during mechanical ventilation.

4. In pregnant women, compression of the inferior vena cava can cause a decrease in venous return and cardiac preload and may result in hypotension. For this reason, pregnant women with sepsis and or septic shock may need to be placed in the lateral decubitus position to off-load the inferior vena cava *(148)*.
5. Clinical trials conducted in resource-limited settings comparing aggressive versus conservative fluid regimens suggest higher mortality in patients treated with aggressive fluid regimens *(146,147)*. Refer to the WHO-ICRC *Basic emergency care* (Shock module) for an initial approach and management of shock in resource-limited settings *(72)*.

Do not use hypotonic crystalloids, starches or gelatins for resuscitation.

Remark:

Starches are associated with an increased risk of death and acute kidney injury compared with crystalloids. The effects of gelatins are less clear, but they are more expensive than crystalloids *(92,149)*. Hypotonic (vs isotonic) solutions are less effective at increasing intravascular volume. Surviving Sepsis guidelines also suggest albumin for resuscitation when patients require substantial amounts of crystalloids, but this conditional recommendation is based on low-quality evidence *(92)*.

In adults, administer vasopressors when shock persists during or after fluid resuscitation. The initial blood pressure target is MAP ≥ 65 mmHg in adults and improvement of markers of perfusion.

In children, administer vasopressors if signs of fluid overload are apparent or the following persist after two fluid bolus:

- **signs of shock such as altered mental state;**
- **bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and HR < 70 bpm or > 150 bpm in children);**
- **prolonged capillary refill (> 2 seconds) or feeble pulses;**
- **tachypnoea; mottled or cool skin or petechial or purpuric rash; increased lactate; oliguria persists after two repeat boluses;**
- **or age-appropriate blood pressure targets are not achieved *(93)*.**

Remarks:

1. Vasopressors (i.e. norepinephrine, epinephrine, vasopressin and dopamine) are most safely given through a central venous catheter at a strictly controlled rate, but it is also possible to safely administer them via peripheral vein *(150)* and intraosseous needle. Monitor blood pressure frequently and titrate the vasopressor to the minimum dose necessary to maintain perfusion and prevent side-effects. A recent study suggests that in adults 65 years or older a MAP 60–65 mmHg target is equivalent to ≥ 65 mmHg *(151)*.
2. Norepinephrine is considered the first-line treatment in adult patients; epinephrine or vasopressin can be added to achieve the MAP target. Because of the risk of tachyarrhythmia, reserve dopamine for selected patients with low risk of tachyarrhythmia or those with bradycardia.
3. In children, epinephrine is considered the first-line treatment, while norepinephrine can be added if shock persists despite optimal dose of epinephrine *(93)*.

If central venous catheters are not available, vasopressors can be given through a peripheral IV, but use a large vein and closely monitor for signs of extravasation and local tissue necrosis. If extravasation occurs, stop infusion. Vasopressors can also be administered through intraosseous needles.

If signs of poor perfusion and cardiac dysfunction persist despite achieving MAP target with fluids and vasopressors, consider an inotrope such as dobutamine.

Remark:
No RCTs have compared dobutamine with placebo for clinical outcomes.

14. Prevention of complications in hospitalized and critically ill patients with COVID-19

Please find new recommendation on the use of existing care bundles in this chapter as the first recommendation, and new recommendation on anticoagulation for thromboprophylaxis in this chapter as the third recommendation.

Conditional recommendation for

For patients with COVID-19 who are critically ill, with or without invasive mechanical ventilation, we suggest the use of existing care bundles (defined as three or more evidence informed practices delivered together and consistently to improve care; (see Evidence to decision for examples), chosen locally by the hospital or ICU and adapted as necessary for local circumstances (conditional recommendation, very low certainty).

Evidence to decision

Benefits and harms — Some benefits

Indirect evidence in patients without COVID-19 suggest that some care bundles may improve patient-important outcomes, such as mortality, but the effects vary depending on the specific bundle, and the population targeted. The certainty of evidence is generally low to very low. Examples of care bundles in the critically ill include those for reducing delirium and improving cognition and sleep (reviewed in *(152)*; other information available at https://www.icudelirium.org/medical-professionals/overview), preventing VAP *(153)*, treating sepsis (reviewed in http://links.lww.com/CCM/C326), preventing central venous catheter infection *(154)*, and preventing pressure ulcers (https://www.nice.org.uk/guidance/cg179). Details of selected other bundles reviewed by the Cochrane Collaboration in their review of the literature are in Annex 3. The effect on other outcomes is uncertain.

Potential harms of bundles include the administrative burden of initial implementation, ongoing training, and monitoring of performance (very low certainty).

Certainty of the evidence — Very low

The evidence review consisted of a rapid review by the Cochrane Collaboration, supplemented by references provided by GDG members. The Cochrane review found very low certainty evidence in support of a mortality reduction with implementation of care bundles in critically ill patients. Supplementary references provided low to very low certainty evidence for important effects on mortality with bundles to reduce delirium *(152)*, prevent VAP *(153)*, treat sepsis (http://links.lww.com/CCM/C326), and prevent central venous catheter infection *(154)* and pressure ulcers (https://www.nice.org.uk/guidance/cg179). All evidence reviewed was indirect, from non-COVID-19 populations.

Values and preferences	No substantial variability expected

Applying the agreed values and preferences, the GDG inferred that the majority of well-informed patients would want to receive care bundles, locally adapted as necessary and applicable to their situation, given the low to very low certainty evidence suggesting a reduction in mortality and very low certainty of harm.

Resources and other considerations	Important considerations

Care bundles may contain practices that require adaptation to implement in all settings, depending on their contents. For example, early mobilization and rehabilitation as part of a care bundle to reduce delirium may require additional training, and central line insertion may require multiple sterile towels or a sterile gown placed on the patient, if large sterile drapes are not available.

Justification

When moving from evidence to the conditional recommendation in favour of care bundles for critically ill patients with COVID-19, the panel emphasized the low to very low certainty evidence of reduction in mortality and possible administrative burdens for implementation. The GDG recognized that hospital or ICUs may select among existing care bundles and adapt them to local circumstances as required, based on contextual factors of resource considerations and feasibility. The GDG judged that considerations of accessibility and impact on health equity would not alter the recommendation. The GDG was not aware of ongoing studies of care bundles in the critically ill COVID-19 population.

Subgroup analyses

The panel did not find any evidence bearing on the question of subgroup effects across patients with different levels of disease severity or between children and adults. In other words, the conditional recommendation is applicable across all these subgroups.

Applicability

Special populations

None of the reviewed studies of care bundles enrolled children, and therefore the applicability of this recommendation to children is uncertain. However, the panel thought that the implementation of relevant care bundles for children with COVID-19 would have similar effects to care bundles in adults. Similarly, the panel concluded that the recommendation applies to pregnant women.

Practical info

The GDG made a conditional recommendation in favour of care bundles for critically ill patients with COVID-19. Existing care bundles for critically ill patients include those for reducing delirium and improving cognition and sleep (reviewed in *(152)*; other information available at https://www.icudelirium.org/medical-professionals/overview), preventing VAP *(153)*, treating sepsis (reviewed in http://links.lww.com/CCM/C326), preventing central venous catheter infection *(154)*, and preventing pressure ulcers (https://www.nice.org.uk/guidance/cg179). For some bundles, observational data have shown variable association between the bundle components and patient important outcomes *(155)*. Even in currently accepted care bundles, the components may change as the evidence base evolves. Hospitals and ICUs should choose bundles for which adherence is likely to be high.

Uncertainties

Monitor multiple RCTs in process in patients with COVID-19.

PICO (16.2)

Population: Patients with COVID-19 and ARDS or viral pneumonia who are critically ill in ICU, with or without invasive ventilation. Populations of children (defined <18 years) and adult patients (≥18 years)
Intervention: Existing validated care bundles*, chosen locally by the hospital or ICU, adapted to local circumstances, and felt to be appropriate for patients with COVID-19 as specified above. *A care bundle is defined as three or more evidence informed practices delivered together and consistently to improve care.
Comparator: Not using existing care bundles

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No care bundles	Care bundles	**Certainty of the evidence** (Quality of evidence)	**Plain text summary**
Mortality (randomized trials) at 6 months	Relative risk: 0.75 (CI 95% 0.53–1.06) Based on data from 180 patients in 1 study	**489** per 1000	**367** per 1000 Difference: **122 fewer per 1000** (CI 95% 259 fewer – 29 more)	**Very low** Due to very serious indirectness. Due to very serious imprecision[a]	ICU care bundles possibly reduce mortality.
Mortality (observational studies) 28 days or to hospital discharge	Relative risk: 0.75 (CI 95% 0.65–0.86) Based on data from 1258 patients in 7 studies	**359** per 1000	**269** per 1000 Difference: **90 fewer per 1000** (CI 95% 126 fewer – 50 fewer)	**Very low** Due to very serious indirectness. Due to very serious imprecision[b]	ICU care bundles possibly reduce mortality.
Administrative burden	Based on data from 0 patients in 0 studies			**Very low**	Care bundles may be associated with an appreciable administrative burden.
Impingement on physician autonomy	Based on data from 0 patients in 0 studies			**Very low**	Care bundles may be associated with an impingement of physician autonomy.

[a] **Indirectness: very serious. Imprecision: very serious.**
[b] **Indirectness: very serious. Imprecision: very serious.**

Thromboembolism

Coagulopathy is common in patients with severe COVID-19, and both venous and arterial thromboembolism have been reported *(41,42,156,157,158)*.

Monitor patients with COVID-19, for signs or symptoms suggestive of thromboembolism, such as stroke, deep venous thrombosis, pulmonary embolism or acute coronary syndrome. If these are clinically suspected, proceed immediately with appropriate diagnostic and management pathways.

Thromboprophylaxis

Conditional recommendation for

In hospitalized patients with COVID-19, without an established indication for higher dose anticoagulation, we suggest administering standard thromboprophylaxis dosing of anticoagulation rather than therapeutic or intermediate dosing (conditional recommendation, very low certainty).

Evidence to decision

Benefits and harms Important harms

Therapeutic or intermediate dosing of anticoagulation, compared with prophylactic dosing of anticoagulation, possibly reduces mortality (very low certainty) and pulmonary embolism and probably increases the risk of major bleeding (moderate certainty for therapeutic anticoagulation; low certainty for intermediate dosing of anticoagulation). The effects on other outcomes are uncertain.

The absolute reductions in risks of mortality and pulmonary embolism, and the absolute increase in risk of major bleeding, are likely to be higher in patients with severe or critical illness due to COVID-19, who may have a higher baseline risk of these outcomes compared with patients with mild or moderate illness.

Certainty of the evidence Very low

For reduction in mortality and pulmonary embolism, the panel considered the evidence in favour of therapeutic or intermediate dosing of anticoagulation to be of very low certainty, due to serious imprecision (confidence intervals included both important benefit and important harm) and risk of bias (confounding in observational studies; no randomized trials).

For avoidance of major bleeding, the panel considered the evidence in favour of standard thromboprohylaxis dosing, compared with therapeutic anticoagulation, to be of moderate certainty. This judgment was based on low-certainty evidence in observational studies in COVID-19 that was upgraded to moderate certainty based on a large body of supportive indirect evidence at low risk of bias (randomized trials of therapeutic anticoagulation for other indications).

For the comparison of standard thromboprophylaxis dosing compared with intermediate dosing of anticoagulation, the evidence for avoidance of major bleeding was rated as low certainty.

The panel acknowledged that reporting of ongoing randomized trials of therapeutic and intermediate dosing of anticoagulation, compared with standard thromboprophylaxis dosing, over the next several months were highly likely to upgrade the certainty of evidence and may lead to changes in recommendations.

Values and preferences Substantial variability is expected or uncertain

The majority of GDG members inferred that most well-informed patients would not want to receive therapeutic or intermediate dosing of anticoagulation given the very low certainty evidence suggesting a possible reduction in mortality and pulmonary embolism and the low certainty (for intermediate dosing of anticoagulation) or moderate certainty (for therapeutic anticoagulation) of increased risk of major bleeding. A minority of GDG members believed that some well-informed patients would choose to receive intermediate dosing of anticoagulation, given the very low certainty evidence suggesting a possible reduction in mortality and pulmonary embolism and the low certainty of increased risk of major bleeding.

Resources and other considerations Important considerations

Unfractionated heparin sodium and low molecular weight heparins such as enoxaparin are relatively inexpensive and are listed on the WHO Model List of Essential Medicines; but availability is variable. Shortages may reduce the availability of low molecular weight heparins in some settings. In low-resource settings, management of bleeding complications in patients receiving anticoagulant dosing higher than that used for standard thromboprophylaxis may be challenging due to limited coagulation testing and transfusion capacity.

Justification

When moving from evidence to the conditional recommendation in favour of standard thromboprophylaxis anticoagulation for patients with moderate, severe, and critical COVID-19, the panel emphasized the very low certainty evidence of reduction in mortality or pulmonary embolism with higher anticoagulant dosing. The panel recognized that the evidence supporting an increased risk of major bleeding was dominated by studies of therapeutic anticoagulation rather than intermediate dosing. The GDG panellists anticipated variability in patient values and preferences, and judged that other contextual factors, such as resource considerations, accessibility, feasibility and impact on health equity would not alter the recommendation. The panel acknowledged that ongoing randomized trials are expected to add substantially to the evidence base over the next several months.

Subgroup analyses

The panel did not find any evidence bearing on the question of subgroup effects across patients with different levels of disease severity, between children and adults, by different anticoagulant regimens (including agent, dose and duration), and therefore did not make any subgroup recommendations. In other words, the conditional recommendation is applicable across all these subgroups.

Applicability

Special populations

None of the studies enrolled children, and therefore the applicability of this recommendation to children is uncertain. However, the panel did not think that children with COVID-19 would respond any differently to therapeutic or intermediate intensity anticoagulation. One observational study enrolled pregnant women, with very low certainty evidence in this population for a possible reduction in mortality. The panel thought that pregnant women would have a similar risk of increased bleeding as non-pregnant individuals. Therefore, the panel concluded that the recommendation applies to pregnant women. Safe anticoagulants for the fetus in pregnancy include unfractionated heparin and low molecular weight heparin, which do not cross the placental barrier.

Practical info

Therapeutic dosing of anticoagulation refers to the dose used for treatment of acute venous thromboembolism; intermediate dosing is commonly interpreted as twice the standard thromboprophylaxis dose. The GDG made a conditional recommendation in favour of standard thromboprophylaxis dosing of anticoagulation in patients with COVID-19 who do not have an established indication for higher dose anticoagulation.

Patients on standard thromboprophylaxis dosing of anticoagulation do not require monitoring, except for platelet count monitoring after 5–7 days if unfractionated heparin is used. Dosing should be adjusted according to body weight/BMI and renal function according to local protocols. For example, if renal failure is present, patient should receive unfractionated heparin or reduced dose of low molecular weight heparin.

Suggested dosing of standard thromboprophylaxis is as follows:

Enoxaparin 40 mg by subcutaneous injection every 24h:
- Prophylactic dosages (non-weight adjusted) in low body weight (women < 45 kg, men < 57 kg) may lead to a higher risk of bleeding. Careful clinical observation is advised.
- If BMI > 40 kg/m^2 or weight > 120 kg: enoxaparin 40 mg by subcutaneous injection every 12h.

Unfractionated heparin (UFH) 5000 units by subcutaneous injection every 8 or 12h:
- If BMI > 40 kg/m^2 or weight > 120 kg: 7500 units q12h or 5000 units every 8h.

Tinzaparin 4500 units/day if BMI < 40 kg/m^2 or weight < 120 kg; 9000 units/day if BMI > 40 kg/m^2 or weight > 120 kg.

Dalteparin 5000 units/day BMI < 40 kg/m^2 or weight < 120 kg; 5000 units every 12h if BMI > 40 kg/m^2 or weight > 120 kg.

Fondaparinux 2.5 mg by subcutaneous injection every 24h.

Exoxaparin and unfractionated heparin are both on the WHO Model List of Essential Medicines; enoxaparin has the advantage of daily dosing. The suggested duration of standard thromboprophylaxis is until hospital discharge.

If therapeutic dosing is prescribed, clinicians should be aware of the increased risk of bleeding, including major bleeding requiring transfusion (e.g. gastrointestinal) or clinically significant bleeding even if transfusion is not required (e.g. intracranial). These increased risks may also occur with intermediate dosing of anticoagulants, especially in the presence of other risk factors for bleeding. Heparin-induced thrombocytopenia associated with thrombosis is also a risk of unfractionated heparin and, less commonly, low molecular weight heparin.

Potential agents for therapeutic and intermediate intensity anticoagulation include low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, or fondaparinux. Factors influencing the choice of agent include availability of laboratory monitoring (needed for unfractionated heparin), requirement for rapid reversibility (favours unfractionated heparin), presence of severe renal dysfunction (favours unfractionated heparin), interaction with other drugs used to treat COVID-19 (especially direct oral anticoagulants), convenience (least with unfractionated heparin, most with direct oral anticoagulants), and suspicion of heparin-induced thrombocytopenia (favours fondaparinux or direct oral anticoagulants).

For therapeutic or intermediate intensity anticoagulation, patients should have baseline creatinine, platelet count, prothrombin time or international normalized ratio, and partial thromboplastin time. Patients on therapeutic dosing of unfractionated heparin require monitoring of partial thromboplastin time or anti-factor Xa levels and ideally platelet count. Patients on warfarin require monitoring of international normalized ratio.

PICO (16.1)
Population: Hospitalized patients without an indication for therapeutic anticoagulation
Intervention: Anticoagulation at therapeutic or intermediate intensity
Comparator: Anticoagulation at prophylactic intensity

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Anticoagulation at prophylactic intensity	Anticoagulation at therapeutic or intermediate intensity	**Certainty of the evidence** (Quality of evidence)	**Plain text summary**
Mortality at 14 days	Hazard Ratio: 0.86 (CI 95% 0.73–1.07) Based on data from 2626 patients in 1 studies	Difference: **19.0 fewer** (CI 95% 38.0 fewer – 3.0 more)		**Very low** Due to very serious risk of bias. Due to very serious imprecision[a]	Therapeutic or intermediate intensity anticoagulation possibly reduces mortality.
Pulmonary embolism at 14–28 days	Odds Ratio: 0.09 (CI 95% 0.02–0.57) Based on data from 82 patients in 1 studies	Difference: **16.0 fewer** (CI 95% 15.0 fewer – 7.0 fewer)		**Very low** Due to very serious risk of bias. Due to very serious imprecision[b]	Therapeutic or intermediate intensity anticoagulation possibly reduces pulmonary embolism.
Major bleeding at 4–12 days		Effect estimates ranged from OR 1.42 (matched case control) to 3.89 (retrospective cohort). Risk differences ranged from: 7 fewer per 1000 to 46 more per 1000		**Moderate** Upgraded due to all plausible confounding would have reduced the effect[c]	Therapeutic or intermediate intensity anticoagulation probably increases major bleeding.

[a] **Risk of bias: very serious. Imprecision: very serious.**
[b] **Risk of bias: very serious. Imprecision: very serious.**
[c] **Upgrade: All plausible confounding would have reduced the effect.** Upgraded from low certainty evidence due to large body of relevant indirect evidence.

This summary of findings table was generated from a living systematic review (www.hematology.org/COVIDguidelines) based on data accessed on 1 December 2020.

Prevention of other complications

Table 14.1 shows interventions to prevent complications in hospitalized and critically ill patients with COVID-19. They are based on Surviving Sepsis *(92)* or other guidelines *(153,159,160,161)*, and are generally limited to feasible recommendations based on high-quality evidence. Recent publications have encouraged best practices to continue during the COVID-19 outbreak *(162)*. See the WHO *Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation* for practical tools to assist implementation *(73)*.

Table 14.1 Interventions to prevent complications in hospitalized and critically ill patients with COVID-19

Anticipated outcome	**Interventions**
Reduce days of invasive mechanical ventilation	• Use weaning protocols that include daily assessment for readiness to breathe spontaneously • Minimize continuous or intermittent sedation, targeting specific titration endpoints (light sedation unless contraindicated) or with daily interruption of continuous sedative infusions • Early mobilization • Implementation of the above as a bundle of care (may also reduce delirium); such as the **A**wakening and **B**reathing **C**oordination, **D**elirium assessment/management, and **E**arly mobility (ABCDE)
Reduce incidence of ventilator-associated pneumonia	• Oral intubation is preferable to nasal intubation in adolescents and adults • Keep patient in semi-recumbent position (head of bed elevation 30–45º) • Use a closed suctioning system; periodically drain and discard condensate in tubing • Use a new ventilator circuit for each patient; once patient is ventilated, change circuit if it is soiled or damaged, but not routinely

	• Change heat moisture exchanger when it malfunctions, when soiled, or every 5–7 days
Reduce incidence of catheter-related bloodstream infection	• Use a checklist with completion verified by a real-time observer as a reminder of each step needed for sterile insertion and as a daily reminder to remove catheter if no longer needed
Reduce incidence of pressure ulcers	• Turn patient every 2 hours
Reduce incidence of stress ulcers and GI bleeding	• Give early enteral nutrition (within 24–48 hours of admission) • Administer histamine-2 receptor blockers or proton-pump inhibitors in patients with risk factors for GI bleeding. Risk factors for GI bleeding include mechanical ventilation for ≥ 48 hours, coagulopathy, renal replacement therapy, liver disease, multiple comorbidities, and higher organ failure score
Reduce the development of antimicrobial resistance	• Utilize de-escalation protocols as soon as patient is clinically stable and there is no evidence of bacterial infection
Reduce the development of adverse drug effects	• Expose patient to empiric antimicrobial therapy for the shortest time possible, to prevent nephrotoxicity, cardiac and other side-effects from unnecessary antimicrobial use
Promote appropriate antimicrobial prescribing and use during the COVID-19 pandemic *(163)*	• Do not prescribe antibiotics to suspected or confirmed COVID-19 patients with low suspicion of a bacterial infection, to avoid more short-term side-effects of antibiotics in patients and negative long-term consequences of increased antimicrobial resistance

Adverse effects of medications

Careful consideration should be given to the numerous, clinically significant side-effects of medications that may be used in the context of COVID-19, as well as drug-drug interactions between medications, both of which may affect COVID-19 symptomatology (including effects on respiratory, cardiac, immune and mental and neurological function). Both pharmacokinetic and pharmacodynamic effects should be considered.

Remarks:

1. The risk of relevant side-effects and drug-drug interactions relating to COVID-19 symptomatology include sedation, cardiotoxicity via QTc-prolongation and respiratory suppression, and these may be dose-dependent (i.e. increase with escalating doses). For this reason, care should be taken that minimum effective doses of medications with dose-dependent negative effects are used and for the shortest durations possible.
2. Use medications that carry the least risk possible for drug-drug interactions with other medications the person may be receiving. Psychotropic medications with sedative proprieties, such as benzodiazepines, can worsen respiratory function. Some, psychotropic medications have QTc-prolonging activity (such as some antipsychotics and some antidepressants). Use medications that carry the least risk possible for side-effects that may worsen COVID-19 symptomatology, including sedation, respiratory or cardiac function, risk of fever or other immunological abnormalities, or coagulation abnormalities.

15. Therapeutics and COVID-19

For the most up to date clinical practice guideline on therapeutics and COVID-19 see WHO website and BMJ website and MAGICapp.

By 17 December 2020 this guideline contains the following recommendations:

- Strong recommendations against the use of hydroxychloroquine and lopinavir/ritonavir in patients with COVID-19, regardless of disease severity.
- A strong recommendation for systemic corticosteroids in patients with severe and critical COVID-19.
- A conditional recommendation against systemic corticosteroids in patients with non-severe COVID-19.
- A conditional recommendation against remdesivir in hospitalized patients with COVID-19.

We recommend that the use of unproven drugs not be administered as treatment or prophylaxis for COVID-19, outside of the context of clinical trials.

Remarks:

Outside of clinical trials, the following criteria should be met for access to investigational therapeutics: 1) no proven effective treatment exists; 2) it is not possible to initiate clinical studies immediately; 3) data providing preliminary support of the intervention's efficacy and safety are available, at least from laboratory or animal studies, and use of the intervention outside clinical trials has been suggested by an appropriately qualified scientific advisory committee on the basis of a favourable risk–benefit analysis; 4) the relevant country authorities, as well as an appropriately qualified ethics committee, have approved such use; 5) adequate resources are available to ensure that risks can be minimized; 6) the patient's informed consent is obtained; and 7) the emergency use of the intervention is monitored and the results are documented and shared in a timely manner with the wider medical and scientific community *(164)*.

16. Treatment of other acute and chronic infections in patients with COVID-19

The prevalence of acute coinfections or secondary infections coinciding with COVID-19 has not been adequately described but appears to be low *(104)*, and will be based on local factors and endemic or other emerging infections *(77,111,112,163)*. Antibiotic overuse increases the risk of emergence and transmission of multidrug-resistant bacteria. Infections with multidrug-resistant bacteria are more difficult to treat, and associated with increased morbidity and mortality.

Acute coinfections with bacteria

We recommend for patients with suspected or confirmed mild COVID-19, against the use of antibiotic therapy or prophylaxis.

We recommend for patients with suspected or confirmed moderate COVID-19, that antibiotics should not be prescribed unless there is clinical suspicion of a bacterial infection.

We recommend for patients with suspected or confirmed severe COVID-19, the use of empiric antimicrobials to treat all likely pathogens, based on clinical judgment, patient host factors and local epidemiology, and this should be done as soon as possible (within 1 hour of initial assessment if possible), ideally with blood cultures obtained first. Antimicrobial therapy should be assessed daily for de-escalation.

Remarks:

1. For patients with severe disease, early and appropriate empiric antimicrobial therapy *(92)* can be administered in the emergency unit and/or pre-hospital setting. Empiric antibiotic treatment should be based on the clinical diagnosis (community-acquired pneumonia, health care-associated pneumonia (if infection was acquired in health care setting) or sepsis), local epidemiology and susceptibility data, and national treatment guidelines. Choose antibiotics with the least ecologic impact based on data and guidance from your own institution, region or country (e.g. of the Access group of the AWaRe classification) *(113)*. The AWaRe classification categorizes antibiotics into three different groups (Access, Watch and Reserve) based on their indication for common infectious syndromes, their spectrum of activity, and their potential for increasing antibiotic resistance. The AWaRe classification is a tool for antibiotic stewardship at local, national and global levels with the aim of optimizing antibiotic use and reducing antibiotic resistance.
2. Empiric antibiotic therapy should be de-escalated on the basis of microbiology results and clinical judgment. Regularly review the possibility of switching of intravenous to oral route of administration and provide targeted treatment based on microbiologic results.
3. Duration of empiric antibiotic treatment should be as short as possible; generally 5–7 days.
4. An increase in antibiotic use during the pandemic may cause adverse reactions such as *Clostridioides difficile* infections, with clinical disease ranging from diarrhoea and fever to colitis *(165)*. Antibiotic stewardship programmes should be put into place or continue among COVID-19 patients.

Acute coinfections with other pathogens (not bacteria)

Treatment of other coinfections may be based on a laboratory-confirmed diagnosis or epidemiological and clinical criteria.

Remarks:

1. In malaria endemic areas, when a malaria RDT is also positive, antimalarials should be initiated as soon as possible as per local protocol *(66)*.
2. When there is ongoing suspected or confirmed local circulation of seasonal influenza, empiric therapy with a neuraminidase inhibitor (i.e. oseltamivir) should be considered for patients with severe disease or at risk for severe influenza, and given as soon as possible.
3. If TB coinfection is suspected or confirmed, then follow local TB treatment protocols *(69)*.

Chronic infections

It is currently unknown whether immunosuppression caused by chronic coinfections such as human immunodeficiency virus (HIV) puts persons at greater risk for severe COVID-19. However, people living with HIV with advanced disease have an increased risk of opportunistic infections (notably TB) *(166)* and related complications in general. Facility-based HIV testing services should continue and those newly diagnosed should start antiretroviral therapy as soon as possible. For people living with HIV already on treatment, continuity of antiretroviral therapy and prophylaxis for coinfections is essential, with multi-month prescribing.

17. Management of neurological and mental manifestations associated with COVID-19

People with COVID-19 are at increased risk for neurological, neuropsychiatric, and mental manifestations (see Chapter 1. Background). Neuropsychiatric manifestations such as delirium/encephalopathy and neurological manifestations such as stroke may be presenting features without respiratory symptoms (see Table 6.1). In addition to acute neurological manifestations, Guillain-Barré syndrome, acute disseminated encephalomyelitis, and acute haemorrhagic leukoencephalitis-like presentations may occur weeks after the acute stage of infection *(46)*. Moreover, there may be potential for longer term neurological consequences such as cognitive impairment *(167)* and/or post-intensive care syndrome (PICS). Further research is needed in order to fully characterize these complications.

Anxiety and depressive symptoms constitute common reactions for people in the context of COVID-19 diagnosis, especially for those who may be hospitalized, due to concerns for one's own health or the health of others, the need for physical isolation (which can lead to social isolation), potential risk of death, concerns over the risk of infecting others, and concerns over leaving family members alone who may need care. Stressors particular to COVID-19 include: fear of falling ill and dying, fear of being socially excluded/placed in quarantine, loss of livelihood and loss of loved ones, and feelings of helplessness, boredom and loneliness due to being isolated. These stressors may trigger new symptoms or exacerbate underlying mental or neurological conditions. Pre-existing mental, neurological or substance use disorders increase the risk of becoming severely ill or of death, or of having long-term complications due to COVID-19 *(84,85,168,169,170,171)*. People with COVID-19 are also at higher risk for sleep problems owing to acute stress responses, as well as additional reasons for those who are hospitalized such as environmental factors, invasive medical procedures (e.g. mechanical ventilation) and the frequent combination of multiple medications possibly disrupting sleep patterns *(172)*.

Delirium

We recommend, in patients with COVID-19, that measures to prevent delirium, an acute neuropsychiatric emergency, be implemented; and patients be evaluated using standardized protocols, for the development of delirium. If detected, then immediate evaluation by a clinician is recommended to address any underlying cause of delirium and treat appropriately.

Remarks:

1. Manage any underlying cause of delirium by monitoring oxygenation and fluid status, correcting metabolic or endocrine abnormalities, addressing coinfections, minimizing the use of medications that may cause or worsen delirium, treating withdrawal from substances, understanding and minimizing the effects of any harmful drug-drug interactions and maintaining normal sleep cycles as much as possible *(173)*.
2. In patients receiving invasive ventilation, minimize continuous or intermittent sedation, targeting specific titration endpoints (light sedation unless contraindicated) or with daily interruption of continuous sedative infusions, to reduce delirium *(173)*.
3. In patients experiencing agitation (defined as marked restlessness or excessive motor activity, often accompanied by anxiety), use calming communication strategies and attempt to reorient the person. Acute pain due to physical illness or air hunger should be considered as triggers for agitation and need to be addressed immediately. If the person continues to be agitated despite the strategies described above and is experiencing severe distress, it may be necessary to use psychotropic medications *(174)*.
4. When using antipsychotic medications for agitation, consider side-effects that may worsen symptomatology, including sedation, respiratory or cardiac function, risk of fever or other immunological abnormalities, or coagulation abnormalities and any potential drug-drug interactions between these and other medications. Use minimum effective doses of antipsychotic medications at the lowest frequency and for the shortest duration possible, with doses adjusted according to age, medical co-morbidities and degree of distress *(174)*. For severe agitation, low doses of haloperidol (administered orally or by intramuscular injection) can be considered, while carefully monitoring for adverse effects such as QT prolongation and extrapyramidal symptoms *(174)*.
5. If haloperidol is contraindicated due to the patient's clinical condition (e.g. prolonged QT interval, recent myocardial infarction, Parkinson's Disease, Lewy-Body dementia, etc.), other antipsychotic medications with safer cardiovascular profiles may be used after careful consideration of other risks (such as respiratory suppression or sedation) and drug-drug interactions *(175)*.
6. If the patient remains severely agitated despite the strategies described above, benzodiazepines can be added, with preference given to those with shorter half-lives and lower risk of drug-drug interactions (such as lorazepam); lowest doses should be used and for the shortest duration possible. The intravenous route should be avoided *(175)*.

Stroke

Patients presenting with rapidly developing neurological symptoms suggestive of stroke should be evaluated as soon as possible and standard stroke protocols should be followed including systemic thrombolysis and/or intra-arterial thrombectomy, if indicated. Signs and symptoms of stroke can include weakness of limbs or face, sensory loss, speech difficulties, impairment of vision, ataxia, confusion, or decreased consciousness. Standard IPC measures must be followed during the clinical evaluation, neuroimaging or procedures for patients with stroke.

Remark:

Strokes can be missed in severely sick or unresponsive ICU patients and a low threshold for further evaluation (including neuroimaging) is recommended for acute neurological worsening.

Mental health and psychosocial support

We recommend providing basic mental health and psychosocial support (MHPSS) for all persons with suspected or confirmed COVID-19 by asking them about their needs and concerns, and addressing them *(176)*.

Remarks:

1. Basic psychosocial support skills are essential for management of all patients and they represent an integral part of the care to be provided for different groups, including children, older adults, pregnant women and others affected by COVID-19 *(177)*.
2. This recommendation is consistent with the Inter-Agency Standing Committee briefing note about mental health and psychosocial aspects of COVID-19 *(176)*, and guidance on basic psychosocial skills for COVID-19 responders *(177)*, and WHO recommendations on providing access to support based on psychological first aid principles to people in acute distress exposed recently to a traumatic event *(178)*.
3. Ask people about their needs and concerns around diagnosis, prognosis, and other social, family or work-related issues. Listen carefully, try to understand what is most important to the person at this moment, and help them work out what their priorities are and link them with relevant resources and services.
4. Give accurate information on the person's condition and treatment plans in easily understood and non-technical language, as lack of information can be a major source of stress. Help people address urgent needs and concerns, and help with decision-making, as necessary. Help connect people with loved ones and social support, including through phone or internet as appropriate.
5. MHPSS and follow up should continue after the person is discharged from hospital to ensure their symptoms are not worsening and they are continuing to do well. This can be provided through telehealth, where available and appropriate.
6. Given the stress that COVID-19 may create at individual and family levels, the high prevalence of common mental health conditions among women in the antenatal and postpartum period, and the acceptability of programmes aimed at them, interventions for MHPSS targeted to mothers need to be more widely implemented. Prevention services should be available in addition to services that treat mental health conditions.
7. Parents and caregivers who may need to be separated from their children, and children who may need to be separated from their primary caregivers, should have access to appropriately trained health or non-health workers for MHPSS. MHPSS should be appropriately adapted for the needs of children, taking into consideration their social and emotional development, learning and behaviour *(176)*.

We recommend prompt identification and assessment for anxiety and depressive symptoms in the context of COVID-19 and to initiate psychosocial support strategies and first-line interventions, for the management of new anxiety and depressive symptoms.

Remarks:

1. For people who are experiencing symptoms of anxiety, basic psychological skills such as psychological first aid stress management, and brief psychological interventions based on the principles of cognitive behavioural therapy should be considered *(178,179)*.
2. For relieving anxiety causing severe distress that is not responsive to psychosocial support strategies, benzodiazepines can be considered, specifically in the hospital setting. Benzodiazepines should only be used with extreme caution with preference for those with shorter half-lives and lower risk of drug-drug interactions (such as lorazepam). Lowest doses should be used and for the shortest duration possible; high doses and longer term use should be avoided. Benzodiazepines carry the risks of confusion and respiratory suppression, may worsen traumatic stress reactions, can produce tolerance and dependence, and are known to be prescribed indiscriminately in many emergencies *(174)*.
3. For people who are experiencing symptoms of depression, brief psychological interventions based on the principles of cognitive behavioural therapy, problem-solving treatment and relaxation training can be considered *(180)*. Consider using remote mental health support (i.e. telephone therapy) when access to regular services is disrupted.

4. If a person's anxiety or depressive symptoms persist beyond recovery from COVID-19 and/or discharge from the hospital, then an underlying anxiety or depressive disorder may be suspected, and a mental health professional should be consulted and these conditions should be managed appropriately. Refer to the *mhGAP Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings (181)*.
5. It is important to ask about thoughts or acts of self-harm, particularly during COVID-19, due to risk factors for self-harm and suicide such as sense of isolation, loss of a loved one, job, or financial loss and hopelessness. Remove possible means of self-harm, activate psychosocial support, follow up with the person, and consult a mental health professional as necessary. Refer to the *mhGAP Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings (181)*.
6. To ensure comprehensive care and based on the initial assessment, following discharge, link the person to employment, education, social services (including housing) and other relevant sectors *(181)*.
7. Cognitive-behavioural therapy with a trauma focus, eye movement desensitization and reprocessing or stress management should be considered for adults with post-traumatic stress disorder (PTSD) *(182)*.

We recommend psychosocial support strategies as the first-line interventions for management of sleep problems in the context of acute stress.

Remarks:

1. Sleep hygiene advice (including avoiding the use of psychostimulants such as caffeine, nicotine or alcohol), and stress management (including relaxation techniques and mindfulness practices) are effective in reducing sleep problems and may be offered. Psychological interventions based on the principles of cognitive behavioural therapy may also be considered.
2. For people who are hospitalized for COVID-19, additional causes of insomnia may include environmental factors (e.g. excessive light and noise at night), anxiety, persistent cough, delirium, agitation, pain or air hunger. Identifying and promptly addressing underlying causes should be prioritized before using any pharmacological sleep aids.

18. Noncommunicable diseases and COVID-19

Pre-existing NCDs, including cardiovascular disease, diabetes, chronic respiratory disease, hypertension, obesity and cancer, have been identified as independent risk factors for death (see Table 6.1).

We recommend when caring for patients with suspected and confirmed COVID-19 that have underlying NCDs to continue or modify previous medical therapy according to the patient's clinical condition.

Antihypertensive drugs should not routinely be stopped in patients with COVID-19, but therapy may need to be adjusted based on general considerations for patients with acute illness, with particular reference to maintaining normal blood pressure and renal function.

Remark:

SARS-CoV-2 uses the ACE 2 receptor for entry into cells. It has been suggested that antihypertensive drugs that exert their effect by inhibiting ACE or blocking the ACE 2 receptor may either aggravate or ameliorate the clinical course of patients with COVID-19 *(183)*. To date, there are no studies that can substantiate this, and it is generally advised to continue these medications unless there are other reasons to stop these (e.g. hyperkalaemia, hypotension or acute deterioration in renal function) *(184)*.

19. Rehabilitation for patients with COVID-19

At the outset of the pandemic, the rehabilitation needs for patients recovering from COVID-19 were based on evidence from the critical care population and long-term sequelae in SARS-CoV-1 survivors *(185,186,187,188,189,190,191,192,193,194,195,196)*. Post-intensive care syndrome (PICS) refers to a range of impairments including physical deconditioning, and cognitive and mental health impairments. The COVID-19 patients who are at higher risk of ICU admission are also those at higher risk to develop PICS, i.e. older persons with underlying diseases such as diabetes, hypertension, increased frailty and other chronic disorders *(197)*. Intensive care unit-acquired weakness is ubiquitous in ARDS survivors, as it is in critically ill COVID-19 patients who required prolonged sedation *(198)*, and recovery may be incomplete at 5 years after ICU discharge *(199)*. Some studies suggest that cognitive impairment ranges from 70–100% at hospital discharge, 46–80% at 1 year, and 20% at 5 years. Mood disorders including depression and PTSD are also sustained and prevalent *(199)*. For ARDS survivors, a reduced exercise capacity persists in the context of relatively preserved pulmonary function at 1 year *(200)*. In SARS-CoV-1 survivors, pulmonary function at 1-year is reported to be normal in 63%, mildly reduced in 32% and moderately impaired in 5%, with abnormalities characterized by restrictive patterns and reduced carbon monoxide diffusing capacity *(201)*.

The following symptoms have been reported 4–8 weeks after discharge from the hospital in both ICU admitted COVID-19 patients and non-ICU admitted COVID-19 patients: new illness-related fatigue, breathlessness, PTSD symptoms, pain, voice change, cough, dysphagia, anxiety, depression, and problems with concentration, memory and continence. Patients admitted to ICU had greater prevalence of symptoms in almost all reported symptom domains than COVID-19 patients not admitted to ICU *(202)*. More than half of all COVID-19 patients who had been hospitalized, regardless of their clinical management, reported persistence of fatigue at 60 days since the onset of symptoms *(202,203)*.

With progression of the pandemic and the follow up of patients who have not been critically ill, new evidence is emerging about COVID-19 related persistent symptoms, which have parallels with other coronavirus diseases. Some patients with SARS-CoV-1 infection went on to develop a long-term illness with widespread pain, fatigue, depression and sleep disturbance *(204,205)*. PTSD has also been described after SARS-CoV- 1 infection *(205,205)*.

Early findings report, most commonly reported ongoing symptoms (regardless of hospitalization status) are fatigue, muscle ache, shortness of breath and headache at a follow up of 4 months *(205)*. Not returning to usual health within 2–3 weeks of testing was reported by approximately one third of symptomatic adults in an outpatient setting *(206)*. A study reported that at 3 months after the onset of symptoms, one third of non-hospitalized patients were to some degree dependent on others for personal care *(207)*.

In addition, several complications from COVID-19 have been reported in different clinical domains, resulting from a thrombotic event (such as ischaemic stroke and ischaemic heart disease), direct invasion (such as myocarditis, myositis, and meningitis) or an immune-mediated reaction (such as Guillain-Barré syndrome). While many of these complications are amenable for rehabilitation, they are not addressed in this chapter. Clinicians and rehabilitation professionals can refer to existing clinical practice guidelines for the appropriate management of these sequelae.

COVID-19 is a multisystem disease which, in certain cases, will require full multidisciplinary team rehabilitation to enable recovery *(208)*.

In hospitalized patients, during the acute phase of illness, rehabilitation professionals may provide interventions that relieve respiratory distress, prevent complications and support communication.

Remarks:

1. Decision on when to start rehabilitation should be determined by a multidisciplinary team taking into account the patient's medical status *(209)*. Ensure that appropriate IPC is available at designated rehabilitation areas caring for patients with COVID-19 that remain infectious. Make optimal use of digital and/or written information for the instruction of patients *(141)*. Telehealth may play a role in the acute and subacute phases, in which face-to-face rehabilitation is costly, risky, and impractical *(210)*. Consider strategies for communication with and engagement of families during physical distancing *(211)*.

2. Early mobilization is recommended for all patients with severe risk of functional limitations, resulting from frailty or ICU-acquired weakness *(117)*. In ICU, early mobilization should be part of a bundle of care (See Chapter 12 and 13 on management of critical COVID-19 for new recommendation on bundles), and appropriate levels of activity would be based on the Richmond Agitation-Sedation Scale *(141)*. Monitor oxygen saturation levels closely as desaturation may occur. To identify every next level of mobility the ICU mobility scale can be used.
3. See Chapter 12 (Management of critical COVID-19: ARDS) for examples of respiratory interventions that may be considered.
4. Communication challenges may result from voice and speech disorders that are often linked with intubation or a cognitive impairment. Augmented communication strategies may assist, and where available, refer for speech and language therapy.
5. COVID-19 patients with dysphagia are at risk of aspiration. Dysphagia is common post-extubation and the presumed aspiration prevalence for the general critical care population is 10–25% at ICU discharge *(185)*. Referral to an appropriately trained health professional such as a speech and language therapist, for additional breathing exercises, vocal exercises, and eating and drinking exercises where available *(212)*.
6. Patients with COVID-19 have demonstrated improved mobility at hospital discharge and higher probability of discharging home with increased frequency and longer mean duration of physical therapy visits *(213)*. Some reports have found that early aerobic exercises may not be well tolerated and result in rapid desaturation in COVID-19 inpatients. Exercise training may have to start with gradual functional exercises, using no or minimal equipment *(141)* including an active range of motion exercises, balance exercises, and walking with or without a walking aid. When (assisted) exercises are well tolerated while lying supine, the rehabilitation professional may proceed with exercises while sitting, and then standing *(141)*.

Prior to hospital discharge, COVID-19 patients should be screened for rehabilitation needs in order to facilitate onward referral.

Remarks:

1. Hospitalized COVID-19 patients may have ongoing rehabilitation needs which prevent safe discharge or require continued rehabilitation services. These needs can be based on physical deconditioning, and respiratory, swallow, cognitive and mental health impairments. Consider the context of the person's individual situation, including social support and home environment when making decisions about a course of intervention or support needs.
2. When indicated from screening, further assessment of rehabilitation needs can be based on a basic set of measures that cover potentially affected functioning domains. This includes, but is not limited to: respiratory function (such as respiratory rate and SpO_2), mobility (such as ICU mobility scale), muscle strength (such as Medical Research Council sumscore), balance (such as Berg balance scale), dysphagia (such as fluid and food trials), and activities of daily living (ADL) (such as Barthel index). Additional tests might be helpful based on a first screening for mental and cognitive impairment (such as Montreal Cognitive Assessment, Hospital Anxiety and Depression Scale, PTSD Checklist-5).
3. When the patient is ready for discharge, evaluate the need of an assistive device (such as a mobility aid) and oxygen requirements at rest and during exertion. Oxygen desaturation on exertion may happen during the recovery phase, even during physical exercise of moderate activity, and is unrelated to the oxygen saturation at rest and the degree of dyspnoea *(214)*. An example of a rapid exercise test to assess desaturation on exertion is the 1-minute sit-to-stand test *(215)*.
4. Where continued rehabilitation needs are identified, refer for inpatient, outpatient or community-based follow up as indicated and according to the type and severity of rehabilitation needs. When a patient does not require inpatient rehabilitation but would benefit from rehabilitation follow up post-discharge, refer to outpatient or community-based services according to local service availability. Consider which options have the least barriers to attendance/service utilization and, where available and appropriate, refer to services delivered through telehealth *(210)* particularly where IPC measures prevent in-person consultations.
5. Information, including documentation, should be communicated between hospitals and to other hospital-based or community rehabilitation services and primary care services *(209)*.
6. Ensure patients are provided with education and information resources for self-management management of COVID-19 symptoms, especially when barriers to accessing rehabilitation follow up are anticipated (patient leaflet https://www.who.int/publications/m/item/support-for-rehabilitation-self-management-after-covid-19-related-illness).

Patients with COVID-19, should be provided with education and support for the self-management of breathlessness and resumption of activities, both in a hospitalized and a non-hospitalized setting caring for COVID-19.

Remarks:

1. Education about control of breathing can support COVID-19 patients to those recovering from respiratory illness, especially those troubled by breathlessness. Patients may be advised to adopt positions, such as high side lying and forward lean sitting, and breathing techniques, such as pursed lip breathing and square box breathing, that help to manage breathlessness. Adequate walking pace regulation is recommended to reduce breathlessness and to prevent desaturation on exertion. Severe shortness of breath that is not relieved by positioning and breathing techniques requires medical investigation.
2. All rehabilitating patients should be educated about resuming everyday activities conservatively at an appropriate pace that is safe and manageable for energy levels within the limits of current symptoms and should not be pushed for post-exertional fatigue. A gradual increase in exercise should be based on symptoms.
3. For patients with COVID-19 that also have underlying cardiovascular or pulmonary conditions, resumption of exercise should be done after consultation with appropriate health professionals *(208,216,217)*. COVID-19 patients with confirmed cardiac involvement need a cardiac evaluation before resuming exercise.
4. Resuming sports gradually should also be guided by appropriate health professionals, an example is provided for return-to-play guideline for myocarditis *(208,216,217)*.

For patients who have been discharged from the hospital or patients who have been managed at home and experience persistent symptoms and/or limitations in functioning, screen for physical, cognitive and mental impairments, and manage accordingly.

Remarks:

1. Patients with COVID-19, regardless of the disease severity, might present with persistent symptoms and a functional decline which may not be obviously apparent (such as a cognitive impairment). Consult with family members or caregivers about health-related premorbid functional difficulties and compare with their current presentation.
2. Screening may include a full history, evaluation of pre-existing health conditions, observation of the patient performing functional tasks, and a symptom-based questionnaire or easily administered screening tool *(218)* (such as Timed Up and Go test for physical function, Whooley questions for depression, Generalized Anxiety Disorder 2-item for anxiety, and Mini-Cog for cognition). Rapid exercise tests for exertional desaturation should not be attempted outside a supervised care setting if resting oximeter reading is < 96% *(215)*.
3. When resources permit, define and clinically assess impairment types by functional domains, including respiratory function (such as spirometry, diffusing capacity of the lungs for carbon monoxide, Medical Research Council dyspnoea scale), cardiovascular function (such as 6 minutes walking distance), swallowing function (such as dysphagia severity scale), musculoskeletal function (such as hand grip strength, Medical Research Council sumscore), cognitive functioning (such as Montreal Cognitive Assessment, Mini-Mental State Examination), and mental functioning (such as Hospital Anxiety and Depression Scale, PTSD checklist-5, Impact of Event Scale-Revised). Additional tests may be indicated for pain, fatigue, and difficulties with ADL *(218)*.
4. Late deterioration of COVID-19 may still occur and late onset inflammatory, thromboembolic and autonomic complications including pulmonary embolism, heart attack, heart failure and stroke have been reported. Rehabilitation or health staff should be alerted and referred to specialist, as part of multidisciplinary, coordinated care pathway.

Provide individualized rehabilitation programmes from subacute to long term according to patient needs. The prescription and provision of rehabilitation programmes should be guided by persistent symptoms and functional limitations.

Remarks:

1. COVID-19 related impairments, such as fatigue, muscle weakness and cognitive impairment, might impact the performance of ADLs. As patients regain strength and fitness, autonomy in ADLs will improve, but some will need to accept additional support from a caregiver for a time. Provide ADL training and consider home modifications (such as grab bars in the shower and toilet, handrails along stairs) and the provision of an assistive product (such as a mobility aid, shower chair, over-toilet frame), as needed.
2. The training principles of comprehensive pulmonary rehabilitation programmess apply for COVID-19 patients with persistent fatigue, reduced exercise capacity and breathlessness *(140,214,219)*. COVID-19 population needs patient-tailored supervised programmes that are flexible to adapt for patients with gas exchange abnormalities *(140,214,219,220)* guided by baseline oxygen needs at rest and during exercise.
3. Patients with physical deconditioning and muscle weakness should start with exercises that support recovery in daily functioning. Start with active range of motion exercises, and when tolerated, proceed with progressive muscle strengthening, typically offered with resistance training. Return to physical exercise should always be guided by symptoms *(216)*.
4. For patients having difficulties with memory, concentration and problem solving, education should be provided, and advice on strategies to help establish expectations (including from family members) and to alleviate stress and anxiety. Cognitive restorative rehabilitation may support with cognitive exercises (such as memory exercises, puzzles, games, reading) and compensation tools such as prompts (e.g. lists and notes) and breaking down activities. Encourage participation in daily activities that are meaningful for the patient.
5. For patients with anxiety, depression and PTSD, basic mental health and psychosocial support by appropriately trained health or non-health workers should be provided. See Chapter 17 on neurologic and mental manifestations *(218,221,222)*.
6. For patients with persistent pain, a multidisciplinary approach is recommended in order to provide pain management according to the principles of the biopsychosocial model.

20. Caring for women with COVID-19 during and after pregnancy

The results of a living systematic review (as of 6 October 2020) show that pregnant and recently pregnant women with COVID-19 appear to be less likely to be symptomatic (0.28, 95% CI 0.13 –0.62; 4 studies; 462 051 women), or manifest common symptoms such as fever, dyspnoea and myalgia, compared with non-pregnant women of reproductive age *(53)*. These findings are largely influenced by studies of pregnant women who were managed in hospitals for any reason, with limited data on women during early pregnancy or postpartum.

Pregnant women with COVID-19 are more likely to experience any type of preterm birth (OR=1.47, 95% CI 1.14–1.90; 18 studies; 8549 women) compared with pregnant women without the disease. Overall rates of spontaneous preterm birth in pregnant women with COVID-19 is broadly similar to those observed during the pre-pandemic period. A third of all neonates born to mothers with COVID-19 were admitted to the neonatal intensive care unit (NICU) (33%) and were at increased risk of NICU admission for any indication (OR=4.89, 95% CI 1.87–12.81; 10 studies, 5873 neonates) compared with those born to mothers without COVID-19.

Transmission of SARS-CoV-2 may be possible in utero or intrapartum, but most neonatal infections reported so far seem to have occurred in the postnatal period *(53)*. However, available studies varied in the rigor of ascertaining mother-to-child transmission of SARS-CoV-2, limiting interpretation of these results.

This section builds on existing recommendations from WHO on pregnancy and infectious diseases and provides additional remarks for the management of pregnant and recently pregnant women.

We recommend all pregnant women with history of contact with a person with confirmed COVID-19 be carefully monitored considering asymptomatic transmission of COVID-19.

Pregnant or recently pregnant women with suspected or confirmed mild COVID-19 may not require acute care in hospital, unless there is concern for rapid deterioration or an inability to promptly return to hospital; but isolation to contain virus transmission is recommended, and can be done at a health facility, community facility or at home, according to established COVID-19 care pathways.

Pregnant or recently pregnant women with moderate or severe COVID-19 require acute care in the hospital, as there is concern for rapid deterioration that may warrant supportive care for severe respiratory morbidity; and/or interventions to improve maternal and fetal survival.

Remarks:

1. Counsel pregnant and recently pregnant women about maternal and newborn signs, including COVID-19 danger signs and maternal perception of decreased fetal movements, and advise them to seek urgent care if they develop any worsening of illness or other danger signs, such as danger signs of pregnancy (including: bleeding or leaking fluid from the vagina, blurry vision, severe headaches, weakness or dizziness, severe abdominal pain, swelling of face, fingers, feet, inability to tolerate foods or liquids, convulsions, difficulty in breathing, decrease in fetal movements). Update birth preparedness and complication readiness plans so they know when and where to seek care.
2. In pregnant and postnatal women that are being cared for at home in self-isolation, self-care interventions should be encouraged. Routine antenatal or postnatal health visits in health facilities should be postponed, and delivery of antenatal and postnatal counselling and care, should instead be conducted via alternative platforms such as home-based, phone or telemedicine *(223,224)*. If postponed, health visits should be rescheduled until after the period of self-isolation following national guidelines and advice, and in consultation with the health care provider. For women requiring abortion services, consider alternative modes of service delivery, including self-management of medical abortion up to 12 weeks' gestation, where women have access to accurate information and to a health care provider at any stage of the process. Postponing abortion care may lead to increased morbidity and mortality where individuals resort to unsafe abortion practices as abortion service delivery is time-bound by gestational limits prescribed by the law *(225).* See the *WHO Consolidated guideline on self-care interventions for health (226).*
3. Counsel women about healthy diet, mobility and exercise, intake of micronutrients for herself and her infant, tobacco use and second-hand smoke exposure, use of alcohol and other substances, as per WHO guidelines on antenatal and postnatal care. Clinical enquiry about the possibility of gender-based violence should be strongly considered, where there is the capacity to provide a supportive response (including referral where appropriate) and where the WHO minimum requirements are met. See resource *(227)*.
4. When caring for pregnant and recently pregnant women with underlying NCDs or pregnancy-induced conditions (e.g. gestational diabetes, pregnancy-induced hypertension) continue or modify previous medical therapy according to the woman's clinical condition.

Pregnant and recently pregnant women with suspected, probable or confirmed COVID-19, should have access to woman-centred, respectful skilled care, including midwifery, obstetric, fetal medicine and neonatal care, as well as mental health and psychosocial support, with readiness to care for maternal and neonatal complications.

Remarks:

1. Woman-centred, respectful, skilled care refers to care organized for and provided to all women in a manner that maintains their dignity, privacy and confidentiality, ensures freedom from harm and mistreatment, and enables informed choice. During labour and childbirth this includes a companion of choice, pain relief, mobility during labour and birth position of choice.
2. Screen birth companions using the standardized case definition. If the companion has suspected or confirmed COVID-19, arrange for an alternative, healthy birth companion in consultation with the woman. Emphasize to any and all companions the importance of IPC measures during labour, childbirth and the mother's and newborn's postnatal stay in the health facility, including appropriate training on and use of PPE and movement restriction in the health care facility.

Mode of birth should be individualized, based on obstetric indications and the woman's preferences. WHO recommends that induction of labour and caesarean section should only be undertaken when medically justified and based on maternal and fetal condition. COVID-19 positive status alone is not an indication for caesarean section. See *WHO recommendations for induction of labour (228)*

Remarks:

1. Emergency birth and pregnancy termination decisions are challenging and based on many factors such as gestational age, severity of maternal condition, and fetal viability and well-being.
2. Interventions to accelerate labour and childbirth (e.g. augmentation, episiotomy, operative vaginal birth) should only be undertaken if medically justified and based on maternal and fetal clinical condition. See *WHO recommendations: intrapartum care for a positive childbirth experience (229).*
3. Delayed umbilical cord clamping (not earlier than 1 minute after birth) is recommended for improved maternal and infant health and nutrition outcomes. The risk of transmission of COVID-19 through blood is likely to be minimal. There is no evidence that delaying cord clamping increases the possibility of viral transmission from the mother to the newborn. The proven benefits of a 1–3 minute delay, at least, in clamping the cord outweigh the theoretical, and unproven, harms.
4. Individualized decisions should be taken about postponing planned (elective) induction or caesarean section in pregnant women with suspected or confirmed mild COVID-19 *(227).*

Pregnant and recently pregnant women who have recovered from COVID-19 and been released from the COVID-19 care pathway, should be enabled and encouraged to receive routine antenatal, postpartum, or postabortion care, as appropriate. Additional care should be provided if there are any complications.

Remarks:

1. All pregnant women with or recovering from COVID-19 should be provided with counselling and information related to the potential risk of adverse pregnancy outcomes.
2. Women's choices and rights to sexual and reproductive health care should be respected regardless of COVID-19 status, including access to contraception and safe abortion to the full extent of the law *(225).*

21. Feeding and caring for infants and young children of mothers with COVID-19

Relatively few cases have been reported of infants confirmed with COVID-19; those that have been reported experienced mild illness. Of 115 mother-child pairs from 17 articles where the mother is confirmed to be infected with COVID-19, 13 children had COVID-19 (4 breastfed, 5 formula-fed, 2 mix-fed, 2 unreported feeding practice). Twenty mothers had breastmilk samples tested for the presence of SARS-CoV-2 RNA particles by RT-PCR; 7 of them had children with COVID-19 (2 breastfed,1 formula fed, 2 mix-fed, 2 unreported). Of the 20 with breastmilk tested, 18 had negative results and 2 had positive results. One of the two mothers whose breastmilk sample was positive for SARS-CoV-2, had a mix-fed child who was not infected with COVID-19; the other one had a child with COVID-19 (feeding practice was not reported) *(230,231,232,233,234,235,236,237,238,239,240)*.

Breastfeeding protects against morbidity and death in the post-neonatal period and throughout infancy and childhood. The protective effect is particularly strong against infectious diseases that are prevented through both direct transfer of antibodies and other anti-infective factors and long-lasting transfer of immunological competence and memory. See WHO *Essential newborn care and breastfeeding (241).* Therefore, standard infant feeding guidelines should be followed with appropriate precautions for IPC.

Recommendations on the care and feeding of infants whose mothers have suspected or confirmed COVID-19 promote the health and well-being of the mother and infant. Such recommendations must consider not only the risks of infection of the infant with the COVID-19 virus, but also the risks of serious morbidity and mortality associated with not breastfeeding or the inappropriate use of breastmilk substitutes as well as the protective effects of skin-to-skin contact and kangaroo mother care. In light of the current

evidence, WHO has concluded that mothers with suspected or confirmed COVID-19 should not be separated from their infants. Mother-infant contact and holding enhances thermoregulation and other physiological outcomes, significantly reduces mortality and morbidity, and improves child and parental attachment. Overall, the recommendation to keep mothers and their children together is based on several important benefits that outweigh the potential (and likely mild) harms of COVID-19 transmission to the child.

We recommend that mothers with suspected or confirmed COVID-19 should be encouraged to initiate and continue breastfeeding. From the available evidence, mothers should be counselled that the benefits of breast-feeding substantially outweigh the potential risks of transmission.

Remarks:

1. WHO recognizes that the recommendation for an infected mother to be in close contact with her baby may appear to contradict other IPC measures that include isolation of persons infected with COVID-19 virus *(53)*. However, the balance of risks is significantly different for infants than for adults. In infants, the risk of COVID-19 infection is low, the infection is typically mild or asymptomatic, and the consequences of not breastfeeding or separation of mother and child can be significant. At this point it appears that COVID-19 in infants and children represents a much lower risk to survival and health than the other infections and conditions that breastfeeding is protective against. This protection is especially important when health and other community services are themselves under pressure. In contrast, the risks associated with COVID-19 in adults are much higher and more severe. Improved communication is needed to address the uncertainties and confusion among programme managers, health workers and communities on this issue.
2. See Table 21.1 below for recommendations when mother with COVID-19 is caring for infant.

Table 21.1. Summary of recommendations when mother with COVID-19 is caring for infant

	Interventions
Mother infant contact at birth	Mothers should not be separated from their infants unless the mother is too sick to care for her baby. If the mother is unable to care for the infant another competent family caregiver should be identified. Mother and infant should be enabled to remain together while rooming-in throughout the day and night and practise skin-to-skin contact, including kangaroo mother care, especially immediately after birth and during establishment of breastfeeding, whether they or their infants have suspected or confirmed COVID-19 virus infection. Neonates born to mothers with suspected or confirmed COVID-19 should be breastfed within 1 hour of birth. Mothers should apply appropriate IPC. Early and uninterrupted skin-to-skin contact between mothers and infants should be facilitated and encouraged as soon as possible after birth, while applying necessary measures for IPC. This applies also to infants who are born preterm or low birth weight. If the newborn or infant is ill and requires specialist care (such as neonatal unit), arrangements should be made to allow the mother free access to the unit, with appropriate IPC measures. Earlier initiation of breastfeeding results in greater benefits. This may be relevant to mothers who give birth by caesarean section, after an anaesthetic, or those who have medical instability that precludes initiation of breastfeeding within the first hour after birth.
During early childhood	Infants should be breastfed exclusively during the first 6 months after birth, as breastmilk provides all the nutrients and fluids they need. From 6 months of age, breastmilk should be complemented with a variety of adequate, safe and nutrient-dense foods. Breastfeeding should continue up to 2 years of age or beyond. Breastfeeding counselling, basic psychosocial support and practical feeding support should be provided to all pregnant women and mothers with infants and young children if they or their infants and young children have suspected or confirmed COVID-19 infection.

If feeding is interrupted	In situations when severe illness in a mother prevents her from caring for her infant or prevents her from continuing direct breastfeeding, mothers should be encouraged and supported to express milk, and the breastmilk provided safely to the infant, while applying appropriate IPC measures. In the event that the mother is too unwell to breastfeed or express breastmilk, explore the viability of feeding with donor human milk. If this is not possible, consider wet nursing (defined as another woman breastfeeds the child) or appropriate breastmilk substitutes, informed by feasibility, safety, sustainability, cultural context, acceptability to mother and service availability. Mothers who are not able to initiate breastfeeding during the first hour after delivery should still be supported to breastfeed as soon as they are able. Assistance should be provided after recovery for relactation to re-establish a milk supply and continue breastfeeding.
Practices the mother should perform during all infant and childcare	Perform frequent hand hygiene with soap and water or alcohol-based hand rub, especially before contact with her child. Perform respiratory hygiene: sneeze or cough into a tissue and immediately dispose of the tissue. Hands should immediately be washed with soap and water or alcohol-based hand rub. Clean and disinfect surfaces with which the mother has been in contact. Wear a medical mask until symptom resolution and criteria for release from isolation have been met. Additionally, breastfeeding mothers should be helped to clean her chest with soap and water if she has been coughing on it before breastfeeding. She does not need to wash her breasts prior to every breastfeed. While mothers are recommended to wear medical masks, if the mother does not have a medical mask, she should still be encouraged to continue breastfeeding as the benefits of breastfeeding outweigh the potential risks of transmission of the virus when breastfeeding while applying other IPC measures.
Best practices for breast-feeding	Health facilities providing maternity and newborn services should enable a mother to breastfeed for as often and for as long as she wishes. Minimizing disruption to breastfeeding will require health care practices that enable a mother to breastfeed. All mothers should receive practical support to enable them to initiate and establish breastfeeding and manage common breastfeeding difficulties. This support should be provided by appropriately trained health care professionals and community-based lay and peer breastfeeding counsellors. There should be no promotion of breastmilk substitutes, feeding bottles and teats, pacifiers or dummies in any part of facilities providing maternity and newborn services, or by any of the staff. Health facilities and their staff should not give feeding bottles and teats or other products that are within the scope of the International Code of Marketing of Breast-milk Substitutes and its subsequent related WHA resolutions, to infants. If the mother is too unwell to breastfeed or express breastmilk, explore the best alternatives to breastfeeding a newborn or young infant, in priority order, as follows: 1) donor human milk should be fed if available from a human milk bank; 2) if supplies are limited, prioritize donor human milk for preterm and low birth weight newborns; 3) wet nursing may be an option depending on acceptability to mothers and families, availability of wet nurses and services to support mothers and wet nurses. COVID-19 testing of a woman who is a potential wet nurse is not required. Prioritize wet nurses for the youngest infants. In settings where HIV is prevalent, prospective wet nurses should undergo HIV counselling and rapid testing where available. In the absence of testing, if feasible, undertake HIV risk assessment. If HIV risk assessment or counselling is not possible, facilitate and support wet nursing; 4) breastmilk substitutes may be used as a last resort.

22. Caring for older people with COVID-19

Older age has been reported as a risk factor for increased mortality in those affected by COVID-19. Other risk factors that have been reported are: smoking, diabetes, hypertension, cardiovascular, cancer, chronic lung disease, and functional decline *(242,243,244)*. Since older people are often affected by these conditions, they are potentially at the highest risk for fatality. Furthermore, the majority of long-term care service users are older people with multiple underlying conditions and weak immune systems, which make them more susceptible to severe COVID-19 and poor outcomes *(245)*. Refer to the WHO policy brief *Preventing and managing COVID-19 across long-term care services (245)* and WHO guidance *Integrated care for older people (ICOPE) (246)* for person-centred and coordinated model of care.

We recommend that older people be screened for COVID-19 at the first point of access to the health system, be recognized promptly if they are suspected to have COVID-19 and treated appropriately according to established COVID-19 care pathways. This should occur in all settings where older people may seek care; included but not limited to facility-based emergency units, primary care, prehospital care settings and LTCFs.

Remarks:

1. Older patients may present with atypical symptoms (including delirium) of COVID-19, especially those with cognitive decline and dementia *(247,248)* (see Table 6.1); health workers should take this into account during the screening process.
2. Provide accessible information to older people and their caregivers on clinical manifestation of COVID-19 including atypical symptoms, how to monitor symptoms, as well as when and how to seek care.

Identify if there is an advance care plan for patients with COVID-19 (such as desires for intensive care support) and respect their priorities and preferences. Tailor the care plan to be in line with patients' expressed wishes and provide the best care irrespective of treatment choice.

We recommend a review of medication prescriptions to reduce polypharmacy and prevent medicine interactions and adverse events for those being treated with COVID-19.

Remarks:

1. Older people are at greater risk of polypharmacy, as a result of newly prescribed medications, inadequate medication reconciliation, and a lack of coordination of care, all of which increases the risk of negative health consequences. If medications are prescribed for mental and neurological manifestations of COVID-19 in older people, this should be done with extreme caution given the increased susceptibility to drug side-effects and drug interactions with other prescribed medications.
2. Over 20% of adults over 60 years have pre-existing mental or neurological conditions for which they may already be taking medications before infection *(249)*. If a person has a previously diagnosed mental or neurological condition and is already on medications, consider how these medications (or withdrawal from them) may affect their COVID-19 symptoms. Stopping or adjusting the dosage of medications in people with COVID-19 are decisions that require careful risk-benefit analyses and when possible, consultation with a specialist is advised.

Ensure multidisciplinary collaboration among physicians, nurses, pharmacists, physiotherapists, occupational therapists, social workers, mental health and psychosocial providers, community workers and other health care professionals in the decision-making process to address multimorbidity and functional decline *(246,250,251)*.

Remarks:

1. Physiological changes with age lead to declines in physical and mental capacities such as malnutrition, cognitive decline, depressive symptoms, and those conditions interact at several levels. These interactions require an integrated approach to the screening, assessment and management of older people *(246)*.

2. Person-centred care including geriatric, psychosocial, and palliative care by a multidisciplinary team, with a careful evaluation of baseline conditions and functions, and disease severity, followed by frequent reassessments, ensures the provision of the appropriate level of care *(252,253)*.
3. Hearing loss and vision impairments become more prevalent among older people and may pose a communication barrier, especially when masks prevent lip reading and decrease vocal clarity. Cognitive decline may also need to be considered when communicating with older patients. Such impairments should be identified early so that health workers involved in their care can adjust their communication accordingly *(254)*.
4. Older people who experience COVID-19, including those admitted to ICU and/or treated with protracted oxygen therapy and bed rest, are more likely to experience pronounced functional decline and require coordinated rehabilitation care after acute hospitalization (see Chapter 19. Rehabilitation for patients with COVID-19).
5. Ensure that chronic infections are diagnosed and treated appropriately in older people. Other infections such as TB may mimic or co-exist with COVID-19 and therefore pass unrecognized, causing increased mortality *(67,68,69)*.

23. Palliative care and COVID-19

Palliative care is a multifaceted, integrated approach to improving the quality of life of adults and paediatric patients and their families facing the problems associated with life-threatening illness such as COVID-19. Palliative care focuses on prevention and relief of suffering by means of early identification, assessment and treatment of physical, psychosocial and spiritual stressors. Palliative care includes but is not limited to end-of-life care *(255)*. Palliative interventions should be integrated with curative treatment *(255)*. Basic palliative care, including relief of dyspnoea or other symptoms and social support, should be practised by all doctors, nurses, social workers and others caring for persons affected by COVID-19, adult or child *(255,256)*. Refer to the WHO guide *Integrating palliative care and symptom relief into responses to humanitarian emergencies and crises (255)*.

We recommend to identify, in all patients with COVID-19, if they have an advance care plan for COVID-19 (such as desires for intensive care support) and respect their priorities and preferences to tailor the care plan and provide the best care irrespective of treatment choice.

Palliative care interventions should be made accessible at each institution that provides care for persons with COVID-19.

Remarks:

1. Appropriate interventions should be accessible at each institution that provides care for persons with COVID-19. Efforts should be made to assure accessibility of interventions at home *(255)*.
2. Palliative care includes but is not limited to end-of-life care. Palliative interventions should be integrated with curative treatment. Basic palliative care, including relief of dyspnoea or other symptoms and social support, should be practised by all doctors, nurses, social workers and others caring for persons affected by COVID-19.
3. In hospitals, palliative care does not require a separate ward or department. Palliative care can be provided in any setting.
4. Consider non-pharmacologic and pharmacologic interventions (such as opioids) for relief of dyspnoea that is refractory to treatment of the underlying cause (i.e. oxygen therapy, escalation of respiratory support, corticosteroids) and/or as part of end-of-life care *(257)*. The narrow therapeutic margin of opioids in the management of dyspnoea requires that opioids are prescribed in accordance with evidence-based treatment protocols and that patients are closely monitored to prevent negative unintended effects due to inappropriate use of opioids. Where opioids are used, preference should be given for compounds less likely to cause delirium in medically ill patients. Providers should reference their institutional standards regarding the potential use of opioids for dyspnoea in patients with COVID-19.

5. Relieving spiritual and psychological suffering is an important aspect of palliative care. Visits from relatives and spiritual counsellors should be facilitated, especially for patients near to the end of life. This may include employing a range of techniques such as voice/video calls.
6. Palliative care is a person-centred approach; therefore all patients and families should be actively included in the decision-making processes about escalation of care. Medical decisions, where possible, should respect the priorities and preferences of patients, and should always be clearly explained to patients and relatives.

24. Care of COVID-19 patients after acute illness (new chapter)

New evidence is emerging about COVID-19 related persistent symptoms, which have parallels with other coronavirus diseases *(204)*.

The clinical characterization of mid- and long-term effect of COVID-19 remain to be clearly described and understood. In hospitalized patients, ICU and non-ICU, there are reports of new illness-related fatigue, breathlessness, PTSD symptoms, pain, voice change, cough, dysphagia, anxiety, depression, and problems with concentration, memory and continence. Patients admitted to ICU had greater prevalence of symptoms in almost all reported symptom domains than COVID-19 patients not admitted to ICU *(202)*. As well, more than half of all COVID-19 patients who had been hospitalized, regardless of their clinical management, reported persistence of fatigue at 60 days since the onset of symptoms *(202,203)*.

Early findings report, most common ongoing symptoms (regardless of hospitalization status) are fatigue, muscle ache, shortness of breath and headache at a follow up of 4 months *(205)*. Not returning to usual health within 2–3 weeks of testing was reported by approximately one third of symptomatic adults in an outpatient setting *(206)*. A study reported that at 3 months after the onset of symptoms, one third of non-hospitalized patients were to some degree dependent on others for personal care *(207)*.

Best Practice Statement

Patients who have had suspected or confirmed COVID-19 (of any disease severity) who have persistent, new, or changing symptoms should have access to follow-up care.

Remarks:

Recognition

- All patients (and their caregivers) with COVID-19 should be counselled to monitor for resolution of signs and symptoms. If any one or more of these persist, or patient develops new or changing symptom, then to seek medical care according to national (local) care pathways.
- This includes counselling about acute life-threatening complications, such as pulmonary embolism, myocardial infarction, dysrhythmias, myopericarditis and heart failure, stroke, seizures and encephalitis *(54,258)* for which they should seek emergency care.
- Patients with severe and critical COVID-19 may develop post-intensive care syndrome (PICS), with a range of impairment including (but not limited to) physical deconditioning, cognitive, and mental health symptoms. See Chapter 19. Rehabilitation for patients with COVID-19 for more details on PICS.

Management

- National (local), coordinated care pathways should be established that can include primary care providers (i.e. general practitioners), relevant specialists, multidisciplinary rehabilitation professionals, mental health and psychosocial providers, and social care services.
- Management should be tailored according to patient needs and be coordinated.
- Management interventions include addressing promptly life-threatening complications. For non-life-threatening complications, management may entail education, advice on self-management strategies (i.e. breathing techniques, pacing), caregiver support and education, peer-to-peer groups, stress management, stigma mitigation and home modification; prescription of rehabilitation programmes, and/or specialty management.
- See Chapter 19. Rehabilitation for patients with COVID-19 for recommendations regarding screening, assessment and rehabilitation interventions to facilitate onward referrals for inpatient, outpatient, or community-based follow up, to ensure continuity during transitions of care.

Evidence to decision

Values and preferences	No substantial variability expected

Applying the agreed values and preferences, the GDG inferred that well-informed patients would consider the possible harms associated with COVID-19 follow-up to be negligible, and that ensuring access to care is an important value to consider.

Resources and other considerations	Important considerations

National (local), coordinated care pathways should be established that can include primary care providers (i.e. general practitioners), relevant specialists, multidisciplinary rehabilitation professionals, mental health and psychosocial providers, and social care services. Alternative delivery platforms such as home-based phone, telemedicine, or community outreach teams may be used.

Justification
Applicability
Special populations
Considerations should be made when following up special populations such as older persons (see Chapter 22. Caring for older people with COVID-19), and children and their caregivers.

Practical info
Uncertainties
Further research on mid- and long-term sequelae of COVID-19 is a priority. Some items identified include:

- A consensus case definition to facilitate global surveillance, diagnosis, management and research to be convened by WHO.
- Detailed clinical characterization of mid- and long-term sequelae, using standardized tools for data collection (see Chapter 27. Clinical research during the COVID-19 pandemic).
- Multidisciplinary approach to research which involves patients and communities affected with COVID-19.
- Impact of therapeutics on longer term outcomes.

25. Ethical principles for optimum care during the COVID-19 pandemic

Ethics are central to the clinical care of COVID-19 patients in the same way that ethics pertain to all patients. Clinical care involves using clinical expertise to do what is best for patients within a relationship of care. This section provides a brief introduction to some of the ethical considerations that are important to remember in the context of COVID-19 *(259,260)*.

Ethical considerations that impact all persons affected by COVID-19

Equal moral respect: Every person is equally valuable. Treatment and care decisions should be based on medical need and not on irrelevant or discriminatory features such as **ethnicity, religion, sex, age, disability or political affiliation**. Patients with similar health problems or symptoms must receive equal treatment and care. Showing moral respect means involving patients and their caregivers in decision-making to the greatest extent possible, explaining options and limitations in treatment.

Duty of care: Every patient is owed the best possible care and treatment available in the circumstances. Even when resources need to be rationed during a crisis, health care professionals and frontline workers have a duty of care to promote their patients' welfare within available resources. Health care professionals and frontline workers are also owed a duty of care. In this regard, appropriate PPE for health care professionals and frontline workers should be provided to promote their safety and well-being. This is a benefit to them but also to the whole of society by ensuring that they are available to support the clinical response for as long as possible.

Non-abandonment: It follows from consideration of equal moral respect and duty of care, that no person in need of medical care should ever be neglected or abandoned. Care will extend to families and friends of patients and options to maintain communication with them should be explored. Palliative care must be accessible for all patients with respiratory failure for whom ventilatory support will be withheld or withdrawn.

Protection of the community: Appropriate IPC should be in place, respected and enforced. Such actions protect patients, health care professionals and the community. During a pandemic the focus should be on both clinical care for patients and the promotion of public health.

Confidentiality: All communications between patient and clinician must remain confidential except in the case of compelling public health concerns (e.g. contact tracing and surveillance etc.) or other accepted justifications for breach of confidentiality. Private individual information must be kept secure unless it is a justified breach.

We recommend that hospitals and health systems at local, regional, national and global level plan prepare and be ready to surge clinical care capacity (staff, structure, supplies and systems) in order to be able to provide appropriate care of all COVID-19 patients and maintain essential health services *(61,261)*.

Allocation of scarce resources: We recommend that each institution should establish a plan for what to do in situations of resource scarcity to cover the allocation or access to critical medical interventions (such as oxygen, intensive care beds and/or ventilators). Such a plan should establish a clear overall aim.

Decision-making regarding allocation: Part of planning for scarcity is ensuring that a fair system of decision-making for allocation is in place.

Remarks:

1. Personnel familiar with the medical triage criteria and allocation protocols, who are distinct from the clinical treating team are one option. Allocation decisions should be done according to the established plan and regularly reviewed. If necessary, there should be a reallocation of a resource that was previously allocated where it is not proving beneficial.
2. For example, the aim might be to ensure the best possible use of limited resources based upon chosen medical criteria. Triage criteria should seek to balance medical utility and equity, and ease of implementation. The same criteria should be applied for all patients with similar levels of need, regardless of COVID-19 status.

We recommend that it be clear when decision-making will move from routine allocation to pandemic allocation, so that institutions do not move too soon to restrict access in anticipation of possible future scarcity that might not arise.

Remarks:

1. It should be clear what the “tipping point” is to change to pandemic allocation (e.g. a declaration by a ministry of health, or hospitals reaching ICU bed and ventilator capacity). This should take into account maximizing surge clinical capacity.
2. Whatever method is chosen should be subject to a fair process, such as using the following procedural principles:
    - **Inclusiveness:** Input should be obtained from the most affected population(s).
    - **Transparency:** The mechanism should be easily accessible and understandable at an elementary school level and in all major languages in the institution’s catchment area.
    - **Accountability:** A mechanism should be available to review the application of an approved triage protocol, or requests to review a particular decision, in light of novel or updated clinical information or other concerns.
    - **Consistency:** Allocation principles should be applied consistently.

We recommend that caregivers should be:

- **Given access to adequate training in caregiving, including IPC.**
- **Given access to appropriate and adequate PPE.**
- **Exempted from travel restrictions that would preclude caring for the patient.**
- **Be given access to psychological, social and spiritual care, and also to respite and bereavement support as needed.**

Remark:
Caregivers are at risk for the same types of psychological, social and spiritual distress as patients. They are also at risk for becoming infected. Basic mental health and psychosocial support should be provided for all caregivers by asking them about their needs and concerns, and addressing them *(262)*.

26. Reporting and coding during the COVID-19 pandemic (mortality and morbidity)

All coding advice is available in the official WHO languages and can be found together with more detail for classification purposes at https://www.who.int/standards/classifications/classification-of-diseases/emergency-use-icd-codes-for-covid-19-disease-outbreak. See Table 26.1 and 26.2 for details.

Table 26.1 Morbidity and mortality coding for COVID-19 in ICD-10 and ICD-11

ICD**ICD**	**Description of codes**	
ICD -10	An emergency ICD-10 code of "U07.1 COVID-19, virus identified" is assigned to a disease diagnosis of COVID-19 confirmed by laboratory testing. An emergency ICD-10 code of "U07.2 COVID-19, virus not identified" is assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available. Both U07.1 and U07.2 may be used for mortality coding and tabulation as cause of death.	
ICD-11	The code for the confirmed diagnosis of COVID-19 is RA01.0. The code for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.1.	

A set of additional categories has been agreed to be able to document or flag conditions that occur in the context of COVID-19. Both, 3-character and 4-character codes have been defined to respond to the different levels of coding depth that is in place in different countries. The categories below will not be seen in primary tabulation of the single underlying cause of death. They may be used in multiple cause of death analysis and reporting.

Table 26.2 Coding for conditions occurring in context of COVID-19 in ICD-10 and ICD-111

ICD -10	1. U08 Personal history of COVID-19 U08.9 Personal history of COVID-19, unspecified Note: This optional code is used to record an earlier episode of COVID-19, confirmed or probable that influences the person's health status, and the person no longer suffers of COVID-19. This code should not be used for primary mortality tabulation. 2. U09 Post COVID-19 condition U09.9 Post COVID-19 condition, unspecified Note: This optional code serves to allow the establishment of a link with COVID-19. This code is not to be used in cases that still are presenting COVID-19. 3. U10 Multisystem inflammatory syndrome associated with COVID-19 U10.9 Multisystem inflammatory syndrome associated with COVID-19, unspecified
ICD-11	RA02 Post COVID-19 condition RA03 Multisystem inflammatory syndrome associated with COVID-19 QC42/RA01 Personal history of COVID-19

For mortality we recommend the use of emergency ICD codes as outlined in the *International guidance for certification and coding of COVID-19 as cause of death (263).*

Remarks:

1. The primary goal is to identify all deaths due to COVID-19. A death due to COVID-19 is defined for surveillance purposes as a death resulting from a clinically compatible illness, in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID-19 disease (e.g. trauma). There should be no period of complete recovery from COVID-19 between illness and death. A death due to COVID-19 may not be attributed to another disease (e.g. cancer) and should be counted independently of pre-existing conditions that are suspected of triggering a severe course of COVID-19.
2. Specification of the causal sequence leading to death in Part 1 of the certificate is important. For example, in cases when COVID-19 causes pneumonia, sepsis and acute respiratory distress; then pneumonia, sepsis and acute respiratory distress should be included, along with COVID-19, in Part 1. Certifiers should include as much detail as possible based on their knowledge of the case, from medical records, or about laboratory testing *(263).*
3. The use of official terminology, COVID-19, should be used for all certification of this cause of death. COVID-19 should be recorded on the medical certificate as cause of death for all decedents where the disease caused, or is assumed to have caused, or contributed to death. This helps to reduce uncertainty for the classification or coding and to correctly monitor these deaths.

27. Clinical research during the COVID-19 pandemic

A living mapping and systematic review of COVID-19 studies are available *(264)*. For more information about the WHO research roadmap see https://www.who.int/teams/blueprint/covid-19.

We recommend to collect standardized clinical data on all hospitalized patients to improve understanding of the natural history of the disease and contribute data to the WHO Global COVID-19 Clinical Data Platform (see website for details).

Remarks:

1. Member States are invited to contribute anonymized clinical data to the WHO Global COVID-19 Clinical Data Platform; contact: COVID_ClinPlatform@who.int to get log-in credentials. This will serve to inform the public health and clinical response.
2. Four case record forms (CRFs) are now available: These can be accessed on the WHO website *(265)*.
   - Rapid CRF
   - Pregnancy CRF
   - Multisystem inflammatory syndrome temporally associated with COVID-19 CRF
   - Follow up CRF.
3. Clinical characterization research protocols are also available *(266).*

The WHO Solidarity trial is a randomized clinical trial that is a currently enrolling. For more information see the WHO website *(267)*.

Remark:
Older age is reported to be a predictor of mortality in patients with COVID-19. The systematic exclusion of older adults from research activities or from accessing investigational therapeutic agents is not justified *(260).*

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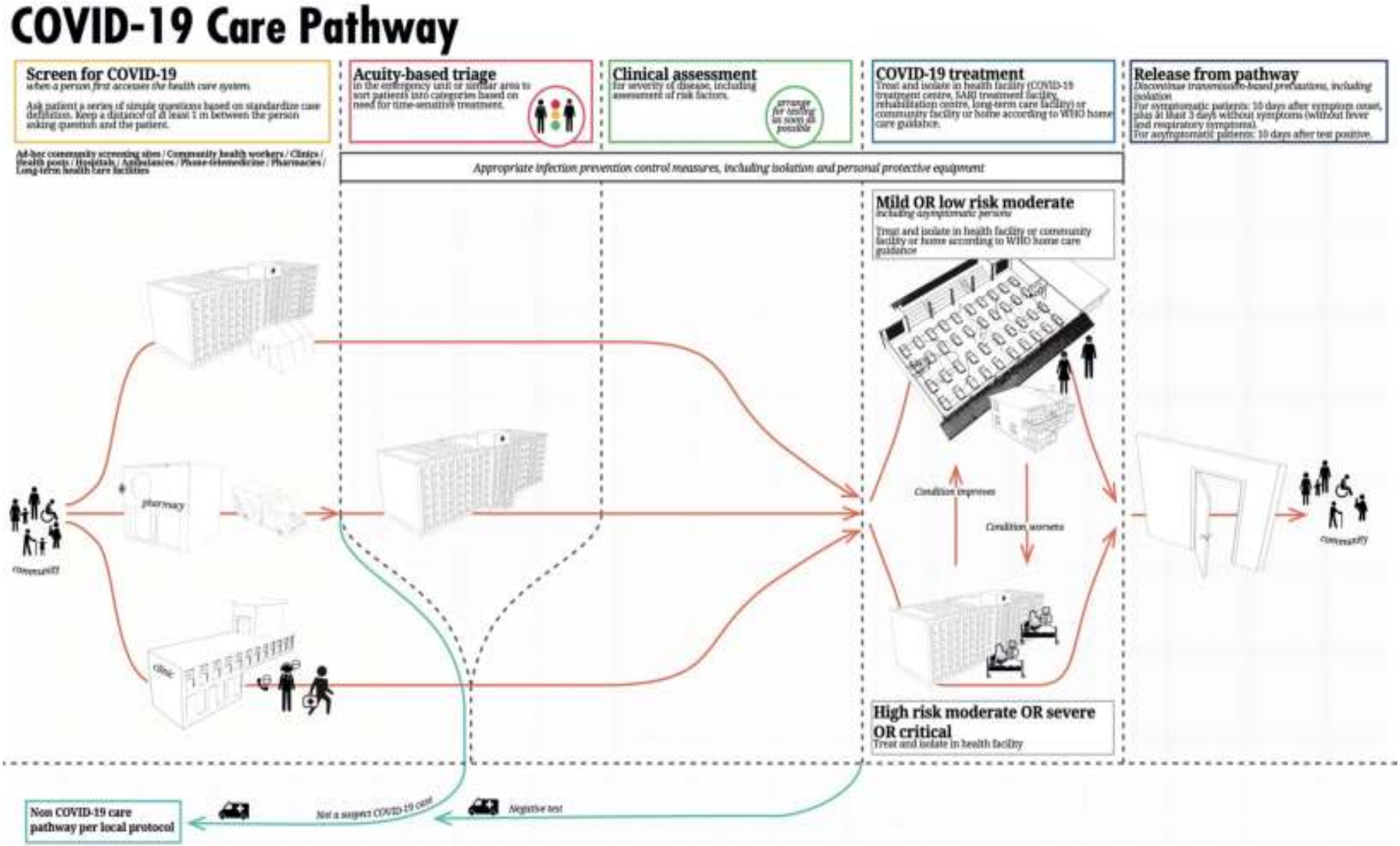
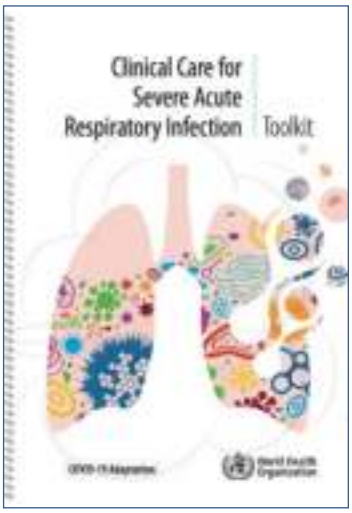
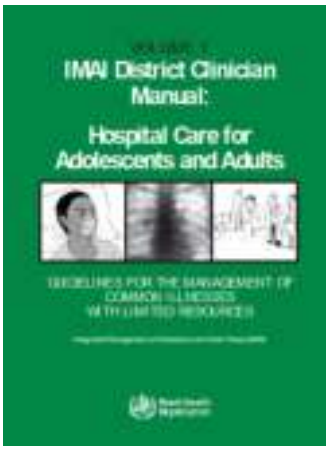
Annex 1: COVID-19 care pathway



Annex 2: Resources for supporting clinical management of COVID-19

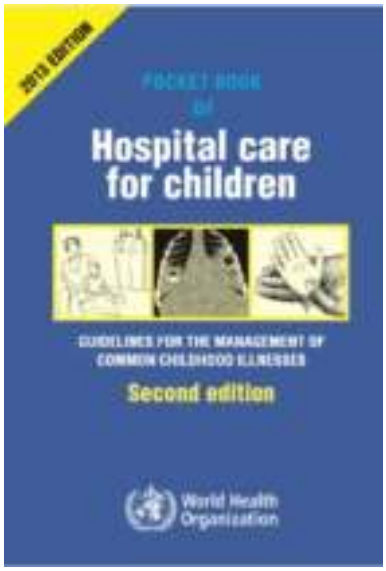


Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation (2020)
This toolkit is intended for clinicians working in acute care hospitals in low- and middle-income countries, managing adult and paediatric patients with acute respiratory infection, including severe pneumonia, acute respiratory distress syndrome, sepsis and septic shock. The main objective is to provide some of the necessary tools that can be used to care for the critically ill patient from hospital entry to hospital discharge.
https://www.who.int/publications/i/item/clinical-care-of-severe-acute-respiratory-infections-tool-kit



IMAI District clinician manual: hospital care for adolescents and adults. Guidelines for the management of common illnesses with limited resources (2011)
The manual is written for clinicians working at the district hospital (first-level referral care) who diagnose and manage sick adolescents and adults in resource-constrained settings. It aims to support clinical reasoning, and to provide an effective clinical approach and protocols for the management of common and serious or potentially life-threatening conditions at district hospitals. The target audience includes doctors, clinical officers, health officers and senior nurse practitioners. It has been designed to be applicable in both high and low HIV prevalence settings.
https://www.who.int/hiv/pub/imai/imai2011/en/

WHO-ICRC Basic emergency care: approach to the acutely ill and injured (2018)
Developed by WHO and ICRC, in collaboration with the International Federation for Emergency Medicine, *Basic emergency care (BEC): approach to the acutely ill and injured* is an open-access training course for frontline health care providers who manage acute illness and injury with limited resources. The BEC package includes a Participant Workbook and electronic slide decks for each module. Integrating the guidance from WHO Emergency Triage, Assessment and Treatment (ETAT) for children and the Integrated Management of Adult/Adolescent Illness (IMAI), BEC teaches a systematic approach to the initial assessment and management of time-sensitive conditions where early intervention saves lives.
https://www.who.int/publications/i/item/basic-emergency-care-approach-to-the-acutely-ill-and-injured



Pocket book of hospital care for children: guidelines for the management of common childhood illnesses (second edition) (2013)
For use by doctors, nurses, and other health workers caring for children at first-level referral hospitals with basic laboratory facilities and essential medicines. These guidelines focus on the management of the major causes of childhood mortality in most developing countries, including pneumonia, and also cover common procedures, patient monitoring, and supportive care on the wards.
https://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/

Oxygen therapy for children (2016)
A bedside manual for health workers to guide the provision of oxygen therapy for children. The manual focuses on the availability and clinical use of oxygen therapy in children in health facilities to guide health workers, biomedical engineers and administrators. It addresses detection of hypoxaemia, use of pulse oximetry, clinical use of oxygen, delivery systems, and monitoring of patients on oxygen therapy. The manual also addresses the practical use of pulse oximetry, and oxygen concentrators and cylinders.
http://www.who.int/maternal_child_adolescent/documents/child-oxygen-therapy/en/

Technical specifications for oxygen concentrators (2015) Provides an overview of oxygen concentrators and technical specifications to aid in selection, procurement, and quality assurance. It highlights the minimum performance requirements and technical characteristics for oxygen concentrators and related equipment that are suitable for the use in health facilities.
https://www.who.int/medical_devices/publications/tech_specs_oxygen-concentrators/en/

WHO-UNICEF technical specifications and guidance for oxygen therapy devices (2019)
The purpose of this document is to increase access to quality products to ensure the supply of oxygen, especially in low- and middle-income countries and low-resource settings within countries from all income groups. It aims to support ministries of health to ensure that oxygen supply is available, as well as to raise awareness of the importance of appropriate selection, procurement, maintenance, and use of medical devices, both capital equipment and single-use devices.
https://www.who.int/medical_devices/publications/tech_specs_oxygen_therapy_devices/en/

Healthcare Workers
Testing
Vaccination
Clinical Care
Test Clinical Tips
Patient Care Guidance
Therapeutic Options
Ending Home Isolation
Duration of Isolation and Precautions for Adults
Care for Patients at Home
Discharging COVID-19 Patients
Providing Family Planning Services
Care for Pregnant Women
Care for Breastfeeding People
Care for Newborns
Care for Children
Telephone Nursing Guide
Late Sequelae of COVID-19
Infection Control
First Responders
Exposure in Healthcare Settings
Optimizing PPE Supplies
Crisis Planning & Operations
Non-Hospital Settings
FAQs
Get Healthcare Settings Updates
Guidance for COVID-19
Communication Resources
What's New

Get Email Updates

To receive email updates about COVID-19, enter your email address below.

Email Address

What's this? | Submit

The current website is optimized for the latest versions of Chrome, Edge, Firefox, and Safari.

Interim Guidance on Duration of Isolation and Precautions for Adults with COVID-19

Last Updated July 22, 2021

Summary of Recent Changes

Updates as of February 13, 2021

As of February 13, 2021

- Added recommendations for duration of isolation and precautions for severely immunocompromised adults.
- Added information on recent reports of variants of concern in the United States.

Assuming evidence supports ending isolation and precautions for adults with any disease severity 10 days after symptom onset, CDC is considering updating its recommendations to state that fever should resolve and symptoms recommended to present transitional or mild (i.e. not severe, like shortness of breath, prolonged isolation and unnecessary use of laboratory testing. Recommendations for ending isolation and precautions should be date and not a calendar date, to avoid confusion.

CDC recommends that all people, regardless of symptoms and regardless of whether or not they have been tested for recent COVID-19 in the past, continue to use all recommended prevention strategies (i.e., wear masks, stay at least 6 feet away from others, avoid crowds, and wash hands frequently).

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- Key Findings
- Duration of Isolation and Precautions
- Recommendations
- Assessment
- References

Summary of Key Findings

1. Considerations of SARS-CoV-2 RNA in upper respiratory specimens decline after onset of symptoms.[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,612,613,614,615,616,617,618,619,620,621,622,623,624,625,626,627,628,629,630,631,632,633,634,635,636,637,638,639,640,641,642,643,644,645,646,647,648,649,650,651,652,653,654,655,656,657,658,659,660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677,678,679,680,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,720,721,722,723,724,725,726,727,728,729,730,731,732,733,734,735,736,737,738,739,740,741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,760,761,762,763,764,765,766,767,768,769,770,771,772,773,774,775,776,777,778,779,780,781,782,783,784,785,786,787,788,789,790,791,792,793,794,795,796,797,798,799,800,801,802,803,804,805,806,807,808,809,810,811,812,813,814,815,816,817,818,819,820,821,822,823,824,825,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840,841,842,843,844,845,846,847,848,849,850,851,852,853,854,855,856,857,858,859,860,861,862,863,864,865,866,867,868,869,870,871,872,873,874,875,876,877,878,879,880,881,882,883,884,885,886,887,888,889,890,891,892,893,894,895,896,897,898,899,900,901,902,903,904,905,906,907,908,909,910,911,912,913,914,915,916,917,918,919,920,921,922,923,924,925,926,927,928,929,930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,946,947,948,949,950,951,952,953,954,955,956,957,958,959,960,961,962,963,964,965,966,967,968,969,970,971,972,973,974,975,976,977,978,979,980,981,982,983,984,985,986,987,988,989,990,991,992,993,994,995,996,997,998,999,1000,1001,1002,1003,1004,1005,1006,1007,1008,1009,1010,1011,1012,1013,1014,1015,1016,1017,1018,1019,1020,1021,1022,1023,1024,1025,1026,1027,1028,1029,1030,1031,1032,1033,1034,1035,1036,1037,1038,1039,1040,1041,1042,1043,1044,1045,1046,1047,1048,1049,1050,1051,1052,1053,1054,1055,1056,1057,1058,1059,1060,1061,1062,1063,1064,1065,1066,1067,1068,1069,1070,1071,1072,1073,1074,1075,1076,1077,1078,1079,1080,1081,1082,1083,1084,1085,1086,1087,1088,1089,1090,1091,1092,1093,1094,1095,1096,1097,1098,1099,1100,1101,1102,1103,1104,1105,1106,1107,1108,1109,1110,1111,1112,1113,1114,1115,1116,1117,1118,1119,1120,1121,1122,1123,1124,1125,1126,1127,1128,1129,1130,1131,1132,1133,1134,1135,1136,1137,1138,1139,1140,1141,1142,1143,1144,1145,1146,1147,1148,1149,1150,1151,1152,1153,1154,1155,1156,1157,1158,1159,1160,1161,1162,1163,1164,1165,1166,1167,1168,1169,1170,1171,1172,1173,1174,1175,1176,1177,1178,1179,1180,1181,1182,1183,1184,1185,1186,1187,1188,1189,1190,1191,1192,1193,1194,1195,1196,1197,1198,1199,1200,1201,1202,1203,1204,1205,1206,1207,1208,1209,1210,1211,1212,1213,1214,1215,1216,1217,1218,1219,12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Ministry of Health

COVID-19 Quick Reference Public Health Guidance on Testing and Clearance

This information can be used to help guide decision making on testing and clearance of contacts of cases or individuals suspected or confirmed to have COVID-19. This information is current as of March 5, 2021 and may be updated as the situation on COVID-19 continues to evolve. At this time, there are no changes to the routine management of COVID-19 cases or contacts based on their vaccination history. This will be re-evaluated and updated as further information is available.

Who should be tested for COVID-19?

Please refer to the COVID-19 Provincial Testing Guidance Update.

Diagnosing COVID-19

Please refer to the current Ontario Case Definition for information on confirmed, probable and reinfection cases.

Please refer to Public Health Ontario Test Information Sheets on:

- COVID-19 – PCR
- COVID-19 – Serology
- COVID-19 – Variant of Concern (VoC) Surveillance

For details on the assessment of laboratory results in the context of the clinical and epidemiological context of an individual, please refer to the Management of Cases and Contacts of COVID-19 in Ontario.

Point-of-care (POC) testing refers to testing that employs a COVID-19 medical device authorized by the Minister of Health (Canada) for point-of-care use and is also often referred to as 'rapid testing'. Some point-of-care testing (POCT) assays, both molecular and antigen tests, are now approved by Health Canada. All antigen POCT results that are preliminary positives require parallel or confirmatory testing at a licensed laboratory. All POCT preliminary positives and final positives from antigen and molecular tests must be reported to the local public health unit according to the *Health Protection and Promotion Act* (HPPA) and are actionable for initiating clinical and public health management (see Appendix 9: Management of Individuals with Point of Care Results). However, the confirmatory laboratory test result should be used to direct final clinical and public health management. False negatives may be more likely with POCT assays than laboratory-based assays. Depending on the clinical context of testing, final positive and negative POCT results may still require parallel/repeat testing using a laboratory-based NAAT to guide case and public health management (see Appendix 9: Management of Individuals with Point of Care Results for more details).

Asymptomatic testing for COVID-19

- An asymptomatic individual who has been advised by local public health to get tested due to exposure to a case or as part of an outbreak investigation should be tested within 14 days from their last exposure.
    - If the contact has their negative specimen collected on day 0 to day 6 of their quarantine period, they should repeat specimen collection on or after day 10 of their 14 day quarantine period. If the contact has their negative specimen collected on day 7 to day 14, then repeat testing is not recommended.
    - Contacts must remain in quarantine for the full 14 days from last exposure, regardless of negative test results.
    - Re-testing should be conducted if the asymptomatic individual who initially tested negative develops symptoms consistent with COVID-19.

Reinfection

- Re-testing after clearance should be based on clinical indications for testing (e.g., in the context of new symptoms compatible with COVID-19), or as directed in the context of new high-risk exposures or outbreak investigations.
- An asymptomatic individual that **previously had laboratory-confirmed COVID-19 AND was cleared**, should generally **not be re-tested** for asymptomatic surveillance purposes due to persistent shedding.
- Previously cleared individuals should continue to follow public health guidance for COVID-19 prevention, including self-isolating after new high risk exposures to unrelated cases.

- If there is uncertainty as to whether a new positive after clearance represents a potential new infection or persistent shedding, repeat testing as soon as possible.
- For confirmation of reinfection, please follow the **Ontario Case Definition**.

Criteria for when to discharge someone with probable or confirmed COVID-19 from isolation

- For each scenario, isolation after symptom onset should be for the duration specified **provided that the individual is afebrile (without the use of fever-reducing medications), and symptoms are improving for at least 24 hours**. Absence of cough is not required for those known to have chronic cough or who are experiencing reactive airways post-infection.
- If an individual has tested positive but has never had symptoms, isolation recommendations should be **based on date of specimen collection**.
- If an asymptomatic individual has tested positive AND has a prior history of symptoms compatible with COVID-19, clearance should still be based on specimen collection date. At the discretion of the local public health unit, the period of communicability and clearance may be based on symptom onset date depending on timing of symptoms (e.g., recent symptoms) and likelihood that symptoms were due to COVID-19 (e.g., known exposure to a confirmed COVID-19 case prior to symptom onset).
- After an individual completes their isolation period, they should continue to practice physical distancing measures and use of masking for source control as recommended for everyone at this time.

Approaches to Clearing Cases (including cases with variants of concern)

Approach	When to Use	Instructions
Non-Test Based Waiting **10 days** from symptom onset (or 10 days from specimen collection date if persistently asymptomatic)	Mild to moderate illness AND no severe immune compromise	Can discontinue isolation after **10 days from symptom onset** (or 10 days from positive test collection date if never had symptoms), provided that the individual is afebrile (without the use of fever-reducing medications) and symptoms are improving for at least 24 hours. Absence of cough is not required for those known to have chronic cough or who are experiencing reactive airways post-infection. Mild to moderate illness includes the majority of cases of COVID-19, and includes all those who do not meet the definition of severe illness or severe immune compromise (below).
Non-Test Based Waiting **20 days** from symptom onset (or 20 days from specimen collection date if asymptomatic and severe immune compromise)	Severe illness (requiring ICU level of care) **OR** severe immune compromise	Can discontinue isolation **20 days from symptom onset** (or 20 days from positive test collection date if asymptomatic and severe immune compromise), provided that the individual is afebrile (without the use of fever-reducing medications) and symptoms are improving for at least 24 hours. Absence of cough is not required for those known to have chronic cough or who are experiencing reactive airways post-infection. Studies informing this approach did not have a consistent definition of severe illness or severe immune compromise. For the purposes of a clearance assessment: • **Severe illness** is defined as requiring ICU level of care for COVID-19 illness (e.g., respiratory dysfunction, hypoxia, shock and/or multi-system organ dysfunction). • Examples of **severe immune compromise** include cancer chemotherapy, untreated HIV infection with CD4 T lymphocyte count <200, combined primary immunodeficiency disorder, taking prednisone >20 mg/day (or equivalent) for more than 14 days and taking other immune suppressive medications. • Factors such as advanced age, diabetes, and end-stage renal disease are generally not considered severe immune compromise impacting non-test based clearance.

Approach	When to Use	Instructions
Test Based Two consecutive negative specimens tested by a NAAT, collected at least 24 hours apart	Not routinely recommended, but may be used at the discretion of a hospital to discontinue precautions for admitted patients	Continue isolation until **2 consecutive negative specimens tested by a NAAT and collected at least 24 hours apart**. • Testing for clearance may begin after the individual has become afebrile and symptoms are improving for at least 24 hours. Absence of cough is not required for those known to have chronic cough or who are experiencing reactive airways post-infection. • If swab remains positive, test again in approximately 3-4 days. If swab is negative, re-test in 1-2 days (and at least 24 hours apart). • Tick the box labelled 'Other' and clearly write 'For clearance of disease' on the PHO Laboratory COVID-19 Test Requisition, or clearly write this on the requisition if submitting to another laboratory. • Serological testing cannot be used for test based clearance. • Test based clearance should not be used in an attempt to reduce the length of isolation.

Recommendations for Health Care Workers Return to Work

- Health care workers (HCWs) should follow **isolation and clearance with a non-test based approach;** if they have required hospitalization during the course of their illness, a test based approach may be used at the discretion of the hospital while they are admitted (see above). Some HCWs may be directed to have test based clearance by their employer/Occupational Health and Safety.
- Symptomatic HCWs awaiting testing results must be off work
- Asymptomatic HCWs awaiting testing results may continue to work using the appropriate precautions recommended by the facility, which will depend on the reason for testing (i.e., asymptomatic HCW is not on self-isolation following a high-risk exposure)
- Asymptomatic HCWs exposed to a symptomatic household member should isolate until the symptomatic individual has received a negative COVID-19 test result or an alternative diagnosis from their healthcare provider. If testing is not conducted then the HCW should self-isolate for 14 days from last exposure.

In **exceptional circumstances** where clinical care would be severely compromised without additional staffing, an earlier return to work under work self-isolation may be considered for an asymptomatic HCW who is self-isolating due to a high-risk exposure.

In **exceptionally rare circumstances** where clinical care would be severely compromised without additional staffing, an earlier return to work of an asymptomatic COVID-19 positive HCW that has not been cleared may be considered under work self-isolation recognizing the HCW may still be infectious (see table below). Any COVID-19 positive worker who is, in an exceptionally rare circumstance, being allowed to return to work earlier than would otherwise be the case must not pose a risk to other workers or patients.

Work self-isolation means maintaining self-isolation measures outside of work for 14 days from their last exposure (for contacts with high-risk exposures); or 10 days from symptom onset (or 10 days from positive specimen collection date if consistently asymptomatic) for cases. While at work, the HCW must adhere to universal masking recommendations, maintain physical distancing (remaining greater than 2m/6 ft from others) except when providing direct care, and perform meticulous hand hygiene. These measures at work are required to continue until non-test based clearance (or test based clearance if required by employer/Occupational Health and Safety). The COVID-19 positive HCW should ideally be cohorted to provide care for COVID-19 positive patients/residents if possible. The HCW on work self-isolation should not work in multiple locations.

Work Self-Isolation Guidelines

Symptoms at/around time of testing	Test Result	Instructions
Yes	Positive	• Work self-isolation could start after a minimum of 72 hours after illness resolving, defined as resolution of fever (without the use of fever-reducing medications) and improvement in respiratory and other symptoms
Yes	Negative	• May return to work 24 hours after symptom resolution • If the HCW was self-isolating due to an exposure at the time of testing, return to work should be under work self-isolation until 14 days from last exposure
Never symptomatic at time of test	Positive	• If there has been a recent potential exposure (e.g., tested as part of an outbreak investigation or other close contact to a case), work self-isolation (i.e., return to work) could start after a minimum of 72 hours from the positive specimen collection date to ensure symptoms have not developed in that time, as the positive result may represent early identification of virus in the pre-symptomatic period • If there is a low pre-test probability (e.g., there has been no known recent potential exposures such as tested as part of surveillance and no other cases detected in the facility or on the unit/floor, depending on the facility size), see Public Health Management of Cases and Contacts of COVID-19 in Ontario for repeat testing guidance. If follow-up testing is negative, the HCW is cleared and can return to work as per usual.

Recommendations for Return to Work in Non-Health Care Settings

- Return to work for workers who are confirmed or probable cases and work in non-health care settings requires clearance as outlined earlier in this document and in the Public Health Management of Cases and Contacts of COVID-19 in Ontario guidance.
- Workers are not required to provide proof of a negative test result (by NAAT) or a positive serological test result to their employers in order to return to work. It is expected that workers who have tested positive abide by public health direction and advice on when they would be considered clear to return to work.
- Return to work for workers who are self-isolating due to a high-risk exposure can occur after the end of their self-isolation period.
- Asymptomatic workers exposed to a symptomatic household member should isolate until the symptomatic individual has received a negative COVID-19 test result or an alternative diagnosis from their healthcare provider. If testing is not conducted then the worker should self-isolate for 14 days from last exposure.

Work Self-Isolation in Non-Health Care Settings

- Work self-isolation should NOT be considered for confirmed or probable COVID-19 cases in non-healthcare settings (including asymptomatic positive workers within their isolation period), for large workplace outbreaks, for large numbers of exposed workers in a given workplace, or for any worker linked to an outbreak where workers also live in a congregate living setting.
- There may be **exceptional circumstances** where the Public Health Unit may consider work self-isolation for workers who are in self-isolation from a high-risk exposure, excluding the scenarios outlined above. This should be done in consultation with the Ministry Emergency Operations Centre and Public Health Ontario.
- Work self-isolation is generally **not** recommended for any workers in non-healthcare settings due to the potential for contacts with high risk exposures to be infectious, and barriers to ensuring appropriate and consistent infection prevention and control measures to prevent transmission.
    - Considerations for exceptional circumstances could include:
        - health and safety, and ethics and equity, including whether the worker(s) serve a “critical” function, and promoting the well-being of and minimizing harm to the self-isolating worker, other workers and the community
        - minimizing risk related to transportation to and from work (e.g., no carpooling / ride-sharing or public transit use); the availability of alternatives to work-self isolation (e.g., work from home, alternate staff)
        - availability of in-house supports for training and monitoring of correct PPE use at the workplace

        - whether required IPAC measures can be implemented including whether there are barriers to measures such as: symptom screening, physical distancing, appropriate PPE use and masking for source control
    - To be in compliance with the Occupational Health and Safety Act, the employer must take into consideration the safety of all workers and take all steps reasonable in the circumstances to protect their workers.

Appendix 9: Management of Individuals with Point-of-Care Testing Results

Version 3.0 March 5, 2021

Key Updates

- Updated Table 1 & 2 (page 4-6)
- Updates to reflect changes to LSCCLA and HPPA for point-of-care testing (throughout)
- Minor updates to Public Health Management section (page 7-8)

Point-of-care testing (POCT) refers to testing that employs a COVID-19 medical device authorized by the Minister of Health (Canada) for point-of-care use and is also referred to as 'rapid testing'. Some POCT assays, both molecular and antigen tests, are now approved for use by Health Canada and available in Ontario. This Appendix to the Management of Cases and Contacts of COVID-19 in Ontario provides information on the public health management of SARS-CoV-2 results from POCT assays.

Notification to the Public Health Unit

- A positive result issued from an **antigen** POCT assay is considered a **preliminary positive result** and must be reported to the local public health unit (PHU), in accordance with the *Health Protection and Promotion Act*.
- Where a Health Canada approved **molecular POCT** assay has been reviewed and approved for final reporting by the Ministry of Health, results can be issued and reported to the local public health unit as **final.**
    - See Table 1 below for the specific clinical scenarios where a POCT final report can be issued. Molecular POCT assays currently being deployed by the Ministry of Health include: GeneXpert® Xpress SARS-CoV-2 and ID NOW™ COVID-19.
    - All positive molecular COVID-19 POCT results must be reported to the local PHU in which the person from whom the specimen was taken resides, in accordance with the *Health Protection and Promotion Act*.

    - Physicians and practitioners performing antigen or molecular COVID-19 POCT are required under section 25 of the *Health Protection and Promotion Act* to report positive COVID-19 test results, including a preliminary positive result from antigen POCT, as soon as possible after the positive test result is obtained.
    - Laboratory operators are required under section 29 of the *Health Protection and Promotion Act* to report positive COVID-19 test results as soon as possible after the positive test result is determined.
- Where possible, results from molecular COVID-19 POCT should be entered into the Ontario Laboratories Information System (OLIS) for reporting to the PHU through Case and Contact Management. If OLIS entry is not possible, individuals performing COVID-19 molecular POCT must report all positive results directly to the local PHU through an alternate secure manner (e.g., electronic fax).

Confirmatory Testing for POCT Assays

- Any positive **antigen** COVID-19 POCT result is considered preliminary, regardless of the setting it is obtained in, and requires additional testing such as parallel (i.e. dual swab collection at the same time as POC specimen collection) or repeat (i.e. subsequent swab collection following POC testing) testing using a laboratory-based nucleic acid amplification test (NAAT).
- Health Canada-approved molecular COVID-19 POCT for which positive results have been approved as final by the Ministry of Health do not necessarily require confirmatory testing, and are sufficient for classifying the case as 'confirmed'. However, additional testing may be recommended for further clinical/public health management of the case (see Table 1 below).
- **Additional testing using a laboratory-based NAAT is recommended in the following scenarios**:
    - **Negative** molecular POCT result in **high** pre-test probability settings. These include :
        - persons (symptomatic or asymptomatic) who are contacts of confirmed cases;
        - symptomatic persons tested when community prevalence is high (e.g. >10% of NAAT tests are SARS-CoV-2 positive);

        - symptomatic persons beyond the early phase of illness (e.g., beyond 7 days of symptom onset).
    - **Positive** molecular COVID-19 POCT result in symptomatic or asymptomatic persons in an **isolated or remote** community for which the positive molecular COVID-19 POCT result is the first recent positive case identified in the community.
    - All POCT done in the setting of an **outbreak**, including symptomatic or asymptomatic patients. Parallel collection should be performed in this scenario.
- For more guidance on interpretation of POCT results and when parallel or subsequent repeat testing is recommended, see the MOH's COVID-19 Quick Reference Public Health Guidance on Testing and Clearance and the COVID-19 Provincial Testing Guidance Update.

Case Classification

- Additional testing for confirmation through standard laboratory-based NAAT testing should be obtained for preliminary positive results from antigen COVID-19 POCT assays until further evaluation of their test performance.
- Final case status (Probable, Confirmed or Does Not Meet Case Definition) should be based on the confirmatory laboratory-based NAAT result, and the timing of that specimen relative to the initial specimen collection (see Table 1 below).

Table 1: Interpretation and Classification of Results from Molecular Point-of-Care Testing (POCT) Assays Approved for Final Reporting

Clinical/Exposure History	Final Molecular POCT Result*	Initial Case Classification	Confirmatory laboratory NAAT result	Final Case Classification
Symptomatic individual without known contact with a positive case (includes school-aged children with 1 or more symptoms)	Positive	Confirmed	Not required, but if collected and indeterminate	Confirmed case
			Not required, but if collected within 24 hours of POC test and is negative***	Does not meet case definition
	Negative	Does not meet case definition**	Not required, but if collected and is positive	Confirmed case
			Not required, but if collected and indeterminate	Probable case
			Not required, but if negative or invalid	Does not meet case definition
Any individual (symptomatic or asymptomatic) with known contact with a positive case	Positive	Confimed	Not required, but if collected and is positive, indeterminate, or invalid	Confirmed case
			Not required, but if collected within 24 hours of POC test and is negative***	Does not meet case definition
	Negative	N/A	Confirmatory testing is required, and if positive	Confirmed case
			Confirmatory testing is required, and if negative	N/A- Individual remains as a contact
			Confirmatory testing is required. If not performed or indeterminate, repeat confirmatory testing	N/A - Individual would remain as a contact until repeat test result is available

Clinical/Exposure History	Final Molecular POCT Result*	Initial Case Classification	Confirmatory laboratory NAAT result	Final Case Classification
Asymptomatic individual without known contact with a positive case	Positive	Probable	Confirmatory testing is required, and if positive	Confirmed case
			Confirmatory testing is required, if collected within 24 hours of POC test and is negative***	Does not meet case definition
			Confirmatory testing is required and is indeterminate or invalid	Probable case
	Negative	N/A	N/A	Does not meet case definition

* If POCT result is 'invalid', repeat testing as per manufacturer's direction

**Consideration should be given to clinical and/or exposure history, disease prevalence in the community, and the risk/vulnerability of the population to determine if confirmatory testing is warranted in these scenarios.

*** Confirmatory testing that is negative, and obtained >24 hours after a positive POCT specimen, may represent a true change in case status (positive to negative), or that the POCT positive result was a false positive. Interpretation and subsequent case management should be based on the context of the case, and their clinical and epidemiological situation.

Table 2: Interpretation and Classification of Results from Antigen Point-of-Care Testing (POCT)

Description	Antigen POCT Result*	Initial Case Classification	Confirmatory Laboratory NAAT Result**	Confirmatory specimen obtained ≤24 hours after specimen for preliminary result	Final Case Classification
Asymptomatic individual without known contact with a positive case (screening test)	Positive	Probable	Positive	Yes or No	Confirmed case
			Negative	Yes	Does not meet case definition
			Negative	No	Probable***
			Not performed or invalid	N/A	Probable
	Negative	Does not meet case definition	Not required or recommended, but if collected and test is negative	Yes or No	Does not meet case definition
			Not required or recommended, but if collected and test is positive	Yes or No	Confirmed case

* If POCT result is 'invalid', repeat testing as per manufacturer's direction

** If confirmatory test is 'indeterminate', follow public health case and contact management guidance on the management of indeterminate results.

*** Negative confirmatory laboratory-based specimens collected >24 hours after preliminary positive specimen should be interpreted in the context of the time between the initial preliminary positive and confirmatory specimen, and the pre-test probability of the individual based on their clinical and epidemiological context.

Public Health Management

- A **final positive** result from a Health Canada approved molecular COVID-19 POCT assay should be classified as a **confirmed case** of COVID-19 and PHUs should conduct case and contact management.
- A **positive result** on a serology POCT does not need to be reported to or actioned by the PHU.
- A **preliminary positive** result from a Health Canada approved antigen COVID-19 POCT assay should be considered a **probable case** of COVID-19 and PHUs should initiate case and contact management while awaiting confirmatory test results.
    - Probable cases should be advised that confirmatory testing is pending, and if confirmatory testing is negative, they may discontinue self-isolation as per the Quick Reference Guidance on Testing and Clearance.
    - Contacts of these probable cases should be advised that confirmatory testing is pending, and if confirmatory testing is negative, they may no longer be considered a contact and can discontinue self-isolation.
    - Preliminary positives should initiate outbreak assessment/management actions as appropriate to the case and context, and in a manner that they may be quickly discontinued if confirmatory testing is negative.
- If confirmatory testing is negative, from a specimen obtained ≤24 hours after the specimen was obtained for the preliminary positive result, PHUs should update the case classification from probable to '**Does not meet'** case definition and case and contact management can be discontinued.
- Confirmatory testing that is negative, and **obtained >24 hours** after a preliminary positive specimen, may represent a true change in case status (positive to negative), or that the preliminary positive was a false positive. Interpretation and subsequent case management should be based on the context of the case, and their clinical and epidemiological situation.
    - Individuals who were **symptomatic at/around the time of initial testing**
        - In general, continue management as a probable case as a change in case status (positive to negative) cannot be excluded,

including continuation of case isolation and contact self-isolation.

- Individuals who were tested as an **asymptomatic contact with high risk exposure** to a case AND remain asymptomatic:
    - If specimen collection was ≤24 hours of the initial preliminary positive, can discontinue public health management as a probable case, including contact self-isolation. However, the individual should continue to self-isolate based on their exposure to a case. Case classification should be updated to 'does not meet' case definition.
    - If specimen collection was >24 hours after initial preliminary positive, in general, case and contact management as a probable case should be continued as a change in case status cannot be ruled out. However, based on the clinical and epidemiological context of the case and their overall pre-test probability, case status could be updated to 'does not meet' case definition based on a negative confirmatory specimen collected >24 hours after the initial preliminary positive specimen.

Interim guidance on the use of the Abbott ID NOW™ instrument and COVID-19 assay

on behalf of the Canadian Public Health Laboratory Network and the Canadian Society of Clinical Chemists

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Introduction

This document, prepared October 26, 2020, provides interim guidance on the use of the Abbott ID NOW™ instrument and coronavirus disease 2019 (COVID-19) assay in the context of the Canadian public health system.

The Abbott ID NOW COVID-19 assay is an isothermal nucleic acid amplification technology intended for the qualitative detection of nucleic acid from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral ribonucleic acid (RNA) in direct nasal, nasopharyngeal or throat swabs from individuals who are suspected of COVID-19 by their healthcare provider. While already in widespread use globally, there are several reports of a reduced sensitivity associated with the test when compared with other laboratory-developed tests (LDTs) or commercially available nucleic acid amplification tests (NAAT) such as the Cepheid GeneXpert™ based assay (1). The use of a lower sensitivity test, even a real-time transcription polymerase chain reaction (RT-PCR) method, carries risks to decision-making that can only be offset by the magnitude of possible benefits. It must be understood that a significantly greater degree of diagnostic uncertainty will be introduced/remain with use of the Abbott ID NOW assay, relative to the conventional RT-PCR methods commonly used in Canada at the time of writing. These guidelines will be updated periodically as more information is available regarding test sensitivity in different settings (surveillance, screening, diagnosis) and in the overall context of infection with SARS-CoV-2.

Many of these guidelines may also be applied to other less sensitive molecular and rapid antigen-based tests that may be approved for use in the future.

Key messages

- Health Canada provided approval for use of the Abbott ID NOW COVID-19 assay (October 2020).
- The intended use for this assay as outlined by Health Canada is as follows:
  - The Abbott ID NOW COVID-19 assay performed on the Abbott ID NOW instrument is a rapid molecular *in vitro* diagnostic test utilizing an isothermal nucleic acid amplification technology intended for the qualitative detection of nucleic acid from the SARS-CoV-2 viral RNA in direct nasal, nasopharyngeal or throat swabs from individuals who are suspected of COVID-19 by their healthcare provider within **the first seven days** of the onset of symptoms.
  - Results are for the identification of SARS-CoV-2 RNA. The SARS-CoV-2 RNA is generally detectable in respiratory samples during the acute phase of infection. Positive results are indicative of the presence of SARS-CoV-2 RNA; clinical correlation with patient history and other diagnostic information is necessary to determine patient infection status. Positive results do not rule out bacterial infection or co-infection with other viruses.
  - Negative results should be treated as preliminary and, if inconsistent with clinical signs and symptoms or necessary for patient management, should be tested with different authorized or cleared molecular tests. Negative results do not preclude SARS-CoV-2 infection and should not be used as the sole basis for patient management decisions. Negative results should be considered in the context of a patient's recent exposures, history and the presence of clinical signs and

symptoms consistent with COVID-19.
    - The Abbott ID NOW COVID-19 test is intended for use by medical professionals or trained operators who are proficient in performing tests using the Abbott ID NOW instrument in laboratory and point-of-care (POC) settings.
- The performance of the assay should be verified in the field before recommending its use. This is critical since data obtained from pre-market evaluations cannot account for the variability in training and quality of sample collection that follows use in a broader population. Therefore, clinical performance must continue to be monitored.
- The "in-field" performance characteristics of the Abbott ID NOW is still under evaluation in Canada; however, data about the nature of the technology from other jurisdictions suggest that the tests have lower sensitivity but comparable specificity to other LDTs and commercial NAAT assays. Although, the rapid nature of the assays makes it suitable for POC applications, these performance characteristics, combined with the incidence of infection within the population being tested, must be considered when interpreting the results.
- In discussion with provincial and territorial laboratory directors, the use of this test must be carefully considered.
    - At this time, until further data is collected, because of the decreased sensitivity, all negatives should be considered preliminary negatives.
    - Owing to an expected higher rate of false negatives, it is recognized that reflexive laboratory-based testing of preliminary negatives from the Abbott ID NOW COVID-19 testing depending on its proposed use) will likely introduce an additional burden to reference laboratories already facing enormous testing volumes.
- This document outlines scenarios where the Abbott ID NOW COVID-19 testing may prove useful, should the expected performance characteristics be confirmed.

Current approach to severe acute respiratory syndrome coronavirus 2 testing in Canada

Since the emergence of SARS-CoV-2, testing has been a key pillar of Canada's response to the pandemic. The broad use of testing, as part of an array of public health measures, led to a flattening of the epidemic curve in the spring of 2020, demonstrating the value of testing as a part of the COVID-19 response. To date, testing has relied on molecular (i.e. RT-PCR) testing performed on a nasopharyngeal sample (NP) or alternate respiratory sample collected by a healthcare professional. **This testing method currently remains the gold standard for diagnosing SARS-CoV-2 infection in Canada.**

Considerations for the use of the Abbott ID NOW COVID-19 assay

It is critically important to understand the timing of specimen collection in relation to symptom onset since the sensitivity of the test is not expected to be uniform over the course of infection. Data suggest that viral shedding may begin 2–3 days before the symptoms peak—around the time of symptom onset—and then gradually declines over time thereafter (2,3).

During the first seven days of infection, viral loads are likely to be above the limit of detection for the Abbott ID NOW assay. Although the time of post-symptom onset still needs to be carefully considered. It is also important to understand test performance in relation to the time since a potential exposure when the test is being used for rapid contact tracing (e.g. how many days after exposure might one expect to have viral loads that can be optimally detected using the Abbott ID NOW?).

Notwithstanding the difference in the performance profile, other features of the Abbott ID NOW (including but not limited to; faster turnaround time, lower per-test cost, ability to do the test in a setting by non-professionals on a more frequent basis) suggest that it could have an important role to play in the next phase of the pandemic response.

It is important for public health, microbiology and infectious diseases experts to identify the scenarios where the use of the Abbott ID NOW may further strengthen the public health response by expanding access to testing beyond existing indications and increasing capacity for molecular detection of SARS-CoV-2. Furthermore, establishing mechanisms to allow a new POC test to report into the public health system efficiently is critical (see "Reporting of results and Quality Control" section below).

Balancing test sensitivity against other considerations

The intrinsic performance characteristics of the Abbott ID NOW are not the only factors determining its utility. **The final interpretation of a test must take into account the performance parameters, the prevalence of infection, predictive values and the intended use of the test result.** Therefore, the tolerance for sensitivity and specificity thresholds will vary based on the reason for testing and the expected action that would follow either a positive or a negative result.

In scenarios where critical decisions and actions rely on a test result (e.g. a symptomatic resident in a long-term care home, a patient in an intensive care unit [ICU] who requires immediate treatment), the recommended test would be the most accurate test. At the time of writing, the indicated (best) test would be RT-PCR performed on a NP sample or on a lower respiratory tract sample in patients with evidence of pneumonia. However, there may be circumstances where a rapid POC test can be permissible and enhance testing capacity to support the public health response, particularly when the demand for RT-PCR testing exceeds laboratory capacity or is otherwise unavailable or in situations where a symptomatic individual may otherwise be lost to follow-up.

Clinical situations where infection is prevalent in the community: When the prevalence of infection is high, and the access to RT-PCR testing is unavailable (i.e. northern, remote and isolated [NRI] communities) or when the results are delayed beyond 48 hours because testing demand is exceeding laboratory capacity issues, a POC test may provide an option that will positively impact public health or clinical management. Here the intended use is for early diagnosis of infection. In this situation, a positive result will allow for early implementation of public health measures and contact tracing or clinical management decision-making. Although there will be a need to further evaluate, preliminary data suggests that performance of the Abbott ID NOW in early infection (1–5 days post-symptom onset) may be similar to RT-PCR in terms of sensitivity and performance. However, negative results should be confirmed using conventional NAAT as soon as possible as clinical decisions cannot be made based solely on the Abbott ID NOW test because of the lowered negative predictive value associate with reduced test sensitivity.

Clinical situations where infection is not prevalent in the community and high sensitivity is not the main consideration: There may be alternative settings where a less sensitive test may be acceptable. Although the Abbott ID NOW is currently approved for testing symptomatic individuals within the first seven days of symptom onset, monitoring of asymptomatic individuals who are at risk of introducing infection into high risk settings (e.g. long-term care, correctional facilities) could be considered. Modelling data suggest that testing protocols that incorporate repeated and frequent re-testing of individuals could be effective (4). Here the intended use of a POC test is for monitoring infection in individuals that may not otherwise be able to be tested with the same frequency due to challenges with testing capacity. Due to the potential reduction in pre-test probability of a positive result, the test would need to be confirmed using a laboratory-based NAAT. The purpose of this requirement for confirmation is to reduce the potential for negative factors associated with a false positive test (unnecessary removal from work, stigma that may be associated with infection, etc.).

Proposed use scenarios

At this time, it is not possible to provide an exhaustive list of all cases where the Abbott ID NOW assay might be of benefit. Several scenarios are given as examples below, but are not meant to be proscriptive.

Scenario 1: Northern, remote and isolated settings

The NRI communities face additional barriers to timely test results due to transportation time required to deliver a specimen to a testing laboratory. Given the importance of accurately identifying new cases in NRI communities to prevent spread of SARS-CoV-2 in the face of limited healthcare resources, RT-PCR testing is the recommended test for these settings. While there have been extraordinary efforts to date to bring high quality POC PCR testing to NRI communities (e.g. Cepheid GeneXpert test), significant challenges remain. First and foremost is the ongoing short supply of the GeneXpert COVID-19 test cartridges. The availability of a relatively low complexity POC solution with an anticipated higher test allocation may be an attractive option as a screen-in test to conserve GeneXpert test cartridges for the testing of symptomatic individuals. In this two-test algorithm, if a sample is shown to be positive using the Abbott ID NOW assay, then appropriate actions can quickly be put in place, while negative results can be confirmed on the highly sensitive Cepheid GeneXpert or in a reference laboratory. This may also be useful in other settings where rapid, accurate results are required (e.g. staging for medical procedures in hospitals involving symptomatic patients). This may have additional benefit in allowing the prioritization of GeneXpert test cartridges for NRI communities.

Scenario 2: Early outbreak identification and investigation

While the use of a less sensitive test would not be recommended for the exclusive management of an outbreak, testing of symptomatic individuals and their direct contacts with the Abbott ID NOW assay can be useful for the early identification of possible outbreaks.

- Testing can be done as part of suspected outbreak identification and investigation where patients can be tested rapidly on site if faster preliminary results will help inform and expedite public health action (triage of patients and contact tracing). This may be particularly relevant in situations where a symptomatic individual may otherwise be lost to follow-up.
    - This would always be followed by confirmatory PCR testing, although this requirement could be revisited to determine if ongoing testing is needed.

Scenario 3: Asymptomatic testing in high risk settings

An additional broad category for use of the Abbott ID NOW includes situations that involve the prospective monitoring of asymptomatic individuals for introduction of SARS-CoV-2 into high risk settings. Note that such a proposed monitoring role for non-PCR testing technologies is referred to as "screening" in some other documents on COVID-19 testing strategies. At this time, the market authorization for the Abbott ID NOW from Health Canada—Medical Devices Bureau is focused on symptomatic testing in the early phase of disease, so the use of this test in a monitoring context will require clinical validation. The frequency of repeat testing is not yet defined (see below).

- Repeated testing of workers in congregated settings to prevent introduction or to minimize the chance of spread within a site, including:
  - Large processing plants
  - Long-term care facilities
  - Homeless shelters
  - Farm/migrant workers
  - Inmates in correctional facilities
- The Abbott ID NOW could be used for prospective testing of low-risk, asymptomatic visitors and staff entering congregated settings.
- Important additional considerations for the use of Abbott ID NOW include the following:
  - Testing would always need to be done in the context of PCR confirmatory testing of all positive cases
  - Reflexive PCR testing of preliminary negative cases needs to be carefully considered and is not being recommended at this time due to the significant impact it would have on current testing capacity in laboratories already facing enormous testing volumes
  - The frequency of repeat testing will need to be carefully examined to ensure the testing strategy can correctly identify individuals during a high viral period early in infection
  - The use of alternative specimen collection (rather than with oral or nasal swabs included with the Abbott ID NOW) may be more acceptable for collecting samples from asymptomatic individuals than NPs

These situations represent scenarios where frequent entries and exits multiply the potential introduction of the virus into high risk settings known to facilitate the rapid spread of infection. It is not yet possible to articulate the implementation approach that best supports the public health goals of testing (case identification, isolation contact tracing, etc.). It is clear that a false negative test can occur early in infection even with the most sensitive RT-PCR methods. As such, repeat testing may be necessary to detect infection in cases with high clinical suspicion of disease. The Abbott ID NOW assay may offer ease of use, the ability to conduct testing outside traditional laboratory settings and rapid time to results to enable frequent testing and offset the reduced sensitivity.

Approach to the potential use of the Abbott ID NOW assay

How the results from the Abbott ID NOW assay are interpreted and how it impacts public health and clinical management of patients need to be considered. To do this, it is critical that end users understand the prevalence of infection in the population they are testing. This necessitates a robust surveillance system that communicates regularly with the end users.

Positive result

Positive results should be considered "preliminary positive" until confirmed using a reference RT-PCR method. While the Abbott ID NOW assay is expected to have high specificity, false positives can be expected, particularly if the prevalence of infection in the population tested is low, thus decreasing the pre-test probability of the assay. All patients with a positive result will require isolation. If the confirmatory RT-PCR is negative, discontinuation of isolation can be considered depending on the clinical context that generated the initial test.

Negative result

In interpretation of a negative Abbott ID NOW result, the clinical context of the test (asymptomatic versus symptomatic) and the pre-test probability of infection must be considered. In patients where the pre-test probability of COVID-19 remains high (e.g. known contact, high community transmission), then the individual should undergo confirmatory testing using RT-PCR to direct further management. If the pre-test probability is low, then the individual can be monitored in the absence of isolation and reference testing.

Frequency of testing

As highlighted above, the Abbott ID NOW assay is ideally used in surveillance/screening programs where individuals get repeat tests to account for a lack in sensitivity. If the Abbott ID NOW is used in a monitoring approach, the ideal frequency of testing remains to be defined. The effectiveness of this strategy is dependent upon several associated factors, including the proportion of asymptomatic infections, the sensitivity of the assay and the time to results (assuming that self-isolation would occur once a positive test is identified).

Reporting of results and quality assurance

The use of the Abbott ID NOW will most likely occur outside of a laboratory environment. The current anticipated market authorizations are expected to require oversight of the testing

procedure by a trained healthcare professional, at least in the short term. It will be essential that a mechanism for reporting of results into the public health system and/or laboratory system be developed to ensure appropriate data capture and quality control, and to support public health action.

It is critical that quality assurance practices be considered when implementing POC testing, regardless of the perceived simplicity of the test. Where POC testing is implemented outside a hospital environment, sites are recommended to partner with local accredited laboratories for ongoing guidance and oversight. The laboratory director and partnering laboratories will guide sites to ensure important quality assurance practices are in-place.

Examples of quality assurance practices that must be considered:

- Training and ongoing authorization of staff who will perform POC testing
- Initial and ongoing reagent validation prior to clinical use
- Quality control practices for regular monitoring of test performance
- Proficiency testing to monitor overall testing practices at a site
- Troubleshooting issues with tests and/or devices
- Reporting of results

Critical scientific questions

The science continues to evolve daily as unprecedented global investment in research and development continues. Despite this, several critical questions remain to inform the use of new tests such as the Abbott ID NOW and sample types.

- How do these tests perform in "real life"?
  - Most submissions for approval have used simulated samples to evaluate the tests. This creates uncertainty about the true performance when applied to patients. There must be a verification of performance by comparing the real-life performance of intended use in the field compared with the traditional nucleic acid amplification methodology.
- How frequently is testing required to close the sensitivity gap?
  - This requires understanding of the dynamics of the test over time. It will be important to determine the frequency of testing to best mitigate the risk of cases being missed due to the lower sensitivity of the Abbott ID NOW.
  - At what threshold of community transmission is repeat testing in specific environments beneficial?
- How do lower sensitivity tests and lower sensitivity sample types interact?
  - If the NP swab is considered the gold standard, then what is the impact on sensitivity of using a less sensitive specimen for testing? How do the assays compare when an oral or nasal swab or alternative sample type such as a saline gargle is used?
  - If oral and/or nasal swabs are used as an alternative to the NP swab, the impact must be evaluated to inform potential for use.

Competing interests

None.

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How long are people with COVID-19 infectious?

Source: Emerging Sciences Group of the Public Health Agency of Canada. Emerging Evidence on COVID-19: Rapid Review of Infectious Period. September update. Full report available from: phac.emergingsciencesecretariat-secretariatdessciencesemergentes.aspc@canada.ca

Background: COVID-19 cases need to be isolated long enough to prevent further transmission but no longer than needed. Determining the infectious period of COVID-19 is complicated by four factors: 1) people can be diagnosed when they are symptomatic, pre-symptomatic or asymptomatic, 2) the common diagnostic test, RT-PCR, is accurate for diagnosis as it is able to detect viral genetic material, but it cannot document when someone is no longer infectious because it cannot distinguish whether viral particles are still infectious or not, 3) cell culture is the best way to confirm whether infectious virus is present, but it takes time and requires specialized laboratory facilities, and 4) although transmission is primarily respiratory, virus has been found in feces and eye secretions.

Methods: Twenty databases and key websites were searched for relevant reviews, peer-reviewed publications and preprints up to August 31, 2020. Keywords included: "Shedding", "Viral dynamics", "Viral clearance", "Viable", "Culture", "Infectivity", "SARS-CoV-2 detection", "Infectious Period", "Communicability period", "Recurrence", and "Re-positive". Data from studies were extracted into evidence tables on risk of infection, severity of disease and mortality and organized by asymptomatic, pre-symptomatic, symptomatic, recurrent or reinfection, as well as culture versus RT-PCR and sample source (e.g. respiratory, fecal, etc.).

Results: Over 1,000 citations were screened and relevant full texts were reviewed. There were some good quality prospective cohort studies, but the majority of publications were case reports and observational studies of contact tracing; many of these were preprints and are at high risk of bias. Due to their number and preliminary nature, not all case reports were summarized.

Symptomatic infectious period, N=107 studies

CULTURE (that measures viable virus): N=18 studies and two systematic reviews:

- Respiratory
  - Mild illness: Cultures from respiratory samples—taken from the time of self-reported symptom onset—have documented viral shedding for 8–10 days with a peak in viral load ranging from just before to during the first week after onset of illness.
  - Severe illness: Culture from respiratory samples have documented cases of prolonged viable viral shedding (18–32 days). These cases are typically individuals who are either immunocompromised or have multiple chronic underlying health conditions. These studies usually include single cases or small sample sizes and many are still in preprints.
  - Feces: SARS-CoV-2 has been cultured from the fecal/rectal samples of confirmed cases, however the length of viable virus shedding and whether it is a potential transmission route remains unclear.

RT-PCR (that measures viral RNA): N=88 studies and six systematic reviews:

- Nasopharyngeal swabs: Most studies show RT-PCR tests become negative within 14–20 days of self-reported symptom onset.
  - Prolonged viral RNA shedding (up to 83 days) have been reported. Multiple studies have found this is positively associated with severity of COVID-19 and older age. Once these cases have clinically recovered, cultures have not detected viable virus and there has been no evidence of transmission.
- Stool samples: Stool samples can remain positive a few days to four weeks longer than respiratory samples.
- Eye swabs: SARS-CoV-2 RNA has been identified in the eye up to 22 days post onset of self-reported symptoms.

Pre-symptomatic infectious period, N=25 studies

- CULTURE: Viable virus has been cultured from respiratory samples 1–6 days prior to symptom onset and from the rectum as early as three days before symptom onset.
- RT-PCR has detected COVID-19 virus RNA from respiratory samples 1–7 days (2.5 days on average) before symptom onset.

Asymptomatic infectious period, N=25 studies

- CULTURE and RT-PCR: Viable virus and viral RNA was highest during the first week of infection and declined in subsequent weeks. Based on the current evidence, the total infectious period of asymptomatic cases appears to be similar to, or shorter than, mildly symptomatic cases; viral loads have been similar.

Recurrent viral shedding in convalescent period, N=55 studies

- CULTURE and RT-PCR: Only one culture study found viable virus in a recurrent case. Multiple case reports and observational RT-PCR studies have detected recurrent viral RNA shedding in people who were asymptomatic in the convalescent period, typically within seven days of two consecutive negative RT-PCR results. Following recurrence, patients remained viral RNA positive for approximately 1–8 days, but no evidence of transmission was reported.

Reinfection, N=2 studies

- Two studies have been published with compelling evidence that reinfection can occur. In both cases genetic analysis confirmed the virus from the first and second infection were different. This appears to be rare.

Conclusion: Across studies, similar viral loads have been reported for asymptomatic, pre-symptomatic, and symptomatic cases. Mild cases are typically no longer infectious 10 days after diagnosis. More severe cases are generally infectious for at least 20 days; when these cases are no longer infectious can only be confirmed by viral culture.

Cell-based culture of SARS-CoV-2 informs infectivity and safe de-isolation assessments during COVID-19

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Summary: Isolation of SARS-CoV-2 in cell-based culture may be used as a surrogate marker for infectivity and inform de-isolation protocols in the management of COVID-19, particularly in persons where SARS-CoV-2 RNA is persistently detected by nucleic acid testing despite clinical recovery.

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ABSTRACT

Background

The detection of SARS-CoV-2 RNA by real-time polymerase chain reaction (PCR) in respiratory samples collected from persons recovered from COVID-19 does not necessarily indicate shedding of infective virions. By contrast, the isolation of SARS-CoV-2 using cell-based culture likely indicates infectivity, but there are limited data on the correlation between SARS-CoV-2 culture and PCR.

Methods

One hundred and ninety-five patients with varying severity of COVID-19 were tested (outpatients [n=178]), inpatients [n=12] and critically unwell patients admitted to the intensive care unit [ICU; n=5]). SARS-CoV-2 PCR positive samples were cultured in Vero C1008 cells and inspected daily for cytopathic effect (CPE). SARS-CoV-2-induced CPE was confirmed by PCR of culture supernatant. Where no CPE was observed, PCR was performed on day four to confirm absence of virus replication. Cycle threshold (Ct) of the day four PCR ($Ct_{culture}$) and the PCR of the original clinical sample (Ct_{sample}) were compared, and positive cultures were defined where Ct_{sample} - $Ct_{culture}$ was $\geq$3.

Findings

Of 234 samples collected, 228 (97%) were from the upper respiratory tract. SARS-CoV-2 was only successfully isolated from samples with Ct_{sample} $\leq$32, including in 28/181 (15%), 19/42 (45%) and 9/11 samples (82%) collected from outpatients, inpatients, and ICU patients, respectively. The mean duration from symptom onset to culture positivity was 4.5 days (range 0-18). SARS-CoV-2 was significantly more likely to be isolated from samples collected from inpatients (p<0·001) and ICU patients (p<0·0001) compared with outpatients respectively, and in samples with lower Ct_{sample}.

Conclusion

SARS-CoV-2 culture may be used as a surrogate marker for infectivity and inform de-isolation protocols.

Keywords: COVID-19; SARS-CoV-2; viral culture; infection control; de-isolation

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Introduction

In late December 2019, a cluster of pneumonia cases of unknown etiology were reported in Hubei Province, China [1]. The causative agent, a novel betacoronavirus, now known as SARS-CoV-2, was isolated on January 7, 2020 [2] and the genetic sequence January 10, 2020 enabling the rapid development of diagnostic assays for COVID-19 (the disease caused by SARS-CoV-2) to be available within a month of the outbreak's notification to the World Health Organization (WHO) [3]. Effective control of SARS-CoV-2 transmission requires widespread testing, isolation, contact tracing of infected persons and other non-pharmaceutical interventions [4], particularly in the absence of effective SARS-CoV-2-specific antivirals and vaccines. Nucleic acid testing such as real-time reverse transcriptase polymerase chain reaction (PCR) is the predominant diagnostic method to confirm infection, however, the detection of SARS-CoV-2 RNA may not always indicate the presence or shedding of viable virus with replicative capacity and, by implication, transmissibility [5]. The diagnostic value of culture in the routine management of COVID-19 is limited by requirements of isolation to be performed under physical containment laboratory level 3 (PC3) biosafety conditions [6], technical expertise, turnaround times (TATs), and costs. However, the ability to culture SARS-CoV-2 has important roles in providing adequate positive control material for the development, validation, evaluation and quality assurance of SARS-CoV-2 diagnostic assays; supporting the development of vaccines and therapeutic agents, and enabling research into viral virulence and transmission.

Despite clinical recovery, there are a proportion of patients where SARS-CoV-2 RNA remains detectable for many days to weeks [5]. The relationship between persistent PCR positivity and virus viability is important in understanding the natural history and pathogenesis of SARS-CoV-2 infection, and whether truly persistent infection occurs. This has significant implications for the release of infected persons from quarantine, particularly for those who reside in high-risk settings such as aged care, mental health and correctional facilities, or work with at-risk population groups such as

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healthcare workers (HCWs). Persistent SARS-CoV-2 RNA detection also has implications for patient isolation and bed management, the safe use of non-invasive ventilation and ongoing requirements for appropriate use of personal protective equipment for HCWs when caring for such patients.

We investigated the correlation between SARS-CoV-2 culture and PCR results from respiratory tract samples collected from persons with COVID-19 to guide the safe de-isolation of those with persistently positive PCRs.

Methods

SARS-CoV-2 PCR and cell culture results of respiratory tract samples received between March 1 and April 22, 2020 were analysed. Samples were inoculated into cell culture as part of (i) routine laboratory protocol at the start of the epidemic; (ii) if collected from patients admitted to the ICU and (iii) if requested by attending physicians (usually due to persistent PCR positivity in an individual awaiting release from quarantine) or public health physicians as part of outbreak investigations.

Sample types

Samples were collected from the upper respiratory tract (URT; nasopharyngeal swabs and combined nose and throat swabs) and lower respiratory tract (LRT; sputum, endotracheal aspirate, non-bronchoscopic bronchoalveolar lavage). URT swabs were received in 1-3 mL of viral or universal transport media (UTM), Amies transport media, or dry; stored at +4°C and tested within 12 hours of specimen receipt.

SARS-CoV-2 nucleic acid detection

RNA was extracted from 200µL of respiratory tract samples using the MagNA Pure 96 instrument's Viral NA Small Volume Kit (Roche Diagnostics GmbH, Mannheim, Germany) following the "Pathogen Universal Protocol" (elution volume, 100µL) according to the manufacturers' instructions. SARS-CoV-2 nucleic acid amplification and detection were performed using the LightCycler® 480 II System

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(Roche Diagnostics, Rotkreuz, Switzerland). The primers and probes, mastermix composition and cycling conditions used are outlined in (Table 2, Supplementary). Each PCR assay included a negative (RNAse-free water), positive (10^{-3} dilution of a SARS-CoV-2-positive cell culture supernatant) and internal control (human beta-globin gene). Cycle threshold (Ct) of positive samples were recorded.

SARS-CoV-2 gene targets included E, RdRp, N, M, and ORF1ab for samples from ICU patients; and between one and four of E, RdRp, N and ORF1ab for all other samples. Global shortages of reagents and consumables influenced the targets tested. The total number of samples tested per target were: one (n=24), two (n=115), three (n=22), four (n=62) and five targets (n=11).

SARS-CoV-2 culture of respiratory tract samples

Samples with detectable SARS-CoV-2 RNA were inoculated into cell culture under PC3 conditions [4] on the same day or stored at +4°C for inoculation the following day. Vero C1008 (Vero 76, clone E6, Vero E6 [ECACC 85020206]) cells were seeded at 1-3 x 10^4 cells/cm^2 with Dulbecco's minimal essential medium (DMEM; LONZA, Alpharetta, GA, USA) supplemented with 9% foetal bovine serum (FBS; HyClone™, Cytiva, Sydney, Australia) in 25cm^2 cell culture flasks or Costar® 24-well clear TC-treated multiple well plates (Corning®, Corning, NY, USA). The medium was changed within 12 hours for DMEM containing 1% FBS with the addition of penicillin, streptomycin and amphotericin B deoxycholate to prevent microbial overgrowth and then inoculated with 500µL (cell culture flasks) or 200µL (24-well plates) of clinical sample. Plates were sealed with AeraSeal™ Film (Excel Scientific, Inc., Victorville, CA, USA) to minimize evaporation, spillage, and well-to-well cross-contamination. Inoculated cultures were incubated at 37^0C in 5% CO_2 for 5 days (day 0 to 4) and observed daily for CPE, 200µL of viral culture supernatant was collected on days 1, 2, 3 and 4 for the ICU cohort and on day 4 for all other samples.

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Where CPE was observed (generally within 2-3 days post-inoculation), SARS-CoV-2 replication was confirmed by PCR. Terminal sampling and PCR testing of culture supernatant was performed on day 4 as CPE may not be observed despite active viral replication, as seen with SARS-CoV [7]. Day 4 was chosen for terminal sampling as this was the optimal time for reading the endpoint as determined by the 50% tissue culture infective dose ($TCID_{50}$) assay below. Additionally, with no medium change and using a concentration of amphotericin B (2.5µg/mL), cell monolayer breakdown was observed from day 5 onwards in some cultures.

SARS-CoV-2 nucleic acid detection in cell culture supernatant

SARS-CoV-2 RNA was extracted from 200µL of culture supernatant using the EZ1 Advanced XL platform and EZ1 Virus Mini Kit v2.0 (Qiagen, Valencia, CA, USA) according to the manufacturers' instructions. SARS-CoV-2 PCR was then performed as above.

Determination of $TCID_{50}$

A primary isolate, SARS-CoV-2/01/Human/NSW Australia|EPI_ISL_407893|2020-01-24 (GISAID), was titrated in serial one log dilutions (from 10^{-1} to 10^{-8}) to obtain a $TCID_{50}$ using 24-well culture plates of Vero C1008 cells. The plates were observed daily for CPE using an inverted optical microscope for five days, and wells were considered positive if any characteristic altered cell foci were seen (Figure 4, Supplementary). The end-point titres were calculated according to the Reed and Muench method [8] based on four replicates for titration, and the infectious virus titre of our SARS-CoV-2 stock was 1 x $10^{6.5}$ infectious particles per 200µL (Figure 1).

Determination of virus replication and Ct cut-off for virus viability in cell culture supernatant

To clarify the significance of the Ct of culture supernatant in the absence of CPE, a dilutional series of virus stock was run (as per $TCID_{50}$) and SARS-CoV-2 RNA detection by PCR targeting six genes (E, RdRp, M, N, ORF1ab and ORF1b) at each dilution was performed (Figure 1). This allowed the limit of detection (LoD) of viral culture $TCID_{50}$ to be compared to the LoD of the various PCR gene targets

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and demonstrated that the highest Ct reflective of non-viable virus was 37·29 with the ORF1b gene target. Using the same targets, the dilution series indicated a change in 1 log dilution of virus concentration correlated with a change in Ct of approximately ±3. This was also confirmed when testing synthetic plasmids using real-time quantitative PCR assays demonstrated that a 1 log difference in viral load corresponded to a change in Ct of 3·44 ± 0.16. Furthermore, a Ct of 34 and 37 correlated with viral loads of approximately 100 copies/mL and 10 copies/mL, respectively, a difference of 1 log (data not shown).

Positive viral cultures were defined as (i) CPE visualized and SARS-CoV-2 RNA detected from culture supernatant, or (ii) no CPE visualized but a decrease between the Ct of the original sample (Ct_{sample}) and day 4's terminal culture supernatant ($Ct_{culture}$) of ≥3 (equivalent to a 1 log increase in virus quantity), i.e. Ct_{sample} - $Ct_{culture}$ ≥3 = culture positive. Conversely, negative viral cultures were defined as (i) CPE not visualised, and no SARS-CoV-2 RNA detected from the culture supernatant, or (ii) no CPE visualized in culture and Ct_{sample} - $Ct_{culture}$ <3. Where SARS-CoV-2 RNA was detected in terminal sampling, we surmise that Ct_{sample} - $Ct_{culture}$ <3 was due to residual inoculated clinical sample and not replicating virus. This is supported by the initial rise in $Ct_{culture}$ on day 1 compared to Ct_{sample} on day 0 (Figure 2). In addition, no viral replication was identified with blind passaging of the first 20 cultures without CPE and Ct_{sample} - $Ct_{culture}$ <3, indicating the absence of viable virus. By contrast, SARS-CoV-2 replication was demonstrated by CPE and detectable RNA in subsequent passaging of samples without initial CPE but where Ct_{sample} - $Ct_{culture}$ was ≥3.

Statistical analyses

Welch's t-test, two-tailed hypothesis with 95% confidence intervals (95% CI) was used to compare the mean Ct of URT and LRT samples (Figure 6, Supplementary) of culture positive (with or without CPE) and culture negative samples (Figure 5, Supplementary), and to determine the mean Ct of the N gene in each week of culture (Figure 3). Fisher's exact test was used to determine significance in

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culture positivity rates between different cohorts with 95% CI, (Table 1) and the difference between the culture positive samples per week (Figure 3). Mann-Whitney U test, two-tailed hypothesis (95% CI) was used to compare the date of symptom onset in culture positive and negative patients (Figure 7, Supplementary) and to compare the median Ct of the N gene in each week (Figure 3). *p*-values <0·05 were considered statistically significant.

Results

Of 234 samples (228 [97%] from the URT) collected from 195 persons with COVID-19, 11 (5%), 42 (18%) and 181 (77%) were from 178 outpatients, 12 inpatients not requiring ICU and five ICU patients, respectively (Table 1). SARS-CoV-2 was isolated from 56 (24%) samples, with CPE observed and SARS-CoV-2 RNA detected in 46 (20%) samples. No CPE was observed in 10 (4%) samples but fulfilled the Ct_{sample} - $Ct_{culture}$ ≥3 criteria to define positivity. Whole genome sequencing failed to identify specific SARS-CoV-2 lineages A (A, A.1-A.5) or B (B, B.1-B.9 and B.11) where CPE was absent [9]; furthermore the samples were not collected from any epidemiologically linked clusters (data not shown). Mean Ct of the N gene were significantly lower in CPE positive cultures when compared to both CPE negative but PCR positive cultures (25·01 vs 27·75, *p* <0·001) and negative cultures (25·01 vs 36·87, *p* <0·001) (Figure 5, Supplementary).

The highest Ct for the N gene target in any clinical sample where SARS-COV-2 was successfully cultured was 32. Based on this result and the Ct cut-off value of 37 determined by PCR of $TCID_{50}$ dilutions, and incorporating a 1 log margin of error, we were confident that any clinical sample with a Ct of ≥37 was not indicative of viable virus (Figure 1). SARS-CoV-2 was significantly more likely to be isolated in inpatients compared to outpatients (45% vs 15%, *p*<0·001), and ICU compared with other inpatients (82% vs 45%, *p*=0·04) or outpatients (82% vs 15%, *p*<0·001) (Table 1). Serial sampling of ICU patients and testing multiple gene targets demonstrated the variability in Ct when SARS-CoV-2 RNA was detected, with the E gene generally giving the lowest Ct and N gene the

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highest (Figure 2 and Figure 6, Supplementary) in this cohort. There was consistent correlation over time between targets and concordance with the selected definition for culture positivity (Figure 2).

Of note, SARS-CoV-2 was isolated 17 and 18 days post-symptom onset in a 36 year old female patient with hypothyroidism; no other samples were culture-positive beyond 10 days after symptom onset (Figure 3). The mean Ct across all cultures increased as time from symptom onset increased (Figure 3). Using the N gene as a representative target, cultures were significantly more likely to be positive from samples collected within the first week after symptom onset compared to the second week (80% vs 45%, p=0·002), and between the second and third week (45% vs 4%, p<0·001) (Figure 3).

Ct values of the most frequently used target (N gene) ranged from 17·56 to 40, mean=34·16, IQR (29·21 –39·37). Mean Ct of the N gene was significantly lower in LRT compared with URT samples (26·76 vs 34·41, p<0·001) (Figure 6, Supplementary). No significant difference was observed for the other targets, potentially due to a type II error.

In clinical samples where SARS-CoV-2 was isolated, the mean duration between symptom onset and sample collection was 4·5 days (median 3·5, range 0-18). By contrast, the mean duration between symptom onset and sample collection in culture negative samples was 20 days (median 18·4, range 3-29; p<0·001) (Figure 7, Supplementary).

Discussion

Detection of SARS-CoV-2 RNA by PCR has been the primary diagnostic method to confirm COVID-19. As an indicator of infectivity, the absence of detectable SARS-CoV-2 RNA in respiratory tract samples is utilized in many jurisdictions as a requirement for release of persons with COVID-19 from quarantine [10]. In Australia, infected persons from high-risk settings (including but not limited to HCWs) are required to have two consecutive negative SARS-CoV-2 tests at least 24 hours apart

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before being allowed to return to such settings [11]. Whilst there are reports of persistent or prolonged PCR positive results in recovered persons [12,13], few have provided robust data to support that they are no longer infectious. Furthermore, there is substantial variability in the duration of PCR positivity (up to 28 days after symptom onset) [12], resulting in individuals (including HCWs) being isolated for prolonged periods given the potential risks of virus transmission. As the detection of SARS-CoV-2 RNA in respiratory samples does not necessarily indicate viable infectious virions, we examined the correlation between the Ct of PCR positive samples and viral culture, a surrogate marker for infectivity. The Australian National Guidelines for Public Health Units also recommends that viral culture results be considered when deciding on the release of persons from quarantine following COVID-19 [11].

We successfully isolated SARS-CoV-2 from upper and lower respiratory tract samples collected from persons with acute COVID-19 and correlated the yield of cell culture with PCR Ct values. Similar to other reports [14,15] we demonstrate that the threshold Ct where culture will be successful is <32 for the N gene target. However, this Ct is specific for our laboratory and we would recommend that diagnostic laboratories correlate their Ct values with culture results due to the variable analytical performance between different SARS-CoV-2 PCR assays [16,17].

The cell culture method described herein relies not only on detection of CPE but incorporates PCR testing into the workflow. We demonstrate that virus with replicative capacity can be isolated and detected despite the absence of CPE by correlating the Ct of cell culture supernatant with the Ct of the original clinical samples where SARS-CoV-2 was detected. This effect was not due to any SARS-CoV-2 genotypes, however further genetic analysis may be warranted. This provides a more objective and sensitive measure of virus isolation as the detection of CPE can be subtle or absent due to low levels of virus that result in a delayed rise in virus load beyond day four in the cell lines used. This may assist in improving workflows in laboratories processing large numbers of cell

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cultures or those with reduced capacity to detect CPE. A Ct_{sample} cut-off >32 in our laboratory correlates with non-viable virus; and in the absence of CPE, a Ct_{sample} - $Ct_{culture}$ value <3 also indicates an absence of viral replication, suggesting these individuals could be safely released from isolation.

We have demonstrated that culture yield is improved when samples are collected as close to the date of symptom onset as possible, and that virus isolation is more likely in patients with more severe illness requiring admission to hospital or the ICU compared to outpatients. A previous study determined that virus may be isolated up to six days prior to symptom onset [18], however our study did not include such a cohort. Given the TATs , culture results of samples collected from persons during the pre-symptomatic stage would not be available in a meaningful timeframe to guide clinical management but would provide laboratory evidence of pre-symptomatic or asymptomatic SARS-CoV-2 transmission. We showed culture positivity out to 18 days post-symptom onset in one patient, which is ten days longer than previous findings from Singapore [15]. As paired URT and LRT samples were not collected concurrently in this study, we were not able to ascertain the relationship between the two in the context of de-isolation assessments. In the majority of persons that have clinically recovered from COVID-19, LRT samples may not be available, particularly in the absence of sputum production.

We did not assess whether SARS-CoV-2 replication in the absence of CPE occurs in cell lines other than Vero C1008 cells, However, this has been described in MEK and COS cell lines during the isolation of SARS-CoV [7]. The culture-positive samples demonstrating no CPE but detectable virus replication by PCR were predominantly seen in the ICU cohort with approximately half collected from the LRT. Given the small sample size we were unable to determine whether other factors (e.g. concurrent infections, antimicrobial use) may have affected detection of CPE in these samples. Due to the limited volume of clinical sample received, culture was not set up in duplicate however quality

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control to ensure the sensitivity of the cells was undertaken with a stock of titred virus to ensure a consistent LoD was maintained.

The performance of our inhouse SARS-CoV-2 assay was comparable to the Roche cobas® SARS-CoV-2 (Roche Diagnostics, Rotkreuz, Switzerland), (data not shown). Due to reagent shortages, not all samples or culture supernatants were able to be tested with all five SARS-CoV-2 gene targets (E, RdRp, M, N and ORF1ab). Nevertheless, we hypothesize that the findings using the N target would be similar for the other targets as a similar pattern was observed where testing of multiple targets were performed (Figure 2). Nucleic acid extraction from the primary sample and culture supernatant was performed on the MagNA Pure 96 and EZ1 Advanced XL instruments, respectively. Previous evaluations of automated nucleic acid extraction instruments for non-SARS-CoV-2 respiratory viruses showed superiority of the EZ1 Advanced XL compared to the MagNA Pure 96 [19], but there are limited data on the performance of extraction instruments for SARS-CoV-2. We were unable to ascertain if different swab types or UTM affected either PCR or culture results. This study also did not investigate why certain individuals shed SARS-CoV-2 RNA for longer periods compared to others, nor were we able to determine whether there were any factors such as immunosuppression that may have explained prolonged viral shedding, and further research is recommended to address these questions.

In summary, viral culture may assist clinicians to release from isolation individuals who have recovered clinically but remain persistently or intermittently positive SARS-CoV-2 by PCR. Whilst there is limited availability of cell culture in most clinical diagnostic laboratories, this capacity adds important insights not provided by molecular methods and should be maintained in reference laboratories to guide clinical management and de-isolation.

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NOTES

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Conflict of interest

None declared

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Table 1: Patient demographics and sample characteristics.

	ICU	Inpatients (non-ICU)	Outpatients (Non-admitted)	Total
Number of patients	5	12	178	195
Average age in years (range)	58 (36-76)	43 (22-78)	40 (18-71)	40 (8-78)
Male gender	3 (60%)	8 (70%)	136 (77%)	147 (75.4%)
Number of samples	11	42	181	234
URT	6	40	181	227 (97%)
LRT	5	2	0	7 (3%)
Average days from symptom onset to sample collection (range)	7 (0-20)	7 (1-16)	12 (0-29) **	11 (0-29)
Culture Positive with CPE	6 (55%)	17 (40%)	23 (12%)	46 (20%)
Culture Positive without CPE	3 (27%)	2 (5%)	5 (3%)	10 (4%)
TOTAL Culture Positive	9 (82%)	19 (45%)	28 (15%)	56 (24%)
TOTAL Culture Negative	2 (18%)	23 (55%)	153 (85%)	178 (76%)

*ICU: intensive care unit; URT: upper respiratory tract; LRT: lower respiratory tract; CPE: cytopathic effects

** Time of symptom onset was unavailable for 56 samples collected from outpatients as part of contact investigations who were either asymptomatic or had no symptom onset date recorded.

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FIGURE LEGENDS

Figure 1: PCR Ct cut-off value for non-viability of clinical samples and for determination of culture positive versus negative in the absence of CPE. A. Culture positivity rate by clinical sample PCR Ct value: No clinical samples with PCR Ct values >32 resulted in positive viral cultures. Safety margin of 1 log viral load less than this and concordant with B. was 37. **B. Culture supernatant PCR Ct values by gene target for $TCID_{50}$ dilutions:** indicates differential sensitivity of PCR depending on target gene. Red line at $10^{-6.5}$ indicates limit of detection by $TCID_{50}$. Ct for ORF1b target of 37.29 (bold) chosen as highest Ct representative of non-viable virus.

Figure 2: Representative samples from ICU cohort demonstrating target-dependent change in Ct values over four days of culture in **A**. A positive culture *with* CPE, **B.** A positive culture *without* CPE but Ct_{sample} - $Ct_{culture}$ ≥3, and **C.** a negative culture (no CPE, PCR positive but Ct_{sample} - $Ct_{culture}$ <3). Target genes: E, RdRp, M, N and ORF1ab.

Figure 3: Comparison of Culture Positive and Negative samples and Days since symptom onset with the clinical sample N gene Ct value.

** Note: This figure excludes 56 samples where date of symptom onset was unknown (patient asymptomatic, or the date of symptom onset not recorded).

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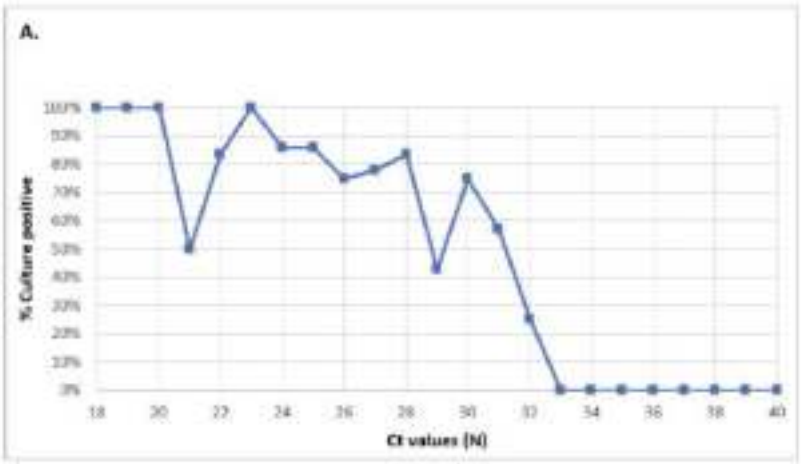
Figure 1A - B

A.



B.

TCID50	WHO E GENE	WMD M GENE	WMD N GENE	RDRP	CHINA CDC ORF1AB	WMD ORF1B
NEAT	12.45	18.6	18.14	16.22	12.09	14.54
1.00E-01	15.81	21.87	22.35	19.97	15.3	18.22
1.00E-02	18.31	25.12	25.52	23.12	18.63	21.56
1.00E-03	20.13	28.24	28.86	25.8	22.2	24.81
1.00E-04	21.58	31.57	32.21	27.62	25.49	28.19
1.00E-05	NEG	34.65	34.7	28.04	28.64	31.54
1.00E-06	NEG	35.59	36.71	NEG	32.19	34.63
1.00E-07	NEG	36.46	36.74	NEG	34.88	37.29
1.00E-08	NEG	NEG	NEG	NEG	NEG	NEG

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Figure 2A – B – C

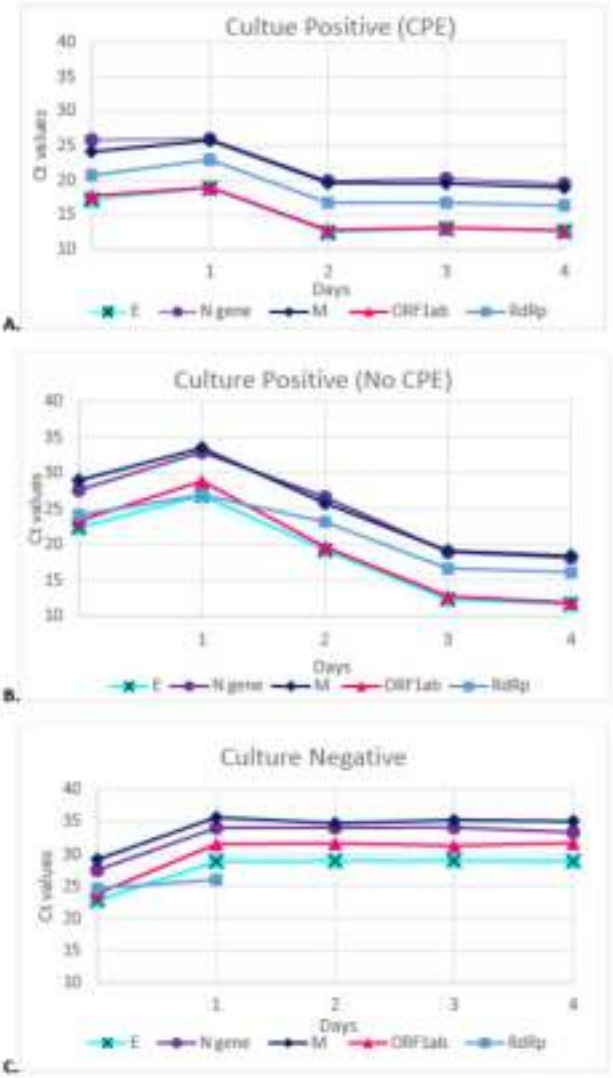

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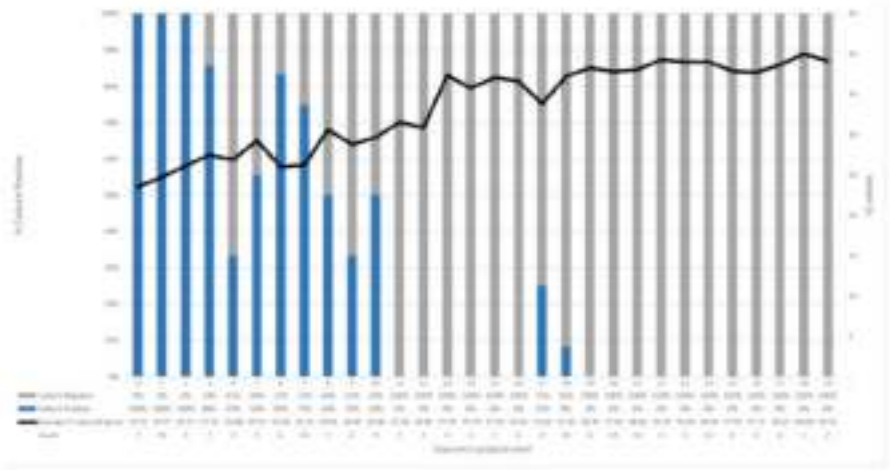
Figure 3



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Article

Real Time PCR and Culture-Based Virus Isolation Test in Clinically Recovered Patients: Is the Subject Still Infectious for SARS-CoV2?

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Abstract: Background. The highly variable manifestation of the COVID-19 disease, from completely asymptomatic to fatal, is both a clinical and a public health issue. The criteria for discharge of hospitalized patients have been based so far on the negative result of Real-Time Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) tests, but the persistence of viral fragments may exceed that of the integral virus by weeks. The aim of our study was to verify the clearance of the virus at viral culture in patients hospitalized for COVID-19 that have clinically recovered but are still positive on nasopharyngeal swab. Methods. The study was conducted in hospitalized patients with positive RT-PCR on nasopharyngeal swab. Patients included were from asymptomatic to severe cases and performed nasopharyngeal control swabbing on day 14 for asymptomatic patient or at least three days after remission of symptoms. RT-PCR positive specimens were sent to a biosafety level 3 laboratory for viral culture. Results. We performed a combined analysis of RT-PCR and a highly sensitive in vitro culture from 84 samples of hospitalized patients. The average age was 46 ± 20.29, and 40.5% of the subjects had radiologically confirmed pneumonia, with average PaO_2 of 72.35 ± 12.12and P/F ratio of 315 ± 83.15. Ct values for the N gene were lower in the first swab than in the control one ($p < 0.001$). The samples from 83 patients were negative at viral culture, and RT-PCR on the respective supernatants always confirmed the absence of viral growth. Conclusions. Our preliminary results demonstrate that patients clinically recovered for at least three days show the viral clearance at viral culture, and presumably they continued to not be contagious.

Keywords: cell culture; COVID-19; RT-PCR; SARS-CoV-2; viral transmission

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1. Introduction

Since the outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, the increase in the number of cases that have reported positive to diagnostic tests has increased the impact on healthcare and on global public costs. In several areas, the rise in the absolute number of people tested positive to SARS-CoV-2 has been correlated to a higher number of tests performed in the general population, in accordance with improved contact tracing. As a higher transmission in younger subjects has been observed, as compared to the earlier phases of the pandemic, in the current wave, we are able to directly keep track of a greater number of mild and asymptomatic cases [1].

Studies have shown a wide variability in the sensitivity of Real-Time Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) protocols for the detection of SARS-CoV-2, with a false negative rate ranging from 2% (95% CI, 0.3 to 7.9%) to 39.8% (95% CI, 30.2 to 50.2). This variability seems to be at least partially related to the difference in the reagents (i.e., primer sets, buffers, and enzymes, and laboratory kit components in general) that are used [2], but also to the sample type/location, operator, and sample storage time/temperature, as well as the nucleic acid extraction method used [3].

A crucial point in the management of coronavirus disease 2019 (COVID-19), at patient as well as at population level, is to define the exact kinetics of viral shedding and infectiousness. Little is known about the minimal viral load needed to trigger a state of disease, be it completely asymptomatic or overt COVID-19. Furthermore, we currently do not know the clinical meaning of the detection of a certain level of the virus with current diagnostic molecular tests in a general individual, i.e., whether he or she is a potential carrier and what the odds are that they could be, as well as the probability of them developing an overt syndrome. Conversely, to date, detecting positivity to a test for SARS-CoV-2 in a patient with overt disease does not give clear information about how much he or she is actually contagious. A clear frame could shed new light on the kinetics of the viral replication in each host, and possibly give information about why and how some individuals remain completely asymptomatic while others develop a fatal disease. Most importantly, understanding viral dynamics would have a clear impact on the management of COVID-19 at a population level, as it would form the basis of optimized individual isolation timing and social distancing as well as discharge criteria from the hospital.

In addition, many cases have been described of subjects who remain positive to the RT-PCR on nasopharyngeal swab, even many days after the onset of the disease, despite no longer having symptoms. More interestingly, it is not infrequent that patients who have been discharged with repeatedly negative RT-PCR results show again (weakly) positive RT-PCR results at random control swabs, raising concern about the possible need of again establishing isolation measures to avoid the risk of infection transmission from these subjects who have a "viral clearance" from the respiratory system.

Only a few studies, though, have investigated the correlation between RT-PCR cycle thresholds (Ct) and the actual cultivability of the virus from the same samples in vitro.

The aim of our study is to verify, through viral culture, the true persistence of the active, and therefore potentially infecting, virus during the follow-up of patients affected by COVID-19 when they are clinically recovered, including in the analysis of the correlation between Ct cycles and cultivability of virus in vitro patients showing a broad spectrum of clinical severity, i.e., from asymptomatic to severely ill.

2. Methods

This study was conducted in patients hospitalized from 1 August to 30 September 2020 in the Respiratory Diseases and Infectious Diseases Units at the University Hospital "Policlinico Riuniti" in Foggia, Italy. Upon entering the emergency room (ER), chest X-ray, laboratory tests, blood gas analysis, and nasopharyngeal swab for SARS-CoV-2 were performed. Patients were admitted to our ward after a positive RT-PCR result on nasopharyngeal swab (T0).

During the hospital stay they underwent standard care medication (corticosteroids, enoxaparin, mucolytics and antibiotics) and oxygen or non-invasive ventilation, according to their clinical condition.

A nasopharyngeal control swab was performed on day 14 if the patient was completely asymptomatic or at least three days after remission of symptoms (T1) and therefore declared "clinically recovered". This definition includes complete weaning from oxygen therapy or ventilator support and no main symptoms of infection (no fever, no dyspnea, SaO_2 stably above 96% in room air), with laboratory values compatible with only iatrogenic effect (e.g., mild leukocytosis from corticosteroids) and mild elevation of D-dimers, though nonetheless highly reduced from the time of admission. In this case, patients could be discharged from hospital if he or she was negative at nasal swab.

This schedule is based on the national discharge guidelines that needed a negative result of RT-PCR performed on nasopharyngeal swabs on two consecutive days. It is also based on a highly improbable negative RT-PCR in the first 14 days of hospital stay. We further investigated four clinically recovered patients who were persistently positive, requiring more than 1 month of hospitalization. In the case of positive RT-PCR, the nasopharyngeal swabs were sent to a biosafety level 3 (BSL-3) laboratory for viral culture.

This study was approved by our Institutional Review Board (Dir 389-20). All patients' data were collected in the context of routine clinical care, and written informed consent was signed at admission according to hospital policy.

2.1. Specimen Processing and Analysis

2.1.1. RT-PCR

Viral RiboNucleic Acid (RNA) was extracted from nasopharyngeal swabs within 2 h of collection, using the STARMag 96 × 4 Universal Cartridge kit with the Microlab NIMBUS IVD instrument, according to the manufacturer's instructions (Seegene Inc. Seoul, Korea). Amplification and detection of target genes (N, E, and RdRP) was performed using the commercially available kit AllplexTM 2019-nCoV Assay (Seegene Inc. Seoul, Korea) with the CFX96TM instrument (Bio-Rad, Hercules, CA). The cycle threshold (Ct) of each RT-PCR reaction was extracted from the Seegene Viewer software, used for results interpretation, and recorded into a dedicated Excel database. The test was considered positive when at least one of the three investigated genes had a Ct below 40. As the N gene assay resulted 10 times more sensitive that the ORF1b gene for detecting viral infection [4], the viral loads were estimated basing on the Ct values for the N target using the ΔCt method (Ct sample—Ctref: = ΔCt − N), as previously described [5].

2.1.2. Virus Isolation

For SARS-CoV-2 isolation, the Vero E6 cell line (African green monkey kidney cells) was used [6,7]. Cells were cultured in Eagle's minimal essential medium (EMEM) (Life Technologies, Carisbad, CA, USA) supplemented with 10% (vol/vol) fetal bovine serum (FBS) (Life Technologies, Carisbad, CA, USA), and 100 U/mL penicillin and streptomycin (Life Technologies, Carisbad, CA, USA).

For the virus isolation from swab, cells were plated into a 25 cm^2 cell culture flasks (Corning, CLS430168) at a confluency of 70–80% in 6 mL EMEM with 6% FBS and incubated overnight at 37 °C. The following day, 1500 µL of the swab medium was incubated with 500 µL of an antibiotic solution (2000 U/mL of penicillin/streptomycin and 300 U/mL of neomycin) for 1 h at room temperature. The 2 mL of suspension was then inoculated on the monolayer of the VeroE6 cells. The flask was incubated at 37 °C for 1 h.

After incubation, 4 mL of EMEM with 6% fetal bovine serum (FBS) was added and incubated again at 37 °C for 72 h [8]. Each day, 200 µL of EMEM were collected from each flask for biomolecular testing. The EMEM 6%FBS was replaced every 72 h. The observation lasted for a week. The result was defined on the basis of cytopathic effect (subjective reading) combined with the positivity of the RT-PCR test (objective reading) in supernatant. All procedures for viral culture followed the laboratory biosafety guidelines.

2.1.3. Definition of the Sensitivity Level of the Isolation Test

To establish a sensitive procedure for virus isolation in cell culture, two viral suspensions obtained from two SARS-CoV-2 Italian patients containing known virus concentrations (100 $TCID_{50}$) were tested.

Serial dilutions of both suspensions were made to obtain infectious viral particles at various concentrations in 2 mL of EMEM containing 6% FBS. Each virus dilution was seeded on a Vero E6 cell monolayer and incubated at 37 °C. After one hour of incubation, a further 4 mL of EMEM 6% FBS was added and, at the same time, 200 µL of the supernatant were taken, on which the RNA extraction and the RT-PCR test were carried out to verify the value of the starting Ct. For each viral dilution, four tests were performed.

Every 24 h, the infected cell monolayer was visually inspected by light microscopy to check for the presence of cytopathic effect, and 200 µL of supernatant were collected, on which the RNA extraction and the RT-PCR test were carried out to verify the Ct value. After 72 h from the beginning of the incubation, the medium was replaced.

For each time point, one step reverse transcription PCR was performed to detect the RdRp gene, as described by Corman, V.M. et al. [9], as this target is the most specific one for the detection of Sars-CoV-2. Briefly, viral RNA was extracted from medium by QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany), following the manufacturer protocol.

A 25-µL reaction was set up containing 5 µL of RNA, 12.5 µL of the 2× reaction buffer provided with the Superscript III one step RT-PCR system with Platinum Taq Polymerase (Invitrogen, Carlsbad, CA, USA), 1 µL of reverse transcriptase/Taq mixture from the kit, 0.4 µL of a 50 mM magnesium sulfate solution, 1.5 µL of Forward primer (10 µM, GTGARATGGTCATGTGTGGCGG), 2 µL of Reverse primer (10µM, CARATGTTAAASACACTATTAGCATA), and 0.5 of probe (10 µM FAM-CAGGTGGAACCTCATCAGGAGATGCBBQ).

All oligonucleotides were synthesized and provided by Invitrogen (Carlsbad, CA, USA). Thermal cycling was performed at 55 °C for 10 min for reverse transcription, followed by 95 °C for 3 min and then 45 cycles of 95 °C for 15 s and 58 °C for 30 s.

Overall, the experiment lasted 120 h. Infectious virus was considered to be present in those wells that showed a combined reduction of the Ct value and the presence of a cytopathic effect. Isolation in flasks with 10, 5, and 1 viral infecting doses occurred within 72 h in all cases. In the tests carried out using 0.5 and 0.1 viral infecting doses, only one isolation occurred within 72 h in the 0.5 dose group, and one isolation occurred at 96 h in the 0.1 dose group (Tables 1 and 2).

Table 1. Data relating to cytopathic effect of each dilution detected at 72, 96, and 120 h of incubation.

Infectious Viral Doses (TCID50)	72 h	96 h	120 h	72 h	96 h	120 h
	Cytopathic Effect	Result of Tests	Cytopathic Effect	Cytopathic Effect	Result of Tests	Cytopathic Effect
10	YES	Positive 4/4—end test				
5	YES	Positive 4/4—end test				
1	YES	Positive 4/4—end test				
0.5	NO	Negative 4/4—continue test	YES NO	Positive 1/4—end test Negative 3/4—continue test	NO	Negative 3/3—end test
0.1	NO	Negative 4/4—continue test	YES NO	Positive 1/4—end test Negative 3/4—continue test	NO	Negative 3/3—end test

Notes: (Median Tissue Culture Infectious Dose (TCID50)).

Table 2. Data resulting from the comparison of cytopathic effect and Ct values obtained by PCR analyses in relation to the different infectious viral doses used to standardize the test. The indicated Ct values are the average medium ones, obtained by the four replicates.

Infectious Viral Doses (TCID50)		72 h	96 h	120 h
	Starting Ct (RdRp)	Ct Value (RdRp)	Ct Value (RdRp)	Ct Value (RdRp)
10	27.33	12.31	-	
5	28.60	12.10	-	
1	24.42	17.13	13.73	-
0.5	30.77	32.56	36.02	Negative
0.1	32.67	34.67	34.46	Negative

Notes: Cycle thresholds (Ct) of the *RdRp* gene. Median Tissue Culture Infectious Dose (TCID50).

2.2. Statistical Analysis

All analysis was performed using SPSS 26 software (IBM, Armonk, NY, USA). Numerical data were represented with mean ± standard deviation, while categorical variables were represented as counts and percentage. Any statistical differences in the laboratory data of population at baseline and nasopharyngeal control swab were performed using *t*-test paired samples or Mann–Whitney U–test, as appropriate. A *p*-value of less than 0.05 was considered statistically significant.

3. Results

We selected 84 subjects whose nasopharyngeal swab was still RT-PCR-positive at T1. Table 3 summarizes the characteristics of the subjects at baseline. The average age was 46 ± 20.29, (19.1% female), 51.2% of patients were African, and the remaining were Caucasian. At admission, 40.5% of the subjects had radiologically confirmed pneumonia, the overall average PaO_2 was 72.35 ± 12.12, $PaCO_2$ 36.2 ± 5.2, with an average P/F ratio of 315 ± 83.15. Five percent of patients underwent oxygen therapy, and 9.6% underwent high flow nasal cannulae (HFNC) or continuous positive airway pressure (CPAP) ventilation.

Table 3. Characterization of the study group at baseline (N = 84).

Patient Characteristics	
Age, years	46.07 ± 20.29
Females, n (%)	16 (19.1)
African, n (%)	43 (51.2)
Current or former smoker, n (%)	24 (28.6)
Comorbidities, n (%)	
Asthma or COPD	3 (3.6)
Chronic cardiac disease	27 (32.2)
Diabetes	10 (12)
Alzheimer	5 (6)
Chronic neurological disease	8 (9.6)
Radiographic feature, n (%)	
Pneumonia	34 (40.5)
Respiratory failure, n (%)	
Oxygen therapy	13 (15.5)
HFNC or CPAP	8 (9.6)

Continuous data are expressed as mean ± standard deviation, numerical as count (percentage). Notes: COPD: chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; HNFC: high nasal flow cannulae.

Nasopharyngeal swabs were performed, on average, on day 19.95 ± 5.71 in 80 patients, while in four persistently positive cases these were performed at day 41, 43, 50, and 70, respectively. As expected, Ct values for the N gene were lower in the first nasopharyngeal swab than in the control one (26.04 ± 5.26 vs. 35.59 ± 3.95, $p < 0.001$—Table 4, Figure 1). The first group of patients became negative after two consecutive swabs, about 10 days after culture (29.50 ± 9.17), while the four persistently positive patients needed 53, 61, 72, and 104 days, respectively, to obtain a double negative response.

Table 4. Comparison between laboratory characteristics of patients at T0 and at T1 (interval of 19.95 ± 5.71 days).

Parameters	T0			T1		
	Min	**Max**	**Mean ± SD**	**Min**	**Max**	**Mean ± SD**
Laboratory tests and blood gas analysis						
WBCs (10^3/uL)	1.068	15.6	6.243 ± 3.209	2.4	13.5	6.013 ± 2.724
Lymphocytes (10^3/uL)	0.099	2.504	0.993 ± 0.613	1.082	2.541	1.576 ± 0.543 **
D-dimer (ng/mL)	180	5918	1037.68 ± 1206.56	181	1849	691.82 ± 463.45 *
ESR (mm/h)	4	126	40.63 ± 36.543	5	77	30.88 ± 28.62 *
IL-6 (pg/mL)	1.59	139.4	22.55 ± 35.68	1.39	8.2	4.25 ± 2.25 **
CRP (mg/L)	0.1	307.2	57.13 ± 84.64	0.3	108.3	16.41 ± 30.83 **
pH	7.32	7.58	7.44 ± 0.05	7.43	7.51	7.46 ± 0.02 **
PaO_2 (mmHg)	46	90	72.35 ± 12.12	59	89	76 ± 8.70 *
$PaCO_2$ (mmHg)	24	46	36.2 ± 5.21	32	43	36.9 ± 3.84
P/F ratio (mmHg)	110	428.6	315 ± 83	245.8	423.8	358.39 ± 49.73 **
RT-PCR NcT value						
	14.5	38.9	26.04 ± 5.26	17.40	38.9	35.59 ± 3.95 **

Data are expressed as mean ± standard deviation, with the minimum and maximum values found. * $p < 0.05$, ** $p < 0.01$ vs. baseline. Notes: CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IL-6: Interleukin 6; NcT: cycle thresholds (Ct) of *N* gene; $PaCO_2$: partial pressure of arterial carbon dioxide; P/F ratio: arterial partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2); WBCs: white blood cells.

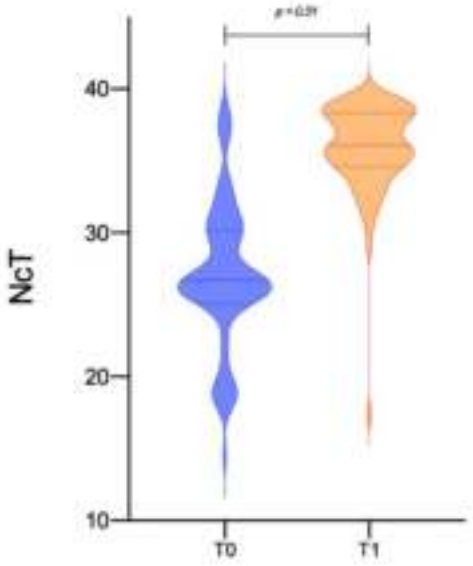

Figure 1. Comparison of cycle threshold (Ct) values at T0 (positive nasopharyngeal swab at hospital admission) and at T1 (nasopharyngeal control swab at clinical recovery performed after 19.95 ± 5.71 days from T0) for the *N* gene in a population of 84 patients described by Violin plot).

Using a sensitive virus culture method able to detect even fractions of viral infectious units, the samples from 83 patients were negative at viral culture, and the RT-PCR on the respective supernatants always confirmed the absence of viral growth (Figure 2a). Only in one case (1.19%) a cytopathic effect was observed in the corresponding cell culture at 96 h post-seeding (Figure 2b), and a relevant reduction of the viral load (increase of Ct from 31 to 38) in RT-PCR was also observed. However, the patient had a presumably delayed clearance because he was affected by Acute Myelogenous Leukaemia (AML) when he acquired the SARS-CoV-2 infection and was under chemotherapy treatment; this subject resulted negative to a nasopharyngeal swab ten days later.

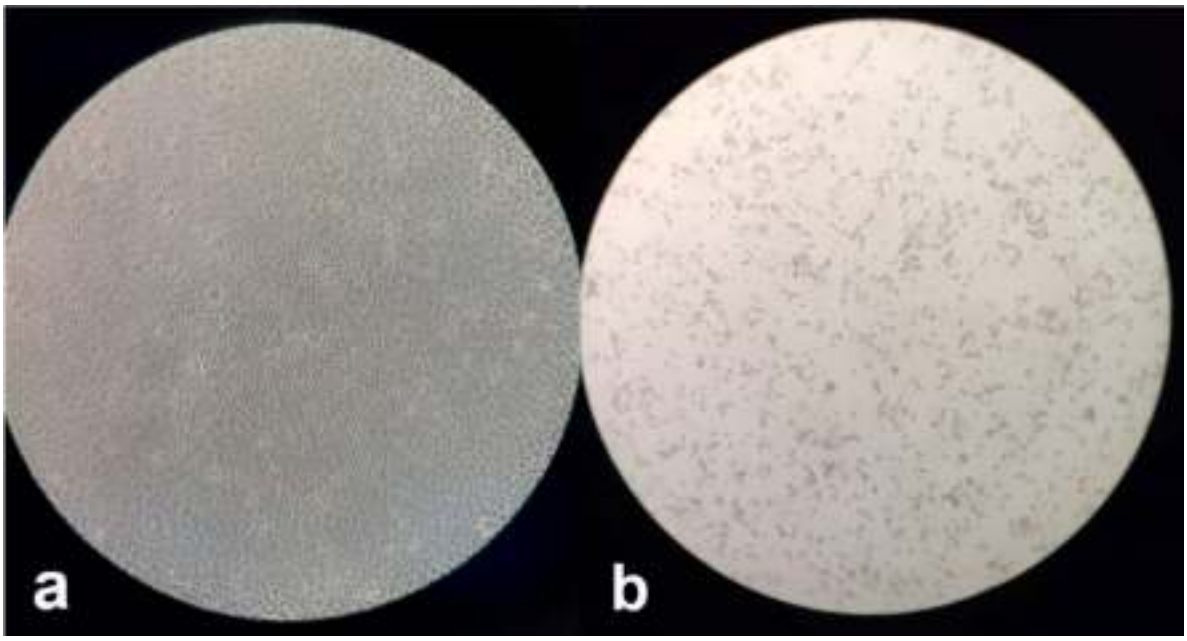

Figure 2. Viral cultures examined by a microscope at 5× magnification: (**a**) Absence of viral growth, as shown by complete confluence of Vero E6 cells; (**b**) Cytopathic effects consisting of rounding and detachment of cells in Vero E6 cell cultures at 96 h post-seeding.

4. Discussion

This study shows that the positivity of RT-PCR on nasopharyngeal swab performed during a follow up check in recovered COVID-19 patients about 20 days after symptoms onset does not coincide with the presence of the infectious virus established with the virus culture method. The main implication of these findings is that clinically recovered patients, in >98% of cases, are no longer contagious, despite the presence of vestigial virus components detected by RT-PCR. Since the beginning of the pandemic, many studies have tried to estimate the infectivity according to the clinical features and to the viral load detected by diagnostic RT-PCR [10,11]. According to an analysis made by He et al. [12], the infectiousness of COVID-19 peaks early, around the onset of symptoms, and declines within 8 days, as proven by analyzing serial time intervals between symptoms onset in two individuals in a contagious chain.

The most reliable method for COVID-19 diagnosis is RT-PCR [13] based on the detection of nucleic acid from the SARS-CoV-2 in upper and lower respiratory specimens (such as nasopharyngeal or oropharyngeal swabs, sputum, lower respiratory tract aspirate, bronchoalveolar lavage, and nasopharyngeal wash/aspirate or nasal aspirate). Ct values may be converted to Log10 RNA copies/mL using calibration curves based on quantified sample RNA transcripts, providing a quantitative result [14].

Huang et al. [15] studied 60 specimens from 50 patients, performing RT-PCR for genes E, N, and Nsp12, as well as in vitro virus cultivation on Vero E6 cells. The specimens resulting positive in culture had significantly higher Ct values for all three genes. They

further proved that the analysis of structural and non-structural genes in both culturable and non-culturable samples might help to identify actively replicating viruses.

La Scola et al. [16] highlighted a correlation between Ct values and the probability of isolating the virus in vitro; from a group of 183 samples, virus isolation always (100%) occurred in swabs with a Ct between 13 and 17, and viral growth was never observed with Ct > 34.

Arons et al. [17] analyzed specimens from 76 residents in a skilled nursing facility and found that, after classification on symptoms, no significant difference was observed in the Ct values of patients, and there was no significant difference according to symptoms intensity. The analysis was performed with RT-PCR on nucleocapsid gene regions N1 and N2. A parallel in vitro test of viral culture found no virus rescue after 9 days from symptoms onset.

Wölfel et al. [14] performed RT-PCR for E and RdRp genes and in vitro culture of nasopharyngeal swab, sputum, sera, and stool samples from none patients with mild disease. They found that RT-PCR can result positive for as long as 28 days from symptoms onset. No virus could be cultivated from samples collected after 8 days, and could also never be cultivated for viral loads with less than 10^6 copies of RNA. Despite the small size of the study population, the time for virus isolation success, estimated via a probit model, was 9.78 days (CI 8.45–21.78). Notably, they observed an earlier peak of shedding in the nasal-pharyngeal swab as compared to sputum, and this was higher in intensity in patients with pneumonia. Urine and serum samples never showed viral growth in vitro, while stool samples showed a prolonged viral RNA shedding, extending far beyond the virus isolation window.

Bullard et al. [18] performed a comparison between SARS-CoV-2 viral culture on Vero cells with RT-PCR; they analyzed 90 samples (nasopharyngeal and endotracheal swabs) from patients at different time points from symptoms onset (0 to 21 days) and observed that no virus growth is obtained, either after 8 days from symptoms onset or when Ct > 24 on RT-PCR. For each 1 unit increase of Ct, the odds ratio of infectivity decreased by 32%, while, for each day increase from symptoms onset, the decrease was by 37%. The limits to this study are that only one gene (E) has been analyzed and no longitudinal analysis has been performed.

In a pre-print work by Van Kampen et al. [19], a study of samples from 129 patients with severe/critical disease has shown a possible longer infectious viral shedding as compared to mild and moderate cases. They observed a correlation between viral load and the probability of isolating the virus in vitro. A reduction to less than 5% of this probability was observed for viral loads of less than 10 copies or after 15.2 days after symptoms onset.

In our study, the culture from the swabs of positive patients is able to define the presence of live and viable viral particles within 96 h from the seeding on Vero E6 monolayer cells. Furthermore, the sensitivity of the test is confirmed by the fact that, even with dilutions in which 0.5 and 0.1 infectious viral particles are expected to be present, 25% of the cultures provided successful virus isolation. These results confirm the viral isolation method as the most sensitive and specific one, and it is considered the gold standard according to classical virological methods, capable of discriminating persons that harbor the live infectious virus from those that probably harbor dead virus particles or fragments of viral RNA not yet detected by RT-PCR.

Compared to the studies in the literature, our preliminary results demonstrate that patients clinically recovered for at least three days showed the viral clearance at viral culture, and presumably they continued to not be contagious. There is no doubt that both the RT-PCR and the viral culture have limits, so non-infectivity cannot be excluded with absolute certainty, and genomic and sub-genomic RNAs analysis could provide more evidence about the real infection risk. Deeper studies are necessary to better evaluate this aspect. However, according to our results, and in line with the data that emerged from the other few studies performed on cell cultures, we can suppose that it might not be strictly necessary to perform control swabs to demonstrate the clearance of the virus when patients

have clinically recovered for at least three days. Further studies, involving patients with a shorter time of recovery, that is, earlier than 14 days of hospitalization, might conclusively prove this observation and significantly shorten the length of hospitalization as well as time of social isolation.

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Abbreviations

COVID-19, coronavirus disease 2019; CPAP, continuous positive airway pressure; Ct, cycle thresholds; EMEM, Eagle's minimal essential medium; HFNC, high flow nasal cannulae; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Asymptomatic transmission of covid-19

What we know, and what we don't

Allyson M Pollock, [1] James Lancaster[2]

The UK's £100bn "Operation Moonshot" to roll out mass testing for covid-19 to cities and universities around the country raises two key questions. How infectious are people who test positive but have no symptoms? And, what is their contribution to transmission of live virus?

Unusually in disease management, a positive test result is the sole criterion for a covid-19 case. Normally, a test is a support for clinical diagnosis, not a substitute. This lack of clinical oversight means we know very little about the proportions of people with positive results who are truly asymptomatic throughout the course of their infection and the proportions who are paucisymptomatic (subclinical), presymptomatic (go on to develop symptoms later), or post-infection (with viral RNA fragments still detectable from an earlier infection).

Earlier estimates that 80% of infections are asymptomatic were too high and have since been revised down to between 17% and 20% of people with infections.[1 2] Studies estimating this proportion are limited by heterogeneity in case definitions, incomplete symptom assessment, and inadequate retrospective and prospective follow-up of symptoms, however.[3] Around 49% of people initially defined as asymptomatic go on to develop symptoms.[4 5]

It's also unclear to what extent people with no symptoms transmit SARS-CoV-2. The only test for live virus is viral culture. PCR and lateral flow tests do not distinguish live virus. No test of infection or infectiousness is currently available for routine use.[6-8] As things stand, a person who tests positive with any kind of test may or may not have an active infection with live virus, and may or may not be infectious.[9]

The relations between viral load, viral shedding, infection, infectiousness, and duration of infectiousness are not well understood. In a recent systematic review, no study was able to culture live virus from symptomatic participants after the ninth day of illness, despite persistently high viral loads in quantitative PCR diagnostic tests. However, cycle threshold (Ct) values from PCR tests are not direct measures of viral load and are subject to error.[10]

While viral load seems to be similar in people with and without symptoms, the presence of RNA does not necessarily represent transmissible live virus. The duration of viral RNA shedding (interval between first and last positive PCR result for any sample) is shorter in people who remain asymptomatic, so they are probably less infectious than people who develop symptoms.[11]

Viral culture studies suggest that people with SARS-CoV-2 can become infectious one to two days before the onset of symptoms and continue to be infectious up to seven days thereafter; viable virus is relatively short lived.[7] Symptomatic and presymptomatic transmission have a greater role in the spread of SARS-CoV-2 than truly asymptomatic transmission.[1 2 12 13]

The transmission rates to contacts within a specific group (secondary attack rate) may be 3-25 times lower for people who are asymptomatic than for those with symptoms.[1 12 14 15] A city-wide prevalence study of almost 10 million people in Wuhan found no evidence of asymptomatic transmission.[16] Coughing, which is a prominent symptom of covid-19, may result in far more viral particles being shed than talking and breathing, so people with symptomatic infections are more contagious, irrespective of close contact.[17] On the other hand, asymptomatic and presymptomatic people may have more contacts than symptomatic people (who are isolating), underlining the importance of hand washing and social distancing measures for everyone.

Missed opportunity

By failing to integrate testing into clinical care, we have missed an important opportunity to better understand the role of asymptomatic infection in transmission. Given the variation in prevalence and testing strategies by region, the proportions of people with positive and negative test results should be published alongside the purpose of the testing strategy and the population tested (screening healthy populations in schools, universities, and health and social care, or testing people with symptoms). Government regulations on recording the age, ethnicity, sex, and place of residence of people with positive results must also be followed.[18]

Searching for people who are asymptomatic yet infectious is like searching for needles that appear and reappear transiently in haystacks, particularly when rates are falling.[19] Mass testing risks the harmful diversion of scarce resources. A further concern is the use of inadequately evaluated tests as screening tools in healthy populations.[20]

The UK's testing strategy needs to be reset in line with the Scientific Advisory Group for Emergencies' recommendation that "Prioritising rapid testing of symptomatic people is likely to have a greater impact on identifying positive cases and reducing transmission than frequent testing of asymptomatic people in an outbreak area."[21]

Testing should be reintegrated into clinical care with clinical and public health oversight and case definitions based on clinical diagnosis. Carefully designed prospective studies of cases and contacts are needed to estimate transmission rates by people

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with and without symptoms. These should include careful investigations of outbreaks—for example, testing all contacts of people with a clear history of exposure, especially in high risk environments such as nursing homes, prisons, and other institutional settings.

Coronavirus infection surveys by the Office for National Statistics[22] and the REACT survey[23] could be expanded to include clinical follow-up of participants combined with tests of viral load and viral cultures. The absence of strong evidence that asymptomatic people are a driver of transmission is another good reason for pausing the roll out of mass testing in schools, universities, and communities.

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Group A Streptococci Among School-Aged Children: Clinical Characteristics and the Carrier State

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ABSTRACT. *Objective.* **A 4-year longitudinal study of school-aged children was conducted to describe the clinical characteristics and epidemiologic features of infections with group A streptococci (GAS).**

Methods. **Between 1998 and 2002, surveillance throat cultures were performed twice per month (October to May) for a cohort of elementary school children in Pittsburgh, Pennsylvania. In addition, throat cultures were obtained during any respiratory illness. Erythromycin and clindamycin susceptibility testing was performed for all isolates. Molecular typing was performed with field-inversion gel electrophoresis. Representative isolates from each field-inversion gel electrophoresis group were *emm* typed. Strict definitions were used to characterize each GAS infection. Children were classified into 4 categories each year, ie, single episode, recurrent episodes, carriers of GAS, and no infections.**

Results. **A total of 48 to 100 children per year were studied for 4 years; 61 (49%) were male. The mean age was 9.6 years (range: 5–15 years). A total of 5658 throat cultures were performed; 878 (15.5%) were positive for GAS. Antimicrobial agents were used to treat 209 episodes of infection. Thirteen *emm* types were observed during the 4-year period. GAS were isolated most often from children who were carriers; isolates from single episodes were next most common. Children carried a single *emm* type for a mean of 10.8 weeks (range: 3–34 weeks). Carriers were likely to be classified again as carriers in subsequent years and frequently switched *emm* types. Sixty-two percent of the children had ≥1 year with no infections.**

Conclusions. **GAS infections are common among school-aged children. The majority of positive throat cultures observed in this longitudinal study were obtained from children who were carriers of GAS. Carriers switched *emm* types but tended to become carriers repeatedly during the study. Practitioners should consider treating children known to be GAS carriers when they develop a new illness that is consistent with streptococcal pharyngitis, because they may acquire new *emm* types and be at risk for rheumatic heart disease. *Pediatrics* 2004;114:1212–1219; *group A streptococcus, surveillance, epidemiology, pharyngitis, carrier.***

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ABBREVIATIONS. GAS, group A streptococci; FIGE, field-inversion gel electrophoresis; CFU, colony-forming units.

Group A streptococci (GAS) (*Streptococcus pyogenes*) are the most common cause of bacterial pharyngitis among children and adults.[1] They are the leading cause of acquired heart disease among children throughout the world, and increasingly they are a major cause of deaths attributable to bacterial sepsis among both children and adults.[2–4]

Children are the major reservoir of GAS and are the target population for pharyngitis, as well as the suppurative and nonsuppurative complications caused by GAS.[2] They represent the pool from which adults with severe invasive disease acquire their infections.[4] The peak age incidence for infections caused by GAS is between 5 and 15 years. The frequency of GAS infections decreases markedly after 15 years of age unless large numbers of young adults from diverse locations are assembled in close quarters, as in military settings.[5]

GAS were previously grouped into >100 different serotypes with a typing system based on the M-protein in the cell wall. A recent alternative to serotyping is the designation of *emm* type by sequencing the 5′-terminal end of the *emm* gene.[6] It is not known whether children develop repeated infections with the same or different *emm* types of GAS. There is limited understanding of why and how children become immune to infection with GAS. Previous studies of large cohorts of children were performed before the availability of *emm* typing, when the majority of isolates could not be serotyped for the M-proteins.[7–10] The purpose of this longitudinal study was to describe the epidemiologic features of GAS infections in a group of school-aged children, with the use of modern molecular methods.

METHODS

Setting and Participants

A longitudinal study of the epidemiologic features of GAS infections in a private, tuition-supported, elementary school was initiated in 1998. This school serves 285 children and is located in Pittsburgh, Pennsylvania. Forty percent of the children who attend have parents who are faculty members of the University of Pittsburgh. Children attend kindergarten through grade 8. They are divided into 3 major cohorts according to age, ie, 5–7 years, 8–10 years, and 11–15 years. Within each group, there are 4 homerooms. Placement for each instructional setting (eg, math and reading) is based on readiness rather than age or grade level. Therefore, there is significant mixing between groups of students. Class size is limited to 24 students, and most classes have 12 to 15 students. All classrooms were represented in the study.

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All students attending the school were invited to join the study, but participation was voluntary. All students who were willing to participate were enrolled. The protocol was approved by the institutional review board of Children's Hospital of Pittsburgh, as well as by the school. Informed consent was obtained from ≥1 of the parents of the children who participated. The children provided assent.

Processing of Throat Cultures

Throat cultures were performed for each child approximately every 2 weeks during each school year, from October through May. Each child underwent a minimum of 17 cultures per school year. A throat culture was also performed each time a child developed a new respiratory illness, to ensure the identification of all new acquisitions of GAS. Study personnel were "on call," and an ill child was examined within 1 day after the identification of a new respiratory illness. If a child saw his or her personal physician because of an illness, then a throat culture was performed by the practitioner and retrieved by study personnel. Follow-up cultures were performed 2 to 4 days after completion of antimicrobial therapy for all new acquisitions of GAS that were treated. Follow-up cultures were performed 1 week after the initial culture when new positive cultures for GAS were not treated.

Throat culture specimens were obtained with a rayon-tipped swab (BBL Becton Dickinson, Sparks, MD), transported to the laboratory within 2 hours, and processed the same day with standard techniques, as described previously.[11] Beginning in October 2000, the relative numbers of GAS colonies were indicated on a scale of 1 to 4 (1+, <10 colony-forming units (CFU); 2+, >10 CFU but <50 CFU; 3+, >50 CFU but streptococci not predominant; 4+, streptococci predominant). More than 90% of the throat swabs were obtained by the principal investigator (J.M.M.); the processing of throat cultures was overseen by 1 senior laboratory technician (K.A.B.).

Typing of the GAS Isolates

The genetic relatedness of the GAS strains was investigated with field-inversion gel electrophoresis (FIGE), a type of pulsed-field gel electrophoresis, with previously described methods.[12,13] A 4-mm slice of each GAS plug was initially digested with 24 units of *Sma*I in 1× restriction buffer (New England Biolabs, Beverly, MA). Similar digestions were conducted with *Apa*I and/or *Eag*I, in their respective restriction buffers, for isolates that could not be digested with *Sma*I.[11]

The migration of DNA bands was compared with that of the λ ladder standard. Bands within the 50- to 250-kilobase range were used for analysis. Comparison of banding patterns was performed with visual inspection, and interpretation of clonal relatedness was based on guidelines proposed by Tenover et al.[14] One or more representative isolates from each FIGE type from each year and 4 erythromycin-resistant strains from the third year were selected and sent to the Centers for Disease Control and Prevention for *emm* typing.[6]

Susceptibility Testing

GAS isolates were screened initially for their susceptibility to erythromycin and clindamycin with the Kirby-Bauer disk diffusion test (BBL Becton Dickinson), on Mueller-Hinton agar with 5% sheep's blood, according to published guidelines and as described previously.[11,15] The minimal inhibitory concentration was then determined with the E-test (AB Biodisk, Piscataway, NJ) for isolates that were either intermediate or resistant in susceptibility to erythromycin or clindamycin. To screen for the mechanism of resistance, double-disk diffusion tests were performed.[16] Resistance to erythromycin was classified as an inducible MLS_B phenotype, a constitutive MLS_B phenotype, or an M phenotype. All GAS isolates were stored at −70°C for later use.

Definitions

Physical examination of the pharynx was performed for each throat culture specimen obtained. At the time of culture sample collection, the child was questioned regarding his or her symptoms, with a standard data sheet. In addition to the symptoms reported by the child, information regarding symptoms was solicited from a parent for each illness visit. The physical examination results, as well as the symptoms, were documented in a database. When any throat culture was positive for GAS, the principal investigator (J.M.M.) called a parent within 48 hours after obtaining the positive result. A standard instrument was used to assess symptoms and duration.

Each child was classified into 1 of 4 categories for each school year. The following definitions were used for each subject from whom an isolate of GAS was recovered. A child was classified as a carrier if GAS were recovered from ≥2 sequential surveillance cultures obtained ≥1 week apart in the absence of symptoms. Children were assigned to this category if they were ever GAS carriers during a school year. This included children who cleared their carriage and later had a single throat culture positive for GAS, with or without symptoms. A child was categorized as having recurrent episodes if either clinical or subclinical acquisitions of GAS were documented and separated by a minimum of 1 negative culture (and a 3-week interval) while the child was not receiving antimicrobial therapy. This designation was independent of GAS typing results. A child was designated as having had a single episode if a single positive throat culture was preceded and followed by negative throat cultures during a single school year. Children whose throat cultures were negative for GAS throughout a single school year were designated as having no infections.

All episodes of GAS-positive throat cultures were classified as being either clinical or subclinical. Clinical episodes were those associated with any respiratory symptoms. Typical episodes were those in which sore throat was a prominent complaint. Atypical episodes were those in which the child reported the new onset of rhinorrhea and/or cough, without sore throat. Subclinical episodes occurred when a child with a single positive throat culture had no symptoms.

The outcome of each episode of classic GAS pharyngitis (in which sore throat was the prominent complaint) was classified both clinically and bacteriologically in follow-up evaluations, on the basis of the result of the throat culture and the presence of clinical symptoms. An episode was defined as a clinical cure if the child no longer had symptoms of pharyngitis, as a clinical failure if the child had persistent symptoms of pharyngitis, as a bacteriologic cure if the child had a negative follow-up throat culture for GAS, and as a bacteriologic failure if the child had a positive follow-up throat culture for GAS of the same FIGE type as the initial infection. Each episode in which a child experienced a second positive culture after a bacteriologic cure was classified as a new acquisition if the child had a throat culture that was positive for GAS with a different FIGE pattern or *emm* type, compared with the child's previous GAS isolate, or as a reacquisition if the child had a throat culture that was positive for GAS with the same FIGE pattern or *emm* type as the child's previous GAS isolate. Duration of carriage was defined as the length of time between the first positive culture of one *emm* type and the first negative culture or the first positive culture with a new *emm* type during the school year.

Treatment

Patients with new respiratory complaints of sore throat or rhinorrhea (with or without sore throat) and a new positive throat culture for GAS were treated with orally administered penicillin V or amoxicillin by a single study physician (J.M.M.). Children with rhinorrhea without sore throat were treated only if the child's previous 2 throat cultures were known to have been negative for GAS. This decision was made because western Pennsylvania is known to have a high incidence of acute rheumatic fever and many children diagnosed as having rheumatic fever do not recall an antecedent sore throat.[17–19] Unlike clinical practice, the circumstances of the study afforded the opportunity to identify readily episodes of new acquisition of GAS.

The dose of penicillin V or amoxicillin used for all children was 500 mg twice per day for 10 days. At the beginning of the longitudinal study, erythromycin or azithromycin was prescribed only for children who were allergic to penicillin. Beginning in February 2001, either cephalexin or clindamycin was used for patients who were allergic to penicillin or amoxicillin. These medications were dosed on a milligrams per kilogram basis for a 10-day course, with the exception of azithromycin, which was used for 5 days. Treatment was not prescribed when a surveillance culture was positive for an asymptomatic child. No attempts were made to eradicate the carrier state.

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Statistical Methods

Data were entered into a Microsoft Access (Microsoft, Redmond, WA) database. All of the data from the laboratory and a random sample of 10% of the entries were double-checked for accuracy. Calculations were made with STATA 7 (Stata Corp, College Station, TX). χ^2 analysis was used for comparisons of dichotomous variables, and the *t* test was used for comparisons of continuous variables.

RESULTS

Demographic Characteristics of the Study Population

A total of 125 children participated in this longitudinal study at some time between October 1998 and May 2002. Figure 1 summarizes the subjects' entry into and departure from the study. Of the 125 children, 33 (26%) were monitored for 4 years, 50 (40%) were monitored for 3 years, 22 (18%) were monitored for 2 years, and 20 (16%) were monitored for only 1 year.

Forty-nine percent of the students were male; 73% were white, 13% Asian, 7% Hispanic, and 7% black. The demographic features of the children in each study year were similar to those of the school as a whole. The mean age of subjects for the entire study was 9.6 years (range: 5-15 years).

Laboratory Results

Table 1 shows the number of cultures that were performed in each year of the study and the number and percentage that were positive for GAS. The modest increase in the proportion of positive cultures was significantly different when year 3 was compared with years 1 and 4. No isolate of GAS was determined to be resistant to clindamycin. In the first 2 years of the study (1998–2000), there were no isolates that were resistant to erythromycin. However, as previously reported, 156 of 318 GAS isolates (49%) and 126 of 238 GAS isolates (53%) in years 3 and 4 of the study, respectively, were found to be resistant to erythromycin.[11] Table 2 shows the distribution of *emm* types of the GAS isolates for the 4 years. Thirteen different *emm* types circulated during the 4-year study period, with an average of 9 *emm* types per year. The predominant *emm* type was different each year for the first 3 years. The most prominent *emm* type in year 2 was not observed among the cohort in the previous year. In January of year 3, an erythromycin-resistant strain was isolated for the first time

TABLE 1. Comparison of the Percentages of GAS-Positive Throat Cultures According to Study Year

Year	No. of Children	No. of Throat Cultures Performed	No. (%) of Throat Cultures Positive for GAS
1998–1999	48	860	115 (13.4)
1999–2000	75	1340	208 (15.5)
2000–2001	100	1794	318 (17.7)
2001–2002	96	1664	237 (14.2)
Total		5658	878 (15.5)

The majority of children were monitored for 2 or 3 years. All *P* values were not significant except for comparisons of the numbers of positive cultures for years 1998–1999 versus 2000–2001 ($P = .004$) and 2000–2001 versus 2001–2002 ($P = .005$).

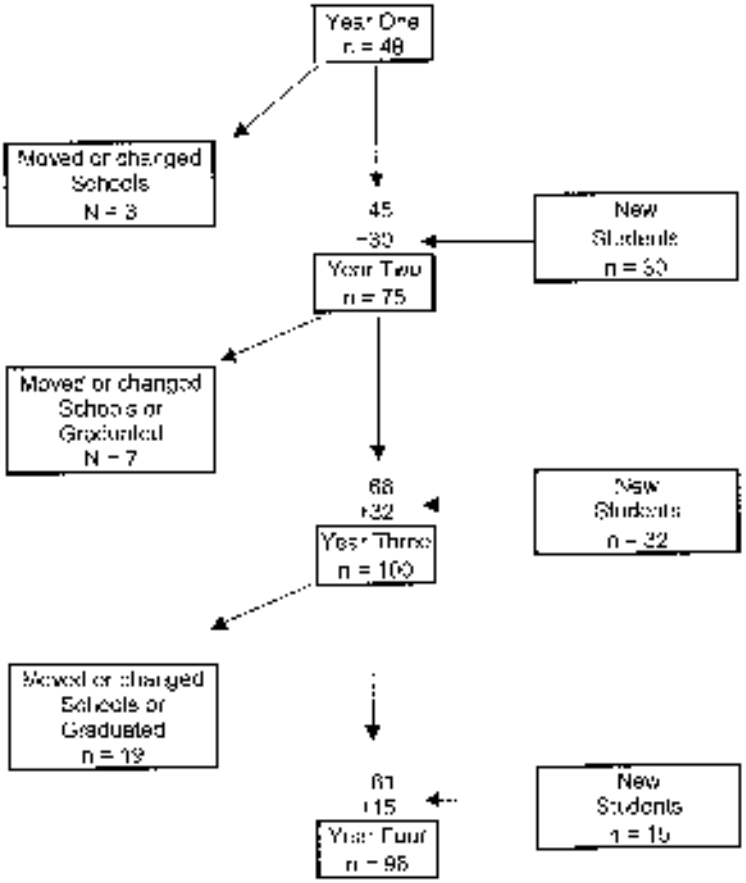

Fig 1. Entry and departure of participants during the 4-year study.

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TABLE 2. Distribution of *emm* Types of the GAS Isolates Recovered in the 4 Years of the Study

emm Type	No. of Isolates (%)			
	Year 1 (n = 115), 1998–1999	Year 2 (n = 208), 1999–2000	Year 3 (n = 318), 2000–2001	Year 4 (n = 238), 2001–2002
1	9 (8)	6 (3)	6 (2)	19 (8)
3*	0	6 (3)	16 (5)	18 (8)
4*	35 (30)	19 (9)	0	0
5*	5 (4)	5 (3)	25 (8)	10 (4)
6*	2 (2)	20 (10)	156 (49)	130 (55)
12	0	1 (0.5)	0	32 (13)
22	0	0	1 (0.5)	0
28	0	90 (46)	34 (11)	12 (5)
29	53 (46)	17 (8)	11 (3)	0
75*	3 (3)	10 (5)	8 (2.5)	2 (1)
77	0	0	3 (1)	0
89*	0	33 (16)	58 (18)	13 (5)
94	0	1 (0.5)	0	0
Total *emm* types	6	11	10	8

* There were ≥2 FIGE patterns observed for each of these *emm* types.

(*emm* 6, M phenotype, and *mef(A)* positive).[11] This became the predominant strain during years 3 and 4 of the study. There were 22 *emm* 6 isolates in years 1 and 2 of the study; however, they were not resistant to erythromycin and they had different FIGE patterns, compared with the epidemic strain.

The density of GAS was recorded for each throat culture after October 2000. Density did not correlate with clinical category. For children with typical symptoms, 33% of the throat cultures were 1+ positive and 45% were 4+ positive; for children with no symptoms, 39% of the cultures were 1+ positive and 24% were 4+ positive; for children with atypical symptoms, 54% of the cultures were 1+ positive and 21% were 4+ positive.

Classification of Isolates According to Symptoms

Each child with a positive culture for GAS was classified according to symptoms, with strict definitions. No symptoms were present (carriers plus transient subclinical infections) at the time of recovery for the majority of isolates (75%; range: 74–80% for each year). For the remaining positive cultures, 18% (range: 10–20% for each year) were associated with typical symptoms and 7% (range: 6–10% for each year) were associated with atypical symptoms. Overall, 8% of all episodes of illnesses associated with nasal congestion and/or cough but without sore throat were positive for GAS. This number excludes illnesses among children who were already known to be GAS carriers. There were no significant differences in the mean ages of children with no symptoms, typical symptoms, and atypical symptoms.

Children experienced episodes of acute GAS pharyngitis throughout the school year. The number of episodes of positive throat cultures associated with typical symptoms was examined according to the month of the year for each year of the study. In years 2, 3, and 4, there was a bimodal distribution of cases; the month in which episodes associated with typical symptoms peaked was variable (December, February, or April). The seasonal occurrence of episodes of GAS-positive throat cultures associated with typical symptoms and a new *emm* type was not different between children who were classified as GAS carriers and children who were not classified as carriers (P = .49).

Clinical Characteristics of Streptococcal Infections

Every child was classified into 1 of 4 groups for each year, ie, single episode, recurrent episodes, carrier, and no infections. The relative frequencies of each of the 4 categories were constant for the 4 years of the study. Little variation in the frequency of a given category was observed from year to year (Table 3). The most common classification was children with no infections (38-46%), whereas the least common category was recurrent infections (6-14%).

Fifty-six children were classified as experiencing a single episode in ≥1 school year. For the children with single episodes, 56% were associated with typical symptoms, 21% with atypical symptoms, and 23% with no symptoms. Forty of these children were monitored for ≥1 year after their single episode. Only 3 (8%) experienced a single episode in the following school year; in each case, the second episode involved a different *emm* type. Ten of the 40 children (25%) became carriers in the subsequent year, whereas 25 children (63%) had no infections in the subsequent year.

Recurrent episodes were very uncommon. They were observed for only 22 children during the 4-year period; most had only 2 episodes in 1 study year (Table 4). No more than 7 children had recurrent episodes in any given year. Twenty of the 22 children with recurrent episodes were monitored for ≥2 years, and only 2 of those children had recurrent

TABLE 3. Comparison of the Clinical Characteristics of the Children in the 4 Years of the Study

Classification	No. of Children (%)			
	1998–1999 (N = 48)	1999–2000 (N = 75)	2000–2001 (N = 100)	2001–2002 (N = 96)
No infections	18 (38)	29 (39)	39 (39)	44 (46)
Carriers	13 (27)	23 (31)	32 (32)	28 (29)
Single clinical infection	10 (21)	16 (21)	23 (23)	17 (18)
Recurrent infections	7 (14)	7 (9)	6 (6)	7 (7)

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TABLE 4. Characteristics of Children With Recurrent Episodes of Infection With GAS in a Single Study Year

	No. of Patients	No. With 2 Episodes	No. With 3 Episodes	No. of Pairs of Isolates	Same *emm* Type	Different *emm* Types
Year 1	7	4	3	10	4	6
Year 2	6	5	1	7	3	4
Year 3	6	4	2	6	4	2
Year 4	7	7	0	7	4	3
Totals	26*	22	4	30	15	15

The data in the right 2 columns should add up to the number of pairs of isolates that were compared in each year. For example, in year 1 there were 4 children who had 2 episodes each; therefore, there was 1 pair of isolates to compare for each child, for a total of 4 comparisons. In year 1, there were 3 children who had 3 episodes each. For these children, the first isolate was compared with the second isolate and the second isolate was compared with the third isolate. Each child who experienced 3 episodes had 2 pairs to compare, for a total of 6 pairs in this group. For year 1, there were 4 + 6 = 10 pairs of GAS isolates to compare. The number of pairs of GAS isolates compared is indicated.
* Twenty-two different children; 2 children had recurrent episodes in each of 3 years.

episodes in subsequent years. Children were treated with an antibiotic in 19 of the episodes because they were associated with clinical symptoms. Fifty percent of recurrent episodes were with different *emm* types. The mean time between infections was 9.33 weeks (SD: 7.59 weeks), with a range of 3 to 29 weeks. Recurrent episodes with the same *emm* type versus a different *emm* type were equally likely to occur independently of 1) the interval between episodes (<30 or >30 days apart) ($P = .71$), 2) the symptoms with the first episode ($P = .73$), and 3) whether the child received an antibiotic for the first episode ($P = .5$). For children who experienced recurrences with the same *emm* type, the 2 isolates had identical FIGE types. All children with recurrences with different *emm* types also had different FIGE types. All of the children who had recurrent episodes experienced a clinical and bacteriologic cure before the second episode of infection. There were only 3 children with a single negative throat culture between episodes of GAS with the same *emm* type. For all of these children, both episodes had typical symptoms and were treated promptly with an antibiotic. The mean time between episodes of the same *emm* type for all children was 10.68 weeks, and the mean time between episodes of different *emm* types was 8.84 weeks; these values were not significantly different.

Seventy-seven children completed ≥1 study year with no infections. Twenty-eight of the 50 children (56%) monitored for >1 year continued to have no infections in subsequent study years. Twenty-two of these 50 children (44%) were monitored for 4 years. Three had no infections during the entire 4-year period. Three had no infections in 3 years, and 12 had no infections in 2 years.

Carriers of GAS accounted for 27 to 32% of the cohort in each year of the study. The mean prevalence of carriers calculated according to month was 15.9% (SD: 4.99%; range: 4.2-26%). Eleven of the 13 children who were carriers in year 1 of the study were monitored for all 4 years. Ten of the 11 (91%) were carriers in subsequent years of the study. Seven were carriers for all 4 years, 1 for 3 years, and 2 for 2 years. If children were carriers in their first year of the study, then they were significantly more likely to continue to be carriers, compared with children who were not carriers in their first year ($P < .0001$).

Fifty-three children were classified as GAS carriers at least once. Of these 53 children, 24 (45%) had a positive throat culture when their first culture was performed; they were identified as carriers at study entry. The remaining 29 children began with negative throat cultures for GAS. Thirteen of these 29 children (45%) had typical symptoms at the time of their first positive throat culture. The remaining 16 (55%) had atypical symptoms or were asymptomatic when their first carrier culture was positive. Children who were classified as carriers had variable numbers of throat cultures that were positive during that school year; 29% had <25% of all throat cultures positive for GAS, 32% had 25% to 50% of all throat cultures positive, 21% had 50% to 75% of throat cultures positive, and 18% had >75% of all throat cultures positive for GAS.

Thirty-one of the 53 children who were carriers during ≥1 school year switched *emm* types at some point. There were 107 episodes in which these 31 children switched from carrying one *emm* type to carrying a different *emm* type during a single school year. Sixteen of the 107 episodes (15%) were associated with typical clinical symptoms at the time of type switching. Most episodes of switching (85%) were not associated with any clinical symptoms. Occasionally, a child who was a carrier of one *emm* type had a clinical infection with a second *emm* type and then resumed carriage with the first *emm* type. Three children switched *emm* types 7 times in the 4 years of the study.

The mean duration of carriage of one *emm* type was 10.8 weeks (SD: 9.1 weeks; range: 2-34 weeks). By definition, the duration of carriage could not be longer than 1 school year (34 weeks), because throat cultures were not performed during the summer break. However, there were 21 occurrences in which a child was noted to carry the same *emm* type in the last throat culture of one school year and the first throat culture of the following school year. If we presume that these children remained carriers of that *emm* type throughout the summer (June to September), then the maximal duration of carriage of one *emm* type was 127 weeks. For those 21 episodes, the

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range was 24 to 127 weeks, with a mean duration of 49 weeks.

Treatment

There were 209 episodes that were treated with an antibiotic. Of these, 78% involved typical symptoms of classic streptococcal pharyngitis. Eighty-six percent of these were treated with amoxicillin or penicillin, 7% were treated with azithromycin (before February 2001), 5% were treated with clindamycin, and 2% were treated with cephalexin. No clinical treatment failures were observed.

DISCUSSION

In clinical practice, the assignment of GAS as the cause of an episode of pharyngitis is based on temporal association. A child is considered to have streptococcal pharyngitis if he or she has a sore throat and a positive rapid diagnostic test or culture for GAS. Although microbiologic confirmation is essential, the recovery of GAS does not establish causality. The tests do not distinguish carriage of GAS in a child with pharyngitis attributable to another cause from an acute infection caused by GAS. To establish causality, it is theoretically necessary to demonstrate the host's response to the infection in the form of antibody production. However, this antibody response (serologic evidence of infection) does not occur for 2 to 3 weeks. Furthermore, the antibody response is frequently aborted with appropriate early antibiotic therapy.[20] The unique contribution of this study is the acquisition of systematic longitudinal data for school children, which overcomes the problems of interpretation of sporadic data obtained in clinical situations. All children in this cohort were accurately classified, during each year of the study, into 4 categories, ie, single episodes, recurrent episodes, carriers, and no infections.

Longitudinal studies that described the epidemiologic features of GAS infections among school children and in families were conducted previously.[7–10] However, the lack of available antisera and molecular typing systems when those studies were performed prevented precise tracking of infections. In 1 study, as many as 90% of the GAS isolates were nontypeable.[10] The inability to type the GAS isolates prevented the accurate categorization of episodes in which GAS were recovered. In contrast, the use of FIGE techniques and *emm* typing in our study, in conjunction with careful physical examinations and determination of clinical symptoms, allowed precise classification of each episode of infection/colonization with GAS.

One of the original goals of this investigation was to study how immunity to GAS is acquired. We hypothesized that a single infection with a given *emm* type would provide partial or complete immunity to reinfection with the same *emm* type. Recurrent infections were relatively uncommon among the subjects in this study. Approximately one-half of the recurrent episodes were caused by a GAS isolate of the same *emm* type as the first infection, independent of both the time between episodes and previous antibiotic treatment. This suggests that a single infection with a specific *emm* type may not be sufficient to induce type-specific immunity or that early treatment may abort the development of type-specific immunity. However, because recurrent episodes proved to be the least common of the clinical manifestations of infection with GAS, we are limited in our ability to speculate about the induction of immunity. A larger study of children presenting with symptomatic GAS pharyngitis will be necessary for determination of the epidemiologic features of recurrent episodes.

Although recurrent episodes were least common, single episodes were frequent. When a child had a single episode in 2 subsequent school years, the episodes always involved different *emm* types. These children might have acquired some type-specific protection. Many single episodes were typical in clinical presentation; however, 21% were atypical and 23% were completely asymptomatic. Some children had a single positive throat culture temporally associated with a clinical constellation that resembled a viral upper respiratory tract infection. The association of the clinical syndrome of rhinorrhea and GAS warrants additional study, to determine whether a causal relationship exists and to assess the potential implications of this relationship.

An intriguing observation in this study was that almost 40% of children remained uninfected each school year, despite the fact that they resided within this reservoir of GAS infection. The mean age of children with no infections was similar to that of the group as a whole. More than one-half of those who were uninfected in 1 year remained free of infection in a subsequent year. The local and systemic mechanisms that provide protection under these circumstances remain unknown. Protection may be based on mucosal immunity to the specific portion of the M-protein, local or systemic immunity to the conserved portion of the M-protein, or local production of peptides with antibacterial properties.[21,22]

The traditional definition of a GAS carrier is an asymptomatic individual with a positive throat culture and no serologic response. A second accepted definition is an asymptomatic child with a GAS-positive throat culture after completion of an appropriate course of antimicrobial treatment. In an effort to maintain participation in this study, serologic data were not sought from enrolled subjects. Instead, meticulous tracking of throat culture results, GAS typing, and correlation with the presence of clinical symptoms permitted accurate classification of each positive throat culture and each child. Demonstration of the persistence of identical GAS isolates with time, in the absence of any symptoms, provides strong evidence that a child is a GAS carrier.[23] This is independent of the relative number of GAS colonies found on the culture plate or serologic information.

Carriers of GAS constituted the largest group of children with positive throat cultures in our study. The prevalence of carriage varies dramatically according to the setting in which it is studied. In previous longitudinal studies like our own, carriage rates were reported to be extremely high (up to 25%).[7–10] In contrast, carriage rates evaluated in clin-

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ical practice or as part of a therapeutic trial were reported to be 2.5% to 11.5%.[24–27] Our study showed the prevalence of carriage to be 27% to 32% over the course of a school year, with an average point prevalence of 15.9% for any given month of the study (range: 4.2–26%). When the point prevalence is compared with the results of clinical practice studies, the results appear to be similar. Longitudinal studies may enhance the identification of carriers because asymptomatic children undergo repeated cultures. Furthermore, symptomatic children in our study were treated primarily with penicillin and amoxicillin. Some authors think that treatment with these antimicrobial agents may result in higher carrier rates after episodes of symptomatic infection, compared with other antimicrobial drugs.[27]

There are few studies that describe the natural history of pharyngeal carriage with GAS. Our data show that carriage is both common and persistent. The duration of carriage of a single *emm* type persisted between 3 and 123 weeks. Children who cleared the carrier state spontaneously demonstrated that they were likely to become carriers again. Ten of 11 children who were GAS carriers in the first year and were monitored over time remained carriers. This phenomenon has not been noted previously and may suggest a GAS carrier phenotype. Furthermore, the use of molecular markers in our study permitted recognition of the frequent changes in *emm* types among children who were carriers. Occasionally, the acquisition of a new *emm* type by a GAS carrier was associated with clinical symptoms. Usually, the children continued to carry the new strain; rarely, they reverted to carriage of their original *emm* type.

The observation that children who are carriers of GAS often acquire infection with new *emm* types has implications for the clinical approach for children who are known to be carriers. Although the conventional teaching has been that children who are carriers of GAS are not at risk to develop acute rheumatic fever,[28] children may be at risk when they acquire new *emm* types. It was recognized previously that 5% of children who are thought to be carriers have a serologic response to infection with GAS.[29] We hypothesize that this may be explained by the acquisition of a new *emm* type. On the basis of these observations and because we practice in an area of the country with a high rate of acute rheumatic fever,[17–19] we now routinely treat all infections associated with a GAS-positive throat culture among children with typical symptoms (sore throat and absence of cough and nasal congestion), even if the child is known to be a carrier of GAS. Practitioners in other areas of the country with similarly high rates of acute rheumatic fever should consider this approach.

Thirteen different *emm* types were identified among pharyngeal isolates of GAS during this 4-year study period. There are relatively few data on the distribution and frequency of various *emm* types among children with pharyngitis. Data from North Carolina showed that 6 M types caused most disease in that community between October 1993 and May 1994.[30] Haukness et al[31] found 12 *emm* types in 63 GAS isolates from 3 clinical offices in the Chicago area, during a 3-week period. Data from a study of GAS isolates obtained between September 2001 and May 2002 in the Pittsburgh community showed 7 different *emm* types among the erythromycin-resistant isolates.[32] Information that is available regarding invasive strains suggests that there is substantial overlap in the predominant *emm* types causing disease in different locations.[33] Because invasive strains generally reflect the predominant pharyngeal strains, it is anticipated that there will be substantial overlap in the *emm* types causing pharyngeal infections in different geographic areas. A comparison of the *emm* types of pharyngeal strains recovered in different geographic areas would provide important insights into the epidemiologic features of GAS infections at a national level.

The study population in this private school might be different from populations found in neighborhood, public, or religious schools in the United States, which might limit the generalizability of these data. There is substantial mixing of students at different grade levels, because instructional settings are based on readiness rather than age. In addition, these children are from many different school districts and >20 different zip codes. They have contact with children in their neighborhoods who do not attend the same school. On one hand, this may allow exposure to a greater number of *emm* types, compared with children in more traditional public school settings; on the other hand, because all children did not participate in the study, it is possible that the number of *emm* types circulating in the school has been understated. The fact that a single individual obtained 90% of the throat swabs and that all of the cultures were processed in the laboratory by a single senior technician minimizes the variability in collection and interpretation of throat cultures.

GAS-positive throat cultures are very common among school-aged children. The majority of positive throat cultures in this longitudinal study were obtained from children who proved to be carriers of GAS. Their cultures were not associated with the symptoms of GAS pharyngitis or with acute infection. This supports the recommendation of both the American Academy of Pediatrics and the Infectious Disease Society of America that only children who present with typical symptoms should have a rapid streptococcal test or throat culture performed to detect the presence of GAS.[23,34] Although children with GAS infections may present with atypical respiratory symptoms, until there is the capability of rapidly distinguishing acutely infected patients from carriers, testing for GAS should be performed selectively in clinical settings.

This study has allowed us to describe the various clinical and subclinical manifestations of infection with GAS among school-aged children. The factors that govern the clinical expression of streptococcal infection are unknown. How and why some children regularly incorporate GAS as part of their normal flora is also unknown. Neither local nor systemic mechanisms that protect against acquisition of streptococcal infection have been delineated. Despite our

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long familiarity with this resurgent pathogen, many questions remain to be answered.

ACKNOWLEDGMENTS

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Group A Streptococci Among School-Aged Children: Clinical Characteristics and the Carrier State

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Prevalence of Streptococcal Pharyngitis and Streptococcal Carriage in Children: A Meta-analysis

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KEY WORDS
Streptococcus, carriage, pediatrics, prevalence, meta-analysis

ABBREVIATIONS
GAS—group A *Streptococcus*
CI—confidence interval

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WHAT'S KNOWN ON THIS SUBJECT: The prevalence of group A streptococcal pharyngitis and carriage has not been systematically studied.

WHAT THIS STUDY ADDS: In this meta-analysis the authors provide clinicians with quantitative estimates of the prevalence of GAS infection and carriage in children of various ages.

abstract

OBJECTIVES: Prevalence estimates can help clinicians make informed decisions regarding diagnostic testing of children who present with symptoms of pharyngitis. We conducted a meta-analysis to determine the (1) prevalence of streptococcal infection among children who presented with sore throat and (2) prevalence of streptococcal carriage among asymptomatic children.

METHODS: We searched Medline for articles on pediatric streptococcal pharyngitis. We included articles in our review when they contained data on the prevalence of group A *Streptococcus* (GAS) from pharyngeal specimens in children who were younger than 18 years. Two evaluators independently reviewed, rated, and abstracted data from each article. Prevalence estimates were pooled in a meta-analysis and stratified according to age group.

RESULTS: Of the 266 articles retrieved, 29 met all inclusion criteria. Among children of all ages who present with sore throat, the pooled prevalence of GAS was 37% (95% confidence interval [CI]: 32%–43%). Children who were younger than 5 years had a lower prevalence of GAS (24% [95% CI: 21%–26%]). The prevalence of GAS carriage among well children with no signs or symptoms of pharyngitis was 12% (95% CI: 9%–14%).

CONCLUSIONS: Prevalence rates of GAS disease and carriage varied by age; children who were younger than 5 years had lower rates of throat cultures that were positive for GAS. *Pediatrics* 2010;126: e557–e564

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Clinicians are frequently faced with the decision of whether to obtain a pharyngeal swab for rapid antigen testing and/or culture to assess for the presence of group A *Streptococcus* (GAS) pharyngitis. Because GAS can lead to serious sequelae, particularly rheumatic fever, clinicians may be inclined to test children with the slightest suspicion of pharyngitis. Conversely, it is widely known that a subgroup of asymptomatic children have GAS detected in the pharynx as part of their flora (hereinafter referred to as carriers of GAS).

Knowledge of the prevalence of GAS infection among various subgroups of children can assist clinicians in selecting children who are likely to benefit from additional diagnostic testing. Using prevalence rates as an estimate of the previous probability of disease is the first step in evidence-based practice. In children with a very low pretest probability of GAS pharyngitis, routine diagnostic testing is not necessary. In such children, an indiscriminate approach to diagnostic testing might lead to more harm than benefit, especially if the rate of carriage of GAS is high. Prevalence estimates also help clinicians in the interpretation of test results and in the treatment of children with suspected GAS pharyngitis. We conducted a meta-analysis of the prevalence of GAS infection and carriage with the aim of providing clinicians with quantitative estimates for children of various ages.

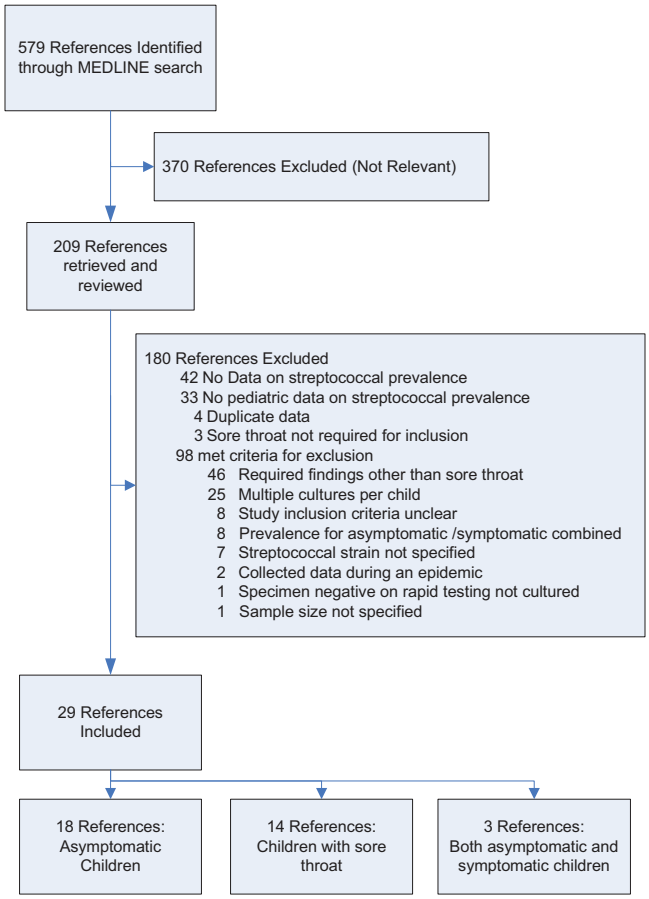

FIGURE 1
Flow diagram outlining the study selection process.

METHODS

We searched Medline (1950 through November 4, 2008) for articles on GAS pharyngitis or asymptomatic carriage in children who were younger than 18 years (Fig 1). Search terms included the following: Streptococcus infections (MeSH), streptococc*, pharyngitis, sore throat, strep throat, throat culture, tonsillitis, tonsillopharyngitis, subclinical, carrier*, carriage, coloni*, prevalence, incidence, and epidemiology. We reviewed full-text versions of articles that might contain data regarding prevalence of GAS infection and/or carriage. Only articles that were written in English, French, Italian, Spanish, and German were reviewed. Two evaluators (Drs Shaikh and Leonard) independently abstracted data from each article.

Explicit a priori inclusion and exclusion criteria were applied. We included an article when it reported data on the prevalence of GAS in children who presented to a clinician for evaluation of sore throat. Only studies that used throat cultures as the gold standard were included; studies in which rapid antigen tests were used were included only when specimens that were negative on the rapid antigen test were sent for culture confirmation. Although streptococcal grouping is ideally determined by using latex agglutination in a microbiological laboratory, sensitivity to bacitracin is often used in an office setting; therefore, we decided to include studies that used either test and to investigate whether the results differed on the basis of the test used. Because we were interested in the point prevalence of GAS, not the incidence of GAS over time, longitudinal studies in which the same child was cultured multiple times were excluded.

We excluded studies that (1) did not specifically identify the *Streptococcus* as group A, (2) included only children who lived in isolated communities or residential homes, (3) reported on an unusual epidemic of GAS, (4) included

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a large proportion (>30%) of children who had received antibiotics before the throat culture, and (5) required children to have signs and symptoms other than sore throat (eg, required fever). We excluded studies that did not describe the exact signs and symptoms required for patient enrollment. For example, some of the studies reviewed stated that enrollment was based on the presence of "pharyngitis." Because pharyngitis may be defined in many ways, when no additional clarification was provided in the methods, these studies were excluded.

Because various studies enrolled children of various ages, we planned to group the studies into 2 clinically relevant age categories: <5 years and 5 to 18 years. In a number of articles, however, the lower age cutoff was not specified (eg, "we enrolled children ≤15 years of age"). Because it is likely that the majority of the children in these studies were school-aged children, we analyzed all articles that included school children together despite the different lower age cutoffs used and examined the effect of the age cutoff on the prevalence rates. Finally, when the original study presented data stratified by age, we used the data in each stratum; therefore, data from 1 article may appear in several analyses. We also examined studies that reported streptococcal prevalence among asymptomatic children; however, studies that included both asymptomatic and symptomatic children were excluded when data for the groups could not be separated.

Quality Rating

We adapted a quality assessment system for prevalence articles.[1] Two investigators (Drs Shaikh and Leonard) assessed each study independently to determine whether (1) the study was prospective, (2) the study was consecutive (defined as the systematic and unbiased enrollment of potentially eligible patients), and (3) children who had recently (≤30 days) used antibiotics were excluded. We assessed these quality indicators separately for each article; a total quality score was not calculated.[2]

Statistical Methods

Prevalence was calculated by dividing the number of children with positive cultures for GAS by the number of children who underwent throat swabs.[3] We pooled the prevalence estimates by using standard meta-analytic techniques. All reported confidence intervals (CIs) represent the 95% CIs. We planned regression analyses with regard the following factors: lower age limit of children included in the study (see previous section), setting (emergency department versus outpatient clinic), and country (United States/Canada/Europe/Australia versus others), study quality (prospective, consecutive, excluded recent antibiotic use), and year of publication.

We also examined the effect of seasonality on prevalence rates by comparing streptococcal prevalence from studies that enrolled children during their respective winter season (November through April in the northern hemisphere and May through September in the southern hemisphere) with studies that enrolled children during the entire year. For this particular analysis, only studies that were conducted in cities that were not located between the Tropic of Cancer and the Tropic of Capricorn were included.

Data were imported into Stata 10.1, and a pooled estimate of GAS prevalence was calculated by using a random-effects model with inverse-variance weighting by using the DerSimonian and Laird method.[4] Statistical heterogeneity between and within groups was measured by using the χ^2 test for heterogeneity.

Because prevalence is clearly affected by the spectrum of patients included, we expected to find significant heterogeneity among studies. To deal with heterogeneity, we used meta-regression to identify subgroups in which pooling may be acceptable. Meta-regression, a modification of linear regression, investigates the extent to which heterogeneity among studies is related to various study characteristics. Finally, we used Galbraith plots to assess visually which studies were the most heterogeneous.

To evaluate the weight of particular articles on the pooled estimates, we performed influence analysis. This method recalculates the pooled prevalence estimate omitting 1 study at a time. We also conducted sensitivity analysis by examining the effect of (1) restricting the analysis to studies conducted in the United States or Canada, (2) restricting the analysis to studies that were conducted in an outpatient setting, and (3) excluding the most heterogeneous studies.

RESULTS

Description of Articles

A total of 515 articles were found through the described search strategy. From these, we retrieved 209 that were relevant for full-text review (Fig 1). Twenty-nine articles met all criteria for inclusion; 14 reported the prevalence of GAS recovered from children who presented with sore throat, 18 reported the prevalence of GAS carriage among asymptomatic patients, and 3 reported both.

Prevalence of GAS Among Children With Sore Throat

There was significant heterogeneity ($P < .001$) among the estimates from the 14 studies that reported data on the prevalence of GAS among children with sore throat (Table 1). On

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TABLE 1 Prevalence of GAS Infection Among Children Presenting With Sore Throat

Source	Age Range, y	*N*	Setting	Country	Prevalence (%)
All ages					
Romoin et al,[15] 2005	5–12	916	Clinic	Egypt/Croatia/Brazil	33
McIsaac et al,[16] 2004	3–17	454	Clinic	Canada	34
McIsaac et al,[17] 2000	3–14	158	Clinic	Canada	35
de Silva et al,[18] 1998	3–12	137	Clinic	Sri Lanka	45
McIsaac et al,[19] 1998	3–14	94	Clinic	Canada	36
Gunnarsson et al,[11] 1997	3–15	106	Clinic	Sweden	34
Dobbs et al,[20] 1996	4–11	86	Clinic	Ireland	48
Dagnelie et al,[21] 1993	4–14	80	Clinic	Netherlands	58
Pichichero et al,[22] 1992	<18	65 463	Clinic	United States	23
Hoffman et al,[23] 1992	≤14	466	Clinic	Denmark	42
Reed et al,[24] 1990	<19	375	ED	United States	33
Reed et al,[25] 1988	2–12	136	Clinic	United States	32
Feery et al,[26] 1976	6–16	47	Clinic	Australia	45
Forsyth et al,[27] 1975	≤14	213	Clinic	United States	31
Pooled prevalence (95% CI)					37 (32–43)
Younger than 5 y					
Romoin et al,[15] 2005	2–5	894	Clinic	Egypt/Croatia/Brazil	24
Gunnarsson et al,[11] 1997	0–2	40	Clinic	Sweden	18
Feery et al,[26] 1976	0–5	30	Clinic	Australia	17
Pooled prevalence (95% CI)					24 (21–26)

ED indicates emergency department.

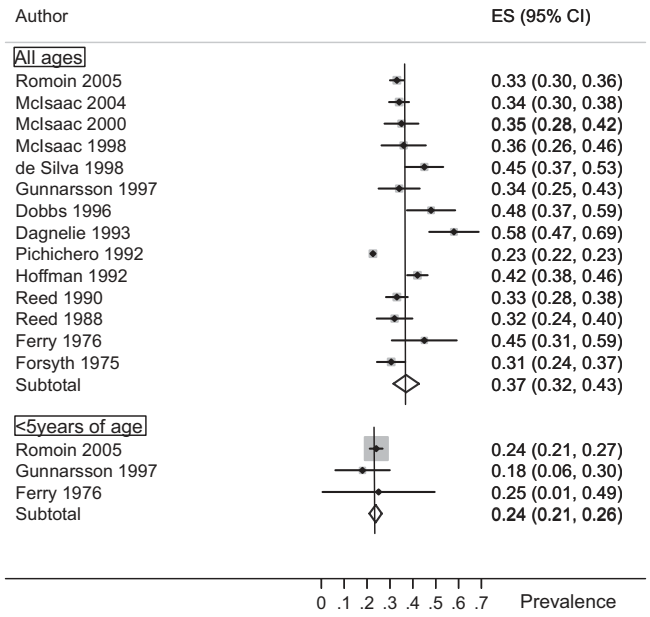

FIGURE 2
Prevalence (rectangles), 95% CI (lines), and pooled prevalence rate (diamonds) of streptococcal pharyngitis in children with sore throat, stratified by age.

stratified analysis, prevalence of GAS carriage was lower in studies that included only children who were younger than 5 years as compared with studies that included children of all ages ($P = .026$). Accordingly, we present separate analyses for GAS according to age group (Fig 2).

Only 3 studies provided data on the prevalence of GAS in children who had sore throat and were younger than 5 years (Fig 2). There was no heterogeneity among the estimates ($P = .6$) from these 3 studies, and the pooled prevalence of GAS was 24% (95% CI: 21%–26%).

Fourteen studies presented data on the prevalence of GAS among children of all ages with sore throat. The pooled prevalence of GAS from these studies was 37% (95% CI: 32%–43%). There was substantial heterogeneity among these studies ($P < .001$). To explore the reasons for this heterogeneity, we conducted meta-regression and sensitivity analysis. On meta-regression, there was no association between publication year, study quality, season, country, antibiotic use, laboratory test used to determine streptococcal group, or clinical setting and prevalence estimates. Influence analysis showed that omission of no single study significantly affected the pooled prevalence values. The Galbraith plot identified the populations studied by Dagnelie and Pichichero as the most heterogeneous; however, exclusion of 1 or both of these studies did not significantly alter the results; the prevalence of GAS was 36% (95% CI: 33%–39%) with both studies excluded. Sensitivity analysis revealed that prevalence of GAS was very similar when the analysis was restricted to studies that were conducted in the United States or Canada (37% [95% CI: 31%–43%]). Restricting the analysis to studies that were conducted in an outpatient setting also did not change the estimated significantly (38% [95% CI: 32%–43%).

Prevalence of GAS Carriage Among Asymptomatic Children

Eighteen studies presented data on GAS carriage among asymptomatic children who were younger than 18 years (Table 2). There was significant heterogeneity among the estimates from the studies ($P < .001$).

On stratified analysis, prevalence of GAS carriage was found to be lower in studies that included only children who were younger than 5 years as compared with studies that included children of all ages. Accordingly, we

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TABLE 2 Prevalence of GAS carriage Among Asymptomatic Children

Source	Age Range, y	*N*	Setting	Country	Prevalence (%)
All ages					
Unceta et al,[28] 2005	0.5–14	413	Clinic	Spain	12
Kim et al,[29] 2004	School aged	581	School	Korea	17
Fazeli et al,[30] 2003	6–13	1588	School	Iran	11
Gür et al,[31] 2002	6–16	1161	School	Turkey	14
Attia et al,[32] 2001	1–18	194	Clinic/ED	United States	15
Jasir et al,[33] 2000	School-aged	1885	School	Iran	21
Pichichero et al,[34] 1999	2–16	227	Clinic	United States	3
Gunnarsson et al,[11] 1997	3–15	565	School	Sweden	10
Edmond et al,[35] 1996	4–17	85	ED	Australia	5
Cimolai et al,[a] 1991	2–18	247	Clinic	Canada	13
Lieu et al,[36] 1988	1–17	100	ED	United States	20
Hofkosh et al,[37] 1988	3–15	414	Clinic	United States	5
Reed et al,[25] 1988	2–12	96	Clinic	United States	26
McMillan et al,[38] 1986	4–18	307	Clinic	United States	12
Ginsburg et al,[39] 1985	5–14	622	Clinic	United States	5
Karoui et al,[40] 1982	6–16	1041	School	Kuwait	10
Feery et al,[26] 1976	6–16	26	Clinic	Australia	15
Koshi et al,[41] 1971	<15	110	Clinic	India	5
Pooled prevalence (95% CI)					12 (9–14)
Younger than 5 y					
Gunnarsson et al,[11] 1997	0–2	216	School	Sweden	3
Edmond et al,[35] 1996	0–3	50	ED	Australia	10
Ginsburg et al,[39] 1985	0–5	740	Clinic	United States	2
Feery et al,[26] 1976	0–5	30	Clinic	Australia	17
Pooled prevalence (95% CI)					4 (1–7)

ED indicates emergency department.

[a] Cimolai N, Morrison BJ, MacCulloch L, Smith DF, Hlady J. Beta-haemolytic non-group A streptococci and pharyngitis: a case-control study. *Eur J Pediatrics*. 1991;150:776–779

present separate analyses for GAS carriage according to age group (Fig 3).

Only 4 studies provided data on the prevalence of GAS carriage in asymptomatic children who were younger than 5 years. Although there was some remaining heterogeneity among the estimates from these 4 studies ($P = .04$), the small sample of studies did not allow for meaningful meta-regression or sensitivity analysis. The pooled prevalence of GAS from these studies was 3.8% (95% CI: 1%–7%).

Eighteen studies provided data on the prevalence of GAS carriage among children of all ages. The pooled prevalence of GAS carriage in these studies was 12% (95% CI: 9%–14%). There was substantial heterogeneity among these studies ($P < .001$). On meta-regression, none of the variables investigated (see Methods) was associated with the prevalence estimates. Influence analysis showed that omission of no single study significantly changed the pooled prevalence estimates. The Galbraith plot identified the populations studied by Jasir and Pichichero as the most heterogeneous; however, exclusion of 1 or both of these studies did not significantly alter the results; the pooled prevalence with both studies excluded was 11% (95% CI: 9%–13%). Sensitivity analysis revealed that the pooled prevalence was very similar when the analysis was restricted to studies that were conducted in the United States or Canada (11% [95% CI: 7%–15%).

DISCUSSION

This study demonstrates that children who present with sore throat have a high probability of having GAS pharyngitis: 37% of children who presented to an outpatient clinic or emergency department with sore throat were found to have a throat culture that was positive for GAS. The prevalence of GAS in an unselected, office-based adult population has been estimated to be in the range of 5% to 10%.[5] The relatively high probability of GAS disease and acute rheumatic fever in school-aged children, as compared with adults and children who are younger than 5 years, suggests that testing of school-aged children who present with sore throat is beneficial. This is in accordance with the strategies endorsed by the Committee on Infectious Diseases of the American Academy of Pediatrics,[6] the American Heart Association,[7] and the Infectious Disease Society of America.[8]

Only 3 studies provided data on the prevalence of GAS in children who were younger than 5 years and had a sore throat. In those studies, 24% of children who were younger than 5 years and presented with sore throat were positive for GAS; however, because acute rheumatic fever occurs infrequently among preschool children,[9] more data are needed to determine whether routine testing in this age group is justified. It may be the case that presence of other risk factors (eg, age >3 years, older sibling with GAS infection, other signs and symptoms) can be used to select a subgroup of children who have sore throat and would benefit from routine testing.

Twelve percent of children who were older than 5 years were found to be carriers of GAS. This is in agreement with previous epidemiologic studies to date.[10–14] Because it is not possible to distinguish between a child who has a viral infection and is a carrier for GAS and a child who has an acute streptococcal infection and because the prevalence of GAS carriage is relatively high in the school-aged population (~1 in 8), children who have repeated episodes of sore throat and continue to test positive for GAS should be carefully evaluated. Although posttreatment cultures are unnecessary in the majority of patients with GAS pharyngitis,[7] in selected children with recurrent pharyngitis, posttreatment test-

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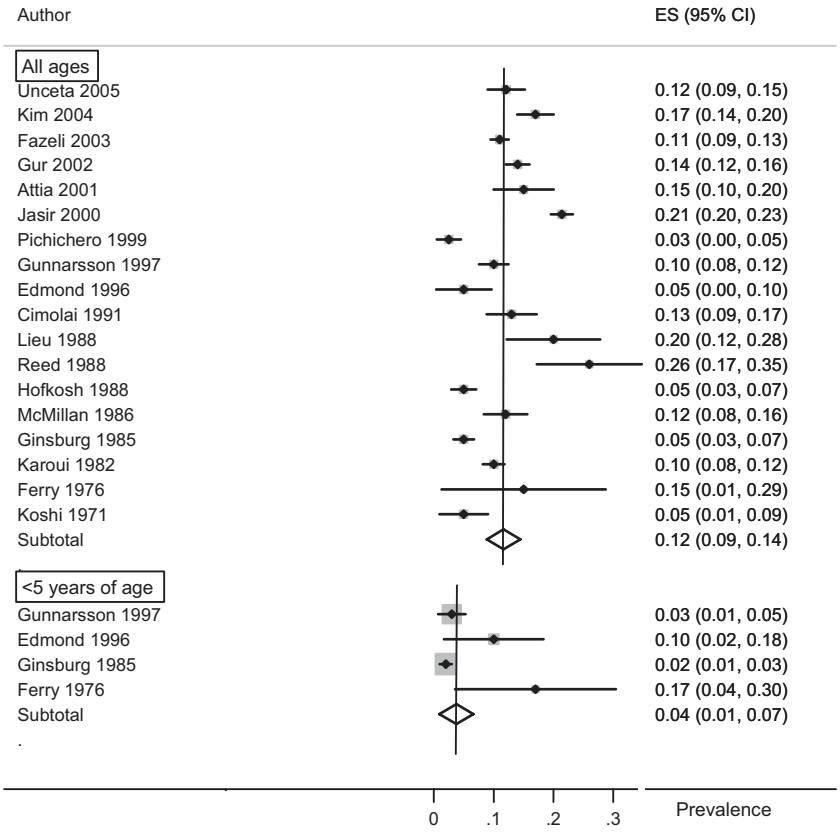

FIGURE 3
Prevalence (rectangles), 95% CI (lines), and pooled prevalence rate (diamonds) of streptococcal carriage in asymptomatic children, stratified by age.

ing may help to differentiate children with true recurrent GAS pharyngitis from carriers; children who are carriers are likely to have persistent GAS even after being treated with appropriate antimicrobial agents.

A somewhat surprising finding was that the prevalence of GAS infection and carriage did not vary significantly among studies that enrolled children only in the winter and those that enrolled children all year. Previous longitudinal studies, which are clearly better at identifying seasonal trends, have convincingly documented that GAS is a seasonal disease. There may be 2 reasons that this seasonality was not observed in our analysis. First, prevalence of GAS was not stratified by season in most of the articles. As such, we could not compare prevalence rates from the winter months with the prevalence rates in the rest of the year. Rather, we compared studies that enrolled children only during the winter with studies that enrolled children all year long. No studies enrolled children during the summer months only. In studies that enrolled children throughout the year, the majority of children were likely to have been enrolled during the winter months; therefore, because of how the data were reported, we were limited in our ability to discern seasonal trends in the data; our data do not conflict with the well-documented seasonality of GAS pharyngitis.

Our analysis had several limitations. The first limitation relates to the paucity of studies with data on children who were younger than 5 years. Additional study on the prevalence of GAS in preschool children is warranted. Second, the heterogeneity among studies could be considered a limitation. We used our clinical judgment and results of the meta-regression analysis to determine when studies were "too different" to be pooled. For example, rather than blindly pooling data from all of the studies, we present data for less heterogeneous subgroups of patients on the basis of age. Much of the remaining heterogeneity is likely attributable to the differences in implicit criteria used by investigators during enrollment. This would have led to differences in the clinical spectrum of patients who were included in various studies. In other words, although all studies met our inclusion criteria, the severity of symptoms of the children enrolled may have varied on the basis of the approach of the investigators or the objectives of the study. Nevertheless, by conducting a comprehensive review of the literature and by using strict a priori inclusion and exclusion criteria, our results provide a more complete picture of GAS prevalence than has previously been reported. Our results were robust to changes in the assumptions tested by sensitivity analyses, and the pooled estimates have relatively narrow CIs.

CONCLUSIONS

This study provides important information for the clinician regarding the expected prevalence of GAS from pharyngeal specimens obtained from children with sore throat and from children who are asymptomatic. The pooled prevalence values presented in this study can be used as an estimate of baseline probability and provide a basis for an evidence-based approach to the treatment of children with this frequently occurring condition.

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Dr Shaikh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Prevalence of Streptococcal Pharyngitis and Streptococcal Carriage in Children: A Meta-analysis

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CanLII

R. v. Mabior, 2012 SCC 47 (CanLII), [2012] 2 SCR 584

Date:	2012-10-05
File number:	33976
Other citations:	434 NR 341 — [2012] 11 WWR 213 — 284 Man R (2d) 114 — [2012] EXP 3544 — 96 CR (6th) 1 — 290 CCC (3d) 32 — 268 CRR (2d) 39 — 103 WCB (2d) 905 — EYB 2012-212075 — JE 2012-1903 — [2012] SCJ No 47 (QL) — [2012] ACS no 47
Citation:	R. v. Mabior, 2012 SCC 47 (CanLII), [2012] 2 SCR 584, <https://canlii.ca/t/ft1pq>, retrieved on 2021-05-10

SUPREME COURT OF CANADA

CITATION: R. *v.* Mabior, 2012 SCC 47, [2012] 2 S.C.R. 584

DATE: 20121005
DOCKET: 33976

BETWEEN:

Her Majesty The Queen
Appellant
and
Clato Lual Mabior
Respondent
- and -
Canadian HIV/AIDS Legal Network, HIV & AIDS Legal Clinic Ontario, Coalition des organismes communautaires québécois de lutte contre le sida, Positive Living Society of British Columbia, Canadian AIDS Society, Toronto People With AIDS Foundation, Black Coalition for AIDS Prevention, Canadian Aboriginal AIDS Network, British Columbia Civil Liberties Association, Criminal Lawyers' Association of Ontario, Association des avocats de la défense de Montréal and Institut national de santé publique du Québec
Interveners

CORAM: McLachlin C.J. and LeBel, Deschamps, Fish, Abella, Rothstein, Cromwell, Moldaver and Karakatsanis JJ.

REASONS FOR JUDGMENT: (paras. 1 to 110)	McLachlin C.J. (LeBel, Deschamps, Fish, Abella, Rothstein, Cromwell, Moldaver and Karakatsanis JJ. concurring)

Her Majesty The Queen *Appellant*

v.

Clato Lual Mabior *Respondent*

and

Canadian HIV/AIDS Legal Network,
HIV & AIDS Legal Clinic Ontario, Coalition des organismes communautaires québécois de lutte contre le sida, Positive Living Society of British Columbia, Canadian AIDS Society, Toronto People With AIDS Foundation,
Black Coalition for AIDS Prevention, Canadian Aboriginal AIDS Network,
British Columbia Civil Liberties Association,
Criminal Lawyers' Association of Ontario,
Association des avocats de la défense de Montréal and
Institut national de santé publique du Québec *Interveners*

Indexed as: R. *v.* Mabior

2012 SCC 47

File No.: 33976.

2012: February 8; 2012: October 5.

Present: McLachlin C.J. and LeBel, Deschamps, Fish, Abella, Rothstein, Cromwell, Moldaver and Karakatsanis JJ.

ON APPEAL FROM THE COURT OF APPEAL FOR MANITOBA

Criminal law — Aggravated assault — Consent — Fraud — Non-disclosure of HIV status — Accused undergoing antiretroviral therapy and having protected and unprotected sexual relations knowing he was HIV-positive — Whether approach outlined in R. v. Cuerrier, 1998 CanLII 796 (SCC), [1998] 2 S.C.R. 371, remains valid in determining whether fraud vitiates consent to sexual relations — Whether non-disclosure of HIV status in circumstances where no realistic possibility of transmission exists can constitute fraud vitiating consent — Criminal Code, R.S.C. 1985, c. C-46, ss. 265(3)(c), 268, 273.

M was charged with nine counts of aggravated sexual assault based on his failure to disclose his HIV-positive status to nine complainants before having sex with them (ss. 265(3)(*c*) and 273 *Cr. C.*). None of the complainants contracted HIV. The trial judge convicted him on six of the counts and acquitted him on the other three, on the basis that sexual intercourse using a condom when viral loads are undetectable does not place a sexual partner at "significant risk of serious bodily harm", as required by *Cuerrier*. The Court of Appeal varied the decision, holding that either low viral loads or condom use could negate significant risk. This reduced to two the

counts on which M could be convicted, and the Court of Appeal entered acquittals on the four remaining counts. The Crown appealed the acquittals.

Held: The appeal should be allowed in part and the convictions in respect of the complaints by S.H., D.C.S. and D.H. should be restored. The appeal should be dismissed in respect of the complaint by K.G.

This Court, in *Cuerrier*, established that failure to disclose that one has HIV may constitute fraud vitiating consent to sexual relations under s. 265(3)(*c*) *Cr. C.* Because HIV poses a risk of serious bodily harm, the operative offence is one of aggravated sexual assault (s. 273 *Cr. C.*). To obtain a conviction under ss. 265(3)(*c*) and 273, the Crown must show, beyond a reasonable doubt, that the complainant's consent to sexual intercourse was vitiated by the accused's fraud as to his HIV status. The test boils down to two elements: (1) *a dishonest act* (either falsehoods or failure to disclose HIV status); and (2) *deprivation* (denying the complainant knowledge which would have caused him or her to refuse sexual relations that exposed him or her to a significant risk of serious bodily harm). Failure to disclose may amount to fraud where the complainant would not have consented had he or she known the accused was HIV-positive, and where sexual contact poses a significant risk of or causes actual serious bodily harm.

Two main criticisms of the *Cuerrier* test have been advanced: first, that it is uncertain, failing to draw a clear line between criminal and non-criminal conduct, and second, that it either overextends the criminal law or confines it too closely — the problem of breadth. While it may be difficult to apply, the *Cuerrier* approach is in principle valid. It carves out an appropriate area for the criminal law — one restricted to "significant risk of serious bodily harm". The test's approach to consent accepts the wisdom of the common law that not every deception that leads to sexual intercourse should be criminalized, while still according consent meaningful scope.

The *Cuerrier* requirement of "significant risk of serious bodily harm" should be read as requiring disclosure of HIV status if there is a realistic possibility of transmission of HIV. This view is supported by the common law and statutory history of fraud vitiating consent to sexual relations, and is in line with *Charter* values of autonomy and equality that respect the interest of a person to choose whether to consent to sex with a particular person or not. It also gives adequate weight to the nature of the harm involved in HIV transmission, and avoids setting the bar for criminal conviction too high or too low. If there is no realistic possibility of transmission of HIV, failure to disclose that one has HIV will not constitute fraud vitiating consent to sexual relations under s. 265(3)(*c*).

The evidence adduced in this case leads to the conclusion that, as a general matter, a realistic possibility of transmission of HIV is negated if: (i) the accused's viral load at the time of sexual relations was low *and* (ii) condom protection was used. This general proposition does not preclude the common law from adapting to future advances in treatment and to circumstances where risk factors other than those considered in this case are at play.

Here, the four complainants all consented to sexual intercourse with M, and testified that they would not have had sex with him had they known he was HIV-positive. M had intercourse by vaginal penetration with the four complainants, during which he ejaculated. At the time of intercourse with the complainants S.H., D.C.S. and D.H., M had a low viral load but did not use a condom. Consequently, those convictions should be maintained. As regards K.G., the record shows that M's viral load was low. When combined with condom protection, this did not expose K.G. to a significant risk of serious bodily harm. This conviction must accordingly be reversed.

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Applied: *R. v. Cuerrier*, 1998 CanLII 796 (SCC), [1998] 2 S.C.R. 371; **referred to:** *R. v. D.C.*, 2012 SCC 48, [2012] 2 S.C.R. 626; *Proprietary Articles Trade Association v. Attorney-General for Canada*, 1931 CanLII 385 (UK JCPC), [1931] A.C. 310; *Reference re Validity of Section 5(a) of the Dairy Industry Act*, 1948 CanLII 2 (SCC), [1949] S.C.R. 1, aff'd 1950 CanLII 342 (UK JCPC), [1951] A.C. 179; *Lord's Day Alliance of Canada v. Attorney General of British Columbia*, 1959 CanLII 42 (SCC), [1959] S.C.R. 497; *The Queen v. Sault Ste. Marie*, 1978 CanLII 11 (SCC), [1978] 2 S.C.R. 1299; *Boggs v. The Queen*, 1981 CanLII 39 (SCC), [1981] 1 S.C.R. 49; *Skoke-Graham v. The Queen*, 1985 CanLII 60 (SCC), [1985] 1 S.C.R. 106; *R. v. Roy*, 2012 SCC 26, [2012] 2 S.C.R. 60; *R. v. Beatty*, 2008 SCC 5, [2008] 1 S.C.R. 49; *The Queen v. Clarence* (1888), 22 Q.B.D. 23; *R. v. Flattery* (1877), 13 Cox C.C. 388; *R. v. Dee* (1884), 15 Cox C.C. 579; *R. v. Bennett* (1866), 4 F. & F. 1105, 176 E.R. 925; *R. v. Sinclair* (1867), 13 Cox C.C. 28; *Hegarty v. Shine* (1878), 14 Cox C.C. 124, aff'd 14 Cox C.C. 145;

Papadimitropoulos v. The Queen (1957), 98 C.L.R. 249; *R. v. Harms* (1943), 1943 CanLII 146 (SK CA), 81 C.C.C. 4; *Bolduc v. The Queen*, 1967 CanLII 57 (SCC), [1967] S.C.R. 677; *R. v. Petrozzi* (1987), 1987 CanLII 2786 (BC CA), 35 C.C.C. (3d) 528; *R. v. Lee* (1991), 1991 CanLII 7351 (ON SC), 3 O.R. (3d) 726; *R. v. Ssenyonga* (1993), 1993 CanLII 14680 (ON SC), 81 C.C.C. (3d) 257; *State v. Marcks*, 41 S.W. 973 (1897), and 43 S.W. 1095 (1898); *State v. Lankford*, 102 A. 63 (1917); *United States v. Johnson*, 27 M.J. 798 (1988); *United States v. Dumford*, 28 M.J. 836 (1989); *R. v. Maurantonio*, 1967 CanLII 317 (ON CA), [1968] 1 O.R. 145; *R. v. Sharpe*, 2001 SCC 2, [2001] 1 S.C.R. 45; *Application under s. 83.28 of the Criminal Code (Re)*, 2004 SCC 42, [2004] 2 S.C.R. 248; *R. v. Ewanchuk*, 1999 CanLII 711 (SCC), [1999] 1 S.C.R. 330; *R. v. B.*, [2006] EWCA Crim 2945, [2007] 1 W.L.R. 1567; *R. v. Mwai*, [1995] 3 N.Z.L.R. 149; *R. v. Find*, 2001 SCC 32, [2001] 1 S.C.R. 863; *R. v. Spence*, 2005 SCC 71, [2005] 3 S.C.R. 458; *Twining v. Morrice* (1788), 2 Bro. C.C. 326, 29 E.R. 182; *Conolly v. Parsons* (1797), 3 Ves. 625n; *Walters v. Morgan* (1861), 3 De G. F. & J. 718, 45 E.R. 1056; *R. v. McCraw*, 1991 CanLII 29 (SCC), [1991] 3 S.C.R. 72; *R. v. Jones*, 2002 NBQB 340, [2002] N.B.J. No. 375 (QL); *R. v. J.A.T.*, 2010 BCSC 766 (CanLII).

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APPEAL from a judgment of the Manitoba Court of Appeal (Steel, MacInnes and Beard JJ.A.), 2010 MBCA 93, 258 Man. R. (2d) 166, 261 C.C.C. (3d) 520, 79 C.R. (6th) 1, [2011] 2 W.W.R. 211, [2010] M.J. No. 308 (QL), 2010 CarswellMan 587, setting aside convictions for aggravated sexual assault entered by McKelvey J., 2008 MBQB 201, 230 Man. R. (2d) 184, [2008] M.J. No. 277 (QL), 2008 CarswellMan 406. Appeal allowed in part.

Elizabeth Thomson and *Ami Kotler*, for the appellant.

Amanda Sansregret and *Corey La Berge*, for the respondent.

Jonathan Shime, *Corie Langdon*, *Richard Elliott* and *Ryan Peck*, for the interveners the Canadian HIV/AIDS Legal Network, the HIV & AIDS Legal Clinic Ontario, Coalition des organismes communautaires québécois de lutte contre le sida, the Positive Living Society of British Columbia, the Canadian AIDS Society, the Toronto People With AIDS Foundation, the Black Coalition for AIDS Prevention and the Canadian Aboriginal AIDS Network.

Michael A. Feder and *Angela M. Juba*, for the intervener the British Columbia Civil Liberties Association.

P. Andras Schreck and *Candice Suter*, for the intervener the Criminal Lawyers' Association of Ontario.

François Dadour, for the intervener Association des avocats de la défense de Montréal.

Lucie Joncas and *François Côté*, for the intervener Institut national de santé publique du Québec.

The judgment of the Court was delivered by

THE CHIEF JUSTICE —

I. Overview

[1] This case raises the issue of whether an HIV-positive person who engages in sexual relations without disclosing his condition commits aggravated sexual assault.

[2] Sex without consent is sexual assault under s. 265 of the *Criminal Code*, R.S.C. 1985, c. C-46. *R. v. Cuerrier*, 1998 CanLII 796 (SCC), [1998] 2 S.C.R. 371, establishes that failure to advise a partner of one's HIV status may constitute fraud vitiating consent. Because HIV poses a risk of serious bodily harm, the operative offence is one of aggravated sexual assault, attracting a maximum sentence of life imprisonment: *Cuerrier*, at para. 95; ss. 265, 268 and 273 *Cr. C.*

[3] While *Cuerrier* laid down the basic requirements for the offence, the precise circumstances when failure to disclose HIV status vitiates consent and converts sexual activity into a criminal act remain unclear. The parties ask this Court for clarification.

[4] I conclude that a person may be found guilty of aggravated sexual assault under s. 273 of the *Criminal Code* if he fails to disclose HIV-positive status before intercourse and there is a realistic possibility that HIV will be transmitted. If the HIV-positive person has a low viral count as a result of treatment and there is condom protection, the threshold of a realistic possibility of transmission is not met, on the evidence before us.

II. Background

[5] The respondent, Mr. Mabior, lived in Winnipeg. His house was a party place. People came in and out, including a variety of young women. Alcohol and drugs were freely dispensed. From time to time, Mr. Mabior had sex with women who came to his house, including the nine complainants in this case.

[6] Mr. Mabior did not tell the complainants that he was HIV-positive before having sex with them; indeed, he told one of them that he had no STDs. On some occasions, he wore condoms, on others he did not. Sometimes the condoms broke or were removed, and in some cases, the precise nature of the protections taken is unclear. Eight of the nine complainants testified that they would not have consented to sex with Mr. Mabior had they known he was HIV-positive. None of the complainants contracted HIV.

[7] Mr. Mabior was charged with nine counts of aggravated sexual assault (and other related offences), based on his failure to disclose to the complainants that he was HIV-positive. In defence, Mr. Mabior called evidence that he was under treatment, and that he was not infectious or presented only a low risk of infection at the relevant times.

[8] The trial judge convicted Mr. Mabior of six counts of aggravated sexual assault (2008 MBQB 201, 230 Man. R. (2d) 184). She acquitted him on the other three, on the basis that sexual intercourse using a condom when viral loads are undetectable does not place a sexual partner at "significant risk of serious bodily harm", as required by *Cuerrier*.

[9] Mr. Mabior appealed from these six convictions; the Crown did not appeal from the three acquittals. The Manitoba Court of Appeal varied the trial judge's decision, holding that *either* low viral loads *or* condom use could negate significant risk (2010 MBCA 93, 258 Man. R. (2d) 166). This reduced to two the counts on which Mr. Mabior could be convicted, and the Court of Appeal entered acquittals on the four remaining counts. The Crown appeals these acquittals. Mr. Mabior has not cross-appealed against the two convictions upheld by the Court of Appeal.

III. The Legislation

[10] Sections 265 and 273 of the *Criminal Code* provide:

> **265.** (1) A person commits an assault when
>
> (*a*) without the consent of another person, he applies force intentionally to that other person, directly or indirectly;
>
> . . .
>
> (2) This section applies to all forms of assault, including sexual assault . . . and aggravated sexual assault.
>
> (3) For the purposes of this section, no consent is obtained where the complainant submits or does not resist by reason of
>
> . . .
>
> (*c*) fraud;
>
> . . .
>
> **273.** (1) Every one commits an aggravated sexual assault who, in committing a sexual assault, wounds, maims, disfigures or endangers the life of the complainant.
>
> (2) Every person who commits an aggravated sexual assault is guilty of an indictable offence and liable
>
> . . .
>
> (*b*) in any other case, to imprisonment for life.

IV. The Issues

[11] The issues are as follows:

A. What is the correct interpretation of "fraud" vitiating consent to sexual activity in s. 265(3)(*c*) of the *Criminal Code*?

(1) Problems with the existing interpretation of "fraud" vitiating consent:

(a) Uncertainty;

(b) Breadth.

(2) Guides to interpretation:

(a) The purposes of the criminal law;

(b) The common law and statutory history of fraud vitiating consent to sexual relations;

(c) *Charter* values;

(d) The experience of other common law jurisdictions.

(3) Finding a solution:

(a) The active misrepresentation approach;

(b) The absolute disclosure approach;

(c) A case-by-case fact-based approach;

(d) Judicial notice;

(e) Relationship-based distinctions;

(f) The reasonable partner approach;

(g) An evolving common law approach.

(4) Realistic possibility of HIV transmission.

V. Discussion

A. *What is the Correct Interpretation of "Fraud" Vitiating Consent to Sexual Activity in Section 265(3)(c) of the Criminal Code?*

(1) Problems With the Existing Interpretation of "Fraud" Vitiating Consent

[12] This Court considered "fraud" under s. 265(3)(*c*) 14 years ago in *Cuerrier*. The majority test in *Cuerrier* may be stated in different ways, but boils down to two elements: (1) *a dishonest act* (either falsehoods or failure to disclose HIV status); and (2) *deprivation* (denying the complainant knowledge which would have caused her to refuse sexual relations that exposed her to a significant risk of serious bodily harm).

[13] We are invited to revisit the *Cuerrier* test by the parties and by the Manitoba Court of Appeal in this case and the Quebec Court of Appeal in the companion case of *R. v. D.C.*, 2012 SCC 48, [2012] 2 S.C.R. 626. Two main criticisms of the *Cuerrier* test are advanced: first, that it is uncertain, failing to draw a clear line between criminal and non-criminal conduct (uncertainty), and second, that it either overextends the criminal law or confines it too closely — the problem of breadth.

[14] I turn first to the criticism that the *Cuerrier* test is uncertain. It is a fundamental requirement of the rule of law that a person should be able to predict whether a particular act constitutes a crime at the time he commits the act. The rule of law requires that laws provide in advance what can and cannot be done: Lord Bingham, *The Rule of Law* (2010). Condemning people for conduct that they could not have reasonably known was criminal is Kafkaesque and anathema to our notions of justice. After-the-fact condemnation violates the concept of liberty in s. 7 of the *Canadian Charter of Rights and Freedoms* and has no place in the Canadian legal system.

[15] The *Cuerrier* test gives rise to two uncertainties — what constitutes "significant risk" and what constitutes "serious bodily harm"? These terms are broad and different people can and do read them in different ways.

[16] About "significant risk", some people say that virtually any risk of serious bodily harm is significant. Others argue that to be significant, the risk must rise to a higher level. These debates centre on statistical percentages. Is a 1% risk "significant"? Or should it be 10% or 51% or, indeed, .01%? How is a prosecutor to know or a judge decide? And if prosecutors, defence counsel and judges debate the point, how — one may ask — is the ordinary Canadian citizen to know? This uncertainty is compounded by the fact that a host of variables may affect the actual risk of infection.

[17] Debate has also surrounded the requirement that the risk be one of "serious bodily harm". Some sexually transmitted diseases ("STDs") involve little beyond treatable temporary discomfort. Yet even that discomfort, while it persists, may be serious from the perspective of the victim. Other STDs, like HIV, are extremely serious, involving permanent and life-altering symptoms, and in some cases death. Between these two extremes lie many other STDs, some more debilitating than others. Which are sufficiently serious to attract the sanction of the criminal law? *Cuerrier* offers no clear answer.

[18] The uncertainty inherent in the concepts of significant risk and serious bodily harm is compounded by the fact that they are interrelated. The more serious the nature of the harm, the lower the probability of transmission need be to amount to a significant risk of serious bodily harm, it is argued. So it is not simply a matter of percentage of risk and seriousness of the potential disease. It is a matter of the two as they relate to each other.

[19] What emerges is a complex calculus that makes it impossible, in many cases, to predict in advance whether a particular act is criminal under s. 265(3)(*c*) or not. The second major criticism of *Cuerrier* relates to the scope of the conduct it catches. The danger of an overbroad interpretation is the criminalization of conduct that does not present the level of moral culpability and potential harm to others appropriate to the ultimate sanction of the criminal law. A criminal conviction and imprisonment, with the attendant stigma that attaches, is the most serious sanction the law can impose on a person, and is generally reserved for conduct that is highly culpable — conduct that is viewed as harmful to society, reprehensible and unacceptable. It requires both a culpable act — *actus reus* — and a guilty mind — *mens rea* — the parameters of which should be clearly delineated by the law.

(2) Guides to Interpretation

[20] As for all issues of statutory interpretation, the basic question is what Parliament intended. That intention is discovered by looking at the words of the provision, informed by its history, context and purpose.

[21] The words of s. 265(3)(*c*) do not on their face reveal much about how Parliament intended "fraud" to be interpreted. The concept was taken by Parliament from the common law.

[22] The interpretation of "fraud" vitiating consent to sexual relations is informed by four considerations: (a) the purposes of the criminal law; (b) the common law and statutory history of the concept; (c) *Charter* values, particularly equality, autonomy, liberty, privacy and human dignity; and (d) the experience of other common law jurisdictions. I will consider each in turn.

(a) *The Purposes of the Criminal Law*

[23] The interpretation of fraud vitiating consent to sexual relations should further the purposes of the criminal law, notably identifying, deterring and punishing criminal conduct, defined by a wrongful act and guilty mind. Morality infuses the criminal law. But the law does not seek to criminalize all immorality. The principal objective of the criminal law is the public identification of wrongdoing *qua* wrongdoing which violates public order and is so blameworthy that it deserves penal sanction: *Proprietary Articles Trade Association v. Attorney-General for Canada*, 1931 CanLII 385 (UK JCPC), [1931] A.C. 310 (P.C.); *Reference re Validity of Section 5(a) of the Dairy Industry Act*, 1948 CanLII 2 (SCC), [1949] S.C.R. 1, aff'd 1950 CanLII 342 (UK JCPC), [1951] A.C. 179 (P.C.); *Lord's Day Alliance of Canada v. Attorney General of British Columbia*, 1959 CanLII 42 (SCC), [1959] S.C.R. 497; *The Queen v. Sault Ste. Marie*, 1978 CanLII 11 (SCC), [1978] 2 S.C.R. 1299; *Boggs v. The Queen*, 1981 CanLII 39 (SCC), [1981] 1 S.C.R. 49; *Skoke-Graham v. The Queen*, 1985 CanLII 60 (SCC), [1985] 1 S.C.R. 106.

[24] The law draws a sharp distinction between civil wrongdoing and criminal wrongdoing. Criminal conduct requires both a wrongful act and a guilty mind. It requires "a significant fault element": *R. v. Roy*, 2012 SCC 26, [2012] 2 S.C.R. 60, at para. 32. As Charron J. stated for the majority of this Court in *R. v. Beatty*, 2008 SCC 5, [2008] 1 S.C.R. 49, at para. 34:

> If every departure from the civil norm is to be criminalized, regardless of the degree, we risk casting the net too widely and branding as criminals persons who are in reality not morally blameworthy. Such an approach risks violating the principle of fundamental justice that the morally innocent not be deprived of liberty.

The potential consequences of a conviction for aggravated sexual assault — up to life imprisonment — underline the importance of insisting on moral blameworthiness in the interpretation of s. 265(3)(*c*) of the *Criminal Code*.

(b) *The Common Law and Statutory History of Fraud Vitiating Consent to Sexual Relations*

[25] The common law history of fraud vitiating consent to sexual relations reveals three periods. The early cases support the view that failure to disclose to a partner the fact that one has a serious sexually transmitted disease could constitute fraud vitiating consent to sexual relations, resulting in convictions for rape or assault. This was reversed in *The Queen v. Clarence* (1888), 22 Q.B.D. 23 (Cr. Cas. Res.), which held that fraud was confined to deception as to the sexual nature of the act or as to the identity of the male sexual partner. In the post-*Charter* era, a return to a broader view of fraud vitiating consent is appropriate.

[26] The first recorded cases to look at the problem before us took a generous approach to consent to sexual intercourse — one that accepted that sexual partners (always women in those days) were entitled to refuse sexual intercourse and should not be tricked into it by deceit. The courts adopted a flexible approach to "fraud" vitiating consent to sexual relations. Without attempting to define the term, they showed themselves willing to extend the term to fundamental aspects of sexual intercourse.

[27] For example, in *R. v. Flattery* (1877), 13 Cox C.C. 388 (C.C.A.), a conviction of rape was upheld for a man operating a booth at a fair who had obtained sex from a girl of 19 on the pretext of medical treatment. It was held that the victim's consent to physical contact with the accused was vitiated by his fraud, because she had only consented to a surgical operation, and not to a sexual act.

[28] Similarly, early common law cases accepted that impersonation of the spouse — falsely pretending to be the victim's husband — could constitute fraud vitiating consent. In *R. v. Dee* (1884), 15 Cox C.C. 579 (Cr. Cas. Res. Ir.), O'Brien J. left no doubt on this issue:

> That brings us back to the question which in law is the crime of rape. The crime is the invasion of a woman's person without her consent, and I see no real difference between the want of consent and the act being against her will, which is the language of the indictment, though the distinction is taken by Lord Campbell, or between the negation of consent and positive dissent. Whether the act of consent be the result of overpowering force, or of fear, or of incapacity, or of natural condition, or of deception, it is still want of consent, and the consent must be, not consent to the act, but to the act of the particular person — not in the abstract, but in the concrete . . . . [p. 598]

[29] In *R. v. Bennett* (1866), 4 F. & F. 1105, 176 E.R. 925 (West. Cir.), similar reasoning was applied to hold that concealment of venereal disease amounted to fraud vitiating consent:

> An assault is within the rule that fraud vitiates consent, and therefore, if the prisoner, knowing that he had a foul disease, induced his niece to sleep with him, intending to possess her, and infected her, she being ignorant of his condition, any consent, which she may have given, would be vitiated, and the prisoner would be guilty of an indecent assault. [p. 925]

[30] Again in *R. v. Sinclair* (1867), 13 Cox C.C. 28, the Central Criminal Court found fraud vitiating consent for non-disclosure of gonorrhœa, stating that if the complainant "would not have consented if she had known the fact, then her consent is vitiated by the deceit practised upon her, and the prisoner would be guilty of an assault" (p. 29).

[31] These cases evinced a generous approach to the issue of consent and when deceit might vitiate it, an approach that respected the right of the women involved to choose whether to have intercourse or not. However, this jurisprudence was shortly to be set aside, in a series of cases which culminated in *Clarence*. To read these cases is to enter a world foreign to modern sensitivities — the world of Victorian morality.

[32] The case that announced the change was *Hegarty v. Shine* (1878), 14 Cox C.C. 124 (H.C.J. Ir. (Q.B.D.)), a civil case involving an action for assault. Mr. Shine, the master of the house, had sexual relations with his domestic servant over a period of two years. She became pregnant and had a child. Both she and the child were infected with syphilis. The court dismissed the action against Mr. Shine on the basis of *ex turpi causa non oritur actio* — the plaintiff was the victim of her own immoral act, which the law could not condone. On the matter of fraud, the majority stated that the doctrine of fraud was confined to *mistake as to whether the act was sexual or not*: "In the case before us the defendant actively consented to the very thing, that is to say, sexual intercourse, with full knowledge and experience of the nature of the act" (p. 130). The appeal court ((1878), 14 Cox C.C. 145) confirmed that only deceit as to the nature of the act could vitiate consent. The court emphasized the pitiable condition of the victim, but concluded the law could not assist her.

[33] The point of no return for the earlier, more open view of fraud was reached in *Clarence*. That case confirmed that fraud could vitiate consent to sexual relations only if the complainant was deceived as to the *sexual nature* of the act or as to the identity of the man. The facts were simple. The couple were married. The husband did not tell his wife he had gonorrhœa and infected her. The husband was charged with assault and unlawful infliction of bodily harm.

[34] The fact that 13 judges sat suggests the case was viewed as important. The court divided nine to four, and the husband was acquitted. The majority held that fraud in the context of sexual relations had been interpreted too broadly by the earlier cases, and that it was necessary to limit its application to situations where the complainant was deceived as to the sexual nature of the act or as to the identity of the man. This produced a rule that was to prevail for almost 100 years that fraud could not vitiate consent to sexual intercourse unless it went to the "sexual nature of the act" or to the identity of the sexual partner.

[35] The opinion of Stephen J. encapsulates the view of the majority in *Clarence*. Stephen J. found that the offence of unlawful infliction of bodily harm could not apply to the case. While the act posed by the husband was indeed unlawful — infecting one's wife was forbidden by the law relating to marriage since it constituted cruelty and could be evidence of adultery —, it could not be said that it constituted infliction of bodily harm. Indeed, the words "infliction of bodily harm" were construed as requiring a physical assault. Stephen J. found that infecting a person with a disease did not constitute such an assault.

[36] Stephen J. went on to consider the question of obtaining sexual relations by fraud. He expressed the view that the only fraud capable of vitiating consent to sexual relations was fraud as to the nature of the act of intercourse, or as to the identity of the sexual partner. If the victim knew the act was sexual, and was not deceived as to the identity of her partner, she could not complain that she had been deceived and her "consent" fraudulently obtained. Stephen J. commented briefly that neither *Bennett* nor *Sinclair* could be relied upon as precedent.

[37] The reasons of Pollock B., also in the majority, added that sexual acts done by a husband to his wife cannot be unlawful (pp. 63-64). The husband possessed conjugal rights over his wife to which she had consented by marrying him. Once married, the wife had no right to refuse her husband's demands. Since sexual acts between spouses were lawful, Pollock B. reasoned, all such acts done by a husband — including those characterized by cruelty — must be lawful.

[38] The *Clarence* test was accepted throughout the common law world and prevailed until recent times. The strictness with which it was applied is illustrated by a 1957 decision of the Australian High Court, *Papadimitropoulos v. The Queen* (1957), 98 C.L.R. 249. The accused had induced the complainant to have sexual intercourse by duping her into believing that they were legally married. He was acquitted of the charge of rape. The court summed up the law as follows:

> To say that in having intercourse with him she supposed that she was concerned in a perfectly moral act is not to say that the intercourse was without her consent. To return to the central point; rape is carnal knowledge of a woman without her consent: carnal knowledge is the physical fact of penetration; it is the consent to that which is in question; such a consent demands a perception as to what is about to take place, as to the identity of the man and the character of what he is doing. But once the consent is comprehending and actual the inducing causes cannot destroy its reality and leave the man guilty of rape. [Emphasis added; p. 261.]

[39] The views of the majority in *Clarence* were reflected in the first Canadian *Criminal Code* in 1892 (S.C. 1892, c. 29). Parliament defined fraud for purposes of rape and indecent assault narrowly, by restricting it to "false and fraudulent representations as to the nature and quality of the act": ss. 259(*b*) and 266. The *Code* thus incorporated the concerns of the majority in *Clarence*. The deceitful act was limited to "false and fraudulent representations" by opposition to simple concealment, and the subject of the fraud was limited to the "nature and quality of the act". As a consequence, Canadian courts accepted *Clarence* as settled law and continued to hold that only active fraud as to the nature of the act, i.e. fraud as to its sexual character, or as to the identity of one's sexual partner constituted fraud vitiating consent to sexual intercourse: see, e.g., *R. v. Harms* (1943), 1943 CanLII 146 (SK CA), 81 C.C.C. 4 (Sask. C.A.); *Bolduc v. The Queen*, 1967 CanLII 57 (SCC), [1967] S.C.R. 677.

[40] In 1983, Parliament amended the *Criminal Code* to create the present s. 265(3)(*c*): S.C. 1980-81-82-83, c. 125, s. 19. This amendment was part of a major overhaul of the law of sexual offences which aimed, *inter alia*, at protecting the integrity of the person and eliminating sexual discrimination in the criminal law. The new provision referred simply to "fraud", dropping the qualifying phrases "false and fraudulent representations" and "nature and quality of the act". Arguably, this change evidenced Parliament's intent that "fraud" should be read more broadly than it had been in the past. However, courts continued to apply a restrictive interpretation to the term: see *R. v. Petrozzi* (1987), 1987 CanLII 2786 (BC CA), 35 C.C.C. (3d) 528 (B.C.C.A.); *R. v. Lee* (1991), 1991 CanLII 7351 (ON SC), 3 O.R. (3d) 726 (Gen. Div.); *R. v. Ssenyonga* (1993), 1993 CanLII 14680 (ON SC), 81 C.C.C. (3d) 257 (Ont. Ct. (Gen. Div.)).

[41] Occasionally, a more generous approach surfaced as to when fraud could vitiate consent to sexual relations. For instance, American caselaw was more inclined to convict the accused of assault or rape on facts similar to those in *Clarence*: *State v. Marcks*, 41 S.W. 973 (Miss. 1897), at p. 973, and 43 S.W. 1095 (1898), at pp. 1097-98; *State v. Lankford*, 102 A. 63 (Del. Ct. Gen. Sess. 1917), at p. 64; *United States v. Johnson*, 27 M.J. 798 (A.F.C.M.R. 1988), at p. 804; *United States v. Dumford*, 28 M.J. 836 (A.F.C.M.R. 1989), at p. 839. And in Canada, in *R. v. Maurantonio*, 1967 CanLII 317 (ON CA), [1968] 1 O.R. 145 (C.A.), Hartt J. (*ad hoc*) held that "the words 'nature and quality of the act' . . . should not be so narrowly construed as to include only the physical action but rather must be interpreted to encompass those concomitant circumstances which give meaning to the particular physical activity in question" (p. 153). But these were minority voices.

[42] There are not many cases on the books, to be sure. One understands why when one considers the practical implications of the *Clarence* test. The cases where a woman consents to sex but thinks it is *not* sex or that it is sex with a different man are necessarily rare. Submitting to a medical examination only to discover it is a sexual encounter might be such a case; the complainant does not consent to the sexual act but to a medical procedure. Under *Clarence* and its progeny, if the woman consented to the sexual act with the given man, no matter what the deceit, the man could not be convicted for his act. It is not surprising that the legal lexicon contains few

cases dealing with fraud vitiating consent. The stark fact was that in all but rare cases fraud could not vitiate consent.

[43] Canadian common law on fraud vitiating consent to sexual relations has now entered a third, post-*Clarence* era. *Charter* values of equality, autonomy, liberty, privacy and human dignity require full recognition of the right to consent or to withhold consent to sexual relations. Fraud under s. 265(3)(*c*) must be interpreted with these values in mind. The *Clarence* line of jurisprudence, which confined fraud to the question of whether the complainant knew the act was sexual or not, is no longer appropriate in the Canadian context. To hold that a complainant consents to the risk of an undisclosed serious disease because he or she knew the act was sexual affronts contemporary sensibilities and contemporary constitutional values.

(c) *Charter Values*

[44] Courts must interpret legislation harmoniously with the constitutional norms enshrined in the *Charter*: *R. v. Sharpe*, 2001 SCC 2, [2001] 1 S.C.R. 45, at para. 33; *Application under s. 83.28 of the Criminal Code (Re)*, 2004 SCC 42, [2004] 2 S.C.R. 248, at para. 35. *Charter* values are always relevant to the interpretation of a disputed provision of the *Criminal Code*.

[45] The *Charter* values of equality, autonomy, liberty, privacy and human dignity are particularly relevant to the interpretation of fraud vitiating consent to sexual relations. The formerly narrow view of consent has been replaced by a view that respects each sexual partner as an autonomous, equal and free person. Our modern understanding of sexual assault is based on the preservation of the right to refuse sexual intercourse: sexual assault is wrong because it denies the victim's dignity as a human being. Fraud in s. 265(3)(*c*) of the *Criminal Code* must be interpreted in light of these values.

[46] As we have already seen, prior to the adoption of the *Charter* in 1982 and the reform of sexual offences in 1983, courts took a restrictive view of how lack of consent to sexual relations could be established and how consent could be negated by fraud. Rules of evidence and procedure, like the ancient rule that non-consent must be supported by evidence of a "hue and cry" in the neighbourhood immediately after the alleged sexual assault, or the willingness of judges to infer consent from dress or prior sexual experience, systemically biased the trial process in favour of finding consent. In like fashion, the jurisprudence, post-*Clarence*, took a narrow view of fraud capable of vitiating consent, holding that it went only to the sexual nature of the act, and that it did not apply to married women, who were bound to submit to their husbands in all circumstances.

[47] Post-*Charter* Canadian law has repudiated this crabbed view of consent and fraud. Amendments to the *Criminal Code* have removed the evidentiary burdens and presumptions that once made proof of lack of consent difficult. Courts have held that judges may not infer consent from the way the complainant was dressed or the fact that she may have flirted: *R. v. Ewanchuk*, 1999 CanLII 711 (SCC), [1999] 1 S.C.R. 330. And in 1998, *Cuerrier* signaled a return to a generous interpretation of fraud capable of vitiating consent.

[48] In keeping with the *Charter* values of equality and autonomy, we now see sexual assault not only as a crime associated with emotional and physical harm to the victim, but as the wrongful exploitation of another human being. To engage in sexual acts without the consent of another person is to treat him or her as an object and negate his or her human dignity. Although the *Charter* is not directly engaged, the values that animate it must be taken into account in interpreting s. 265(3)(*c*) of the *Criminal Code*.

(d) *The Experience of Other Common Law Jurisdictions*

[49] The parties and a number of interveners have relied on the approach of foreign legal systems to support their positions.

[50] A survey of comparative law shows that common law jurisdictions criminalize the *actual sexual transmission* of HIV, when the HIV-positive person is aware of his or her serologic status and when the partner does not give informed consent to the risk of infection. Several jurisdictions treat transmission of HIV following non-disclosure as offences involving bodily harm, rather than as sexual offences. Such transmission has been prosecuted on the following legal grounds: in England, for reckless infliction of bodily injury, under s. 20 of *The Offences against the Person Act, 1861*, 24 & 25 Vict., c. 100; in the Australian state of Victoria, for "[c]onduct

endangering life" (s. 22 of the *Crimes Act 1958* (Vic.)); and in New Zealand, for, *inter alia*, "reckless disregard for the safety of others" that "causes grievous bodily harm" (s. 188(2) of the *Crimes Act 1961*, No. 43). See I. Grant, "The Prosecution of Non-disclosure of HIV in Canada: Time to Rethink *Cuerrier*" (2011), 5 *M.J.L.H.* 7, at pp. 31-41.

[51] However, deception that exposes a partner to a *risk of transmission* — but that does not ultimately result in transmission — is not criminalized in many jurisdictions. In England, exposing one's partner to HIV without advising of HIV status does not vitiate consent. Fraud vitiates consent only if it goes to "the nature or purpose of the relevant act", which excludes deception as to HIV status: *R. v. B.*, [2006] EWCA Crim 2945, [2007] 1 W.L.R. 1567, at para. 12. Theoretically, s. 18 of *The Offences against the Person Act, 1861*, which criminalizes intentional infliction of harm, could be used in England to punish non-disclosure of HIV-positive status as a form of *attempted* intentional infliction of harm. However, the high evidentiary burden "of proving that someone actually intended to transmit HIV through sex (as opposed to intending to have unprotected sex)" places a prohibitive onus on the Crown (Grant, at p. 32).

[52] In Australia, six of the nine jurisdictions do not criminalize exposure absent transmission. Of the three jurisdictions that criminalize exposure to a risk of transmission (*Crimes Act 1958* (Vic.), ss. 22 and 23; *Criminal Law Consolidation Act 1935* (S.A.), s. 29; *Criminal Code Act* (N.T.), ss. 174C and 174D), two (Victoria and the Northern Territory) apply lesser criminal offences for cases where no actual transmission resulted from exposure.

[53] In New Zealand, liability hinges, *inter alia*, on whether transmission occurs. Absent transmission, the failure to disclose HIV-positive status prior to sexual relations attracts the lesser offence of criminal nuisance (s. 145 of the *Crimes Act 1961*; *R. v. Mwai*, [1995] 3 N.Z.L.R. 149 (C.A.)).

[54] Professor Grant summarizes the contrast between the Canadian approach and the approach taken by England, Australia and New Zealand as follows:

> In Canada, the same charge of aggravated (sexual) assault is typically used regardless of the nature of the deception, whether the virus is transmitted, or whether there is an isolated incident of non-disclosure or an ongoing course of non-disclosure. . . . In all other jurisdictions [canvassed in this study], the offence is characterized as the infliction of bodily harm, and not as non-consensual sexual contact. [p. 42]

[55] In sum, while the experience of other jurisdictions is not conclusive, it sounds a note of caution against extending the criminal law beyond its appropriate reach in this complex and emerging area of the law.

(3) Finding a Solution

[56] We have discussed the need for a clear and appropriately tailored test for fraud vitiating consent in s. 265(3)(*c*) of the *Criminal Code*, in the context of failure to disclose HIV-positive status. With a view to meeting that need, we have canvassed four guides to construing the provision — the proper ambit of the criminal law, the common law and statutory background of the concept of fraud, *Charter* values and the approach to non-disclosure of HIV status adopted in other countries. This brings us to the nub of the question before us — when, precisely, should non-disclosure of HIV status amount to fraud vitiating consent under s. 265(3)(*c*)?

[57] The four interpretational considerations suggest that the *Cuerrier* test is valid from the perspective of principle and impact. The *Cuerrier* test, to recap, requires proof of two elements: (1) a dishonest act; and (2) deprivation. It defines the first element broadly in terms of either misrepresentation or non-disclosure of HIV, and the second element equally broadly in terms of whether the act poses a "significant risk of serious bodily harm".

[58] While it may be difficult to apply, the *Cuerrier* approach is in principle valid. It carves out an appropriate area for the criminal law — one restricted to "significant risk of serious bodily harm". It reflects the *Charter* values of autonomy, liberty and equality, and the evolution of the common law, appropriately excluding the *Clarence* line of authority. The test's approach to consent accepts the wisdom of the common law that not every deception that leads to sexual intercourse should be criminalized, while still according consent meaningful scope.

While *Cuerrier* takes the criminal law further than courts in other common law jurisdictions have, it can be argued other courts have not gone far enough: see L. H. Leigh, "Two cases on consent in rape" (2007), 5 *Arch. News* 6.

[59] Some interveners challenge the use of the criminal law in the case of HIV on the ground that it may deter people from seeking treatment or disclosing their condition, thereby increasing the health risk to the carrier and those he has sex with. On the record before us, I cannot accept this argument. The only "evidence" was studies presented by interveners suggesting that criminalization "probably" acts as a deterrent to HIV testing: see, e.g., M. A. Wainberg, "Criminalizing HIV transmission may be a mistake" (2009), 180 *C.M.A.J.* 688. Other studies suggest little difference in reporting rates in states that criminalized and did not criminalize behaviour: S. Burris, et al., "Do Criminal Laws Influence HIV Risk Behavior? An Empirical Trial" (2007), 39 *Ariz. St. L.J.* 467, at p. 501. The conclusions in these studies are tentative, and the studies were not placed in evidence and not tested by cross-examination. They fail to provide an adequate basis to justify judicial reversal of the accepted place of the criminal law in this domain.

[60] It follows that *Cuerrier* should not be jettisoned. The problems of uncertainty and appropriate reach that have emerged in its application should be addressed, but to the extent possible within the general framework of *Cuerrier*. This brings us to the suggestions for dealing with the problems of uncertainty and overbreadth that have arisen in applying *Cuerrier*.

(a) *The Active Misrepresentation Approach*

[61] It is argued that one way to correct the uncertainty and reach problems in *Cuerrier*'s application is to narrow the concept of dishonest act to active deception — a clear misrepresentation or a lie in response to a clear question.

[62] This approach would go a long way to remedying the problem of uncertainty. A person would know that unless they made a positive misrepresentation or lied in response to a clear question, they would not be committing a crime. And it would also remedy the perceived problem of overbreadth; the narrower definition of fraud would prevent those who may inadvertently or negligently fail to disclose HIV status from being criminalized.

[63] This approach has some support. My concurring reasons in *Cuerrier* defined fraud as arising when "the person represents that he or she is disease-free" (para. 72, Gonthier J. concurring). This "active deception" approach has been viewed favourably by some: see Leigh, at p. 7.

[64] The approach, however, also suffers from difficulties. The first is that it may be difficult to distinguish between active deception and passive deception by non-disclosure. Everything depends on the circumstances. This approach's sensitivity to context blurs the line between criminal and non-criminal conduct. Conversations leading up to sexual acts are not always models of clarity. People tend not to use precise language. Gestures may supplant language. For example, is the shake of the head in response to a partner's question about HIV a positive representation that one does not have HIV? Moreover, there may be circumstances where the partner may reasonably infer absence of disease from prior conversations or circumstances. To be sure, trial judges can untangle complicated fact situations and decide if there has been a positive misrepresentation. But the fact remains that this marker may not fully or fairly capture the deception that underlies a particular fraud, and may be a difficult test to apply in practice.

[65] Second, there is arguably no principled distinction between active deception and passive deception. Should the trusting wife who does not ask a direct question as to HIV status of her partner be placed in a worse position than the casual date who does? The point from the complainant's perspective is that in either case she would not have given her consent had the deception not occurred. Fraud is fraud, whether induced by blatant lies or sly deceit.

(b) *The Absolute Disclosure Approach*

[66] The Crown submits that all HIV-positive people should be required to disclose the fact to all sexual partners in all cases. This amounts to removing the "significant risk of serious bodily harm" requirement from the second element of the *Cuerrier* test.

[67] This approach provides a clear test, solving the problem of uncertainty. However, its solution to the problem of breadth is less convincing. This approach arguably casts the net of criminal culpability too widely. People who act responsibly and whose conduct causes no harm and indeed may pose no risk of harm, could find themselves criminalized and imprisoned for lengthy periods. Moreover, this approach seems to expand fraud vitiating consent in s. 265(3)(*c*) further than necessary, by defining it as simple dishonesty and effectively eliminating the deprivation element of fraud. Finally, this absolute approach is arguably unfair and stigmatizing to people with HIV, an already vulnerable group. Provided people so afflicted act responsibly and pose no risk of harm to others, they should not be put to the choice of disclosing their disease or facing criminalization.

(c) *A Case-by-Case Fact-based Approach*

[68] The respondent argues that the *Cuerrier* "significant risk of serious bodily harm" test remains a workable test, but seeks to clarify it by emphasizing that it is simply a statement of what the evidence must establish to support a finding of fraud under s. 265(3)(*c*). A "significant risk of serious bodily harm" must be established by medical evidence in each case. The question is whether at the time of the sexual act in question, the particular act posed a significant risk of transmitting HIV. This typically requires the Crown to call expert evidence as to the accused's viral count at the time of the offence as well as risks associated with any condom protection used. The trial judge must be satisfied that the evidence establishes beyond a reasonable doubt that the accused's conduct at the moment of the offence posed a significant risk of serious bodily harm. Any doubt must be resolved in favour of the accused.

[69] While respectful of the rights of accused persons, this approach does not remedy the problems of uncertainty and reach that make *Cuerrier* difficult to apply. The process would be onerous. In every case, medical experts would have to be called. Lengthy examination and cross-examination would have to take place. Trial judges would have to spend long hours assessing the evidence to determine if it establishes a "significant risk of serious bodily harm" at the time of the alleged offence. Finally, the risk of conflicting judgments could render the process unfair from a systemic standpoint. The court of appeal, while accepting the trial judge's conclusions on the evidence, might take a different view on the mixed question of fact and law of whether the risk was "significant". Years may pass in legal no-man's-land with no one knowing whether the accused is guilty or not guilty. Enormous costs, both for the prosecution and the defence, would be run up. This case illustrates all these problems.

(d) *Judicial Notice of the Effect of Condom Use*

[70] To mitigate the uncertainties of the fact-based *Cuerrier* test, the respondent suggests that courts can take judicial notice of the fact that condom use always negates a significant risk of serious bodily harm.

[71] Before a judge can take judicial notice of a fact, the fact must be shown to be so "notorious" or in modern parlance, "accepted", that no reasonable person would dispute it: *R. v. Find*, 2001 SCC 32, [2001] 1 S.C.R. 863, at para. 48; *R. v. Spence*, 2005 SCC 71, [2005] 3 S.C.R. 458, at para. 53. Yet the record here is replete with debate about whether use of a condom alone negates significant risk of serious bodily harm, and the controversy is exacerbated by the rapidly changing state of the science and by the fact-specific nature of risk. Judicial notice is not available here and cannot form the basis for formulating general propositions relating to the factual issue of risk, in the absence of indisputable consensus.

(e) *Relationship-based Distinctions*

[72] Another way of narrowing the *Cuerrier* "significant risk of serious bodily harm" approach to fraud under s. 265(3)(*c*) is to confine it to special relationships. It has been suggested in the commercial context that failure to disclose may amount to fraud when parties have a relationship of trust, quasi-trust or confidence: B. L. Nightingale, *The Law of Fraud and Related Offences* (loose-leaf). The distinction could conceivably be extended to relationships where one party is vulnerable, like the young often intoxicated women who had sex with Mr. Mabior in this case. This approach assumes that sexual partners who do not ask about STDs bear a risk of exposing themselves to HIV, unless a relationship of trust exists between them.

[73] The law of fraud in commercial situations provides some support for this approach. Originally, the common law and courts of equity did not regard mere silence, standing on its own without some other form of

conduct which induced a false belief in another, as being fraudulent: *Twining v. Morrice* (1788), 2 Bro. C.C. 326, 29 E.R. 182; *Conolly v. Parsons* (1797), 3 Ves. 625n (Ch.); *Walters v. Morgan* (1861), 3 De G. F. & J. 718, 45 E.R. 1056. However, over time, equity recognized specific circumstances warranting a positive duty to disclose material facts, including a relationship of trust, quasi-trust or confidence.

[74] Against this approach, it can be argued that it narrows "fraud" under s. 265(3)(*c*) too much. Is there a good reason for compelling disclosure to one's wife but not to a casual date? Where the concern is the contraction of a life-altering disease, the answer is no.

[75] Historically, fraud capable of vitiating consent to sexual intercourse has not followed the patterns of commercial fraud. The special context of sexual fraud raises unique concerns. This has generally resulted in a narrower approach to fraud, marked by its own peculiar considerations. The relationship between the parties in a particular case has tended not to figure among them. The closest the law has come to a relationship-based approach are the suggestions in Victorian times that wives and prostitutes — for different reasons relating to the mores of the time — could never assert fraud vitiating consent to sexual intercourse: see *Clarence*. Such ideas strike the modern ear, attuned to equality, as offensive.

(f) *The Reasonable Partner Approach*

[76] Yet another possibility is to define "fraud" under s. 265(3)(*c*) as what a reasonable and informed person in the position of the HIV-positive person's potential partner would expect. The test would be objective, but based on the circumstances of the particular case, including the type of relationship the parties had.

[77] This approach has the advantage of taking into account the expectations of the parties as they existed on the facts of the case. In this sense, it is fairer than a test that is based on a general norm presumed to apply in all cases. An HIV-positive person may be expected to understand the expectations of his partner in the particular circumstances at hand, and act accordingly.

[78] This approach also recognizes that allocation of responsibility for protecting against transmission of sexual diseases may vary with relationships and with the passage of time. One of the historic difficulties in formulating a test for fraud vitiating consent to sexual relations has been the variation in social norms and expectations over time. In Victorian times, husbands were held to be incapable of committing fraud vitiating consent, since wives had no right to refuse consent to sexual intercourse with their husbands. In more recent times, some argue that expectations have shifted from the view that an infected person bears all the responsibility for the sexual health of both partners, to the view that each party is responsible for his or her own sexual health. A contextually grounded reasonableness approach would avoid these problems by tailoring the result to the relationship from which the criminal charge arises.

[79] Again, however, the approach can be criticized. The most telling criticism is that it does not lay down a clear test for fraud, leaving people uncertain as to where the line lies between criminal conduct and non-criminal conduct. Unless the partners have themselves established the lines, the HIV-positive person is left to infer from the nature of the relationship what his potential partner, acting reasonably, would expect.

[80] This leads to a second criticism — overreach of the criminal law, and its correlative, unfairness to the accused. In the heat and anticipation of the sexual moment, assessments of what a reasonable partner would expect may be mistaken. Is the person then to be criminalized and sent to prison for perhaps years, for what is at its base the result of misjudgment? Such may be the consequence of the reasonable partner expectation test.

(g) *An Evolving Common Law Approach*

[81] This leaves the option of building greater certainty into the *Cuerrier* test by indicating when the significant risk test is met in terms of principle and concrete situations. Such an approach is consistent with the incremental role of common law courts in adapting the contours of an offence to the requirements of justice and practical application.

[82] The question, building on *Cuerrier*, is: when do sexual relations with an HIV-positive person pose a "significant risk of serious bodily harm"? In answering this question, the facts as found by the trial judge

should be accepted, absent palpable and overriding error. Whether those facts establish a "significant risk of serious bodily harm" is a question of law: see C.A., at para. 37. The terms "serious bodily harm" mean "any hurt or injury, whether physical or psychological, that interferes in a substantial way with the integrity, health or well-being of a victim": *R. v. McCraw*, 1991 CanLII 29 (SCC), [1991] 3 S.C.R. 72, at p. 88. Of course, actual transmission of HIV constitutes serious bodily harm.

[83] The courts below answered this question of law differently. The trial judge took the approach that any risk of transmission of HIV, however small, constitutes "significant risk of serious bodily harm" (see reference to the trial judge's reasons, at C.A. para. 66). The Court of Appeal, by contrast, held that "significant risk" connoted a high risk of transmission of HIV. In its view "significant risk of serious bodily harm" under *Cuerrier* requires a "significant or high risk" (para. 80) — the "opposite of evidence of a 'high probability' of no infectiousness" (para. 127).

[84] In my view, a "significant risk of serious bodily harm" connotes a position between the extremes of no risk (the trial judge's test) and "high risk" (the Court of Appeal's test). Where there is a *realistic possibility of transmission of HIV*, a significant risk of serious bodily harm is established, and the deprivation element of the *Cuerrier* test is met. This approach is supported by the following considerations.

[85] First, "significant risk of serious bodily harm" cannot mean any risk, however small. That would come down to adopting the absolute disclosure approach, with its numerous shortcomings, and would effectively read the word "significant" out of the *Cuerrier* test.

[86] Second, a standard of "high" risk does not give adequate weight to the nature of the harm involved in HIV transmission. "Significant risk" in *Cuerrier* is informed both by the risk of contraction of HIV and the seriousness of the disease if contracted. These factors vary inversely. The more serious the nature of the harm, the lower the probability of transmission need be to amount to a "significant risk of serious bodily harm".

[87] Third, as discussed earlier in considering guides to interpretation, a standard of realistic possibility of transmission of HIV avoids setting the bar for criminal conviction too high or too low. A standard of any risk, however small, would arguably set the threshold for criminal conduct too low. On the other hand, to limit s. 265(3)(*c*) to cases where the risk is "high" might condone irresponsible, reprehensible conduct.

[88] Fourth, the common law and statutory history of fraud vitiating consent to sexual relations supports viewing "significant risk of serious bodily harm" as requiring a realistic possibility of transmission of HIV. This history suggests that only serious deceptions with serious consequences are capable of vitiating consent to sexual relations. Interpreting "significant risk of serious bodily harm" in *Cuerrier* as extending to any risk of transmission would be inconsistent with this. A realistic possibility of transmission arguably strikes the right balance for a disease with the life-altering consequences of HIV.

[89] Fifth, the values of autonomy and equality enshrined in the *Charter* support an approach to fraud vitiating consent that respects the interest of a person to choose whether to consent to sex with a particular person or not. The law must strike a balance between this interest and the need to confine the criminal law to conduct associated with serious wrongs and serious harms. Drawing the line between criminal and non-criminal misconduct at a realistic possibility of transmission arguably strikes an appropriate balance between the complainant's interest in autonomy and equality and the need to prevent over-extension of criminal sanctions.

[90] Finally, interpreting "significant risk of serious bodily harm" as entailing a realistic possibility of transmission of HIV is supported by a number of cases. Apart from the trial reasons in this case, we have been referred to no case holding that "significant" means any risk, however small. To be sure, not many cases have considered the point. But the few that have are worth noting. In *R. v. Jones*, 2002 NBQB 340, [2002] N.B.J. No. 375 (QL), the court held that a risk of transmission of hepatitis C between 1.0 and 2.5% was "so low that it cannot be described as significant" (para. 33). And in *R. v. J.A.T.*, 2010 BCSC 766 (CanLII), the trial judge stated that "[a] significant risk means a risk that is of a magnitude great enough to be considered important" (para. 56).

[91] These considerations lead me to conclude that the *Cuerrier* requirement of "significant risk of serious bodily harm" should be read as requiring disclosure of HIV status if there is a realistic possibility of

transmission of HIV. If there is no realistic possibility of transmission of HIV, failure to disclose that one has HIV will not constitute fraud vitiating consent to sexual relations under s. 265(3)(*c*).

[92] The test of realistic possibility of transmission proposed in these reasons is specific to HIV. As discussed above, "significant risk" depends both on the degree of the harm and risk of transmission. These two factors vary inversely. A treatable sexually transmitted disease that does not seriously alter a person's life or life-expectancy might well not rise to the level of constituting "serious bodily harm", and would also fail to meet the requirement of endangerment of life for aggravated sexual assault under s. 273(1). Where the line should be drawn with respect to diseases other than HIV is not before us. It is enough to note that HIV is indisputably serious and life-endangering. Although it can be controlled by medication, HIV remains an incurable chronic infection that, if untreated, can result in death. As such, the failure to advise a sexual partner of one's HIV status may lead to a conviction for aggravated sexual assault under s. 273(1) of the *Criminal Code*. (This said, it may be that with further medical advances, the death rate may decline to the point where the risk of death is virtually eliminated, reducing the offence to sexual assault *simpliciter* under s. 271(1) of the *Criminal Code*. Similarly, the day may come when researchers will find a cure for HIV, with the possible effect that HIV will cease to cause "serious bodily harm" and the failure to disclose will no longer fall under the category of fraud vitiating consent for the purposes of sexual assault.)

(4) Realistic Possibility of HIV Transmission

[93] A review of the case law pertaining to fraud vitiating consent to sexual relations leads to the following general principle of law: the *Cuerrier* requirement of a "significant risk of serious bodily harm" entails a *realistic possibility of transmission of HIV*. This applies to all cases where fraud vitiating consent to sexual relations is alleged on the basis of the non-disclosure of HIV-positive status.

[94] This leaves the question of when there is a realistic possibility of transmission of HIV. The evidence adduced here satisfies me that, as a general matter, a realistic possibility of transmission of HIV is negated if (i) the accused's viral load at the time of sexual relations was low, *and* (ii) condom protection was used.

[95] The conclusion that low viral count coupled with condom use precludes a realistic possibility of transmission of HIV, and hence does not constitute a "significant risk of serious bodily harm" on the *Cuerrier* test, flows from the evidence in this case. This general proposition does not preclude the common law from adapting to future advances in treatment and to circumstances where risk factors other than those considered in this case are at play.

[96] In this case, the evidence accepted by the trial judge was that Mr. Mabior had intercourse by vaginal penetration with the four complainants, during which he ejaculated. The accused underwent antiretroviral treatment on a regular basis, but he only wore condoms occasionally. Mr. Mabior's medical record also shows that he had been successfully treated for gonorrhœa and had no sexually transmitted infections at the time of intercourse with the four complainants other than HIV. Based on this evidence, three factors were relevant to risk: baseline risk for vaginal intercourse when the male partner is HIV-positive; reduction in risk with condom use; and antiretroviral therapy. I will consider each in turn.

[97] As the Court of Appeal noted, baseline risk of HIV transmission per act of vaginal intercourse with an infected male partner (i.e. the risk of transmission based on the male ejaculating, without a condom, having a normal unreduced viral load) varies from study to study. Dr. Smith's written report put the risk at 0.05% (1 in 2000) to 0.26% (1 in 384) (p. 4). Ms. McDonald, a public health nurse, testified about the Manitoba Health post-exposure protocol, which puts risk per act at 0.1% (1 in 1000). A systemic review and meta-analysis of 43 publications comprising 25 different study populations, put the risk in high-income countries at 0.08% per sexual act (1 in 1250): M.-C. Boily, et al., "Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies" (2009), 9 *Lancet Infect. Dis.* 118.

[98] It is undisputed that HIV does not pass through good quality male or female latex condoms. However, condom use is not fail-safe, due to the possibility of condom failure and human error. Dr. Smith testified that consistent condom protection reduces the risk of HIV transmission by 80%, relying on the widely accepted Cochrane review: S. C. Weller and K. Davis-Beaty, "Condom effectiveness in reducing heterosexual HIV transmission" (2002), 1 *Cochrane Database Syst. Rev*. CD003255. It was pointed out that the 80% reduction in the

transmission risk refers to consistent condom use: the reduction may be larger for consistent *and* correct condom use, but this has not been verified empirically.

[99] The Court of Appeal, in applying a "high risk" approach, held that condom use reduces the risk of HIV transmission "below the level of significance" (para. 87). However, in my view, the evidence does not establish that condom protection alone precludes a *realistic possibility* of transmission, the standard proposed here. According to the expert evidence, the risk might still fall above the "negligible" threshold: Dr. Smith's report, at p. 6.

[100] This brings us to the final factor, antiretroviral therapy. As noted by the Court of Appeal, the transmissibility of HIV is proportional to the viral load, i.e. the quantity of HIV copies in the blood. The viral load of an untreated HIV patient ranges from 10,000 copies to a few million copies per millilitre. When a patient undergoes antiretroviral treatment, the viral load shrinks rapidly to less than 1,500 copies per millilitre (low viral load), and can even be brought down to less than 50 copies per millilitre (undetectable viral load) over a longer period of time. This appears to be scientifically accepted at this point, on the evidence in this case.

[101] Dr. Smith explained in his report that antiretroviral therapy is not a safe-sex strategy, and that "it is highly advisable that persons even with an undetectable viral load who are having sex with more than one partner unfailingly and correctly use a condom" (pp. 5 and 7). The most recent wide-scale study on this issue, relied on by a number of interveners, concludes that the risk of HIV transmission is reduced by 89 to 96% when the HIV-positive partner is treated with antiretrovirals, irrespective of whether the viral load is low or undetectable: M. S. Cohen, et al., "Prevention of HIV-1 Infection with Early Antiretroviral Therapy" (2011), 365 *New Eng. J. Med.* 493. This evidence indicates that antiretroviral therapy, alone, still exposes a sexual partner to a realistic possibility of transmission. However, on the evidence before us, the ultimate percentage risk of transmission resulting from the combined effect of condom use *and* low viral load is clearly extremely low — so low that the risk is reduced to a speculative possibility rather than a realistic possibility.

[102] In reaching this conclusion, I use *low* viral load, rather than *undetectable* viral load, as one of the factors for determining risk. This avoids the evidentiary difficulties associated with establishing an *undetectable* viral load. Dr. Smith presented evidence that various factors such as common infections and treatment issues may lead to fluctuations in a person's viral load. So-called "spikes" or "blips" bring the viral load of a person treated with antiretrovirals above the detectable level. Furthermore, detectability depends on the accuracy of ever-developing technology: a viral load that assays do not detect today, might very well be detectable by future assays. Finally, it must be observed that Dr. Smith did not accept, and presented as controversial, the 2008 announcement by the Swiss Federal Commission for HIV/AIDS that an HIV-positive person with an undetectable viral load is not sexually infectious (p. 5). As he noted, this statement is subject to important qualifications, based only on a review of scientific literature, and requires corroborating research.

[103] This leads to the conclusion that on the evidence before us, the combined effect of condom use *and* low viral load precludes a realistic possibility of transmission of HIV. In these circumstances, the *Cuerrier* requirement of significant risk of serious bodily harm is not met. There is no deprivation within the meaning of *Cuerrier* and failure to disclose HIV status will not constitute fraud vitiating consent under s. 265(3)(*c*) of the *Criminal Code*.

(5) Summary

[104] To summarize, to obtain a conviction under ss. 265(3)(*c*) and 273, the Crown must show that the complainant's consent to sexual intercourse was vitiated by the accused's fraud as to his HIV status. Failure to disclose (*the dishonest act*) amounts to fraud where the complainant would not have consented had he or she known the accused was HIV-positive, and where sexual contact poses a significant risk of or causes actual serious bodily harm (*deprivation*). A significant risk of serious bodily harm is established by a realistic possibility of transmission of HIV. On the evidence before us, a realistic possibility of transmission is negated by evidence that the accused's viral load was low at the time of intercourse and that condom protection was used. However, the general proposition that a low viral load combined with condom use negates a realistic possibility of transmission of HIV does not preclude the common law from adapting to future advances in treatment and to circumstances where risk factors other than those considered in the present case are at play.

[105] The usual rules of evidence and proof apply. The Crown bears the burden of establishing the elements of the offence — a dishonest act and deprivation — beyond a reasonable doubt. Where the Crown has made a *prima facie* case of deception and deprivation as described in these reasons, a tactical burden may fall on the accused to raise a reasonable doubt, by calling evidence that he had a low viral load at the time and that condom protection was used.

B. *Application*

[106] With respect to the four counts before us, the complainants all consented to sexual intercourse with the accused. Each of the complainants testified that they would not have had sex with the accused had they known that he was HIV-positive. The only issue is whether their consent was vitiated because he did not tell them that he had HIV.

[107] The trial judge found the accused guilty of aggravated sexual assault on the four counts where it was established that his viral load was not undetectable or no condom was used. The Court of Appeal set aside the convictions on the basis that *either* an undetectable viral load *or* condom protection would suffice.

[108] As set out above, at this point in the development of the common law, a clear test can be laid down. The absence of a realistic possibility of HIV transmission precludes a finding of fraud vitiating consent under s. 265(3)(*c*) of the *Criminal Code*. In the case at hand, no realistic possibility of transmission was established when the accused had a low viral load and wore a condom. It follows that the appeal should be allowed insofar as the decision of the Court of Appeal conflicts with this conclusion.

[109] The accused had a low viral load at the time of intercourse with each of S.H., D.C.S. and D.H., but did not use a condom. Consequently, the trial judge's convictions on these counts should be maintained. This leaves K.G. The trial judge convicted on the ground that, although the accused used a condom at the time of the encounter, his viral load "was not suppressed" (para. 128). As discussed, the combination of a low viral load — as opposed to an *undetectable* viral load — and of condom use negates a realistic possibility of transmission, on the evidence in this case. The record shows that the accused's viral load was low at the time of sexual relations with K.G. When combined with condom protection, this low viral load did not expose K.G. to a significant risk of serious bodily harm. The trial judge's conviction on this count must be reversed.

[110] I would allow the appeal in part and restore the convictions in respect of the complaints by S.H., D.C.S. and D.H. I would dismiss the appeal in respect of the complaint by K.G.

Appeal allowed in part.

Solicitor for the appellant: Attorney General of Manitoba, Winnipeg.

Solicitor for the respondent: Legal Aid Manitoba, Winnipeg.

Solicitors for the interveners the Canadian HIV/AIDS Legal Network, the HIV & AIDS Legal Clinic Ontario, Coalition des organismes communautaires québécois de lutte contre le sida, the Positive Living Society of British Columbia, the Canadian AIDS Society, the Toronto People With AIDS Foundation, the Black Coalition for AIDS Prevention and the Canadian Aboriginal AIDS Network: Cooper & Sandler, Toronto.

Solicitors for the intervener the British Columbia Civil Liberties Association: McCarthy Tétrault, Vancouver.

Solicitors for the intervener the Criminal Lawyers' Association of Ontario: Schreck Presser, Toronto.

Solicitors for the intervener Association des avocats de la défense de Montréal: Poupart, Dadour, Touma et Associés, Montréal.

Solicitors for the intervener Institut national de santé publique du Québec: Desrosiers, Joncas, Massicotte, Montréal.

CanLII

R. v. N.G., 2020 ONCA 494 (CanLII)

Date: 2020-08-05

File number: C66296

Citation: R. v. N.G., 2020 ONCA 494 (CanLII), <https://canlii.ca/t/j91b3>, retrieved on 2021-05-10

WARNING

The President of the panel hearing this appeal directs that the following should be attached to the file:

An order restricting publication in this proceeding under ss. 486.4(1), (2), (2.1), (2.2), (3) or (4) or 486.6(1) or (2) of the *Criminal Code* shall continue. These sections of *the Criminal Code* provide:

> 486.4(1) Subject to subsection (2), the presiding judge or justice may make an order directing that any information that could identify the victim or a witness shall not be published in any document or broadcast or transmitted in any way, in proceedings in respect of
>
> (a) any of the following offences;
>
> (i) an offence under section 151, 152, 153, 153.1, 155, 159, 160, 162, 163.1, 170, 171, 171.1, 172, 172.1, 172.2, 173, 210, 211, 213, 271, 272, 273, 279.01, 279.011, 279.02, 279.03, 280, 281, 286.1, 286.2, 286.3, 346 or 347, or
>
> (ii) any offence under this Act, as it read at any time before the day on which this subparagraph comes into force, if the conduct alleged involves a violation of the complainant's sexual integrity and that conduct would be an offence referred to in subparagraph (i) if it occurred on or after that day; or
>
> (iii) REPEALED: S.C. 2014, c. 25, s. 22(2), effective December 6, 2014 (Act, s. 49).
>
> (b) two or more offences being dealt with in the same proceeding, at least one of which is an offence referred to in paragraph (a).
>
> (2) In proceedings in respect of the offences referred to in paragraph (1)(a) or (b), the presiding judge or justice shall
>
> (a) at the first reasonable opportunity, inform any witness under the age of eighteen years and the victim of the right to make an application for the order; and
>
> (b) on application made by the victim, the prosecutor or any such witness, make the order.
>
> (2.1) Subject to subsection (2.2), in proceedings in respect of an offence other than an offence referred to in subsection (1), if the victim is under the age of 18 years, the presiding judge or justice may make an order directing that any information that could identify the victim shall not be published in any document or broadcast or transmitted in any way.
>
> (2.2) In proceedings in respect of an offence other than an offence referred to in subsection (1), if the victim is under the age of 18 years, the presiding judge or justice shall
>
> (a) as soon as feasible, inform the victim of their right to make an application for the order; and
>
> (b) on application of the victim or the prosecutor, make the order.

(3) In proceedings in respect of an offence under section 163.1, a judge or justice shall make an order directing that any information that could identify a witness who is under the age of eighteen years, or any person who is the subject of a representation, written material or a recording that constitutes child pornography within the meaning of that section, shall not be published in any document or broadcast or transmitted in any way.

(4) An order made under this section does not apply in respect of the disclosure of information in the course of the administration of justice when it is not the purpose of the disclosure to make the information known in the community. 2005, c. 32, s. 15; 2005, c. 43, s. 8(3)(b); 2010, c. 3, s. 5; 2012, c. 1, s. 29; 2014, c. 25, ss. 22,48; 2015, c. 13, s. 18..

486.6(1) Every person who fails to comply with an order made under subsection 486.4(1), (2) or (3) or 486.5(1) or (2) is guilty of an offence punishable on summary conviction.

(2) For greater certainty, an order referred to in subsection (1) applies to prohibit, in relation to proceedings taken against any person who fails to comply with the order, the publication in any document or the broadcasting or transmission in any way of information that could identify a victim, witness or justice system participant whose identity is protected by the order. 2005, c. 32, s. 15.

COURT OF APPEAL FOR ONTARIO

CITATION: R. v. N.G., 2020 ONCA 494
DATE: 20200805
DOCKET: C66296

Lauwers, Trotter and Fairburn JJ.A.

BETWEEN

Her Majesty the Queen

Respondent

and

N.G.

Appellant

Wayne A. Cunningham, for the appellant

Grace Choi, for the respondent

Richard Elliott and Ryan Peck, for the interveners, the HIV Legal Network, HIV & AIDS Legal Clinic Ontario and Coalition des organismes communautaires québécois de lutte contre le SIDA

Heard: February 12, 2020

On appeal from the conviction entered on November 15, 2017 by Justice Edward E. Gareau of the Superior Court of Justice.

Fairburn J.A.:

OVERVIEW

[1] Over a period of many months, after being diagnosed with HIV and warned about the need to disclose his HIV status to sexual partners, the appellant engaged in repeated acts of vaginal sexual intercourse with three different women. The appellant wore condoms but did not disclose his HIV-positive status and was not on antiretroviral medication. The complainants testified that they would not have

consented to having sexual intercourse with the appellant had they been aware of his HIV-positive status.

[2] The appellant was charged with multiple offences, including three counts of aggravated sexual assault. The trial focused on whether the appellant's failure to disclose his HIV status to the complainants, prior to sexual intercourse, constituted fraud vitiating their consent to that sexual activity in accordance with the principles laid down in *R. v. Mabior*, 2012 SCC 47, [2012] 2 S.C.R. 584. Although one of the complainants was diagnosed with HIV after her sexual relationship with the appellant, there was no proof that she contracted the virus from him.

[3] *Mabior* holds that an accused may be found guilty of aggravated sexual assault under s. 273(1) of the *Criminal Code*, R.S.C. 1985, c. C-46, if he or she fails to disclose an HIV-positive status to a sexual partner, consent to the sexual activity would not have been given had the sexual partner known about that status, and there exists a "realistic possibility of transmission" of HIV during that sexual activity: *Mabior*, at para. 4. The unanimous court in *Mabior* determined that a realistic possibility of HIV transmission is "negated" where two factors come together and work in combination: (a) the non-disclosing person's viral load (the quantity of HIV circulating in his or her blood) at the time of sexual relations is "low"; and (b) a condom is used during the sexual activity in question: *Mabior*, at paras. 94, 103-4.[1]

[4] While the trial judge found as a fact that the appellant used a condom during every act of vaginal sexual intercourse, it is indisputable that the appellant did not have a "low" viral load during a number of those acts of intercourse.

[5] Unable to argue that he met the two-prong test for negating the realistic possibility of transmission of HIV, the appellant instead argued that the *Mabior* test should be changed to reflect the fact that condom use alone is sufficient to negate the realistic possibility of transmission. The trial judge rejected the call to adapt the *Mabior* test and found the appellant guilty on all three counts of aggravated sexual assault.

[6] The appellant then brought a reopening application, at which he sought to introduce expert evidence that use of a condom alone negated any realistic possibility of transmission. The trial judge heard and dismissed the application to reopen the trial. Convictions were entered and the appellant was sentenced to 42 months in custody.

[7] In this court, the appellant renews his argument and seeks to buttress it with fresh evidence. For the reasons that follow, I would dismiss the appeal.

[8] While there is much to be said for the fact that there have been significant medical and scientific strides in our understanding of HIV transmission and treatment in recent years, strides that may well inform the proper direction of the criminal law in the future, I do not accept that the *Mabior* judgment rests on a flawed understanding of the effectiveness of condoms at preventing HIV transmission. The appellant's dispute with *Mabior* rests on the central legal underpinnings of that decision. As I will explain, the reasons for those underpinnings were carefully explained by the unanimous court in *Mabior* and it is not for this court to upend them.

BACKGROUND FACTS

I. The Sexual Activity with A.G.

[9] The appellant and A.G. met on a dating website. She estimated that they had vaginal intercourse 10 to 12 times between September 2013 and October 2014. That activity took place in public parks, behind a school, in the back seats of motor vehicles, and once at A.G.'s home.

[10] A.G. testified that she also performed fellatio on the appellant about 75 or 80 percent of the time that they also had sexual intercourse. He did not use a condom during the fellatio. He sometimes would ejaculate in her mouth and she would swallow his semen.

[11] A.G. testified the appellant always wore a condom during the vaginal intercourse. She recalled bringing the condoms and thought the appellant may have also brought them sometimes. The appellant would put condoms on himself after he had an erection. A.G. could not recall a condom breaking.

[12] When A.G. found out about the appellant's HIV-positive status, she "died a little bit inside." She felt suicidal while awaiting test results to determine whether she had contracted the disease. She ultimately tested negative. She testified that she would not have consented to any sexual activity with the appellant had she known his HIV-positive status.

II. The Sexual Activity with A.C.

[13] The appellant also met A.C. through a dating website. Their sexual relationship involved mutual oral sex without condoms. It also involved vaginal sexual intercourse. That activity took place between July 2013 and March 2014. Although much of their sexual activity took place at A.C.'s home, the appellant and A.C. also had intercourse outside in the bushes and on the ground. During certain periods of time, they had intercourse a couple of times a week.

[14] A.C. said that the appellant would bring his own condoms and put them on. She said that she could hear the package open and saw them "being disposed [of] because most times I would give him the Kleenex, he'd put it in the Kleenex, and I would throw it away". Like A.G., she would not have consented to engaging in sexual activity with the appellant had she known his HIV status. This was particularly true given that she had her own serious health issues at the time.

[15] Although A.C. tested positive for HIV in October 2014, there was no finding that she contracted the disease from the appellant.

III. The Sexual Activity with N.W.

[16] The appellant's brother introduced N.W. to the appellant. N.W. testified about numerous incidents of oral sex and at least one incident of vaginal intercourse that took place at her home somewhere between December 2013 and January 2014. The trial judge found that a condom was used during sexual intercourse.

[17] Like the other complainants, N.W. testified that she would not have consented to engaging in any sexual activity with the appellant had he disclosed his HIV-positive status to her.

IV. The Uncontroverted Facts About the Appellant's Viral Load

[18] Health authorities informed the appellant about his HIV-positive status on October 20, 2013. At that point, his sexual relationships with A.G. and A.C. had already started. The appellant was told about the risks of transmission, the importance of using condoms, and the need to disclose his HIV-positive status to all sexual partners.

[19] The appellant did not start taking antiretroviral medication until April 3, 2014, over five months after diagnosis. Despite having been specifically warned about the risk of transmission and need for disclosure, the appellant continued in his sexual relationships with A.C. and A.G., and started his sexual relationship with N.W., without disclosing to any of them.

[20] Between his initial diagnosis and his first viral load reading after beginning antiretroviral drugs, the appellant's viral load ranged between 11,345 and 27,868 copies of HIV in a millilitre of blood, well above the 1,500 copies described as "low" in *Mabior*. The higher the number, the greater the risk of transmission: *Mabior*, at para. 100. By October 29, 2014, the appellant's viral load had become non-detectable.

[21] Therefore, there is no dispute in this case that the appellant was having vaginal sexual intercourse with the complainants during a time when his viral load was not low within the meaning of *Mabior*.[2] Accordingly, despite his use of condoms, the appellant failed to meet the *Mabior* test for negating a realistic possibility of transmission of HIV during those sexual acts.

V. Defence Expert at Trial: Dr. Wendy Wobeser

[22] The defence called an infectious disease specialist, Dr. Wendy Wobeser. She was qualified to give opinion evidence in the following areas: (a) biology and treatment of HIV; (b) the risk of transmission of HIV; and (c) the general area of infectious diseases.

[23] Dr. Wobeser testified that HIV is a necessary precursor to Acquired Immune Deficiency Syndrome ("AIDS"). Given the advances in science and the availability of antiretroviral medication, today, very few people with HIV develop AIDS. Even so, Dr. Wobeser testified that HIV remains a serious, life-endangering infection if not treated properly.

[24] The most significant risk factors for a person with HIV transmitting the infection through sexual activity are: (a) whether a condom is used; (b) the person's viral load; (c) whether the person is undergoing antiretroviral therapy; and (d) the type of sexual activity undertaken. She testified that vaginal-penile intercourse is less likely to result in transmission of the virus than anal intercourse, with anal intercourse being the highest risk sexual activity for transmission.

[25] Where condoms are used, and "everything works", Dr. Wobeser testified that the risk of HIV transmission is zero. She referred to a study that was cited in *Mabior* with reference to the effectiveness of condoms at preventing transmission: Susan C. Weller and Karen Davis-Beaty, "Condom Effectiveness in Reducing Heterosexual HIV Transmission" (2002), 1 Cochrane Database Syst. Rev. CD003255

["Cochrane Review"]. Relying upon the Cochrane Review, she referred to the fact that, in the "real world", condom use reduces the baseline risk (the actual rate at which something occurs in a given population) of HIV transmission by 80 to 85 percent.

PROCEEDINGS BELOW

I. Reasons for Judgment at Trial

[26] Relying upon Dr. Wobeser's evidence, the trial judge accepted as a fact that, where condoms work, the risk of transmission of HIV is "zero". Even so, he concluded that condoms only provide 80 to 85 percent effectiveness in the "real world", and probably closer to the 80 percent range. As the trial judge said:

> The act of sexual intercourse is not a theoretical concept where theoretical statistics and theories should be applied. It is, rather, a real life action where real life scenarios and real life numbers should be applied. In theory, if all is perfect it may very well be that condom use is 100% effective in [preventing the transmission of] the HIV virus, but the sexual act between two people is not a theoretical experience; it is a real life action where realistic approaches should be taken especially when it concerns the realistic possibility of the transmission of the HIV virus, which is still a life threatening virus if left untreated.

[27] The trial judge rejected as unpersuasive the reasoning in another trial decision where an accused was acquitted of aggravated sexual assault on the basis of condom use alone: see *R. v. Thompson*, 2016 NSSC 134, 373 N.S.R (2d) 167, rev'd but not on this point 2018 NSCA 13, 359 C.C.C. (3d) 222.[3] He also felt bound by this court's decisions in *R. v. Felix,* 2013 ONCA 415, 307 O.A.C. 248 and *R. v. Mekonnen,* 2013 ONCA 414, 299 C.C.C. (3d) 134, two cases that applied the *Mabior* rule for negating the realistic possibility of HIV transmission.

[28] While the trial judge accepted that a great deal has changed in relation to antiretroviral therapy, a subject I will return to later, he concluded that "when the scientific evidence as a whole is examined with respect to condom use in real life situations", nothing had changed since *Mabior*. Therefore, he found:

> Since there is not the combined effect of a low viral load and condom use at the time [the appellant] had sexual intercourse with A.C., A.G., and N.W., there exists, in law, a realistic possibility of HIV transmission during the occurrences of sexual intercourse that [the appellant] had with A.C., A.G., and N.W. [Emphasis in original.]

[29] The appellant was found guilty of three counts of aggravated sexual assault.

II. The Reopening Application

[30] After being found guilty of three counts of aggravated sexual assault, the appellant brought an application to reopen the trial. In support of that application, the appellant filed the affidavit of Dr. John Richard Middleton Smith, the same expert who testified in *Mabior.* Like Dr. Wobeser at trial in this case, during his evidence in *Mabior,* Dr. Smith relied upon the Cochrane Report to estimate the reduction in the baseline risk of HIV transmission when condoms are used. As the court noted in *Mabior,* at para. 98: "Dr. Smith testified that consistent condom protection reduces the risk of HIV transmission by 80%, relying on the widely accepted Cochrane review."

[31] On the reopening application at trial, Dr. Smith said that his thinking on the risks associated with the sexual transmission of HIV where condoms are used has evolved since he testified in *Mabior*. Adopting a passage from a consensus statement prepared by Canadian experts in the field of HIV, Dr. Smith now emphasizes that "when correctly used and no breakage occurs, condoms are 100% effective at stopping the transmission of HIV" (emphasis added): see *Loufty*, *et al.*, "Canadian Consensus Statement on HIV and its Transmission in the Context of Criminal Law" (2014), 25:3 Can J. Infect Dis. Med. Bicrobiol. 135 ["Canadian Consensus Statement"].

[32] Dr. Smith now underscores that the 80 to 85 percent effectiveness rate for condoms, as reflected in the Cochrane Review, is only applicable at a population level and, in his view, should no longer be used for assessing individual risk on a per sex act basis. As he said:

> It is simply incorrect to state that in [an] individual case condoms are only 80-85% effective. In my opinion an individual who always uses a condom and is careful in its use can be almost 100% sure that the HIV virus will not be transmitted.

…

> In my opinion, it is agreed amongst the medical profession, that as far as science has been able to determine, condoms are near 100% effective in preventing HIV transmission if correctly used. I say near 100% because of the negligible prospect that even when properly used, there may be an unknown problem with the condom that allows transmission of bodily fluid. [Emphasis added.]

[33] In the trial judge's view, Dr. Smith's evidence added nothing new to the evidence of Dr. Wobeser that, where condoms work perfectly, the HIV transmission rate is zero. The trial judge concluded, though, that the condom error rate across the population is still an important consideration when determining the realistic possibility of transmission of HIV because sexual intercourse takes place in the "real world" where condoms do not always perform perfectly. Accordingly, he concluded that Dr. Smith's evidence was insufficiently cogent to be granted admission on the reopening application. The application was dismissed, and the matter proceeded to sentencing.

ANALYSIS

I. Overview

[34] In challenging his convictions, the appellant returns to the same argument he made at trial and on the reopening application. He contends that the *Mabior* requirement that condom use be coupled with a low viral load in order to negate a realistic possibility of transmission of HIV overshoots the mark. He says that condom use alone should be sufficient to negate the realistic possibility of transmission because "consistent and correct" condom use creates a zero percent chance of transmission.

[35] Although the appellant acknowledges that in rare situations condoms will fail, he says that this failure is strictly owing to incorrect usage. Therefore, according to the appellant, where a condom is used, regardless of the level of the HIV-positive sexual partner's viral load, condom usage alone should be sufficient to negate the realistic possibility of HIV transmission. To displace that presumption, the appellant contends that it should fall to the Crown to prove condom failure.

[36] At the same time, and importantly, the appellant is not prepared to acknowledge that the criminal law necessarily has a role to play in the wake of condom failure. He argues that all issues surrounding the mechanics of such proof, and whether proof of condom failure could even rise to the level of criminality, be left to another day. Therefore, I refer to the appellant's position on this appeal as a condom-alone rule.

[37] Although they put it slightly differently, the interveners join the appellant in the position that "correct" condom use alone should be able to negate the *Mabior* threshold of a realistic possibility of transmission. They ask this court to "conclude as a matter of law", that:

> (i) condom use *per se* can negate a realistic possibility of transmission for the purpose of the criminal law, and
>
> (ii) there is no realistic possibility of transmission in the case of correct condom use (i.e., "the integrity of the condom is not compromised and the condom is worn throughout the sex act in question"). [Emphasis in original. Footnote omitted.]

[38] To be clear, this case is not about advances in the understanding around the non-transmissibility of HIV in the context of a suppressed or undetectable viral load. In particular, it does not raise the question of whether a suppressed or undetectable viral load, standing on its own, should now be sufficient to negate the realistic possibility of transmission.

[39] The sole issue that this court is asked to resolve in this case is whether, at law, the use of a condom alone – despite the presence of a non-low or perhaps even high viral load – should remove HIV non-disclosure cases from the reach of the criminal law, barring proof that the condom failed in some way. The record before this court addressed that issue alone, and the legal argument followed suit.

[40] The appellant makes two broad arguments in support of his position that it is open to this court to set aside the *Mabior* finding that condom use alone does not negate the realistic possibility of HIV transmission. He maintains that this court can arrive at a different conclusion than *Mabior* on this point because, in determining the rate at which condoms fail to protect against the baseline risk of HIV transmission, the Supreme Court of Canada (a) relied upon Dr. Smith's approach to population-level statistics, an approach that Dr. Smith no longer endorses; and (b) relied upon what are in hindsight flawed statistics.

[41] In support of his argument, the appellant relies upon the evidence of Dr. Smith at the reopening application, as well as evidence contained within a fresh evidence record on appeal. Together, I will refer to all of this evidence as the "new evidence".

[42] The appellant acknowledges that if he is unsuccessful in having his fresh evidence admitted on appeal, then it is unrealistic to expect that this court will find error with the trial judge's decision to exclude Dr. Smith's evidence on the reopening application. His position on this point is a sensible one, particularly given that the tests for the admission of evidence on a reopening application and on appeal align.

[43] In a judge alone trial, a finding of guilt can be vacated prior to the sentence being imposed or other final disposition made, but this should only occur in "exceptional circumstances and where it is clearly called for": *R. v. Lessard* (1976), 1976 CanLII 1417 (ON CA), 30 C.C.C. (2d) 70 (Ont. C.A.), at p. 73. Where an application to reopen a trial is predicated on the admission of further evidence, the well-known *Palmer* test for the admission of fresh evidence on appeal applies: *R. v. Palmer*, 1979 CanLII 8 (SCC), [1980] 1 S.C.R. 759, at p. 775; *R. v. Kippax*, 2011 ONCA 766, 286 O.A.C. 144, at para. 63, leave to appeal refused, [2012] S.C.C.A. No. 92. The *Palmer* criteria are now commonly understood as reflected in a three-part test:

> Is the evidence admissible under the operative rules of evidence?
>
> Is the evidence sufficiently cogent in that it could reasonably be expected to have affected the result?
>
> What is the explanation offered for the failure to adduce the evidence at trial and should the explanation affect the admissibility of the evidence on appeal?

Truscott (Re), 2007 ONCA 575, 226 O.A.C. 200, at para. 92; *R. v. Reeve,* 2008 ONCA 340, 236 O.A.C. 92, at para. 66.

[44] The central question in this appeal is whether the trial judge erred when he concluded that Dr. Smith's evidence was insufficiently cogent to be granted admission on the reopening application.[4] There are three aspects to the cogency consideration:

> Is the evidence relevant in that it bears upon a decisive or potentially decisive issue at trial?
>
> Is the evidence credible in that it is reasonably capable of belief?
>
> Is the evidence sufficiently probative that it could reasonably, when taken with the other evidence adduced at trial, be expected to have affected the result?

Truscott, at para. 99.

[45] The first two cogency requirements are clearly met in this case.

[46] First, the new evidence bears upon a decisive issue at trial, being whether the appellant's use of condoms negated the realistic possibility of transmission of HIV despite his viral load.

[47] Second, there is no dispute that the new evidence is credible. No one suggests otherwise.

[48] The real question is whether, when considered against all of the evidence at trial, the new evidence is "sufficiently probative" to allow this court to change the *Mabior* rule, so that condom use alone can negate the realistic possibility of HIV transmission, thereby requiring acquittals to be entered. I see no error in the trial judge's conclusion that Dr. Smith's evidence was insufficiently cogent to be granted admission on the reopening application. There is nothing in the fresh evidence on appeal that changes my view in that regard.

II. The *Mabior* Rule for Fraud Vitiating Consent

[49] In order to understand the appellant's position about why condom use alone should negate the realistic possibility of transmission, it is first necessary to understand how the Supreme Court of Canada came to reject that very suggestion in *Mabior.* I will start by reviewing the *Mabior* test and how it came to be. I will then address the narrow basis upon which that test can be revisited by lower courts, after which I will explain why, in my view, the appellant's arguments for adapting the test must fail.

1. From *Cuerrier* to *Mabior*

[50] A range of criminal offences have been used to prosecute HIV non-disclosure cases in Canada, such as criminal negligence causing bodily harm, common nuisance, administering a noxious substance, attempted murder, murder, and various degrees of assault and sexual assault.[5] A report prepared by the Department of Justice suggests that aggravated sexual assault is the most frequently prosecuted offence in this context: Canada, Department of Justice, *Criminal Justice System's Response to Non-Disclosure of HIV* (2017), at p. 15 ["Department of Justice Report"].

[51] This case, *Mabior*, and *Mabior's* predecessor, *R. v. Cuerrier,* 1998 CanLII 796 (SCC), [1998] 2 S.C.R. 371, are all cases involving convictions for aggravated sexual assault. The reasons must be considered within that offence-based context. Therefore, to understand the *Mabior* rule that lies at the centre of this appeal, it is necessary to first understand how consent operates in the context of sexual assault prosecutions involving HIV non-disclosure.

[52] Consent to sexual activity constitutes the voluntary agreement to "engage in the sexual activity in question": *Criminal Code*, s. 273.1(1). Consent must be freely given, constituting the "conscious agreement of the complainant to engage in every sexual act in a particular encounter": *R. v. J.A.*, 2011 SCC 28, [2011] 2 S.C.R. 440, at para. 31.

[53] Consent as defined in s. 273.1(1) of the *Criminal Code* is not to be "considered in the abstract": *R. v. Barton,* 2019 SCC 33, at para. 88. Rather, as set out in *R. v. Hutchinson,* 2014 SCC 19, [2014] 1 S.C.R. 346, at paras. 55, 57, and recently reinforced in *Barton,* at para. 88, consent is linked to the "sexual activity in question", which encompasses "the specific physical sex act", "the sexual nature of the activity", and the "identity of the partner". It does not, though, include the "conditions or qualities of the physical act, such as … the presence of sexually transmitted diseases". See also: *R. v. Kirkpatrick,* 2020 BCCA 136, at para. 89, *per* Bennett J.A. (majority).

[54] Even where the requirements of s. 273.1(1) are met – the complainant has agreed to the specific physical sex act, the sexual nature of the act, and the identity of the sexual partner – this does not end the inquiry into whether consent has been given. This is where ss. 265(3) and 273.1(2) of the *Criminal Code* come into play, setting out the circumstances where consent is deemed not to have been given: *R. v. Ewanchuk*, 1999 CanLII 711 (SCC), [1999] 1 S.C.R. 330, at para. 36.

[55] As first addressed in *Cuerrier*, HIV non-disclosure cases prosecuted as aggravated sexual assault engage directly with s. 265(3)(c) of the *Criminal Code*, dealing with fraud capable of vitiating consent:

> For the purposes of this section, no consent is obtained where the complainant submits or does not resist by reason of
>
> …
>
> (c) fraud.

[56] Seven judges sat in *Cuerrier* and three judgments emerged. Cory J. held the plurality. His decision set the course for how the fraud component in s. 265(3)(c) operates to vitiate consent where certain criteria are present in HIV non-disclosure cases. Like *Mabior* and this case, *Cuerrier* also involved HIV non-disclosure in the context of acts of vaginal-penile sexual intercourse.

[57] Expressing concern over casting the criminal net too widely, Cory J. determined that HIV non-disclosure could only constitute fraud capable of vitiating consent if two things were proven: (a) a deception; and (b) a deprivation or risk of deprivation.

[58] The deception component of s. 265(3)(c) can be proven through either an active lie about one's HIV status, or silence as to that status: *Cuerrier*, at para. 126.

[59] The deprivation component can be proven through actual harm (the actual transmission of the virus) or through a "risk of deprivation" (a risk of transmission of the virus). A "risk of deprivation" means that the complainant did not contract HIV through the sexual activity in question but was placed at risk of contracting the disease during that activity. It is the "risk of deprivation" component of the element of fraud under s. 265(3)(c) that has attracted substantial attention in the context of HIV non-disclosure cases.

[60] Where the prosecution is relying upon only a risk of deprivation to vitiate consent (as in *Cuerrier, Mabior*, and this case), according to *Cuerrier,* the risk must rise to the level of a "significant risk of serious bodily harm": at paras. 128, 135. See also: *Hutchinson*, at para. 34.

[61] In time, that test proved somewhat elusive and difficult to apply, resulting in concerns regarding the inconsistent application of the test and the overbroad application of the criminal law: *Mabior*, at paras.

13-15. These concerns eventually resulted in two different appellate courts specifically asking the Supreme Court of Canada for clarification on the test: *R. v. Mabior*, 2010 MBCA 93, 245 Man. R. (2d) 81, at para. 152; *R. v. D.C.*, 2010 QCCA 2289, 270 C.C.C. (3d) 50, at para. 121.

[62] The Supreme Court answered that call in *Mabior*.[6]

[63] The parties and interveners in *Mabior* advanced various models for solving the perceived difficulties arising from the *Cuerrier* test. Each model was rejected by the court, including the suggestion by Mr. Mabior that judicial notice be taken of the fact that "condom use always negates a significant risk of serious bodily harm": *Mabior,* at para. 70.

[64] Ultimately, the Supreme Court refused to jettison the *Cuerrier* test. Instead, the court opted to clarify the meaning of that test for purposes of finding a sufficient risk of deprivation to vitiate consent in the context of HIV non-disclosure. The court concluded that a significant risk of serious bodily harm is established where there exists a "realistic possibility of transmission of HIV": *Mabior,* at paras. 4, 84, 91, 93, 104, 108. In other words, where a person fails to disclose his or her HIV-positive status before engaging in sexual intercourse, in circumstances where there exists a realistic possibility of HIV transmission, a deception and risk of deprivation will align such that fraud will be capable of vitiating the unwitting sexual partner's consent.

[65] In an effort to provide even further clarity in the law, the *Mabior* court went on to explain, at para. 94, that where two factors come together to form a symbiotic relationship, the realistic possibility of HIV transmission will be negated:

> This leaves the question of when there is a realistic possibility of transmission of HIV. The evidence adduced here satisfies me that, as a general matter, a realistic possibility of transmission of HIV is negated if (i) the accused's viral load at the time of sexual relations was low *and* (ii) condom protection was used [Italics in original, underline added.]

[66] In other words, *Mabior* made clear that if a person's viral load is "low" during sexual relations and a condom is used during those relations, the realistic possibility of HIV transmission will be negated. Therefore, as a matter of criminal law, *Mabior* clarified that where these two things align, there will be no realistic possibility of HIV transmission, thereby removing the risk of deprivation necessary for consent to be vitiated under s. 265(3)(c) of the *Criminal Code*.

[67] While the *Mabior* decision places the burden on the Crown to establish the dishonest act and risk of deprivation beyond a reasonable doubt, the court made the practical observation, at para. 105, that where the Crown establishes a *prima facie* case of deception and deprivation, a tactical burden may shift to the accused to trigger the two-part test:

> The usual rules of evidence and proof apply. The Crown bears the burden of establishing the elements of the offence – a dishonest act and deprivation – beyond a reasonable doubt. Where the Crown has made a *prima facie* case of deception and deprivation as described in these reasons, a tactical burden may fall on the accused to raise a reasonable doubt, by calling evidence that he had a low viral load at the time and that condom protection was used. [Emphasis added.]

[68] The application of the test to the facts of *Mabior* assists in understanding how it is intended to operate. The court allowed the appeal insofar as the decision of the Court of Appeal had conflicted with the test. This led to the reinstatement of convictions where, despite Mr. Mabior's low viral load, he did not use a condom during vaginal sexual intercourse: *Mabior*, at paras. 108-9. See also this court's application of this test for negating a realistic possibility of HIV transmission in *Felix*.

[69] Having completed this review of the *Mabior* rule that is under challenge in this appeal, and before moving on, it is perhaps worth emphasizing the crux of HIV non-disclosure cases prosecuted as aggravated sexual assaults. The essence of the crime lies in the failure to disclose one's HIV-positive status to an unwitting sexual partner in circumstances where there exists a realistic possibility of transmission of the virus to that unwitting partner. In my view, what is criminalized is the unilateral imposition of risk of very serious harm onto another person without offering the at-risk party an opportunity to decide whether to assume that risk, or how to manage that risk, before making a decision to proceed.

2. The Importance of *Stare Decisis*

[70] The principle of *stare decisis* casts a long shadow in this case and, as I will explain, governs the result.

[71] There are sound reasons for why, except in limited circumstances, lower courts do not depart from precedents of higher courts. At the forefront of those reasons is the need for certainty in the law. As noted in *Canada (Attorney General) v. Bedford*, 2013 SCC 72, [2013] 3 S.C.R. 1101, at para. 38:

> Certainty in the law requires that courts follow and apply authoritative precedents. Indeed, this is the foundational principle upon which the common law relies.

[72] Despite the importance of certainty in the law, and the need to follow precedent in order to achieve that certainty, where the factual underpinnings guiding a legal decision give way, so too may the principle of *stare decisis.* Indeed, the *Mabior* decision makes specific note of this fact.

[73] *Mabior* is clear that the means by which a realistic possibility of HIV transmission can be negated – condom use combined with a low viral load – represents a conclusion that is inextricably linked to the factual record before the court: see, for instance, paras. 94, 95, 101, 103, 109. The decision is also clear that the court was alive to the fact that this approach to negating risk is directly linked to science and medicine, both disciplines that are inherently dynamic in nature and ever on the move toward better health outcomes.

[74] Recognizing that medical and scientific developments may take place in the future, the court extended – twice over – a specific invitation to lower courts to, if necessary, adapt the means by which a realistic possibility of HIV transmission can be negated:

> The general proposition that a low viral load combined with condom use negates a realistic possibility of transmission of HIV does not preclude the common law from adapting to future advances in treatment and to circumstances where risk factors other than those considered in the present case are at play. [Emphasis added.]

Mabior, at para. 104. See also para. 95.

[75] The appellant argues that the *Mabior* invitation to adapt is this court's gateway to reconsidering the factors that must be at play before a realistic possibility of transmission can be negated. I do not agree.

[76] While I accept that the *Mabior* decision leaves it open to lower courts to adapt the criteria necessary to negate a realistic possibility of HIV transmission, it does so in a way that is consistent with the principles of *stare decisis.* In my view, the invitation to adapt is directly linked to "future advances in treatment and to circumstances where risk factors other than those considered" in *Mabior* are at play. In other words, the invitation to adapt is linked to potential changes to the factual pillars upon which *Mabior* rests, in circumstances where those pillars are particularly susceptible to change.

[77] As I will shortly explain, though, the appellant's argument in favour of a condom alone rule rests on a challenge, not to the factual pillars upon which *Mabior* rests, but to the legal foundation upon which the decision rests.

[78] Although I take no final view on the matter, because it extends beyond the scope of this judgment, it is noteworthy that since *Mabior* was decided, it is arguable that the factual underpinnings of the decision have already changed, although not in relation to the effectiveness of condoms. There appears to have been significant changes involving the understanding around the ability to transmit HIV with a suppressed or undetectable viral load. The record in this case includes references to the post-*Mabior* medical and scientific communities' broad consensus that it is no longer considered possible to transmit HIV with a suppressed or undetectable viral load: see *Barre-Sinoussi et al.*, "Expert Consensus Statement on the Science of HIV in the Context of Criminal Law" (2018), 21:7 J. Int'l AIDS Society e25161, at s. 2.1 ["International Consensus Statement"]; Canadian Consensus Statement, at pp. 136-7.

[79] So widely accepted is that view today that it appears some prosecution services across the country have now put policies in place directing Crown counsel not to prosecute HIV non-disclosure cases any longer in circumstances where the HIV-positive partner's viral load is either suppressed (a level defined within those policies) or undetectable: see e.g., Federal: Office of the Director of Public Prosecution, *Directive* (30 November 2018) [Federal Prosecution Policy]; Ontario: Ministry of the Attorney General, "D. 33 Sexual Offences Against Adults: Sexually Transmitted Infections and HIV Exposure Cases", in *Crown Prosecution Manual* (December 1, 2017); British Columbia: Prosecution Service, "Sexual Transmission, or Realistic Possibility of Transmission, of HIV, in *Crown Counsel Policy Manual* (April 16, 2019).

[80] Lower courts have also started acknowledging that viral loads below a defined level, standing on their own, are sufficient to negate the realistic possibility of HIV transmission: see e.g., *R. v. Vatcher* (November 22, 2019), Ottawa, 0411-998-17-51-27 (Ont. C.J.); *R. v. J.T.C.*, 2013 NSPC 105, at paras. 55-

56, 63, 99-101; *R. v. J.T.C.*, 2013 NSPC 88, at paras. 14-15, 17, 19-21; *R. v. C.B.*, 2017 ONCJ 545, at paras. 87, 90-92, 99; *Thompson*, at paras. 97, 132-134.

[81] Without weighing in on the matter, as it is not before us, the apparent evolution in the medical and scientific communities' understandings around the transmissibility of HIV in the face of suppressed or undetectable viral loads illustrates precisely the kind of evolution the *Mabior* court left open for consideration in the future. This is the kind of situation where *stare decisis* would not bind lower courts to the *Mabior* rule.

[82] In my view, the new evidence in this case is not of a similar type. Its primary focus is not upon changes to the factual backdrop upon which the *Mabior* decision rests. Rather, its primary focus is upon desired changes to the legal foundations upon which the *Mabior* decision rests.

III. The New Evidence Does Not Add Anything New

1. The New Evidence

[83] At the reopening application, Dr. Smith expressed that he has changed his mind since *Mabior* about the appropriateness of using population-level statistics when considering the risk of HIV transmission in the context of the criminal law. He reinforced this view in his fresh evidence on appeal.

[84] As reflected in the *Mabior* decision, Dr. Smith provided evidence that the baseline risk of HIV transmission per act of unprotected vaginal-penile sexual intercourse (no condom and a non-low viral load), where the male partner is HIV-positive, varies from "study to study", but is somewhere between 1 in 2,000 and 1 in 384. The court also summarized other evidence, suggesting that the baseline risk of transmission in these circumstances ranges from 1 in 1,000 to 1 in 1,250: *Mabior*, at para. 97. In this case, Dr. Wobeser referred to this baseline risk of transmission as around 8 in 10,000.

[85] The Supreme Court relied upon the Cochrane Review, as put forward by Dr. Smith in *Mabior*, for the proposition that "consistent" condom use can reduce that baseline risk by 80 percent: *Mabior*, at para. 98. The court concluded that, despite the reduction in risk of transmission provided by condom use, something more was required to negate the "realistic possibility of transmission": *Mabior*, at para. 99. That something more is a low viral load.

[86] Contrary to his *Mabior* evidence, Dr. Smith now eschews the use of the Cochrane Report – predicated on population-level statistics – to determine the effectiveness of condoms at reducing the risk of HIV transmission. Dr. Smith now opines that: "it is incorrect to state that in any individual case condoms are only 80% to 85% effective" because, in his current view, correct and consistent condom use leads to 100 percent protection from transmission when considered on a per act basis where nothing goes wrong.

[87] While Dr. Smith acknowledges that condoms do fail from time-to-time, it is his view that the law should only consider what happened in each individual case. As he puts it: "[o]ne has to find out the truth of what occurred" and the "legal system should not be dealing with cases where there [has] not been transmission". He says that, instead, the legal system should only "function" by looking at the "outcome of the event", rather than the risk going into the event.

[88] In formulating his opinion, Dr. Smith relies upon a number of reports, including the Canadian Consensus Statement, where HIV physicians and medical researchers have expressed a similar view. That report is aimed at addressing what the authors perceive to "be at stake in individual criminal cases" and "does not extend to HIV transmission at a population level in relation to HIV prevention efforts" (emphasis added): at p. 136.

[89] Within that context, the authors focus upon condoms that are "used correctly" and where "no breakage occurs." The authors specifically point out that their opinion is based upon the assumption that the "condom was applied to the penis and worn throughout sex, and that no condom breakage occurred": at p. 136.[7] Assuming these prerequisites are met, the Canadian Consensus Statement says "condoms are 100% effective at stopping the transmission of HIV": at p. 136.

[90] Dr. Smith also relies upon the International Consensus Statement to a similar end. That report was prepared by 20 HIV scientists from different regions across the world. "Correct" condom use is defined as a condom being worn throughout the sex act and its integrity not being compromised: International Consensus Statement, at s. 2.2.

[91] Bearing that definition in mind, the International Consensus Statement concludes that when a condom is correctly used, in an individual act of sexual intercourse, there is zero risk of transmission of HIV because bodily fluids containing the virus, like blood, semen, pre-seminal fluid, vaginal and anal fluids, cannot come into direct contact with sites in the body of an HIV-negative person where infection

can be initiated, like mucous membranes or damaged tissue: International Consensus Report, at ss. 2.1 and 2.2.

[92] Finally, Dr. Smith relies upon the Department of Justice Report, that concludes with a recommendation that the criminal law should "generally not apply to persons living with HIV who … are not on treatment but use condoms … because the realistic possibility of transmission test is likely not met" (emphasis added): at p. 30. The appellant points out that in response to that report, the Attorney General of Canada adapted its policy direction to federal prosecutors, suggesting that the Director "shall generally not prosecute…where the person has not maintained a supressed viral load but used condoms or engaged only in oral sex or was taking treatment as prescribed, unless other risk factors are present" (emphasis added): see Federal Prosecution Policy.

[93] The Crown responds with evidence from two other experts: (a) Dr. William Yarber, a health behavioural scientist with specialized knowledge in the area of male condoms and problems with usage; and (b) Dr. David Fisman, the current Head of the Division of Epidemiology at the University of Toronto, with an expertise in, among other things, the epidemiology of sexually transmitted diseases including HIV. As will be explained later, Dr. Yarber catalogues the multiple challenges associated with "correct" condom use and the difficulties in achieving a perfect latex barrier to transmission. Among other things, Dr. Fisman addresses the importance of using population-level statistics when determining the risk of transmission associated with a sexual activity before it is undertaken.

2. There is No Basis to Revisit the Supreme Court's Reliance on Population-Level Statistics

[94] The appellant points to the following sentence from *Mabior*, at para. 98, to suggest that the court did not understand what he argues the new evidence shows, that consistent and correct condom use makes for a zero risk of transmission:

> Dr. Smith testified that consistent condom protection reduces the risk of HIV transmission by 80%, relying on the widely accepted Cochrane review …. It was pointed out that the 80% reduction in the transmission refers to consistent condom use: the reduction may be larger for consistent *and* correct condom use, but this has not been verified empirically. [Emphasis added.]

[95] The appellant and interveners argue that the new evidence now verifies empirically that consistent and correct condom use brings the risk of HIV transmission to zero and *Mabior* should be adapted accordingly. Although they accept that some people are irresponsible condom users, they argue that the lack of due care on the part of others should not be visited upon responsible condom users. In other words, the criminal law should not be used to punish those who correctly use their condoms because those individuals do not place their sexual partners at risk.

[96] The interveners clearly and helpfully summarize this position in the following passage reproduced from their factum:

> By definition, population-level estimates factor in instances where condoms are not used correctly; those instances reduce the overall observed effectiveness, at the population level, of condoms for HIV prevention. It is unfair to convict an individual condom user – whose correct use of a condom would mean zero risk of transmission – on the basis of a population-level estimate that condoms are "only" 80% effective in reducing the risk of transmission (already an exceedingly small per-act risk), particularly in the absence of a finding that that individual engaged in incorrect condom use. [Emphasis added.]

[97] In my view, there are three overarching difficulties with the appellant and interveners' position: (a) the position conflates "consistent and correct" condom use with the ideal scenario in which condoms function perfectly, thereby failing to account for real-world situations in which condoms do not function perfectly; (b) it is contrary to the principles underlying epidemiology and the criminal law; and (c) it is inconsistent with the *Charter* values animating the *Mabior* rule.

a. "Consistent and Correct" Condom Use Does Not Mean Zero Risk of Transmission

[98] First, the position conflates fundamentally different concepts. The term "correct condom use" is used as if it were a proxy for knowing in advance that a condom would be used perfectly and that the condom would function perfectly. These are not the same things.

[99] There is no dispute that a perfectly functioning latex condom provides a perfect barrier to HIV transmission. Indeed, the Supreme Court of Canada well appreciated this fact in *Mabior*, as reflected at

para. 98 of the decision: “It is undisputed that HIV does not pass through good quality male or female latex condoms”.

[100] But, as the Supreme Court of Canada also understood, condoms do not always work as they are intended to work: “condom use is not fail-safe, due to the possibility of condom error and human error”: *Mabior,* at para. 98. Indeed, from time-to-time, despite the very best intentions and efforts of sexual partners, condoms sometimes fail to work. Dr. Smith agreed during cross-examination that it is “not possible to know prior to a sexual encounter whether perfect or correct use versus condom failure may happen.”

[101] Indeed, this court recently captured this concept in *R. v. Boone,* 2019 ONCA 652, at para. 122:

> Dr. Tyndall agreed with Dr. Remis that condom use reduced the risk of transmission overall by about 80 percent. Dr. Tyndall also testified that if the condom was properly applied and did not malfunction during use, the risk reduction approached very near 100 percent. Of course, no one could know ahead of any particular sexual activity whether the condom would malfunction in some way.

[102] There is an ample record on appeal, primarily led through Dr. Yarber’s affidavit evidence, testimony, and accompanying reports, that supports the fact that sometimes condoms slip, break, leak, and otherwise fail. These events can happen despite efforts to the contrary.

[103] As the respondent points out, multiple experts in this case, including Dr. Wobeser, Dr. Smith, and Dr. Yarber, provided evidence demonstrating just how many things can go wrong with male latex condoms, including:

- Using a condom that has expired
- Using a condom that has been incorrectly stored, including in a pocket and sat on
- Using a condom that has been exposed to excessive heat
- Opening a condom package in a way that damages the condom
- Not squeezing the air out of the tip of the condom before application in order to leave a sufficient reservoir for semen
- Not rolling the condom onto the entire penis
- Using improper lubrication that can damage the condom
- Withdrawing the penis in a way that results in the condom slipping off or spilling semen
- Reusing a condom.

[104] Moreover, these problems can be magnified when condoms are used in less than perfect settings, such as when they are applied in the dark, in small spaces, in awkward positions, or under the influence of intoxicants. To adopt an expression used by the trial judge in this case, in the “real world”, even despite the best of intentions, things can and do go wrong with condom usage.

[105] In fact, this case involves precisely some of those “real world” kinds of circumstances that may lean more heavily toward things going wrong: sexual intercourse taking place in locations that are less than conducive to the careful handling of this piece of latex, including in the dark in cars, parks, bushes, and school yards.

[106] In addition, condom failure incidents are not always obvious. While some condom failure may come to the attention of the sexual participants, this is not always the case. As Dr. Fisman points out:

> You don’t have a biophysics lab present at the bedside after two people have sex so that you can look and see, is there any compromise of the condom’s integrity… and some of it may well be unrecognized because you’re talking about potentially very small quantities of fluid and very small particles.

[107] Indeed, the chances of noticing condom failure might be further minimized where one party to the sexual act has no knowledge that there is a risk of HIV transmission should the condom fail. Where a complainant is unaware of the risk, he or she may not be as vigilant with the condom use as might otherwise be the case.

[108] Again, the circumstances of this case underscore that fact. By way of example, A.C. testified that the appellant usually brought his own condoms, put them on himself and disposed of them. She did not pay much attention to the procedure. In fact, she was not even sure if the condoms contained ejaculate when they came off: “It was dark, so I couldn’t tell. The lights were always off.” As it turns out, unbeknownst to her, those condoms that she paid so little attention to were her sole line of defence against the baseline risk of HIV transmission because the appellant had not started taking antiretroviral medication during the many months while they were engaged in sexual acts.

[109] Accordingly, “correct” usage does not necessarily mean that the condom functioned perfectly. Even in situations where there is a well-intentioned effort to achieve perfect usage, things can and do go wrong.

b. Assessing Risk from a Population Level is Consistent with Epidemiology and the Criminal Law

[110] What the appellant and interveners are really looking for is a legal rule that favours determining the realistic possibility of transmission by looking to the actual effectiveness of condoms at the exact time they are used. As the appellant argued on appeal, it should be for the Crown to prove beyond a reasonable doubt that a condom failed before the criminal law could even possibly apply.

[111] This argument is inconsistent with risk assessment from an epidemiology perspective and is also inconsistent with the legal underpinnings of *Mabior.*

[112] As Dr. Fisman explains, looking to population-level statistics to predict risk at an individual level is the “premise that underpins the entire field of epidemiology” and is “crucial” to predicting “the risk for an individual person.” Any other approach assesses risk from an *ex post facto* perspective, one where the harm arising from the risk has either happened or not. As Dr. Fisman explains:

> [I]t’s very difficult to talk about probabilities when you are talking about an individual, because the event either happens or doesn’t happen with an individual, it’s a 0 or a 1. Whereas in a population we can get into estimation of risks. … Post hoc you know with certainty what happened, but it’s sort of horse-and-barn-door stuff, it’s nonmodifiable, which is why it’s important to have estimates of risk ex-ante.

[113] In contrast, I read Dr. Smith’s evidence as essentially supporting the idea that, for purposes of the criminal law, risk of HIV transmission should only be assessed based upon the “outcome of the event”. When asked about whether population data has some relevance to informing the “predictive probability of transmission” of the virus, he answered: “Well, I think in terms of preventive health education it would, but in terms of just legal system it would not.”

[114] Dr. Smith confirmed that this is his view of “how the legal system should function.” He went even further and provided his opinion that the “legal system” should not be dealing with cases involving only risk of transmission:

> I think that the legal system should not be dealing with cases where there [has] not been transmission. Personally, I think it would be reasonable for the legal system to deal with cases where there has been transmission.

[115] Of course, that is not a scientific or medical conclusion, but a legal one that is antithetical to the reasoning in both *Cuerrier* and *Mabior.* In my view, Dr. Smith’s evidence contains no new information about the effect of condom use on HIV transmission rates; rather, what has changed is his opinion that the criminal law should approach these risks differently than the Supreme Court chose to in those cases.

[116] Although the appellant and interveners do not go quite as far as Dr. Smith by suggesting that only transmission cases should fall within the reach of the criminal law, they heavily rely upon his evidence to advance the position that the risk of transmission should only be looked at from an after-the-fact perspective. They argue that, at its highest, an after-the-fact inquiry should be made into whether the complainant was actually put at risk. This stands in direct opposition to the current forward-looking *Mabior* approach to assessing whether there exists a realistic possibility of HIV transmission at the time when the unwitting sexual partner offers his or her consent to the sexual activity in question.

[117] In my view, their position is really a request to conduct a “case-by-case” approach to risk assessments in HIV non-disclosure cases. That approach was specifically rejected in *Mabior* because of the inherent lack of predictability that would result from any such approach: *Mabior*, at paras. 68-69. Indeed, it is that very kind of approach that led to great uncertainty in the wake of *Cuerrier* and why *Mabior* came along to inject certainty into this complex area of the law.

[118] It is important that the criminal law be predictable. People need to know with some degree of certainty, before they engage in conduct, whether that conduct will be labelled criminal or not. The desire in *Mabior* to provide clarity in the operation of the criminal law is one of the foundational principles upon which the decision rests, and one that pushed toward a clear and easily applied test for when the realistic possibility of transmission of HIV would be negated: *Mabior*, at paras. 14, 19.

[119] The appellant's and interveners' suggestion that the law move toward an assessment of whether there was a risk of transmission of HIV during a specific sexual encounter, based on whether condoms actually slipped, leaked, broke, or otherwise malfunctioned, would return the law in HIV non-disclosure cases to the undesirable world of uncertainty.

[120] Moreover, I do not accept the appellant's suggestion that the criminal law is designed only to address what actually happens as a result of what people do, not the risk they potentially put others at while doing it. Indeed, there are examples of the criminal law addressing its attention to risks before they materialize.

[121] As the respondent points out, drinking and driving and unsafe storage of firearm offences constitute two examples of the criminal law specifically targeting perceived risk of harm before that risk is actually visited upon others.

[122] I do not wish to be taken as suggesting that drinking and driving or unsafe storage of firearms offences are perfect analogies to HIV non-disclosure sexual assault-based offences. There is one important difference between them. When it comes to drinking and driving and unsafe storage of firearms offences, members of the public are not given the choice to voluntarily assume the risks associated with those activities. When it comes to HIV non-disclosure cases, though, members of the public are given that choice. The key is that they need to know there is a risk before they can choose to assume that risk.

[123] HIV non-disclosure cases are therefore targeted at the deception involved in unilaterally placing complainants at risk without giving them the choice to voluntarily assume that risk and decide how to best manage that risk.

[124] To this end, I would add the crime of fraud to this discussion. Indeed, the essential elements of fraud were discussed at some length in *Cuerrier* and, with some adaptation, formed the genesis of the approach to how fraud can vitiate consent in the HIV non-disclosure context: *Cuerrier*, at paras. 114-17. Drawing upon the court's prior authorities setting out the elements of fraud, including reference to *R. v. Théroux*, 1993 CanLII 134 (SCC), [1993] 2 S.C.R. 5, Cory J. emphasized in *Cuerrier* that the "essential elements of fraud are dishonesty, which can include non-disclosure of important facts, and deprivation or risk of deprivation" (emphasis added): at para. 116. In other words, a risk of deprivation to one's economic interests, through dishonest means, is sufficient for fraud. Take away the dishonesty and someone can voluntarily assume the risk of financial harm.

[125] *Cuerrier* took the same risk approach to HIV non-disclosure, by focussing on the risk to the complainant at the time that the consent is dishonestly procured. Take away the dishonesty and someone can voluntarily assume the risk of HIV transmission.

c. Assessing Risk from a Population Level is Consistent with *Charter* Values

[126] *Mabior* reflects an exquisitely difficult balance between the rights of those living with HIV and the rights of those offering their consent to sexual activities without all of the information they need and would like to make that decision.

[127] On the one hand, the court emphasized that the stigma attaching to a criminal conviction in this context should be "reserved for conduct that is highly culpable" in nature: *Mabior,* at para. 19. On the other hand, the court emphasized the *Charter* values of equality, autonomy, privacy, liberty, and bodily integrity, all of which promote respect for sexual participants and their dignity as human beings: see *Mabior*, at para. 45. See also *Ewanchuk*, at paras. 27-28; *Barton*, at paras. 88-90, 109. These are the *Charter* values animating the *Mabior* decision and underpinning the complainant's right to be informed of a partner's HIV status in the circumstances described in *Mabior.*

[128] It is against that backdrop that the court spoke of "[o]ur modern understanding of sexual assault", one that "is based on the preservation of the right to refuse sexual intercourse" and the need to interpret s. 265(3)(c) within that context: *Mabior,* at para. 45.

[129] In my view, the use of population-level statistics to assist in determining the risk of HIV transmission during condom-use-alone sexual intercourse is entirely consistent with our modern notion of consent to sexual activity and what may operate to vitiate that consent.

[130] From a consent perspective, it makes sense to consider the risk of HIV transmission during a sexual act from a forward-looking perspective. After all, if risk is to be looked at after condom failure, then

the complainant has already been put at risk without having voluntarily assumed that risk. This hindsight approach to risk, after the risk has been involuntarily and unknowingly assumed, would do little for the modern-day notion of consent and the preservation of the "right to refuse intercourse". In my view, the *Mabior* rule is about preventing the consenting party from having the risk of contracting an indisputably serious, life-altering disease unilaterally imposed upon him or her in the first place: *Mabior,* at para. 88.

[131] While I accept that HIV is now a manageable disease, it remains incurable and indisputably chronic, such that it could change the entire course of a sexual partner's life: Canadian Consensus Statement, at p. 138; International Consensus Report*,* at s. 2; Department of Justice Report, at pp. 3-6. While AIDS can be avoided, to date, HIV cannot be cured: Department of Justice Report, at p. 3. Among other health complications, HIV requires antiretroviral medication, leaves a person susceptible to other infections because of the immune system impairment, and brings about periods of ill health and disability: Department of Justice Report, at pp. 5-6.

[132] It is only by resorting to population-level statistics that forward-looking risk can be assessed.

3. The Risk of Condom Failure in the Cochrane Review is Not Overinflated

[133] The appellant also argues that the population-level statistics contained in the Cochrane Review are suspect. First, he says that those statistics – as relied upon by the Supreme Court of Canada in *Mabior* and by Dr. Wobeser at trial – are predicated on groups of "always condom users" and "never condom users".

[134] As for the always condom users, the appellant argues that there is likely some social acceptability bias embedded in the statistics because it involves self-reporting, where people will be motivated to suggest they took appropriate precautions prior to becoming seroconcordant (the non-HIV-positive sexual partner moving to a positive status). This would lead to some people reporting using condoms when they did not actually use condoms, causing some instances of transmission from sex without condoms to be recorded as transmission from sex with condoms. That could lead to condoms appearing less effective than they actually are.

[135] The appellant also suggests that there may have been some difficulties with some of the underlying studies informing the Cochrane Review. For instance, in one of the studies, where there had been four seroconversions involving people who claimed to have always used condoms, the authors of that study noted that there had been "improper or incomplete condom use" in a number of the cases. In another study, the appellant suggests that, because of the way in which the seroconversions were assigned to specific time frames, it may be that it had the effect of misclassifying the effectiveness of condoms. He argues that some seroconversions were assigned to timeframes during which the couple reported always using condoms, but transmission may have occurred during an earlier timeframe when they were not using condoms. Again, if this occurred, it would lead to condoms appearing less effective than they actually are.

[136] This argument is rooted in the suggestion that, even if it was right for the Supreme Court to assess the risk of transmission of HIV with the use of population-level statistics, it was wrong to have uncritically accepted the Cochrane Review as accurately containing the condom failure error rate across the population.

[137] The respondent relies upon the evidence of Dr. Yarber, an expert on condom use and failure rates. The appellant challenges Dr. Yarber's numbers, arguing that, in fact, the rates for condom breakage, leakage, slippage, late application, and early removal events are much smaller than he suggests.

[138] The respondent disputes the appellant's characterization of the statistics, claiming they are actually much higher than the appellant suggests. Relying upon a study that Dr. Yarber co-authored, the respondent suggests that condom use errors must be considered in light of studies showing the combined rates for different types of condom failure together, some of which are well over the 20 percent range: *Sanders et al.*, "Condom use errors and problems: a global view" (2012), 9 Sexual Health 81, at p. 90. That is, the chance of the condom slipping *or* breaking *or* otherwise failing – the chance of the condom failing in some way – can be over 20 percent.

[139] I do not intend to address the specific statistics for condom slippage, breakage, leakage, and the like. At the end of the day, in my view, the Cochrane Review relied upon by the Supreme Court in *Mabior* has not been shaken in any meaningful way by the new evidence here.

[140] Indeed, Dr. Smith acknowledged during cross-examination on the reopening application that the Cochrane Review is a meta-analysis that remains "widely respected as a valiant attempt to measure the average risk of transmission in the real world". Dr. Smith also referred to the Liu Study that suggests

much lower rates of transmission with condom use, but the validity of that study has been called into question. Dr. Fisman provides evidence that the study is highly questionable and, in fact, is "out of keeping with scientific consensus": see *Liu*, *et al.*, "Effectiveness of ART and Condom Use for Prevention of Sexual HIV Transmission in Serodiscordant Couples: A Systematic Review and Meta-Analysis" (2014) 9:11 PLoS ONE e111175. "Serodiscordant" means one partner is infected and the other is not.

[141] I agree that the Cochrane Review, as Dr. Smith suggested on the reopening application, is still "widely accepted". Indeed, the Public Health Agency of Canada performed a synthesis of current medical evidence relating to HIV transmission rates published in 2018 and relied in part on data from the Cochrane Review: *Traversy LeMessurier*, *et al.*, "Risk of Sexual Transmission of Human Immunodeficiency Virus with Antiretroviral Therapy, Supressed Viral Load and Condom Use: A Systematic Review" (2018), 190, Can. Med. Assoc. J. E1350. An earlier version of that synthesis was also relied upon by the Department of Justice in determining the rate of HIV transmission when condoms are used alone: Department of Justice Report, at p. 8. The International Consensus Statement also relied on the Cochrane Review: see fns. 17, 22, 69.

[142] According to Dr. Fisman, whose evidence I accept, the Cochrane Review represents a "reasonable" assessment of condom effectiveness across the population, "as imperfect as that is." For every act of vaginal intercourse, the Cochrane Review concluded that condom use resulted in an 80.2 percent relative reduction in HIV transmission, the best-case estimate being 94.2 percent and the worst-case estimate being 35.4 percent. In other words, as Dr. Fisman put it, condoms "could be better than we think they are" or they could be "worse than we think they are." Indeed, the Cochrane Review itself acknowledges that condom effectiveness could be under- or overestimated by the study and, importantly, the Supreme Court of Canada had that evidence before it when *Mabior* was decided.

[143] Even if the reduction rate for the transmission of HIV is slightly higher than what the Cochrane Review suggests, the fact remains that, from an admissibility perspective, that new evidence is not sufficiently cogent to be granted admission.

[144] While the appellant quarrels with the precise reduction in risk of transmission arising from condom use alone, even if he is right, his position cannot succeed. To this end, it is notable that the Supreme Court decided that the potential reduction in baseline HIV transmission rates arising from the taking of antiretroviral medication was in the range of 89 to 96 percent: *Mabior*, at para. 101. Yet the court was not satisfied that even that level of reduction in baseline risk of transmission could qualify as negating the realistic possibility of HIV transmission.

[145] Therefore, even if I were to accept (which I do not), that at a population level, the use of condoms alone reduce the risk of transmission of HIV up to even the 96 percent mark, on the *Mabior* analysis, that would still be insufficient, on its own, to negate the court's view of what constitutes a realistic possibility of transmission.

[146] I conclude this section by making two practical observations in response to the appellant's and interveners' characterization of the *Mabior* decision as criminalizing an "infinitesimal" risk of transmission. They emphasize that the baseline risk of HIV transmission is so "infinitesimal" that it cannot possibly rise to the level of a realistic possibility of harm, let alone when that baseline risk is pulled down by another at least 80 percent through condom use. I note that the appellant and interveners are not alone in that position: Martha Shaffer, "Sex, Lies, and HIV: Mabior and the Concept of Sexual Fraud" (2013), 63 U. Toronto L.J. 466, at pp. 472-73; Isabel Grant, "The Over-Criminalization of Persons with HIV" (2013), 63 U. Toronto L.J. 475, at pp. 479-80.

[147] It is important to note, though, that the argument suggesting that there is only an "infinitesimal" risk of transmission arises from statistics predicated on two things: (a) a per-sex-act consideration of risk; and (b) only the baseline risk relating to vaginal-penile intercourse.

[148] First, the baseline statistic for risk of transmission in *Mabior* is based upon a single act of vaginal-penile intercourse. As pointed out by Dr. Wobeser, though, that risk repeats itself with every repeated act of sexual intercourse. Therefore, even if the per-act baseline risk, as reduced by condom use, could be called "infinitesimal", one cannot lose sight of the fact that the risk adds up over time. In other words, even if the risk of engaging in a behaviour with an infected partner once could be called infinitesimal, when that behaviour is repeated, so too is the risk of transmission.

[149] As Dr. Fisman explained, the risk is "cumulative with each sexual act", meaning that following a number of sex acts involving the same serodiscordant couple, the "Bernoulli (or coin-toss) model" would apply. The "risk of the event occurring at least once would be estimated using a formula" that applies an "exponent equivalent to the number of sex acts that have occurred". Put simply, the risk of transmission exponentially increases with each sexual act involving the same serodiscordant couple.

[150] In my view, the repeated risk of harm that comes with each act of sexual intercourse between the same serodiscordant couple partially informs the *Mabior* rule that condom use alone does not negate the "realistic possibility of transmission". While some HIV non-disclosure cases involve one-time encounters, others involve repeated acts of sexual intercourse where there is no disclosure made to the unwitting partner, such as the acts of vaginal sex with A.G. and A.C. in this case. Clearly, the cumulative risk for these complainants rose with each act of intercourse.

[151] Second, I would make the observation that, when it comes to sexual intercourse, the baseline transmission rates differ somewhat significantly between vaginal and anal intercourse. One systemic review, adopted in the Department of Justice Report, at p. 10, places the baseline transmission rate for "receptive vaginal intercourse" (risk to the receptive partner) at 8 in 10,000 (0.08 percent), while it places the transmission rate of "receptive anal intercourse" at 138 in 10,000 (1.38 percent). See also International Consensus Statement, at ss. 2.3.2. and 2.3.3.

[152] In my view, these two factors, cumulative risk over many sex acts, and differing baseline risks depending upon the nature of the sex acts, informs the wisdom of the *Mabior* approach in creating a singular, easy-to-understand, and easy-to-apply rule for the application of the criminal law. Under the present *Mabior* regime, the criminal law cannot apply differently based upon the nature of a sexual act or the number of times those acts take place within the same serodiscordant couple. Any other approach would carry serious implications in terms of equality and return this already complex area of the law to the world of uncertainty.

[153] Accordingly, while the statistical backdrop for the *Mabior* decision may be at the low end of what is meant by a realistic possibility of transmission, there are other scenarios to which the statistical backdrop looks much different.

IV. Policy Reasons to Change *Mabior*

[154] I will conclude by addressing the interveners' arguments about policy. As they say, it is "bad public policy to criminalize people who use condoms." They advance four arguments in support of that position. They maintain that the criminalization of HIV non-disclosure where condoms are used:

- is too blunt an instrument because the HIV-positive person's conduct is not truly blameworthy in nature, particularly given that the risk of HIV transmission in these circumstances is non-existent or negligible at worst;
- ignores scientific evidence and results in "state-sanctioned stigma and discrimination against people living with HIV";
- has the effect of contributing to a broad societal misunderstanding about HIV and serves to exacerbate the stigma surrounding the disease, all of which can work to the detriment of public health; and
- compounds the disadvantage of already significantly disadvantaged groups.

[155] There is no doubt that the criminal law is the bluntest of instruments, properly reserved for only those situations where conduct is so morally blameworthy that it deserves to be labelled "criminal".

[156] Nor can there be any doubt that the stigma associated with a criminal conviction only compounds the difficulties of those living with HIV, an already vulnerable group, many of whom come from historically marginalized and disadvantaged situations: See e.g. Department of Justice Report, at p. 4.

[157] The fact is that there are many different models for how to approach HIV non-disclosure cases. Some of those other models were reviewed by the Supreme Court of Canada in *Mabior*: at paras. 49-55. And, as noted in *Mabior,* at para. 51, there are few jurisdictions that criminalize deception that only exposes a partner to the risk of transmission (as opposed to actual transmission).

[158] Not only is the deception that exposes a sexual partner to a risk of transmission criminalized in Canada, but the most frequently chosen path of prosecution is by way of the most serious sexual offence known to law: aggravated sexual assault, an offence punishable by up to life in prison.

[159] Although this appeal raises the singular issue of the effectiveness of condoms at preventing HIV transmission, there is much to be said for the fact that other things may have changed since *Mabior*. A prime example of change involves the current understanding around suppressed and undetectable viral loads. This significant change is reflected in the policies of some Attorneys General in Canada not to prosecute matters involving these circumstances. There are others, like the federal Attorney General, who have also started to put in place specific condom-related prosecution policies, directing that, as a

"general" rule, there be no prosecutions in situations where condoms are used as long as there are no other risk factors present.

[160] The ability of the common law to adapt is important in this context. Even so, the interveners' arguments call upon this court to overturn the clear legal result in *Mabior* based upon policy arguments.

[161] While there may come a day where there is a reconsideration of the intersection between the law of aggravated sexual assault and HIV non-disclosure risk of transmission cases, this is not that case. The sole issue raised in this appeal relates to the suggestion that, since *Mabior,* there have been changes to how we should understand the effectiveness of condoms at preventing HIV transmission. To that end, I adopt the trial judge's observation that "when the scientific evidence as a whole is examined with respect to condom use in real life situations, nothing has changed in the past five years from the time *Mabior* was decided in 2012 to the present day".

[162] The *Mabior* decision reflects the Supreme Court's appreciation for the fact that perfectly operating latex condoms provide a perfect barrier to the transmission of HIV. It also reflects the court's understanding that sex happens in the real world and that, in that world, human error and condom failure are concerns across the population. It also reflects the court's decision to criminalize the risk of transmission from a forward-looking perspective, one that takes into account the need for certainty in the criminal law. Finally, it accommodates an interpretation of s. 265(3)(c) of the *Criminal Code* that is consistent with our modern notion of consent to sexual activity.

[163] In my view, there is nothing in the new evidence that reveals a change in the facts upon which *Mabior's* legal reasoning rests. The fresh evidence on appeal is not cogent and is not admissible. The trial judge did not err in excluding Dr. Smith's evidence on the reopening application.

CONCLUSION

[164] On consent, I would amend count 3 on the indictment to reflect the offence commencing on October 20, 2013 and continuing to June 24, 2014.

[165] I would dismiss the fresh evidence application. I would dismiss the appeal.

Released: "P.L." August 5, 2020

"Fairburn J.A."
"I agree. P. Lauwers J.A."
"I agree. Gary Trotter J.A."

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[1] Although the *Mabior* decision does not specifically define what constitutes a low viral load, it describes a viral load of less than 1,500 copies of HIV present in a millilitre of blood as "low": at para. 100.
[2] Although the complainants in this case testified about also having had condomless oral sex with the appellant, the trial judge's reasons focus on the risks of transmission associated with the acts of vaginal intercourse. Therefore, these reasons are similarly focused on the acts of vaginal sexual intercourse.
[3] The appellant and interveners also draw this court's attention to the trial decision in *Thompson,* what they put forward as the only post-*Mabior* decision that suggests that condom-use alone (combined with no ejaculation) is sufficient to negate the realistic possibility of HIV transmission.
[4] The respondent also raises a concern about the final prong of the *Palmer-Truscott* test: diligence. In my view, there is no need to address that concern given that the appeal fails on the cogency element.
[5] See, for instance, cases that include convictions for offences in addition to aggravated sexual assault: *R. v. Iamkhong*, 2009 ONCA 478, 250 O.A.C. 220; *R. v. Booth*, 2005 ABPC 137, 382 A.R. 116; *R v. Boone*, 2019 ONCA 652; *R. v. Aziga*, 2011 ONSC 4592, appeal as of right filed. See also, Department of Justice Report, at pp. 11 and 13.
[6] *R. v. D.C.*, 2012 SCC 42, [2012] 2 S.C.R. 626, was released at the same time as *Mabior,* simply applying the *Mabior* test to the facts of that case.
[7] The new evidence on appeal is focused upon male condoms. As this case involved the use of male condoms, I remain similarly focused.

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Chapter 12 - Contact Follow-up and Outbreak Management in Tuberculosis Control

Elizabeth Rea, MD, MSc, FRCPC

Paul Rivest, MD, MSc

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Key Messages/Points

- Only respiratory tuberculosis (TB), with limited exceptions, is infectious; contact follow-up should be carried out for both sputum smear-negative and smear-positive cases. The objective of contact follow-up is to identify and treat any secondary cases, and to identify contacts with latent TB infection (LTBI) in order to offer preventive treatment. Source-case investigation is recommended for children under 5 years old with a diagnosis of active TB disease.
- Interviews with the infectious case to identify contacts should include questions about locations/activities of potential exposure as well as specific named contacts. The discussion of site-based, social network contact investigation as well as the section on contact follow-up in homeless populations has been expanded from the 6th edition of the Standards.
- Prioritization of contact follow-up is recommended by the infectiousness of the source case, extent of exposure and immunologic vulnerability of those exposed. Thus, the most effort is put into contacts who are most at risk of being infected and/or most at risk of developing active TB (tuberculosis) disease if infected.
- The classic concentric-circle approach to contact follow-up is no longer recommended. Rather, the initial follow-up should include non-household contacts from the outset when case infectiousness and contact vulnerability indicate, rather than waiting.
- Contacts may be grouped as follows:

  High priority
  - household contacts plus close non-household contacts who are immunologically vulnerable, such as children under 5 years.

Medium priority

- close non-household contacts with daily or almost daily exposure, including those at school and work.

Low priority

- casual contacts with lower amounts of exposure.

- For smear-positive/cavitary/laryngeal TB (tuberculosis), it is recommended that the initial contact follow-up include both high- and medium-priority contacts. For smear-negative, non-cavitary pulmonary TB (tuberculosis), the initial contact follow-up should be for high-priority contacts only. In both situations, contact investigation is iterative: it should be expanded if the initial follow-up results indicate that transmission has occurred.
- A single evaluation at least 8 weeks after the end of exposure (with tuberculin skin testing [TST (tuberculin skin testing)] and symptom assessment) is recommended in most non-household contact settings, in order to maximize participation and minimize overdiagnosis of "conversion" related to boosting. Initial plus 8 week post-exposure TST (tuberculin skin testing) is recommended for household and other high-priority contacts. Two-step TST (tuberculin skin testing) is not recommended in the setting of a contact investigation.
- TST (tuberculin skin testing) is no longer recommended as a primary assessment tool in the contact follow-up of elderly residents in long-term care, in whom it is less reliable and for many of whom the risks of treatment of LTBI (latent TB infection) in old age will outweigh any benefit. The focus for these individuals should be on early detection of secondary cases.

Introduction

The first priority of TB (tuberculosis) control programs is always recommended to be the early identification and successful treatment of all TB (tuberculosis) cases. This is because treatment rapidly reduces the risk of TB (tuberculosis) transmission to others. The next priority should be evaluation and follow-up of close contacts of active cases in order to identify secondary cases, source cases in some situations and those with recently acquired LTBI (latent TB infection), to offer this group treatment [1-3]. Typically, 1%-2% of close contacts are found to have active disease at the time of contact investigation [4].In addition, about 5% of newly infected contacts will develop active disease within 2 years of exposure [5-8]. TB (tuberculosis) programs in North America typically find a median of 4 (average 6) close contacts for each TB (tuberculosis) case [4] [9].

Reporting of active TB (tuberculosis) is required in all Canadian jurisdictions. In part this is to ensure that contact investigation can be carried out quickly, in an organized, collaborative manner.

With limited exceptions, only TB in the respiratory tract is infectious and requires contact investigationFootnote 10.Patients who present with nonrespiratory disease can also have concomitant respiratory involvement; thus it is important for all TB patients to have chest radiography (and sputum testing if there are any respiratory symptoms or chest x-ray abnormalities) as part of their medical work-up. Patients with miliary TB are often culture-positive on sputum or other airway secretions and occasionally smear-positiveFootnote 11.Induced sputum cultures have been found to be positive in up to 50% of cases of pleural TB, even in the absence of pulmonary disease on chest x-rayFootnote 12.Therefore, both miliary and pleural TB should also be considered as potentially contagious.

Factors associated with TB transmission are outlined in Chapter 2, Pathogenesis and Transmission of Tuberculosis. Cases who are sputum smear-positive or have cavitary disease on chest x-ray are significantly more infectious than smear-negative or non-cavitary casesFootnote 2 Footnote 8 Footnote 9. Adolescence, adult age, coughing, sneezing and singing also increase the risk of transmissionFootnote 1.Transmission is rarely thought to occur outdoors; however, indoor environments that are poorly ventilated, dark and damp can lead to increased concentration and survival of Mycobacterium tuberculosisFootnote 13 Footnote 14. In infected contacts who are vulnerable because of young age (under 5 years), HIV or other causes of significant immune suppression infection may progress quickly to active disease;Footnote 8 early diagnosis often depends on good contact follow-up.

Contact investigation often demands considerable time, expertise and coordination. It is usually best carried out by public health/ TB (tuberculosis) control authorities in collaboration with treating clinicians and other providers. Anxiety, stigma and lack of knowledge about TB (tuberculosis) among those exposed may be major issues. Provision of clear, credible and consistent information about TB (tuberculosis) and the contact follow-up plan is important.

Definitions

Index case: the first case or initial active case from which the process of contact investigation begins.

Source case: the person who was the original source of infection for secondary case(s) or contacts. The source case can be, but is not necessarily, the index case.

Contact: a person identified as having been exposed to an active case of disease. The closeness and duration of exposure usually corresponds with the risk of becoming infected.

Objectives of Contact Investigation

Contact investigation has three main objectives. In order of priority these are as follows:

1. Identify and initiate treatment of secondary cases of active TB (tuberculosis) disease.
2. Identify and treat the source case who infected the index case, if the index case is under 5 years old.
3. Identify contacts with LTBI (latent TB infection) in order to offer preventive treatment.

Principles of Contact Investigation

Prioritize the Work

This is the most important principle. It is advisable to prioritize by the infectiousness of the source case, extent of exposure and immunologic vulnerability of those exposed. Thus, the most effort can be put into contacts who are most at risk of being infected and/or most at risk of developing active TB (tuberculosis) disease if infected. Contact investigation is iterative: it should be expanded if initial follow-up results indicate that transmission has occurred.

Rapid Initiation of Contact Investigation

Rapid evaluation of close contacts allows prompt identification of those who already have active disease and, if active disease has been excluded, allows initiation of treatment of LTBI (latent TB infection) for newly infected contacts before disease occurs.

As soon as a suspected case of TB (tuberculosis) has been reported, it is advisable for public health authorities to ensure that all the medical investigations to confirm the diagnosis and determine the degree of infectiousness are under way (chest radiography plus sputum collection as necessary, even for patients with suspected extrapulmonary TB (tuberculosis)) and that the patient is in airborne infection isolation. Initiation of adequate TB (tuberculosis) treatment is the most effective way to rapidly decrease infectiousness and the risk to others. If the clinical suspicion of pulmonary TB (tuberculosis) is sufficiently strong to begin TB (tuberculosis) treatment pending microbiologic confirmation, then investigation of household contacts should also begin promptly, especially for any children under 5 years old, HIV (human immunodeficiency virus)-infected contacts and others at high risk of disease progression if infected [10].A positive nucleic acid amplification test result is sufficient grounds to begin contact investigation (refer to Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance). Investigation of contacts beyond the high-priority group (refer below) should always await microbiologic confirmation of the diagnosis.

Assessment of Transmission Risk

Infectiousness of the index case

The single greatest factor determining the extent of contact investigation is the degree of infectiousness of the index case. Neither drug-resistant TB nor coinfection with HIV increases the infectiousness of the case; therefore, the recommended approach and prioritization of the contact investigation is the same. However, treatment of LTBI among contacts should be guided by the drug sensitivity pattern of the source case.

Sputum status is the most reliable indicator of infectiousness. The "worst" (i.e. most positive) result is used to evaluate infectiousness [15].Cases of laryngeal TB (tuberculosis) are considered four to five times more contagious than smear-positive pulmonary cases, as they are likely to have a large number of bacteria due to extensive concurrent pulmonary disease [1] [16] [17].

Cavitary disease on chest x-ray has been repeatedly linked to higher infectiousness, independent of smear status. Chest CT (computed tomography) may detect smaller, early cavitation that is not apparent on the chest x-ray; however, it is not clear whether these individuals are as infectious as those who have cavitation visible on chest x-rayFootnote 10.

Coughing is the least reliable indicator of infectiousness but is generally linked to it, particularly within households. There are several well-documented clusters of TB (tuberculosis) transmission related to cough-inducing medical procedures and to smoking crack cocaine [18].Singing and similar activities (e.g. playing wind instruments) are also associated with increased risk of transmission [19].

In general, children under age 10 with TB (tuberculosis) are not considered infectious. However, in unusual circumstances, even very small children can transmit TB (tuberculosis) - for example, if there has been contamination and inadequate cleaning of respiratory equipment [20].By contrast, adolescents can be very effective transmitters of TB (tuberculosis), partly because they can have extensive disease by the time it is diagnosed, and particularly because in high school they can have large numbers of contacts [21] [22]. It is recommended that any child presenting with adult-type pulmonary TB (tuberculosis) (cough, cavitation on chest x-ray, smear-positive sputum) should be considered infectious and contact investigation undertaken.

Source case investigation

When active TB (whether pulmonary or extrapulmonary) is diagnosed in any child under 5 years old, an immediate search for an infectious source case close to the child is recommendedFootnote 10.Most often the source case is an adolescent or adult in the household, or other care-giver. Source case investigation is also recommended when a cluster of TST conversions is identified in an institutional setting with no known source case. However, source case investigations usually give very low yield; even for young children a source case is identified

in less than half of investigationsFootnote 10 Footnote 23. Source-case investigation is not recommended for adult TB cases, nor for children or adults who are well but have a positive TST result on a routine screening (outside of an institutional cluster of TST conversions, as above).

Nonrespiratory TB is considered noninfectious, so long as concurrent pulmonary disease has been ruled out; no contact follow-up is necessary. Rare exceptions involve aerosolizing medical procedures (e.g. autopsy, high-pressure irrigation of draining TB abscesses). Source-case investigations for nonrespiratory TB are not recommended other than for children under 5 years old, as aboveFootnote 10.

Likely period of infectiousness

Cases of pulmonary TB (tuberculosis) are generally considered to become infectious at the time of onset of cough or worsening of a baseline cough. If no cough is reported or if the duration is difficult to determine, the onset of other symptoms attributable to TB (tuberculosis) may be used to estimate the onset of infectiousness. In practice, however, it is often difficult to know with certainty when symptoms began.

Generally, priority should always be given to contact tracing during the period when the TB (tuberculosis) patient had respiratory symptoms (e.g. a cough). However, guidelines published by the US Centers for Disease Control and Prevention [10] recommend that the patient with smear-positive or symptomatic disease should be considered to have been infectious for 3 months before onset of respiratory symptoms or the first positive finding consistent with TB (tuberculosis), whichever is longer. Asymptomatic cases with a negative smear and no cavities seen on chest x-ray should be considered infectious 4 weeks before the date that TB (tuberculosis) was suspected. However, these guidelines are based on expert opinion rather than clear epidemiologic evidence.

For contact follow-up purposes, the period of infectiousness ends when the index case is in effective airborne isolation from others (this may be before or after diagnosis) or is no longer infectious, whichever comes first. Refer to Chapter 15, Prevention and Control of Tuberculosis Transmission in Health Care and Other Settings, for a description of when isolation may be discontinued for a suspected or confirmed TB (tuberculosis) case.

Degree of exposure to the index case

The interview of an infectious TB (tuberculosis) patient for contact tracing is one of the most important parts of the investigation. It takes considerable skill and is most successful when done by staff with training/experience in public health interview techniques [24].Trust and rapport are important for full disclosure, and the initial interview can also lay the foundation for long-term adherence to TB (tuberculosis) treatment. Face-to-face interviewing, in privacy, is ideal. Most TB

(tuberculosis) patients in Canada were born in countries with high TB (tuberculosis) incidence or in First Nations/Inuit communities (refer to Chapter 1, Epidemiology of Tuberculosis in Canada), so language and cultural perceptions about TB (tuberculosis) and health are very important. Interviews are best carried out in the language the patient is most comfortable with. It is recommended that a professional interpreter or an objective third party (not a family member) be used for interpretation if possible, either in person or participating by telephone. Interviewers should always be respectful and sensitive to patient concerns and beliefs about TB (tuberculosis), should incorporate education about TB (tuberculosis) and stress the confidentiality of contact investigations. Note that legislation may permit or require release of information about the case's diagnosis to specific individuals (e.g. to public health authorities) or in specific circumstances. For example, although precautions can be taken to avoid identification of the case in public or to contacts, some information may have to be shared with selected individuals (e.g. a school principal) in order to identify or reach contacts and ensure that they too get the medical follow-up they need.

Ideally, the treating physician and laboratory should report all new or suspect cases of TB (tuberculosis) to the appropriate public health authority within 48 hours. The first public health communication with a new infectious patient (and/or the health care providers if the patient is hospitalized) should ideally begin within 1 calendar day of the case being notified. The purpose of this brief initial communication is to achieve adequate airborne isolation, provide any urgent support, identify the household contacts and direct any who are ill to immediate TB (tuberculosis) assessment. Interviewing to determine the full set of contacts should be initiated within 3 working days. Interviewing is usually best extended over two (or more) sessions, a week or more apart, as the patient becomes more familiar with public health staff, and the initial stress and anxiety over the diagnosis are resolving. Proxy or supplemental interviews (ideally with patient permission) with family, close friends, coworkers, etc., may be helpful if patients are unable or unwilling to participate. It is important to include questions about the places where the case spends time regularly, not just names of individual people, and to get contact details whenever possible (name, alias/nickname, phone, address, email, age, nature of interaction).

Interviews to identify contacts should include the following information:

- Any contact with children and their ages
- Any contact with immunosuppressed people (HIV (human immunodeficiency virus) positive, cancer patients, etc.)
- Description of the household/congregate setting; household contacts and their ages (includes anyone who regularly sleeps in the home)
- Close friends and relatives who are seen at least once per week - how often, for how long?

- Work or school location and description of setting (type of work, size of room, ventilation, etc.)
- Transportation to work/school - bus, car-pool, etc.
- Place of worship, clubs, sports teams, recreation programs or hobbies
- Any other places or groups the case has regularly been in or with while infectious
- Any contacts who are ill with potential TB (tuberculosis) symptoms or who have known TB (tuberculosis)
- Any major events (e.g. weddings, funerals, parties) the case attended while infectious
- Any recent travel or visitors staying at the home within the previous 2 years - if so obtain details

A site visit to assess the home is strongly recommended, even if the initial interview is carried out in hospital (for feasibility of home isolation, identification of additional household contacts, identification of any social/practical issues relevant to treatment adherence, etc.). Site visits to the school or workplace and other exposure locations are also very helpful to make contact follow-up decisions (environmental characteristics such as size, layout, use of the space and ventilation; interviews with a direct supervisor can help to identify potential contacts). Discretion is important, as a site visit may precipitate unnecessary anxiety and/or lead to a breakdown of confidentiality and repercussions for the case. In this regard, it is advisable to arrange site visits directly with senior personnel, such as a school principal, division manager or occupational health manager and emphasize with them the importance of maintaining confidentiality as much as possible. Refer to Site-based screening below.

There are so many variables in TB transmission that it is very difficult to quantify the amount of exposure that constitutes a significant riskFootnote 25.In theory, there is no amount of exposure to infectious TB that is absolutely without risk; in practice, each case should be evaluated on its specific characteristics. For context, one study of almost 3,000 contacts demonstrated that TST-positive contacts had a mean of 65 hours more exposure than TST-negative contactsFootnote 26.By contrast, in an outbreak investigation among university students exposed to an index case with laryngeal and cavitary pulmonary TB, the risk of infection per hour of exposure was over 1% in many classes; some contacts converted with as little as 3-4 hours of exposure per weekFootnote 27.Exposure in cramped, ill-ventilated spaces may lead to transmission in much shorter exposure times, and genetic fingerprinting has occasionally discovered apparent transmission following close but very brief exposureFootnote 28.

Organized and Systematic Contact Investigation: Prioritizing Contacts

An organized, systematic approach will allow the TB program to put the most effort into those contacts at most risk. In the 6th edition of the Standards, the traditional "concentric circle" approach to prioritizing TB contact follow-up emphasized starting with contacts who have the most exposure (e.g. household contacts) and expanding stepwise to those with progressively less exposure whenever there is evidence of transmission, until the level of TB infection reaches background rates. However, this approach does not take into account contacts who may have less extensive exposure but, if infected, are immunologically vulnerable to rapid development of active TB. It can also lead to long delays in appropriate contact follow-up when the index case is already known to be highly infectious. A fundamental difficulty is that transmission can be very difficult to evaluate when the background rate of positive TST results is unknown or is high (for example, people who immigrated to Canada from high-incidence countries). This is often the case in Canada, where the majority of TB cases - and many of their close contacts - are foreign-born; it is also the context in many Aboriginal communities. A strictly concentric circle approach can also be difficult to apply in complex congregate settingsFootnote 22 Footnote 29.

Instead, recommended priorities for initial contact follow-up and criteria for expansion are outlined below. These are guidelines: it is always important to consider the specific circumstances, work from first principles of TB (tuberculosis) transmission and re-evaluate according to the results of the investigation as they become available.

For TB (tuberculosis) follow-up purposes, contacts may be categorized as follows:

Household contacts are those who regularly sleep in the same household as the infectious case on an ongoing basis (e.g. three or more times per week). This may include members of an extended family, room-mates, boarders, "couch-surfers," etc. Household members often have the greatest exposure to the TB (tuberculosis) case [8] [22] [26].

Close non-household contacts are those who have regular, extensive contact with the index case and share breathing space daily or almost daily but do not sleep in the same household most of the time. Close non-household contacts may include caregivers, regular sexual partners, close friends or extended family. They also include daycare and primary/secondary school classroom contacts, and coworkers who work in close proximity, particularly in small rooms. The amount of time that high school classmates spend in the same room as the case will depend on the number of shared courses; prioritize those who share the most actual time together. Similarly, in almost all workplaces it is possible (and important) to define the group of colleagues who spend the most time in the same air space as the case. Regular contacts in specialized health care settings such as dialysis units or rehabilitation programs may also qualify. It is not social closeness to the

TB case but, rather, the amount of time in a shared airspace that is the critical issue. For example, computer personnel may report working very closely with others in their group but spend little time together in shared air space if the work is largely done electronically.

Casual contacts are those who spend time regularly but less frequently with the infectious case. These may include high school classmates who share fewer courses with the case, classmates in college/university classes, less exposed colleagues at work; members of a club, team, weekly children's play-group or other social/recreational/religious group; extended family members who are seen occasionally; other students on a school bus.

Community contacts are those living in the same community or attending the same school or workplace but in a different classroom or area of the workplace. Individuals who have only transient or occasional exposure are in this group.

The highest priority contacts are those with the most exposure and those with the highest risk of progression to active TB (tuberculosis) if infected, as follows:

- household contacts, including those exposed as "household members" in congregate settings such as homeless shelters, jails and long-term care facilities (generally, room-mates or cell-mates)
- contacts who are close non-household or casual contacts AND who are at high risk of progression of LTBI (latent TB infection) to TB (tuberculosis) disease, e.g. age under 5 years, HIV (human immunodeficiency virus), dialysis, transplant, silicosis (refer to Chapter 4, Diagnosis of Latent Tuberculosis Infection, and Chapter 6, Treatment of Latent Tuberculosis Infection)
- contacts exposed (i.e. without an N95 mask) during bronchoscopy, sputum induction, autopsy or other aerosolizing medical procedures (refer to Chapter 15).

Medium-priority contacts are the close non-household contacts who are not at high risk of rapid progression from LTBI (latent TB infection) to active TB (tuberculosis). Most close non-household contacts fall into the medium-priority group.

Casual contacts are low priority. It is generally recommended that the investigation be expanded to this group only if there is evidence of transmission or the case is considered to be extremely infectious (e.g. laryngeal TB, refer to Chapter 2, Transmission and Pathogenesis of Tuberculosis). However, the specific circumstances should always be considered. For example, a choir group meeting once per week may pose significantly more risk than a weekly outdoor soccer game; children riding on long daily school bus routes in winter, when windows are usually closed, may have considerable exposureFootnote 30.

It is rare for community contacts to need investigation (e.g. an entire school beyond the exposed classrooms, general customers of grocery stores or fast-food restaurants)Footnote 31.Such an extensive investigation should be undertaken only in very unusual circumstances; consultation with experienced public health colleagues is advised.

For respiratory TB (tuberculosis) cases who are sputum smear-positive, or have cavitary disease, or have laryngeal TB (tuberculosis), the initial investigation should include both high priority and medium priority contacts. If there is evidence of transmission (refer below) within these two groups, consideration should be given to expanding contact follow up to casual contacts. *For laryngeal TB (tuberculosis)*, also consider including any casual contacts (social/recreational groups, etc.) from the outset [10].

For smear negative respiratory TB (tuberculosis) cases, household members should always be assessed in the initial contact investigation, along with any other high-priority contacts. However, investigation should be expanded to medium-priority contacts (e.g. other close non-household contacts) only if there is evidence of transmission [10] [15].

High-priority contacts should be assessed for both smear-negative and smear-positive cases. Whenever possible, initial assessment (TST (tuberculin skin testing) and symptom assessment, then medical assessment and chest radiography if the TST (tuberculin skin testing) result is ≥5 mm or the patient is symptomatic, plus sputum if symptomatic or the chest x-ray is abnormal) of the high-priority contacts should begin within 7 working days of their being identified as contacts and be completed within 1 month. High-priority contacts should ideally have both an initial and a second TST (tuberculin skin testing) (at least 8 weeks from the last day of exposure) to identify conversion. Participation rates for TB (tuberculosis) skin testing may be higher if it is done directly by TB (tuberculosis) program staff, at home or at a TB (tuberculosis) clinic [10].

Especially among non-household contacts, participation rates often drop significantly between initial and post-8-week screenings as the level of initial concern declines. Thus, in most non-household settings it is most practical to aim for a single round of screening after 8 weeks from the break in contact. In populations in which many people have prior exposure to TB (tuberculosis) or BCG vaccination (e.g. immigrants from high-incidence countries), this also avoids false TST (tuberculin skin testing) "conversion" related to boosting. If casual contacts are investigated, only a single TST (tuberculin skin testing) after 8 weeks from the last day of exposure is recommended [32].

Expanding Contact Investigation

Transmission is considered to have occurred if a secondary case is identified in any contact, if there are any TST (tuberculin skin testing) converters, if the prevalence rate of TST (tuberculin skin testing) >10 mm among contacts is significantly higher than expected (for example, 60% among contacts when the expected prevalence rate is 40%, refer to Table 1) or if a child contact under age 5 years is infected without another probable source. TST (tuberculin skin testing) results in Canadian-born contacts, particularly children, may be the most useful in assessing transmission. A TST (tuberculin skin testing) result is considered positive in contacts with a TST (tuberculin skin testing) result of 5 mm or greater or in converters who have had an increase of 6 mm from a previous TST (tuberculin skin testing) result of 5-9 mm. A history of BCG vaccination does not alter the interpretation of the TST (tuberculin skin testing) results (refer to Chapter 4, Diagnosis of Latent Tuberculosis Infection, for more information). When there is evidence of transmission, the contact investigation should first address any high-priority contacts who have not yet been assessed and investigate moderate-priority contacts if this has not already been done. Consideration should then be given to expanding to casual contacts. Genotyping to compare index and secondary cases should be requested, but further contact tracing should not be delayed while results are pending.

Table 1. Expected range of prevalence of TST (tuberculin skin testing) results (≥10 mm induration) in various Canadian populations [A]

Population	Expected range of prevalence of TST (tuberculin skin testing) ≥10 mm (%)		
	BCG status not specified	BCG vaccinated	Non-BCG vaccinated
Canadian-born non-Aboriginal children [B]	N/A	N/A	1-3
Canadian-born non-Aboriginal adults	13	65	7
Canadian-born Aboriginal children	5-29	6-25	0-5
Canadian-born Aboriginal adults	14-30	29-50	17-21
Foreign-born children	15-23	N/A	N/A
Foreign-born adults	53-61	73	25
Health care workers	11-46	27-77	5-18
Residents of long-term care facilities (age ≥60)	6-25	71	18
Residents of homeless shelters	45	N/A	N/A
Correctional facility inmates	12-72	90	63
Correctional facility staff	5-33	N/A	N/A

Population	Expected range of prevalence of TST (tuberculin skin testing) ≥10 mm (%)		
	BCG status not specified	**BCG vaccinated**	**Non-BCG vaccinated**
Injection drug users (TST (tuberculin skin testing) ≥5 mm)	31	N/A	N/A
Injection drug users (TST (tuberculin skin testing) ≥10 mm)	66	N/A	N/A
People with pre-existing medical conditions (TST (tuberculin skin testing) ≥5 mm)	14-24	N/A	N/A
People with pre-existing medical conditions (TST (tuberculin skin testing) ≥10 mm)	18-26	N/A	N/A
Overall community	6-36	N/A	N/A

N/A = Non applicable

A Based on *Compendium* of Latent Tuberculosis Infection (*LTBI (latent TB infection)*) Prevalence Rates in Canada, Public Health Agency of Canada, 2012 (for an electronic copy of the full compendium, contact *TB_surveillance@phac-aspc.gc.ca)*.

B Although the Aboriginal status was not specified in the study, it was assumed that the vast majority of the reference population belonged to the Canadian-born non-Aboriginal category.

There is often pressure on a public health department or physician to initiate widespread contact investigation - e.g. to an entire school - from the outset. If this is done, however, it is often impossible to interpret the results of a positive TST (tuberculin skin testing) result (or interferon gamma release assay [IGRA (Interferon Gamma Release Assay)]) in individual patients. Contacts may then be mistakenly identified as recently infected and the investigation expanded yet further. This can also lead to widespread concern about the risk of transmission to community contacts. If expansion of the investigation beyond high- and medium-priority groups is considered, the decision should be based on evaluation of any evidence of transmission in the initial investigation, the probability of finding infected individuals among less exposed contacts and the likelihood that these casual contacts will follow up on screening and LTBI (latent TB infection) treatment recommendations. Contacts with less exposure have a positive TST (tuberculin skin testing) prevalence rate that is usually four to eight times less

than that among household contacts [4] [8] [33] [34]. Also, contact participation rates in TB (tuberculosis) screening, follow-up and LTBI (latent TB infection) treatment tend to be lower in less close contacts, contacts of less infectious cases and in adults compared with children [35].

Additional Approaches to Contact Tracing

DNA genotype fingerprinting:

DNA fingerprinting is available to all Canadian TB control programs, on request or routinely, through the public health laboratories. It can be a useful adjunct to epidemiologic investigations to confirm or disprove suspected linkages between cases and to evaluate potential specimen mix-upsFootnote 36 Footnote 37. It can be particularly helpful in populations in which contact follow-up is challenging and resource intensive, such as the homeless; routine use of fingerprinting for homeless cases may identify linkages not otherwise suspected and guide expanded contact investigationFootnote 38 Footnote 39. Rapid fingerprinting techniques (spoligotyping, MIRU [Mycobacterium Interspersed Repetitive Units]) are helpful to quickly identify or rule out potential new cases in evolving clusters or outbreaks. Fingerprinting can also be very useful, and reassuring, in the evaluation of potential clusters if the results do not show matching outside known household secondary cases.

Location-based contact investigation and social network analysis:

All cases should routinely be asked about the locations where they spend time. Particularly when infectious cases are unable or unwilling to name specific contacts, or when cases are occurring without identifiable exposure risks or sources, identifying locations where the case spent time may be more productive than traditional name-based approaches [40].Investigations have identified transmission occurring at bars, crack use sites, etc., [41-43] which can then be targeted for broad location-based screening clinics and TB (tuberculosis) education/outreach. Epidemiologic links among cases can be enhanced when questions about common locations are included in case interviews.

Social networks analysis examines the social relationships between cases and contacts to identify settings and behaviours that characterize transmission events. Social network analysis has been extensively studied in sexually transmitted infections and more recently in the study of TB (tuberculosis) outbreaks [40] [43-45]. Formal social network analysis, using special computer software, may be particularly helpful in outbreaks (refer to Pajek-Program for Large Network Analysis).

Site-base screening and congregate settings:

In some settings, it is far more practical and feasible to carry out contact investigation for an entire group (such as a class at school or coworkers in a work setting) than attempt to identify the specific individuals who were most exposed. Practical factors, such as the ability to reliably measure the degree of exposure of different individuals in the setting, the administrative ability to provide efficient testing and TB (tuberculosis) education, and the ramifications of extending the investigation to a larger group later if it becomes necessary, should be taken into account in deciding on the extent and number of people to be tested. Similarly, in certain settings (e.g. shelters for the homeless) in which contacts may be difficult to identify or to find, it may be helpful to do wider testing from the outset.

School, workplace and other congregate setting investigations are usually best carried out on site. This leads to higher participation rates among contacts, better communication and less anxiety; it is usually the most effective and efficient way of carrying out the investigation and obtaining the necessary information. However, for this type of investigation it is important to be very organized. The following approach is recommended:

- Identify a single individual at the setting who will be responsible for organizational aspects of the contact investigation and act as liaison, usually a school principal, workplace manager or occupational health manager.
- Protect the confidentiality of the index case (Note investigations should be carried out in compliance with relevant legal/legislative requirements, and that provincial/territorial legislation may permit disclosure in specific circumstances). This may not be easy; there may be considerable pressure for details, and in many situations others may be able to guess the identity of the case. Particularly if the identity of the case is widely known or suspected, enlist the help of setting personnel (e.g. the principal or manager) to plan for successful reintegration of the TB case once noninfectious.
- Visit the site beforehand to get a sense of the environment and organize the screening arrangements; get input from the setting's liaison person to ensure that screening is carried out at a time and in a way that offers the best opportunity for contacts to come to the screening.
- Check that adequate staffing will be available for the screening.
- Include key players at the site, such as occupational health services, human resources or other administrative staff, and union health and safety representatives in planning and communication; they may benefit from information about TB ahead of a general information session as others will likely look to them for advice.
- Prepare a communication plan; identify one individual who will be responsible for media and communications to the general public if necessary; alert public health

communications staff.

- Offer general information/education sessions about TB and the contact follow-up for all parents/employees/residents before the screening sessions; if the number of contacts is relatively small, a separate session specifically for them may be helpful.
- Identify the referral plan for contacts who are TST positive or symptomatic; treat all contacts referred for medical evaluation consistently, ideally by a limited number of health care providers working in coordination with public health. It can be confusing and alarming for a group of contacts if the work-up and treatment advice are inconsistent from person to person.
- Ensure the results of the medical evaluation are provided promptly to the appropriate public health authority.

Contact investigations carried out in work or school settings may be associated with high levels of anxiety. Good organization, communication and transparency (to the extent possible while protecting case confidentiality) are critical aspects of all site-based or expanded contact investigations. Anxiety and misinformation can be minimized by limiting the delay between contacting the site and conducting testing, ensuring that key people at the setting get the same information at the same time, and by holding general education sessions about TB (tuberculosis) and the investigation plan. Communication from all personnel involved in the investigation should be clear, credible and consistent, especially with regard to the actual level of risk involved, interpretation of the TST (tuberculin skin testing) and decisions regarding treatment of LTBI (latent TB infection).

A standard approach to the evaluation of contacts for the presence of active disease and evidence of recent infection:

All identified contacts should be interviewed systematically regarding their exposure to the case, presence of symptoms, risk factors for progression to active TB (tuberculosis) if infected and history of treatment of TB (tuberculosis) or LTBI (latent TB infection). If there are any concerns, rapid evaluation to exclude active TB (tuberculosis) should be carried out. Once active disease has been excluded, contacts should receive a TST (tuberculin skin testing) unless there is a history of prior treatment of TB (tuberculosis) or a documented prior positive TST (tuberculin skin testing) result. The TST (tuberculin skin testing) should be carried out and interpreted regardless of BCG vaccination status. A TST (tuberculin skin testing) of 5 mm or more is considered positive for contacts. Refer also to Chapter 4, Chapter 6 and Chapter 9, Pediatric Tuberculosis.

Note that TB (tuberculosis) assessment of contacts may involve TST (tuberculin skin testing) or an IGRA (refer to Chapter 4, Diagnosis of Latent Tuberculosis Infection).

A two-step TST (tuberculin skin testing) is not recommended in the setting of a contact investigation: Skin test conversion can occur as early as 3 weeks after exposure, and it will generally be impossible to differentiate between true TST (tuberculin skin testing) conversion and a boosted reaction in the setting of a contact investigation (refer to Chapter 2 and Chapter 4). This is another reason why only those with significant exposure should be considered contacts.

Window treatment of LTBI for those most susceptible: Contacts who are at very high risk of progression to active disease if infected (children under 5 years; HIV positive or other immunosuppressed individuals) should receive window prophylaxis in the interval between a negative initial TST result and the definitive TST at least 8 weeks after the last day of exposure because of the high risk of progression to active TB if infected. Refer to Chapter 6 and Chapter 9 for additional information.

Evaluation of Contact Investigation:

The results of each contact investigation should be reviewed as they become available, to guide expansion and/or additional follow-up efforts. In addition, program-wide outcomes should be reviewed annually. Along with qualitative assessment of successes and challenges, they are important elements for program evaluation and future planning. Key indicators should include the following:

- initial list of contacts for each infectious TB case, completed within 7 calendar days;
- assessment of close contacts completed and LTBI treatment started, if indicated and not contraindicated or refused, within 28 calendar days;
- proportion of contacts with a diagnosis of LTBI who begin treatment;
- proportion of contacts beginning treatment for LTBI who complete treatment; and
- proportion of contacts completing LTBI (latent TB infection) treatment who show active TB (tuberculosis) disease within 2 years after completion.

Summary Points

Recommended Steps in Contact Investigation and Follow-Up

1. The treating physician and laboratory should report all new or suspected cases of TB (tuberculosis) within 48 hours to the appropriate public health authorities.
2. Each new active case should be interviewed by public health authorities to identify household and other close contacts promptly. TB (tuberculosis) programs should prioritize contacts by the infectiousness of the source case, the extent of the exposure and the risk of progression to active TB (tuberculosis) if infected.

3. Each contact should be interviewed regarding the circumstances and duration of exposure, presence of symptoms, previous history of tuberculosis, TB (tuberculosis) exposure and prior TST (tuberculin skin testing).
4. Public health authorities and the treating physician should collaborate to ensure that contacts with no previous history of TB (tuberculosis) or documented positive tests receive a TST (tuberculin skin testing) and symptom assessment.
5. In the context of contact investigation, a positive TST (tuberculin skin testing) result is 5 mm or greater on initial or repeat testing, or an increase of at least 6 mm from a previous TST (tuberculin skin testing) of 5-9 mm. A history of BCG vaccination does not alter the interpretation of the skin test results for contacts. TST (tuberculin skin testing) should be repeated at least 8 weeks after the last exposure for all high-priority contacts who had an initial negative test. Refer to Chapter 4, Diagnosis of Latent Tuberculosis Infection, for guidance.
6. A medical evaluation to rule out active TB should be performed for all contacts who have symptoms compatible with TB; a positive TST result, whether before exposure or at initial or repeat testing; and (regardless of the results of the initial TST) all children under age 5, as well as contacts who are HIV seropositive or severely immunocompromised, according to the recommendations in Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance, Chapter 9, Pediatric Tuberculosis, and Chapter 10, Tuberculosis and Human Immunodeficiency Virus. This should include chest radiography, plus sputum collection as indicated.
7. Once active TB (tuberculosis) has been ruled out, treatment of LTBI (latent TB infection) should be offered according to the recommendations in Chapter 6, Treatment of Latent Tuberculosis Infection, Chapter 9, Pediatric Tuberculosis, and Chapter 10, Tuberculosis and Human Immunodeficiency Virus.
8. Public health authorities should determine the need to extend the contact investigation on the basis of the contagiousness of the index case, the results of the investigation of high-priority contacts and the nature of the exposure of additional contacts.
9. Extended contact investigations should be carried out in a systematic and organized manner; public health/TB control should coordinate these investigations.

The results of the contact investigation should be evaluated by the TB (tuberculosis) management program.

Contact Investigations in Special Settings

Homeless and Underhoused People and Those with Drug Addictions

Contact tracing for cases who are homeless, heavy users of illicit drugs and other highly marginalized individuals is very challenging and resource intensive. It is easy to become frustrated and overwhelmed. These challenges can be made more manageable and successful by recognizing that such cases are not "business as usual," keeping priorities clearly in mind, training staff and allocating adequate resources.

Many homeless TB (tuberculosis) cases may suffer from alcoholism, drug addiction or mental illness, which complicates the management of their TB (tuberculosis) [46].They may have poor access to health services and multiple medical comorbidities, resulting in delayed TB (tuberculosis) diagnosis, worsening of the disease, prolonged periods of infectiousness and thus large numbers of contacts who need to be assessed. High baseline prevalence rates of TST (tuberculin skin testing) positivity also mean that a large number of contacts will require further assessment and possible treatment of LTBI (latent TB infection) [47-51].

Information that is easily collected from other individuals with TB can prove very difficult to gather from homeless individuals. They may not know the names of friends/associates or only a street name, or where to find them; recall may be severely limited by addiction or mental illness and sometimes by mistrust of authorities. Drug users may be very reluctant to implicate those they use drugs with for fear of legal prosecution. It may be most productive to try to identify any particularly close friends by name and otherwise to focus on setting-based follow-up. Cases may be highly mobile, with many locations exposed. Shelters may have bed logs, which can be used to identify room-mates; in large shared rooms, prioritize those who spent the most nights with the case and slept closest. Bear in mind that ventilation patterns, including fans, can affect transmission. Rooming houses (also known as single-room occupancy hotels) are often very cramped and poorly ventilated. Homeless shelters may be closed during the day; ask about meals, drop-in centres providing services for the homeless (day-use shelters), libraries, bars, parks, etc. Shelter staff or social service agency workers may be able to identify daily patterns, or friends, and family of the case. If there are gaps in the available history during the infectious period, it may also be worthwhile to check for recent hospitalizations or detainment in a correctional facility. It will be extremely helpful to involve staffs who are familiar with the local homeless sector in contact follow-up.

Homeless contacts are often difficult to locate, and have significant challenges following through on screening, medical evaluation, and preventive treatment for LTBIFootnote 52.Non-judgmental and supportive TB staff, and judicious use of incentives and enablers may help increase participation rates. Active participation and encouragement from trusted staff at the shelter or day-program (e.g. a drop-in centre or soup kitchen) during screening clinics is especially helpful. Persistence and flexibility are critical. Someone who is not co-operative one

day may be willing to participate another time; interventions which can be carried out on-site or in a single session generally have more success than those involving extra visits or travel (e.g. sputum collection on site, portable chest x-ray , IGRA vs TST planting and reading)Footnote 53-55. The primary focus should generally be on early detection of secondary cases; LTBI should be assessed and treated only if individuals meet the medical and social criteria for treatment of LTBI.

Refer also to Chapter 15, Prevention and Control of Tuberculosis Transmission in Health Care and Other Settings, for additional discussion on the prevention of TB (tuberculosis) in homeless shelters.

Correctional Facilities

Residents of correctional facilities often have a higher prevalence of TB infection and disease; large outbreaks of TB have occurred in prisons in the United States, Russia and elsewhereFootnote 56-58. Older facilities in particular are often overcrowded and poorly ventilated, increasing the risk of spread. Some residents have comorbid medical conditions, such as HIV infection, that increase progression of TB infection to active disease; mental illness and mistrust of authorities can make clinical assessment difficult.

When an infectious case of TB (tuberculosis) is identified in a correctional facility, contacts can include fellow inmates and employees at the facility, transportation staff, visitors, courthouses, and family or community members exposed before the case was incarcerated. Multiple corrections facilities may be involved, as both provincial and federal inmates are often moved between sites, and both case and contacts may have had multiple incarcerations during the infectious period [45].However, where inmates are given a TST (tuberculin skin testing) on admission and/or annually, these results may be available as a baseline for contact follow-up. To assist in the identification of contacts, correctional facilities should track inmate transfers, releases and movement within a facility and within the system.

Levels of anxiety may be very high among corrections staff during a TB investigation and have sometimes resulted in facility closures or work stoppages. Ongoing relationships with local public health/TB control staff can help mitigate this. It is extremely helpful to include senior corrections staff, particularly chiefs/directors of health care, and union health and safety representatives early in planning and communication; if multiple facilities are involved, provincial/territorial or senior federal corrections officials should be included. If suspect cases are identified during contact follow-up, they should be removed from the general

ranges/shared cells pending diagnostic confirmation. Suspect and confirmed infectious cases should be kept in airborne isolation rooms if available within correctional facilities or transferred to hospital.

Correctional Service Canada has developed guidelines for TB (tuberculosis) prevention and control in institutions that house inmates sentenced to 2 years or longer. Contact publichealth@csc-scc.gc.ca to obtain a copy.

Health Care Institutions

Hospital TB (tuberculosis) contact follow-up benefits from close coordination and collaboration between public health/TB (tuberculosis) control staff and hospital infection control/occupational health staff. While almost every type of health care institution has been implicated in nosocomial transmission, there is very little by way of published hospital contact follow-up studies to guide thoughtful contact follow-up [59-61]. Unless the contact investigation is conducted in an organized, systematic fashion, with the basic principles of transmission in mind, it may result in hundreds of "contacts" with limited or unknowable exposure and often dismal participation and follow-up completion rates. It is often very useful to measure air exchange rates in specific hospital exposure locations, in order to help prioritize contact follow-up. It is also important to confirm whether there were any unprotected aerosolizing procedures, such as intubation, carried out on the infectious case (i.e. when staff did not use N95 masks). Some types of patients are extremely vulnerable (e.g. transplant patients) and even short exposures may be relevant (refer to Chapter 6). Visitors to the case and to room-mates may have significant exposure. Hospital infection control and occupational health departments often take advantage of TB (tuberculosis) exposures to get staff TST (tuberculin skin testing) documentation up to date, but within this larger group of staff being tested it is important to distinguish those who have the most actual exposure to the infectious case - particularly if there are conversions detected. Pooling the results of contact follow-up within and outside of the hospital can help to focus the investigation and determine the need, if any, for expansion. Notification of contacts may come from the hospital and/or public health authority, and testing can be done by the hospital, public health authority or personal physicians, but the plan should be agreed on by all parties to avoid confusion and gaps.

Individuals who are immunosuppressed are at much higher risk of TB disease after infection with TB; thus, TB exposures in specialty services or clinics may pose an especially high risk. For example, among dialysis patients in British Columbia, the annual rate of TB was 25 times higher than among age-matched population controlsFootnote 62.Nosocomial transmission of TB to people with HIV is well documented in both inpatient and outpatient settingsFootnote 63 Footnote 64. Refer to Chapter 4, Diagnosis of Latent Tuberculosis Infection, Chapter 6,

Treatment of Latent Tuberculosis Infection, and Chapter 10, Tuberculosis and Human Immunodeficiency Virus, for additional information on assessment and management of these contacts. Also, refer to Chapter 15, Prevention and Control of Tuberculosis Transmission in Health Care and Other Settings.

Long-Term Care

Many of the same issues for hospitals apply to TB (tuberculosis) exposures in long-term care facilities. For residents who are contacts of an infectious case of TB (tuberculosis), the most critical follow-up is assessment for active disease through careful symptom evaluation, chest radiography and sputum testing. Diagnosis of active TB (tuberculosis) in the elderly can be difficult, and expert clinical consultation may be necessary. Gastric washings may be easier to obtain than spontaneous or induced sputum in demented or very elderly residents. TST (tuberculin skin testing) is not recommended as a primary contact assessment tool for residents over 65 years [65].Interpretation of TST (tuberculin skin testing) results in the elderly is often complicated by both immune suppression and the potential for boosting related to remote TB (tuberculosis) exposure or BCG [66-69]. As well, for many elderly contacts the risks of LTBI (latent TB infection) treatment outweigh the potential benefits. However, contacts among staff and visitors ≤65 years old should receive a TST (tuberculin skin testing). In the absence of secondary cases, their results are likely to be a more reliable indicator of transmission in the facility.

Remote Communities

Contact investigation in a remote community may be especially challenging. Access to diagnostic tests, staffing, TB expertise and resources may be difficult. In remote First Nations or Inuit communities there may also be significant language and cultural barriers to successful contact tracing. Nowhere are organization, education, communication and a collaborative, nonjudgmental approach more important. The provincial/territorial TB program, the local public health/TB control program, Health Canada's First Nations and Inuit Health Branch if it is involved in the delivery or funding of health services in the community, local health care providers and the community should work closely together to identify secondary cases and contacts quickly, and then to see that they are properly managed over the duration of medical investigation and treatment. A mobile or portable radiography unit may need to be brought to the community; liberal use of sputum screening may also be useful in coordination with the public health laboratory. Otherwise, a special effort should be made to facilitate the timely transport of people with suspected TB to a larger medical centre

for investigation. Directly observed preventive therapy is a treatment option for newly infected contacts in First Nations and Inuit communitiesFootnote 70.Also, refer to Chapter 14, Tuberculosis Prevention and Care in First Nations, Inuit and Métis Peoples.

Contacts During Air Travel and Other Public Transport

The World Health Organization (WHO (World Health Organization)) publishes guidelines [71] outlining the procedures for notifying certain contacts of people with infectious TB (tuberculosis) who have travelled on an international flight with a total duration of ≥8 hours within the previous 3 months. The 8 hour duration is based on epidemiologic studies reviewed in the WHO guidelines. In Canada, reports of people with TB (tuberculosis) who report a history of air travel while infectious should be made to the Public Health Agency of Canada (PHAC (Public Health Agency of Canada)) through the provincial/territorial TB (tuberculosis) program (even if the flight occurred more than 3 months ago, as passenger records are usually still available). The reporting form and detailed guidelines can be found at Public Health Agency of Canada, Reporting Forms website. The report to PHAC should be made as soon as possible (even if culture and antibiotic sensitivity results are still pending), as this speeds up the process of risk assessment and securing the necessary passenger information from the airline. However, a systematic review of 12 studies suggests that the value of actively screening airplane passengers is limited [72].

The few published reports of contact tracing after exposure to TB (tuberculosis) on buses and trains indicate that transmission is sometimes possible on repeated daily exposure, such as on school buses or on long-distance trips [73].Such events appear to be rare, involving highly infectious cases and specific environmental circumstances (e.g. daily travel on a crowded long-duration school bus route in winter). There is no evidence to support contact tracing related to local public transportation, particularly given the logistic hurdles and considerable inefficiency of contact tracing in these circumstances [73].

Possible Contact with Infectious TB (tuberculosis) Cases During Residence or Travel in a Country with High TB (tuberculosis) Incidence

Refer to Chapter 13, Tuberculosis Surveillance and Screening in Selected High-Risk Populations.

Management of a TB (tuberculosis) Outbreak

TB outbreaks generally last for several years; response and control are major undertakings [74-76]. In addition, outbreaks are more likely to occur in already challenging settings, such as homeless, impoverished, or other marginalized populations, isolated Inuit or First Nations

communities, etc [44] [54]

Definition

The definition of an outbreak of any disease is the occurrence of more cases in a given population than expected in a given time. Spatial or temporal associations may suggest ongoing transmission and an outbreak. TB (tuberculosis) outbreaks may be identified only retrospectively, after cases have been found to be linked epidemiologically or by genetic analysis. Any such clustering within the last 2 years should suggest a possible outbreak and prompt further investigation.

The following working definition of outbreak for planning investigations is based on that proposed by the U.S. Centers for Disease Control and Prevention: [22]

- During and because of a contact investigation, two or more of the identified contacts are diagnosed as secondary cases of active TB; or
- Any two or more cases occurring within 1 year of each other are discovered to be linked, but the linkage is recognized outside of a contact investigation. For example, two patients who received a diagnosis of TB (tuberculosis) independently, outside of a contact investigation, are found to work in the same office, yet they were not previously identified as contacts of each other. A more extreme example is when a second generation of transmission has already occurred at the time an index case is diagnosed - i.e. secondary cases have already generated their own secondary cases. The linkage between cases should be confirmed by genotyping results if cultures are available.

This definition emphasizes the pace of secondary cases occurring and the ability of the TB (tuberculosis) program to keep up with multiple contact investigations. In practice, the ability of the local TB (tuberculosis) program to manage a growing cluster of TB (tuberculosis) cases and the concurrent contact investigations in a timely way, within its usual operations, is also a key factor in determining whether or not to consider the situation an outbreak for response purposes. Most situations that have been recognized as TB (tuberculosis) outbreaks involve chains of many more than two secondary cases, or one previously unrecognized link to a secondary case, and extend over several years. The above definition is an operational one intended to help identify and contain rapidly evolving clusters. Note that a slower cluster of linked cases that spans several years may still require heightened TB (tuberculosis) program response for an identifiable population group yet not be an "outbreak" by the above definition.

Goals

The goals of the investigation and management of an outbreak of TB (tuberculosis) are as follows:

- to promptly identify the source case or cases, so that the risk of ongoing transmission of infection is rapidly reduced by isolation and initiation of appropriate treatment
- to rapidly identify new cases of active TB (tuberculosis) within the at-risk population, and initiate airborne isolation and treatment
- to identify people with recently acquired LTBI (latent TB infection), so that preventive therapy can be given before active disease develops.

Managing an Outbreak

Organization and resources

Given the scale and duration of most TB (tuberculosis) outbreaks, it is important that there be adequate staffing and resources for investigation and management from the onset of the response efforts. Assistance from outside the TB (tuberculosis) program may be necessary. Advice from experienced colleagues who have managed TB (tuberculosis) outbreaks elsewhere can be invaluable.

The following components are recommended in any TB (tuberculosis) outbreak response:

- an identified outbreak manager, appointed for the duration, with overall responsibility for management and coordination of the outbreak response;
- public health/TB control staff to register and case-manage patients with TB, define infectiousness, coordinate the investigation and provide consultation and communication with those in the field;
- sufficient field staff to carry out the contact investigation and follow-up; for outbreaks dispersed across remote communities, mobile specialized teams may be an effective strategy to support local staff;
- information technology (IT)/database and epidemiologic support;
- consistent, coordinated clinical and diagnostic supports with expertise in TB; prompt, local access to chest radiography of adequate quality, identified medical consultants with expertise in TB to review chest radiology, evaluate patients for TB, hospitalize if necessary, and manage suspected cases and contacts in a consistent manner, without delay; for remote communities telemedicine links (including review of digital radiology) can be extremely effective, hospital facilities that can offer airborne isolation rooms, diagnostic examinations and treatment without delay, links to public health laboratories for specialized supports (arrangements to handle larger numbers of specimens,

fingerprinting, etc.), rapid and safe transportation of specimens and, if necessary, patients;
- sufficient case-management and DOT staff to provide supervision of the complete course of drug treatment for all active cases - at least 1 year's additional staffing after the outbreak is over may be required;
- communications personnel to provide regular updates to the media and community on the status of the investigation;
- staff and resources to carry out the evaluation.

Roles and responsibilities

It is crucial, from the onset of the investigation, that the roles of all those involved in the investigation and management are clearly defined. Establishing an outbreak coordinating group, including the key individuals from public health/TB (tuberculosis) control, clinical expert care, hospitals, laboratory, the affected community and communications, can be very helpful. Collaboration and regular feedback among all levels of health care are important. There should be clear agreement to be followed in the investigation and the management of suspected cases and contacts, and written protocols.

Communication with health care providers

Local health care providers, particularly those who are most likely to first see new cases of TB (tuberculosis) in the outbreak population (emergency room, primary care in the outbreak neighbourhood, etc.) are key partners. Presentation at medical rounds, written notification about the outbreak and other ongoing communication will help to raise the index of clinical suspicion for TB (tuberculosis), provide up-to-date information about TB (tuberculosis) diagnosis and management, and help decrease barriers to care, including early hospitalization for suspected infectious cases when necessary.

Staff training

Given the scale of TB outbreaks and response, many staff involved may not be experienced in TB work; including training and education/clinical rounds at all the organizations involved in the response plan can be helpful.

Prompt isolation and treatment of cases of active disease

An outbreak should markedly raise the index of clinical suspicion for TB (tuberculosis) when anyone in the affected community presents with compatible symptoms, particularly for respiratory (i.e. infectious) TB (tuberculosis). All suspected infectious cases should be

promptly isolated - in hospital if necessary - and investigated to confirm the diagnosis and the degree of infectiousness. Suspect cases should not return to congregate settings until infectious TB (tuberculosis) has been ruled out.

Case-finding, identification of source case, and contact investigation

In outbreaks among homeless and other marginalized populations, outreach street nursing, primary care clinics on site at shelters or other homeless services, and other low-threshold types of care are often critical for early diagnosis [44, 75, 75, 76]. Shelter staff may be the first to identify an ill resident; training about TB and infection control precautions, basic symptom screening on admission, and mechanisms to rapidly isolate and refer suspect TB cases for medical evaluation should be implemented.

If not apparent, the source case or cases should be identified through aggressive investigation of all symptomatic individuals in the at-risk community. Once the initial investigation is under way, a review of the history of TB (tuberculosis) in the community is important. Review of "old cases" by provincial/territorial and local public health/TB (tuberculosis) programs may identify previously inadequately treated cases. In some circumstances it may be helpful to locate and reassess previously identified high-risk contacts who were lost to follow-up or did not take or complete treatment for LTBI (latent TB infection).

In small communities or in closed settings it may be more efficient to screen the entire community or those in the facility at baseline, especially as it may be difficult to determine the exact level of contact in a small, close-knit community. In some settings, especially if members are very mobile, offering on-site active case-finding (sputum and/or chest radiography as well as symptom screening) on an ongoing basis over an extended period of time may be the only way to ensure that most contacts are identified and screened [53-55, 75-77]. Many remote communities have members who travel back and forth frequently to other communities; tracking these individuals is particularly difficult, yet they can be a conduit to spread the outbreak to additional communities. Coordination and shared follow-up arrangements with TB programs in these other communities may be very helpful in the assessment and management of mobile contacts and cases.

In populations in which treatment of LTBI (latent TB infection) is not realistic as a major outbreak control strategy, the primary emphasis should be on early detection and treatment-to-cure of active cases, rather than extensive efforts to do skin testing. Examples include elderly residents (over 65 years) in long-term care facilities and some homeless populations (e.g. older alcoholics). Also, refer to Chapter 15.

A heightened index of clinical suspicion and perhaps case finding efforts should be maintained for several years after the outbreak subsides, as there is usually a pool of recently infected people remaining in the community. It may be possible to follow infected contacts who refuse or are not eligible for treatment of LTBI (latent TB infection) in order to detect early TB (tuberculosis) disease (e.g. periodic clinical assessment for 2 years after exposure).

Data management and epidemiologic support

Contact investigation and management in a TB (tuberculosis) outbreak is very data-heavy. Tracking hundreds of contacts, often through multiple sites and assessments, demands a good database and IT support. Rapid, thoughtful evaluation of the aggregate results as they become available requires a dedicated epidemiologist.

Identify fundamental causes

TB (tuberculosis) outbreaks mainly take place in settings where rapid transmission is possible - inadequate housing (overcrowding, inadequate ventilation) and prolonged infectiousness often related to limited health care access. A high prevalence of vulnerability factors among contacts accelerates the development of secondary cases: the presence of many young children, diabetes and other causes of immunosuppression, smoking, malnutrition, etc. In facility-based outbreaks (homeless shelters, hospitals, jails) a systematic assessment of conditions and practices, including ventilation, may identify areas for intervention (also, refer to Chapter 15). Individual cases can be treated and cured, but it is very difficult to contain outbreaks or reduce endemically high rates of TB (tuberculosis) without addressing the fundamental causes. These aspects, too, should be recognized, and when possible addressed in the outbreak response.

Community outreach and education

TB (tuberculosis) outbreaks can be anxiety-provoking and stigmatizing. Often they take place in a context of limited or inaccurate information about TB (tuberculosis) and sometimes quite negative cultural/historical associations. All these can prolong the situation through delayed diagnosis if individuals either do not recognize the significance of their symptoms or are afraid to receive a diagnosis of TB (tuberculosis). It is crucial to provide information about TB (tuberculosis) and the outbreak response to the affected community or setting as early as possible in the investigation of the outbreak, with regular updates for them and for the general local population. The information should be in a style and format that is accessible and takes into account the cultural and practical setting of those affected. Standard materials

may need to be adapted, ideally with input from community members. Peer outreach may be very useful, particularly for hard-to-reach individuals. This will help reduce the level of anxiety and will likely lead to greater cooperation and adherence to recommendations.

Evaluate the process and outcome of the outbreak investigation

Ongoing evaluation and a formal evaluation at the end of the outbreak, including both the process and outcome of the outbreak investigation, are crucial. DNA genotyping of isolates may be useful in identifying the presence of an outbreak, mapping its extent and evaluating the results of the outbreak investigation and control. Identification of key contributing factors, often social determinants of health, may point to future non-TB (tuberculosis)-specific interventions.

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Chapter 15: Canadian Tuberculosis Standards 7th Edition: 2014 – Prevention and control of Tuberculosis transmission in health care and other settings

Chapter 15 - Prevention and Control of Tuberculosis Transmission in Health Care and Other Settings

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Key Messages/Points

- The scope of this chapter includes hospitals; other health care settings; and residential and community care settings.
- Health care organizations and individual health care workers (HCW (healthcare workers) (health care workers)s) have a shared responsibility to apply effective tuberculosis infection prevention and control measures.
- The risk of health care associated transmission of *M. tuberculosis* varies with the type of setting, HCW (healthcare workers) occupational group, patient care activity, patient/resident/client population and the effectiveness of tuberculosis (TB (tuberculosis)) infection prevention and control measures.
- The most important contributors to health care associated transmission of *M. tuberculosis* are patients with unrecognized, respiratory TB (tuberculosis) disease. Hence, the most important element of any TB (tuberculosis) management program is rapid diagnosis, isolation and start of effective therapy for these patients.
- Remote and isolated health care settings in which at-risk populations are cared for should have access to resources to facilitate implementation of essential administrative, environmental and personal protective controls.

Major Recommendations

- All health care settings should have a TB (tuberculosis) management or infection prevention and control program supported at the highest administrative level. This involves a hierarchical approach to infection prevention and control measures categorized as administrative, environmental and personal protection controls.
- Airborne precautions should be initiated immediately for everyone with suspected or confirmed respiratory TB (tuberculosis) disease admitted to a hospital. The criteria for discontinuation of airborne precautions include the following: establishment of an alternative diagnosis, clinical improvement, adherence to effective therapy,

sputum smear and/or culture conversion, and drug-susceptibility tests that indicate fully sensitive organisms or low clinical suspicion of drug resistance.

- U.S. National Institute for Occupational Safety and Health (NIOSH (National Institute for Occupational Safety and Health) (National Institute for Occupational Safety and Health))-certified respirators (N95 or higher filter class) should be used by HCW (healthcare workers)s providing care for or transporting patients with suspected or confirmed respiratory TB (tuberculosis) disease.
- Masks should be used by patients/people with suspected or confirmed respiratory TB (tuberculosis) disease when outside an airborne infection isolation room.
- Baseline tuberculin skin testing (TST (tuberculin skin testing)) is recommended for all HCW (healthcare workers)s in health care and community care settings. Recommendations for periodic and serial (repeated) TST (tuberculin skin testing) for HCW (healthcare workers)s vary with the setting. Interferon-gamma release assays are not recommended for serial testing.

Introduction and General Principles

While the incidence of tuberculosis (TB (tuberculosis)) in Canada is generally low, exposure to people with unsuspected active respiratory TB (tuberculosis) disease followed by transmission of *M. tuberculosis* does occur in health care settings [1] [2]. A survey of TB (tuberculosis) control services in all Canadian provinces and territories in 2008 reported a total number of 1,562 cases of active TB (tuberculosis) disease and 11,935 people treated for latent TB (tuberculosis) infection (LTBI (latent TB infection)) [3]. Approximately 50% of people with active TB (tuberculosis) disease in this survey were admitted to hospital for an average of 21 days. Although the overall number of people admitted to Canadian health care facilities with active TB (tuberculosis) disease is low, both health care and community settings (e.g. homeless shelters and drop-in centres) serving at-risk populations continue to pose a hazard for the transmission of *M. tuberculosis* [4] [6]. Populations at risk of active TB (tuberculosis) disease include people with a history of active TB (tuberculosis) disease; staff and residents of homeless shelters; urban poor; staff and inmates of correctional facilities, including previously incarcerated people; injection drug users; people born in Canada prior to 1966; Aboriginal Canadians; people infected with human immunodeficiency virus (HIV (human immunodeficiency virus)); those born or previously residing in countries with a high TB (tuberculosis) incidence (in Asia, Eastern Europe, Africa and Latin America); and HCW (healthcare workers)s serving these at-risk groups [7] [10].

Literature reviews show that the incidence of LTBI (latent TB infection) among HCW (healthcare workers)s increases with certain occupational risk factors, including number of years working in health care settings where patients with active respiratory TB (tuberculosis) are cared for, providing direct care to those with respiratory TB (tuberculosis) disease, working in emergency departments or medical wards, providing services for patients infected with HIV (human immunodeficiency virus), and participating in aerosol-generating medical procedures (e.g. sputum induction and bronchoscopy) on individuals with TB (tuberculosis) [5] [11] [12].

In hospitals, clinics, community care centres and correctional facilities, where people congregate and share indoor air (in the same room or via the building ventilation system), the risk of *M. tuberculosis* transmission can be increased if ventilation and other infection prevention and control measures are inadequate. In addition, exposure to people with active, undiagnosed and untreated respiratory TB (tuberculosis) disease has resulted in high rates of positive TST (tuberculin skin testing) results in HCW (healthcare workers)s [1] [2] [5] [13]. Reported TB (tuberculosis) outbreaks within health care facilities are often due to failure to implement appropriate TB (tuberculosis) infection prevention and control measures [4]. These observations have heightened concerns and resulted in the formulation of recommendations for the prevention of health care associated transmission of *M. tuberculosis* to HCW

(healthcare workers)s, patients and visitors [7] [14] [15]. A review of the literature suggests that implementation of a full hierarchy of infection prevention and control measures in many hospitals, as recommended in published guidelines, has led to successful reduction in *M. tuberculosis* transmission [5] and is therefore considered integral to preventing transmission in hospitals, other health care settings, and residential and community care facilities.

This chapter reviews factors that determine or affect transmission of *M. tuberculosis* within hospitals, other health care settings, and residential and community care settings while focusing on measures to prevent transmission. The term HCW (healthcare workers)s refers to individuals in health care settings who provide health care or support services, such as physicians, nurses, nurse practitioners, paramedics, emergency first responders, respiratory therapists, unregulated health care providers, clinical instructors, students, volunteers, and housekeeping, dietary and maintenance staff [16].

Recommendations are based, as much as possible, on published evidence to date. However, the evidence applicable to infection prevention and control of *M. tuberculosis* that is based on randomized controlled trials, generally considered the strongest level of evidence, is limited. This type of study design is generally not feasible or practical when analyzing risk factors or situations involving natural exposure (e.g. TB (tuberculosis) outbreaks). As a result, the majority of the available evidence comes from observational studies, such as cohort or case-control studies, and from qualitative analyses of outbreaks. This chapter cites the evidence base from these primary studies, as well as from several published literature reviews [5] [9] [17] and from a systematic review that includes recommendations from the US Centers for Disease Control and Prevention (CDC (Centers for Disease Control and Prevention)) [7]. Recommendations are itemized in boxes, tables or algorithms with the strength of the recommendation and the quality of its evidence indicated (refer to Preface for explanation of rating). Where detailed information is beyond the scope of this chapter or further references are of interest, refer to the relevant chapter(s) in this book.

Determinants of Transmission of Mycobacterium tuberculosis

Aerosolization of infectious *M. tuberculosis* bacteria occurs when individuals with respiratory TB (tuberculosis) disease cough, sneeze, sing, play wind instruments or speak. Cough-inducing procedures (e.g. bronchoscopy, sputum induction) as well as some laboratory and autopsy procedures can also cause aerosolization of mycobacteria. Once infectious *M. tuberculosis* bacteria are aerosolized, they are carried throughout a room or building by air currents and can be inhaled by another individual, with the possibility of resulting in TB (tuberculosis) infection. Although the risk of transmitting *M. tuberculosis* is highly variable, the presence of certain factors (refer to section Factors associated with increased risk of transmission of *M. tuberculosis bellow*) predicts an increased transmission risk. In general, the more of these factors present, the greater the risk of *M. tuberculosis* transmission. For further discussion on determinants of *M. tuberculosis* transmission, refer to Chapter 2, Transmission and Pathogenesis of Tuberculosis.

Factors Associated with Increased Risk of Transmission of *M. tuberculosis*

- **Patient factors**
  - Respiratory (pulmonary or laryngeal) disease [A]
  - Number of Patients with Respiratory TB (tuberculosis) Disease [A]
  - Respiratory secretions that are acid-fast bacteria (AFB (acid-fast bacteria)) smear positive
  - Presence of cough
  - HIV (human immunodeficiency virus) infection [A]
  - Atypical manifestations of disease
- **Diagnostic/laboratory risk factors**

- Cough-inducing procedures, e.g. sputum induction, bronchoscopy or administration of aerosolized therapies
- Delayed diagnosis [A]
- Autopsy and preparation of pathology specimens
- Improper handling of laboratory specimens containing *M. tuberculosis*

- **Treatment factors**
  - Incorrect, ineffective or no therapy [A]
  - Delayed treatment
- **Environmental factors**
  - Inadequate ventilation to remove airborne infectious *M. tuberculosis* [A]
  - Inadequate TB (tuberculosis) infection prevention and control measures for containment of *M. tuberculosis*
  - Duration of exposure and proximity to infectious patient [A]
  - Overcrowding [A]
  - Absence of sunlight
  - High humidity

A
These factors are discussed below.

Respiratory (Pulmonary or Laryngeal) TB (tuberculosis) Disease

People with laryngeal TB (tuberculosis) disease show the highest infectivity of all forms of TB (tuberculosis). While most people with nonrespiratory TB (tuberculosis) alone are not infectious, it is important to exclude concomitant respiratory involvement, which occurs in a significant proportion of those with nonrespiratory TB (tuberculosis) [18]. Pleural TB (tuberculosis) disease in the absence of concomitant respiratory involvement is not considered infectious, refer to Chapter 2, Transmission and Pathogenesis of Tuberculosis.

Number of Patients with Respiratory TB (tuberculosis) Disease

It is generally understood that the number of hospitalized patients with respiratory TB (tuberculosis) disease, particularly before diagnosis and treatment, is an important determinant of institutional transmission risk. Results from one study involving 17 acute-care hospitals in Canada showed that with effective implementation of infection prevention and control measures the number of patients might not be the best indicator of transmission risk. In this study, institutional risk of *M. tuberculosis* transmission was found to be better correlated with delayed diagnosis and treatment [19] .Thus, prompt diagnosis followed by early isolation and appropriate treatment has a mitigating effect on this risk factor [5].

HIV Infection

There is no clear evidence that people infected with *M. tuberculosis* are more infectious if they are coinfected with HIV (human immunodeficiency virus). However, there will often be rapid development of active TB (tuberculosis) disease, [20] and HIV (human immunodeficiency virus)-related TB (tuberculosis) disease will often have atypical clinical manifestations, leading to delayed diagnosis. The increased risk of *M. tuberculosis* transmission by this population is related to the potential for delayed isolation if the index of suspicion for respiratory TB (tuberculosis) disease is low. Also, refer to Chapter 10, Tuberculosis and Human Immunodeficiency Virus.

Delayed Diagnosis

Refer to section "Identification of patients with active respiratory TB (tuberculosis) within hospitals" in this chapter.

Incorrect, Ineffective or No Therapy

The administration of incorrect or ineffective therapy or no therapy at all contributes to the risk of transmission. Refer to Chapter 5, Treatment of Tuberculosis Disease.

Inadequate Ventilation

The exchange of indoor air with outdoor air reduces the risk of infection by diluting the concentration of viable airborne *M. tuberculosis* bacteria present [1]. Theoretically, the risk of transmission should decrease exponentially with increasing fresh-air ventilation.

Duration of Exposure and Proximity to Infectious Patient

The risk of TB (tuberculosis) infection varies with duration of exposure, form of tuberculous disease and type of patient care activity. In one study, an hour of exposure during bronchoscopy on a patient with unrecognized smear-positive disease resulted in a 25% risk of infection [12] and in another study exposure to a patient with laryngeal TB (tuberculosis) resulted in a 1.7% risk of infection per hour [21]. Even when the relative risk of infection is low, repeated exposure can lead to a higher cumulative risk. For example, if a HCW (healthcare workers) is exposed for 1 hour each week, the cumulative risk can approach 100% after 10 years of repeated exposure.

Overcrowding

Overcrowding contributes to transmission in settings like homeless shelters and correctional facilities. The relative importance of select factors (such as overcrowding, duration of exposure and proximity to infectious people in a confined space) to *M. tuberculosis* transmission has not been quantitatively described in the literature, but some reports suggests that their impact is highly variable [22].

Risk Classification

Health Care Settings

The risk of health care associated transmission of *M. tuberculosis* to HCW (healthcare workers)s, patients (or residents) and visitors varies with the type of setting, occupational group, effectiveness of TB (tuberculosis) infection prevention and control measures, and patient/resident population [7]. A review of the community profile of TB (tuberculosis) disease, as well as the risk category of the health care facility and unit, can be used to conduct facility and/or unit risk assessments. This provides a framework for institutions to predict whether their workers are at increased risk of TB (tuberculosis) exposure so that the necessary infection prevention and control strategies can be implemented.

An approach to classifying risk of *M. tuberculosis* transmission in health care settings is described in Table 1. The risk categories presented have been modified from previous classifications [4] [23] and are based upon review of the available literature [7]. While the number of people with respiratory TB (tuberculosis) disease in a facility during a year is considered a key determinant of transmission risk, the likelihood of exposure to any one patient or resident can vary considerably among facilities. To account for this, the classification below is based on the number of active patient or resident beds and number of cases of respiratory TB (tuberculosis) disease diagnosed in the facility in a typical year.

Table 1. Risk classification for health care settings

Risk category	Facility size	Number of active TB (tuberculosis) cases present annually
Low	Hospitals: ≥200 beds	<6
	Hospitals: <200 beds	<3
	Long-term care institutions including homes for the aged, nursing homes, chronic care facilities, hospices, retirement homes, designated assisted living centres and any other collective living centre	<3
Not considered low	Hospitals: ≥200 beds	≥6
	Hospitals: <200 beds	≥3
	Long-term care institutions (as listed above)	≥3
	Infirmaries in correctional facilities [A]	≥3

A
Correctional facilities that have never reported active TB (tuberculosis) cases can be considered low risk.

HCW (healthcare workers) Activities

Patient care activities performed by HCW (healthcare workers)s are associated with varying degrees of exposure risk and subsequent infection with *M. tuberculosis* (Refer to section Risk categories for activities performed by health care workers). This risk increases with the duration of exposure and higher amounts of airborne mycobacteria. As a result, it is recommended that HCW (healthcare workers)s perform a risk assessment prior to interactions with people suspected of or confirmed as having active TB (tuberculosis) disease [16]. This risk assessment involves evaluating the likelihood of exposure to *M. tuberculosis* for a specific patient care activity, with a specific patient, in a specific environment and under particular conditions. This is referred to as a point-of-care risk assessment and is described in a recent publication from the Public Health Agency of Canada (PHAC) [16]. The assessment informs HCW (healthcare workers)s' decisions regarding the appropriate infection prevention and control measures needed to minimize the risk of exposure for themselves, other HCW (healthcare workers)s, patients and visitors.

Risk Categories for Activities Performed by Health Care Workers

- **High-risk activities**
  - Cough-inducing procedures (such as sputum induction)
  - Autopsy
  - Morbid anatomy and pathology examination
  - Bronchoscopy
  - Mycobacteriology laboratory procedures, especially handling cultures of *M. tuberculosis*
- **Intermediate-risk activities**
  - Work requiring regular direct patient contact on units (such as emergency departments) where patients with respiratory TB (tuberculosis) disease may be present [A]
  - Work in pediatric units where patients with TB (tuberculosis) may be admitted [B]
  - Cleaning of rooms of patients with respiratory TB (tuberculosis) disease
- **Low-risk activities**
  - Work requiring minimal patient contact (such as clerical, reception and administration)
  - Work on units where patients with respiratory TB (tuberculosis) disease are unlikely to be present [C]

A

This includes work done by all HCW (healthcare workers)s in these units.

B

Pediatric patients with respiratory TB (tuberculosis) disease should be considered infectious until infectiousness is ruled out by radiography and negative acid-fast bacteria sputum smears in patient, parents or caregivers. Refer to section "Isolation considerations for pediatric patients" in this chapter and Chapter 9, Pediatric Tuberculosis.

C

Classification of such units as low risk may be inaccurate if the population they are serving has a high incidence of TB (tuberculosis) (e.g. patients born or previously residing in countries with a high TB (tuberculosis) incidence or other at-risk populations). Some of the longest delays in diagnosis may occur in such settings.

Laboratory Personnel Handling *M. tuberculosis*

There are risks associated with handling *M. tuberculosis* in the laboratory that are not typically present in health care settings. Compared with the general population, laboratory HCW (healthcare workers)s have been found to have a greater risk of acquiring LTBI (latent TB infection) [7]. Although this risk stems mainly from aerosol formation during specimen or isolate manipulation, other mechanisms of transmission have been described in this setting. At the time of publication of these Standards, PHAC's Laboratory of Biosafety and Biosecurity was in the process of preparing a biosafety guideline, *Mycobacterium tuberculosis* Complex (MTBC (Mycobacterium tuberculosis Complex)) Biosafety Directive. Refer to Appendix D for details on laboratory standards. Recommendations on safe laboratory procedures, training programs, infection control plans, respiratory protection, TST (tuberculin skin testing) screening for personnel and safe transportation of samples are also available from other sources [7] [24] [25].

Prevention and Control of Transmission of *M. Tuberculosis*

Current recommendations for the prevention of health care associated transmission of *M. tuberculosis* involve a hierarchical approach to infection prevention and control measures, including the following:

- **Administrative controls** - institutional policies or measures that aim to reduce the time between the arrival of people with respiratory TB (tuberculosis) disease at a health care facility, diagnosis of their condition and placement in an airborne infection isolation room (AIIR (airborne infection isolation room) (airborne infection isolation room)). The purpose of these policies is to provide overarching protection for all HCW (healthcare workers)s, patients and visitors in a facility. Administrative control measures include occupational health programs incorporating skin testing of HCW (healthcare workers)s for LTBI (latent TB infection) after exposure and at regular intervals, access to treatment of LTBI (latent TB infection), exclusion of HCW (healthcare workers)s with respiratory TB (tuberculosis) disease, facility and unit risk assessments, as well as a HCW (healthcare workers) education program. Details on performing a risk assessment and on HCW (healthcare workers) education can be found elsewhere [7] [16].
- **Environmental (engineering) controls** - environmental measures to reduce the likelihood of exposure of HCW (healthcare workers)s, other patients and visitors to viable airborne *M. tuberculosis*. These include mechanical ventilation systems (to supply clean air) in patient care areas, use of ultraviolet germicidal irradiation (UVGI (ultraviolet germicidal irradiation)) and high-efficiency particulate air (HEPA (high-efficiency particulate air)) filters.
- **Personal protection controls** - measures directed to individual HCW (healthcare workers)s either to prevent infection (such as use of respirators) or to prevent disease if infected (such as detection and treatment of LTBI (latent TB infection)).

Each control measure is further explained below.

Administrative Controls within Hospitals

Recommendations

(*Conditional recommendations, based on very weak evidence*)

All hospitals, regardless of risk category, should have a TB (tuberculosis) Management Program (or TB (tuberculosis) Infection Prevention and Control Program) supported at the highest administrative level with components detailed below. This program may be facilitated through existing infection prevention and control programs with administrative responsibility clearly delineated.

Other health care settings may refer to the hospital TB (tuberculosis) Management Program to identify procedures that are applicable to the setting.

Tuberculosis Management Program

The goal of a TB (tuberculosis) management program is to prevent *M. tuberculosis* transmission to HCW (healthcare workers)s, patients and visitors.

Risk Assessment

The first step of an effective TB (tuberculosis) management program in a hospital or other health care setting should be to perform an organizational risk assessment in order to decrease the risk of patient and HCW (healthcare workers) exposure to and acquisition of *M. tuberculosis*. The exposure risk for HCW (healthcare workers)s engaged in different activities should be evaluated during this assessment. For further information on an organizational risk assessment, refer to a recent PHAC publication [16].

In hospitals of all risk categories, the following features should be in place as components of the TB (tuberculosis) management program:

- Policies and procedures should clearly delineate administrative responsibility for developing, implementing, reviewing and evaluating various program components. The evaluation should include quality control and audits for all components of administrative, environmental and personal protection controls. Personnel with responsibility for the program within the facility should be designated.
- Policies and procedures should be in place for rapid identification, isolation and treatment of patients; reduction of health care associated transmission through environmental controls; and protection of staff through appropriate use of personal protective equipment, education and TST (tuberculin skin testing).
- An annual review of the indices of health care associated transmission should be done. This includes (i) TST (tuberculin skin testing) conversion rates among HCW (healthcare workers)s; (ii) the total number of people with respiratory TB (tuberculosis) disease admitted annually; (iii) the number of occupational exposure episodes (i.e. admitted individuals with respiratory TB (tuberculosis) disease who were not placed under airborne precautions while receiving care); and (iv) the number of previously admitted patients whose TB (tuberculosis) was diagnosed only at autopsy.
- An annual summary of the clinical, epidemiologic and microbiologic features of patients whose TB (tuberculosis) is diagnosed within the hospital should be made available to HCW (healthcare workers)s caring for these patients. This will increase awareness of which patients in the population served are at risk of respiratory TB (tuberculosis) disease and the clinical manifestations.
- Additional considerations (such as higher index of suspicion or increased vigilance to prevent transmission before diagnosis) are recommended when caring for immunocompromised patients, whose infection may

carry a higher risk of progression from LTBI (latent TB infection) to active TB (tuberculosis) disease. This includes patients in oncology, HIV and haemodialysis units or clinics.

In hospitals that are not considered low risk (Table 1), the following additional items should be in place as components of the TB (tuberculosis) Management Program:

- The hospital Infection Prevention and Control Committee (or other appropriate existing committee) should be given responsibility for the TB (tuberculosis) management program. Committee members should include people with day-to-day responsibility for infection prevention and control. There should also be representation from senior administration; occupational health and safety; laboratory, nursing and medicine; and other health disciplines or groups as needed (e.g. respiratory technology, public health, central supply, housekeeping, laundry, pharmacy, physical plant and maintenance).

In low-risk hospitals (Table 1), the following additional items should be in place as components of the TB (tuberculosis) management program:

- The TB (tuberculosis) management program may consist of screening protocols for diagnosis in patients with symptoms of respiratory TB (tuberculosis) disease and pre-arrangement to transfer all such patients to another centre where appropriate environmental measures are available.
- In hospitals with a transfer-out policy, there should be at least one separate, well-ventilated area [26] or a single room with the door closed, away from high-risk patients, [16] where patients can be maintained until they are transferred.
- Hospital administrators in collaboration with appropriate jurisdictional authorities, should coordinate the planning of adequate numbers of hospitals with resources to receive such patients with minimum delay.

Education of HCW (healthcare workers)s

A very important component of any TB (tuberculosis) management program is education of HCW (healthcare workers)s on how to protect themselves from exposure to *M. tuberculosis*. HCW (healthcare workers)s should be educated about TB (tuberculosis) infection prevention and control measures at the time of hiring and periodically thereafter. Education for HCW (healthcare workers)s should be relevant to their duties. For health care professionals, this should include awareness of epidemiologic and medical risk factors for TB (tuberculosis), signs and symptoms of active TB (tuberculosis) disease (respiratory and nonrespiratory) and mechanisms of transmission. All HCW (healthcare workers)s, including orderlies, housekeeping and maintenance staff, should be educated to respect signage and to understand the importance of administrative, environmental and personal protection controls in the prevention of transmission.

Identification of Patients with Respiratory TB (tuberculosis) Disease Within Hospitals

Delayed diagnosis occurs in almost half of all hospitalized patients in whom respiratory TB (tuberculosis) disease is subsequently detected. This often results in significant exposure for HCW (healthcare workers)s and other patients. One study found that for each unrecognized case of respiratory TB (tuberculosis) disease, an average of 24 HCW (healthcare workers)s were exposed [27]. Certain locations within the hospital, such as emergency departments, are a frequent point of first contact with the health care system for people with undiagnosed respiratory TB (tuberculosis) disease [28] [29]. This was observed in a Canadian study: from 1994 to 1998, 47% of 250 people with TB (tuberculosis) made a total of 258 visits to emergency departments during the 6 months before their diagnosis [28].

Recommendations

(Conditional recommendations, based on strong evidence)

- A cough of 2- 3 weeks' duration with or without weight loss and fever in a person belonging to one of the at-risk groups below should prompt a thorough investigation to determine whether active respiratory TB (tuberculosis) is the cause: [7] [10]
    - People with a history of active TB (tuberculosis);
    - Staff and residents of homeless shelters;
    - The urban poor;
    - Staff and inmates of correctional facilities and previously incarcerated people;
    - Injection drug users;
    - Aboriginal Canadians residing in communities with high TB (tuberculosis) rates;
    - People infected with HIV (human immunodeficiency virus);
    - People born in Canada and other low TB (tuberculosis) incidence countries prior to 1966;
    - People born or previously residing in countries with a high TB (tuberculosis) incidence in Asia, Eastern Europe, Africa and Latin America;
    - People with high risk factors listed in Chapter 6, Table 1;
    - HCW (healthcare workers)s serving at-risk groups.

To consider someone a suspect for active respiratory TB (tuberculosis) disease (for investigation and/or initiation of airborne precautions), cough of 2 weeks duration is a more sensitive criterion, but cough of 3 weeks duration will be more specific. Selection of 2 or 3 weeks as the criterion depends on the local experience and epidemiology of TB (tuberculosis).

The TB (tuberculosis) incidence rate in Canada prior to 1966 was similar to that in a high TB (tuberculosis) incidence country (refer to Chapter 1, Epidemiology of Tuberculosis in Canada) thus the inclusion of this birth cohort as an at-risk group.

Concomitant respiratory TB (tuberculosis) disease should be ruled out in cases of nonrespiratory TB (tuberculosis). Refer to Chapter 2, Transmission and Pathogenesis of Tuberculosis, and Chapter 7, Nonrespiratory Tuberculosis.

Prompt diagnosis of active respiratory TB (tuberculosis) can be a major challenge if the clinical features of TB (tuberculosis) are atypical, such as negative AFB (acid-fast bacteria) sputum smears, non-cavitary lesions on chest radiograph and the absence of cough and sputum production [19]. Atypical features of respiratory TB (tuberculosis) disease are more frequently observed in the elderly and people who are immunocompromised because of medical conditions (renal failure, HIV (human immunodeficiency virus)) or therapy (steroids, anti-tumour necrosis factor). Refer to Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance.

Airborne Precautions for Patients with Suspected or Confirmed Respiratory TB (tuberculosis) Disease

Recommendations

(Strong recommendations, based on strong evidence)

- Airborne precautions should be initiated as soon as possible for all those with suspected or confirmed respiratory TB (tuberculosis) disease who are admitted to a hospital.
- Patients (including children of any age) who show signs and symptoms of TB (tuberculosis), or whose respiratory secretions, e.g. sputum or bronchial alveolar lavage, have yielded AFB (acid-fast bacteria), or who have a chest radiograph indicative of active TB (tuberculosis) should be immediately isolated in an AIIR (airborne infection isolation room). Refer to Figure 1.

Recommendations

(Conditional recommendations, based on very weak evidence)

- Once airborne precautions have been initiated, the patient should remain in the AIIR (airborne infection isolation room) until isolation is discontinued by designated medical personnel. Patients kept under airborne precautions can leave an AIIR (airborne infection isolation room) for medical reasons.
- A patient may be allowed to leave an AIIR (airborne infection isolation room) but only if it can be ensured that he or she adheres to airborne precautions; these include the proper wearing of a mask.
- Refer to Figure 1 for detailed recommendations.

In the absence of an AIIR (airborne infection isolation room), the patient should be placed into a single room (with the door closed and a portable air filtration unit used if available) until transfer to a facility where an AIIR (airborne infection isolation room) is available. Airborne precautions also include the use of respirators by HCW (healthcare workers)s caring for patients with suspected or confirmed active TB (tuberculosis) disease.

Isolation Considerations for Pediatric Patients

If isolation in the hospital is necessary for young children (under 5) with suspected or confirmed respiratory TB (tuberculosis) disease, it should be noted that they likely acquired their disease from adult family contacts, who may pose a risk to HCW (healthcare workers)s and other patients while visiting. Thus, for these patients, considerations for infection prevention and control in the hospital should include potentially infectious family members [30] [31]. Visitors (limited to immediate adult family or guardians) should be screened by symptoms and radiography for active TB (tuberculosis) disease and should wear a mask during visits (when not in the AIIR (airborne infection isolation room)) until active TB (tuberculosis) disease is ruled out. Refer to Chapter 9, Pediatric Tuberculosis, for information on TB (tuberculosis) infection and disease in children.

Figure 1. Recommended steps for isolation for suspected or confirmed active respiratory TB (tuberculosis) disease in hospital[A]

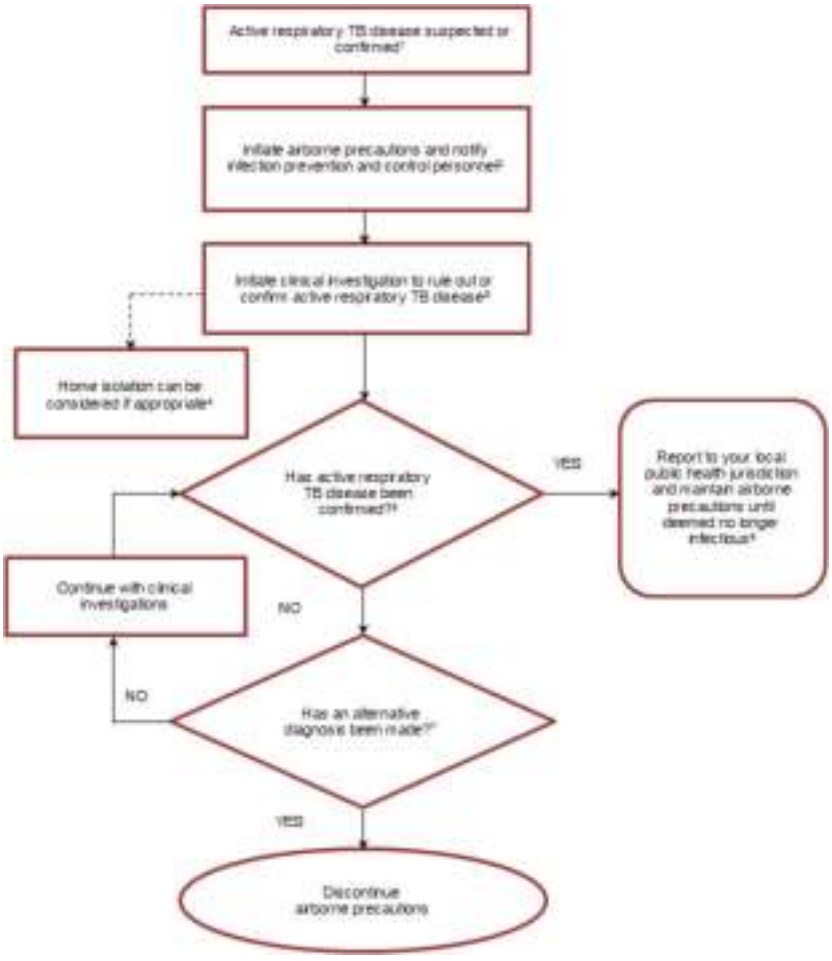

Figure 1. Legend

A) Includes infirmaries in correctional facilities

1) It is recommended that patients suspected of having active respiratory TB (tuberculosis) disease be isolated immediately rather than wait for confirmation of disease prior to initiating airborne precautions.

Airborne precautions are recommended during procedures that may generate aerosols from wound drainage in non-respiratory active TB (tuberculosis) disease.

Refer to Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance.

2) Airborne precautions include (in addition to routine practices):

- placement in an AIIR (airborne infection isolation room);
- respirator use by healthcare workers and if deemed necessary, by visitors also;
- mask use by patient when out of AIIR (airborne infection isolation room);
- restriction of patient to AIIR (airborne infection isolation room) except for medically essential procedures;
- education of patient, families and visitors on the precautions.

Visitors should be restricted to immediate family or guardians. Visiting family or guardians of pediatric patients should be screened for active respiratory TB (tuberculosis) disease. Visits by children under age five and immunocompromised persons should be discouraged.

3) Cough inducing procedures (e.g., sputum specimen collection, sputum induction) should be performed in an AIIR (airborne infection isolation room).
Refer to Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance, for details of clinical investigations.

4) Refer to Figure 2 Legend for conditions for home isolation.

5) The examination of smears of respiratory specimens for acid-fast bacteria is widely used as a presumptive rapid test, however mycobacterial culture provides a definitive diagnosis of active TB (tuberculosis) disease.

6) Airborne precautions may be discontinued when the patient has clinical evidence of improvement, three consecutive negative sputum smears for acid-fast bacteria and there is evidence of adherence to at least two weeks of effective therapy. Multi-drug resistant TB (tuberculosis) cases and those with mono-resistance to rifampin (RMP (rifampin)) should have three consecutive negative sputum cultures after six weeks of incubation prior to discontinuing airborne precautions.

7) Airborne precautions can be discontinued if another diagnosis is made (e.g., cancer, non-tuberculous pneumonia) and concomitant active respiratory TB (tuberculosis) disease is considered unlikely.

AIIR (airborne infection isolation room): airborne infection isolation room

Transport of Patients with Suspected or Confirmed Respiratory TB (tuberculosis) Disease

Recommendations

(Conditional recommendations, based on very weak evidence)

- Prior to transport, HCW (healthcare workers)s involved in patient transport, transport personnel and the receiving health care facility should be advised of the infectious state of the patient.
- Patients should be escorted by a HCW (healthcare workers) during transport/transfer of patients from one facility to another or within a facility.

- Patients with respiratory TB (tuberculosis) disease should wear a mask, and HCW (healthcare workers)s involved in transport should wear a respirator (Refer to section "Respirators and masks").
- If transport between facilities is required, patients should not use public transport.
- Patients should be transported in well-ventilated vehicles (i.e. with the windows open when possible).
- Where air transport is required (e.g. from remote settings), transport personnel should refer to their organization's policies on medical transport of patients with airborne infections.

Preventing Patient-to-Patient Transmission of *M. tuberculosis* Within Hospitals

Measures should be taken to reduce the risk of *M. tuberculosis* transmission to people within the hospital, including patients, HCW (healthcare workers)s, other staff, volunteers and visitors. Until placement in an AIIR (airborne infection isolation room), a patient with suspected or confirmed active respiratory TB (tuberculosis) should wear a mask as a source control measure to prevent viable *M. tuberculosis* from being disseminated (refer to section "Respirators and masks"). Source control measures, patient placement in a single room and limiting of patient movement all contribute to reducing the risk of patient-to-patient transmission [16]. When availability of single rooms is limited, priorities for placement of patients should be determined by risk assessment. Patients with suspected or confirmed respiratory TB (tuberculosis) disease have priority and should not share rooms with each other, since their strains and levels of infectivity may be different [16].

A review of HCW (healthcare workers)s' LTBI (latent TB infection) screening records for conversions as well as patient surveillance data and medical records for cases of respiratory TB (tuberculosis) disease can help to identify whether patient-to-patient transmission occurred before initiation of airborne precautions. This possibility should be considered under the following circumstances: [7]

- A high proportion of people with respiratory TB (tuberculosis) disease were admitted to or examined in the same setting during the year preceding onset of their disease.
- Isolates from multiple patients in the same health care facility have identical anti-mycobacterial susceptibility and molecular genotypes.
- An increase occurred in the number of people with drug-resistant respiratory TB (tuberculosis) disease compared with the previous year (applicable if the transmission was from a drug-resistant patient).

Refer to Chapter 12, Contact Follow-up and Outbreak Management in Tuberculosis Control, for further information.

Discontinuation of Airborne Precautions

Institutional policies should designate people with the authority (e.g. the infection prevention and control personnel) to discontinue airborne precautions as well as manage both breaches of and adherence to airborne precautions.

Recommendations

(*Strong recommendations, based on moderate evidence*)

Suspect TB (tuberculosis) cases

- Airborne precautions may be discontinued if three successive samples of sputum (spontaneous or induced) are negative on smear unless TB (tuberculosis) is still strongly suspected and no other diagnosis has been made [24] [32] [33].

Note: Where feasible, three sputum specimens (either spontaneous or induced) can be collected on the same day, a minimum of 1 hour apart with at least one of them taken in the early morning. As previously done, the evidence used to inform sputum collection recommendations for discontinuation of airborne precautions originates from

available studies related to diagnosis of respiratory TB (tuberculosis) disease. Refer Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance for the current evidence base.

A single negative AFB (acid-fast bacteria) smear from bronchial alveolar lavage does NOT definitively exclude respiratory TB (tuberculosis) disease; three induced sputa provide superior yield for the diagnosis and therefore are preferred to a single bronchoscopy. Refer Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance, for further explanation and references.

Confirmed TB (tuberculosis) cases

Although the degree and duration of infectiousness of patients after initiation of effective therapy remains unclear, it is known that effective therapy (i.e. therapy with two or more drugs to which the TB (tuberculosis) organisms are susceptible) will rapidly reduce cough and the number of viable bacteria in the sputum.
Note: Drug susceptibility test results are usually available within 4 weeks in a smear-negative, culture-positive case and 3 weeks in a smear-positive case; this confirms the effectiveness of therapy to date. Refer to Appendix D on Tuberculosis and Mycobacteriology Laboratory Standards: Services and Policies.

Recommendations
(*Strong recommendations, based on moderate evidence*)

Confirmed TB (tuberculosis) cases

- **Patients with smear-negative, culture-positive drug-susceptible respiratory TB (tuberculosis):**

  These patients should be kept under airborne precautions until there is clinical evidence of improvement and a minimum of 2 weeks of effective therapy has been completed. Patients may be discharged to home isolation for the period requiring airborne precautions provided there is clinical improvement, drug-resistant TB (tuberculosis) is not suspected and there is no contraindication for home isolation (refer to Figure 2).
- **Patients with smear-positive, culture-positive drug-susceptible respiratory TB (tuberculosis):**

  These patients should be kept under airborne precautions until there is clinical evidence of improvement, evidence of adherence to at least 2 weeks of effective multidrug therapy based on the known antibiotic sensitivity of the patient's organism, and three consecutive negative AFB (acid-fast bacteria) sputum smears [34]. Patients may be discharged to home isolation for the period requiring airborne precautions provided there is clinical improvement, drug-resistant TB (tuberculosis) is not suspected and there is no contraindication for home isolation (Figure 2).

Note: Specimens can be collected within 1 hour of each other on the same day, with at least one of them taken in the early morning. As previously done, the evidence used to inform sputum collection recommendations for discontinuation of airborne precautions originates from available studies related to diagnosis of respiratory TB (tuberculosis) disease. Refer to Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance for the current evidence base. In patients who are no longer able to spontaneously produce a sputum specimen, sputum induction is useful and appropriate. More invasive testing, such as bronchoscopy, is not recommended for monitoring response to therapy.

Although smear-positive patients are still potentially infectious, their household contacts have already been heavily exposed and are often receiving therapy for LTBI (latent TB infection) when discharge from hospital is being considered. Thus, the risk of further transmission to these contacts should be balanced by the social, mental and physical health benefits of the patient's return home.

Recommendations

(*Strong recommendations, based on moderate evidence*)

Confirmed TB (tuberculosis) cases

- **Patients with persistent smear-positive sputa:** Patients may be discharged to home isolation for the period requiring airborne precautions provided there is clinical improvement, drug-resistant TB (tuberculosis) is not suspected and there is no contraindication for home isolation (Figure 2). If sputum specimens continue to be culture-positive after 4 months of anti-tuberculosis treatment or if culture results become positive after a period of negative results, drug susceptibility tests should be repeated and a TB (tuberculosis) expert consulted [7].
- **Patients known to have active multidrug-resistant TB (tuberculosis) or mono-resistance to RMP (rifampin)**: These patients should be kept under airborne precautions for the duration of their hospital stay or until three consecutive sputum cultures (not smears) are negative after 6 weeks of incubation. Also refer to Chapter 8, Drug-resistant Tuberculosis.

Figure 2. Recommended steps for isolation for suspected or confirmed active respiratory TB (tuberculosis) disease in the home

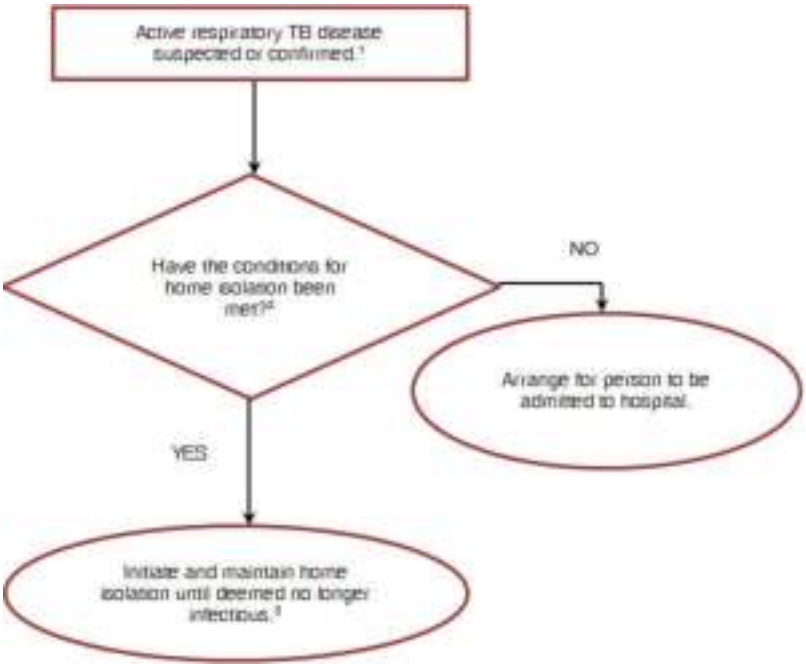

Figure 2. Legend

1) Refer to Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance.
The person being assessed for active respiratory TB (tuberculosis) disease should wear a mask. HCW (healthcare workers)s should wear a respirator when sharing a common airspace with the person.

2) Conditions for home isolation:

- Supervised therapy, if indicated, has been arranged;
- The person does not share a common airspace with non-household members (e.g., rooming house) and the household air is not being recirculated to other housing units (e.g., apartment complex);
- All household members have been previously exposed to the person. If any household members are TST (tuberculin skin testing) negative, they should be informed and understand the potential risks;

- No children under the age of 5 or persons with immunocompromising conditions are present in the home (an exception would be if they are receiving prophylaxis or treatment for active TB (tuberculosis) disease or latent TB (tuberculosis) infection);
- No visitors should be allowed in the home except for HCW (healthcare workers)s;
- The person is counselled on and is willing and able to comply with limitations to their movement outside of the home (e.g., does not go to work, school or any other public indoor environment);
- The person should not be allowed to use any form of public transportation (if absolutely necessary, a taxi can be used to attend essential healthcare appointments provided the person is wearing a mask);
- The person should be allowed to ambulate outdoors since the risk of transmission is negligible provided they are not in very close contact with susceptible individuals for prolonged periods of time.

3) Home isolation may be discontinued when the patient has clinical evidence of improvement, three consecutive negative sputum smears for acid-fast bacteria and there is evidence of adherence to at least 2 weeks of effective therapy. Multi-drug resistant TB (tuberculosis) cases and those with mono-resistance to RMP (rifampin) should have three consecutive negative sputum cultures after 6 weeks of incubation prior to discontinuing home isolation. HCW (healthcare workers)s: health care workers.

Environmental (Engineering) Controls Within Hospitals

Ventilation Guidelines

Ventilation recommendations for AIIR (airborne infection isolation room)s and select areas in hospitals are of critical importance because of their impact on reducing the risk for health care associated transmission of *M. tuberculosis*. Increasing air changes per hour (ACH (air changes per hour)) from 1 ACH (air changes per hour) to 6 ACH (air changes per hour) will result in four to five times more rapid clearing of infectious microorganisms from the air within a room. However, further increases above 6 ACH (air changes per hour) will have progressively less effect, and increases above 12 ACH (air changes per hour) may provide minimal additional benefit [29] [35]. In general, as air exchange rates are increased, there are increased costs for building and maintaining the ventilation system.

A number of recognized organizations have made recommendations regarding ventilation levels to reduce the risk of health care associated transmission of airborne pathogens, including *M. tuberculosis* and varicella-zoster viruses [7] [36] [37]. These organizations have published different ventilation standards for AIIR (airborne infection isolation room)s and other patient care areas within hospitals (refer to Table 2). Differences among these recommendations are not based on consideration of different evidence but, rather, on the risk-benefit assessment of each organization. Refer to Table 2 for current ventilation recommendations by different organizations.

General hospital areas

It is important to ensure that there is adequate ventilation in general (i.e. non-isolation) areas such as inpatient rooms and examination or treatment rooms. This is because people with unsuspected respiratory TB (tuberculosis) disease may be placed in them, posing a risk of transmission to other patients and HCW (healthcare workers)s [1]. Recent literature on room ventilation rates has not provided definitive evidence for the ideal number of ACH (air changes per hour) to prevent transmission of TB (tuberculosis) in non-isolation rooms within hospitals [38].

Airborne infection isolation rooms (all hospitals except low risk with transfer-out policy)

Measures to ensure that adequate ventilation is in place are outlined below and are also discussed in more detail in other guidelines [7] [16].

Recommendations

(Strong recommendations, based on moderate evidence)

- With the exception of rooms in which operative procedures are done, the direction of air flow should be inward from the hall into the room (negative pressure), and then the air should be exhausted outdoors. If an anteroom is used, the air from both the anteroom and patient room should be exhausted outdoors [16]. To achieve this, the ventilation system should be designed to function such that the anteroom and/or the AIIR (airborne infection isolation room) are at lower pressure relative to the hallway outside. An anteroom is not essential if the pressure differential is adequate. Refer to the CDC (Centers for Disease Control and Prevention) (Centers for Disease Control and Prevention)'s recent recommendations on pressure differentials [7].
- Windows and doors should be kept closed at all times, including during and after aerosol-generating procedures (long enough for air clearance in the room). Opening the window may cause reversal of the direction of air flow, depending upon the prevailing wind direction and outdoor temperature.
- Air should be exhausted to the outdoors through a dedicated exhaust system, ideally exiting from the roof of the building. It is important that the exhausted air does not re-enter the building or an adjacent occupied building. If the air will be recirculated, or if the exhausted air could re-enter the building, it should be passed through a HEPA (high-efficiency particulate air) filter before being exhausted [7]. Within existing facilities, use of HEPA (high-efficiency particulate air) filtration units that recirculate air back into the room and/or ultraviolet germicidal irradiation (which has bactericidal activity against *M. tuberculosis)* may be adjunctive methods to remove or reduce viable airborne *M. tuberculosis*; these are discussed later in this chapter.
- The rate of air changes and direction of air flow should be verified at least every 6 months when the room is not being used as an AIIR (airborne infection isolation room). When the AIIR (airborne infection isolation room) is in use, the direction of air flow should be verified daily using electronic pressure monitors, and should be recorded. Where electronic monitors are unavailable, such as in older buildings, in resource-constrained settings or in temporary isolation settings, smoke tubes placed at all four corners of the door can be used [16].
- The number of AIIR (airborne infection isolation room)s required in hospitals not considered low risk should be based on the number of patients admitted each year with suspected respiratory TB (tuberculosis) disease. In organizations with very few admissions for TB (tuberculosis), the number of AIIR (airborne infection isolation room)s should be decided by the organizational authorities according to an analysis of AIIR (airborne infection isolation room) utilization in the previous 2 or 3 years. The Canadian Thoracic Society suggests one or two more AIIR (airborne infection isolation room)s than what was needed in the past at peak times. Appropriate resources should be made available to hospitals that will have such rooms and therefore receive patients with respiratory TB (tuberculosis) disease.

Sputum induction and administration of aerosolized pentamidine (all hospitals)

Recommendations

(Strong recommendations, based on moderate evidence)

- The smaller the room where these procedures are performed the easier and more practical it is to achieve required ventilation levels. Ideally, specially constructed "booths" (which are commercially available) should be used.
- Doors and windows should remain closed during and after the procedure, long enough for air clearance in the room (refer to Table 3).
- The air should be exhausted through a dedicated exhaust system or HEPA (high-efficiency particulate air) filtered.

Bronchoscopy and autopsy (all hospitals)

Areas where these procedures are performed tend to be much larger, making it difficult to achieve consistently high levels of ventilation with an inward direction of air flow. The increased risk of transmission associated with these activities warrants the significant expenditures required to achieve higher ventilation requirements.

Recommendations

(Strong recommendations, based on moderate evidence)

- Doors and windows should remain closed during and after the procedure, long enough for air clearance in the room (refer to Table 3).
- The air should be exhausted through a dedicated exhaust system or HEPA (high-efficiency particulate air) filtered.

Table 2. Ventilation recommendations for selected areas in health care facilities

Area	Number of mechanical air changes per hour Recommending agency				Direction of air movement (all agencies) [A]
	CTS (Canadian Thoracic Society) (2013)	CSA (2010)	CDC (Centers for Disease Control and Prevention) (Centers for Disease Control and Prevention) (2005)	ASHRAE (2008) in FGI (2010)	
Autopsy suite	12	20	12	12	Inward
Bronchoscopy room	6-12 [B]	20	12	12	Inward
Sputum induction/pentamidine aerosol					
Emergency department (waiting rooms)	2 [C]	12 15	12-15	12	Inward
Trauma				15	
Radiology waiting rooms	2 [C]	9	12-15	12	Inward
Operating room or surgical room	15	20	15	20	Outward
Airborne infection isolation rooms [D]					
Existing buildings	6	[E]	6	[F]	Inward
New buildings	9	12	12	12	
General patient care/non-isolation rooms	2 [C]	6	[G]	4 [H]	N/A

Area	Number of mechanical air changes per hour Recommending agency				Direction of air movement (all agencies) [A]
	CTS (Canadian Thoracic Society) (2013)	CSA (2010)	CDC (Centers for Disease Control and Prevention) (Centers for Disease Control and Prevention) (2005)	ASHRAE (2008) in FGI (2010)	

CTS (Canadian Thoracic Society)
Canadian Thoracic Society

CSA
Canadian Standards Association [36]

CDC (Centers for Disease Control and Prevention)
US Centers for Disease Control and Prevention [7]

ASHRAE
American Society of Heating Refrigeration and Air-conditioning Engineers [37]

FGI
Facilities Guidelines Institute [37]

A
Direction of airflow from hallway or corridor relative to space; inward means from hallway into room. The US CDC (Centers for Disease Control and Prevention) (Centers for Disease Control and Prevention) provides further detail on direction of airflow specific to some inpatient settings, such as emergency departments and surgical suites/operating rooms [7].

B
Six ACH (air changes per hour) for existing room and 12 ACH (air changes per hour) for new constructions.

C
Note that the CTS (Canadian Thoracic Society) recommendations for these areas were developed following a systematic review of the available evidence on ventilation rates for preventing transmission of *M. tuberculosis*. The scope of the review included general hospital areas, emergency departments, as well as trauma and radiology waiting rooms.

D
Air-cleaning devices may be used to increase the equivalent ACH (air changes per hour).

E
Portable or fixed HEPA (high-efficiency particulate air) filtration units may be used as a temporary measure to help older facilities achieve the minimum required number of air exchanges per hour, but the facilities should be considered for upgrade. Refer to CSA document for details [36].

F
Portions of a structure can be renovated if facility operation and patient safety in the renovated areas are not jeopardized by existing features of sections retained without complete corrective actions. Refer to ASHRAE document for details [37].

G
Not stated, no recommendation made specific to these areas.

H
Recommendation is for patient corridor.

Note that the CTS (Canadian Thoracic Society) ventilation recommendations in Table 2 should be considered a minimum, as the CSA recommends higher ventilation rates for all areas. The CTS (Canadian Thoracic Society) recommendations were developed on the basis of a systematic review of currently available published evidence. Specific ACH (air changes per hour) rates are not recommended here; rather, Table 2 provides health care organizations with current recommendations provided by various organizations. In deciding which recommendations to implement, hospital administrators may need to take into account factors such as resources, facility design and available scientific evidence. The current paucity of evidence for adequate ACH (air changes per hour) rates to prevent transmission of *M. tuberculosis* and gaps in existing literature indicate that further research is needed in this area.

Entering rooms after generation of infectious aerosols has ended or patient with respiratory TB (tuberculosis) disease has been discharged

Health care workers often ask when it is safe to enter a room previously occupied by a patient with respiratory TB (tuberculosis) disease without needing to wear a respirator or when a procedure room can be used for another patient after generation of infectious aerosols has ceased. As shown in Table 3, this is dependent upon the level of ventilation in the room (expressed as ACH (air changes per hour)), if room sizes are relatively similar.

Table 3. Time needed (by number of air changes per hour) to remove airborne microorganisms after generation of infectious droplet nuclei has ceased [A]

Air changes per hour	Minutes required for removal of airborne microorganisms	
	99% removal	99.9% removal
2	138	207
4	69	104
6	46	69
12	23	35
15	18	28
20	14	21
50	6	8

A
This table was adapted from the CDC (Centers for Disease Control and Prevention) (Centers for Disease Control and Prevention) recommendations [7].

The values apply to a room in which the generation of aerosols has ceased, and ongoing mixing of the air in the room is assumed. Consideration should also be given to keeping the relative humidity of the air in the hospital at ≤60%. This range has been cited to minimize environmental contamination and provide acceptable indoor air quality [7].

Cleaning of rooms

If a room previously occupied by a patient with respiratory TB (tuberculosis) disease has been ventilated for the appropriate amount of time (refer to Table 3), the routine hospital cleaning procedures used in non-isolation rooms may be used for terminal cleaning of AIIR (airborne infection isolation room)s [7] [16]. If a room is still in use during cleaning, housekeeping personnel should wear a respirator (refer to section "Respirators and masks" below).

Ultraviolet Germicidal Irradiation

There is good evidence that short wave ultraviolet germicidal irradiation (UVGI (ultraviolet germicidal irradiation)) has excellent bactericidal activity against *M. tuberculosis* and can reduce infectious droplet concentrations by an amount equivalent to ventilation with 20 ACH (air changes per hour), depending upon the room volume and type of lights used [39]. Upper-room UVGI (ultraviolet germicidal irradiation) is considered a supplement or adjunct to ventilation [40]. Use of UVGI (ultraviolet germicidal irradiation) has been controversial because of potential skin cancer and eye damage. However, the risk of skin cancer with new, commercially available UVGI (ultraviolet germicidal irradiation) units is essentially eliminated. Possible eye complications can be avoided by proper installation of these units above head height, as well as a schedule of regular inspection and maintenance. A detailed review of the use of UVGI (ultraviolet germicidal irradiation) was published in 2010 [41]. This technology is being used with increasing frequency in settings such as homeless shelters to reduce airborne infectious microorganisms without the cost of renovating the heating, ventilation and air conditioning (HVAC (heating, ventilation and air conditioning)) system. For further information on the safe and effective use of UVGI (ultraviolet germicidal irradiation), including proper installation above head height and maintenance, refer to the recent CDC (Centers for Disease Control and Prevention) (Centers for Disease Control and Prevention) guidance document for using upper-room UVGI (ultraviolet germicidal irradiation) to control spread of *M. tuberculosis* in health care settings [40]. Use of UVGI (ultraviolet germicidal irradiation) may be considered in bronchoscopy and sputum induction rooms, emergency departments, autopsy areas and HIV (human immunodeficiency virus) clinics if ventilation is inadequate and cannot be upgraded. It can also be used where exposure is unpredictable, such as emergency departments in hospitals that are not considered low risk (refer to Table 1).

High-efficiency Particulate Air (HEPA (high-efficiency particulate air)) Filtration

HEPA (high-efficiency particulate air) filtration can be used to filter the exhaust from airborne infection isolation rooms, bronchoscopy suites or rooms where sputum induction is performed. Small HEPA (high-efficiency particulate air) units, either fixed or portable, may also be used to filter recirculated air in a room without the need for an increase in the amount of outdoor air supplied. HEPA (high-efficiency particulate air) filters require careful monitoring and regular change, as clogged filters will result in decreased efficacy. People performing maintenance and replacing filters on any ventilation system that is probably contaminated with *M. tuberculosis* should wear a respirator [7] (refer to section "Respirators and masks"). For further information on HEPA (high-efficiency particulate air) filtration and details on safety issues when handling spent filters, refer to the CDC (Centers for Disease Control and Prevention) (Centers for Disease Control and Prevention) guidelines [7].

With both UVGI (ultraviolet germicidal irradiation) and HEPA (high-efficiency particulate air) filtration environmental controls, regular maintenance (including procedures for installation, removal and disposal) and corresponding documentation are necessary.

Personal Protection Controls Within Hospitals

Personal protection controls are the final level in the hierarchy of control measures for preventing health care associated transmission of *M. tuberculosis.*

Respiratory Protection Program

Respiratory protection is one element of personal protection control measures. All hospitals should have a respiratory protection program in place. An essential component of the program involves selecting appropriate NIOSH (National Institute for Occupational Safety and Health)-certified respirators for HCW (healthcare workers)s, as discussed below. For cost-efficiency purposes, it is also important to provide respirator models with inherently

good fit characteristics, as these have been shown to fit more than 90% of workers [42] [43]. The health care organization should ensure that appropriate respirators are available as needed for use by HCW (healthcare workers)s, other staff and visitors, contractors, etc., and that masks, as needed for use by patients with respiratory TB (tuberculosis) disease, are available.

Another essential component of a hospital respiratory protection program is education of HCW (healthcare workers)s regarding the occupational risk of TB (tuberculosis) and the role of respiratory protection in reducing that risk.

Respirators and Masks

Respiratory protection of HCW (healthcare workers)s involves the use of a respirator with a filter class equivalent to or higher than an N95, to prevent inhalation of aerosols containing infectious microorganisms. The most widely used respirators by HCW (healthcare workers)s in North America are the NIOSH (National Institute for Occupational Safety and Health)-certified half-facepiece disposable respirators with an N95 filter class, commonly referred to as N95 respirators [15] [16]. These respirators are certified to filter 95% of particles of diameter 0.3 microns (µm) or larger with less than a 10% leak, thus protecting wearers against airborne infectious microorganisms such as *M. tuberculosis.* [7] [44]

A mask (either surgical or procedure) is used as a physical barrier. Masks are worn by HCW (healthcare workers)s to protect their skin and mucous membranes (nose and mouth) from droplets from an infected patient (or source). Masks are not designed for respiratory protection of HCW (healthcare workers)s as they are less than 50% effective in filtering small droplet nuclei (1-5 microns) containing *M. tuberculosis* [45].

Masks worn by patients with respiratory disease serve as a source control measure to trap the droplets that these patients expel. There is concern that because masks are loose-fitting they may allow the escape of airborne droplets (particularly during coughing); tight-fitting respirators, on the other hand, may be uncomfortable for patients (particularly those with limited respiratory reserve).

It is recommended that in all hospitals, including those with a transfer-out policy for cases of active TB (tuberculosis) disease, N95 respirators should be available for HCW (healthcare workers)s whenever a patient is suspected of or confirmed to have respiratory TB (tuberculosis) disease. This is particularly important because most low-risk hospitals will not have AIIR (airborne infection isolation room)s in which to house patients while awaiting transfer.

Fit Testing

Fit testing is used to determine whether a particular size and model of respirator fits a given person by assessing leakage around the face-respirator seal. Each time HCW (healthcare workers)s put on a respirator, a user seal check (according to manufacturer's instructions) is required to determine whether the respirator is properly sealed to the face. When TB (tuberculosis) patients are housed in AIIR (airborne infection isolation room)s, the contribution of respirators in preventing TB (tuberculosis) transmission to HCW (healthcare workers)s appears to be minimal [46]. Hence, despite published literature on fit testing [47] [49] there is insufficient evidence showing that a fit testing program results in reduced risk of health care associated transmission of *M. tuberculosis*. Nevertheless, most Canadian jurisdictions require fit testing for HCW (healthcare workers)s to determine their ability to obtain a satisfactory seal during respirator use [50]. HCW (healthcare workers)s are referred to jurisdictional requirements regarding the processes and frequency of fit testing. In the absence of requirements, consult provincial/territorial public health authorities.

Respirator recommendations for HCW (healthcare workers)s

(Strong recommendations, based on strong evidence)

- NIOSH (National Institute for Occupational Safety and Health) (National Institute for Occupational Safety and Health)-certified respirators (N95 or higher filter class) should be used by HCW (healthcare workers)s providing care to patients with suspected or confirmed respiratory TB (tuberculosis) disease.
- NIOSH (National Institute for Occupational Safety and Health) (National Institute for Occupational Safety and Health)-certified respirators (N95 or higher filter class) should be used by HCW (healthcare workers)s involved in the transport of patients suspected of or confirmed as having respiratory TB (tuberculosis) disease, e.g. paramedics.
- Refer to jurisdictional requirements for fit testing of respirators.

Mask recommendations for patients

(Strong recommendations, based on strong evidence)

- Masks should be used by patients with suspected or confirmed respiratory TB (tuberculosis) disease when leaving their AIIR (airborne infection isolation room)s.
- Masks should be used by patients with suspected or confirmed respiratory TB (tuberculosis) disease during transfer to a different location.

Screening for LTBI (latent TB infection) as Part of Infection Prevention and Control in Hospitals

Baseline TST (tuberculin skin testing) (all HCW (healthcare workers)s in all health care facilities)

The importance of conducting proper baseline TST (tuberculin skin testing) for all potentially exposed HCW (healthcare workers)s in all health care settings cannot be overemphasized. At the time of employment, many HCW (healthcare workers)s may already be TST (tuberculin skin testing) positive because of prior exposure, particularly HCW (healthcare workers)s born or previously residing in countries with high TB (tuberculosis) incidence who may have been exposed and infected before moving to Canada. In addition, older Canadian-born HCW (healthcare workers)s in some provinces/territories may have received bacille Calmette-Guérin (BCG) vaccination, which can interfere with TST (tuberculin skin testing) results. Prior exposure to *M. tuberculosis,* nontuberculous mycobacterial infection or BCG vaccination can result in a boosting phenomenon that is misdiagnosed as a TST (tuberculin skin testing) conversion. The occurrence of boosting phenomena has been documented in 3% to 10% of Canadian HCW (healthcare workers)s [13] [51]. Therefore, a two-step TST (tuberculin skin testing) is recommended (refer to Chapter 4, Diagnosis of Latent Tuberculosis Infection). PHAC has developed a compendium of the expected prevalence of TST (tuberculin skin testing) positivity in various Canadian populations; refer to Chapter 12, Contact Follow-up and Outbreak Management in Tuberculosis Control, for a summary table from the compendium.

Periodic TST (tuberculin skin testing) (specific clinical personnel in hospitals not considered low risk or those performing high-risk activities in all health care settings)

Recommendations for serial screening of specific HCW (healthcare workers)s for LTBI (latent TB infection) are given in the box below. Periodic TST (tuberculin skin testing)s should not be performed on previously TST (tuberculin skin testing)-positive HCW (healthcare workers)s as there is no value in doing so; rather, they should be referred for medical evaluation by a physician experienced in TST (tuberculin skin testing) interpretation and treatment of LTBI (latent TB infection), and should also be educated on the signs and symptoms of active TB (tuberculosis) disease (refer to Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance). Information on performing a TST (tuberculin skin testing), the definition of skin test conversion and management of the TST (tuberculin skin testing)-positive worker can be found in Chapter 4. Diagnosis of Latent Tuberculosis Infection.

Post-exposure TST (tuberculin skin testing) (all hospitals)

Any HCW (healthcare workers) who has unprotected exposure (termed an exposure episode) to a patient eventually confirmed to have respiratory TB (tuberculosis) disease should be considered at risk of having been infected. This includes situations in which a patient with undiagnosed respiratory TB (tuberculosis) disease was not in an AIIR or was cared for by a HCW (healthcare workers) who was not wearing a respirator. Exposure could also occur when such patients are not treated for a sufficient amount of time or with an effective regimen before isolation is discontinued.

Recommendations for screening HCW (healthcare workers)s for LTBI (latent TB infection)
(Strong recommendations, based on moderate evidence)

- Baseline two-step TST (tuberculin skin testing) for all HCW (healthcare workers)s upon starting work. An exception applies where documented results of a prior two-step TST (tuberculin skin testing) exist, in which case a single-step TST (tuberculin skin testing) should be given and prior TST (tuberculin skin testing) results transcribed into the HCW (healthcare workers)'s health record.
- Annual TST (tuberculin skin testing) for HCW (healthcare workers)s (with negative baseline TST (tuberculin skin testing)s) involved in intermediate-risk activities in health care settings not considered low risk and those involved in high-risk activities in all health care settings (refer to Tables 2 and 3).

Note: After 2 or more years of annual screening, if the annual risk of infection (based on TST (tuberculin skin testing) conversion rate in those screened) is shown to be less than 0.5%, consideration could be given to reducing the frequency of screening to every other year or to developing criteria that restrict annual screening to fewer workers who are at higher risk, and not testing the remaining workers except after exposure.

Recommendations for screening HCW (healthcare workers)s for LTBI (latent TB infection)
(Strong recommendations, based on moderate evidence)

Post-exposure:

- Single TST (tuberculin skin testing) 8 weeks after exposure for TST (tuberculin skin testing)-negative HCW (healthcare workers)s exposed to people with respiratory TB (tuberculosis) disease without adequate protection.
- For previously TST (tuberculin skin testing)-positive HCW (healthcare workers)s exposed to people with respiratory TB (tuberculosis) disease without adequate protection:
  - Refer for medical evaluation and educate on signs and symptoms of active TB (tuberculosis) disease. Refer Chapter 3, Diagnosis of Active Tuberculosis and Drug Resistance.
  - For HCW (healthcare workers)s with a history of BCG (Bacille Calmette-Guérin) vaccination, refer Chapter 4, Diagnosis of Latent Tuberculosis Infection, for information on the use of interferon-gamma release assays.

Protocols for TST (tuberculin skin testing) can be found in Chapter 4, Diagnosis of Latent Tuberculosis Infection.

Any HCW (healthcare workers) who has unprotected exposure (termed an exposure episode) to a patient eventually confirmed to have respiratory TB (tuberculosis) disease should be considered at risk of having been infected. This includes situations in which a patient with undiagnosed respiratory TB (tuberculosis) disease was not in an AIIR (airborne infection isolation room) or was cared for by a HCW (healthcare workers) who was not wearing a respirator. Exposure could also occur when such patients are not treated for a sufficient amount of time or with an effective regimen before isolation is discontinued.

Interferon-gamma release assay (IGRA (Interferon-gamma release assay))

The use of IGRA for serial (repeated) testing of HCW (healthcare workers)s is not recommended because serial testing studies have shown high rates of conversions and reversions, unrelated to exposure or treatment. There is no consensus on the appropriate cut-offs for deciding on IGRA conversions and reversions, and data show substantial variability in IGRA results around the cut-off used for LTBI (latent TB infection) diagnosis. Thus, TST (tuberculin skin testing) is the preferred test for serial testing for new LTBI (latent TB infection) (refer to Chapter 4, Diagnosis of Latent Tuberculosis Infection, for details).

IGRAs may be useful for confirming a positive TST (tuberculin skin testing) in low-risk HCW (healthcare workers)s who are found positive on baseline TST (tuberculin skin testing) as part of their pre-employment screening.

BCG vaccination

The efficacy of BCG vaccination against *M. tuberculosis* has varied from zero to more than 80% in randomized controlled trials [52]. As a result, it is not recommended that HCW (healthcare workers)s be routinely vaccinated with BCG. Refer to Chapter 16, Bacille Calmette-Guérin (BCG) Vaccination in Canada, for details about the vaccine. The issue more relevant to most health care settings in Canada is how to interpret a positive TST (tuberculin skin testing) or IGRA when there is a history of BCG vaccination in adulthood (refer to Chapter 4, Diagnosis of Latent Tuberculosis Infection, for information on this). Also, refer to The Online TST (tuberculin skin testing)/IGRA interpreter External Link. A summary of the provincial and territorial usage of BCG over time is available from PHAC at the Tuberculosis Prevention and Control External Link website and a BCG world atlas is available at BCG World Atlas: A Database of Global BCJ Vaccination Policies and Practices External Link.

Adherence to TB (tuberculosis) Infection Prevention and Control Measures

Low adherence to TB (tuberculosis) infection prevention and control measures by HCW (healthcare workers)s and to treatment of LTBI (latent TB infection) by both HCW (healthcare workers)s and patients will impede TB (tuberculosis) prevention efforts. Pre-employment screening for active TB (tuberculosis) disease is not sufficient to prevent *M. tuberculosis* transmission incidents involving HCW (healthcare workers)s in health care settings. Periodic HCW (healthcare workers) screening, recommended as above, and a high index of suspicion coupled with early assessment of HCW (healthcare workers)s with symptoms suggestive of TB (tuberculosis) are needed. Employers have reported greater success in encouraging HCW (healthcare workers)s to participate in screening programs when they are performed in conjunction with some other required activity (e.g. orientation, WHMIS (Workplace Hazardous Materials Information System) [Workplace Hazardous Materials Information System] training, employee updates, vaccination days) [14]. Administrative controls such as HCW (healthcare workers) training and education, in addition to a convenient schedule and location for screening, can increase adherence to TB (tuberculosis) infection prevention and control measures [7] [53].

Infection Prevention and Control of *M. Tuberculosis* in Specific Units and Populations Within Hospitals

Specific Units

All patients exhibiting signs and symptoms of TB (tuberculosis) in a hospital setting should be assessed to rule out active TB (tuberculosis) disease. In certain units, special consideration is required to prevent the transmission of TB (tuberculosis) to HCW (healthcare workers)s, other patients and visitors. A unit that treats or cares for at-risk patients (e.g. chemotherapy, HIV and dialysis units) should have a plan in place for how it will manage a patient with respiratory TB (tuberculosis) disease so that the patient's treatment is not interrupted and other people are not exposed.

Recommendations for Screening HCW (healthcare workers)s for LTBI (latent tuberculosis infection)
(Strong recommendations, based on strong evidence)

- **Intensive care unit (ICU (Intensive care unit)):** Every patient with suspected or confirmed respiratory TB (tuberculosis) disease who requires care in an ICU should be placed in an appropriately ventilated AIIR (airborne infection isolation room) within the ICU. If this is not available, arrangements should be made to transfer the patient to a facility with an AIIR (airborne infection isolation room) within the ICU as quickly as possible. For patients requiring intubation and mechanical ventilation, an appropriate bacterial filter should be placed on the endotracheal tube to prevent contamination of the ventilator and the ambient air [16]. When endotracheal suctioning is performed a closed suction apparatus should be used.
- **Emergency department:** A high index of suspicion for TB (tuberculosis) is required when assessing patients presenting with signs and symptoms of respiratory TB (tuberculosis) disease. Such patients should be immediately transferred to an AIIR (airborne infection isolation room). If such a room does not exist within the emergency department but exists elsewhere in the hospital, patients should be promptly transferred to this room until respiratory TB (tuberculosis) disease has been excluded (refer to section "Transport of patients with suspected or confirmed active respiratory TB (tuberculosis)").
- **Surgery:** Surgery should either be postponed (if feasible) until the TB (tuberculosis) patient is no longer considered infectious or scheduled to allow adequate ventilation of the room after surgery (refer to Table 3). Surgery is sometimes required in patients with multidrug-resistant or extensively drug resistant TB (tuberculosis), or to drain tuberculous abscesses. Because of the presence of infectious mycobacteria (and anaesthesia gases), the air supplied to the operating room should be exhausted to the outside and not exit the room to other patient care areas. HCW (healthcare workers)s should wear appropriate respirators (refer to section "Respirators and masks"). Post-operative recovery of the patient with suspected or confirmed respiratory TB (tuberculosis) disease should take place in the operating room or in an AIIR (airborne infection isolation room).

Special Populations

There are certain individuals whose immunocompromising conditions or immunosuppressive therapy places them at higher risk of progression from LTBI (latent TB infection) to active TB (tuberculosis) disease [7] [54]. They include HIV-infected individuals, transplant patients, people undergoing anti-tumour necrosis factor therapy and those undergoing dialysis or treatment for renal disease. A high incidence of LTBI (latent TB infection) and anergy has been reported among patients with chronic renal failure requiring dialysis [55] [56]. The risk of active TB (tuberculosis) disease in this population appears to be high in the first 6 to 12 months after dialysis is initiated [56]. Providing care for patients in a specialized clinic or in other settings might require special considerations, a higher index of suspicion for respiratory TB (tuberculosis) disease or increased vigilance to prevent transmission before diagnosis. Refer to Chapters 10 and 13 for further information. The CDC (Centers for Disease Control and Prevention) (Centers for Disease Control and Prevention) provides guidance on infection prevention and control considerations for dialysis units [7].

Prevention of Transmission of *M. Tuberculosis* Within Other Health Care Settings

Although the principles of TB (tuberculosis) infection prevention and control are the same across the continuum of health care, there is variation in the risk associated with different settings, and thus modification of the control measures applied is required. The availability of control measures needs to be considered when recommending interventions to prevent transmission of TB (tuberculosis) in non-hospital health care settings.

Long-term Care Facilities

Long-term care (LTC (long-term care)) facilities include homes for the aged, nursing homes, chronic care facilities, hospices, retirement homes, designated assisted living centres and any other collective living centre. Residents of LTC (long-term care) facilities are considered to be at the same risk as other populations in the community, with the exception of those belonging to at-risk groups (Refer to "Identification of patients with active respiratory TB (tuberculosis) within hospitals"). Due to the decreasing utility of TST (tuberculin skin testing) to diagnose LTBI (latent TB infection) after age 65 and the increasing risk of adverse effects from LTBI (latent TB infection) treatment in this age group, screening with a posterior-anterior and lateral chest x-ray for active TB (tuberculosis) is preferred upon admission for those over 65 years old. Refer to Chapter 12, Contact Follow-up and Outbreak Management in Tuberculosis Control, for further discussion and references. A baseline 2-step TST (tuberculin skin testing) is still recommended upon admission for those 65 years old and under who also belong to an identified at-risk group. Detailed screening recommendations for both HCW (healthcare workers)s and residents in LTC (long-term care) facilities are provided in Table 4.

Ambulatory Care/Outpatient Clinics

Ambulatory care settings include locations where health services are provided to patients who are not admitted to inpatient hospital units. This includes, but is not limited to, outpatient diagnostic and treatment facilities (e.g. diagnostic imaging, phlebotomy sites, pulmonary function laboratories, TB (tuberculosis) treatment facilities), community health centres or clinics, physician offices and offices of allied health professionals (e.g. physiotherapists) [7] [16]. If the patient mix includes members of at-risk populations, a high index of suspicion should be maintained for the presence of respiratory TB (tuberculosis) disease. Refer to section "Identification of patients with active respiratory TB (tuberculosis) within hospitals" for a description of this population.

Recommendations

(Conditional recommendations, based on weak evidence)

- If possible, visits by people with suspected or confirmed respiratory TB (tuberculosis) disease should be postponed until no longer infectious.
- If a visit cannot be postponed, it should be scheduled at the end of the day to minimize exposure to others, and, when possible, staff should be alerted of these visits to allow for prompt use of precautions [16].
- The patient should be provided with a mask before arrival or immediately upon reception to be worn until an AIIR (airborne infection isolation room) becomes available. If unavailable, the patient should be temporarily assessed or treated in a single room with the door closed, away from vulnerable patients, and transferred as soon as medically feasible to a facility with AIIR (airborne infection isolation room)s if admission is required [16].
- HCW (healthcare workers)s caring for people with suspected or confirmed respiratory TB (tuberculosis) disease in outpatient clinics should wear a respirator (Refer to section "Respirators and masks").
- Refer to Table 4 for further infection prevention and control recommendations for this setting.

Paramedics and Other Emergency Medical Services

Exposure to airborne infectious agents remains a substantial hazard for emergency medical services (EMS (emergency medical services)) providers. Such exposure can occur during resuscitation or routine transportation of patients.

Recommendation

(Strong recommendation, based on strong evidence)

EMS providers should wear appropriate respirators when attending to people with suspected or confirmed respiratory TB (tuberculosis) disease. Refer to section "Transport of patients with suspected or confirmed active respiratory TB (tuberculosis)."

Remote and Isolated Health Care Settings

In remote and isolated communities there are many challenges to TB (tuberculosis) infection prevention and control. Resource limitations may result in difficulties with access to adequate diagnostic facilities for bacteriologic examinations and chest radiography. In some remote and isolated First Nations and Inuit communities, the average TB (tuberculosis) incidence rates are high but vary considerably among communities [57]. Refer to Chapter 14, Tuberculosis Prevention and Care in First Nations, Inuit and Métis Peoples.

Respiratory TB (tuberculosis) disease should be ruled out for anyone presenting with unexplained cough for more than 2 weeks with or without fever, unexplained weight loss, hemoptysis, loss of appetite and night sweats. This requires a chest radiograph and analysis of three sputum smears for AFB (acid-fast bacteria). The most important measure for infection prevention and control is a high index of suspicion in members of at-risk populations (refer to section "Identification of patients with active respiratory TB (tuberculosis) within hospitals") with rapid use of diagnostic procedures (including sputum examinations and chest radiography) and early initiation of therapy. If chest radiography is difficult to organize because patients must fly out of the community, then sending sputum samples for AFB (acid-fast bacteria) smear and TB (tuberculosis) culture may be a more rapid way to make a diagnosis.

Recommendations

(Strong recommendations, based on moderate evidence)

- In high-prevalence areas where primary care nurses may be required to collect sputum samples for examination for AFB (acid-fast bacteria), they should wear a respirator and separate themselves from the area where the person is providing the sputum specimen.
- Health care facilities that care for at-risk populations should have access to resources that will facilitate implementation of essential administrative, environmental and personal protective controls.
- Refer to Table 4 for further infection prevention and control recommendations for this setting.

Where resources remain limited because of lack of the infrastructure needed to implement necessary infection prevention and control measures, strategies used in low-resource countries could be implemented: [58]

- Schedule visits from people with suspected or confirmed respiratory TB (tuberculosis) disease at the end of the day or after regular hours.
- If patients needing medical attention cannot be transferred to a facility with an AIIR (airborne infection isolation room), cohort smear- positive TB (tuberculosis) patients, provided they are receiving treatment and there is no suspicion of drug resistance (or the prevalence of drug-resistance is known to be very low) [26].
- Establish effective out-patient services with community-based treatment programs (in homes) to complete treatment started in the hospital, especially where AIIR (airborne infection isolation room)s are unavailable [58].
- When outdoor temperature permits, use natural ventilation to assist in reducing the risk of transmission of airborne pathogens. The World Health Organization has produced evidence-based guidelines on natural ventilation with minimal hourly ventilation rates [59].

Home Care Settings

Home care is delivered to patients who reside in their home or a community care residence. *M. tuberculosis* transmission to HCW (healthcare workers)s who work in home-based health care settings has been documented with recommendations developed to prevent transmission [7]. The room in the home where the patient spends considerable amounts of time should be well ventilated [16].

Recommendations

(Conditional recommendations, based on very weak evidence)

- Home care agencies in consultation with public health authorities should develop a system for screening at-risk clients for signs of respiratory TB (tuberculosis) disease before and during visits, thus facilitating earlier diagnosis and use of appropriate infection prevention and control measures.
- HCW (healthcare workers)s caring for clients with respiratory TB (tuberculosis) disease at home should wear a respirator (refer to section "Respirators and masks").
- HCW (healthcare workers)s should not perform cough-inducing or aerosol-generating medical procedures on clients with suspected or confirmed infectious TB (tuberculosis) disease, because recommended infection prevention and control measures will probably not be in place in the home [7].
- Refer to Table 4 for further infection prevention and control recommendations for this setting.
- Refer to Figure 2 on home isolation and Chapter 5, Treatment of Tuberculosis Disease.

Prevention of Transmission of *M. Tuberculosis* Within Residential and Community Care Settings

While guidance is available on preventing *M. tuberculosis* transmission in health care settings, less has been written about prevention in community care settings, even though the incidence of LTBI (latent TB infection) and active TB (tuberculosis) disease in these settings exceeds that in the general population who are not receiving care [60].

Adult Day Care Centres

For the purposes of these guidelines, adult day care facilities include basic or specialized day care centres for adults or other special adult populations requiring care. Adult day care services often include group programs designed to meet the social and health needs of functionally and/or cognitively impaired adults. Examples of clients include individuals with Alzheimer's disease, developmental disabilities, traumatic brain injury, mental illness, vision and hearing impairments [37]. Refer to Table 4 for screening recommendations for clients and employees. These recommendations apply only to clients who expect to use these services for 4 or more hours per week or for 150 or more hours per year.

Homeless Shelters and Drop-in Centres

Recent extended outbreaks of *M. tuberculosis* in homeless and under-housed individuals in Canada and the United States highlight the risk of ongoing transmission within this population [61] [62]. Overcrowding increases transmission risk, as does failure to recognize signs and symptoms of respiratory TB (tuberculosis) disease and inability to take immediate steps to prevent transmission. An upsurge in foreign-born homeless people in Canada could present an increased risk of drug-resistant strains being introduced into the homeless shelter system [6]. Employees and regular volunteers of shelters are at increased risk of becoming infected with TB (tuberculosis) because of frequent exposure to undiagnosed cases, compounded by inadequate ventilation. Screening for LTBI (latent TB infection) among the homeless can be labour intensive and complicated, and adherence to therapy for LTBI (latent TB

infection) is often low in this population. Active case finding can also be challenging, as a large proportion of homeless people may have chronic cough and other symptoms that can imitate those of TB (tuberculosis). Furthermore, following up on contacts of active cases can be extremely difficult.

Primary prevention of TB (tuberculosis) through improved environmental controls is perhaps the most important control strategy. This includes cleaning, repair and upgrading of air filter units as well as adding in-duct and upper-air UVGI (ultraviolet germicidal irradiation), which will help reduce the risk of TB (tuberculosis) transmission [63]. Opening windows to improve fresh air ventilation can also result in a dramatic decrease in *M. tuberculosis* transmission, especially in shelters with inadequate ventilation [64]. However, this is not feasible for most of the year in Canada because of cold temperatures. Guidelines to assist shelter operators and staff in reducing the risk of *M. tuberculosis* transmission in homeless shelters have been published [64] [65].

Recommendations

(Conditional recommendations, based on very weak evidence)

- With support from local public health authorities, homeless shelters should develop and implement a TB (tuberculosis) management program that provides education to staff, volunteers and clients.
- Refer to Table 4 for further infection prevention and control recommendations for this setting.

Addiction Treatment Centres

A high prevalence of positive TST (tuberculin skin testing) concurrent with increasing duration of injection drug use has been documented in this population. In addition, drug users have also been shown to have an increased risk of progression from LTBI (latent TB infection) to active TB (tuberculosis) disease [10]. The benefit of TST (tuberculin skin testing) screening for this high-risk population in terms of follow-up medical evaluation and adherence to therapy has been low [10]. Incentives have been shown to be a consistent and effective strategy for increasing participation in TB (tuberculosis) screening as well as educational activities for this population [10] [66]. Refer to Table 4 for further recommendations for this setting.

In populations known to have poor rates of return for TST (tuberculin skin testing) reading (e.g. homeless individuals and intravenous drug users), use of IGRAs can help achieve a higher rate of test completion and follow-up, although completion of LTBI (latent TB infection) treatment may still be challenging.

Prevention of Transmission of *M. Tuberculosis* Within Correctional Facilities

The following is based in part on the Correctional Service Canada (CSC (Correctional Service Canada)) guidelines for TB (tuberculosis) prevention and control in institutions in which inmates are sentenced to 2 years or longer [67]. At the time of publication of this Standard, the CSC (Correctional Service Canada) guidelines were under revision. An additional resource is the guideline published by the CDC (Centers for Disease Control and Prevention) (Centers for Disease Control and Prevention) on the prevention and control of TB (tuberculosis) in US correctional and detention facilities [68]. It should be noted that the recommendations below were developed mainly for federal facilities, as TB (tuberculosis) prevention and control activities and capacity vary across Canada for provincial/territorial correctional facilities. The latter facilities generally have more inmates, most of whom have shorter stays than inmates in federal facilities. The shorter duration of incarceration in provincial/territorial facilities, make it more difficult to implement recommendations developed for federal facilities.

The risk of TB (tuberculosis) transmission is higher in correctional facilities as a result of several factors:

1. The prevalence of LTBI (latent TB infection) among correctional facility inmates is higher than in the average Canadian population.
2. The risk of reactivation of LTBI (latent TB infection) to active TB (tuberculosis) disease is increased because of the higher prevalence of HIV (human immunodeficiency virus) infection, other comorbidities, previous or current cigarette smoking, and alcohol and injection drug abuse in this population.
3. Diagnosis may be delayed because of poor use of medical services.
4. Ventilation is often inadequate because of recirculation of air and a lack of open windows. This is more common in older prisons that were built to achieve security, not airborne infection control.
5. The density of inmates may be high (crowding).
6. Transfer of inmates within and between facilities may be frequent.

TB (tuberculosis) Control Program for Correctional Facilities

It is recommended that the first step of a TB (tuberculosis) management program in a correctional facility should be to perform an institutional risk assessment in order to decrease the risk of inmate and staff exposure to and acquisition of *M. tuberculosis*. This risk assessment is based on the baseline TB (tuberculosis) status of inmates and staff and an annual review of active respiratory TB (tuberculosis) cases diagnosed among inmates (and, if any, among staff). This involves inquiries into the medical and TB (tuberculosis) history as well as risk factors and symptoms. Past TB (tuberculosis)-related history should be collected, if necessary, by accessing a comprehensive electronic medical database. The history should be reviewed carefully, including results of previous TST (tuberculin skin testing)s and any chest radiography, as should prior treatment of LTBI (latent TB infection) or active TB (tuberculosis) disease. Incomplete treatment should prompt a thorough evaluation of the possibility of active TB (tuberculosis) disease by means of chest radiography, medical evaluation and sputum analysis for AFB (acid-fast bacteria) smears and cultures. Active case finding by symptom check is recommended for inmates on admission (baseline) and annually thereafter. At all other times a high index of suspicion should be maintained in order to minimize delays in the diagnosis of active respiratory TB (tuberculosis). Suspicion should be particularly high if the inmate has a prior history of TB (tuberculosis), even if treatment was judged to have been adequate, since actual adherence to treatment may have been suboptimal, leading to increased risk of relapse.

AIIR (airborne infection isolation room)s exist across Canada in CSC (Correctional Service Canada) facilities with at least one per geographic/administrative region. The direction of air flow should be into the room, and the air should then be exhausted outdoors. This should be verified when the room is occupied. For treatment of LTBI (latent TB infection) in inmates and staff, refer to Chapter 6, Treatment of Latent Tuberculosis Infection.

Recommendations

(Strong recommendations, based on strong evidence)

- Inmates who are suspected of having respiratory TB (tuberculosis) disease should be placed immediately in an AIIR (airborne infection isolation room) until TB (tuberculosis) is ruled out or they have received sufficient treatment and are deemed no longer infectious (Refer to Figure 1).
- Inmates and staff who are exposed to people with respiratory TB (tuberculosis) disease should be investigated in close collaboration with local public health authorities using the principles outlined in Chapter 12, Contact Follow-up and Outbreak Management in Tuberculosis Control.
- Refer to Table 4 for further infection prevention and control recommendations for this setting.
- If an inmate is discharged while still being treated for active TB (tuberculosis) disease, follow-up should be arranged directly with local public health authorities, so that supervised treatment is not interrupted, even for a day.

Table 4. Summary of recommendations for TB (tuberculosis) infection prevention and control measures in non-hospital settings

For the purposes of this table, "people with infectious TB (tuberculosis)" refers to people with suspected or confirmed respiratory TB (tuberculosis) disease unless otherwise indicated.

Facility/setting	Administrative controls	Environmental controls [A]	Personal respiratory protection controls	Screening and surveillance [B]
Long-term care (homes for the aged, nursing homes, chronic care facilities, hospices, retirement homes, designated assisted living centres and any other collective living centre)	Facility risk assessment by retrospective review of all TB (tuberculosis) cases in preceding 5 years and all available TST (tuberculin skin testing) results for staff and volunteers. This should inform the decision to routinely screen residents. Educate staff about TB (tuberculosis) symptoms, risk factors and infection prevention and control measures [C]. People with infectious TB (tuberculosis) should be transported as soon as possible to an appropriate medical facility and should not return to the setting until they are no longer infectious.	CTS (Canadian Thoracic Society): 2 ACH (air changes per hour) CSA: 4 ACH (air changes per hour) CDC (Centers for Disease Control and Prevention) (Centers for Disease Control and Prevention): NR (no recommendation for ACH) FGI/ASHRAE: 2-6 ACH (air changes per hour)	Respirators for HCW (healthcare workers)s in contact with people with infectious TB (tuberculosis) [D]. Mask for people with infectious TB (tuberculosis) if not in airborne infection isolation room (AIIR (airborne infection isolation room)) and during transport.	**Employees/volunteers [E]:** Baseline screening upon hire or placement using two-step TST (tuberculin skin testing) [F]. Annual TST (tuberculin skin testing) unless conversion rate is shown to be ≤0.5% [G]. **Residents/clients:** Baseline posterior-anterior and lateral chest radiography on admission for people >65 years old from identified populations [H]. Baseline two-step TST (tuberculin skin testing) upon admission for identified population £65 years old [F]. Annual TST (tuberculin skin testing) not necessary. Facility risk assessment/local epidemiology should inform decision [I].

Facility/setting	Administrative controls	Environmental controls [A]	Personal respiratory protection controls	Screening and surveillance [B]
Ambulatory care and outpatient clinics Refer to Table 2 for ACH (air changes per hour) recommendations for AIIR (airborne infection isolation room)	Signage at entry requesting use of surgical mask by people with respiratory symptoms that suggest infection. High index of suspicion if signs and symptoms of active TB (tuberculosis) disease. Schedule visit by people with infectious TB (tuberculosis) for end of day.	CTS (Canadian Thoracic Society): 2 ACH (air changes per hour) CSA: 6-9 ACH (air changes per hour) CDC (Centers for Disease Control and Prevention) (Centers for Disease Control and Prevention): NR (no recommendation for ACH) FGI/ASHRAE: 6 ACH (air changes per hour)	Respirators for HCW (healthcare workers) in contact with people with infectious TB (tuberculosis) [D]. Mask for people with infectious TB (tuberculosis) if not in AIIR (airborne infection isolation room) or during transport.	**Employees/volunteers [E]:** Baseline screening upon hire or placement using two-step TST (tuberculin skin testing) [F]. Annual TST (tuberculin skin testing) not necessary. **Patients**: Refer to Chapter 13, Tuberculosis Surveillance and Screening in High-risk Populations, for information on which individuals should be screened.
Clinic or nursing station etc. in remote and isolated settings or communities Refer to Table 2 for ACH (air changes per hour) recommendations for AIIR (airborne infection isolation room)	Schedule visits for people with infectious TB (tuberculosis) at the end of the day or after hours. Educate staff on TB (tuberculosis) symptoms, risk factors and infection control measures. Community-based treatment program (refer Figure 2 on home isolation). Patient with infectious TB (tuberculosis) who cannot be medically managed at home should be transferred	CTS (Canadian Thoracic Society): 2 ACH (air changes per hour) and/or UVGI (ultraviolet germicidal irradiation) to supplement CSA: 6-9 ACH (air changes per hour) CDC (Centers for Disease Control and Prevention) (Centers for Disease Control and Prevention):	Respirators for HCW (healthcare workers)s in contact with people with infectious TB (tuberculosis) [D]. Mask for people with infectious TB (tuberculosis) if outside the home.	**Employees/volunteers [E]:** Baseline screening upon hire or placement using two-step TST (tuberculin skin testing) [F]. Annual TST (tuberculin skin testing) if previously negative and people with infectious TB (tuberculosis) are being seen in the facility. Otherwise, annual TST (tuberculin skin testing) is not necessary [G].

Facility/setting	Administrative controls	Environmental controls [A]	Personal respiratory protection controls	Screening and surveillance [B]
	to an appropriate hospital as soon as possible.	NR (no recommendation for ACH)		
		FGI/ASHRAE: 6 ACH (air changes per hour) Natural ventilation where no mechanical ventilation exists and weather permits.		**Patients**: Refer to Chapter 13, Tuberculosis Surveillance and Screening in High-Risk Populations, regarding which individuals should be screened upon admission.
Home care	Educate staff on TB (tuberculosis) symptoms, risk factors and infection prevention and control measures. Refer to Figure 2 for home isolation recommendation.	ACH (air changes per hour): NA (not applicable) People with infectious TB (tuberculosis) should not share common airspace with non-household members. Use of natural ventilation when weather permits.	Respirators for HCW (healthcare workers)s in contact with people with infectious TB (tuberculosis) [D]. Mask for people with infectious TB (tuberculosis) if leaving home for necessary appointment.	**Employees/volunteers [E]:** Baseline screening upon hire or placement using two-step TST (tuberculin skin testing) [F]. Annual TST (tuberculin skin testing) if employee's results were previously negative and agency provides care for people with infectious TB (tuberculosis). Otherwise, annual TST (tuberculin skin testing) is not necessary [G]. **Clients**: NA (not applicable)
Adult day care centres	Refer to recommendations for long-term care (LTC (long-term care)) above.	NR (no recommendation for ACH)	Refer LTC (long-term care) above.	Refer to recommendations for LTC (long-term care) above.

Facility/setting	Administrative controls	Environmental controls [A]	Personal respiratory protection controls	Screening and surveillance [B]
Homeless shelters **Drop-in centres** **Addiction treatment centres**	TB (tuberculosis) management program. Educate staff on TB (tuberculosis) symptoms, risk factors and infection prevention and control measures. Head-to-foot bed arrangement. Incentives and enablers may be considered to encourage resident screening for LTBI (latent TB infection). People with infectious TB (tuberculosis) should be immediately placed in a separate room, transported to an appropriate health care facility and returned only when they are no longer infectious.	CTS (Canadian Thoracic Society): 6 or 0.708 m^3/min/person [J]. CSA: NR (no recommendation for ACH) CDC (Centers for Disease Control and Prevention) (Centers for Disease Control and Prevention): 25 cubic feet of outside air/minute/person FGI/ASHRAE: NR (no recommendation for ACH) Maintenance and upgrade of HVAC (heating, ventilation and air conditioning) filter units as required. UVGI (ultraviolet germicidal irradiation) [L] Use of natural ventilation where no mechanical ventilation exists	Respirators for HCW (healthcare workers)s performing medical assessment of people with infectious TB (tuberculosis) prior to transfer for medical care [D]. Mask for people with infectious TB (tuberculosis) pending and during transport to a health care facility.	**Employees/volunteers [E]:** Baseline screening upon hire or placement using two-step TST (tuberculin skin testing) [F]. Annual TST (tuberculin skin testing) if negative [G].

Facility/setting	Administrative controls	Environmental controls [A]	Personal respiratory protection controls	Screening and surveillance [B]
		and weather permitting.		**Clients**: Refer to Chapter 13, Tuberculosis Surveillance and Screening in High-risk Populations, for information on which individuals should be screened. In outbreaks consider outbreak case finding.
Correctional facilities	Airborne precautions (refer to Figure 1 legend) for people with infectious TB (tuberculosis) until deemed no longer infectious. Supervised therapy for people with infectious TB (tuberculosis). Educate inmates on importance of completing therapy and on precautions. High index of suspicion for active respiratory TB (tuberculosis). If possible, separate housing of symptomatic new inmates until screened for respiratory TB (tuberculosis) disease. Health teaching for people with respiratory TB (tuberculosis) disease to increase isolation and treatment adherence.	General inmates areas: CTS (Canadian Thoracic Society): 2 ACH (air changes per hour) CSA: NR (no recommendation for ACH) CDC (Centers for Disease Control and Prevention) (Centers for Disease Control and Prevention): 6-12 ACH (air changes per hour) FGI/ASHRAE: NR (no recommendation for ACH) AIIR (airborne infection isolation room) : Refer to Table 2	Respirators for HCW (healthcare workers)s and prison staff in contact with people with infectious TB (tuberculosis) [D]. Mask for people with infectious TB (tuberculosis) if not in AIIR (airborne infection isolation room) or during transport.	**Employees/volunteers:** Baseline screening upon hire or placement using two-step TST (tuberculin skin testing) [E]. Baseline assessment for signs, symptoms and risk factors for TB (tuberculosis). Annual TST (tuberculin skin testing) if negative [G]. Annual assessment for signs and symptoms of active TB (tuberculosis) disease.

Facility/setting	Administrative controls	Environmental controls [A]	Personal respiratory protection controls	Screening and surveillance [B]
		for ACH (air changes per hour) recommendations for non-isolation rooms and AIIR (airborne infection isolation room) in the infirmary. HEPA (high-efficiency particulate air) filtration [K]. UVGI (ultraviolet germicidal irradiation) [K]		**Inmates**: If >1 year stay, baseline screening at admission using two-step TST (tuberculin skin testing) [F]. Returning inmates receive a single-step TST (tuberculin skin testing). Annual TST (tuberculin skin testing) thereafter (if TST (tuberculin skin testing) negative) and assessment of risk factors for active TB (tuberculosis) disease [G]. Annual assessment of signs and symptoms for inmates with positive TST (tuberculin skin testing) or history of TB (tuberculosis), and medical examination for inmates with symptoms of active TB (tuberculosis) disease. If <1 year stay, assess for symptoms and signs of TB (tuberculosis), past history of TB (tuberculosis) and known immunosuppression at admission. If any of these is present, chest radiography and medical evaluation should be done.

Table 4. Legend

AIIR (airborne infection isolation room)
airborne infection isolation room

ACH (air changes per hour)

Facility/setting	Administrative controls	Environmental controls [A]	Personal respiratory protection controls	Screening and surveillance [B]

air changes per hour

NA (not applicable)
not applicable

NR (no recommendation for ACH)
no recommendation for ACH (air changes per hour)

A
Recommendations for ACH (air changes per hour) are from the Canadian Thoracic Society (CTS (Canadian Thoracic Society)), [15] Canadian Standards Association (CSA), [36] US Centers for Disease Control and Prevention (CDC (Centers for Disease Control and Prevention) (Centers for Disease Control and Prevention)), [7] [68] [69] and Facilities Guidelines Institute/American Society of Heating Refrigeration and Air-conditioning Engineers (FGI/ASHRAE) [37]. Consult the reference document for complete ACH (air changes per hour) recommendations prior to implementing.

B
If an exposure episode occurs in any of the settings in this table, post-exposure screening should be conducted. Refer to Chapter 4, Diagnosis of Latent Tuberculosis Infection, and Chapter 12, Contact Follow-up and Outbreak Management in Tuberculosis Control, for information on post-exposure TST (tuberculin skin testing) protocol and contact investigation respectively. It is recommended that the investigation be done in close collaboration with the local public health/TB (tuberculosis) control authorities.

C
Various facility operators can contact their regional public health office for resources that can be used to educate staff on control measures for TB (tuberculosis). Some educative materials can be found at the Curry International Tuberculosis Center, About TB (tuberculosis) External Link, website.

D
Respirators should be NIOSH (National Institute for Occupational Safety and Health) (National Institute for Occupational Safety and Health)-certified and filter at least 95% of particles of diameter 0.3 micron or larger with less than a 10% leak (e.g. N95 respirators).

E
A regular volunteer may be defined as one who expects to work 150 or more hours during the coming year, meaning approximately a half day per week. Volunteers expecting to work less than 150 hours during the coming year should be tested if they are known to belong to an at-risk population group listed in the section "Identification of patients with active respiratory TB (tuberculosis) within hospitals" in this chapter. If volunteers have a history of active TB (tuberculosis), or a history of a chest x-ray suggesting possible past TB (tuberculosis), or have symptoms consistent with active TB (tuberculosis) (fever, cough for more than 2 weeks with or without fever, unexplained weight loss, hemoptysis, loss of appetite and night sweats), they should be referred for full medical evaluation rather than simply a TST (tuberculin skin testing).

F
A one-step TST (tuberculin skin testing) may be given to people who meet the following criteria: (1) documented results of a prior two-step TST (tuberculin skin testing) with a result of <10 mm at any time in the past, (2) documented, single negative TST (tuberculin skin testing) result within the past 12 months or (3) two or more documented negative TST (tuberculin skin testing) results at any time, the most recent one being less than 12 months ago. If prior results exist, these should be transcribed into the person's health record. Staff with a positive TST (tuberculin skin testing) at baseline screening do not need to be re-tested but should be assessed by a physician knowledgeable in the treatment of LTBI (latent TB infection). Such staff should also be instructed to promptly report any symptoms suggesting TB (tuberculosis) disease, such as cough of more than 2 weeks' duration with or without fever, night sweats or weight loss.

G

Facility/setting	Administrative controls	Environmental controls [A]	Personal respiratory protection	Screening and surveillance [B]
Refer to Chapter 4, Diagnosis of Latent Tuberculosis Infection, for TST (tuberculin skin testing) protocol. If a HCW (healthcare workers) or staff member has an exposure episode following which he/she is tested as a contact of a person with confirmed active respiratory TB (tuberculosis) and found negative, the HCW (healthcare workers) or staff's next annual test should be 12 months after the negative result. All TST (tuberculin skin testing) conversions should be reported to the local public health authority, as this may be indicative of TB (tuberculosis) transmission within a facility. HCW (healthcare workers) or staff with a positive TST (tuberculin skin testing) on annual screening should be assessed by a physician knowledgeable in the treatment of LTBI (latent TB infection). They should also be instructed to promptly report any symptoms suggesting TB (tuberculosis) disease (as per jurisdictional requirements), such as cough of more than 2 weeks' duration with or without fever, night sweats or weight loss.				

H

Applies to people known to belong to an at-risk population group listed in the section "Identification of patients with active respiratory TB (tuberculosis) within hospitals" in this chapter.

I

The decision to routinely screen (annually or otherwise) should be based on past incidence of active TB (tuberculosis) in the resident population served by the institution. For example, were there any active TB (tuberculosis) cases within the past 10 years?

J

Natural ventilation recommended for areas frequented by clients, use whichever is higher.

K

Adjunctive use of HEPA (high-efficiency particulate air) filtration units and UVGI (ultraviolet germicidal irradiation) can be considered in AIIR (airborne infection isolation room)s, especially in older correctional facilities where it is not practical or feasible to achieve the recommended levels of natural ventilation.

L

Shelters that cannot afford upgrades to their HVAC (heating, ventilation and air conditioning) systems to provide recommended air exchange rates should consider appropriately placed UVGI (ultraviolet germicidal irradiation) systems, as these can achieve equivalent air exchanges at a fraction of the cost [64].

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Chapter 2: Canadian Tuberculosis Standards 7th Edition: 2014 – Pathogenesis and transmission of Tuberculosis

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Chapter 2 - Pathogenesis and Transmission of Tuberculosis

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Chapter 2 - Pathogenesis and Transmission of Tuberculosis

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Key Messages/Points

- Infection with *Mycobacterium tuberculosis* is acquired by inhalation of bacilli-containing droplet nuclei small enough (diameter 1-5 microns) to reach the alveoli.
- Through innate immune mechanisms, alveolar macrophages eradicate the bacteria in some individuals; in others, the bacteria are able to replicate and establish tuberculosis (TB) infection. Bacterial factors and host genetic factors that promote or limit acquisition of infection are not well understood.
- After infection with *M. tuberculosis*, early primary TB (tuberculosis) disease develops in 5% of people unless they first receive treatment for latent infection. Rapid progression to primary active TB (tuberculosis) is most frequent in infants and young children, and in people with immune compromise.
- In another 5% of infected people there is later development of reactivation TB (tuberculosis) in the absence of treatment for latent TB (tuberculosis) infection (LTBI (latent TB infection)). Risks are much higher for people with immune compromise, notably HIV infection.
- In the remaining 90% progression to active disease never occurs.
- Intact cell-mediated immunity (CMI (cell-mediated immunity)) is required to control and contain *M. tuberculosis* infection. Beyond evident clinical and radiographic risk

factors, it is impossible to predict which infected people will ultimately develop active TB (tuberculosis).

- Transmission of *M. tuberculosis* occurs, with very few exceptions, via droplet nuclei, which can then be inhaled by those who are exposed. For this reason, only those with active pulmonary and/or laryngeal TB (tuberculosis) are likely to be contagious.
- The probability of transmission increases with the following:
  - bacterial burden (smear positivity), cavitary and upper lung zone disease, and laryngeal disease;
  - amount and severity of cough in the source case;
  - duration of exposure;
  - proximity to the source case;
  - crowding and poorer room ventilation;
  - delays in diagnosis and/or effective treatment.
- The most effective way to reduce transmission is to diagnose and treat patients with active TB (tuberculosis) disease as soon as possible.

Pathogenesis

The pathogenesis and transmission of TB (tuberculosis) are inter-related. *M. tuberculosis* is almost exclusively a human pathogen. How it interacts with the human host determines its survival. From the perspective of the bacterium a successful host-pathogen interaction is one that results in pathogen transmission. Initial infection is usually self-limited and followed by a variable period of latency, which ultimately, in a proportion of those infected, results in infectious pulmonary TB (tuberculosis). Transmission from a case of infectious pulmonary TB (tuberculosis) is by the airborne route in minute droplets of moisture that become increasingly reduced by evaporation, creating "droplet nuclei" [1].

Evolution of Initial Infection and Host Response

At the time of initial infection, the distribution of inhaled droplet nuclei in the lung is determined by the pattern of regional ventilation. It thus tends to follow the most direct path to the periphery and to favour the middle and lower lung zones, which receive most of the ventilation [2]. In immunocompetent hosts, it is theorized that alveolar macrophages ingest the *M. tuberculosis* organisms and may or may not destroy them, depending on the degree to which phagocytosing cells are nonspecifically activated, on host genetic factors

and on resistance mechanisms in the bacteria [3]. If bacteria are successfully cleared, then test results will remain negative on the tuberculin skin test (TST (tuberculin skin test)) or interferon-gamma release assay (IGRA (interferon-gamma release assay)).

When innate macrophage microbicidal activity is inadequate to destroy the initial few bacteria of the droplet nucleus they replicate logarithmically, doubling every 24 hours until the macrophage bursts to release the bacterial progenyFootnote 3. New macrophages attracted to the site engulf these bacilli, and the cycle continues. The bacilli may spread from the initial lesion via the lymphatic and/or circulatory systems to other parts of the body. After a period lasting from 3 to 8 weeks the host develops specific immunity (cell-mediated immunity [CMI] and delayed-type hypersensitivity [DTH]) to the bacilli, and individuals typically show positive results on the TST or IGRA. The resulting M. tuberculosis-specific lymphocytes migrate to the site of infection, surrounding and activating the macrophages there. As the cellular infiltration continues, the centre of the cell mass, or granuloma, becomes caseous and necrotic. Radiographically demonstrable fibrocalcific residua of the initial infection include a Ghon focus (a calcified granuloma in the lung) alone or in combination with a calcified granulomatous focus in a draining lymph node (Ghon complex)Footnote 4 Footnote 5. Infection and immune conversion are usually asymptomatic; any symptoms that do occur are self-limited. In a small proportion of those infected, erythema nodosum (a cutaneous immunologic response to an extracutaneous TB infection) or phlyctenular conjunctivitis (a hypersensitivity reaction) may develop.

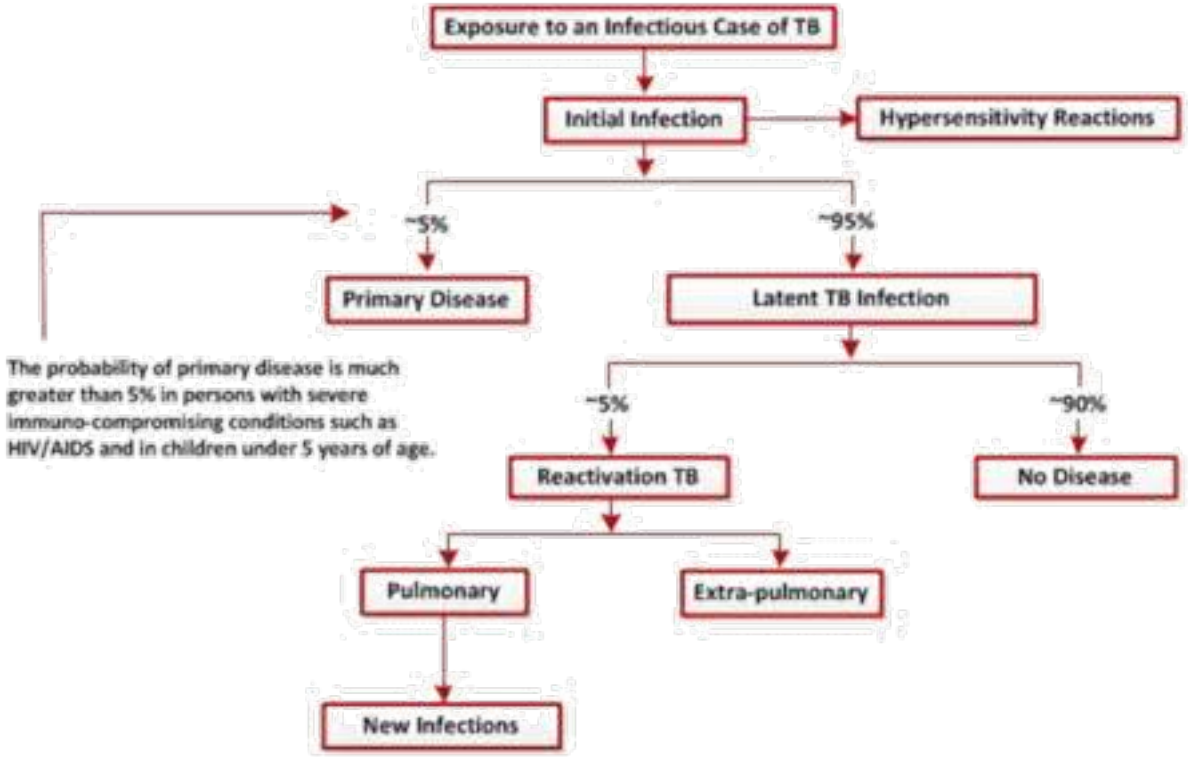
Early Disease Progression (Primary TB (tuberculosis))

A proportion of those who are recently infected are unable to contain the infection despite the stimulation of CMI (cell-mediated immunity) and DTH, and there is progression to disease in a matter of months. Such early disease progression is a function of age and immunologic response, disease being especially likely to occur in young children and the immunocompromised. A progressive Ghon focus, disseminated (miliary) disease and central nervous system disease may occur as early as 2 to 6 months after infection in infants and the severely immunocompromised [6] [7]. Uncomplicated and asymptomatic lymph node disease (hilar or mediastinal lymphadenopathy without airway involvement) may also occur in the first 2-6 months of infection, although there is debate about whether this should be called active disease (refer to Chapter 9, Pediatric Tuberculosis) [6] [8].

At 4-12 months after infection, early disease manifestations include complicated lymph node disease (airway compression, expansile caseating pneumonia, infiltration of adjacent anatomic structures), pleural disease (most commonly a lymphocyte-predominant exudative effusion) and peripheral lymphadenitis (usually in the neck) [6]. In immunocompetent children and adolescents early disease is more likely to manifest as intrathoracic adenopathy and in adults as a unilateral pleural effusion. In severely immunocompromised people of any age (e.g. those with advanced HIV or AIDS), early disease may manifest as intrathoracic adenopathy [9] [10]. Rarely, in newly infected people who are 10 years of age or older (pubertal) adult-type pulmonary disease (refer to Figure 1) or other types of extrapulmonary TB (tuberculosis) (for example bone and joint TB (tuberculosis)) may develop within the first 24 months of infection [11].

While early disease progression may or may not result from lympho-hematogenous spread, late disease progression (refer to Figure 1) is almost always the result of the lympho-hematogenous spread of bacilli. Recent infection with early disease progression probably accounts for many cases of TB (tuberculosis) in recently arrived immigrants [12]. For purposes of disease reporting, everyone with a diagnosis of TB (tuberculosis) made within 18-24 months of infection is considered to have "primary" disease (on balance about 5% of those infected). Those newly infected people in whom TB (tuberculosis) does not develop within this period of time will either be left with LTBI (latent TB infection) and will never experience disease (on balance about 90% of those infected) or, after a variable period of latency, they will develop late disease progression (on balance about 5% of those infected, refer to Figure 1).

Figure 1. The Pathogenesis of Tuberculosis in the Infected Host
(Adapted from the 6th Edition of the Canadian TB (tuberculosis) Standards)



▶ Text Equivalent - Figure 1

Latent Tuberculosis Infection (LTBI (latent TB infection))

In the classical concept of LTBI (latent TB infection), *M. tuberculosis* bacteria are believed to survive for years in Ghon foci and complexes and in the small granulomas or solid caseous material of lympho-hematogenously seeded foci. Presumably, local conditions, an intact CMI (cell-mediated immunity) or the presence of inhibitors result in conditions unfavourable to replication. Recent mapping of the complete genome sequence of the bacterium demonstrates that the organism has the potential to synthesize enzymes involved in anaerobic metabolism [13]. Although rapid death and autolysis occur after abrupt depletion of oxygen, the organism can shift into a state of dormancy if allowed to settle through gradual reductions in oxygen tension [14] [15]. Therefore, although *M. tuberculosis* thrives in an aerobic environment, it possesses the genetic and biochemical capability of anaerobic survival and can persist experimentally in oxygen-depleted media. Tubercle formation, with its oxygen-depleted environment, is a defining characteristic of TB (tuberculosis). LTBI (latent TB infection) is usually identified by a positive TST (tuberculin skin test) or IGRA (interferon-gamma release assay) in the absence of active disease (refer to Chapter 4, Diagnosis of Latent Tuberculosis Infection).

More recently LTBI (latent TB infection) and active TB (tuberculosis) have been considered as two ends of a spectrum of states ranging from asymptomatic infection to overt disease [16] [17]. In this more nuanced concept, patients whose LTBI (latent TB infection) progresses to overt disease may pass through a continuum of asymptomatic intermediate states with detectable manifestations indicative of disease [16]. Such asymptomatic disease states frequently remain undiagnosed, and their manifestations and duration are mostly dependent on host immune response. Defining these intermediate states in concrete terms is considered to be important for pragmatic reasons, as they might have an impact upon the performance of TB (tuberculosis) biomarkers or other diagnostic measures and could also present targets for therapeutic interventions [16] [18].

Reinfection

The elegant studies of Ferguson strongly suggest that it takes up to 18 months after the initial infection for CMI to matureFootnote 19. During this period of time a reinfection carries the same risk of disease as the initial infection, perhaps explaining why disease is much more common in newly infected close contacts of smear-positive cases than it is in newly infected close contacts of smear-negative cases - the former having a greater likelihood than the latter of repeated exposure and reinfectionFootnote 20-22. Reinfection of immunocompetent hosts that occurs 18 months or more after the initial infection carries a much lower risk of progression to TB disease, estimated to be 21% of the risk of an initial infection progressing to diseaseFootnote 22. It is not known whether this is because prior infection without development of overt disease is simply a marker for people who are less susceptible to disease development or better able to overcome it once it has developed. Nevertheless, in highly endemic areas the majority of TB cases occurring in those with prior LTBI may be due to reinfection rather than reactivation; in Canada, where repeat exposure is much less common, most active TB reflects reactivation and not reinfectionFootnote 23-25. In the severely immunocompromised host, reinfection and initial infection carry a similarly high risk of disease regardless of when the reinfection occurred (refer to Chapter 6, Treatment of Latent Tuberculosis Infection).

Late Disease Progression (Reactivation TB (tuberculosis))

In Canada, most TB (tuberculosis) is understood to be "reactivation" TB (tuberculosis), i.e. occurring 18-24 months or more after the initial infection. It usually presents as adult-type pulmonary disease (upper lung zone fibrocavitary disease - previously referred to as postprimary TB (tuberculosis) - beginning in small foci that are the result of remote lympho-hematogenous spread), although it may also present as extrapulmonary TB (tuberculosis). As mentioned earlier, adult-type pulmonary TB (tuberculosis) may on occasion be a manifestation of primary TB (tuberculosis) or a reinfection. In any population group, reactivation of LTBI (latent TB infection), leading to reactivation TB (tuberculosis), is much more likely to occur in people who are immunocompromised.

There are a number of theories, most of them speculative, as to why adult-type pulmonary TB (tuberculosis) tends to localize in the upper lung zones. These are described elsewhere [2] [5]. People with a history of untreated or inadequately treated pulmonary TB (tuberculosis) or a "high-risk" lung scar (upper lung zone fibronodular abnormality) on chest radiograph are understood to have a higher bacillary burden than those without such a history/radiograph, and to be at increased risk of reactivation TB (tuberculosis) [26] [27].

From the standpoint of public health and the organism's survival as a species, adult-type pulmonary TB (tuberculosis) is the most important phenotypic expression of the disease. Patients with adult-type pulmonary TB (tuberculosis) are much more likely to show lung cavitation, created when caseous material liquefies (possibly related to hydrolytic enzymes released from inflammatory cells during their destruction and DTH to tuberculin-like proteins) and erodes into the bronchi [28]. Within the unique extracellular environment of cavities, host defences are ineffectual, and bacteria multiply in large numbers. Because cavities are open to, and discharge their contents into, nearby bronchi these same bacteria are directly communicable to the outside air when the patient coughs. Transmission from patients with adult-type pulmonary TB (tuberculosis) is facilitated by the concurrent involvement of both the airways and their contiguous pulmonary blood supply at sites of disease in the lung. This minimizes the respiratory limitation experienced by the patient, extending the life of the host within the community and creating further opportunities for transmission before the patient either seeks medical attention or succumbs [29].

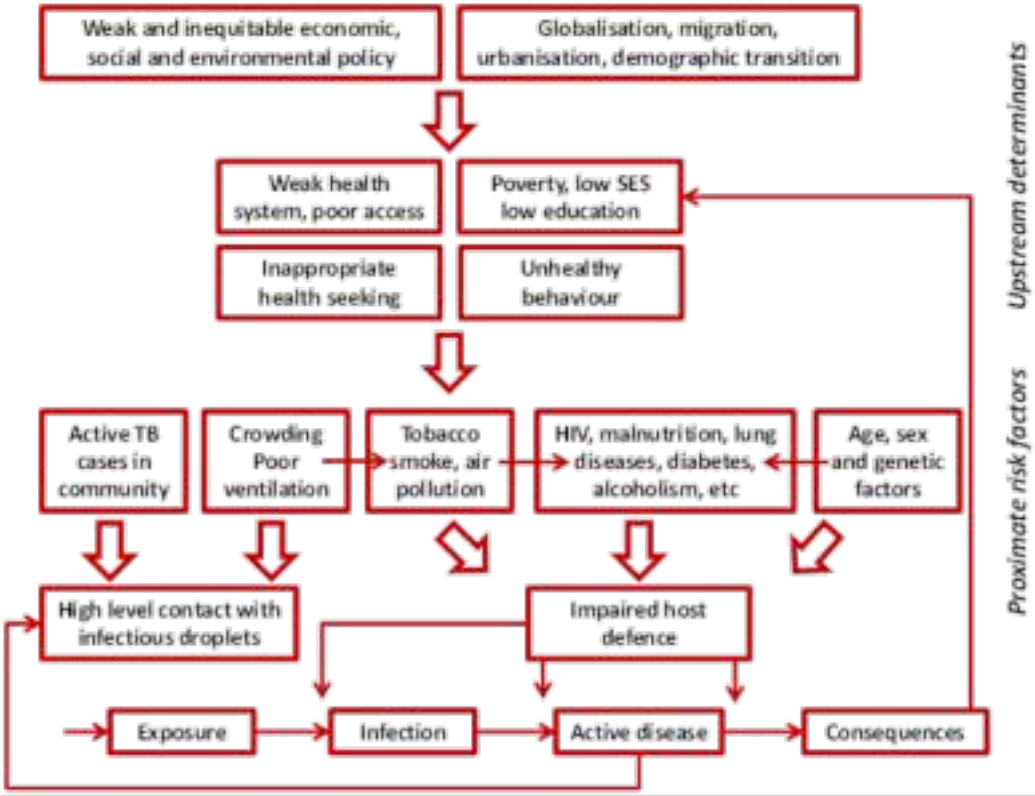
Extrapulmonary TB (tuberculosis)

Outside of the extrapulmonary sites of disease alluded to in the section Early Disease Progression and cases of bone and joint TB, whose timeline from infection to disease in children may be as short as a year, most extrapulmonary TB is reactivation disease. Extrapulmonary TB or combined pulmonary and extrapulmonary TB is more common in those who are severely immunocompromised; in those coinfected with HIV the occurrence of extrapulmonary TB increases as the CD4 count decreases (refer to Chapter 7, Non-respiratory Tuberculosis)Footnot9 Footnote 10.

Risk Factors for Progression from Infection to Disease

The risk of transition from LTBI (latent TB infection) to active TB (tuberculosis), primary or reactivation, is largely dependent on the immune competency of the host. Age and sex appear to directly affect the immunologic response and the risk of disease: morbidity is greater among young children (<5 years of age), especially infants, among young adults, especially females, and among older adults, especially males. In high-burden countries, the population attributable fraction of undernutrition for TB (tuberculosis) is 27% according to the WHO [30]. The seasonality of TB (tuberculosis) (with the highest incidence in spring and early summer) has been attributed to reduced sunlight and vitamin D deficiency during the winter months in some studies but not in others [31-33]. Ethnic differences have been offered as factors determining host immune response, with some support [34], but differences among ethnic groups in all clinical forms of TB (tuberculosis) are probably best explained as phase differences in an epidemic wave [35]. All races initially exposed in an epidemic as a group are equally susceptible, but eventually death and survival outcome select out people who are relatively more resistant. A growing body of evidence suggests that host genetic factors are important in determining susceptibility to TB (tuberculosis) [36-38]. Most important from a clinical perspective are the many medical conditions that are well known to affect host immunologic response and increase the risk of progression from LTBI (latent TB infection) to active TB (tuberculosis) disease. These are reviewed in detail in Chapter 6, Treatment of Latent Tuberculosis Infection. To identify entry points for interventions aimed at addressing TB (tuberculosis) risk factors as well as social determinants, Lönnroth and colleagues developed a framework for proximate risk factors and upstream determinants of TB (tuberculosis) (refer to Figure 2) [39].

Figure 2. Framework for proximate risk factors and upstream determinants of TB (tuberculosis) [39]



▶ Text Equivalent - Figure 2

Transmission [40-43]

M. tuberculosis is communicable from one human to another mainly by the aerosol route and rarely through ingestion or percutaneous inoculation (e.g. through laboratory or hospital accident). Bovine TB (tuberculosis), which in the past was caused by ingestion of milk heavily infected by *M. bovis* that then penetrated the mucosa of the oropharynx or the gastrointestinal tract, has been largely eradicated as a result of the pasteurization of milk and the tuberculin testing of cattle, followed by the slaughter of animals found to be infected.

The reservoir for M. tuberculosis is humans. Other animals, in particular primates, may be infected but are rarely a source of infectionFootnote 40-43. Droplet nuclei, sometimes referred to as "the quanta of contagion", are created by forceful expiratory efforts, such as coughing, sneezing, singing, playing wind instruments and even speaking. Before droplets reach the airspace of a room and have had an opportunity to evaporate down to a "droplet nucleus" their numbers can be reduced by wearing a simple gauze (surgical) mask or covering the mouth and nose during coughing. Certain procedures, for example, bronchoscopy, sputum induction, processing of specimens, autopsy and

even irrigation or other manipulation of tuberculous abscesses, may also produce infectious aerosols. The droplets have an extremely slow settling rate (0.5 mm per second or less), which permits their transport by air currents, duct systems or elevator shafts for significant distances from the source case. Large particles settle quickly and are either not inhaled by contacts or, if inhaled, are trapped in the mucus of the upper airway. If the organism reaches the trachea and bronchi it is usually swept back to the larynx by ciliary action and cough, and then swallowed. For practical purposes, only the droplet nuclei in the size range 1 to 5 microns reach the terminal air spaces or alveoli; each is understood to contain only a few bacteria. In most instances only one such droplet nucleus is believed to be responsible for establishing infection in the host. Bacteria that are lodged on fomites (linen, furniture, books, floors) do not constitute a significant source of infection: most die quickly through the action of drying, heat or sunlightFootnote 5 Footnote 40-43.

The rate of transmission can be measured by the percentage of close contacts (household and non-household) whose TST (tuberculin skin test) or IGRA (interferon-gamma release assay) responses are converted from negative to positive or in whom active TB (tuberculosis) disease develops. The percentage will depend on the number of infectious droplet nuclei per volume of air (infectious particle density) and the length of time that the uninfected individual spends breathing that air. In the past, drug susceptibility patterns and phage typing of *M. tuberculosis* isolates have helped to confirm the transmission between source case and contact. More recently, DNA fingerprinting of *M. tuberculosis* isolates has greatly refined the identification of this relation [44].

Because of the highly variable latency period of *M. tuberculosis* infection it is difficult to precisely document transmission using currently available tools. People found to have positive TST (tuberculin skin test)s and/or IGRA (interferon-gamma release assay)s during contact investigation may have been infected in the past (remotely) rather than by the recent source case of concern, though for contact management and public health purposes these contacts are treated as if recently infected if there is no way to determine the duration of infection. DNA fingerprinting techniques will only detect transmission to the small group of people in whom active disease develops following transmission. If most TB (tuberculosis) disease in a community reflects recent/ongoing transmission, the first priority for public health authorities should be to prevent further

transmission. On the other hand, if most TB (tuberculosis) reflects reactivation of remotely acquired infection, the priority should shift to identification and treatment of people with LTBI (latent TB infection), notably those with risk factors for reactivation.

Patient, Pathogen and Environmental Determinants of Transmission

Several patient, pathogen and environmental factors determine whether transmission occurs, largely by affecting the number of infectious droplet nuclei per volume of air (refer to Table 1). Although the probability of being infected after contact with an infectious source decreases with decreasing duration and decreasing closeness of contact, the absolute number of casual contacts infected may exceed the number of infected close contacts, since the former may far outnumber the latter [45]. DNA fingerprint data have highlighted the limits of contact tracing in settings where there is exposure of a large number of people unknown to source cases and in settings where social connections are tenuous at best [46] [47]. At this point very little is known about what, if any, host determinants influence the acquisition of initial infection after inhalation of a droplet nucleus. Some individuals are able to achieve complete or "sterile" elimination of *M. tuberculosis* bacteria rather than developing latent infection [48]. Observational studies suggest that BCG vaccination in infancy offers some protection against infection with *M. tuberculosis* as detected by an IGRA (interferon-gamma release assay) [49-52].

Table 1. Patient, pathogen and environmental factors affecting transmission

Patient	Pathogen	Environment
Disease type	Strain variability	Indoor/outdoor
Pulmonary Smear-positive/smear-negative Cavitary/non-cavitary on CXR [A] Typical/atypical on CXR Laryngeal		Air circulation/ventilation Sunlight
Extrapulmonary		Proximity to the source case
Symptomatology		Duration of exposure
Delayed diagnosis		

[A]CXR = chest radiograph

Patient	Pathogen	Environment
Treatment		
ACXR = chest radiograph		

Patient Factors

With rare exception (e.g. transmission related to an inadequately sterilized bronchoscope or a needle stick injury), transmission requires that a TB (tuberculosis) patient be able to produce airborne infectious droplets [41-43]. This most often limits the potential for transmission to adolescent or adult patients with adult-type pulmonary TB (tuberculosis). Younger children can on occasion be infectious [53], but as a general rule they have few bacilli in their lesions, often do not produce sputum and rarely have communicable disease [54]. Of patients with TB (tuberculosis) involving the respiratory tract not all are equally efficient at transmission.

1. Sputum smear status

Patients with smear-positive/culture-positive pulmonary TB (tuberculosis) are more infectious than patients with smear-negative/culture-positive pulmonary TB (tuberculosis), and the latter are more infectious than patients with smear-negative/culture-negative pulmonary TB (tuberculosis) (refer to Table 2 for a summary of the epidemiologic studies on the risk of infection in household [close] contacts grouped according to the bacteriologic status of the source cases) [55-62]. Sputum that is smear-positive contains 5,000 or more organisms per millilitre of sputum [57] [58] [63] [64] Patients with smear-positive bronchoalveolar lavage fluid are considered just as infectious as those with smear-positive sputum [65]. Smear-positive induced sputum is for practical purposes considered to indicate the same degree of contagiousness as smear-positive spontaneously expectorated sputum, though there are currently no data that prove this assertion [55]. With the use of molecular epidemiologic tools the relative transmission rate of smear-negative compared with smear-positive patients has been determined to be 0.17-0.22 or roughly one-fifth the likelihood of transmission [66] [67]. In addition to the greater infectivity of smear-positive cases, as mentioned in the section Pathogenesis, the risk of disease after infection from a smear-positive case is greater, by virtue of the higher probability of repeated infection, than it is after infection from a smear-negative case.

Table 2. [A] Risk of infection among household (close) contacts according to bacteriologic status of index case (pulmonary TB (tuberculosis) only)

Ref no.	Year of survey	Location	Contacts		Number and % infected contacts by bacteriologic status of index case						General population % positive PPDB [B]
					S+C+		S+C+		S+C+		
			Age	Total no.	N	%+	N	%+	N	%+	
56	1949-56	England	0-14	545	262	63%	126	21%	157	18%	13%
57	1950-53	England	0-14	823	374	65%	228	27%	221	18%	22%
58	1963-64	Holland	all ages	858 [C]	391	20%	467	1%	-	-	<< 1%
20	1966-71	Canada-Whites	0-19	2406	1210	38%	655	12%	541	10%	2%
NA	NA	Canada Aboriginals	0-19	1168	592	45%	377	31%	199	27%	NA
59	1967-69	Rotterdam	0-14	134	40	50%	43	5%	51	8%	1%
60	1969	USA	all ages	130	88	44%	14	21%	28	14%	NA
61	1971-74	USA	all ages	761	504	46%	257	28%	-	-	NA
62	1975-77	USA	all ages	541	368	40%	173	27%	-	-	NA

AAdapted from reference number 55

BTaken from the same reference, i.e. a comparable reference population

Ref no.	Year of survey	Location	Age	Contacts: Total no.	Number and % infected contacts by bacteriologic status of index case: S+C+ N	S+C+ %	S-C+ N	S-C+ %	S+C+ N	S+C+ %	General population % positive PPD[B]

[B] taken from the same reference, i.e. a comparable reference population.

[C] In this study contacts were considered infected only if tuberculin conversion and/or primary TB (tuberculosis) had been documented.

S = smear, C = culture, PPD = purified protein derivative

2. Disease type on plain chest radiograph

Pulmonary TB (tuberculosis) patients with cavitation on chest radiograph are more infectious than pulmonary TB (tuberculosis) patients without cavitation after bacteriologic findings have been taken into account [68-70]. Pulmonary TB (tuberculosis) patients with "typical" chest radiographic findings (upper lung zone disease, with or without cavitation, and no discernable intrathoracic adenopathy) are more infectious than pulmonary TB (tuberculosis) patients with "atypical" chest radiographic findings (all others) [71].

3. Laryngeal disease

Patients with laryngeal TB (tuberculosis) are more infectious than those with pulmonary TB (tuberculosis) [72]. Most patients with laryngeal TB (tuberculosis) (hoarseness associated with inflammation and ulceration of the vocal cords) have far advanced pulmonary disease upstream from the larynx [73].

4. Symptomatology

In general, normal breathing produces few infectious particles, a bout of coughing or five minutes of speaking in a normal tone produce many more, and a sneeze produces the most [74] [75]. The likelihood that household contacts will be infected increases with the frequency of cough in the source case [60]. When the aerial infectivity of the droplets from smear-positive patients was evaluated by artificially atomizing sputum and exposing guinea pigs to a standard dose, there was marked variability in the infectivity of aerosolized sputum, perhaps explaining the extraordinary heterogeneity of infectiousness among patients with smear-positive pulmonary TB (tuberculosis) [76-78]. Thus, although patients may appear to have an equal number of bacteria in their sputum, the physical and chemical properties of their sputum, as well as their effectiveness as an aerosolizer, may determine whether they produce a large or small number of droplet nuclei. The role of smoking, allergy or coincidental viral upper respiratory tract infection in aerosol formation is unknown [79].

5. Delayed diagnosis

The number of contacts and the duration of exposure of each contact may increase as time to diagnosis increases. The longer the duration of symptoms in the source case the greater the risk of transmission [65].

6. Treatment

Effective treatment (refer to Chapter 5, Treatment of Tuberculosis Disease) appropriate to the drug susceptibility test results rapidly reduces cough frequency and sputum bacillary counts [60] [80]. Even faster than the rate of decrease of the latter is the rate of decrease of bacillary counts in cough-generated aerosol cultures [81]. With treatment those bacteria that continue to be expectorated may be expected to be less metabolically active and/or are inhibited by the drugs, two effects that may decrease the chances of the organism establishing an infection in the host [76] [82]. However, in theory, any residual viable bacteria in respiratory secretions can be transmitted, although the chances of this occurring decrease rapidly with effective treatment [83]. Given the frequency of drug resistance, the determination that treatment is effective in reducing the infectiousness of a given patient should reflect objective clinical, radiographic and/or microbiologic improvement, and not simply time elapsed since treatment initiation.

Pathogen Factors

Data are emerging to suggest that one or more virulence properties of *M. tuberculosis* may affect its ability to be transmitted [84]. For example, one strain may be better suited than another to overcoming the innate resistance of the host. Although drug-resistant strains have shown reduced virulence in animal models [85], clinical evidence of their transmissibility is compelling [86-89], and for practical purposes they should be considered just as transmissible as drug-susceptible strains. Beijing/W strains have been reported to be hypervirulent, but indices of transmission have been found to be no greater in patients with these strains than in those without them [90].

Environmental Factors

Outdoor exposures are very unlikely to result in transmission unless the source and the susceptible person are in talking distance. Bacillary dispersion is immediate, and sunlight rapidly kills any viable bacilli [91] [92]. For practical purposes outdoor exposures are not investigated during a contact tracing exercise.

1. Air circulation and ventilation

Given a defined number of bacteria expelled into the air, the volume of air into which the bacteria are expelled determines the probability that a susceptible individual breathing that air will become infected. A high concentration of viable bacteria in the inhaled air of the contact is favoured by indoor exposure, poor ventilation or recirculation of air, and little sunlight (ultraviolet rays). Ventilation dramatically dilutes the concentration of infectious droplet nuclei (refer to Chapter 15, The Prevention and Control of Tuberculosis Transmission in Health Care and Other Settings, for further information on clearance times).

2. Proximity to the source case

Proximity to the source case is also a determinant of transmission. Related to this is overcrowding: if, as a result of there being many people in a room, an individual is forced into close proximity with an infectious case his or her risk of infection is likely to increase.

3. Duration of exposure

Because of the dilution of infected air and the low concentration of infectious droplet nuclei, the duration of exposure required to ensure that transmission occurs is commonly prolonged (days, months or even years), and yet reports have confirmed that exposures as short as a few minutes may be sufficient to infect a close contact. The latter would appear to be supported by the high proportion of active cases that deny any history of exposure.

Measures to Prevent Transmission

The highest priority should be given to early diagnosis and prompt, effective treatment of the source case together with isolation of the patient when necessary. The insidious development of symptoms in most cases of TB (tuberculosis) commonly results in a delay of weeks or months before the patient presents for diagnosis. At that point, when the patient is often at his or her most infectious, any further delay caused by the physician, nurse or system allows unnecessary transmission to others. Maintaining an appropriate awareness of TB (tuberculosis) among health care providers is thus critical to reducing transmission and initiating early prevention and treatment. Administrative and engineering controls that aim to reduce exposure in health care and other congregate settings complement--but cannot replace--prompt diagnosis and

appropriate therapy. Methods once thought to be important in preventing the transmission of TB (tuberculosis) - disposing of such personal items as cloths or bedding, sterilizing fomites, using caps and gowns, gauze or paper masks, boiling dishes and washing walls - are unnecessary, because they have no bearing on airborne transmission.

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RESEARCH ARTICLE

Mass Gatherings and Respiratory Disease Outbreaks in the United States – Should We Be Worried? Results from a Systematic Literature Review and Analysis of the National Outbreak Reporting System

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Abstract

Background

Because mass gatherings create environments conducive for infectious disease transmission, public health officials may recommend postponing or canceling large gatherings during a moderate or severe pandemic. Despite these recommendations, limited empirical information exists on the frequency and characteristics of mass gathering-related respiratory disease outbreaks occurring in the United States.

Methods

We conducted a systematic literature review to identify articles about mass gathering-related respiratory disease outbreaks occurring in the United States from 2005 to 2014. A standard form was used to abstract information from relevant articles identified from six medical, behavioral and social science literature databases. We also analyzed data from the National Outbreaks Reporting System (NORS), maintained by the Centers for Disease Control and Prevention since 2009, to estimate the frequency of mass gathering-related respiratory disease outbreaks reported to the system.

Results

We identified 21 published articles describing 72 mass gathering-related respiratory disease outbreaks. Of these 72, 40 (56%) were associated with agriculture fairs and Influenza A H3N2v following probable swine exposure, and 25 (35%) with youth summer camps and pandemic Influenza A H1N1. Outbreaks of measles (n = 1) and mumps (n = 2) were linked to the international importation of disease. Between 2009 and 2013, 1,114 outbreaks were reported to NORS, including 96 respiratory disease outbreaks due to Legionella. None of these legionellosis outbreaks was linked to a mass gathering according to available data.

Conclusion

Mass gathering-related respiratory disease outbreaks may be uncommon in the United States, but have been reported from fairs (zoonotic transmission) as well as at camps where participants have close social contact in communal housing. International importation can also be a contributing factor. NORS collects information on certain respiratory diseases and could serve as a platform to monitor mass gathering-related respiratory outbreaks in the future.

Introduction

Mass gatherings create environments conducive to the transmission of infectious disease including pandemic influenza. [1–11]. Some mass gatherings such as outdoor sporting events may involve limited social mixing and are held in settings with ample ventilation. Other mass gatherings, however, can involve significant social mixing over several days such as professional conferences and music festivals [1–4]. Intensely crowded settings can lead to high secondary attack rates even when a circulating pathogen has a relatively low transmission probability [1–4]. Travelers to mass gatherings can not only introduce an infectious disease to a previously unaffected area, but can also amplify transmission at the gathering and further disseminate transmission following their return home. This was recently demonstrated by the propagation of the first wave of the 2009 H1N1 pandemic (pdm09H1N1) following a large Easter holiday gathering in Iztapalapa, Mexico [6]. Similar mass gatherings have been linked to the propagation of the Great Pandemic in 1918 and the Asian Flu Pandemic in 1957 [7–8].

During future influenza pandemics or other public health emergencies in the United States, state and local public health officials will have to consider modifying, postponing, or cancelling mass gatherings. This decision could depend on the severity of the pandemic as well as the timing, duration and size of the event and whether people will be traveling to and from the event from other (affected or not-yet-affected) communities [12]. If the risk of severe disease is low, then other non-pharmaceutical interventions could be recommended to minimize the potential for disease transmission. Despite these recommendations, limited empirical information exists on the frequency and characteristics of mass gathering-related respiratory disease outbreaks in the United States.

To address this gap, we conducted a systemic review of the published literature and analyzed the National Outbreak Reporting System (NORS) database maintained by the United States (U.S.) Centers for Disease Control and Prevention (CDC) since 2009 [13]. The objectives of this project included describing the frequency of mass gathering-related respiratory disease outbreaks occurring in the United States, highlighting the likely causes of these outbreaks, and documenting any patterns or shared characteristics across the identified outbreaks.

Methods

Data collection

Definitions. Mass gatherings can be defined as large events involving more than 1,000 persons in a specific location for a shared purpose [14]. We applied this definition in our literature review but also included camp sessions of at least 100 participants because the cumulative aggregation of participants over the camp season can easily exceed 1,000 persons. Because NORS does not include a specific field for mass gatherings, we analyzed data from the NORS database

for outbreaks involving person-to-person transmission and transmission at camps, conferences, banquets, sporting events, and religious locations. Information on the setting for outbreaks involving other modes of transmission (e.g. water-borne) is not routinely reported to NORS. For all reported outbreaks, we used the number of persons exposed to approximate size of the mass gathering. We deferred to the author's definition of outbreak in our literature review. Disease events reported to NORS were assumed to meet CDC's outbreak definitions [13].

Systematic Literature Review. Six medical, behavioral, and social science literature databases were searched for relevant articles published from January 1, 2005 to December 31, 2014. These included Medline® (National Library of Medicine) and five non-Medline databases: Embase® (Excerpta Medica Database, Elsevier), Global Health, CAB Abstracts, Web of Science, and Scopus. A CDC reference librarian performed the initial search using the following strategy: ((mass OR public OR large OR general OR sport* OR community OR public) ADJ2 (gather* OR event* OR assembl* OR meeting*)) OR concert* OR theater* OR auditorium* OR amphitheater* OR Olympic* OR (world ADJ cup) OR festival* OR carnival* OR ((country OR county OR state OR world) ADJ fair*) OR world expo OR amusement park* OR cruise ship*AND Influenza OR pneumonia OR SARS OR flu OR H1N1 OR H3N2 OR coronavirus OR tuberculosis OR TB OR ((lung* OR respiratory) ADJ2 (infection* OR virus*)) OR MERS OR measles OR mumps OR acute respiratory syndrome OR legionnaires OR legionella OR infectious OR communicable OR illness OR disease* AND (transmission* OR outbreak OR epidemi* OR pandemic* OR cluster*) AND (at least one of the states in the United States).

To identify publications about outbreaks occurring at recreational, religious, cultural, and academic camps, the same search was repeated using the keywords (camp OR camping) AND Influenza OR pneumonia OR SARS OR flu OR H1N1 OR H3N2 OR coronavirus OR tuberculosis OR TB OR ((lung* OR respiratory) ADJ2 (infection* OR virus*)) OR MERS OR measles OR mumps OR acute respiratory syndrome OR legionnaires OR legionella OR infectious OR communicable OR illness OR disease* AND (transmission* OR outbreak OR epidemi* OR pandemic* OR cluster* OR spread) AND (at least one of the United States). We included "ADJ" as an adjacency operator to command the database to search for a word (or words) near another word within a certain number of words. For example, (mass ADJ2 outbreak) searched for the word "mass" within two words of the word "outbreak" picking up "mass outbreak" OR "outbreak during mass event". The search query varied slightly across the six databases (S1 File).

Only articles written in English were eligible for inclusion. Duplicate articles identified during the initial database search were removed prior to aggregating results in an EndNote file. The titles and abstracts of the remaining articles were reviewed by one person and categorized as relevant if the title included one or a combination of the following terms: mass gathering (or a specific event or setting associated with mass gatherings) and outbreak (or a specific syndrome or infection). The article was also included if the abstract, if available, described information on the occurrence of an infectious disease or illness at a mass gathering (or specific event or setting associated with mass gatherings). Articles on enteric or skin infections were excluded.

We reviewed each article that met the criteria in full. If the manuscript addressed our project objectives, then we completed a standard abstraction form for the article title, publication date, mass gathering name, venue type, dates, location, approximate size, and pathogen involved as well as the number of probable and confirmed cases, age groups of cases, likely outbreak cause and response of mass gathering organizers. At a minimum, each article included in our final analysis described the following: 1) purpose of gathering, 2) month and year of gathering, 3) location or venue type (indoor or outdoor), 4) type of syndrome or infectious disease outbreak, 5) number of confirmed or probable cases, 6) information on the index case(s), and 7) possible cause(s) of the outbreak. If not mentioned in the article, the approximate size of the mass

gathering was obtained by contacting the corresponding author or the mass gathering organizer. All project types were eligible for inclusion including outbreak investigation reports, case series, cross-sectional surveys, case-control studies, and intervention studies. No additional quality criteria for article inclusion were applied due to the variability in the study types [15]. Articles describing modeling studies, outbreaks on conveyances or at schools or businesses, policy papers, and outbreaks occurring before 2005 were excluded. We focused on mass gathering-related outbreaks occurring between 2005 and 2014 to provide a sufficiently long time frame to detect any trends or patterns before, during, and after the 2009 H1N1 pandemic while limiting results from the initial literature search criteria to a manageable size. Information from completed abstraction forms were entered into an Access database and imported into SAS for analysis.

National Outbreak Reporting System. NORS is a web-based national surveillance system for enteric waterborne, foodborne, person-to-person, animal associated, and environmental disease outbreaks as well as non-enteric waterborne outbreaks [13]. Health departments can voluntarily report outbreaks due to any other cause not mentioned above. NORS was fully deployed in 2009 and is maintained by CDC. We analyzed data from the NORS database for outbreaks involving person-to-person transmission that occurred between January 2009 and December 2013. Data describing water-borne outbreak were available through December 2012 only. Other available data included investigation methods, outbreak onset dates, number of exposed participants, total number of confirmed and probable cases, geographic location of the outbreak, and etiology, if known. Data were provided in an Access database and then imported into SAS (version 9.3, Cary, NC) for analysis.

Analysis

We generated descriptive statistics on the frequency, type, size, venue, geographic spread and dates of mass gathering-related respiratory disease outbreaks identified from the literature review and NORS database. Additional qualitative analysis was performed on information abstracted from the literature review on the causes of the outbreaks. No personal identifying information on individual patients was collected.

Ethics Approval

The project was reviewed by CDC's Human Subjects Research Office and approved as a public health evaluation activity.

Results

Published literature

The literature database search resulted in 835 articles (475 and 360 using the general mass gathering and camping keywords, respectively) (Table 1). We identified 54 articles as relevant from the initial review of titles and abstracts and included 9 additional articles identified from the references of these 54 articles. Of these 63 total articles, 21 were included in our analysis following full review [16–36]. We excluded 42 articles primarily because the article did not report a respiratory disease outbreak (n = 18, 43%) or was not related to a mass gathering (n = 9, 21%).

The 21 articles included 18 manuscripts describing 14 individual mass gathering-related respiratory disease outbreaks (the same outbreak could be described in more than one article) and three articles [21, 25, 36] describing pathogen-specific summaries of outbreaks across different settings and included 59 additional mass gathering-related outbreaks (Table 2, S2 File).

Table 1. Categorization of the published literature reviewed for identifying mass gathering-related respiratory disease outbreaks in the United States, January 1, 2005–December 31, 2014.

	General Mass Gatherings	Camps	From References	Total
Literature database search results[a]	475	360	—	835
Relevant from title and abstract review	38	16	9	63
Included following full article review	7	11	3	21
Excluded articles after full review				
Duplicate	3	2	0	5
Not found	0	2	0	2
Not respiratory disease outbreak	17	1	0	18
Not mass gathering	4	0	5	9
Animal health	4	0	1	5
Not in United States	1	0	0	1
Experiment	2	0	0	2

[a]Databases included Medline® (National Library of Medicine) and five non-Medline databases: Embase® (Excerpta Medica Database, Elsevier), Global Health, CAB Abstracts, Web of Science, and Scopus.

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Thus, we identified 72 different mass gathering-related respiratory disease outbreaks. Of these, 1 occurred in 2005, 3 in 2007, 27 in 2009, 1 in 2011, 40 in 2012, and none in 2013 or 2014.

Fairs. More than half (n = 44, 61%) of the 72 identified outbreaks occurred at state or county agricultural fairs (Table 3). All of these fairs were large multiday events ranging between 5 to 12 days with a mean daily attendance of 33,000 persons (personal communication on subset of fairs for which data were available: Marla Calico, International Association of Fairs and Exhibitions). Forty outbreaks were reported between 2011 and 2012 and involved transmission of Influenza A H3N2v at fairs across 9 states. The largest outbreak occurred at an agricultural fair in Indiana and resulted in 73 confirmed and probable cases. In this, as well as other H3N2v outbreaks, the majority of case-patients reported close contact with swine at the agricultural fairs, though additional but limited secondary person-to-person transmission was detected [33–36]. Children and adolescents less than 18 years of age represented the largest percentage of case-patients (92%) during these outbreaks [36]. Three outbreaks of Influenza A H1N1 (3SIV) occurred at agricultural fairs in 2007 in Ohio, Illinois, and Michigan [20–21]. The swine barn housed 235 pigs belonging to 133 exhibitors and was closed as a result of the outbreak in Ohio [20]. A single case of Influenza A H3N2 (3SIV) was detected in a 12-year old boy after attending an agricultural fair in Kansas in 2009.

Camps. Twenty-seven (38%) of the 72 identified outbreaks occurred at residential recreational, academic, or cultural camps. Each lasted for three days or more and involved either Influenza A (H1N1) (n = 25) [22–29] or mumps (n = 2) [16–17, 30–31]. The size of most camp sessions was small, ranging between 100 to 600 campers and staff. Nineteen (76%) of the 25 Influenza A H1N1 (pdm09H1N1) outbreaks were reported from an online survey of 2009 summer camp participants in Maine [25]. In this survey, camp-related outbreaks (defined as having at least three confirmed cases of pdm09H1N1) were statistically associated with having both a larger number of camp participants per session and a larger number of campers per cabin. The six other camp-related pdm09H1N1 outbreaks occurred in North Carolina (n = 3) [22–23, 27–28], Louisiana (n = 1) [24], Alabama (n = 1) [26], and Washington State (n = 1) [29]. One outbreak involved 119 cases occurring across two clusters in a multi-camp setting at a North Carolina university with more than 7,900 participants [32–33]. The authors found that this transmission occurred rapidly during academic camps and was likely due to close and frequent

Table 2. Relevant articles about mass gathering-related respiratory disease outbreaks listed by year of outbreak and pathogen, identified from a literature review of articles published during 2005 and 2014.

Year[a]	Pathogen	Transmission	Type of Gathering	Location	Size of Gathering[b]	Length of Gathering (Days)	Estimated Number of Cases[c]	Age of Cases (Years)	Factors in outbreak	Reference
2005	Mumps	Person-to-person	Camp	New York	541	52	31	10–41	International importation of infectious case; Delayed diagnosis and reporting; Close social mixing and contact in communal housing/ activities	CDC [16]; Schaffzin JK, et al. [17]
2007	Measles	Person-to-person	Sporting event	Pennsylvania	265,000	10	7[d]	12–53	International importation of infectious case; Contact with susceptible persons before and during travel and at event.	CDC [18]; Chen TH, et al. [19]
2007	Influenza A H1N1 (3SIV)	Animal (zoonotic)	Fair	Ohio	Unknown	Unknown	24	Unknown	Contact with swine	Killian ML, et al. [20]
2007	Influenza A H1N1 (3SIV)	Animal (zoonotic)	Fair	Multiple—Ohio[e]; Illinois; Michigan	Unknown	Unknown	4[f]	16 mos —48 yrs	Visiting near swine barn or contact with swine	Shinde V [21]
2009	Influenza A H1N1	Person-to-person	Camp	North Carolina	1,650[g]	56	67[h]	Unknown	Close social mixing/ contact in communal housing	CDC [22]
2009	Influenza A H1N1	Person-to-person	Camp	North Carolina	700	7	52[i]	> 10	Close social mixing and contact in communal housing/activities	Doyle TJ, et al [23]
2009	Influenza A H1N1	Person-to-person	Camp	Louisiana	217	4[j]	59	5–69	Increased risk among participants with hematologic and oncologic conditions; Close social mixing and contact in communal housing/activities	Morrison C, et al. [24]
2009	Influenza A H1N1	Person-to-person	Camp	Multiple—Maine	Unknown	Unknown	19 outbreaks of influenza-like-illness and ≥3 confirmed cases	Unknown	Close social mixing and contact in communal housing/activities; Number of campers per session and per cabin	Robinson S, et al. [25]
2009	Influenza A H1N1	Person-to-person	Camp	Alabama	800[k]	28	15[k]	8–14[k]	Close social mixing and contact in communal housing/activities	Kimberlin D, et al. [26]
2009	Influenza A H1N1	Person-to-person	Camp	North Carolina	7,906[l]	73	119[m]	9–68	Close social mixing and contact in communal housing/activities including in classroom	Tsalik E, et al. [27]; Tsalik E, et al. [28]
2009	Influenza A H1N1	Person-to-person	Camp	Washington	145	6	60[n]	> 10	Close social mixing and contact in communal housing/activities	Sugimoto JD, et al. [29]
2009	Mumps	Person-to-person	Camp	New York	400	40	25[o]	9–30	International importation of infectious case; close social mixing and contact in communal housing/ activities	CDC [30]; CDC [31]

(*Continued*)

Table 2. (*Continued*)

Year[a]	Pathogen	Transmission	Type of Gathering	Location	Size of Gathering[b]	Length of Gathering (Days)	Estimated Number of Cases[c]	Age of Cases (Years)	Factors in outbreak	Reference
2009	Influenza A H3N2 (SIV)	Animal (zoonotic)	Fair	Kansas	Unknown	Unknown	1	12	Contact with swine	Cox CH, et al. [32]
2011	Influenza A H3N2v	Animal (zoonotic)	Fair	Pennsylvania	~70,000	7	89[p]	Unknown	Contact with swine	CDC [33]; Wong KK, et al. [34]
2012	Influenza A H3N2v	Animal (zoonotic)	Fair	Indiana	Unknown	7	4	Unknown	Contact with swine	CDC [35]
2012	Influenza A H3N2v	Animal (zoonotic)	Fair	Multiple—Illinois; Indiana[e]; Maryland; Michigan; Minnesota; Ohio; Pennsylvania; Wisconsin	~21,000–1.7 million[q]	5–12[q]	From 1 to 73 (across 39 fairs reporting cases)	3 months—74 years	Visiting fair or contact with swine; Increased transmissibility of H3N2v (reassortant with M gene from pdm09H1N1)	Jhung MW, et al. [36]

[a]Reflects year during which initial outbreak-related case(s) were detected and reported.

[b]Estimated size of gathering obtained from article, personal communication with corresponding author or communication with the International Association of Fairs and Exhibitions (IAFE).

[c]Reflects case counts reported in the manuscript. Attack rates, when available, are reported in S2 File.

[d]Includes measles cases resulting from travel-related transmission.

[e]Indicates second reference to same outbreak.

[f]Includes only laboratory confirmed cases of Influenza A H1N1 (3SIV).

[g]Size and length of gathering combined across multiple-camps and 2 sessions.

[h]65 camp participants with influenza-like-illness across two camp sessions; 2 participants confirmed with Influenza A H1N1 during second session.

[i]Among 212 camp participants completing survey; 52 cases includes 49 camp participants (12 of whom were laboratory confirmed) and 3 identified from household contacts of ill camps participants.

[j]Camp closed early due to number of participants with influenza-like-illness and confirmation of 4 participants with Influenza A H1N1.

[k]Combined across 4 two-week sessions. In 3rd session, 12 cases identified (including 4 confirmed with Influenza A H1N1). In 4th session, 3 cases confirmed with Influenza A H1N1; cases aged 8 to 14 years.

[l]Numerous academic and recreational camps on university campus with length varying from 3 to 73 days, all camps closed early due to identified illnesses.

[m]Across two clusters; first involving 3 camps and 64 cases and second involving 2 camps and 55 cases.

[n]Includes 49 camp participants (from 96 campers responding to survey) and 11 additional cases among household contacts (of 136 household contacts from 41 households with an ill camper). Five camp participants confirmed with Influenza A H1N1.

[o]Outbreak spread to other counties in New York and New Jersey for total of 1,523 mumps cases.

[p]Includes 3 confirmed, 4 probable, and 82 suspected cases of Influenza A H3N2v.

[q]Estimates from IAFE based on available data from subset of fairs reporting Influenza A H3N2v cases; at time of project, no standards existed for calculating fair attendance.

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contact during classroom time and social mixing outside of class. Two camps (the university camp in North Carolina [27–28] and a camp for children with hematological and oncological conditions in Louisiana [24]) closed early due to the large number of participants presenting influenza-like-illness (ILI).

Two mumps outbreaks were identified in this review—both occurred at a camp for boys in upstate New York following international importations of infectious mumps cases from the United Kingdom. The first outbreak took place in 2007 and resulted in 31 cases among 541 campers and staff; the staff represented 60% of all case-patients [16–17]. The second occurred

Table 3. Frequency of mass gathering-related respiratory disease outbreaks identified from the published literature[a] by setting, pathogen, and mode of transmission, January 1, 2005–December 31, 2014.

Setting	Pathogen	Mode of Transmission	Outbreak Frequency
Fairs	Influenza A H3N2v	Zoonotic[b]	40
	Influenza A H1N1 (3SIV)	Zoonotic	3
	Influenza A H3N2 (SIV)	Zoonotic	1
Camps	Influenza A H1N1	Person-to-person	25
	Mumps	Person-to-person	2
Sporting events	Measles	Person-to-person	1
Total			72

[a]From 21 reviewed articles.

[b]Minimal person-to-person transmission detected.

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in 2009 and caused 25 cases among 400 campers and staff [30–31]. In both outbreaks, transmission was associated with prolonged close contact in communal housing and camp activities despite a two-dose MMR vaccination coverage > 85% among school-aged campers. A delay in mumps diagnosis also likely contributed to the 2007 outbreak. During the 2007 outbreak, camp activities were either cancelled or postponed [16–17]. These outbreaks resulted in substantial community transmission when campers returned home—more than 1,500 community cases (including 19 hospitalizations) occurred in New York and New Jersey in 2009 [30–31].

Sporting events. The final mass gathering-related outbreak identified in this review involved measles transmission at an international youth sporting event in Pennsylvania [18–19]. The youth sporting event outbreak was caused by the international importation of measles in a participant from Japan and resulted in six additional cases of measles. The index case from Japan infected three others before or during travel to Pennsylvania and a fourth case at the sporting event. The remaining two cases subsequently contracted measles in another state from the case-patient infected at the sporting event. Public health officials worked with event organizers to provide post-exposure measles-mumps-rubella (MMR) vaccination to close contacts of case-patients without documentation of at least two doses of measles vaccine or who were negative for measles IgG antibody [19].

Four of the 34 articles excluded from our analysis described health events at six large mass gatherings in Arizona between 2008 and 2011 [37], at Kansas Speedway NASCAR racing events between 2007 and 2010 [38], at the annual New York State Fair between 2004 and 2008 [39] and at a large (>40,000 participants) summer camp in Virginia in 2005 [40]. Analysis of syndromic surveillance data and/or onsite clinic records maintained at these gatherings identified heat or dehydration-related illnesses, injuries, and enteric infections as the most frequently reported conditions at these mass gatherings; no infectious respiratory disease outbreaks were detected. Additionally, no single-day mass gathering-related outbreaks were identified in our review.

National Outbreak Reporting System

Between 2009 and 2013, 1,114 outbreaks were reported to NORS (Table 4). This included 96 infectious respiratory disease outbreaks due to Legionella—all of which were reported as water-borne outbreaks (Legionella is not easily transmitted between human hosts). None of these outbreaks was linked to mass gatherings in our analysis. No other respiratory disease outbreaks were reported to NORS.

Table 4. Outbreaks reported to CDC's National Outbreak Reporting System (NORS), 2009–2013, by year and mode of transmission.

Mode of Transmission	2009 (%)	2010 (%)	2011 (%)	2012 (%)	2013 (%)	Total (%)
Foodborne	118 (62)	148 (58)	133 (61)	142 (58)	154 (74)	695 (62)
Waterborne[a]	51 (27)	78 (31)	66 (30)	71 (29)	—	266 (24)
Person-to-person[b]	10 (5)	17 (7)	6 (3)	16 (7)	25 (12)	74 (7)
Animal contact	10 (5)	12 (5)	13 (6)	14 (6)	15 (7)	64 (6)
Environmental	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)
Unknown/indeterminate	0 (0)	0 (0)	0 (0)	0 (0)	14 (7)	14 (1)
Total	190	255	218	243	208	1,114

[a]At time of analysis, 2013 waterborne disease outbreak data were not available. Waterborne transmission includes 96 legionellosis outbreaks; none were linked to mass gatherings.

[b]Person-to-person outbreaks (n = 74) were due to Norovirus (45), *Escherichia* (3), *Salmonella* (1), *Shigella* (1), and *Campylobacter* (1). The remaining 23 outbreak reports were missing etiology information.

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Discussion

To the best of our knowledge, this is the first effort to describe the frequency and characteristics of mass gathering-related respiratory disease outbreaks occurring in the United States. Mass gathering-related respiratory disease outbreaks appeared to be relatively rare during our 10-year project period, but were reported from agricultural fairs (zoonotic transmission) and summer camps where participants had close social contact in communal housing. Though legionellosis outbreaks were more common, none of these water-borne outbreaks was linked to a mass gathering in our analysis. The type and duration (multi-day events with communal housing) of mass gatherings could be important factors in mass gathering-related respiratory disease outbreaks. International participation may be a contributing factor for certain diseases.

As anticipated, we identified several mass gathering-related pdm09H1N1 outbreaks involving school-aged children [41]. These persons are a high-risk age group for the novel 2009 influenza virus. Compared to other settings, influenza transmission among children and teenagers is more likely to occur within households, school classes, peer groups, and sports teams [42–44]—all of these social mixing opportunities are prominent at summer camps. Children and adolescents can easily have more than 20 close contacts with other children lasting 5 minutes of more during a typical school day [45]. Both the number and duration of close contacts could be higher in residential camps. This is supported by the outbreaks reported from Maine where the camp size and the number of campers per cabin were associated with influenza outbreaks [25]. Though respiratory disease transmission can occur at summer camps, influenza transmission during the summer (in the United States) outside a pandemic is uncommon; pdm09HIN1 was circulating since early spring and was involved a number of school-based outbreaks in states reporting camp-related influenza outbreaks in summer 2009. No respiratory illnesses were detected from a syndromic surveillance system implemented at a large school-aged summer camp in Virginia in 2005 [40].

The majority of the other mass gathering-related respiratory disease outbreaks identified in this project occurred at agricultural fairs and was caused by Influenza A H3N2v. Prior to 2011–2012, human Influenza A (SIV) infections were rare; however, the H3N2v outbreaks resulted from the reassortment of swine Influenza A H3N2 virus and Influenza A pdm09H1N1 in the swine population, raising concerns about sustained human-to-human transmission and increased risk in the pediatric population [46]. Though only minimal human-to-human transmission of H3N2v was detected, close and repeated contact between humans and livestock at the estimated 2,380 agricultural fairs (personal communication: Marla J. Calico, International

Association of Fairs and Exhibitions) that take place each year in the United States could create future opportunities for zoonotic transmission of influenza viruses as well as other possible respiratory infections [34, 36]. The syndromic surveillance system using emergency department chief complaint data was analyzed to detect the initial H3N2v outbreak in Indiana (personal communication: Shawn Richards, Indiana State Department of Health). This highlights the usefulness of such systems to rapidly detect temporal or spatial clusters of unusual health events associated with fairs and other mass gatherings.

The mumps and measles outbreaks demonstrate the importance of close collaboration between public health officials and mass gathering organizers to assess health risks to participants. As recommended in the articles, camp and sporting event organizers should verify immunization histories of all registered participants and team members [17, 31]. This is particularly important for measles, which is highly contagious through aerosolized viral particles; other control and prevention measures are likely to be ineffective. Organizers should also obtain information on disease transmission in the home countries of participants. These pre-gathering activities can help with the early case detection and outbreak prevention. The 2007 mumps outbreak, for example, was attributed to the international importation of mumps in a staff member followed by the delayed recognition of suspected mumps cases and prolonged and close contact between campers in communal housing [16–17].

NORS was developed to capture outbreaks related to enteric infections such as Norovirus, Shigella, and Salmonella as well as non-enteric waterborne diseases such as Legionnaires—an infection caused by a bacterium found naturally in the environment [47]. Though we could use exposure setting (e.g., camps, conference, etc.) as a proxy for mass gathering, this exposure setting was only reported for outbreaks involving person-to-person transmission. The 96 reported legionellosis outbreaks were unrelated to mass gatherings according to available data. A previous review of environmental and waterborne outbreaks reported to NORS between 2011 and 2012 indicated that the 4 (22%) of the 18 legionellosis outbreaks occurred at hotels; however, there was no additional information to determine on whether visitors or detected cases were involved in hotel-based conferences or other mass gatherings [48].

No other mass gathering outbreak due to pdm09H1N1 or other respiratory diseases was identified in this project including at large mass gatherings in Arizona, Kansas, New York, and Virginia [37–40]. This is consistent with previous assessments of international mass gatherings such as the Olympics that detected only marginal increases above baseline in the incidence of all infectious diseases including influenza with infections primarily limited to competitors and staff [5, 47]. Though we assume that all mass gatherings could increase the transmission of respiratory diseases, this may not be the case for diseases transmitted through infectious droplets where the probability of close and adequate contact (i.e., $<$ 6 feet for influenza) with an infectious person may be too low for efficient transmission [49]. Even at large mass gatherings involving out-of-town visitors such as the May 2009 convocation speech in Arizona (during which no respiratory disease outbreaks were detected) [37], most participants likely stayed at hotels or at other low-density accommodations rather than in cabins or at campgrounds [5, 49]. In addition, many of these gatherings have well organized and pre-assigned seating. This could further reduce the 'crowdedness' and likelihood of close and prolonged contact with infectious persons [5]. This can be contrasted to the type of communal housing and social mixing associated with camp outbreaks described here. Variability in susceptibility among attendees as well as in the timing of the gathering in relation to local respiratory disease activity also likely play a role in transmission [9].

Our findings have several limitations. First, only a small percentage of outbreaks are likely reported in the literature. We used a broad database search criteria to minimize this limitation and identify all possible articles describing mass gathering-related respiratory disease

outbreaks. Second, some outbreaks may not be identified as outbreaks. Active or passive surveillance likely influences the number of infectious respiratory disease outbreaks identified and reported. For example, active surveillance for variants of influenza viruses at fairs following the initial H3N2v outbreak in 2011 could have increased the number of outbreaks detected from this setting. In addition, while multiday residential-based mass gatherings can facilitate transmission, these settings may also help identify cases and an emerging outbreak through close monitoring of known participants. In non-residential settings, other non-disease related factors including crowd mood, age, weather, and alcohol and drug use could influence the use of illness-related medical services. These factors could further increase the variability of health event reporting [14]. Third, some respiratory diseases with longer incubation periods and many subclinical infections are unlikely to be identified during the mass gathering. Symptoms could appear once the participants have returned home and are then rarely linked or reported to the appropriate surveillance system [9, 49].

Advances in technology such as crowdsourcing applications (e.g. Flu Near You at URL: https://flunearyou.org and GermTrax at URL: http://germtrax.com) [50] as well as an increased use of social media along with real-time outbreak and syndromic event reporting could help address some of the surveillance limitations at mass gatherings. In Brazil, for example, a smart phone application was developed allowing persons attending the 2014 FIFA World Cup to provide information on their daily health status. This information was automatically aggregated into reports that were reviewed daily to identify potential infectious disease clusters or outbreaks [51]. Monitoring social media including Twitter was used to identify potential health issues and communicate accurate information about disease transmission during the 2012 London Olympics [52]. These approaches can complement other surveillance systems such as collection and analysis of syndromic event data from emergency department visits or onsite medical clinics [37]. Integration of these various platforms through a web-based system could allow public health officials to rapidly detect unusual disease activity [10, 53] even at smaller mass gatherings [54–55]. Recent research has also focused on the use of radio frequency identification devices [56–57] as well as video analysis technology [58] to capture social mixing and contact patterns at mass gatherings. These contact data can be used to simulate or model the transmission of various infectious disease pathogens including pandemic influenza. Simulations or mathematical models can help describe the risk of potential outbreaks and highlight where and when enhanced disease transmission mitigation at mass gatherings should be considered.

Finally, NORS was developed primarily to capture outbreaks related to enteric infections as well as non-enteric waterborne diseases such as Legionnaires. Voluntary reporting of other types outbreaks likely impacted the probability of identifying mass gathering related respiratory disease outbreaks from the NORS database. However, because state and local health departments are familiar with this system, NORS could incorporate standard mass gathering and additional outbreak definitions and serve as a platform to monitor mass gathering-related respiratory outbreaks in the future.

Conclusion

We identified a relatively small number of mass gathering-related respiratory disease outbreaks occurring in the United States between 2005 and 2014. This could suggest a low risk of respiratory disease transmission at most types of gatherings—even during a pandemic. However, because not all outbreaks are reported in the published literature or to NORS, a follow-up state and local health department assessment on the number and characteristics of mass gathering-related respiratory disease outbreaks could help validate or complement the findings reported

here. Additional research to strengthen existing surveillance approaches to detect outbreaks and better quantify the social mixing patterns at different mass gatherings could provide additional insight into the types of mass gatherings at greatest risk of respiratory disease outbreaks.

Supporting Information

S1 File. Literature database search strategy.
(PDF)

S2 File. Summary information from articles included in systematic literature review.
(PDF)

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Author Contributions

Conceived and designed the experiments: JJR TP JS.

Performed the experiments: JJR TP JS.

Analyzed the data: JJR TP JS.

Contributed reagents/materials/analysis tools: JJR TP JS.

Wrote the paper: JJR TP JS.

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Outbreaks associated to large open air festivals, including music festivals, 1980 to 2012

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In the minds of many, large scale open air festivals have become associated with spring and summer, attracting many people, and in the case of music festivals, thousands of music fans. These festivals share the usual health risks associated with large mass gatherings, including transmission of communicable diseases and risk of outbreaks. Large scale open air festivals have however specific characteristics, including outdoor settings, on-site housing and food supply and the generally young age of the participants. Outbreaks at large scale open air festivals have been caused by *Cryptosporium parvum, Campylobacter spp., Escherichia coli, Salmonella enterica, Shigella sonnei, Staphylococcus aureus*, hepatitis A virus, influenza virus, measles virus, mumps virus and norovirus. Faecal-oral and respiratory transmissions of pathogens result from non-compliance with hygiene rules, inadequate sanitation and insufficient vaccination coverage. Sexual transmission of infectious diseases may also occur and is likely to be underestimated and underreported. Enhanced surveillance during and after festivals is essential. Preventive measures such as immunisations of participants and advice on-site and via social networks should be considered to reduce outbreaks at these large scale open air festivals.

Introduction

Mass gathering (MG) medicine is an emerging specialty [1] that includes effective strategies and planning to address health security and risks associated with MGs. The number of attendees that classifies an event as a 'mass gathering' is wholly arbitrary. Definitions vary greatly, with some sources specifying any gathering to be a MG when more than 1,000 individuals attend, whereas others require the attendance of as many as 25,000 people to qualify [2]. Outbreaks, however, occur irrespective of the size of a gathering and are described not only in settings such as private parties, weddings, and other events involving fewer than 1,000 attendees, but also in large MGs, such as religious MGs, attended by millions of people [3]. In addition to the number of people, MGs are events at a specific site for a definite time which may greatly vary between different MGs. These gatherings might be planned or unplanned and recurrent or sporadic.

Although large scale open air festivals have become important spring and summer activities and attract thousands of people, they are probably neglected, particularly music festivals, in terms of public health attention, as well as surveillance and prevention of infectious disease strategies, compared to other categories of MGs such as sport or religious events. Indeed, most of the literature on MGs in this respect, has addressed health issues related to very large MGs, including the Hajj [2] and the Olympic Games [4].

A characteristic of large scale open air festivals, including music festivals, may be that they are not always organised and managed by professionals and may involve inexperienced volunteers as staff members. Music festivals in particular have also specific characteristics, including outdoor settings, on-site housing and food supply, the young age of the participants, recreational motivations, and the potential for excessive alcohol or drug consumption, which may notably increase the risk of sexually transmitted infections (STIs) [5] and possibly of other infectious diseases.

A total of 858 music festivals were recorded worldwide in 2012 in choosefest database (www.choosefest.com/). The largest music festivals were in Europe where 13 of the 20 top international festivals occur (Table 1). Most festivals take place over a three to four day period with the longest lasting 11 days. Attendance for the top 20 festivals in terms of size ranges from 17,000 to 175,000 per day. According to a survey conducted in the United Kingdom (UK) during the year 2009, the total number of visits to UK music festivals was estimated to exceed 7.7 million attendees, including overseas and domestic participants combined (www.ukmusic.org/assets/media/UK%20Music%20-Music%20Tourism.pdf). Music festivals, which may involve as many as 400,000 cumulated attendees, share the usual health risks associated with large MGs, including communicable and non-communicable diseases [6-8]. A mean percentage of 1.5% attendees at music festivals seek medical care during these events, and the highest proportion recorded of attendees seeking care was 10% [9-12]. This situation may have an impact on local healthcare facilities, especially

Table 1

Top 20 international music festivals by estimated attendance per day, 2012

Festival	Location	Duration (days)	Estimated attendance per day
Glastonburry	Worthy Farm, Pilton, Shepton Mallet, Somerset, United Kingdom	5	175,000
Roskilde	Roskilde, Denmark	4	110,000
Rock Werchter	Werchter, Belgium	4	110,000
Rock al Parque	Bogota, Colombia	4	88,600
T in the Park	Balado, Kinross-Shire, Scotland	3	85,000
Summerfest	Henry Maier Festival Park, Milwaukee, Wisconsin, United States	11	82,000
Exit	Petrovaradin Fortess, Novi Sad, Vojvodina, Serbia	4	75,000
Coachella	Coachella, California, United States	3	75,000
Reading-Leads Festival	Reading, Leads, United Kingdom	3	75,000
Sziget	Budapest, Hungary	6	65,000
Pukkelpop	Kiweit-Hasselt, Belgium	3	62,500
Pinkpop	Landgraaf, Netherlands	3	60,000
Big Day Out	Gold Coast, Sydney, Melbourne, Adelaide, Perth, Australia and Auckland, New Zealand	11	56,000
Burning Man	Black Rock Desert, Nevada, United States	7	50,000
Bonnaroo	Great Stage Park, Manchester, Tennessee, United States	4	40,000
Fuji Rock	Naebi Ski Resort, Japan	3	40,000
Hurricane	Scheeßel, Lower Saxony, Germany	3	40,000
Downlaod	Donington Park, United Kingdom	3	37,000
Benicassim	Benicassim, on the coast between Valencia and Barcelona, Spain	4	32,000
Wireless	Hyde Park, London, United Kingdom	3	17,500

Sources: http://www.wikifestivals.com/wiki/list-international-music-festivals-attendance, http://www.cnbc.com/id/42150834/The_Worlds_s_Biggest_Music_Festivals, http://en.wikipedia.org/wiki/Music_festivals.

in terms of the workload on local hospitals, as found in Punchestone Racecourse, Ireland in 2004 [13]. During the Oxegen festival, which had 80,000 attendees over three days, a 45% increase in admissions to the emergency department (mainly for trauma) was observed at Nass General Hospital, with 51% of these admissions treated as inpatients. Interestingly, 47% of these patients had consumed alcohol and/or drugs [13].

A comprehensive review on outbreaks in relation to large scale open air festivals is missing. The objective of this report is to summarise the evidence related to the substantial challenges posed by communicable diseases to the organisers of large scale open air festivals, including music festivals, and outline details of infections resulting from faecal-oral, respiratory and sexual transmission. Opportunities to control these outbreaks are discussed.

Methods

Definition of large scale open air festivals

Outbreaks in the setting of an open air festival, including a music festival or other art festival, village festival, cultural festival, university, religious events and large weddings were included.

Case reports and human/non-human experimental laboratory studies were excluded from the review. Outbreaks in relation with sport events, Hajj pilgrimage, food festivals, fairs or occurring in the setting of cruise ship, school, restaurant or hotel (including weddings at restaurants or hotels) were excluded because they were reviewed elsewhere [6-8].

Search strategy

To retrieve information on the transmission of infectious diseases and outbreaks during large scale open

air festivals, we first conducted a literature search using the MEDLINE database (www.ncbi.nlm.nih.gov/pubmed), from 1980 to July 2012, cross-referencing the following terms: 'mass gatherings', 'festivals' or 'music festivals' and 'infection' or 'infectious diseases' or 'outbreak'. Only studies published in English, but one in Serbian, were included in this review. Relevant systematic and narrative reviews were also utilised for useful background information. Subsequently, the reference lists of the systematic reviews and other identified papers were scanned for potentially relevant primary studies that could be considered for inclusion in the review. Additional search was conducted using ProMED-mail (www.promedmail.org) cross-referencing the following terms: 'festivals' or 'music' and through Google (www.google.fr) and Yahoo (fr.yahoo.com) general search-engines cross-referencing the terms: 'festivals' or 'music festivals' and 'infectious' or 'outbreak'.

Results

Using our search strategy, 107 articles were retrieved through MEDLINE and scanning of reference lists, and 23 of these were relevant to our subject from a review of titles, abstracts, and full text of the articles obtained. Pro-MED mail search allowed identifying only three relevant outbreaks that were already retrieved through MEDLINE. Google and Yahoo search retrieved respectively 31,900,000 and 12,400,000 hits, using 'festival' and 'outbreaks' terms; 6,670,000 and 11,300,000 hits, using 'music festival' and 'outbreaks' terms and 558,000 and 200,000 hits, using 'music festival' and 'infectious' terms. Given the poor relevance of search results obtained through Google and Yahoo, no further analysis was conducted using these two search-engines.

Outbreaks and infectious diseases occurring during large scale open air festivals were classified into three categories: (i) faecal-oral transmission and gastrointestinal diseases, (ii) respiratory transmission and respiratory infections and (iii) blood-borne and sexually transmitted diseases.

Faecal-oral transmission and gastrointestinal diseases

A total of 10 outbreaks of gastrointestinal infections associated with faecal-oral transmission in the context of large scale open air festivals were retrieved and are summarised in Table 2. Of these five were linked to music festivals. Outbreaks of *Cryptosporium parvum, Campylobacter, Escherichia coli, Salmonella enterica, Shigella sonnei, Staphylococcus aureus*, hepatitis A virus and norovirus infections have been described over the last two decades in the United States (US), Canada, Europe and Japan and have been as well associated with events including 350 attendees, as with open air festivals involving as many as 80,000 participants. In some outbreaks, the attack rate was close to 50% of attendees, such as in Shigella outbreaks [14,15] or gastroenteritis outbreaks due to norovirus [16].

Failures of hand-washing hygiene among food handlers suspected to be infected by the infectious agent lead to the contamination of food and were an important route of transmission for gastrointestinal diseases at large scale open air festivals [14,17-19]. A lack of respect for food hygiene rules has also been observed during such festivals [17,18,20]. Factors that contribute to gastrointestinal outbreaks at these festivals include (i) excessive production of food beyond the safe food production capacity [17], (ii) preparation of meals by a large number of volunteer food handlers [14,18], and (iii) the sale of food prepared under unsanitary conditions, sometimes by vendors without a license [19-21]. Moreover, during a lunchtime concert in Cardiff, the most likely cause of the outbreak of norovirus infection was vomit contaminating inadequately cleaned and disinfected hard surfaces, carpets and soft furnishings [16].

Another important factor associated with the risk of gastrointestinal infections is the lack of adequate sanitation. Inadequate sanitation was the cause of the contamination of drinking water during the annual meeting of the Rainbow Family in the US in 1987, resulting in a large outbreak of shigellosis [15]. Inadequate sanitation associated with limited access to running water for hand washing has also been reported as the source of gastrointestinal outbreaks [14].

Unusual transmissions of gastrointestinal diseases have also occurred during large scale open air festivals. An outbreak of Escherichia coli O157 was reported during the Glastonbury music festival in England and was linked to mud contaminated by infected cattle. Heavy rain had turned the site into a quagmire, and attendees had high levels of contaminated mud on their hands and faces [22]. Additionally, a swimming pool at an accommodation during a dance festival in Canada was identified as the source of an outbreak of diarrhoea due to *Cryptosporidium parvum* [23].

Overall, the estimated incidence of gastrointestinal diseases per 100,000 attendees ranged from nine to more than 55,000 during the outbreaks included in this review.

Respiratory transmission and respiratory infections

Infections acquired by respiratory routes reported in the literature in association with nine large scale open air festivals are described in Table 3. Of these, three were music festivals.

Influenza outbreaks have been reported at music festivals [24-27], with the potential for the spread of new influenza viruses in some cases [27,28]. In Serbia in 2009, 40% of the pandemic influenza A(H1N1)pdm09 cases were linked to the Exit festival [26]. Interestingly, during 2009, influenza A(H1N1)pdm09 outbreaks were recorded at three of the top six music festivals (>100,000 cumulated attendees) in Europe (Rock

Table 2

Outbreaks of gastrointestinal diseases associated with large scale open air festivals, 1987–2008

Reference	Event	Place	Year	Size (cumulated number of attendees) and type of attendees[a]	Pathogen involved	Case numbers	Estimated incidence per 100,000 attendees	Indication of patient age	Source of outbreak	Mode of transmission	Favouring factors
[15]	Annual meeting Rainbow Family	Nantahala National Forest, United States	1987	12,700	*Shigella sonnei*	Estimated >7,000; nationwide dissemination (3 States)	55,118	Mean patient age: 27 years	Inadequate sanitation	Food-borne, water-borne, person-to-person	Inadequate sanitation
[14]	Michigan Women's Music Festival	Michigan, United States	1988	6,403 women	*Shigella sonnei*	3,175 primary cases (278 ill staff and 2,897 ill attendees); 182 secondary cases; 117 hospitalisations	45,244	Mean patient age: 31 years	Uncooked tofu salad	Food-borne and person-to-person	Limited access to soap and running water for hand washing and large number of non-professional food handlers
[20]	Glastonbury music festival	South west England	1992	70,000	*Campylobacter*	72	103	Age range of the majority of patients: 20–30 years	Unpasteurised milk	Food-borne	Lack of respect for food hygiene rules
[22]	Glastonbury music festival	South west England	1997	80,000	*Escherichia coli* 0157	7	9	Mean patient age: 21 years	Mud (contaminated by cattle faeces)	Direct contact	Grazing of cattle on site two days before the event and heavy rain
[16]	Lunchtime concert	Cardiff, England	1999	1,229 children	Norovirus	>300	24,410	Primary school students	Vomits inappropriately cleaned	Direct contact	Vomit inappropriately cleaned
[23]	Ukrainian Dance Festival	Dauphin, Manitoba, Canada	2001	430 dancers, >450 spectators	*Cryptosporidium parvum*	59 (2 hospitalisations)	13,111	Mean patient age: 23 years	Swimming pool	Faecal-oral	Swimming pool in one accommodation
[17]	San Juan Festival	Catalonia, Spain	2002	ND	*Salmonella enterica*	1,435 (117 hospitalisations)	ND	Age range of 24% of patients: 1–24 years; of 35%: 25–44 years	Pastry with vanilla cream	Food-borne	Exceeded food production capacity
[19]	Youth camp	Australia	2003	350	Hepatitis A virus	21	6,000	Median patient age: 16 years	Coleslaw	Food-borne	Infected food handler
[21]	Outdoor concerts 'jam bands'	United States (9 States)	2003	1,200–82,000	Hepatitis A virus	25	31–2,083	Median patient age: 23 years	Unknown	Person-to-person, food-borne	Unknown
[18]	Nagoya University Festival	Japan	2008	50,000	*Staphylococcus aureus*	75 (staff and attendees)	150	ND	Crepes	Food-borne	Lack of respect for food hygiene rules

ND: not determined.

[a] When attendees were of a certain type.

Table 3

Outbreaks of respiratory transmissions and infections associated with large scale open air festivals, 2006–2010

Reference	Event	Place	Year	Size (cumulated number of attendees)	Outbreak type	Number of cases and description	Estimated incidence per 100,000 attendees	Age of patients as specified	Favouring factors/ consequence
[31]	Easter Youth Festival	Carinthia, Austria	2006	ND	Mumps virus	214 cases (143 confirmed, 71 probable)	ND	Age range of 80% of patients: 16–30 years	Occurrence in unvaccinated people
[32]	Annual village festival	Navarra, Spain	2006	› 4,500	Mumps virus	19 primary cases; 58 secondary cases	422	Age range: 18–37 years	Failure in immunisation by Rubini strain
[28]	World Youth Day (religious meeting)	Sydney, Australia	2008	500,000	Numerous influenza virus strains (A and B)	100 confirmed cases	20	Median age: 21 years	Community strains from Australia that were rarely isolated before World Youth Day 2008 were frequently identified among pilgrims; novel influenza viruses were introduced
[27]	Iztapalapa Passion Play (religious meeting)	Iztapalapa, Mexico	2009	>2 million	Influenza A(H1N1) pdm09 virus	38 cases; of 202 cases of influenza A(H1N1) pdm09 in Mexico from 1 to 5 May 2009, 38 originated from the Iztapalapa Passion Play meeting	2	Age range of 32% of patients: 5–19 years; of 28%: 20–29 years	Local and national spread, start of the pandemic influenza A(H1N1)pdm09
[24]	Rock Werchter (music festival)	Belgium	2009	113,000	Influenza A(H1N1) pdm09 virus	14 confirmed cases; 30 ILI cases	12	Mean age: 23 years	International spread
[25]	Sziget Festival (music festival)	Budapest, Hungary	2009	390,000	Influenza A(H1N1) pdm09 virus	8 confirmed cases; 14 ILI cases	2	Mean age: 21 years (personal communication, Dr Peter Felkai, January 2010)	International spread
[26]	Exit Festival (music festival)	Novi Sad, Serbia	2009	165,000	Influenza A(H1N1) pdm09 virus	49 confirmed cases	30	Age range of 42% of patients: 20–29 years	During 2009, 40% of influenza A(H1N1) pdm09 cases in Serbia were linked to this festival
[29]	Taizé (religious meeting)	France	2010	3,500	Measles virus D4-Manchester	13 primary cases; 17 secondary cases; 7 tertiary cases	371	Median age for primary cases: 17 years; for secondary cases: 15 years; for tertiary cases: 13 years	Low vaccine coverage
[30]	Wedding	Andalucia, Spain	2010	ND	Measles virus	25 primary cases; 58 secondary cases	ND	97% of patients ›16 years-old	Low vaccine coverage

ILI: Influenza-like illness; ND: not determined.

Werchter, Belgium; Sziget Festival, Hungary; and Exit Festival, Serbia).

In 2010, 13 primary measles cases were identified among unvaccinated persons aged between nine and 32 years-old in 11 districts in Germany. All cases had attended religious meetings in Taizé, France [29]. This outbreak illustrates the risk of long distance spread of infectious diseases associated with international large scale open air festivals. The same year, 25 primary cases of measles had been reported from Granada, southern Spain, of whom 22 were unvaccinated children under the age of 15 years [30]. This outbreak involved a subpopulation with low vaccination coverage and parents with ideological objections to vaccination participating to a large wedding reception [30]. Secondary cases were documented in both outbreaks.

An outbreak of mumps occurred in Austria in 2006 involving 214 individuals. Nearly half of the cases for whom vaccination status was known occurred in non-vaccinated persons, another 40% were vaccinated with one dose of vaccine. The majority of cases (80%) occurred in persons between 16 and 30 years of age with a peak in the age group of 21 to 25 years (42%). Considering the minimum incubation period of 10 to 14 days, the mumps outbreak probably originated with virus transmissions to susceptible individuals at a village Easter festival [31]. In 2006 too, a mumps outbreak including 19 primary cases was recorded in a village in Spain. Patients' ages ranged between 18 and 37 years and 94% of the patients reported attending the annual festival held in the village. 58 secondary cases were reported [32].

Overall, the estimated incidence of confirmed respiratory infections per 100,000 attendees ranged from two to more than 420 during the outbreaks included in this review.

Sexual and blood transmission of infectious diseases

During music festivals, the risk of transmission of sexual or blood-borne infections is considered important, but this consideration is mainly speculative. Indeed, this risk is difficult to assess. Some of these infections have long incubation periods, making it difficult to relate the infection to the event. Despite the lack of evidence for the transmission of such diseases at festivals, the consumption of drugs and alcohol during music festivals is known to be high and may lead to at-risk behaviours, particularly unprotected sexual behaviours [5,33,34]. To our knowledge, the sexual-risk behaviour of participants during music festivals has been evaluated at several times only during the Big Day Out, one of the biggest music festivals in Australia [33,35]. Among sexually active participants, 43% reported not using a condom because of alcohol use [33]. Knowledge of STIs was poor overall [33]. In this young population (89% in the age group 16–24 years), surveillance of STI risk behaviour between 2005 and 2008 indicated that reporting having had a recent STI test increased from 23% in 2006 to 32% in 2008 [35]. Attempts to test for Chlamydia infection during the Big Day Out in 2009 has not been effective, with only 21% of participants returning the test and only one diagnosed case of Chlamydia infection [36].

Discussion

We describe various outbreaks related to large scale open air festivals, highlighting the fact that at these gatherings of people where the majority of attendees are aged 15 to 30 years, transmission of infections occurs at local, national [15,17,21] and international levels [24,25,29], as found during larger MGs [8]. Within open air festivals, music festivals contributed a large proportion of the outbreaks.

The outbreaks published in MEDLINE and ProMED are probably a tiny and heavily biased subset of all outbreaks associated with large scale open air festivals. This constitutes a limitation of our study and may explain the geographical repartition of the outbreaks included in our review. Unfortunately, general search-engines like Google and Yahoo are not sufficiently accurate tools to further identify outbreaks. Even the US Centers for Disease Control and Prevention foodborne outbreak online database (wwwn.cdc.gov/foodborneoutbreaks/Default.aspx) does not allow a distinction between festivals, fairs, and other temporary or mobile services.

During large scale open air festivals, respiratory infections can easily be transmitted due to overcrowded conditions which may contribute to the spread of new influenza viruses, as reported during the 2009 pandemic [25,26]. The risk of transmission and of the introduction of new strains of viruses in countries hosting MGs or large scale open air festivals has been documented at such events [8,27,28]. Therefore, risk assessment and the establishment of preventive strategies should be implemented in preparation for large scale open air festivals, as for other MGs. Measles is one of the most contagious human diseases, with a basic reproduction number ranging from 7.7 to 15 in a susceptible population [37]. Increased numbers of cases have recently been observed in young adults, notably in Europe [38]. Therefore, it is not surprising that measles outbreaks have occurred during youth festivals [29,30]. Interestingly, although immunisation programmes are required for certain MGs, such as the Hajj [8], there is no immunisation recommendation for large scale open air festivals.

Outbreaks of vaccine-preventable diseases, including hepatitis A, influenza, measles and mumps, have been reported in connection with large scale open air festivals [19,21,24,25,29-32] and could have been prevented by adequate vaccination coverage in the populations taking part. Although meningitis outbreaks have not been associated with large scale open air festivals, they have been described in the context of

the Hajj [8]. Vaccination against meningococcus may be considered for young people planning to participate in a large scale open air festival. The use of drugs and alcohol is common at large open air festivals and may theoretically increase the risk of transmission of STIs and blood-borne diseases [5,13,33].

A high incidence of Shigella, norovirus, *Cryptosporidium parvum* and hepatitis A virus infections was found among attendees of large scale open air festivals where outbreaks were reported compared to their respective incidence in the general population, suggesting that increased transmission of gastrointestinal infections may also occur in these settings. In contrast, no evidence for substantial increased risk of outbreaks of gastrointestinal infectious diseases was found during large international sport events notably due to proper sanitary supervision of food preparation and of water sources in these events [39]. Among previous outbreaks of gastrointestinal diseases reported at large scale open air festivals, the role of inadequate sanitation has been highlighted [14,15]. Good sanitation is therefore critical even at the smallest gatherings, where the organisation is often non-professional. Respect for hygiene rules for food handling is also critical to avoid food-borne disease transmission. In particular, the role of volunteers in food preparation should be examined. They constitute a potential risk because they are not trained in the necessary hygiene measures [14].

The discrepancy between sport events and large scale open air festivals in terms of infectious diseases may also be the consequence of the relatively short duration of sport events which frequently last shorter than one day, with many participants moving to other locations at the end of the event and who do not live on site [39]. In contrast, large scale open air festivals last several days with most attendees staying on site during the event, sharing accommodations and sanitations. In an old study conducted in 1972, the overall incidence of communicable diseases was 75 per 100,000 attendees during a 2.5 day music festival and 580 per 100,000 during a seven day-long music festival, suggesting that the length of exposure is a contributing factor to transmission of infectious diseases in the specific setting [10].

To prevent infectious diseases, communication and on-site advice about infectious risks should be implemented and hand-washing hygiene, cough etiquette and condom use should be promoted. Reminding people before festivals to check whether they have been immunised for certain vaccine preventable diseases including measles, mumps and influenza should be promoted. To prevent STIs and blood-borne diseases, campaigns involving the free distribution of condoms and syringes for intravenous drug users may be proposed.

Finally, surveillance after large scale open air festivals with participant recall may be implemented to better address infectious disease threats of international concern at the earliest possible stages. Social networks such as Twitter or Facebook can assist with active surveillance (e.g. public health outreach on Twitter or Facebook for people reporting health related issues in the host city during a festival and for people participating in a festival). Social media can function also as a method of passive surveillance (e.g. analysis of geographically tagged tweets). Mobile phones, particularly mobile internet use, facilitate the availability of real-time information at any time and nearly anywhere in the world to the general public and may be useful in this context [4]. Surveillance could also be operated through specialised networks reporting on travel-associated diseases, including GeoSentinel [40] and EuroTravnet [41]; however participation to large scale open air festival and MGs is not documented specifically at the moment in these databases.

Conclusions

Infections related to large scale open air festivals may be under-reported given the important number of these festivals worldwide. Alternatively these could also possibly be overestimated due to 'common sense' assumptions about conditions at festivals. We assume that most outbreaks probably remain unnoticed and underreported. The relationship between infections and festivals may be difficult to establish, especially for diseases with long-incubation periods and international events, as the participants spread worldwide. Cases could have been classified under 'travel-related' infections since participation to festivals or other MGs is usually not documented in surveillance networks records. We cannot give an estimate of the frequency of communicable diseases during large scale open air festivals, because of the relative paucity of published data. The creation of an online event and patient registry should overcome this gap [42].

During an event, syndromic surveillance associated with the use of adequate laboratory facilities may help to recognise the first cases of an outbreak although the value of syndromic surveillance during MGs is highly debated [43].

Preventive measures including immunisation of people participating in large scale open air festivals and targeted on-site advice about food hygiene, hand hygiene, cough etiquette and the use of condoms may be considered. However, the effectiveness of such preventive measures in the context of MGs has not been established and research is needed before this could be recommended [44]. Finally, strict adherence to food safety protocols and adequate sanitation should be promoted to prevent gastrointestinal diseases. The presence of on-site medical staff has proven to be cost-effective in improving the medical management of injuries and other health issues, such as infections [45].

Conflict of interest

The authors have no conflict of interest.

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REVIEW

Outdoor Transmission of SARS-CoV-2 and Other Respiratory Viruses: A Systematic Review

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Background. While risk of outdoor transmission of respiratory viral infections is hypothesized to be low, there are limited data on SARS-CoV-2 transmission in outdoor compared to indoor settings.

Methods. We conducted a systematic review of peer-reviewed papers indexed in PubMed, EMBASE, and Web of Science and preprints in Europe PMC through 12 August 2020 that described cases of human transmission of SARS-CoV-2. Reports of other respiratory virus transmission were included for reference.

Results. Five identified studies found a low proportion of reported global SARS-CoV-2 infections occurred outdoors (<10%) and the odds of indoor transmission was very high compared to outdoors (18.7 times; 95% confidence interval, 6.0–57.9). Five studies described influenza transmission outdoors and 2 adenovirus transmission outdoors. There was high heterogeneity in study quality and individual definitions of outdoor settings, which limited our ability to draw conclusions about outdoor transmission risks. In general, factors such as duration and frequency of personal contact, lack of personal protective equipment, and occasional indoor gathering during a largely outdoor experience were associated with outdoor reports of infection.

Conclusions. Existing evidence supports the wide-held belief that risk of SARS-CoV-2 transmission is lower outdoors but there are significant gaps in our understanding of specific pathways.

Keywords. coronaviruses; SARS-CoV-2; COVID-19; transmission; outdoor.

Recommendations about methods to curb transmission of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) beyond wearing masks and maintaining social distance have varied, especially regarding outdoor transmission [1]. This variability reflects a general lack of information on how SARS-CoV-2 is transmitted outdoors.

Outdoor spaces generally allow for more physical distancing, which mitigates the risk of virus transmission through larger respiratory droplets [2]. Outdoor spaces allow for airflow, ventilation, and lack of recycled air, which all minimize the theoretical risk of aerosol transmission through smaller respiratory droplets. While aerosol spread in community settings is controversial, emerging data suggest that indoor recycled air can spread SARS-CoV-2—with examples of spreading events in a restaurant in Guangzhou [3], at an indoor choir practice in Skagit, Washington, United States [4], at a South Korean call center [5], at meat-packing plants in the United States [6], and in a nursing home in the Netherlands [7]. In areas with low ventilation, aerosolized droplets have the capacity to linger for longer before being inhaled or falling to a surface, which could result in fomite transmission [8]. In enclosed environments, low humidity, air conditioning, and low UV light may all contribute to longer survival of viral particles [9]. Outdoor environments also generally have fewer high-touch surfaces that may harbor the virus. UV light, present outdoors from sunlight, results in a 10-fold decrease in virus survival on surfaces [10]. Finally, indoor environments may increase host susceptibility; the low indoor humidity has been associated with slower host ciliary clearance and complications such as pneumonia, and lack of sunlight has been associated with lower vitamin D levels [11]. For these reasons, the risk of virus transmission in outdoor locations has been hypothesized to be lower than in indoor spaces.

We sought to quantify the risk of SAR-CoV-2 transmission in outdoor settings. We conducted a systematic review of the literature on transmission of SARS-CoV-2 to better understand the risks of outdoor transmission. Where data were available, we estimated the risk of outdoor compared to indoor transmission. Anticipating a paucity of data on SARS-CoV-2, we chose a broad search strategy that included other human betacoronaviruses and respiratory viruses.

METHODS

Search Strategy and Selection Criteria

Data for this review were identified by searches of PubMed, EMBASE, Web of Science, as well as preprints available in

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Europe PMC [12]. Details of our search strategies and eligibility criteria can be found in our protocol published on 3 August 2020 on PROSPERO (ID, 183826: www.crd.york.ac.uk/prospero/). The search was conducted on 17 June 2020, and because of the rapidly expanding data on SARS-CoV-2, the search was repeated to include most-recent literature on 12 August 2020.

Exposures and Outcomes

The exposure of interest—outdoor gatherings—was defined as persons congregating outdoors for work, social, or recreational activities (see Supplementary Material 1 for our full search strategy). The outcome of interest included cases of transmission of SARS-CoV-2 or other respiratory viruses identified by a case report, illness, or mortality. We also included secondary outcomes of clusters or outbreaks of cases. Our search included any viral infection that can be spread by respiratory droplets and, in addition to SARS-CoV-2, included the other 2 recognized human betacoronaviruses (SARS-CoV-1 and Middle east respiratory syndrome-CoV), human influenza viruses, adenoviruses, rhinoviruses, human metapneumoviruses, and respiratory syncytial virus.

We included studies (experimental or observational with empirical data collection) that described human-to-human transmission of respiratory viruses between humans in an outdoor setting, any review of these studies, and any study (experimental or observational) that compared respiratory viral transmission among humans in an outdoor versus indoor settings.

We excluded reviews of previously published data, studies of exclusively indoor outbreaks, outdoor outbreaks within animal populations or between animals and humans, and outbreaks where the site of transmission was not listed or was unclear. We also excluded studies limited to built environments (homes, apartment buildings, military barracks), hospitals, or forms of transportation (airplanes, trains, buses, cars, ships).

Data Selection and Extraction

After removing duplicate records, 1 author (T. C. B.) reviewed all downloaded citations based on their titles and prespecified inclusion criteria. A second author (M. M.) reviewed a 5% random sample of the excluded titles (rejected from initial search results) for quality control. Two authors (T. C. B. and N. R.) then independently screened the titles, abstracts, and descriptor terms and compared and discussed discrepancies until consensus was reached; a third author (M. M.) served as an arbiter when needed. Two authors (T. C. B. and N. R.) then independently inspected the full texts of the remaining studies for relevance based on exposure, design, and outcome measures to select the included papers, and discussed discrepancies until consensus was reached with a third author (M. M.) serving as arbiter. We used Endnote X9.3.2 (Clarivate Analytics) and Rayyan (Qatar Computing Research Institute, Doha, Qatar) web-based software to manage search results [13].

Two authors (T. C. B. and N. R.) extracted the following data from each paper into a prepiloted data extraction form in Excel spread sheets: complete citation, study location, study design, details of participants (risk group or groups, sample size), exposure details (type of gathering, characteristics of gathering place, number of people, duration, proportion of time spent outdoors, amount if any of indoor transmission, how the nonexposure state (indoors) was defined, outcomes (numerators and denominators associated with each outcome, definitions and descriptions of outcomes provided in papers, details of how outcomes were assessed, individual cases of infection and/or large spreading events, mortality), methodological details (sample characteristics, how the information was gathered, how the outbreak was investigated), and details related to bias assessment.

RESULTS

The combined searches yielded 10 912 unique citations, of which 12 studies met our inclusion criteria. Nine studies were identified from the 17 June 2020 search, 2 from the 12 August 2020, and 1 from a targeted search. Out of the 12 that met our inclusion criteria, 5 were pertaining to SARS-CoV-2 (Table 1 and Table 2), 5 reported on influenza or influenza-like viruses (Table 3), and 2 reported on adenovirus transmission. Of note, 33 studies were excluded because they did not specify the location of transmission (Supplementary Material 2). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram is shown in Figure 1.

Five studies related to SARS-CoV-2 transmission found that less than 10% of reported transmission occurred in outdoor settings, less than 5% of cases were related to outdoor occupations, and the odds of transmission or super-spreading are much lower outdoors (Table 1) [14–17].

Of 318 identified outbreaks involving 3 or more cases in China reported to local Municipal Health Commissions from 4 January to 11 February 2020, Qian et al found that all occurred in indoor environments [14]. They reported a single transmission that occurred outdoors (1 case of outdoor transmission out of 7324 total reported cases). This report, however, might be affected by strict interventions prohibiting mass gatherings outdoors, which likely contributed to the low number of cases contracted outdoors. Additionally, relying on local health department reports may have led to underestimates of the total number of transmissions, especially those that were asymptomatic [14].

Nishiura et al [16] analyzed the transmission pattern of coronavirus disease 2019 (COVID-19) reported through 28 February 2020 (11 clusters and sporadic cases) in Japan. They concluded that the odds of a primary case transmitting COVID-19 in a closed environment were 18.7 times greater (95% confidence interval [CI], 6.0–57.9) compared to outdoor setting (defined as an open-air environment). The odds of a single case spreading

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Table 1. Comparison of Respiratory Virus Transmission Outdoors Compared to Indoors Ordered by Virus Studied

Outcome	Virus Studied	Estimate of Effect		Relative Estimate of Effect	Number of Participants in the Study
		Outdoor	Indoor		
Number of cases [14]	SARS-CoV-2	2/7324 cases	7322/7324 cases	<1% of transmissions happened outdoors	7324 cases, totaling 318 outbreaks
Number of cases [15]	SARS-CoV-2	4/103 cases	99/103 cases	5% of work-related cases occurred outdoors	103 possible work-related cases among a total of 690 local transmissions
Odds of transmission [16]	SARS-CoV-2	Raw data not available	Raw data not available	Odds of transmission in closed environments 18.7 (95% CI, 6.0–57.9) times greater than in open air	110 cases: 27 primary cases and 83 secondary cases
Number of super-spreading events and odds of transmission[a] [16]	SARS-CoV-2	1/7 super-spreading events	6/7 super-spreading events	Odds ratio of super-spreading in closed environments: 32.6 (95% CI, 3.7–289.5)	110 cases: 27 primary cases and 83 secondary cases
Number of cases [17]	SARS-CoV-2	95/10 926 cases	10 831/10 926 cases	<1% of transmissions happened outdoors	10 926 cases, totaling 201 events of transmission
Number of cases [18]	H1N1 2009 influenza	0/3 cases	24/29 cases	Of 32 total people in a holiday camp, 29 traveled together in a train wagon	32 people at a holiday camp
Mortality [19]	H1N1 1918 influenza	28/820 deaths sleeping in hammocks outside, 34.1 persons/1000	39/267 deaths sleeping in cabins inside, 146.1 persons/1000	Risk ratio 4.28 (95% CI, 2.69–6.81)	Total 1217 people on the ship

Abbreviations: CI, confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Super-spreading defined as events where the number of secondary cases generated by a single primary case is greater than the 95th percentile of the distribution (ie, transmission to 3 or more persons).

to 3 or more individuals, which they defined as a super-spreader event, in closed environments compared to open air was 32.6 (95% CI, 3.7–289.5). This report, however, included no description of the context or location of the outdoor transmission nor were any raw data provided. It is unclear whether this report is relying on proportions, which again may be subject to the fact that fewer people would have been outdoors during winter months in Japan.

Leclerc et al [17] reviewed 201 transmission clusters of COVID-19 worldwide that had been reported up to 30 March 2020. The vast majority of these transmissions were associated with indoor or indoor/outdoor settings (197/201 clusters or 21/22 locations). The 1 outdoor setting was at multiple construction sites in Singapore, where 4 outbreaks occurred. Leclerc's updated results by August 12, from non-peer reviewed sources, additionally revealed one transmission occurred while jogging in Codogno, Italy, and twenty cases in an outdoor park in Münster, Germany (Table 4).

Lan et al [15] investigated 103 possible work-related cases of COVID-19 among a total of 690 local cases in 6 Asian countries or regions, including Hong Kong, Japan, Singapore, Taiwan, Thailand, and Vietnam. In this paper, construction workers in Singapore constituted only 5% of the total work-related transmissions. While this paper did not explicitly state whether the location of work-related transmission was outdoor or indoors, it was included based on Leclerc's classification of the same construction workers as an outdoor setting. This does not rule out that that transmission may have occurred in indoor locations at construction sites.

Szablewski et al [20] report SARS-CoV-2 transmission at an overnight camp in Georgia, United States, where attack rates increased with increasing length of time at the camp, and with cohousing. Staff members, who stayed the longest at the camp, had the highest attack rate (56%). The outbreak was clustered by cabin assignments, which suggests a high likelihood of transmission in indoor spaces during overnight cabin stays rather than during outdoor activities during the day. The authors state that nonpharmaceutical interventions such as cohorting and adults wearing masks during the day, were not protective, although no further information is given about this claim.

While there is high heterogeneity in the studies describing outdoor transmission of SARS-CoV-2, the studies we found highlight the conditions of outdoor exposure and transmission. The location and context of SARS-CoV-2 transmissions reported in this review are summarized in Table 4. Among these are examples of transmissions at a gathering in a park, but over multiple days with the same people, and at a camp, which lasted for several days and had indoor housing components.

Five other studies included in Table 3 describe outdoor transmission of influenza or influenza-like viruses. Summers et al [19] conducted a historical analysis of a large outbreak of the 1918 influenza virus on a military troop ship in July 1918. The outbreak involved over 1000 of the 1217 crew members and caused 68 deaths. Analysis of factors that might have contributed to

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Table 2. Studies Reporting Outdoor SARS-CoV-2 Transmission

Reference	Location and Date	Sample Description	Design	Outcomes Measured	Outdoor Exposure	Outdoor Findings	Indoor Findings	Bias
Qian et al 2020 [14]	320 prefectural cities, China, 4 January to 11 February 2020	7324 cases, 318 outbreaks	Retrospective analysis of all public health reports from local Municipal Health Commission website to determine location of transmission	Location of transmissions, clusters, and outbreaks. Cluster defined as 3 or more infections that appear linked to the same infection venue. Outbreak defined as a cluster in which a common index patient is suspected. Outbreaks were organized by relationship and also by location.	Open air	One outdoor transmission involving 2 cases in Shangqiu, Henan: a 27-year-old man had a conversation outdoors with an individual who had returned from Wuhan	Of 318 identified outbreaks that involved 3 or more cases, they all occurred in indoor environments	Relied on heterogenous case reports of the local health department, which might have missed cases because of differential allocation of resources or internal biases. Additionally, the data were collected partly after lockdown (started 23 January 2020 in Wuhan), after which most people were indoors.
Nishiura et al 2020 [16]	7 prefectures in Japan, start date 28 February 2020	110 cases (27 primary cases, 83 secondary cases); 7 super-spreading events identified	Retrospective case investigation using contact tracing data	Location and number of transmissions from primary to secondary cases. Super-spreading events defined as number of secondary cases generated by a single primary case is greater than the 95th percentile of the distribution (ie, transmission to 3 or more persons)	Open air	Odds of transmission in a closed environment was 18.7 times greater compared to an open-air environment (95% CI, 6.0–57.9). Odds ratio of super-spreading events in closed environments was as high as 32.6 (95% CI, 3.7–289.5). One super-spreading event occurred outdoors (not described).	Of 7 super-spreading events, 6 (85.7%) took place in closed environments	Small sample size and no raw data provided to support calculations of odds. Limitations were not discussed in the manuscript. Not peer-reviewed at the time of review.
Leclerc et al 2020 [17]	Multiple world-wide locations, as of 30 March 2020	201 events of transmission (clusters)	Review of all documented transmission clusters (world-wide) using literature review and open-source strategies	Settings of transmission clusters for 201 events	22 types of settings were determined. Outdoor locations were defined as outdoor, while locations that were a mixture were defined as indoor/outdoor. Indoor locations were defined as indoor.	The transmissions in the only outdoor setting occurred in 4 outbreaks at outdoor construction sites in Singapore, totaling 95 cases. Updated results additionally revealed 1 transmission occurred while jogging in Codogno, Italy (nonpeer reviewed source) and 20 cases in an outdoor park in Münster, Germany (nonpeer reviewed source)	10/22 locations defined as indoor/outdoor, 11/ 22 defined as indoor. Total 197 events occurred in these settings, totaling 10 831 cases	Included reports from some nonpeer reviewed sources (eg. local media outlets for the jogging and outdoor park transmission reports), which might have been individually influenced by recall bias and poor methodology. While the study conducted a systematic review, additional sources were collected using an open-source strategy, which might have been affected by selection bias of respondents.

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Table 2. Continued

Reference	Location and Date	Sample Description	Design	Outcomes Measured	Outdoor Exposure	Outdoor Findings	Indoor Findings	Bias
Lan et al 2020 [15]	6 Asian regions: Hong Kong, Japan, Singapore, Taiwan, Thailand, and Vietnam, 23 January–14 March 2020	690 locally transmitted cases	Observational study, extracted confirmed COVID-19 cases from governmental investigation reports. Only locally transmitted (nonimported) cases were included. Transmission period was extended to 40 d from primary case.	Number of cases per occupation across country/area and stratified into early (first 10 d) and late (11-40 d) transmission periods	Workplace largely outdoors	A total of 103 possible work-related cases were determined to be outdoors among a total of 690 local transmissions. Of workers that might be prevalently outdoors, 5% of cases were construction workers. Tour guides (5% of cases) might also be considered to have occurred partly outdoors.	The 5 occupation groups with the most cases were health care workers (22%), drivers and transport workers (18%), services and sales workers (18%), cleaning and domestic workers (9%), and public safety workers (7%).	The exact outdoor/indoor makeup of the location of transmission was not described. This is in part due to the fact that the transmission source was not always known, and detailed occupational histories were also not always known. Also, none of the reports arose from systematic testing of high-risk occupations, rather from individual case reports, which might have been affected by biased and heterogenous reporting mechanisms from different regions.
Szablewski et al 2020 [20]	Overnight camp in Georgia, United States, 17–27 June 2020	During 17–20 June the overnight camp held orientation for 138 trainees and 120 staff members; staff members remained for the first camp session, scheduled 21–27 June, and were joined by 363 campers and 3 senior staff members on 21 June. Children and adults attended.	Retrospective case investigation (MMWR)	Positive test result for SARS-CoV-2 (symptomatic and asymptomatic)	Camp attendees were cohorted by cabin and engaged in a variety of indoor and outdoor activities, including daily vigorous singing and cheering	On 24 June a staff member tested positive to SARS-CoV-2. Test results were later available for 344 attendees; among these, 260 (76%) were positive. The percentage of transmission that developed solely outdoors was not investigated.	Median cabin attack rate was 50% among 28 cabins that had 1 or more cases (on average, each cabin housed 15 people). Attack rate was highest in the larger cabin, suggesting the main location of transmission was in the cabins.	Attack rates are likely an underestimate because cases might have been missed among persons not tested or whose test results were not reported. Some cases may have resulted from transmission occurring before or after camp attendance. Exact details of outdoor activities versus indoor were not described.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; MMWR, Morbidity and Mortality Weekly Report; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Table 3. Studies Reporting Other Outdoor Respiratory Virus Transmission Ordered by Infection Identified

Reference	Virus	Location and Date	Sample Description	Design	Outcomes Measured	Outdoor Exposure	Outdoor Findings	Indoor Findings	Bias
Figueroa et al 2017 [22]	Respiratory disease outbreaks	United States, 2009–2014	18 mass gatherings in 8 states	Data were collected on mass-gathering–related respiratory disease outcomes; 50 state health departments and 31 large local health departments were contacted via online assessment; 43 (53%) of 81 health jurisdictions responded	Outbreak was defined as 1 or more cases of an infectious respiratory disease. Mass gathering (exposure) was defined as a planned or unplanned congregation of 1000 or more persons in either an indoor or outdoor venue for a common purpose.	Mass gatherings were defined as indoors or indoor/outdoors	All reported outbreaks occurred at multiday mass gathering events. For influenza A (H1N1) attack rates at 2 summer camps were 1.4% and 4.8%. Attack rate for a religious event was 19.5%. At a sporting event in the spring, it was 3.3% but only included athletes. Attack rate of influenza A (H3) at another summer camp was 0.02%.	At a professional conference in the winter, which was likely to be mostly indoors, attack rate was of 21.0%. Probable factors that affected attack rates were participant density and susceptibility, rather than gathering size alone. Use of nonpharmaceutical interventions might have been an additional factor.	Low response rate (around 50%) by state health departments, while there was no response from local health departments. There might be responder bias, given that departments that experienced mass gathering outbreaks might have been more willing to respond. Details of each mass gathering and their indoor/outdoor locations are not described.
Rainey et al 2016 [21]	Respiratory disease outbreaks	United States, 2005–2014	21 published articles describing 72 mass-gathering–related respiratory disease outbreaks. 1114 outbreaks reported to NORS	6 medical, behavioral, and social science literature databases were analyzed to extract relevant articles. NORS was also analyzed to estimate the frequency of mass-gathering–related respiratory disease outbreaks.	Mass gatherings were defined as large events involving more than 1000 persons in a specific location for a shared purpose. Definition of outbreak was deferred to the author's definition. Half of the reported outbreaks were related to a zoonotic source and were excluded. 38% of the outbreaks occurred at a variety of camps.	The authors did not specify outdoor vs indoor location of mass gathering	Close social mixing and contact in communal housing/activities were associated with all other outbreaks identified. They concluded that multiday mass gatherings with indoor residential overnight components can facilitate transmission.	All reported outbreaks in summer camps had social contact and communal housing, none reported without a housing component	Search strategy might have not captured studies that did not use the word outbreak, and might have missed any outbreak not captured by surveillance systems (eg. smaller outbreaks, of diseases with longer incubation periods). While indoor and outdoor characteristics of mass gatherings were discussed, exact amount of time spent outdoors compared to indoors not delineated.
Botelho-Nevers et al 2013 [23]	Disease outbreaks (including respiratory disease)	Open-air mass gatherings worldwide, 1980–2012	9 published articles about respiratory infections at large, outdoor mass gatherings, festivals, or music festivals	Literature search using PubMed and MEDLINE database, with cross-referencing using search engines such as Google and Yahoo	Outbreaks in the setting of open-air gatherings	Mass gatherings defined as generally outdoors, but which may have onsite indoor housing and food supply	4 outbreaks of influenza A (H1N1) and 1 of influenza A and B were found. Overall, the estimated incidence of confirmed respiratory infections of influenza per 100 000 attendees ranged from 2 to 30. The discrepancy between sport events, which seem to have lower incidence, and large-scale open-air festivals in terms of infectious diseases may also be the consequence of the relatively short duration of sports events, which frequently last shorter than 1 day.	No exclusively indoor events were included	The infections related to large open-air festivals may be underreported, given difficulty in ascertaining exact location of transmission and sporadic surveillance systems. The search strategy of only using ProMed and MEDLINE might have limited the amounts of results that might otherwise be available on other reporting/surveillance agencies.

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Table 3. Continued

Reference	Virus	Location and Date	Sample Description	Design	Outcomes Measured	Outdoor Exposure	Outdoor Findings	Indoor Findings	Bias
Pestre et al 2012 [18]	2009 H1N1 Influenza	Summer camp in France, August 2009	32 persons participated in the holiday camp; 29 of them traveled in the same train wagon	Retrospective case investigation	Infection of H1N1 influenza	Individuals who did not travel in the same train wagon	The outbreak involved 21 children and 3 adults who had all travelled together in the same wagon. The 3 individuals that did not take the same train wagon and were immediately thereafter in contact with the 24 infected individuals at camp did not experience influenza symptoms.	Out of 29 individuals who took the same train wagon, 21 children and 3 adults experienced symptoms	Conditions of outdoor versus indoor activities at camp were not described. Given this, the comparison between indoor (train wagon) and outdoor (camp) exposure assumes that a majority of time at camp, as compared to the train wagon, was outdoors. Measurement of cases might have been affected by timing of testing and/or presence of asymptomatic cases. Limitations were not discussed.
Summers et al 2010 [19]	1918 Influenza	His Majesty's New Zealand Transport military troop ship in Sierra Leone, July 1918	1217 persons onboard	Retrospective historical outbreak analysis	Mortality	Sleeping in hammocks as opposed to cabins with bunks	Of 1217 persons onboard, over 1000 suspected cases of influenza, 68 deaths. Mortality rate for persons that slept in hammocks outdoors was 28/820 or 34.1 persons/1000 population.	Mortality rate for persons that slept in cabins with bunks was 39/267 (146.1 persons/1000 population). The difference between hammocks was significant (crude RR, 4.28; 95% CI, 2.69–6.81). Density did not seem to be a contributing factor.	Historical evidence used in this paper is subject to transcription and/or recording errors, lack of case definitions, and approximate estimates of case numbers. While it is hinted that hammocks were in higher ventilated zones outdoors as compared to cabins, the exact location of hammocks was not described.

Abbreviations: CI, confidence interval; NORS, National Outbreaks Reporting System; RR, relative risk.

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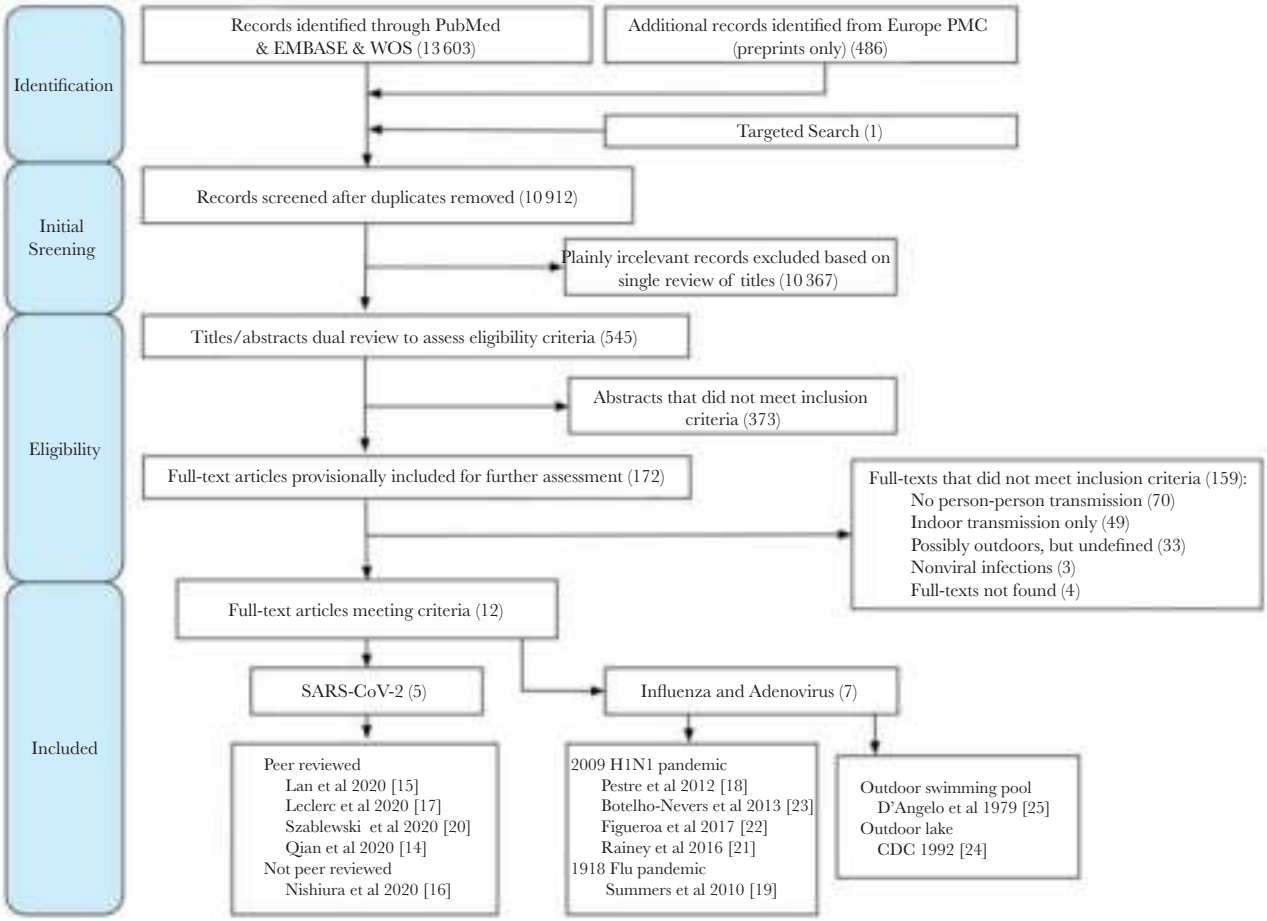

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram for the study. Abbreviations: CDC, Centers for Disease Control and Prevention; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOS, Web of Science.

mortality revealed a significant association between individuals who slept indoors, in cabins with bunks (mortality of 146.1/1000 population), versus individuals who slept in hammocks in open-air areas (mortality of 34.1/1000 population). This study is of particular interest because the duration of exposure and distance between individuals was held constant. This was one of the few studies that investigated potential confounders such as age and social class—mortality changed with age, but not with social class or rurality. Age did not change the discrepancy in deaths seen outdoors compared to indoors.

Pestre et al [18] conducted a retrospective analysis of a 2009 H1N1 influenza outbreak at a summer camp in France. Investigations revealed that all febrile individuals had travelled together in the same train passenger car to reach camp, suggesting that the enclosed space facilitated transmission. The 3 individuals out of 32 that had not travelled in the same train wagon as all the other participants never developed symptoms, even though they were still present at camp for 2 days with all other infected individuals—presumably mostly in outdoor spaces.

Finally, 3 reports about respiratory illnesses at mass open-air gatherings emphasized that while influenza outbreaks were uncommon, the duration of the event (multiday over single day) and communal housing were risk factors for outbreaks (Table 3) [21–23]. Rainey et al concluded that all reported outbreaks in summer camps had social contact and communal housing; none were reported without a shared housing component [21]. Of note, no single-day mass-gathering–related outbreaks were detected in the 72 outbreaks they detail. Figueroa et al also did not identify any single-day event-related outbreaks [22]. Botelho et al found 4 outbreaks of influenza A (H1N1) and 1 of influenza A and B; all events with an outbreak were multiday sport events while single-day events had none [23].

Two articles discussed adenovirus outbreaks associated with lakes [24] and outdoor swimming pools [25]. In both studies respiratory viral infection occurred in swimmers and in others who did not swim, such as fellow camp attendees and family members, suggesting human-to-human transmission prevalently occurring outdoors.

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Table 4. Outdoor Conditions Where COVID-19 Was Transmitted

Setting	Description of Transmission	Purely Outdoors?	Use of Nonpharmaceutical Interventions[a]
Overnight summer camp [20]	Outbreak of 260 cases during an overnight camp in Georgia. Everyone tested negative for COVID-19 ≤12 days prior to coming to camp. While exact outdoor activities were not described, the overnight component suggests that the attack rate increased with length of time spent at the camp. This was shown by staff members, who were present at camp the longest, having the highest attack rate (56%). Attack rate associated with being adult, length of stay, and being in a cabin together. Median attack rate in the cabins, 50%; overall attack rate, 44%.	No	Yes. They state the NPI was not effective. NPIs were cohorting of attendees by cabin (≤ 26 persons), staggering of cohorts for use of communal spaces, physical distancing outside cabin cohorts, and enhanced cleaning and disinfection, especially of shared equipment and spaces. Cloth masks were required for staff members. Evidently, these interventions were not effective at preventing a majority of cases.
Conversation in outdoor setting [14]	One outdoor transmission involving 2 cases in Shangqiu, Henan: a 27-year-old man had a conversation outdoors with an individual who had returned from Wuhan. No secondary or tertiary cases from this transmission were reported	Yes	Unknown
Outdoor construction sites [15, 17]	Four outbreaks at outdoor construction sites in Singapore, involving a total of 95 cases [17]. 5 cases of construction workers in Singapore [15]. Details of exact location of transmission were not described. Details of indoors versus outdoors unknown. However, in Leclerc et al [17] building sites were described as outdoor settings.	Unknown	Unknown
Jogging outdoors [17]	1 transmission while jogging in Codogno, Italy (reported by local news media, cited in Leclerc et al [17] open source database)	Yes	Unknown
Outdoor park [17]	20 cases in an outdoor park in Münster, Germany (reported by local news media, cited in Leclerc et al [17] open source database). The members of the extended family, who had been living in different houses in the Angelmodde district of Munster, were suspected to have met often on a playground in the Osthuesheide district. The activities of the family were not described, but it was described as a repeated exposure over days.	Yes	Unknown

Abbreviations: COVID-19 coronavirus disease 2019; NPI, nonpharmaceutical intervention.
[a]Such as masks, physical distance, cohorting.

DISCUSSION

While the studies included in this review were highly heterogeneous, ranging in methodology, definition of outdoor transmission, and virus studied, several common factors were identified. The studies with direct comparison of SARS-CoV-2 location of transmission reported dramatically lower proportions occurring outdoors. The exact determinants of outdoor transmission that can be gleaned from this review are limited, the cases of outdoor transmission of SARS-CoV-2 we identified were affected by the duration of exposure, frequency of exposure, density of gathering, whether masks were used, and were confounded by the possibility of indoor transmission.

Historical evidence gleaned from influenza outbreaks further support the lower risk of transmission outdoors. Summers et al showed that influenza mortality on a ship was significantly lower outdoors (sleeping in hammocks) compared to indoors (sleeping in cabins) [19]. While mortality does not provide direct information about transmission, it serves as a useful proxy. Outcomes from several investigations of influenza outbreaks during mass outdoor gatherings suggest that outdoor, single-day events without communal sleeping arrangements have lower risks of influenza transmission than multiday events with indoor components [21–23].

These findings, as well as reports of influenza outbreaks and adenovirus outbreaks in outdoor bodies of water, suggest that while outdoor transmission is less common than indoor, it is not impossible. Case reports identified after our review had been completed provide further evidence that high-density outdoor gatherings, particularly with low mask use, may lead to higher transmission rates. Miron et al noted that incidence of COVID-19 cases was significantly higher in 14 out of 20 counties that had a large outdoor gathering 15 days prior [26]. Dave et al estimated that in the 3 weeks following the start of the Sturgis motorcycle rally on 7 August 2020, in South Dakota, a multiday event with 500 000 participants, cases grew more in counties with weak mitigation policies than those with strong mitigation policies (such as closure of restaurants and bars, or mask-wearing mandates) as participants returned to their homes [27]. In contrast, although COVID-19 rates increased in the 3 weeks following the mass protests in the United States [28], the uptick in cases due to these events was less than expected because social distancing and masking measures were more widespread [29]. The importance of protective measures is further exemplified by the outdoor outbreak that occurred at the White House Rose Garden event on 26 September 2020, where few of the 200 attendees were wearing masks or maintaining social distancing measures [30].

Of note, our search did not find any studies on the transmission of COVID-19 in settings of outdoor agricultural work. In California, prevalence of COVID-19 for agricultural workers is 2 to 3 times higher than the rate for workers in all other industries [31]. The experience of agricultural workers suggests

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that crowded working or sleeping conditions may be a substantive risk factor for transmission, but the contribution of work in outdoor spaces to transmission risk has not been assessed. We found that outdoor, single-day events without communal sleeping arrangements have lower risks of transmission compared to multiday, mass outdoor gatherings in the spread of influenza [21–23].

To better characterize the risks of outdoor SARS-CoV-2 exposure, future studies should fill the research gaps we have identified in this review. First, many research studies we identified did not report the location of transmission at all. This may be because understanding relationships between cases is more important than the location of interaction, or may be related to practical challenges in contact tracing outdoors. Second, it is difficult to isolate an outdoor exposure to a virus. While outdoor gatherings could be largely safe, if they are accompanied by time in indoor locations, such as cabins or trains, it might be challenging to identify the exact location of transmission. In the report by Szablewski et al, which was included in our review, while the summer camp may have been largely outdoors, it does not preclude exposure in the dining halls or cabins. As for construction sites, once a building is framed and enclosed, it may be considered indoor work, which may in fact be the majority of the work. Third, in many reports published early in the SARS-CoV-2 pandemic, the measured outcome was illness or death due to viral infection, not SARS-CoV-2 infection itself, which was rarely assessed. If asymptomatic infections are more likely to occur outdoors, this could represent a systematic bias. Fourth, the definition of being outdoors is ambiguous, and the effect of exposure is likely modified by variable proximity to and contact with others. Fifth, to test the hypothesis that the risk of infection is lower outdoors, future research should collect data about time spent indoors versus outdoors. Given that 90% of time is spent indoors in high- and middle-income countries [32], it would be expected that 90% of transmission occurs indoors, all else being equal. Lastly, there are few data that examine how respiratory droplets spread outdoors, such as how far they travel during running, biking, or during windy conditions. A study examined these variables but was calculated with no account of ventilation, sunlight, or humidity [33].

Finally, most of the transmission events we identified in the literature did not report the socioeconomic status of those impacted. Spreading events often occur in settings where marginalized and disempowered populations live or work such as lower-income, higher-density urban settings, work settings such as meat-packing plants, or even prisons [34]. While there are multiple reasons for the disproportionate impacts of COVID-19 in these populations, we postulate that lack of opportunity to move high-risk activities outdoors may be one of them [35, 36]. While it was our intention to further explore this hypothesis by analyzing subgroup socioeconomic and ethnicity data in the studies included in this review, the studies did not include these metrics.

Future studies could compare SARS-CoV-2 case rates at outdoor gatherings to known rates for indoor gatherings. There are several examples of studies that estimate the risk of indoor transmission [37–39], which have ranged from 10.3% (95% CI, 5.3%–19.0%) in a study of train travel in China to 78% in a church in Arkansas [38]. Accurate estimation of the risk of outdoor transmission will require determining person-time at risk for infection, incidence rate ratios, and more nuanced information about the exposure environment; these data are still lacking.

Better understanding of how SARS-CoV-2 is transmitted outdoors is needed to inform sound policies that reconcile shelter-in-place orders with the many health benefits associated with time spent outdoors [40]. This is particularly relevant to outdoor parks and recreation agencies, which seek clear guidance on how being outdoors has a low risk of transmission. Other policy implications are to encourage moving essential activities outdoors, with appropriate masking and social distancing measures, given that transmission can still occur outdoors. The long-term and potentially deleterious social and emotional effects of school closures can be potentially mitigated if, for example, it is known that outdoor schooling is a viable alternative. Finally, encouraging outdoor time may serve as a harm reduction model in allowing people to congregate, and therefore better tolerate long-term shelter in place mandates.

This systematic review has several limitations. The few and heterogenous studies on outdoor transmission of respiratory viruses had used various metrics, exposures, and outcomes, making it challenging to compare findings quantitatively. The low proportion of outdoor COVID-19 cases may reflect the general decrease in outdoor activities since strict lockdowns were enacted in the countries surveyed. Relying on reports of symptomatic infections may underrepresent asymptomatic cases that occur outdoors. If the viral inoculum affects the severity of respiratory viral infection, an outdoor exposure may reduce the viral inoculum to which the individual is exposed and therefore the subsequent clinical impact of the disease. If this theory were true for SARS-CoV-2, it may increase the proportion of infections that are asymptomatic [41]. The studies in this review did not contain much information about potential confounders such as the age of infected individuals, activities in which they participated, ethnicity, or social class. There was minimal information on mitigation efforts such as masks and social distancing and how that may have impacted/influenced viral transmission. This review did not explicitly include gray literature (such as case reports from health departments, lay newspaper sources) in its search strategy, as other comprehensive reviews of transmissions have done [17]. Including preprints may have decreased our risk of information bias.

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CONCLUSION

While it has been acknowledged that spending time outside has general health benefits, our review posits that there are also benefits in reducing transmission of SARS-CoV-2 by reducing exposure time (substituting time indoors with time outdoors). These results suggest that moving activities to outdoor settings may reduce infections and ultimately save lives. However, it is important to note that infections are possible outdoors and the advantage may be overtaken by relaxed mitigation efforts.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)

16-24 February 2020

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I. The Mission

Goal and Objectives

The overall goal of the Joint Mission was to rapidly inform national (China) and international planning on next steps in the response to the ongoing outbreak of the novel coronavirus disease (COVID-19[1]) and on next steps in readiness and preparedness for geographic areas not yet affected.

The major objectives of the Joint Mission were as follows:

- To enhance understanding of the evolving COVID-19 outbreak in China and the nature and impact of ongoing containment measures;
- To share knowledge on COVID-19 response and preparedness measures being implemented in countries affected by or at risk of importations of COVID-19;
- To generate recommendations for adjusting COVID-19 containment and response measures in China and internationally; and
- To establish priorities for a collaborative programme of work, research and development to address critical gaps in knowledge and response and readiness tools and activities.

Members & Method of Work

The Joint Mission consisted of 25 national and international experts from China, Germany, Japan, Korea, Nigeria, Russia, Singapore, the United States of America and the World Health Organization (WHO). The Joint Mission was headed by Dr Bruce Aylward of WHO and Dr Wannian Liang of the People's Republic of China. The full list of members and their affiliations is available in Annex A. The Joint Mission was implemented over a 9-day period from 16-24 February 2020. The schedule of work is available in Annex B.

The Joint Mission began with a detailed workshop with representatives of all of the principal ministries that are leading and/or contributing to the response in China through the National Prevention and Control Task Force. A series of in-depth meetings were then conducted with national level institutions responsible for the management, implementation and evaluation of the response, particularly the National Health Commission and the China Centers for Disease Control and Prevention (China CDC). To gain first-hand knowledge on the field level implementation and impact of the national and local response strategy, under a range of epidemiologic and provincial contexts, visits were conducted to Beijing Municipality and the provinces of Sichuan (Chengdu), Guangdong (Guangzhou, Shenzhen) and Hubei (Wuhan). The field visits included community centers and health clinics, country/district hospitals, COVID-19 designated hospitals, transportations hubs (air, rail, road), a wet market, pharmaceutical and personal protective equipment (PPE) stocks warehouses, research institutions, provincial health commissions, and local Centers for

[1] In the Chinese version of this report, COVID-19 is referred to throughout as novel coronavirus pneumonia or NCP, the term by which COVID-19 is most widely known in the People's Republic of China.

Disease Control (provincial and prefecture). During these visits, the team had detailed discussion and consultations with Provincial Governors, municipal Mayors, their emergency operations teams, senior scientists, frontline clinical, public health and community workers, and community neighbourhood administrators. The Joint Mission concluded with working sessions to consolidate findings, generate conclusions and propose suggested actions.

To achieve its goal, the Joint Mission gave particular focus to addressing key questions related to the natural history and severity of COVID-19, the transmission dynamics of the COVID-19 virus in different settings, and the impact of ongoing response measures in areas of high (community level), moderate (clusters) and low (sporadic cases or no cases) transmission.

The findings in this report are based on the Joint Mission's review of national and local governmental reports, discussions on control and prevention measures with national and local experts and response teams, and observations made and insights gained during site visits. The figures have been produced using information and data collected during site visits and with the agreement of the relevant groups. References are available for any information in this report that has already been published in journals.

The final report of the Joint Mission was submitted on 28 February 2020.

II. Major findings

The major findings are described in six sections: the virus, the outbreak, transmission dynamics, disease progression and severity, the China response and knowledge gaps. More detailed descriptions of technical findings are provided in Annex C.

The virus

On 30 December 2019, three bronchoalveolar lavage samples were collected from a patient with pneumonia of unknown etiology – a surveillance definition established following the SARS outbreak of 2002-2003 – in Wuhan Jinyintan Hospital. Real-time PCR (RT-PCR) assays on these samples were positive for pan-Betacoronavirus. Using Illumina and nanopore sequencing, the whole genome sequences of the virus were acquired. Bioinformatic analyses indicated that the virus had features typical of the coronavirus family and belonged to the Betacoronavirus 2B lineage. Alignment of the full-length genome sequence of the COVID-19 virus and other available genomes of Betacoronavirus showed the closest relationship was with the bat SARS-like coronavirus strain BatCov RaTG13, identity 96%.

Virus isolation was conducted with various cell lines, such as human airway epithelial cells, Vero E6, and Huh-7. Cytopathic effects (CPE) were observed 96 hours after inoculation. Typical crown-like particles were observed under transmission electron microscope (TEM) with negative staining. The cellular infectivity of the isolated viruses could be completely neutralized by the sera collected from convalescent patients. Transgenic human ACE2 mice and Rhesus monkey intranasally challenged by this virus isolate induced multifocal pneumonia with interstitial hyperplasia. The COVID-19 virus was subsequently detected and isolated in the lung and intestinal tissues of the challenged animals.

Whole genome sequencing analysis of 104 strains of the COVID-19 virus isolated from patients in different localities with symptom onset between the end of December 2019 and mid-February 2020 showed 99.9% homology, without significant mutation (Figure 1).

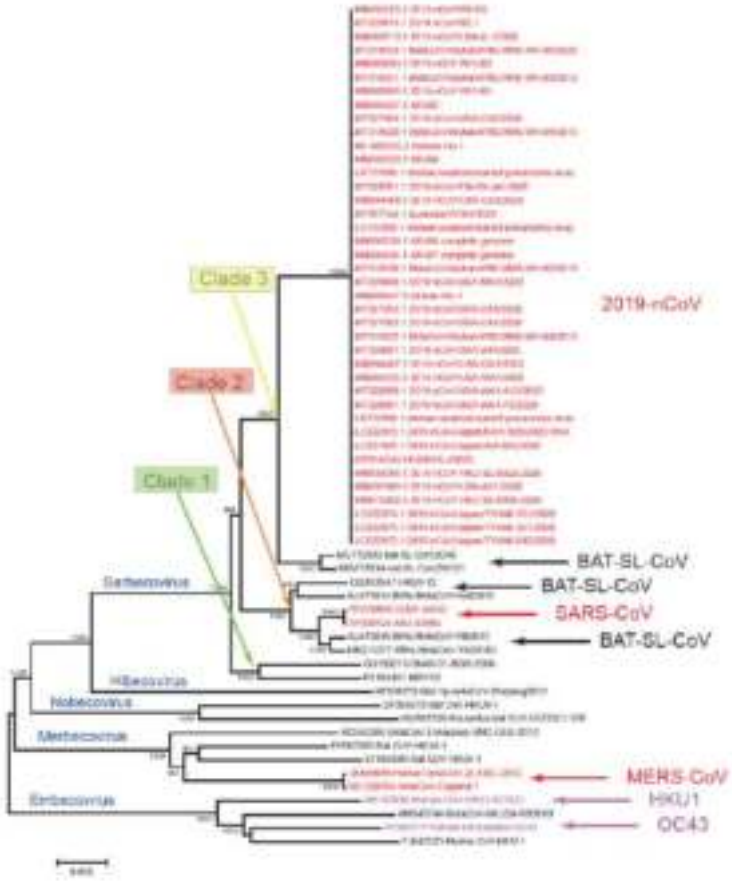

Figure 1. Phylogenetic analysis of the COVID-19 virus and its closely related reference genomes

Note: COVID-19 virus is referred to as 2019-nCoV in the figure, the interim virus name WHO announced early in the outbreak.

Post-mortem samples from a 50-year old male patient from Wuhan were taken from the lung, liver, and heart. Histological examination showed bilateral diffuse alveolar damage with cellular fibromyxoid exudates. The lung showed evident desquamation of pneumocytes and hyaline membrane formation, indicating acute respiratory distress syndrome (ARDS). Lung tissue also displayed cellular and fibromyxoid exudation, desquamation of pneumocytes and pulmonary oedema. Interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes, were seen in both lungs. Multinucleated syncytial cells with atypical enlarged pneumocytes characterized by large nuclei, amphophilic granular cytoplasm, and prominent nucleoli were identified in the intra-alveolar spaces, showing viral cytopathic-like changes. No obvious intranuclear or intracytoplasmic viral inclusions were identified.

The outbreak

As of 20 February 2020, a cumulative total of 75,465 COVID-19 cases were reported in China. Reported cases are based on the National Reporting System (NRS) between the

National and Provincial Health Commissions. The NRS issues daily reports of newly recorded confirmed cases, deaths, suspected cases, and contacts. A daily report is provided by each province at 0300hr in which they report cases from the previous day.

The epidemic curves presented in Figures 2 and 3 are generated using China's National Infectious Disease Information System (IDIS), which requires each COVID-19 case to be reported electronically by the responsible doctor as soon as a case has been diagnosed. It includes cases that are reported as asymptomatic and data are updated in real time. Individual case reporting forms are downloaded after 2400hr daily. Epidemiologic curves for Wuhan, Hubei (outside of Wuhan), China (outside Hubei) and China by symptom onset are provided in Figure 2.

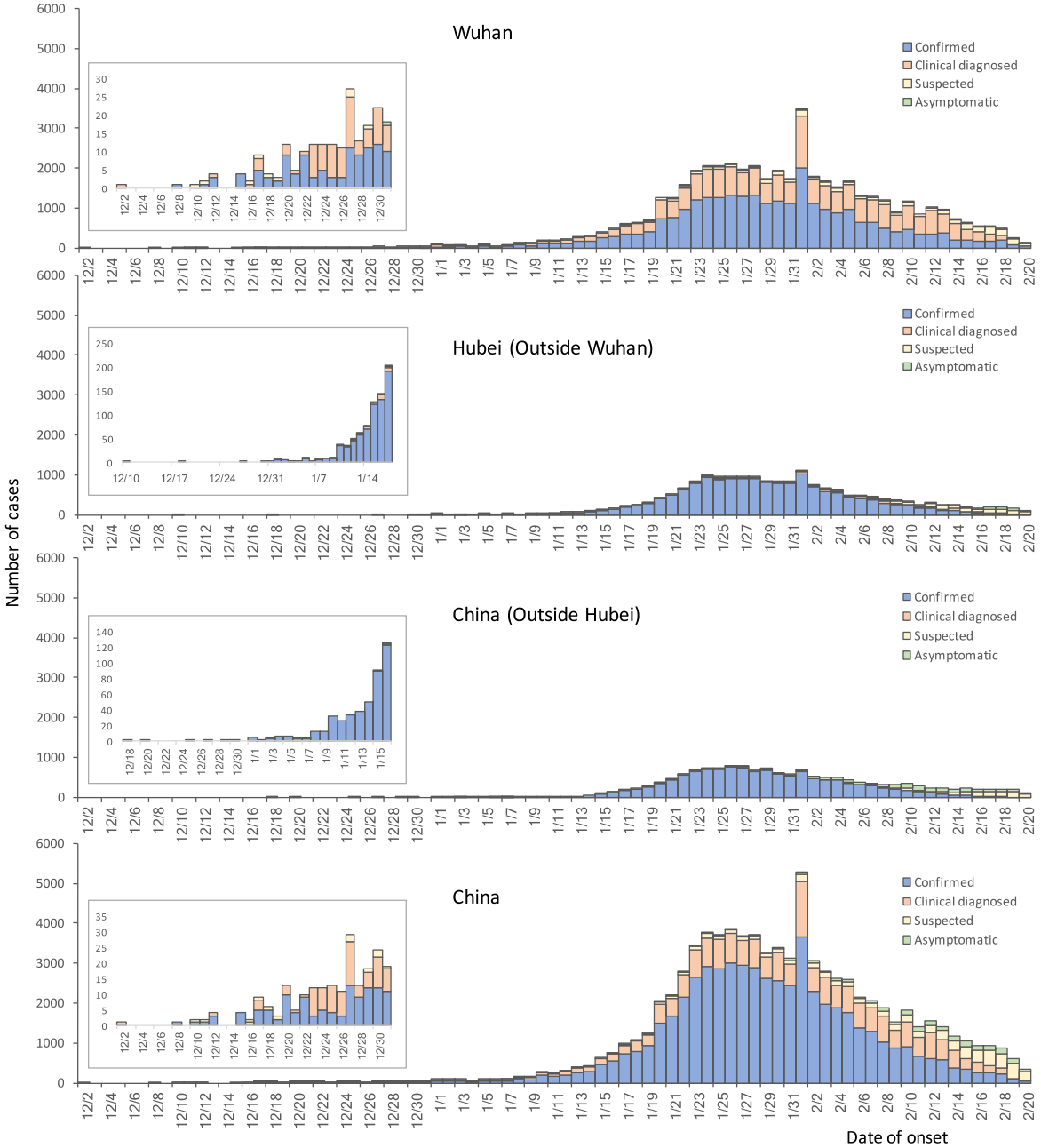

Figure 2 Epidemiologic curve of COVID-19 laboratory confirmed cases, by date of onset of illness, reported in China, as of 20 February 2020

Figure 3 presents epidemic curves of laboratory-confirmed cases, by symptom onset and separately by date of report, at 5, 12, and 20 February 2020. Figures 2 and 3 illustrate that the epidemic rapidly grew from 10-22 January, reported cases peaked and plateaued between 23 January and 27 January, and have been steadily declining since then, apart from the spike that was reported on 1 February (note: at a major hospital in Wuhan, fever clinic patients fell from a peak of 500/day in late January to average 50/day since mid-February).

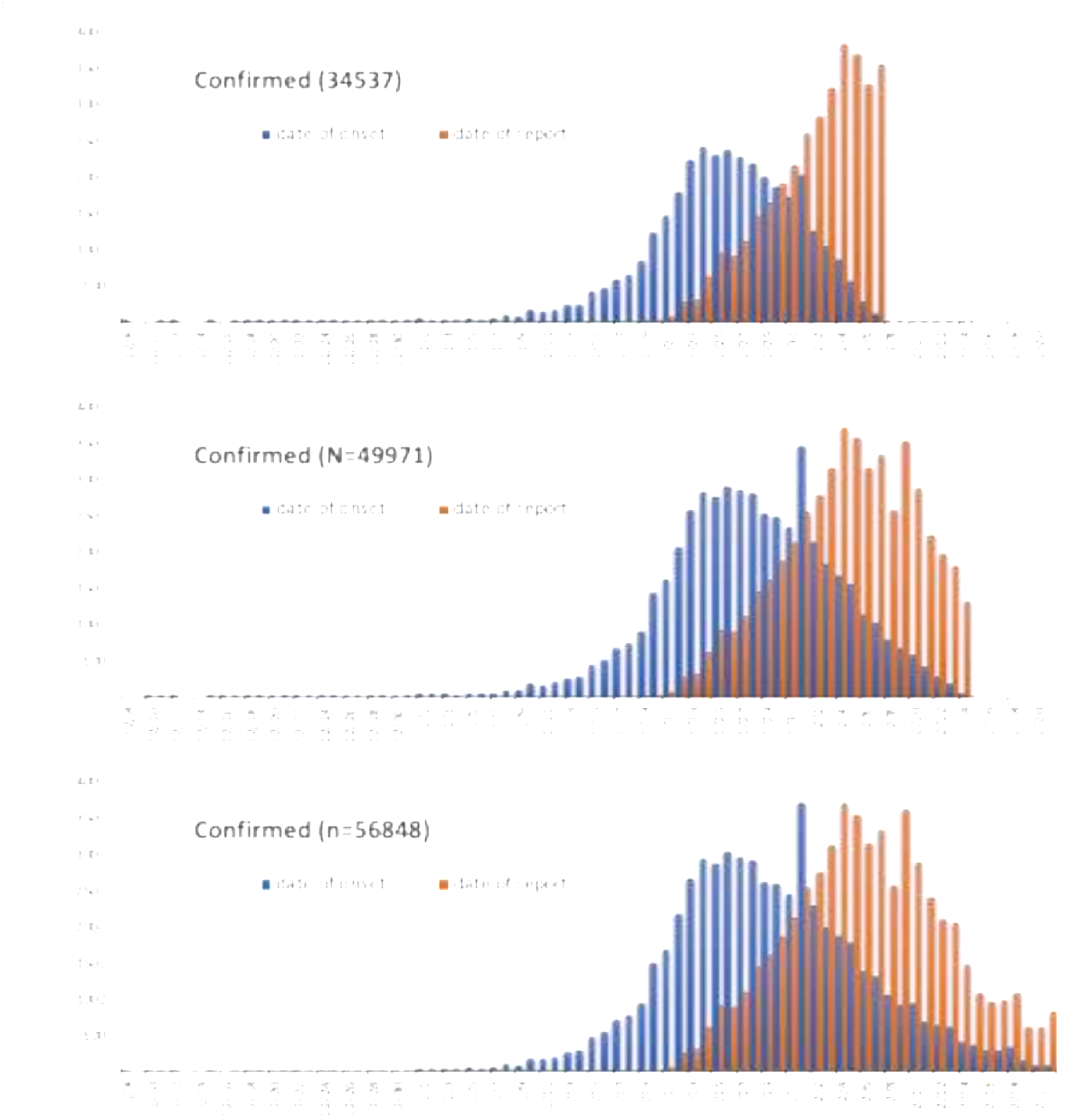

Figure 3. Epidemic curves by symptom onset and date of report as of 5 February (top panel), 12 February (middle panel) and 20 February 2020 (lower panel) for laboratory confirmed COVID-19 cases for all of China

Based on these epidemic curves, the published literature, and our on-site visits in Wuhan (Hubei), Guangdong (Shenzhen and Guangzhou), Sichuan (Chengdu), and Beijing, the Joint Mission team has made the following epidemiological observations:

Demographic characteristics

Among 55,924 laboratory confirmed cases reported as of 20 February 2020, the median age is 51 years (range 2 days-100 years old; IQR 39-63 years old) with the majority of cases (77.8%) aged between 30–69 years. Among reported cases, 51.1% are male, 77.0% are from Hubei and 21.6% are farmers or laborers by occupation.

Zoonotic origins

COVID-19 is a zoonotic virus. From phylogenetics analyses undertaken with available full genome sequences, bats appear to be the reservoir of COVID-19 virus, but the intermediate host(s) has not yet been identified. However, three important areas of work are already underway in China to inform our understanding of the zoonotic origin of this outbreak. These include early investigations of cases with symptom onset in Wuhan throughout December 2019, environmental sampling from the Huanan Wholesale Seafood Market and other area markets, and the collection of detailed records on the source and type of wildlife species sold at the Huanan market and the destination of those animals after the market was closed.

Routes of transmission

COVID-19 is transmitted via droplets and fomites during close unprotected contact between an infector and infectee. Airborne spread has not been reported for COVID-19 and it is not believed to be a major driver of transmission based on available evidence; however, it can be envisaged if certain aerosol-generating procedures are conducted in health care facilities. Fecal shedding has been demonstrated from some patients, and viable virus has been identified in a limited number of case reports. However, the fecal-oral route does not appear to be a driver of COVID-19 transmission; its role and significance for COVID-19 remains to be determined. Viral shedding is discussed in the Technical Findings (Annex C).

Household transmission

In China, human-to-human transmission of the COVID-19 virus is largely occurring in families. The Joint Mission received detailed information from the investigation of clusters and some household transmission studies, which are ongoing in a number of Provinces. Among 344 clusters involving 1308 cases (out of a total 1836 cases reported) in Guangdong Province and Sichuan Province, most clusters (78%-85%) have occurred in families. Household transmission studies are currently underway, but preliminary studies ongoing in Guangdong estimate the secondary attack rate in households ranges from 3-10%.

Contact Tracing

China has a policy of meticulous case and contact identification for COVID-19. For example, in Wuhan more than 1800 teams of epidemiologists, with a minimum of 5 people/team, are tracing tens of thousands of contacts a day. Contact follow up is painstaking, with a high percentage of identified close contacts completing medical observation. Between 1% and 5% of contacts were subsequently laboratory confirmed cases of COVID-19, depending on location. For example:

- As of 17 February, in Shenzhen City, among 2842 identified close contacts, 2842 (100%) were traced and 2240 (72%) have completed medical observation. Among the close contacts, 88 (2.8%) were found to be infected with COVID-19.

- As of 17 February, in Sichuan Province, among 25493 identified close contacts, 25347 (99%) were traced and 23178 (91%) have completed medical observation. Among the close contacts, 0.9% were found to be infected with COVID-19.
- As of 20 February, in Guangdong Province, among 9939 identified close contacts, 9939 (100%) were traced and 7765 (78%) have completed medical observation. Among the close contacts, 479 (4.8%) were found to be infected with COVID-19.

Testing at fever clinics and from routine ILI/SARI surveillance

The Joint Mission systematically enquired about testing for COVID-19 from routine respiratory disease surveillance systems to explore if COVID-19 is circulating more broadly and undetected in the community in China. These systems could include RT-PCR testing of COVID-19 virus in influenza-like-illness (ILI) and severe acute respiratory infection (SARI) surveillance systems, as well as testing of results among all visitors to fever clinics.

In Wuhan, COVID-19 testing of ILI samples (20 per week) in November and December 2019 and in the first two weeks of January 2020 found no positive results in the 2019 samples, 1 adult positive in the first week of January, and 3 adults positive in the second week of January; all children tested were negative for COVID-19 although a number were positive for influenza. In Guangdong, from 1-14 January, only 1 of more than 15000 ILI/SARI samples tested positive for the COVID-19 virus. In one hospital in Beijing, there were no COVID-19 positive samples among 1910 collected from 28 January 2019 to 13 February 2020. In a hospital in Shenzhen, 0/40 ILI samples were positive for COVID-19.

Within the fever clinics in Guangdong, the percentage of samples that tested positive for the COVID-19 virus has decreased over time from a peak of 0.47% positive on 30 January to 0.02% on 16 February. Overall in Guangdong, 0.14% of approximately 320,000 fever clinic screenings were positive for COVID-19.

Susceptibility

As COVID-19 is a newly identified pathogen, there is no known pre-existing immunity in humans. Based on the epidemiologic characteristics observed so far in China, everyone is assumed to be susceptible, although there may be risk factors increasing susceptibility to infection. This requires further study, as well as to know whether there is neutralising immunity after infection.

The transmission dynamics

Inferring from Figures 2 and 3, and based on our observations at the national and provincial/municipal levels during the Joint Mission, we summarize and interpret the transmission dynamics of COVID-19 thus far. It is important to note that transmission dynamics of any outbreak are inherently contextual. For COVID-19, we observe four major types of transmission dynamics during the epidemic growth phase and in the post-control period, and highlight what is known about transmission in children, as follows:

Transmission in Wuhan

Early cases identified in Wuhan are believed to be have acquired infection from a zoonotic source as many reported visiting or working in the Huanan Wholesale Seafood Market. As of 25 February, an animal source has not yet been identified.

At some point early in the outbreak, some cases generated human-to-human transmission chains that seeded the subsequent community outbreak prior to the implementation of the comprehensive control measures that were rolled out in Wuhan. The dynamics likely approximated mass action and radiated from Wuhan to other parts of Hubei province and China, which explains a relatively high R_0 of 2-2.5.

The *cordon sanitaire* around Wuhan and neighboring municipalities imposed since 23 January 2020 has effectively prevented further exportation of infected individuals to the rest of the country.

Transmission in Hubei, other than Wuhan

In the prefectures immediately adjoining Wuhan (Xiaogan, Huanggang, Jingzhou and Ezhou), transmission is less intense. For other prefectures, due to fewer transport links and human mobility flows with Wuhan, the dynamics are more closely aligned with those observed in the other areas of the country. Within Hubei, the implementation of control measures (including social distancing) has reduced the community force of infection, resulting in the progressively lower incident reported case counts.

Transmission in China outside of Hubei

Given Wuhan's transport hub status and population movement during the Chinese New Year (chunyun), infected individuals quickly spread throughout the country, and were particularly concentrated in cities with the highest volume of traffic with Wuhan. Some of these imported seeds generated limited human-to-human transmission chains at their destination.

Given the Wuhan/Hubei experience, a comprehensive set of interventions, including aggressive case and contact identification, isolation and management and extreme social distancing, have been implemented to interrupt the chains of transmission nationwide. To date, most of the recorded cases were imported from or had direct links to Wuhan/Hubei. Community transmission has been very limited. Most locally generated cases have been clustered, the majority of which have occurred in households, as summarized above.

Of note, the highly clustered nature of local transmission may explain a relatively high R_0 (2-2.5) in the absence of interventions and low confirmed case counts with intense quarantine and social distancing measures.

Special settings

We note that instances of transmission have occurred within health care settings prisons and other closed settings. At the present time, it is not clear what role these settings and groups play in transmission. However, they do not appear to be major drivers of the overall epidemic dynamics. Specifically, we note:

(a) **Transmission in health care settings and among health care workers (HCW)** – The Joint Mission discussed nosocomial infection in all locations visited during the Mission. As of 20 February 2020, there were 2,055 COVID-19 laboratory-confirmed cases reported among HCW from 476 hospitals across China. The majority of HCW cases (88%) were reported from Hubei.

Remarkably, more than 40,000 HCW have been deployed from other areas of China to support the response in Wuhan. Notwithstanding discrete and limited instances of nosocomial outbreaks (e.g. a nosocomial outbreak involving 15 HCW in Wuhan), transmission within health care settings and amongst health care workers does not appear to be a major transmission feature of COVID-19 in China. The Joint Mission learned that, among the HCW infections, most were identified early in the outbreak in Wuhan when supplies and experience with the new disease was lower. Additionally, investigations among HCW suggest that many may have been infected within the household rather than in a health care setting. Outside of Hubei, health care worker infections have been less frequent (i.e. 246 of the total 2055 HCW cases). When exposure was investigated in these limited cases, the exposure for most was reported to have been traced back to a confirmed case in a household.

The Joint Team noted that attention to the prevention of infection in health care workers is of paramount importance in China. Surveillance among health care workers identified factors early in the outbreak that placed HCW at higher risk of infection, and this information has been used to modify policies to improve protection of HCW.

(b) **Transmission in closed settings** – There have been reports of COVID-19 transmission in prisons (Hubei, Shandong, and Zhejiang, China), hospitals (as above) and in a long-term living facility. The close proximity and contact among people in these settings and the potential for environmental contamination are important factors, which could amplify transmission. Transmission in these settings warrants further study.

Children

Data on individuals aged 18 years old and under suggest that there is a relatively low attack rate in this age group (2.4% of all reported cases). Within Wuhan, among testing of ILI samples, no children were positive in November and December of 2019 and in the first two weeks of January 2020. From available data, and in the absence of results from serologic studies, it is not possible to determine the extent of infection among children, what role children play in transmission, whether children are less susceptible or if they present differently clinically (i.e. generally milder presentations). The Joint Mission learned that infected children have largely been identified through contact tracing in households of adults. Of note, people interviewed by the Joint Mission Team could not recall episodes in which transmission occurred from a child to an adult.

The signs, symptoms, disease progression and severity

Symptoms of COVID-19 are non-specific and the disease presentation can range from no symptoms (asymptomatic) to severe pneumonia and death. As of 20 February 2020 and

based on 55924 laboratory confirmed cases, typical **signs and symptoms** include: fever (87.9%), dry cough (67.7%), fatigue (38.1%), sputum production (33.4%), shortness of breath (18.6%), sore throat (13.9%), headache (13.6%), myalgia or arthralgia (14.8%), chills (11.4%), nausea or vomiting (5.0%), nasal congestion (4.8%), diarrhea (3.7%), and hemoptysis (0.9%), and conjunctival congestion (0.8%).

People with COVID-19 generally develop signs and symptoms, including mild respiratory symptoms and fever, on an average of 5-6 days after infection (mean incubation period 5-6 days, range 1-14 days).

Most people infected with COVID-19 virus have mild disease and recover. Approximately 80% of laboratory confirmed patients have had **mild to moderate disease**, which includes non-pneumonia and pneumonia cases, 13.8% have **severe disease** (dyspnea, respiratory frequency ≥30/minute, blood oxygen saturation ≤93%, PaO2/FiO2 ratio <300, and/or lung infiltrates >50% of the lung field within 24-48 hours) and 6.1% are **critical** (respiratory failure, septic shock, and/or multiple organ dysfunction/failure). **Asymptomatic infection** has been reported, but the majority of the relatively rare cases who are asymptomatic on the date of identification/report went on to develop disease. The proportion of truly asymptomatic infections is unclear but appears to be relatively rare and does not appear to be a major driver of transmission.

Individuals at **highest risk** for severe disease and death include people aged over 60 years and those with underlying conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease and cancer. Disease in **children** appears to be relatively rare and mild with approximately 2.4% of the total reported cases reported amongst individuals aged under 19 years. A very small proportion of those aged under 19 years have developed severe (2.5%) or critical disease (0.2%).

As of 20 February, 2114 of the 55,924 laboratory confirmed cases have died (**crude fatality ratio** [CFR[2]] 3.8%) (note: at least some of whom were identified using a case definition that included pulmonary disease). The overall CFR varies by location and intensity of transmission (i.e. 5.8% in Wuhan vs. 0.7% in other areas in China). In China, the overall CFR was higher in the early stages of the outbreak (17.3% for cases with symptom onset from 1-10 January) and has reduced over time to 0.7% for patients with symptom onset after 1 February (Figure 4). The Joint Mission noted that the standard of care has evolved over the course of the outbreak.

Mortality increases with age, with the highest mortality among people over 80 years of age (CFR 21.9%). The CFR is higher among males compared to females (4.7% vs. 2.8%). By occupation, patients who reported being retirees had the highest CFR at 8.9%. While patients who reported no comorbid conditions had a CFR of 1.4%, patients with comorbid conditions had much higher rates: 13.2% for those with cardiovascular disease, 9.2% for diabetes, 8.4% for hypertension, 8.0% for chronic respiratory disease, and 7.6% for cancer.

[2] The Joint Mission acknowledges the known challenges and biases of reporting crude CFR early in an epidemic.

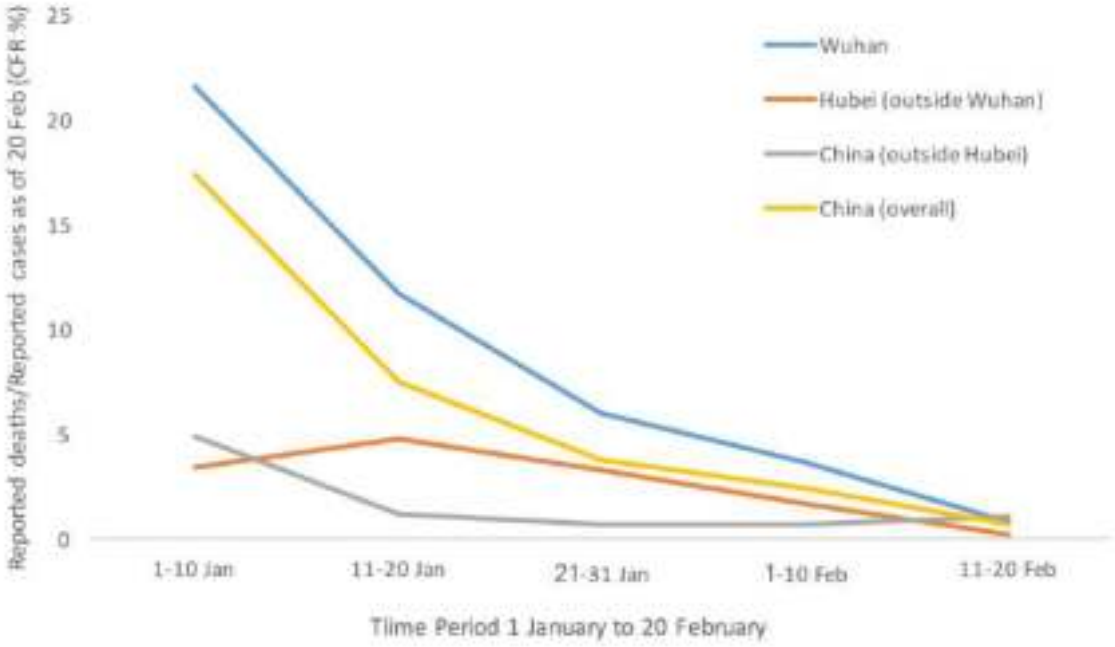

Figure 4 Case fatality ratio (reported deaths among total cases) for COVID-19 in China over time and by location, as of 20 February 2020

Data on the **progression of disease** is available from a limited number of reported hospitalized cases (Figure 5). Based on available information, the median time from symptom onset to laboratory confirmation nationally decreased from 12 days (range 8-18 days) in early January to 3 days (1-7) by early February 2020, and in Wuhan from 15 days (10-21) to 5 days (3-9), respectively. This has allowed for earlier case and contact identification, isolation and treatment.

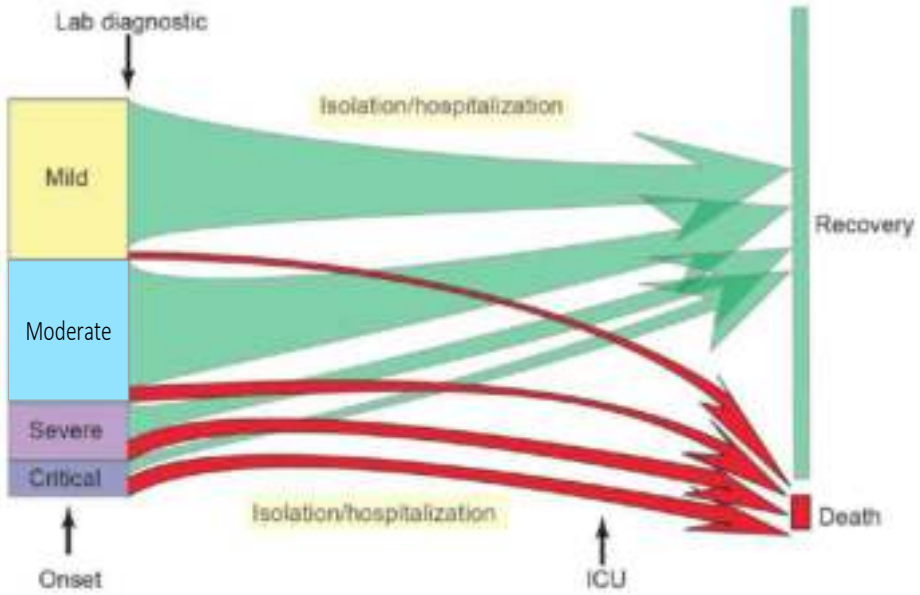

Figure 5. Pattern of disease progression for COVID-19 in China

Note: the relative size of the boxes for disease severity and outcome reflect the proportion of cases reported as of 20 February 2020. The size of the arrows indicates the proportion of cases who recovered or died. Disease definitions are described above. Moderate cases have a mild form of pneumonia.

Using available preliminary data, the median time from onset to clinical recovery for mild cases is approximately 2 weeks and is 3-6 weeks for patients with severe or critical disease. Preliminary data suggests that the time period from onset to the development of severe disease, including hypoxia, is 1 week. Among patients who have died, the time from symptom onset to outcome ranges from 2-8 weeks.

An increasing number of patients have **recovered**; as of 20 February, 18264 (24%) reported cases have recovered. Encouragingly, a report on 20 February from the Guangdong CDC suggests that of 125 severe cases identified in Guangdong, 33 (26.4%) have recovered and been released from hospital, and 58 (46.4%) had improved and were reclassified as having mild/moderate disease (i.e. + milder pneumonia). Among severe cases reported to date, 13.4% have died. Early identification of cases and contacts allows for earlier treatment.

The China response

Upon the detection of a cluster of pneumonia cases of unknown etiology in Wuhan, the CPC Central Committee and the State Council launched the national emergency response. A **Central Leadership Group for Epidemic Response** and the **Joint Prevention and Control Mechanism** of the State Council were established. General Secretary Xi Jinping personally directed and deployed the prevention and control work and requested that the prevention and control of the COVID-19 outbreak be the top priority of government at all levels. Prime Minister Li Keqiang headed the Central Leading Group for Epidemic Response and went to Wuhan to inspect and coordinate the prevention and control work of relevant departments and provinces (autonomous regions and municipalities) across the country. Vice Premier Sun Chunlan, who has been working on the frontlines in Wuhan, has led and coordinated the frontline prevention and control of the outbreak.

The prevention and control measures have been implemented rapidly, from the early stages in Wuhan and other key areas of Hubei, to the current overall national epidemic. It has been undertaken in **three main phases**, with two important events defining those phases. First, COVID-19 was included in the statutory report of Class B infectious diseases and border health quarantine infectious diseases on 20 January 2020, which marked the transition from the initial partial control approach to the comprehensive adoption of various control measures in accordance with the law. The second event was the State Council's issuing, on 8 February 2020, of The Notice on Orderly Resuming Production and Resuming Production in Enterprises, which indicated that China's national epidemic control work had entered a stage of overall epidemic prevention and control together with the restoration of normal social and economic operations.

The first stage

During the early stage of the outbreak, the main strategy focused on preventing the exportation of cases from Wuhan and other priority areas of Hubei Province, and preventing the importation of cases by other provinces; the overall aim was to control the source of infection, block transmission and prevent further spread. The response mechanism was initiated with multi-sectoral involvement in joint prevention and control measures. Wet markets were closed, and efforts were made to identify the zoonotic source. Information on the epidemic was notified to WHO on 3 January, and whole genome sequences of the COVID-19 virus were shared with WHO on 10 January. Protocols for COVID-19 diagnosis and

treatment, surveillance, epidemiological investigation, management of close contacts, and laboratory testing were formulated, and relevant surveillance activities and epidemiological investigations conducted. Diagnostic testing kits were developed, and wildlife and live poultry markets were placed under strict supervision and control measures.

The second stage

During the second stage of the outbreak, the main strategy was to reduce the intensity of the epidemic and to slow down the increase in cases. In Wuhan and other priority areas of Hubei Province, the focus was on actively treating patients, reducing deaths, and preventing exportations. In other provinces, the focus was on preventing importations, curbing the spread of the disease and implementing joint prevention and control measures. Nationally, wildlife markets were closed and wildlife captive-breeding facilities were cordoned off. On 20 January, COVID-19 was included in the notifiable report of Class B infectious diseases and border health quarantine infectious diseases, with temperature checks, health care declarations, and quarantine against COVID-19 instituted at transportation depots in accordance with the law. On 23 January, Wuhan implemented strict traffic restrictions. The protocols for diagnosis, treatment and epidemic prevention and control were improved; case isolation and treatment were strengthened.

Measures were taken to ensure that all cases were treated, and close contacts were isolated and put under medical observation. Other measures implemented included the extension of the Spring Festival holiday, traffic controls, and the control of transportation capacity to reduce the movement of people; mass gathering activities were also cancelled. Information about the epidemic and prevention and control measures was regularly released. Public risk communications and health education were strengthened; allocation of medical supplies was coordinated, new hospitals were built, reserve beds were used and relevant premises were repurposed to ensure that all cases could be treated; efforts were made to maintain a stable supply of commodities and their prices to ensure the smooth operation of society.

The third stage

The third stage of the outbreak focused on reducing clusters of cases, thoroughly controlling the epidemic, and striking a balance between epidemic prevention and control, sustainable economic and social development, the unified command, standardized guidance, and scientific evidence-based policy implementation. For Wuhan and other priority areas of Hubei Province, the focus was on patient treatment and the interruption of transmission, with an emphasis on concrete steps to fully implement relevant measures for the testing, admitting and treating of all patients. A risk-based prevention and control approach was adopted with differentiated prevention and control measures for different regions of the country and provinces. Relevant measures were strengthened in the areas of epidemiological investigation, case management and epidemic prevention in high-risk public places.

New technologies were applied such as the use of big data and artificial intelligence (AI) to strengthen contact tracing and the management of priority populations. Relevant health insurance policies were promulgated on "health insurance payment, off-site settlement, and financial compensation". All provinces provided support to Wuhan and priority areas in Hubei Province in an effort to quickly curb the spread of the disease and provide timely clinical treatment. Pre-school preparation was improved, and work resumed in phases and

batches. Health and welfare services were provided to returning workers in a targeted and 'one-stop' manner. Normal social operations are being restored in a stepwise fashion; knowledge about disease prevention is being popularized to improve public health literacy and skills; and a comprehensive program of emergency scientific research is being carried out to develop diagnostics, therapeutics and vaccines, delineate the spectrum of the disease, and identify the source of the virus.

Knowledge gaps

Since the start of the COVID-19 outbreak, there have been extensive attempts to better understand the virus and the disease in China. It is remarkable how much knowledge about a new virus has been gained in such a short time. However, as with all new diseases, and only 7 weeks after this outbreak began, key knowledge gaps remain. Annex D summarizes the key unknowns in a number of areas including the source of infection, pathogenesis and virulence of the virus, transmissibility, risk factors for infection and disease progression, surveillance, diagnostics, clinical management of severe and critically ill patients, and the effectiveness of prevention and control measures. The timely filling of these knowledge gaps is imperative to enhance control strategies.

III. Assessment

The Joint Mission drew four major conclusions from its work in China and four major conclusions from its knowledge of the broader global response to COVID-19. Recommendations are offered in five major areas to inform the ongoing response globally and in China.

The China Response & Next Steps

1. **In the face of a previously unknown virus, China has rolled out perhaps the most ambitious, agile and aggressive disease containment effort in history. The strategy that underpinned this containment effort was initially a national approach that promoted universal temperature monitoring, masking, and hand washing. However, as the outbreak evolved, and knowledge was gained, a science and risk-based approach was taken to tailor implementation. Specific containment measures were adjusted to the provincial, county and even community context, the capacity of the setting, and the nature of novel coronavirus transmission there.**

   While the fundamental principles of this strategy have been consistent since its launch, there has been constant refinement of specific aspects to incorporate new knowledge on the novel coronavirus, the COVID-19 disease, and COVID-19 containment, as rapidly as that knowledge has emerged. The remarkable speed with which Chinese scientists and public health experts isolated the causative virus, established diagnostic tools, and determined key transmission parameters, such as the route of spread and incubation period, provided the vital evidence base for China's strategy, gaining invaluable time for the response.

As striking, has been the uncompromising rigor of strategy application that proved to be a hallmark in every setting and context where it was examined. There has also been a relentless focus on improving key performance indicators, for example constantly enhancing the speed of case detection, isolation and early treatment. The implementation of these containment measures has been supported and enabled by the innovative and aggressive use of cutting edge technologies, from shifting to online medical platforms for routine care and schooling, to the use of 5G platforms to support rural response operations.

2. **Achieving China's exceptional coverage with and adherence to these containment measures has only been possible due to the deep commitment of the Chinese people to collective action in the face of this common threat. At a community level this is reflected in the remarkable solidarity of provinces and cities in support of the most vulnerable populations and communities. Despite ongoing outbreaks in their own areas, Governors and Mayors have continued to send thousands of health care workers and tons of vital PPE supplies into Hubei province and Wuhan city.**

   At the individual level, the Chinese people have reacted to this outbreak with courage and conviction. They have accepted and adhered to the starkest of containment measures – whether the suspension of public gatherings, the month-long 'stay at home' advisories or prohibitions on travel. Throughout an intensive 9-days of site visits across China, in frank discussions from the level of local community mobilizers and frontline health care providers to top scientists, Governors and Mayors, the Joint Mission was struck by the sincerity and dedication that each brings to this COVID-19 response.

3. **China's bold approach to contain the rapid spread of this new respiratory pathogen has changed the course of a rapidly escalating and deadly epidemic. A particularly compelling statistic is that on the first day of the advance team's work there were 2478 newly confirmed cases of COVID-19 reported in China. Two weeks later, on the final day of this Mission, China reported 409 newly confirmed cases. This decline in COVID-19 cases across China is real.**

   Several sources of data support this conclusion, including the steep decline in fever clinic visits, the opening up of treatment beds as cured patients are discharged, and the challenges to recruiting new patients for clinical trials. Based on a comparison of crude attack rates across provinces, the Joint Mission estimates that this truly all-of-Government and all-of-society approach that has been taken in China has averted or at least delayed hundreds of thousands of COVID-19 cases in the country. By extension, the reduction that has been achieved in the force of COVID-19 infection in China has also played a significant role in protecting the global community and creating a stronger first line of defense against international spread. Containing this outbreak, however, has come at great cost and sacrifice by China and its people, in both human and material terms.

   While the scale and impact of China's COVID-19 operation has been remarkable, it has also highlighted areas for improvement in public health emergency response capacity.

These include overcoming any obstacles to act immediately on early alerts, to massively scale-up capacity for isolation and care, to optimize the protection of frontline health care workers in all settings, to enhance collaborative action on priority gaps in knowledge and tools, and to more clearly communicate key data and developments internationally.

4. **China is already, and rightfully, working to bolster its economy, reopen its schools and return to a more normal semblance of its society, even as it works to contain the remaining chains of COVID-19 transmission. Appropriately, a science-based, risk-informed and phased approach is being taken, with a clear recognition and readiness of the need to immediately react to any new COVID-19 cases or clusters as key elements of the containment strategy are lifted.**

   Despite the declining case numbers, across China every province, city and community visited is urgently escalating their investments in acute care beds and public health capacity. It is crucial that this continues. Fifty thousand infected COVID-19 patient are still under treatment, across the country. However, the Joint Mission has come to understand the substantial knowledge, experience and capacities that China has rapidly built during this crisis. Consequently, it endorses China's working assumption that in most provinces and municipalities it should soon be possible to manage a resurgence in COVID-19 cases, using even more tailored and sustainable approaches that are anchored in very rapid case detection, instant activation of key containment activities, direct oversight by top leadership, and broad community engagement.

   As China works to resume a more normal level of societal and economic activity, it is essential that the world recognizes and reacts positively to the rapidly changing, and decreasing, risk of COVID-19 in the country. China's rapid return to full connectivity with the world, and to full productivity and economic output, is vital to China and to the world. The world urgently needs access to China's experience in responding to COVID-19, as well as the material goods it brings to the global response. It is even more urgent now, with escalating COVID-19 outbreaks outside of China, to constantly reassess any restrictions on travel and/or trade to China that go beyond the recommendations of the IHR Emergency Committee on COVID-19.

The Global Response & Next Steps

1. **The COVID-19 virus is a new pathogen that is highly contagious, can spread quickly, and must be considered capable of causing enormous health, economic and societal impacts in any setting. It is not SARS and it is not influenza. Building scenarios and strategies only on the basis of well-known pathogens risks failing to exploit all possible measures to slow transmission of the COVID-19 virus, reduce disease and save lives.**

   COVID-19 is not SARS and it is not influenza. It is a new virus with its own characteristics. For example, COVID-19 transmission in children appears to be limited compared with influenza, while the clinical picture differs from SARS. Such differences, while based on limited data, may be playing a role in the apparent efficacy of rigorously

applied non-pharmaceutical, public health measures to interrupt chains of human-to-human transmission in a range of settings in China. The COVID-19 virus is unique among human coronaviruses in its combination of high transmissibility, substantial fatal outcomes in some high-risk groups, and ability to cause huge societal and economic disruption. For planning purposes, it must be assumed that the global population is susceptible to this virus. As the animal origin of the COVID-19 virus is unknown at present, the risk of reintroduction into previously infected areas must be constantly considered.

The novel nature, and our continuously evolving understanding, of this coronavirus demands a tremendous agility in our capacity to rapidly adapt and change our readiness and response planning as has been done continually in China. This is an extraordinary feat for a country of 1.4 billion people.

2. **China's uncompromising and rigorous use of non-pharmaceutical measures to contain transmission of the COVID-19 virus in multiple settings provides vital lessons for the global response. This rather unique and unprecedented public health response in China reversed the escalating cases in both Hubei, where there has been widespread community transmission, and in the importation provinces, where family clusters appear to have driven the outbreak.**

   Although the timing of the outbreak in China has been relatively similar across the country, transmission chains were established in a wide diversity of settings, from mega-cities in the north and south of the country, to remote communities. However, the rapid adaptation and tailoring of China's strategy demonstrated that containment can be adapted and successfully operationalized in a wide range of settings.

   China's experience strongly supports the efficacy and effectiveness of anchoring COVID-19 readiness and rapid response plans in a thorough assessment of local risks and of utilizing a differentiated risk-based containment strategy to manage the outbreak in areas with no cases vs. sporadic cases vs. clusters of cases vs. community-level transmission. Such a strategy is essential for ensuring a sustainable approach while minimizing the socio-economic impact.

3. **Much of the global community is not yet ready, in mindset and materially, to implement the measures that have been employed to contain COVID-19 in China. These are the only measures that are currently proven to interrupt or minimize transmission chains in humans. Fundamental to these measures is extremely proactive surveillance to immediately detect cases, very rapid diagnosis and immediate case isolation, rigorous tracking and quarantine of close contacts, and an exceptionally high degree of population understanding and acceptance of these measures.**

   Achieving the high quality of implementation needed to be successful with such measures requires an unusual and unprecedented speed of decision-making by top leaders, operational thoroughness by public health systems, and engagement of society.

Given the damage that can be caused by uncontrolled, community-level transmission of this virus, such an approach is warranted to save lives and to gain the weeks and months needed for the testing of therapeutics and vaccine development. Furthermore, as the majority of new cases outside of China are currently occurring in high and middle-income countries, a rigorous commitment to slowing transmission in such settings with non-pharmaceutical measures is vital to achieving a second line of defense to protect low income countries that have weaker health systems and coping capacities.

The time that can be gained through the full application of these measures – even if just days or weeks – can be invaluable in ultimately reducing COVID-19 illness and deaths. This is apparent in the huge increase in knowledge, approaches and even tools that has taken place in just the 7 weeks since this virus was discovered through the rapid scientific work that has been done in China.

4. **The time gained by rigorously applying COVID-19 containment measures must be used more effectively to urgently enhance global readiness and rapidly develop the specific tools that are needed to ultimately stop this virus.**

COVID-19 is spreading with astonishing speed; COVID-19 outbreaks in any setting have very serious consequences; and there is now strong evidence that non-pharmaceutical interventions can reduce and even interrupt transmission. Concerningly, global and national preparedness planning is often ambivalent about such interventions. However, to reduce COVID-19 illness and death, near-term readiness planning must embrace the large-scale implementation of high-quality, non-pharmaceutical public health measures. These measures must fully incorporate immediate case detection and isolation, rigorous close contact tracing and monitoring/quarantine, and direct population/community engagement.

A huge array of COVID-19 studies, scientific research projects and product R&D efforts are ongoing in China and globally. This is essential and to be encouraged and supported. However, such a large number of projects and products needs to be prioritized. Without prioritizing, this risks compromising the concentration of attention and resources and collaboration required to cut timelines by precious weeks and months. While progress has been made, the urgency of the COVID-19 situation supports an even more ruthless prioritization of research in the areas of diagnostics, therapeutics and vaccines.

Similarly, there is a long list of proposed studies on the origins of COVID-19, the natural history of the disease, and the virus's transmission dynamics. However, the urgency of responding to cases and saving lives makes it difficult for policy makers to consider and act on such comprehensive lists. This can be addressed by balancing studies with the immediate public health and clinical needs of the response. Studies can be prioritized in terms of the largest knowledge gaps that can be most rapidly addressed to have greatest immediate impact on response operations and patient management. This suggests prioritizing studies to identify risk factors for transmission in households, institutions and the community; convenience sampling for this virus in the population using existing surveillance systems; age-stratified sero-epidemiologic surveys; the analysis of clinical case series; and cluster investigations.

IV. Major Recommendations

For China

1. Maintain an appropriate level of emergency management protocols, depending on the assessed risk in each area and recognizing the real risk of new cases and clusters of COVID-19 as economic activity resumes, movement restrictions are lifted, and schools reopen;

2. Carefully monitor the phased lifting of the current restrictions on movement and public gatherings, beginning with the return of workers and migrant labor, followed by the eventual reopening of schools and lifting other measures;

3. Further strengthen the readiness of emergency management mechanisms, public health institutions (e.g. CDCs), medical facilities, and community engagement mechanisms to ensure sustained capacity to immediately launch containment activities in response to any resurgence in cases;

4. Prioritize research that rapidly informs response and risk management decisions, particularly household and health care facility studies, age-stratified sero-epidemiologic surveys and rigorous investigation of the animal-human interface; establish a centralized research program to fast-track the most promising rapid diagnostics and serologic assays, the testing of potential antivirals and vaccine candidates, and Chinese engagement in selected multi-country trials; and

5. As the country with the greatest knowledge on COVID-19, further enhance the systematic and real-time sharing of epidemiologic data, clinical results and experience to inform the global response.

For countries with imported cases and/or outbreaks of COVID-19

1. Immediately activate the highest level of national Response Management protocols to ensure the all-of-government and all-of-society approach needed to contain COVID-19 with non-pharmaceutical public health measures;

2. Prioritize active, exhaustive case finding and immediate testing and isolation, painstaking contact tracing and rigorous quarantine of close contacts;

3. Fully educate the general public on the seriousness of COVID-19 and their role in preventing its spread;

4. Immediately expand surveillance to detect COVID-19 transmission chains, by testing all patients with atypical pneumonias, conducting screening in some patients with upper respiratory illnesses and/or recent COVID-19 exposure, and adding testing for the COVID-19 virus to existing surveillance systems (e.g. systems for influenza-like-illness and SARI); and

5. Conduct multi-sector scenario planning and simulations for the deployment of even more stringent measures to interrupt transmission chains as needed (e.g. the suspension of large-scale gatherings and the closure of schools and workplaces).

For uninfected countries

1. Prepare to immediately activate the highest level of emergency response mechanisms to trigger the all-of-government and all-of society approach that is essential for early containment of a COVID-19 outbreak;

2. Rapidly test national preparedness plans in light of new knowledge on the effectiveness of non-pharmaceutical measures against COVID-19; incorporate rapid detection, largescale case isolation and respiratory support capacities, and rigorous contact tracing and management in national COVID-19 readiness and response plans and capacities;

3. Immediately enhance surveillance for COVID-19 as rapid detection is crucial to containing spread; consider testing all patients with atypical pneumonia for the COVID-19 virus, and adding testing for the virus to existing influenza surveillance systems;

4. Begin now to enforce rigorous application of infection prevention and control measures in all healthcare facilities, especially in emergency departments and outpatient clinics, as this is where COVID-19 will enter the health system; and

5. Rapidly assess the general population's understanding of COVID-19, adjust national health promotion materials and activities accordingly, and engage clinical champions to communicate with the media.

For the public

1. Recognize that COVID-19 is a new and concerning disease, but that outbreaks can managed with the right response and that the vast majority of infected people will recover;

2. Begin now to adopt and rigorously practice the most important preventive measures for COVID-19 by frequent hand washing and always covering your mouth and nose when sneezing or coughing;

3. Continually update yourself on COVID-19 and its signs and symptoms (i.e. fever and dry cough), because the strategies and response activities will constantly improve as new information on this disease is accumulating every day; and

4. Be prepared to actively support a response to COVID-19 in a variety of ways, including the adoption of more stringent 'social distancing' practices and helping the high-risk elderly population.

For the international community

1. Recognize that true solidarity and collaboration is essential between nations to tackle the common threat that COVID-19 represents and operationalize this principle;

2. Rapidly share information as required under the International Health Regulations (IHR) including detailed information about imported cases to facilitate contact tracing and inform containment measures that span countries;

3. Recognize the rapidly changing risk profile of COVID-19 affected countries and continually monitor outbreak trends and control capacities to reassess any 'additional health measures' that significantly interfere with international travel and trade.

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Annexes

A. WHO-China Joint Mission Members

Bruce AYLWARD	Team Lead WHO-China Joint Mission on COVID-19, Senior Advisor to the Director-General, World Health Organization, Geneva, Switzerland
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Zhongze WU	Director, Compliance and Enforcement Division, Department of Wildlife Conservation, National Forestry and Grassland Administration
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Lei ZHOU	Chief and Researcher, Branch for Emerging Infectious Disease, Public Health Emergency Center, Chinese Center for Disease Control and Prevention

B. Summary Agenda of the Mission

Dates	Location	Activities
10-15 February 2020 (Advance Team)	Beijing	Advance Team and WHO Country team meetings with national counterparts and institutions
16 February 2020	Beijing	Meeting with the full international team for briefing at the WHO Country office
	Beijing	Workshop at the National Health Commission (NHC) with relevant departments of the Joint Prevention and Control Mechanism of the State Council
17 February 2020	Beijing	Site visit to Beijing Ditan Hospital
	Beijing	Site visit to Anhuali community and health service station, Anzhen street, Chaoyang District, Beijing
	Beijing	Workshop with Chinese Center for Disease Control and Prevention
18 February 2020 (Guangdong Team)	Shenzhen, Guangdong	Shenzhen customs at the airport
	Shenzhen, Guangdong	Shenzhen No.3 People's Hospital
	Shenzhen, Guangdong	Shenzhen Center for Disease Control and Prevention
	Shenzhen, Guangdong	Meeting at Tencent
19 February 2020 (Guangdong Team)	Shenzhen, Guangdong	Qiaoxiang community
	Shenzhen to Guangzhou	Visit to Futian High-speed Train Station, and travel to Guangzhou by train
	Guangzhou	Guangzhou Panyu Sanatorium
	Guangzhou	Guangdong Laboratory of Regenerative Medicine and Health
	Guangzhou	Guangzhou Tiyudongzhihui wet market
	Guangzhou	First Workshop with The People's government of Guangdong Province
20 February 2020 (Guangdong Team)	Guangzhou	Guangdong Provincial Center for Disease Control and Prevention
	Guangzhou	Renmin road campus of Guangzhou Women and Children Medical Center
	Guangzhou	The second Workshop with The People's government of Guangdong Province
18 February 2020 (Sichuan Team)	Beijing to Chengdu	
	Sichuan	Site visit to Chengdu Shuangliu International Airport
		Meeting with the Governor of Sichuan Provincial People's Government
		Site visit to Yong'an Township Central hospital with fever clinic
		Site visit to home community of Yong'an township
19 February 2020 (Sichuan Team)		Symposium with provincial and municipal authorities
		Sichuan Center for Disease Control and Prevention
		Site visit to West China Hospital- Designated COVID-19 hospital
20 February 2020 (Sichuan Team)		Site visit to Chengdu Women and Children's hospital
		Site visit to Pharmaceutical Logistics center
		Site visit to East Chengdu railway station

		Site visit to Chengdu Public Health Clinical Centre- Designated COVID 19 hospital
Sichuan and Guangdong teams reconvene in Guangzhou		
21-24 February 2020		Analyze major findings; Meetings of the WHO-China Joint mission to finalize the report
Feb 22 (Wuhan Team)	Guangzhou to Wuhan	Select team members only
23 February (Wuhan Team)		Site visit to Guanggu Campus of Wuhan Tongji Hospital
		Site visit to Mobile Cabin Hospital in Wuhan Sports Center
		Workshop with relevant departments of the Joint Prevention and Control Mechanism of Hubei Province
		Feedback Meeting with Minister Ma, NHC at the Wuhan Conference Center
24 February 2020	Guangzhou to Beijing	Finalize report, WHO-Joint Press conference in Beijing

C. Detailed Technical Findings

Response management, case and contact management, risk communication and community engagement

The response structures in China were rapidly put in place according to existing emergency plans and aligned from the top to the bottom. This was replicated at the four levels of government (national provincial, prefecture and county/district).

Organizational structure and response mechanism

Response activation at the national level: COVID-19 prevention and control mechanisms were initiated immediately after the outbreak was declared and nine working groups were set up to coordinate the response: a) Coordination b) Epidemic prevention and control c) Medical treatment d) Research e) Public communication f) Foreign affairs g) Medical material support h) Life maintenance supplies and i) Social stability. Each working group has a ministerial level leader. Emergency response laws and regulations for the emergency response to public health emergencies, prevention and control of infectious diseases have been developed or updated to guide the response.

Response activation in provinces: Each province set up a similar structure to manage the outbreak. The response is organized at the levels of national, provincial, prefecture, county/district and the community. By 29 January, all provinces across China had launched the highest level of response for major public health emergencies.

Response Strategy

A clear strategy was developed, and goals were well articulated and communicated across the entire response architecture. This strategy was rapidly adapted and adjusted to the outbreak, both in terms of the epidemiological situation over time and in different parts of the country.

The epidemiological situation has been used to define location into four areas:

- In areas without cases, the strategy in these areas is to "strictly prevent introduction". This includes quarantine arrangements in transportation hubs, monitoring for temperature changes, strengthening of triage arrangements, use of fever clinics, and ensuring normal economic and social operations.
- In areas with sporadic cases, the strategy is focused on "reducing importation, stopping transmission and providing appropriate treatment".
- In areas with community clusters, the strategy is focussed on "stopping transmission, preventing exportation, and strengthening treatment".
- In areas with community transmission, the strictest prevention and control strategies are being implemented, the entry and exit of people from these areas has been stopped and public health and medical treatment measures are comprehensively strengthened.

Main control measures implemented in China

The main control measures implemented in China are as follows and are illustrated in Figures 6A-6D, representing the national level response and examples of the response at the Provincial and municipal levels:

Monitoring and reporting: COVID-19 was included in the statutory reporting of infectious diseases on 20 January and plans were formulated to strengthen diagnosis, monitoring, and reporting.

Strengthening ports of entry and quarantine: The Customs Department launched the emergency plan for public health emergencies at ports across the country and restarted the health declaration card system for entry and exit into cities as well as strict monitoring of the temperature of entry and exit passengers.

Treatment: For severe or critical patients, the principle of "Four Concentrations" was implemented: i.e. concentrating patients, medical experts, resources and treatment into special centres. All cities and districts transformed relevant hospitals, increased the number of designated hospitals, dispatched medical staff, and set up expert groups for consultation, so as to minimise mortality of severe patients. Medical resources from all over China have been mobilized to support the medical treatment of patients in Wuhan.

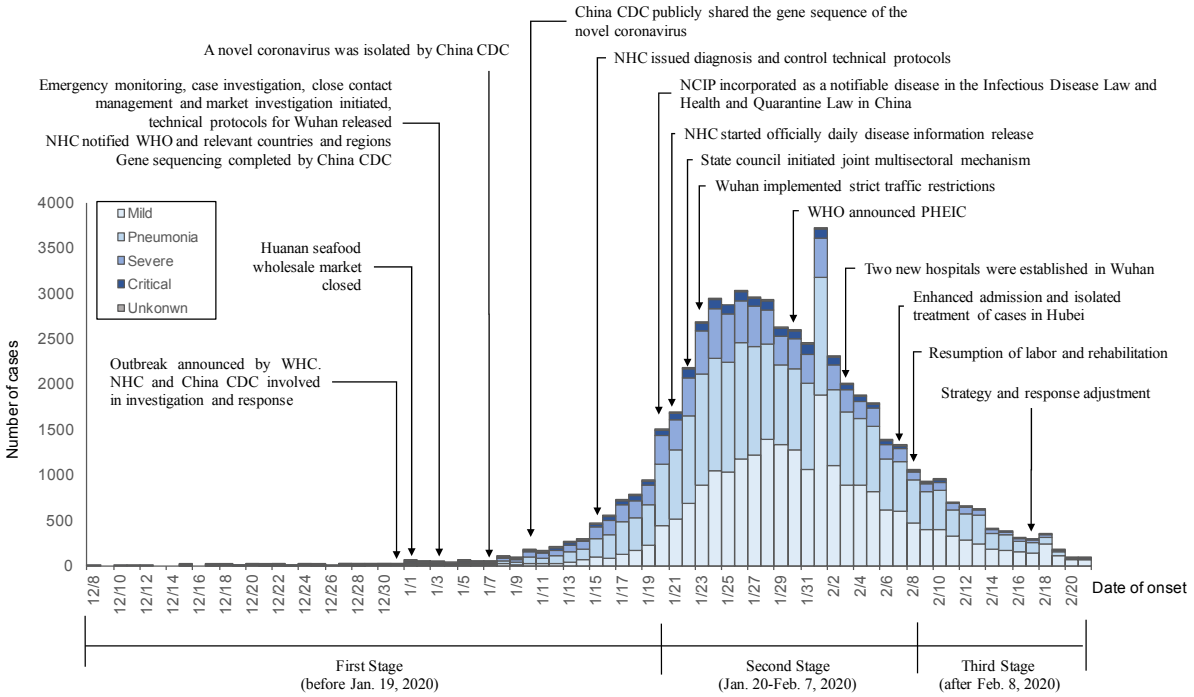
Epidemiological investigation and close contact management: Strong epidemiological investigations are being carried out for cases, clusters, and contacts to identify the source of infection and implement targeted control measures, such as contact tracing.

Social distancing: At the national level, the State Council extended the Spring Festival holiday in 2020, all parts of the country actively cancelled or suspended activities like sport events, cinema, theatre, and schools and colleges in all parts of the country postponed re-opening after the holiday. Enterprises and institutions have staggered their return to work. Transportation Departments setup thousands of health and quarantine stations in national service areas, and in entrances and exits for passengers at stations. Hubei Province adopted the most stringent traffic control measures, such as suspension of urban public transport, including subway, ferry and long-distance passenger transport. Every citizen has to wear a mask in public. Home support mechanisms were established. As a consequence of all of these measures, public life is very reduced.

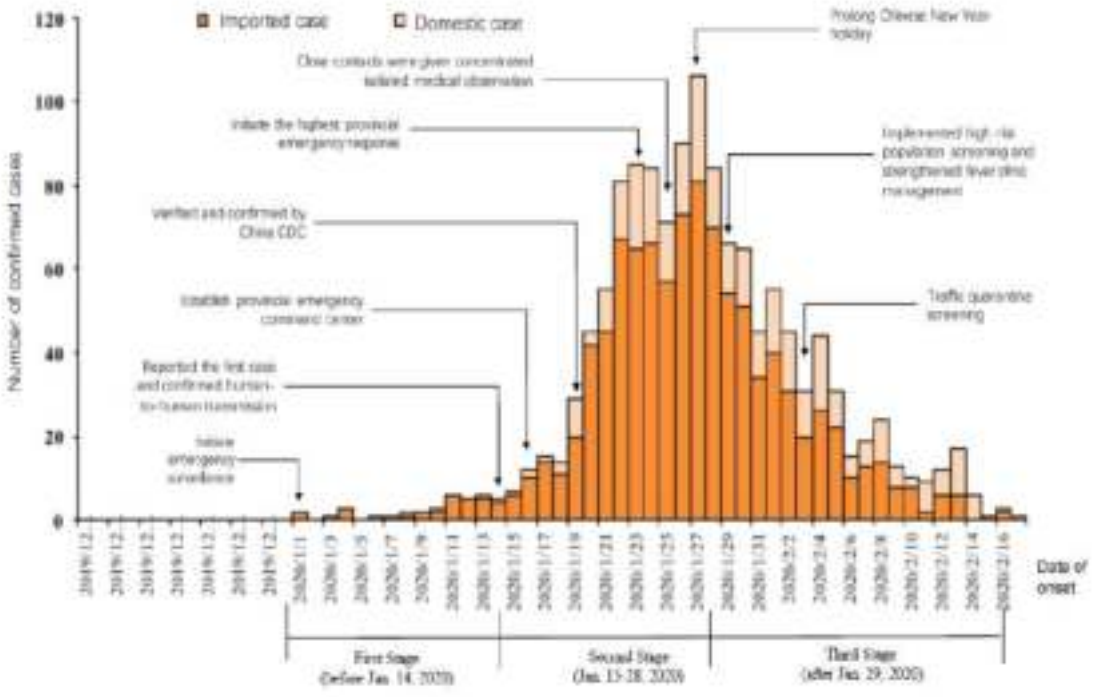
Funding and material support: Payment of health insurance was taken over by the state, as well as the work to improve accessibility and affordability of medical materials, provide personal protection materials, and ensure basic living materials for affected people.

Emergency material support: The government restored production and expanded production capacity, organized key enterprises that have already started to exceed current production capacity, supported local enterprises to expand imports, and used cross-border e-commerce platforms and enterprises to help import medical materials and improve the ability to guarantee supplies.

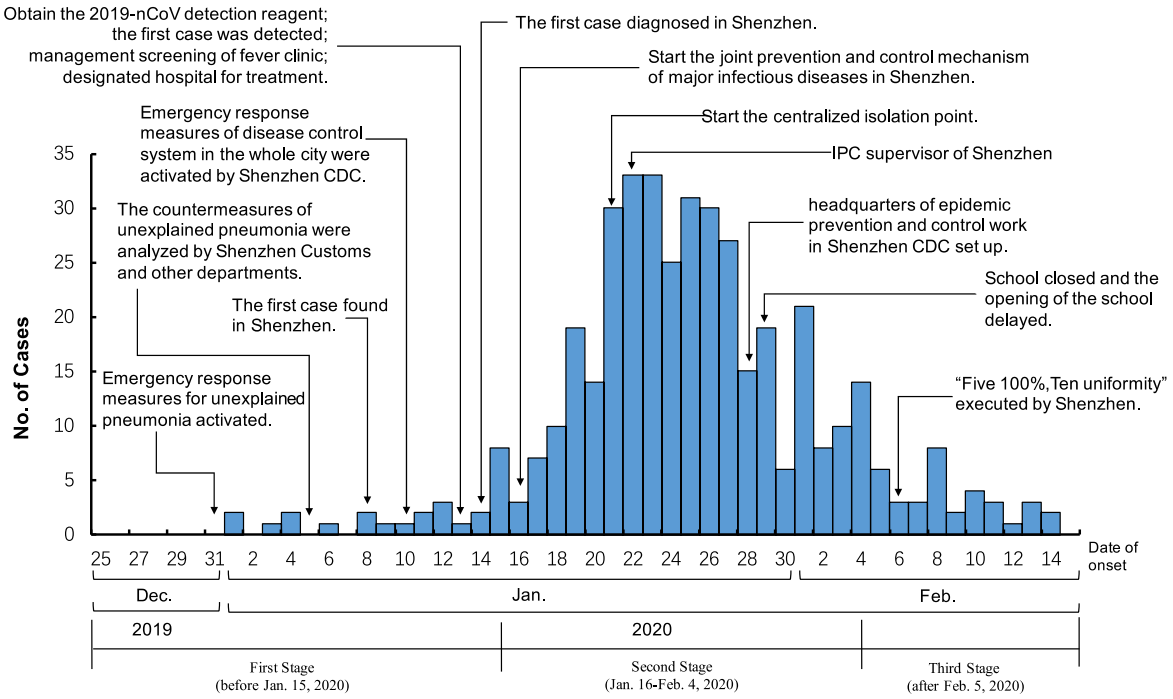
A


China CDC publicly shared the gene sequence of the novel coronavirus
A novel coronavirus was isolated by China CDC
NHC issued diagnosis and control technical protocols
Emergency monitoring, case investigation, close contact management and market investigation initiated, technical protocols for Wuhan released
NHC notified WHO and relevant countries and regions
Gene sequencing completed by China CDC
NCIP incorporated as a notifiable disease in the Infectious Disease Law and Health and Quarantine Law in China
NHC started officially daily disease information release
State council initiated joint multisectoral mechanism
Wuhan implemented strict traffic restrictions
WHO announced PHEIC
Mild
Pneumonia
Severe
Critical
Unkonwn
Huanan seafood wholesale market closed
Two new hospitals were established in Wuhan
Enhanced admission and isolated treatment of cases in Hubei
Resumption of labor and rehabilitation
Outbreak announced by WHC. NHC and China CDC involved in investigation and response
Strategy and response adjustment
Number of cases
Date of onset
First Stage (before Jan. 19, 2020)
Second Stage (Jan. 20-Feb. 7, 2020)
Third Stage (after Feb. 8, 2020)

B


Imported case
Domestic case
Number of confirmed cases
Date of onset

C



D

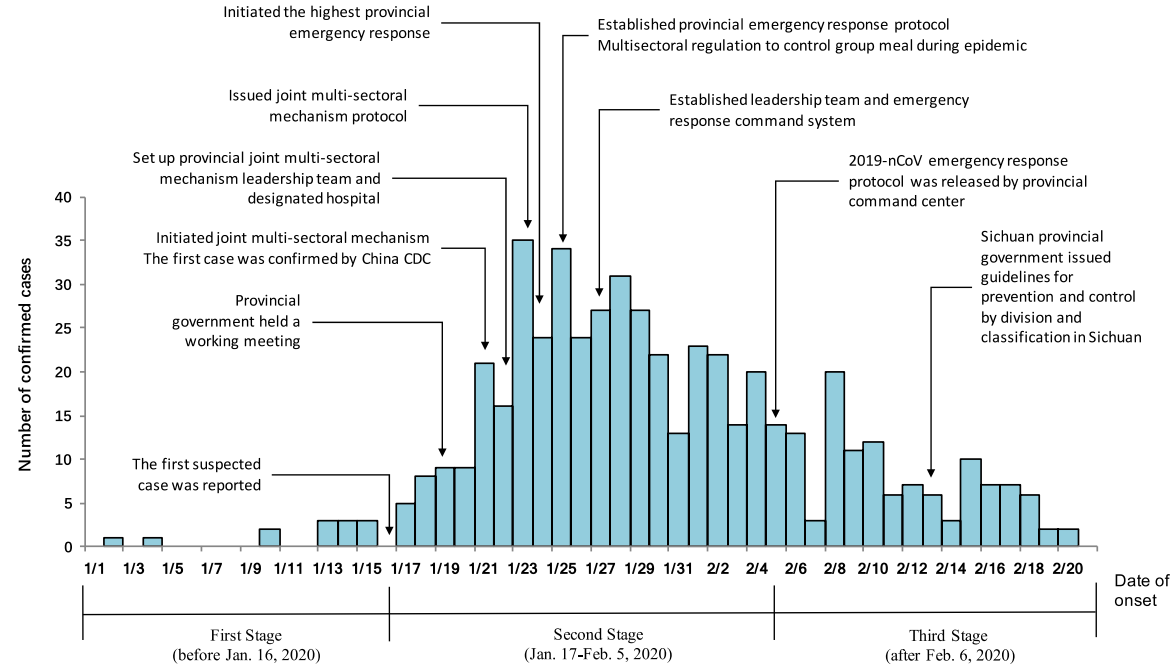


Figure 6. COVID-19 epidemic curves and major intervention measures in China as implemented at a) the national level b) in Guangdong province, c) in Shenzhen municipality and d) in Sichuan province

Risk communications (information release, public and media communications)

International and interregional cooperation and information sharing: From 3 January 2020, information on COVID-19 cases has been reported to WHO daily. Full genome sequences of the new virus were shared with WHO and the international community immediately after the pathogen was identified on 7 January. On 10 January, an expert group involving Hong Kong, Macao and Taiwanese technical experts and a World Health Organization team was invited to visit Wuhan. A set of nucleic acid primers and probes for PCR detection for COVID-19 was released on 21 January.

Daily updates: The National Health Commission announces the epidemic situation every day and holds daily press conferences to respond to emerging issues. The government also frequently invites experts to share scientific knowledge on COVID-19 and to address public concerns.

Psychological care: This is provided to patients and the public. Governments at all levels, NGOs and all sectors of society developed guidelines for emergency psychological crisis intervention and guidelines for public psychological self-support and counselling. A hotline for mental health services has been established for the public.

IT platform: China has capitalized on the use of technology, big data and AI for COVID-19 preparedness, readiness and response. Authoritative and reliable information, medical guidance, access to online services, provision of educational tools and remote work tools have been developed in and used across China. These services have increased accessibility to health services, reduced misinformation and minimized the impact of fake news.

Social mobilization and community engagement

Civil society organizations (community centers and public health centers) have been mobilized to support prevention and response activities. The community has largely accepted the prevention and control measures and is fully participating in the management of self-isolation and enhancement of public compliance. Community volunteers are organized to support self-isolation and help isolated residents at home to solve practical life difficulties. Measures were taken to limit the movement of the population through home-based support. Up to now, outside of Hubei, 30 provinces have registered and managed more than 5 million people coming from Wuhan.

Clinical case management and infection prevention and control

The main **signs and symptoms** of COVID-19 include fever, dry cough, fatigue, sputum production, shortness of breath, myalgia or arthralgia, sore throat, and headache. Nausea or vomiting has been reported in a small percentage of patients (5%). On 14 February, China CDC described the clinical features, outcomes, laboratory and radiologic findings of 44 672 laboratory-confirmed cases. Only 965 (2.2%) were under 20 years of age and there is just one recorded death (0.1%) in this age group. Most patients (77.8%) were aged 30 to 69 years. Patients aged over 80 years had a CFR of 14.8%. The CFR was highest in those with

comorbidities including cardiovascular, diabetes, chronic respiratory disease, hypertension and cancer.

As opposed to Influenza A(H1N1)pdm09, **pregnant women** do not appear to be at higher risk of severe disease. In an investigation of 147 pregnant women (64 confirmed, 82 suspected and 1 asymptomatic), 8% had severe disease and 1% were critical.

Severe cases are defined as tachypnoea (≧30 breaths/ min) or oxygen saturation ≤93% at rest, or PaO2/FIO2 <300 mmHg. **Critical cases** are defined as respiratory failure requiring mechanical ventilation, shock or other organ failure that requires intensive care. About a quarter of severe and critical cases require mechanical ventilation while the remaining 75% require only oxygen supplementation.

China has a principle of **early identification**, early isolation, early diagnosis and early treatment. Early identification of suspect cases is critical to containment efforts and occurs via a process of temperature screening and questioning at entrances to many institutions, communities, travel venues (airports, train stations) and hospitals. Many hospitals have fever clinics that were established and maintained since the SARS outbreak. In China, laboratory tests were originally requested according to the case definitions, which included an epidemiological link to Hubei or other confirmed cases. However, more recently, a more **liberal clinical testing regimen** allows clinicians to test with a low index of suspicion.

Suspect cases are isolated in normal pressure single rooms, wear a surgical mask (for source control). Staff in China wear a cap, eye protection, n95 masks, gown and gloves (single use only). In Wuhan it is necessary for most suspects to be cohorted in a normal pressure isolation ward. Staff wear PPE continuously, changing it only when they leave the ward.

PCR test results are returned the same day. If positive, patients are transported to designated hospitals (including negative pressure ambulances in some cities). All patients, including the mild and asymptomatic, with a positive test are admitted. The designated hospitals are known and are strategically placed with at least one per district/county. Positive cases are cohorted by gender. Negative tested patients are managed based on clinical needs. All patients are evaluated with a respiratory multiplex to look for other diagnoses. This can add to the reassurance that a negative COVID-19 test reflects a lack of infection with COVID-19.

In Wuhan, there are 45 **designated hospitals**, 6 of which are designated for critical patients, and 39 for severe patients and/or any patients >65 years old. There are an additional 10 temporary hospitals reconstructed from gymnasium and exhibition centers, which are for mild patients. Other surge measures undertaken in Wuhan include two new temporary hospitals with 2600 beds, plus many makeshift hospitals to increase bed capacity. Bed capacity within Wuhan has increased to >50,000.

Patients are treated according to the **National Clinical guidelines** (edition 6) released by the China National Health Commission (NHC). There are no specific antiviral or immune modulating agents proven (or recommended) to improve outcomes. All patients are monitored by regular pulse oximetry. The guidelines include supportive care by clinical category (mild, moderate, severe and critical), as well as the role of investigational

treatments such as chloroquine, phosphate, lopinavir/ritonavir, alpha interferon, ribavirin, arbidol. The application of intubation/invasive ventilation and ECMO in critically ill patients can improve survival. The Joint Mission Team was told of ECMO use in four patients at one hospital with one death and three who appeared to be improving. Clearly, though ECMO is very resource consumptive, any health system would need to carefully weigh the benefits. There is widespread use of Traditional Chinese Medicines (TCM), for which the affects must be fully evaluated.

Patients with COVID-19 are not permitted **visitors**. Staff use coveralls, masks, eye cover, and gloves, removing PPE only when they leave the ward.

Patients are discharged after clinical recovery (afebrile >3 days, resolution of symptoms and radiologic improvement) and 2 negative PCR tests taken 24 hours apart. Upon discharge, they are asked to minimise family and social contact and to wear a mask. There are expectations of clinical trial results within a matter of weeks, which will see further opportunities for treatment.

There are guidelines for **elderly care** specifically targeting prevention in individuals and introduction of COVID-19 to nursing homes.

Training programmes by video conference nationally are scaled up to inform staff of best practice and to ensure PPE usage. **Clinical champions** are created to disperse knowledge and provide local expertise.

Maintenance of usual healthcare activities is maintained by hospital zoning (e.g. clean/contaminated sections of the healthcare facility).

Laboratory, diagnostics and virology

The virus found to cause COVID-19 was initially isolated from a clinical sample on 7 January. It is notable that within weeks following the identification of the virus, a series of reliable and sensitive **diagnostic tools** were developed and deployed. On 16 January, the first RT-PCR assays for COVID-19 were distributed to Hubei. Real-time PCR kits were distributed to all the provinces on 19 January and were provided to Hong Kong SAR and Macao SAR on 21 January. Information regarding viral sequences and PCR primers and probes was shared with WHO and the international community by China CDC on 12 January 2020. To facilitate product development and research on the new virus, COVID-19 virus sequences were uploaded to the GISAID Database by China.

By 23 February, there were 10 kits for detection of COVID-19 approved in China by the NMPA, including 6 RT-PCR kits, 1 isothermal amplification kit, 1 virus sequencing product and 2 colloidal gold antibody detection kits. Several other tests are entered in the emergency approval procedure. Currently, there are at least 6 local producers of PCR test kits approved by NMPA. Overall, producers have the capacity to produce and distribute as many as 1,650,000 tests/week.

Specimens from both the upper respiratory tract (URT; nasopharyngeal and oropharyngeal) and lower respiratory tract (LRT; expectorated sputum, endotracheal aspirate, or bronchoalveolar lavage) are collected for COVID-19 testing by PCR.

COVID-19 virus has been detected in respiratory, fecal and blood specimens. According to preliminary data from Guangzhou CDC as of 20 February, virus can initially be detected in upper respiratory samples 1-2 days prior to symptom onset and persist for 7-12 days in moderate cases and up to 2 weeks in severe cases. Viral RNA has been detected in feces in up to 30% of patients from day 5 following onset of symptoms and has been noted for up to 4-5 weeks in moderate cases. However, it is not clear whether this correlates with the presence of infectious virus. While live virus has been cultured from stool in some cases, the role of fecal-oral transmission is not yet well understood. COVID-19 has been isolated from the clinical specimens using human airway epithelial cells, Vero E6 and Huh-7 cell lines.

Serological diagnostics are rapidly being developed but are not yet widely used. Joint Mission members met with local research teams at the China CDC, Guangzhou Regenerative Medicine and Health Guangdong Laboratory. The teams reported on the development of tests for IgM, IgG and IgM+IgG using rapid test platforms utilizing chemiluminiscence. ELISA assays are also under development.

Research & Development

The government of China has initiated a series of major emergency research programs on virus genomics, antivirals, traditional Chinese medicines, clinical trials, vaccines, diagnostics and animal models. Research includes fundamental basic research and human subjects research. For the purpose of this report, human studies are limited to those involving IRB approval and informed consent. Other forms of human subjects investigations are included in the sections on epidemiology in this report. Well-focused, robust research conducted in the setting of an outbreak has the potential of saving many lives by identifying the most effective ways to prevent, diagnose and treat disease.

Since the COVID-19 virus has a genome identity of 96% to a bat SARS-like coronavirus and 86%-92% to a pangolin SARS-like coronavirus, an animal source for COVID-19 is highly likely. This was corroborated by the high number of RT-PCR positive environmental samples taken from the Huanan Seafood Market in Wuhan.

At least 8 **nucleic acid-based methods** for direct detection of COVID-19 and two colloidal gold antibody detection kits have been approved in China by the NMPA. Several other tests are close to approval. It will be important to compare the sensitivities and specificities of these and future serologic tests. Development of rapid and accurate **point-of-care tests** which perform well in field settings are especially useful if the test can be incorporated into presently commercially available multiplex respiratory virus panels. This would markedly improve early detection and isolation of infected patients and, by extension, identification of contacts. **Rapid IgM and IgG antibody testing** are also important ways to facilitate early diagnosis. Standard serologic testing can be used for retrospective diagnoses in the context of serosurveys that help better understand the full spectrum of COVID-19 infection.

A variety of **repurposed drugs and investigational drugs** have been identified. Screening NMPA approved drug libraries and other chemical libraries have identified novel agents. Hundreds of clinical trials involving remdesivir, chloroquine, favipiravir, chloroquine, convalescent plasma, TCM and other interventions are planned or underway. Rapid completion of the most important of these studies is critical to identifying truly effective therapies. However, evaluation of investigational agents requires adequately powered, randomized, controlled trials with realistic eligibility criteria and appropriate stratification of patients. It is important for there to be a degree of coordination between those conducting studies within and beyond China.

The development of a safe and effective **vaccine** for this highly communicable respiratory virus is an important epidemic control measure. Recombinant protein, mRNA, DNA, inactivated whole virus and recombinant adenovirus vaccines are being developed and some are now entering animal studies. Vaccine safety is of prime concern in the area of coronavirus infection in view of the past experience of disease enhancement by inactivated whole virus measles vaccine and similar reports in animal experiments with SARS coronavirus vaccines. It will be important that these vaccine candidates rapidly move into appropriate clinical trials.

The ideal **animal model** for studying routes of virus transmission, pathogenesis, antiviral therapy, vaccine and immune responses has yet to be found. The ACE2 transgenic mouse model and Macaca Rhesus model are already used in research laboratories. Systematically addressing which models can accurately mimic human infection is required.

There is a global rush for masks, hand hygiene products and other personal protective equipment. The relative importance of **non-pharmaceutical control measures** including masks, hand hygiene, and social distancing require further research to quantify their impact.

There are distinct patterns of intra-familial transmission of COVID-19. It is unclear whether or not there are host factors, including genetic factors, that influence susceptibility or disease course. COVID-19 has a varied clinical course and a precise description of that course is not available. In addition, the long-term consequences of COVID-19 are unknown. An observational cohort study of patients with COVID-19 enrolled from the time of diagnosis (with appropriate controls) could provide in-depth information about clinical, virologic and immunologic characteristics of COVID-19. Table 1 summarizes priority research areas with immediate to longer term goals.

Table 1 Priority research areas with immediate, intermediate and longer-term goals

Immediate Goals	Intermediate Goals	Long-term goals
Diagnostics: RNA assays, antibody & antigen assays, point of care detection	Diagnostics: Multiplex diagnostic platforms	Diagnostics: Prognostic markers
Therapeutics: Remdesivir, favipiravir, chloroquine, plasma, TCM	Therapeutics: intravenous immunoglobulin (IVIg)	Therapeutics: Innovative approaches (CRISPR-CAS; RNAi; Cell-based; positive hits from library screening)
Vaccines: Development of animal models	Vaccines: mRNA candidates and candidate viral vectors	Vaccines: inactivated candidates and subunit candidates

D. Knowledge Gaps

Knowledge gaps and key questions to be answered to guide control strategies include:

Source of infection

- Animal origin and natural reservoir of the virus
- Human-animal interface of the original event
- Early cases whose exposure could not be identified

The pathogenesis and virulence evolution of the virus

Transmission dynamics

- Modes of Transmission:
    - Role of aerosol transmission in non-health care settings
    - Role of fecal-oral transmission
- Viral shedding in various periods of the clinical course in different biological samples (i.e. upper and lower respiratory tract, saliva, faeces, urine)
    - Before symptom onset and among asymptomatic cases
    - During the symptomatic period
    - After the symptomatic period / during clinical recovery

Risk factors for infection

- Behavioral and socio-economic risk factors for infection in
    - Households / institutions
    - the Community
- Risk factors for asymptomatic infection
- Risk factors for nosocomial infection
    - among health care workers
    - among patients

Surveillance and monitoring

- Monitoring community transmission through existing
    - ILI surveillance
    - SARI surveillance
- The outbreak trend and intervention dynamics
    - Basic reproduction numbers in various stages of the epidemic
    - The epidemic's relation to seasonality

Laboratory and diagnostics

- Sensitivity and specificity of different nucleic acid (PCR, NAATs and rapid tests), antibody and antigen tests
- Post-infection antibody titers and the duration of protection
- Sero-prevalence among
    - Health care workers
    - General population
    - Children

Clinical management of severe and critically ill patients

- Value of ECMO in the management of critically ill patients
- Best practice using mechanical ventilation in the management of critically ill patients
- Re-evaluation of the role of steroids in the management of severe and critically ill patients
- Identification of factors associated with successful clinical management and outcome
- Determination of the effectiveness of Traditional Chinese Medicines (TCM)
- Determination the effectiveness of additional investigational treatment options (e.g. intravenous immunoglobulin/IVIg, convalescent plasma)

Prevention and control measures

- Key epidemic indicators that inform evidence-based control strategy decision making and adjustments
- Effectiveness of infection prevention and control (IPC) measures in various health care settings
- Effectiveness of entry and exit screening
- Effectiveness of the public health control measures and their socio-economic impact
    - Restriction of movement
    - Social distancing
    - School and workplace closures
    - Wearing mask in general public
    - Mandatory quarantine
    - Voluntary quarantine with active surveillance

E. Operational & Technical Recommendations

Operational/programmatic recommendations

- Reassess risk and capacities based on different stages of the outbreak; approve different measures during the different phases of the response; assess different stages of the response; reach a balance between response and social development
- Initiate a timely scientific evidence based, efficient and flexible joint multi-sectoral mechanism, which is driven by strong government leadership

Technical recommendations

Epidemiology and transmission

- Continue enhanced surveillance across the country through existing respiratory disease systems, including ILI, SARI or pneumonia surveillance systems
- Prioritize early investigations, including household transmission studies, age-stratified sero-epidemiologic surveys including children, case-control studies, cluster investigations, and serologic studies in health care workers

Severity

- Continue to share information on patient management, disease progression and factors leading to severe disease and favorable outcomes
- Review and analyze the possible factors associated with the disease severity, which may include:
    - natural history studies to better understand disease progression in mild, severe and fatal patients
    - medical chart reviews about disease severity among vulnerable groups, (e.g. those with underlying conditions, older age groups, pregnant women and children) to develop appropriate standards of care
    - evaluation of factors leading to favorable outcomes (e.g. early identification and care)

Clinical care and infection prevention and control

- Suspect patients who have not yet been tested should be isolated in single normal pressure rooms; cohorting of positive cases is acceptable
- Physicians and all health care workers need to maintain a high level of clinical alert for COVID-19
- For affected countries, standardize training for clinical care and IPC and scale with the development of local (e.g. district level) experts
- Ensure concurrent testing for other viral pathogens to support a negative COVID-19 test
- Ensure maintenance of usual and essential services during the outbreak

- Ensure processes are in place for infection prevention among the most vulnerable, including the elderly
- Ensure readiness to provide clinical care and to meet IPC needs, including:
    a. anticipated respiratory support requirements (e.g. pulse oximeters, oxygen, and invasive support where appropriate)
    b. national guidelines for clinical care and IPC, revised for COVID-19
    c. nationally standardised trainings for disease understanding and PPE use for HCWs
    d. community engagement
    e. PPE and Medication stockpiles
    f. early identification protocols; triage, temperature screening, holding bays (triage, including pulse oximetry)
    g. treatment protocols including designated facilities, patient transportation
    h. enhanced uptake of influenza and pneumococcal vaccine according to national guidelines
    i. laboratory testing
    j. rapid response teams

Laboratory and virology

- Continue to perform whole genome analysis of COVID-19 viruses isolated from different times and places, to evaluate virus evolution
- Conduct pathogenesis studies using biopsy/post-mortem specimens of COVID-19 patients or infected animal models
- Evaluate available nucleic acid PCR diagnostics
- Rapidly develop and evaluate rapid/point-of-care diagnostics and serologic assays
- Conduct further study to interpret the result of positive COVID-19 RNA detection in feces in patients recovering from COVID-19
- Enhance international cooperation, especially in terms of biosafety and information sharing for increased understanding of the COVID-19 virus and traceability of the virus
- Consider monitoring proinflammatory cytokines via multiplex assays to predict the development of “cytokine storm”

Research and development

- Additional effort should be made to find the animal source, including the natural reservoir and any intermediate amplification host, to prevent any new epidemic foci or resurgence of similar epidemics

- Efforts should be made to consistently evaluate existing and future diagnostic tests for detection of COVID-19 using a harmonized set of standards for laboratory tests and a biorepository that can be used for evaluating these tests
- Consider the establishment of a centralized research program in China to oversee that portfolio and ensure the most promising research (vaccines, treatments, pathogenesis) are adequately supported and studied first; program staff dedicated to the clinical research would work at the clinical research site(s) to decrease the research workload of the clinicians at the site
- Consider including one or more sites within China in the ongoing and future multi-center, international trials; Chinese investigators should be actively engaged in international trials
- Continue to develop additional animal models, making every effort to ensure these mimic human infection and virus transmission as closely as possible
- Conduct studies to determine which of the commonly used forms of PPE are most effective in controlling the spread of COVID-19

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Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study

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Summary

Background Rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China, prompted heightened surveillance in Shenzhen, China. The resulting data provide a rare opportunity to measure key metrics of disease course, transmission, and the impact of control measures.

Methods From Jan 14 to Feb 12, 2020, the Shenzhen Center for Disease Control and Prevention identified 391 SARS-CoV-2 cases and 1286 close contacts. We compared cases identified through symptomatic surveillance and contact tracing, and estimated the time from symptom onset to confirmation, isolation, and admission to hospital. We estimated metrics of disease transmission and analysed factors influencing transmission risk.

Findings Cases were older than the general population (mean age 45 years) and balanced between males (n=187) and females (n=204). 356 (91%) of 391 cases had mild or moderate clinical severity at initial assessment. As of Feb 22, 2020, three cases had died and 225 had recovered (median time to recovery 21 days; 95% CI 20–22). Cases were isolated on average 4·6 days (95% CI 4·1–5·0) after developing symptoms; contact tracing reduced this by 1·9 days (95% CI 1·1–2·7). Household contacts and those travelling with a case were at higher risk of infection (odds ratio 6·27 [95% CI 1·49–26·33] for household contacts and 7·06 [1·43–34·91] for those travelling with a case) than other close contacts. The household secondary attack rate was 11·2% (95% CI 9·1–13·8), and children were as likely to be infected as adults (infection rate 7·4% in children <10 years *vs* population average of 6·6%). The observed reproductive number (*R*) was 0·4 (95% CI 0·3–0·5), with a mean serial interval of 6·3 days (95% CI 5·2–7·6).

Interpretation Our data on cases as well as their infected and uninfected close contacts provide key insights into the epidemiology of SARS-CoV-2. This analysis shows that isolation and contact tracing reduce the time during which cases are infectious in the community, thereby reducing the *R*. The overall impact of isolation and contact tracing, however, is uncertain and highly dependent on the number of asymptomatic cases. Moreover, children are at a similar risk of infection to the general population, although less likely to have severe symptoms; hence they should be considered in analyses of transmission and control.

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Introduction

Since emerging in Wuhan, China, in December, 2019,[1] the coronavirus disease 2019 (COVID-19) epidemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has progressed rapidly into a pandemic. COVID-19 is characterised by fever, cough, fatigue, shortness of breath, pneumonia, and other respiratory tract symptoms,[2–4] and in many cases progresses to death. As of April 15, 2020, there have been 1914916 confirmed cases and 123010 deaths reported worldwide.[5] Most cases were initially confined to Hubei province in China, but there has since been substantial spread not only elsewhere in China but worldwide. A rapid and robust response by the global scientific community has described many important aspects of SARS-CoV-2 transmission and natural history,[1,2,6–8] but key questions remain.

If well tracked, early introductions of an emerging pathogen provide a unique opportunity to characterise its transmission, natural history, and the effectiveness of screening. Careful monitoring of cases and low probability of infection from the general community enables inferences, important to modelling the course of the outbreak, that are difficult to make during a widely disseminated epidemic. In particular, we can make assumptions about when and where cases were likely to have been infected that are impossible when the pathogen is widespread. Furthermore, during these early phases, uninfected and asymptomatic contacts are often closely tracked, providing important information about transmission and natural history. Combined, these data on early introductions can be used to give insights into the natural history of the disease,[9]

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For the Chinese translation of the abstract see Online for appendix 1

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Research in context

Evidence before this study

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been accompanied by a substantial increase in research and publications ranging from transmissibility of SARS-CoV-2 to clinical characteristics of the infection. As of March 23, 2020, our search of PubMed using keywords ("COVID-19" OR "SARS-nCoV-2" OR "novel coronavirus") AND ("serial interval" OR "incubation period" OR "attack rate") yielded 14 articles that have estimated either the serial interval or incubation period of coronavirus disease 2019 (COVID-19) and one that investigated the secondary attack rate. However, most of these estimates have come from either Wuhan or publicly available case data; in both instances, incomplete capture of infections and cases might have produced biased estimates.

Added value of this study

This study is, to our knowledge, the first analysis of SARS-CoV-2 transmission and COVID-19 natural history based on a large primary dataset of cases and close contacts, for which the mode of surveillance (ie, symptom-based versus contact-based) was sufficiently documented and RT-PCR testing was nearly universal. We present one of the first estimates of the serial interval, secondary household attack rate, and dispersion (ie, tendency towards super spreading) for SARS-CoV-2 based on active surveillance data. We found that the attack rate does not differ significantly by age, with on average 7% of close contacts becoming infected, around 80% of these contacts showing any symptoms, and 3% of infections manifesting severe disease at initial assessment. We also found that contact-based surveillance in Shenzhen reduced the duration an infected individual transmits in the community by 2 days. These findings are important for understanding the burden of COVID-19 and for strategic planning across the world.

Implications of all the available evidence

These results shed further light on how SARS-CoV-2 is transmitting, how severe it is, and how effective control measures can be in specific contexts. We provide a key piece of evidence supporting intensive contact tracing and highlighting that children might be an important target for interventions aimed at reducing transmission, even if they do not get sick.

	Contact-based surveillance (n=87)	Symptom-based surveillance (n=292)	Unknown or other (n=12)	Total (n=391)	p value
Sex					
Female	63 (72%)	131 (45%)	10 (83%)	204 (52%)	<0·0001
Male	24 (28%)	161 (55%)	2 (17%)	187 (48%)	..
Age					
0–9 years	13 (15%)	6 (2%)	1 (8%)	20 (5%)	<0·0001
10–19 years	5 (6%)	6 (2%)	1 (8%)	12 (3%)	..
20–29 years	11 (13%)	23 (8%)	0 (0%)	34 (9%)	..
30–39 years	15 (17%)	71 (24%)	1 (8%)	87 (22%)	..
40–49 years	9 (10%)	49 (17%)	2 (17%)	60 (15%)	..
50–59 years	10 (12%)	63 (22%)	1 (8%)	74 (19%)	..
60–69 years	20 (23%)	60 (21%)	6 (50%)	86 (22%)	..
≥70 years	4 (5%)	14 (5%)	0 (0%)	18 (5%)	..
Severity					
Mild	18 (21%)	82 (28%)	2 (17%)	102 (26%)	0·03
Moderate	66 (76%)	180 (62%)	8 (67%)	254 (65%)	..
Severe	3 (3%)	30 (10%)	2 (17%)	35 (9%)	..
Symptomatic					
No	17 (20%)	8 (3%)	0 (0%)	25 (6%)	<0·0001
Yes	70 (80%)	284 (97%)	12 (100%)	366 (94%)	..
Fever					
No	25 (29%)	34 (12%)	2 (17%)	61 (16%)	0·0002
Yes	62 (71%)	258 (88%)	10 (83%)	330 (84%)	..

Table 1: **Demographic and clinical characteristics of cases by contact-based versus symptom-based surveillance**

See Online for appendix 2

transmission characteristics,[10] and the unseen burden of infection.[11]

Here, we use data collected by the Shenzhen Center for Disease Control and Prevention (Shenzhen CDC) on 391 cases of COVID-19 and 1286 of their close contacts to characterise key aspects of its epidemiology outside of Hubei province. We characterise differences in demographics and severity between cases identified through symptom-based surveillance and monitoring of close case contacts, and estimate the time to key events, such as confirmation, isolation, and recovery. Using data from contact tracing, we characterise SARS-CoV-2 transmission by estimating key values, such as the household secondary attack rate, serial interval, and observed reproductive number (R).

Methods

Case identification

On Jan 8, 2020, Shenzhen CDC identified the first case of pneumonia with unknown cause and began monitoring travellers from Hubei province for symptoms of COVID-19. Over the next 2 weeks this surveillance programme expanded to include travellers from Hubei regardless of symptoms, patients at local hospitals, and individuals detected by fever screening in neighbourhoods and at local clinics. Suspected cases and close contacts were tested for SARS-CoV-2 by RT-PCR of nasal swabs at 28 qualified local hospitals, ten district-level CDCs, and two third-party testing organisations, with final confirmation done at the Guangdong Provincial Center for Disease Control and Prevention (Guangdong CDC) or Shenzhen CDC (appendix 2 p 11). Close contacts were identified through contact tracing of a confirmed case and were defined as those who lived in the same apartment, shared a meal, travelled, or socially interacted with an index case 2 days before symptom onset. Casual

	Outcome: symptom-based surveillance						Outcome: moderate or severe assessment					
	Univariate regression			Multivariate regression			Univariate regression			Multivariate regression		
	OR	2·5%	97·5%	OR	2·5%	97·5%	OR	2·5%	97·5%	OR	2·5%	97·5%
Sex												
Female	Ref	..	..	Ref	..	..	Ref	..	..	Ref	..	..
Male	3·23	1·93	5·53	3·06	1·77	5·44	1·30	0·82	2·07	1·37	0·85	2·22
Age												
0–9 years	0·07	0·02	0·23	0·08	0·02	0·25	0·88	0·30	2·77	0·67	0·22	2·23
10–19 years	0·19	0·05	0·77	0·17	0·04	0·76	1·08	0·28	5·27	0·88	0·22	4·40
20–29 years	0·33	0·12	0·89	0·37	0·13	1·02	0·65	0·28	1·56	0·61	0·26	1·49
30–39 years	0·75	0·31	1·77	0·8	0·32	1·93	1·17	0·58	2·37	1·15	0·57	2·33
40–49 years	0·86	0·32	2·33	0·79	0·29	2·19	1·27	0·58	2·83	1·21	0·55	2·72
50–59 years	Ref	..	..	Ref	..	..	Ref	..	..	Ref	..	..
60–69 years	0·48	0·2	1·08	0·44	0·18	1·04	1·50	0·72	3·16	1·43	0·68	3·03
≥70 years	0·56	0·16	2·25	0·45	0·12	1·89	1·41	0·45	5·43	1·28	0·40	4·96
Severity												
Mild	Ref	..	..	Ref	..	..	..	..	..	..	..	..
Moderate	0·6	0·33	1·05	0·51	0·26	0·94	..	..	..	..	..	..
Severe	2·2	0·68	9·84	1·51	0·42	7·23	..	..	..	..	..	..
Fever												
No	Ref	..	..	..	..	..	Ref	..	..	..	..	..
Yes	3·06	1·69	5·49	..	..	..	0·94	0·49	1·75	..	..	..
Symptomatic												
No	Ref	..	..	..	..	..	Ref	..	..	..	..	..
Yes	8·62	3·68	21·89	..	..	..	0·51	0·15	1·39	0·55	0·29	1·01
Surveillance method												
Contact-based	..	..	..	..	..	..	Ref	..	..	..	..	..
Symptom-based	..	..	..	..	..	..	0·67	0·37	1·17	..	..	..

OR=odds ratio.

Table 2: **Association of clinical and demographic factors with mode of detection and severity at initial assessment**

contacts (eg, other clinic patients) and some close contacts (eg, nurses) who wore a mask during exposure were not included in this group.

Symptomatic cases were isolated and treated at designated hospitals regardless of RT-PCR test results. Asymptomatic individuals who tested positive were quarantined at centralised facilities. Close contacts and travellers from Hubei who tested negative were quarantined at home or a central facility, and monitored for 14 days. RT-PCR testing was required for all close contacts at the beginning of isolation, and release was conditional on a negative RT-PCR result. Basic demographics, signs and symptoms, clinical severity, and exposure history were recorded for all confirmed cases.

Here, we analyse confirmed cases identified by the Shenzhen CDC between Jan 14 and Feb 12, 2020, and close contacts of cases confirmed before Feb 9, 2020.

This work was done in support of an ongoing public health response, and hence was determined not to be human subjects research after consultation with the Johns Hopkins Bloomberg School of Public Health institutional review board. Data collection is part of the continuing public health investigation of an emerging outbreak and therefore the individual informed consent was waived. The study was approved by the ethics committees of Shenzhen CDC. Analytical datasets were constructed in an anonymised manner, and all analysis of personally identifiable data took place onsite at the Shenzhen CDC.

Epidemiological and clinical characteristics of cases

We defined symptom-based surveillance to include symptomatic screening at airport and train stations, community fever monitoring, home observation of recent travellers to Hubei, and testing of patients admitted to hospital. Contact-based surveillance is the identification of cases through monitoring and testing of close contacts of confirmed cases, independently of their symptom presentation. By protocol, those in the contact-based group were tested for SARS-CoV-2 infection regardless of symptoms, whereas those in the other categories were tested only if they showed signs or symptoms of disease.

At the first clinical assessment, data were recorded on 21 signs and symptoms (appendix 2 p 1), and disease severity was assessed. Cases with fever, respiratory symptoms, and radiographic evidence of pneumonia were classified as having moderate symptoms. Cases

were classified as having severe symptoms if they had any of the following: breathing rate 30 breaths per min or higher; oxygen saturation level 93% or lower at rest; oxygen concentration level PaO_2/FiO_2 (ratio of arterial oxygen partial pressure to fractional inspired oxygen) 300 mm Hg (1 mm Hg=0·133 kPa) or lower; lung infiltrates higher than 50% within 24–48 h; respiratory failure requiring mechanical ventilation; septic shock; or multiple organ dysfunction or failure. All other symptomatic cases were classified as mild.

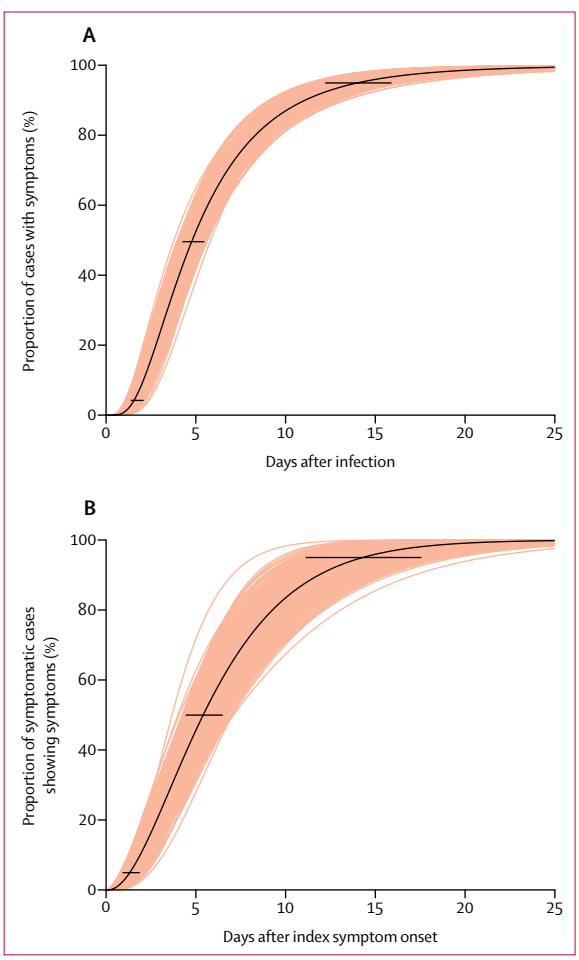

Figure 1: **Incubation period and serial interval of COVID-19**
(A) Proportion of cases who developed symptoms of coronavirus disease 2019 (COVID-19) by days after infection (ie, the cumulative distribution function of the incubation period). (B) Proportion of cases infected by an index case who developed symptoms by a given number of days after the day of symptom onset of the index case (ie, the cumulative distribution function of the serial interval). The maximum-likelihood estimates for the parametric distribution of the cumulative distribution function are shown, along with 1000 parametric bootstrap estimates of the cumulative distribution function. The median incubation period of COVID-19 is estimated to be 4·8 days (95% CI 4·2–5·4). 5% of cases who develop symptoms will do so by 1·6 days (95% CI 1·3–2·0) after infection, and 95% by 14·0 days (12·2–15·9). We estimated that the median serial interval of COVID-19 is 5·4 days (95% CI 4·4–6·5). 5% of infected cases who develop symptoms will do so by 1·3 days (95% CI 0·9–1·9) after symptom onset of the index case, and 95% by 14·3 days (11·1–17·6).

Relationships between demographics, mode of detection, and symptom severity were assessed and characterised with χ^2 tests, and simple and multiple logistic regression.

Timing of key events

Distributions were fit to the timing of key events in each confirmed case's course of infection and treatment. The time from infection to symptom onset (incubation period) was assumed to be log-normally distributed and estimated as previously described.[12–14] We determined the left and right boundaries on the possible exposure and symptom onset times. Cases who recently travelled to Hubei were assumed to have been exposed while there. Cases without a recent travel history but with exposure to a confirmed case were assumed to be exposed from the time of earliest to latest possible contact with that case. Only cases for whom we could identify the earliest and latest possible time of exposure and who had a date of symptom onset were included in the analysis.

Time between symptom onset and recovery was estimated by use of parametric survival methods. Patients who had not recovered were considered to be censored on Feb 22, 2020, or at the time of death. All other delay distributions were estimated by directly fitting parametric distributions to time between symptom onset or arrival in Shenzhen, and confirmation, isolation, or admission to hospital. Confidence intervals were calculated with bootstrapping or standard parametric estimators.[15]

Transmission characteristics

Transmission was characterised by examining the relationship between confirmed cases and their infected and uninfected close contacts. The household secondary attack rate was calculated as the percentage of household contacts (those sharing a room, apartment, or other sleeping arrangement) who were later confirmed to have SARS-CoV-2 infection. The distribution of serial intervals (the time between symptom onset in the confirmed case and their infected contacts) was calculated by fitting parametric distributions to the time of symptom onset in clear case–contact pairs. The mean R and distribution of individual reproductive numbers (ie, the number of secondary infections caused by each case) were calculated from the number of secondary infections observed among close contacts of each index case, with ambiguities resolved through multiple imputation (appendix 2 p 11). The relative odds of transmission among contacts of various types were estimated by use of conditional logistic regression and random-effects models, to account for differing numbers of possible infected individuals in each risk group. When assessing the impact of characteristics of infected individuals, we only included risk sets where a single potential infected individual was clearly identifiable. Confidence intervals were estimated by use of bootstrapping or standard parametric approaches.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Shenzhen CDC had full access to all the data in the study, and all corresponding authors share the final responsibility for the decision to submit for publication.

Results

Between Jan 14 and Feb 12, 2020, the Shenzhen CDC confirmed 391 cases of SARS-CoV-2 infection (table 1). Of 379 with a known mode of detection, 292 (77%) were detected through symptom-based surveillance. Overall, there were approximately equal numbers of male and female cases (187 *vs* 204). The mean age of the population was 45 years, and 307 (79%) of 391 cases were adults aged 30–69 years. At the time of first clinical assessment, most cases were mild (102 [26%] of 391) or moderate (254 [65%] of 391), and only 35 (9%) were severe. 330 (84%) of 391 cases had fever at the time of initial assessment, while 25 (6%) of 391 had no signs or symptoms. As of Feb 22, 2020, final clinical outcomes were known for 228 of 391 cases in our data, with three who had died (all captured through symptom-based surveillance) and 225 who had recovered.

A larger proportion of cases detected through symptom-based surveillance were male (161 [55%] of 292 *vs* 24 [28%] of 87) and aged 20–69 years (266 [91%] of 292 *vs* 65 [75%] of 87) than were those detected through contact-based surveillance (tables 1, 2). At the time of the first clinical assessment, 25 (29%) of 87 cases in the contact-based surveillance group did not have fever, and 17 (20%) of 87 had no symptoms. By contrast, 258 (88%) of 292 in the symptom-based surveillance group had fever, and only eight reported no symptoms.

In multiple logistic regression, male sex was associated with severe symptoms (odds ratio [OR] 2·5 [95% CI 1·1–6·1]). The probability of severe symptoms increased slightly with age, although only individuals aged 60–69 years had a significantly increased risk compared with the reference category, individuals aged 50–59 years (OR 3·4 [95% 1·4–9·5]).

Based on 183 cases with a well defined period of exposure and symptom onset (appendix 2 p 8), we estimated the median incubation period for COVID-19 to be 4·8 days (95% CI 4·2–5·4; figure 1, appendix 2 p 2),

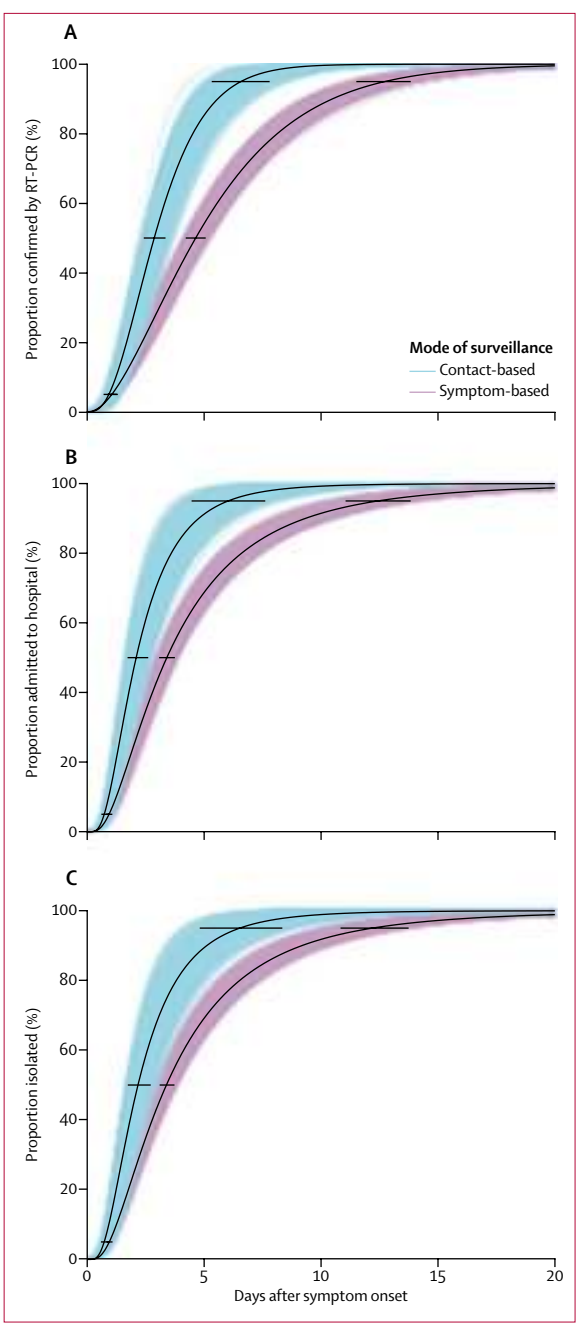

Figure 2: **Time between symptom onset and SARS-CoV-2 confirmation (A), admission to hospital (B), and isolation among cases (C) detected by contact-based and symptom-based surveillance**

The maximum-likelihood estimates for the parametric distribution of the cumulative distribution function are shown, along with 1000 parametric bootstrap estimates of the cumulative distribution function. Panel A shows estimates of the proportion of cases who are confirmed by RT-PCR, according to the number of days after symptom onset. We estimated that 50% of cases detected through symptom-based surveillance were confirmed by RT-PCR within 4·6 days (95% CI 4·2–5·0) after symptom onset, and 95% were confirmed by RT-PCR within 12·7 days (11·5–13·8) after symptom onset. Contact-based surveillance reduced the days from symptom onset to RT-PCR confirmation to 2·9 days (95% CI 2·4–3·4) in 50% of cases and to 6·6 days (5·3–8·0) in 95% of cases. Panel B shows estimates of the proportion of cases who were admitted to hospital, according to the number of days after symptom onset. We estimated that 50% of the cases detected through symptom-based surveillance were admitted to hospital by 3·4 days (95% CI 3·1–3·8) after symptom onset, and 95% by 12·4 days (10·9–13·8). Contact-based surveillance reduced the days from symptom onset to hospital admission to 2·1 days (95% CI 1·7–2·6) in 50% of cases, and 6·0 days (95% CI 4·5–7·5) in 95% of cases. Panel C shows estimates of the proportion of cases isolated, according to number of days after symptom onset. We estimated that 50% of cases detected through symptom-based surveillance were isolated by 3·4 days (95% CI 3·1–3·7) after symptom onset, and 95% by 12·2 days (95% CI 10·8–13·6). Contact-based surveillance reduced the days from symptom onset to isolation to 2·2 days (95% CI 1·7–2·6) in 50% of cases, and to 6·5 days (4·7–8·2) in 95% of cases.

	Number of cases*	Number infected	Attack rate (95% CI)	Univariate regression			Multivariate regression		
				Odds ratio	2·5%	97·5%	Odds ratio	2·5%	97·5%
Sex									
Female	558	58	10·4% (8·1–13·2)	Ref	..	..	..	..	..
Male	486	26	5·3% (3·7–7·7)	0·43	0·21	0·86	..	..	..
Age									
0–9 years	148	11	7·4% (4·2–12·8)	2·33	0·38	14·05	..	..	..
10–19 years	85	6	7·1% (3·3–14·6)	3·50	0·53	23·24	..	..	..
20–29 years	114	7	6·1% (3·0–12·1)	4·91	0·74	32·64	..	..	..
30–39 years	268	16	6·0% (3·7–9·5)	1·84	0·34	9·80	..	..	..
40–49 years	143	7	4·9% (2·4–9·8)	3·46	0·55	21·92	..	..	..
50–59 years	110	10	9·1% (5·0–15·9)	Ref	..	..	..	..	..
60–69 years	130	20	15·4% (10·2–22·6)	5·68	1·01	32·09	..	..	..
≥70 years	72	7	9·7% (4·8–18·7)	4·26	0·64	28·44	..	..	..
Contact type: household									
No	456	4	0·9% (0·3–2·2)	Ref	..	..	Ref	..	..
Yes	686	77	11·2% (9·1–13·8)	15·10	3·69	61·69	6·27	1·49	26·33
Contact type: travel									
No	824	63	7·6% (6·0–9·7)	Ref	..	..	Ref	..	..
Yes	318	18	5·7% (3·6–8·8)	9·13	1·85	45·08	7·06	1·43	34·91
Contact type: meal									
No	435	20	4·6% (3·0–7·0)	Ref	..	..	Ref	..	..
Yes	707	61	8·6% (6·8–10·9)	23·01	2·51	211·2	7·13	0·73	69·32
Contact frequency									
Rare	230	1	0·4% (0·02–2·4)	<0·0001	0	Inf	..	..	..
Moderate	305	9	3·0% (1·6–5·5)	Ref	..	..	..	..	..
Often	555	71	12·8% (10·3–15·8)	8·8	2·58	30·06	..	..	..

SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. Inf=infinity. *15 confirmed close contacts were excluded from this analysis because contact tracing reports for the negative close contacts in the same clusters were missing. Close contacts with missing data on sex, age, contact types, or contact frequency not shown.

Table 3: **Group-specific attack rates and risk factors for SAR-CoV-2 infection among close contacts**

and estimated that 95% of those who develop symptoms will do so within 14·0 days (95% CI 12·2–15·9) of infection. We estimated that about 5·0% of cases who develop symptoms would not show symptoms until 14 days after infection.

Based on 228 cases with known outcomes, we estimated that median time to recovery was 20·8 days (95% CI 20·1–21·5). We estimated that the median time to recovery was 22·4 days (95% CI 20·8–24·1) in individuals aged 50–59 years, and was estimated to be significantly shorter in younger adults (eg, 19·2 days in individuals aged 20–29 years; appendix 2 pp 3, 10). In multiple regression models including sex, age, baseline severity, and method of detection, in addition to age, baseline severity was associated with time to recovery (appendix 2 p 3). Compared to cases with mild symptoms, those with severe symptoms had a 41% (95% CI 24–60) longer time to recovery (appendix 2 p 3). As of Feb 22, 2020, three cases had died. These deaths occurred 35–44 days from symptom onset and 27–33 days from confirmation.

Cases detected through symptom-based surveillance were confirmed on average 5·5 days (95% CI 5·0–5·9) after symptom onset (figure 2, appendix 2 p 2), whereas those detected by contact-based surveillance were confirmed on average 3·2 days (95% CI 2·7–3·8) after symptom onset. 17 (5%) of 342 cases with a known onset date and start date of quarantine were isolated before developing symptoms. Among those isolated after developing symptoms, the symptom-based surveillance group was, on average, isolated 4·6 days (95% CI 4·1–5·0) after symptom onset, whereas the contact-based surveillance group was isolated 2·7 days (2·1–3·3) after symptom onset. Hence, contact-based surveillance was associated with a 2·3-day (95% CI 1·5–3·0) decrease in time to confirmation and a 1·9-day (1·1–2·7) decrease in time to isolation. The mean time between symptom onset and admission to hospital was similar to time between symptom onset and isolation in both the symptom-based and contact-based surveillance groups (figure 2, appendix 2 p 2).

191 (64%) of 298 travellers developed symptoms after arriving in Shenzhen, with a mean time from arrival to symptom onset of 4·9 days (95% CI 4·2–5·5; appendix 2 p 2). Those developing symptoms before arrival or on the day of arrival were confirmed as cases on average 4·5 days (95% CI 3·8–5·1) after arrival, and isolated on average 3·1 days (2·5–3·7) after arrival.

Overall, 1286 close contacts were identified for index cases testing positive for SARS-CoV-2 between Jan 14 and Feb 9, 2020, with 244 (84%) of 292 cases having at least one close contact. 622 (95%) of 653 close contacts with known dates for the period when they were under quarantine were followed up for 12 days or longer. 98 of the close contacts tested positive for SARS-CoV-2 infection by RT-PCR, and one had presumptive infection. Assuming those with a missing test result were uninfected, we found that the secondary attack rate was 11·2% (95% CI 9·1–13·8) among household contacts and 6·6% (5·4–8·1) overall (the secondary attack rate increased to 14·9% [12·1–18·2] among household contacts and 9·7% [7·9–11·8] overall if those with missing results were removed from the denominator). In multiple conditional logistic regression analysis of contact types, household contact (OR 6·3; 95% CI 1·5–26·3) and travelling together (OR 7·1; 1·4–34·9) were significantly associated with infection (table 3). Reporting contact that occurred often was also associated with increased risk of infection compared with moderate-frequency contact (OR 8·8; 95% CI 2·6–30·1; table 3).

Attack rates were similar across all age categories of infected contacts (table 3), although we observed some indication of elevated attack rates in older age groups (figure 3). Notably, the rate of infection in children younger than 10 years (7·4%) was similar to the population average (6·6%). There was no significant association between probability of infection and age of the index case. Surprisingly, in univariate analysis a longer time in the community before isolation was associated with a reduced risk of causing infections (data not shown). However, this association was no longer significant after adjusting for contact frequency and type.

Based on 48 pairs of cases with a clear relationship between the index case and secondary case and time of symptom onset, we estimated that the serial interval is gamma distributed with a mean of 6·3 days (95% CI 5·2–7·6) and an SD of 4·2 days (95% CI 3·1–5·3; figure 1B, appendix 2 p 2). Hence, 95% of secondary cases were expected to develop symptoms within 14·3 days (95% CI 11·1–17·6) of their infector. This estimate includes the effect of isolation on truncating the serial interval. Stratified results show that if the infected individual was isolated less than 3 days after infection the average serial interval was 3·6 days, increasing to 8·1 days if the infected individual was isolated on the third day after symptom onset or later (appendix 2 p 3).

The mean number of secondary cases caused by each index case (ie, the observed reproductive number, *R*), was 0·4 (95% CI 0·3–0·5). The distribution of individual *R* values was highly over-dispersed, with 80% of infections being caused by 8·9% (95% CI 3·5–10·8) of cases (negative binomial dispersion parameter 0·58; 95% CI 0·35–1·18).

We examined the potential impact of surveillance and isolation through truncating the infectious period.

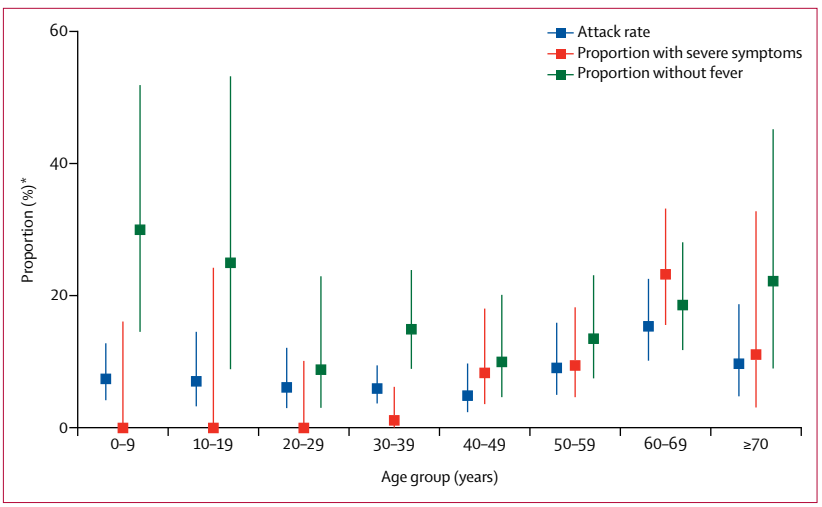

Figure 3: **Attack rate among close contacts, baseline severity, and proportion of cases without fever at initial assessment by age group**

*Proportion of close contacts for attack rate; proportion of all cases for those with severe symptoms or no fever at initial assessment.

Because of the scarce understanding of infectious periods following SARS-CoV-2 infection, we considered a range of possible infectious periods where infectiousness varies over time and follows a gamma distribution (appendix 2 p 11). We defined the mean infectious day (ie, the average number of days after symptom onset that an infected individual is expected to infect a secondary case) as the weighted mean of the infectious period, where each day is weighted by relative infectiousness. We considered periods where the mean infectious day is less than 15 days after symptom onset (roughly the period of SARS and early SARS-CoV-2 reports),[16,17] and assumed that R_0=2·6 and that isolation effectively ends the infectious period. Under these assumptions we found that if the mean infectious day is greater than 5 days, then it might be possible to bring *R* below one in cases detected by symptom-based surveillance, and the same can be accomplished by contact-based surveillance if the mean infectious day is greater than 3 days (appendix 2 p 9). For the impact of passive surveillance alone to achieve our observed *R* of 0·4, we projected that the mean infectious day must be at least 5·5 days (and likely greater) after symptom onset.

Even if transmission is completely eliminated in the group captured by surveillance (eg, if we could get perfect surveillance on the day of symptom onset), assuming R_0=2·6, the cases captured by surveillance must, if not isolated, be expected to cause 61% of onward transmission to achieve local elimination by surveillance and isolation alone (appendix 2 p 9).

Discussion

This analysis of early SARS-CoV-2 cases and their close contacts in Shenzhen, China, provides insight into the natural history, transmission, and control of this disease.

The values estimated provide the evidentiary foundation for predicting the impact of this virus, evaluating control measures, and guiding the global response. Analyses of how cases are detected, and use of data on individuals exposed but not infected, indicate that infection rates in young children are not lower than the population average (even if rates of clinical disease are). We were able to directly estimate important transmission parameters, and show that, at least among observed contacts, transmission rates are low. Estimates of the distribution of time between symptom onset and case isolation by surveillance type reveal that heightened surveillance combined with case isolation could plausibly account for these low rates of transmission. These results paint a positive picture of the impact of heightened surveillance and isolation in Shenzhen. However, uncertainty in the number of asymptomatic cases missed by surveillance and their ability to transmit SARS-CoV-2 must temper any hopes of stopping the COVID-19 pandemic by these measures.

This work further supports the understanding of COVID-19 as a disease with a fairly short incubation period (mean 4–6 days) but a long clinical course,[2,7,18] with patients taking many weeks to die or recover. Notably, however, we estimate a higher proportion of cases taking 14 days or more to develop symptoms (5%) than estimated in the study by Lauer and colleagues (1%).[6]

Focusing on cases detected through contact-based surveillance adds nuance to previous characterisations of COVID-19. Since RT-PCR testing of contacts is near universal, we can assume these cases are more reflective of the average SARS-CoV-2 infection than cases detected through symptomatic surveillance. In the contact-based surveillance group, any tendency for cases to be male or older (beyond the underlying population distribution) disappears. Furthermore, in this group, 20% of cases were asymptomatic at the time of first clinical assessment and nearly 30% did not have a fever. This observation is consistent with a reasonably high rate of asymptomatic carriage, but lower than that suggested by some modelling studies,[19] although RT-PCR has imperfect sensitivity.[20]

In Shenzhen, SARS-CoV-2 transmission most probably occurred between very close contacts, such as individuals sharing a household. However, even in this group fewer than one in six contacts (ie, secondary attack rate 11–15%) were infected, and overall we observed far fewer than one (0·4) onward transmission per primary case. As noted above, low transmission levels might in part be due to the impact of isolation and surveillance, but it is equally likely that unobserved transmission has some role. We also estimated reasonably high rates of overdispersion in the number of cases caused by each infected individual, leaving open the possibility that large COVID-19 clusters can occur even if surveillance and isolation are forcing R below one—events that could potentially overwhelm the surveillance system.

This work has numerous limitations. As in any active outbreak response, the data were collected by multiple teams under protocols that, by necessity, changed as the situation developed. Hence, there might be noise and inconsistency in definitions. Notably, the definition of a confirmed case changed to require symptoms near the end of our analysis period (Feb 7), but sensitivity analyses show that truncating the data at this point does not qualitatively influence results (appendix 2 pp 5–6). It is, likewise, impossible to identify every potential contact an individual has, so contact tracing focuses on those close contacts who are most likely to be infected; hence our R is assuredly lower than the true reproductive number in the population. Asymptomatic travellers will be missed by symptom-based surveillance and, even if they are tested, some asymptomatic contacts might be missed because of the imperfect sensitivity of the RT-PCR test.[20] Recovery time in Shenzhen is likely to be inflated because cases are required to be isolated for 2 weeks and release is conditional on a negative RT-PCR test. Although guidelines for contact tracing and case detection are supposed to be implemented across the country, whether the impact of contact tracing can be generalised to other parts of China depends on a range of factors, including local testing capacity and surveillance resources.

As SARS-CoV-2 continues to spread, it is important that we continue to expand our knowledge about its transmission and natural history. Data from the early phase of local outbreaks, when detailed contact tracing is possible and sources of infection can still be reliably inferred, are particularly powerful for estimating critical values pertinent to describing transmission and the natural history of a disease. This is especially true when information about uninfected contacts and mode of detection is used, as we have done here. The resulting estimates provide important inputs for interpreting surveillance data, evaluating interventions, and setting public health policy.

Contributors

YoW, SM, XZ, ZZ, XL, LW, WG, CC, XT, XW, YuW, SH, and TF collected the data. JL, QB, SAT, and CY did statistical analyses, and drafted the manuscript and figures. TZ, BS, YS, JZ, TM, and CY collected and cleaned data. QB, TM, JL, and TF conceived the study and supervised data collection.

Declaration of interests

We declare no competing interests.

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CANADA COVID-19 WEEKLY EPIDEMIOLOGY REPORT

28 MARCH TO 03 APRIL 2021 (WEEK 13)

Published: 09 April 2021

39 639 (↑28%) New cases reported in the last 7 days[a]	**195 (↓8%)** New deaths reported in the last 7 days[a]
5 663 (↑28%) Average number of cases reported daily in the last 7 days[a]	**28 (↓8%)** Average number of deaths reported daily in the last 7 days[a]
115 653 (↑6%) Average number of tests performed daily in the last 7 days[b]	**5.1% (↑0.8)** Percentage of positive tests in the last 7 days[b]

[a]Source: Provincial and Territorial Ministry of Health (MOH) websites as of 03 April 2021

[b]Source: National Microbiology Laboratory (NML) data for laboratory analyses as of 03 April 2021

Note: The percentages are calculated based on the difference in the total number of cases, deaths, or tests in the past 7 days compared to the prior 7 days, divided by the number of cases, deaths, or tests in the prior 7 days. The change in the percentage of positive tests is based on the difference in percentage points compared to the previous week.

KEY MESSAGES

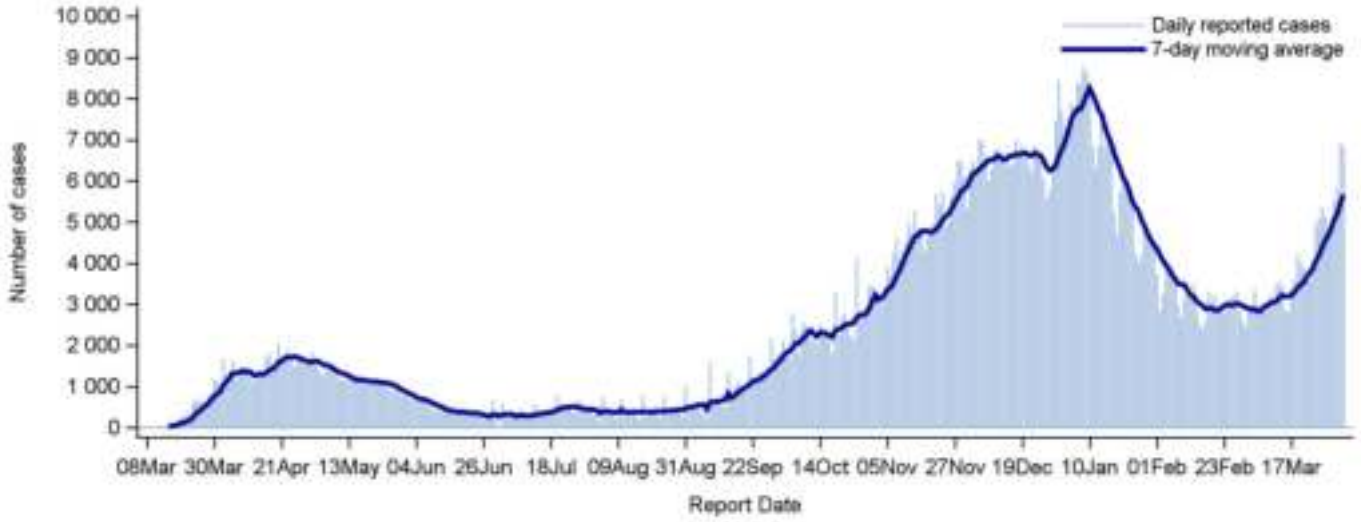
- In Canada, there was an average of **5 663 new cases reported daily** during the week of 28 March to 03 April (week 13), representing a **28% increase** compared to the previous week (week 12: 21 March to 27 March).
- British Columbia, Alberta, Saskatchewan, Ontario, Québec and Newfoundland and Labrador reported **increases in weekly numbers**, compared to the previous week.
- **Daily rates of cases per 100 000 population have increased among most age groups during the past week**. Among both males and females, case rates remain highest among individuals in the 20 to 39 year age group and lowest among individuals in the 80 years and older age group.
- **Long-term care facilities and retirement residences** continue to be the most commonly reported outbreak setting in Canada, and account for the greatest proportion of outbreak related cases and deaths.
- During week 13, **an average of 115 653 tests were performed daily** for COVID-19 across Canada. The weekly percentage of tests positive was **5.1%**, an increase from the previous week.
- There was an average of **28 new deaths reported daily** during week 13, representing an **8% decrease** compared to the previous week.
- **The number of hospitalizations and ICU admissions increased during week 13**. On 03 April 2021, there were 2 250 cases hospitalized and 801 cases in ICU, representing a 5% increase in the seven-day moving average of hospitalized cases and a 16% increase in the seven-day moving average of ICU admissions compared to one week prior.
- The overall cumulative hospitalization rate (including ICU admissions) is 139 cases per 100 000 population, with **the highest rates observed among those aged 80 years and older** (1 013 cases per 100 000 population).
- According to forecasting, between **1 093 510 to 1 150 910 cumulative reported cases** and **23 290 to 23 710 cumulative reported deaths** are expected by 18 April 2021.

NATIONAL DEMOGRAPHICS AND TRENDS

NATIONAL TRENDS IN CASES

- During week 13, a total of 39 639 cases of COVID-19 were reported in Canada, an average of 5 663 cases per day.
- The number of new cases represents a 28% increase compared to week 12.
- Since early March 2021, the number of new cases reported has consistently increased, with 6 822 new cases reported on 03 April 2021 (Figure 1).

Figure 1. Daily number of reported COVID-19 cases in Canada (and 7-day moving average), as of 03 April 2021 (N= 1 001 658)



Source: Provincial and Territorial MOH websites as of 03 April 2021

Note: The 7-day moving average is a trend indicator that captures the arithmetic mean of the daily reported cases over the previous seven days. The moving average helps smooth out day-to-day variability in reporting, filtering out the "noise" of short-term fluctuations. Fluctuations can be attributed to retrospective data, non-reporting on the weekends or provinces or territories reporting cases at a reduced frequency. Spikes in cases may be due to regular reporting variations (e.g. lower reporting on weekends or holidays), or periodic reporting of previous cases by provinces and territories.

Most provinces and territories, with the exception of Northwest Territories and Nunavut, reported new cases during week 13 (Table 1):

- The weekly number of new cases decreased in Manitoba, New Brunswick, Nova Scotia and Prince Edward Island, compared to the previous week. No change was observed in Yukon.
- The weekly number of new cases increased in British Columbia, Alberta, Saskatchewan, Ontario, Québec and Newfoundland and Labrador, compared to the previous week.
- Cases increased by 31% in Ontario and 33% in Québec, compared to the previous week. Together, these provinces accounted for about 64% of the cases reported during week 13.
- Cumulatively, Ontario reported the highest number of cases (n=358 558), while Québec has the highest incidence rate at 3 673.2 cases per 100 000 population.

Table 1. Trends of new cases in Canada and by province or territory, as of 03 April 2021

Province/Territory	Total number of cases (as of 03 April)[a]	Average number of cases reported daily (week 13)	Weekly number of cases reported		Percent change (%)[b]	Crude rate per 100 000 population (as of 03 April)
			21 March to 27 March (week 12)	28 March to 03 April (week 13)		
British Columbia	103 031	917	5 271	6 418	22%	2 001.5
Alberta	151 359	809	4 317	5 663	31%	3 423.0
Saskatchewan	34 323	220	1 324	1 540	16%	2 912.0
Manitoba	34 352	69	604	485	-20%	2 490.6
Ontario	358 558	2 552	13 609	17 866	31%	2 433.5
Québec	314 958	1 081	5 703	7 564	33%	3 673.2
Newfoundland and Labrador	1 020	1	1	5	400%	195.4
New Brunswick	1 641	10	82	70	-15%	210.0
Nova Scotia	1 732	3	27	23	-15%	176.9
Prince Edward Island	160	1	8	4	-50%	100.2
Yukon	74	0	1	1	0%	176.0
Northwest Territories	42	0	0	0	N/A	93.0
Nunavut	395	0	0	0	N/A	1 003.7
Canada[c]	**1 001 658**	**5 663**	**30 947**	**39 639**	**28%**	**2 635.5**

Source: Provincial and Territorial MOH websites as of 03 April 2021

[a] The number of cases includes the total confirmed and probable cases.

[b] The percentage is calculated based on the difference in the total number of cases in the past 7 days compared to the prior 7 days divided by the number of cases in the prior 7 days. Note that for provinces/territories with low case counts, an increase or decrease of only a few cases leads to a large percentage change. If the denominator is zero, the percent change cannot be calculated.

[c] Includes 13 cases identified in repatriated travelers (Grand Princess Cruise ship travelers) who were under quarantine in Trenton in March 2020.

Age-standardized rates take into account the differences in population size and age structure between provinces and territories to allow for more valid comparisons of COVID-19 spread in Canada.

Table 2 presents the age-standardized incidence rate by province or territory during week 13.

- Saskatchewan reported the highest age-standardized incidence rate (127.4 cases per 100 000 population).
- The second and third-highest age-standardized incidence rates were reported by Ontario (126.3 cases per 100 000 population) and British Columbia (125.2 cases per 100 000 population).

Table 2. Age-standardized incidence rates by province or territory for week 13

Province/Territory	Age-standardized incidence rate per 100 000 for week 13
British Columbia	125.2
Alberta	64.8
Saskatchewan	127.4
Manitoba	25.6
Ontario	126.3
Québec	75.1
Newfoundland and Labrador	N/A*
New Brunswick	N/A*
Nova Scotia	2.5
Prince Edward Island	3.8
Yukon	4.5
Northwest Territories	0.0
Nunavut	0.0
Canada	95.7**

Source: Detailed case information received by PHAC from provinces and territories, standardized to the July 1 2020 post-census population estimate.
*Age-standardized incidence could not be calculated as data was either not reported or partially reported to PHAC during week 13.
**The age-standardized incidence rate for Canada only includes provinces and territories for which data was available for week 13.
Note: Data are analyzed based on PHAC report date.

Table 3 outlines the total number of new cases, resolved cases, and deaths reported during week 13.

- Of the provinces and territories that reported new cases during week 13, all reported more new cases than new resolved cases.

Table 3. Summary of new COVID-19 cases, resolved cases, and deaths reported in Canada, and by province or territory, during week 13

Province/Territory	New cases	New resolved cases	New deaths
British Columbia	6 418	3 866	11
Alberta	5 663	2 210	14
Saskatchewan	1 540	1 208	6
Manitoba	485	418	5
Ontario	17 866	12 075	120
Québec	7 564	5 428	39
Newfoundland and Labrador	5	2	0
New Brunswick	70	27	0
Nova Scotia	23	16	0
Prince Edward Island	4	3	0
Yukon	1	0	0
Northwest Territories	0	0	0
Nunavut	0	0	0
Canada	**39 639**	**25 253**	**195**

Source: Provincial and Territorial MOH websites as of 03 April 2021

DEMOGRAPHIC DISTRIBUTION[a]

[a] Detailed case information received by PHAC from provinces and territories
Note: Data are analyzed based on PHAC report date.

- Cases for which PHAC received detailed individual case-level information during week 13 (n=34 754) ranged in age from less than one year to 102 years of age. The median age was 34 years, no change from what was observed during week 12.
- Table 4 presents a summary of the age and gender distribution of COVID-19 cases reported to PHAC during week 13:
    - Fifty-nine percent (59%) were individuals under 40 years of age.
    - The highest proportions of cases by age group were observed among those aged 0-19 years (22%) and 20-29 years (20%).
    - The highest age specific incidence rates were observed among those 20-29 and 30-39 years of age.

Table 4. Age, gender distribution, and rate of COVID-19 cases reported to PHAC, during week 13

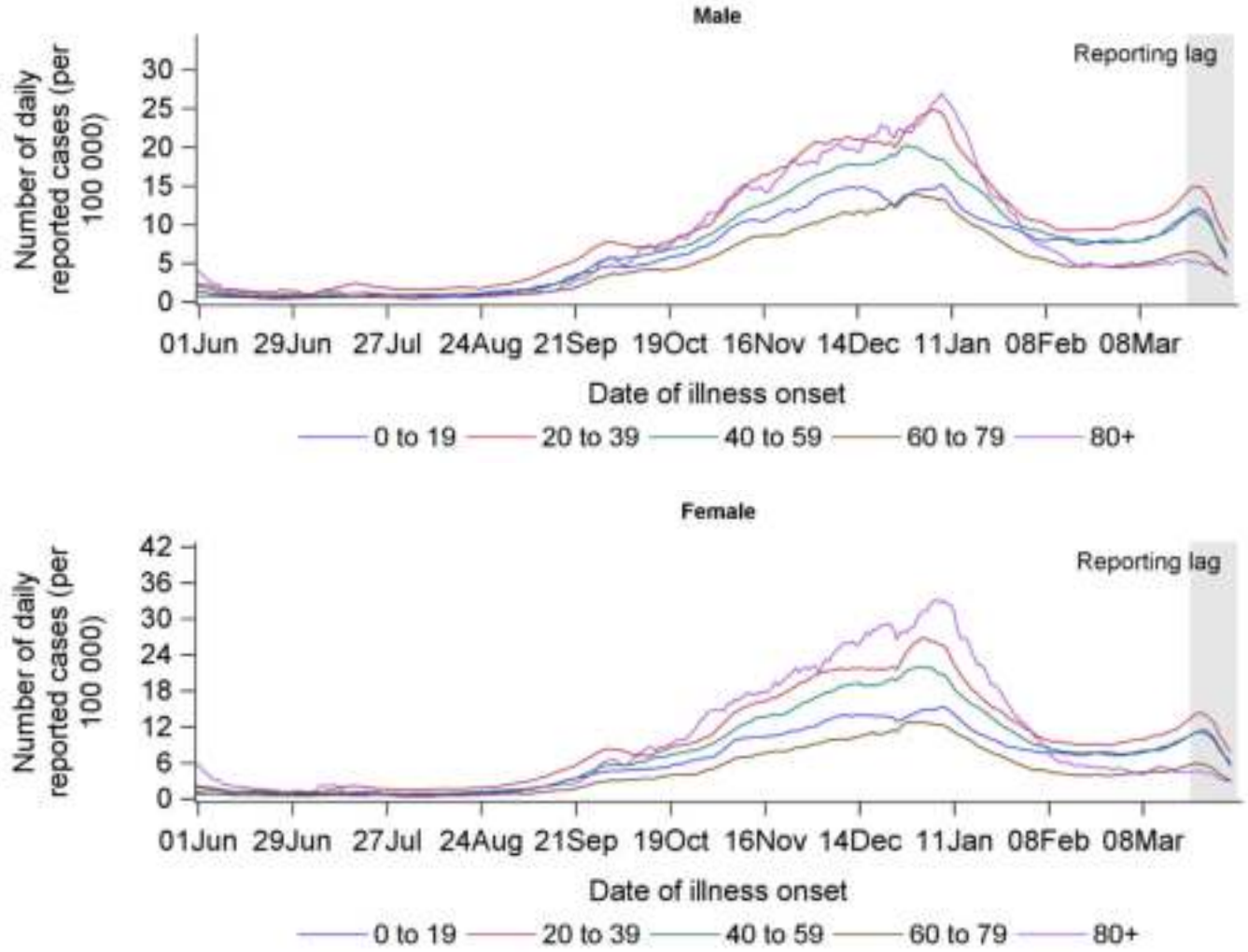
Age groups	Female			Male			Total[a]		
	n	%	Rate	n	%	Rate	n	%	Rate
≤ 19	3 945	22%	99.2	4 100	22%	98.5	8 045	22%	98.8
20-29	3 418	19%	138.6	3 644	20%	136.9	7 062	20%	137.7
30-39	2 893	16%	110.2	3 099	17%	116.2	5 992	17%	113.2
40-49	2 662	15%	108.7	2 659	14%	110.6	5 321	15%	109.6
50-59	2 289	13%	87.6	2 421	13%	93.7	4 710	13%	90.7
60-69	1 374	8%	56.9	1 538	8%	66.6	2 912	8%	61.6
70-79	679	4%	42.9	630	3%	44.2	1 309	4%	43.6
80+	396	2%	40.0	320	2%	47.5	716	2%	43.0
Total	17 656	100%	92.3	18 411	100%	97.5	36 067	100%	94.9

Source: Detailed case information received by PHAC from provinces and territories during week 13. Rates are presented per 100 000 individuals in the given age group based on the 1 July 2020 post-census population estimate.
[a] Cases not identified as male or female were removed from the total due to small numbers.
Note: Data are analyzed based on date reported to PHAC. Note that there is a period of time (lag time) where it is expected that cases have occurred but have not yet been reported nationally. Therefore, COVID-19 cases reported to PHAC during week 13 may include cases that occurred (based on date of illness onset, or lab related dates) in previous weeks.
Note: Cases with missing gender or age were excluded. Where available, gender data was used; when gender data was unavailable, sex data was used. Reliable data on gender diverse respondents are unavailable due to small counts.

Figure 2 presents cases by date of illness onset, stratified by gender and adjusted for population at the national level.

- Daily rates of cases have increased for most age groups in recent weeks; this follows the large decline observed since early January 2021.
- Daily rates of cases continue to remain highest among individuals in the 20 to 39 year age group for males and females. This age group has consistently been the highest since 20 January 2021 for males and 03 February 2021 for females.
- Daily rates of cases are lowest among individuals in the 80 years and older age group for both genders. The incidence rates for this age group are 1.9 times lower for males and 2.2 times lower for females compared to the 20 to 39 year age group.

Figure 2. Daily rate of cases per 100 000 population, by age and gender, from 1 June 2020 to 03 April 2021



Source: Detailed case information received by PHAC from provinces and territories. Rates are calculated based on the 1 July 2020 post-census population estimate.

Note: The shaded area represents a period of time (lag time) where it is expected that cases have occurred but have not yet been reported nationally. The earliest of the following dates were used as an estimate: Onset date, Specimen Collection Date, Laboratory Testing Date, Date Reported to Province or Territory, or Date Reported to PHAC.

Note: Where available, gender data was used; when gender data was unavailable, sex data was used. Reliable data on gender diverse respondents are unavailable due to small counts.

SYNDROMIC SURVEILLANCE

FLUWATCHERS

FluWatchers is an online health surveillance system that relies on volunteer reports to track the spread of Influenza-like illness (ILI) and symptoms compatible with COVID-19 across Canada. Some of the more commonly reported symptoms of COVID-19 include a new or worsening cough, fever or feeling feverish; therefore, reports of a minimum of cough or fever are being used to track COVID-19 within the FluWatchers system.

During week 13, 12 081 participants reported into the FluWatchers system. A total of 194 participants (1.6%) reported symptoms of cough or fever.

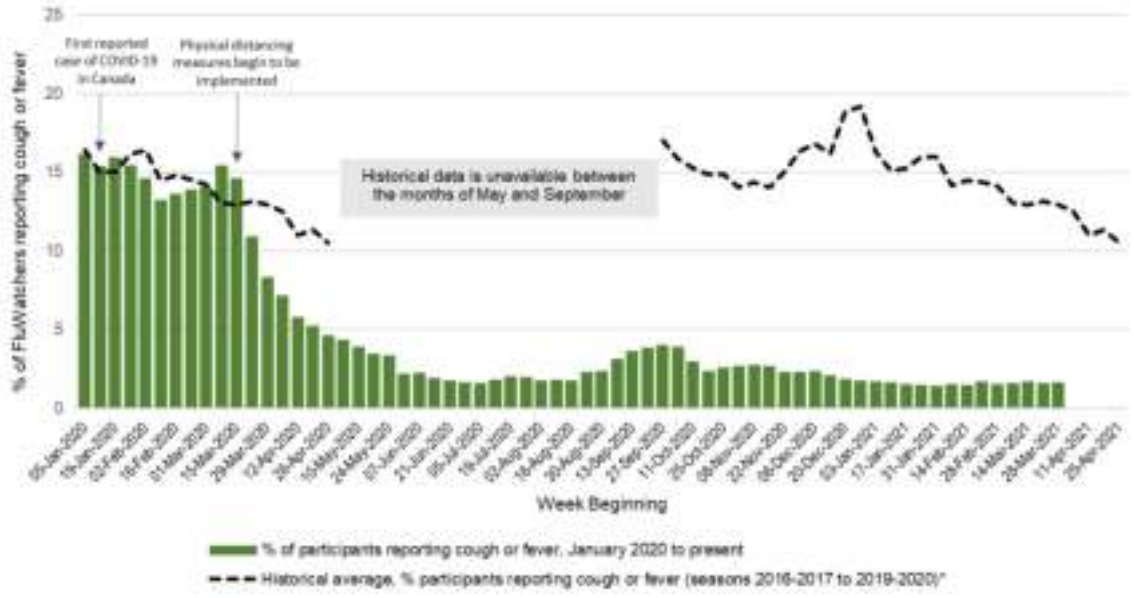
From mid-December 2020 to late-January 2021, FluWatchers activity was on a slow decline, despite increasing COVID-19 activity at the time. In recent weeks, activity due to seasonal respiratory viruses has been low and stable, COVID-19 activity has begun to increase and FluWatchers activity has slightly increased as well. Symptoms reports by FluWatchers participants remain below seasonal norms for this time of year.

Among the 194 participants reporting cough or fever:

- 88 (45%) sought medical attention;
- 76 (39%) were tested - 4 tests were positive for COVID-19 (8 tests had unknown results at the time of reporting)

Syndromic data captured by FluWatchers is sensitive to all circulating respiratory viruses, including COVID-19. The FluWatchers program is measuring total respiratory virus activity in the community. FluWatchers participants are a self-selected subset of the Canadian population that may not be representative of the Canadian population; thus, under representing the true measure of COVID activity in the population.

Figure 3. Percentage of FluWatchers Participants Reporting Cough or Fever (N=12 081 during week 13)



*Historical data is unavailable between the months of May and September. From January 2020 to May 2020, the historical epidemiological curve contains data from seasons 2016-2017 to 2018-2019. From October 2020 onwards, the historical epidemiological curve contains data from seasons 2016-2017 to 2019-2020; however, data from March 8, 2020 to May 2, 2020 are excluded from the historical epidemiological curve.

TRANSMISSION

TEMPORAL DISTRIBUTION BY EXPOSURE CATEGORY[a]

[a] Detailed case information received by PHAC from provinces and territories

During week 13, exposure and date of illness onset information was available for 20 329 cases. Of these:

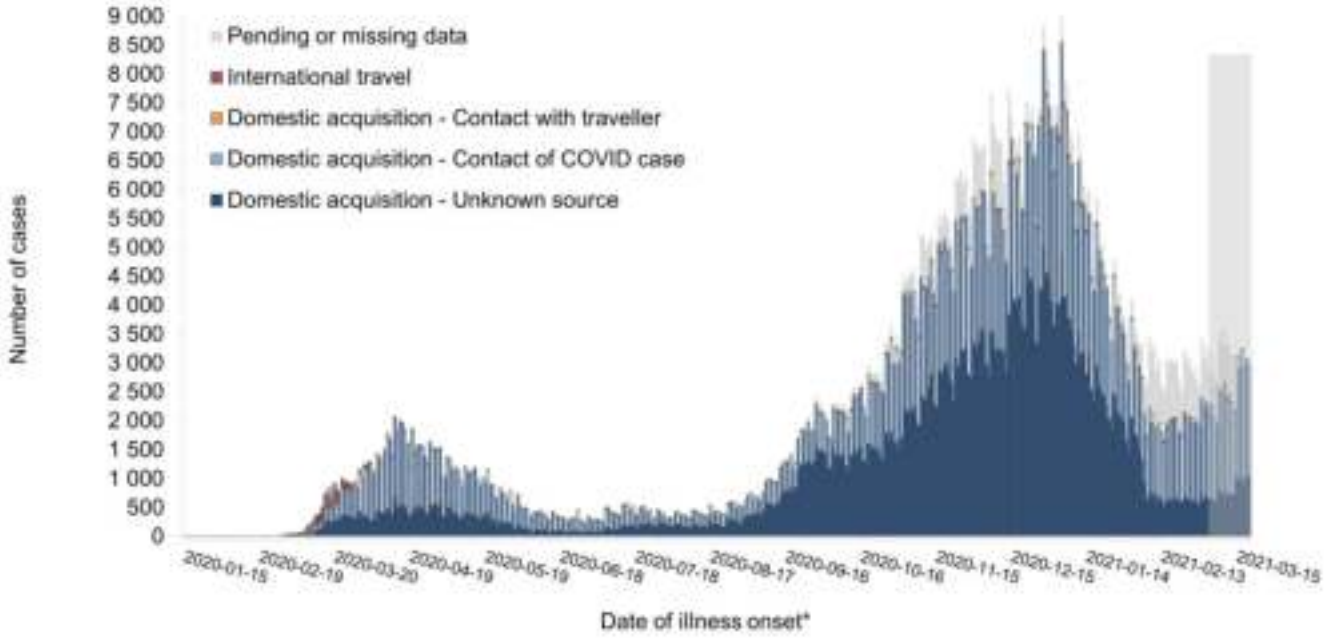
- 13 398 cases (66%) reported exposure in Canada to a known COVID-19 case;
- 6 820 cases (34%) reported exposure in Canada to an unknown source;
- 43 cases (<0.5%) reported exposure to a traveller; and
- 68 cases (<0.5%) reported having travelled outside of Canada during the exposure period.

Jurisdictions update exposure status on an ongoing basis as case investigations are completed and may result in changes to the percent distributions by exposure type for previous weeks (Figure 4).

Of the 883 392 cases submitted as of 03 April 2021 with information on the source of exposure and date of illness onset:

- 418 343 cases (47%) reported exposure in Canada to a known COVID-19 case;
- 449 898 cases (51%) reported exposure in Canada to an unknown source;
- 6 771 cases (1%) reported exposure to someone who had travelled; and
- 8 380 cases (1%) reported having travelled outside of Canada during the exposure period.

Figure 4. Number of reported COVID-19 cases in Canada, by date of illness onset and exposure category as of 03 April 2021 (n=991 533)



Source: Detailed case information received by PHAC from provinces and territories

* The earliest of the following dates were used as an estimate: Onset date, Specimen Collection Date, Laboratory Testing Date, Date Reported to Province or Territory, or Date Reported to PHAC.

Note: The shaded area represents a period of time (lag time) where it is expected that cases have occurred but have not yet been reported nationally. There is missing information for exposure variables from several provinces and territories.

INTERNATIONAL TRAVEL EXPOSURES[a]

[a] Detailed case information received by PHAC from provinces and territories

In Canada, the first cases of COVID-19 were attributed to international travel exposures. On 14 March 2020, the Government of Canada published a global Travel Health Notice advising Canadians against non-essential travel and advised Canadians abroad to return to Canada. By 21 March 2020, the Government of Canada prohibited all non-essential travel into Canada by foreign nationals. Since that time, the proportion of COVID-19 cases associated with international travel decreased from 22.3% (n=3 883) of all cases in March 2020 to 0.4% (n=127) in May 2020, and increased slightly over the summer months but has remained low since the fall (Table 5 and Figure 5). Since the spring of 2020, there have been significant efforts to enact border restrictions to reduce COVID-19 import to Canada.

As of 03 April 2021, 0.9% of cases with known exposure (n=8 380) have been associated with international travel. Since 01 July 2020, the United States, Mexico, and India are the top countries identified by cases that reported international travel during their exposure period.

Table 5. Number and percentage of COVID-19 cases associated with international travel by month of illness onset[a], as of 03 April 2021

Month	Number of COVID-19 cases associated with international travel	Percentage of COVID-19 cases associated with international travel[b]
January 2020	7	18.9%
February 2020	71	37.2%
March 2020	3 883	22.3%
April 2020	510	1.1%
May 2020	127	0.4%
June 2020	218	1.9%
July 2020	351	2.7%
August 2020	257	1.9%
September 2020	213	0.5%
October 2020	314	0.4%
November 2020	443	0.3%
December 2020	607	0.3%
January 2021	836	0.5%
February 2021	252	0.4%
March 2021	291	0.4%
Total	**8 380**	**0.9%**

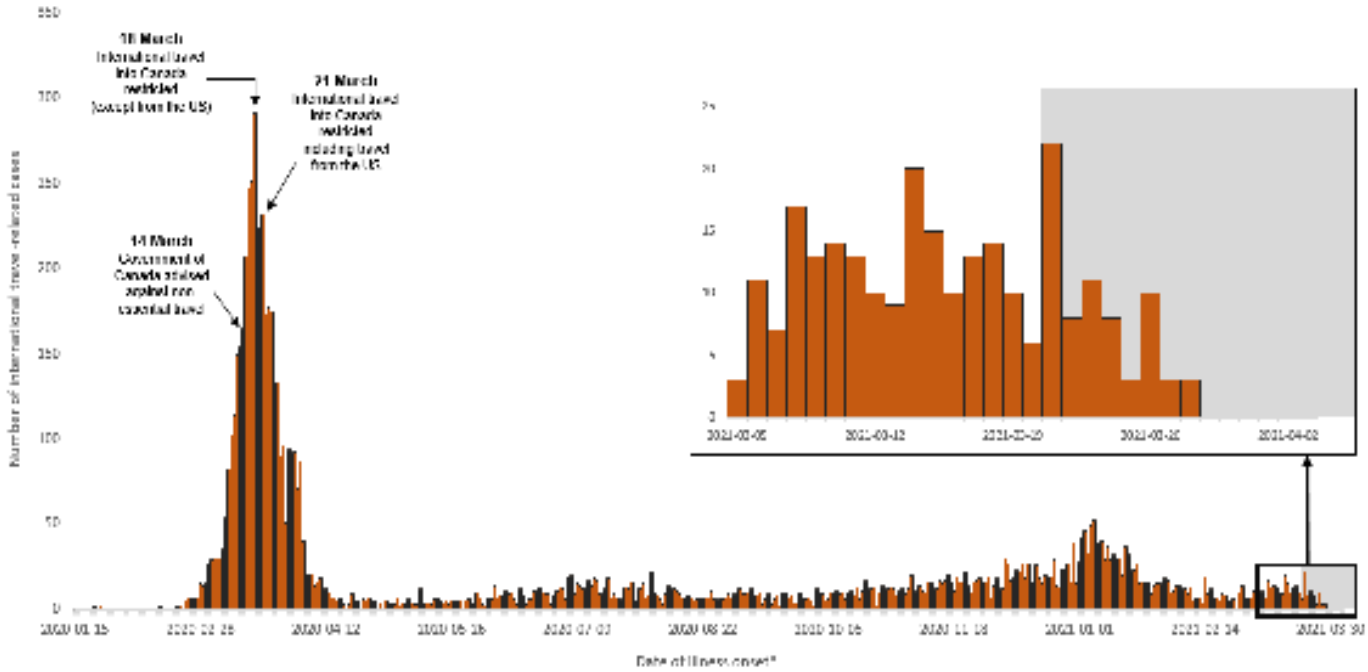
Source: Detailed case information received by PHAC from provinces and territories

Note: This is an underestimate of the total number of cases among returning travelers as exposure history are not available for all cases and not all jurisdictions have consistently reported exposure history to PHAC throughout the COVID-19 pandemic.

[a]The earliest of the following dates were used as an estimate: Onset Date, Specimen Collection Date, Laboratory Testing Date, Date Reported to Province or Territory, or Date Reported to PHAC.

[b]Only includes cases that have information on exposure.

Figure 5. Number of international travel-related COVID-19 cases in Canada, by date of illness onset[a] (n= 8 380) as of 03 April 2021



Source: Detailed case information received by PHAC from provinces and territories

* The earliest of the following dates were used as an estimate: Onset date, Specimen Collection Date, Laboratory Testing Date, Date Reported to Province or Territory, or Date Reported to PHAC.

Note: The shaded area represents a period of time (lag time) where it is expected that cases have occurred but have not yet been reported nationally.

Note: This is an underestimate of the total number of cases among returning travellers as exposure history are not available for all cases and not all jurisdictions have consistently reported exposure history to PHAC throughout the COVID-19 pandemic.

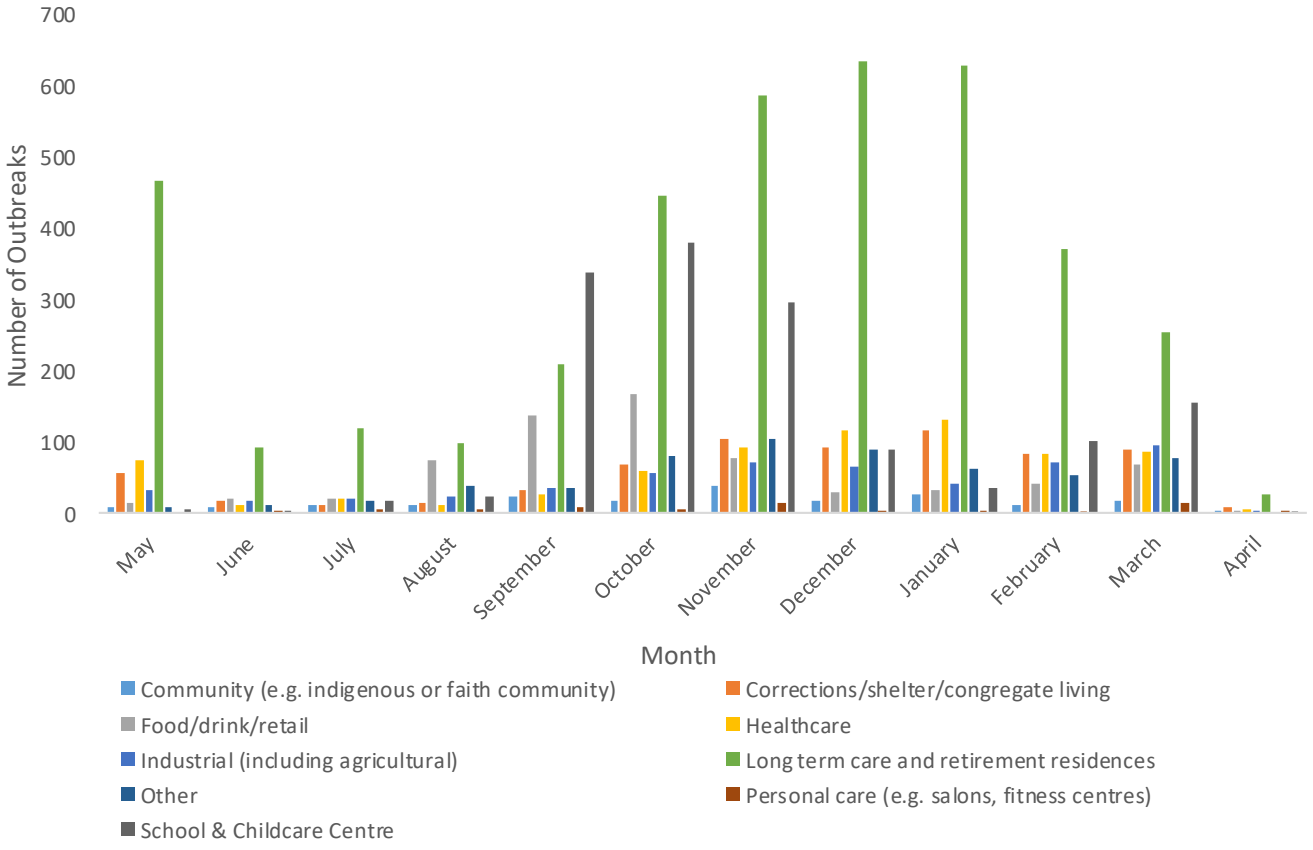
OUTBREAKS

Outbreaks have been a significant source of the spread of COVID-19 in Canada, and point to vulnerabilities in closed and crowded settings.

- Outbreaks have been detected in congregate living, workplace, and agricultural work settings, and namely in long-term care settings, meat processing plants, hospitals, small communities, and among farmworkers.
- Outbreaks continue to be observed in high-risk settings involving closed spaces, crowded places and close contact situations.
- Long-term care facilities and retirement residences continue to be the most commonly reported outbreak setting in Canada, and continue to account for the greatest proportion of outbreak related cases and deaths. This has been a consistent monthly trend with the exception of September, where reports of outbreaks in schools and childcare centres exceeded those in long-term care facilities and retirement residences.

Figure 6 and Table 6 identify common locations of outbreaks, as well as the number of cases and deaths associated with each.

Figure 6. Number of new outbreaks by setting as of 03 April 2021



Source: Publicly reported outbreak data, including Provincial and Territorial websites, as of 03 April 2021
Note: Schools with only one case, or those for which information on number of cases is unknown, have been excluded

Table 6. Total number of COVID-19 outbreaks, cases, and deaths by outbreak setting in Canada as of 03 April 2021[a]

Outbreak setting	Total number of outbreaks reported	Total number of cases reported	Total number of reported deaths	Outbreaks Reported in past 7 days
Community[b]	203	10 391	89	5
Corrections/shelter/congregate living	735	12 933	226	15
Food/drink/retail	685	2 489	3	20
Healthcare	765	10 648	812	18
Industrial (including agricultural)[c]	539	11 938	24	17
Long term care and retirement residences	4 430	66 863	12 473	61
Personal Care[d]	60	610	0	7
School & Childcare Centre[e]	1 438	8 199	1	31
Other[f]	585	5 331	6	17

Source: Publicly reported outbreak data, including Provincial and Territorial websites, as of 03 April 2021

[a]This is not an all-inclusive list and is subject to change based on current and active outbreak locations reported.

[b]Community includes population centres, Indigenous communities, Mennonite, Reserves, and small city outbreaks.

[c]The number of outbreaks in Windsor-Essex have been grouped into one cluster; industrial settings include: automotive manufacturing, distribution/processing facilities, worker camps, waste management/recycling, warehouse, etc.

[d]Personal care refers to personal care services, such as hair salons, nail salons, etc.

[e]Child and youth care include daycare centres and day camps; excludes any facilities that report only one case. Schools with only one case, or those for which information on number of cases is unknown, have been excluded

[f]Other groups together outbreaks in settings not listed in the categories above, for example social gatherings, office workplaces, recreational facilities, etc.

Note: These categories include both current and retrospective outbreak data.

LABORATORY-CONFIRMED COVID-19 DETECTION

During week 13, a total of 809 571 tests were performed, with an average of 115 653 tests performed daily for COVID-19 across Canada. The weekly percentage of tests positive during week 13 was 5.1%, an increase of 0.8% from the previous week (Table 7).

Table 7. Summary of COVID-19 tests performed in Canada, by province or territory, for week 13

Province/Territory	Cumulative number of tests performed as of 03 April 2021	Week 13 (28 March to 03 April, 2021)			
		Weekly number of tests performed	Average number of tests performed daily	Average # of tests performed daily per 1 000 population	Weekly percentage of tests positive[1]
British Columbia	2 222 958	61 093	8 728	1.7	10.4%
Alberta	3 746 782	80 346	11 478	2.6	7.5%
Saskatchewan	679 507	24 319	3 474	2.95	6.6%
Manitoba	598 266	12 269	1 753	1.27	4.7%
Ontario	12 630 159	353 513	50 502	3.43	5.3%
Québec	7 308 657	242 176	34 597	4.03	3.3%
Newfoundland and Labrador	223 240	3 977	568	1.09	0.2%
New Brunswick	269 376	7 763	1 109	1.42	1%
Nova Scotia	437 783	20 312	2 902	2.96	0.1%
Prince Edward Island	127 300	3 296	471	2.95	0.1%
Yukon	8 616	87	12	0.29	0%
Northwest Territories	16 195	308	44	0.97	0.6%
Nunavut	9 921	112	16	0.41	0%
Canada	**28 278 760**	**809 571**	**115 653**	**3.04**	**5.1%**

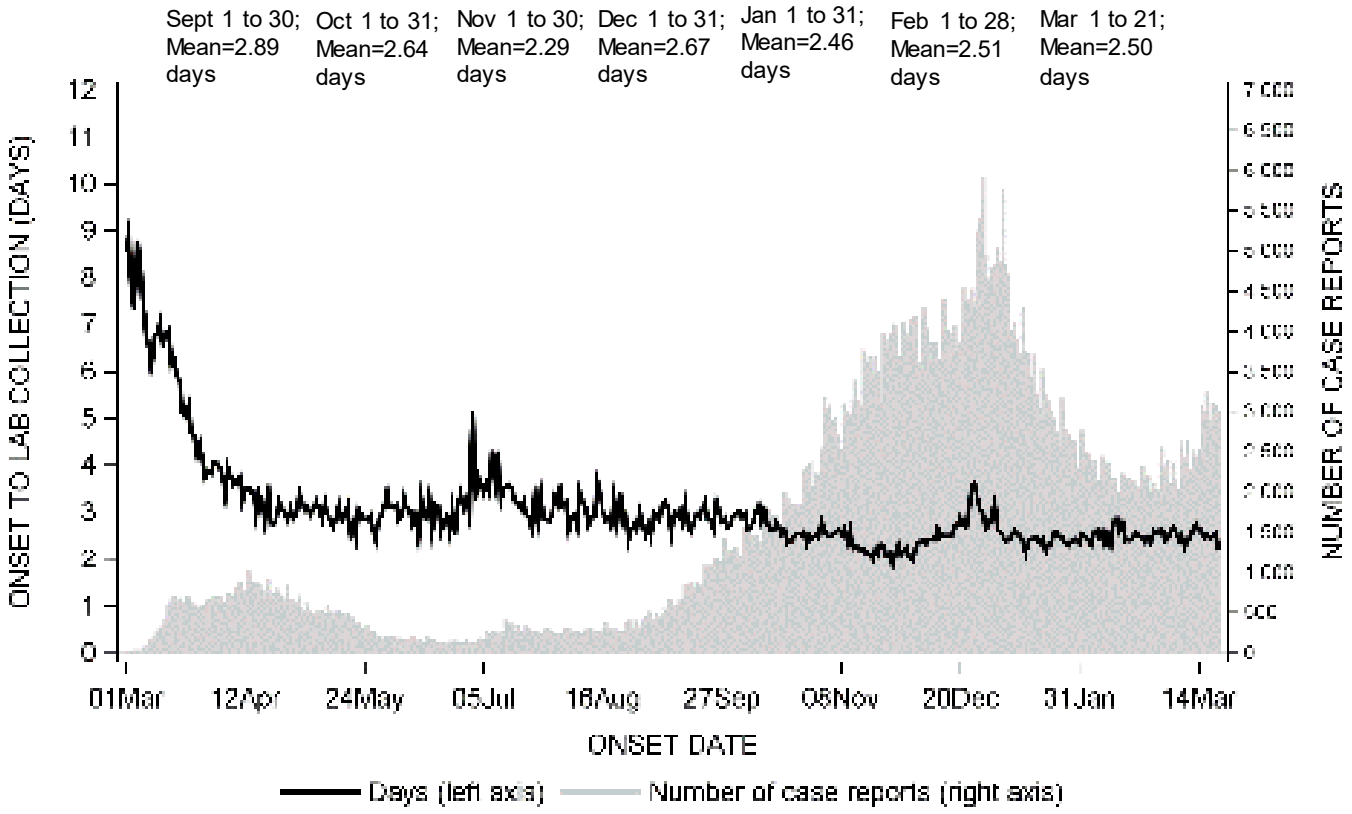
Source: NML Data for laboratory analyses as of 03 April 2021

[1] Weekly percentage of tests positive is calculated by dividing the total positive tests in the past 7 days by the total tests performed in the past 7 days

Note: Laboratory testing numbers may be an underestimate due to reporting delays and may not include additional sentinel surveillance or other testing conducted in the province or territory.

The mean time from symptom onset to lab specimen collection was 2.50 days in March 2021. This is similar to the mean of 2.51 days in February 2021 (Figure 7).

Figure 7. Onset date to laboratory collection date for cases reported to PHAC as of 03 April 2021



Source: Detailed case information received by PHAC from provinces and territories
Note: Date of symptom onset to date of specimen collection intervals of >15 days are deemed outliers, and not included in this figure.

SEVERITY INDICATORS

HOSPITALIZATIONS, INTENSIVE CARE, AND DEATHS

During week 13, detailed case information on hospitalization status was available for 18 578 cases. Among these cases:

- **700 (4%)** were hospitalized (including ICU admission), of whom:
  - **87 (12%)** were admitted to ICU.

Among the total number of hospitalizations reported during week 13 for which age information was available, 24% (n=166/695) were 40 to 59 years of age, 41% (n=287/695) were 60 to 79 years of age, and 21% (n=143/695) were 80 years and older (Table 8).

As of 03 April 2021, case information on hospitalization status was available for 694 621 cases, where:

- **52 835 (8%)** were hospitalized (including ICU admission), of whom:
  - **9 337 (18%)** were admitted to ICU.

Since the beginning of the pandemic, the 60 to 79 year age group has accounted for the highest proportion of cases hospitalized and admitted to ICU, followed closely by the 80 years and older age group (see table A5 in annex for cumulative counts).

Table 8. Number of COVID-19 cases hospitalized, and admitted to ICU, overall and by gender and age group, reported to PHAC during week 13[a]

Age groups	Hospitalized – non-ICU			Hospitalized – ICU		
	Female	Male	Total	Female	Male	Total
≤ 19	11	10	21	0	1	1
20-39	30	39	69	2	6	8
40-59	66	82	148	8	10	18
60-79	107	136	243	16	28	44
80+	61	66	127	9	7	16
Total	275	333	608	35	52	87

Source: Detailed case information received by PHAC from provinces and territories

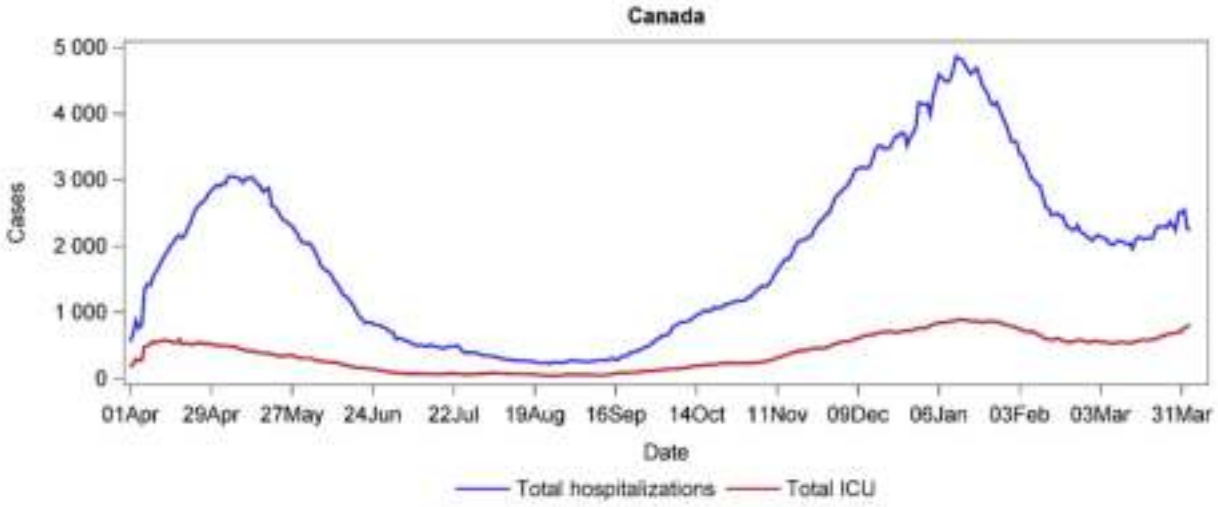
[a] Data are analyzed based on date reported to PHAC. Note that there is a period of time (lag time) where it is expected that cases have occurred but have not yet been reported nationally. Therefore, COVID-19 cases reported to PHAC during week 13 may include cases that occurred (based on date of illness onset, or lab related dates) in previous weeks.

Note: Non-ICU hospitalizations and ICU counts are mutually exclusive. Cases with missing gender, sex or age were excluded. Where available, gender data were used; when gender data were unavailable, sex data were used. Reliable data on gender diverse respondents are unavailable due to small counts.

Following a sharp decline in hospitalizations, and stabilized numbers of ICU admissions since early January 2021, the number of hospitalizations and ICU admissions have begun to increase (Figure 8). On 03 April 2021, there were 2 250 cases hospitalized and 801 cases in ICU, representing a 5% increase in the seven-day moving average of hospitalized cases and a 16% increase in the seven-day moving average of ICU admissions compared to one week prior.

Based on detailed case information received by PHAC from provinces and territories, the overall cumulative hospitalization rate (including ICU admissions) is 139 cases per 100 000 population, with the highest rates observed among those aged 80 years and older (1 013 cases per 100 000 population).

Figure 8. Number of COVID-19 cases in hospital and ICU daily in Canada, as of 03 April 2021



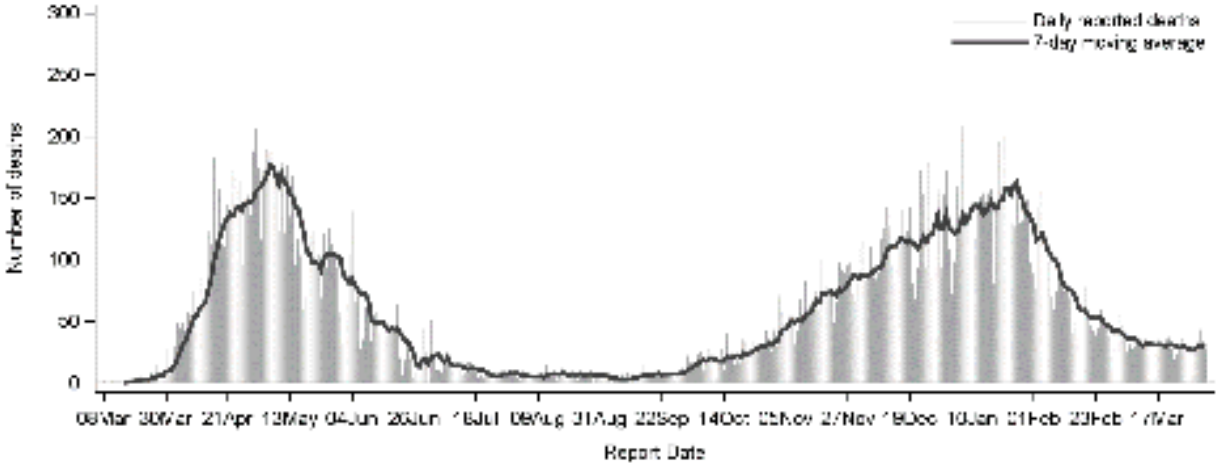
Source: Provincial and Territorial MOH websites as of 03 April 2021

During week 13, there were 195 COVID-19 related deaths reported in Canada.

- This represents an 8% decrease compared to the previous week.
- This amounts to an average of 28 deaths reported per day, compared to an average of 30 deaths per day during the previous week.
- There has been an overall decreasing trend in the number of deaths observed since late January 2021 (Figure 9).

Of the deaths reported during week 13, jurisdictions submitted case-level information to PHAC for 27 deaths, of which 18 (67%) were male and 96% were aged 60 years and older. To date, deaths are highest among those aged 80 years and older (Table A4 in the annex, cumulative counts).

Figure 9. Daily number of COVID-19 related deaths reported in Canada (and 7-day moving average), as of 03 April 2021 (N=23 050)



Source: Provincial and Territorial MOH websites as of 03 April 2021

Note: The 7-day moving average is a trend indicator that captures the arithmetic mean of the daily reported deaths over the previous seven days. The moving average helps smooth out day-to-day variability in reporting, filtering out the "noise" of short-term fluctuations. Fluctuations can be attributed to retrospective data or provinces or territories reporting cases at a reduced frequency.

CANADIAN ACUTE CARE HOSPITALS

Laboratory-confirmed COVID-19-associated hospitalizations in Canada are monitored through two sentinel hospital-based systems:

1. Canadian Nosocomial Infection Surveillance Program (CNISP) *
2. Serious Outcomes Surveillance Network of the Canadian Immunization Research Network (CIRN-SOS) **

NOTE: * denotes data from CNISP and ** data from CIRN-SOS

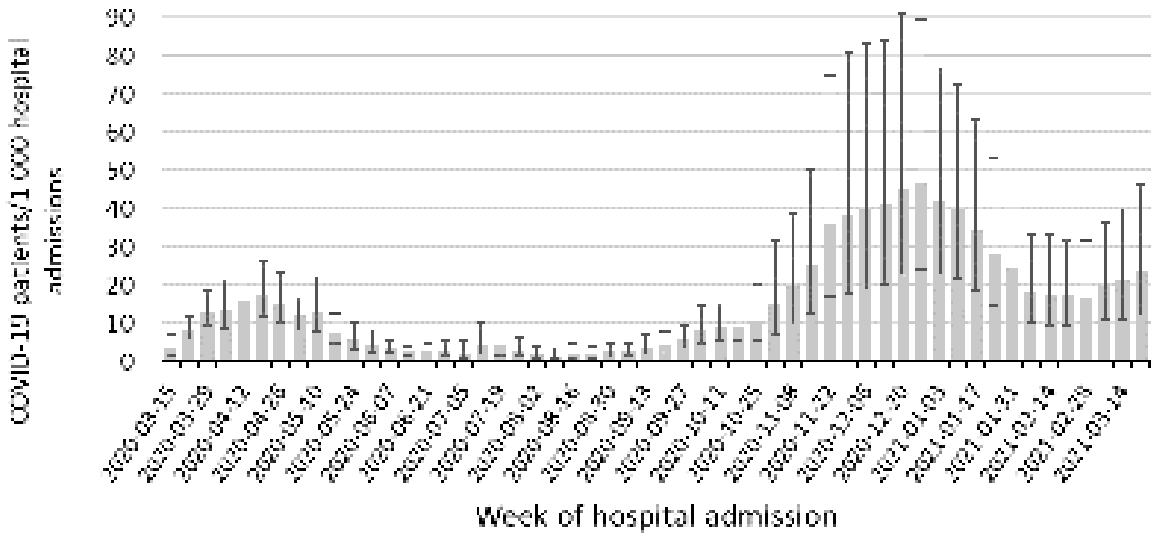
Key Findings*

- Among all patients hospitalized with COVID-19 since March 2020:
  - 20% have been admitted to the ICU (3 082/15 731)
  - 12% required mechanical ventilation (1 931/15 731)
  - <1% received extracorporeal membrane oxygenation (ECMO) (141/15 731)
  - 15% have died (all-cause mortality) (2 356/15 731)
- The median age of patients hospitalized with COVID-19 was 68 years (range 0-104 and 4% are pediatric (<18 years) (554/15 731)
- Males accounted for 54% of hospitalized patients (2 185/4 063)

Hospitalization Rates

- The weekly rate of new laboratory-confirmed COVID-19 patients per 1 000 hospital admissions was 23.8 for the most recent week of 21 March 2021 (Figure 10). The weekly incidence rate of hospitalizations has increased each week since the week of 28 February 2021 (Figure 10).

Figure 10. National rates of laboratory-confirmed COVID-19 patients per 1 000 admissions with 95% confidence intervals (n=15 731)*



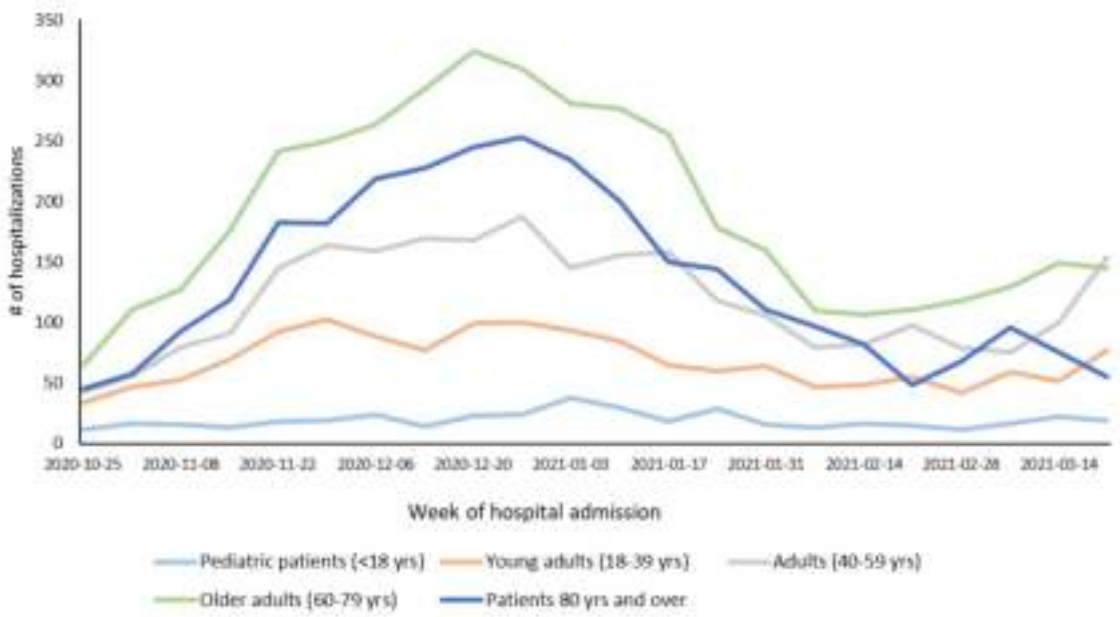
[a] Includes data from the 151 hospitals that have participated in all weeks of aggregate data collection. Denominator data are estimated using 2020 annual patient admissions.*

Hospitalization Trends

AGE *

- There was an increase observed in the number of hospitalizations among young adults (18-39 years) and adults (40-59 years) in the most recent week of 21 March 2021, with adults (40-59 years) accounting for the greatest number of hospitalizations for that week (Figure 11).
- Hospitalizations among patients 80 years and over have continued to decrease since the week of 07 March 2021 (Figure 11).
- Hospitalizations among pediatric patients (<18 years) have fluctuated, but consistently remained low (Figure 11).

Figure 11. Weekly number of new laboratory-confirmed COVID-19 patients by age group (n=11 728)*



CLINICAL PROGRESSION **

Time from symptom onset to hospital admission:

- Median length of time from symptom onset to hospital admission was shortest at 3 days among patients aged 80+ years (n=745), compared to 4 days among patients aged 16-39 years (n=162), 5 days among patients aged 60-79 years (n=852) and 6 days among patients aged 40-59 years (n=417).

Length of hospital stay:

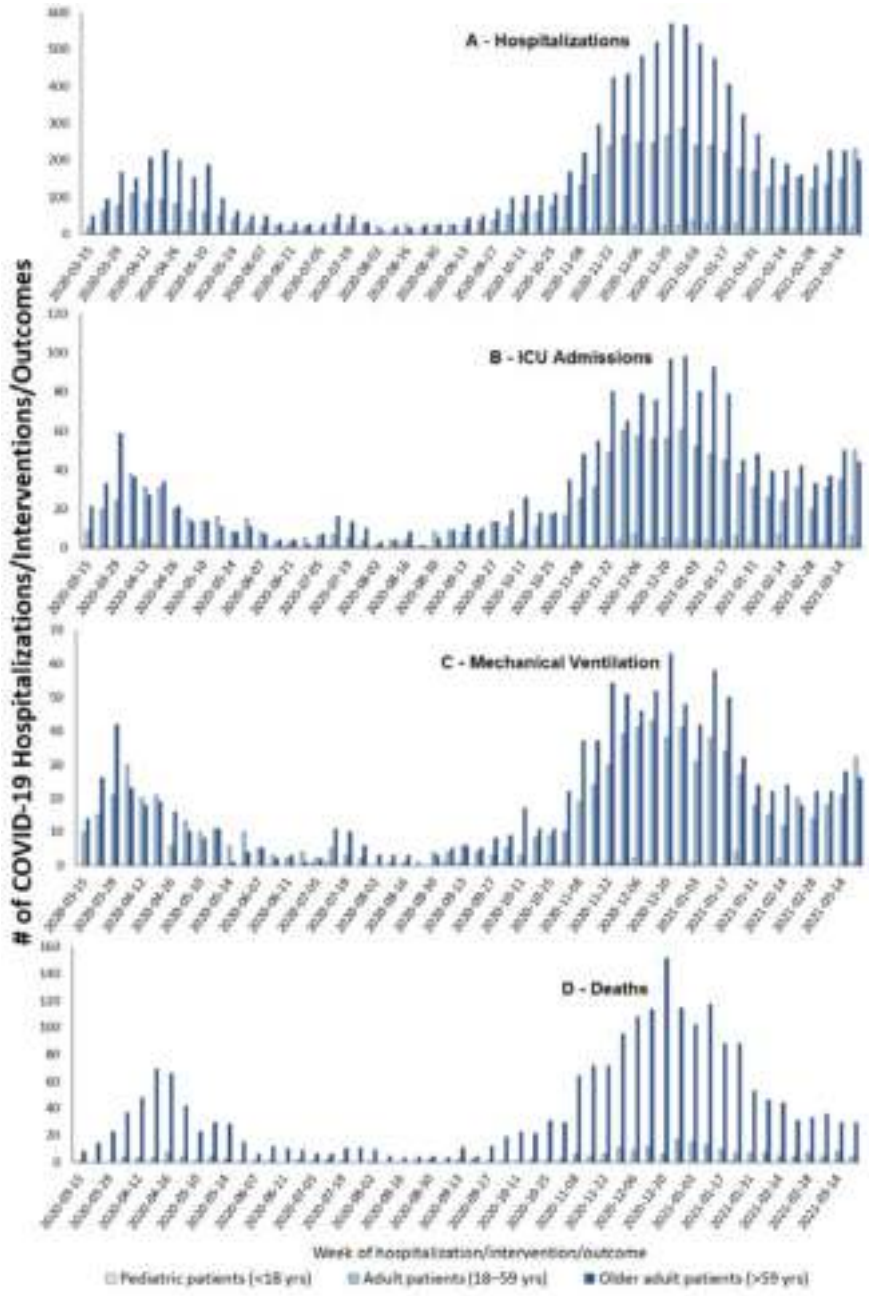
- Median length of hospital stay was longest among patients aged 80+ years (median=12 days, n=658) and patients aged 60-79 years (median=11 days, n=738). Values were comparatively lower for patients aged 40-59 years (median=6 days, n=352) and 16-39 years (median=4 days, n=134).

Note: Patients hospitalized before symptom onset were excluded from 'time from symptom onset to hospital admission' calculations. Length of stay is calculated as the time (in days) between date of hospital admission and date of outcome (including discharge, transfer, status change to alternate level of care, and death).

INTERVENTIONS/OUTCOMES *

- The number of new weekly hospitalizations, ICU admissions, and patients receiving mechanical ventilation have each increased since the week of 28 February 2021. Note that the increase observed in the most recent week of 21 March 2021 was largely driven by adult patients (18-59 years), as these measures all decreased among older adult patients (>59 years) (Figure 12).
- The number of deaths have remained relatively stable in recent weeks (Figure 12).

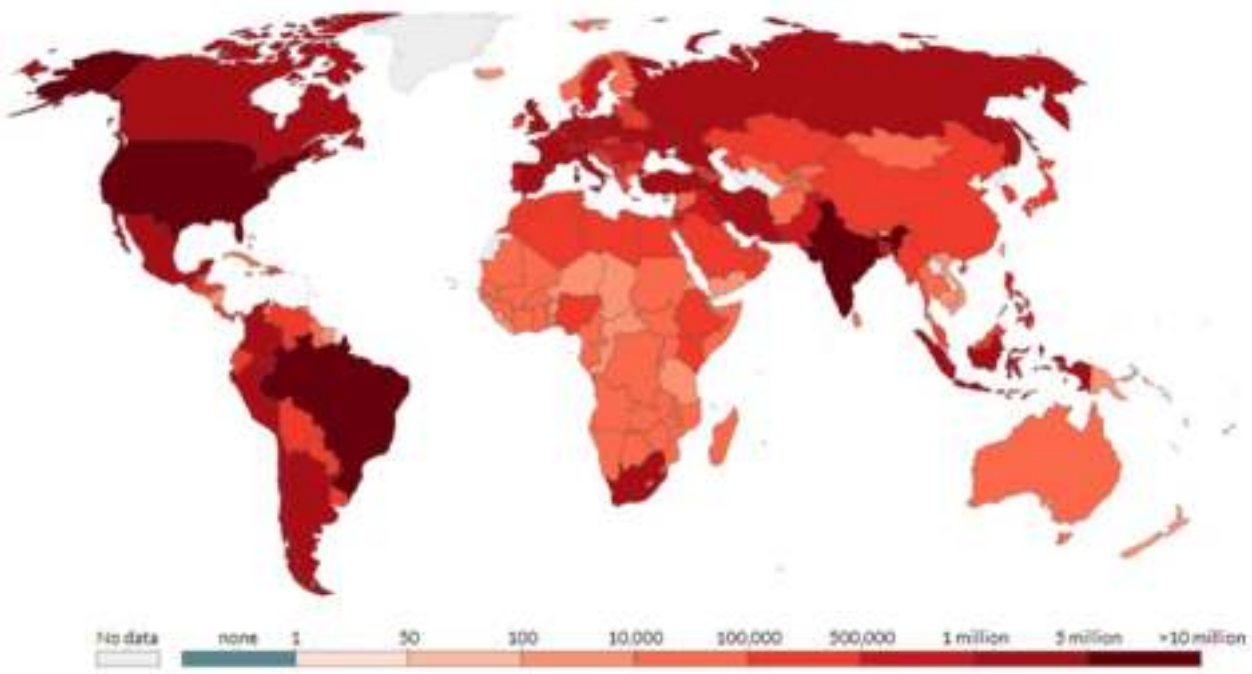
Figure 12. Weekly number of new laboratory-confirmed COVID-19 patients that were admitted to hospital (A; n=15 731), ICU (B; n=3 082), required mechanical ventilation (C; n=1 931), and deceased (D; n=2 356), by age group*



INTERNATIONAL

- As of 03 April 2021, there are over 129 million global cases of COVID-19 with over 2.8 million reported deaths (Figure 13).
- The region of Europe accounts for the highest number of cases reported.
- The following five countries account for the largest proportion of cases reported globally in the past 14 days:
    - Brazil (n=1 003 138)
    - India (n=886 379)
    - United States (n=885 934)
    - France (n=490 035)
    - Turkey (n=452 358)
- Canada's cases account for approximately 0.8% of all cases reported globally since the beginning of the pandemic.

Figure 13. International map of COVID-19 cases as of 03 April 2021 (n=129 943 007)

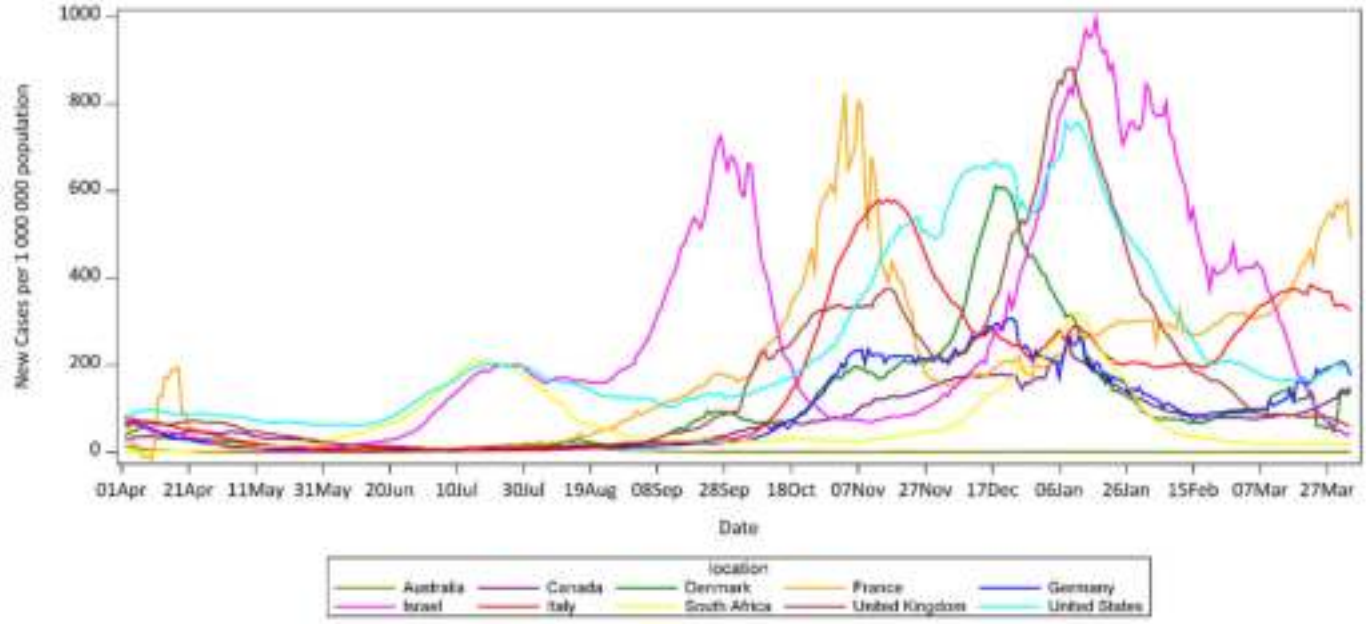


Source: Our World in Data – Coronavirus Pandemic (COVID-19) - https://ourworldindata.org/coronavirus

France continues to experience the highest rates of new cases compared to other countries, with 489.2 new cases per 100 000 population on 03 April 2021. Italy and the United States are second and third highest, with 325.6 and 195.2 new cases per 100 000 population, respectively.

Daily rates of cases in Canada are steadily increasing with 149.2 cases per 100 000 population on 03 April 2021. The rates of new cases in Canada are 3.3 times lower than France, 2.2 times lower than Italy, and 1.2 times lower than the United States.

Figure 14. Weekly new cases of COVID-19 in Canada compared to other countries as of 03 April 2021 (7-day moving average, population-adjusted)



Source: OurWorldInData, as of 03 April 2021

Up-to-date country-specific risk levels are found on travel health notices. For more information on COVID-19 internationally, please refer to the World Health Organization's COVID-19 Situation Report.

MODELLING

Estimates of transmission rates in Canada: Effective reproductive rate (*Rt*)

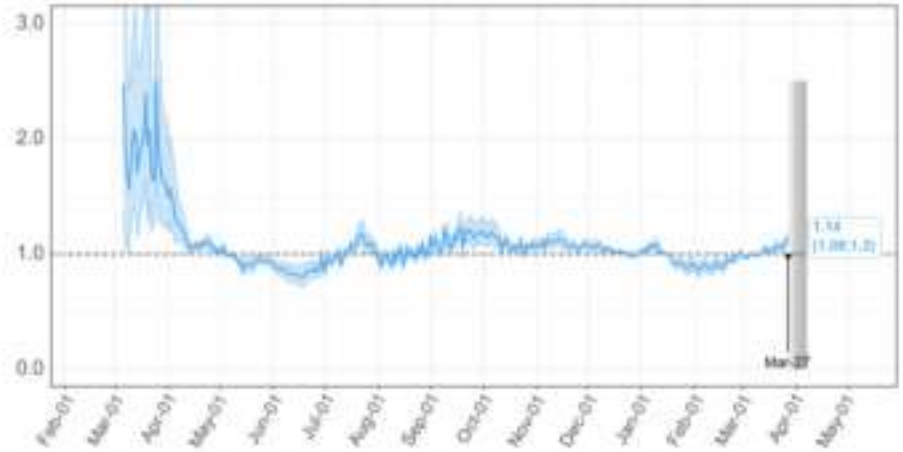
Rt is the time variable reproduction rate, representing the average number of newly infected people for each infected person. If Rt is less than 1 at a particular time (t), than the average number of people infected by one infected person is less than one, so the epidemic is being brought under control. If Rt is greater than 1, the average number of people infected by one infected person is greater than one, and the epidemic is growing. A value of Rt above 1 indicates that there is active community transmission, meaning that the disease will continue to spread in the population. The higher the Rt value, the faster the disease is spreading, which leads to an increase in the incidence of new cases.

However, there are some limitations to consider. As the epidemic continues, the Rt may not capture the current state of the epidemic with low case burden and the value must be interpreted based on the current landscape. The Rt can easily fluctuate when case numbers are low. It is also an average Rt for a population and does not point to local outbreaks driving case counts. Since the method used to calculate Rt is highly sensitive to the reported number of new cases, community outbreaks within specific provinces and territories will cause the estimated Rt value in that respective region to be higher, which may not always accurately depict overall transmission in the province or territory as a whole.

Figure 15 shows the Rt over time.

- In 2020, the reproductive rate was hovering under 1 in May and early June, followed by fluctuations in July. In early August, the Rt increased until the end of September when it decreased to just above 1. Between October 2020 and January 2021, the Rt fluctuated just above 1 with a slight increase in early November and early January. Starting in mid-January 2021, the Rt decreased to below 1, indicating that the epidemic was reducing nationally.
- Since early February 2021, the Rt has begun to slowly increase. The national Rt was 1.14 on 27 March 2021, an increase from 1.07 during the previous week.

Figure 15. Reproductive rate in Canada based on date of case report



Source: Calculated from detailed case information received by PHAC from provinces and territories
Note: Fluctuations are attributed to provincial and territorial reporting delays and non-reporting on the weekends

FORECASTING

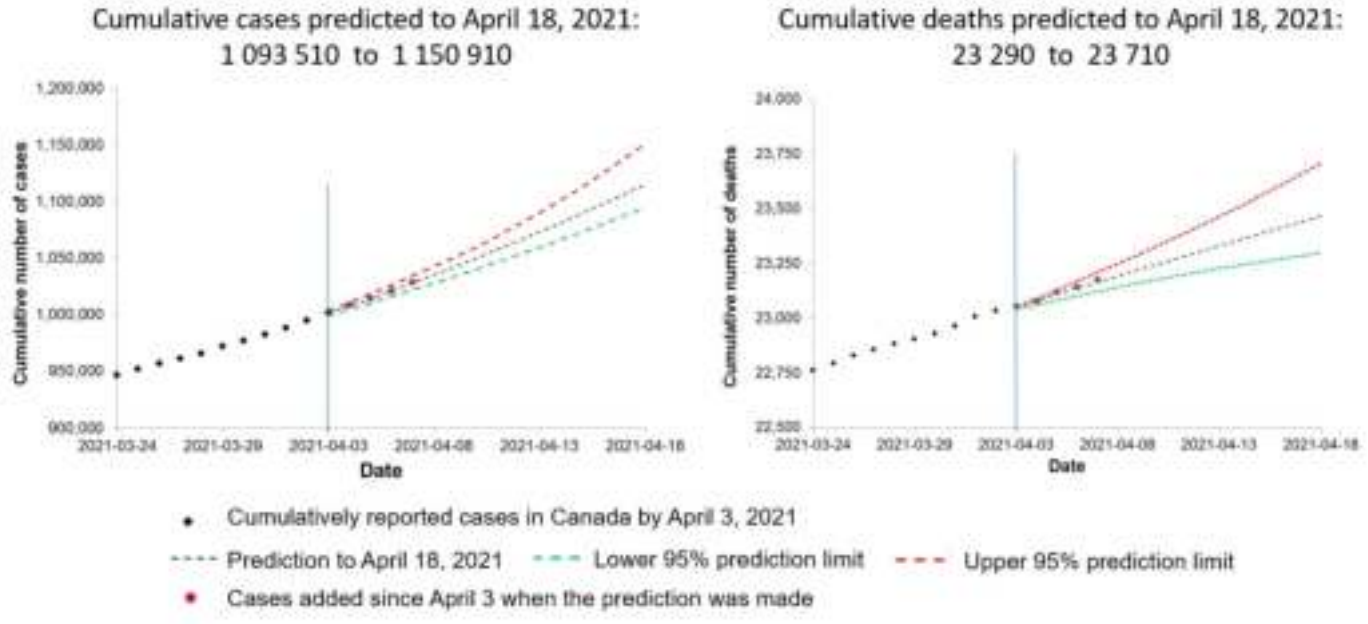
Canada's approach to modelling:

Models cannot predict the course of the COVID-19 pandemic, but can help us understand all possible scenarios, support decisions on public health measures and help the health care sector plan for these scenarios.

Forecasting models use data to estimate how many new cases can be expected in the coming weeks. Figure 16 below shows the projected number of cases and deaths in Canada, with a 95% prediction interval calculated to 18 April 2021, using available data as of 03 April 2021.

- According to forecasting, between 1 093 510 to 1 150 910 cumulative reported cases and 23 290 to 23 710 cumulative reported deaths are expected by 18 April 2021.
- The black dots represent actual data (cumulative cases and cumulative deaths) prior to 03 April 2021 and the dashed lines show the predicted trajectories after that date.
- It is important to communicate uncertainties in the predictions. The red and green lines represent the upper and lower limits with 95% confidence, respectively.
- If the added data points since 03 April 2021 stay between the red and green lines, it means both (i) the prediction model is performing as expected; (ii) data generated by the epidemic and reporting mechanisms are as expected.
- If the added data points since 03 April 2021 fall outside these limits, especially above the red line, the model detects unexpected signals that require further epidemiologic investigation.

Figure 16. Projected numbers to 18 April 2021 and 95% prediction intervals based on data reported as of 03 April 2021



For more information, please visit: https://www.canada.ca/en/public-health/services/diseases/coronavirus-disease-covid-19/epidemiological-economic-research-data/mathematical-modelling.html

TECHNICAL NOTES

The data in the report are based on information from various sources described below. The information presented for case-based analyses, trend analyses and laboratory analyses are available as of **03 April 2021 at 4 p.m. EDT.**

DATA SOURCES AND DATA CAVEATS

Epidemiological data received by PHAC

Some of the epidemiological data for this report are based on detailed case information received by PHAC from provinces/territories (P/Ts). This information is housed in the PHAC COVID-19 database. Case counts and level of detail in case information submitted to PHAC varies by P/T due to:

- Possible reporting delay between time of case notification to the P/T public health authority and when detailed information is sent/received by PHAC.
- Preliminary data may be limited and data are not complete for all variables.
- Data on cases are updated on an ongoing basis after being received by PHAC and are subject to change.
- Variation in approaches to testing and testing criteria over time within and between P/Ts.
- The lag time from illness onset to PHAC report date is approximately two weeks and data within this period is subject to change.

Note: Missing data for hospitalizations, ICU admissions, and deceased were not included in calculations. Unless calculations were broken down by age and gender, cases with missing values for age and gender were included. P/Ts may define gender differently and some may be referring to biological sex. Case severity is likely underestimated due to underreporting of related variables, as well as events th at may have occurred after the completion of public health reporting, and therefore is not captured in the case report forms. Transmission data should be interpreted with caution as information on exposure are missing from several provinces and territories.

Provincial and territorial case counts

P/T information on case counts, resolved cases, and deaths associated with COVID-19 are collected from publicly available P/T websites, generally from the P/T ministry of health. Case definitions may vary by P/T.

- National COVID-19 case definitions are provided by PHAC for the purpose of standardized case classification and reporting. PHAC's national case definitions can be found here: https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/health-professionals/national-case-definition.html
- Only cases and deaths meeting P/T's definition for case classification are reported. For details on case definitions, please consult each P/T ministry of health website.

Laboratory information

Data on the number of tests conducted in each P/T are received from the National Microbiology Laboratory.

- Laboratory testing numbers may be an underestimate due to reporting delays and may not include additional sentinel surveillance or other testing performed. They are subject to changes as updates are received.

Outbreak data

Reporting delays and gaps in information that are available at the federal level present difficulties in reporting on local outbreaks. To ensure timely information is available, PHAC utilizes web-scraping techniques to gather outbreak data from media and P/T public health agency websites. There are several important limitations to these data:

- A nationally standardized outbreak definition does not yet exist. Cluster definitions vary according to P/T. The methods for defining an outbreak are currently in development and may change over time.
- The data do not represent all outbreaks that have occurred in Canada over the course of the pandemic, but they do provide a summary of clusters reported via non-traditional data sources. Data collection on outbreaks began 12 March 2020.
- Case-level data are generally not available for outbreaks detected via non-traditional data sources. Information presented is at the aggregate level only.

Population data

- Canadian population data from Statistics Canada Population estimates on 1 July 2020 are used for age-standardized and age-specific rate calculations.

International data

International data are retrieved from the European Centre for Disease Prevention and Control (ECDC) Situation update and Our World in Data.

- Given that the pandemic is rapidly evolving and the reporting cycles from government sources are different, the case numbers may not necessarily match what is being reported publicly. Rather, this reflects what is publicly available from the sources listed above.
- International comparisons should be interpreted with caution. Number of tests conducted, indications for testing, and diagnostic capacity by country have a large influence on total number of reported cases. Therefore, the data displayed may not represent the true incidence of disease within each country.

Canadian Acute-Care Hospitalization Data

Canadian Nosocomial Infection Surveillance Program (CNISP) collects information on hospitalized patients across all age groups (pediatric and adult).

- As of 27 March 2021, CNISP has collected weekly aggregate data on 15 731 adult and pediatric patients hospitalized with COVID-19 from 151 hospitals across all 10 provinces and 1 territory.
- CNISP has conducted surveillance among 56 hospitals across 10 provinces and 1 territory and as of 12 March 2021 has collected case-level data on 4 063 adult and pediatric patients hospitalized with COVID-19

Serious Outcomes Surveillance Network of the Canadian Immunization Research Network (CIRN-SOS) collects information on hospitalized adult patients aged 16 years or older.

- As of 1 April 2021, CIRN-SOS has collected case-level data on 2 950 adult patients (≥16 years) hospitalized with COVID-19 across 9 hospital sites in Alberta, Ontario, Québec, and Nova Scotia.
- Denominators may be lower depending on variable completeness.

*** denotes data from CNISP and ** data from CIRN-SOS**

ANNEX

Table A1. Cumulative number of COVID-19 cases, resolved cases, and deaths reported in Canada by province or territory, as of 03 April 2021

Province/Territory	Total cases	Total resolved cases	Total deaths
British Columbia	103 031	91 732	1 463
Alberta	151 359	138 560	1 994
Saskatchewan	34 323	31 744	436
Manitoba	34 352	32 162	938
Ontario	358 558	327 940	7 428
Québec	314 958	294 560	10 684
Newfoundland and Labrador	1 020	1 006	6
New Brunswick	1 641	1 457	30
Nova Scotia	1 732	1 634	66
Prince Edward Island	160	147	0
Yukon	74	71	1
Northwest Territories	42	42	0
Nunavut	395	391	4
Canada[a]	**1 001 658**	**921 459**	**23 050**

Source: Provincial and Territorial MOH websites

[a] Includes 13 cases identified in repatriated travelers (Grand Princess Cruise ship travelers) who were under quarantine in Trenton in March 2020. Update on their status is not available.

Table A2. Age-standardized incidence rates of COVID-19 cases, by province or territory, as of 03 April 2021

Province/Territory	Cumulative age-standardized incidence rates (per 100 000 population)
British Columbia	1 944.0
Alberta	3 296.6
Saskatchewan	2 904.6
Manitoba	2 477.9
Ontario	2 440.2
Québec	3 632.5
Newfoundland and Labrador	201.0
New Brunswick	179.2
Nova Scotia	172.5
Prince Edward Island	98.9
Yukon	126.9
Northwest Territories	97.7
Nunavut	930.6
Canada	**2 611.1**

Source: Detailed case information received by PHAC from provinces and territories, standardized to the July 1 2020 post-census population estimate

Note: Data are analyzed based on date reported to PHAC.

Table A3. Cumulative age and gender distribution of COVID-19 cases reported to PHAC, as of 03 April 2021

Age group	Female			Male			Total[a]		
	n	%	Rate	n	%	Rate	n	%	Rate
≤ 19	84 158	17%	2 115.2	89 518	18%	2 151.5	173 676	18%	2 133.7
20-29	90 880	18%	3 684.0	94 289	19%	3 543.1	185 169	19%	3 610.9
30-39	80 405	16%	3 063.4	78 453	16%	2 940.8	158 858	16%	3 001.6
40-49	75 824	15%	3 095.9	68 928	14%	2 865.8	144 752	15%	2 981.9
50-59	67 167	13%	2 571.2	64 828	13%	2 510.2	131 995	13%	2 540.9
60-69	40 054	8%	1 657.4	43 254	9%	1 871.8	83 308	8%	1 762.2
70-79	23 850	5%	1 508.6	23 296	5%	1 636.0	47 146	5%	1 569.0
80+	41 849	8%	4 224.6	22 188	5%	3 296.6	64 037	6%	3 849.2
Total	**504 187**	**100%**	**2 637.0**	**484 754**	**100%**	**2 566.8**	**988 941**	**100%**	**2 602.1**

Source: Detailed case information received by PHAC from provinces and territories

[a] Cases not identified as male or female were removed from the total due to small numbers.

Note: Cases with missing gender, sex or age were excluded. Where available, gender data was used; when gender data was unavailable, sex data was used. Reliable data on gender diverse respondents are unavailable due to small counts.

Table A4. Cumulative age and gender distribution of COVID-19 deaths reported to PHAC as of 03 April 2021

Age group	Female	Male	Total[a]
≤ 19	2	4	6
20-39	44	75	119
40-59	327	506	833
60-79	2 475	3 799	6 274
80+	8 885	6 869	15 754
Total	**11 733**	**11 253**	**22 986**

Source: Detailed case information received by PHAC from provinces and territories

[a] Cases not identified as male or female were removed from the total due to small numbers.

Note: Cases with missing gender, sex or age were excluded. Where available, gender data was used; when gender data was unavailable, sex data was used. Reliable data on gender diverse respondents are unavailable due to small counts.

Table A5. Cumulative age and gender distribution of cases hospitalized, and admitted to ICU reported to PHAC as of 03 April 2021

Age groups	Hospitalized – non-ICU			Hospitalized – ICU		
	Female	Male	Total	Female	Male	Total
≤ 19	350	370	720	55	68	123
20-39	2 266	1 652	3 918	318	374	692
40-59	3 397	4 657	8 054	884	1 593	2 477
60-79	6 766	8 373	15 139	1 642	3 162	4 804
80+	8 660	6 948	15 608	542	688	1 230
Total	**21 439**	**22 000**	**43 439**	**3 441**	**5 885**	**9 326**

Source: Detailed case information received by PHAC from provinces and territories

[a] Cases not identified as male or female were removed from the total due to small numbers.

Note: Cases with missing gender, sex or age were excluded. Where available, gender data was used; when gender data was unavailable, sex data was used. Reliable data on gender diverse respondents are unavailable due to small counts.

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ORIGINAL ARTICLE

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Indoor transmission of SARS-CoV-2

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Abstract

It is essential to understand where and how severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is transmitted. Case reports were extracted from the local Municipal Health Commissions of 320 prefectural municipalities in China (not including Hubei Province). We identified all outbreaks involving three or more cases and reviewed the major characteristics of the enclosed spaces in which the outbreaks were reported and their associated indoor environmental aspects. Three hundred and eighteen outbreaks with three or more cases were identified, comprising a total of 1245 confirmed cases in 120 prefectural cities. Among the identified outbreaks, 53.8% involved three cases, 26.4% involved four cases, and only 1.6% involved ten or more cases. Home-based outbreaks were the dominant category (254 of 318 outbreaks; 79.9%), followed by transport-based outbreaks (108; 34.0%), and many outbreaks occurred in more than one category of venue. All identified outbreaks of three or more cases occurred in indoor environments, which confirm that sharing indoor spaces with one or more infected persons is a major SARS-CoV-2 infection risk.

KEYWORDS

COVID-19, crowding, indoor environments, indoor hygiene, outbreak, SARS-CoV-2

1 | INTRODUCTION

In less than 4 months, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spreads rapidly to all countries worldwide. By the end of June 2020, it had infected more than 10 million people and, by developing into coronavirus disease 2019 (COVID-19), had caused or contributed to the deaths of half a million people.[1] Understanding where and how person-to-person SARS-CoV-2 transmission occurs is essential for effective intervention.

The once-in-a-century COVID-19 pandemic has occurred in the age of artificial intelligence and big data. Many clusters/outbreaks were identified via contact tracing by local health authorities in China and elsewhere using both traditional and new technologies. The identification of these clusters allowed health authorities to quarantine close contacts for effective intervention and provided an opportunity to study the characteristics of where and how these clusters occurred. The first COVID-19 patient was identified in Wuhan in December 2019, and the largest number of confirmed Chinese cases occurred in Hubei Province, of which Wuhan is the provincial capital.[2] Since January 20, 2020, the local health authorities of cities outside Hubei have reported online the details of most identified cases of infection. These were nearly only cases of SARS-CoV-2 infection that had progressed to actual disease (ie, COVID-19) and necessitated hospitalization, as by February 11, 2020, our knowledge of asymptomatic infection was non-existent.

In this study, we identified the outbreaks from these case reports from the local Municipal Health Commissions of 320 prefectural cities (municipalities) in China, not including Hubei Province, between January 4 and February 11, 2020. We also reviewed the major characteristics of the enclosed areas in which these outbreaks

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were determined to have occurred and their associated indoor environmental aspects.

2 | METHODS

We collected descriptions of each confirmed case from the local Municipal Health Commission website of 320 prefectural cities in mainland China, not including Hubei province. Each local Municipal Health Commission gave daily descriptions of the confirmed cases. The case descriptions generally included age, sex, venue of infection, symptoms, date of symptom onset, hospitalization, and confirmation and history of exposure. Many described cases also included patient's trajectory and relationship with other confirmed cases, and clusters had often already been identified. We consulted nationwide websites, except for those of cities in Hubei Province, and collected all available data up to February 11, 2020. Data from a few major cities—Beijing, Shanghai, and Guangzhou—were not included in our analysis due to insufficient case descriptions. Case descriptions from Hong Kong, Macao, and Taiwan were collected from their respective health authorities. We input the data into a database and conducted cross-validation to insure data reliability.

A total of 7324 cases with the minimum required descriptions (ie, the information listed above) were found; these accounted for 66.7% of the 10 980 confirmed non-Hubei cases in China by February 11, 2020.[3] In this study, we defined a *cluster* as an aggregation of *three* or more cases that appeared to be linked to the same infection venue (eg, an apartment, an office, a school or a train) during a period in which people were insufficiently close proximity. We defined an *outbreak* as a cluster in which a common index patient was suspected, and we excluded tertiary and higher-generation infections in counting the number of cases involved. We also excluded outbreaks that involved only two cases, to exclude possible spouse-to-spouse transmission and to reduce the workload due to the large number of clusters or outbreaks with two cases. We also identified the index patient(s) of the identified outbreaks and their date of symptom onset.

We divided the identified outbreaks into categories for further analysis. First, the following six categories of infection venues were considered: homes (apartments and villas), transport (eg, normal and high-speed trains, private cars, buses, passenger planes, taxis, and cruise ships), restaurants and other food venues, entertainment venues (gyms, mah-jong halls, card houses, tea houses, and barbershops), and shopping venues (shopping malls and supermarkets), and an additional miscellaneous category (eg, hospitals, hotel rooms, unspecified communities, and thermal power plants). Second, the following four categories of infected individuals were considered based on their relationship: family members, family relatives, socially connected individuals, and socially non-connected individuals. A socially connected relationship was defined as one that existed between individuals who had possibly been in close contact due to friendships, acquaintances, or jobs, but did not include family connections (family members or relatives). A socially non-connected relationship was defined as one with no social connection or family connection.

Practical Implication

- The indoor environments in which we live and work are the most common venues in which SARS-CoV-2 is transmitted.
- There is a need to improve the hygienic and ventilation conditions of these indoor environments to decrease the transmission of airborne infectious diseases.
- Given that there is an association between crowding and infection, in the post-pandemic future, we need to reflect deeply on the need for a healthy indoor environment.

3 | RESULTS

We identified 318 outbreaks involving 1,245 infected individuals in 120 cities. The top three cities (Table S2) were Shenzhen, Guangdong (24 outbreaks, 7.5%; 84 cases, 6.7%), Chongqing (16 outbreaks, 5.0%; 61 cases, 4.9%) and Bozhou, Anhui (nine outbreaks, 2.8%; 35, 2.8%). The average number (±standard deviation) of cases per outbreak was 3.92 ± 1.65. More than half (171;53.8%) of the 318 identified outbreaks involved three cases, more than a quarter (84; 26.4%) involved four cases, and only five (1.6%) outbreaks involved ten or more cases. Table S1 briefly describes four outbreaks, including the largest outbreak, which occurred in a shopping mall in Tianjin (21 cases).

Among the 318 outbreaks, 129 involved only family members, 133 involved family relatives, 29 involved socially connected individuals, 24 involved socially non-connected individuals, and only three involved multiple relationships. In addition to family members, family relatives and socially connected individuals constituted a large proportion of the infected cases (Figure 1A).

Eighty-three of the 318 identified outbreaks had multiple possible venues, which meant either that the exact venue of infection could not be identified or that more than one venue was involved in the infection. If we double- or triple-count these venues, we have a total of 416 infection venues for 318 outbreaks (Figure 1B). Among the 318 outbreaks, 254 (79.9%) occurred in a home (one in a villa; all others in apartments), 108 (34.0%) occurred on transport, 14 occurred at a restaurant or other food venue, seven occurred at an entertainment venue, and seven occurred at a shopping venue (shopping mall and supermarket), with an additional 26 occurring at a miscellaneous venue (eg, hospital, hotel room, unspecified community, and thermal power plant). Among the 235 outbreaks with an exact venue, 188 occurred in a home, 18 occurred on transport, 10 occurred at a restaurant,

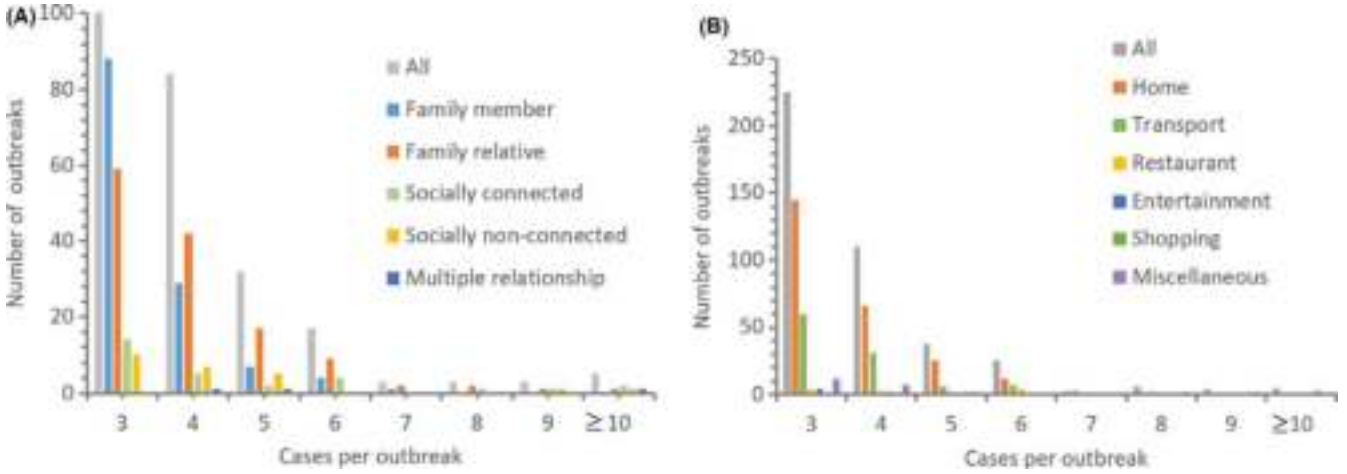
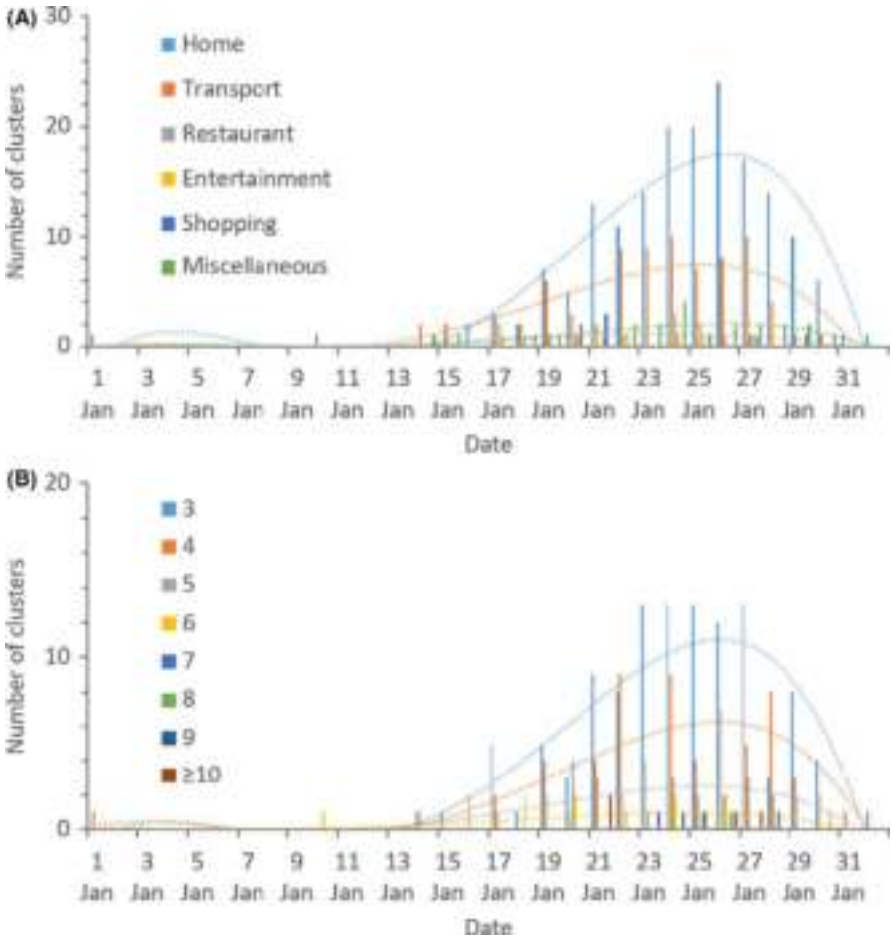


FIGURE 1 Distribution of all identified 318 outbreaks (A) involving confirmed cases of different relationships and (B) for each category of the 416 venues

FIGURE 2 Occurrence of outbreaks on median dates of infectious period for 231 actual outbreaks (A) in different categories for 300 venues and (B) with different numbers of cases in each outbreak on median dates of infectious period



six occurred at an entertainment venue, and seven occurred at a shopping venue, with an additional six occurring at a miscellaneous venue. For the 83 outbreaks with multiple possible venues, a total of 181 venues were identified (2.18 venues per outbreak). Among the 181 venues, 66 were homes, 90 were a form of transport, 4 were restaurants, 1 was an entertainment venue, and 20 were miscellaneous venues.

Most of the 254 home outbreaks comprised three to five cases (145 with three cases, 66 with four cases, and 25 with five cases). The average number of cases was 3.7 for outbreaks at homes, 3.8 for outbreaks on transport, 4.9 for outbreaks at food venues, 3.6 for outbreaks at entertainment venues, 8.7 for outbreaks at shopping venues, and 4.4 for outbreaks at miscellaneous venues. The proportion of large outbreaks was high for shops and food venues, possibly

because more susceptible individuals were present in these venues than in homes. Shopping and entertainment venues were each associated with only seven outbreaks. This suggests that it will be difficult to implement preventive measures in places that are frequented by large numbers of susceptible individuals if exact transmission routes are uncertain. In this context, it may be useful to provide further details of the seven outbreaks in shopping venues, as these had the highest average number of cases. There was one super-spreading event (outbreak) in a shopping center involving 21 cases, and there were also two outbreaks involving 10 cases (Table S1). In these three outbreaks, two of the index patients were shopping assistants in the shopping centers and one was a vegetable trimmer in the supermarket. These were all low-end shopping venues, where we suspect that the ventilation was poor or insufficient, at least for the 21-case outbreak; however, we have no direct evidence for this. In contrast, the index patient might have been a super-spreader, because the nature of the shopping assistants' job placed them in close contact with many people for a long duration. In the third case, the virus might have been present on the raw vegetables and thus been transferred to the vegetable trimmer.

Between December 29, 2019, and January 31, 2020, we also identified 231 outbreaks with known start and end dates of the suspected infectious period (Figure 2A). The identified outbreaks peaked between January 23 and 28 (Figure 2A), which coincides with the celebration period of the Chinese New Year (CNY). CNY 2020 lasted from New Year's Eve on January 24 to the Lantern Festival (ie, the 15th of Lunar January) on February 8. The official holiday in mainland China was from January 24 to 30, 2020. The peak date for the number of transport outbreaks was 1 to 2 days earlier than that for the home outbreaks as people traveled home for CNY.

Because home outbreaks dominated, the changes in the temporal profile of the number of cases (Figure 2A) closely followed that of the home outbreaks (Figure 2B). However, for outbreaks with more than six cases, no particular pattern was identified over time, which suggests a sporadic nature.

Among the 231 outbreaks with a known suspected infectious period, 126 included a known date of symptom onset for the index patient (Figure 3). We further divided those 126 outbreaks into two subgroups according to the index patient's symptom-onset date, as follows: on or before January 28 (96 outbreaks) and after January 28 (30 outbreaks). The average time from symptom onset to the end of the infectious period was 3.76 ± 4.42 days for those on and before January 28 and 0.87 ± 2.80 days for those afterward. The significant reduction in the average time from symptom onset to the end of the infectious period between these subgroups suggests the effectiveness of the early detection and isolation policy, which also explains the sharp decline in cases of infection after January 28.

Information is available on both the age and sex of the index patient for 139 outbreaks (Figure 4). Eighty-six outbreaks (62%) had a male index case, and 53 (38%) had a female index case. The average number of infected patients (excluding the index case) was approximately 3 for most age groups (3 for minors [ie, <18 years of age], with only one outbreak; 2.79 for young adults [ie, 18-35 years of age],

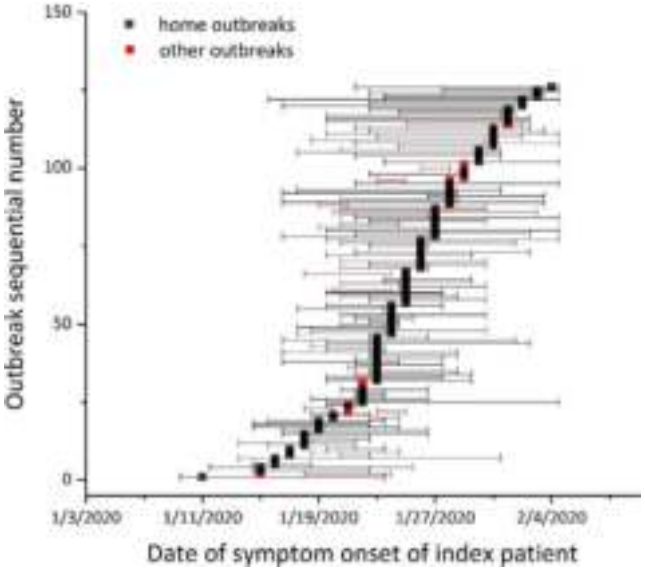


FIGURE 3 One hundred and twenty-six outbreaks with both possible starting and end infectious dates and date of symptom onset of index patient. Non-home outbreaks are shown in red

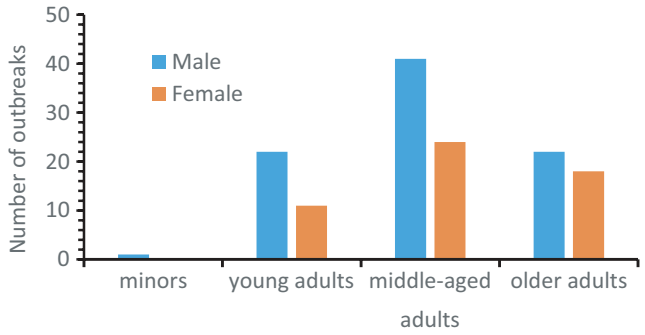


FIGURE 4 One hundred and thirty-nine outbreaks with information on the age of the index patient. Minors (<18 y old), young adults (18-35 y old), middle-aged adults (36-55 y old), senior adults (>55 y old)

in 33 outbreaks; and 3.11 for middle-aged adults [ie, 36-55 years of age], in 65 outbreaks). The average number of infected patients was 2.58 for senior adults [ie, >55 years of age], in 40 outbreaks. We were interested to note that among the outbreaks with a middle-aged index case, a female index case infected an average of 3.71 others, while a male index case infected 2.75 others. The dominant middle-aged group of reported index cases likely reflects the fact that returned migrant workers from Wuhan constituted the major pool of source patients in provinces outside Hubei.

4 | DISCUSSION

The first salient feature of the 318 identified outbreaks that involved three or more cases is that they all occurred in indoor environments. Although this finding was expected, its significance has not been

well recognized by the community or by policymakers. In a modern civilization, our lives and work are indoors. The transmission of SARS-CoV-2 from infected individuals to susceptible individuals is mainly an indoor phenomenon.

The emergence of homes as the most common COVID-19 outbreak venue in China is not surprising. During the COVID-19 epidemic in mainland China, homes became temporary quarantine places. Our estimated home dominance of 79.9% is close to the official estimate of 83% of the so-called household clusters among the nearly 1000 clusters (not outbreaks) defined by the China National Health Commission.[4] After Wuhan announced its city lockdown on January 23, the warning message spread throughout the country. People in provinces outside Hubei also began to stay at home. Most Chinese families have one child, and some families may also include grandparents. The relatively low number of cases in these home outbreaks might be considered an advantage of the compulsory home quarantine because transmission was limited to a small number of family members. Similar stay-at-home policies have now been implemented elsewhere during the pandemic. Most urban homes are high-rise apartments, while rural homes may be single-family detached houses. Modern urban homes may be mechanically ventilated, while older homes are typically naturally ventilated. It is unfortunate that detailed characteristics of the homes in which the infections occurred are not available.

The rising trend shown before the peak period in Figure 2 was likely due to the introduction of imported cases due to the Spring Festival travel season (Chunyun in Chinese), a period around CNY during which many people leave the cities in which they work to visit their rural families. The 2020 Chunyun brought people from the epicenter Wuhan to their home cities before Wuhan's lockdown on January 23. Social and family gatherings continued after January 23 in most cities outside Hubei. Interventions such as contact tracing and confinement of estates, villages, and individual buildings were implemented gradually in most cities outside Hubei immediately after CNY, which explains the sharp declining curve after January 28. The significant reduction in the average time from symptom onset to the end of the infectious period between the before January 28 subgroup and after January 28 subgroup suggests the effectiveness of the early detection and isolation policy and explains the sharp decrease in infections after January 28.

Our study does not rule out outdoor transmission of the virus. However, among our 7324 identified cases in China with sufficient descriptions, only one outdoor outbreak involving two cases occurred in a village in Shangqiu, Henan. A 27-year-old man had a conversation outdoors with an individual who had returned from Wuhan on January 25 and had symptom onset on February 1. This outbreak involved only two cases.

The second salient feature of the 318 identified outbreaks is the relatively small number of outbreaks that involved 10 or more cases. The largest outbreak occurred in a Tianjin shopping mall and involved 21 cases, although Wu et al[5] reported 25 cases (Table S1). This is distinct from the 2003 SARS-CoV epidemic, during which seven major super-spreading events in Hong Kong and Singapore alone were identified to involve as many as 329 cases and super-spreading events dominated the epidemic.[6] The occurrence of many small outbreaks (in terms of the number of cases) in the COVID-19 pandemic suggests a different transmission pattern from that of the 2003 SARS-CoV epidemic. Some viral, epidemiological, and environmental factors may have contributed to this difference between the 2003 SARS-CoV epidemic and the current COVID-19 pandemic. However, a number of large super-spreading events were later reported elsewhere in the world, including 94 people who were infected in an 11th-floor call center in Seoul with 216 employees,[7] and 32 confirmed and 20 probable secondary cases after a 2.5-hour choir practice attended by 61 persons in Skagit County, Washington.[8] We cannot pinpoint the exact transmission routes of these identified outbreaks. During the early phase of the pandemic, most health authorities advised that the SARS-CoV-2 was transmitted mainly by close contact and via the fomite route (eg, China NHC[9] and US CDC[10]). The China NHC also suggested that long-range aerosol transmission may occur when certain conditions are met, such as in crowded enclosures or spaces with poor ventilation. By 5 November 2020, the US CDC[11] suggested that "It is possible that COVID-19 may spread through the droplets and airborne particles that are formed when a person who has COVID-19 coughs, sneezes, sings, talks, or breathes. There is growing evidence that droplets and airborne particles can remain suspended in the air and be breathed in by others, and travel distances beyond 6 feet (for example, during choir practice, in restaurants, or in fitness classes). In general, indoor environments without good ventilation increase this risk."

We do not have data on the hygiene conditions, such as ventilation rates and human densities, of the infection venues of the 318 outbreaks studied here. The exact location of the infection venues and the necessary parameters such as the floor area or the number of occupants were not provided in the case reports. Instead, we reviewed the current design standards of thermal and ventilation conditions, occupant density, and close-contact behavior in the various indoor environments discussed here (Table S3). The required ventilation rates vary significantly among homes, offices, trains, and buses. We note that the current ventilation rate guidelines in these environments do not consider infection control. For example, the required ventilation rate is only 3.9 L/s per person in shopping malls and 2.8 L/s per person in public buses, whereas a ventilation rate of at least 8-10 L/s is required for good indoor air quality.[12] The review showed that a rate as high as 25 L/s per person may be needed.[12] Some existing buildings are probably crowded, poorly ventilated, and unhygienic. A comprehensive review of ventilation conditions in Chinese indoor environments by Ye et al[13] showed that the CO_2 concentration can reach 3500 pp min some buildings. The design and operation of buildings have also been under pressure to reduce energy use[14] and increase human productivity. Balancing the need for energy efficiency, indoor environmental quality and health in both urban planning and building design have not been easy.[15] The quality of indoor environments might be sacrificed by putting a greater focus on cost than on health.

Close-contact behavior and occupant density in the various indoor environments discussed are also reviewed in Table S3. Frequent close contact occurs indoors, and buildings have high-touch surfaces.[16-19] Unfortunately, we do not have detailed data on surface-cleaning and hand-hygiene conditions in these indoor environments, but fomite transmission must nevertheless be considered in designing preventive approaches.

This study has limitations. We only studied outbreaks in China, where very strict intervention measures were implemented. We relied fully on the case reports of the local health authorities in each city, and variation exists in the details and the quality of their original epidemiological investigations. We also made no attempt to access any of the infection venues, and the details of each of these indoor spaces remains unknown.

This study shows that the individual indoor environments in which we live and work are the most common venues in which the virus of the once-in-a-century-pandemic is transmitted among us. An individual infected in one building may infect others in the building(s) that he or she later visits. People are in constant contact as they move from one indoor space or building to another, which creates an indoor contact network through which a virus can spread.[20] The buildings and transport cabins in various parts of the world are thus connected and facilitated the spread of the COVID-19 pandemic virus.

The association between crowding and infection has been known since Pringle.[21] The most dramatic example in the current pandemic might be in the cruise ship outbreak on the crowded Diamond Princess, of which the peak basic production number was predicted to be 11[22] or 14.8[23] before quarantine and much higher than elsewhere. The world's first statutory housing policy, the Artisans and Labourers Dwellings Act 1875[24] was developed following 19th-century empirical evidence that crowding led to a high incidence of infectious disease. A recent systematic review by the World Health Organization also found an association between crowding and infection.[25] A *Lancet* editorial in 2018 declared "[t]he right to a healthy home."[26] One WHO meeting also declared that "everyone has the right to breathe healthy indoor air"[27] and that "the provision of healthy indoor air should not compromise global or local ecological integrity, or the rights of future generations".[28] We hope that in the post-pandemic future, mankind will reflect deeply on the need for a healthy indoor environment.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

H. Qian, T. Miao, and Y. Li contributed equally. Y. Li and H. Qian contributed to study design, hypothesis formulation, and coordination. L. Liu, X. Zheng, and D. Luo contributed to data collection and initial data analyses. H. Qian and T Miao contributed to major data analyses. Y. Li wrote the first draft of the paper, and H. Qian and T. Miao contributed to major revision. All of the other authors contributed to revision.All of the authors approved the submitted version and have agreed to be personally accountable for their own contributions.

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DATA AVAILABILITY STATEMENT

Available to interested readers by contacting Dr. Li (e-mail, liyg@hku.hk).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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SARS-CoV-2 concentrations and virus-laden aerosol size distributions in outdoor air in north and south of Italy

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ABSTRACT

The COVID-19 disease spread at different rates in the different countries and in different regions of the same country, as happened in Italy. Transmission by contact or at close range due to large respiratory droplets is widely accepted, however, the role of airborne transmission due to small respiratory droplets emitted by infected individuals (also asymptomatic) is controversial. It was suggested that outdoor airborne transmission could play a role in determining the differences observed in the spread rate. Concentrations of virus-laden aerosol are still poorly known and contrasting results are reported, especially for outdoor environments. Here we investigated outdoor concentrations and size distributions of virus-laden aerosol simultaneously collected during the pandemic, in May 2020, in northern (Veneto) and southern (Apulia) regions of Italy. The two regions exhibited significantly different prevalence of COVID-19. Genetic material of SARS-CoV-2 (RNA) was determined, using both real time RT-PCR and ddPCR, in air samples collected using PM_{10} samplers and cascade impactors able to separate 12 size ranges from nanoparticles (diameter D < 0.056 μm) up to coarse particles (D > 18 μm). Air samples tested negative for the presence of SARS-CoV-2 at both sites, viral particles concentrations were <0.8 copies m^{-3} in PM_{10} and <0.4 copies m^{-3} in each size range investigated. Outdoor air in residential and urban areas was generally not infectious and safe for the public in both northern and southern Italy, with the possible exclusion of very crowded sites. Therefore, it is likely that outdoor airborne transmission does not explain the difference in the spread of COVID-19 observed in the two Italian regions.

1. Introduction

The pandemic of COVID-19 disease, due to the novel coronavirus SARS-CoV-2, was firstly reported in a cluster in Wuhan (China) in December 2019 and it rapidly spread all around the World. By June 27 (2020), infected cases reached 9,660,902 individuals and 491,195 deaths worldwide (https://covid19.who.int/). Starting from February 2020 it was clear that spread of the disease happened in specific outbreak areas and that significant differences were observed in COVID-19 prevalence and fatality rate in different countries and in different regions of the same country. In Europe, Italy was the first country severely hit, with the majority of cases observed in northern Italy and a much smaller number of cases observed in central and, especially, southern Italy. The rapid spread of SARS-CoV-2 and these spatial differences raised important questions regarding the mechanisms of transmission and the role potentially played by airborne transmission. It has also been suggested that airborne transmission could be responsible of the different COVID-19 prevalence observed in northern and southern Italy because of the different dispersion conditions in the two areas (Conticini et al., 2020; Setti et al., 2020). The Po Valley area in northern Italy is characterised, especially during winter period, by low wind speed accompanied to long periods of stable conditions with shallow mixing layers (Ferrero et al., 2010) and this limit both transport (because of limited ventilation) and dispersion of pollutants (because of limited turbulence) favouring large pollutant concentrations near the ground. Venice area, in the northeast of Italy is located near the sea and it has a typical circulation of air masses (Contini et al., 2015) with prevalent winds coming from NNE-NE directions (from the Alps

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mountains) mainly during the night and winds coming from SSE-SE during the day (from the Adriatic Sea). In contrast, Apulia region in southern Italy has a local meteorology characterised by greater solar radiation, compared to the Po Valley, increasing thermal turbulence and strong winds that favour transport and dilution of pollutants (Cesari et al., 2018). This difference in dispersion conditions could, in principle, influence the concentrations of virus-laden particles in outdoor air.

The spread of SARS-CoV-2 by contact (direct or indirect through contaminated surfaces) is widely accepted, however, the relative importance of airborne transmission is still controversial (Contini and Costabile, 2020; Domingo et al., 2020; Klompas et al., 2020; Morawska and Cao, 2020; Prather et al., 2020). Particles are emitted during sneezes, cough, respiration, speaking, singing, and shouting. In case of infected individuals, these particles could contain viable virus as happens for other respiratory viruses (Milton et al., 2013; Yan et al., 2018), including other coronaviruses such as NL63, OC43, 229E, and HKU1 (Leung et al., 2020). Sneezing and coughing are mainly associated with symptomatic individuals, however, emissions during respiration and speaking could happen also for asymptomatic individuals that have typically a viral load comparable to that of symptomatic patients (Lavezzo et al., 2020). Large respiratory droplets (conventionally with diameter $D > 5$ μm) settle faster than they evaporate, contaminating the immediate vicinity of the infected individuals. In contrast, small droplets (i.e. $D < 5$ μm) evaporate faster than they settle, leaving dry residuals (also called droplet nuclei) which might contain virus aggregates, proteins, and mineral salts (Asadi et al., 2020; Borouiba, 2020). Droplet nuclei can remain suspended in air for longer time compared to large droplets and potentially contribute to airborne transmission (Allen and Marr, 2020; Morawska and Cao, 2020; Martano, 2020).

The probability of airborne transmission is different in outdoor and indoor environments and depends on several parameters; the most important are: (i) concentration and size distribution of virus-laden particles in air; (ii) the fraction of viable viral particles; (iii) the minimum viral load necessary to transmit the infection by inhalation in susceptible individuals. The lifetime of aerosolized SARS-CoV-2 could be 3 h under laboratory controlled conditions (van Doremalen et al., 2020), but it could be less in outdoors depending on the degradation of the virus due to local meteorology conditions (Ratnesar-Shumate et al., 2020). The minimum infectious dose, expressed in viral RNA copies inhaled, is not defined for SARS-CoV-2 in current scientific literature. However, referring to the studies on SARS-CoV-1, the dose of airborne virus copies (i.e. the quantum) necessary to cause infection in 63% of susceptible individuals is variable between 10 and 100 and it is possible to assume an average of 20 for SARS-CoV-2 (Buonanno et al., 2020). Current knowledge of concentration and size distribution of virus-laden aerosol in air is extremely scarce and contrasting results have been observed. In outdoors, measurements in Wuhan (Hu et al., 2020; Liu et al., 2020) showed concentrations below the detection limit, except for crowded areas; while, a study conducted in Bergamo (north of Italy) identified traces of viral RNA in 23% of the analysed PM_{10} samples without quantifying the concentrations (Setti et al., 2020). Concentrations of viral particles in indoor environments (mainly measured in hospitals and quarantine areas) seems to be higher (Hu et al., 2020; Liu et al., 2020; Santarpia et al., 2020) than those observed in outdoors. However, other studies showed no detectable concentrations even in proximity of quarantined COVID-19 patients (Faridi et al., 2020; Ong et al., 2020).

This work tries to fill the gap in knowledge regarding atmospheric concentrations of virus-laden particles in Italy. It is focused on the analysis of concentration and size distribution of SARS-CoV-2 virus-laden aerosol in outdoor air, comparing data collected in the Veneto region (north Italy) and Apulia region (south Italy), to asses a possible role of outdoor airborne transmission in the difference of COVID-19 spread rate observed in north and south of Italy. Measurements were performed simultaneously in the two regions, collecting air samples using both PM_{10} samplers and cascade impactors. SARS-CoV-2 presence was determined looking for genetic material (RNA) using both real-time RT-PCR and droplet digital PCR (ddPCR) methods (Corman et al., 2020; Suo et al., 2020).

2. Methods

2.1. Samples collection

Aerosol sampling was simultaneously carried out from 13th to 27th of May 2020, in two different Italian regions: Veneto (in the northeaster Italy) and Apulia (in the southeaster Italy). In Veneto, samples were collected at the Scientific Campus of Ca' Foscari University (45°28′47″N, 12°15′12″E, Mestre-Venice, Italy). The site is located in a working/residential area of Mestre, characterized by some major potential sources of particulate matter: high density residential areas; heavily trafficked roads; the industrial area of Porto Marghera, and an international airport (Squizzato et al., 2016). In Apulia, measurements were performed at the Lecce Environmental-Climate Observatory (ECO, 40.3°N 18.1°E; 36 m a.s.L.), located at the Institute of Atmospheric Sciences and Climate of the National Research Council (ISAC-CNR), inside the University Campus, at about 4 km (WSW) from the urban area of Lecce (Dinoi et al., 2020). The area, considered an urban background site, is affected by the integrated contribution of local anthropogenic sources (mainly road traffic and biomass burning) and by the long-range transport of natural and anthropogenic dust (Cesari et al., 2016, 2018).

During both sampling campaigns, two different samplers were used. In Venice, PM_{10} samples were collected using a low volume aerosol sampler (Skypost PM-TCR Tecora) equipped with a sequential sampler (Charlie) that operates at flow rate of 38.3 L min^{-1}. The sampling period for each sample was about 48 h, with a total average air volume of 110 m^3 per sample. A second simultaneous sampling was performed using a model 110 MOUDI cascade impactor with an average flow of 30 L min^{-1}. The inlet of the impactor has a nominal cut-off size of 18 μm, and the nominal cut-off sizes of the 10 impaction stages are: 10, 5.6, 3.2, 1.8, 1.0, 0.56, 0.32, 0.18, 0.10 and 0.056 μm. A back-up filter collected particles with aerodynamic diameter <0.056 μm. The sampling period for each impactor sample was about 6 days, with a total average air volume of about 250 m^3 per sample. This setup for data collection with the impactor was already successfully used in other measurement campaigns (Cesari et al., 2020).

In Lecce, the 48-h PM_{10} samples were collected using a low volume (38 L min^{-1}) sampler (SWAM 5a Dual Channel Monitor-FAI Instruments). Size-segregated samples were collected with a rotating model 120 MOUDI-II™ cascade impactor, operating at 30 L min^{-1} for about 6 days for each sample, to separate particles of different aerodynamic diameters in the same twelve intervals used in the Venice site.

At both sites, quartz fibre filters were used, after a decontamination process with a 4 h pre-combustion at 400 °C in a muffle furnace. In total, 12 PM_{10} filters (6 for each site) and 48 impactor filters (24 for each site) were collected. In addition, 4 field blank filters were obtained for each site, 2 for the PM_{10} sampler and 2 for the cascade impactor. All samples were vacuum packed in sealed sterile petri dishes and frozen at −25 °C immediately after sampling for conservation until the successive analysis. Laboratory analysis started within four days from the end of collection period.

It has been chosen to use both, PM_{10} samplers and cascade impactors, because it is important to know the size distribution of virus-laden particles to effectively understand the risk of airborne transmission. Sub-micrometric particles (in the accumulation mode <1 μm) could remained suspended in atmosphere for longer time compared to larger particles that have a greater deposition velocity. Therefore, particles in the accumulation mode could contribute to airborne transmission more than coarse particles and there are limited indication on this aspect in current studies. In Liu et al. (2020) in indoor environments in hospitals in China SARS-CoV-2 RNA was detected also in the size range 0.25–1 μm, instead, in the indoor measurements in Singapore hospitals (Chia

et al., 2020) the smallest aerodynamic size fraction that contained detectable levels of SARS-CoV-2 was 1–4 μm.

2.2. Analytical method for RNA detection

RNA extraction for PCR experiments was achieved using Total RNA Purification Kit (Norgen Biotek Corp.) with a modified protocol to increase yield. Each filter was cut and placed inside a 2 mL centrifuge tube containing 1 mL of Phosphate Buffer Solution (PBS) pH 7.4. The tube was sealed and put in a sonicator water bath (Elmasonic S10H) for 30 min. Aerosol particles were separated from the quartz filter by centrifugation using a mini syringe placed in a collection tube. The obtained pellet, for each filter processed, was resuspended by 350 μL of supernatant, according to the manufacturer's protocol. The final eluted solutions (about 70 μL in total) were stored frozen at −80 ± 2 °C until PCR analysis that was performed within four days from extraction.

Molecular analysis for the detection of SARS-CoV-2 was carried out using real-time RT-PCR and Droplet Digital PCR (ddPCR) technologies. According to World Health Organization (WHO), real-time RT-PCR represents the gold standard for the diagnosis of SARS-CoV-2. Recently, ddPCR has demonstrated the best performance to detect SARS-CoV-2, because it reduces the false negatives (Suo et al., 2020).

Real-time RT-PCR for SARS-CoV-2 was carried out on a CFX96™ Real-Time system (Bio-Rad, Italy) using COVID-19 PCR DIATHEVA Detection kit (Diatheva, Cartoceto, PU, Italy) based on the WHO guideline (Corman et al., 2020). The COVID-19 PCR DIATHEVA Detection kit is a One-Step real-time reverse transcription (RT-PCR) multiplex assay based on fluorescent-labelled probe used to confirm the presence of SARS-CoV-2-RNA by amplification of RdRp and E gene. The kit provides all the reagents required for the analysis, PCR positive and PCR negative controls included. 5 μL of extracted RNA were added to 15 μL of Master mix for each sample and analysed according to kit instructions. Undiluted and 1:10 diluted samples were tested. In each run, two negative controls (molecular grade water) and a positive control were added. The interpretation of the sample results was done according to kit instructions. The limit of detection (LOD) of the COVID-19 PCR DIATHEVA Detection kit was previously defined through analysis of standard material RNA of SARS-CoV-2 and was equal to 10 copies/μL.

The ddPCR assays were performed using Bio-Rad SARS-CoV-2 ddPCR kit on QX200™ Droplet Digital™ PCR system (Bio-Rad, Italy). The Bio-Rad SARS-CoV-2 ddPCR is a reverse transcription (RT) droplet digital PCR (ddPCR) test designed for the qualitative detection of RNA from SARS-CoV-2. The assay includes the 2019-nCoV CDC ddPCR Triplex Probes and the One-Step RT-ddPCR Advanced Kit for Probes. The 2019-nCoV CDC ddPCR Triplex Probes contains specific oligonucleotide primers and probes for SARS-CoV-2 (N1 and N2), the same as those reported by Center for Disease Control and Prevention (CDC), mapping on regions of the virus nucleocapsid (N) gene into a single assay multiplex to enable a one-well reaction. The reaction mixtures were partitioned into approximately 20,000 droplets using a QX200 Droplet Generator™ (Bio-Rad, Italy) with the random dispersal of target nucleic acids into the droplets. The PCR assays were conducted in a C1000 Touch™ Thermal Cycler (Bio-Rad, Italy), according to kit instructions. After amplification, the droplets were individually assayed using the QX200™ Droplet Reader™. The fluorescence data were then analysed by the QuantaSoft v1.7 Software and QuantaSoft Analysis Pro v1.0 Software (Bio-Rad, Italy) to determine the presence of SARS-Cov-2 N1 and N2 in the specimen. The LOD of the Bio-Rad SARS CoV-2 ddPCR test was declared by the manufacturer in 0.625 copies/μL for targets N1 and N2.

The efficiency of the extraction procedure was evaluated through the recovery of a process control, a virus added prior to acid nucleic extraction. Mengo virus strain MC_0, supplied by Istituto Superiore di Sanità (ISS, Rome, Italy), is a murine virus of the *Picornaviridae* family, a non-enveloped positive-sense ssRNA virus. The efficiency of the extraction method was evaluated comparing the Ct values obtained for Mengovirus on samples extracts. In detail, 10 μL of Mengovirus was added prior to extraction to (i) 1 mL of PBS (reference sample); (ii) 1 mL of PBS with a blank filter and (iii) 1 mL of PBS with an exposed environmental filter. Each condition was run in duplicate. The detection of Mengovirus was carried out on a CFX96™ Real-Time system (Bio-Rad, Italy) using amplification conditions, primers and probe and reagents RNA UltraSense™ One-Step Quantitative RT-PCR System (Life Technologies, Carlsbad, California, US) (Pintó et al., 2009). Results indicate an average recovery of 49% (±5%).

3. Results and discussion

The outbreak of COVID-19 in Italy has resulted in 239,961 confirmed cases and 34,708 fatalities as of 27th June 2020. The transmission of SARS-CoV-2 was exceptionally severe in Veneto region (Fig. 1), with maximum active cases (i.e. currently infected individuals) of 10,800 on 16th April (about 10% of the overall Italian cases) over a population of 4.9 million people. Apulia region (southern Italy) reached the maximum of active cases on the 3rd of May with 2,955 cases (3% of the overall Italian cases) over a population of 4.0 million people. At the beginning of sampling period (13th May) Veneto and Apulia regions were affected by 5,020 and 2,322 active cases, respectively. These official numbers likely underestimate the real contagions. In Italy, cumulatively, 2.2–3.5 million individuals seem to have been infected as of May 4th, giving an attack rate of 3.6%-5.8% of the population (Flaxman et al., 2020).

During sampling, the average temperature was 19.6 °C (±1.4 °C) in Venice and 21.0 °C (±1.9 °C) in Lecce; the average relative humidity was 69% (±9.5%) in Venice and 56% (±9.8%) in Lecce. No precipitations were observed at the two sites during the sampling period.

PM_{10} and $PM_{2.5}$ concentration levels at the two sites are shown in Fig. 2. The national lockdown in Italy (indicated as phase I) included the period between 10th March and 17th May, even if there were some differences of restrictive measures during this period. Successively, there was the post-lockdown divided in what we called phase II and phase III in Fig. 2. Phase II was from 18th May until 3rd June and it was a re-opening with several limitations (cinema and theatres closed, travels among different regions were interdict, employees of public administrations remained diffusely on smart working). During phase III it was removed the restriction of travels among different regions and a significant fraction of employees of public administrations started to work on offices again. Our measurements started near the end of the phase I and continued during phase II of the post-lockdown period. The concentrations of PM_{10}, averaged over the whole measurement period, were 17.2 ± 5.2 μg m^{-3} (average ± standard deviation) in Venice, as provided by the Regional Agency of Environmental Prevention and Protection of Veneto (ARPAV) and 27.0 ± 14.8 μg m^{-3} in Lecce. The average concentrations of $PM_{2.5}$ were 9.8 ± 2.5 μg m^{-3} in Venice and 8.3 ± 2.3 μg m^{-3} in Lecce. High PM_{10} concentration are determined in Lecce at the beginning of sampling period (13–18 May 2020), while the values of $PM_{2.5}$ were comparable at the two sites (Fig. 2). This was due to a contribution of coarse particles due to African dust advection, that influenced only southern regions of Italy, contributing mainly to PM_{10} but not significantly to $PM_{2.5}$.

The existence of SARS-CoV-2 in aerosol samples was determined through the detection of its genetic material (RNA) in collected samples. Air samples were extracted at the Istituto Zooprofilattico Sperimentale della Puglia e della Basilicata (IZSPB), COVID-19 laboratory for the Apulia region. All extracts were firstly analysed using real-time RT-PCR and were negative showing no detectable presence of SARS-CoV-2 RNA. The detection limit of the method, referred to the extracted solutions, was 10 genome copies μL^{-1}. Successively, the same extracts were also analysed using the most sensitive technique available in the laboratory, the ddPCR, lowering the detection limit to 0.625 genome copies μL^{-1} and all samples tested negative for the presence of viral RNA.

The LODs (genome copies μL^{-1}) were transformed in thresholds for atmospheric concentrations of viral particles (expressed in copies/m^3)

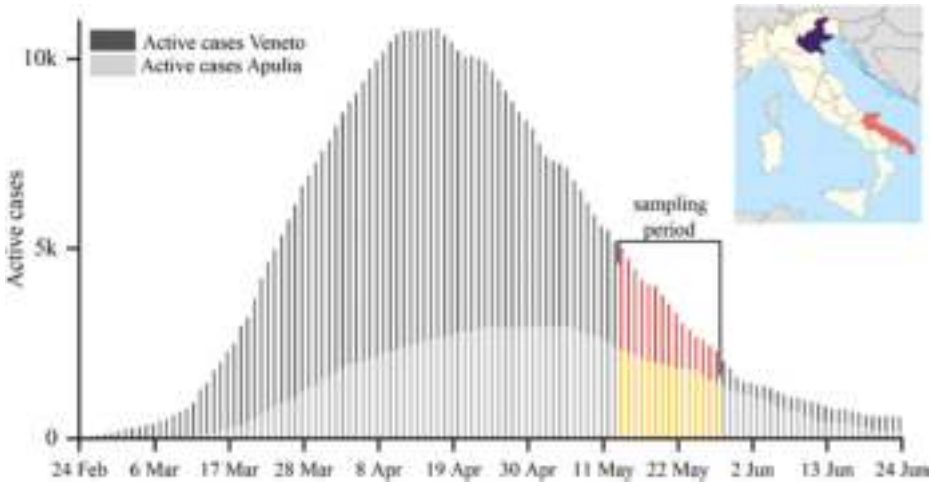

Fig. 1. Daily number of infected individuals observed in Veneto and Apulia regions during COVID-19 outbreak in Italy. The measurement sites are shown together with sampling period.

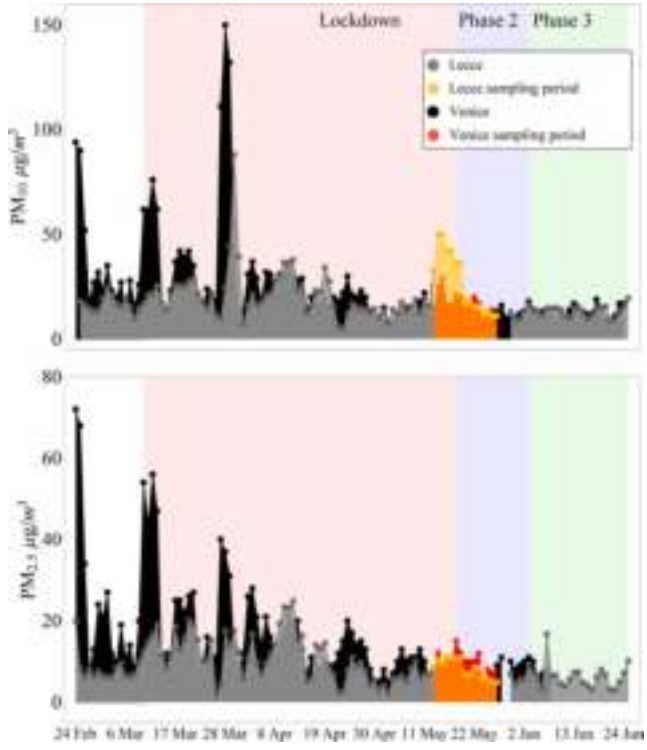

Fig. 2. Comparison of PM_{10} (top) and $PM_{2.5}$ (bottom) concentrations at the two sites evidencing the sampling period. The lockdown period (phase I) and the post-lockdown (phase II and II) are reported.

using the same approach employed for determination of concentration threshold of a chemical component of aerosol samples. Specifically, the LOD was transformed in a threshold of viral particles contained in a single filter (i.e. RNA copies per filter) considering the total volume of extraction solutions (about 70 μL) and the efficiency of the methodology (i.e. the recovery). These numbers were then normalised using the sampled volume to obtain the concentration threshold in copies m^{-3}. The concentration of virus-laden aerosol in PM_{10} samples was <0.8 copies m^{-3} at both sites during the sampling period. The size-segregated concentrations from nanoparticles ($D < 0.056$ μm) up to coarse particles ($D > 18$ μm) were <0.4 copies m^{-3} at both sites.

These results are comparable with those found in outdoor residential area in Wuhan (China) during the pandemic (Liu et al., 2020). Liu et al. (2020) collected air samples suing both samplers and cascade impactors, between February and March 2020, in public areas in outdoor as well as in indoor in quarantine areas. Samples collected in outdoor residential areas tested negative (<3 copies m^{-3}) with the exclusion of crowded zones in proximity of hospitals in which concentrations up to 11 copies m^{-3} were detected. Hu et al. (2020) found no viral RNA in air samples collected in residential community and an open public area (not crowded sites) in Wuhan (China). The analysis reported by Setti et al. (2020) shows that 23% of the 34 PM_{10} samples collected between February and March in outdoor in northern Italy (Bergamo) tested positive for SARS-CoV-2 RNA, however, concentrations of virus-laden particles were not evaluated. Results reported here suggest that in outdoor conditions, and excluding crowded areas, it is unlikely a role of airborne transmission of COVID-19.

The risk could be larger in community indoor environments where a certain number of infected individuals could be present in closed environments with limited ventilation. In this case, concentrations of virus-laden aerosol seems to be larger compared to outdoor, even if some contrasting results have been obtained. Liu et al. (2020) found SARS-CoV-2 RNA concentrations up to 42 copies m^{-3} in hospitals and quarantine areas in Wuhan (China) with a fraction of these viral particles in the fine size range (0.25–1 μm). Chia et al. (2020) found detectable SARS-CoV-2 genetic material in air in indoor COVID-19 patient care areas in Singapore in the size range >1 μm. Lednicky et al. (2020) found viable SARS-CoV-2 was isolated from air samples collected 2 to 4.8 m away from the patients in samples collected at the Student Health Care Center (SHCC, University of Florida, USA). Santarpia et al., 2020 found detectable concentrations of viral RNA in 63% of the samples collected in indoor at the Medical Center of the University of Nebraska (where COVID-19 patients were quarantined) with concentrations up to 2.86 copies L^{-1}). Instead, Faridi et al. (2020) did not detect SARS-CoV-2 in ten air samples collected in patient rooms of the largest hospital in Iran. In Singapore, air samples collected in a quarantine area with three patients tested negative for the presence of SARS-CoV-2 RNA (Ong et al., 2020). The possible larger risk of community indoor environments compared to outdoors could be mitigated by the use of face masks and the ventilation of closed spaces with outdoor air.

4. Conclusions

The results found indicate that outdoor atmospheric concentrations of SARS-CoV-2 were very small (<0.8 copies m^{-3}) in both northern and southern Italy. The same applies for each size range investigated with the impactor, which gave virus-laden aerosol concentrations <0.4 copies m^{-3}. The measurements were taken in a period when the number

of active cases (i.e. infected individuals) in the two regions were not at the maximum values (Fig. 1), thereby, it is possible to assume that higher concentrations (up to a factor 2 on average for Venice) were likely be present during the period of maximum spread of contagion. The average typical threshold of about 20 virus copies is necessary (Buonanno et al., 2020) to make a quantum of virus (i.e. the dose of airborne droplet nuclei that, if inhaled, is able to cause infection in 63% of susceptible persons). Considering a typical inhalation rate of about 1 m^3/h, as average between rest and light exercise (Adams, 1993), the concentrations would be low to spread the contagion via airborne transmission even assuming the mentioned increase of a factor 2.

Therefore, it is possible to conclude that outdoor air in residential and urban areas was generally not infectious and safe for the public in both northern and southern Italy, with the possible exclusion of very crowded sites. In addition, outdoor airborne transmission of SARS-CoV-2 was likely not the main cause of the difference in diffusion rates of COVID-19 observed during outbreaks in north and south of Italy.

Author contributions

D. Contini, A. Gambaro, G. La Salandra conceptualized the study design; E. Barbaro, E. Gregoris, M. Feltracco collected samples in Venice and contributed to data post-processing; M. Conte, A. Dinoi collected samples in Lecce and contributed to data post-processing; D. Chirizzi, G. Ciccarese, G. La Salandra, and G. La Bella carried out the laboratory tests. All authors collaborated to interpretation of results, wrote, read, commented, and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Kitchener Court File No.: CV-21-00000095-0000
St. Thomas Court File No.: CV-21-08

ONTARIO
SUPERIOR COURT OF JUSTICE

B E T W E E N:

THE ATTORNEY GENERAL OF ONTARIO

Applicant (Responding Party)

-and-

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHUURMAN, DEAN WANDERS, RANDY FREY, HARVEY FREY and DANIEL GORDON

Respondents (Moving Parties)

A N D B E T W E E N:

HER MAJESTY THE QUEEN IN ONTARIO

Applicant (Responding Party)

-and-

THE CHURCH OF GOD (RESTORATION) AYLMER, HENRY HILDEBRANDT, ABRAM BERGEN, JACOB HIEBERT, PETER HILDEBRANDT, SUSAN MUTCH, ELVIRA TOVSTIGA, and TRUDY WIEBE

Respondents (Moving Parties)

AFFIDAVIT OF DR. RICHARD SCHABAS
(Sworn May 29, 2021)

I, RICHARD SCHABAS, of the [redacted] in the Province of Ontario, MAKE OATH AND SAY:

1. I am a retired physician with specialist qualification in Public Health, and as such have knowledge of the matters hereinafter deposed to.

2. I also have specialist qualification in Internal Medicine and a Master's degree in Epidemiology. I practised clinical medicine for forty years, initially as a general practitioner and then as a general internist. I practised public health for twenty-five years at a local and provincial level, including ten years as Ontario's Chief Medical Officer of Health, between 1987 and 1998.

3. I worked in hospital management as Chief of Staff at York Central Hospital and was directly involved in the 2003 SARS outbreak. I have held academic appointments at three Ontario universities - Toronto, Waterloo and Queen's. I gave testimony at three Royal Commissions on public health issues - the Krever Commission on blood safety, the O'Connor Commission on Walkerton and the Campbell Commission on SARS. I have contributed to 28 peer reviewed published papers.

4. My curriculum vitae is attached hereto and marked as **Exhibit "A".**

5. The Moving Parties' counsel contacted me about providing expert testimony in support of their motion to set aside the enforcement order against them. I have been asked to address the following issues surrounding the virus SARS-CoV-2 and Covid-19 disease:

    a. **Data analysis** -- How serious is Covid-19? How does it compare to previous pandemics? What does the data tell us about who this disease is impacting? Can you put this into context so we can understand the severity of Covid across various demographics and relative to other causes and numbers of deaths?

    b. **Public health & policy** -- Do current public health responses reflect the data and analysis noted in your answer to question 1? What should public health be concerned with? Have our "lockdown" measures been in keeping with previous public health practices, standards and plans for

pandemic management? Are population-wide lockdowns an appropriate public health response? If not, why not?

c. **Lockdown harms** -- Has an appropriate cost/benefit analysis been done by the government? Do lockdowns work in preventing unnecessary mortality? What are the unintended or ignored secondary consequences and harms? What are the public health concerns with curtailing the activities of healthy people or those with limited risk?

d. **Limits on gatherings** -- Should Ontarians be allowed to attend religious services, gather with their families and friends, go to restaurants or small businesses, and peacefully protest? What is the data on outbreaks in these settings? Do we know whether this translates into hospitalizations and/or deaths? Is a limit of 10-persons based on any scientific and evidentiary foundation? Is it appropriate, from a public health perspective, for governments to make all decisions on risk assessment or tolerance on behalf of individual citizens?

6. I acknowledge that in preparing this report and providing expert evidence, the Moving Parties' counsel explained that my role is to assist the court to determine the matters in issue. I further acknowledge that it is my duty to provide evidence that is fair, objective and non-partisan and to opine only on matters that are within my area of expertise. This duty prevails over any obligation that I may owe to any party on whose behalf I am engaged.

7. Covid-19 is a novel respiratory virus that has caused a global outbreak over the past 16 months. Public health has been preoccupied by its response to Covid-19. The issues around Covid-19 are complex and much of the science is uncertain. Ontario has responded to Covid-19 with a variety of restrictive measures generally characterized as "lockdown". Many of these measures have been arbitrary and capricious. I will focus on the specific issue of restricting the size of religious gatherings.

8. “Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.”[1] A wholistic view of health has long been a cornerstone of public health practice. For the past year public health in Ontario has obsessed with controlling just one disease to the detriment of all other diseases and other aspects and determinants of health. The ability to practice religion in a time-honoured fashion is important to the mental and social well-being of many people. Not allowing some people to practice their religion in person is bad for their health.

9. “First do no harm.”[2] Many lockdown measures, including restrictions on normal religious practices, cause substantial harm. When a medical intervention can cause harm there is an onus to show strong evidence that the intervention is both necessary and is effective. Furthermore, there is a responsibility to take all reasonable measures to mitigate the harms from the intervention. There is no strong evidence that limiting the size of religious gatherings is necessary and effective to control Covid-19. Ontario public health has rigidly applied the same rules to all public gatherings regardless of the relative harms.

10. The measures broadly described as lockdown were mostly invoked in a period of panic in March 2020. Covid-19 was suddenly and unexpectedly causing large outbreaks in Western Europe and, in Italy at least, threatened the integrity of health care. Spurious mathematical models posited a microbiological apocalypse with tens of millions of deaths in a matter of a few months. China first and then Italy locked down. And then, in a matter of days, so did we. We did this without any substantial scientific foundation, and we did it without any clear idea of our goals and objectives other than a vague notion of “flattening the curve”.

11. Public health has relied heavily on mathematical models in its Covid response. These models are inherently simplistic and are dependent on unreliable inputs.[3] The most contentious input into the models was (and is) the estimate of the Infection Fatality Rate (IFR). The models that drove our response in Covid-19 used IFR estimates of about 1% (one in one hundred). Analysis based on

seroprevalence studies shows that the actual IFR was much lower at 0.23% or less.[4] Perceptions, however, remained anchored at a much higher rate. For example, Dr. David Fisman, a prominent Canadian modeller, in his testimony to the Health Committee of the House of Commons on May 20, 2020, a transcript of which is attached hereto and marked as **Exhibit "B"** to this Affidavit, used an IFR estimate of 1.2% to project 280,000 deaths from Covid-19 in Canada. In my opinion, a more reasonable estimate of IFR in Canada at that time was at least four times lower and since two-thirds of our deaths occurred in Long Term Care the IFR for people living in the general community was much lower again - probably in the range of 0.1-0.2% (one death in a thousand to one in five hundred people infected. Immunization of vulnerable people has probably pushed Canada's IFR well below 0.1%.

12. A mathematical model is only a hypothesis. To qualify as a scientific hypothesis, an hypothesis must make testable predictions. To be relied upon for public policy, a model must demonstrate that it can make accurate predictions.

13. The models used for Covid-19 do not make testable predictions. They produce a range of values that is so broad they cannot be disproven. This is not scientific.

14. Typically, public health has been directed by the worst-case predictions of the models. These worst-case predictions are consistently wrong and often wildly wrong. This is true not only for Ontario but also for jurisdictions such as Sweden, Brazil and Florida that have used much less restrictive measures. Mathematical models for other infectious diseases have a track record of wildly wrong predictions - SARS, H5N1 (bird flu) and H1N1 influenza are examples. Models that have not proven themselves reliable should not determine public health policy.

15. These lockdown measures had never been employed before on this scale and duration, anywhere, ever. They were not envisioned by our plans for pandemic influenza that our governments and public health had spent years developing. Pandemic influenza plans should have been the template for our response to Covid-19 because Covid-19 is very similar in its disease dynamics to a severe

influenza pandemic. Instead, these carefully crafted plans were abandoned in the blink of an eye.

16. Canada's plan for pandemic influenza embraces two overarching principles. First, to minimize the impact of death and illness, not just death and illness from the pandemic infection. Second, to minimize the disruption of normal life.[5] Attached hereto and marked as **Exhibit "C"** to this Affidavit is a copy of the Canadian Influenza Pandemic Preparedness: Planning Guidance for the Health Sector report, dated August 2018.

17. Ontario specifically endorsed these principles in the Ontario Plan for an Influenza Pandemic, March 2013 (p. 10).[6] The 4th chapter of the plan, pertaining to Public Health Measures, is attached hereto and marked as **Exhibit "D"** to this Affidavit.

18. Ontario's response to Covid-19 abandoned both of these principles. The focus has been almost exclusively on the pandemic infection Covid-19, virtually ignoring all other causes of illness, disability and death. The disruption of society has been profound and, unlike with pandemic influenza where any disruptions were expected to last a few weeks, with Covid-19 these disruptions have lasted interminably - now well over a year and with no end in sight.

19. The World Health Organization identified several potential interventions that were "not recommended in any circumstance", including contact tracing, quarantine, entry and exit screening and border closure.[7] Notwithstanding the parallels between the Covid-19 pandemic and an influenza pandemic, and the lack of any new evidence, Canada and Ontario adopted precisely these measures in their panicked reaction.

20. Lockdown measures were not based on strong science. Nor has there been any serious effort by governments to the evaluate the effectiveness of the different components of lockdown. Worst of all, we entered into lockdown without any clear goals and objectives. As a result, lockdown in various forms has continued for more than a year causing great harm[8] and dubious benefit.[9,10]

21. The harms from lockdowns are real and substantial - harms to education, to employment, to business, to arts and culture, to social interactions and to quality of life.

22. A recent report from Statistics Canada[11] confirms that the period of lockdown corresponds to a substantial increase in non-Covid deaths. While the number of these deaths is only about 15% of the number of Covid deaths during the same period, the non-Covid deaths are predominantly in younger people suggesting that the impact on years of life lost, a valid and important epidemiological measure, may be similar to deaths caused by Covid. Furthermore, we can expect the mortality impact of lockdown to stretch on for many years to come. Lockdown has scarred a generation.

23. Covid-19 has proven to be a serious public health problem. There have already been close to three million reported deaths worldwide and it is likely that more than a one billion people have already been infected - perhaps closer to two billion. However, to understand the public health significance of these numbers they need to be put in some context. Since about 60 million people die every year,[12] three million deaths represents about 3% (one in thirty) of global deaths over 17 months. Covid-19 deaths have been disproportionately among the frail elderly, particularly among the institutionalized frail elderly. Therefore the impact on premature mortality - potential years of life lost - has been substantially less than 3%. For comparison, almost two million people - overwhelming children - will die this year and every year from diarrheal illness[13] making a much greater impact on premature mortality, this year and every year, than Covid-19.

24. Canada has had about 25,000 deaths attributed to Covid-19. About 300,000 people die every year in Canada from all causes - on average about 800 deaths every day. Deaths from Covid-19 represent about 7% (one in fifteen) of all deaths in Canada during this period and, because of the high average age and frailty of people dying from Covid-19, the impact on premature mortality is almost certainly less than this. Furthermore, since two-thirds of deaths from Covid-19 in Canada

have been in LTC residents, there have been about 7,000 deaths in people living in the community spread over two waves of the disease, i.e., about 3,500 Covid-19 community deaths per wave. This is comparable to the number of deaths we would expect in a typical annual wave of seasonal influenza. This means that, while Covid-19 is a significant public health problem, the risk it poses to the vast majority of Canadians is not out of keeping with other more familiar problems, such as influenza. Outside of LTC, for every person who had died from Covid-19 in Canada, about 40 people have died from something else.

25. Tobacco addiction accounts for an estimated 40,000 preventable deaths every year in Canada - about twice the number of deaths we have seen from Covid-19. Taking into account the relatively younger average age of people who die from the effects of tobacco, the impact of tobacco addiction on premature mortality is likely four to eight times greater than Covid-19 in the past year. Tobacco addiction has had this tragic impact every year for seventy years and there is no end in sight. Tobacco addiction dwarfs Covid-19 as a threat to public health.[14,15,16]

26. A global outbreak of a novel respiratory virus is not unique. There were similar outbreaks in 1957 (H2N2 “Asian Flu”) and 1968 (H3N2 “Hong Kong Flu”). The Asian Flu is estimated to have caused between one and four million deaths globally in its first wave alone.[17] Asian Flu then returned on a seasonal basis for ten years causing many more deaths. In 1957 the global population was one-third what it is now and the proportion over 65 was about one-half current. Adjusting for population differences, an outbreak of comparable severity in 2021 would be expected to kill 6 to 24 million people in its first year. Covid-19 has not come close to this.

27. Any interaction between two people carries a risk of transmitting Covid-19. Since people must interact for us to continue living, we must balance risk of Covid transmission with the costs of intervention.

27. Large, indoor public gatherings can pose a risk of Covid transmission. Virtually all jurisdictions have taken some measures to control these sorts of gatherings.

However, there is very little real evidence beyond anecdote to support this concern. Furthermore, the specific measures to limit the spread of Covid-19 in these settings - including the size of the permitted gatherings and the rules of procedure - are highly variable between jurisdictions. There are no established, evidence-based protocols. The devil is in the details.

28. It is wrong for Ontario to limit arbitrarily the size of all religious gatherings. Instead, public health should work constructively with religious congregations to find ways to allow religious services to continue to function at an acceptable risk. Examples could include determining attendance limits based on characteristics of the venue, social distancing, screening at entrance, masks, limited singing, improved ventilation and shorter services.

29. There have been case reports of clusters of Covid-19 transmission events traced to religious gatherings reported from various jurisdictions. However, to assess the level of risk it is important to compare these instances with documented spread to the total number of attendances at religious gatherings - undoubtedly many billions globally. Covid-19 can spread in religious gatherings, but the rate appears to be negligible, based on Public Health Ontario's own data.[18] Furthermore, in many of these anecdotal reports of Covid-19 spread at religious gatherings, there was clear evidence of practices such as over-crowding, choir singing or poor ventilation that contributed to the risk.

30. To estimate the risk of contracting Covid-19 by attending a religious service in Ontario it is necessary to have an estimate of the number of people infected at religious services (numerator) and the number of people attending (denominator). I don't have access to either of these pieces of data for Ontario. However, there is some useful data from Manitoba that can advise this estimate. Specifically, in an affidavit[19] in a similar legal proceeding, a government epidemiologist was only able to identify a single Covid-19 fatality linked to a religious service over the past year. I have no direct data for the denominator but if I assume that during this period on average 10% of Manitobans attended a religious service weekly, this would

represent about six million attendances over the past year. One death in six million attendances is a very low risk, roughly the equivalent to the risk of death from driving 40 miles. Even a risk an order of magnitude higher would not, in my opinion, be sufficient to justify the inflexible restrictions on religious gatherings. For some people, a tiny risk of death or serious illness from Covid-19 (or driving their car to church) is worth facing for the benefit of attending a religious service.

31. There are many plausible explanations for the low risk of Covid-19 death from attendance at a religious gathering, based on the Manitoba experience. It is not essential to untangle these possible explanations to change public health policy. The proof of the pudding is in the eating.

32. A properly managed religious gathering in Canada would carry only a very small risk of Covid-19 transmission. Public health should reasonably allow gatherings of this type. People attending should be advised about the potential risk and people at increased risk of serious complications from Covid-19, based on age or infirmity, should be advised not to attend, although the choice should be left up to the individual. The impact of these events on Covid-19 transmission should be monitored and further measures adjusted based on evidence.

33. There have been two major developments with regard to Covid-19 in the past four months - vaccines and “variants”.

34. Safe and effective vaccines became available starting in late 2020. Ontario, quite appropriately, initially focused on immunizing Long Term Care residents and staff and then on the elderly. Although our vaccine roll-out has been slower than some other jurisdictions, we are already seeing remarkable benefits. Individuals who have been immunized are almost entirely protected from serious illness or death from Covid-19 and are much less likely to transmit the virus.

35. The “variants” represent the natural evolution of Covid-19 in response to the reproductive pressure from population immunity. The “variants” are somewhat more infectious than the original Covid-19 virus. The more infectious a virus the

less effective any lockdown measures. Furthermore, the current “variants” are almost certainly just the beginning of the changes in Covid-19. It has already shown itself capable of evolving quickly and there is no reason to expect the process to stop. On the contrary, as population immunity from infection and immunization increases globally, the reproductive pressure on the virus will increase and we can expect the process of evolution to, if anything, speed up.

36. This puts us on a very slippery slope with regard to lockdown measures. If we persist with this strategy we will need to be more and more stringent measures with less and less impact. Lockdown is a path that takes us nowhere.

37. Perhaps the greatest error public health has made in managing Covid-19 is the use of fear as a tool of public policy. This is short-sighted, cynical, and counterproductive. The great majority of Canadians - those under age sixty and healthy people to an older age - face about the same risk of dying from Covid-19 as they would from influenza.

38. The fear generated by public health messaging makes religion even more important to the health of believers. Promoting fear and then denying people their means of dealing with fear compounds the harm.

39. The science about many important aspects of Covid-19 is still uncertain. The non-pharmaceutical interventions that collectively constitute lockdown are not based on high-quality scientific evidence. Public health authorities have been required to make decisions to deal with a crisis in the context of scientific uncertainty. These decisions are of necessity based on judgement as much as science. Fair enough. However, when public health takes actions that are not based on strong science these actions need to be nuanced, flexible, balanced and constantly under review.

40. Ontario has applied a different standard for liquor stores than for other retail stores. It should use the same nuanced approach for religious services. There is no strong evidence that an arbitrary limit on the size of religious gatherings is an important element of Covid-19 control. There is no strong evidence that larger religious

based on strong science these actions need to be nuanced, flexible, balanced and constantly under review.

40. Ontario has applied a different standard for liquor stores than for other retail stores. It should use the same nuanced approach for religious services. There is no strong evidence that an arbitrary limit on the size of religious gatherings is an important element of Covid-19 control. There is no strong evidence that larger religious gatherings cannot be held at an acceptable risk, particularly with the full cooperation of the religious group. The harms from the arbitrary limits on the size of religious gatherings are obvious and substantial.

41. I make this affidavit *bona fide*.

SWORN REMOTELY by videoconference by Dr. Richard Schabas at [redacted] before me at the City of London, in the County of Middlesex, this 25th day of May, 2021 in accordance with O.Reg. 431/20 Administering Oath or Declaration Remotely

A Commissioner, etc.

LISA D.S. BILDY
BARRISTER & SOLICITOR

DR. RICHARD SCHABAS

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19. The Queen's Bench Winnipeg Centre. File No. CI 20-01-29284. Affidavit of Carla Loeppky. March 4, 2021

EXHIBIT A

This is Exhibit "A" referred to
in the Affidavit of
Dr. Richard Schabas
Sworn before me this 27th day
of May A.D., 2021
A Commissioner for Oaths in and for Ontario

LISA D.S. BILDY
BARRISTER & SOLICITOR

May 7, 2021

CURRICULUM VITAE:

RICHARD SCHABAS MD, MHSc, FRCPC

Professional Experience:

2008-2016	Antibiotic Steward Campbellford Memorial Hospital Campbellford, Ontario
2005-2016	Medical Officer of Health Hastings and Prince Edward Counties Health Unit Belleville, Ontario
2005-2016	Consultant in Internal Medicine Campbellford Memorial Hospital Campbellford, Ontario
2003-2005	Chief of Staff York Central Hospital Richmond Hill, ON
1997-2007	President Schabas Associates Inc. Health Consultants
2001-2002	Vice President, Medical Affairs GlycoDesign Inc.
2000-2001	Vice President, Corporate Development GlycoDesign Inc.
1998-2001	Head, Division of Preventive Oncology Cancer Care Ontario
1997	Director of Screening Programs Cancer Care Ontario
1987-98	Chief Medical Officer of Health and Director, Public Health Branch,

Ontario Ministry of Health

1983-87 Medical Officer of Health,
Borough of East York Health Unit,
Toronto, Ontario

1981-99 Consultant in Internal Medicine
Orthopaedic and Arthritic Hospital,
Toronto, Ontario

1983-97 Consultant in Internal Medicine
Eastwood Medical Clinic
Toronto, Ontario

1977-78 General Practitioner,
Parry Sound, Ontario

Degrees:

1983 Fellowship in the Royal College of Physicians and Surgeons of Canada in Community Medicine (now called Public Health and Preventive Medicine)

1982 Master's in Health Sciences,
University of Toronto

1982 Fellowship in the Royal College of Physicians and Surgeons of Canada in Internal Medicine

1976 Medical Doctor (with Honours)
University of Toronto

1970 General Certificate of Education (Advanced) in History, English Literature and Geography,
University of London Board,
London, England

Academic Appointments:

2007-2016 Associate Professor
Faculty of Medicine
Queen's University

1996-2009 Associate Professor,
Department of Public Health Sciences,
Faculty of Medicine,

University of Toronto

1994-2000 Adjunct Associate Professor,
Department of Health Studies and Gerontology,
University of Waterloo

1987-1996 Assistant Professor,
Department of Biostatistics and Preventive Medicine,
Faculty of Medicine,
University of Toronto

1983-1987 Lecturer,
Department of Biostatistics and Preventive Medicine,
Faculty of Medicine,
University of Toronto

Previous Appointments (Selected List):

2003-2005 Infection Control Committee
York Central Hospital (Chair)

2001-2002 Health Policy Sub-committee
BIOTECanada

1998-1999 Ontario Expert Panel on Colorectal Cancer Screening (vice Chair)

1998-1999 Expert Panel on Cancer Epidemiology in Cape Breton (Chair)
Cancer Care Nova Scotia

1998-1999 Ontario Tobacco Strategy Expert Panel

1998 Expert Panel on Hepatitis C Epidemiology (Chair)
Health Canada

1998 Multidisciplinary Assessment Committee for New Opportunities
Canadian Foundation for Innovation

1997-1998 Steering Committee (Chair)
Canadian Consensus Conference on a National Immunization Records System
Health Canada

1987-1998	Advisory Committee on Communicable Diseases (Chair) Ontario Ministry of Health
1987-1998	Residency Committee, Community Medicine Program, Faculty of Medicine, University of Toronto
1987-1998	Federal/Provincial Advisory Committee on Occupational and Environmental Health
1993-1998	Editorial Board, "Health News", University of Toronto
1996-1997	Federal/Provincial/Territorial Implementation Team National Blood Agency
1996-1997	Board of Directors Canadian Blood Agency
1994-1997	Children At Risk Advisory Committee, Laidlaw Foundation
1996	Federal/Provincial/Territorial Working Group on Blood Governance (Co-chair)
1994-1996	Provincial (Ontario) Cancer Network
1994-1997	Advisory Committee, Centre for Health Economics and Policy Analysis, McMaster University
1994	Task Force on the Primary Prevention of Cancer (Miller Report)
1992-1994	Expert Advisory Committee National Population Health Survey
1988-1992	Federal/Provincial Advisory Committee on Community Health (Chair, 1992)
1990-1992	National Health Information Council

1990	Canadian Delegation, World Health Assembly, Geneva, Switzerland
198619-92	Public Health Committee Ontario Medical Association
1987-1991	Provincial (Ontario) Advisory Committee on AIDS
1987-1988	Expert Advisory Committee on Immunization, College of Physicians and Surgeons of Ontario
1983-1987	Health Protection and Promotion Committee, Metropolitan Toronto District Health Council
1985-1987	Emergency Services Committee, Metropolitan Toronto District Health Council
1986-1987	Working Group on AIDS Services, (Chair) Metropolitan Toronto District Health Council,
1985-1987	Executive Committee, Association of Local Official Health Agencies

Consultation Contracts for Schabas Associates Inc.(Selected List)

Biochem Pharma: Adviser on influenza vaccine issues

Cameco Corporation: Adviser on epidemiology

Canadian Blood Agency: Observer, GAT Task Force, June 25, 1998, Washington D.C.

Canadian Cancer Society: Cancer Control in Canada: Strategic Priorities for the Next Decade

Capital Health Authority (Edmonton, Alberta): Strengthening Population Health

Health Canada:

Biotechnology Surveillance, Centre for Surveillance Coordination
Health Protection Branch Surveillance Project

Setting Priorities in Public Health

Canadian Consensus Conference on a National Immunization Records System

Expert Panel on Hepatitis C Epidemiology

Expert Opinion of Canadian Red Cross Society Frozen Blood Samples

Laboratory Centre for Disease Control Business Plan Development (with HDP Consultants)

Evaluation of the Canadian Health Network

Surveillance Transition: Principles of Data Collection

Ontario Ministry of Health:

Ministerial adviser on blood issues

Primary Care Reform

Aventis Pasteur Ltd: Advisor on vaccine issues

Hospital Appointments:

2005-	Campbellford Memorial Hospital Campbellford, Ontario
2002-2005	York Central Hospital Richmond Hill, Ontario
1981-1999	Orthopaedic and Arthritic Hospital, Toronto, Ontario
1983-1987	Toronto East General and Orthopaedic Hospital, Toronto, Ontario
1977-1978	Parry Sound District General Hospital, Parry Sound, Ontario
1977-1978	St. Joseph's Hospital, Parry Sound, Ontario

Professional Training:

1981-1983	Senior Resident in Community Medicine, University of Toronto
1980-1981	Senior Resident in Internal Medicine, Wellesley Hospital, Toronto, Ontario
1979-1980	Junior Resident in Internal Medicine, Toronto General Hospital, Toronto, Ontario
1978-1979	Junior Resident in Internal Medicine, Women's College Hospital, Toronto, Ontario
1976-1977	Rotating Intern, St. Joseph's Hospital, Toronto, Ontario

Scientific Publications:

I. Peer Reviewed Journals:

Schabas, Fisman and Schabas,*Control of Clostridium difficile-associated diarrhea by antibiotic stewardship in a small community hospital*. Canadian Journal of Infectious Diseases and Medical Microbiology. 2012;23(2):82-83.

Schabas, *Is the Quarantine Act relevant*? CMAJ 2007; 176: 1840 - 1842

Schabas, *Severe acute respiratory syndrome: Did quarantine help?* Canadian Journal of Infectious Diseases and Medical Microbiology July/August 2004, Volume 15, Number 4

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Schabas, *SARS: prudence, not panic.* CMAJ 2003 168: 1432-1434

Schabas, *Colorectal Screening - Time to Act.* CMAJ 2003 168: 178-179

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Schabas *"Promoting Heart Health Promotion."* Canadian Journal of Public Health 87(Supplement 2) November/December 1996

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II. Other Journals:

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Schabas, *"Don't Chase Phantom Flu."* Globe and Mail, 2006

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Heinmann, Mikel, Naus, Goel, Tischler, Carlson, Schabas, Pasut, Borczyk, Krishnan, *"Meningococcal Disease in Ontario During the Winter of 1988-1989."* Canadian Diseases Weekly Report, 1989

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Barretto, Chung-James, and Schabas, *"An outbreak of Rubella in a Toronto High School."* Ontario Diseases Surveillance Report, 1983

Public Reports as Chief Medical Officer of Health:

1996: Tobacco - sounding the alarm
increasing smoking rates in Ontario teenagers, attributable to tax cuts and cigarette promotion are a public health crisis - this report recommends wide-ranging action to curtail this problem

1995: Immunization - the next steps
a review of the successes in immunization and a strategic plan for expansion of Ontario's immunization program, with a second dose measles catchup, a hepatitis B high school catchup and introduction of a pneumococcal program

1994: Opportunities for Health - progress against cancer

a description of the epidemiology and etiologies of cancer - a discussion of strategies for cancer control - a strong emphasis for promotion of non-smoking and healthy eating as our best means of controlling cancer - over 100,000 copies distributed

1993: Opportunities for Health - promoting heart health
a description of the underlying determinants of ischemic heart disease - smoking, blood cholesterol, blood pressure, body weight and physical activity - their distribution in Ontario and strategies for promoting heart health - over 100,000 copies distributed

1992: Opportunities for Health - a report on youth
an analysis of the main health challenges facing year old in Ontario with wide-ranging policy recommendations in areas of tobacco control, alcohol abuse, fitness, nutrition, pregnancy planning, control of sexually transmitted diseases, motor vehicle crashes and mental health promotion

1991: Tobacco and Your Health
a descriptive review of the patterns of tobacco use in Ontario and their health impacts over 200,000 copies distributed

Research:

1996- Co-Investigator (Rena Mendelson, Principal Investigator)
Ontario Nutrition Survey
Health Canada Grant (Project #E311212)

1994- Principal Investigator (with Prof. R. Cameron, Prof. Susan Elliot, and Prof.M. Taylor)
Canadian Heart Health Initiative - Ontario Project
National Health Research and Development Program Grant
1991-93 Principal Investigator
Ontario Heart Health Survey
National Health Research and Development Program Grant

1985-87 Principal Investigator (with Dr. John Frank)
A study to test of efficacy of the Schick test and tetanus ELISA antibody in determining primary immunization

Awards:

2006 Smoke Free Champion Award
Association of Local Official Health Agencies/Ontario

Public Health Association

1997 Amethyst Award for outstanding achievement in the Ontario public service

1997 *Salute to the City* Award
Presented to honour the 20th Anniversary of the Toronto Eaton Centre

1990 Distinguished Service Award
Association of Local Official Health Agencies

1981 Milton H. Brown Award
Department of Biostatistics and Epidemiology,
Faculty of Medicine,
University of Toronto

Public Presentations (Selected List):

2010 SARS, H5N1 and H1N1 – three panic-demics
Curso Internacional de Medicina Interna de America del Norte
Mexico City, Mexico

2009 H1N1 – What lies Ahead
Ontario Agency for Health Protection and Promotion
Toronto

SARS – The Real Story
Internal Medicine Interest Group
Faculty of Medicine
Queen's University
Kingston Ontario
SARS – Did Quarantine Work?
American Association for the Advancement of Science
Washington DC

2007 Confessions of a Public Health Doctor
Public Health Interest Group
Faculty of Medicine
Queen's University
Kingston Ontario

Does Vitamin D Prevent Cancer?
Department of Public Health Sciences
University of Toronto

SARS, the Precautionary Principle and Public Health
Centre de recherche en droit public
Université de Montréal

2006 Pandemic Planning in Perspective
Continuing Professional Development
Queen's University
Kingston, Ontario

Flu Fraud
Pandemics and the Media
Department of Public Health Sciences
University of Toronto

Prudent Pandemic Planning
Plenary Panel on Pandemic Planning
National Healthcare Leadership Conference
Victoria, British Columbia

2004 Toronto SARS Outbreak
National University of Ireland
Galway, Ireland

My Biotech Career – a cautionary tale
Dublin Molecular Medicine Centre
Dublin Ireland

Lessons from SARS
Department of Public Health Sciences
University of Toronto

2003 Lessons from SARS
Ontario SARS Commission
Toronto

Lessons from SARS
SARS Symposium
University of Toronto

SARS Lessons from the Toronto Outbreak
International Science Symposium on SARS
Beijing, China

Why Public Health in Canada Fails
University of Toronto Alumni Lecture
Canadian Public Health Association Annual Meeting
Calgary, Alberta

The Future of Public Health in Canada
Canadian Institutes for Health Research Symposium
Calgary Alberta

Colorectal Cancer Screening
Medical Rounds
York Central Hospital

Opportunities for Cancer Prevention
Department of Health Studies and Gerontology
University of Waterloo
Waterloo, Ontario

2002 Controversies in Cancer Screening
Annual Clinic Day
Toronto East General Hospital

Politics of Colorectal Cancer Screening
McGill Conference on GI Cancers
Montreal, Quebec

Colorectal Cancer Screening
Cape Breton Cancer Symposium
Sydney Nova Scotia

Feasibility of Eradication of *H.pylori* to Prevent Stomach Cancer
Cancer Care Ontario Workshop, Toronto
Progress Towards a National Immunization Registry

National Immunization Conference
Victoria, British Columbia

2001 Cancer Prevention
Helping Hands Conference
North Bay, Ontario

Colorectal Cancer Screening
Canadian Digestive Diseases Week
Banff, Alberta

2000 Updates in Oncology - Screening
Royal Victoria Hospital
Barrie, Ontario

1999 "Colorectal Cancer Screening - What's ahead for Ontario?"
Focus on the Future Conference
Thunder Bay, Ontario

Colorectal Cancer Screening
Fabian Curry Memorial Clinic Day
Minet, Ontario

"Politics, the Environment and Cancer in Cape Breton."
Joint Preventive Oncology Seminar
Toronto

"Colorectal Cancer Screening - What's ahead for Ontario?"
Annual Preventive Oncology Seminar
Cancer Care Ontario
Toronto

"Preventive Oncology at Cancer Care Ontario."
Ontario Hospital Association
Toronto

1998 "Colorectal Cancer Screening - What's ahead for Ontario?"
Annual General Meeting
Ontario Association of Gastroenterology
Toronto

"Colorectal Cancer Screening - What's ahead for Ontario?"

Colorectal Cancer Symposium
Ottawa Regional Cancer Centre and University of Ottawa
Ottawa, Ontario

Labelle Lecture (Responder)
McMaster University
Hamilton, Ontario

"The Evolving Role of the Community Medicine Specialist" (panel chair)
Annual Meeting
Royal College of Physicians and Surgeons of Canada
Toronto

"Adolescent and Adult Pertussis" (afternoon chair)
Canadian Public Health Association
Toronto

1997 "The State of Public Health in Ontario" (keynote speaker)
Ontario Public Health Association Annual Conference
Kingston, Ontario

"Public Health and the Health of Population"
University of Waterloo

"Public Health and Who Does What"
Annual Meeting
Association of Local Public Health Agencies
Hamilton, Ontario

"What Ahead for Public Health"
Spring Exchange
Ontario Society of Nutrition Professionals in Public Health
Kempenfelt Bay, Ontario

"Genetic Screening and Public Policy"
Association of Genetic Colleagues of Ontario
Mississauga, Ontario

"Promoting Heart Health" (keynote speech)
Peel Heart Health Network,Mississauga, Ontario
"Public Health and Environmental Health"
Seminar, Diploma Program in Environmental Health
McMaster University

"Public Health in the Age of Krever"
2nd National Conference on Communicable Disease Control
Canadian Public Health Association
Toronto

"Ministry of Health and the Blood System"
Update on Transfusion Medicine
Michener Institute and the Canadian Red Cross Society
Toronto

"Immunization Update"
Saturday at the University Series
University of Toronto

Keynote Address
Tobacco Control Enforcement Conference
Toronto

"Community Health Research and Public Health Policy"
Panel presentation
Community Health Research Day
University of Toronto

1996 "Barriers to Implementation and Achievement of National Goals"
(plenary presentation) and
"An Anti/Anti Immunization Panel" (breakout session)
Canadian National Immunization Conference
Health Canada
Toronto, Ontario

"Program Evaluation in Public Health (panel presentation)
Association of Public Health Epidemiologists in Ontario Workshop
Toronto, Ontario

"Tobacco - sounding the Alarm" (keynote presentation) and
"Public Health Reform" (concurrent session) and
"Community Action and Public Health in Ontario" (panel presentation)
Ontario Public Health Association Annual Conference
Toronto, Ontario

"Priorities for Tobacco Control in Ontario" (panel presentation)
Preventive Oncology Seminar
Ontario Cancer Treatment and Research Foundation
Toronto, Ontario

"Restructuring Public Health"
Association of Local Official Health Agencies Annual Conference
Gananoque, Ontario

"Cancer Control and Public Health"
Future Directions in Cancer Control
University of Toronto

"Public Health and Confidentiality"
Health Information and Privacy
Canadian Institute of Law and Medicine
Toronto, Ontario

1995 "Immunization - the next steps" (keynote presentation) and "Future Directions in Public Health" (panel presentation),
Ontario Public Health Association Annual Conference
London, Ontario

"Promoting Heart Health Promotion"
Canadian Conference on Dissemination Research
University of British Columbia

2nd International Heart Health Conference
Barcelona, Spain
presented three papers and one poster about the Canadian Heart Health Initiative - Ontario Project

1994 "Implementing New Vaccine Programs"
National Conference on Immunization in the 90's
Health Canada

1992 "What is Safer Sex"
Annual Conference
Canadian Public Health Association
"Understanding Population Health"
Annual Conference

Ontario Public Health Association

1989 "New Directions for Public Health in Ontario"
Annual Conference
Canadian Public Health Association

1987 "High Risk versus Population Strategies - a debate"
Annual Conference
Ontario Public Health Association

1986 "Planning for Change in Public Health"
Annual Conference
Ontario Public Health Association

Educational Activities (University of Toronto):

Supervision of Community Medicine Residents: Joel DeKoven, Robert Gin, Medhat Gindi, Paul Gully, Robert Kyle, Verna Mai, Paul Martiquet, Cordell Neudorf, Lynn Noseworthy, Howard Njoo, Sandor Demeter, Elizabeth Richardson, Eric Young, Shelley Deeks, Troy Herrick, Donna Reynolds, David Buckeridge, Matthew Hodge, Christine Kennedy

Supervision of MHSc Students: Jane Colonna, Walter Ewing, Bromwyn Mears, Anthony Shardt, Catherine Whiting, Luba Wolchuk, Barbara Stolz, Jennifer Bridge, Paul Alexander

Course Lectures: Canada's Health Care System, Health Administration, Health Politics

Course Seminars: Cancer Epidemiology

Educational Activities (other)

1996 "Public Health and Environmental Health" (seminar)
Diploma Program in Environmental Health
McMaster University

Memberships:

Canadian Medical Association
Canadian Medical Protective Association
College of Physicians and Surgeons of Ontario
Ontario Medical Association

Medical Staff Association, York Central Hospital
Royal College of Physicians and Surgeons of Canada

EXHIBIT B

This is Exhibit " B " referred to
in the Affidavit of
Dr. Richard Schabas

Sworn before me this 29th day
of May A.D., 2021

A Commissioner for Oaths in and for Ontario

LISA D.S. BILDY
BARRISTER & SOLICITOR

HOUSE OF COMMONS
CHAMBRE DES COMMUNES
CANADA

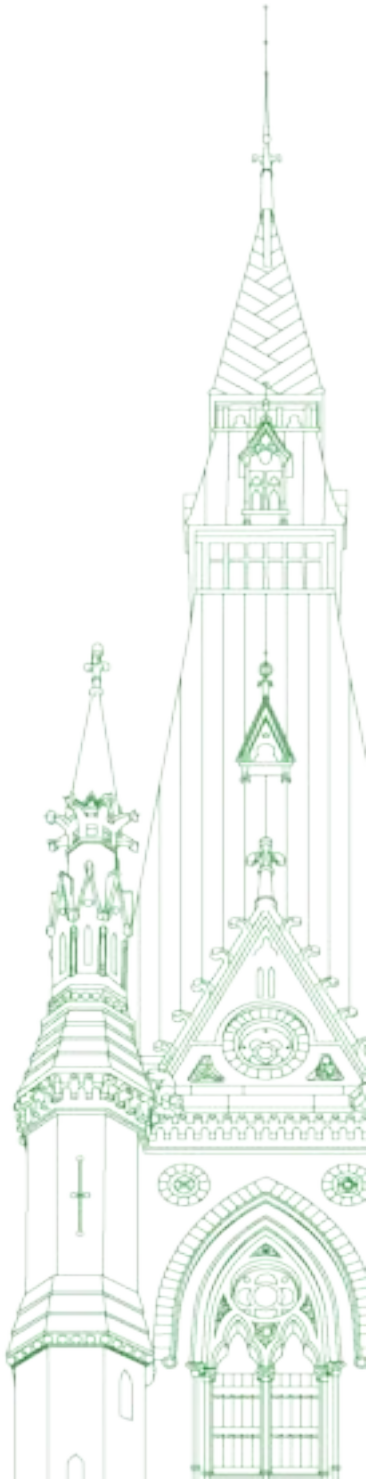
43rd PARLIAMENT, 1st SESSION

Standing Committee on Health

EVIDENCE

NUMBER 022

Wednesday, May 20, 2020



Chair: Mr. Ron McKinnon

Standing Committee on Health

Wednesday, May 20, 2020

● (1615)

[*English*]

The Chair (Mr. Ron McKinnon (Coquitlam—Port Coquitlam, Lib.)): I now call this meeting to order.

I'd like to welcome everyone to meeting number 22 of the House of Commons Standing Committee on Health. Pursuant to the orders of reference of April 11 and April 20, 2020, the committee is meeting for the purpose of receiving evidence concerning matters related to the government's response to the COVID-19 pandemic.

In order to facilitate the work of our interpreters and ensure an orderly meeting, I would like to outline a few rules to follow.

First, interpretation in this video conference will work very much like in a regular committee meeting. You have the choice at the bottom of your screen of floor, English or French. Please speak slowly and clearly and hold your microphone in front of your mouth.

If you will be speaking in both official languages, please ensure that the interpretation is listed as the language you will speak in before you start. For example, if you're going to speak in English, please switch to the English feed and then speak. This allows for better sound quality for interpretation.

Before speaking, please wait until I recognize you by name. For witnesses, the questioner will basically identify who they would like to respond to the questions. When you're ready to speak, click on the microphone icon to activate your mike. Should members need to request the floor outside of their designated time for questions, they should activate their mike and state that they have a point of order.

As a reminder, all comments by members and witnesses should be addressed through the chair. Should any technical challenges arise, please advise the chair or the clerk immediately and the technical team will work to resolve them. It may be necessary to suspend the meeting in such cases in order to sort things out.

Before we get started, could everyone check on the upper right-hand corner of their screen if they're using a personal computer. In the top right-hand corner there's a choice between speaker view and gallery view. Gallery view will ensure that all video participants can see each other.

I'd now like to welcome our witnesses. Each witness will have 10 minutes for an opening statement, followed by the usual rounds of questions from members. First, as an individual, we have Dr. Amir Attaran, professor, faculty of law, University of Ottawa. As an individual, we have Dr. David Fisman, professor of epidemiology, University of Toronto; and as an individual, Dr. Richard Schabas, former chief medical officer of health for Ontario. From BlueDot we have Dr. Kamran Khan, chief executive officer and founder; and from Dynacare we have Vito Ciciretto, president and chief executive officer.

Welcome everyone. Thank you for joining us today.

We will begin with Dr. Attaran. Welcome back. You have 10 minutes. Please go ahead.

Professor Amir Attaran (Professor, Faculty of Law, University of Ottawa, As an Individual): Thank you.

Good afternoon, ladies and gentlemen. Thank you for having me back at the health committee. I hope you've been well.

Mr. Tony Van Bynen (Newmarket—Aurora, Lib.): Mr. Chair, I'm sorry. The interpretation is overriding the English language.

The Chair: Dr. Attaran, are you on the appropriate translation channel? You should be on the channel for the language you're speaking.

Prof. Amir Attaran: I'm sorry, I forgot that. Let's start over.

The Chair: Thank you.

Prof. Amir Attaran: Good afternoon, ladies and gentlemen.

Thank you for having me back at the health committee. I hope you've been well and that your families have been keeping safe.

When we last met, Canada was in a full lockdown, and I strove to explain how we might get out of it. I offered a road map for exiting the lockdown gradually. That road map remains valid. First, a nationwide lockdown to bring disease transmission to virtually nil, and simultaneously a massive push to increase testing and contact tracing by a factor of ten or more, followed by a sequence of gradual reopenings and infection wavelets that are well calibrated by disease forecasts and monitored by testing to minimize deaths. No competent expert disagrees with this basic strategy.

I said that following this road map would be long and difficult, and I reassured you that there is light at the end of the tunnel. Sadly, some weeks on, today I am here to tell you that the light seems dimmer than I imagined, not for scientific reasons, but for political reasons, which you can fix.

As you know, countries like Australia, Denmark, New Zealand and Norway are executing successful reopenings. Meanwhile, Canada is flying somewhat blind because provincial and federal governments have still not solved their massive failure to co-operate in sharing and analyzing epidemiological data. Without data and analysis, many experts think reopening is arriving too early in some places like Toronto, which will kill people needlessly, and arriving too late in others, like Kingston or the Maritimes, after crippling the economy and ballooning the deficit. This isn't good.

My goal today is to offer a frank reality check, franker than Dr. Tam and Dr. Nemer delivered. I was saddened and frustrated that yesterday many of you asked excellent questions, but got evasive and, at times, mealy-mouthed answers. Please feel free to ask me those same questions. If I can help, I promise I will.

First, let's start with some data and the big question. Is Canada really bending the curve? The answer is sort of.

Many Canadians think we have done well because we are better than the United States, a country that has no public health care, vocal COVID-19 deniers and a president who recommends injecting bleach. The Americans are obviously not the right comparison for us. It's better to compare Canada with other wealthy countries, especially confederations, because they have federal-provincial complications like our own.

Please turn to the line graph I've provided to the committee. It's one of two graphs that were provided.

This graph shows confirmed COVID-19 cases, adjusted for population, starting on the day that a country exceeded the threshold of one case per million population. Canada was the last country to face COVID-19. That's luck, and it gave us extra time to prepare and the benefit of learning from others who went before us. With those advantages we achieved a lower infection peak. However, we come to the question of bending the curve down, we're doing poorly. Instead of the successful nosedive the graph shows for France, Germany, Spain or Switzerland, which they achieved despite a faster and higher peak than ours, our curve looks more like an undulating plateau that gradually drops off like a bunny ski hill. By May 18, our daily confirmed cases were tied with those on April 4. Between those dates are weeks of squandered time, lives and money, the latter being around $12 billion a week to the macro economy.

● (1620)

I find the comparison with Australia the most interesting. It proves that Canada could have done better. It is a large confederation of states, much like our own provinces, and it crossed the threshold of one case per million just one day before we did. In other words, we started off tied, but instead of dithering, Australia smacked down its curve hard and fast. Its results are almost as impressive as South Korea’s, which many reckon to be the world’s most successful country. Now Australia is opening thoroughly, and we are not, so the costs of this failure are just massive. The next time you hear the Prime Minister and Dr. Tam say that Canada is bending the curve, be skeptical. Be much more skeptical than you have been.

Let’s now talk about testing. You heard from nearly everyone that Canada is doing a poor job and that without more and faster testing it is impossible to reopen without unnecessarily risking and losing Canadian lives. The scientific goal is not simply testing the sick, but over-testing the vulnerable and anyone else who might have come been contact with the sick so as to isolate them for 14 days and nip outbreaks in the bud, yet Canada’s testing remains awful, especially in Ontario and Quebec.

The bar graph I furnished to the committee shows over-testing as the ratio of total COVID-19 tests per positive test. The higher that ratio, the better the chance of spotting infections and avoiding outbreaks. If one chooses not to worry about the price of testing—and one shouldn’t, because testing costs peanuts compared to hospitalizations or lockdowns—then it is far better to test too much than too little.

On this measure of testing, Canada lags behind not just top performers like Australia and South Korea, but also behind Ethiopia, Rwanda, Kenya, Cuba and Ghana. We are such testing tightwads that low-income countries in Africa surpass us. Africans also outclass Canada on contact tracing. Addis Ababa’s extensive testing and contact tracing puts Montreal and Toronto to shame.

For Canada to be beaten by the world's poorest countries has got to puncture the myth of competence and success. It cannot be that Canada lacks Africa's scientists, laboratories, equipment or chemicals, any of that. No. The reason we have failed is the cupidity and stupidity of certain governments, and this is where I put my constitutional lawyer hat on to talk about federalism. American lawyers have a great saying. They say that the Constitution is not a suicide pact, but I'm afraid, ladies and gentlemen, that during a killer pandemic our usually accepted federal-provincial relations can turn into a suicide pact.

I believe that our most fundamental failing right now is that pandemic responses are handicapped by a mythological, schismatic view of federalism. Thus, when provinces withhold epidemiological data or do a poor job of testing, collectively we grumble, we shrug and we mutter that health is provincial, but this is wrong. Speaking as a constitutional lawyer, health is actually a shared federal/provincial jurisdiction. The Supreme Court is dead clear about that. It says, "Health is a jurisdiction shared by both the provinces and the federal government." That's our Supreme Court, and it's perfectly accurate.

I think it is good for the federal government to let provinces run their show, and that's normally how it should work, but I'll suggest that a pandemic is not normal. There comes a point when the federal government must step in, the point where provincial actions are killing Canadians. If our country cannot show that once-in-a-century flexibility, then, yes, we are turning the Canadian Constitution into a suicide pact.

I know that what I've just said will be outrageously controversial. I'm sorry, but as a person who loves this country, I cannot let obvious mistakes pass and kill my neighbours.

● (1625)

Let me close with three recommendations.

First, Parliament must pressure cabinet into taking legal steps to force provinces to share epidemiological data. These are the data that scientists like Dr. Fisman and Dr. Khan absolutely need to keep me, you and your loved ones alive as this lockdown lifts. Parliament gave cabinet the power to demand data in section 15 of the Public Health Agency of Canada Act, but the Prime Minister has not used that power. It's frankly pathetic.

Second, demand that the Public Health Agency of Canada set minimum standards for things like testing. We cannot remain stuck behind Africa. Come on. It was only last week that the Prime Minister proposed a national testing strategy. That is much too late. We need it now.

The Chair: Dr. Attaran, you're at 11 minutes. Could you wrap up, please?

Prof. Amir Attaran: Sure.

Third, sign an accord with the provinces on co-operating throughout this pandemic. In Australia, the prime minister and the premiers signed a COVID accord on March 13, and the Vikings have killed this thing. Those Australian Vikings have put it down.

It's unbelievable that two months later, Canadian governments still have no COVID accord.

I'll close there. I hope you take these suggestions in the spirit they are intended, not to gore anyone's sacred cow, but to save the lives of the Canadians we love.

Thank you for hearing me.

● (1630)

The Chair: Thank you, Dr. Attaran.

We go now to Dr. Fisman.

Dr. Fisman, please go ahead. You have 10 minutes.

Dr. David Fisman (Professor of Epidemiology, University of Toronto, As an Individual): Honourable committee members, thank you for the privilege of appearing before you.

The last several months have offered us as a country extraordinary challenges. As an epidemiologist, internist and parent, these challenges have subsumed every part of my work life and my personal life. I haven't hugged my kids since mid-March. I have watched patients admitted to hospital with mild breathing difficulties and have seen these same patients wheeled into the intensive care unit 72 hours later. My colleagues have cared for married couples, and have had to tell the surviving spouse of the death of their partner while on clinical rounds. I've had the gratifying experience of watching our modelling work influence policy. I've also experienced the annoyance of watching epidemiological data abused, misused and distorted in support of various political, economic and social agendas.

The challenges I have faced pale next to those faced by many Canadians, those who have lost their jobs or lost their loved ones, often without the chance to hold hands or say goodbye. They pale next to the challenges faced by those who have worked at essential jobs under pressure from employers but without access to adequate personal protective equipment. We've watched extraordinary leadership from senior public health officials across the country. Here I'd like to single out the clear, compassionate messaging from Drs. Henry, Hinshaw and Tam for special praise.

We have also struggled with more limited leadership in other provinces. Here I would note in particular the failure of provincial public health officials in Ontario to act swiftly and courageously to stop the spread of COVID-19 in long-term care facilities, the failure to clearly articulate that COVID-19 was spreading in our communities in early March, and the failure to keep up with the best epidemiological evidence on important issues like transmission of disease by individuals with few or no symptoms.

So yes, we have seen many challenges, some of which we have met and some of which we have not. My group prepares forecasts for several federal and provincial colleagues each morning. We have documented a reproduction number for the epidemic in Canada of below one since around May 9, 2020. That's a hopeful sign. The reproduction number of an epidemic, the number of new cases created by an old case, is an index of epidemic growth and decline. A sustained reproduction number of below one suggests that this first wave of the COVID-19 pandemic is approaching an end in Canada.

I have been concerned by how this encouraging turn of events has been interpreted by some to mean that this wave is ending in spite of, rather than because of, the patient and selfless actions of many Canadians who've experienced hardship, isolation and deprivation in order to distance themselves from workplaces, friends and family. In Canada we have seen health care systems stretched and challenged, but we have not witnessed the tragic overflow of intensive care units as has occurred in Wuhan, Lombardy, New York and Madrid.

Make no mistake, our failure to experience these tragedies does not mean that models were wrong. Cities around the world that failed to react to approaching epidemics as promptly as Canadian cities did have experienced astounding surges in mortality—a 300% increase in deaths in New York, 75% in Stockholm, 460% in Bergamo, and a 100% increase in mortality in London. We reacted to approaching disaster in time to avert the worst of this first wave, but in our two largest cities, Montreal and Toronto, we still have several hundred individuals in intensive care units.

Now we face what I'll refer to as the “paradox of prevention”. By preventing widespread infection in the country, we've maintained susceptibility in the population, which leaves us vulnerable to future epidemic waves. This is the defining paradox of public health. Our fundamental deliverable is the non-occurrence of events. Those of us who work in the field are accustomed to having our outputs taken for granted. To note one familiar example, vaccination programs are criticized because their very success means we don't experience outbreaks. Perhaps a silver lining to this episode, moving forward, will be a greater appreciation of what public health provides us in normal times.

To go back to our successful avoidance of even greater tragedy in Canada in March and April, having achieved this important success, we need to move forward with economic revitalization. I think the presentation of our choice as economic revitalization versus prevention of disease transmission is a Hobson's choice or false dichotomy. We can't ignore our economy, but we won't have robust revitalization without strong surveillance systems and health protection measures. A frightened and grieving population will not drive a strong economy. In the United States, data assembled by JP-Morgan Chase show clearly that declines in spending are strongly linked to levels of disease activity.

● (1635)

The bedrock on which revitalization rests will be public health surveillance and laboratory testing. We can't see this epidemic without testing, and we can't fight an epidemic that we cannot see.

The virus is a slippery foe, and it's a study in contradictions. I call it Schrödinger's coronavirus. It's dangerous and it's lethal, but it causes mild illness and even infection without symptoms. It kills over 7% of the Canadians with recognized infection, but it gives most children a free pass.

Asymptomatic and presymptomatic infections are a Trojan horse that gives entry to congregate settings like long-term care and retirement homes, health care facilities, prisons and food processing plants. Once it's spreading in these institutions, it can take a terrible toll, as we have seen in long-term care facilities.

We can look around the world for successful responses to this epidemic and emulate best practices, but we can also emulate best practices here in our own country. Colleagues in Newfoundland have controlled COVID-19 rapidly; they tell us to hunt the virus and be proactive. Colleagues in British Columbia teach us how important clear strategy and communication are in this fight. Alberta can show us how to scale up testing, and our northern territories can show us how to protect isolated remote communities. Saskatchewan has shown us how to deal swiftly with growing outbreaks to prevent geographic spread of infection.

But I do believe that our most potent weapon in the fight is testing. Work by my colleague, Dr. Ashleigh Tuite, shows that without aggressive testing, control measures like contact tracing are likely to be fruitless, as we will only perform contact tracing on tested cases. If we fail to test at scale, we will miss too many additional cases for contact tracing to change the dynamics of the epidemic. It will simply be a waste of resources. If we test at scale, we can keep the epidemic in our sight and move toward economic revitalization while keeping Canadians safe.

Testing will be our eyes and ears as we move forward to open our economy, but the laboratory is a tool that needs to be used differently in different settings. We need to establish regular testing regimens for those who work in congregate settings with vulnerable individuals, especially in long-term care and in hospitals. Testing in a stable and consistent way allows us to estimate the reproduction number of the epidemic and know when we're headed back into exponential growth. We want to find all the cases we can. That's how we prevent sparks from turning into forest fires.

Hospitalizations and deaths are easy to see, but they're lagging indicators. Instituting control policies once those are surging means that we've already missed the boat. We can use non-traditional surveillance tools, too, like web-based syndromic surveillance, and even surveillance of sewage for coronavirus levels, as is already being done in other countries. Situational awareness will keep us safe as our economy comes back to life.

We can also demand more of our country. This epidemic shows us that having laboratories with 21st century diagnostic technology, but public health information systems that depend on fax machines from 1995, will hold us back. We can demand more transparency from our leaders. As action by the public is central to disease control, it's important that the public be kept in the loop and made to feel like they're on the team. Indeed, they are the team.

We need clear, transparent benchmarks across the country on testing, on turnaround times for case reporting and contact tracing and for the reproduction numbers that will be used to determine when we need to strengthen distancing and when we can loosen it. We will have more setbacks; the countries with the strongest response programs in the world have all suffered them. We will too. I'd ask you not to throw your hands up and let the virus win.

Don't let uncertainty distract you from the mission. Uncertainty is to be expected for a disease that's been in humans for 24 weeks. Don't let smug professors bully you about the absence of randomized controlled trial evidence for control of a disease that has only existed for half a year. We can acknowledge uncertainty and be humble about this disease, but always put the lives and livelihoods of Canadians at the forefront when we make our decisions.

Thank you for the opportunity to answer your questions today.

● (1640)

The Chair: Thank you, Dr. Fisman.

We go now to Dr. Schabas.

Please go ahead. You have 10 minutes.

Dr. Richard Schabas (Former Chief Medical Officer of Health for Ontario, As an Individual): Mr. Chair and members of the committee, it's a privilege to speak with you today.

I'm a retired physician. I practised medicine for 40 years in two specialties: public health and internal medicine. I worked in local public health for 15 years. I was Ontario's chief medical officer of health for 10 years. I was directly involved in the 2003 SARS outbreak as the chief of staff of York Central Hospital. I have published academic and popular articles on relevant subjects, such as SARS, quarantine and bird flu.

Canadians on the whole enjoy a wonderful standard of health, resting on the foundation of the social determinants of health: education, employment and our social fabric. Anything that threatens these foundations threatens our public health.

Canada is now faced with both a tragedy and a crisis. The tragedy is caused by COVID, a respiratory virus. It has the potential to cause the deaths of tens of thousands of Canadians, overwhelmingly old and infirm.

The crisis is caused by our attempts to control that virus. The crisis has the potential to cause severe and lasting damage to the fabric of our country's economy, education, social and cultural institutions, and mental health that will have repercussions for our public health for decades.

The tragedy is a natural disaster that saddens me and saddens us all. The crisis is a self-inflicted wound that frankly terrifies me. It offends social justice, because the burden of the crisis falls disproportionately on children, young families and blue-collar workers. The more we focus exclusively on COVID, the greater the danger to our public health.

The best analogy to the COVID outbreak is the H2N2 Asian flu pandemic that swept around the world in the fall of 1957. Asian flu caused more disease and a much higher death rate, especially in younger people, than COVID. Asian flu killed between one million and two million people in a matter of a few months in a world population one-third the size of today's. That's the equivalent of three million to six million deaths today, many more than from COVID. Asian flu was a tragedy, but it wasn't a crisis, because 60 years ago people responded differently. Some modest control measures were taken, but they were very temporary. The world moved on.

Perspective isn't very popular with COVID, but I think it's important. We get spooked by COVID deaths because every day we see the numbers for COVID, but not for anything else. Death is a common phenomenon in our world. Almost 300,000 Canadians will die this year, like every year, from cancer, heart disease, stroke, motor vehicle crashes, suicide and a myriad of other causes. Since mid-March, for every Canadian outside long-term care who has died of COVID, 50 Canadians have died of something else.

We have frightened people. Predictably, the media has led the way. But public health has also frightened people, I think, to promote better compliance with social distancing. This was wrong for two reasons: first, it's cynical; and second, it now will make it that much harder to step down.

My wife and I live in Toronto. When we walk our dog, we see two kinds of people— those like us who have done the math and aren't really frightened by COVID, and those who think walking the streets is dangerous. But there's a third group, the people in our building whom we haven't seen for two months who are too terrified to even go outside. Getting them to re-enter the world will be a tremendous challenge.

The only reliable defence against a respiratory virus is immunity. You can get immunity from being infected or you can get it from a vaccine. A safe and effective vaccine would be wonderful, but it would be foolish to build public policy around expectations of a vaccine any time soon. Any strategy that doesn't take us towards immunity ultimately leads us nowhere. So long as the disease is circulating elsewhere, it's coming back here too. Provincial or national elimination is a false promise.

● (1645)

Population immunity leading to herd immunity is a natural phenomenon not an intervention, not an experiment. Herd immunity is what has controlled every other respiratory virus. We will get there sooner or later with COVID. The policy challenge is to mitigate the worst effects of the disease while protecting the real determinants of our health: education, employment and our social fabric.

We have better information about COVID than we did two months ago. We know that COVID is very serious, certainly much more serious than I, for one, expected. However, it's also not the apocalypse that some of the models had predicted, not even remotely close. The comparison should be with 1957, not 1918.

We know that our health care system can cope. A combination of expanded capacity, better treatment strategies, and triage mean that the apparent capacity crisis in Italy has not been repeated here or really anywhere else. We know that the great majority of people in Canada are at very little personal risk of death from COVID. For virtually everyone under the age of 60 and for people without serious comorbidities to a much older age, the risk of death from COVID infection is not materially different from the risk of dying from influenza. We are two populations: the frail elderly for whom COVID is a deadly disease and the great majority for whom it is not.

Canada's experience in the last two months has been problematic. We seem to have been reasonably effective at reducing infection in the community, but we have not been effective in protecting the institutionalized, frail elderly because of a massive failure of infection control in some facilities. As a consequence, we have had many deaths, but we have relatively little population immunity.

The COVID outbreak in the northern hemisphere has been on the wane since late March—for almost two months. The policy tide worldwide is now towards reopening. Canada will be swept along.

My real concern is that the virus will return, probably in September, and that our attempts to control it with widespread testing and contact tracing will probably fail. I've worked long enough in public health to understand the limitations of contact tracing as a disease control strategy, particularly for a disease like COVID.

However, when this strategy fails, will we panic and lockdown again, this time indefinitely, or will we respond in a more measured and rational way? We have some time to prepare. If plan A is based on testing and contact tracing, we need a plan B. What should we do now?

First, we need to identify those things that are fundamentally non-negotiable. Education, which requires the reopening of schools, and employment, which requires that many people return physically to work, should be top of the list, along with access to medical and dental care.

Second, we need to be clear that we are pursuing the policy of mitigation not elimination. With mitigation, we can tolerate an increase in cases when we open up now, and again when the disease resurges in the fall. We will regard community spread as inevitable and as a step towards population immunity.

Third, we need to do serious policy work to identify those aspects of social distancing that are effective, acceptable and sustainable. Canada's latest fad is for non-medical masks, based on the thinnest of evidence. Let's think carefully before we change ourselves into a society that hides its face in public.

Fourth, we must develop better strategies to protect the vulnerable, particularly better infection control in long-term care institutions. This alone will go a long way towards reducing mortality.

Fifth, we need to change our messaging to the public to better reflect their real risk of serious illness and death so that people will be willing to come out of isolation and resume normal life.

Sixth, we need to look for ways to develop public health policy nationally. We need a national, not a federal, public health agency that engages the provinces with the federal government as equal partners.

Thank you.

● (1650)

The Chair: Thank you, Dr. Schabas.

We'll go now to Dr. Khan from BlueDot. You have 10 minutes.

Dr. Kamran Khan (Professor of Medicine and Public Health, University of Toronto, Chief Executive Officer and Founder, BlueDot): Good afternoon, ladies and gentlemen, and thank you for inviting me to be a part of this important discussion today.

First let me introduce myself and tell you a bit about my background and its relevance to today's meeting. My name is Kamran Khan, and I'm a physician trained in internal medicine, infectious diseases, and preventive medicine and public health. I practise medicine and am an epidemiologist who has been studying outbreaks and emerging infectious diseases at St. Michael's Hospital in Toronto for the past 17 years. I'm a professor of medicine and public health at the University of Toronto and am the founder and CEO of a digital health company called BlueDot.

What has motivated me to dedicate my professional life as a clinician, an academic and an entrepreneur to the field of emerging infectious diseases? Twenty years ago, I began my training in infectious diseases and public health in New York when West Nile virus arrived in the city and began its westward march across the continent. Two years later, shortly after the terrorist attacks of September 11, 2001, anthrax was weaponized and dispersed through the U.S. postal system, reminding us that deadly outbreaks can arise from deliberate acts. After returning to my home in Toronto two years later, a coronavirus known as SARS spread from mainland China to dozens of cities and countries around the world, including Toronto, where it triggered a deadly outbreak that lasted four very long months. While the world had never seen an outbreak quite like SARS before, it was clear that this wouldn't be the last time.

The world is changing in ways that are driving the emergence and spread of dangerous diseases, but it's also changing in other ways that can play to our advantage. The rise of big data, the advent of artificial intelligence and emerging digital technologies offer us the raw materials needed to literally spread knowledge around the world faster than any outbreak. This was the inspiration for BlueDot's founding six and a half years ago, to build a digital global early warning system for infectious diseases that can transform how the world prepares for and responds to tomorrow's inevitable infectious disease threats, whether they arise from Mother Nature, accidents or deliberate acts.

The early warning system we have developed at BlueDot serves three key objectives: first, to detect infectious disease threats as early as possible to buy ourselves valuable time; second, to assess their potential for global spread and impact so that we can channel our finite resources to the right place at the right moment; third, to empower a wider array of decision-makers, from government to health care to the private sector, with timely insights so that together we can mobilize highly effective, efficient and coordinated responses.

To detect threats at their earliest stages, our early warning system processes vast amounts of online data in 65 languages, searching for early signals of outbreaks involving over 150 different diseases and syndromes, 24 hours a day, 365 days a year. The surveillance engine does not rely solely on official news of outbreaks reported by government agencies, but also analyzes unofficial information generated through digital media, health blogs and other online sources.

This engine picked up an article in Chinese on the morning of December 31, 2019, reporting on an outbreak of pneumonia of an unknown cause in Wuhan, China. This event certainly captured my attention, given the number of parallels to the emergence of SARS in 2003. Within a few seconds of detecting the outbreak in Wuhan, our system analyzed the flight schedules and anonymous itineraries of hundreds of thousands of travellers departing Wuhan on commercial flights for destinations around the world. Given our early concerns about this outbreak, my team submitted results of this analysis for publication in an open access, peer-reviewed scientific journal on January 8, 2020, in order to make this data freely available for anyone to access. This analysis accurately identified many of the cities outside of mainland China that were among the first to confirm cases of COVID-19.

As cases of COVID-19 arrived in North America, our team began generating insights to support public health efforts to mitigate domestic transmission of this virus within our communities. These analyses made use of anonymous location data generated from mobile apps to understand the movements of populations—critical insights for public health officials to optimize and strategically make use of their finite human resources across the country and over time.

It's worth noting that BlueDot only makes use of third party data that is anonymized, adheres to all legal and regulatory requirements, and is aggregated up to the level of populations. These location data have been used for years in sectors from urban planning to transportation to retail, among others. Here, we're making use of them for the sole purpose of safeguarding communities and protecting lives during the midst of a pandemic.

● (1655)

At BlueDot, our diverse team, comprising physicians, veterinarians, epidemiologists, geographers, ecologists, data scientists and engineers, has been diligently working for the past six and a half years leveraging data, advanced analytics and emerging digital technologies to develop innovative solutions that are capable of generating insights to mitigate risks from infectious disease threats in our rapidly changing world. But insights are only meaningful if they are translated into action, and that translation can only happen through partnerships.

In this regard, BlueDot has a long-standing partnership with Global Affairs Canada, going back to 2014, in which we have been building and implementing digital systems to manage infectious disease risks across the Association of Southeast Asian Nations. In 2019 we began a partnership with the Public Health Agency of Canada, channelling our efforts to mitigate domestic risks from global infectious diseases. Now, as the COVID-19 pandemic evolves into new phases, we continue to work together to mitigate its impacts across the country.

I'd like to conclude by saying that Mother Nature is sending us a message. A confluence of forces in our rapidly changing world—population growth, urbanization, the industrialization of agriculture, the disruption of wildlife ecosystems, climate change and increases in global population mobility—is accelerating the emergence and global spread of infectious diseases with unprecedented consequences. As global citizens, this is a reality we have to confront, or we risk finding ourselves in the same precarious position we are in today a few years down the road.

We have also learned that outbreaks move incredibly fast in our hyper-connected world. If we want to remain a step ahead, we are going to have to move even faster. Thankfully, we have what is needed to generate powerful insights: access to diverse and novel data, and human intelligence coupled with artificial intelligence to derive meaning from these complex data.

We need to translate insights into actions that reach across the whole of society. Governments empowered with timely insights will be better able to protect their citizens and economies from dangerous global infectious diseases. Hospitals and health care providers will be better able to protect themselves and the rest of us from these very same diseases. Businesses will be better able to protect the lives and livelihoods of their employees and customers. Creating an ecosystem to manage these risks together is not only possible, but, in my opinion, necessary.

A final thought to leave with you is that our most valuable resource is time, and it is a non-renewable resource. When we get through COVID-19—and we will—the question for all of us will be whether we will use every day of peacetime to prepare for the next inevitable threat with the same sense of urgency with which we are responding to COVID-19 today.

Thank you for the opportunity to share my thoughts with this committee.

The Chair: Thank you, Dr. Khan.

We go now to Mr. Ciciretto, president and chief executive officer of Dynacare.

Go ahead, please. You have 10 minutes.

Mr. Vito Ciciretto (President and Chief Executive Officer, Dynacare): Good afternoon. Thank you, Mr. Chair and members of the House of Commons Standing Committee on Health, for your invitation to this very important meeting. I hope that each of you and your families are healthy and well. It is a privilege to be with you today on behalf of Dynacare to discuss the Canadian response to the COVID-19 pandemic.

At Dynacare, we believe that life is precious. Our mission is to support the health of Canadians with commitment and care. That is why we do what we do. Our 2,900 Dynacare employees deliver the highest level of clinical and scientific testing to provide the necessary information that supports the diagnosis, treatment and well-being of Canadians. Each and every day we provide testing and medical laboratory services to over 32,000 Canadians across the country, amounting to over 11 million tests annually. We operate 200 convenient and accessible specimen collection centres in Ontario, Manitoba and Quebec. We operate seven state-of-the-art laboratories in four Canadian provinces. We report over 500 critical results requiring immediate action by physicians.

Our goal is to inspire confidence in Canadians when it comes to managing their health and well-being. To achieve this, we have elevated the patient experience at our specimen collection centres. We continuously innovate by introducing new and improved test methodologies such as genetic testing; liquid-based cytology; non-invasive prenatal testing; and the piloting of Pixel, a self-collection test methodology utilized in remote rural communities. We have introduced patient-friendly diagnostic testing reports and digital apps that help Canadians better manage their health journeys.

This unprecedented pandemic has highlighted that the work we do at Dynacare matters now more than ever. We are very proud to play a critically important role in supporting the provincial public health authorities of Ontario, Manitoba and Quebec in their efforts to control this pandemic. Since March 25, our talented scientific and laboratory professionals at Dynacare have conducted over 40,000 COVID-19 molecular tests across these provinces, including COVID-19 testing for members of vulnerable and priority populations, such as those in emergency shelter systems, residents of long-term care facilities, EMS first responders and health care workers.

Even throughout this pandemic, Dynacare has continued to operate its laboratories and accept patients at our collection sites for urgent non-COVID-19 testing. In addition to the provision of COVID-19 testing, our community laboratory infrastructure has helped to alleviate pressure on provincial public health systems and hospitals. In particular, our medical couriers have quickly and safely transported COVID-19 test specimens from screening and assessment centres to Dynacare, public health and hospital laboratories. On behalf of the provincial public health labs, we have delivered negative COVID-19 test results to over 25,000 patients. We have supported vulnerable populations by establishing designated Dynacare specimen collection sites for immunocompromised patients and for COVID-19 positive patients. We have engaged in non-COVID-19 sample collection at long-term care facilities.

Our employees have rallied behind Dynacare's response to this pandemic and, as such, we celebrate the many acts of compassion through our Dynacare health care heroes social media campaigns. Our people are the ones who have truly stepped up.

The COVID-19 testing system has generally been working well with strong collaboration among public health agencies, community laboratories and hospitals. But, as with any unprecedented and rapidly evolving environment, there are challenges and opportunities for improvement.

The technical nature of the nasopharyngeal collection process, along with the required swabs that are employed in the collection of a COVID-19 sample, have been rate-limiters in terms of testing and have increased the demand for PPE. At over 200 collections centres, Dynacare has over 850 phlebotomists who are not authorized to collect samples using the current collection devices.

● (1700)

By employing alternative specimen collection procedures used in other countries, our team can support provincial screening. To this end, Dynacare is embarking on a study with Sunnybrook Occupational Health to validate alternative sample collection methods using saliva and front-of-nose collected specimens. The results of this study are expected within a few weeks.

Second, shortages of testing reagents and collection kits were common early in this pandemic. Due to increased vendor production and the proactive response of our supply chain team, we appear to have sufficient supply for our current volume of testing. However, in order to support expanded testing needs, our intention is to increase testing capacity, both through new collection techniques and through supply chain preparedness. Global demand has made it very difficult to secure additional testing capacity and reagent supply on a timely basis. Vendor allocation practices drive more test capacity and reagent to jurisdictions that have been more severely impacted by the COVID-19 virus than Canada has.

It's important to everyone at Dynacare that at the end of every laboratory test we perform there is a person—a mom, a dad, a daughter, a friend. It is not uncommon for our dedicated teams of employees to go above and beyond the call of duty by helping to secure a replacement test requisition for a patient, by leading a drive-by convoy to acknowledge the efforts of front-line health care workers at hospitals, or by making extended efforts to contact a patient with a critical result.

We treasure the value that our dedicated employees bring to the health care system, and we go to great lengths to take care of them. Notwithstanding the significant drop in non-COVID-19 test volumes during this pandemic, we have not thus far implemented furloughs, layoffs or reductions in base pay, due to our long-term philosophy and government wage programs. We are very proud of this and believe that it positions us well for the future. As doctors' offices and clinics reopen, as elective surgeries start again, as insurers and employers resume regular activities, Dynacare will be in a position to meet the laboratory testing needs of our patients and clients and support our health systems across Canada.

Unquestionably, our workplace will be defined by a new normal, with new social distancing and PPE protocols that will protect our patients and our people. As the number of patients requiring service continues to increase, these new protocols will demand the need to adapt, and we will.

Across Canada, some provinces are slowly beginning to open back up in ways that we would not characterize as business as usual. In the absence of a vaccine and lack of scientific consensus on the potential for immunity to the COVID-19 virus, some employers are expressing concern that their workplaces could be prone to COVID-19 outbreaks. Employers across a number of sectors, including food and beverage production, natural resources, manufacturing and many more have expressed an interest in the provision of COVID-19 testing at their own cost. Dynacare's priority will always be supporting health systems in responding to the emergency presented by COVID-19. As the economy opens up, we see a need to work with industry to avoid workplace outbreaks as a means to limiting the community spread of COVID-19.

Key to restarting the Canadian economy is high-quality antibody testing, which can determine whether an individual has been exposed to the COVID-19 virus. Public health authorities, in conjunction with medical and scientific experts, are working to determine how COVID-19 antibody testing could be applied.

This past week, two COVID-19 antibody tests were approved by Health Canada. Dynacare is currently working with two additional vendors who will be seeking Health Canada approval for an antibody test. A community laboratory like Dynacare is very well positioned to support large-scale provincial COVID-19 antibody testing surveillance programs through its extensive specimen collection network of 200 centres, our well-equipped laboratory facilities and our extensive logistics network. We do this every day—efficiently, effectively and with compassion.

In public health emergencies, those in poor health or with underlying chronic conditions are often the most vulnerable.

● (1705)

For many, the COVID-19 pandemic has emphasized the importance of keeping Canadians healthy and decreasing the prevalence of chronic conditions such as cardiovascular disease, lung disease, metabolic syndrome and diabetes.

At Dynacare, we believe that life is precious, and we look forward to continuing to improve the health of Canadians by providing ongoing support to provincial health care systems and through health and well-being programs at Canadian workplaces both through the COVID-19 pandemic and beyond.

Thank you again for the opportunity to address this committee.

Take care and be well.

The Chair: Thank you, Mr. Ciciretto.

We'll start our rounds of questioning now. We will do three rounds. We will start the first round with Ms. Jansen.

Ms. Jansen, please go ahead. You have six minutes.

Mrs. Tamara Jansen (Cloverdale—Langley City, CPC): Thank you to everybody for all your presentations. That was very wholesome. It was great.

I'd like to start with Professor Attaran. I found your written submission very interesting, and I had to chuckle when you pointed out the fact that some hospitals are still faxing in their data. My first foray into state-of-the-art technology on the farm was when we bought a fax machine back in 1992, 28 years ago.

However, in order to stay in business, we obviously had to invest in better and better data collecting technology. I have to say that I was completely shocked to find out from previous witness testimony at this committee that our health care system doesn't have a real-time data collection system in place, especially considering the different recommendations that have been made following previous pandemics.

We have had several witnesses come to this committee and beg us to find a way to move forward with a pan-Canadian data collection system that works in real time. A system like this could help us on so many different levels, not just during a pandemic, but it seems there is this fear that sharing information in this way will compromise the autonomy of provincial and local health authorities.

In your opinion, is there not a way to ensure that each provincial and regional jurisdiction can continue to make decisions that make sense for them while still sharing their data and helping the country with a more informed pandemic response?

● (1710)

Prof. Amir Attaran: What a great question, thank you.

On the question of sharing epidemiological data, it's like this: If you had a number of people who had pieces of a map of a minefield, would you tolerate them not sharing that data? I think you'd probably want to have a map of the entire minefield, not just your little patch of it, if you were setting out on a journey.

The current situation is as foolish as that. Each province has a certain amount of data about the outbreak within its borders, and it can either contribute that piece to modelling exercises or not, and depending on whether it does so or not, we have a better or worse view of the epidemic.

The answer to your question lies in a legal part as well as an administrative part. Legally it's very simple. Cabinet just needs to use section 15 of the Public Health Agency of Canada Act and issue an order in council that data must be provided, period.

Parliament gave it that power. It simply leaves me speechless that the current cabinet hasn't used it. That is something I hope you follow up.

Mrs. Tamara Jansen: Okay, I have a really short amount of time, sorry.

Prof. Amir Attaran: I'm sorry.

Mrs. Tamara Jansen: Okay, I appreciate that.

You mentioned in your submission the dysfunction that we have in sharing data, and, again, being from a business background.... I worked in the retail sector for many years, and our spring season was always very short. We had an eight-week period across multiple provinces, so that meant timely data was absolutely critical to make these decisions on where to send what product and when. We were able to take into consideration those regional differences to ensure the right assets were sent to the right place at just the right time, and we know the technology is available for a pan-Canadian data system.

Yesterday Dr. Tam mentioned that PHAC has no choice, and now you are mentioning they actually do under section 15, so it strikes me that, if Statistics Canada is able to aggregate information about Canadians without violating privacy rights, surely the health care system can do the same.

Prof. Amir Attaran: Statistics Canada can do the same, too. They could build the system inside of about a couple of weeks, I'm told, but they need the mandate from cabinet. That is what's missing. There you go.

Mrs. Tamara Jansen: Okay.

Prof. Amir Attaran: I will just add one last thing to this. There was a time in this country when the federal government did provide a contract to somebody to develop such an epidemic data reporting system. It was given to IBM Canada. The system did not function, and they are the same ones who are behind Phoenix, so there is not a good history here.

Mrs. Tamara Jansen: Okay. Thank you.

I've asked numerous witnesses if they would give PHAC a grade on their pandemic response. So far no one has been willing to give me a straight answer. I've been hearing of some backlash by PHAC to those who are vocally critical in their response to the pandemic.

Are you willing to give me a grade, or could that disadvantage you in your work in some way?

Prof. Amir Attaran: My grade is a C-minus or a D. And there is retaliation, yes. Since the last time I appeared in front of this committee, and was negative about some of those efforts, I was asked to join a grant application with people from PHAC. I understand they said they wouldn't participate unless I stood off it, which I did willingly because I didn't want to cause trouble for my colleagues. But I don't feel there should be retaliation against witnesses simply for providing our democratic government what we think is the truth.

Mrs. Tamara Jansen: Okay. Thank you for that direct answer. I appreciate that.

Yesterday, Dr. Nemer talked about the task forces she set up to tackle the Canadian pandemic response. She mentioned that, although she could share the agendas, she couldn't share the deliberations or findings because they are secret. I believe other countries around the world that have set up similar task forces are sharing their research papers publicly, which helps us all.

Do you think the findings of these task forces should also be public so we can have that timely data sharing for a better pandemic response?

● (1715)

Prof. Amir Attaran: I can't even believe that's a question. Of course, it has to be public. Science is always conducted in public. If you look at a country like Switzerland, they too have a task force on COVID, a scientific task force. If you go to the website over two dozen public reports by that task force are published. If Switzerland, little Switzerland, can get two dozen reports out of their task force by now, why does Canada have zero? It's shameful.

The Chair: Thank you.

Mr. Fisher, please, go ahead. You have six minutes.

Mr. Darren Fisher (Dartmouth—Cole Harbour, Lib.): Thank you, Mr. Chair.

Dr. Fisman, you have a wealth of experience in the battle against infectious diseases, yet you've publicly explained that predictions you made earlier this year on the virus were wrong. I think we can both agree that hindsight is 20/20. There's been a lot of discussion at this committee about why certain decisions were made in the early days of this virus.

I wonder if you could explain to this committee, and to Canadians, about the difficulties of making predictions around a novel virus, and why what's considered the best advice one day can change and evolve so quickly the next?

Dr. David Fisman: I think part of the difficulty relates to the fact that viruses are the troublemakers, and Dr. Khan alluded to this. The troublemakers tend to be RNA viruses, that's their genetic material that comes from animals. RNA viruses are very good at mutating. What we see with this virus, which is a cousin of SARS 1, and bears a lot of similarity to SARS 1, is that it behaves differently in important ways. Being 80% similar can still translate into some very important differences, but some very important similarities.

What we tend to see, what we almost always see with infectious diseases as they emerge, is we find out about hot spots first. Typically we have this sense of the virus being more virulent than it ultimately turns out to be. That's certainly been the case with some outbreaks. What we saw with this virus, also initially, was it looked a lot like SARS based on the information we knew from China. I've acknowledged publicly I think my biggest mistake was thinking it really was looking like SARS in China. We did some forecasting on how the Chinese seemed to be doing in controlling it, and we accurately forecasted that it would be done in Wuhan by early March. That was right, but the difficulty was we didn't see Iran coming. Once you saw this in Iran, you knew the game was over, and this was going to disseminate around the world.

They're all the same, but they're all different. When you look at some of the key parameters, as we talk about, with these diseases, which let you sort of predict how things are going to play out, some important numbers include the reproduction number of the disease, the number of new cases per old case. This virus turns out to be a real trickster, in that it's got what's called an overdistributed reproduction number, where many cases are dead ends but some individual cases make 40 secondary cases. You see that play out again and again, whether it's in nursing homes, on cruise ships or in restaurants. As you know, there's the single individual in Korea who infected 40 secondary cases and sparked a massive outbreak in the city of Daegu.

That makes it difficult. It also provides a potential vulnerability for the virus in terms of control, because once you get rid of those large gatherings that make super-spreading events difficult, the virus becomes much less transmissible. The initial case fatality that we saw coming out of China—that's deaths per case—was listed as 2.4%. Of course, deaths go up slowly with this thing, because people die in the ICU. The China case fatality I think at this point is 5% or 6%. We're at 7% in Canada.

As for what we know now, we've been helped a lot in this regard by data from Spain from last week, from a national seroprevalence study, where they were able to find both the recognized and the unrecognized infections. About 5% of the country of Spain has had this, with 27,000 deaths. Now we're able to go from a case fatality in Spain, which is deaths per recognized case, down to an infection fatality rate, which in Spain we now are pretty sure is about 1.2%, based on seroprevalence data.

The fact that Spain is at 5% prevalence 30,000 deaths in, with an infection fatality rate of 1%, makes me very concerned about some of Dr. Schabas's remarks in terms of moving towards herd immunity. We think that we'd hit herd immunity at 60% to 70% of Canadians infected. Seventy per cent of Canadians infected is 28 million people, and 1% of that is 280,000 Canadians dead. I would note that the failure to have mass mortality in Canada to date relates to the public health response.

I would also note that we can do this because we've shown around the country that we can control this disease without just letting it rip and pushing for herd immunity, as they're doing in Sweden. We've seen competence in British Columbia. We've seen tremendous competence in Atlantic Canada and on the Prairies. We can do this. We just need to get the job done.

Throwing your hands up and saying that we're going to follow Stockholm, Sweden, which is currently leading Europe in per capita mortality, is not the way to go, in my opinion.

● (1720)

Mr. Darren Fisher: Thank you. I had other questions for you, and I think we've run out the clock—

Dr. David Fisman: I'm sorry.

Mr. Darren Fisher: —but I do want to say that this is excellent and very thoughtful testimony, and I want to thank you for that, Doctor.

Dr. David Fisman: Thank you.

Mr. Don Davies (Vancouver Kingsway, NDP): Mr. Chair, I have a point of order.

I'm still somewhat shocked at the evidence I heard from Dr. Attaran about him potentially being discriminated against or having retribution threatened against him as a result of this testimony before the health committee. All of us, as members of this committee, have an interest in upholding the integrity of this committee and ensuring that all witnesses who come before us can give us the sincere, unvarnished benefit of their opinion, particularly when we're talking about science.

I would like to ask that this committee formally request that Dr. Attaran indicate to us full details of what has occurred by PHAC or Stats Canada, or whoever it was, to ensure that the integrity of this committee is upheld at all times.

The Chair: Thank you, Mr. Davies.

Under our current operating mandate, we don't have the authority to do that. We can certainly invite him to submit all of the evidence, all of the allegations he has, to us or to the Speaker of the House. We would be unable to deal with a matter of this kind in our current operating situation.

Mr. Don Davies: Mr. Chair, if I might—

Mr. Robert Kitchen (Souris—Moose Mountain, CPC): Mr. Chair—

Mr. Don Davies: —I would vehemently dispute that. This committee is mandated to receive evidence. It's clearly in the consent order of the House of Commons. If we have evidence before us that witnesses are being pressured or intimidated against not giving evidence, that is a direct interference with the precise mandate of this committee.

On the record, I'm happy to ask Dr. Attaran to provide those details, but for the record, I want to state in the strongest terms possible that it is absolutely the prerogative and mandate of this committee to ensure that we uphold the integrity of our process. Any time we hear that a witness may have been intimidated, or harmed in any way, for simply accepting the invitation from us to come and give us the benefit of their testimony, it's absolutely part of the pith and substance of this committee, and I will pursue this matter fully once we get that information from Dr. Attaran.

The Chair: Thank you, Mr. Davies. Your point is well taken. I will take the matter under advisement and—

Mr. Robert Kitchen: Mr. Chair, I have a point of order.

The Chair: Dr. Kitchen, go ahead.

Mr. Robert Kitchen: Mr. Chair, I'm 100% behind what Mr. Davies said, but my point of order extends further than that. We as committee members are here to present and ask questions, to protect our witnesses as well as ourselves, and to make certain that we have that protection. If we do not have that as a committee, the questions and points that we may bring up can be held against us, and that's just not acceptable. How can we function as a committee if that's not the place?

● (1725)

Mr. Matt Jeneroux (Edmonton Riverbend, CPC): Mr. Chair, just to add on to that, if you could point us in some direction as to why you don't think we have these powers to be able to do that in this committee....

I disagree with you. I agree with Mr. Davies that it's within the mandate of this committee to ask for that testimony.

If you can point us in that direction, please do. If you can't, then I suggest we allow Mr. Davies to proceed with his point of order.

The Chair: Your points are well taken. It should be pointed out that all testimony before this committee, when it's operating in official capacity, is privileged. We have parliamentary privilege. Any repercussions that follow from that would be a serious matter, but our mandate is solely to receive evidence.

We are explicitly allowed to move motions relating to the invitation and scheduling of witnesses. We do not have the authority at this time to undertake a motion to demand information about matters such as this, but I certainly would welcome Dr. Attaran's information if he should provide it.

I wonder if our clerk would like to give an opinion on this.

[*Translation*]

Mr. Luc Thériault (Montcalm, BQ): Mr. Chair, I would like to raise a point of order.

Professor Attaran seems to want to add a comment. Perhaps he could clarify what it is, which could help you deliberate further. I would be prepared to let him speak quickly, since I thought I saw him raise his hand. So I would like us to hear what he has to say. Then you could deliberate on that.

[*English*]

The Chair: Witnesses aren't able to participate in the committee on points of order, but as I said, I will welcome his information. I invite him to bring it to the committee, to send it to the committee.

The clerk will be looking into this matter and will come back to us at a later time with an opinion. In the interim, I will reserve judgment and suggest that we carry on with the testimony.

Mr. Thériault, please go ahead. You have six minutes.

[*Translation*]

Mr. Luc Thériault: Thank you, Mr. Chair.

I am going to address Professor Attaran first. These days, we can say that science is being tossed around a lot. All decisions are supposedly made in the name of science. One might even think that it is being used more to justify some political dithering.

Mr. Attaran, on page 3 of your brief, you say the following:

> ...the Prime Minister hesitated, perhaps because of the scientifically inaccurate advice from his Minister of Health, that closing the borders to slow the disease down is “very ineffective.”

Some people argue that border closures have no significant effect in stopping the spread of the disease. I understand you disagree. Should the borders—especially the U.S. border—have been closed much sooner?

Did we have all the information we needed to make that decision? If not, what would have been required to make that decision as quickly as possible? What is the reason for the conflicting scientific advice?

Prof. Amir Attaran: You are right that scientific issues are often politicized, and that was the case with the border closure.

In my view, the purpose of closing the border is to protect us, especially in the case of the U.S. border. However, as you already know, the WHO says that it is almost useless, and the minister said that it is useless, but I disagree.

I know that, after the disaster we are now experiencing, we will rethink these issues. In Africa, for example, the borders between countries were quickly closed. They learned that lesson from the Ebola crisis. Now we see that nations are more protected. The infection rate in Kenya and Rwanda, for example, is lower than it would normally be. So it works.

● (1730)

Mr. Luc Thériault: Some witnesses have told us that we cannot fall behind in the case of this virus. The fact that the incubation period is often 14 days means that, since the beginning of the pandemic, we have constantly been feeling that we are playing catch-up. So I imagine that things should have been done differently and that decisions should have been made much more quickly.

You were talking about structural and systemic difficulties related to the Confederation and the inability of the scientific community and public health authorities to work in a coordinated manner and in real time with respect to sharing data.

What is the point of not working together? What justifies it? You gave the example of Ontario during the SARS episode. What is the point of those provinces or Quebec not working together? I have trouble understanding that.

Prof. Amir Attaran: I don't understand it either. It's almost dangerous to think of our Confederation as 10 provinces that are not connected through their biomedical resources, especially considering the virus that's connecting us right now. You are right.

Mr. Luc Thériault: How could legislating or establishing regulations be more effective? I'm trying to understand the motivation behind this inefficiency.

Prof. Amir Attaran: To answer more effectively, I have to speak in English. May I?

Mr. Luc Thériault: Yes, of course.

[*English*]

Prof. Amir Attaran: I'm sorry, but some of the legal words I don't know in French. I try.

The order in council that would be necessary to make data exchange mandatory between the federal government and the provinces is not a controversial thing. It is something that Parliament put into the law in, I believe, 2004 or 2005. Simply put, it should be used. We should not let our preconceptions about the appropriateness of what the province may do, or what the federal government may do, stand in the way of the clear reading of the law. You, as parliamentarians, created that law on sharing, and I'm grateful to you for doing so. It's a very useful tool, but it does need to be used.

I think Dr. Fisman would probably be able to add something to this.

Dr. David Fisman: I'm not sure, though I could add my perspective as a researcher based in Toronto since 2006.

What I've always found astounding is the failure to make accessible data that are paid for, assembled and cleaned on the public dime available to Canadians in a manner that doesn't threaten anyone's privacy or well-being. I've found that astounding for a long time.

A lot of my work, since I've come to Toronto, uses the national hospital discharge survey from the United States, which is pretty similar to the stuff you get from CIHI, except that if you ask for the data online from the CDC, they will FedEx it to you and pay for the FedEx, whereas if you ask for the same stuff from CIHI, you pay them. I don't understand it.

There's a much deeper issue here than COVID, and I thank my colleague for flagging it. We have a culture of what I call data hugging in Canada, and it does need to change. It harms us all.

● (1735)

The Chair: Thank you, Mr. Thériault.

We will now go to Mr. Davies.

Mr. Davies, please go ahead for six minutes.

Mr. Don Davies: Thank you.

Dr. Fisman, last week you were interviewed on TVO and you said, “I think there are a lot of folks who are itching to declare victory and open things up again, which is a bit of a problem because the reason that infections are subsiding is because we have distancing in place.” Are you concerned that some provinces and territories may be moving too rapidly to open?

Dr. David Fisman: I think my own province is, and I appreciate tremendously the pressure our premier is under. I think he's done a marvellous job given the cards he's been dealt, but I'm also aware there are a lot of folks who want to get back to business.

I'm not sure whether doing a screen share on Zoom is part of parliamentary committees, but we are looking at reproduction numbers here in Ontario. That is the number of new cases per old case. What we see is that the disease has clearly surged over the last week in Toronto, particularly in Peel. Part of that is from the liberalized use of testing, which drives the numbers up. Part of that is probably from the anticipation of greater economic opening. I think we may get a couple of rude bumps along the way, but ultimately distancing will be our parachute. If things start to look too grim, they'll be able to close things back down again, but, yes, I'm concerned that there's tremendous momentum to get folks back to business.

There's a lot of economic activity that could resume safely in the province of Ontario. Ontario is a big place. It's bigger than France, and we have regions.... Dr. Attaran referred to the city of Kingston. It has had one or two cases over the last 10 days but is subject to the same blanket lockdown as Toronto and Peel, which have had a couple of hundred cases a day. I think more—

Mr. Don Davies: I'd like to direct you to some of the things we should be doing.

You also said in the interview, “Predictably, as we reopen, we’ll see a resurgence of disease.”

Dr. David Fisman: Right.

Mr. Don Davies: That's exactly what we've seen in Korea and in Germany this week, two places that controlled their initial epidemic faster than we did and are moving toward revitalization. They've seen resurgences, just as Singapore did before them and just as Wuhan did last week.

What do you recommend we do, given that you see resurgences? What steps should we be taking to get in front of that, if there are any?

Dr. David Fisman: The resurgences will happen. It's just how this works. It's simple math. The reproduction of a disease is number of contacts times the probability of transmission per contact times how long a person is infectious for. We can forget about immunity right now, because immunity is low. Even if it's 5%, it's too low to bring the reproduction number down. Therefore, as contacts go up, the reproduction number predictably goes up.

The Chair: Doctor, could you please hold the mike?

Dr. David Fisman: My apologies.

We're going to go too far. We're going to try to open things up and go too far. That's why we need strong surveillance systems, to see that as it happens.

Mr. Don Davies: I want to move to testing. Maybe you and Dr. Attaran can comment on this.

We hear repeatedly at this committee, from every expert, that we have to test, test, test, and that it's key to getting control of this disease and reopening. However, we've barely done a million tests since January. Wuhan is gearing up to do a million tests per day. We're behind Germany. We're behind South Korea. In fact, we're at barely half of Dr. Tam's target of 60,000 tests a day.

Why are we unable to test at the rate that all experts are telling us we need to? Where is the problem here?

Dr. David Fisman: I don't know. Mr. Ciciretto is an expert on how labs work and could probably give you a more meaningful answer than I could.

We do work with local public health units. My concern at the moment is that it's not just the testing. If people are saying we're going to do contact tracing once we open up and we're going to track the contacts of cases as they did in Korea—I think they had a couple of hundred secondary cases associated with a nightclub outbreak—I don't think we could do that.

We have lags all the way along and it gets back to the 1990s technology where it takes time to test, the tests get faxed, it takes a while for them to percolate through the public health system and—

● (1740)

Mr. Don Davies: I'm sorry to interrupt, but I want to give Dr. Attaran a chance to weigh in on this too.

Other countries are testing at much higher rates. Why can't Canada do it?

Prof. Amir Attaran: Again, I am not a testing expert. What I can say is that it's obviously a systemic and administrative problem, because for Ethiopia or Rwanda to be surpassing us in testing.... They're getting the reagents and supplies from somewhere. They are pulling it off.

I did mention the city of Addis Ababa, the capital of Ethiopia. They have actually sent health workers around to every door in the city already to interview people about their travel or exposure history and test them if necessary. If Ethiopia can do that, I refuse to believe Canada can't. We just need to understand better—and I'm not the person to give you the answer—what the administrative holdup is in the testing, but it's clearly administrative not scientific.

Mr. Don Davies: Thank you, Dr. Attaran.

I have one quick question for you.

Your chart spoke for itself. The question I have is why is Canada performing below comparative countries like Australia and other countries you mentioned. Your chart clearly shows we are. What are the reasons for that?

Prof. Amir Attaran: In terms of bending the curve, or the testing, specifically?

Mr. Don Davies: Bending the curve.

Prof. Amir Attaran: In terms of bending the curve, Dr. Fisman can be more detailed on this, but it's clear that we have not adopted as rigorous a lockdown as some other countries have. We've also had a slow-burning problem in the care homes and this has taken what could have been a sharp peak and broadened it into something of a plateau.

I am very uncomfortable with the fact that we are opening up without the testing at the necessary level, or the tracing. I'm not saying I don't want to open up. I hate being locked up as much as anyone else—you should see my children. There has to be groundwork done, and it is the fact that the governments of this country—some of them, especially the federal government—just haven't done the groundwork.

Mr. Don Davies: Thank you.

The Chair: That ends round one.

We will start round two.

Mr. Jeneroux, please go ahead. You have five minutes.

Mr. Matt Jeneroux: Thank you, Mr. Chair.

Thank you to the witnesses for joining us here again today.

I want to address Dr. Khan and some of the comments you made. In particular, I am hoping to get a grasp on when BlueDot—obviously ahead of the curve, early on—provided the first data regarding the coronavirus to the Public Health Agency of Canada.

Dr. Kamran Khan: As I mentioned in my opening remarks, our surveillance system had picked this up on December 31. You may also be aware that the Public Health Agency of Canada has a platform called the Global Public Health Intelligence Network, GPHIN. There are some parallels with the platform we're using. I think we may be using a bit more machine learning and artificial intelligence in our system.

I believe, with respect to awareness of the event in Wuhan, this was at a similar time; I believe it was around the end of December or beginning of January. We have had, as I mentioned, a relationship with the Public Health Agency, going past detection of threats and then looking at dispersion, how they might spread and where they might go next. All of the systems that we use internally—software systems, all of the internal data on commercial flights, passenger movements around the planet—are accessible by the Public Health Agency. This is part of our partnership.

I also did share the results of some of our analysis directly with Dr. Tam back in early January—I believe it may have been January 4 or 5, a few days after the new year. I communicated some of our initial findings and then had a follow-up meeting, I think, around the January 9 or 10 to discuss some of this in person.

● (1745)

Mr. Matt Jeneroux: What information did you provide exactly? Did you provide that information from December 31 that you had attributed to the beginning of this?

Dr. Kamran Khan: Because the Public Health Agency already has a surveillance system and GPHIN had picked up news of the outbreak in Wuhan around the same time as BlueDot, we didn't send them that information because it was something they already had access to. But we have been working with the Public Health Agency around contextualizing this.

Understanding that something is appearing in the world is very different from understanding what risk it presents to Canada and where those risks are greatest at the particular moment. Is it in British Columbia, in Halifax, or somewhere else?

We shared some of our findings on the movements of travellers across the world with Dr. Tam and her office and then met in person to discuss some of the results and, more broadly, really, the need for systems. We had some earlier comments about data internally within Canada. We're clearly not a closed population; we are a microcosm of the world, one of the most connected populations on earth.

It was critical for us to have better systems not only to detect threats but also to quickly assess what risks they present, so that we could be a step ahead and mobilize our resources, heighten our surveillance in the right places at the right time, and to share with you the specifics of the risks associated with the events in Wuhan. That was really just a few days after New Year's in early January.

Mr. Matt Jeneroux: Did you make any recommendations at that time about shutting down borders and what that would mean to Dr. Tam, and perhaps her team?

Dr. Kamran Khan: We discussed obviously what the risks were, but, of course, as you remember, in early January we didn't even know this was the coronavirus. Clearly it caused enough concern from our end just because there were some parallels with the SARS event that had emerged in late 2002 in Guangdong. We had some concerns given the parallels with SARS.

However, as more information became available, as soon as we knew this was a novel coronavirus, we did follow up directly with Dr. Tam and her office. Obviously, they were aware, but our concerns at that point were that we knew the last two novel coronaviruses, MERS and SARS, had killed a third and 10% of their patients, respectively. They have no known vaccines, no known effective antivirals.

A novel coronavirus means that the whole world is susceptible, and that's a lot of fuel for an outbreak, and it's in the middle of wintertime, which is when you have respiratory illnesses. Given the signal-to-noise ratio and the detection of this behind a whole background of febrile illnesses, that certainly caused us quite a bit of concern.

The last point I will make is that I believe it was on January 13 when the first case was reported in Bangkok. By the way, coincidentally, it was the top city that we had identified as being at risk. At that moment we knew this was not a few dozen cases. In order for there for cases to be showing up in a city of 11 million, we had to be dealing with hundreds, maybe even thousands of cases. That was really the moment we became quite concerned, but of course with emerging diseases, unfortunately, you learn as you go. You don't have all the answers and you have to make decisions as new information becomes available.

The Chair: Thank you, Mr. Jeneroux.

Mr. Matt Jeneroux: Mr. Chair, do you mind if I request that Dr. Khan share that early information he provided to the Public Health Agency with the committee?

The Chair: Sure.

Mr. Matt Jeneroux: Thanks.

Dr. Kamran Khan: I'd be happy to do that.

The Chair: Thank you, Mr. Jeneroux.

We go now to Dr. Jaczek.

Dr. Jaczek, please go ahead for five minutes.

Ms. Helena Jaczek (Markham—Stouffville, Lib.): Thank you very much, Chair.

Thank you to all the witnesses. This session has certainly been fascinating. There has been a real divergence of views, especially from the first three witnesses.

Thank you, all three, for your very considered opinions. We go from one extreme, with Dr. Attaran saying that we haven't gone nearly far enough, to Dr. Schabas saying that perhaps we have gone too far.

Speaking as a member of this committee, of course we're very interested in all of your opinions, but part of what we need to do is to find some commonality, to find where there is agreement. The area where there seems to be agreement, and that we have heard a great deal about from many witnesses, is that there needs to be more of a national data surveillance system as it relates to public health. It's been exemplified by many of you that in fact provinces are collecting data differently. Even in the use of the case definition, there has been a difference from province to province.

Dr. Schabas, given all of your experience, and having known you for so very many years in the trenches, in both urban and rural settings, I will address this question to you. At the end of your remarks, you made a comment in relation to a national surveillance system. I'd like to hear from you on what kind of data you would like to see and where the important areas are that need to be collected. I'm sure you've had to make decisions based on inadequate data, or not as much data as you would like to have had, on many occasions. Could you flesh out for us how you see that national surveillance system?

● (1750)

Dr. Richard Schabas: Thank you, Helena, and thank you again for arranging my invitation to this meeting. It's been great. It's been fascinating listening to David and Amir. Maybe at some point I'll have a chance to rebut some of the other things that have been said.

On the notion of having a national agency, we were always very envious of the Americans. They had the Centers for Disease Control, a highly respected agency that led and that took the high ground. It was where everyone turned to for advice and direction and guidelines. We had the old Laboratory Centre for Disease Control at Health Canada. There were some very good people there, but it didn't have the same clout—

The Chair: Dr. Schabas, could you speak a little bit closer to the mike and maybe a little bit slower for the interpreters?

Dr. Richard Schabas: I'm sorry.

The idea emerged almost 20 years ago—I actually wrote an editorial in the Canadian Medical Association Journal on this—of really proposing a national agency that would fulfill some of those roles. I think we had an opportunity 15 years ago after SARS, when there was this surge in interest in public health and improving our national public health capacity, which led to the—

The Chair: Pardon me, Dr. Schabas.

The interpretation has stopped. We'll suspend for a minute until that resumes.

● (1750)

_____(Pause)_____

● (1755)

The Chair: The meeting has now resumed.

Dr. Schabas, please carry on.

Dr. Richard Schabas: As I was saying, 15 years ago, the vision I had hoped we would adopt was not so much one of a federal agency, but a national agency. We had some resources with the federal government, but it was also a time when Ontario was developing Public Health Ontario and British Columbia was augmenting the BCCDC.

There was a real advantage in developing a sense of co-operation between the federal government and the provinces, because the reality is that the provinces collect the data and the provinces make most of the public health decisions. You don't have the federal authority to tell them what to do. They're going to do what they want to do. The only way to get consistency in a truly national approach to a problem like this is to get people to buy in, to get people to be willing to do it because they think it's the right thing to do and because the prestige of the direction they're getting from the national agency is sufficient for them to.... I'm not going to say fall in line, but be consistent with their approach.

We don't ever expect everything to be the same. Here's a great example: Why should British Columbia be doing with COVID what Quebec is doing? They are very different sorts of situations. I think we would all be much happier if we knew there was a common purpose, common objectives and a common directive.

I'm hoping, maybe a little naively, that there will be another surge in interest in public health—I'm sure there will be—after the COVID crisis comes and goes. I hope we rethink how we set things up. That's not a criticism of the Public Health Agency of Canada. I just think it would function better if it was better integrated with the provincial agencies and if the provinces and the federal government were truly partners in this.

The Chair: Dr. Jaczek, your time is pretty much up but because of the problem in the middle, I'll give you one more question.

Ms. Helena Jaczek: Thank you, Chair.

Dr. Khan, perhaps I can ask you. Obviously you and BlueDot have been very helpful to the Public Health Agency of Canada. What kinds of interactions have you and BlueDot had with the provincial agencies, such as Public Health Ontario?

● (1800)

Dr. Kamran Khan: We have had interactions with the ministry of health in Ontario and have been actively working with the province there. At BlueDot, we're a team of about 50 people. We're also working via Global Affairs Canada—

The Chair: I'm sorry, Dr. Khan. Please adjust your microphone.

Dr. Kamran Khan: I'm so sorry about that.

We are also working with Global Affairs Canada to support capacity building—as I mentioned in my opening remarks—in 10 countries in Southeast Asia. We're working with the State of California.

In many regards I think we would be very eager to support public health responses across the country and work closely with the provinces and territories. We've had, in some ways, an issue with respect to capacity to do this in the midst of the COVID-19 pandemic. However, we have had engagement at the federal level, and are producing analytics across the entire country on a week-over-week basis, and also with the Province of Ontario.

I'm not sure if that answers your question, but a lot of the analytics are focused on understanding issues related to social distancing and how that is related to epidemic activity. Also, keep in mind that while today we're in a bit of a lockdown, as the economy reopens and we have a highly susceptible population, we're going to have to start.... We may find ourselves in the same place as New Zealand in the future, where we have to start looking outward again and start to think about introductions that could trigger the next wave.

We've been involved in supporting both an internal look and tackling this in our own backyards, as well as monitoring the global situation and potential introductions.

The Chair: Thank you, Dr. Jaczek.

Dr. Kitchen, it's over to you for five minutes, please.

Mr. Robert Kitchen: Thank you, Mr. Chair,

Thank you, everybody, for your presentations today. They've been greatly appreciated.

Dr. Attaran, yesterday I spoke to Dr. Tam and asked her a question about data sharing between the provinces and organizations with the federal government. You've answered a lot of those questions I had for you, but further to that, I was asking her about demographic data, in particular how New York City has come up with a lot more demographic information, etc. She indicated to me that it's on the Public Health Agency of Canada's website, so I took the opportunity this morning to go onto that site. With some help from my staff, I finally managed to find some information on that.

They talk about updating the data as of today and about 4,201 cases of clinical presentations, and of those, 561 cases or 13% were clinically or radiologically diagnosed with pneumonia. My point about that is it provides a lot of information and then, all of a sudden, I find a little bit further down a little statement: “The epidemiology update is based upon information received for 38,746 cases. Not all data fields are complete, only cases with data available are included.” The bottom line is they're providing inappropriate information on the data that we have.

How is it that we ask you or other epidemiologists to come up with data and provide modelling when we put this out with inappropriate information?

Prof. Amir Attaran: Dr. Kitchen, thank you for a very intelligent question. You're exactly right. You mentioned there were roughly 38,000 cases in the data that you looked at. I'm going by memory here, but I think we've had about 80,000 cases reported in Canada so far, so that's under 50%. What that means is that at the high-water mark, anyone like Dr. Fisman or Dr. Khan doing modelling, or me when I do it in my amateurish way, are working with less than half a deck.

Mr. Robert Kitchen: Right, and—

Prof. Amir Attaran: There are obvious problems with that.

Mr. Robert Kitchen: When the Public Health Agency is making these decisions based on World Health Organization data, which is maybe coming in from China or wherever, which is inappropriate, again how do you come up with that proper information?

Dr. Fisman, do you have any comments?

● (1805)

Dr. David Fisman: I'll tell you, my group at University of Toronto call ourselves “data raccoons”, because we've sort of managed to thrive for about 15 years on data that most people regard as garbage, so it's sort of a bit of the normal state of affairs for us with public health data analysis. The stuff we have is pretty good by our standards.

Working with folks here in Ontario, there's been a modelling table convened over the last few weeks. We've been given access to case files. There's a lot you can learn, but there are also a lot of fields that are missing. We could potentially do better, but I think it's also important to remember that those fields are being filled in by very harried front-line public health epidemiologists.

I suspect that what you're seeing from the Public Health Agency of Canada is that they're putting out the data where they have complete fields, and that it's their way of dealing with missing data. Missing data is just part of epidemiologic data analysis. It happens no matter how good the data are that you have. I'd sort of want to know more about how they've made those decisions, but sometimes it's good enough.

Mr. Robert Kitchen: That's a challenge, though, when you don't have proper data and you don't understand that.

I'm going to go on a little bit further.

Mr. Ciciretto, you talked about high-quality antibody testing. We've heard a lot from you today and all of the witnesses about testing. Last week Health Canada approved the first serological test for detecting antibodies in those who contracted or may have contracted COVID-19. The approved serological test comes from an Italian biotechnology company.

Do we have the capacity to produce these tests domestically? Do you know that?

Mr. Vito Ciciretto: The answer to the question is, we do have capacity. The particular test that was approved was from a company called DiaSorin. We don't have that testing platform, in particular, so that's critical. Could we acquire it? Yes, we could acquire it.

There are other companies that we're working with right now, large diagnostics organizations that are looking to get Health Canada approval as well for a serological test. Once that happens, I have 200 collection centres and 850 phlebotomists who can collect those samples and bring them into a laboratory and onto existing test platforms that we have today that could do that testing quickly, efficiently and accurately.

The Chair: Thank you, Dr. Kitchen.

We'll go now to Mr. Kelloway.

Go ahead. You have five minutes, please.

Mr. Mike Kelloway (Cape Breton—Canso, Lib.): Thanks, Mr. Chair.

Hello, colleagues.

I want to say a really special thank you to the witnesses today. I'll echo Dr. Jaczek's that it's interesting to see such a rich series of viewpoints, insights, opinions and also backgrounds in a variety of areas. I really appreciate it. It's very illuminating.

Dr. Khan, I find your work very fascinating in terms of the technology you use. I don't necessarily want to look to the past but to potentially a second or third wave.

Can you talk about how your technology may be able to be used to track and identify, in many ways, a second or third wave? Could you illuminate a little bit what the biggest risk factor is that could trigger the next wave?

Dr. Kamran Khan: Maybe the way I could sort of frame what we have been building with the metaphor of a smoke detector and fire extinguisher. For six and a half years, we've been building systems to be able to detect threats early, because we know, as I mentioned, that time is our most valuable resource.

To be able to quickly go from detection to what kind of risks we are facing—not just from the dispersion of the disease, but what kind of disruption might occur—is very important because diseases spread around the world all the time. They don't all cause outbreaks or pandemics. That is a complex requirement because every disease behaves differently. Zika virus is different from Ebola, which is different from COVID-19 or measles for that matter.

We've been spending a number of years building up that capacity to have a bird's-eye view of what's happening around the planet, to be able to relate it to geographies across the planet, and to do this in, really, a matter of seconds.

With respect to once an outbreak starts to spread and is now occurring locally, this is where we have been using—again, I want to underscore, anonymously—just the pings, the digital locations from hundreds of millions of mobile apps and mobile devices.

That kind of information can help us understand. Ultimately, this is a virus that spreads, as Dr. Fisman mentioned, through the movements and interactions of people. These are really rich datasets—over three billion data points a day—that can really allow us to understand how those movements are occurring so that we can then start to anticipate how the epidemic might evolve. It also allows us to generate insights about some of the non-pharmaceutical interventions like physical distancing or recommendations for quarantine. Are those being adhered to at a population level?

I do want to highlight that we're not tracking anyone who is infected or their contacts. We're looking at population movement.

With respect to going forward to the next wave, I think the simple reality is that no one really quite knows what this is going to look like or exactly how it's going to unfold. We are dealing with a completely novel disease. Certainly, we have concerns that as we get into the latter months in the fall.... We know that coronaviruses tend to be in cooler, drier climates where they may be more efficiently transmitted. As that occurs, currently we are relating a lot of this mobility data to understanding how the epidemic curve is evolving. Perhaps there are lessons that we can learn about which geographies and which locations seem to be opening up society in such a way that they can, you know, generate some sense of normalcy and some kind of economic activity without having an exponential increase in the epidemic. I think that's really the $6,400 question. How do we do this gracefully? How do we thread the needle?

These are things that I, candidly speaking, don't know anyone has the answers for just yet. I think it goes back to the point that surveillance, testing and monitoring are critically important, because as we start to reopen society, it is going to be incredibly important for us to be watching very closely what the response is in terms of epidemic activity and transmission.

I hope that I perhaps have given you a little bit of a sense of what we're thinking going forward.

● (1810)

Mr. Mike Kelloway: You have.

I think you mentioned measuring disruption in society. Maybe I'm miscategorizing that.

Can you unpack that a bit?

Dr. Kamran Khan: Yes, thank you. It's a really big and very important issue.

The four Ds that we work on are detection, dispersion, disruption and dissemination. Detection speaks for itself, early detection. Dispersion mean, how do these things leap across continents in hours? How do we anticipate the next move? Without getting into a lot of detailed epidemiology, what sometimes is called the infectious disease triangle is a disruption or an outbreak that really lies at the crossroads of the characteristics of the microbe or the germ itself, the characteristics of the population, and the environmental conditions.

The Zika virus is not going to spread here locally in Toronto, because there's no mosquito and it's too cold; it might spread in Miami in July, but maybe not in January. That is a very complex set of data and we're bringing in hundreds of data sources, from real-time satellite data to insect observations, demographics, etc. We can do this for over 100 different diseases so we can try to get a sense of whether the necessary ingredients are there for this to actually cause a disruption, an outbreak.

As you can imagine, this is not a data problem. It requires deep subject matter expertise integrated with deep data analytical expertise and data science. This is the area we're actively involved in. We're well on our path and well on our way, but this is a formidable challenge that really is going to take years.

The Chair: Thank you, Mr. Kelloway.

Mr. Mike Kelloway: Thank you very much.

The Chair: We go now to Mr. Thériault.

Mr. Thériault, please go ahead for two and a half minutes.

[*Translation*]

Mr. Luc Thériault: Thank you, Mr. Chair.

My question is for Professor Fisman. Perhaps Mr. Schabas can express his opinion as well.

We do not yet have a vaccine or antivirals. Serological tests are just beginning. Faced with the desire for reopening, we have suddenly and a little hastily seen the notion of herd immunity appear. But there is no real certainty about the exact data, about the connection between COVID-19 and herd immunity.

Can you tell us where we are at in terms of knowledge or studies on herd immunity with COVID-19? Can you describe the situation?

If reopening were at an ideal rate, would we achieve herd immunity? At what rate would we need to achieve it to make everything safe?

● (1815)

[*English*]

Dr. David Fisman: Thank you very much.

There are a lot of moving parts here. Herd immunity can be approximated as a function of the reproduction number of the disease. The higher the reproduction number, the more people need to be immune if the disease is not to take off. That's why we see measles outbreaks when vaccine levels fall off just a little bit, because the reproduction number for measles in a susceptible population is about 20. You can get about 20 new cases from an old case.

This is a much less infectious disease. The reproduction number is somewhere between two and three. That means you need somewhere between half and two-thirds of the population to be immune to have herd immunity, so that if you bring an infectious case into the population you won't don't have an epidemic.

Where are we right now? We don't know. I've been doing a running meta-analysis on seroprevalence studies as they've come out. I'm up to about 50 of them. You can compare antibody prevalence in populations to what those communities think they have going on in the number of cases they have. It's called a cumulative meta-analysis, just adding study to study to study. The long and short of it is that I think we probably detect about 7% of cases. We have an inflation factor of somewhere between tenfold and twentyfold.

If we look at Canada with 80,000 recognized cases, that would be somewhere between 800,000 and 1.6 million cases in reality. That puts us—I'm going to get hung up in trying to do the math on the fly—at 4%.

If we're there now, New York is well ahead of us. New York has good seroprevalence data. They're at about 15%, but they had to go through hell to get there. They did experience a wholesale collapse of hospital systems in much of the city, including the Bronx and Queens, to get to 15%. That means they might be able to get to 50%, 60%, or 70% herd immunity by going through that a few more times. I don't think they will allow that to happen. They've lost approximately 20,000 New Yorkers of all ages, I would add, to get to that point.

What we have to do right now—a lot of countries around the world, indeed a lot of provinces in Canada, show us that we can knock this disease down to low levels and then we can use good public health practice. I agree with Dr. Schabas that you can't do contact tracing if you're having 200 cases a day, as we are in Toronto. It's just too much. If you're having five cases a day, you sure can. If you're testing a lot, you sure can. You need to use the distancing to knock the reproduction number down. We're still at around one in Quebec and Ontario. I would add that the Canadian epidemic, at this point, is a Quebec and Ontario epidemic. The other provinces have got the job done at this point. If you can do that, then we can start to use other public health measures, like contact tracing, to keep a lid on this and get through the summer and allow the economy to reopen.

We haven't touched on masks at all. There's pretty good ecological evidence at this point that the countries that are doing much better than us are mostly mask-adopting countries. You can argue the science, and we can have a symposium in five years about who was right, or we can use the precautionary principle and move towards masks now, which I think Dr. Tam has started to do.

We can do a lot to keep that reproduction number low and reopen our economy to a degree, and muddle through.

Exciting stuff is happening with vaccines. There are RNA vaccines that weren't on the table 10 years ago. There's a really exciting live virus vaccine from the U.K., where AstraZeneca, the pharmaceutical company, is manufacturing the vaccine at scale while the trials go on. If the trials are a success, they're going to have millions of doses ready to put into people's arms.

We need to avoid mass death situations until we can get through to a point where we can effectively deal with this pandemic. We will, but it's a matter of tenacity, patience and competence, and that's very patchy across the country. Some places have shown it; other places haven't. I'm sad to tell you that I feel that my province, at a provincial level, is one of the places that hasn't shown that, although individual local public health units have really shone and distinguished themselves.

● (1820)

The Chair: Thank you, Mr. Thériault.

We go now to Mr. Davies for two and a half minutes, please.

Mr. Don Davies: Thank you.

Dr. Fisman, last week, you stated, “I continue to be concerned that there hasn't been enough attention given to epidemiology in kids. I know folks are starting to study that in Germany and Switzerland, but we haven't really studied it in North America.” Then you said, “For those of us who have been really concerned about the possibility that children may be important vectors of this disease..”.

Given that we haven't done much research in North America and your concern that children may be important vectors, how do we square that with sending our kids back to school?

Dr. David Fisman: Honestly, it's a dilemma.

I think I mentioned earlier that the signature of this disease is that it takes off with big gatherings, so there's a lot you can probably reopen economically, safely, if you stay away from large gatherings of people. The one big gathering that's really, really tough to cancel—and which has huge economic implications—is at schools. That's the hardest thing.

The reason to be concerned about aggregating kids is that we see evidence from other respiratory infectious diseases that kids don't die of them, but they are tremendously good at transmitting these diseases.

Mr. Don Davies: That being the case, why would we be sending kids, who are vectors of this disease, to gather in large gatherings and to come back to homes where they may be in contact with seniors?

I don't see what the dilemma is there. What is the dilemma?

Dr. David Fisman: I think the idea is that economically it holds a country back. Even if we have 40% of our workforce able to work from home, for the parents, it's often difficult to get their jobs done if they're minding children in parallel.

However, yes, it's an issue. Countries like Korea have kept their schools closed. Hong Kong continues to have its schools closed. I think they're just starting to reopen, because they have approximately zero cases at this point.

I think places with good public health leadership have done it very cautiously. Kids are the transmitters of infectious disease for many respiratory diseases, even if they themselves tend not to be sick from them.

Mr. Don Davies: Thank you.

Dr. Khan, I will go quickly to you.

I know you did a commendable job. An article in U of T News said that BlueDot was among the first to warn the world of a potentially dangerous new illness, COVID-19. You rang the alarm on December 31, 2019, before both the U.S. Centers for Disease Control and Prevention or the World Health Organization. You also predicted the next 11 cities that the novel coronavirus would hit.

You're quoted as saying, “We didn’t necessarily know it would be of this size.... But what we did know is that it had the ingredients.”

Approximately when were you aware that COVID-19, or the novel coronavirus, had the potential for serious, significant, widespread transmission?

Dr. Kamran Khan: I think the point—and this is sort of a gradient—was literally December 31. First seeing that information certainly caused some alarm. Around the middle of January—and I'd have to double-check the exact date—was when the first case showed up in Bangkok.

I'll give you a bit of a sense of the increasing concern.

When we learned that this was a novel coronavirus, I believe somewhere around January 8 or so, there was concern for all the reasons I mentioned earlier, MERS and SARS, and comparing those: no vaccine, no effective antivirals, no underlying immunity and we were in the middle of flu season.

What we had been learning up until that point is that the number of cases being reported in China were in the dozens. When the case showed up in Bangkok, which was the top place we had concerns about because of the movement of travellers from Wuhan out into the region, in a city of 11 million.... The math doesn't work if you have a case show up in another city and knowing the volume of travellers who were leaving. That was the moment for me and our team, when we were really quite concerned.

Again, we didn't have all the answers, but we were quite concerned that this was a novel coronavirus. The outbreak was much larger than it appeared to be. This inevitably told us this was not just a spillover event. This was not just the people who were at the market who became infected. If there were hundreds or thousands of cases, this had to be something that was more efficiently being spread from person to person.

It was roughly around the middle of January that we had serious concerns about how this might unfold.

● (1825)

The Chair: Thank you.

That brings round two to a close. We start round three with Mr. Webber.

Mr. Webber, go ahead, please, for five minutes.

Mr. Len Webber (Calgary Confederation, CPC): Thank you, Mr. Chair, and thank you to all our presenters, whose opening remarks were very interesting indeed.

My first question is for you, Dr. Attaran. Thank you for sharing with the committee your paper on the pandemic data sharing. In this paper, you mentioned the SARS issue back in 2003 and how the World Health Organization demanded epidemiological data from Canada about the scope of the epidemic back then, particularly in Toronto. The problem was that Canada had no way to fulfill the World Health Organization's demand because of the jurisdictional fight that you described today with regard to data sharing.

Because of that, Health Canada was in no position to answer the World Health Organization's questions, so they grew afraid of Canada. They thought that Canada was concealing this epidemiological data, which then resulted in the World Health Organization recommending against travel to Canada, making Canada one of only two countries—that and China—that they sanctioned back then.

Sadly, I see this occurring again. Dr. Attaran, do you see this occurring? What will the implications be of being sanctioned once again?

Prof. Amir Attaran: Mr. Webber, you summarized that exactly right. Back in SARS, there were two countries in the world that got slammed with a WHO travel advisory, and we were one. China, not exactly having been honest, shall we say, was the other. Now, we weren't trying to deceive, the way China was. We were just unable to be honest. We were unable to get the data from Ontario to Ottawa and then onward to Geneva, where the WHO is.

Nothing has changed. That is a risk that could repeat itself. Yesterday, I believe it was Dr. Kitchen who asked about the multilateral information sharing agreement, which is an accord between the provinces and the federal government to share data. It is so secretive and ineffectual that to this day we don't know which provinces have signed that agreement and which have not. Can you believe it?

As for the Public Health Agency, I've asked them that question directly. Which provinces have signed the information sharing agreement and which haven't? They won't answer the question. Parts of that agreement actually stand in the way of data analysis, the sort that Dr. Fisman does. Under that agreement, provinces have to give their permission before analyses using their data can be published, which means that they have the ability to suppress analyses that can save lives. It's terrible.

Mr. Len Webber: It's unbelievable, Dr. Attaran, it really is. Thank you for sharing your testimony today.

Dr. Fisman, again, thank you as well, and thank you for your work, your commitment and your sacrifices, too, along with those of all health care workers in Canada. Thanks to all of them.

You've talked about some of the best practices around the country. It's in Nova Scotia, I think, that you indicated they hunt the virus, and you also talked about how in Saskatchewan they deal swiftly with and contain areas of outbreak.

Then you talked about Alberta and how they've scaled up their testing and are the most potent and aggressive testing province in the country. I'm just at odds here. I don't understand. How come Alberta can do it but the rest of Canada cannot? Where are they getting their testing material? What's their secret in Alberta?

● (1830)

Dr. David Fisman: Do you know what? I'm not sure to what extent I can talk about private conversations in this public forum but, as I speak to colleagues across the country, what is clear to me is that the places that got the job done were aware of their deficiencies as laboratory systems and worked with commercial partners to automate processes in their labs. It's one thing to be testing 100 specimens a day. It's another to be testing 10,000 a day.

I think that the laboratories that are able to have high throughput here, and—Mr. Ciciretto is probably the better one to answer this question—we do have folks in the country who know this stuff. From the time the specimen arrives until the report goes out to the public health unit, not by fax but electronically, operations can be tremendously streamlined so you don't get the bottlenecks that we've had in Ontario.

I think a lot of the problems got blamed on the supply chain but clearly, as the supply chain has cleared up, it's still a rocky ride. In Ontario there have been a lot of politics as well. I think you see that. You've had access to some testing data via the modelling process. You see that there's still this hugging going on where, even as testing is supposed to get dispersed out to hospital labs and private labs, it's still getting hugged by the public health laboratory system.

I think, in a time of national crisis, it's time to check your ego and work with whoever you can work with. Essentially, the folks in Newfoundland.... It was a remarkable experience to interact with them. Perhaps this is a size thing, but it seemed a lot to me like an ego thing. They have a provincial working group that has some former politicians, some leaders from health, leaders from business and a couple of academics, and they're all at the table and they're all exchanging ideas. It reminds me of the children's story, *Stone Soup*, where everyone brings something and puts something in. At the end of that, they all have a good soup to enjoy together.

That's how they do it in Newfoundland. It was a revelation to me, as someone coming from Ontario who's used to being asked for information that then goes off into a dark place and you're never really sure who's seen it, used it or responded to it. It's just a very different way of doing business, and I think it's served them well. They got the idea of hunting the virus from Iceland. They looked over to the east and thought, “Well, you know we've got Canada over to the west and we've got this other country over to the east, and the country to the east is doing a bang-up job. Let's talk to them.”

I think being humble and looking for folks who are doing this better than you, and learning from them, is part of the magic.

Mr. Len Webber: Absolutely, it is.

The Chair: Thank you.

Mr. Van Bynen, go ahead, please. You have five minutes.

Mr. Tony Van Bynen: Thank you, Mr. Chair. Thank you, Dr. Fisman, for joining our committee today. It's so refreshing to hear such a wide variety of perspectives, and that certainly helps us to develop a good understanding of the situation that we're trying to find some solutions for.

It's my understanding that you co-authored a study that examined the impact of enhanced contact tracing and restrictive physical distancing measures in comparison to a combination of enhanced contact tracing and less restrictive distancing measures.

Could you please share with the committee the findings of your study and what the implications may be?

Dr. David Fisman: I think what you're referring to was our paper in the Canadian Medical Association Journal, CMAJ, in March. Our model looks a lot like most other models by competent modelling groups. It looks like the publication by a guy named Steve Kissler, in Science, that happened about a month after.

What we projected was that reducing transmission through a variety of means can knock down the reproduction number of the disease and prevent intensive care units from overflowing. Something we learned.... We didn't really anticipate that a lot of deaths in Ontario would come in the long-term care facilities. We knew that long-term care facilities were vulnerable, but we assumed, as we were doing our modelling, that people would try to protect them, which turned out not to be the case.

What we've found is that various combinations of case identification with contact tracing or straight physical distancing are sufficient to knock the reproduction number down enough that ICUs don't overflow. This has been the case in Canada, which is wonderful.

Moving forward, we now have a second iteration of that model in press, in a journal called Annals of Internal Medicine. Thanks to the provincial modelling table, we've been able to calibrate the model. That means we've fit the model to real data. We couldn't do that beforehand because we didn't have an epidemic to fit it to. We can fit it to ICU occupancy in Ontario and can fit it to hospital deaths. The long-term care stuff is very challenging to try to fit into any sort of model. What we see is that, basically, the lower disease activity goes and the slower we reopen, the longer it will be before we have a resurgence.

In our paper in March, in the Canadian Medical Association Journal, my colleague, Dr. Ashleigh Tuite, who I've referenced previously and is a brilliant modeller, came up with the idea of dynamic social distancing, which depends on really good public health surveillance, so that you know when your hospital is starting to fill up again and when you have to strengthen distancing measures. I really think the group at Harvard, who we're friends with, may have copied that from us. That came out in the Science paper as well a couple of weeks later. It's this idea—and journalists refer to it as surfing the wave—that we're likely to go up and down and up and down with this disease for a while until we have a vaccine, which may come sooner than I ever would have imagined.

● (1835)

Mr. Tony Van Bynen: Thank you.

Yesterday I asked Dr. Tam about the provinces and territories and their plans to reopen their economies, as well as people starting to leave their homes as the weather gets nicer. As a follow-up, with the information obtained from your study in mind, what are your thoughts on how this can be implemented safely?

Dr. David Fisman: This is not our work. There's a marvellous mathematician at Waterloo by the name of Chris Bauch who has a paper looking at regional reopening in Ontario as opposed to blanket policies, with the outcome of interest being how we can minimize the amount of time in lockdown.

I think some organic reopening is happening anyway as the weather gets better, and that's all right. This doesn't seem to be an infectious disease that spreads particularly well in parks or as people are out enjoying themselves, as long as they're maintaining a bit of distance. This disease really continues to show that it likes big crowds and indoor places. I think our most recent superspreader event here in Ontario was among greenhouse workers in Chatham, which fits the description to a T: 50 people were infected working in a greenhouse. When folks are in small groups and there's a low upper bound on the number of people they're working with—we call that “work bubbles”—or when folks are enjoying themselves outside to stay fit, going to parks or enjoying the outside with their kids, that generates minimal risk for us.

What we do need is good, strong surveillance systems—and this circles back to our initial conversation about testing—that let us know when we're getting into danger again, as we were in March. I do think we're going to struggle in the fall. Again, there's a lot of hindsight at this point. This thing emerged in January, but we didn't really get serious about it until March, and I think we're going through that again. Anyone who looks at disease dynamics for a living can tell you that we're in a lull now but the disease is probably going to be coming back in September or October. We have some golden time now to get prepared for a likely resurgence in the fall. I think we need to build those surveillance systems and get much better at this by the time we get to the fall, because we're going to have to be more nimble then. There's much we can do, and there's much we can do safely if we avoid large gatherings.

The bubble idea—and a lot of corporations have already instituted this— is simply that if you divide people up into relatively small teams, they don't work simultaneously in the office and there's a deep clean between when teams are in the office, you have an upper bound on how many people are going to get infected if someone comes into the bubble with infection.

I think there's a lot of ingenuity and a lot of wiggle room in reopening the economy safely, as long as we have the surveillance systems that allow us to see when we're getting back into trouble.

The Chair: Thank you.

Ms. Jansen, please go ahead. You have five minutes.

Mrs. Tamara Jansen: Dr. Khan, I'm curious about your thoughts, as a infectious disease specialist, on the current deal that Health Canada has made with China on developing a COVID-19 vaccine.

The announcement mentioned that the National Research Council is working with CanSino Biologics to advance a vaccine, which is being developed jointly with the People's Liberation Army. Apparently Health Canada has even approved the first human clinical trial that will be run at Dalhousie University in spite of the fact that CanSino has not published any data from its first trial phase for any sort of public scrutiny.

This really shocked me. Vaccine development cycles are normally 10 to 15 years, and the shortest ever was four years. Our Five Eyes intelligence alliance has raised concerns regarding China's transparency regarding this particular pandemic. They even denied, initially, human-to-human contact. And some whistle-blowers have disappeared.

If we want Canadians to buy into a COVID-19 vaccine, wouldn't it make more sense to be working with a more trustworthy partner on this sort of thing? Does it strike you as being dangerous?

● (1840)

Dr. Kamran Khan: Thank you for the question. I'm going to try to see if I can tackle it.

With respect to vaccine development and partnerships, I would say that I'm not fully aware of all the details of how Canada is looking at vaccine development, perhaps, with the Government of China or with scientific groups in China.

I think all of the points that you've raised are very important. Clearly, there is a race to get to a vaccine as quickly as possible, not only from a preventative standpoint but also to develop therapeutics.

I think I'm probably not well equipped to speak to the broader ethical issues here. I'm just less informed about the specifics of this particular circumstance.

But clearly, the points that you're raising around transparency are critical in any scientific endeavour. I think that is a critical issue.

I'm not sure if, perhaps, Vito or others want to chime in on that.

Mrs. Tamara Jansen: My time is limited. I have another question, but not specifically for you.

Going back to Professor Attaran, you mentioned that we could ask you questions about yesterday's meeting.

I asked Dr. Tam about her flip-flop on the use of masks. Up until early April, Dr. Tam stated that an asymptomatic person shouldn't wear a mask. It didn't work. It might even be harmful. Then on April 6, she changed her mind and said that a mask was good for additional protection.

Her response to my question on why her message changed was that, apparently, new evidence had come to light.

As this was a respiratory pathogen, I imagine that out of the abundance of caution, masks would have been helpful right from the beginning.

In your opinion, what sort of new evidence has come to light over the course of this pandemic that would substantively change the way we consider the effectiveness of masks as prophylactics?

Prof. Amir Attaran: There's no easy way for me to say this, but Dr. Tam was not being truthful.

In the week or 10 days.... Pardon me, I don't know the exact time span between her statement that masks were not to be recommended to the public and then changing her view to give permissive guidance that masks of a non-medical sort could be used. In that short period of, as I say, about a week or 10 days, there was no new evidence that emerged to justify that change.

There have been additional studies of masks, of course, some of it biophysics, what particle size will penetrate a mask in what conditions. But there was definitely not in that crucial window a game-changing study.

Mrs. Tamara Jansen: I have a really quick question. My time is almost out.

You provided a chart in your submission that showed that Australia and, I believe, South Korea had much better pandemic trajectories than Canada did. As with all catastrophic emergencies, there's never just one thing that goes wrong that causes the tragedy, and I assume that's the same when things go right.

What, in your estimation, are the critical things that ensured better outcomes in those countries compared to Canada?

Prof. Amir Attaran: Australia, for instance, was very quick at cutting off travel with China. It did so at the same time as President Trump did, but for sounder reasons than Mr. Trump.

It was also incredibly quick at organizing coordination between the states—the provinces, if you will—and the federal government. As I mentioned, they signed an accord on co-operation on March 13. Such an accord doesn't exist in this country yet.

The Australians have, generally speaking, a very strong sense of biosecurity because they are an island continent and they have honed that over years. They're much more attuned to risks coming in from abroad than we have been. The error of not being tougher on travel sooner is one that we will, of course, regret for many years to come.

The Australians also, I feel, were extraordinarily good at their social distancing. Now, precise measures of how aggressive social distancing is are hard to come by. Dr. Fisman would be able to speak to that far better than I could, but even from my inexpert point of view on this, it's clear the Australians did take the social distancing more seriously early on than did Canadians, and that has had an effect.

● (1845)

The Chair: Thank you.

Ms. Sidhu, go ahead, five minutes.

Ms. Sonia Sidhu (Brampton South, Lib.): Thank you, Chair.

Thank you everyone for coming today.

As you know, I really like all the witnesses. Yesterday Dr. Tam and her team were here.

This committee has really been focusing on supporting Canadians and how we can better help all Canadians.

Today I really want to say thank you to all the witnesses and my first question is to Dr. Khan.

You talked about the rigorous factor and triggering the next wave. Can you explain to the committee how your technology can be used to track second or third waves of COVID-19? What do you see as the biggest risk that's coming?

Dr. Kamran Khan: In the technology that we've developed, and I'm going back to that metaphor of smoke detector and fire extinguisher, we've really been focusing much more on developing the early warning systems that could give us a signal that there is a threat coming.

COVID-19 is here now and we're all very well aware of it and we're now sort of more in firefighting mode, grabbing the fire extinguisher to put fires out.

From the standpoint of our technology, the area where we are supporting public health decisions is around an understanding of population movements and how that relates to the transmission of COVID-19 across the country.

With respect to the next set of waves, I have two thoughts. One is clearly the vast majority of the population in Canada remains susceptible, as we've heard. We either could see an uptick in cases later in the fall because of a variety of factors including climate conditions and dynamics of how people are interacting, or we could find ourselves in a similar position to some countries like Australia and New Zealand, where imported cases become the catalyst for another wave.

So we're going to have to be thinking both internally and externally. These are a couple of examples of how our technology is looking internally within the country domestically as well as globally.

Ms. Sonia Sidhu: Thank you.

My next question is for Mr. Ciciretto. Your company is based in Brampton. Your company recently moved to providing COVID-19 test results online instead of over the phone. How has that increased the efficiency of your testing process?

In Canada today, 1.3 million people have been tested. What do you think? How has online reporting instead of over the phone reporting increased the efficiency of your testing process?

Mr. Vito Ciciretto: The ability to transmit results directly from an analyzer onto your laboratory information system and into provincial health repositories is critical from at least two perspectives. One is from a timeliness perspective. As soon as that test result is available you want to make sure that you're able to release it.

The second and perhaps even more important perspective has to do with accuracy. The minute that there's any type of human interaction, of taking a manual result from a machine and then transmitting it onto a computer, there's always that risk of error, and that's not something you want, obviously.

● (1850)

Ms. Sonia Sidhu: Dr. Fisman, as you know the Public Health Agency has its opinion on non-medical masks.

You also mentioned the mask adoption strategy; how is this beneficial to Canadians?

Dr. David Fisman: We don't know but we can be highly suspicious that it would help us a lot. Especially if we can get the reproduction number of the disease down to around one. That's a tipping point. At that tipping point, very small changes in infection transmissibility can really make the epidemic fall through the floor and go away.

What you have to remember about masks and disease like this is that masks work in both directions. They reduce the likelihood that you get infectious particles into your nose, mouth and eyes potentially, if you keep your hands off your face. They also prevent you from infecting other people. Probably the more important part with this disease is the reduction of transmission, which happens very efficiently even with cloth masks. The reason that's so important with this particular disease is that what we know of the work of Gabriel Leung and his colleagues in Hong Kong, which was published in Nature about a month ago, is they estimate about 44% of transmissions in Hong Kong occur in presymptomatic individuals. Those are people who are going to feel sick tomorrow, but they feel just fine today. They haven't changed their behaviour.

Masks can be extremely impactful because if I'm wearing a mask and I become infectious but I don't know it yet, I don't infect you. Everybody wants to wear a mask to protect themselves from other people. I'm fine to have folks leverage that to get the masks on. It's pretty clear. There's a reason why surgeons wear masks in the operating room because they block extrusion of respiratory droplets that infect with bacteria the patients they're operating on. This would be the same idea except out in public you're wearing a mask not to protect yourself necessarily—although it might—but to protect other people from you if you're infectious but don't have symptoms.

As I say, we've had reproduction numbers in Ontario and Quebec, which is basically where our epidemic lives now, rumbling along around a reproduction number of one. In Ontario it's been there since early April, we just can't seem to get it down. If anything knocks that reproduction number down to 0.7 or 0.6, we're going to get back to a lot more rapid economic opening up. We're going to be able to open up more. The lower we keep that reproduction number, the more we'll be able to open up the economy while still staying safe.

To me it's a no-brainer. We can argue about class 1A evidence or what have you. We can have a symposium about this in five years and decide what exactly the science shows. But now is the time for action.

As Professor Attaran said, we're burning through $12 billion a week. Getting masks on Canadians and teaching them how to use them is change from between the couch cushions relative to what we're burning through by keeping our society closed. To me it's worth the gamble.

● (1855)

The Chair: Thank you.

We go now to Mr. Desilets for two minutes and a half, please.

[*Translation*]

Mr. Luc Desilets (Rivière-des-Mille-Îles, BQ): Thank you, Mr. Chair.

My thanks to all the witnesses for joining us. The content they have shared with us is very interesting.

My first question is for—

[*English*]

The Chair: Pardon me, Mr. Desilets, your sound is bad as well.

Could you try and unplug your headset and plug it back in?

I will suspend for a minute.

● (1855)

_____(Pause)_____

● (1900)

The Chair: I declare this meeting resumed.

Please go ahead, Mr. Thériault, on behalf of Mr. Desilets.

[*Translation*]

Mr. Luc Thériault: Okay.

Earlier, when I asked Dr. Fisman a question, I noticed that Dr. Schabas was reacting. I think he wants to answer the question.

It had to do with the rate of safe reopening that Canada should adopt in order to have herd immunity, given that we don't have a vaccine yet, we don't have antivirals, and we are just beginning serological testing.

My question is for Dr. Schabas.

[*English*]

Dr. Richard Schabas: One really profoundly unfortunate thing about what's happened in Canada, where we in fact did the lockdown in advance of our outbreak, unlike many places in western Europe or in the United States, is that in a sense we've had the worst of both worlds. We have achieved very little herd immunity, certainly no more than 5%, at least in the whole country, yet we've had a lot of deaths. We've had a lot of deaths because of the outbreaks in the long-term care homes. The population death rate in the city of Montreal is twice as high as it is in Stockholm, Sweden and is starting to close in on the city of New York. It's not been a very happy experience.

There were two kinds of outbreaks. There was the long-term care outbreak, which drives mortality, and then there's the community outbreak, where there has been very little mortality.

The fundamental question is: Is it safe to reopen in the presence of active disease? No, not in the sense that we're not going to see more COVID disease. We will. When we start to open up, we are going to see more COVID disease.

The whole thrust of my presentation is to look at it the other way. Is it safe not to open up? We talked, and one of the earlier questions was: When are we going to open the schools? Why are we opening the schools? There's going to be more COVID spread. Well, the reason you open schools is that children have to go to school. It's a fundamental right of children to have an education. If we deprive a whole generation of children of six months or a year of education, we're going to be paying the public health price for that for years to come.

There is no nice solution. Dr. Fisman and Dr. Attaran talk about doing more testing and contact tracing, something which, by the way, has never been done to control a respiratory virus. It may work well on a spreadsheet; the real world is more complicated. I hope they're right. I hope they're right and that works, but the real world is a rather more complicated place.

I was just going to say what I'm really worried about is that when they try the strategy and the disease resurges in the fall and the strategy fails, as I believe it almost certainly will, we can't go back into this kind of lockdown because we will do more long-term damage to our public health than COVID-19 could ever do.

● (1905)

The Chair: Thank you, Mr. Thériault.

We go now to Mr. Davies.

Mr. Don Davies: Thank you.

Dr. Schabas, you wanted a chance to explain, so I'm going to put a few things to you. After SARS, you wrote, “In the unlikely event of another SARS outbreak in Canada, public health officials should quarantine no one.” Now, our current pandemic is a SARS outbreak. The virus is SARS-CoV-2. We fought it mainly with lockdown and quarantine. My first question is, are you standing by your extraordinary statement that we should quarantine no one?

Before I get to that, I want to contrast that. In 1990, when you were Ontario's chief medical officer, you classified HIV as a virulent disease, which is the worst category of characterization, and you recommended that we forcibly confine people with HIV who may have had sex with someone else, even if they used a condom and even if they disclosed that to their partner.

My final piece, before I let you answer, is that you said that we should treat this more like the 1957 flu, but the fatality rate in the 1957 flu was about 0.1%, which is about one-twelfth that of COVID-19.

Throwing all those together, can you help me understand your point of view?

Dr. Richard Schabas: I'll try to remember all of them.

First of all, let me start with the SARS 1 and the quarantine. I was talking about SARS 1. SARS 1 was a disease that was not transmissible asymptomatically and was not even transmissible in its early symptomatic stage, so quarantine made zero sense with SARS 1, and my hope was that it wouldn't happen again.

Yes, we've used it widely in SARS 2. Whether it's really been very effective, or whether it's a useful tactic, because as I've said before, you can maybe flatten the curve.... In fact, I'm quite impressed by our ability to implement quarantine, and I think it probably has to some degree flattened the curve, but the question is ultimately to what end? The virus isn't going anywhere, and unless the measures you're using to flatten the curve are somehow sustainable in the long term, I'm not sure they really get us anywhere.

On the third question, as related to HIV, yes, I had recommended it. I didn't do it. It wasn't up to me. I had recommended to the minister that it be classified in the same category as diseases like tuberculosis, syphilis, gonorrhea and hepatitis B. It was a classification that would give a judge the authority to incarcerate someone who was deliberately spreading the disease. That was the context of it. It actually never happened, and that's not quarantine. Please understand that quarantine is when you lock someone up who you think is incubating the disease.

Case isolation, which is a totally different thing, is that when you know somebody has the disease, you take steps to isolate them. I'm not recommending that we do this for HIV. That's a different context. That's what we do, in fact, when people have COVID or we have good reason to believe they have COVID. We isolate them. That's not quarantine. Quarantine is when you lock them up when you think you're incubating them.... The term “quarantine” itself derives from the 40 days of Lent. That's a medieval strategy and, by and large, I think it belongs back in the Middle Ages.

● (1910)

The Chair: Thank you.

Mr. Don Davies: I have a point of privilege to raise before we adjourn, Mr. Chair.

I would like to move a motion that this committee inquire into reports that a witness appearing before the health committee, Dr. Amir Attaran, may have been threatened, punished, intimidated or otherwise harmed by the Public Health Agency of Canada, Statistics Canada or the federal government in some other form, because of testimony he has given at the health committee, and to determine if a prima facie issue of privilege has been raised and, if so, report such findings to the Speaker of the House.

Mr. Chair, I'm quoting from Bosc and Gagnon, which says this:

> ...the intimidation of a committee witness has also been found to be a prima facie breach of privilege. In 1992, a witness who had testified before a subcommittee was advised by a Crown corporation employee that the issue of her testimony was being referred to the corporation's legal department. The witness informed a Member, who raised a question of privilege in the House. The matter was found by Speaker Fraser to be prima facie contempt and was referred by the House to the Standing Committee on House Management for consideration.

In its report, the committee said this:

> The protection of witnesses is a fundamental aspect of the privilege that extends to parliamentary proceedings and those persons who participate in them. It is well-established in the Parliament of Canada, as in the British Parliament, that witnesses before committees share the same privileges of freedom of speech as do Members. Witnesses before parliamentary committees are therefore automatically extended the same immunities from civil or criminal proceedings as Members for anything that they say before a committee. The protection of witnesses extends to threats made against them or intimidation with respect to their presentations before any parliamentary committee.

Mr. Chair, I could go on. There are many more. I move that there has been a violation of my privileges as a member of this committee, and I would ask that you act on the motion that I have moved.

The Chair: Mr. Davies, you're in a point of order. You can't make a motion on a point of order.

As far as the question of privilege goes, as I mentioned earlier, I believe that's out of scope for our authority to conduct these video conference meetings. We are restricted to solely receiving evidence relating to the government's response to COVID-19, and we are also allowed to make motions regarding the invitation of witnesses.

Certainly, as I've mentioned before, I will take the matter under advisement. I will look for a legal opinion from the clerk and from the legal clerk as well, and we can take this up at another time. I'll take that under advisement and—

Ms. Sonia Sidhu: Mr. Chair, I would like to raise a point of order.

There were comments made in testimony today that I believe break parliamentary language. It was deeply disrespectful to call Canada's public servant untruthful. That comment should be removed from the committee record.

The Chair: Thank you for that point of order.

Certainly, we are bound by the rules of Parliament in our conduct here. I would certainly urge all participants, going forward, to be prudent in their language.

Thank you, everybody. I'd like to—

Mr. Matt Jeneroux: Mr. Chair, this is to Mr. Davies' point of order.

The Chair: Go ahead.

Mr. Matt Jeneroux: I'm reading the motion adopted by the House of Commons in the sitting on Tuesday, March 24, 2020. Section (i) states the following:

> ...if committee is not satisfied with how the government is exercising its powers under the Act, it may adopt a motion during a meeting by videoconference or teleconference to report this to the House by depositing a report with the Clerk of the House which shall be deemed to have been duly presented to the House on that day;

I would point to you, Mr. Chair, and also the clerk, to reference that point when coming back and addressing Mr. Davies' question of privilege.

Mr. Don Davies: If I might, Mr. Chair—

The Chair: I'm sorry, I—

Mr. Don Davies: —I want to be very clear that I am not raising a point of order. I am raising an issue of privilege.

I can further quote that it says in the—

The Chair: Just hold on, Mr. Davies.

Thank you, Mr. Jeneroux, for your contribution.

I believe you did start your remarks, Mr. Davies, on a point of order. You then went into a question of privilege. It's kind of beside the point. I will take under advisement your motion. We will get back to you once I have a ruling from the law clerk.

● (1915)

Mr. Don Davies: Mr. Chair, with respect, it's very important that you....

You're misunderstanding my point. Earlier I raised a point of order. I am now raising a question of privilege. That's what I did in my second intervention. You clearly have the power, in fact you have the duty, to receive my question of privilege as it's raised in committee, because this is where I have to raise that.

I'm happy for you to go back and reflect on it, but I want to be very clear that I am raising a question of privilege and I am asking for your consideration of the motion that I have moved.

The Chair: Thank you, Mr. Davies. As I said, I will take the matter under advisement. We will get back to the committee in due course.

Mr. Don Davies: Thank you.

The Chair: Thank you, everybody.

Thank you to our witnesses. It's been a lively and robust discussion. Thank you for sharing so much of your time with us and for putting up with our technical issues.

Thank you to the House staff and the technical people for being with us to work through those issues and thank you to the members for all the great questions.

Have a good day, all, and thank you.

The meeting is adjourned.

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EXHIBIT C

This is Exhibit "C" referred to
in the Affidavit of
Dr. Richard Schabas

Sworn before me this 29th day
of May A.D., 2021

A Commissioner for Oaths in and for Ontario

LISA D.S. BILDY
BARRISTER & SOLICITOR

Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector

August 2018

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Preface

Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector (CPIP) is a federal, provincial, and territorial (FPT) guidance document that outlines how jurisdictions will work together to ensure a coordinated and consistent health-sector approach to pandemic preparedness and response. CPIP consists of a main body, which outlines overarching principles, concepts, and shared objectives, as well as a series of technical annexes that provide operational advice and technical guidance, along with tools and checklists on specific elements of pandemic planning. The CPIP main body and its annexes are intended to be used together.

CPIP was first published in 2004. In 2006, the Pan-Canadian Public Health Network (PHN) Council approved an updated version of CPIP as an evergreen document to be updated as required. In 2009, Canada’s pandemic preparedness planning efforts were tested for the first time, with the emergence of the H1N1 influenza pandemic. In 2012, a CPIP renewal process was initiated by the PHN Council. This latest version of CPIP, was approved by FPT Deputy Ministers of Health 2014, with further update in 2018. It incorporates evidence from H1N1 lessons learned reviews conducted at the FPT and international levels and by various stakeholder groups, and scientific advances. As an evergreen document, the CPIP main body and each annex will be reviewed every 5 years, with updates made between review cycles, if necessary.

Since 2012, The CPIP Task Group (CPIP TG) has overseen the CPIP renewal process.The CPIP TG consists of members with expertise in the areas of pandemic and seasonal influenza, pandemic preparedness planning and response, emergency management, epidemiology, public health, virology, bioethics, immunization, surveillance, and laboratory diagnosis.

The updated CPIP allows for a more flexible and adaptable response to future pandemics, providing scope for provinces and territories (PT) to adapt their own plans and responses to local and regional circumstances. The title of the document also has changed, from Canadian Pandemic Influenza Plan for the Health Sector to Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector, to more accurately reflect its role and intended use as a guidance document.

CPIP now supports a risk-management approach and includes new concepts such as pandemic impact assessment, descriptions of pandemic scenarios of varying impact, and identification of triggers for a Canadian response. It also better reflects Canada's geographic, demographic, cultural, and socio-economic diversity and the imperative for planners to take this diversity into account. CPIP has been subject to extensive FPT government review and targeted stakeholder consultations. Stakeholders included national-level organizations representing health professionals, emergency preparedness and first responders, community services, the private sector, and Indigenous peoples.

1.0 Introduction

1.1 Background

Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector (CPIP) provides planning guidance to prepare for and respond to an influenza pandemic. Influenza pandemics (subsequently referred to as pandemics) are unpredictable but recurring events that occur when a novel influenza virus strain emerges, spreads widely and causes a worldwide epidemic. Unfortunately, it is not possible to predict the anticipated impact of the next pandemic or when it will occur.

Planning for a prolonged and widespread health emergency of unpredictable impact is challenging but essential. It requires a "whole of society" response and the coordinated efforts of all levels of government in collaboration with their stakeholders.

Pandemic planning activities within the health sector in Canada began in 1983. The first Canadian pandemic plan was completed in 1988 and was followed by several updates. In 2004, the Canadian Pandemic Influenza Plan for the Health Sector was published as the result of extensive collaboration among FPT and other stakeholders. Before this version, the last major update to the CPIP and its annexes occurred in 2006.

The 2009 influenza A (H1N1) pandemic (subsequently referred to as the 2009 pandemic) provided the first real test of Canada's pandemic preparedness planning efforts. Collaboration among all levels of government and stakeholders was unprecedented compared with previous events like the Severe Acute Respiratory Syndrome (SARS) outbreak in 2003. The public health and health care systems were stressed but in most instances were able to cope. Antiviral stockpiles were deployed and pandemic vaccine was administered to millions of Canadians. There were, however, many challenges identified in this experience.

Canada's pandemic planning continues to evolve on the basis of research, emerging evidence and the lessons learned from the 2009 pandemic. The value of building on seasonal influenza surveillance systems and control measures is well recognized. Making these systems and measures as robust as possible in the interpandemic period will help prepare for a strong pandemic response.

1.2 Purpose

CPIP's overall purpose is to provide planning guidance for the health sector for pan-Canadian preparedness and response, in order to achieve Canada's pandemic goals:

> First, to minimize serious illness and overall deaths, and second to minimize societal disruption among Canadians as a result of an influenza pandemic.

The main body of CPIP provides strategic guidance and a framework for pandemic preparedness and response, whereas the CPIP annexes provide operational advice and technical guidance, along with tools and checklists. As an evergreen document, CPIP will be updated as required to reflect new evidence and best practices.

It is important to note that CPIP is not an actual response plan. Rather, it is a guidance document for pandemic influenza that can be used to support an FPT all-hazards health emergency response approach. While CPIP is specific to pandemic influenza, much of its guidance is also applicable to other public health emergencies.

1.3 Audience and Scope

CPIP is pan-Canadian pandemic planning guidance for the health sector developed under the guidance of a group of Canadian experts. The primary audiences are the FPT ministries of health together with other ministries that have health responsibilities. While it is anticipated that CPIP's strategic direction and guidance will inform FPT planning in order to support a consistent and coordinated response across jurisdictions, PTs have ultimate responsibility for planning and decision-making within their respective jurisdictions. CPIP also serves as a reference document for other government departments, non-governmental organizations (NGOs) engaged in health issues, and other stakeholders.

While CPIP provides pandemic planning guidance, it does not address business continuity preparedness or overall management of a health emergency. These activities are critical for an effective pandemic response; however they are more appropriately addressed in the emergency plans of individual jurisdictions and organizations. Neither does CPIP address pandemic preparedness and response in the non-health sectors (e.g., community and social services, public safety), although some of its content may be a useful reference.

1.4 Changes in This Version

There have been considerable changes to CPIP since the 2006 version in both format and content.The strategic nature of the information in the main body of the planning guidance has been strengthened and lessons learned from the 2009 pandemic have been incorporated. While the overall pandemic goals remain the same, new objectives have been added along with a set of principles to support the response. These are accompanied by a discussion of ethical considerations pertaining to pandemic preparedness and response, and consideration of the implications of Canada's diversity and the needs of vulnerable persons. Roles and responsibilities for each level of government have been described more explicitly.

The new CPIP outlines a risk management approach to support a flexible and proportionate response. Risk management involves setting the best course of action in an uncertain environment by identifying, assessing, acting on and communicating risks. Information has been added about what is known and what is uncertain about pandemic influenza. The planning assumptions have been updated, and four hypothetical planning scenarios have been developed to illustrate the importance of developing plans and response strategies that are flexible and can

be adapted as circumstances require. CPIP also provides triggers for action that are based on novel virus emergence and pandemic activity in Canada rather than the global World Health Organization (WHO) phases. Finally, content has been updated in each of the specific response areas.

The CPIP technical annexes are being renamed according to their subject (e.g., Surveillance, Vaccine) instead of being named alphabetically. As part of the CPIP renewal process, it is intended that each of the technical annexes will be revised.

2.0 Context for Planning

2.1 Understanding Pandemic Influenza

2.1.1 Influenza and the Origin of Pandemics

While there are four types of influenza virus (A, B, C and D), only influenza A and B viruses cause seasonal outbreaks in humans, and only influenza A viruses have been known to cause pandemics. Aquatic birds are the natural hosts for influenza A viruses, although a wide range of species can be infected and significant disease outbreaks can occur in poultry, pigs and other species. Most of these animal influenza virus strains do not cause disease in humans although occasional human (zoonotic) infections occur, usually through close contact with infected poultry or animals.

Influenza pandemics or worldwide epidemics occur when an influenza A virus to which most humans have little or no immunity acquires the ability to cause sustained human-to-human transmission leading to community-wide outbreaks. Such a virus has the potential to spread rapidly worldwide, causing a pandemic. [1]

These novel viruses may arise through genetic reassortment (a process in which animal and human influenza genes mix together) or genetic mutation (when genes in an animal virus change, allowing the virus to easily infect humans). Pigs can become infected with influenza viruses from different species and act as a “mixing vessel” to facilitate the reassortment of genes from different viruses.

Not all novel influenza viruses evolve into pandemic viruses. Some novel subtypes, like the avian A (H5N1) virus, have caused sporadic human cases on an ongoing basis since 1997 but have not gained the ability to spread easily in humans. As the overall human case fatality rate for A (H5N1) infections has been over 50%, [2] there are concerns about the potential of a high impact human pandemic if this virus gains the capacity to spread easily between people.

2.1.2 Typical Pandemic Characteristics

Historical evidence suggests that influenza pandemics occur three to four times per century. In the last 100 years there were four pandemics separated by intervals of 11 to 41 years. They varied greatly in their impact, as measured by illness and deaths. The 1918-1919 pandemic had a high impact, killing an estimated 30,000 to 50,000 people in Canada and 20 to 50 million people worldwide. The impact of the 1957 and 1968 pandemics was considered moderate, whereas the 2009 pandemic had a lower impact.

Pandemics of the Last 100 Years, subtypes and common names:

1918-1919:	H1N1 “Spanish flu”
1957-1958:	H2N2 “Asian flu”
1968-1969:	H3N2 “Hong Kong flu”

2009:	H1N1 "Influenza A(H1N1) 2009"

While every pandemic is different, some common characteristics can be recognized:

- The pattern of disease is different in pandemics than in seasonal influenza.
- Pandemics may arrive outside of the usual influenza season and typically have more than one wave of illness.
- The total duration of a pandemic is likely to be 12 to 18 months.
- During a pandemic, the new pandemic virus replaces other circulating influenza strains. Afterwards, the pandemic strain becomes part of (and may dominate) the mix of seasonal influenza A viruses.
- During seasonal influenza, most hospitalizations and deaths occur in the elderly and persons with underlying health conditions, whereas, in a pandemic, disproportionately more severe disease and death is seen in young people and in persons without underlying health conditions. [3]
- There is a gradual reversion back to the typical seasonal morbidity and mortality pattern over the decade following the pandemic.

During the 1918-1919 pandemic, 99% of influenza-associated deaths in the United States (US) were in persons under 65 years of age and nearly half of these among previously healthy adults 20-40 years of age. In subsequent pandemics, the proportion of influenza-associated deaths in the US in persons under 65 years of age was 36% (1957-58), and 48% (1968-69). [4] In the 2009 pandemic 70% of reported deaths in Canada were in persons under 65 years of age. [5]

2.1.3 Pandemic Impact

The term “severity” is often used to describe both severity of disease in individuals (clinical severity) and the overall “severity” of a pandemic in a population. In CPIP, the term **severity** is used to describe clinical severity of disease in individuals and **impact** is used to describe the effects of a pandemic on the population.For planning and response purposes, describing the “impact” of a pandemic on the population is a more meaningful approach than talking about its “severity”. It is acknowledged that this usage may vary from the approach of some other authorities. For example, the WHO uses the term “pandemic severity” for what CPIP terms “impact” but the concepts are the same. [6]

Severity refers to clinical severity of disease in an individual (e.g., mild, moderate or severe disease).

Impact refers to the effects of a pandemic on a population (e.g., low, moderate, or high impact).

Pandemics vary in their impact, as do seasonal influenza outbreaks, although usually on a higher scale of magnitude. A low impact pandemic might resemble moderate to severe seasonal influenza outbreaks, although its epidemiological profile would be different in important ways as previously described. In contrast, pandemics of moderate to high impact could result in high rates of illness and death across the country and would severely challenge the health care sector. They could also disrupt the normal functioning of society and put people with limited resources and support systems into a more vulnerable state.

Numerous factors can affect pandemic impact. These are outlined below and described in more detail in Appendix A:

- Viral factors are perhaps the most important. These characteristics of the virus itself are usually described as transmissibility (ability to spread) and virulence or clinical severity (the ability to cause severe disease). Transmissibility can be defined in terms of both the extent and the speed of spread and it can vary by season and setting.

- Factors affecting population vulnerability include pre-existing population immunity, the presence of underlying health conditions, or unexpected new risk factors for severe disease. Impact may be increased in vulnerable populations, including among Indigenous peoples, or settings such as remote communities, homeless shelters and overcrowded housing.
- Response factors include the effectiveness of interventions (e.g., public health measures, vaccine, and antiviral medications), the health care system response (e.g., access, surge capacity), and risk communications, along with the extent of public adoption of desired behaviours and social mobilization.

The impacts of a pandemic in psychosocial terms may be acute in the short term but can also undermine the long-term psychological well-being of the population. Psychosocial issues are not only experienced by those who become ill; distress permeates through the family and the community (e.g. financial stress due to economic downturns, caregiver burnout, occupational stresses, stigma/social exclusion).

The range of issues associated with psychosocial planning is broad involving all levels of government and multiple planning partners, including humanitarian actors such as community-based organizations, government authorities and NGOs and are closely aligned with the practice of risk communication [7].

2.2 Uncertainties and Unpredictability

Influenza is unpredictable - every influenza season and every pandemic is different. These uncertainties make pandemic planning challenging and highlight the need for flexibility and adaptability. Some of the major unknown areas about the next pandemic are the following:

- When the next pandemic will occur - although historically pandemics have occurred three to four times per century, there is no predictable interval. It should not be assumed that the 2009 pandemic has provided a respite during which preparedness efforts can be relaxed.
- Where it will emerge - while most seasonal influenza strains emerge in East/Southeast Asia, [8] the same is not true for pandemic influenza; the 2009 pandemic emerged in Mexico. An influenza pandemic could emerge anywhere in the world, and there may be very little lead time before Canada is extensively involved.
- What the nature of spread will be - pandemics often first arrive outside the usual influenza season (e.g., in late spring or summer) and typically have more than one wave of infection. However, this is not true in all circumstances or in all areas. A small first wave is often followed by a larger second wave, but the relative size of pandemic waves may vary. The speed of spread may also vary - pandemic waves can be intense or more spread-out over time. An intense wave would put more stress on the health care system.
- What its characteristics will be - the basic characteristics of the next pandemic virus are unknown, including its antigenic type (e.g., H2, H5, H7), its transmissibility and virulence, and the age groups and clinical groups most affected.
- What its impact will be - the last four pandemics demonstrated that population impact can vary from low to high and is not the same in all populations or settings. It is important to consider all possibilities and make plans adaptable for different circumstances. This will help ensure that the response is proportional to the evolution of the pandemic in any specific community.
- What effect interventions will have - typical seasonal influenza interventions are expected to be effective during the pandemic. However, the novel virus could be resistant to antiviral medications and/or pandemic vaccine production could be delayed or unsuccessful. The extent of vaccine uptake and adoption of public health measures is also unknown. Furthermore, interventions could have unintended consequences.

2.3 Lessons Learned from the 2009 Pandemic

There were many important epidemiological observations from the 2009 pandemic to take into account in future planning and response. These include the speed with which cases and sporadic outbreaks appeared in Canada after the novel virus was first detected and the early involvement of some remote and isolated communities, with severe disease in some First Nations communities. There was considerable variation in the timing and intensity of pandemic waves, especially the first wave, across the country. Although the symptoms were similar, age groups affected and risk conditions varied from seasonal influenza. Greater impact was seen in pregnant women and Indigenous peoples, and persons with morbid obesity were newly recognized as being at high risk for complications. For the duration of the pandemic, seasonal influenza strains were replaced by the pandemic strain and as with previous pandemics, it was not certain whether this single A strain dominance would continue in the 2010/2011 influenza season, A (H3N2) and B strains began to re-circulate and the pandemic virus became the seasonal A (H1N1) strain.

A number of challenges were identified in the national response. Surveillance demands were very heavy from the start, and were accentuated by the lack of linked information systems in some jurisdictions, unclear protocols for sharing information, and limited capacity for epidemiological analysis. The process for release of the National Antiviral Stockpile (NAS) was uncertain. There was high demand for critical care and ventilators for affected children and adults. Preparation and timely approval of concise national guidelines was difficult. The pandemic immunization program faced challenges with uncertain timelines for vaccine delivery, prioritization of vaccine supply, logistics of local campaigns and communication of changing recommendations.

On the positive side, previous planning processes and relationship-building led to unprecedented FPT collaboration and many successful stakeholder engagement efforts. Existing surveillance systems, like FluWatch, and ready-to-use hand hygiene and respiratory etiquette campaigns were valuable. Mathematical modeling was successfully used to support decision-making in some areas (e.g., recommendations for vaccine prioritization) and it was recognized that a number of other areas would benefit from modeling (e.g. predicting pandemic impact).

Following the pandemic, the Government of Canada (GC) [9] and most PT governments conducted lessons learned reviews. In addition, the Standing Senate Committee on Social Affairs, Science and Technology held extensive hearings on the response. [10] Some common themes emerging from these reports and recommendations were identified to improve preparedness, such as:

- streamlined FPT governance structure and clarification of roles and responsibilities;
- improved scalability and adaptability of response, with triggers to activate and deactivate specific responses while taking into account the variable impact and timing of the pandemic in different geographic regions;
- development of integrated electronic information management systems;
- strengthened surveillance systems and epidemiological capacity;
- collaborative processes to develop and strengthen guidance documents for health care workers (HCW) and other stakeholders to establish timely availability, accessibility, consistency and cultural sensitivity of messages;
- strategies to communicate risk, uncertainty and changing information;
- active participation of all stakeholders in pandemic preparedness and response;
- strengthened linkages with primary care and other front-line service providers;
- development of mechanisms for rapid funding and research priority-setting, multi-jurisdictional studies and centralized ethics approval for multi-centre studies;
- mechanisms to integrate new research findings into evidence-informed practice; and
- regular and rigorous testing of plans at all levels.

2.4 Understanding Canada's Diversity

Canada's geographic features and population diversity can create challenges in mounting an effective response to a public health emergency. Canada is a huge country geographically with communities that range in size from large cities to small rural and remote settlements. The proportion of people living in rural areas in Canada (18.9%) is low in comparison to other developed countries and is steadily declining. The proportion of the rural population, however, varies greatly (from 14% to 53%) from one province or territory to another. It is lowest in British Columbia and Ontario and is highest in the Atlantic provinces and the territories. [11]

Canada is diverse in terms of language, religious beliefs, ethnicity, culture and lifestyle. Canada's Indigenous peoples make up almost 4% of the population, the second highest percentage in the world after New Zealand. [12] While many Indigenous peoples live in remote and isolated communities in the North, about half live in urban areas. The median age of Canada's Indigenous peoples is considerably younger than that of non-Indigenous peoples (27 years compared with 40 years respectively). [13]

The proportion of foreign-born people in Canada is one of the highest in the world at 20%, [14] most of whom settle in large cities. Toronto and Vancouver now have over 40% visible minority populations and Montreal has 16%. [15] In addition there are many temporary residents, such as foreign workers and foreign students.

The needs of remote and isolated communities may be greater than other communities because of geographic isolation and health, social, environmental, economic and cultural considerations. These may affect the baseline health status and thus increase the vulnerability of their residents. In addition, some remote and isolated communities lack basic amenities, such as household access to running water, that are assumed to be present when public guidance like hand hygiene is issued. It is important to consider these factors, along with limited access to health care and transportation challenges, when planning for all aspects of the pandemic response in remote and isolated communities. Similar concerns may affect urban marginalized or vulnerable populations.

There are individuals within all jurisdictions whose needs are not fully addressed by traditional services or who cannot comfortably or safely access and use standard resources. Examples of these vulnerable persons include, but are not limited to, individuals who are:

- physically or mentally disabled (e.g., visually or hearing impaired, mobility limitations, cognitive disorders);
- limited or non-English or French speaking;
- low literacy;
- geographically, culturally or socially isolated;
- low income;
- medically or chemically dependent;
- homeless or street-involved;
- housebound or frail seniors; and
- new immigrants and refugees. [16]

It may not be a single one of these conditions that determines the degree of vulnerability, but rather a combination of them under certain circumstances [17].

Studies indicate that there is a social gradient of risk during influenza pandemics, based on social vulnerabilities that are likely to lead to increased exposure to infection, risk of basic human needs not being met, insufficient support and/or inadequate treatment. [18] Vulnerable populations might become more marginalized if pandemic health services are streamlined into standard approaches to reach the general population.

Within the nationally coordinated pandemic response it is important to allow sufficient local flexibility to address the unique needs of vulnerable populations. Detailed influenza-specific planning guidance has been developed for vulnerable populations in Canada. [19, 20] These referenced documents should be useful for FPT and regional/local planners.

Responsibility for planning for vulnerable populations is often unclear and although public health is typically involved, inclusion of all relevant stakeholders is important for comprehensive planning and buy-in. It is important for planners to address the unique needs of their jurisdiction. This begins with identifying populations and settings associated with increased risk of illness or severe outcomes from pandemic influenza along with persons who might need tailored prevention and care services during a pandemic. Specific planning considerations include information needs (e.g., language, cultural style and methods of dissemination); access to assessment, treatment (including antiviral medications) and convalescence support; access to vaccine; and need for support for activities of daily living.

2.5 Ethical Considerations

This section summarizes the more important ethical considerations in pandemic planning but is not intended to be an actual ethical framework. Ethical considerations are also addressed more specifically in various CPIP annexes with supporting tools and frameworks where available.

In Canada, ethical considerations are increasingly taken into account in the development of health policy. Ethical analysis helps to identify the ethical issues and determine how to do the right thing in a fair, just and transparent way. Many of the issues encountered in pandemic preparedness and response involve balancing rights, interests and values. Examples include decisions over resource allocation; prioritization guidelines for pandemic vaccine and antiviral medications; adoption of public health measures that may restrict personal freedom; roles and obligations of HCWs and persons providing medical first response, as well as their employers; the potential need for triage in the provision of critical care; and responsibilities to the global community. [21]

The application of ethical reasoning to pandemic preparedness and response begins with identifying and prioritizing the ethical questions in the issue under consideration. Analysis should include reflection on the ethical considerations associated with the options, taking into account the societal versus individual interests and values that are at stake. Ethical tensions are inevitable. When weighing the options, it is important to be guided by the Canadian pandemic goals.

As pandemic planning initiatives fall within the domain of public health, they are guided by a code of ethics that is distinct from traditional clinical ethics. [22] Whereas clinical ethics focuses on the health and interests of individuals, public health ethics focuses on the health and interests of a population. When a health risk like a pandemic affects a population, public health ethics predominates, and a higher value is placed on collective interests.

In practical terms, this means there should be an emphasis placed on trust and solidarity. Successful public health activities require relationship-building and can contribute to creating and maintaining trust between individuals, populations and health authorities. Solidarity is the notion that we are all part of a greater whole, whether an organization, a community, nation or the globe. Another important consideration is reciprocity, meaning that those who face disproportionate burdens in their duty to protect the public (e.g., HCWs and other workers who are functioning in a health care capacity, for example police or fire personnel who are providing medical first response) are supported by society, and that to the extent possible those burdens are minimized.

The concept of stewardship is also closely related to trust. Stewardship refers to the responsible planning and management of something entrusted to one's care, along with making decisions responsibly and acting with integrity and accountability. Trust, stewardship and the proper building of relationships also mean that the power conferred to government and health authorities will not be abused. For example, if restrictions are deemed essential for proper risk management, they must be effective and proportional to the threat, meaning that they should be imposed only to the extent necessary to prevent foreseeable harm. These restrictions should also be counterbalanced with supports to minimize the burden on those individuals affected.

The concepts of equity and fairness are very important to Canadians. In a pandemic context, they lead to a number of considerations. As much as possible, benefits and risks should be fairly distributed through the population. This may be difficult, however, in some circumstances, such as a pandemic that differentially affects certain populations or a very severe pandemic if resources are in short supply. Decisions should take health inequities into account and try to minimize them, rather than make them worse. Access to necessary health care may be restricted in a health crisis; however, available resources (e.g., vaccine and antiviral medications) should be distributed in a fair and equitable way. What will constitute fair and equitable distribution will be context dependent. Therefore the transparency and reasonableness of decision-making processes are important.

Good decision-making processes are also essential for ethical decision-making. They involve the following: [23], [24]

- openness and transparency - the process is open for scrutiny, and information about the basis for decisions and when and by whom they were made is publicly accessible;
- accountability - being answerable for decisions;
- inclusiveness - stakeholders are consulted, views are taken into account, and any disproportionate impact on particular groups is considered; and
- reasonableness - decisions should not be arbitrary but rather be rational, proportional to the threat, evidence-informed and practical.

2.6 Legal Considerations

The legal considerations that arise in the context of pandemic preparedness and response are varied and complex. International laws as well as FPT legislation will be relied upon during both the preparedness and responses phases of a pandemic.

2.6.1 International Requirements

International Health Regulations (2005)

The current International Health Regulations (2005) [IHR (2005)] came into force in 2007. They provide a framework for monitoring and enhancing global public health capacity and international communication regarding potential public health emergencies of international concern (PHEIC). The aim of the IHR (2005) is to prevent the international spread of disease while limiting interference with international traffic and trade. The IHR (2005) also establish a more effective and transparent process for WHO and its Member States (including Canada) who are States Parties to the Regulations, to follow when determining and responding to a PHEIC. Most importantly, they broaden the scope of international collaboration to include any existing, re-emerging or new disease that could represent an international threat.

The IHR (2005) include obligations for States Parties to:

- develop core capacity for surveillance and response;
- establish a national focal point (NFP) as the contact point for WHO on all IHR matters; and

- notify WHO of all potential PHEIC within specified time frames.

In order for Canada to meet the IHR (2005) requirements, all levels of government must collaborate. In Canada, PTs use established protocols to report influenza infections of international concern to the Public Health Agency of Canada (PHAC), which is Canada's NFP. After an initial assessment if notification is required, PHAC communicates with the WHO. Reportable influenza-related events include cases of human influenza caused by a new subtype as well as cases having potential international public health implications that meet the notification criteria established under Annex 2 of the IHR (2005). WHO then re-assesses the event to determine whether the event constitutes an actual PHEIC. The first PHEIC declared by the WHO under the IHR (2005) was the influenza A (H1N1) pandemic in 2009.

Pandemic Influenza Preparedness Framework

The Pandemic Influenza Preparedness Framework (PIP Framework) for the sharing of influenza viruses and access to vaccines and other benefits was adopted by the World Health Assembly in 2011. The PIP Framework aims to improve the sharing of influenza viruses with pandemic potential and to achieve more predictable, efficient and equitable access for countries in need of life-saving vaccines and medicines during future pandemics.

Under the Framework, Member States, including Canada, are responsible for:

- ensuring the timely sharing of influenza viruses with human pandemic potential with the Global Influenza Surveillance and Response System (GISRS);
- contributing to the pandemic influenza benefit-sharing system; and
- continuing to support the GISRS.

2.6.2 Federal Legislation

The Emergency Management Act (2007), section 6(1), makes each minister accountable to Parliament for a government institution responsible to identify the risks that are within or related to his or her area of responsibility and prepare emergency management and response plans with respect to those risks; to maintain, test and implement those plans; and to conduct exercises and training in relation to them.

In accordance with responsibilities under the Act, the federal Minister of Health is primarily responsible for developing, testing and maintaining mandate-specific emergency plans for the federal Health Portfolio, which includes Health Canada (HC) and PHAC. These emergency plans outline the federal response to national public health threats or events such as major disease outbreaks (including an influenza pandemic), and to the health effects of natural disasters or major chemical, biological, radiological, nuclear and explosive (CBRNE) events.

Furthermore, the Quarantine Act (2005) strives to prevent the introduction and spread of communicable diseases into and out of Canada by providing the Minister of Health with the authority, including enforcement mechanisms, to take public health measures as required. Pandemic Influenza Type A is listed in the Act's Schedule of Diseases.

2.6.3 Provincial/Territorial Legislation

Health emergency management in the PTs in Canada is governed by legislation specific to each jurisdiction. This legislation requires the PT governments to have comprehensive emergency plans respecting preparation for, response to and recovery from emergencies and disasters, including those with potential impact on critical infrastructure. Important health emergency management powers are also found in public health legislation.

The 2009 pandemic provided an opportunity to identify problems or gaps in existing legislation (including public health legislation) that should be addressed in order to respond more effectively to a future pandemic. An effective response requires an authority to establish appropriate leadership for a coordinated response, along with

authority for PT and local public health officials to implement appropriate control measures. Planners should ensure that they will have authority to mount an effective response whether or not an emergency is officially declared.

3.0 Canada's Approach to Pandemic Influenza

3.1 Goals and Objectives

Goals serve an important purpose in guiding preparedness and response, and in prioritizing the use of resources if necessary. Canada's goals for pandemic preparedness and response are:

> First, to minimize serious illness and overall deaths, and second to minimize societal disruption among Canadians as a result of an influenza pandemic.

These national goals were originally presented in the Canadian Pandemic Influenza Plan for the Health Sector, which was endorsed by FPT Ministers of Health in 2004. The goals, and their sequence, had undergone extensive deliberation by FPT pandemic planners and other stakeholders. A survey carried out as part of the Canadian Program of Research on Ethics in a Pandemic (CanPREP) found that over 90% of participants agreed that the most important goal of pandemic influenza preparations was saving lives. [25] During the 2009 pandemic, the pandemic goals were invaluable in guiding aspects of the response.

The supporting objectives for the health sector are as follows:

1. **Minimize serious illness and overall deaths by**
    - reducing the spread of infection through promotion of individual and community actions;
    - protecting the population through provision of pandemic vaccine and implementation of other public health measures; and
    - providing treatment and support for large numbers of persons while maintaining other essential health care.
2. **Minimize societal disruption by**
    - supporting the continuity of health care and other essential services;
    - supporting the continuation of day-to-day activities as much as possible and promoting a return to normal community functioning as soon as possible;
    - maintaining trust and confidence through
        - support of evidence-informed decision-making by collection, analysis and sharing of surveillance and other scientific information; and
        - communication of appropriate and timely advice to decision-makers, health professionals and the public; and
    - supporting a coordinated response by working collaboratively with all levels of government and stakeholders.

3.2 Guiding Principles and Approaches

The following principles underpin Canadian pandemic preparedness and response activities and decision-making:

- Collaboration - all levels of government and health care stakeholders need to work in partnership to produce an effective and coordinated response. This implies adopting consistent and collaborative approaches to

planning, response and recovery, and having an effective FPT decision-making process. It also implies involvement of stakeholders in these steps.

- Evidence-informed decision-making - decisions should be based on the best available evidence to the extent possible. It is recognized that other factors also enter into decision-making, such as legal and institutional constraints, values, costs and availability of resources. [26]
- Proportionality - the response to a pandemic should be appropriate to the level of the threat.
- Flexibility - actions taken should be tailored to the situation and subject to change as new information becomes available. The pan-Canadian approach should be consistent, although patterns of spread may mean that regional and local jurisdictions will require flexibility in terms of the scale and timing of their response.

In addition to these main guiding principles, Canadian pandemic planning and response activities are also guided by:

- A precautionary/protective approach - this approach is particularly applicable in the early stages of a pandemic when evidence-informed decision-making is not possible due to lack of data and the uncertainty of an evolving event. This means taking timely and reasonable preventive action, proportional to the threat and evidence-informed to the extent possible. This does not mean that in the absence of evidence, all actions must be taken; rather, it means that as emerging evidence reduces uncertainty, evidence-informed actions may supersede those precautionary measures taken at the outset.
- Use of established practices and systems to the extent possible - it is extremely difficult to implement new ways to do things during an emergency. Effective seasonal influenza responses support a strong pandemic response, as well-practised strategies and processes can be rapidly ramped up to manage the pandemic.
- Ethical decision-making - ethical principles and societal values should be explicit and embedded in all decision-making, including the processes used to reach decisions. It is especially important to ensure that all actions respect ethical guidelines tailored to the concerns of public health, while respecting the rights of individuals as much as possible.

3.3 Coordination of National Preparedness and Response

The global nature of a pandemic requires a response that differs from many other types of emergency. Traditionally, the responsibility to deal with an emergency is placed first on the individual/household to manage the effects of the emergency as it affects them, and then on successive levels of government as the resources and expertise of each are needed. Public Safety Canada is responsible for coordinating the whole of government response when the federal government is involved in the response to an emergency. Within the PTs a similar function is performed by the appropriate ministry or emergency measures organization.

In a pandemic situation, a pan-Canadian whole-of-government response is required so that all potential resources can be applied to minimizing the pandemic's negative health, social and economic impacts. Pandemic plans should be aligned across jurisdictions to facilitate successful FPT collaboration during a pandemic.

The following sections provide a high-level overview of FPT health emergency planning and response relevant to pandemics.

3.3.1 Emergency Management Frameworks and Plans

The GC has in place a coordinated system of federal emergency management frameworks, systems and emergency response plans, many of which can be accessed at Public Safety Canada's web site. These plans are based on the four components of the emergency management continuum (prevention and mitigation,

preparedness, response and recovery) and they use an all-hazards approach. Emergency response plans for the federal Health Portfolio are part of this GC system.

The FPT health sector also has a system of frameworks and emergency response plans parallel to those of the federal health sector, that are comprehensive and flexible enough to address any type of national health emergency. The development and maintenance of some of these documents, including CPIP, is overseen by the PHN.

The federal and FPT emergency management plans are supported by various operational annexes and guidance documents. These are nested under the generic all-hazards emergency response plans and deal with more specific threats.

3.3.2 Pan-Canadian Coordination of the Pandemic Health Sector Response

Because a pandemic is a significant health event, the FPT ministries of health have the primary mandate for the health sector response in their respective jurisdiction and act as advisor for other sectors on health issues.

At the federal level, the Centre for Emergency Preparedness and Response (CEPR) at PHAC is the Health Portfolio's focal point for coordinating and providing a wide range of emergency management services with other federal departments, PT governments, NGOs and the private sector. CEPR is responsible for the Health Portfolio Operations Centre (HPOC) in Ottawa and its linkages to other operational centres at the FPT level.

Coordination of the FPT ***health sector response*** to a pandemic will follow the governance structure outlined in the FPT Public Health Response Plan for Biological Events (FPT-PHRPBE). The FPT-PHRPBE is complementary to and used in conjunction with existing jurisdictional planning and response systems.

The FPT-PHRPBE is intended to bridge the gap between PT public health response plans and federal health response plans by providing a single, common overarching governance framework for the FPT health sector that can be applied, in full or in part, during a significant public health event requiring a coordinated FPT response, such as an influenza pandemic.

The FPT-PHRPBE defines a flexible FPT governance mechanism that identifies escalation considerations and response levels for a scalable response, and to improve effective engagement amongst public health, health care delivery and health emergency management authorities during a coordinated FPT response. This will ensure that at the time of a response, notification processes and inter-jurisdictional information-sharing will be enhanced; public and professional communication will be addressed; and advance planning and decision-making between and amongst multiple jurisdictions will be facilitated.

Finally, as the effects of a pandemic are not exclusive to the health system, it is critical for FPT governments and emergency management partners to use a common approach in responding to a pandemic. Emergency social services (e.g. non-medical services considered essential for the immediate physical and social well-being of people affected by disasters) should be coordinated within the broader PT response and aligned with health system activities.

3.3.3 North American Plan for Animal and Pandemic Influenza

The North American Plan for Animal and Pandemic Influenza (NAPAPI) outlines how Canada, Mexico and the US intend to work together to combat an outbreak of animal influenza or an influenza pandemic in North America. The NAPAPI addresses both animal and public health issues, including early notification and surveillance, joint outbreak investigation, epidemiology, laboratory practices, medical countermeasures (e.g., vaccine and antiviral

medications), personnel sharing and public health measures. It also addresses border and transportation issues. While the NAPAPI is not legally binding, it reflects strong commitments by the countries involved to work collaboratively.

3.4 Pandemic Roles and Responsibilities

Collaboration in pandemic planning and response is strengthened by having clearly defined and well-understood roles and responsibilities. While this section focuses on government responsibilities, it is acknowledged that other partners also have important roles and responsibilities in a pandemic. These partners include the non-health sector, private sector, NGOs, municipalities and local/regional health authorities, and international organizations. Similarly, members of the general public bear responsibility for keeping themselves informed and for cooperating with measures to reduce the spread of illness.

3.4.1 World Health Organization

WHO's pandemic roles and responsibilities are outlined in the WHO pandemic influenza risk management guidance document and include: [27]

- coordination of the international response under the IHR (2005), including conducting global risk assessments;
- communication of the global situation using the global pandemic phases;
- declaration of a PHEIC and pandemic as required under the IHR;
- provision of information and support to affected States Parties;
- selection of the pandemic vaccine strain and determination of when to move from seasonal to pandemic vaccine production; and
- provision of oversight and support for implementation of the PIP Framework.

3.4.2 Canada - FPT Governments

Responsibility for health services in Canada is shared across all levels of government. High-level roles and responsibilities for FPT governments are outlined below; more detailed information about roles and responsibilities for specific response components can be found in the CPIP annexes. It is recognized that responsibilities for federal populations, which are summarized at the end of this section, are complex and evolving.

A. International aspects

International aspects of influenza management and liaison are a federal responsibility.

The federal government is responsible for:

- acting as the national focal point for the WHO on all IHR (2005) matters and managing all international aspects of pandemic preparedness and response;
- providing travel health notices and other health related information relevant to international travel; and
- exercising powers under the Quarantine Act to protect public health by taking comprehensive measures to help prevent the introduction and spread of communicable diseases in Canada. Such measures may include, but are not limited to, the screening, examining and detaining of arriving and departing international travellers, conveyances (e.g., airplanes and cruise ships) and their goods and cargo.

B. Collaboration, communication, information sharing and policy recommendations

While PT governments are responsible for communications plans and messaging within their jurisdictions, a coordinated pan-Canadian pandemic response requires collective infrastructures, response capacities and coordinated activities.

The federal government is responsible for:

- ensuring that risk assessments for novel and pandemic viruses are prepared and communicated as required; and
- facilitating the coordination of the overall pan-Canadian response to a pandemic.

FPT governments will work collaboratively to:

- coordinate and support the process required for development and periodic updating of CPIP and its annexes, for which PHAC acts as the custodian;
- assess capacity gaps for a pan-Canadian response and address gaps as necessary;
- align federal pandemic plans for federal populations, (see Section F for federal populations), with PT plans, where relevant;
- assess surveillance capacity, standards and protocols and modify as necessary;
- assess laboratory capacity, standards and protocols and modify as necessary;
- establish and support pan-Canadian policies and recommendations on the use of antiviral medications and vaccine during a pandemic;
- develop and implement public health guidance;
- ensure development and dissemination of clinical care guidance;
- develop a pan-Canadian communication strategy that reflects Canadian linguistic, literacy and cultural characteristics and allows for the alignment of messaging by FPT jurisdictions where appropriate;
- establish protocols for the sharing of relevant information, including but not limited to FPT plans and drafts; surveillance information; jurisdictional communications, strategies and messaging; and pandemic response interventions and impacts; and
- identify and address rapid research response priorities and leverage their respective research undertakings.

C. Antiviral medications and influenza vaccine

The federal government is responsible for:

- providing regulatory authorization to market antiviral medications and influenza vaccines;
- acting as the focal point for vaccine manufacturers and international regulatory collaboration;
- providing regulatory authorization to conduct clinical trials;
- negotiating with manufacturers and establishing contracts for the FPT purchase of antiviral medications and vaccine for pandemic purposes;
- national monitoring of adverse reactions to antiviral medications and vaccines; and
- providing antiviral medications and vaccine to those federal populations not covered by arrangements for PT provision.

PT governments are responsible for maintenance, monitoring, distribution and administration of antiviral medications and vaccine in their respective jurisdictions. They will work collaboratively to:

- provide antiviral medications and, when available, vaccine to recommended populations;
- share information regarding the distribution and use of antiviral medications and vaccines in their respective jurisdictions; and
- monitor and report adverse vaccine reactions.

The PT governments are also responsible for the distribution of vaccines and antiviral medications to most federal populations, but this varies by federal population and jurisdiction (see section F on federal populations).

FPT governments will work collaboratively to develop strategies to mitigate the effects of insufficient or delayed antiviral drug and/or vaccine supply, should such a situation arise.

D. Health sector preparedness and response

Health sector preparedness and response remains the responsibility of each jurisdiction. In some jurisdictions responsibility for emergency social services also falls to the health sector.

PT governments are responsible for:

- ensuring that PT pandemic plans (or all-hazards plans depending on the jurisdiction) are developed, tested and periodically updated;
- considering the content and intent of CPIP in the development of their PT jurisdictional plans;
- communicating and engaging with the general public, media and stakeholder groups about their respective plans; and
- activating PT pandemic or all-hazards plans.

The federal government has similar responsibilities for federal departments within the health sector and for federal populations in collaboration with the PTs (see section F on federal populations).

E. Health care provision

The provision of health care is an essential component of pandemic response and is primarily a PT responsibility.

PT governments are responsible for:

- developing plans to increase surge capacity in order to care for affected persons in their jurisdiction;
- providing health care services for persons within their jurisdiction, including for federal populations while leveraging agreements that are in place (federal populations and federal responsibility are covered in the next section);
- developing and maintaining memoranda of understanding and protocols as needed, preferably before the pandemic, to facilitate interprovincial/territorial movement of patients and licensed health care professionals during a pandemic and other aspects of mutual aid;
- developing, as necessary, a strategy for collecting and monitoring data on health care service use;
- ensuring the provision of medications, supplies and equipment required for provision of pandemic health care services; and
- working collaboratively to establish protocols and guidelines for prioritizing health care services during times of high service demand and staff or supply shortages in the respective jurisdiction.

The federal government is responsible for:

- ensuring the provision of health services, medications, supplies and equipment for specified federal populations/employees who normally access federally operated health care services;
- facilitating access to surge capacity, including from federal programs, employees and resources, to support PT responses if required;
- mobilizing medical supplies in the National Emergency Strategic Stockpile (NESS) as surge capacity to support PT responses; and
- facilitating the acquisition of extra medical supplies through Public Services and Procurement Canada and other federal agencies as appropriate.

F. Federal populations

Federal populations are those populations for which the federal government either provides health care and benefits, goods and/or services or reimburses the cost of providing health care and benefits. With the exception of the Canadian Forces which has its own distinct health care system for active members, the needs of federal populations must be integrated into PT pandemic planning activities in order to establish a comprehensive and coordinated pandemic response.

Federal populations include the following:

- First Nations on-reserve, inclusive of First Nations who have assumed responsibility for health services under a transfer agreement;
- active members of Canadian Forces;
- federal offenders or inmates of federal penitentiaries;
- refugee claimants, protected persons, detainees under the Immigration and Refugee Protection Act, rejected refugee claimants, and other specified populations; and
- Canada-based staff at missions abroad.

The federal government is responsible for:

- supporting the provision and distribution of medications, supplies and equipment to federal populations, as noted in the list above, through existing FPT distribution and administration systems.

The federal government will work collaboratively with PT governments to:

- ensure that access to pandemic health services for all federal populations is available on the same basis as is provided to other residents of Canada, while leveraging agreements that are in place. This involves but is not limited to access to antiviral medications, influenza vaccines and supplies needed for provision of pandemic health care services; and
- facilitate the coordination of federal planning for federal populations with PT pandemic plans.

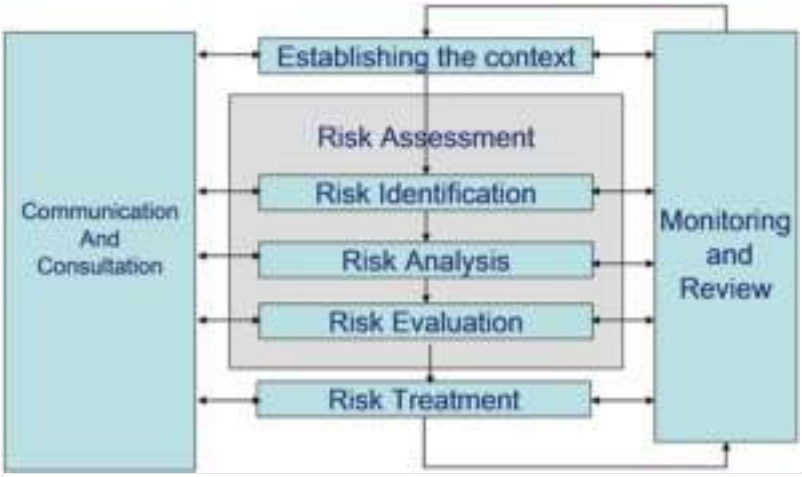
3.5 Risk Management Approach

3.5.1 Overview

Risk management is a systematic approach to setting the best course of action in an uncertain environment by identifying, assessing, acting on and communicating risks. A risk management approach provides a useful framework for addressing the uncertainties inherent in pandemic planning and response. Risk management supports the CPIP planning principles of evidence-informed decision-making, proportionality, and flexibility; and a precautionary/protective approach when there is uncertainty early in an event.

Figure 1 provides a graphic overview of the risk management process as outlined in ISO 31000, the international standard for risk management. The individual steps involved in risk management are then briefly described.

Figure 1 - ISO 31000 Risk Management Process [28]



▶ Figure 1 - ISO 31000 Risk Management Process - Text Equivalent

Risk assessment is a central component of risk management. Its purpose is to provide evidence-informed information and analyses for making informed decisions on how to treat particular risks and select between options. There are three parts to risk assessment:

- Risk identification involves identifying what might happen, or what situations might exist that could affect achievement of the objectives of the organization or system.
- Risk analysis involves analysing the risks in terms of their probability and potential impact (who is affected and to what extent). This analysis helps identify the planning considerations and options for each component of the response. The analysis should also assess the public's perception of risk and how it could influence the risk management response, so that communications strategies and messaging can be tailored appropriately.
- Risk evaluation involves determining the significance of the level and type of risk in order to make decisions about future actions. Ethical, legal, financial and other considerations are also inputs to the decisions. Decisions may include the need and priorities for treatment, whether an activity should be undertaken or which of a number of paths should be followed.

Risk treatment follows risk assessment and involves identifying and recommending risk treatment options, i.e. options for management or control. Risk treatment options should include steps that need to be taken in advance, as well as potential actions at the time of the pandemic.

Communication and consultation are also integral parts of the risk management process. Effective communication with stakeholders should facilitate adequate understanding of the risk management decision-making process, ensure that the process is transparent and help people to make informed decisions. A risk communications plan should be developed at an early stage.

Monitoring and review are important for assessing factors that could change over time and for documenting effectiveness of interventions. Such reviews should lead to periodic updates of the risk assessment.

3.5.2 Risk Management Considerations in Pandemic Planning and Response

Given the large number of variables that are involved in influenza pandemic planning, comprehensive risk management is challenging. The four pandemic planning scenarios described in section 3.7 can assist with risk identification by providing a starting point to think through the risks that would be associated with pandemics of varying impact and their implications.

It is also worthwhile to anticipate key decisions that will need to be taken during the pandemic to help guide the development and analysis of options. It is also worthwhile to clarify ahead of time and to the extent possible what level(s) of government should be involved with which types of decision when the time comes. Examples of these key decisions are as follows:

- what is the scale of the response;
- whether (and when) to escalate or de-escalate the response;
- when, what and how to communicate with the public;
- what amount of vaccine and the formulation(s) to order;
- how vaccine use should be prioritized;
- what public health interventions should be used, when and within which populations, and whether they need to be adjusted over time;
- what influenza testing and treatment strategies to recommend and whether they need to be adjusted over time; and
- what supplementary assessment and treatment services might be needed and, if necessary, when they should be started and stopped.

Anticipating key decisions should be accompanied by identification of the types and sources of information required for decision-making. Establishing robust surveillance for seasonal influenza establishes baselines, develops capacity and provides a platform for escalation during the pandemic.

Anticipating key decisions should also lead to development of relevant options for risk treatment. From a pandemic preparedness perspective, examples of risk treatment include continuity of operations planning; establishment of stockpiles for antiviral medications and other key supplies; development of advance contracts for pandemic vaccine; strengthening influenza surveillance systems, diagnostic and analytical capacity; establishment of protocols for pandemic research; and establishment of communications networks to plan effective and coordinated risk communications strategies.

When a pandemic occurs, planning scenarios are replaced by a real event and response activities will be guided by the available evidence. During the initial stages, little may be known about the likely pandemic impact or the populations most at risk. Many decisions will have to be made before solid information is available and then adjusted, if necessary, as more becomes known, keeping in mind that it is often difficult to scale back a response. As the evidence emerges over time, understanding of the situation will continue to change as new information becomes available and will always be incomplete. A risk management approach will be used throughout the response by all responders. Risk assessments will provide key input into FPT decision-making by identifying what is known at that point in time, what might occur and when, and the major areas of uncertainty.

PHAC will facilitate development of timely and credible risk assessments to support FPT decision-making. These formal risk assessments will be conducted at the start of the pandemic to inform the initial response and then periodically as new information emerges (e.g., at the end of a pandemic wave). Risk assessments will address key information needs, including viral characteristics, the anticipated or experienced impact on the health care system and community, age and risk groups most affected, occurrence of antiviral resistance and estimated effectiveness of control measures. As the pandemic progresses, there will be questions about likely occurrence of more pandemic waves, whether new risk factors are emerging and whether the response should be escalated or de-escalated. Appendix B identifies relevant considerations for initial and ongoing pandemic risk assessments and identifies potential sources for the supporting information.

3.6 Planning Assumptions

This section on planning assumptions and section 3.7 on pandemic planning scenarios describe two important tools for pandemic planning. These tools provide distinct but complementary approaches.

Identifying planning assumptions is a way to deal with uncertainty. Assumptions provide a useful framework for planning but should not be regarded as predictions. While planning assumptions are rooted in evidence to the extent possible, [29], [30] they are basically educated guesses. As the pandemic unfolds, emerging evidence is used to guide the response. Informing the planning assumptions identified below is the WHO's Pandemic influenza risk management interim guidance (2013), the UK's Scientific summary of pandemic influenza & its mitigation (2011) and discussions from the Canadian Pandemic Influenza Preparedness Planning Assumptions Workshop held in 2011.

3.6.1 Origin and Timing

- The next pandemic could emerge anywhere in the world and at any time of year.
- There may be no lead time before the novel virus reaches Canada.
- The first peak of illness in a geographic area within Canada could occur within weeks of first detection of the novel virus in that area. The first peak in mortality is expected to be several weeks after the peak in illness.

3.6.2 Transmission

- The pandemic virus will behave like seasonal influenza viruses in significant ways:
  - incubation period - is expected to last from one to three days;
  - period of communicability - adults are infectious from 24 hours before and up to five days from the onset of symptoms, and children may be infectious for up to seven days. Longer periods have been found, especially in persons with immune compromising conditions;
  - methods of transmission - mainly by large droplet and contact (direct and indirect) routes; the role of airborne transmission is unclear.
- Transmission is expected to be relatively lower in spring and summer than in fall and winter (the general pattern of transmission in temperate countries).
- Transmission is possible from asymptomatic persons but is greater when symptoms, such as coughing, are present and viral shedding is high (i.e., early in the symptomatic period).

3.6.3 Pandemic Epidemiology

- Most communities will experience two or more pandemic waves of different magnitudes. In any locality, the length of each wave will be from several weeks to a few months but may vary by community.
- There will be geographic variability with regard to the timing and intensity of waves, although multiple jurisdictions will be affected simultaneously.
- The pandemic is expected to last 12 to 18 months.
- The novel virus is expected to displace other circulating seasonal strains during the pandemic. After the pandemic, the pandemic virus will continue to circulate as a seasonal strain. It may completely replace previously circulating seasonal influenza A subtypes or continue as one of several circulating seasonal A subtypes.
- Relatively more severe disease and mortality is expected to occur in the young and in persons without underlying health conditions compared to seasonal influenza.

3.6.4 Clinical Features

- Population clinical attack rates (averaged across all age groups) are expected to be 25% to 45% over the course of the pandemic.
- Clinical symptoms are expected to develop in about two-thirds of people who are infected with the pandemic influenza virus.
- The general, uncomplicated clinical picture is expected to be the same as for seasonal influenza: respiratory symptoms, fever and abrupt onset of muscle ache, fatigue and headache or backache.
- Persons at high risk for complications from seasonal influenza [31] are expected to also be at increased risk of severe disease and complications from pandemic influenza infection, although additional risk groups may emerge.

3.6.5 Impact and Interventions

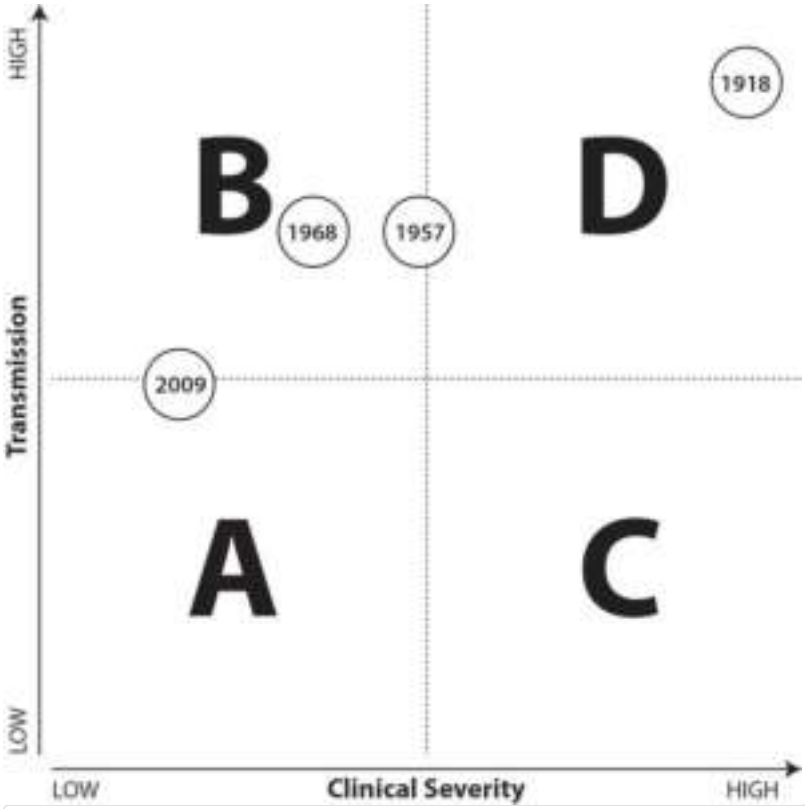
- Impact will vary across communities, and vulnerable populations are expected to be affected more severely.
- Workplace absenteeism may be higher than the estimated clinical attack rate because of caregiving or concern about personal safety in the workplace in addition to worker illness.
- Vaccine is expected to be available in time to have an impact on the overall pandemic but will not be available for the first wave.
- Personal hygiene measures are expected to help to reduce transmission between individuals and within households and other settings.

3.7 Pandemic Planning Scenarios

This section discusses another important tool for pandemic planning. The use of multiple planning scenarios is specifically intended to support the planning principles of evidence-informed decision-making, proportionality, and flexibility; and a precautionary/protective approach.

Planning scenarios provide a starting point to think through the implications and risks that would be associated with pandemics of varying population impact. Scenarios can also be used for exercises and training in support of pandemic plans. To help with risk identification, four pandemic planning scenarios have been developed that describe potential pandemic impacts varying from low to high. Figure 2 displays the four scenarios in a two-by-two table and estimates where the past four pandemics might be placed, according to an analysis conducted by the US Centers for Disease Control and Prevention (CDC). [32]

Figure 2 - Framework for the planning scenarios, with previous pandemics placed as per CDC analysis [33]



▶ Figure 2 - Framework for the planning scenarios, with previous pandemics placed as per CDC analysis - Text Equivalent

Scenario A (low impact) - this scenario involves an influenza virus with low transmissibility (ability to spread) and low virulence (clinical severity). Its impact is comparable to that of moderate to severe seasonal influenza outbreaks or the 2009 pandemic. It might be expected to stress health care services.

Scenario B (moderate impact) - this scenario involves an influenza virus with high transmissibility and low virulence. Its impact is worse than seasonal influenza in terms of numbers ill, which would be expected to stress health care services through sheer volume. High absenteeism would put all sectors and services under pressure.

Scenario C (moderate impact) - this scenario involves an influenza virus with low transmissibility and high virulence. Its impact is worse than seasonal influenza outbreaks in terms of severe clinical illness, which would be expected to stress critical care health services. The high virulence could cause significant public concern and may lead to people staying home from school and work.

Scenario D (high impact) - this scenario involves an influenza virus with high transmissibility and high virulence, and its anticipated impact is much worse than that of seasonal influenza outbreaks. It would cause severe stress on health care services, and high absenteeism would put all sectors and services under extreme pressure.

There are several important points to note about the scenarios:

- Whatever the pandemic impact, the epidemiological picture is expected to be significantly different from that of seasonal influenza, in that relatively more severe disease and mortality will occur in the young and in persons without underlying health conditions compared to seasonal influenza. [34]
- The four basic scenarios do not incorporate all of the potential factors (or “what-ifs”) that can affect the impact of a pandemic and should be considered in risk assessment. Some of these factors are population-wide and could affect all scenarios (such as seasonality, pre-existing immunity or antiviral resistance), whereas others might be setting-specific (such as planning for a remote community). See Appendix A for more details about

these additional factors and their potential impact. Additional risks may also be identified as planners consider all stages of the pandemic and components of the proposed response.

Table 1 provides some added description to the scenarios for planning purposes, along with potential impact considerations associated with each scenario.

Table 1 - Description and potential impact of the four pandemic planning scenarios

	Pandemic scenario			
Nature of impact	**A (low impact)**	**B (moderate impact)**	**C (moderate impact)**	**D (high impact)**
Basic virus characteristics	Low transmissibility/ low virulence	High transmissibility/ low virulence	Low transmissibility/ high virulence/	High transmissibility/ high virulence
Nature and scale of illness	• Similar numbers as in moderate or severe seasonal influenza outbreaks • Mild to moderate clinical features (in most cases)	• Higher number of cases than large seasonal outbreak but similar clinical severity • Overall increased numbers needing medical care and with severe disease	• Similar number of cases as with large seasonal outbreak but illness is more severe • Overall increased numbers needing medical care and with severe disease	• Large numbers of people ill • High proportion with severe disease
Impact on health care services	• Ambulatory and acute-care services stressed but able to cope • ICUs at capacity • Public health and laboratory services stressed • Long-term care may or may not be affected (depending on pre-existing immunity)	• Ambulatory and acute-care services very stressed • Health care services no longer able to continue all activities • ICUs under severe pressure • Long-term care may or may not be affected • Settings with limited surge capacity (e.g., nursing stations) may be even more stressed	• Ambulatory and acute-care services very stressed • Health care services no longer able to continue all activities • ICUs under severe pressure • Long-term care may or may not be affected • Settings with limited surge capacity e.g., nursing stations) may be even more stressed	• Health care services may be overwhelmed • Ambulatory services fully stretched • Hospitals able to provide only emergency services • Triaging necessary for critical care services • Collapse of services could lead to higher mortality than expected • Settings with limited surge capacity (e.g., nursing stations) may be highly stressed

Nature of impact	Pandemic scenario			
	A (low impact)	**B (moderate impact)**	**C (moderate impact)**	**D (high impact)**
Broader societal impact	• Limited workplace disruption • Some school disruption • Elevated public concern	• High workplace absenteeism • Some services experience pressures • Schools likely disrupted • Some supply chain problems • Elevated public concern • Surges in need for health care services.	• Potential workplace absenteeism and school disruption from fear of exposure • Considerable public concern over occurrence of very severe disease	• High absenteeism • Services and businesses under extreme pressure • Potentially severe supply chain problems • Could disrupt provision of basic services • Extreme public concern and psychosocial distress • Mass fatalities may overwhelm death care services (e.g. funeral homes,mortuaries)
Economic impact	Minimal if any	Productivity may be affected	Productivity may be affected	Very high

Initial period when impact is unknown - A formal scenario has not been proposed for the initial period when the pandemic has not yet been characterized in terms of its potential impact. However, some of the possible observations for this preliminary period are as follows:

- sporadic cases and limited outbreaks may be occurring;
- there will likely be elevated demand on telephone information lines, ambulatory care and laboratory services;
- public health services may be stressed;
- elevated media and public concern can be anticipated;
- international travel and trade could be disrupted; and
- there could be increased demand and shortages of publicly available supplies, e.g., infection control and basic emergency supplies, antivirals.

3.8 Pandemic Phases and Triggers for Action

3.8.1 WHO Pandemic Phases

Pandemic phases were introduced into pandemic plans to assist planning and serve as triggers for action, thus supporting the principles of flexibility and proportionate response. Previous Canadian pandemic plans incorporated the WHO pandemic phases, with additional designations proposed to identify activity levels within Canada.

After the 2009 pandemic, the IHR Review Committee [35] recognized that the WHO pandemic phases had presented challenges in interpretation and were used in different ways - as a planning tool, as a method to describe the global situation and/or as an operational tool to trigger action. The Committee recommended simplifying the WHO phase structure and separating operational considerations at country level from the WHO global preparedness plan and its phases.

WHO's 2013 pandemic guidance [36] describes the four phases that WHO will use to communicate a high-level global view of the evolving picture. The phases reflect WHO's risk assessment of the global situation regarding each influenza virus with pandemic potential that is infecting humans. The four global phases are:

- Interpandemic phase - the period between influenza pandemics;
- Alert phase - when influenza caused by a new subtype has been identified in humans. This phase is characterized by extra vigilance and careful risk assessment;
- Pandemic phase - the period of global spread of human influenza caused by a new subtype. Movement between the interpandemic, alert and pandemic phases may occur quickly or gradually;
- Transition phase - reduction of the assessed risk resulting in de-escalation of global actions.

The global phases and their application in risk management are distinct from (1) the determination of a PHEIC under the IHR (2005) and (2) the declaration of a pandemic. These are based upon specific assessments and can be used for communication of the need for collective global action, or by regulatory bodies and/or for legal or contractual agreements, should they be based on a determination of a PHEIC or on a pandemic declaration. [37]

As pandemic viruses emerge, countries face different risks at different times and should therefore rely on their own risk assessments, informed by the global phases, to guide their actions. The uncoupling of national actions from global phases is necessary since the global risk assessment, by definition, will not represent the situation in each country.

3.8.2 Canada's Approach to Pandemic Phases and Triggers for Action

Canada's response to the novel/pandemic virus will relate to its presence and activity levels in this country, which may not coincide with the global picture. Therefore, the WHO global phases will not be used to describe the situation in Canada or be used as triggers for action in Canadian jurisdictions. While the triggers for action described below may parallel some of the global WHO phases, it is not expected that they will line up exactly. For example, Canada might be well into the first pandemic wave before WHO announces the global pandemic phase (as happened in the 2009 pandemic) or conversely Canada might be still anticipating the first domestic outbreaks when the pandemic phase announcement is made.

In the 2009 pandemic, there was considerable variation in pandemic wave activity across Canada and even within PTs, in terms of both timing and intensity. This was particularly apparent in the first wave making blanket descriptions, triggers or responses inappropriate.

Describing pandemic activity

Descriptive terms such as the start, peak and end of a pandemic wave, will be used instead of phase terminology to describe pandemic activity in the country or in a jurisdiction within Canada. Pandemic wave activity can be further characterized for jurisdictions of any size using FluWatch definitions for no activity, sporadic activity, localized activity and widespread activity. [38]

Triggers for action

Triggers for action provide guidance for initiation of FPT activities and for their modification and cessation. Pandemic response should be appropriate to the local situation, so it is important that triggers and related actions be applied at PT or regional/local level as appropriate to the situation. Potential triggers for action in Canadian jurisdictions during the initial alert stages and the pandemic itself are identified in Table 2. The typical actions listed are at a high level; more detailed triggers for individual response components can be found in the annexes. Note that the triggers are not necessarily linear; for example, not all jurisdictions may find their capacity exceeded and therefore some may not need to invoke that particular trigger.

Table 2 - Pandemic Triggers and Typical Accompanying Actions

Trigger	Typical actions for consideration	Comments
Novel virus causing human cases detected somewhere in the world (no or limited transmission)	• Preparations to enhance surveillance within Canada • Intelligence gathering from affected areas • Relevant public and health sector communications	Tailored communications to health sector and general public continue throughout the response
Novel virus with sustained human transmission detected somewhere in the world	• Enhanced surveillance by PTs within Canada • Intelligence gathering from affected areas; preliminary risk assessment • Development of specific laboratory diagnostics • Enhancement of illness prevention messages and other public health measures (e.g., hand hygiene, respiratory etiquette) as appropriate • Confirmation of pandemic vaccine arrangements with manufacturer	Pandemic may be imminent or have already started
Novel/pandemic virus (with sustained human transmission) first detected in Canada	• Continuation of above activities • Activation of health emergency response protocols • Detailed investigations of early cases to determine epidemiological and clinical characteristics and inform risk assessment • Arrangements for antiviral access/strategic deployment of NAS • Provision of clinical guidelines and public health advice	Depending on circumstances, activation of health emergency protocols might already have occurred

Trigger	Typical actions for consideration	Comments
Novel/pandemic virus detected in PT or local jurisdiction	• Treatment of cases • Ramping up health sector capacity to deal with increasing number of cases • Additional public health measures (e.g., school closures) as appropriate • Preparation for vaccine distribution, administration and monitoring • Ongoing surveillance to monitor influenza activity and epidemiological analysis to characterize pandemic • Relevant public and health sector communications • Assess need for supportive emergency and social services (e.g. reception centres, volunteers, faith-based organizations)	Escalation of activities as pandemic activity moves from sporadic cases into full pandemic wave, followed by de-escalation as it wanes
Demands for service start to exceed available capacity	• Further escalation of surge capacity • Prioritization or triage of services as needed • Implementation of broader public health measures (e.g., banning of large gatherings)	May not reach this level in any or all jurisdictions
The pandemic wave wanes and demand for service falls to more normal levels	• Preparation for a resurgence of influenza • Replenishing of supplies as needed in anticipation of another wave • Evaluation of response and revision of plans as required • Preparation for immunization program • Ongoing surveillance to detect resurgence • Assessment of the psychosocial impact on the population (e.g. workforce resiliency, mental health, social cohesion) of the first wave	
Pandemic vaccine is available for administration	• Administration of vaccine as quickly as possible • Monitoring of vaccine uptake, safety and effectiveness	

Trigger	Typical actions for consideration	Comments
Second or subsequent pandemic wave arrives	• Treatment of cases • Continuation of immunization if already started • Ongoing surveillance to monitor influenza activity, antiviral resistance and strain changes	
Pandemic is over and normal activities resume	• Completion of pandemic studies and reports • Evaluation of response and revision of plans as required • Return to more normal operations • Preparation for post-pandemic seasonal influenza	• Identification of lessons learned and their incorporation into pandemic planning are critical activities in the recovery from a pandemic

4.0 Key Components of Pandemic Influenza Preparedness and Response

This chapter provides a high-level overview of the major components of influenza preparedness and response. Each section of the chapter describes the purpose and strategic approach of one of the response components and demonstrates how it supports the overall pandemic goals. Detailed operational guidance and tools for each component can be found in the respective CPIP annex.

All parts of the health sector, including public health, will be under stress during a pandemic. Advance planning, training and exercises will greatly assist in handling this increased demand on health services, staffing, resources and supplies and in providing the best possible clinical outcomes for persons ill with influenza. Continuity of operations and surge capacity planning are key components of health sector preparation, together with strong infection prevention and control and occupational health programs within each organization that provides health services.

Public health authorities play a leadership role in their jurisdiction in pandemic preparedness, response and recovery. They are responsible for communication to the public, the health sector and other stakeholders. The public health response to a pandemic also includes surveillance (both epidemiological and laboratory), the provision of pandemic vaccine and antiviral medications, and the application of public health measures such as promotion of personal and social distancing measures to reduce spread in households and the community.

In planning for the delivery of health services, it is important to encompass the entire continuum of care from medical first response to critical care, and to include community health partners. Planning for the provision of health care needs to be linked with public health and community-wide partners so that interdependencies can be identified and addressed.

The health care system includes workers of many disciplines, who will be at varying levels of risk during an influenza pandemic. HCWs are defined broadly as individuals who provide health care or support services in the health care setting, such as nurses, physicians, dentists, nurse practitioners, paramedics, medical laboratory workers, other health professionals, temporary workers from agencies, unregulated health care providers,

students, volunteers and workers who provide support services (e.g., food, laundry, housekeeping). The concepts and advice that are provided for HCWs also apply to other workers who are functioning in a health care capacity, for example police or fire personnel who are providing medical first response.

4.1 Surveillance

The purpose of pandemic surveillance is to provide decision-makers with the timely information they need for an effective response. Pandemic surveillance uses data obtained through routine and enhanced surveillance activities (e.g., data from sources such as laboratories, PT partners, hospital networks and sentinel practitioners) together with information from special studies to obtain a comprehensive and timely epidemiological picture of the pandemic.

These pandemic surveillance programs will monitor parameters such as:

- the geographic spread of the novel/pandemic virus across Canada;
- the trend of disease occurrence as it rises and falls within each PT and across the country;
- the intensity and impact of the pandemic (e.g., clinical cases, hospitalizations and deaths; severe clinical syndromes and associated risk groups; and demands on the health system); and
- changes in the antigenicity and antiviral sensitivity of the virus.

Strategic approach

A risk management approach to an influenza pandemic requires access to timely information, analysed and presented in a way that is useful to decision-makers. Epidemiological and laboratory surveillance data are key components of the formal risk assessments that will be produced to inform the response. One of the most critical needs is an early assessment of the potential impact of the pandemic so as to prepare the health care system and to plan interventions that are proportional to the situation. Systems or studies to produce the early impact assessment and other required information need to be in place before the pandemic.

Pandemic surveillance should be built on existing surveillance systems for seasonal influenza, which involve an extensive network of surveillance partners and are practised every year.

During a pandemic, collection of additional surveillance elements may be required to identify risk factors for severe disease and populations at increased risk. Targeted surveillance activities may be required for remote and isolated communities, including many Indigenous communities, to describe outbreaks appropriately in these regions. Other special studies (e.g., seroprevalence surveys) will be needed to inform decision-making.

Surveillance activities will need to be adapted in response to rapidly evolving situations; they may be streamlined, expanded or scaled down depending on information needs at particular times within the evolving pandemic. The scope of the pandemic and the urgency of information needs will require expedited and secure electronic data transfer and enhanced capacity for data analysis and interpretation.

More details about pandemic surveillance strategies and activities can be found in the Surveillance Annex.

4.2 Laboratory Services

Laboratory-based surveillance is an integral part of monitoring influenza activity. Because the signs and symptoms of influenza are similar to those caused by other respiratory pathogens, laboratory testing must be conducted to diagnose influenza definitively. Rapid identification of a novel influenza virus and timely tracking of virus activity throughout the duration of the pandemic are critical to the success of a pandemic response. In the early stages of a pandemic, laboratory services also contribute to appropriate clinical treatment.

The purpose of laboratory services during a pandemic is to:

- identify the first cases of a novel influenza strain occurring in Canada;
- support public health surveillance by monitoring the geographic spread of disease and the impact of interventions;
- facilitate clinical management by distinguishing patients infected with the pandemic influenza virus from those with other respiratory diseases;
- monitor circulating influenza viruses for antiviral resistance and strain characteristics; and
- assess influenza vaccine match and support vaccine effectiveness studies.

Strategic approach

The pandemic laboratory response is built on the principles of collaboration, flexibility and use of established practices and systems. As part of annual influenza surveillance, all public health laboratories and other laboratories that routinely test for influenza submit aggregate data weekly during the influenza season to the National Microbiology Laboratory (NML). These data are collated and disseminated by PHAC through the Respiratory Virus Detection Surveillance System and FluWatch. In addition, public health laboratories and other designated laboratories across the country submit isolates to the NML to monitor for antigenic changes within the circulating viruses. This information is shared with international partners through GISRS. Sustaining these relationships and strengthening capacity within the laboratory system during the interpandemic period will support a timely and effective pandemic response.

During a pandemic, influenza testing laboratories will support epidemiological efforts to track the spread and trends of the pandemic, monitor antiviral resistance and support clinical management. The Canadian Public Health Laboratory Network (CPHLN) will support public health and diagnostic laboratories by providing recommendations and best practices for specimen collection and testing for the novel influenza virus. The NML will share protocols, reagents and proficiency panels to ensure that test methods are capable of detecting the new virus. Molecular testing is the primary method used for the diagnosis of influenza.

Antiviral resistance will be monitored and outcomes will inform clinical management of patients. Antiviral resistance testing is conducted primarily at the NML, as well as some provincial laboratories.

The laboratory response will be adjusted as the pandemic progresses. Initially the NML will be heavily engaged in characterization of the novel virus and development of diagnostic reagents. All laboratories should anticipate high test volumes initially as the novel virus spreads across the country. During peak periods, laboratories will need to prioritize specimen collection to prevent overload. At this point, diagnosis of influenza in the community will be made primarily by clinical assessment; however, testing to support the management of certain patients (e.g., those requiring admission to hospital) will be expected to continue together with identification of outbreaks and surveillance. If ongoing monitoring shows increasing levels of antiviral resistance, more testing may be necessary to support clinical management of severely ill patients, especially those not responding to treatment.

Throughout the pandemic, public health, diagnostic and research laboratories, including those involved in the Canadian Immunization Research Network (CIRN), will also play an important role in supporting studies to better understand the novel pandemic virus and its impact.

More details about pandemic laboratory strategies and activities can be found in the Laboratory Annex.

4.3 Public Health Measures

Public health measures are non-pharmaceutical interventions that can be taken by individuals and communities to help prevent, control or mitigate pandemic influenza. Public health measures range from actions taken by individuals (e.g., hand hygiene, self-isolation) to actions taken in community settings and workplaces (e.g., increased cleaning of common surfaces) to those that require extensive community preparation (e.g., pro-active school closures). The purpose of public health measures is to:

- reduce transmission of the novel/pandemic virus, thereby helping to reduce the overall size of the outbreak and the number of severely ill cases and deaths; and
- slow the rate of transmission in order to reduce the peak burden on the health care system and buy time in anticipation of vaccine.

Strategic approach

Public health measures are typically implemented at the community level. The responsibility and legislative authority for implementing public health measures belong to the relevant PT and local public health authorities, with the exception of international border and travel related issues for which the federal government is responsible. In addition, the Canadian Forces Health Services is responsible for implementing public health measures on all Canadian Forces establishments/bases/wings/stations across Canada and for Canadian Forces personnel deployed abroad.

There are important concepts to consider when planning and implementing public health measures. The measures should be used in combination to provide “multi-layered protection”, as the effectiveness of each measure on its own may be limited. Actions should be tailored to the anticipated pandemic impact and the local situation, supporting the principles of flexibility and proportionality. Some measures, like hand hygiene and respiratory etiquette, are applicable in all pandemics. Other measures (e.g., proactive school closures and travel restrictions) might be used only in moderate- to high-impact situations, as they can be associated with significant societal and economic costs.

A risk management approach will help weigh the potential advantages of particular interventions against their disadvantages and unintended consequences. Decisions about which measures to deploy also raise fundamental ethical challenges. For example, when considering restrictive measures, it is important to balance respect for autonomy against protection of overall population health. In such situations, the principles of proportionality, reciprocity and flexibility are involved, with a view to safeguarding individual freedom to the extent possible while promoting protection against the health and societal consequences of influenza infection.

There are several types of public health measures for jurisdictions to consider during an influenza pandemic:

- **Individual measures** - Public health advice will be provided to protect well individuals against influenza and prevent ill individuals from spreading infection, e.g., through hand hygiene, cough etiquette, staying home while sick. These measures should already be familiar through annual public health campaigns.
- **Community-based measures** - Guidance will be produced and disseminated to minimize illness and transmission of infection within settings such as workplaces, schools, post-secondary institutions, childcare centres, communal living facilities, remote and isolated communities, camps and cruise ships. Social distancing measures or strategies may be used to minimize close contact among persons in public places, e.g., pro-active school closures; cancellation or modification of public gatherings; and alternative workplace approaches, such as teleconferences and working from home. Because of their potential societal impact, social distancing measures are most applicable in pandemics of moderate to high impact.
- **Border and travel measures** - These interventions include provision of travel health advice, screening of travellers and travel restrictions. Evidence for their effectiveness is limited and their implementation would

depend on the risk assessment and resultant risk/benefit analysis of the actions being considered.

- **Case and contact measures** - Some circumstances involving novel/pandemic viruses may warrant case and contact management by public health authorities. These might include an individual human case or cluster involving a novel virus, suspected human infections associated with an animal influenza outbreak, or initial cases of the pandemic virus in the country or area. The extent of the investigation and recommended measures should be feasible and relevant to the situation.

While aggressive measures (e.g., widespread antiviral use and restriction of movement) to attempt to contain or slow an emerging pandemic in its earliest stages were previously considered possible on the basis of modeling, experience from the 2009 pandemic has resulted in general agreement that such attempts are impractical, if not impossible.

Additional details about public health measures can be found in the Public Health Measures Annex.

4.4 Vaccine

Immunization of susceptible individuals is the most effective way to prevent disease and death from influenza. The purpose of Canada's pandemic vaccine strategy is to:

- provide a safe and effective vaccine for all Canadians as quickly as possible;
- allocate, distribute and administer vaccine as efficiently as possible; and
- monitor the safety and effectiveness of pandemic vaccine.

The phrase "vaccine for all Canadians" is intended to be interpreted broadly. It refers to all persons in Canada (whether or not they are citizens) as well as Canada-Based Staff (CBS), their dependents and Locally Engaged Staff (LES) at Canadian missions abroad and Canadian active duty personnel (Canadian Forces) abroad.

An effective pandemic vaccine strategy is built on strong seasonal influenza immunization programs. The overall impact of the pandemic vaccine strategy will depend on vaccine efficacy and uptake, as well as the timing of vaccine availability in relation to pandemic activity. Using current egg-based vaccine production technology, pandemic vaccine production is expected to take from four to six months, so it is not likely to be available by the time the first pandemic wave reaches Canada. Furthermore, it will become available in stages, which may require prioritization of initial vaccine doses.

Strategic approach

In 2011, Canada entered into a new ten-year contract for pandemic influenza vaccine supply to ensure that there is rapid and priority access to a supply of adjuvanted pandemic influenza vaccine produced in Canada. Canada's pandemic vaccine strategy also includes contracting for a secondary supply of a pandemic vaccine.

Health Canada has developed a regulatory strategy to review and authorize a safe and efficacious pandemic vaccine for use in Canada within the shortest time frame possible. A pan-Canadian approach to pandemic immunization, including prioritization of populations during initial roll-out of the vaccine, will help optimize equitable access and desirable outcomes. Pan-Canadian guidance will include an allocation plan for equitable vaccine distribution, recommendations for pandemic vaccine use and recommendations for prioritization of initial supplies.

Other key elements of the national vaccine strategy include the monitoring of vaccine uptake, adverse events and vaccine effectiveness, building on existing systems such as the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS). Rapid studies will be carried out to confirm or refute vaccine safety concerns.

PTs, Canadian Forces Health Services, and federal departments with the responsibility for immunization should have plans for efficient and timely vaccine administration, including the ability to target key population groups and collect information on vaccine uptake and adverse events. Lessons learned from the 2009 pandemic indicate that vaccine registries and electronic information systems to capture and transmit data are essential tools to support the vaccine program.

More details about the pandemic vaccine program can be found in the Vaccine Annex, including a prioritization framework to guide decision-making if vaccine is expected to be in short supply.

4.5 Antiviral Medications

Antiviral medications can be used to treat influenza cases or to prevent influenza in exposed persons (prophylaxis). Antiviral medications are the only specific anti-influenza intervention available that can be used from the start of the pandemic, when vaccine is not yet available.

Canada's antiviral strategy supports FPT stockpiles of antiviral medications for use in the event of an influenza pandemic, primarily for early treatment and for outbreak control in closed facilities. Early treatment of influenza cases, as early as possible within 48 hours of symptom onset, is recommended in order to reduce the severity and duration of illness, particularly the occurrence of influenza-related complications, hospitalization and death. Early treatment may also help mitigate societal disruption by reducing the duration and severity of illness experienced by workers in the health care and other critical infrastructure sectors.

Strategic approach

There are two national stockpiles in Canada:

- The NAS is a stockpile that is held and managed by the PTs. The NAS is composed of the antiviral medications oseltamivir and zanamivir, with oseltamivir dosage formulations that are appropriate for both adults and children.
- The NESS is a federally owned stockpile of emergency supplies. The NESS is held and managed by PHAC and includes a stockpile of oseltamivir and zanamivir. NESS antivirals are intended to provide surge capacity in support of the PT response during a pandemic.

Federal government departments, such as the Canadian Forces (for active duty personnel) and Global Affairs Canada (for mission staff overseas), hold stockpiles of antiviral medications to meet the anticipated needs of their staff.

Jurisdictions need strategies to facilitate timely access to antiviral medications, particularly for high-risk persons including pregnant women, children (who need special formulations), vulnerable populations, and residents of remote and isolated communities. Pre-positioning of antiviral medications should be considered for some communities to facilitate rapid access (e.g., remote northern communities).

Clinical guidelines have been developed for antiviral use for seasonal influenza. [39] Virus-specific clinical guidance and treatment protocols will need to be developed at the onset of the pandemic, based on pandemic epidemiology and available scientific evidence. Pandemic use will focus primarily on early treatment of influenza cases, particularly persons with severe disease or with risk factors for complications or severe disease. There are limited indications for the use of antiviral medications for prophylaxis during a pandemic, primarily for control of laboratory-confirmed influenza outbreaks in closed health care facilities and other closed facilities or settings where persons at high-risk of complications reside.

Distribution and uptake of antiviral medications should be monitored in real time to optimize appropriate use, identify the need for additional purchases during the pandemic, and support post-pandemic utilization and effectiveness studies. Monitoring adverse reactions and antiviral resistance helps inform decision-makers as to whether changes in the recommendations regarding antiviral use are required. Adverse reaction reports are collected and assessed through the Canada Vigilance Program of the Marketed Health Products Directorate (MHPD) of Health Canada. Ongoing monitoring of antiviral resistance is conducted by the public health laboratory system and reported as part of FluWatch.

More details about antiviral medications and their use in a pandemic can be found in the Antiviral Annex, including a prioritization framework to guide decision-making if antiviral medications are expected to be in short supply.

4.6 Infection Prevention and Control and Occupational Health

A major influenza outbreak may have a substantial impact on the ability of health care organizations to keep those providing or receiving health care services safe. Infection prevention and control (IPC) and occupational health (OH) programs should work together to prevent exposure to and transmission of pandemic influenza during the provision of health care. Working jointly with occupational health and safety committees is essential in meeting these goals. The application of appropriate IPC and OH processes by HCWs and organizations is important in all health care settings along the continuum of care, including but not limited to medical first response, practitioners' offices and other ambulatory care settings, acute care, long-term care and home care settings.

Strategic approach

A timely pandemic response is only possible when an organization and its personnel are experienced in IPC and OH protocols and practices, supported by strong programs. Well-functioning IPC programs should prevent, limit or control the acquisition of health care associated infections for everyone in the health care setting, including patients, HCWs, visitors and contractors. Well-functioning OH programs should identify workplace hazards and support appropriate processes and training to ensure that employees can perform their duties in an environment that minimizes exposure to environmental hazards.

Important elements of IPC and OH programs for pandemic preparedness and response in the health care setting include the following:

- adequate staffing of IPC and OH professionals in the health care organization to conduct education and training for front line staff;
- organizational risk assessments, best carried out in the interpandemic period, to identify engineering, administrative and personal protective equipment (PPE) controls that will best protect patients, HCWs and visitors in the health care setting;
- comprehensive education and training for HCWs in the organization on influenza IPC and OH issues;
- point-of-care risk assessments that are carried out by individual HCWs before they enter a patient's environment or initiate patient care to determine the appropriate PPE, isolation and cohorting strategies for a given patient, during a given intervention, in a specific room, area or facility;
- provision of influenza vaccine to persons working for or being cared for by the organization;
- ongoing surveillance for health care associated infections, including respiratory infections;
- respiratory protection programs to ensure that HCWs who may need to wear a respirator (including N95 respirators) are trained, fit-tested and prepared;
- a wide range of "source control" policies, including a 2-metre spatial separation between infected sources (e.g., patients) and uninfected hosts (e.g., other patients); admission screening; screening of visitors; and

expanded respiratory and hand hygiene programs for HCWs, patients and visitors; and
- systematic administrative practices to enable rapid identification and segregation of patients, HCWs and visitors with symptoms of influenza-like illness (ILI).

For detailed guidance about IPC and OH activities during a pandemic, see the annex on Prevention and Control of Influenza during a Pandemic for all Healthcare Settings.

4.7 Health Care Services

The effective provision of health care provides patients with the right level of care in the right place, at the right time. In a pandemic this means managing an influx of patients with influenza, while maintaining care required for patients with urgent non-influenza conditions. It is necessary for any organization that provides health care to plan for a range of scenarios, including those with very high patient load and potential high staff absenteeism, as demand for health care services may exceed the capacity of the existing system. At the start of a pandemic, early assessment of its anticipated impact will help the health care sector to implement plans to manage the anticipated workload.

Strategic approach

Planning for the delivery of health care in a pandemic is a particular challenge as there is little excess capacity in the Canadian health care system, particularly in remote and isolated communities. Nonetheless surge capacity planning is an essential component of pandemic preparedness for all levels of care, including telephone information lines, primary and ambulatory care practitioners, emergency medical services, hospital and critical care, long-term and palliative care, home care and other community care including death care services (funeral homes, medical examiners, coroners). Surge capacity planning involves development of strategies for enhancing levels of staff and volunteers, equipment and supplies and, potentially, space to accommodate more patients. It also includes consideration of novel approaches to enhancing assessment and care. Surge capacity plans should include regional or even province-wide components.

The 2009 pandemic highlighted the importance of improving integration and coordination so that the health care response functions as a system during an emergency. This involves integration across the continuum of care within a health region and across and among PTs. Integration is facilitated by involving stakeholders from all levels of care in planning and exercises, including emergency medical services, community service providers, volunteer organizations and public health. Electronic information management systems are essential tools for monitoring service delivery and resource utilization across the health care system and transferring information among organizations.

The collection of health care delivery data is an important aspect of seasonal and pandemic influenza surveillance. Monitoring hospital and ICU admissions and ventilator use were added surveillance components in the 2009 pandemic, contributing valuable information on the epidemiology of severe disease and its risk factors. Surveillance of emergency department utilization can indicate when community health services are at or reaching capacity so that other measures can be considered.

Best practices and lessons learned advise that health care organizations and practitioners carry out business continuity planning and maintain strategic reserves of critical equipment and supplies. Detailed plans to store, distribute and track use of stockpiled items should be developed and exercised.

Pandemic-specific issues for health care provision include the following:

- **Self-care instructions** - self-care instructions can empower individuals and families, improve care and optimize the use of the health system; they are useful for dealing with seasonal as well as pandemic influenza. During the 2009 pandemic, many jurisdictions used the media, public announcements and credible websites to promote tools to assist the public on conducting an influenza self-assessment, self-care and when to seek medical attention or go to the hospital.
- **Telephone advice lines** - these were extensively used in the 2009 pandemic to provide information and advice, and to triage people with suspected influenza from those with other respiratory infections. Trained operators directed people to appropriate clinical assessment and care if needed, and helped avoid unnecessary visits to physicians and emergency departments by providing advice on self-care at home. Heavy, and sometimes overwhelming, demand reinforced the necessity for business continuity planning and for operation on a 24/7 basis during a pandemic.
- **Primary care** - the primary care sector will be responsible for the assessment and treatment of ambulatory influenza patients. PTs often face challenges in engaging primary care practitioners, who may not be well linked to the rest of the system. PTs should work with professional associations to develop communications strategies, protocols and guidelines, e.g., for office business continuity planning and IPC. At the time of the pandemic, PTs should anticipate providing primary care practitioners with situation updates, guidance on laboratory testing and clinical management of influenza patients, information on pandemic vaccine (with clear direction on their role in its provision) and access to additional or pre-positioned PPE and supplies. Primary care surge capacity can be enhanced by PT strategies such as new fee codes for telephone advice and prescribing, temporarily allowing practice expansion to patients who are not registered with the practice (when this is not normally permitted), and expanding the role of other health professionals and non-traditional workers (e.g., allowing prescribing of antiviral medications by pharmacists). Influenza assessment centres and alternate care sites may be needed in some communities, particularly in high-impact situations. Responsibility for their establishment is best determined in advance so that appropriate planning can take place.
- **Hospital-based care -** the impact on the acute care sector and the demand for critical care will be influenced by the epidemiology of the pandemic, i.e., the overall numbers with severe disease, the age and risk groups most at risk of severe disease and the dynamics of the pandemic wave (compacted or prolonged), as well as the extent of early antiviral treatment in the community. Critical care planning and preparation for high demand for ventilators or other specialized equipment (e.g., extracorporeal membrane oxygenation) needs special attention. Critical care surge capacity plans should include triage tools that contain both ethical guidance and processes to address bed flow and ventilator utilization. Service needs for paediatric patients (including critical care) and pregnant women should be specifically addressed.
- **Health care in remote and isolated communities** - There may be limited capacity to provide acute care and/or a lack of appropriate medical equipment and services (e.g., ventilators, oxygen therapy) for treating critically ill patients in remote and isolated communities. Under normal circumstances, these needs are met through medical evacuations to acute care facilities in larger centres. However, an increase in medical evacuations could overwhelm the receiving jurisdictions, making it essential to coordinate with receiving jurisdictions and to do everything possible to detect ILI as early as possible and to treat and keep affected persons in the community.
- **Other health care services** - services such as mental health, home care, palliative and hospice care, long-term care and other community health and social services may not be well linked to regional and local pandemic planning processes. Though often overlooked in pandemic planning, their functioning is critical to achieving the pandemic objectives by providing early and appropriate treatment outside of hospitals to those who do

not need acute hospital care. These organizations must be involved in pandemic planning and encouraged to have business continuity plans in place so that they can continue to provide their services to some of the most vulnerable patients in the community with minimal interruption during a pandemic.

During a severe pandemic, death care services may be overwhelmed and local planners may need to consider alternate systems and resources than those that normally manage deaths, such as setting up temporary morgues and delaying funerals/burials. This may cause increased stress or complications in the grieving process for families, particularly when certain religious and/or cultural practices have specific directives about how bodies are managed after death. Planning guidance is available from the WHO, Pan American Health Organization and the International Red Cross on the effective management of mass fatalities during a disaster [40].

4.8 Clinical Care Guidelines

Clinical care involves the assessment and treatment of persons with suspected or confirmed pandemic influenza. The spectrum of illness seen with influenza is broad and ranges from asymptomatic infection to severe illness causing death, which is frequently due to exacerbation of an underlying chronic condition or secondary bacterial pneumonia. Certain aspects of pandemic influenza management may be unfamiliar to some practitioners, and new risk factors and presentations may emerge. Critically ill patients may require extraordinary support measures, some of which may not be universally available in a high-impact pandemic.

Strategic approach

During a pandemic, health care practitioners will need clinical guidelines for assessment, laboratory testing, treatment (including antiviral medications), and management of secondary infections and critically ill patients. Service needs for specific populations (e.g., paediatrics, pregnant women) should be specifically addressed. Guidelines specific to the clinical management of patients in remote and isolated communities should also be available, as there are unique considerations in these settings.

Clinical care guidelines must be timely and user-friendly, and be produced by sources that practitioners consider reliable. Establishing and testing agreed upon approaches for the development of clinical guidelines during the interpandemic period will help to ensure that the necessary processes are in place to support the pandemic response.

4.9 Communications

Communication of information and advice is often the first and most important public health intervention during an emergency. This is especially true for an emerging pandemic, where behaviour change is a central part of risk management. Providing clear and consistent information about the disease, who it affects, how it spreads and ways to reduce risk is an effective way to help reduce the spread of infection before other interventions like vaccine are available. Open and honest public communication also reinforces trust in public health authorities and helps to minimize societal and economic disruption.

Communications planning for an influenza pandemic uses a risk communications approach. [41] It integrates a broad range of communication capacity and expertise, including social marketing, stakeholder consultation and use of social media. It involves collaboration of all partners involved in the pandemic response to deliver consistent, complementary, and effective communications that meet the needs of the public and stakeholders.

For details on the pandemic risk communication approach, see the Communications and Stakeholder Liaison Annex.

Strategic Approach

Pandemic risk communications incorporate the principles of collaboration, proportionality, flexibility and use of established practices and systems. Research conducted during and after the 2009 pandemic reinforced the importance of core risk communication principles such as transparency and stakeholder collaboration in achieving pandemic response objectives. [42]

It is essential to be proactive about communication throughout the pandemic, with information and updates for the media, the public, and other stakeholders. Information may be limited initially and will change as the science evolves and more is learned. The post-2009 pandemic reviews identified difficulties in communicating uncertainty and dealing with changing information, particularly for pandemic vaccine. Therefore, strategies to communicate risk, uncertainty and changing information are critical.

Communicating in ways that demonstrate transparency, cultural sensitivity and use of plain language is essential in building and maintaining public trust. Consistent messaging and “speaking with one voice” will also foster trust and understanding and help avoid confusion.

While communication and messaging within jurisdictions is ultimately a PT responsibility, pandemic communications planning should involve all health partners. The FPT communication response will be coordinated through the PHN Communications Network. Collaboration with nongovernmental, private sector and international organizations is also important. The media should be seen as a key partner and engaged in the interpandemic period as well as during the pandemic.

Communication with the public - Research has demonstrated that risk perception is the strongest indicator of willingness to change behaviour during a public health event, and that it is largely shaped by the public’s emotional response to the event. [43] Monitoring of public perception, information needs and concerns is an important role in the pandemic response and should be planned for. Effective stakeholder identification and engagement will also play a large part in this work. Building relationships with stakeholders in the interpandemic period will help facilitate productive interactions during the pandemic. Federal and PT pandemic communications plans should pay particular attention to reaching vulnerable populations and persons who may have limited access to mainstream media. These groups may require a tailored communications approach, using a variety of formats and delivery mechanisms (e.g., using ethnic media outlets as a conduit to ethno-cultural communities). [44]

Communication with the health care sector - Communications with HCWs and organizations deserves special attention in the planning process. These stakeholders should be engaged in two-way dialogue to help ensure that products and messages meet their needs for timely, clear, concise and relevant communications. Resources should be developed in the interpandemic period so they can be quickly adapted when a pandemic occurs.

For details on the pandemic risk communication approach, see the Communications and Stakeholder Liaison Annex.

4.10 Research

Research plays a key role in addressing knowledge gaps about the influenza virus and effective influenza prevention, treatment and control for both seasonal and pandemic influenza. Much of this research can be carried out in the interpandemic period, but some can only be conducted during a pandemic. Given the potentially long interval between pandemics, it is important not to miss these infrequent but invaluable opportunities and to plan for a rapid research response.

Strategic Approach

Key components of a successful pandemic influenza research strategy include identification of research needs, development and ongoing support of partnerships and research networks, identification of sustained funding sources, and advance establishment of protocols and rapid ethics review processes for pandemic research. Knowledge translation strategies to bring significant findings to decision-makers in a useful and timely way are other key components.

Identification of research needs - It is important that influenza research needs are periodically reviewed and prioritized. This information is helpful to funding agencies like the Canadian Institutes of Health Research (CIHR) and PHAC, and feeds into similar international initiatives by WHO and others. The annexes to this document identify existing research needs in specific areas of the response, such as vaccines and antiviral medications.

Research network - Networks that are created to conduct research in the interpandemic period are well placed to facilitate pandemic research. Provincial public health agencies and PHAC are increasingly collaborating on epidemiological and other public health studies. The Canadian Immunization Research Network (CIRN), a national network of key vaccine researchers is active in ongoing influenza vaccine research projects. The mathematical modeling community has developed several networks and is collaborating more closely with public health. Canadian intensive care researchers have developed international clinical networks, such as the International Forum for Acute Care Trialists (InFACT), that will establish open access protocols, data-sharing processes and ethical frameworks to streamline the response to a new emerging disease or pandemic. These existing networks need ongoing support. As they may not be sufficient to address all of the pandemic research needs, ongoing focus on this aspect is required to ensure readiness for the research response. eds, ongoing focus on this aspect is required to ensure readiness for the research response.

Rapid research response - Special research studies, such as seroprevalence studies and the role of bacterial pathogens in serious outcomes, will be needed to inform pandemic decision-making. As these studies must be mounted quickly, advance planning is critical for their success and timeliness. Leveraging existing partnerships among PHAC, Health Canada, provincial public health agencies, clinical and academic institutions and networks together with populations of research interest such as CIRN and CIHR and engaging them in planning for a rapid research response is essential. Advance plans should include preliminary agreements with potential researchers and development of research protocols and strategies for rapid ethics approval and funding arrangements.

Knowledge translation - Many important decisions must be made quickly during a pandemic. Evidence-informed decision-making requires strong knowledge translation strategies to ensure that existing and new research findings are taken into account. Enabling strategies include compiling research findings from the 2009 pandemic and maintaining up-to-date literature reviews in key areas, such as the effectiveness of public health measures, relevant vaccine studies, and antiviral treatment and resistance. Processes for critical appraisal and dissemination of new research findings should be established in the interpandemic period. Strategies should also be developed to help decision-makers understand and make optimal use of evidence and research.

5.0 Assessment and Evaluation of Pandemic Preparedness and Response

Preparing for and responding to a pandemic is a complex process that requires the coordinated efforts of all orders of government in collaboration with their stakeholders. To ensure that pandemic plans (or all-hazards plans according to the jurisdiction) are comprehensive and effective, jurisdictions should assess their level of preparedness, test their plans regularly and evaluate their pandemic response.

5.1 Assessing Preparedness

Preparedness is a responsibility of individuals, organizations and jurisdictions at all levels. PTs are responsible for preparedness activities that will take place at the PT level and they may also provide advice and/or support to regional and local areas. Assessing the level of pandemic preparedness enables jurisdictions to monitor the progress of their pandemic planning, identify gaps and prioritize future planning efforts. Use of checklists, perhaps coupled with site visits, are potential tools for monitoring progress and levels of preparedness.

It is also important to determine whether responses can be implemented effectively so as to achieve the intended results. Training and exercises should be conducted on a regular basis to maintain preparedness levels as part of a cycle of continuous improvement. Training should also be made a priority for new workers. Exercises can take many forms, ranging from discussion-based activities such as seminars and workshops to larger more complex activities such as activating plans and simulating response activities. It is best for organizations to work their way up to larger exercises. This progression allows organizations to understand their plans better and identify interdependencies, and to make changes and adjustments before attempting a larger, more complicated activity. Following an exercise a formal After Action Report should be prepared, along with an implementation plan to address the gaps identified. Problem areas or weaknesses should be corrected through additional training and/or changes or additions to plans.

In addition to specially designed exercises, seasonal influenza provides annual opportunities for all jurisdictions to test specific components of a plan. For example, seasonal influenza immunization campaigns allow PTs to test rapid distribution of vaccine and supplies while local jurisdictions can practise mass clinic strategies and use of their health emergency management mechanisms to organize the clinic rollout. Other emergencies also provide opportunities to practise and refine components of an effective pandemic response, like command and control and communications.

5.2 Evaluating the Pandemic Response

For future reference, it is important to document completely the processes and activities used and decisions made during the response to the pandemic, along with the outcomes achieved. The response should be evaluated to see if it was carried out as intended and that it led to the desired outcomes. This evaluation helps ensure that lessons learned from the real life event are captured and remain available to inform pandemic plan revisions. The evaluation involves assessment through an After Incident or Lessons Learned report following the pandemic, accompanied by an implementation plan to address the identified gaps. A critical opportunity to evaluate and adjust the response also comes at the end of the first pandemic wave.

In addition to gleaning lessons learned from the pandemic response, it is important to ascertain how well the pandemic response met the goals and objectives of pandemic preparedness and response in Canada. Lessons learned would focus on the assessment of the strategic approach for the key components outlined in this document as a measurement of how well the response met the identified purposes of each of the key components. This higher level and formal evaluation of the pandemic response would involve FPT partners and consider various aspects of the pandemic response. A comprehensive, harmonized approach to pandemic evaluation across jurisdictions should be developed in the interpandemic period so that the main findings and best practices can be identified.

Appendices

Appendix A - Factors Affecting Pandemic Impact

The table lists a series of factors that could affect the impact of a pandemic and describes their potential impact. Consideration of these factors and their potential mitigation will supplement use of the basic planning scenarios and help planners prepare a more adaptable response.

Table - Factors that affect pandemic impact and their potential impact

Category	Factor	Potential impact
Virus characteristics		
Transmissibility	Degree of transmission	High infectivity means that a large number of people will become ill. This would affect absenteeism in schools and workplaces, including health care settings. Health care services would face increased demand. Disruptions in basic services could occur if absenteeism affects critical infrastructure.
	Speed of spread	A concentrated wave with many people ill over a short period would have higher impact on absenteeism and demand for health care than the same number of cases spread over a longer period.
	Season of arrival	Transmission is lower in spring and summer so pandemic waves in that period might be smaller. Higher impact would also be expected with late fall/winter waves due to juxtaposition of usual winter pressures from other viruses and co-circulating bacteria.
Virulence	Clinical severity	High virulence means a high proportion of severe cases among the ill, placing strain on acute and critical care services. The typical pandemic mortality age shift to younger age groups could also increase public concern. Unexpected clinical features could affect provision of acute and critical care.
Population vulnerability		
Population vulnerability	Pre-existing population immunity	Pre-existing population immunity might be present in persons above a certain age due to previous circulation of related strains. This could reduce their risk of infection (although their age might increase their risk of severe disease if they did become ill). Sparing of older persons would significantly reduce overall impact on hospitals and long term care facilities. Higher impact would be anticipated if all age groups are involved.
	Unexpected risk factors	New risk factors for severe disease could mean that more people need health care services. They could also affect vaccine prioritization.
	Special groups and settings	Impact may be increased in high-risk populations or settings (e.g. remote communities, homeless shelters and overcrowded housing). Risk could be elevated because of age, underlying health conditions, poor access to health care, poor socioeconomic conditions, etc.
Response factors		
Public health interventions	Vaccine availability, timing, effectiveness	Timing of vaccine availability in relation to pandemic activity could influence vaccine prioritization and affect uptake. Vaccine impact would be reduced if most people experience illness before vaccine is available.
	Antiviral availability and resistance	Antiviral supply might be insufficient in a very large pandemic. Antiviral drug resistance would reduce supply of effective antiviral medications, thus resulting in need to prioritize use. Supply issues could lead to increased numbers of hospitalizations, severe illness and death.

Category	Factor	Potential impact
	Public health measures	In some circumstances (e.g. virus with lower transmissibility), wide adoption of public health measures could lead to significant reduction in transmission.
Health care system response	Access to care	Good access to primary care and early antiviral treatment would reduce rates of complications and hospitalizations. Lack of access to critical care could increase mortality in seriously ill patients.
	Surge capacity	Lack of surge capacity could affect outcomes if demand for services outstrips supply. Triaging of critical care services would be needed as surge capacity is exceeded. As services become overwhelmed, mortality might increase in both influenza and non-influenza emergency patients.
	Availability of antibiotics and other drugs, supplies	Drug supply problems or antibiotic resistance could affect clinical outcomes. Shortages of infection control supplies could affect viral transmission and increase staff concern.
Risk communications	Behavioural response	Levels of public awareness and understanding and risk perception, along with level of trust in health authorities, could affect degree of adoption (and therefore potential effectiveness) of preventive behaviours such as infection prevention behaviours, social distancing, and uptake of vaccine and antiviral medications.

Appendix B - Pandemic Risk Assessments

The table identifies relevant considerations for initial and ongoing pandemic risk assessments and identifies potential sources of data to generate the information needed. In a pandemic, the Public Health Agency of Canada will prepare or arrange for the risk assessments to be prepared and disseminated.

Table - Pandemic Risk Assessments

Category	What information is needed?		How will this be learned?
	Initial risk assessment	**Ongoing risk assessments**	
Overall response			
Nature of response	• What will be the overall impact?	• Is the impact changing? • How are we coping?	• Estimates/predictions of impact (see sections below)
Characteristics of the virus			
Transmissibility	• How fast will it spread?	• Will there be more than one pandemic wave? • Is transmissibility changing?	• Molecular and genetic studies • Incubation period and generation time • Reproductive number (R0) • Real-time modeling

Category	What information is needed?		How will this be learned?
	Initial risk assessment	**Ongoing risk assessments**	
	• How many will be affected? • See also population vulnerability	• Will follow-up waves be larger or smaller? • When will the next wave begin, peak, end?	• As above • Serological attack rate • Clinical attack rates in various settings
Virulence (clinical severity)	• How severe is the disease? • What proportion of ill people will have complications, need hospitalization, die? • Are there unusual clinical presentations?	• Is disease severity changing?	• Molecular and genetic studies • Rates of hospitalization, intensive care unit (ICU) admission, ventilator use • Case fatality rate/ratio • Clinical case series of persons with severe disease • Outbreak reports
Population vulnerability			
Population vulnerability	• Will all age groups be affected and to what extent?	• How is population immunity changing as the outbreak progresses?	• Levels of pre-existing population immunity • Periodic seroprevalence surveys
	• What are the risk factors for severe disease?	• Are new risk factors/groups emerging?	• Epidemiological studies • Clinical case series • Outbreak reports
	• Are there settings and populations at increased risk?	• Are there additional settings and populations at increased risk? • Are we effectively targeting our interventions? • Any unintended consequences from our interventions?	• Epidemiological studies • PT/NGO feedback • Socioeconomic data
Public health interventions			

Category	What information is needed?		How will this be learned?
	Initial risk assessment	**Ongoing risk assessments**	
Antiviral medications	• Is there antiviral resistance? • Will antivirals be safe? • Will antivirals be effective? • Are we able to effectively mobilize the NAS?	• Are antiviral resistance patterns changing? • Are the antivirals safe? • Are the antivirals effective? • Are the right patients receiving them in a timely way?	• Antiviral susceptibility and resistance testing • Antiviral distribution and uptake • Adverse reaction reports • Effectiveness studies • Distribution reports and special studies
Vaccine	• Will vaccine be safe? • Will vaccine be effective? • When will it be available?	• When will vaccine be available? • Are there changes to the usual high-risk groups? • Is there adequate capacity for rapid immunization? • How can vulnerable groups be reached? • Is pandemic vaccine safe? • Is it effective?	• Early epidemiological studies (re: high-risk groups) • PT monitoring and feedback • Vaccine uptake and effectiveness • AEFI reports
Public health measures	• What is the anticipated impact, including on transmission?	• Are the interventions acceptable? • Are they effective?	• Measures of transmissibility and virulence • Mathematical modeling • Public opinion research • Community surveys
Infection prevention and control (IPC)	• Will the usual IPC measures be effective? • If not or unsure, what additional precautions should be taken?	• Are the usual IPC measures effective? • If not or unsure, what additional precautions should be taken? • Are there unintended consequences?	• Information on incubation period, infectivity, routes of transmission, etc.
System response			

Category	What information is needed?		How will this be learned?
	Initial risk assessment	**Ongoing risk assessments**	
Public health	• What will be the potential impact?	• What is the impact on public health services and health human resources (HHR)? • Are they able to cope?	• Measures of transmissibility and virulence • Surveillance and clinical studies • PT feedback
Community health care	• What will be the potential impact?	• What is the impact on community health care services and HHR? • Are they able to cope?	• Measures of transmissibility and virulence • Surveillance and clinical studies • Information on antiviral resistance • PT feedback • Media monitoring
Acute care services	• What will be the potential impact?	• What is the impact on acute care services and HHR? • Are they able to cope? • What bacterial complications are occurring? • Are the treatment strategies effective?	• Measures of transmissibility and virulence • Surveillance and clinical studies • Information on antiviral and antibiotic resistance • Clinical studies • PT monitoring and feedback • Media monitoring
Long-term care and other community residential care	• Will long-term care or other residential facilities for the elderly or disadvantaged be at significant risk of outbreaks?	• What is the impact on these facilities, their services and HHR?	• Information on pre-existing immunity • Surveillance and outbreak investigations • PT feedback • Media monitoring

Category	What information is needed?		How will this be learned?
	Initial risk assessment	Ongoing risk assessments	
Societal impact	• Will there be significant workplace or school absenteeism? • Will community services be affected?	• What is the impact on schools, businesses, critical infrastructure and other community services? • What is the impact on vulnerable populations? • What is the psychosocial impact on the population? • What is the economic impact?	• Measures of transmissibility and virulence • School and workplace absenteeism surveillance • PT feedback • Media monitoring and public surveys • Clinician surveys • Qualitative studies
Risk communications	• What will be the level of public concern? • What issues will be of most concern?	• What are the levels of public concern? • What issues are of most concern and are we addressing them effectively? • What is the level of public awareness and understanding of the situation?	• Traditional and social media monitoring • Tracking of public inquiries • Public opinion research • Stakeholder feedback (PTs and NGOs)

Footnotes

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Date modified:
2016-02-12

EXHIBIT D

This is Exhibit "D" referred to
in the Affidavit of
Dr. Richard Schabas
Sworn before me this 29th day
of May A.D., 2021

A Commissioner for Oaths in and for Ontario

LISA D.S. BILDY
BARRISTER & SOLICITOR

Ontario Health Plan for an Influenza Pandemic

Chapter 4: Public Health Measures

March, 2013

Ontario

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Emergency Management Branch
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Ontario Health Plan for an Influenza Pandemic

Chapter 4: Public Health Measures

Audience

- individuals responsible for developing, communicating and implementing public health measures within the provincial government, public health units (PHUs) and non-health organizations (e.g., boards of education, schools, summer camps and social service organizations)

Chapter objectives

- to define roles and responsibilities for developing and implementing public health measures during an influenza pandemic
- to describe the framework underlying the public health measures strategy
- to enable the public health sector and non-health organizations to develop and implement public health measures during an influenza pandemic

Public health measures response summary

Response objective: to slow the spread of influenza in Ontario using non-pharmaceutical methods

BEFORE SEVERITY IS KNOWN

Ministry of Health and Long-Term Care (MOHLTC) consults with local, provincial and federal partners to develop and rollout the public health measures strategy

PHUs develop and rollout local public health measures

Voluntary public health measures implemented; of the mandatory public health measures, only case & contact management is implemented

FIGURE 1. PUBLIC HEALTH MEASURES ACTIVITIES STRATIFIED BY SEVERITY

Introduction

Public health measures are non-pharmaceutical interventions that slow the spread of a communicable disease in a community. A key characteristic of public health measures is that they are implemented in non-health settings,[1] such as workplaces, homes, civic spaces (sports arenas, religious institutions), educational settings and community-based social services organizations. Public health measures are individual and group behaviours and the environmental supports that enable and encourage these behaviours. During an influenza pandemic, many people want to play an active role in making their community healthier; by implementing public health measures, everyone can contribute meaningfully to the influenza pandemic response.

Public health measures are commonly used across Ontario during the annual influenza season and other communicable disease outbreaks. Many public health measures used during an influenza pandemic are modifications of existing practices and therefore should be familiar to PHUs, non-health organizations and members of the public.

Roles and responsibilities

Table 1 outlines roles and responsibilities related to public health measures during an influenza pandemic. For a broad overview of roles and responsibilities during an influenza pandemic, see Chapter 1: Introduction.

TABLE 1. PUBLIC HEALTH MEASURES ROLES AND RESPONSIBILITIES

Party	Roles and responsibilities
Public Health Agency of Canada (PHAC)	Provide recommendations on public health measures to provinces and territories Develop and implement public health measures for populations under its jurisdiction (e.g., First Nation communities, members of the Canadian military, federal corrections facilities) Implement travel and border-related public health measures (travel advisories and restrictions, quarantine measures and border closures at international entry points)

[1] When these measures are used in health settings they are termed “infection prevention & control measures”; these measures are discussed in Chapter 5: Occupational Health & Safety and Infection Prevention & Control.

Party	Roles and responsibilities
MOHLTC[2] (through the Ministry Emergency Operations Centre (MEOC))	Develop the provincial public health measures strategy based on PHAC's recommendations and in consultation with provincial and local partners Develop and issue directives,[3] orders and requests as per the HPPA and other relevant provincial legislation Communicate the provincial public health measures strategy to PHUs, other health system partners and provincial ministries Communicate information on public health measures with the public Support PHUs and provincial ministries to implement public health measures in a wide range of settings Collaborate with Public Health Ontario (PHO) to evaluate and refine the provincial public health measures strategy
PHO (through the MEOC)	Provide scientific and technical advice to the MOHLTC Provide scientific and technical advice to PHUs to support the implementation of public health measures, such as developing tools and advising on best practices
Ministry of Labour (MOL)	Provide OHS advice to the MOHLTC (through the MEOC) Enforce the OHSA and its regulations
PHUs[4]	Provide advice to the MOHLTC to support the development, evaluation and refinement of the provincial public health measures strategy Develop, implement and evaluate public health measures based on the provincial strategy Develop and issue orders[5] as per the HPPA

[2] Throughout the OHPIP, the MOHLTC includes the Minister, the Chief Medical Officer of Health (CMOH) and the rest of the MOHLTC. For information on how decisions are made in the MOHLTC during an emergency, see the Ministry Emergency Response Plan.

[3] Directives are sent from the CMOH to health care providers or other health entities as per the Health Protection and Promotion Act (HPPA).

[4] Throughout the OHPIP, PHU includes boards of health, medical officers of health (MOHs) and other PHU health workers (e.g., public health inspectors, epidemiologists, public health nurses, etc.). See the HPPA and Ontario Public Health Standards for more information on the roles and responsibilities of various PHU parties.

Party	Roles and responsibilities
Employers in non-health organizations	Implement public health measures Role model public health measures Follow MOHLTC orders and requests Follow PHU orders
Public	Learn about and follow public health measures Follow MOHLTC and PHU orders

Voluntary and mandatory measures

Some public health measures are required under the HPPA and other provincial and federal legislation. Other measures are considered a best practice, but do not have the weight of legislation backing them. Because of this, public health measures can be categorized into two groups: voluntary public health measures (i.e., without the force of legislation) and mandatory public health measures (i.e., with the force of legislation). Appendix A provides an overview of voluntary and mandatory public health measures that may be implemented during an influenza pandemic.

Regardless of whether they are categorized as voluntary or mandatory, non-health organizations and the public should implement all recommended public health measures during an influenza pandemic.

Preparedness tip

Appendix B includes an overview of planning considerations for PHUs and non-health organizations to support the implementation of public health measures during an influenza pandemic.

Public health measures strategy

The provincial public health measures strategy cannot be finalized until the time of a pandemic as the type and relative significance of each measure depends upon the following factors:

- Evidence – The MOHLTC considers information on the severity of the pandemic, effectiveness of public health measures and the impact of other pandemic response activities (e.g., vaccine availability, effectiveness and uptake rates).
- Legislation – The strategy is based on legislative requirements and responsibilities.

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[5] *This refers to orders made by MOHs and public health inspectors as per the HPPA.*

- Ontario Public Service (OPS) values and ethical principles[6] – The MOHLTC considers the OPS values and other ethical principles during the development of the strategy, including:
  - Proportionality: Restrictions on individual liberty and measures to protect the public from harm should not exceed the minimum required to address the actual level of risk or need in the community. The MOHLTC uses a risk-based approach to consider the proportionality of potential measures to the understood risks and impacts of the pandemic, especially for measures with significant social and economic consequences (e.g., school closures, mass gathering restrictions/ bans). Although some public health measures are easy for an individual to implement, others may involve behaviours that are not routine or that have limited direct benefit to an individual but are of benefit to society.
  - Reciprocity: Society has an ethical obligation to support those who face a disproportionate burden in protecting the public good.
- Health Equity – The MOHLTC considers the needs of vulnerable populations[7] when the public health measures strategy. The strategy strives to reduce or eliminate socially structured differentials in health outcomes, building on broader ideas about fairness, social justice and civil society. For example, the implementation of system-wide school closures has different impacts on groups in society such as single parents/ caregivers, children who participate in school-based nutrition programs, families with low or fixed incomes who cannot afford increased child care costs, and parents who do not have flexible work arrangements, paid vacation or short term leave policies.
- Communication principles – The MOHLTC considers its communication principles when developing the provincial strategy.[8] More restrictive measures require explanation from public health officials as to the reasons for these measures.

While the specifics of the strategy are not known, the public health measures strategy will include the following components:

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[6] Work is underway federally to develop an ethical framework for the Canadian Pandemic Influenza Plan for the Healthcare Sector (CPIP). Future iterations of the Ontario Influenza Response Plan (OIRP) will include an ethical framework that aligns with the CPIP.

[7] The OHPIP defines vulnerable populations as a group of people who, because of the determinants of health, are more likely to be exposed to influenza, more likely to experience a serious impact because of exposure, less likely to benefit from response and recovery measures and/ or who may be negatively affected by response and recovery measures.

[8] The MOHLTC's communication principles include timeliness, transparency, accessibility and credibility.

- Guidance on adapting routine measures – The strategy will include guidance on how PHUs, non-health organizations and members of the public can adapt public health measures they routinely implement during seasonal influenza (see Table 2 for examples of how measures could be adapted).

TABLE 2. EXAMPLES OF ADAPTED PUBLIC HEALTH MEASURES

Activity	Example
Communication	PHUs identify additional public messaging opportunities Employers identify new locations for signage that reinforces specific measures (e.g., hand washing) PHUs make additional media buys to promote public health messages
Role modelling and reinforcement of measures	Boards of education and principals remind parents of the importance of keeping children home when ill Boards of education and principals review and update policies and procedures used when students are ill at school
Modifying and strengthening organization practices	Employers modify sick leave policies to ensure that employees are able to take time off work to care for ill family members Employers ensure there is more frequent cleaning of commonly touched surfaces
Social distancing	Employers extend work from home policies Shelters and daycares modify the placement of sleeping cots to ensure appropriate separation

- Focus on voluntary measures – As possible, the strategy will emphasize voluntary measures; however, mandatory measures may be recommended depending upon the risk posed by the influenza pandemic and the impact of other response activities.
- Environmental supports – The strategy will highlight the importance of ensuring environmental supports are in place to support non-health organizations and the public implement measures.
- Progression of the pandemic – As demonstrated in Table 3, some measures are more likely to be recommended at the beginning stages of an influenza pandemic (before the severity is known), while others are more likely to continue throughout the course of the event.

TABLE 3. ANTICIPATED TIMING OF PUBLIC HEALTH MEASURES

Measure	Beginning stages of the pandemic (before severity is known)	During the pandemic (understanding of severity evolves)
Voluntary public health measures	X	X
Case & contact management	X	
Orders		X

- Recognition of travel restrictions – The strategy will recognize travel restrictions recommended by PHAC, while noting the impact of orders under the HPPA on such restrictions.
- Local variation – The strategy will recognize opportunities for variation in local public health measures because of differences in disease activity, social context (e.g., role of public transit in the local community) and engagement practices (e.g., effective methods of communication for different communities, populations and environments).

Next steps

In the development of the OIRP, the MOHLTC will work with its partners to:

- develop guidance for PHUs on public communications
- engage non-health organizations on implementation of public health measures for influenza
- align the OIRP with the CPIP's ethical framework for decision-making

Appendix A – Sample public health measures

Influenza pandemic public health measures are a modification and intensification of existing good public health practices. Most measures are routinely implemented by PHUs, non-health organizations and the public during seasonal influenza outbreaks and are supported by the guidance provided in the Ontario Public Health Standards.

Public health measures can be organized into two categories: voluntary measures (i.e., measures without the force of legislation) and mandatory measures (i.e., measures with the force of legislation). All recommended public health measures should be fully implemented during an influenza pandemic.

Voluntary public health measures

Behaviours

Voluntary public health measures include the following individual and group behaviours:

- hand hygiene
- respiratory etiquette
- environmental cleaning, especially of frequently touched surfaces such as door handles
- illness isolation, which includes having individuals stay home when sick and implementing social distancing measures within the home when a household member is ill
- social distancing, which involves separation of people to minimize the likelihood of transmitting influenza
- closure of organizations or programs[9]

Environmental supports

During an influenza pandemic, it is critical to equip non-health organizations and the public with the supports they need to implement voluntary public health measures. Information, supportive workplace policies and role modelling are all important to the successful uptake voluntary measures.

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[9] An organization may choose to suspend a program during an influenza pandemic because disease transmission cannot be adequately controlled and the program is not deemed to be critical.

Information

The information provided to non-health organizations and the public will help them implement voluntary behaviours and understand why these measures are important in helping to stop the spread of the influenza pandemic. Core elements include:

- information about the influenza pandemic, such as modes of transmission, risk and impacts
- information about public health measures, including why they are important and how to implement measures at home, in the workplace and elsewhere in the community

Support

In workplaces, supports may include adjustments to policies and procedures in order to help workers enact public health measures. Flexibility in sick leave policies as well as flexible work arrangements are examples of policies that support social distancing. Communication efforts should also be escalated so that changes to policies and procedures are widely understood and effectively implemented.

Role Modelling

Role modelling involves demonstrating behaviours so that the public can emulate them. Role modelling of public health measures by formal and informal leaders in society supports their adoption by normalizing the desired behaviours. Leaders such as school principals, teachers, employers and coaches should be encouraged to personally and publicly adopt these behaviours.

Mandatory public health measures

Mandatory public health measures are extraordinary actions designed to address and counter specific public health threats. Mandatory measures include case & contact management, orders and travel restrictions.

Case & contact management

Case management describes the method, and often formal protocol, where PHU staff follow-up with individuals ill with influenza (i.e., cases) to provide information and strategies to reduce transmission to others. The syndrome that defines a case is communicated through Important Health Notices. This definition may evolve during the influenza pandemic (e.g., during initial stages of the pandemic, the case definition may include travel history).

Contact management involves PHU staff identifying those who may have had close contact with infectious cases (i.e., contacts), notifying them and providing counselling and information to recognize emerging illness.

PHUs perform case & contact management during an influenza pandemic based on the provincial pandemic health measures strategy.

Orders

Authority exists under provincial and federal legislation to order the closure an organization for a period of time and/ or modify activities within an organization. The federal government may issue the closure of spaces under federal jurisdiction, as well as the exclusion of sick individuals from these spaces. The CMOH and MOHs may do the same for spaces under their jurisdiction as described by the HPPA. Organizations and individuals have the legal responsibility to comply with all orders issued by public health officials and to assist in their implementation.

There is other legislation that confers the responsibility for implementing public health measures to leaders outside of the public health sector. For example, the Education Act empowers principals to refuse school admission to those infected or exposed to communicable diseases. The Day Nurseries Act requires daycare operators to note the health status of children in their care, separate sick children from others, and require that parents/ guardians take sick children home.

Appendix B – Selected planning considerations

PHUs should consider in advance of a pandemic how public health measures could be implemented across their jurisdiction. Implementation of public health measures should be based on the PHU's extensive knowledge of their local context and community's needs, existing relationships with local partners, documentation of best practices for implementing public health measures during the annual influenza season and lessons learned from other health promotion activities.

Non-health care settings should similarly consider actions they can take to promote the uptake of public health measures during an influenza pandemic.

Environmental support of voluntary measures

To ensure maximum success, planning for the environmental support of voluntary public health measures should be undertaken by PHUs. This involves:

- audience segmentation and an analysis of appropriate modes of communication (including multilingual and accessible communication tools) for each audience, including vulnerable populations
- identifying the factors that influence and encourage the uptake of public health measures (which can be emphasized in communications)
- applying lessons learned from past experience with public health communications and health promotion programs

Leveraging existing relationships and routine interactions to teach, promote and reinforce the use of public health measures is important. An example is including hand washing lessons as part of a public health nurse's involvement in an Early Years program or as part of an after school program run by a community-based organization.

Closures

Non-health organizations should prepare for the implementation of closures during an influenza pandemic (e.g., school closures, closure of programs in social service organizations). An organization may need to close because of a mandatory public health measure issued by a public health official (e.g., order from the MOH to close the space or program due to the risk posed by the pandemic). However, an organization may also need to close as a result of other events during an influenza pandemic (e.g., the employer decides to close the space or program due to high rates of illness among employees or significant interruptions to public transportation systems).

Regardless of the reason, closures can affect continuity of operations (especially of critical services), employees, the population groups that the organization serves (e.g., students, customers) and secondary populations (e.g., parents of students).

As part of their planning, organizations should work closely with their PHU to better understand the HPPA and how orders under this act would be made and communicated during an influenza pandemic.

Organizations should consider times in the past when they have had to close because of events such as labour disruptions or inclement weather and identify lessons learned that could be applied to an influenza pandemic.

Appendix C – Selected practices from the 2009 influenza pandemic

Public health measures were effectively implemented in a wide range of non-health organizations during the 2009 H1N1 influenza pandemic. Some examples of best practices include the following:

- implementation of hand hygiene stations in arenas and recreation centres
- development of innovative activities to reinforce respiratory etiquette at summer camps and to modify existing policies and procedures to notify parents when campers were ill
- use of internal TV channels by correctional facilitates to share and reinforce educational messaging about the importance of implementing public health measures
- development of culturally appropriate education materials by PHUs for different population groups in their community
    - a PHU redeveloped their educational materials for a specific community that does not support the use of photographs of people – in the redeveloped materials, drawings of stick figures demonstrated how to implement public health measures
- development of strategic community-based communication programs by PHUs
    - a PHU intentionally engaged with leaders and 'information gatekeepers' to promote information about public health measures within their community more effectively
- development of targeted messaging based on community needs
    - a PHU reframed their educational messaging after engaging members from a migrant farm worker community
- development of strategies to implement public health measures in different business and industry settings, such as washing the steering wheels of delivery and service vans
- temporary suspension of some activities by schools and extracurricular programs, such as encouraging players not to shake hands after sports games - in many settings, the traditional handshake was replaced with a team cheer
- reorganization of programming and activities within social services organizations
    - a shelter for people who are homeless and underhoused encouraged guests and residents to sleep 'head to toe' (if in one bed the resident sleeps with their head pointing north, in the next bed, the resident would sleep with their head pointing south) to maintain social distancing measures

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FORM 53

Kitchener Court File No.: CV-21-00000095-0000
St. Thomas Court File No.: CV-21-08

ONTARIO
SUPERIOR COURT OF JUSTICE

B E T W E E N:

THE ATTORNEY GENERAL OF ONTARIO

Applicant (Responding Party)

-and-

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHUURMAN, DEAN WANDERS, RANDY FREY, HARVEY FREY and DANIEL GORDON

Respondents (Moving Parties)

A N D B E T W E E N:

HER MAJESTY THE QUEEN IN ONTARIO

Applicant (Responding Party)

-and-

THE CHURCH OF GOD (RESTORATION) AYLMER, HENRY HILDEBRANDT, ABRAM BERGEN, JACOB HIEBERT, PETER HILDEBRANDT, SUSAN MUTCH, ELVIRA TOVSTIGA, and TRUDY WIEBE

Respondents (Moving Parties)

ACKNOWLEDGMENT OF EXPERT'S DUTY

---

1. My name is Dr. Richard Schabas. I live in Toronto, Ontario.

2. I have been engaged on behalf of the Moving Parties, Trinity Bible Chapel et al. and The Church of God, et al., to provide evidence in relation to the above-noted court proceeding.

3. I acknowledge that it is my duty to provide evidence in relation to this proceeding as follows:

   (a) to provide opinion evidence that is fair, objective and non-partisan;

   (b) to provide opinion evidence that is related only to matters that are within my area of expertise; and

(c) to provide such additional assistance as the court may reasonably require, to determine a matter in issue.

4. I acknowledge that the duty referred to above prevails over any obligation which I may owe to any party by whom or on whose behalf I am engaged.

Date: May 29, 2021

Signature

NOTE: This form must be attached to any expert report under subrules 53.03(1) or (2) and any opinion evidence provided by an expert witness on a motion or application.

Kitchener Court File No.: CV-21-00000095-0000
St. Thomas Court File No.: CV-21-08

HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO	***and***	**CHURCH OF GOD (RESTORATION) AYLMER et al.**
THE ATTORNEY GENERAL OF ONTARIO	***and***	**TRINITY BIBLE CHAPEL et al.**
Applicants		*Respondents*

ONTARIO
SUPERIOR COURT OF JUSTICE

Proceeding commenced at St. Thomas

AFFIDAVIT OF DR. RICHARD SCHABAS

JUSTICE CENTRE FOR CONSTITUTIONAL FREEDOMS

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Kitchener Court File No.: CV-21-00000095-0000
St. Thomas Court File No.: CV-21-08

ONTARIO
SUPERIOR COURT OF JUSTICE

B E T W E E N:

THE ATTORNEY GENERAL OF ONTARIO

Applicant (Responding Party)

-and-

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHUURMAN, DEAN WANDERS, RANDY FREY, HARVEY FREY and DANIEL GORDON

Respondents (Moving Parties)

A N D B E T W E E N:

HER MAJESTY THE QUEEN IN ONTARIO

Applicant (Responding Party)

-and-

THE CHURCH OF GOD (RESTORATION) AYLMER, HENRY HILDEBRANDT, ABRAM BERGEN, JACOB HIEBERT, PETER HILDEBRANDT, SUSAN MUTCH, ELVIRA TOVSTIGA, and TRUDY WIEBE

Respondents (Moving Parties)

AFFIDAVIT OF DR. RICHARD SCHABAS
(Sworn July 23, 2021)

I, RICHARD SCHABAS, of the [redacted] in the Province of Ontario, MAKE OATH AND SAY:

1. I make this affidavit further to my affidavit sworn May 23, 2021, and in reply to the affidavit of Dr. Matthew Hodge, affirmed July 2, 2021.

2. Dr. Hodge states that Ontario's response to Covid-19, including decisions to interfere with religious gatherings, was guided by the "precautionary principle" which states that public health "does not await scientific certainty before taking action to protect" and that this is "particularly relevant during the early stages of a pandemic". He does not propose an alternative standard of evidence that would guide decision-making in these circumstances. This suggests that in his opinion little or no evidence is required before instituting coercive public health measures - that the "precautionary principle" effectively gives public health a blank cheque to do whatever it wants.

3. The traditional evidentiary standard for public health orders in Ontario, from the *Health Protection and Promotion Act*, is reasonable and probable grounds. This standard is not as demanding as the "scientific certainty" of the "precautionary principle", but it is still a high bar. With the exception of immunization, very few if any of the measures and none of the coercive measures used by Ontario public health in response to Covid-19 would meet the reasonable and probable grounds standard.

4. Dr. Hodge says the "burden model" informs his opinion, and that this model takes into account three factors - the prevalence of disease, exposure risk and consequences of infection. The inappropriateness of the "burden model" in advising this issue is obvious. It does not consider the consequences of the intervention.

5. The burden model may provide an appropriate perspective in the typical infectious disease outbreak where the control measures are targeted, reasonable and truly "temporary". Covid-19 and, more specifically, the public health response to Covid-19 are different because the measures taken undermine the fundamental determinants of health (education, employment, social connections) and are not, by any stretch of the imagination, short-lived. Reliance on the "burden model" goes

a long way to explaining the dysfunctional decision-making of Ontario public health.

6. Dr. Hodge's argument that Ontario has insufficient hospital beds to deal with Covid does not stand even rudimentary scrutiny. Ontario had almost 25,000 acute care hospital beds available for use as of April 2020.[1] At no point in the pandemic have Covid patients occupied even 10% of this number.[2] The maximum bed census for Covid-19 (2360 beds on April 20, 2021) was far less than the extra surge capacity (4205 beds) available in April 2020. One can only hope that the Ontario government, considering its concerns about health care capacity, has further enhanced this capacity in the past year. Dr. Hodge's threat of a "health system in which every available bed is occupied by someone infected with COVID-19" should be viewed in this context.

7. Dr. Hodge compares Ontario's overall mortality rate to three other jurisdictions with higher mortality (Sweden, Brazil and Florida) and attributes the difference to Ontario's interventions. This is common practice for defenders of lockdown. The world is a very large place, and it is easy to find anecdotal examples to support both sides of any argument.

8. Ontario and Canada as a whole have had low Covid mortality compared to most European countries, the United States or South America. The reasons for this are unclear. Ontario has indeed had lower Covid mortality than some jurisdictions that have been less coercive with Covid, but it has also had much lower mortality than many jurisdictions in Europe and the United States that have used more severe coercive measures.[3] We need look no further than Canada to see the paradox. British Columbia has been consistently less aggressive than Ontario with Covid control measures and yet has a mortality rate (352/million population) that is 55% lower than Ontario's (638/million population). At the present time there are no restrictions at all for religious services in British Columbia. And Quebec, which employed some of the most stringent measures of all has a death rate (1,321/million population) more than twice as high as Ontario.[4]

9. Dr. Hodge states “transmission risk seems to be highest prior to symptoms appearing, meaning that most infected people will unknowingly infect others before they themselves have symptoms”. He is referring to what is known as “pre-symptomatic transmission.” This statement is false and contrary to the reference he provides.

10. The general scientific consensus is that “most infected people” do not infect anyone. This is the “over-distributed” nature of Covid transmission.[5] The WHO reference provided by Dr. Hodge says, “Laboratory data suggests that infected people appear to be most infectious just before they develop symptoms (namely 2 days before they develop symptoms) and early in their illness.” With regard to people with asymptomatic infections, the WHO says, “While someone who never develops symptoms can pass the virus to others, it is still not clear how frequently this occurs and more research is needed in this area.”

11. Research has in fact been undertaken in the area of pre-symptomatic and asymptomatic transmission. A large, peer-reviewed meta-analysis of 54 studies conducted globally examined transmission from an infected person to another person living in the same home, where people do not wear masks or socially distance.[6] Studying transmission in the household setting gives the most accurate picture of how Covid will spread because of the lack of safeguards present. Symptomatic patients passed on the disease to household members in 18% of instances, while asymptomatic and pre-symptomatic patients passed on the infection in only 0.7% of instances. This makes sense, as the time-period during the pre-symptomatic phase (2 days prior to symptom onset) is relatively short and the symptoms themselves are a critical engine for spread. Covid transmission from patients without symptoms is rare and should not be used to justify restrictions on indoor gatherings.

12. I make this affidavit *bona fide.*

SWORN REMOTELY by videoconference by Dr. Richard Schabas at the [redacted] British Columbia, before me at the City of London, in the County of Middlesex, this 23rd day of July, 2021 in accordance with O.Reg. 431/20 Administering Oath or Declaration Remotely

A Commissioner, etc.

LISA D.S. BILDY
BARRISTER & SOLICITOR

DR. RICHARD SCHABAS

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Kitchener Court File No.: CV-21-00000095-0000
St. Thomas Court File No.: CV-21-08

HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO	***and***	**CHURCH OF GOD (RESTORATION) AYLMER et al.**
THE ATTORNEY GENERAL OF ONTARIO	***and***	**TRINITY BIBLE CHAPEL et al.**
Applicants		*Respondents*

ONTARIO
SUPERIOR COURT OF JUSTICE

Proceeding commenced at St. Thomas

AFFIDAVIT OF DR. RICHARD SCHABAS

JUSTICE CENTRE FOR CONSTITUTIONAL FREEDOMS

[redacted]

Lisa D.S. Bildy [redacted]

[redacted]

Allison Kindle Pejovic

[redacted]

Counsel for the Respondents/Moving Parties

Kitchener Court File No. CV-21-00000095-0000

ONTARIO
SUPERIOR COURT OF JUSTICE

BETWEEN:

THE ATTORNEY GENERAL OF ONTARIO

Applicant

and

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHUURMAN, DEAN WNADERS, RANDY FREY, HARVEY FREY, AND DANIEL GORDON

Respondents

AFFIDAVIT OF DR. DAVID McKEOWN
(Affirmed on July 5, 2021)

I, **DAVID MCKEOWN,** of the [redacted], in the Province of Ontario, **AFFIRM:**

I. Professional Background

1. I am the Associate Chief Medical Officer of Health ("**ACMOH**") with the Ontario Ministry of Health. I have held that position since early 2020 and previously held that position from 2016 to 2017. I am a licensed physician in Ontario and have practiced medicine for 35 years. I have a medical degree from McGill University and a Master's degree in Community Health and Epidemiology from the University of Toronto. I am a certified specialist in Canada and the United States in the areas of public health and preventative medicine. Prior to being appointed ACMOH in 2016, I was the Medical Officer of Health for the City of Toronto for 12 years. Prior to the COVID-19 pandemic, I led local public health responses to the H1N1 pandemic, a major outbreak of Legionnaire's Disease, and the first outbreak of West Nile Virus in Canada.

2. Pursuant to section 81.1 of *Health Protection and Promotion Act*, my responsibilities as ACMOH include acting in the capacity of the Chief Medical Officer of Health when he is unavailable and performing such functions and duties as the Chief Medical Officer of Health may specify in writing. During the COVID-19 pandemic, my responsibilities have included monitoring the spread of COVID-19 in Ontario and advising on the Ontario Government's policy response to the pandemic.

3. As such, I have personal knowledge of the contents of this affidavit. Where in this affidavit I have indicated I have received information from others, I have identified the source of the information and I believe the information to be true.

II. Ontario's Policy Response to the COVID-19 Pandemic

(i) Legislative Background

4. On March 17, 2020, the Premier of Ontario declared an emergency pursuant to section 7.0.1 of the *Emergency Management and Civil Protection Act* ("***EMCPA***"). An "emergency" is defined under section 1 of *EMCPA* as a "situation or an impending situation that constitutes a danger of major proportions that could result in serious harm to persons or substantial damage to property and that is caused by the forces of nature, a disease or other health risk, an accident or an act whether intentional or otherwise."

5. The emergency was declared pursuant to O. Reg. 50/20, which was promulgated under *EMCPA*. That regulation stated that "the outbreak of a communicable disease namely COVID-19 coronavirus disease constitutes a danger of major proportions that could result in serious harm to persons" and that "an emergency is hereby declared pursuant to section 7.0.1 of the Act in the whole of the Province of Ontario." Under *EMCPA*, during a declared emergency, the Lieutenant

Governor in Council may make certain orders that it believes are necessary to address the emergency, subject to the conditions set out in *EMCPA*.

6. On March 24, 2020, O. Reg. 82/20 was promulgated pursuant to the emergency powers under *EMCPA*. Pursuant to that regulation, all non-essential businesses were ordered to close and limits were placed on the operations of other businesses and organizations. Since March 24, 2020, O. Reg. 82/20 has been amended regularly as the pandemic has evolved. In addition, several other orders have been made under *EMCPA* to address the COVID-19 pandemic.

7. Under *EMCPA*, declarations of emergency (and the powers associated with them) are intended to be time limited. In order to ensure the Lieutenant Governor in Council continued to have the power to address the ongoing effects of the pandemic after the emergency declaration terminated, the Legislature enacted the *Reopening Ontario (A Flexible Response to COVID-19) Act, 2020* ("***ROA***"), which was proclaimed into force on July 24, 2020. The *ROA* terminated the provincial emergency and continued a number of orders made under *EMCPA* that were designed to address the COVID-19 pandemic, including O. Reg. 82/20. Since the *ROA* was passed, the Province has amended several orders that were continued under the *ROA* and taken a variety of other public health measures to address the ongoing pandemic.

8. On April 27, 2020, Ontario released its *Framework for Reopening our Province*, which established criteria that Ontario's Chief Medical Officer of Health and other health experts would use to advise the government on the loosening of emergency measures, as well as guiding principles for the safe, gradual reopening of businesses, services and public spaces. The plan contemplated a stage-by-stage approach to reopening the economy.

9. At that time, areas of the province were subject to different restrictions as they moved through three stages of reopening:

- **Stage 1:** Select businesses that were ordered to close or restrict operations would be permitted to reopen with modified operations. Some outdoor spaces, such as parks, would reopen to allow for a greater number of individuals to attend some events (O. Regs. 82/20; O. Reg. 52/20; and O. Reg. 104/20).
- **Stage 2:** More businesses would be permitted to reopen based on risk assessments, more outdoor spaces would reopen, and some larger public gatherings would be permitted (O. Reg. 263/20).
- **Stage 3:** Opening of all workplaces and further relaxing of restrictions on public gatherings (O. Reg. 364/20).

(ii) The Keeping Ontario Safe and Open Framework

10. On November 3, 2020, Ontario released its *Keeping Ontario Safe and Open Framework* ("*Framework*"), which established a modified tiered approach to combatting the pandemic. The *Framework* was intended to allow the province to scale up and scale back public health restrictions on a regional basis in response to surges and waves of COVID-19. It provided a more tailored approach that allowed measures and restrictions to be increased or decreased as required by local epidemiological data.

11. The *Framework* created five zones of public health protection measures, each with varying levels of public health protection measures. The five zones were (1) Green-Prevent; (2) Yellow-Protect; (3) Orange-Restrict; (4) Red-Control; and (5) Grey-Lockdown. Attached as **Exhibit "A"** is a press release dated November 3, 2020, entitled "Ontario Releases COVID-19 Response Framework to Help Keep the Province Safe."

12. The regulations that originally implemented the three stages were amended as follows to implement the various zones:

Zone	Applicable Regulation
Green-Prevent	O. Reg. 364/20
Yellow-Protect	O. Reg. 364/20
Orange-Restrict	O. Reg. 364/20
Red-Control	O. Reg. 263/20
Grey-Lockdown	O. Reg. 82/20

Each of the above-noted regulations has been amended multiple times since the *Framework* was first implemented to respond as needed to the changing COVID-19 situation.

13. Pursuant to O. Reg. 363/20, the Ontario can designate which geographic areas in the province are subject to which level of public health protection measures. The *Framework* provided that several public health indicators would inform any adjustment or tightening of health measures, including weekly incidence of COVID-19, the test positivity rate, the effective reproduction number (Rt), evidence of recent outbreaks, and the level of community transmission.

14. More generally, Ontario's approach to the pandemic has been informed by public health data and by public health professionals. Ontario's priorities when developing the *Framework* included limiting the transmission of COVID-19, avoiding closures while reducing the risk of transmission, keeping schools and childcare open and safe, maintaining health care and public health system capacity, protecting vulnerable populations, and providing additional support to those disproportionately affected by the pandemic.

15. In November and December 2020, Ontario moved various regions into different levels in the *Framework*, depending on the state of the pandemic in those regions. For example:

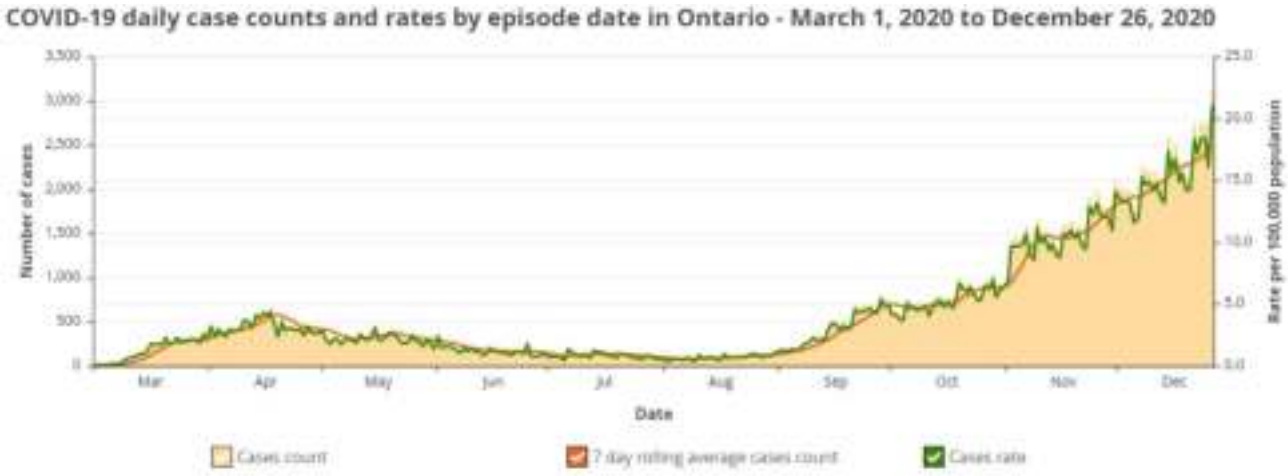
- On November 7, 2020, Peel Region was moved into Red-Control, the second-highest level in the framework. At the request of the local medical officer of health, Toronto remained in a modified Stage 2 under the previous framework.

Attached as **Exhibit "B"** is a press release dated November 6, 2020, entitled "Ontario Moves Public Health Unit Regions into COVID-19 Response Framework to Keep Ontario Safe and Open."

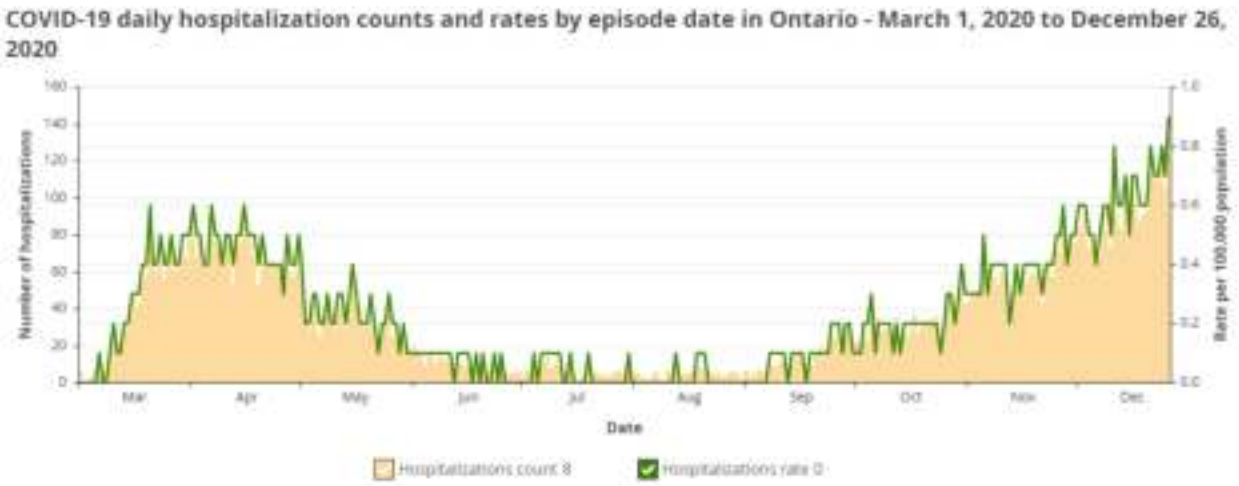
- On November 14, 2020, Toronto, Hamilton, Halton Region, and York Region moved into Red-Control. Attached as **Exhibit "C"** is a press release dated November 13, 2020, entitled "Ontario Updating COVID-19 Response Framework to Help Stop the Spread of COVID-19."
- On November 23, 2020, the City of Toronto and the Region of Peel were moved into Grey-Lockdown, which was at that time the highest level in the framework. Attached as **Exhibit "D"** is a press release dated November 20, 2020, entitled "Ontario Taking Further Action to Stop the Spread of COVID-19."
- On November 30, 2020, Windsor-Essex County Health Unit was moved into Red-Control. Attached as **Exhibit "E"** is a press release dated November 27, 2020, entitled "Ontario Moving Regions to New Levels in COVID-19 Response Framework."
- On December 14, 2020, Windsor-Essex County Health Unit and York Region Health Unit were moved into Grey-Lockdown. Attached as **Exhibit "F"** is a press release dated December 11, 2020, entitled "Ontario Moving Regions to New Levels with Stronger Public Health Measures."

(iii) The Second Provincial State of Emergency

16. In December 2020, there was a significant increase in COVID-19 cases and hospitalizations in Ontario. The graph below from Public Health Ontario ("**PHO**") shows daily COVID-19 cases in Ontario from March 1, 2020 to December 26, 2020:



17. Below is a graph from PHO that shows the number of daily COVID-19 hospitalizations in Ontario from March 1, 2020 to December 26, 2020:



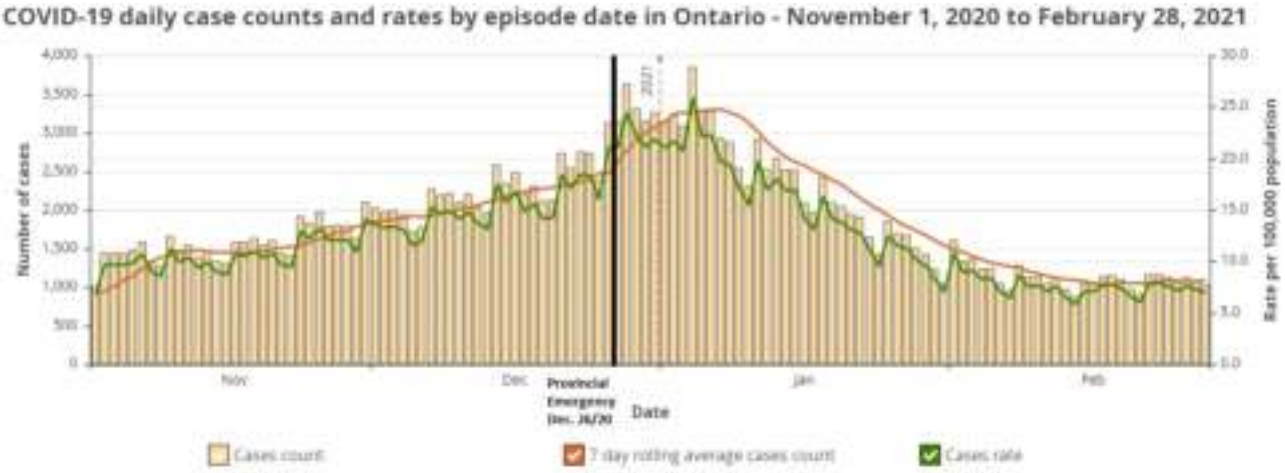
18. On December 21, 2020, the worsening COVID-19 situation led the government to pause the *Framework* and implement a Provincewide Shutdown effective December 26, 2020. Attached as **Exhibit "G"** is a press release dated December 21, 2020, entitled "Ontario Announces Provincewide Shutdown to Stop Spread of COVID-19 and Save Lives."

19. On January 12, 2021, the Premier of Ontario declared a second province-wide state of emergency pursuant to O. Reg. 7/21, which was promulgated under section 7.0.1 of *EMCPA*. The

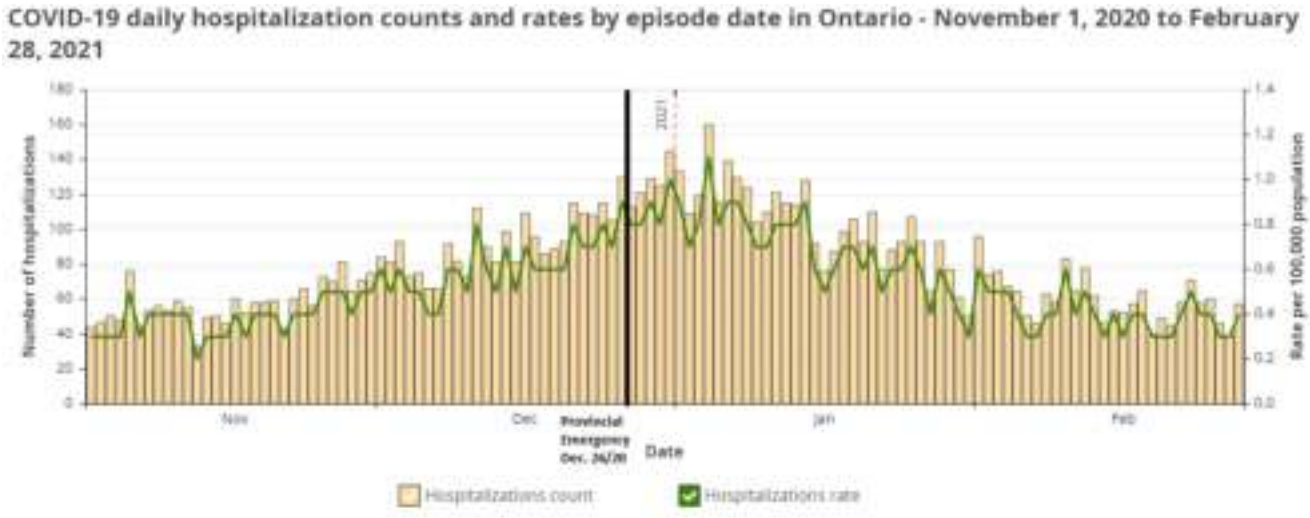
declaration of a state of emergency followed significant increases in the number of COVID-19 cases, hospitalizations and ICU patients in Ontario. Attached as **Exhibit "H"** is a press release dated January 12, 2021, entitled "Ontario Declares Second Provincial Emergency to Address COVID-19 Crisis and Save Lives."

20. During the state of emergency, the *Framework* was temporarily suspended and more stringent measures were put in place province-wide. Among other measures, the Province issued a stay-at-home order requiring everyone to remain at home, with exceptions for certain permitted purposes or activities, such as going to the grocery store or pharmacy, accessing health care services, or performing work that cannot be done remotely. In addition, schools moved to teacher-led remote learning until January 11, 2021 in Northern Ontario, January 25, 2021 in most of Southern Ontario, and February 10, 2021 in the most-affected regions such as Toronto.

21. Shortly after the province implemented the second state of emergency, COVID-19 cases in Ontario began to level off and then steadily decline. According to data from PHO, on December 26, 2021, the rolling 7-day average of new COVID-19 cases in Ontario was 2,488. By February 9, 2021, that number had declined to 1,210. Below is graph from PHO showing the number of new COVID-19 cases in Ontario from November 1, 2020 to February 28, 2021:



22. There was a similar decline in the number of hospitalizations. Below is a graph from PHO showing daily hospitalizations from November 1, 2020 to February 28, 2021:



23. At that time, very few Ontarians had received any COVID-19 vaccinations, as Ontario's vaccine rollout was hampered by a lack of a stable and reliable supply of vaccines from the federal government. According to data from PHO, throughout the entire second state of emergency, less than 2% of the Ontario population had received even a first dose of the vaccine and less than 1% were fully vaccinated.

24. Following a significant decline in COVID-19 cases, the second provincial state of emergency ended on February 9, 2021. At that time, the Province began to gradually transition regions throughout the province from the emergency shutdown measures to revised measures under the *Framework*, as the public health situation in those regions permitted.

25. At the same time, Ontario introduced an "emergency brake" system to allow for immediate action if a public health unit experienced rapid acceleration in COVID-19 transmissions or if its health care system risked being overwhelmed. If that occurred, the Chief Medical Officer of Health, in consultation with the local Medical Officer of Health, could recommend immediately

moving a region into Grey-Lockdown to interrupt transmission. Attached as **Exhibit "I"** is a press release dated February 8, 2021, entitled "Ontario Extending Stay-at-Home Order across Most of the Province to Save Lives."

26. In February and March 2021, Ontario moved various regions into and out of various levels of public health protections, depending on the state of the pandemic in those regions. For example:

- On February 16, 2021, twenty-seven public health regions transitioned out of the shutdown into the revised *Framework*. Four public health regions – City of Toronto, Peel Region, York Region, and North Bay Parry Sound District Health Units – remained in the shutdown in light of the continuing severity of the COVID-19 situation in those regions. Attached as **Exhibit "J"** is a press release dated February 12, 2021, entitled "Ontario Returning 27 Public Health Regions to Strengthened COVID-19 Response Framework."
- On February 22, 2021, York Region returned to the *Framework*, but COVID-19 rates remained too high in the other three regions to justify a similar return to the *Framework*. As well, variants of concern ("VOCs") were starting to spread in the community, particularly in North Bay. Attached as **Exhibit "K"** is a press release dated February 19, 2021, entitled "Stay-at-Home Order Extended in Toronto and Peel Public Health Regions Along with North Bay-Parry Sound"
- On March 1, 2021, Ontario activated the "emergency brake" and returned Thunder Bay District and Simcoe-Muskoka District Health Units to Grey-Lockdown in order to immediately interrupt transmission and contain community spread of VOCs in those regions. Attached as **Exhibit "L"** is a press release dated

February 26, 2021, entitled "Ontario Activates Emergency Brake in Thunder Bay District Health Unit and Simcoe-Muskoka District Health Unit."

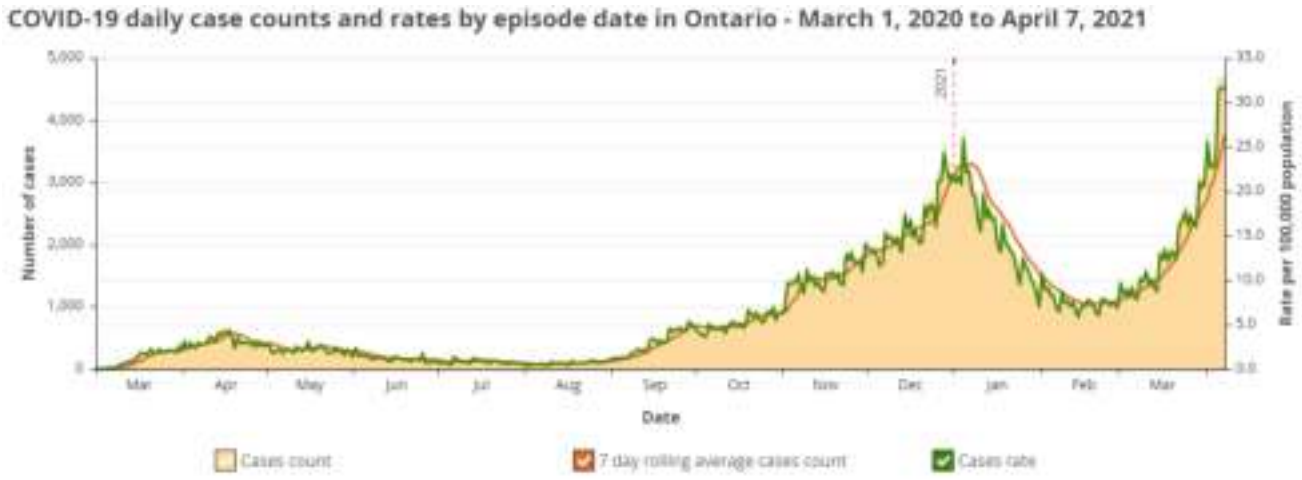
- On March 8, 2021, there was evidence of some improvement in the COVID-19 situation, which permitted the return of Toronto, Peel, and North Bay Parry Sound to the *Framework*. North Bay Parry Sound District Health Unit returned at the Red-Control level. Toronto and Peel, despite making progress, still had higher case rates and returned at the Grey-Lockdown level. Attached as **Exhibit "M"** is a press release dated March 5, 2021, entitled "Toronto, Peel and North Bay-Parry Sound Public Health Regions Returning to Strengthened COVID-19 Response Framework."
- On March 12, 2021, Ontario again activated the "emergency brake" and moved Sudbury District Health Unit to Grey-Lockdown due to a rapid rise in the case rate in that area. Attached as **Exhibit "N"** is a press release dated March 11, 2021, entitled "Ontario Activates Emergency Brake in Sudbury Public Health Region."

(iv) The Third Provincial State of Emergency

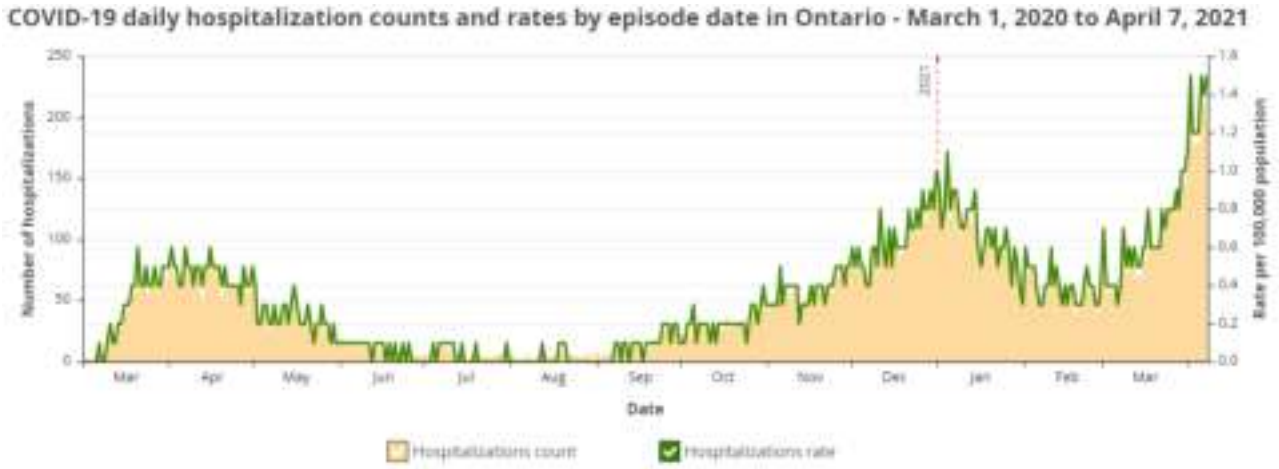
27. In March and April 2021, COVID-19 cases and hospitalizations in Ontario increased rapidly. On March 1, 2021, the average number of new COVID-19 cases reported each day based on a 7-day rolling average was 1,113. By April 1, 2021, the 7-day rolling average of new cases per day had increased to 3,327. By April 12, 2021, that number reached 4,484. By mid-April 2021, there were more patients hospitalized in Ontario as a result of COVID-19 than at any time since the start of the pandemic. Attached as **Exhibit "O"** is an Update on COVID-19 Projections dated April 1, 2021, from the Ontario COVID-19 Science Advisory Table, a group of health

professionals that evaluates and reports on emerging evidence relevant to the COVID-19 pandemic.

28. Below is a graph from PHO of daily COVID-19 cases from March 1, 2020 to April 7, 2021, which shows a significant increase in cases in March and April 2021:



29. The number of hospitalizations followed a similar trend. Below is a graph from PHO that shows daily COVID-19 hospitalizations in Ontario from March 1, 2020 to April 7, 2021:



30. On April 1, 2021, the alarming surge in case numbers and COVID-19 hospitalizations across the province led Ontario, in consultation with the Chief Medical Officer of Health and other

health experts, to implement a provincewide "emergency brake," effective April 3, 2021. Provincial case rates had increased by 7.7% to 101.1 cases per 100,000 people, COVID-19 related ICU admissions had exceeded the peak of the second wave, and hospitals in regional hotspots were beginning to further ramp down scheduled surgeries. Attached as **Exhibit "P"** is a press release dated April 1, 2021, entitled "Ontario Implements Provincewide Emergency Brake."

31. All 34 public health units were moved into the Shutdown Zone. The public health measures applicable in the Shutdown Zone included prohibiting indoor organized public events and social gatherings and limiting the capacity for outdoor organized public events or social gatherings to a 5-person maximum, except for gatherings with members of the same household or of one household and one other person from another household who lives alone. Capacity at weddings, funerals, and religious services, rites or ceremonies was limited to 15% occupancy per room indoors and to the number of individuals who could maintain 2-metre physical distancing outdoors. Ontarians were asked to limit trips outside the home, except for necessities.

32. On April 7, 2021, the Premier of Ontario declared a third province-wide state of emergency pursuant to O. Reg. 264/21, which was promulgated under section 7.0.1 of *EMCPA*. This state of emergency was implemented following rapid increases in COVID-19 cases, hospitalizations, and ICU occupancy in Ontario. For example, the number of COVID-19 hospitalizations in the province increased by 28.2% between the period of March 28 and April 5, 2021. In addition, between March 28 and April 5, 2021, the number of COVID-19 patients in ICUs increased by 25%. There was also an increase in the number of cases that were identified as VOCs, as discussed above. Attached as **Exhibit "Q"** is a press release dated April 7, 2021, entitled "Ontario Enacts Provincial Emergency and Stay-at-Home Order."

33. During this state of emergency, the entire province was in the Shutdown Zone and subject to the health protection measures set out in in O. Reg. 82/20, as well as additional measures, such as a stay-at-home order promulgated under *EMCPA*.

34. The health protection measures that applied during the third state of emergency included:

- the province-wide stay-at-home order, requiring everyone to remain at home except for essential purposes, such as going to the grocery store, accessing health care services, engaging in outdoor exercise, or conducting work that cannot be done remotely;
- limiting the majority of non-essential retailers to curbside pick-up and delivery only;
- restricting access to shopping malls to limited specified purposes;
- restricting discount and big box stores in-person retail sales to essential items;
- imposing more restrictive capacity limits for business or facilities that remain open to the public; and
- limiting restaurants and bars to providing take-out, delivery and drive-through service only.

35. On April 12, 2021, the Province moved elementary and secondary schools to remote learning following the April Break to limit community transmission, take pressure off hospitals, and allow more time to rollout further COVID-19 vaccinations. Attached as **Exhibit "R"** is a press release dated April 12, 2021, entitled "Ontario Moves Schools to Remote Learning Following Spring Break."

36. By April 16, 2021, COVID-19 cases, hospitalizations and ICU occupancy were at their highest levels since March 2020. Attached as **Exhibit "S"** is a graph from the Ontario COVID-19

website showing the number of patients hospitalized and in ICUs in Ontario with COVID-19 from April 2, 2020 to July 5, 2021. Attached as **Exhibit "T"** is an Update on COVID-19 Projections dated April 16, 2021, from the Ontario COVID-19 Science Table.

37. The number of hospitalized patients in an ICU due to COVID-19 also increased significantly. The increase in ICU patients was particularly concerning because it not only threatened the ability of the healthcare system to deal with COVID-19 patients, it also compromised the ability of the healthcare system to care for regular (i.e. non-COVID-19) patients. Attached as **Exhibit "U"** is a table showing the number of COVID-19 cases in ICU and ICU occupancy in Ontario as of April 18, 2021.

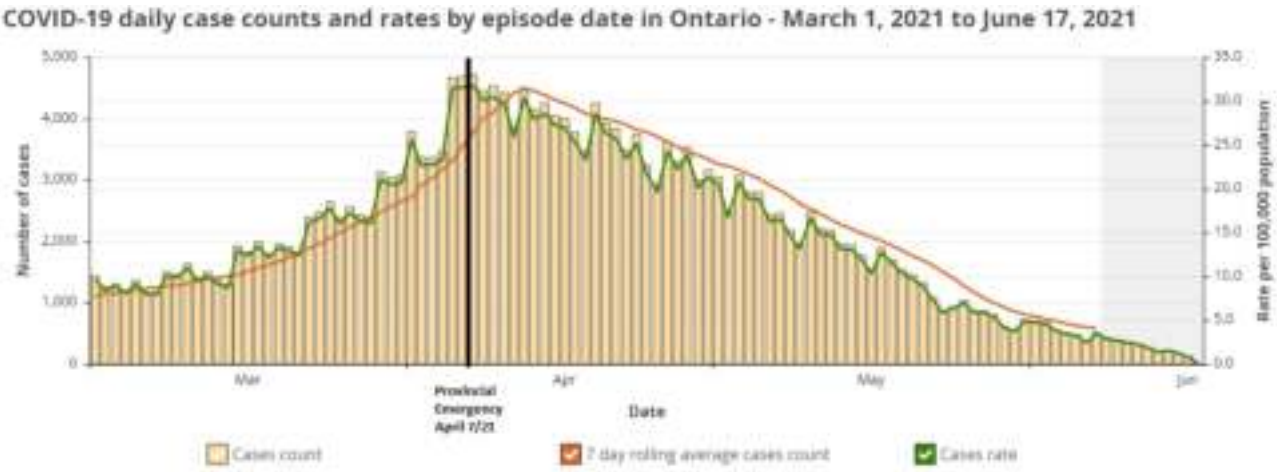
38. Beginning on April 16, 2021, the Province started to implement additional health protection measures, including the following:

- Indoor or outdoor gatherings (other than religious, wedding or funeral services) were only permitted with members of the same household or one other person from outside that household who lives alone or who is a caregiver for any member of the household.
- Indoor or outdoor religious, wedding and funeral services were limited to a maximum of 10 people. Drive-in religious, wedding and funeral services were permitted without any capacity limits.
- Retail stores where in-store shopping was permitted (e.g. supermarkets, grocery stores, convenience stores, indoor farmers' markets, other stores that primarily sell food and pharmacies) were required to operate at no greater than 25% capacity.
- Outdoor recreational amenities, such as golf courses, basketball courts, and soccer fields, were required to close.

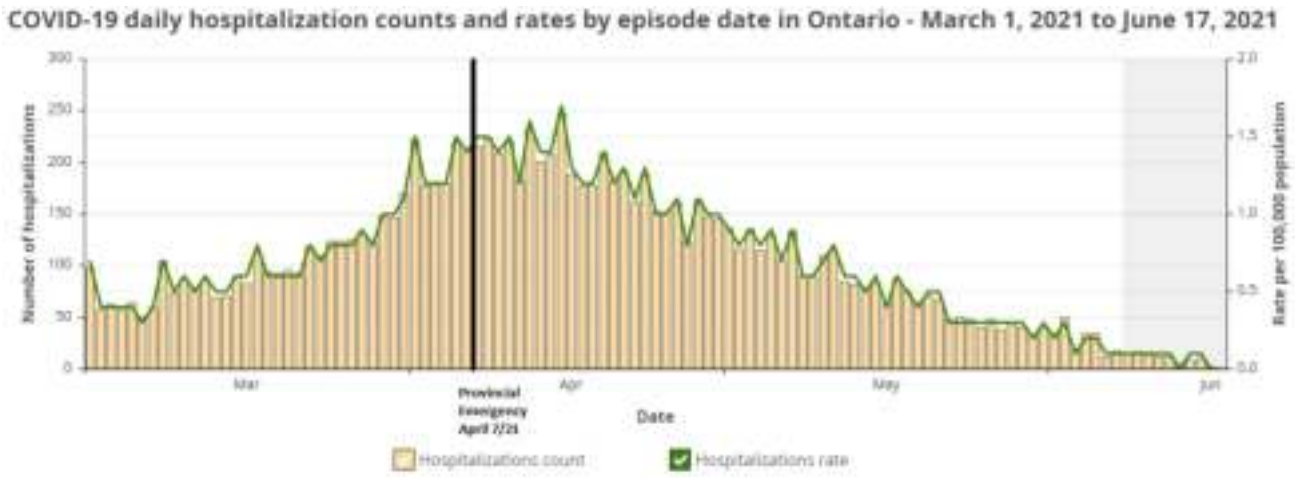
39. In addition, the government restricted travel into Ontario from neighbouring provinces, except for essential purposes, such as work, health care services, transportation of goods, or exercising Aboriginal or treaty rights.

(v) The Reopening Ontario Roadmap

40. Shortly after the Province declared a state of emergency on April 7, 2021, COVID-19 cases in Ontario began to decline. The 7-day rolling average number of daily new cases peaked on April 12, 2021, at 4,484, after which it began to steadily decline. Below is a graph from PHO showing daily new COVID-19 cases in Ontario from March 1, 2021 to June 17, 2021:



41. At the same time, there was a steady decline in the number of hospitalizations. Below is a graph from PHO that shows the number of daily new hospitalizations from COVID-19 from March 1, 2021 to June 17, 2021:



42. The decline in cases and hospitalizations was occurring at a time when the percentage of the Ontario population that had received a COVID-19 vaccine was still relatively low. According to data from PHO, when the Province implemented the third state of emergency on April 7, 2021, less than 3% of the Ontario population was fully vaccinated and only 17% of the population had received a first dose of vaccine.

43. By May 20, 2021, the number of COVID-19 cases had fallen significantly, with the 7-day rolling average of daily new cases dropping to 1,768, down from a high of 4,484 cases on April 12, 2021. Due to the declining number of cases and improvements in other key public health measures, such as hospitalization and ICU capacity, the Ontario government announced a three-step plan to safely reopen the province and end the province-wide stay-at-home order (the "*Roadmap*"). Attached as **Exhibit "V"** is a press release dated May 20, 2021 entitled "Ontario Releases Three-Step Roadmap to Safely Reopen the Province."

44. The *Roadmap* outlines three steps to easing public health measures, which were guided by the following principles:

- **Step 1:** An initial focus on resuming outdoor activities with smaller crowds where the risk of transmission was lower and some retail was permitted with restrictions.

This step included allowing outdoor gatherings of up to ten people, outdoor dining with up to four people per table, and non-essential retail at 15% capacity. Religious services, rites and ceremonies were permitted indoors at 15% capacity and outdoors with the only capacity limit being that participants had to be able to physically distance at least 2 metres. Drive-in religious services, rites and ceremonies were permitted without any capacity limits.

- **Step 2:** Further expanding outdoor activities and resuming limited indoor services with small numbers of people where face coverings are worn, including outdoor gatherings of up to 25 people, outdoor sports and leagues, personal care services where face coverings can be worn and with capacity limits. Religious services, rites and ceremonies are permitted indoors at 25% capacity and outdoors with the only capacity limit being that participants must be able to physically distance at least 2 metres. Drive-in religious services, rites and ceremonies are permitted without any capacity limits.
- **Step 3:** Expanding access to indoor settings, with restrictions, including allowing larger numbers of people in gatherings indoors where face coverings can't always be worn. This will include indoor sports and recreational fitness, indoor dining, museums, art galleries and libraries, and casinos and bingo halls, with some capacity limits. Religious services, rites and ceremonies will be permitted indoors at a capacity which will allow physical distancing .

45. The Reopening Roadmap states that the decision of when to proceed to the next step will be informed by several public health and health system indicators. One of those indicators is the

level of vaccinations in Ontario. The Reopening Roadmap provides that Ontario will not proceed to the next step of reopening until the following vaccinations thresholds have been met:

- **Step 1:** 60% of adults vaccinated with one dose.
- **Step 2:** 70% of adults vaccinated with one dose and 20% vaccinated with two doses.
- **Step 3:** 70% to 80% of adults vaccinated with one dose and 25% vaccinated with two doses.

46. While vaccination rates are a key public health measure that informs Ontario's decision to proceed through the steps of the Reopening Roadmap, they are not the only measure. Other important considerations include the number of hospitalizations, ICU occupancy and the weekly case incidence rates. It should be noted that the protective effects of the vaccine (for both the first and the second dose) take several weeks to develop. It should also be noted that, while the approved COVID-19 vaccines have been shown to be effective in preventing symptomatic illness, the evidence is less clear on the degree to which vaccines prevent asymptomatic transmission. A single dose of vaccine does not provide complete protection against symptomatic illness. Attached as **Exhibit "W"** is a publication from PHO dated April 15, 2021, entitled "Considerations for Public Health Measures for Individuals with Partial Vaccination for SARS-CoV-2."

47. On May 22, 2021, based on the provincewide vaccination rates and improvements in key public health indicators, Ontario lifted the temporary prohibition on some outdoor amenities, including golf courses, soccer fields, tennis and basketball courts, and skate parks. Those outdoor activities were permitted, provided physical distancing could be maintained. No outdoor sports or recreational classes were permitted at that time. Outdoor limits for social gatherings and organized public events were expanded to five people, including with members of different households. All

other public health and workplace safety measures under the provincewide emergency brake remained in effect.

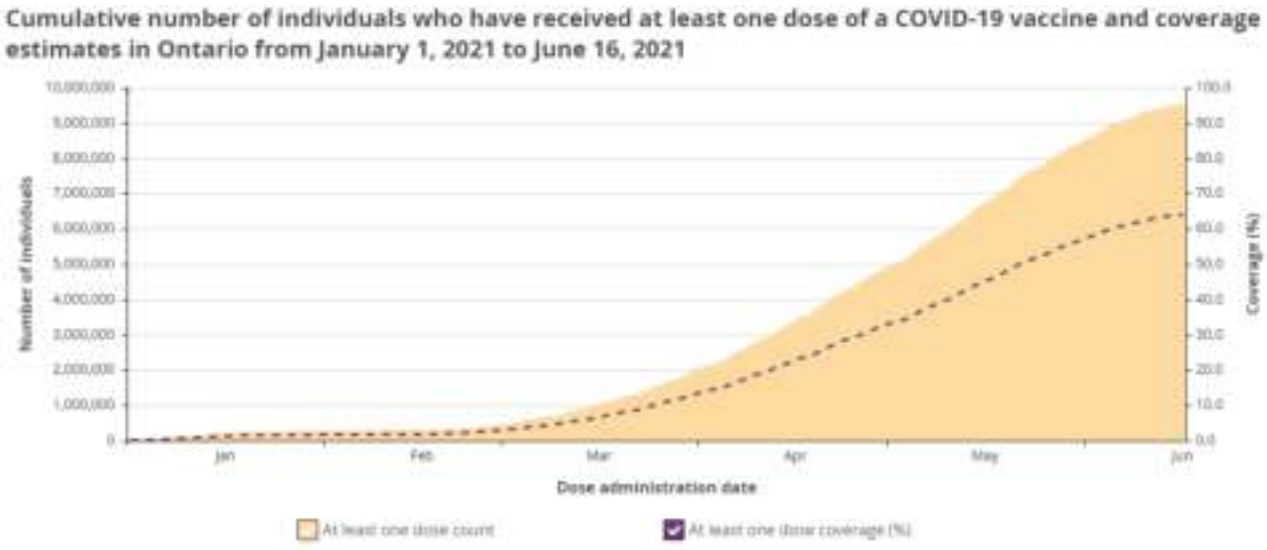
48. On June 2, 2021, based on the provincewide vaccination rates and improvements in key public health indicators, the province-wide stay-at-home order was lifted. All other public health measures existing at that time remained in place, including the restrictions imposed by the third state of emergency order. Attached as **Exhibit "X"** is a press release dated June 1, 2021, entitled "Ontario Maintains COVID-19 Restrictions as Stay-at-Home Order is Set to Expire."

49. On June 9, 2021, based on province-wide vaccination rates and improvements in other key public health indicators, Ontario ended the third state of emergency. On June 11, 2021, the province moved into Step 1 of the *Roadmap*. At that time, the number of cases and hospitalizations were steadily decreasing and over 72% of Ontario adults had received a first dose of a COVID-19 vaccine. There were still 494 patients in Ontario ICUs due to COVID-19, but that number was down from a high of over 800 patients in ICUs in April 2020. Attached as **Exhibit "Y"** is an Update on COVID-19 Projections dated May 20, 2021, from the Ontario COVID-19 Science Table.

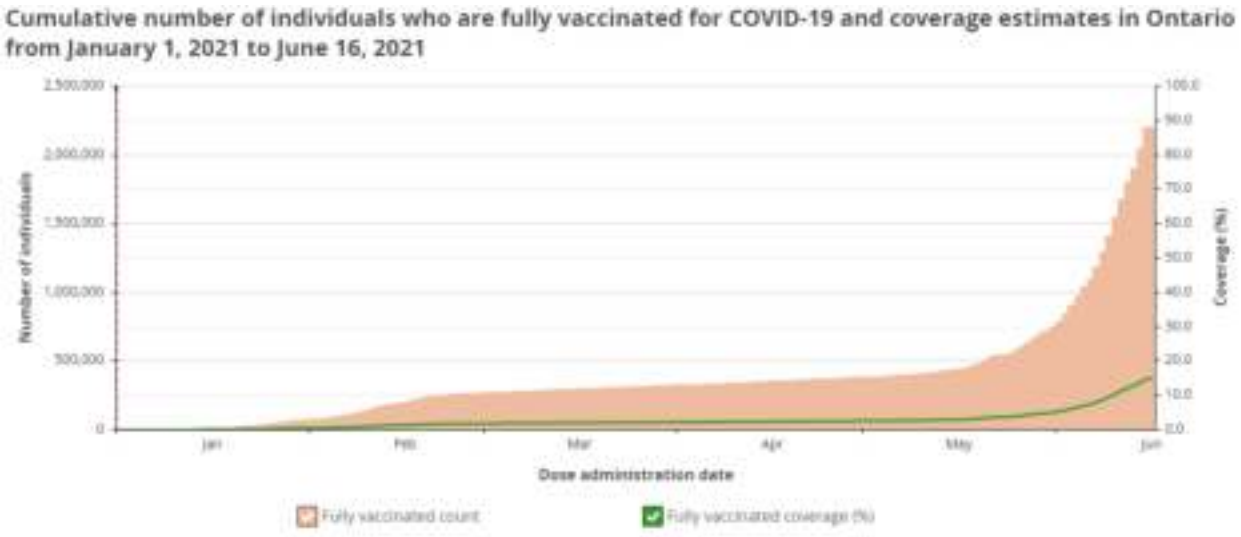
50. Due to high rates of COVID-19 transmission locally, including a rise in the number of cases involving the Delta variant, the Medical Officer of Health for the Porcupine Public Health Unit issued a series of instructions requiring businesses and organizations in the Porcupine Health Unit region to implement enhanced public health measures, beyond those required at Steps 1 and 2 of the Roadmap. The regulations that apply at each Step of the Roadmap state that a person responsible for a business or organization must operate that business or organization in compliance with instructions of public health officials, which includes instructions issued by local Medical

Officers of Health. Attached as **Exhibit "Z"** are the instructions issued by the Porcupine Medical Officer of Health.

51. On June 30, 2021, after having reached the vaccination target of 70% of adults with one dose and 20% of adults with two doses for at least two weeks and with other key public health measures, including hospitalizations, ICU occupancy, and weekly case incidence rates, improving, Ontario moved to Step 2 of the Reopening Roadmap. Below is a graph from PHO showing the number of individuals and rate of first dose vaccinations from January 1, 2021 to June 16, 2021:



52. Below is a graph from PHO showing the number of individuals and rate of second dose vaccinations from January 1, 2021 to June 16, 2021. As noted below, second dose vaccinations did not begin to significantly increase until approximately mid-June 2021. Prior to June 2021, only approximately 3% of Ontarians had received a second dose and most of those individuals were in nursing or long-term care facilities.



53. Step 2 focuses on the resumption of more outdoor activities and limited indoor services with small numbers of people where face coverings are worn, with other restrictions in place. The public health measures applicable at Step 2 include:

- Outdoor social gatherings are permitted up to 25 people;
- Indoor social gatherings are permitted with up to 5 people;
- Indoor religious services, rites or ceremonies are permitted with up to 25% capacity of each particular room. Outdoor religious services, rites or ceremonies continue to be permitted with the only capacity limit being that participants must be able to physically distance at least 2 metres. Drive-in religious services, rites and ceremonies continue to be permitted without any capacity limits;
- Personal care services where face coverings can be worn are permitted at 25% capacity;
- Outdoor sport facilities with spectators are permitted at 25% capacity;
- Outdoor fairs, rural exhibitions and festivals are permitted at 25% capacity;
- Outdoor concert venues, theatres and cinemas are permitted at 25% capacity;

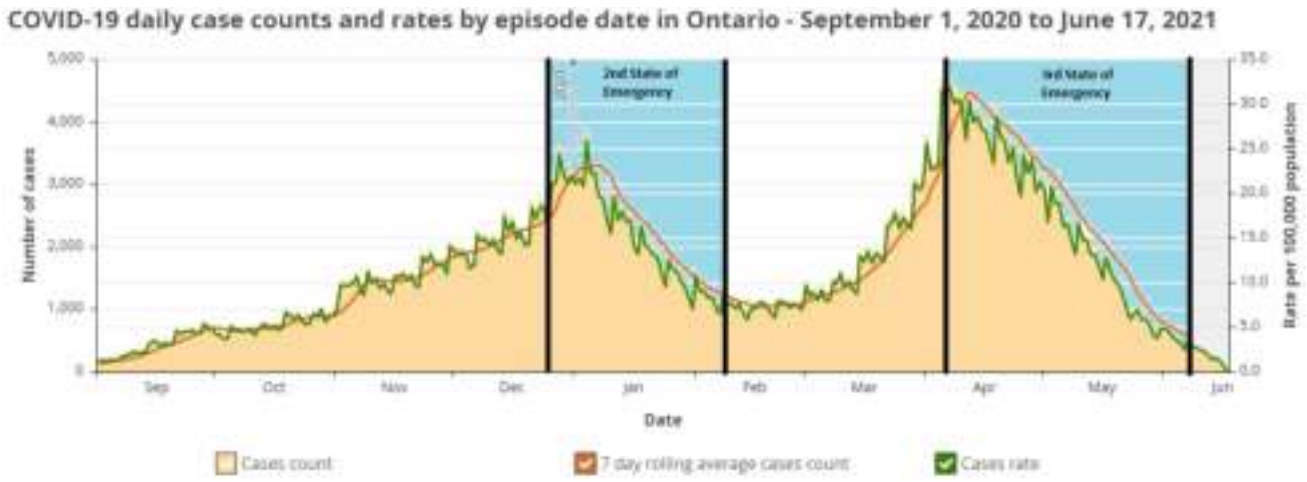
- Essential and other select retail is permitted up to 50% capacity while non-essential retail is permitted up to 25% capacity.

54. On June 29, 2021, the Medical Officer of Health for the Region of Waterloo, Dr. Hsiu-Li Wang, issued instructions, effective June 30, 2021, requiring the Region of Waterloo to maintain Step 1-level restrictions after entering Step 2 with the rest of the province on June 30, 2021. Dr. Wang stated that these measures were necessary due to the high prevalence of the Delta variant in the Region. It is anticipated that these measures will be necessary until approximately mid-July 2021. Attached as **Exhibit "AA"** are the instructions issued by the Waterloo Medical Officer of Health.

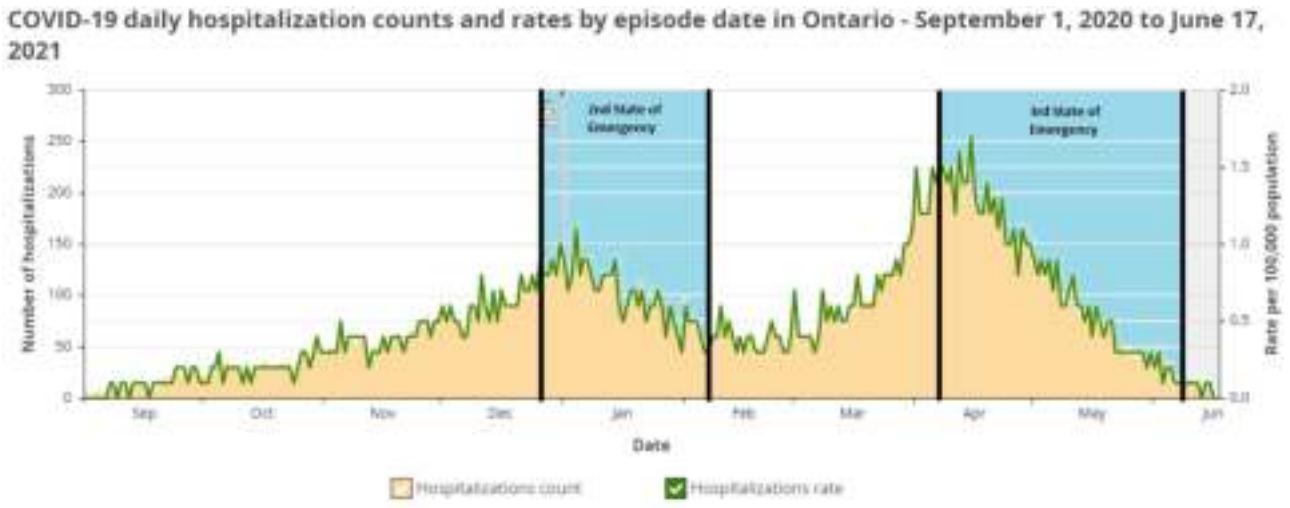
III. The Impact of Ontario's Public Health Measures

55. The public health measures implemented by Ontario had a significant impact on decreasing the transmission of COVID-19 across the province and reducing the strain on the healthcare system. Among other things, the implementation of public health measures during the second and third states of emergency were shortly followed by a substantial decrease in the number of COVID-19 cases and hospitalizations.

56. Both the second and third states of emergency were implemented at times when the number of daily COVID-19 cases was increasing rapidly. Shortly after Ontario implemented each state of emergency, the number of new daily cases started to level off and then steadily decline. This is illustrated in the graph below with data from PHO showing the number of daily new cases from September 1, 2021 to June 17, 2021:



57. The number of daily new hospitalizations followed a similar trend. This is illustrated in the graph below with data from PHO showing the number of daily new hospitalizations from September 1, 2021 to June 17, 2021:



58. In their update to the public on May 20, 2021, the Ontario COVID-19 Science Table stated that "control of the pandemic is improving due to current public health measures." Among other things, the Science Table noted that the percentage of individuals testing positive for COVID-19 decreased following the implementation of the province-wide lockdowns and provincial emergency brake.

59. In short, many key public health indicators showed signs of significant improvement following the implementation of Ontario's strictest public health measures. While there are many factors that contribute to the transmission of COVID-19, this data suggests that Ontario's public health measures decreased the spread of COVID-19 across the province, reduced the overall strain on the healthcare system, and likely saved lives.

IV. Public Health Considerations That Informed Ontario's COVID-19 Policy Response

60. As noted above, as Associate Chief Medical Officer of Health, my responsibilities include monitoring the spread of COVID-19 and advising the Ontario government on its policy response to the pandemic. In that role, I continuously review and assess information related to COVID-19, including published peer-reviewed literature, "scientific grey literature" (i.e. literature published outside of traditional peer-reviewed publishing channels), and publications from PHO. That information informs the advice that I provide, along with others in the office of the Chief Medical Officer of Health, to the Ontario government. I review information and provide advice related to COVID-19 as part of the ordinary exercise of my knowledge, training and experience as Associate Chief Medical Officer of Health.

61. Below are some of the public health considerations that inform Ontario's policy response to the pandemic. These considerations are not exhaustive and no single factor is determinative. It should also be noted that the state of the pandemic is constantly changing and Ontario's policy response must adapt to those changing circumstances. When determining which health protection measures should be implemented to mitigate the spread of the virus, Ontario attempted to use the best information available at the time about the transmissibility of COVID-19, which was also subject to change as research about the virus is being updated regularly.

(i) Methods of COVID-19 Transmission

62. The primary method of transmission of COVID-19 is through direct contact with respiratory droplets from an infected person, which have the potential to be propelled various distances when that person coughs, sneezes, sings, shouts or talks. Transmission occurs predominantly through close contact (2 metres or less) with an infected individual, but transmission over longer distances (more than 2 metres) is possible, although less common. Attached as **Exhibit "BB"** is a document dated December 1, 2020, from PHO entitled "COVID-19 Routes of Transmission," which summarizes some of the evidence related to COVID-19 transmission.

63. Transmission is more likely when people are in close physical proximity with an infected person over a prolonged period of time. The risk of transmission is especially high in settings with poor ventilation or where there is recirculation of unfiltered air, which may allow droplets (or, in some cases, smaller particles known as "aerosols") to travel further distances. For example, there is evidence of high rates of transmission in household settings, where individuals are in close proximity in enclosed areas and physical distancing is not feasible. There is also evidence that indoor settings have a higher risk of transmission relative to outdoor settings, although there remains a risk of transmission when people gather outdoors.

64. Because COVID-19 is spread primarily through close contact with an infected individual, large gatherings, whether indoors or outdoors, present a risk of COVID-19 transmission. The larger the gathering, the greater the likelihood that there will be individuals in that gathering who have COVID-19 and will transmit the virus to others. If individuals in a gathering become infected, they will often transmit the virus to other members of their households. As a result, gatherings of

people from different households present an especially high risk of widespread transmission throughout the population.

65. Certain behaviours may increase the risk of COVID-19 transmission. For example, activities such as singing, shouting, or loud talking can result in more forceful exhalation of droplets (or, in some cases, aerosols), which increases the likelihood of transmitting the virus to others in close proximity and may also increase the distance that droplets or aerosols travel. Attached as **Exhibit "CC"** is a document dated May 21, 2021, from PHO entitled "COVID-19 Transmission Through Large Respiratory Droplets and Aerosols."

66. COVID-19 can be transmitted by people who are pre-symptomatic (i.e. have not yet developed symptoms) or asymptomatic (i.e. never developed symptoms). Some studies have shown that transmission can occur as early as six days before the onset of symptoms, or possibly earlier. As a result, screening for symptoms is insufficient to prevent the spread of COVID-19 when individuals gather in groups, particularly when the level of COVID-19 in the general population is high. Attached as **Exhibit "DD"** is a document dated May 22, 2020, from PHO entitled "Asymptomatic Infection and Asymptomatic Transmission."

(ii) Masks and Physical Distancing

67. There are several measures that can help reduce, but not eliminate, the risk of COVID-19 transmission. One of those measures is mask wearing. Masks have two potential functions. First, they can be used as personal protective equipment ("PPE") to protect the wearer from being exposed to droplets expelled by others who have been infected with COVID-19. Second, they can be used as "source control" to protect others from the wearer by reducing the degree to which a person who is infected with COVID-19 expels droplets.

68. There is evidence that the use of non-medical masks can be an effective form of source control when worn by persons shedding the virus (i.e. it protects others from a mask wearer with COVID-19). A literature review conducted by PHO found that "[m]andatory public mask policies have been associated with a decrease in new COVID-19 cases compared to regions without such policies." Attached as **Exhibit "EE"** is a document dated September 14, 2020, from PHO entitled "Wearing Masks in Public and COVID-19."

69. However, the same review by PHO found that the use of masks to protect the wearer (i.e. as PPE) is "unlikely to be effective in non-healthcare settings." As a result, if one or more infected individuals within a gathering do not wear a mask (or do not wear a mask consistently), the fact that others within the gathering are wearing masks is unlikely to provide sufficient protection against transmission. The efficacy of mask mandates is, therefore, highly dependent on the degree to which participants strictly and uniformly adhere to those mandates, especially in large gatherings or settings with poor ventilation.

70. There is an extremely high degree of variability in the efficacy of non-medical masks in public settings, depending on the materials used and whether the mask is the appropriate fit for the wearer. For example, one review of 42 studies on the effectiveness of non-medical masks in reducing COVID-19 transmission found that the filtration efficiency of non-medical masks (with variable designs and fabrics) ranged from less than 10% to more than 95%. Attached as **Exhibit "FF"** is a document dated February 2, 2021 from PHO entitled "Review of 'Rapid review on the characteristics of effective non-medical face masks in reducing the risk of SARS-CoV-2 transmission.'"

71. Guidance from the World Health Organization ("**WHO**") states that masks should be used as "part of a comprehensive package of prevention and control measures" to limit the spread

of COVID-19. However, that guidance also notes that "the use of a mask alone, even when correctly used…is insufficient to provide an adequate level of protection for an uninfected individual or prevent onward transmission from an infected individual (source control)." Attached as **Exhibit "GG"** is document dated December 1, 2020, from the WHO entitled "Mask use in the context of COVID-19."

72. Another measure that can help reduce, but not eliminate, the risk of COVID-19 transmission is physical distancing. As noted above, respiratory droplets from an infected person have the potential to be propelled various distances when that person coughs, sneezes, sings, shouts or talks. While transmission is most likely to occur through close contact of 2 metres or less, there is evidence that transmission over longer distances can occur, especially in areas with poor ventilation. Behaviours such as singing or loud talking have been shown to increase the distance that droplets can spread. Some studies have suggested that droplets can travel as much as 4 to 8 metres under favourable conditions (see **Exhibit "BB"**).

73. Similar to masks, physical distancing is one part of a comprehensive package of public health measures that can help reduce the transmission of COVID-19 but is insufficient on its own to prevent transmission of COVID-19. Furthermore, the efficacy of physical distancing depends on the degree to which individuals strictly adhere to physical distancing requirements of at least 2 metres. In practice, there will be some circumstances where physical distancing will be unlikely or impractical, such as within households.

(iii) Community Prevalence and Burden on the Healthcare System

74. The risk of COVID-19 transmission in any setting or gathering is related to the baseline level of COVID-19 in the community. The higher the number of COVID-19 cases in the population, the more likely it is that people who participate in a gathering will have COVID-19

and pass it on to others. While some types of gatherings may pose a relatively low risk of transmission when the level of COVID-19 in the population is low, those same gatherings may pose a higher risk of transmission when the level of COVID-19 in the population is high.

75. Ontario's policy response to COVID-19 was also informed by the burdens that the pandemic placed on the healthcare system. Several times during the pandemic, the spread of COVID-19 caused hospitalizations and ICU occupancy to increase significantly. This placed a substantial burden on the healthcare system, as Ontario has limited capacity to treat seriously ill patients who require hospitalization or intensive care. The increase in ICU patients was particularly concerning because it not only threatened the ability of the healthcare system to deal with COVID-19 patients, it also compromised the ability of the healthcare system to care for regular (i.e. non-COVID-19) patients. The diversion of healthcare resources to serve seriously ill patients with COVID-19 also creates a backlog of surgical and other medical treatments for other medical problems.

76. When the burdens on the healthcare system are high, even small increases in transmission within the population can have a significant negative impact on the healthcare system and potentially impact patient care. For example, in April 2021, ICU occupancy in some regions in Ontario was over 86%. At that time, there was a risk that ICU capacity would be stretched beyond its limits, even with small increases in the number of critically ill patients. Within that context, activities that pose a relatively low risk of transmission could significantly increase the burden on an already strained healthcare system.

(iv) Variants of Concern

77. The risk of COVID-19 transmission also depends on the degree of transmissibility of the virus, which has evolved over time as new variants have emerged. Several VOCs have been

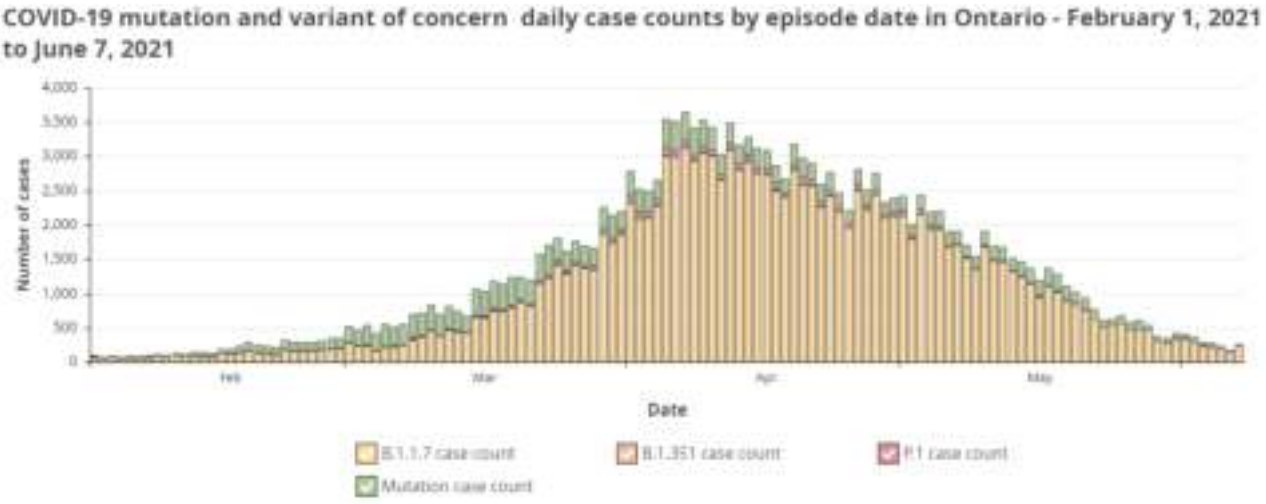
identified that are associated with factors such as increased transmissibility, detrimental change in COVID-19 epidemiology, increased virulence or change in clinical disease presentation, and decreased effectiveness of public health and social measures.

78. There are four VOCs that are particularly concerning in Ontario, namely:

- the B.1.1.7 (Alpha) variant, which was first detected in the United Kingdom;
- the B.1.351 (Beta) variant, which was first detected in South Africa;
- the P.1 (Gamma) variant, which was first detected in Brazil; and
- the B.1.617 (Delta) variant, which was first detected in India.

79. All four of these VOCs are associated with increased transmissibility of COVID-19. The Alpha, Beta and Gamma variants are each estimated to be at least 50% more transmissible than the original COVID-19 virus. Information about the Delta variant is still evolving, but evidence suggests that it is considerably more transmissible than non-variant strains of COVID-19. All four VOCs have been detected in Ontario. Attached as **Exhibit "HH"** is a publication by PHO entitled "Comparing SARS-CoV-2 Variants of Concern (VOCs) as of May 31, 2021." Attached as **Exhibit "II"** is a publication by PHO dated June 16, 2021, entitled "COVID-19 B.1.617 Variant of Concern – What We Know So Far."

80. In February and March 2021, the proportion of cases involving VOCs increased substantially. By April 2021, the Alpha variant had become the dominant strain in Ontario and over 70% of reported cases in the province tested positive for one of the VOCs. Attached as **Exhibit "JJ"** is a graph summarizing the percentage of COVID-19 associated with a VOC from March 31, 2021, to April 13, 2021. Below is a graph from PHO showing the progression of COVID-19 cases with a VOC from February 1, 2021 to June 7, 2021 (excluding the Delta variant):



81. In May and June 2021, there was an increase in the number of cases in Ontario testing positive for the Delta variant. As of June 22, 2021, 975 cases of the Delta variant had been confirmed in Ontario. Attached as **Exhibit "KK"** is the daily epidemiological summary from PHO dated July 3, 2021, which contains data regarding VOCs, including the Delta variant, from January 15, 2020 to July 3, 2021.

V. The Risks of COVID-19 Transmission at Religious Gatherings

82. In light of the factors described above, religious services and gatherings pose a significant risk for the spread of COVID-19. They typically involve large gatherings of people from different households who spend prolonged periods of time (often more than an hour) in the same physical space. That is precisely the scenario that has been shown to be associated with a high risk COVID-19 transmission. That risk is especially high if physical distancing is not strictly observed, if the services are held indoors or in poorly ventilated areas, or if masks are not worn (or not worn consistently or correctly).

83. Religious services are often associated with behaviours that can increase the spread of COVID-19. For example, many religious services involve singing, chanting or praying out loud,

which can increase the spread of droplets that transmit the virus. Religious services are also typically gatherings of families and friends in the same community who know each other well and will be tempted to greet or socialize with each other in violation of physical distancing requirements. While places of worship may take measures to promote physical distancing, in practice good intentions are often outweighed by human nature.

84. The risk of transmission at a religious gathering is not confined to those who attend those gatherings. If someone is infected with COVID-19 at a religious service, it is very likely that he or she will transmit the virus to other members of his or her household who, in turn, may transmit COVID-19 to others in the community.

85. The risk of transmission at religious gatherings increases significantly when the prevalence of COVID-19 in the community is high. The higher the number of COVID-19 cases in the general population, the more likely it is that people who participate in a religious gathering will have COVID-19 and pass it on to others. In addition, when COVID-19 cases in the general population are high, there is a greater burden on the healthcare system. When that occurs, even small amounts of transmission at religious gatherings can have a significant impact on the overall spread of the virus across the province, resulting in an even greater strain on the healthcare system and potentially impacting patient care.

86. Masks and physical distancing can help reduce the risk of COVID-19 transmission but are insufficient to stop the spread of the virus, particularly when the prevalence of COVID-19 in the population is high. As noted above, masks can be highly variable in their effectiveness in non-healthcare settings and their effectiveness decreases if they are ill-fitting or worn inconsistently. In addition, physical distancing of at least 2 metres decreases the likelihood of COVID-19 transmission, but there is evidence that droplets (or in some cases aerosols) can travel farther

distances under some conditions, although transmission at distances of more than 2 metres is less common. Similarly, holding gatherings outdoors can reduce the risk of transmission of the virus, but outdoor transmission can still occur, especially in large gatherings with inconsistent adherence to mask or physical distancing requirements.

VI. The Public Health Measures for Religious Gatherings

87. In order to limit the spread of COVID-19, Ontario implemented several public health restrictions for religious gatherings over the various phases of the pandemic. The objective of those restrictions was to reduce transmission by limiting the number of people who would gather together in close contact and to require participants to take certain precautions, such as mask wearing and physical distancing. The limits that applied to religious gatherings were part of a broader set of measures that applied to a wide variety of businesses, organizations and events throughout the province.

88. The public health measures Ontario has imposed at each stage of the pandemic have been informed by several key indicators, such as weekly incidence of COVID-19, the test positivity rate, the effective reproduction number (Rt), and evidence of recent outbreaks. Where feasible, public health measures have been tailored to the circumstances in each region of the province. During some phases of the pandemic, however, the rapid spread of COVID-19 or the need to discourage travel between different areas of the province required Ontario to implement restrictions that applied across the entire province.

89. I understand that the applicants in these proceedings are challenging the restrictions that applied to religious services in three different public health units ("**PHUs**"): the Niagara PHU, the Southwestern PHU, and the Region of Waterloo PHU. I have summarized below the restrictions that applied to religious gatherings in those PHUs from September 2020 to June 2021.

90. The table below summarizes the capacity limits that applied to religious services, rites or ceremonies in the Niagara PHU:

Capacity Limits for Religious Services, Rite or Ceremonies in the Niagara PHU

Date	Outdoor Services	Indoor Services	Drive-in Services
July 22, 2020 to December 25, 2020	100 people.	30% of room capacity.	Drive-in services permitted without any capacity limit.
December 26, 2020 to February 28, 2021	10 people.	10 people.	Drive-in services permitted without any capacity limit.
March 1, 2021 to March 28 , 2021	100 people.	30% of room capacity.	Drive-in services permitted without any capacity limit.
March 29, 2021 to April 2, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	30% of room capacity.	Drive-in services permitted without any capacity limit.
April 3, 2021 to April 18, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	15% of room capacity.	Drive-in services permitted without any capacity limit.
April 19, 2021 to June 10, 2021	10 people.	10 people.	Drive-in services permitted without any capacity limit.
June 11, 2021 to June 29, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	15% of room capacity.	Drive-in services permitted without any capacity limit.
June 30, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	25% of room capacity.	Drive-in services permitted without any capacity limit.

91. The table below summarizes the capacity limits that applied to religious services, rites or ceremonies in the Southwestern PHU:

Capacity Limits for Religious Services, Rite or Ceremonies in the Southwestern PHU

Date	Outdoor Services	Indoor Services	Drive-in Services
July 13, 2020 to December 25, 2020	100 people.	30% of room capacity.	Drive-in services permitted without any capacity limit.
December 26, 2020 to February 15, 2021	10 people.	10 people.	Drive-in services permitted without any capacity limit.
February 16, 2021 to March 28, 2021	100 people.	30% of room capacity.	Drive-in services permitted without any capacity limit.
March 29, 2021 to April 2, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	30% of room capacity.	Drive-in services permitted without any capacity limit.
April 3, 2021 to April 18, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	15% of room capacity.	Drive-in services permitted without any capacity limit.
April 19, 2021 to June 10, 2021	10 people.	10 people.	Drive-in services permitted without any capacity limit.
June 11, 2021 to June 29, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	15% of room capacity.	Drive-in services permitted without any capacity limit.

Date	Outdoor Services	Indoor Services	Drive-in Services
June 30, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	25% of room capacity.	Drive-in services permitted without any capacity limit.

92. The table below summarizes the capacity limits that applied to religious services, rites or ceremonies in the Waterloo PHU:

Capacity Limits for Religious Services, Rite or Ceremonies in the Waterloo PHU

Date	Outdoor services	Indoor services	Drive-in services
July 17, 2020 to December 25, 2020	100 people.	30% of room capacity.	Drive-in services permitted without any capacity limit.
December 26, 2020 to February 15, 2021	10 people.	10 people.	Drive-in services permitted without any capacity limit.
February 16, 2021 to March 28 2021	100 people.	30% of room capacity.	Drive-in services permitted without any capacity limit.
March 29, 2021 to April 2, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	30% of room capacity.	Drive-in services permitted without any capacity limit.
April 3, 2021 to April 18, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	15% of room capacity.	Drive-in services permitted without any capacity limit.
April 19, 2021 to June 10, 2021	10 people.	10 people.	Drive-in services permitted without any capacity limit.

Date	Outdoor services	Indoor services	Drive-in services
June 11, 2021 to June 29, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	15% of room capacity.	Drive-in services permitted without any capacity limit.
June 30, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	15% of room capacity (pursuant to the instructions discussed at para. 54).	Drive-in services permitted without any capacity limit.

93. The time periods with the lowest (or strictest) capacity limits corresponded to the time periods when the rate of COVID-19 transmission in the Ontario population and the burden on the Ontario healthcare system were at their highest levels. This is consistent with the principles discussed above regarding COVID-19 transmission, including that there are higher risks of COVID-19 transmission in a religious gathering when the baseline number of COVID-19 cases in the general population is higher.

94. Throughout most of the pandemic, the capacity limits for outdoor religious gatherings were higher (or less strict) than the capacity limits for indoor religious gatherings. This is consistent with the evidence that the risk of COVID-19 transmission is generally higher indoors compared to outdoors. However, during some periods when the rate of COVID-19 transmission and the burden on the healthcare system were at their highest, capacity limits for both indoor and outdoor religious gatherings were the same. During those periods, the rate of transmission was so high that outdoor gatherings that would otherwise have posed a relatively small risk of transmission could still have had a significant impact on the overall spread of the virus across the province. The higher the number of COVID-19 cases in the population, the more likely it is that people who participate in a religious gathering will have COVID-19 and pass it on to others. While each individual gathering

may result in a relatively small risk of additional cases, the cumulative impact of many such gatherings could result in a significant increase in transmission across the province.

95. In addition, during the highest risk periods, Ontario's ICUs were approaching full capacity and there was a serious concern that, if the number of new cases and hospitalizations continued to rise, it could overburden the healthcare system and significantly jeopardize patient care. During those time periods of highest risk, it was extremely important to control the spread of COVID-19 at both indoor and outdoor gatherings.

96. It should be noted that the public health measures imposed on indoor and outdoor religious gatherings, even during the highest risk periods, were almost always less strict than the public health measures imposed on other types of gatherings. For example, during the third state of emergency, indoor or outdoor gatherings (other than religious gatherings) were only permitted with members of the same household or one other person from outside that household who lives alone or who is a caregiver for any member of the household. At the same time, religious gatherings were permitted with up to 10 people, which could include members of different households. To take another example, when Ontario moved into Step 1 of the Roadmap, outdoor social gatherings or organized public events (other than religious services) were subject to a capacity limit of 10 people, but outdoor religious services had no capacity limit, provided the participants complied with public health and physical distancing guidelines.

97. There are several reasons why Ontario imposed slightly different measures for religious gatherings. Among other things, the higher capacity limits allowed a small number of people who may not be in the same household to produce and disseminate virtual religious services to a wider community. A capacity limit of 10 people permits a few members of the public (such as readers, cantors, etc.) to assist officiants in conducting the larger online or drive-in services that remained

permitted. Ontario recognizes that religious communities are often a source of support, comfort and guidance for the communities they serve. Religious leaders can provide pastoral and spiritual support during public health emergencies and other health challenges. The public health measures for religious gatherings attempted to allow religious services to continue so that members of religious communities could access the benefits of those services, but with strict capacity limits that mitigate the spread of COVID-19.

VII. Public Health Measures in Other Settings

98. I understand that some of the applicants in these proceedings are arguing that the public health measures that applied to religious gatherings at various stages of the pandemic were not necessary or justified. In support of that argument, I understand that the applicants note that some public health measures that applied to non-religious gatherings or settings, such as essential retail stores, were (in their view) not as strict as the public health measures placed on religious gatherings at certain points during the pandemic.

99. It should be noted that the various restrictions imposed by the Province to reduce the spread of COVID-19 at different times, in different regions of the province, and in different sectors are based on the unique circumstances of each region and sector and the changing nature of the COVID-19 pandemic. Comparing the restrictions that apply in one circumstance to those that apply in another is not a useful or appropriate exercise without taking into account the full context of each circumstance. Every health protection measure implemented by the Province was assessed on its own merits and the factors that apply in determining whether a measure is appropriate in one circumstance may not apply, or may not apply to the same degree, in another.

100. It is important to keep those principles in mind when assessing the public health measures that applied to religious gatherings at various stages of the pandemic. As noted above, religious

gatherings are associated with a combination of risk factors, which may not apply, or may not apply to the same degree, in other settings.

101. Having said that, there are several reasons why Ontario imposed different public health measures on essential retail businesses compared to religious gatherings. Ontario imposed different limits on those retail businesses not because religious worship is any less essential than retail activities, but because religious gatherings typically have characteristics that make them more likely to spread COVID-19 than transient encounters in a retail setting.

102. The behaviour of persons in religious spaces is different than the behaviour of persons in retail spaces. First, people spend, on average, more time at religious gatherings compared to retail settings. It is not uncommon for a person to "run in" to retail stores to quickly purchase a number of small items. In contrast, religious gatherings are often an extended length and typically run for more than an hour, and sometimes for two hours or more. In addition, large groups of people tend to arrive and depart religious services at the same time, which increases crowding, in contrast to retail stores where people typically arrive and depart at many different times.

103. Second, the nature of human interaction in a retail setting tends to be different than human interaction at religious gatherings. Interactions with people outside of a person's household in a retail store are usually brief (e.g. passing someone in a store aisle). In contrast, at religious gatherings, there is often prolonged exposure to the same people sitting together, which presents a greater danger for the spread of the virus, especially if social distancing rules are not followed, the indoor space is not well ventilated, or where face coverings are not worn correctly. Another example is that, in a religious space, people often pray out loud or sing (which is not a concern in retail settings), which increases the risk of transmission.

104. Third, unlike in religious gatherings, there is typically no sense of community in retail settings, such that groups of people would want to greet each other in violation of physical distancing rules. While well-intentioned people at religious gatherings may attempt to physically distance from family and friends, good intentions are often outweighed by human nature. The conflict between the desire to warmly greet friends and family and diligently following physical distancing rules is less of a concern in retail stores.

AFFIRMED by video conference by David McKeown of [redacted], before me at the City of Toronto on the 5th day of July, 2021, in accordance with O. Reg. 431/20, Administer the Oath or Declaration Remotely.

Ryan Cookson

A Commissioner etc.

DAVID MCKEOWN

This is **Exhibit "A"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

NEWS RELEASE

Ontario Releases COVID-19 Response Framework to Help Keep the Province Safe and Open

Government Provides Additional Details on $300 Million to Support Eligible Businesses

November 3, 2020
Office of the Premier

TORONTO — In consultation with the Chief Medical Officer of Health and other health experts, the Ontario government has developed the *Keeping Ontario Safe and Open Framework*. It ensures that public health measures are targeted, incremental and responsive to help limit the spread of COVID-19, while keeping schools and businesses open, maintaining health system capacity and protecting vulnerable people, including those in long-term care.

Details were provided today by Premier Doug Ford, Christine Elliott, Deputy Premier and Minister of Health, Rod Phillips, Minister of Finance, Peter Bethlenfalvy, President of the Treasury Board, and Dr. David Williams, Chief Medical Officer of Health.

"It's clear COVID-19 will be with us for a while, which is why we are putting in place a framework that will protect the health and safety of individuals and families, while avoiding broader closures across the province," said Premier Ford. "This framework, developed in consultation with our health experts, will serve as an early warning system allowing us to scale up and scale back public health restrictions on a regional or community basis in response to surges and waves of COVID-19. By introducing public health measures sooner, we can keep this deadly virus at bay, bend the curve and reclaim a little more of our normal lives."

The framework takes a gradual approach that includes introducing preventative measures earlier to help avoid broader closures and allow for additional public health and workplace safety measures to be introduced or removed incrementally. It categorizes public health unit regions into five levels: Green-Prevent, Yellow-Protect, Orange-Restrict, Red-Control, and Lockdown being a measure of last and urgent resort. Each level outlines the types of public health and workplace safety measures for businesses and organizations. These include targeted measures for specific sectors, institutions and other settings.

"The health and wellbeing of Ontarians is our number one priority. This framework, informed by public health experts, data and the experiences of other jurisdictions, is focused on introducing less invasive measures earlier to stop the spread of COVID-19," said Minister Elliott. "We are committed to being transparent with Ontarians, businesses and local communities as we work together to keep Ontarians safe, while keeping our economy open."

"This framework is critical to ensuring that public health measures are able to help slow the spread of the virus, while also supporting mental health and other social determinants of health," said Dr. Williams. "The framework operates like a dimmer switch, enabling measures and restrictions to be increased and give individuals and families the information they need to adjust their activities and interactions based on local epidemiological data."

As the province continues to expand access to real-time data, enhancements are also being made to Ontario.ca/coronavirus, Ontario's one-stop shop for information on COVID-19. Information about the spread of the virus, and public health and health system capacity will now be available on the website. This includes local cases by public health unit regions, the total number of cases, resolved cases, deaths, and tests completed and how many are positive. The province will continue to add data sets as they become available, such as sources of outbreaks as a subset of overall cases. This information will better help businesses, organizations and local communities access key information to prepare in advance for any changes in their region.

"You deserve to have access to the same information that we have, and that's why our government is enhancing online data and data visualization," said Minister Bethlenfalvy. "Greater transparency means that the people of Ontario have reliable access to the information they need to protect their health, and for businesses to reopen and operate safely. This is another way we're using technology and pursuing innovation to put the people at the centre of government and move Ontario onwards."

To provide the utmost transparency, each public health unit will be classified according to current framework indicators. Proposed classifications based on data for the week of October 26, 2020 can be found below. These will be confirmed by the province on Friday, November 6, 2020 and become effective on Saturday, November 7, 2020 at 12:01 a.m. Final decisions on moving public health unit regions into the framework will be made by the government based on updated data and in consultation with the Chief Medical Officer of Health, local medical officers of health and other health experts, and will be reviewed weekly.

Going forward, the government will continually assess the impact of public health measures applied to public health unit regions for 28 days, or two COVID-19 incubation periods.

Supporting Businesses Affected by COVID-19 Public Health Measures

The Ontario government is making $300 million available to businesses required to close or significantly restrict services in areas subject to modified Stage 2 public health restrictions (Ottawa, Peel, Toronto, and York Region) or, going forward, in areas categorized as Control or Lockdown.

Rebates will cover the period of time that businesses are required to temporarily close or significantly restrict services as a result of being located in areas subject to the targeted modified Stage 2 public health restrictions or, going forward, in areas categorized as Control or Lockdown.

Beginning November 16, 2020, eligible businesses will be able to apply for temporary property tax and energy cost rebates directly to the province through a single, online application portal. Many businesses should expect to receive their rebate payments within a few weeks of finalizing and submitting their completed application. Eligible businesses include restaurants, bars, gyms and cinemas.

"On Thursday, I'll introduce Ontario's 2020 Budget, the next phase of Ontario's Action Plan," said Minister Phillips. "It is a plan that will have three pillars. As we announced yesterday, the first is protect. The second pillar is support, because we know COVID-19 has brought severe challenges and economic difficulties to families and employers. Supporting businesses affected by necessary public health restrictions in regions experiencing a greater risk from COVID-19 is one way we are helping employers manage during these difficult times."

Through Ontario's Property Tax and Energy Cost Rebates program, the government is building on its efforts to ensure eligible businesses receive the financial help they need as a result of targeted provincial public health restrictions.

Public Health Unit Region Classifications

As of November 7, 2020, the province will transition public health unit regions to the new framework. The following proposed classifications for public health unit regions are based on data for the week of October 26, 2020. Updated data will be used for final review by the Chief Medical Officer of Health and approval by Cabinet on Friday, November 6, 2020.

Lockdown:

- No public health unit regions

Red-Control:

- No public health unit regions

Orange-Restrict:

- Eastern Ontario Health Unit;
- Ottawa Public Health;
- Peel Public Health;
- Toronto Public Health (may be delayed in entering Orange-Restrict level until November 14, 2020); and
- York Region Public Health.

Yellow-Protect:

- Brant County Health Unit;
- City of Hamilton Public Health Services;
- Durham Region Health Department; and
- Halton Region Public Health.

Green-Prevent:

- Algoma Public Health;
- Chatham-Kent Public Health;
- Grey Bruce Health Unit;
- Kingston, Frontenac and Lennox & Addington Public Health;
- Haliburton, Kawartha, Pine Ridge District Health Unit;
- Haldimand-Norfolk Health Unit;
- Hastings Prince Edward Public Health;
- Huron Perth Public Health;
- Lambton Public Health;
- Leeds, Grenville & Lanark District Health Unit;
- Middlesex-London Health Unit;
- Niagara Region Public Health;
- North Bay Parry Sound District;
- Northwestern Health Unit;
- Peterborough Public Health;
- Porcupine Health Unit;
- Public Health Sudbury & Districts;
- Region of Waterloo Public Health and Emergency Services;
- Renfrew County and District Health Unit;
- Simcoe Muskoka District Health Unit;
- Southwestern Public Health;
- Thunder Bay District Health Unit;
- Timiskaming Health Unit;
- Wellington-Dufferin-Guelph Public Health; and
- Windsor-Essex County Health Unit.

Quick Facts

- The Ontario government has developed a $2.8 billion COVID-19 fall preparedness plan, *Keeping Ontarians Safe: Preparing for Future Waves of COVID-19*, to ensure the province's health care, long-term care and education systems are prepared for the immediate challenges of the fall, including a second wave of COVID-19 and the flu season.
- If you are concerned you were exposed to COVID-19 or have symptoms, take the online COVID-19 self assessment.
- Get tested if you have symptoms compatible with COVID-19, or if you have been advised of exposure by your local public health unit or through the COVID Alert app. Visit Ontario.ca/covidtest to find the nearest testing location.
- Types of businesses that are eligible for support include restaurants and bars, bingo halls, gaming establishments, casinos, conference centres and convention centres, gyms, facilities for indoor sports and recreational fitness activities, community centres and multi-purpose facilities, museums, performing arts and cinemas and personal care services (with exception of oxygen bars) that were required to close or are subject to significant restrictions under modified Stage 2.
- Businesses that are not eligible are those that were already required to close prior to the introduction of modified Stage 2 public health restrictions, those that were not required to close or restrict services due to modified Stage 2 public health restrictions, and those who do not pay property taxes or energy costs.

Additional Resources

- Ontario Moving Additional Region to Modified Stage 2
- Ontario Implementing Additional Public Health Measures in Toronto, Ottawa and Peel Region
- Property Tax and Energy Cost Rebates
- Visit Ontario's website to learn more about how the province continues to protect the people of Ontario from COVID-19.

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This is **Exhibit "B"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

NEWS RELEASE

Ontario Moves Public Health Unit Regions into COVID-19 Response Framework to Keep Ontario Safe and Open

New approach introduces preventative measures earlier to limit transmission of COVID-19 and avoid broader closures

November 06, 2020
Health

TORONTO — In consultation with the Chief Medical Officer of Health, local medical officers of health, and other health experts, the province intends to move Ontario's public health unit regions to the *Keeping Ontario Safe and Open Framework*. The framework categorizes public health regions into five levels: Green-Prevent, Yellow-Protect, Orange-Restrict, Red-Control, and Lockdown being a measure of last and urgent resort.

"The framework lays out a proactive and graduated response to be applied based on the local situation in each region," said Dr. David Williams, Chief Medical Officer of Health. "By working with the medical officers of health and local authorities on the realities and situations of COVID-19, we want to continue to help protect people's health and wellbeing. We are adapting the public health measures to be as targeted and efficient as possible to stop the spread of the virus, while managing any outbreaks as quickly as possible."

At the request of the local medical officer of health, and with the support of Ontario's Chief Medical Officer of Health, Toronto Public Health would remain in a modified Stage 2 until November 14, 2020.

As of Saturday, November 7, 2020 at 12:01 a.m., public health unit regions would be moved to the following levels:

Lockdown:

- No public health unit regions.

Red-Control:

- Peel Regional Health Unit.

Orange-Restrict:

- Ottawa Public Health; and
- York Region Public Health.

Yellow-Protect:

- Brant County Health Unit;
- City of Hamilton Public Health Services;
- Durham Region Health Department;
- Eastern Ontario Health Unit;
- Haldimand-Norfolk Health Unit;
- Halton Region Public Health;
- Niagara Region Public Health;
- Region of Waterloo Public Health and Emergency Services;
- Simcoe Muskoka District Health Unit; and
- Wellington-Dufferin-Guelph Public Health.

Green-Prevent:

- Algoma Public Health;
- Chatham-Kent Public Health;
- Grey Bruce Health Unit;

- Kingston, Frontenac and Lennox & Addington Public Health;
- Haliburton, Kawartha, Pine Ridge District Health Unit;
- Hastings Prince Edward Public Health;
- Huron Perth Public Health;
- Lambton Public Health;
- Leeds, Grenville & Lanark District Health Unit;
- Middlesex-London Health Unit;
- North Bay Parry Sound District;
- Northwestern Health Unit;
- Peterborough Public Health;
- Porcupine Health Unit;
- Public Health Sudbury & Districts;
- Renfrew County and District Health Unit;
- Southwestern Public Health;
- Thunder Bay District Health Unit;
- Timiskaming Health Unit; and
- Windsor-Essex County Health Unit.

Public health measures required for each level can be found in the *Keeping Ontario Safe and Open Framework*.

For long-term care homes, visitor restrictions remain in effect for the following public health unit regions: Ottawa, Peel, Toronto, and York Region.

"COVID-19 will be with us for awhile, which is why we have put in place a framework that introduces more public health measures sooner to limit transmission of COVID-19 in our communities while avoiding broader closures," said Christine Elliott, Deputy Premier and Minister of Health. "We are committed to being transparent with Ontarians, businesses and local communities as we work together to keep Ontarians safe, while keeping our economy open."

The *Keeping Ontario Safe and Open Framework* takes a comprehensive, whole of government approach by introducing preventative measures earlier to help avoid broader closures and allow for additional public health and workplace safety measures to be introduced or removed gradually. It ensures that public health measures are targeted, incremental and responsive to help limit the spread of COVID-19, while keeping schools and businesses open, maintaining health system capacity and protecting vulnerable people, including those in long-term care.

Trends in public health data will be reviewed weekly. At the same time, the government will continually assess the impact of public health measures for 28 days, or two COVID-19 incubation periods to determine if public health units should stay where they are or be moved into a different level.

The Ontario government is making $300 million available to businesses required to close or significantly restrict services in areas subject to modified Stage 2 public health restrictions, or, going forward, in areas categorized as Control or Lockdown. As a result, businesses in these areas will be able to apply for temporary property tax and energy cost rebates directly to the province through a single, online application portal.

As the province continues to expand access to real-time data, enhancements are also being made to Ontario.ca/coronavirus, Ontario's one-stop shop for information on COVID-19. Information about the spread of the virus, and public health and health system capacity will now be available on the website. This includes local cases by public health unit regions, the total number of cases, resolved cases, deaths, and tests completed and how many are positive. This information will better help businesses, organizations and local communities access key information to prepare in advance for any changes in their region.

Quick Facts

- The framework categorizes public health unit regions into five levels: Green–Prevent, Yellow–Protect, Orange–Restrict, Red–Control, and Lockdown. Each level outlines the types of public health and workplace safety measures for businesses and organizations. These include targeted measures for specific sectors, institutions and other settings.
- Municipalities and local medical officers of health may have additional restrictions or targeted requirements in their region, on top of the public health measures required at their specific level.
- The Ontario government has developed a $2.8 billion COVID-19 fall preparedness plan, *Keeping Ontarians Safe: Preparing for Future Waves of COVID-19*, to ensure the province's health care, long-term care and education systems are prepared for the immediate challenges of the fall, including a second wave of COVID-19 and the flu season.

- On November 5, 2020, the Ontario government released the 2020 Budget, *Ontario's Action Plan: Protect, Support, Recover*, which outlines how the province is protecting people during the COVID-19 pandemic by investing $15.2 billion in health care.
- If you are concerned you were exposed to COVID-19 or have symptoms, take the online COVID-19 self assessment.
- Get tested if you have symptoms compatible with COVID-19, or if you have been advised of exposure by your local public health unit or through the COVID Alert app. Visit Ontario.ca/covidtest to find the nearest testing location.
- To stay safe, you can download the COVID Alert App free from the Apple and Google Play app stores.

Additional Resources

- Ontario Releases COVID-19 Response Framework to Help Keep the Province Safe and Open
- Property Tax and Energy Cost Rebates
- Visit Ontario's website to learn more about how the province continues to protect the people of Ontario from COVID-19.

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This is **Exhibit "C"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

NEWS RELEASE

Ontario Updating COVID-19 Response Framework to Help Stop the Spread of COVID-19

Modelling Shows New Thresholds Needed to Bend the Curve and Keep People Safe

November 13, 2020
Office of the Premier

TORONTO — In consultation with the Chief Medical Officer of Health and the Public Health Measures Table, the Ontario government is taking immediate action to respond to the rapid increase in COVID-19 cases and is updating the *Keeping Ontario Safe and Open Framework*, by lowering the thresholds for each level in the framework. These necessary updates will help limit the spread of COVID-19 while keeping schools open, maintaining health system capacity, protecting the province's most vulnerable, and avoiding broader lockdowns.

Details were provided today by Premier Doug Ford, Christine Elliott, Deputy Premier and Minister of Health, and Dr. David Williams, Chief Medical Officer of Health.

"Our number one priority right now is getting the numbers down and keeping people safe. That's why, on the recommendation of the Chief Medical Officer of Health, we're updating the framework with new thresholds so we can slow the spread of this virus," said Premier Ford. "These adjustments are necessary to respond to the latest evidence we're seeing and we are prepared to make further adjustments as the health experts continue to review the current public health restrictions. We must do whatever it takes to stop our hospitals from being overwhelmed and protect our most vulnerable."

The latest modelling shows that if the number of new cases continues to grow at its current rate, the province could register up to 6,500 new cases per day by mid-December. Within the next two weeks the province will likely exceed its intensive care threshold of 150 beds, under any potential scenario.

The framework changes are in response to the current data and trends, and will lower the threshold for each of the five levels for: weekly incidence rates, positivity rate, effective reproductive number (Rt), outbreak trends and the level of community transmission. Based on these new thresholds, the following public health unit regions would be moved to the following levels in the framework:

- Red-Control:
  - Hamilton Public Health Services
  - Halton Region Public Health
  - Toronto Public Health
  - York Region Public Health

- Orange-Restrict:
  - Brant County Health Unit
  - Durham Region Health Department
  - Eastern Ontario Health Unit
  - Niagara Region Public Health
  - Wellington-Dufferin-Guelph Public Health
  - Region of Waterloo Public Health

- Yellow-Protect:
  - Huron Perth Public Health
  - Middlesex-London Health Unit
  - Public Health Sudbury & Districts
  - Southwestern Public Health
  - Windsor-Essex County Health Unit

Please visit Ontario.ca/COVID19 for the full list of public health region classifications that will come into effect as of Monday, November 16, 2020 at 12:01 a.m. Toronto Public Health will move into the framework on Saturday, November 14, 2020 at 12:01 a.m.

For long-term care homes, visitor restrictions will apply to public health regions within the Orange-Restrict and Red-Control levels in the framework. This will go into effect on Monday, November 16, 2020 at 12:01 a.m.

"Over the last week we have seen an alarming shift in the trends of key public health indicators in regions across the province," said Minister Elliott. "The COVID-19 pandemic continues to evolve, and our government's response must evolve with it. These updates to the COVID-19 Framework will ensure that the necessary targeted measures are in place in hotspots to help stop the spread of the virus and keep our schools and businesses open. Protecting the health and well-being of Ontarians remains our top priority."

The framework takes a gradual approach that includes introducing preventative measures earlier to help avoid broader closures and allow for additional public health and workplace safety measures to be introduced or removed incrementally. It categorizes public health unit regions into five levels: Green-Prevent, Yellow-Protect, Orange-Restrict, Red-Control, and Lockdown being a measure of last and urgent resort.

Ontario's COVID-19 Response Framework has been designed to:

- Be responsive and flexible to latest data;
- Introduce preventative measures earlier to help limit the spread of COVID-19, while keeping schools open, supporting mental health, protecting our most vulnerable, and keeping businesses open where possible;
- Recognize that every community is different and provide the flexibility to allocate resources where they are needed most; and
- Support the ability for local officials to tailor restrictions in their communities based on regional circumstances. The framework serves as a baseline that municipalities and local medical officers of health can build on by imposing additional restrictions or targeted requirements in their region, on top of the public health and workplace safety measures required at their specific level.

"The latest modelling shows a concerning situation in our province. Worldwide we are seeing COVID-19 cases continue to rise, and Ontario is no exception," said Dr. Williams. "It remains critical that everyone continue to strictly follow public health advice to protect yourself and your community. We bent the curve during the first wave and, although it will be challenging, we can do so again through the collective actions of all Ontarians."

Assignments to the current levels would last for a minimum of 28 days or two-incubation periods, at which time the status of these public health unit regions will be reassessed on a weekly basis. However, movement to a more restrictive zone will be considered sooner if there are rapidly worsening trends.

Since the beginning of the outbreak, Ontarians have been playing their part to help bend the curve and stop the spread of the virus. Today more than ever, it is critical for everyone to follow public health advice and strictly comply to the restrictions applied in their regions, especially when connecting with others. The following recommendations apply to all public health unit regions in the province:

- Avoid social gatherings and limit close contacts to your household or the people you live with;
- Adhere to the restrictions in your region on public and private gatherings;
- Maintain two metres of physical distancing from everyone else;
- Wear a face covering indoors and wear one outdoors if physical distancing may not be maintained or if wearing one is required;
- Wash your hands thoroughly and regularly;
- Stay home if you have COVID-19 symptoms, even if they are mild;
- Cover your cough;
- Get tested if you have symptoms compatible with COVID-19, or if you've been advised of exposure by your local public health unit or through the COVID Alert mobile app;
- Individuals and families from higher transmission regions should avoid travel to lower transmission regions, except for essential reasons; and
- Download the COVID Alert mobile app.

In addition, as the province continues to expand access to real-time data, enhancements have been made to Ontario.ca/coronavirus, Ontario's one-stop shop for information on COVID-19. Beginning today, users will now be able to view new, active, resolved, deceased, and total cases, by public health unit, on a map. In addition, the website will now provide Ontarians with an effective reproduction number, as well as enhanced long-term care data. The government will

continue to update the dashboard with relevant data to ensure as much transparency as possible. This information will better help businesses, organizations and local communities access key information to prepare in advance for any changes in their region.

Quick Facts

- Find out what level and which regional public measures are in place for your area.
- The Ontario government has developed a $2.8 billion COVID-19 fall preparedness plan, *Keeping Ontarians Safe: Preparing for Future Waves of COVID-19*, to ensure the province's health care, long-term care and education systems are prepared for the immediate challenges of the fall, including a second wave of COVID-19 and the flu season.
- The Ontario government is making $300 million available to businesses required to close or significantly restrict services in areas subject to modified Stage 2 (Red–Control level) public health restrictions, or, going forward, in Lockdown. As a result, businesses in these areas will be able to apply for temporary property tax and energy cost rebates directly to the province through a single, online application portal.
- If you are concerned you were exposed to COVID-19 or have symptoms, take the online COVID-19 self assessment.
- Get tested if you have symptoms compatible with COVID-19, or if you have been advised of exposure by your local public health unit or through the COVID Alert app. Visit Ontario.ca/covidtest to find the nearest testing location.
- To stay safe, you can download the COVID Alert App free from the Apple and Google Play app stores.

Additional Resources

- Ontario Releases COVID-19 Response Framework to Help Keep the Province Safe and Open
- Property Tax and Energy Cost Rebates
- Visit Ontario's website to learn more about how the province continues to protect the people of Ontario from COVID-19.

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This is **Exhibit "D"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

NEWS RELEASE

Ontario Taking Further Action to Stop the Spread of COVID-19

Province Also Doubling Financial Support for Businesses Affected by Additional Restrictions

November 20, 2020
Office of the Premier

TORONTO — In consultation with the Chief Medical Officer of Health, local medical officers of health, and other health experts, the province is moving certain public health unit regions to new levels in the *Keeping Ontario Safe and Open Framework*, which includes moving Toronto and Peel into Lockdown. These necessary measures are being taken to limit community transmission of COVID-19 in order to keep schools open, safeguard health system capacity, and protect the province's most vulnerable populations.

Details were provided today by Premier Doug Ford, Christine Elliott, Deputy Premier and Minister of Health, Rod Phillips, Minister of Finance, and Dr. David Williams, Chief Medical Officer of Health.

"With the numbers rising rapidly in certain regions, we have to make the tough, but necessary decisions now to protect our hospitals, long-term care and retirement homes, and every person in this province," said Premier Ford. "We cannot afford a province-wide lockdown, so we are taking preventative action today by moving Toronto and Peel into Lockdown level restrictions and other regions into higher levels of restrictions. We need to take decisive action to stop the spread of this deadly virus."

Over the past week, some regions under the Red-Control level have continued to see worsening trends in key indicators, despite having a range of public health measures and restrictions in place since early October. Based on the latest data, the government intends to move Peel Public Health and Toronto Public Health into Lockdown effective Monday, November 23, 2020 at 12:01 a.m. This action is being taken to help stop the spread of COVID-19, while prioritizing the continued opening of schools, child care centres and other key services to the fullest extent possible.

Measures under Lockdown include, but are not limited to:

- Schools, before and after school programs, and child care will remain open;
- Post-secondary schools open for virtual learning with some limited exceptions for training that can only be provided in-person, such as clinical training or training related to a trade;
- No indoor organized public events or social gatherings except with members of the same household. Individuals who live alone, including seniors, may consider having exclusive, close contact with another household;
- Outdoor organized public events or social gatherings limited to a maximum of 10 people;
- Wedding services, funeral services and religious services, rites or ceremonies where physical distancing can be maintained can have up to 10 people indoors or 10 people outdoors;
- Retail permitted to be open for curbside pick-up or delivery only, with certain exceptions such as for supermarkets, grocery stores, pharmacies, hardware stores, discount and big box retailers selling groceries, beer, wine and liquor stores, safety supply stores, and convenience stores, which will be allowed to operate at 50 per cent capacity;
- Restaurants, bars, and food and drink establishments will only be able to provide takeout, drive-through and delivery. Indoor and outdoor dining services are prohibited;
- Personal care services closed;
- Casinos, bingo halls and other gaming establishments closed; and
- Indoor sports and recreational facilities, including pools, closed with limited exceptions.

The Chief Medical Officer of Health and health experts will continue to provide advice to the government using criteria, including:

- Epidemiological indicators such as the number and rate of COVID-19 cases and test positivity;
- Health system capacity indicators including hospital and Intensive Care Unit capacity, access to ventilators and ongoing availability of personal protective equipment;

- Public health sector capacity, including the number of COVID-19 cases and contacts being reached by local public health officials within one day; and
- Ongoing testing of suspected COVID-19 cases, especially of vulnerable populations, to detect new outbreaks quickly.

"As public health indicators continue to worsen in regions across the province, particularly in hotspots like Peel and Toronto, it is clear that more needs to be done to limit community spread of COVID-19," said Minister Elliott. "As we have seen around the world, lockdowns are a difficult but necessary step to stop the spread, safeguard the key services we rely on and protect our health system capacity. With the recent positive news on the development of a vaccine, there is a real hope that we can defeat this deadly virus, but for now we all must continue to follow public health advice and strictly adhere to the restrictions in place."

Based on the latest data, the following public health unit regions will move from their current level in the framework to the following levels effective Monday, November 23, 2020 at 12:01 a.m.:

- Red-Control
  - Durham Region Health Department; and
  - Region of Waterloo Public Health and Emergency Services.

- Orange-Restrict
  - Huron Perth Public Health;
  - Simcoe Muskoka District Health Unit;
  - Southwestern Public Health; and
  - Windsor-Essex County Health Unit.

- Yellow-Protect
  - Chatham-Kent Public Health;
  - Eastern Ontario Health Unit;
  - Grey Bruce Health Unit;
  - Kingston, Frontenac and Lennox & Addington Public Health;
  - Peterborough Public Health; and
  - Thunder Bay District Health Unit.

Please visit Ontario.ca/covidresponse for the full list of public health region classifications.

Trends in public health data will continue to be reviewed weekly to determine if public health units should stay where they are or be moved into a higher level. Public health units will stay in their level for a minimum of 28 days, or two COVID-19 incubation periods, at which time, the government will assess the impact of public health measures to determine if the public health unit should stay where they are or be moved to a different level. The Ministry of Health will continue to communicate regularly with local medical officers of health on local context and conditions to help inform the classification of their public health unit region.

For long-term care homes, visitor restrictions apply to those homes in the public health units that are in the Orange-Restrict level or higher. To further protect the health and safety of those in long-term care homes, staff, essential caregivers and support workers who provide direct care to residents in those regions will be tested more frequently for COVID-19, moving from bi-weekly tests to weekly as of November 23, 2020. In addition, support workers who provide direct care and caregivers in those regions will be asked to provide proof of a negative COVID-19 test result in the past week and verbally attest that they have not subsequently tested positive.

For retirement homes, homes in public health regions that are in Red-Control or higher will be in high alert with visitor restrictions as outlined in the Retirement Homes COVID-19 Visitor Policy. Homes will continue to be notified of their alert status by the Retirement Homes Regulatory Authority.

"Advising regions to move into a lockdown is not a decision we take lightly, but it is one that is needed to ensure the safety of the people of Peel and Toronto," said Dr. Williams. "Now more than ever, it is critical that all Ontarians continue to follow public health advice to help stop the spread of the virus. Everyone has a role to play to protect each other. We are interdependent and nothing can be done without the commitment of each individual, family and community."

To further support public health regions, the province is making additional enforcement mechanisms available to local medical officers of health who have applied additional measures based on their local conditions and needs. The government is amending Ontario Regulation 950 under the *Provincial Offences Act*, allowing for a ticket to be issued for any contravention of a COVID-19 specific communicable disease class order issued by a medical officer of health. The government will also ask the Chief Justice of the Ontario Court of Justice to establish a set fine to be attached to any ticket issued for violating a section 22 order relating to COVID-19 made by a local medical officer of health.

"We are asking Ontarians to familiarize themselves with the restrictions in place, follow the rules and public health guidance, and support enforcement officers who are working to help prevent the further spread of COVID-19," said Solicitor General Sylvia Jones. "Our government will continue to work with law enforcement to ensure they have the tools they need to promote public safety and take the enforcement actions needed to prevent unsafe behaviour."

Additional Supports Available for Businesses Affected by COVID-19 Public Health Measures

The Ontario government is now providing $600 million in relief to support eligible businesses required to close or significantly restrict services due to enhanced public health measures, doubling its initial commitment of $300 million made in the 2020 Budget, Ontario's Action Plan: Protect, Support Recover.

Businesses can apply online for temporary property tax and energy cost rebate grants from the province, via an easy-to-use one-window portal. The rebates will cover the length of time that a business is required to temporarily close or significantly restrict services as a result of being located in an area categorized as Red-Control or Lockdown, or previously categorized as modified Stage 2 public health restrictions. Most businesses can expect to receive their rebate payments within a few weeks of submitting a complete application. A detailed list of eligible businesses, as well as instructions for applying, can be found at Ontario.ca/covidsupport.

The federal and provincial governments have been working collaboratively together to deliver benefits and supports to individuals, families and businesses since the onset of COVID-19. Consistent with this, Ontario will work with the federal government to ensure these supports for businesses in COVID-19 hotspots are available in the most straightforward and seamless way possible by integrating these rebates with the federal Canada Emergency Rent Subsidy (CERS) program.

"We will double the funding we have made available to support employers and jobs affected by the necessary public health measures we are taking to protect people during the second wave," said Minister Phillips. "All of us know a small business owner struggling due to COVID-19. These necessary public health measures we have outlined today will create new challenges — but as we committed in Ontario's Action Plan: Protect, Support, Recover, we will continue to be there to protect jobs and support employers."

Quick Facts

- If you have questions about what will be open or impacts to your business or employment, call the Stop the Spread Business Information Line at 1-888-444-3659.
- Find out what level and which regional public measures are in place for your area.
- Municipalities and local medical officers of health may have additional restrictions or targeted requirements in their region, on top of the public health measures required at their specific level.
- The Ontario government has developed a $2.8 billion COVID-19 fall preparedness plan, Keeping Ontarians Safe: Preparing for Future Waves of COVID-19, to ensure the province's health care, long-term care and education systems are prepared for the immediate challenges of the fall, including a second wave of COVID-19 and the flu season.
- Get tested if you have symptoms compatible with COVID-19, or if you have been advised of exposure by your local public health unit or through the COVID Alert app. Visit Ontario.ca/covidtest to find the nearest testing location.
- To find the right supports, visit COVID-19: Support for People, which has information about the many available and free mental health services and supports.
- To stay safe you can download the COVID Alert App free from the Apple and Google Play app stores.

Additional Resources

- Ontario's Action Plan: Protect, Support, Recover
- Ontario Updating COVID-19 Response Framework to Help Stop the Spread of COVID-19
- Ontario's Action Plan: Responding to COVID-19
- Property Tax and Energy Cost Rebates
- Visit Ontario's website to learn more about how the province continues to protect the people of Ontario from COVID-19.

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This is **Exhibit "E"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

NEWS RELEASE

Ontario Moving Regions to New Levels in COVID-19 Response Framework

Framework Introduces Preventative Measures Earlier to Limit Transmission of COVID-19

November 27, 2020
Health

TORONTO — The Ontario government, in consultation with the Chief Medical Officer of Health, local medical officers of health, and other health experts, is moving five public health regions to new levels with stronger public health measures. These steps are being taken to stop the spread of COVID-19 in order to keep schools open, safeguard health system capacity, and protect the province's most vulnerable populations. The regional levels and specific public health measures are set out in the *Keeping Ontario Safe and Open Framework*.

"The health and safety of all Ontarians is and will always be our top priority, that's why we are following the advice of the Chief Medical Officer of Health and other health experts and making this adjustment today," said Christine Elliott, Deputy Premier and Minister of Health. "Over the last week we have seen a shift in the trends of key public health indicators in regions across the province, and by moving these five regions to a new level in the framework, we can ensure that the necessary targeted measures are in place to stop the spread of the virus and allow us to keep our schools and businesses open."

Based on the latest data, the following public health regions will move from their current level in the framework to the following levels effective Monday, November 30, 2020 at 12:01 a.m.:

- Red-Control
  - Windsor-Essex County Health Unit.
- Orange-Restrict
  - Haldimand-Norfolk Health Unit.
- Yellow-Protect
  - Hastings Prince Edward Public Health
  - Lambton Public Health; and
  - Northwestern Health Unit.

All other public health regions will remain at their current level. Please visit Ontario.ca/covidresponse for the full list of public health region classifications.

For long-term care homes, visitor restrictions apply to those homes in the public health unit regions that are in the Orange-Restrict level or higher. In addition, long-term care homes must implement recently enhanced testing requirements.

Trends in public health data will continue to be reviewed weekly to determine if public health units should stay where they are or be moved into a higher level. Public health units will stay in their level for a minimum of 28 days, or two COVID-19 incubation periods, at which time, the government will assess the impact of public health measures to determine if the public health unit should stay where they are or be moved to a different level. The Ministry of Health will continue to consult regularly with local medical officers of health on local context and conditions to help inform the classification of their public health unit region.

"As we continue in our fight against this second wave of COVID-19, the need to follow public health advice has never been greater," said Dr. David Williams, Chief Medical Officer of Health. "All Ontarians are urged to adhere to the organized public event and social gathering limits in their region and avoid any non-essential travel in order to reduce the risk of exposure and ensure the continued safety of the community."

All Ontarians should avoid close contact with anyone not living in the same household. People who live alone may have exclusive close contact with one additional household to prevent feelings of isolation and mitigate against negative mental health impacts.

The following recommendations apply to all public health unit regions in the province:

- Stay home if you have COVID-19 symptoms, even if they are mild;
- Maintain two metres of physical distancing from everyone else;
- Avoid social gatherings and limit close contacts to your household or the people you live with;
- Adhere to the restrictions in your region on public and private gatherings;
- Wear a face covering indoors and wear one outdoors if physical distancing may not be maintained or if wearing one is required;
- Wash your hands thoroughly and regularly;
- Cover your cough;
- Get tested if you have symptoms compatible with COVID-19, or if you've been advised of exposure by your local public health unit or through the COVID Alert mobile app;
- Individuals and families from higher transmission regions should avoid travel to lower transmission regions, except for essential reasons; and
- Download the COVID Alert mobile app.

Quick Facts

- Find out what level and which regional public measures are in place for your area.
- No matter where you live in the province, the safest way to spend the holidays this year is by only celebrating in person with the people you live with and celebrating virtually with everyone else.
- Get tested if you have symptoms compatible with COVID-19, or if you have been advised of exposure by your local public health unit or through the COVID Alert app. Visit Ontario.ca/covidtest to find the nearest testing location.
- To find the right supports, visit COVID-19: Support for People, which has information about the many available and free mental health services and supports.
- The Ontario government is now providing $600 million in relief to support eligible businesses required to close or significantly restrict services due to enhanced public health measures, doubling its initial commitment of $300 million made in the 2020 Budget, Ontario's Action Plan: Protect, Support Recover.
- If you have questions about what will be open or impacts to your business or employment, call the Stop the Spread Business Information Line at 1-888-444-3659.
- To stay safe, you can download the COVID Alert App free from the Apple and Google Play app stores.

Additional Resources

- Celebrate the Holiday Season Safely
- Ontario Taking Further Action to Stop the Spread of COVID-19
- Ontario’s Action Plan: Protect, Support, Recover
- Property Tax and Energy Cost Rebates
- Visit Ontario’s website to learn more about how the province continues to protect the people of Ontario from COVID-19.

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This is **Exhibit "F"** referred to
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Ryan Cookson

A Commissioner for the Taking of Affidavits

NEWS RELEASE

Ontario Moving Regions to New Levels with Stronger Public Health Measures

Action is being taken to stop the spread of COVID-19 and protect vulnerable people

December 11, 2020
Health

TORONTO — The Ontario government, in consultation with the Chief Medical Officer of Health, local medical officers of health, and other health experts, is moving seven public health regions to new levels with stronger public health measures, including Windsor-Essex County Health Unit and York Region Public Health moving into Grey-Lockdown. These steps are being taken to stop the spread of COVID-19 in order to keep schools open in the regions where in-class learning is permitted, safeguard health system capacity, and protect the province's most vulnerable populations. The regional levels and specific public health measures are set out in the *Keeping Ontario Safe and Open Framework*.

"Moving a region into Grey-Lockdown is not an easy decision, but it is one we needed to make in order to help stop the spread of the virus and safeguard the key services we rely on," said Christine Elliott, Deputy Premier and Minister of Health. "As we enter the holiday season and as the province prepares to receive its first shipment of COVID-19 vaccines, it remains crucial for all Ontarians to continue adhering to public health advice and workplace safety measures to reduce the spread of the virus and keep each other safe."

Based on the latest data, the following public health regions will move from their current level in the framework to the following levels effective Monday, December 14, 2020 at 12:01 a.m.:

- Grey-Lockdown
  - Windsor-Essex County Health Unit; and
  - York Region Public Health.

- Red-Control
  - Middlesex-London Health Unit;
  - Simcoe Muskoka District Health Unit; and
  - Wellington-Dufferin-Guelph Public Health.

- Orange-Restrict
  - Eastern Ontario Health Unit.

- Yellow-Protect
  - Leeds, Grenville and Lanark District Health Unit.

All other public health regions will remain at their current level. Please visit Ontario.ca/covidresponse for the full list of public health region classifications.

"Over the last week, public health indicators in the York and Windsor regions have continued to trend in the wrong direction and it is evident additional measures are needed to help limit the spread of the virus," said Dr. David Williams, Chief Medical Officer of Health. "By making this difficult but necessary decision we can help to ensure that hospitals in these regions can work to provide patients with the care they need when they need it, including the performing of scheduled surgeries and other important procedures."

For long-term care homes, visitor restrictions apply to those homes in the public health unit regions that are in the Orange-Restrict level or higher. In addition, long-term care homes must implement recently enhanced testing requirements.

Trends in public health data will continue to be reviewed weekly to determine if public health units should stay where they are or be moved into a different level. Public health units will stay in their level for a minimum of 28 days, or two COVID-19 incubation periods, at which time, the government will assess the impact of public health measures to determine if the public

health unit should stay where they are or be moved to a different level. The government and the Chief Medical Officer of Health will continue to consult regularly with local medical officers of health on local context and conditions to help inform the classification of their public health unit region.

As we approach the holiday season, the government is urging all Ontarians to continue to follow all required public health measures and public health advice. This includes the following:

- Stay home if you have COVID-19 symptoms, even if they are mild;
- Maintain two metres of physical distancing from anyone outside your household;
- Avoid social gatherings and limit close contacts to your household or the people you live with;
- Adhere to the restrictions in your region on public and private gatherings;
- Wear a face covering indoors and wear one outdoors if physical distancing may not be maintained or if wearing one is required;
- Wash your hands thoroughly and regularly;
- Cover your cough;
- Get tested if you have symptoms compatible with COVID-19, or if you've been advised of exposure by your local public health unit or through the COVID Alert mobile app;
- Individuals and families from higher transmission regions should avoid travel to lower transmission regions, except for essential reasons; and
- Download the COVID Alert mobile app.

No matter where you live in the province, the safest way to spend the holidays this year is by only celebrating in person with the people you live with and celebrating virtually with everyone else. People who live alone may have exclusive close contact with one additional household to help prevent feelings of isolation and mitigate against negative mental health impacts.

The Ontario government is now providing $600 million in property tax and energy cost rebates to support eligible businesses required to close or significantly restrict services due to enhanced public health measures, doubling its initial commitment of $300 million made in the 2020 Budget, Ontario's Action Plan: Protect, Support, Recover. To apply for this funding please visit Businesses: Get help with COVID-19 costs.

Quick Facts

- Find out what level and which regional public measures are in place for your area.
- Learn how to celebrate the holidays safely with the people you live with by visiting Ontario.ca/celebratesafely.
- Get tested if you have symptoms compatible with COVID-19, or if you have been advised of exposure by your local public health unit or through the COVID Alert app. Visit Ontario.ca/covidtest to find the nearest testing location.
- To find the right supports, visit COVID-19: Support for People, which has information about the many available and free mental health services and supports.
- If you have questions about what will be open or impacts to your business or employment, call the Stop the Spread Business Information Line at 1-888-444-3659.
- To stay safe, you can download the COVID Alert App free from the Apple and Google Play app stores.

Additional Resources

- Celebrate the Holiday Season Safely
- Ontario Moving Three Regions to New Levels in COVID-19 Response Framework
- Ontario's Action Plan: Protect, Support, Recover
- Property Tax and Energy Cost Rebates
- Visit Ontario's website to learn more about how the province continues to protect the people of Ontario from COVID-19.

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Ryan Cookson

A Commissioner for the Taking of Affidavits

NEWS RELEASE

Ontario Announces Provincewide Shutdown to Stop Spread of COVID-19 and Save Lives

Government Providing Grants of up to $20,000 to Small Businesses Impacted by New Public Health Measures

December 21, 2020
Office of the Premier

TORONTO — As COVID-19 cases continue to rise at an alarming rate, the Ontario government, in consultation with the Chief Medical Officer of Health and other health experts, is imposing a Provincewide Shutdown. Additional restrictions will be put into place and reinforce that Ontarians should stay at home as much as possible to minimize transmission of the virus and prevent hospitals from becoming overwhelmed. The Provincewide Shutdown will go into effect as of Saturday, December 26, 2020, at 12:01 a.m.

Details were provided today by Premier Doug Ford, Christine Elliott, Deputy Premier and Minister of Health, Stephen Lecce, Minister of Education, Dr. David Williams, Chief Medical Officer of Health, and Dr. Naveed Mohammad, President and CEO, William Osler Health System.

"The number of daily cases continue to rise putting our hospitals and long-term care homes at risk," said Premier Ford. "We need to stop the spread of this deadly virus. That's why, on the advice of Dr. Williams and other health experts, we are taking the difficult but necessary decision to shutdown the province and ask people to stay home. Nothing is more important right now than the health and safety of all Ontarians."

In response to these exceptional circumstances, the Provincewide Shutdown would put in place time-limited public health and workplace safety measures similar to those in other jurisdictions. It would help stop the trend of high COVID-19 transmission in communities, preserve health system capacity, safeguard vulnerable populations and those who care for them, and save lives. Measures include, but are not limited to:

- Restricting indoor organized public events and social gatherings, except with members of the same household (the people you live with). Individuals who live alone may consider having exclusive close contact with one other household.
- Prohibiting in-person shopping in most retail settings - curbside pickup and delivery can continue. Discount and big box retailers selling groceries will be limited to 25 per cent capacity for in-store shopping. Supermarkets, grocery stores and similar stores that primarily sell food, as well as pharmacies, will continue to operate at 50 per cent capacity for in-store shopping.
- Restricting indoor access to shopping malls - patrons may only go to a designated indoor pickup area (by appointment only), essential retail stores that are permitted to be open (e.g. pharmacy, grocery store), or, subject to physical distancing and face covering requirements, to the food court for takeout purchases. Shopping malls may also establish outdoor designated pickup areas.
- Prohibiting indoor and outdoor dining. Restaurants, bars and other food or drink establishments will be permitted to operate by take out, drive-through, and delivery only.

On the advice of the Chief Medical Officer of Health, all Ontarians are advised to stay home as much as possible with trips outside the home limited to necessities such as food, medication, medical appointments, or supporting vulnerable community members. Employers in all industries should make every effort to allow employees to work from home.

The current COVID-19 Response Framework will be paused when the Provincewide Shutdown comes into effect. The impacts of these time-limited measures will be evaluated throughout the 14 days in Northern Ontario and 28 days in Southern Ontario to determine if it is safe to lift any restrictions or if they need to be extended.The Chief Medical Officer of Health will assess and apply lessons learned thus far to the COVID-19 Response Framework to ensure appropriate and effective measures are in place to protect the health of Ontarians and enable economic recovery after the Provincewide Shutdown ends. This will include an assessment of how a revised approach for the safe reopening of retail may be operationalized, according to the latest available evidence.

"This was not an easy decision before the holidays, but we have reached a tipping point," said Minister Elliott. "We continue to see sharp increases in hospitalizations and occupancy in intensive care units is reaching concerning levels. Urgent action must be taken to prevent our health care system from becoming overwhelmed. By implementing a Provincewide Shutdown, we can work to stop the virus in its tracks, safeguard hospital capacity, and save lives."

The government is also providing $12.5 million to implement a High Priority Communities Strategy to contain the virus in high-risk communities. The strategy will take a tailored, community-based approach to fund community agencies in 15 priority communities in the York, Peel, Durham, Ottawa, and Toronto regions. The funding will also allow for the hiring of community ambassadors to make people aware of available services and assistance, for coordination of increased testing opportunities and for the arrangement of wraparound supports for those who are COVID-positive. Additional funding of $42 million will also be available to establish isolation centres.

The province will work with our local municipal partners to establish new isolation centres to help those who may need to isolate following testing.

"We continue to see the number of cases in the province grow and the trends in public health indicators worsen. Additional measures are needed provincewide in order to interrupt this concerning growth," said Dr. Williams. "We must work together to enable everyone to follow these new and time-limited restrictions and protect our health system and our communities."

The government is working to limit the transmission of COVID-19 in workplaces by supporting essential businesses in doing whatever is necessary to keep workers safe. The Ministry of Labour, Training and Skills Development is leading a multi-ministry COVID-19 Safety Team. The team will partner with local authorities to carry out additional enforcement blitzes in sectors where they are needed most.

New School Protocols

While transmission in schools remains low, all publicly funded and private elementary and secondary schools are to move to teacher-led remote learning when students return from the winter break on January 4, 2021. This action is being taken in support of the Government's broader efforts to limit the spread of COVID-19.

Schools located in the following Public Health Unit regions can resume in-person instruction on January 11, 2021 for both elementary and secondary students:

- The District of Algoma Health Unit
- North Bay Parry Sound District Health Unit
- Northwestern Health Unit
- Porcupine Health Unit
- Sudbury and District Health Unit
- Thunder Bay District Health Unit
- Timiskaming Health Unit

For schools in all other Public Health Unit regions, elementary school students are planned to be able to return to in-person learning on January 11, 2021, and secondary school students will continue learning remotely until January 25, 2021, at which point they may resume in-person learning. During this period, child care centres, authorized recreational and skill building programs and home-based child care services will remain open. From January 4-8, 2021, when elementary students move to remote learning, before and after school programs will be closed and emergency child care for health care and frontline workers will be provided. As part of the government's efforts to protect the most vulnerable, boards will be required to make provisions for continued in-person support for students with special education needs who cannot be accommodated through remote learning for whom remote learning is challenging.

"While our schools are not a source of rising community transmission, we can play an important part of the solution to save lives from COVID-19," said Minister Lecce. "During this period, students will pivot to teacher-led online learning, with child care provided for our frontline workers. We are taking proactive and preventative action to protect schools following the holiday break to ensure kids can continue in-class learning — something we believe is so important — for the remainder of the year."

The New Ontario Small Business Support Grant

The government recognizes that small businesses impacted by these necessary public health measures will require additional support so they can continue serving their communities and employing people in Ontario once the COVID-19 pandemic is over. That is why the government is announcing the new *Ontario Small Business Support Grant*, which will provide a minimum of $10,000 and up to $20,000 to eligible small business owners to help navigate this challenging period.

"Ontario's business owners have shown remarkable resolve and ingenuity throughout the pandemic. They know better than anyone what they need to come through this very difficult time, so they can continue to serve and employ people in their communities," said Rod Phillips, Minister of Finance. "The new *Ontario Small Business Support Grant* will provide significant financial support to eligible small business owners in addition to the other supports made available to our small business community."

Small businesses required to close or restrict services under the Provincewide Shutdown will be able to apply for this one-time grant. Each small business will be able to use the support in whatever way makes the most sense for their individual business. For example, some businesses will need support paying employee wages or rent, while others will need support maintaining their inventory.

Eligible small businesses include those that:

- Are required to close or significantly restrict services subject to the Provincewide Shutdown effective 12:01 a.m. on December 26, 2020;
- Have less than 100 employees at the enterprise level; and
- Have experienced a minimum of 20 per cent revenue decline in April 2020 compared to April 2019.

Starting at $10,000 for all eligible businesses, the grant will provide businesses with dollar for dollar funding to a maximum of $20,000 to help cover decreased revenue expected as a result of the Provincewide Shutdown. The business must demonstrate they experienced a revenue decline of at least 20 per cent when comparing monthly revenue in April 2019 and April 2020. This time period was selected because it reflects the impact of the public health measures in spring 2020, and as such provides a representation of the possible impact of these latest measures on small businesses.

Essential businesses that are allowed to remain open will not be eligible for this grant. More information about the *Ontario Small Business Support Grant* is available here. Further details, including how to apply, will be announced in January 2021.

Businesses that are impacted by the Provincewide Shutdown will also be eligible for the property tax and energy cost rebates. In November, the government launched a program to provide rebates to offset fixed costs such as property tax and energy bills for businesses that are required to shut down or significantly restrict services due to provincial public health measures. These rebates will continue to be available for businesses impacted by the Provincewide Shutdown and earlier restrictions. Business can apply for the rebates here.

Quick Facts

- Currently, hospitalizations for COVID-19 have increased by 74 per cent over the last four weeks and are more than 15 times higher than they were at the beginning of September. Intensive care unit (ICU) occupancy for COVID-19 has more than doubled over the last four weeks and is 20 times higher than at the beginning of September.
- Ontario currently has 915 COVID-19 patients requiring acute care, 265 patients in ICU, with 152 on a ventilator.
- Based on the latest modelling data, cases across the province are continuing to grow and the number of people requiring an intensive care bed is projected to rise well above 300 people within the next 10 days.
- Some jurisdictions around the world, including those in Canada have implemented similar time-limited measures to respond to a dramatic resurgence in cases. Based on their experiences, measures of four to six weeks are expected to interrupt transmission of COVID-19 in Ontario.
- Municipalities and local medical officers of health may have additional restrictions or targeted requirements in their region.
- Get tested if you have symptoms compatible with COVID-19, or if you have been advised of exposure by your local public health unit or through the COVID Alert App. Visit Ontario.ca/covidtest to find the nearest testing location.
- The Ontario Small Business Support Grant is part of the Province's more than $13.5 billion in support for people and jobs outlined in the 2020 Budget, Ontario's Action Plan: Protect, Support, Recover. It is also in addition to $4.8 billion to address critical areas to support a strong long-term recovery that helps workers, employers and communities get back on their feet, while building the foundation for recovery and growth.
- To find the right supports, visit COVID-19: Support for People, which has information about the many available and free mental health services and supports.
- To stay safe you can download the COVID Alert App free from the Apple and Google Play app stores.
- To date, as part of the province's COVID-19 immunization program, over 3,000 frontline health care workers have been vaccinated.
- Schools continue to be safe, and according to data reported by school boards, as of Friday, December 18: approximately 99.64 per cent of students in Ontario have not reported a case of COVID-19; approximately 92 per cent of schools across the province have had either no cases or one case reported within the last 14 days; and approximately 80 per cent of schools do not have an case of COVID-19.

Additional Resources

- Ontario Building On Supports for Employers During COVID-19
- Ontario Supporting High Priority Communities
- The Digital Main Street program helps main street businesses build their online presence and reach more customers.
- Property Tax and Energy Cost Rebates
- Visit Ontario's website to learn more about how the province continues to protect the people of Ontario from COVID-19.
- COVID-19: provincewide shutdown
- **If you have questions about what will be open or impacts to your business or employment, call the Stop the Spread Business Information Line at 1-888-444-3659.**

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Learn about the government services available to you and how government works. Learn more

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in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

NEWS RELEASE

Ontario Declares Second Provincial Emergency to Address COVID-19 Crisis and Save Lives

Province Issues Stay-at-Home Order and Introduces Enhanced Enforcement Measures to Reduce Mobility

January 12, 2021
Office of the Premier

TORONTO — In response to a doubling in COVID-19 cases over the past two weeks, the real and looming threat of the collapse of the province's hospital system and alarming risks posed to long-term care homes as a result of high COVID-19 transmission rates, the Ontario government, in consultation with the Chief Medical Officer of Health and other health experts, is immediately declaring a second provincial emergency under s 7.0.1 (1) of the *Emergency Management and Civil Protection Act* (EMPCA).

Details were provided today by Premier Doug Ford, Christine Elliott, Deputy Premier and Minister of Health, Solicitor General Sylvia Jones, Dr. David Williams, Chief Medical Officer of Health, and Dr. Adalsteinn (Steini) Brown, Co-Chair of the Ontario COVID-19 Science Advisory Table.

"The latest modelling data shows that Ontario is in a crisis and, with the current trends, our hospital ICUs will be overwhelmed in a few short weeks with unthinkable consequences," said Premier Ford. "That's why we are taking urgent and decisive action, which includes declaring a provincial emergency and imposing a stay-at-home-order. We need people to only go out only for essential trips to pick up groceries or go to medical appointments. By doing the right thing and staying home, you can stay safe and save lives."

Effective Thursday, January 14, 2021at 12:01 a.m., the government is issuing a stay-at-home order requiring everyone to remain at home with exceptions for permitted purposes or activities, such as going to the grocery store or pharmacy, accessing health care services, for exercise or for work where the work cannot be done remotely. This order and other new and existing public health restrictions are aimed at limiting people's mobility and reducing the number of daily contacts with those outside an immediate household. In addition to limiting outings for these purposes, all businesses must ensure that any employee who can work from home, does work from home.

These new public health measures will help stop the spread of COVID-19 by reducing concerning levels of mobility as the province continues its vaccine rollout and ramps up to mass vaccination when the federal government is able to provide the necessary supply to do so.

Additional Public Health Restrictions

Since the implementation of the Provincewide Shutdown over two weeks ago, the latest modelling trends in key public health indicators have continued to worsen, forecasting an overwhelming of the health system unless drastic action is taken. Escalating case counts have led to increasing hospitalization rates and intensive care unit (ICU) occupancy which has resulted in cancellations of scheduled surgeries and procedures.

Provincial modelling shows growth in COVID-19 cases has accelerated, leading to increased hospitalization rates and ICU occupancy. ICU occupancy by COVID-19 patients is now over 400 beds and is projected to be as high as 1,000 beds by early February which has the potential to overwhelm Ontario's hospitals. The number of COVID-19-related deaths continues to rise and is expected to double from 50 to 100 deaths per day between now and the end of February. Notably, data shows that mobility and contacts between people have not decreased with the current restrictions. A new variant of COVID-19 emerged in November. If community transmission of this variant occurs, Ontario could experience much higher case counts, ICU occupancy and mortality.

In response to the alarming and exceptional circumstances at hand, and to further interrupt the deadly trend of transmission in Ontario communities, hospitals, and long-term care homes, the following additional public health measures will take effect January 13, 2021 at 12:01 a.m.:

- Outdoor organized public gatherings and social gatherings are further restricted to a limit of five people with limited exceptions. This is consistent with the rules during the lockdown during the first wave of COVID-19 in spring 2020 and will allow individuals and families to enjoy time outdoors safely.
- Individuals are required to wear a mask or face covering in the indoor areas of businesses or organizations that are open. Wearing a mask or face covering is now recommended outdoors when you can't physically distance more than two metres.
- All non-essential retail stores, including hardware stores, alcohol retailers, and those offering curbside pickup or delivery, must open no earlier than 7 a.m. and close no later than 8 p.m. The restricted hours of operation do not apply to stores that primarily sell food, pharmacies, gas stations, convenience stores, and restaurants for takeout or delivery.
- Non-essential construction is further restricted, including below-grade construction, exempting survey.

These measures will come into effect between Tuesday January 12, 2021 and Thursday, January 14, 2021, including the provincial declaration of emergency under the EMCPA, orders under that Act, and amendments to regulations under the *Reopening Ontario (A Flexible Response to COVID-19) Act, 2020*.

"Despite our best efforts, COVID-19 is continuing to spread in our communities, our hospitals, our long-term care homes, and our workplaces. We are continuing to see concerning trends across the province, including a tragic number of deaths," said Christine Elliott, Deputy Premier and Minister of Health. "We have made great strides in vaccinating tens of thousands of Ontarians, and we can't let these efforts go to waste. Urgent action is required to break this deadly trend of transmission, ensure people stay home, and save lives."

To help quickly identify and isolate cases of COVID-19 in workplaces and service providers permitted to remain open such as long-term care homes and schools, the province will provide up to 300,000 COVID-19 tests per week to support key sectors such as manufacturing, warehousing, supply chain and food processing, as well as additional tests for schools and long-term care homes. This volume of rapid tests would support antigen screening for up to 150,000 workers per week over the next 4-5 months in Ontario's most critical workplaces. The province is expecting to receive 12 million Panbio tests from the federal government over the next several months and continues to pursue opportunities to purchase additional rapid tests.

"The trends in key public health indicators are continuing to deteriorate, and further action is urgently required to save lives," said Dr. David Williams, Chief Medical Officer of Health. "By strictly adhering to all public health and workplace safety measures, we can reduce the transmission of COVID-19 and keep our loved ones and our communities safe. It will take the collective efforts of us all to defeat this virus."

The government knows that in order to keep Ontarians safe, it is important that they are not forced to leave their homes during the new state of emergency. Ontario is exploring all options available to put a temporary residential evictions moratorium in place, and will have more to say in the coming days.

The additional public health restrictions introduced expand on the existing measures put in place to keep Ontarians safe and healthy.

New Enforcement Measures

The province will provide authority to all provincial offences officers, including the Ontario Provincial Police, local police forces, bylaw officers, and provincial workplace inspectors to issue tickets to individuals who do not comply with the stay-at-home-order, or those not wearing a mask or face covering indoors in places open to the public, subject to limited exceptions, as well as retail operators and companies who do not enforce requirements under orders under the *Reopening Ontario (A Flexible Response to COVID-19) Act* (ROA) or EMPCA. Those who decide not to abide by orders will be subject to a set fine and/or prosecution under both the ROA and EMCPA as applicable.

In addition, all provincial offences officers will have the authority to temporarily close a premise and disperse individuals who are in contravention of gathering limits an order and will be able to disperse people who are gathering, regardless whether a premise has been closed or remains open such as a park.

"Strong, new measures will be enforced to stop the spread of COVID-19," said Solicitor General Sylvia Jones. "We are taking extraordinary action to provide law enforcement officers with the tools and support they need to protect the health and wellbeing of Ontarians."

Schools and Child Care Centres

Based on the advice of the Chief Medical Officer of Health, schools in the following public health units (PHUs) will not return to in-person instruction until February 10, 2021:

- Windsor-Essex

- Peel Region
- Toronto
- York
- Hamilton

By January 20, 2021, the Chief Medical Officer of Health will advise the Ministry of Education on which public health units (PHUs) will be permitted to resume in-person instruction, based on the most up-to-date data and modelling. Before- and after-school programs can be offered when in-person instruction resumes. Schools in northern PHUs will continue to remain open.

To continue to keep students, staff and communities safe, the following new health and safety measures will be put in place for in-person learning:

- Masking for Grade 1-3 and requirements for mask wearing outdoors;
- Enhanced screening protocols; and
- Expanded targeted testing.

The government will also implement new health and safety measures in Ontario child care settings, such as enhanced screening to align with school requirements, voluntary participation in targeted testing and additional infection prevention and control measures to align with schools. These enhancements are in addition to the existing health and safety measures already being implemented in child care settings across the province.

Child care centres for non-school aged children will remain open, and emergency child care for school-aged children will end in approved PHU regions on January 22, 2021 as these elementary schools return to in-person learning.During this extended period of online learning, in areas where in-person elementary learning is suspended, emergency child care will continue for eligible families in regions subject to school closures, as identified by the Chief Medical Officer of Health.

"At the heart of our continued efforts to protect against the spread of COVID-19 in our communities is a firm commitment to return kids to school safely," said Education Minister Stephen Lecce. "Protecting our students, staff and their families is our top priority, and these additional measures build on our comprehensive plan to reopen schools and keep young children in child care safe."

Workplace Safety

The Ministry of Labour, Training and Skills Development is taking additional steps to protect workers with the launch of the "Stay Safe All Day" campaign, focusing workplace inspections in areas of high transmission, including break rooms, and providing new educational materials to employers to

promote safe behaviour before, during and after work.

Evidence gathered from COVID-19 related workplace inspections to date shows the vast majority of employers and workers are following COVID-19 safety requirements when working. However, when in a break room, a vehicle or not on the clock, there is a tendency to forget about the importance of wearing masks, maintaining physical distance and hand hygiene.

As part of the "Stay Safe All Day" campaign, inspectors will use a data-driven approach to focus on workplaces with reported COVID-19 outbreaks, manufacturing businesses, warehouses, distribution centres, food processing operations, construction projects and publicly accessible workplaces deemed essential, such as grocery stores. The Ministry is also using a new data-sharing program, in conjunction with the Ministry of Long-Term Care and the Retirement Regulatory Authority, to focus onsite inspections of long-term-care homes and retirement homes.

"We know the majority of businesses are operating safely and responsibly to protect their workers and customers. But as COVID-19 cases continue to rise, we all need to step up and take additional measures to stop the spread," said Monte McNaughton, Minister of Labour, Training and Skills Development. "This includes increasing our inspections to look at everything workers do both while on the job and throughout the workday."

In the unfortunate event that an employee becomes infected with COVID-19, they may be entitled to federally funded paid sick leave of up to $500 a week for two weeks. Workers can also access Canada's Recovery Caregiver Benefit of up to $500 per week for up to 26 weeks if they are unable to work because they must care for their child under 12 years old or a family member who needs supervised care.

Over the summer, the government enacted a new regulatory amendment that put non-unionized employees on Infectious Disease Emergency Leave during the COVID-19 outbreak any time their hours of work are temporarily reduced by their employer due to COVID-19, ensuring businesses aren't forced to terminate employees after their ESA temporary layoff

periods have expired. As part of the Safe Restart Agreement, the federal government is funding a temporary income support program that allows workers to take up to 10 days of leave related to COVID-19, preventing the risk of further spread in the workplace and allowing workers to focus on their health.

Quick Facts

- The Government of Ontario declared its first provincial emergency in response to COVID-19 on March 17, 2020 which remained in effect until July 24, 2020 when the ROA came into force.
- An emergency declaration pursuant to s. 7.0.1 is terminated 14 days after being made and may be extended for up to a further 14 days by the Lieutenant Governor in Council. Thereafter, extensions require approval of the Legislature, which can extend the declared provincial emergency for additional periods of up to 28 days. Orders made during the declaration of emergency pursuant s. 7.0.2 (4) will automatically terminate after 14 days unless they are extended for additional periods of up to 14 days, while orders pursuant to s. 7.1 can be for a period of up to 90 days and renewed for additional periods of up to 90 days.
- The orders currently in force under the Reopening Ontario (A Flexible Response to COVID-19) Act, 2020 (ROA) remain in effect until January 20, 2021. Under the ROA, orders can be extended for up to 30 days at a time, and the government must continue to report on all order extensions to the Select Committee on Emergency Management Oversight.
- A full list of emergency orders under the EMPCA as well as orders under the ROA can be found on the e-Laws website and at Ontario.ca/alert.
- As of January 10, 2021, there have been 215,782 reported COVID-19 cases and 4,983 related deaths in Ontario.
- Ontario has implemented the largest immunization plan in its history and to date, a total of over 130,000 doses have been administered provincewide.
- Building on the efforts of the targeted testing in Phase 1, the Ministry of Education and the Ministry of Health will work together with Ontario Health, PHUs and school boards to expand access to COVID-19 testing.

Additional Resources

- Ontario Continues to Support Employers and Workers during COVID-19
- Enhancing Public Health and Workplace Safety Measures in the Provincewide Shutdown
- Visit Ontario's COVID-19 vaccine web page to view the latest provincial data and information on COVID-19 vaccines.
- Visit Ontario's website to learn more about how the province continues to protect the people of Ontario from COVID-19.
- If you have questions about what will be open or impacts to your business or employment, call the Stop the Spread Business Information Line at 1-888-444-3659.
- Get tested if you have symptoms compatible with COVID-19, or if you have been advised of exposure by your local public health unit or through the COVID Alert App. Visit Ontario.ca/covidtest to find the nearest testing location.
- To find the right supports, visit COVID-19: Support for People, which has information about the many available and free mental health services and supports.
- To stay safe, you can download the COVID Alert App free from the Apple and Google Play app stores.
- COVID-19: Reopening Schools
- COVID-19 school and child care screening
- Operational Guidance: COVID-19 Management in Schools document.

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This is **Exhibit "I"** referred to
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Ryan Cookson

A Commissioner for the Taking of Affidavits

NEWS RELEASE

Ontario Extending Stay-at-Home Order across Most of the Province to Save Lives

Public Health Units to Gradually Return to the COVID-19 Response Framework

February 08, 2021
Office of the Premier

TORONTO — In consultation with the Chief Medical Officer of Health, the government is moving to a regional approach and maintaining the shutdown in the majority of the public health regions in Ontario, including the Stay-at-Home order and all existing public health and workplace safety measures. When it is safe to do so, the province will gradually transition each region from the shutdown measures to a revised and strengthened *COVID-19 Response Framework: Keeping Ontario Safe and Open* (the "Framework").

Details were provided today by Premier Doug Ford, Christine Elliott, Deputy Premier and Minister of Health, Solicitor General Sylvia Jones, and Dr. David Williams, Chief Medical Officer of Health.

"Our number one priority will always be protecting the health and safety of all individuals, families and workers across the province," said Premier Ford. "But we must also consider the severe impact COVID-19 is having on our businesses. That's why we have been listening to business owners, and we are strengthening and adjusting the Framework to allow more businesses to safely reopen and get people back to work."

To support the province's economic recovery, the government has updated the Framework to allow for a safer approach to retail. Limited in-person shopping in Grey-Lockdown zones will be permitted with public health and safety measures, such as limiting capacity to 25 per cent in most retail settings. In addition, public health and safety measures in retail settings will be strengthened for other levels of the Framework. Individuals will also be required to wear a face covering and maintain physical distance when indoors in a business, with limited exceptions.

Other measures include a requirement for individuals to wear a face covering when attending an organized public event or gathering (where permitted) if they are within two metres distance of another individual who is not part of their household (both indoor and outdoor). All other requirements for gatherings and organized public events would be maintained.

Based on the improving local trends of key indicators, including lower transmission of COVID-19, improving hospital capacity, and available public health capacity to conduct rapid case and contact management, the following three regions will be moving back to the Framework at the Green-Prevent level on Wednesday, February 10, 2021 at 12:01 a.m. and will no longer be subject to the Stay-at-Home order:

- Hastings Prince Edward Public Health;
- Kingston, Frontenac and Lennox & Addington Public Health; and
- Renfrew County and District Health Unit.

Due to the fact that public health trends are improving in some regions faster than others, the current Stay-at-Home order will be amended and individual orders making it applicable to each public health region will be made except for the three above. It is proposed that the Stay-at-Home order will continue to apply to 28 public health regions until Tuesday, February 16, 2021. For Toronto, Peel and York regions, it is proposed that the Stay-at-Home order will continue to apply until Monday, February 22, 2021. Final decisions will be subject to review of the trends in public health indicators at that time.

"While we have seen some progress in our fight against COVID-19, the situation in our hospitals remains precarious and the new variants pose a considerable threat to all of us," said Minister Elliott. "As we cautiously and gradually transition out of the provincewide shutdown, we have developed an emergency brake system giving us the flexibility to contain community spread quickly in a specific region, providing an extra layer of protection."

Recognizing the risk posed by new variants to the province's pandemic response, Ontario is introducing an "emergency brake" to allow for immediate action if a public health unit region experiences rapid acceleration in COVID-19 transmission or if its health care system risks becoming overwhelmed. If this occurs, the Chief Medical Officer of Health, in consultation with

the local medical officer of health, may advise immediately moving a region into Grey-Lockdown to interrupt transmission.

"While we are seeing our numbers trend in the right direction, our situation remains precarious as the variants of concern remain a serious risk," said Dr. Williams. "This is not a re-opening or a 'return to normal' and we must continue to limit close contact to our immediate households and stay at home except for essential reasons. By continuing to follow all public health and workplace safety measures, we can continue to reduce the number of new cases and the strain on our health system."

In addition, the provincial emergency declared under s 7.0.1 of the *Emergency Management and Civil Protection Act* (EMPCA) will be allowed to terminate at the end of February 9, 2021. While the provincewide Stay-at-Home order will cease to apply in some regions as of February 10, 2021, everyone is strongly advised to continue to stay at home, avoid social gatherings, minimize travel between areas with different rules, and limit close contacts to their household. Employers in all industries should continue to make every effort to allow employees to work from home.

Enforcement of residential evictions will remain paused in the public health unit regions where the provincial Stay-at-Home order remains in effect. This will ensure people are not forced to leave their homes. In regions where the Stay-at-Home order is lifted, the regular process for residential eviction enforcement will resume.

Orders currently in force under the EMCPA have been extended to February 23, 2021 and will be extended further if necessary. O.Reg.55/21 (Compliance Orders for Retirement Homes) is currently in effect until February 19, 2021.

"While the declaration of emergency will be ending, the risks posed by COVID-19 and the new variants remain serious concerns," said Solicitor General Jones. "That's why extending the stay-at-home orders for most of the province is necessary to protect our communities, our most vulnerable populations, and stop the spread of COVID-19. We continue to urge all Ontarians to follow public health guidelines and stay home, stay safe, and save lives."

The Chief Medical Officer of Health will continue to consult with public health and other experts, review data, and provide advice to the government on the appropriate and effective measures that are needed to protect the health of Ontarians. Municipalities and local medical officers of health may have additional restrictions or targeted requirements in their region.

Quick Facts

- Provincewide Shutdown measures went into effect on December 26, 2020 to stop the rapid spread of COVID-19 across the province.
- The government declared its second provincial emergency on January 12, 2021 and issued a Stay-at-Home order to reduce mobility and address hospital capacity concerns.
- Ontario has implemented a six-point plan to deal with the new variants which includes mandatory on-arrival testing of international travellers, enhanced screening and sequencing, maintaining public health measures to keep people safe, strengthening case and contact management to track the spread of new cases, enhanced protections for vulnerable populations, and leveraging the latest data to inform public health decisions.
- In January, Ontario's provincial offences officers visited 1,147 big-box stores and other essential retail businesses to ensure businesses are following the public health guidelines and properly protecting workers and customers from COVID-19. 112 tickets were issued to businesses and individuals during three inspection campaigns.
- To support the safe return of in-person learning, Ontario has introduced new measures to continue to protect students and staff against COVID-19 in the classroom.
- Once the shutdown is lifted, visitor restrictions for long-term care homes will once again apply to those homes in the public health regions that are in the Orange-Restrict level or higher. In addition, long-term care homes must implement enhanced testing requirements.
- A full list of emergency orders under the EMPCA as well as orders under the ROA can be found on the e-Laws website and at Ontario.ca/alert.

Additional Resources

- In-Person Shopping at Retail Stores Permitted with Public Health and Safety Requirements in Place
- Find out about the latest public health measures, advice and restrictions.
- To find the right supports, visit COVID-19: Support for People, which has information about the many available and free mental health services and supports.
- Get tested if you have COVID-19 symptoms, or if you have been advised of exposure by your local public health unit or through the COVID Alert App. Visit Ontario.ca/covidtest to find the nearest testing location.
- Visit Ontario's COVID-19 vaccine web page to view the latest provincial data and information on COVID-19 vaccines.
- Visit Ontario's website to learn more about how the province continues to protect the people of Ontario from COVID-19.

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This is **Exhibit "J"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

NEWS RELEASE

Ontario Returning 27 Public Health Regions to Strengthened COVID-19 Response Framework

Province Extending Shutdown and Stay-at-Home Order in Regions at Highest Risk

February 12, 2021
Health

TORONTO — In consultation with the Chief Medical Officer of Health, the Ontario government is transitioning twenty-seven public health regions out of the shutdown and into a revised and strengthened *COVID-19 Response Framework: Keeping Ontario Safe and Open* (the "Framework"). The four remaining public health regions, Toronto Public Health, Peel Public Health, York Region Public Health and North Bay Parry Sound District, will remain in the shutdown, and the Stay-at-Home order and all existing public health and workplace safety measures will continue to apply to these four public health regions.

"The health and safety of Ontarians remains our number one priority. While we are cautiously and gradually transitioning some regions out of shutdown, with the risk of new variants this is not a reopening or a return to normal," said Christine Elliott, Deputy Premier and Minister of Health. "Until vaccines are widely available, It remains critical that all individuals and families continue to adhere to public health measures and stay home as much as possible to protect themselves, their loved ones and their communities."

Based on a general improvement in trends of key indicators, including lower transmission of COVID-19, improving hospital capacity, and available public health capacity to conduct rapid case and contact management, the following public health regions will be moving back to the Framework on Tuesday, February 16, 2021 at 12:01 a.m. and will no longer be subject to the Stay-at-Home order:

Grey-Lockdown:

- Niagara Region Public Health

Red-Control:

- Chatham-Kent Public Health;
- City of Hamilton Public Health Services;
- Durham Region Health Department;
- Halton Region Public Health;
- Middlesex-London Health Unit;
- Region of Waterloo Public Health and Emergency Services;
- Simcoe-Muskoka District Health Unit;
- Southwestern Public Health;
- Thunder Bay District Health Unit;
- Wellington-Dufferin Guelph Public Health; and
- Windsor-Essex County Health Unit.

Orange-Restrict:

- Brant County Health Unit;

- Eastern Ontario Health Unit;
- Haldimand-Norfolk Health Unit;
- Haliburton, Kawartha, Pine Ridge District Health Unit;
- Huron Perth Public Health;
- Lambton Public Health;
- Ottawa Public Health;
- Porcupine Health Unit; and
- Public Health Sudbury and Districts.

Yellow-Protect:

- Algoma Public Health;
- Grey Bruce Health Unit;
- Northwestern Health Unit; and
- Peterborough Public Health.

Green-Prevent:

- Leeds, Grenville and Lanark District Health Unit; and
- Timiskaming Health Unit.

For North Bay Parry Sound District, Peel Public Health, Toronto Public Health and York Region Public Health, it is proposed that the shutdown measures and the Stay-at-Home order will continue to apply until at least Monday, February 22, 2021. Please visit Ontario.ca/covidresponse for the full list of public health region classifications.

After returning to the Framework, public health regions will stay in their level for at least two weeks at which time, the government will assess the impact of public health and workplace safety measures to determine if the region should stay where they are or be moved to a different level. Public health regions will move up through the levels, if necessary, based on the set indicators and thresholds outlined in the Framework.

Visitor restrictions for long-term care homes will once again apply to those homes in the public health regions that are in the Orange-Restrict level or higher. In addition, long-term care homes must implement enhanced testing requirements.

Recognizing the risk posed by new variants to the province's pandemic response, Ontario is introducing an "emergency brake" to allow the Chief Medical Officer of Health, in consultation with the local medical officer of health, to immediately advise moving a region into Grey-Lockdown to interrupt transmission. Local medical officers of health also have the ability to issue Section 22 orders under the *Health Protection and Promotion Act*, to target specific transmission risks in the community.

"While the trends in public health indicators are heading in the right direction, we still have work to do," said Dr. David Williams, Chief Medical Officer of Health. "Everyone is strongly advised to continue staying at home, avoid social gatherings, only travel between regions for essential purposes, and limit close contacts to your household or those you live with."

The Chief Medical Officer of Health will continue to consult with public health and other experts, review data, and provide advice to the government on the appropriate and effective measures that are needed to protect the health of Ontarians.

Quick Facts

- Find out what level and which regional public measures are in place for your area.
- On February 10, 2021, Hastings Prince Edward Public Health, Kingston, Frontenac and Lennox & Addington Public Health, and Renfrew County and District Health Unit moved to the Framework at the Green-Prevent level.

- To help stop the spread of COVID-19 and safeguard health system capacity, Ontarians are strongly urged to continue staying at home and limit trips outside their household and between other regions for essential reasons only, not to gather with individuals outside of their household, and to wear a face covering when within two metres distance of another individual who is not part of their household (both indoor and outdoor) or when required, with limited exceptions.
- Ontario has implemented a six-point plan to deal with the new variants of concern which includes mandatory on-arrival testing of international travelers, enhanced screening and sequencing, maintaining public health measures to keep people safe, strengthening case and contact management to track the spread of new cases, enhanced protections for vulnerable populations, and leveraging the latest data to inform public health decisions.
- To support the province's economic recovery, the government has updated the Framework to allow for a safer approach to retail. Limited in-person shopping in Grey-Lockdown zones will be permitted with public health and safety measures, such as limiting capacity to 25 per cent in most retail settings.
- Digital tools have been an important part of the provincial response to COVID-19. To date, almost 6 million self-assessments have been completed using Ontario's health screening tool to help Ontarians navigate their symptoms and decide on next steps. Now, revised and updated screening tools for workers/employees and customer/visitors will help keep Ontarians safe and healthy by pre-screening for symptoms before leaving for work or to visit a business as the province re-opens. The tools help workplaces and businesses meet screening requirements.
- To support the safe return of in-person learning, Ontario has introduced new measures to continue to protect students and staff against COVID-19 in the classroom.

Additional Resources

- Ontario Extending Stay-at-Home Order across Most of the Province to Save Lives.
- Find out about the latest public health measures, advice and restrictions.
- To find the right supports, visit COVID-19: Support for People, which has information about the many available and free mental health services and supports.
- Get tested if you have COVID-19 symptoms, or if you have been advised of exposure by your local public health unit or through the COVID Alert App. Visit Ontario.ca/covidtest to find the nearest testing location.
- Visit Ontario's COVID-19 vaccine web page to view the latest provincial data and information on COVID-19 vaccines.
- Visit Ontario's COVID-19 information website to learn more about how the province continues to protect the people of Ontario from the virus.

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NEWS RELEASE

Stay-at-Home Order Extended in Toronto and Peel Public Health Regions Along with North Bay-Parry Sound

York Region to Return to Strengthened COVID-19 Response Framework

February 19, 2021
Health

TORONTO — In consultation with the Chief Medical Officer of Health and the local medical officers of health, the Ontario government is maintaining the shutdown, the Stay-at-Home order and all existing public health and workplace safety measures for an additional two weeks in the Toronto and Peel Public Health Regions, along with the North Bay-Parry Sound District. The York Public Health Region will transition out of the shutdown and into the revised and strengthened *COVID-19 Response Framework: Keeping Ontario Safe and Open*.

"Our government's number one priority is the safety of all individuals and families, and that's why we are taking a gradual, cautious approach to returning regions to the Framework," said Christine Elliott, Deputy Premier and Minister of Health. "These are difficult but necessary decisions, in order to protect against COVID-19 variants and maintain the progress we have all made together. Until vaccines are widely available, we continue to urge all Ontarians to follow public health advice and measures, and stay home, stay safe, and save lives."

In the Toronto and Peel Public Health Regions, and the North Bay-Parry Sound District, the shutdown measures and the Stay-at-Home order will continue to apply until at least Monday, March 8, 2021, based on key public health indicators and following consultation with the local medical officers of health. While the Peel and Toronto regions have seen a reduction in COVID-19 transmission from the period of February 8 to 17, 2021, rates still remain too high in the regions, with case rates of 83.4 cases per 100,000 people for Peel and 67.9 cases per 100,000 people for Toronto, both well above the provincial average. During this same period of time, North Bay Parry Sound District has also seen its case rate increase by 11.5 per cent to 14.6 cases per 100,000 people. Variants of concern also remain a serious risk to community transmission and health system capacity.

Based on a general improvement in trends of key indicators, York Region Public Health will be moving back to the Framework at the Red-Control level and will no longer be subject to the Stay-at-Home order. In addition, Lambton Public Health will be moving from the Orange-Restrict level to the Red-Control level as a result worsening public health trends in the region over the past week. These changes will come into effect on Monday, February 22, 2021 at 12:01 a.m.

After returning to the Framework, public health regions are required to stay in their level for at least two weeks. The government will then assess the impact of public health and workplace safety measures to determine if the region should stay where it is or be moved to a different level. Public health regions may be moved to a higher level within the two-week window, if necessary, based on the set indicators and thresholds outlined in the Framework. In addition, Ontario has introduced an "emergency brake" to allow the Chief Medical Officer of Health, in consultation with the local medical officer of health, to immediately advise moving a region into Grey-Lockdown to interrupt transmission.

"While the health indicators have improved enough to allow us to return an additional region to the Framework, we are not yet at the point where we can safely transition back the remainder of the province," said Dr. David Williams, Chief Medical Officer of Health. "Everyone is strongly advised to continue staying at home, avoid social gatherings, only travel between regions for essential purposes, and limit close contacts to your household or those you live with regardless of which level of the Framework you are in."

The Chief Medical Officer of Health will continue to consult with public health and other experts, review data, and provide advice to the government on the appropriate and effective measures that are needed to protect the health of Ontarians.

Quick Facts

- Find out what level and which regional public measures are in place for your area.

- On February 8th the government announced an extension of the shutdown in the majority of public health regions in Ontario and a gradual transition of each region to a revised and strengthened COVID-19 Response Framework when it is safe to do so.
- In addition to the Stay-at-Home orders that apply to the North Bay-Parry Sound District, Toronto and Peel public health regions, the following orders currently in force under the Emergency Management and Civil Protection Act (EMCPA) will be extended to March 8, 2021 and further if necessary: O.Reg 55/21 (Compliance Orders for Retirement Homes), O.Reg 8/21 (Enforcement of COVID-19 Measures), O.Reg. 11/21 (Stay-at-Home Order), O.Reg. 13/21 (Residential Evictions).
- Enforcement of residential evictions will remain paused in the public health regions where the provincial Stay-at-Home order remains in effect.
- Local medical officers of health continue to have the ability to issue Section 22 orders under the Health Protection and Promotion Act, to target specific transmission risks in the community.
- Ontario has implemented a six-point plan to prevent and stop the spread of COVID-19 variants.
- To support the safe return of in-person learning, Ontario has introduced new measures to continue to protect students and staff against COVID-19 in the classroom.

Additional Resources

- Please visit Ontario.ca/covidresponse for the full list of public health region classifications.
- To find the right supports, visit COVID-19: Support for People, which has information about the many available and free mental health services and supports.
- Get tested if you have COVID-19 symptoms, or if you have been advised of exposure by your local public health unit or through the COVID Alert App. Visit Ontario.ca/covidtest to find the nearest testing location.
- Visit Ontario's COVID-19 vaccine web page to view the latest provincial data and information on COVID-19 vaccines.

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NEWS RELEASE

Ontario Activates Emergency Brake in Thunder Bay District Health Unit and Simcoe-Muskoka District Health Unit

Nine Public Health Regions Moving to New Levels in the COVID-19 Response Framework

February 26, 2021
Health

TORONTO — The Ontario government, in consultation with the Chief Medical Officer of Health, is moving nine public health regions to new levels in the *Keeping Ontario Safe and Open Framework* (the "Framework"). This includes activating an "emergency brake" in Thunder Bay District Health Unit and Simcoe-Muskoka District Health Unit to move the regions to Grey-Lockdown to immediately interrupt transmission and contain community spread. Decisions were made in consultation with the local medical officers of health and are based on the trends in public health indicators and local context and conditions.

"While we continue to see the number of cases and other public health indicators lowering in many regions across the province, the recent modelling shows us that we must be nimble and put in place additional measures to protect Ontarians and stop the spread of COVID-19," said Christine Elliott, Deputy Premier and Minister of Health. "With COVID-19 variants continuing to spread in our communities, it is critically important that everyone continues strictly adhering to all public health and workplace safety measures to help contain the virus and maintain the progress we have made to date."

Based on the latest data, the following public health regions will move from their current level in the Framework to the following levels effective Monday, March 1, 2021 at 12:01 a.m.:

Grey-Lockdown

- Simcoe-Muskoka District Health Unit; and
- Thunder Bay District Health Unit.

Red-Control

- Niagara Region Public Health.

Orange-Restrict

- Chatham-Kent Public Health;
- Middlesex-London Health Unit; and
- Southwestern Public Health.

Yellow-Protect

- Haldimand-Norfolk Health Unit; and
- Huron Perth Public Health.

Green-Prevent

- Grey Bruce Health Unit.

Based on the latest assessment of data the "emergency brake" is being used to place Thunder Bay District Health Unit and Simcoe-Muskoka District Health Unit into Grey-Lockdown, helping to stop the spread of the virus and protect public health and health system capacity in the regions. This is due to a rapid worsening in key public health indicators, as well as a high presence of variants in the Simcoe-Muskoka District Health Unit that continue to increase - the highest in the province. As of February 23, 2021, there has been a total of 170 confirmed cases of a variant of concern in this region.

In Peel Public Health, Toronto Public Health, and North Bay Parry Sound District, the Shutdown measures and the Stay-at-Home order will continue to apply until at least Monday, March 8, 2021, with final decisions to be based on key public health indicators and consultation with the local medical officers of health. All other public health regions will remain at their current level. Please visit Ontario.ca/covidresponse for the full list of public health region classifications.

Based on the latest modelling data, the efforts of Ontarians in following public health measures and advice are working to decrease the number of new cases, deaths and hospitalizations across the province. However, with variants of concern continuing to spread, the number of patients requiring hospitalization and intensive care may rise once again if public health measures are not relaxed carefully and gradually. The actions of everyone over the coming weeks will be critical to maintaining the progress communities have made across the province to date.

"Quickly implementing stronger measures to interrupt transmission of COVID-19 is a key component of the government's plan to safely and gradually return public health regions to the Framework," said Dr. David Williams, Chief Medical Officer of Health. "Due to data and local context and conditions in the Simcoe-Muskoka and Thunder Bay Districts, it was necessary to tighten public health measures in these regions to ensure the health and safety of the region at large and stop the spread of the virus."

The Chief Medical Officer of Health will continue to consult with public health and other experts, review data, and provide advice to the government on the appropriate and effective measures that are needed to protect the health of Ontarians.

Quick Facts

- Find out what level and which public health and workplace safety measures are in place for your area.
- To help stop the spread of COVID-19 and safeguard health system capacity, everyone is strongly urged to continue staying at home and limit trips outside their household and between other regions for essential reasons only, not to gather with individuals outside of their household, and to wear a face covering when within two metres distance of another individual who is not part of their household (both indoor and outdoor) or when required, with limited exceptions.
- Recognizing the risk posed by new variants to the province's pandemic response, Ontario has introduced an "emergency brake" to allow the Chief Medical Officer of Health, in consultation with the local medical officer of health, to immediately advise moving a region into Grey-Lockdown to interrupt transmission.
- Local medical officers of health continue to have the ability to issue Section 22 orders under the Health Protection and Promotion Act, and municipalities may enact by-laws, to target specific transmission risks in the community.
- Ontario has implemented a six-point plan to prevent and stop the spread of COVID-19 variants.

Additional Resources

- Stay-at-Home Order Extended in Toronto and Peel Public Health Regions Along with North Bay-Parry Sound.
- To find the right supports, visit COVID-19: Support for People, which has information about the many available and free mental health services and supports.
- Get tested if you have COVID-19 symptoms, or if you have been advised of exposure by your local public health unit or through the COVID Alert App. Visit Ontario.ca/covidtest to find the nearest testing location.
- Visit Ontario's COVID-19 vaccine web page to view the latest provincial data and information on COVID-19 vaccines.
- Visit Ontario's COVID-19 information website to learn more about how the province continues to protect the people of Ontario from the virus.

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Media Contacts

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Ryan Cookson

A Commissioner for the Taking of Affidavits

NEWS RELEASE

Toronto, Peel and North Bay-Parry Sound Public Health Regions Returning to Strengthened COVID-19 Response Framework

Seven Other Public Health Regions Moving to New Levels in the Framework

March 05, 2021
Health

TORONTO — The Ontario Government, in consultation with the Chief Medical Officer of Health, is transitioning Toronto, Peel and North Bay Parry Sound District public health regions out of the shutdown and into the revised and strengthened *COVID-19 Response Framework: Keeping Ontario Safe and Open* (the "Framework"), with the Stay-at-Home order no longer in effect. In addition, seven other public health regions are being moved to new levels in the Framework. All decisions were made in consultation with the local medical officers of health and are based on the latest trends in public health indicators and local context and conditions.

"Our government is taking a safe and cautious approach to returning to the Framework and due to our progress, all regions of the province will soon be out of the provincewide shutdown," said Christine Elliott, Deputy Premier and Minister of Health. "Despite this positive step forward, a return to the Framework is not a return to normal. As we continue vaccinating more Ontarians, it remains critical for everyone to continue to follow public health measures and stay home as much as possible to protect themselves, their loved ones and their communities."

Based on a general improvement in trends of key indicators, North Bay Parry Sound District will be returning to the Framework at the Red-Control level. Toronto Public Health and Peel Public Health are also making progress, but as their case rates still remain high, they will return to the Framework at the Grey-Lockdown level.

In addition, based on the latest data, the following seven public health regions will also be moving to the following levels in the Framework:

Red-Control

- Peterborough Public Health;
- Public Health Sudbury and Districts; and
- Simcoe-Muskoka District Health Unit.

Orange-Restrict

- Haldimand-Norfolk Health Unit; and
- Timiskaming Health Unit.

Yellow-Protect

- Haliburton, Kawartha, Pine Ridge District Health Unit; and
- Renfrew County and District Health Unit.

All changes will be effective Monday, March 8, 2021 at 12:01 a.m. Please visit Ontario.ca/covidresponse for the full list of public health region classifications.

Based on the latest modelling data, the efforts of Ontarians in following public health measures and advice are working to decrease the number of new cases, deaths and hospitalizations across the province. However, with COVID-19 variants of concern continuing to spread, the actions of everyone over the coming weeks will be critical to maintaining the progress communities have made across the province to date.

"While all regions have returned to the Framework, everyone must remain vigilant to help prevent any further increases in transmission," said Dr. David Williams, Chief Medical Officer of Health. "The best defense against the virus and all of its variants of concern remains continuing to stay at home, avoiding social gatherings, only travelling outside of your community for essential purposes, and limiting close contacts to your household or those you live with."

The Chief Medical Officer of Health will continue to consult with public health and other experts, review data, and provide advice to the government on the appropriate and effective measures that are needed to protect the health of Ontarians.

Quick Facts

- Find out what level and which public health and workplace safety measures are in place for your area.
- From the period of February 23 to March 2, 2021, case rates in North Bay Parry Sound District have decreased by 84.6 per cent to 3.1 cases per 100,000 people and the number of hospitalizations has shrunk from 1 to 0.
- In Toronto Public Health the case rates have decreased by 15.7 per cent to 66.4 cases per 100,000 people and hospitalizations have seen an 11.2 per cent decrease. During this same period of time, Peel Public Health has seen its case rates increase by 6.6 per cent to 91.4 cases per 100,000 people. Peel Region has also seen the number of patients with COVID-19 in intensive care decrease from 26 to 19.
- To help stop the spread of COVID-19 and safeguard health system capacity, everyone is strongly urged to continue staying at home and limit trips outside their household and to other regions for essential reasons only, and not to gather with individuals outside of their household. In addition, people are required to wear a face covering when within two metres distance of another individual who is not part of their household (both indoor and outdoor), with limited exceptions.
- Recognizing the risk posed by new variants to the province's pandemic response, Ontario has introduced an "emergency brake" to allow the Chief Medical Officer of Health, in consultation with the local medical officer of health, to immediately advise moving a region into Grey-Lockdown to interrupt transmission.
- Local medical officers of health continue to have the ability to issue Section 22 orders under the Health Protection and Promotion Act, and municipalities may enact by-laws, to target specific transmission risks in the community.
- Emergency orders O.Reg 8/21 (Enforcement of COVID-19 Measures) and O.Reg 55/21 (Compliance Orders for Retirement Homes) currently in force under the Emergency Management and Civil Protection Act (EMCPA) will be extended to March 22, 2021. Emergency orders O.Reg 11/21 (Stay-at-Home Order), O.Reg.89/21 (Stay-at-Home Order Toronto Public Health), O.Reg. 76/21 (Stay-at-Home Order North Bay Parry Sound District), O.Reg. 73/21 (Stay-at-Home Order Peel Public Health) and O.Reg 13/21 (Residential Evictions) will expire and no longer be in effect as of March 8, 2021.

Additional Resources

- Ontario Activates Emergency Brake in Thunder Bay District Health Unit and Simcoe-Muskoka District Health Unit.
- To find the right supports, visit COVID-19: Support for People, which has information about the many available and free mental health services and supports.
- Get tested if you have COVID-19 symptoms, or if you have been advised of exposure by your local public health unit or through the COVID Alert App. Visit Ontario.ca/covidtest to find the nearest testing location.
- Visit Ontario's COVID-19 vaccine web page to view the latest provincial data and information on COVID-19 vaccines.
- Visit Ontario's COVID-19 information website to learn more about how the province continues to protect the people of Ontario from the virus.

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NEWS RELEASE

Ontario Activates Emergency Brake in Sudbury Public Health Region

Immediate action required to interrupt transmission, contain community spread and save lives

March 11, 2021
Health

TORONTO — On the advice of the Chief Medical Officer of Health, the Ontario Government is activating an "emergency brake" in the Public Health Sudbury and Districts region, and moving it to the Grey-Lockdown level in the *Keeping Ontario Safe and Open Framework*. The decision was made due to the concerning trends in public health indicators and in consultation with the local medical officer of health.

"Implementing an emergency brake to immediately interrupt transmission of COVID-19 is a key component of our government's plan to safely and gradually return public health regions to the Framework," said Christine Elliott, Deputy Premier and Minister of Health. "We have seen a rapid rise in the case rate in the Sudbury area, and swift action is needed to protect individuals, families and businesses and save lives."

Based on the latest assessment of data, the "emergency brake" is being used to stop the spread, guard against variants and protect public health and health system capacity in the region. From March 3 to 9, 2021, the region's case rate increased by 54.1 per cent to 75.9 cases per 100,000 people.

The public health region will move to Grey-Lockdown effective Friday, March 12, 2021 at 12:01 a.m.

"As a result of the rapid deterioration of trends in key indicators, the emergency brake is being applied to move Public Health Sudbury and Districts to Grey-Lockdown to help reduce further spread of the virus in the region," said Dr. David Williams, Chief Medical Officer of Health. "We must remain vigilant in adhering to all public health and workplace safety measures to combat the threat posed by variants of concern."

The Chief Medical Officer of Health will continue to consult with public health and other experts, review data, and provide advice to the government on the appropriate and effective measures that are needed to protect the health of Ontarians.

Quick Facts

- Find out what level and which public health and workplace safety measures are in place for your area.
- To help stop the spread of COVID-19 and safeguard health system capacity, everyone is strongly urged to continue staying at home and limit trips outside their household and to other regions for essential purposes only, and not to gather with individuals outside of their household. In addition, people are required to wear a face covering when within two metres distance of another individual who is not part of their household (both indoor and outdoor), with limited exceptions.
- Local medical officers of health continue to have the ability to issue Section 22 orders under the Health Protection and Promotion Act, and municipalities may enact by-laws, to target specific transmission risks in the community.

Additional Resources

- To find the right supports, visit COVID-19: Support for People, which has information about the many available and free mental health services and supports.
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Update on COVID-19 Projections

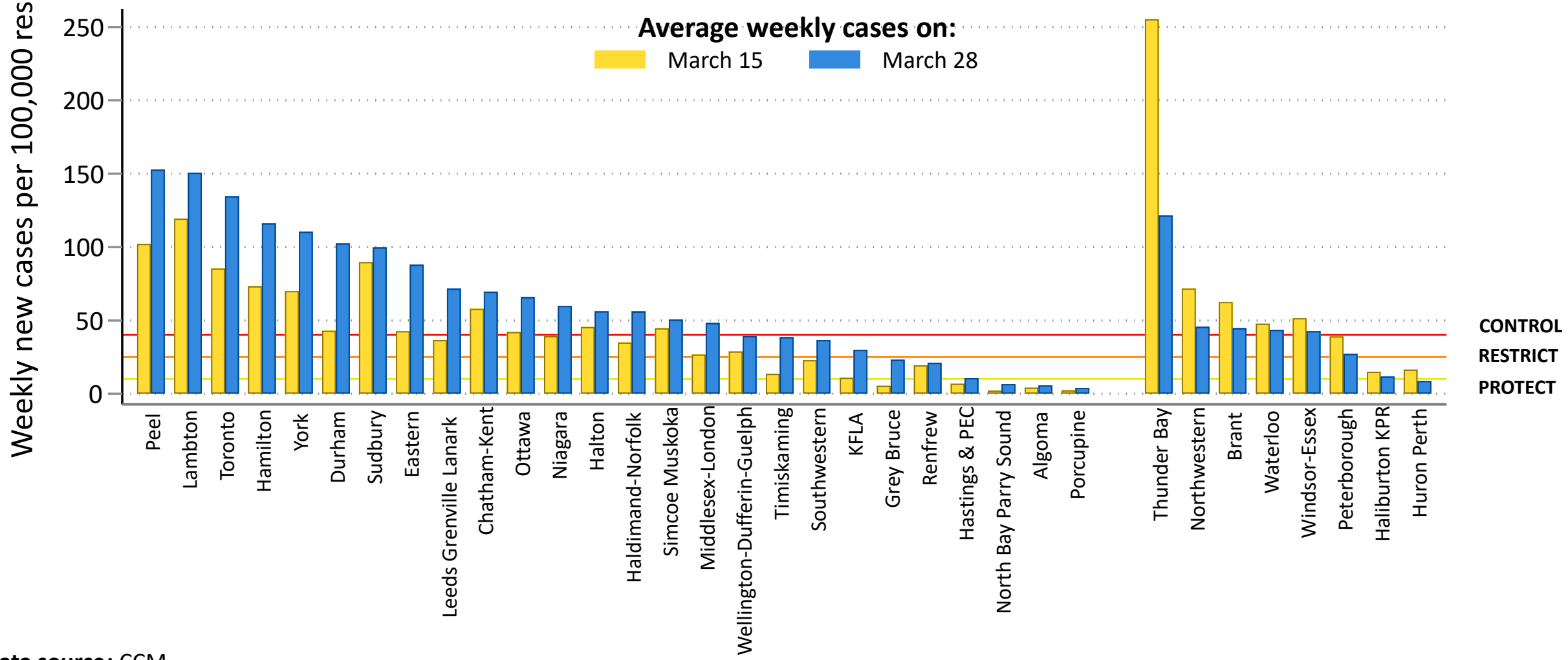
Science Advisory and Modelling Consensus Tables

April 1, 2021

Key Findings

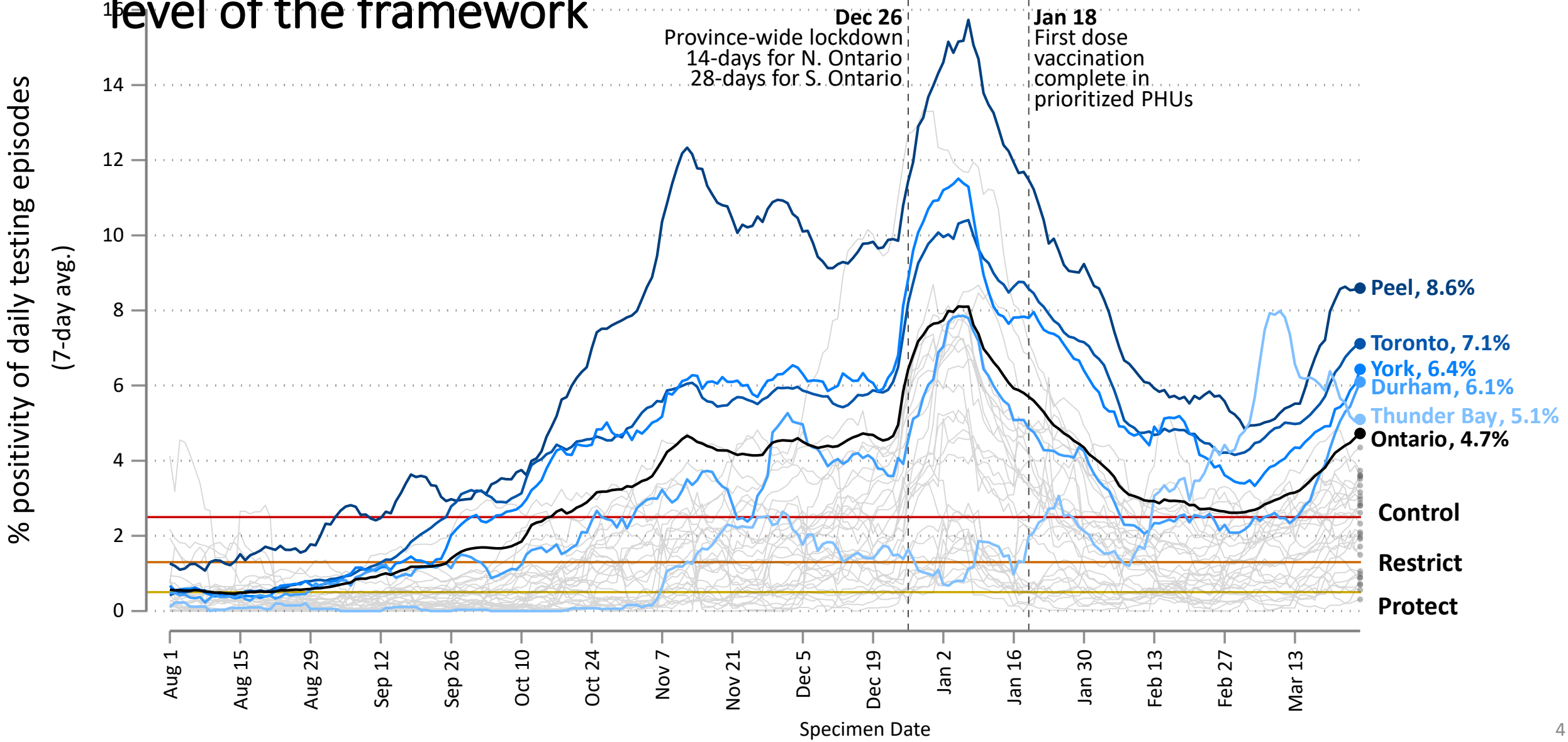
- The **third wave** is here and being **driven by variants of concern**.
- **Younger Ontarians are ending up in hospital.** Risk of ICU admission is **2 x higher** and risk of death is **1.5 x higher** for the B.1.1.7 variant.
- COVID-19 **threatens health system ability to deal with regular ICU admissions** and the ability to care for all patients.
- Vaccination is **not reaching the highest risk communities**, delaying its impact as an effective strategy.
- School disruptions have a significant and highly inequitable **impact** on students, parents and society. Further disruptions should be minimized.
- Stay-at-home orders will control the surge, protect access to care, and increase the chance of the summer Ontarians want.

Cases have increased and are above the second highest level of the framework in most Public Health Units



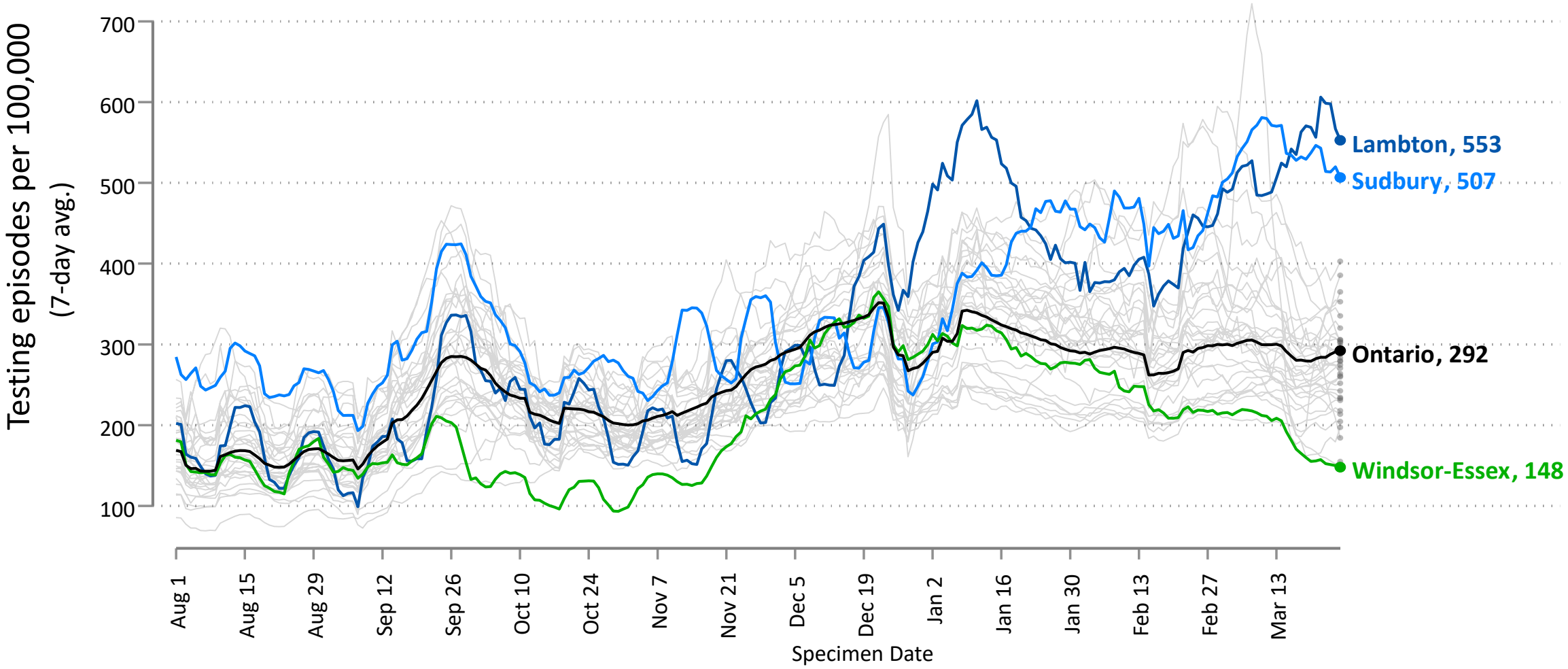
Data source: CCM
Data note: Data for the most recent day have been censored to account for reporting delays

Testing % positivity has increased and is above the second highest level of the framework



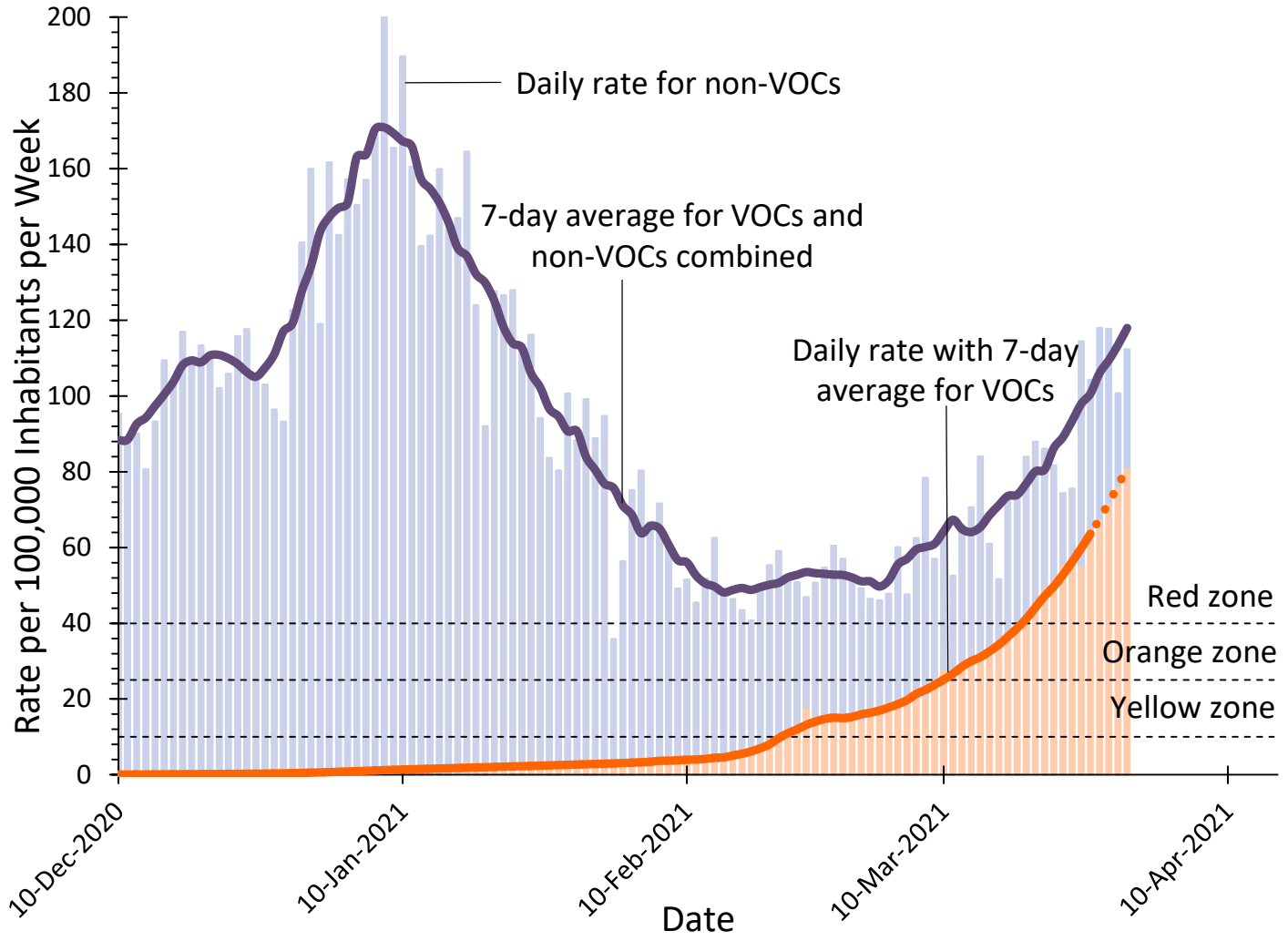
Data source: Ontario Laboratory Information System (OLIS), data up to March 26

Testing rates are flat so case growth is not a result of more testing



Data source: Ontario Laboratory Information System (OLIS), data up to March 26

Cases are increasing. Most new cases are variants of concern.



Variants of concern have more severe consequences and are more fatal

Compared to people infected with the earlier variants, more people with COVID-19 are hospitalized, admitted to ICU, and die if they are infected with the variants of concern.

Short-term case projections depend entirely on system-level public health measures and vaccination

Figure shows example, representative of predictions across 4 models, 3-5 scenarios each.

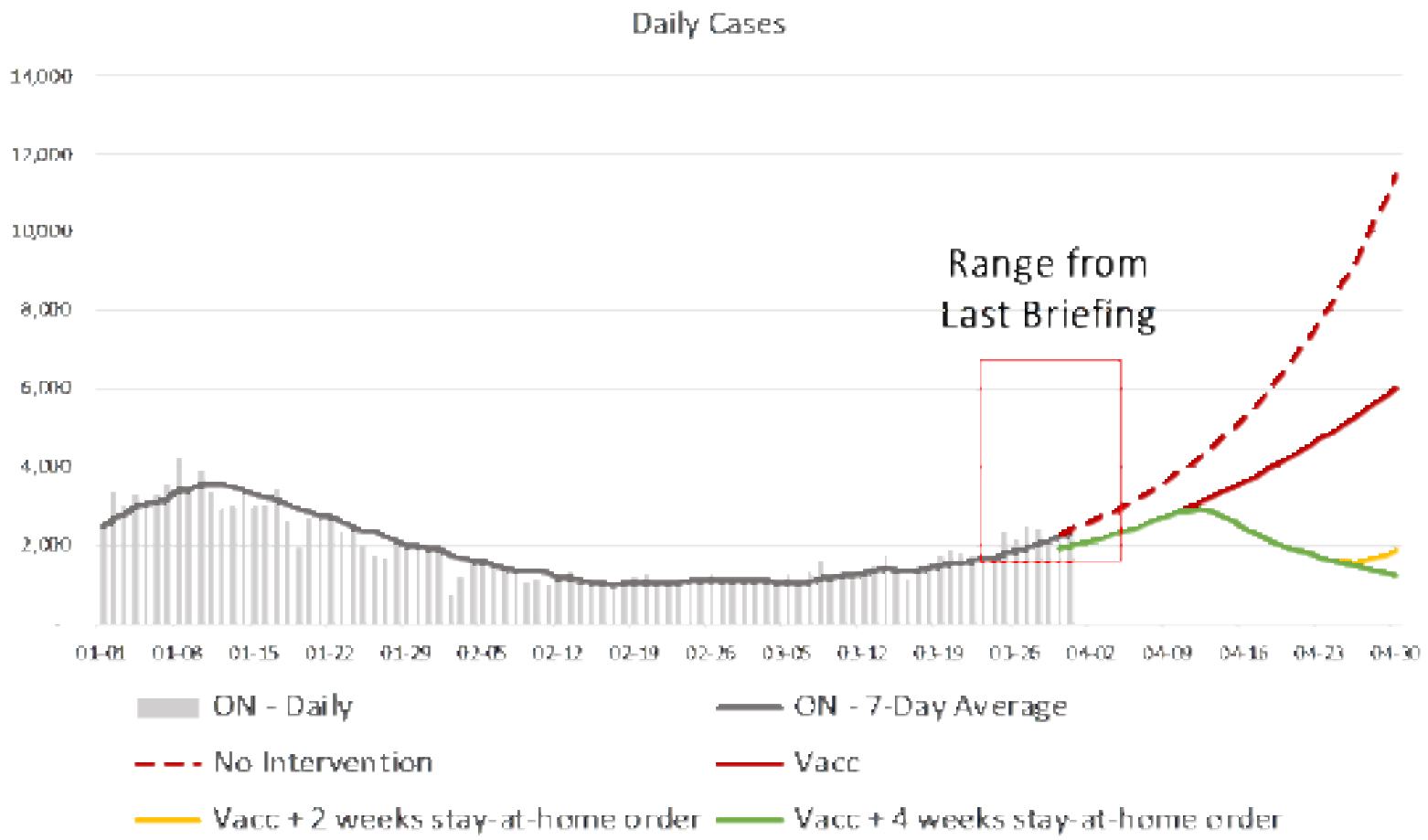
Scenarios:

Stay-at-home order assumptions:

- No stay-at-home
- 2 weeks starting Apr 5
- 4 weeks starting Apr 5

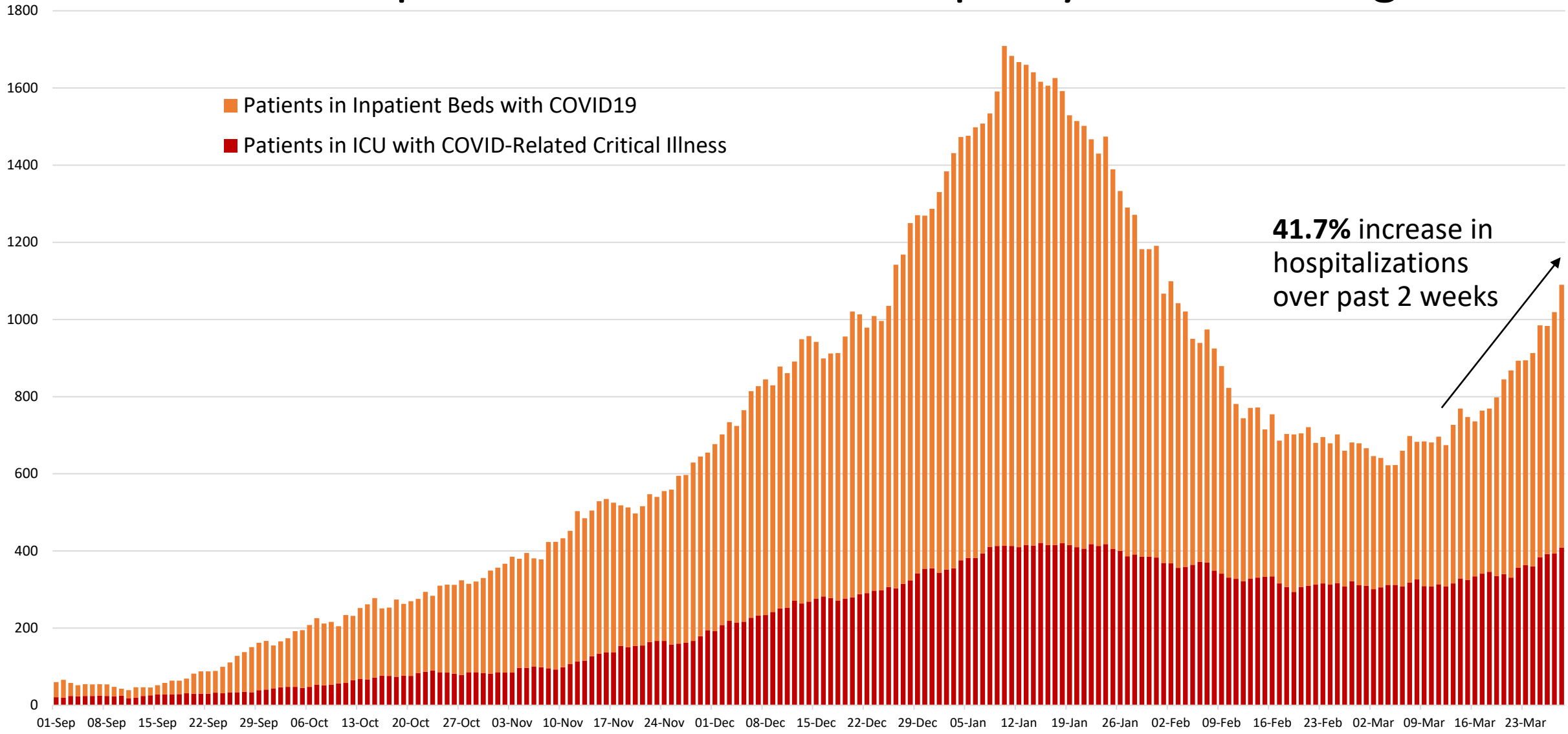
Vaccine assumptions:

- 70% effective in preventing infection
- Administered at constant rate
- Administered randomly to population



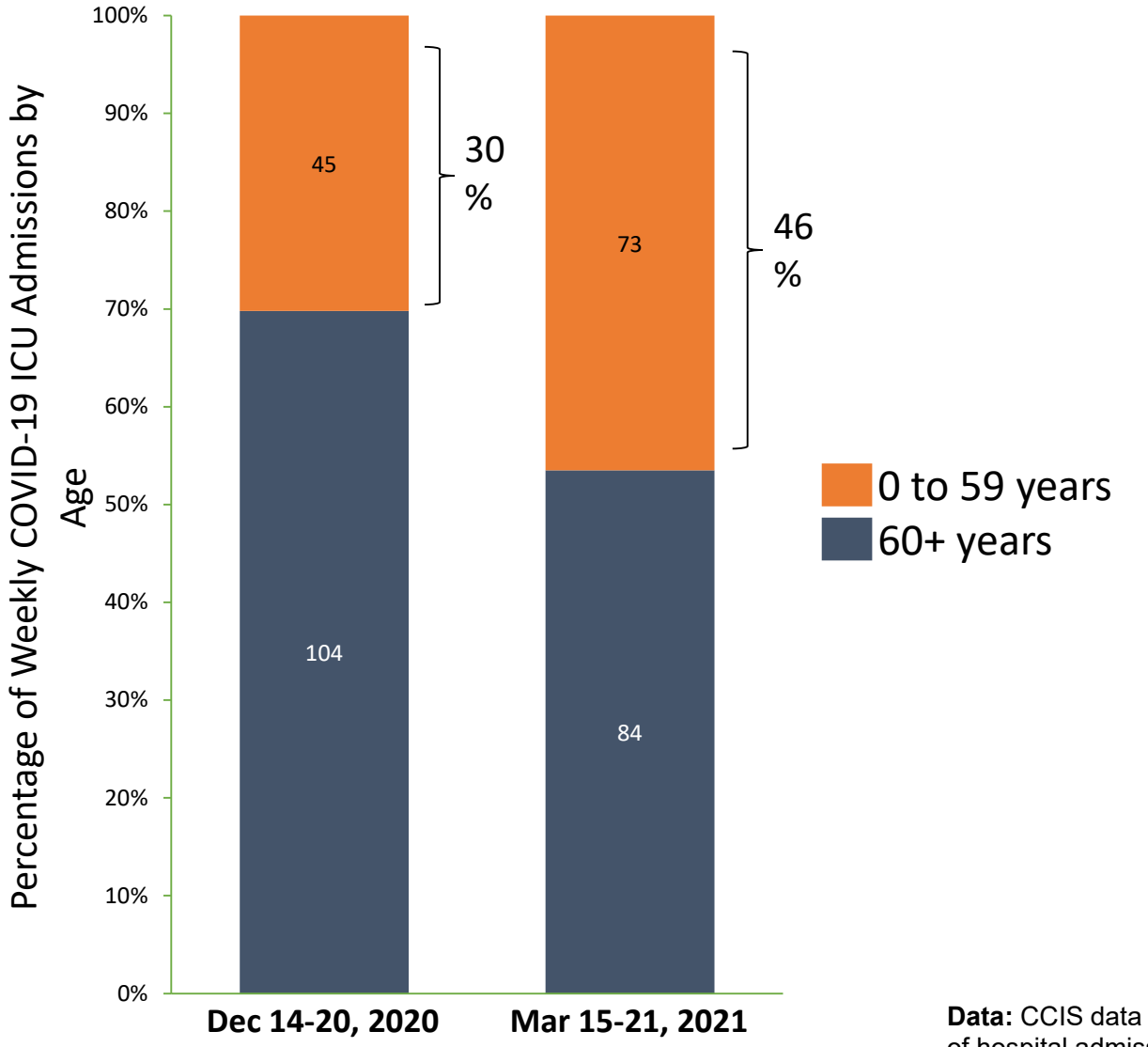
Predictions informed by modeling from COVID-19 ModCollab, Fields Institute, McMasterU, PHO, YorkU
Data (Observed Cases): covid-19.ontario.ca

COVID-19 Hospitalizations and ICU occupancy are increasing



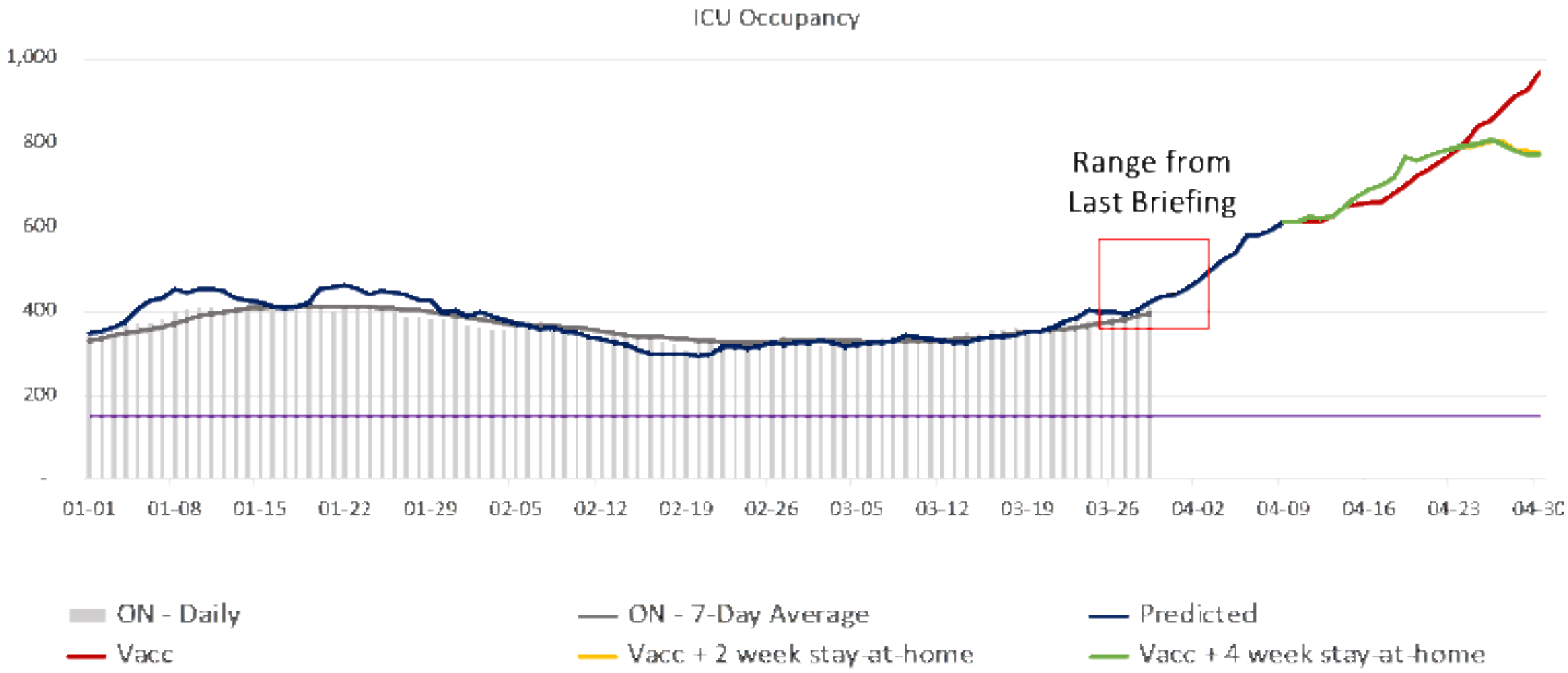
Data Sources: MOH COVID Census and Critical Care Information System

COVID-19 patients admitted to ICU continue to get younger



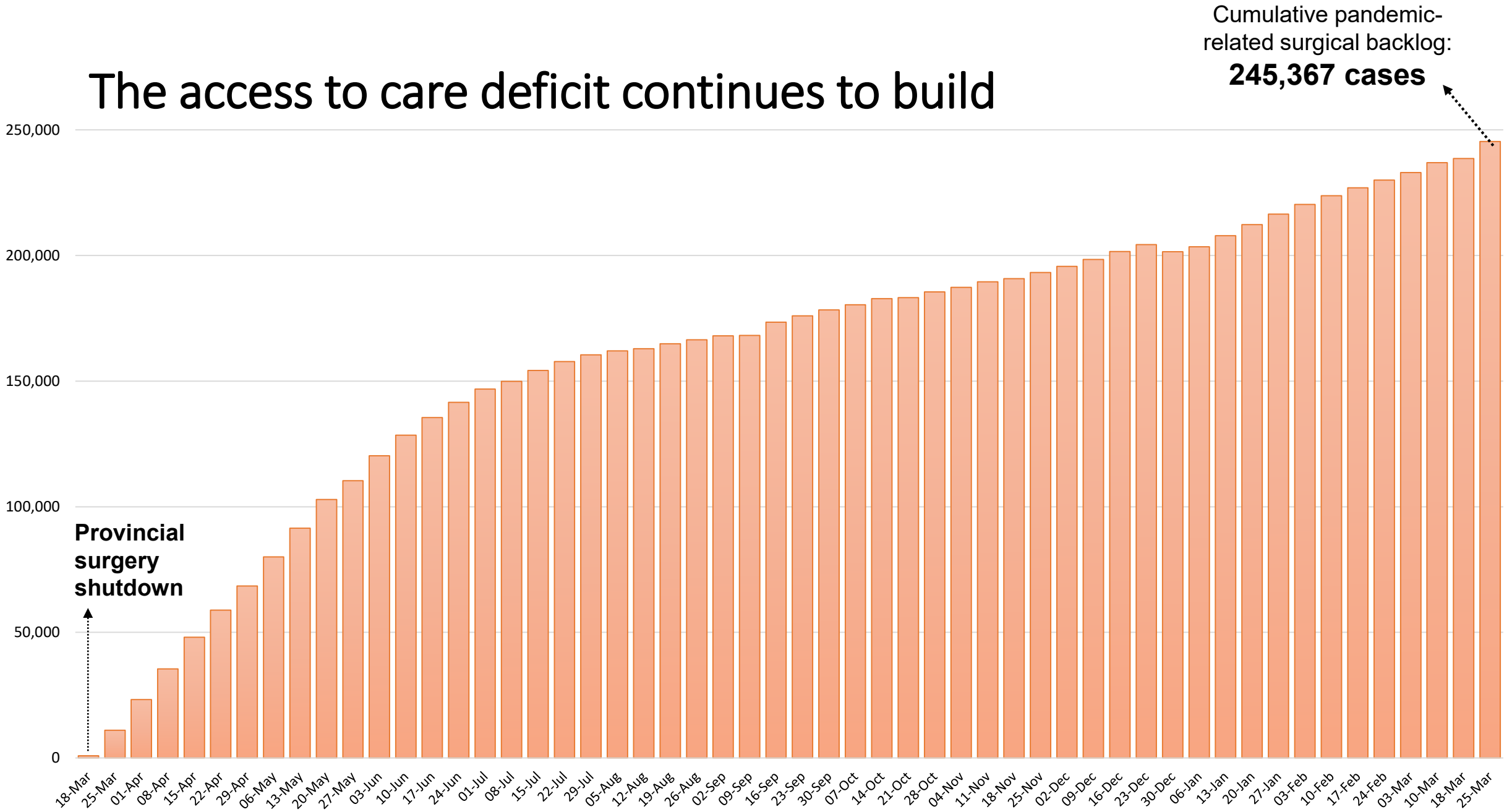
Data: CCIS data up to March 28. Based on date of hospital admission

As with cases, ICU projections depend entirely on system-level public health measures



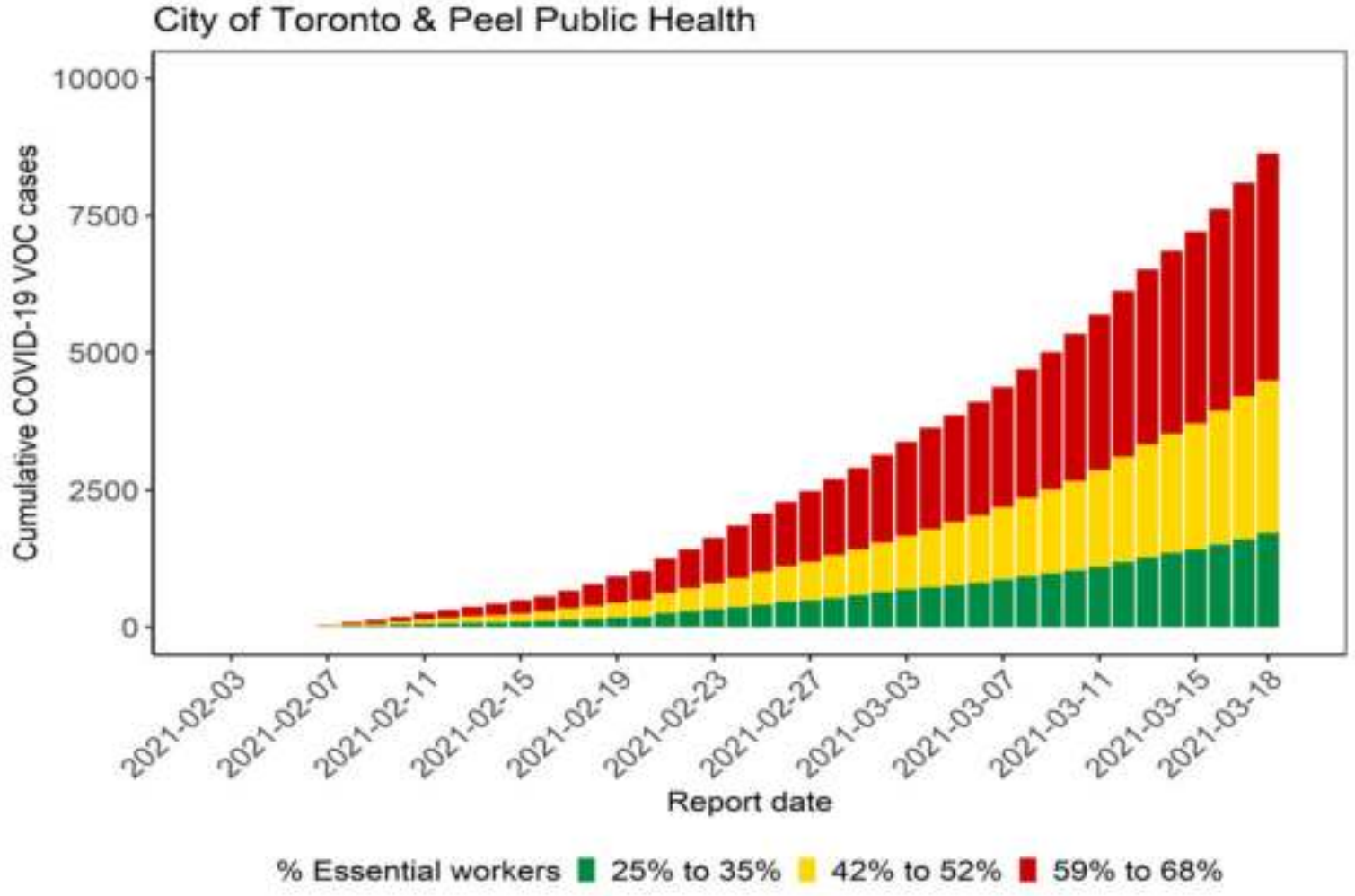
Predictions: COVID-19 ModCollab.
Data (Observed ICU Occupancy): CCSO

The access to care deficit continues to build



Data Source: Wait Times Information System. Backlog estimated based on comparison of 2020/21 with 2019/20 surgical volumes

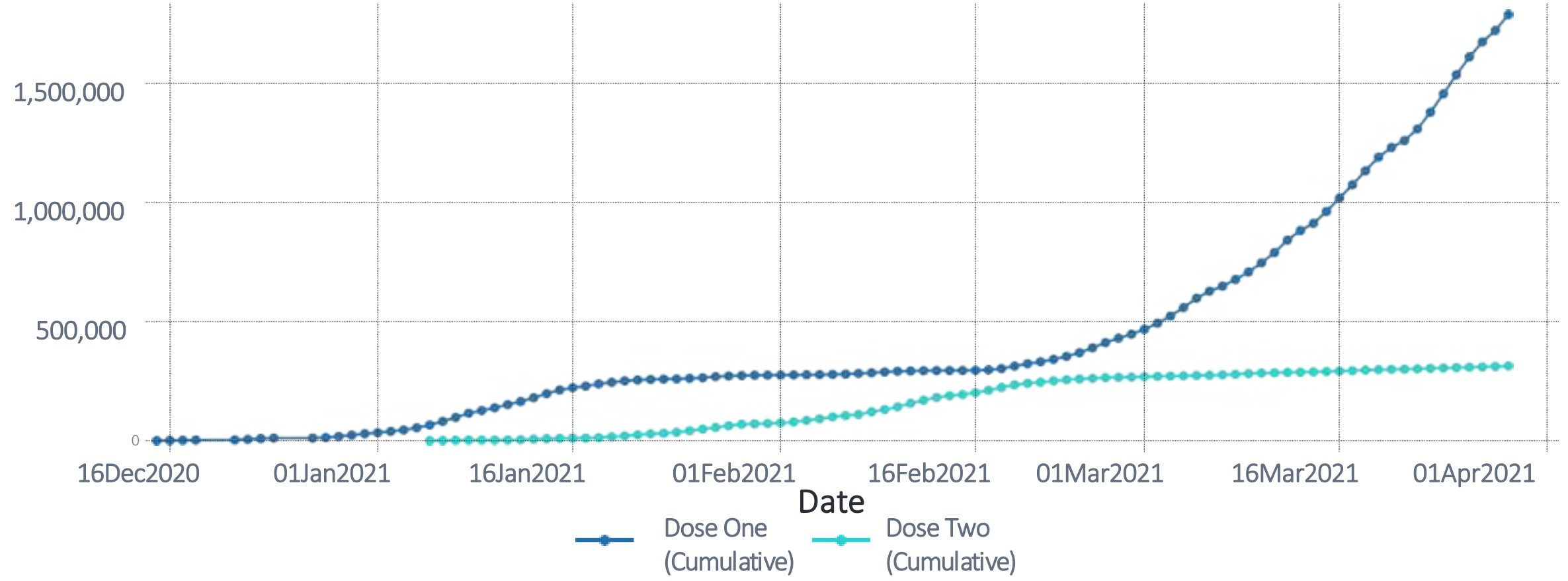
Essential workers are keeping things moving and bearing the brunt of the pandemic. Vaccination and control of workplace outbreaks will be critical.



Source: Chagla Z, Ma H, Sander B, Baral S, Mishra S. (2021). Characterizing the disproportionate burden of SARS-CoV-2 variants of concern among essential workers in the Greater Toronto Area, Canada. https://www.medrxiv.org/content/10.1101/2021.03.22.21254127v1.full.pdf

First dose vaccine coverage expanding but remains incomplete

80 years and older - 17% incomplete; 75-79 years – 40% incomplete; 70-74 years – 72% incomplete



Dose 1 Administered was determined based on the first Time Given for each client.
Dose 2 Administered was determined based on the last Time Given for each client where there is more than 1 dose administered

Vaccination is not reaching the highest risk populations

Figure excludes long-term care vaccination

	Neighbourhood Risk‡ **1** = high incidence of COVID-19 infections → **10** = low incidence of COVID-19 infections										
Age group	1	2	3	4	5	6	7	8	9	10	**Overall**
80+	50%	55%	59%	66%	66%	66%	65%	72%	69%	70%	**64%**
75-79	37%	43%	43%	46%	45%	46%	40%	40%	30%	29%	**39%**
70-74	13%	19%	19%	18%	19%	21%	17%	17%	10%	9%	**16%**
65-69	8%	10%	10%	11%	10%	11%	10%	10%	7%	8%	**9%**
60-64	18%	23%	22%	21%	21%	21%	19%	18%	14%	20%	**20%**
55-59	7%	9%	9%	10%	11%	11%	10%	11%	10%	12%	**10%**
50-54	6%	7%	7%	8%	9%	8%	9%	9%	10%	11%	**8%**
45-49	6%	7%	6%	8%	8%	8%	8%	9%	10%	11%	**8%**
40-44	5%	6%	6%	7%	8%	7%	8%	8%	9%	10%	**7%**
16-39	4%	5%	5%	6%	6%	6%	6%	6%	7%	8%	**6%**
Overall	**8%**	**10%**	**10%**	**11%**	**11%**	**12%**	**11%**	**12%**	**11%**	**13%**	**13%**

School interruptions will have significant impacts on students, families, and society

Economic modeling suggests schooling impacts will have long term economic effects:

- A ~3% drop in lifetime earnings for these cohorts;
- Lost GDP for Canada estimated at 1.6 trillion dollars

Non-COVID health risks include:

- Loneliness & social isolation,
- Loss of structure affecting physical activity, sleep and mental health, and
- Decreased ability to detect neglect or abuse.

All negative impacts are highly inequitable with greater learning loss for students facing greater disadvantage

Source: Kelly Gallagher-Mackay, Elizabeth Dhuey, Lisa Hawke, Lance McCready, Sarah Oates, Prachi Srivastava, and Kathryn Underwood

Key Findings

- The **third wave** is here and being **driven by variants of concern**.
- **Younger Ontarians are ending up in hospital.** Risk of ICU admission is **2 x higher** and risk of death is **1.5 x higher** for the B.1.1.7 variant.
- COVID-19 **threatens health system ability to deal with regular ICU admissions** and the ability to care for all patients.
- Vaccination is **not reaching the highest risk communities**, delaying its impact as an effective strategy.
- School disruptions have a significant and highly inequitable **impact** on students, parents and society. Further disruptions should be minimized.
- Stay-at-home orders will control the surge, protect access to care, and increase the chance of the summer Ontarians want.

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For table membership and profiles, please visit the About and Partners pages on the Science Advisory Table website.

This is **Exhibit "P"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

NEWS RELEASE

Ontario Implements Provincewide Emergency Brake

All 34 Public Health Unit Regions to Move into Shutdown

April 01, 2021
Office of the Premier

TORONTO —The Ontario government, in consultation with the Chief Medical Officer of Health and other health experts, is imposing a provincewide emergency brake as a result of an alarming surge in case numbers and COVID-19 hospitalizations across the province. The provincewide emergency brake will be effective Saturday, April 3, 2021, at 12:01 a.m. and the government intends to keep this in place for at least four weeks.

Details were provided today by Premier Doug Ford, Christine Elliott, Deputy Premier and Minister of Health, Dr. David Williams, Chief Medical Officer of Health, and Dr. Adalsteinn (Steini) Brown, Co-Chair of the Ontario COVID-19 Science Advisory Table.

"We are facing a serious situation and drastic measures are required to contain the rapid spread of the virus, especially the new variants of concern," said Premier Ford. "I know pulling the emergency brake will be difficult on many people across the province, but we must try and prevent more people from getting infected and overwhelming our hospitals. Our vaccine rollout is steadily increasing, and I encourage everyone who is eligible to get vaccinated. That is our best protection against this deadly virus."

Ontario's key indicators and latest modelling show that additional measures must be taken. From March 26 to 28, 2021, provincial case rates have increased by 7.7 per cent to 101.1 cases per 100,000 people. Current COVID-19 related ICU admissions are already over the peak of wave two and hospitals in regional hotspots will need to further ramp down scheduled surgeries. COVID-19 related ICU admissions are projected to exceed 650 beds in a few weeks. These increases are being driven by COVID-19 variants, which are transmitted easily and result in a higher risk of death and hospitalization, including in younger populations.

The provincewide emergency brake would put in place time-limited public health and workplace safety measures to help to stop the rapid transmission of COVID-19 variants in communities, protect hospital capacity and save lives. Measures include, but are not limited to:

- Prohibiting indoor organized public events and social gatherings and limiting the capacity for outdoor organized public events or social gatherings to a 5-person maximum, except for gatherings with members of the same household (the people you live with) or gatherings of members of one household and one other person from another household who lives alone.
- Restricting in-person shopping in all retail settings, including a 50 per cent capacity limit for supermarkets, grocery stores, convenience stores, indoor farmers' markets, other stores that primarily sell food and pharmacies, and 25 per cent for all other retail including big box stores, along with other public health and workplace safety measures;
- Prohibiting personal care services;
- Prohibiting indoor and outdoor dining. Restaurants, bars and other food or drink establishments will be permitted to operate by take-out, drive-through, and delivery only;
- Prohibiting the use of facilities for indoor or outdoor sports and recreational fitness (e.g., gyms) with very limited exceptions;
- Requiring day camps to close; and,
- Limiting capacity at weddings, funerals, and religious services, rites or ceremonies to 15 per cent occupancy per room indoors, and to the number of individuals that can maintain two metres of physical distance outdoors. This does not include social gatherings associated with these services such as receptions, which are not permitted indoors and are limited to five people outdoors.

On the advice of the Chief Medical Officer of Health, all Ontarians are asked to limit trips outside the home to necessities such as food, medication, medical appointments, supporting vulnerable community members, or exercising outdoors with members of their household. Employers in all industries should make every effort to allow employees to work from home.

"Ontario, like many other provinces and jurisdictions around the world, is in the third wave of the COVID-19 pandemic and immediate action is required to help turn the tide," said Christine Elliott, Deputy Premier and Minister of Health. "Implementing a provincewide emergency brake was not an easy decision to make and is not one we take lightly. As we continue to vaccinate more Ontarians, the end is in sight, but right now these necessary measures will help to stop the spread of variants in our communities, protect capacity in our health care system, and save lives."

The current *COVID-19 Response Framework: Keeping Ontario Safe and Open*, will be paused when the provincewide emergency brake comes into effect. The impacts of these time-limited measures will be evaluated throughout the next four weeks to determine if it is safe to lift any restrictions or if they need to be extended. With more than $1.6 billion invested to protect against COVID-19, schools remain safe for students and staff. Keeping schools open is critical to the mental health and well-being of Ontario youth. During the emergency shutdown, schools will remain open for in-person learning with strict safety measures in place. The spring break will continue as planned for the week of April 12. In order to support working families, child care will remain open during the shutdown. Child care settings will continue to adhere to stringent health and safety measures so that they remain safe places for children and staff.

"In the last few weeks a significant increase in COVID-19 cases and variants of concern has been observed across Ontario which has put considerable strain on our public health and health care systems," said Dr. David Williams, Chief Medical Officer of Health. "Implementing a provincewide shutdown is needed to bring the third wave of this pandemic under control so that we can save lives, keep our education system open and allow our vaccination program to take hold."

Quick Facts

- Based on the latest modelling data, variants of concern are continuing to grip the province and drive this third wave of the pandemic. Case rates are rising, younger Ontarians are becoming sicker and ICU capacity is at risk of becoming overwhelmed without stronger public health and workplace safety measures in place.
- The 2021 Budget, *Ontario's Action Plan: Protecting People's Health and Our Economy*, brings the government's total investments to protect the economy to $23.3 billion. This includes an estimated $3.4 billion to support approximately 120,000 small businesses across Ontario via two rounds of the Ontario Small Business Support Grant. Applications for the Ontario Small Business Support Grant have been extended for one week through April 7 and all eligible businesses are encouraged to apply.
- Additionally, the new Ontario Tourism and Hospitality Small Business Support Grant will provide an estimated $100 million in one-time payments of $10,000 to $20,000 to eligible small businesses in the tourism and hospitality sector. Businesses required to close or significantly restrict services due to provincial public health measures can continue to apply for property tax and energy cost rebates. Visit Ontario.ca/COVIDsupport for more information on Ontario's supports for businesses.
- To ensure that every person who requires care in a hospital can access a bed, the government has invested more than $5.1 billion to support hospitals since the start of the pandemic, creating more than 3,100 additional hospital beds and 500 critical care and high intensity medicine beds. This includes $1.8 billion in 2021–22 to continue providing care for COVID-19 patients, addressing surgical backlogs and keeping pace with patient needs through its *Ontario's Action Plan: Protecting People's Health and Our Economy.*
- The province continues to deploy rapid testing in workplaces, including up to 300,000 COVID-19 tests per week for asymptomatic staff in key sectors such as manufacturing, warehousing, supply chain, mining, construction and food processing. More than 4.7 million rapid antigen tests have been sent to over 1,150 workplaces, including 89 essential industry sites, under the Provincial Antigen Screening Program.
- The Ontario government continues to implement its High Priority Communities Strategy to provide targeted supports to communities hardest hit by COVID-19. In these communities 1,000 Community Ambassadors have been mobilized, 30 community testing sites have been opened and nearly 36,000 PPE kits have been distributed to community members.
- Get tested if you have COVID-19 symptoms, or if you have been advised of exposure by your local public health unit or through the COVID Alert App. Visit Ontario.ca/covidtest to find the nearest testing location.
- Emergency orders O. Reg. 55/21 (Compliance Orders for Retirement Homes) and O. Reg. 8/21 (Enforcement of COVID-19 Measures) currently in force, under the Emergency Management and Civil Protection Act, have been extended until April 19, 2021, as the province continues to deal with the impacts of COVID-19.

Additional Resources

- 2021 Budget - Ontario's Action Plan: Protecting People's Health and Our Economy

- The Digital Main Street program helps main street businesses build their online presence and reach more customers.
- Property Tax and Energy Cost Rebates
- Visit Ontario's COVID-19 vaccine web page to view the latest provincial data and information on COVID-19 vaccines.
- Visit Ontario's COVID-19 information website to learn more about how the province continues to protect the people of Ontario from the virus.
- For public inquiries call ServiceOntario, INFOline at 1-866-532-3161 (Toll-free in Ontario only)

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This is **Exhibit "Q"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

NEWS RELEASE

Ontario Enacts Provincial Emergency and Stay-at-Home Order

Additional measures needed to protect health system capacity and save lives during third wave of COVID-19

April 07, 2021
Office of the Premier

TORONTO — The Ontario government, in consultation with the Chief Medical Officer of Health and other health experts, is immediately declaring a third provincial emergency under s 7.0.1 (1) of the *Emergency Management and Civil Protection Act* (EMPCA). These measures are being taken in response to the rapid increase in COVID-19 transmission, the threat on the province's hospital system capacity, and the increasing risks posed to the public by COVID-19 variants.

Details were provided today by Premier Doug Ford, Christine Elliott, Deputy Premier and Minister of Health, Solicitor General Sylvia Jones, and Dr. David Williams, Chief Medical Officer of Health.

"The COVID-19 situation is at a critical stage and we must act quickly and decisively to stay ahead of these deadly new variants," said Premier Ford. "By imposing these strict new measures we will keep people safe while allowing our vaccination program to reach more people, starting with our high risk population and identified hot spots. Although this is difficult, I urge everyone to follow these public health measures and together we will defeat this deadly virus."

Case rates, hospitalizations, and ICU occupancy are increasing rapidly, threatening to overwhelm the health care system. The number of COVID-19 hospitalizations in the province have increased by 28.2 per cent between the period of March 28 and April 5, 2021. In addition, between March 28 and April 5, 2021, Ontario has seen the number of COVID-19 patients in intensive care escalate by 25 per cent. While every action possible is being taken to increase capacity and continue daily surgeries and procedures, the province is reaching a tipping point.

Effective Thursday, April 8, 2021 at 12:01 a.m., the government is issuing a province-wide Stay-at-Home order requiring everyone to remain at home except for essential purposes, such as going to the grocery store or pharmacy, accessing health care services (including getting vaccinated), for outdoor exercise , or for work that cannot be done remotely. As Ontario's health care capacity is threatened, the Stay-at-Home order, and other new and existing public health and workplace safety measures will work to preserve public health system capacity, safeguard vulnerable populations, allow for progress to be made with vaccinations and save lives.

Retail

In addition, the province is also strengthening public health and workplace safety measures for non-essential retail under the provincewide emergency brake. Measures include, but are not limited to:

- Limiting the majority of non-essential retailers to only operate for curbside pick-up and delivery, via appointment, between the hours of 7 a.m. and 8 p.m., with delivery of goods to patrons permitted between 6:00 am and 9:00 pm, and other restrictions;
- Restricting access to shopping malls to limited specified purposes, including access for curbside pick-up and delivery, via appointment, with one single designated location inside the shopping mall, and any number of designated locations outside the shopping mall, along with other restrictions;
- Restricting discount and big box stores in-person retail sales to grocery items, pet care supplies, household cleaning supplies, pharmaceutical items, health care items, and personal care items only;
- Permitting the following stores to operate for in-person retail by appointment only and subject to a 25 per cent capacity limit and restricting allowable hours of operation to between 7 a.m. and 8 p.m. with the delivery of goods to patrons permitted between 6 a.m. and 9 p.m.:
    - Safety supply stores;
    - Businesses that primarily sell, rent or repair assistive devices, aids or supplies, mobility devices, aids or supplies or medical devices, aids or supplies;

    - Rental and leasing services including automobile, commercial and light industrial machinery and equipment rental;
    - Optical stores that sell prescription eyewear to the public;
    - Businesses that sell motor vehicles, boats and other watercraft;
    - Vehicle and equipment repair and essential maintenance and vehicle and equipment rental services; and
    - Retail stores operated by a telecommunications provider or service, which may only permit members of the public to enter the premises to purchase a cellphone or for repairs or technical support.
- Permitting outdoor garden centres and plant nurseries, and indoor greenhouses that engage in sales to the public, to operate with a 25 per cent capacity limit and a restriction on hours of operation to between 7 a.m. and 8 p.m.

These additional and strengthened public health and workplace safety measures will be in effect as of Thursday, April 8, 2021 at 12:01 a.m.

Education

Keeping schools and child care open is critical to the mental health and well-being of Ontario children and youth. Schools and child care will remain open for in-person care and learning in public health regions where it is permitted, with strict safety measures in place.

In addition, beginning next week, education workers who provide direct support to students with special education needs across the province, and all education workers in select hot spot areas, will be eligible to register for vaccination. Vaccinations will commence during the April break starting with priority neighborhoods in Toronto and Peel, then rolling out to priority neighborhoods in other hot spot regions, including York, Ottawa, Hamilton, Halton and Durham. This will be followed by a rollout across the province as supply allows.

"While our government took decisive action by implementing the provincewide emergency brake, more needs to be done to protect against the threats to our health system resources and the continued health and safety of individuals and families across the province," said Christine Elliott, Deputy Premier and Minister of Health. "By further strengthening public health and workplace safety measures, we can work to reduce transmission of the virus while we work to rollout Phase 2 of our vaccine distribution plan, and put more needles in the arms of Ontarians."

"The rapid and increasing spread of COVID-19 and the variants of concern pose significant threats to our health care system and the well-being of Ontarians, requiring immediate and decisive action," said Solicitor General Sylvia Jones. "The declaration of a third provincial emergency is necessary to provide the government with the tools needed to help protect the public, reduce the spread of the virus and save lives."

Vaccinations

As part of Phase Two of its COVID-19 vaccine distribution plan, people living in regions with the highest rates of transmission will be prioritized to receive a vaccine, starting with the most at-risk in the Peel and Toronto public health regions. This initiative will be expanded to additional "hot spot" regions based on established patterns of transmission, severe illness, and mortality.

To support this expanded vaccination effort, mobile teams are being organized to administer vaccines in high-risk congregate settings, residential buildings, faith-based locations, and locations occupied by large employers in hot spot neighbourhoods to individuals aged 18 or over. Pop-up clinics will also be set-up in highly impacted neighborhoods, including at faith-based locations and community centres in those hot spots, in collaboration with public health units and community organizations within those communities. The province will provide additional resources to support these mobile and pop-up clinics in the hardest-hit neighbourhoods.

The government will also extend booking for COVID-19 vaccination appointments to more age groups through its provincial booking system, for public health regions with highly impacted neighbourhoods, on Friday, April 9, 2021. Booking eligibility will be extended to include individuals aged 50 and over for COVID-19 vaccination appointments at mass immunization clinics in high-risk areas as identified by postal code, using the provincial booking system.

Workplace Inspections

Health and safety inspectors and provincial offenses officers will increase inspections and enforcement at essential businesses in regional hot zones to continue protecting essential workers while on the job. There have been 19,500 COVID-related workplace inspections and investigations across the province since the beginning of 2021. During those visits, over 450 COVID-19 related tickets have been issued and OHS inspectors have issued over 14,446 OHS orders and stopped unsafe work related to COVID-19 a total of 24 times.

Rapid Testing

Rapid testing continues to be deployed in workplaces for asymptomatic staff in key sectors such as manufacturing, warehousing, supply chain, mining, construction and food processing. Approximately 5.4 million rapid antigen tests have been sent to over 1,150 workplaces, including 100 essential industry sites, under the Provincial Antigen Screening Program. To encourage the use of these tests under the program, additional outreach will occur to employers in regions with highest rates of transmission to increase access to testing, and the process for enrollment in the screening program will be streamlined to allow for quick access to these supports.

"As we continue to see COVID-19 variants of concern drive this third wave of COVID-19, it is evident stronger public health and workplace measures are needed to help interrupt the spread of the virus," said Dr. David Williams, Chief Medical Officer of Health. "By all of us staying at home, while still taking some time to enjoy the outdoors with the people we live with in our local neighbourhoods and maintaining two metres physical distance from others, we can reduce our mobility, minimize transmission, protect our loved ones and our communities, safeguard health system capacity, and save lives."

Quick Facts

- Over the past week, the province's positivity rate is 5.1 per cent, well above the high-alert threshold of 2.5 per cent, and as of April 6, 2021, there has been a total of 2,483 cases with one of the three variants of concern (VoC). The percent of cases in the last week that tested positive for a mutation or VOC was 63.1 per cent.
- On Saturday April 3, 2021, in response to an alarming surge in case numbers and COVID-19 hospitalizations across the province and in consultation with the Chief Medical Officer of Health, the government imposed a provincewide emergency brake, implementing additional time-limited public health and workplace safety measures, including encouraging remote work in all industries to the greatest extent possible and the closure of additional workplaces, further capacity limits on some essential businesses which are able to remain open, and strengthened advice on limiting trips outside of the home for essential reasons.
- On the advice of the Chief Medical Officer of Health, all Ontarians are asked to limit trips outside the home to necessities such as food, medication, medical appointments, supporting vulnerable community members, or exercising outdoors with members of their household in our their communities. Individuals should remain in their local communities and avoid all non-essential travel – even within the province – and to stay home when ill even with mild symptoms. Employers in all industries should make every effort to allow employees to work from home.
- To ensure that every person who requires care in a hospital can access a bed, the government has invested more than $5.1 billion to support hospitals since the start of the pandemic, creating more than 3,100 additional hospital beds and 500 critical care and high intensity medicine beds. This includes $1.8 billion in 2021–22 to continue providing care for COVID-19 patients, addressing surgical backlogs and keeping pace with patient needs through its Ontario's Action Plan: Protecting People's Health and Our Economy.
- The Ontario government continues to implement its High Priority Communities Strategy to provide targeted supports to communities hardest hit by COVID-19. In these communities 1,000 Community Ambassadors have been mobilized, 30 community testing sites have been opened and nearly 36,000 PPE kits have been distributed to community members.
- Get tested if you have COVID-19 symptoms, or if you have been advised of exposure by your local public health unit or through the COVID Alert App. Visit Ontario.ca/covidtest to find the nearest testing location.

Additional Resources

- Ontario Implements Provincewide Emergency Brake
- Ontario Moving to Phase Two of COVID-19 Vaccine Distribution Plan
- 2021 Budget - Ontario's Action Plan: Protecting People's Health and Our Economy
- The Digital Main Street program helps main street businesses build their online presence and reach more customers.
- Property Tax and Energy Cost Rebates
- Visit Ontario's COVID-19 communications resources web page for resources in multiple languages to help local communication efforts.
- Visit Ontario's COVID-19 vaccine web page to view the latest provincial data and information on COVID-19 vaccines.
- Visit Ontario's COVID-19 information website to learn more about how the province continues to protect the people of Ontario from the virus.
- For public inquiries call ServiceOntario, INFOline at 1-866-532-3161 (Toll-free in Ontario only).

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This is **Exhibit "R"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

NEWS RELEASE

Ontario Moves Schools to Remote Learning Following Spring Break

Continued Rise in COVID-19 Cases Demands Shift to Protect Students and Staff and Slow Community Spread

April 12, 2021
Office of the Premier

TORONTO — The Ontario government, in consultation with the Chief Medical Officer of Health, has made the difficult decision to move elementary and secondary schools to remote learning following the April break. This move has been made in response to the rapid increase in COVID-19 cases, the increasing risks posed to the public by COVID-19 variants, and the massive spike in hospital admissions.

Details were provided today by Premier Doug Ford, Christine Elliott, Deputy Premier and Minister of Health, Stephen Lecce, Minister of Education, and Dr. David Williams, Chief Medical Officer of Health.

"We are seeing a rapidly deteriorating situation with a record number of COVID cases and hospital admissions threatening to overwhelm our health care system," said Premier Ford. "As I have always said we will do whatever it takes to ensure everyone stays safe. By keeping kids home longer after spring break we will limit community transmission, take pressure off our hospitals and allow more time to rollout our COVID-19 vaccine plan."

With appropriate measures in place, schools have been safe places for learning throughout the pandemic, as confirmed by the Chief Medical Officer of Health and local medical officers of health and have demonstrated low rates of in-school transmission. However, increasing rates of community spread pose a threat to the health and safety of school communities. As a result, all publicly funded and private elementary and secondary schools in the province are to move to teacher-led remote learning when students return from the April break on April 19, 2021. Private schools operating in-person this week are to transition to remote learning by April 15, 2021. This action is being taken in support of the Government's broader efforts to limit the spread of COVID-19. Data will be assessed on an ongoing basis and health officials will be consulted to determine when it will be safe to resume in-person learning.

Child care for non-school aged children will remain open, before and after school programs will be closed and free emergency child care for the school-aged children of eligible health care and frontline workers will be provided. To protect the most vulnerable, boards will make provisions for continued in-person support for students with special education needs who require additional support that cannot be accommodated through remote learning.

"This was not a decision we made lightly, as we know how critical schools are to Ontario students. Our priority has always been to keep schools open, however sharply rising community transmission can put our schools and Ontario families at risk," said Minister Lecce. "While Ontario's plan has kept schools safe, as confirmed by the Chief Medical Officer of Health, we are taking decisive and preventative action today to ensure students can safely return to learning in our schools."

Case rates, hospitalizations, and ICU occupancy are increasing rapidly, threatening to overwhelm the health care system. The number of COVID-19 hospitalizations in the province have increased by 22.1 per cent between the period of April 4 and 10, 2021. In addition, during this same period of time, Ontario has seen the number of COVID-19 patients in intensive care increase from 494 to 605.

Since April 8, the province has been under a provincewide Stay-at-Home order, requiring everyone to remain at home except for essential purposes, such as going to the grocery store or pharmacy, accessing health care services (including getting vaccinated), for outdoor exercisewith your household in your home community, or for work that cannot be done remotely. As Ontario's health care capacity is threatened, the Stay-at-Home order, and other new and existing public health and workplace safety measures, will work to preserve public health system capacity, safeguard vulnerable populations, allow for progress to be made with vaccinations and save lives.

With students moving to remote learning, vaccine prioritization of education workers who provide direct support to students with special education needs across the province, and all education workers in select hot spot areas, starting with Peel and Toronto, will continue. Starting today, special education workers across the province and education workers in Peel and Toronto hot spots will be eligible to register for vaccination by calling the provincial vaccine booking line at 1-833-943-3900. More information is available at Ontario.ca/covidvaccine.

It is critically important that as Ontarians receive the vaccine, everyone continues to wear a mask, maintain physical distancing when outside of their immediate household and frequently wash their hands. As well, continue to monitor for symptoms of COVID-19 and get tested if symptoms are present.

"As we continue to see rapid growth in community transmission across the province, it is necessary to take extra precautions and measures to ensure the continued health and safety of students, teachers and their families," said Dr. David Williams, Chief Medical Officer of Health. "As the fight against this third wave of the pandemic continues, everyone must continue following all public health and workplace safety measures and stay at home to prevent further transmission of the virus, so we can once again resume in person learning in our schools."

Quick Facts

- As of April 10, 2021, Ontario currently has 1,646 COVID-19 patients requiring acute care, which includes 605 patients in ICU, with 382 on a ventilator.
- Based on the latest modelling data, cases across the province are continuing to grow and the number of people requiring an intensive care bed is projected to rise to approximately 800 people within the next 10 days.
- Some jurisdictions around the world, including those in Canada have implemented similar time-limited measures to respond to a dramatic resurgence in cases. Based on their experiences, measures of four to six weeks are expected to interrupt transmission of COVID-19 in Ontario.
- Municipalities and local medical officers of health may have additional restrictions or targeted requirements in their region.
- Get tested if you have symptoms compatible with COVID-19, or if you have been advised of exposure by your local public health unit or through the COVID Alert App. Visit Ontario.ca/covidtest to find the nearest testing location.
- Prior to April break, more than 99 per cent of students and staff did not have a current case of COVID-19. Since September, 99.2 per cent of students and 98.6 per cent of staff never reported a COVID-19 case.

Additional Resources

- Visit Ontario's website to learn more about how the province continues to protect Ontarians from COVID-19
- Learn about Ontario’s vaccination program to help protect us against COVID-19.
- Support for parents/students
- COVID-19: enhanced public health and workplace safety measures
- COVID-19 public health measures and advice

Related Topics

Education and Training

Learn about Ontario’s early years, education and training systems. Includes information on child care, elementary schools, secondary schools, colleges, universities, skills training and financial aid. Learn more

Government

Learn about the government services available to you and how government works. Learn more

Health and Wellness

Get help navigating Ontario’s health care system and connecting with the programs or services you’re looking for. Learn more

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Ryan Cookson

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Hospitalized and ICU cases

Each data point shows how many people were hospitalized and how many people who still tested positive for COVID-19 were in the ICU each day. Go to a detailed table that includes people who are in the ICU due to a COVID-19-related illness but no longer test positive for the virus.

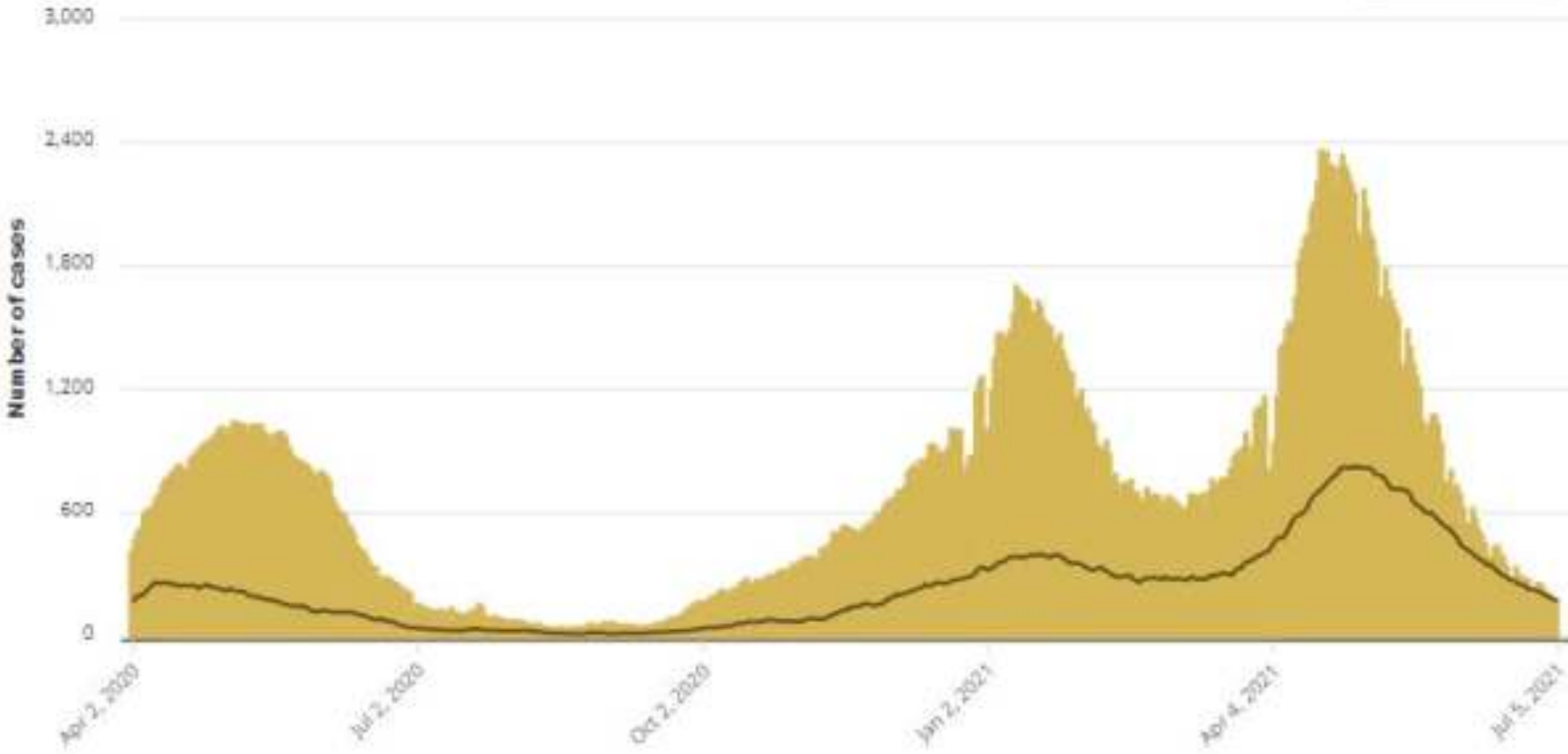
Graph | Table

All time

Hospitalized (including people in ICU)

In ICU (testing positive)

Download



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Ryan Cookson

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Update on COVID-19 Projections

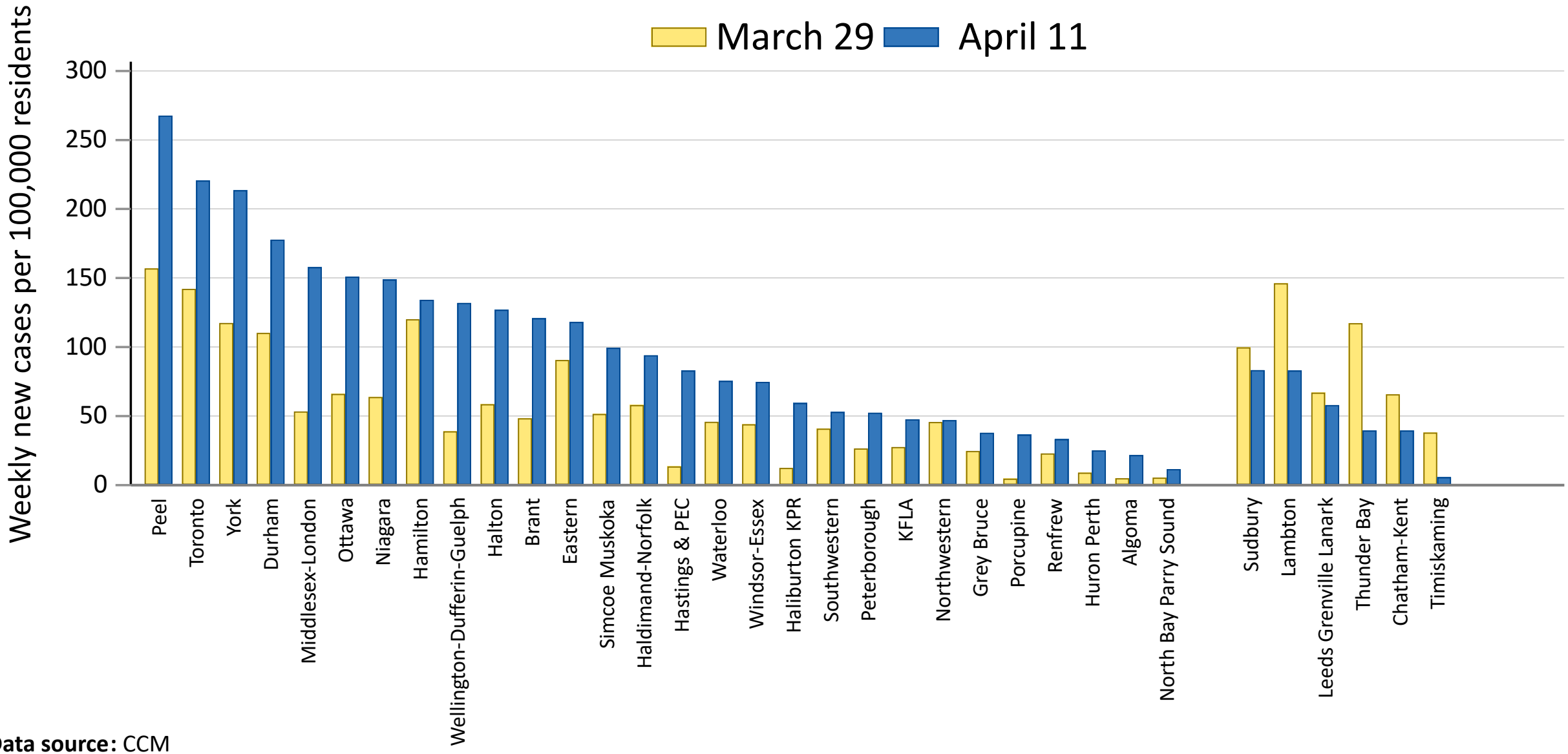
Science Advisory and Modelling Consensus Tables

April 16, 2021

Key Findings

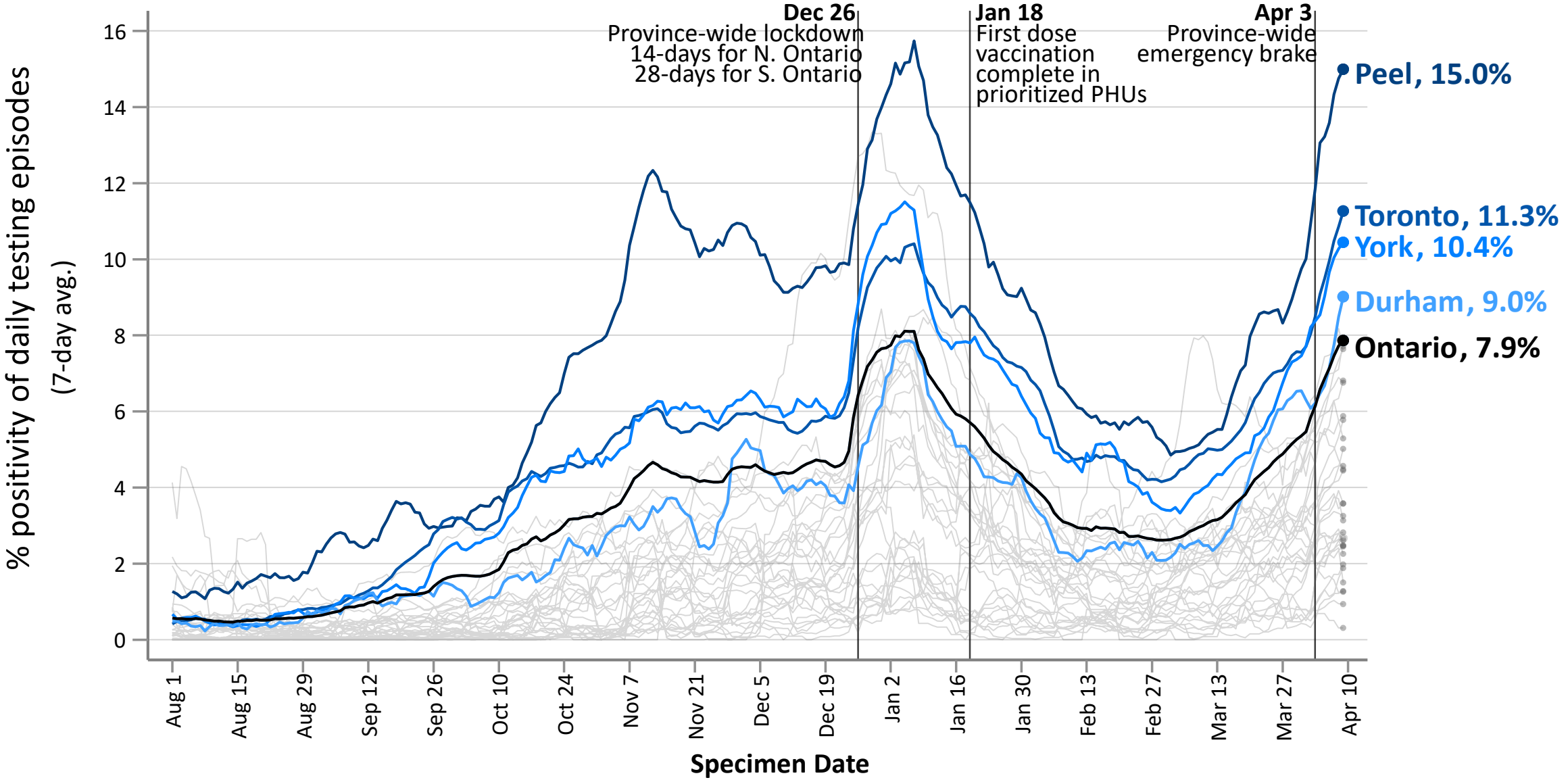
- COVID-19 cases, hospitalizations and ICU occupancy are **at their highest levels since March 2020** and variant cases continue to rise sharply.
- ICU occupancy is **compromising care for all patients.**
- Ontarians can help themselves and others by limiting mobility to truly necessary trips and **always wearing a mask and keeping 6 feet distant** when in contact with anyone outside their household.
- Although improving, vaccination is not reaching people at high-risk fast enough to overcome the level of serious illness in our communities and our hospitals.
- Without stronger system-level measures and immediate support for essential workers and high-risk communities, **high case rates will persist through the summer.**

Cases are **rapidly** increasing in most Public Health Units



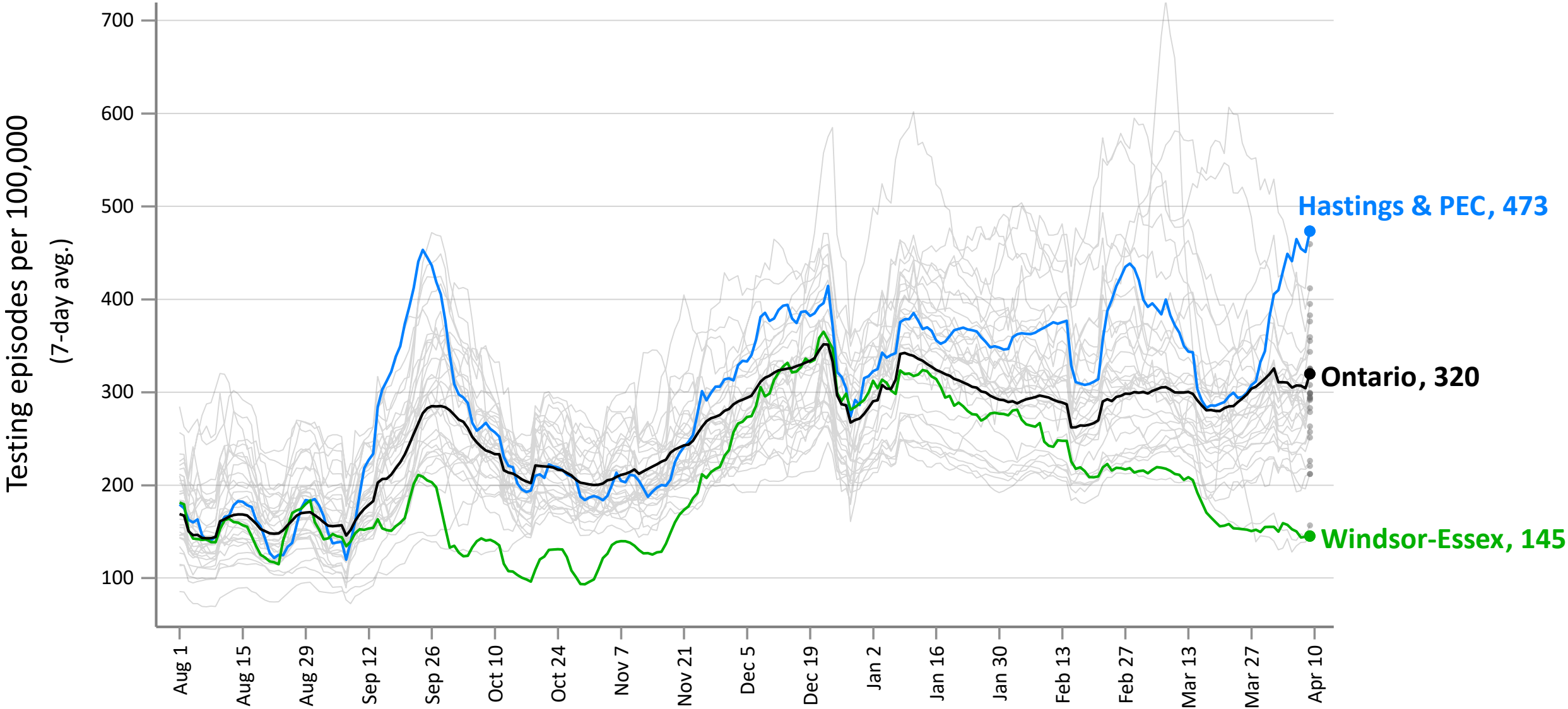
Data source: CCM
Data note: Data for the most recent day have been censored to account for reporting delays

Test positivity rates are increasing across Ontario



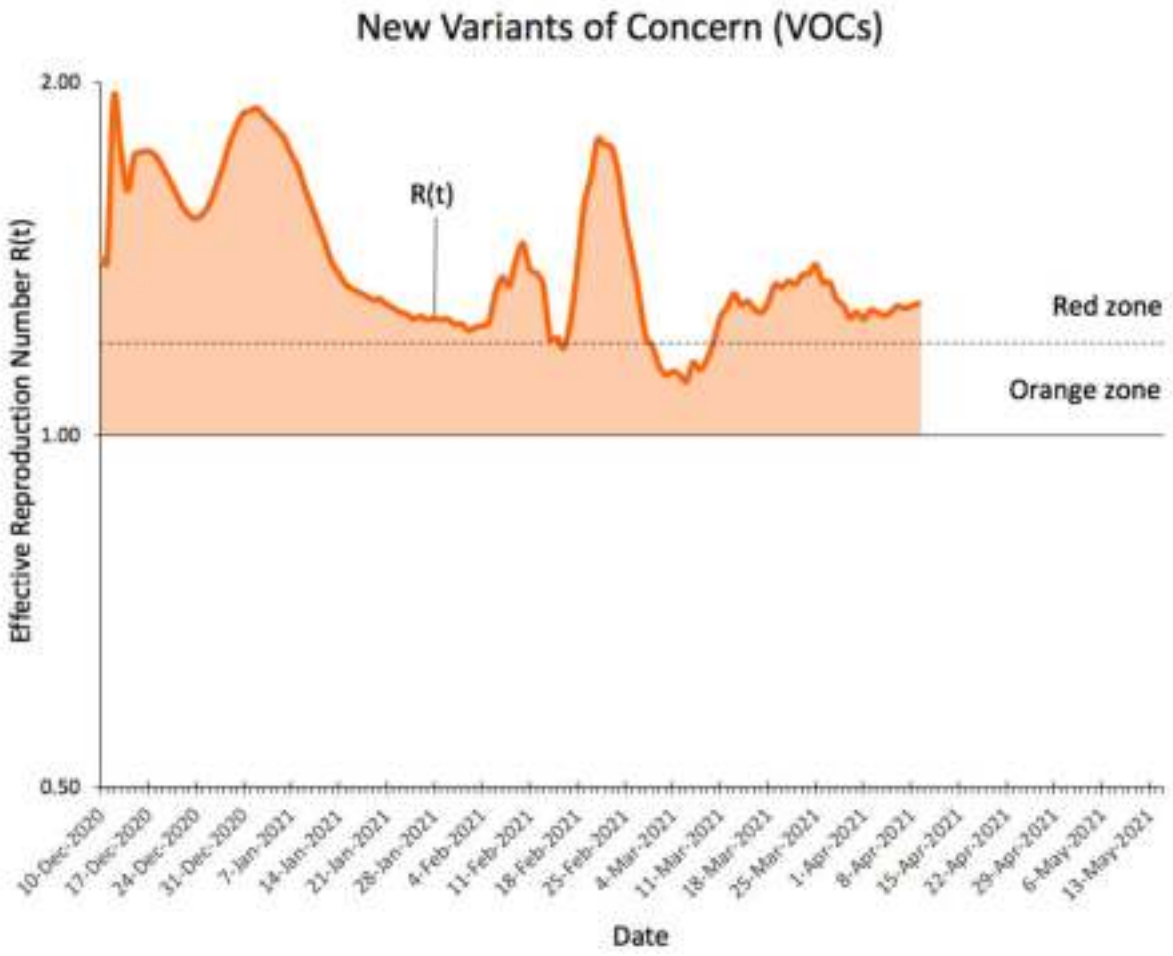
Data source: Ontario Laboratory Information System (OLIS), data up to April 9

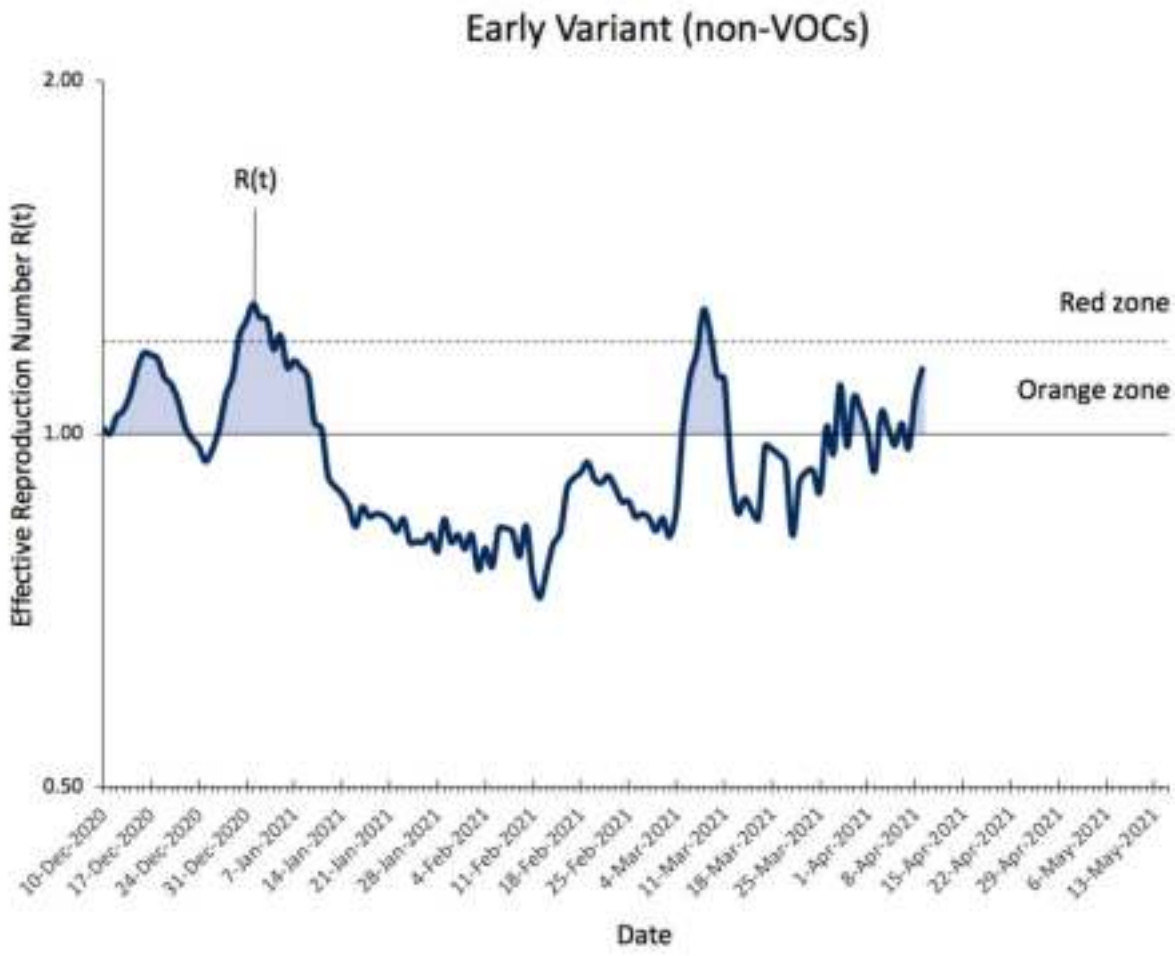
Ontario testing rates are flat – the increase in cases is because there are more cases, not more tests being done



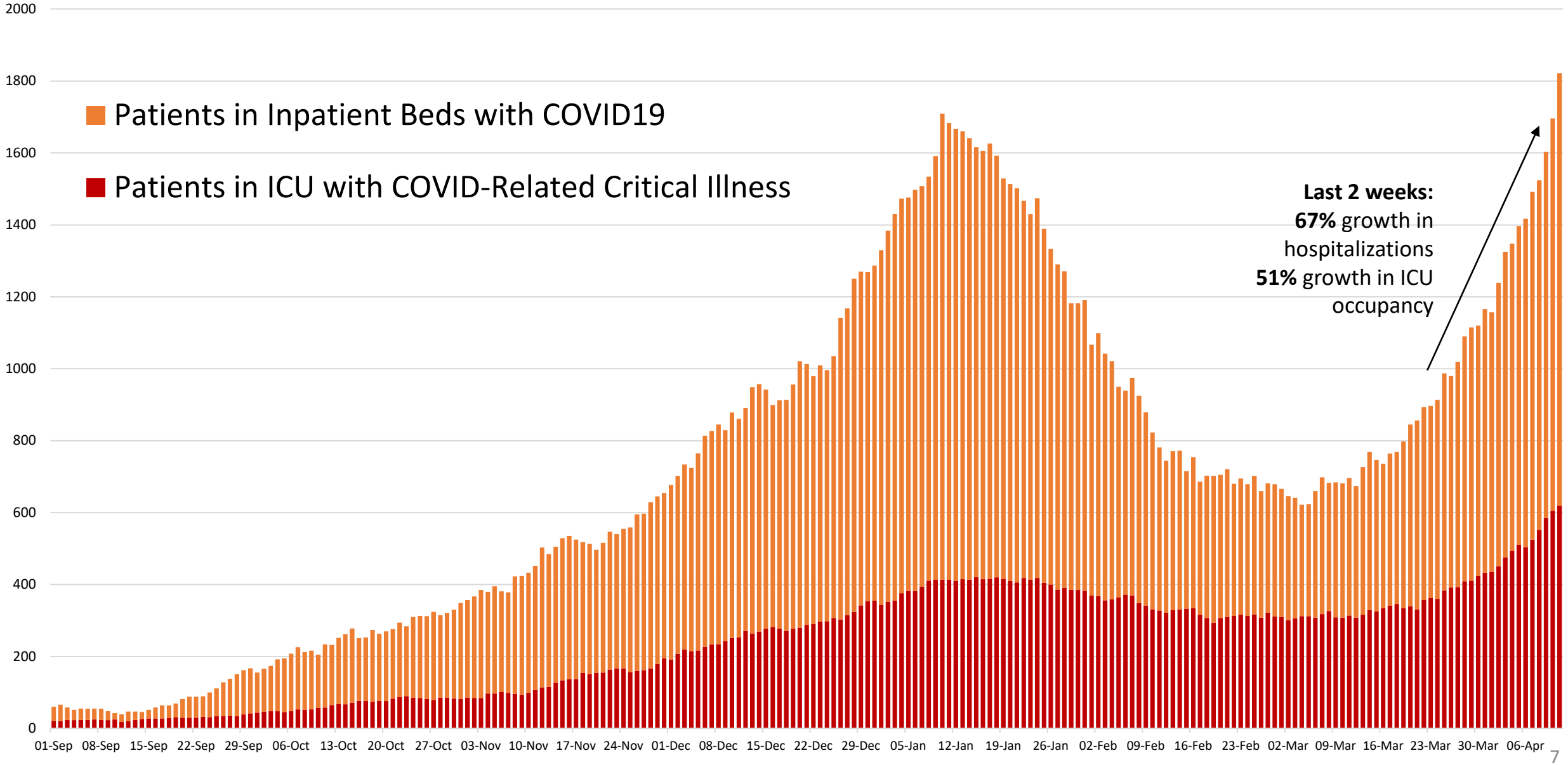
Data source: Ontario Laboratory Information System (OLIS), data up to April 9

The number of variant cases continues to rise and variants now dominate, but even the original strain is rising.





A record number of Ontarians are in hospital due to COVID-19



Data Sources: MOH COVID Inpatient Census and Critical Care Information System

A 6 week stay-at-home order with a vaccination rate of at least 100K doses per day is the only way to flatten the curve.

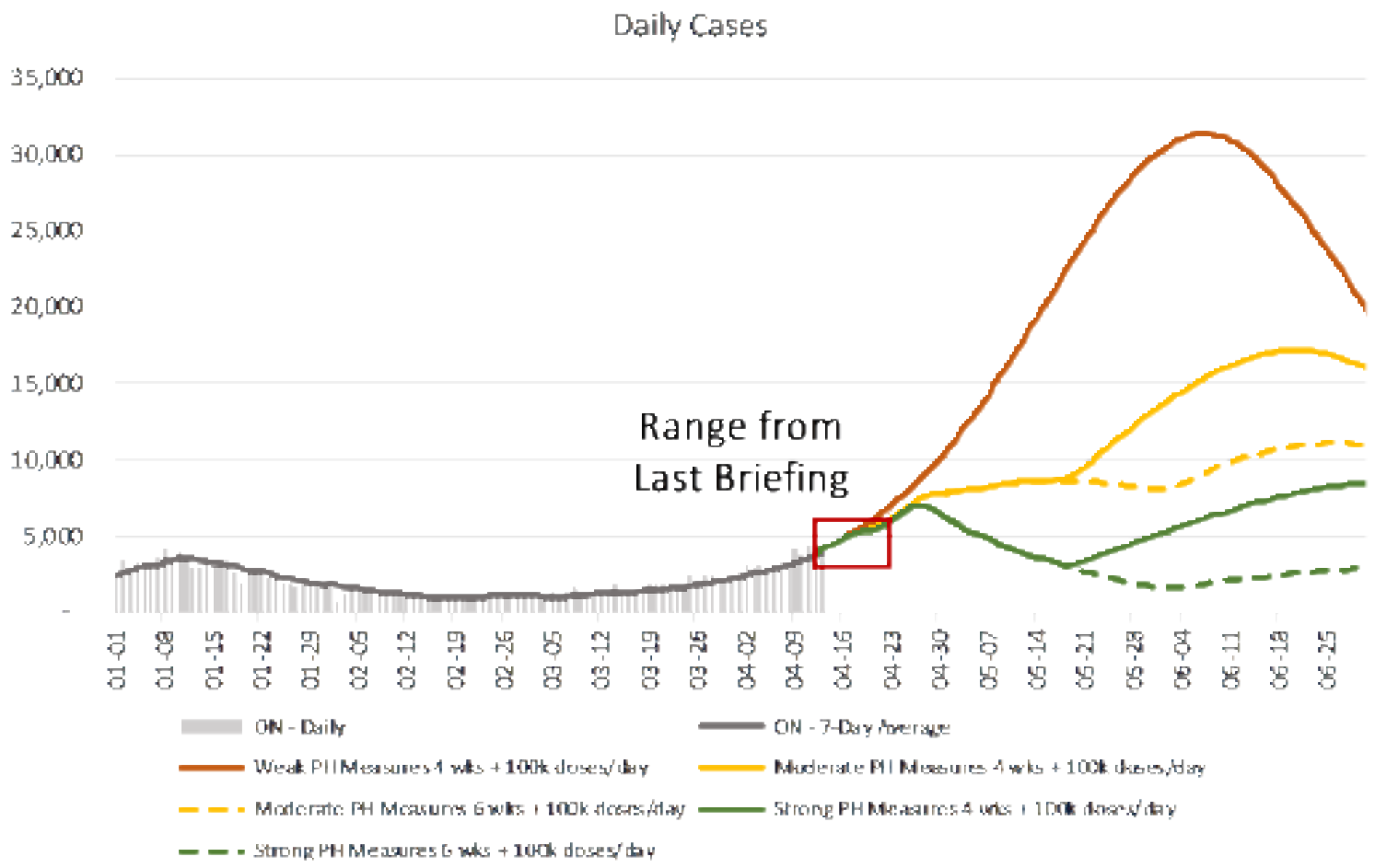
Figure summarizes predictions across 4 models with many scenarios.

Stay-at-home order assumptions:

- 4 or 6 weeks starting Apr 8
- Weak to strong effect on transmission

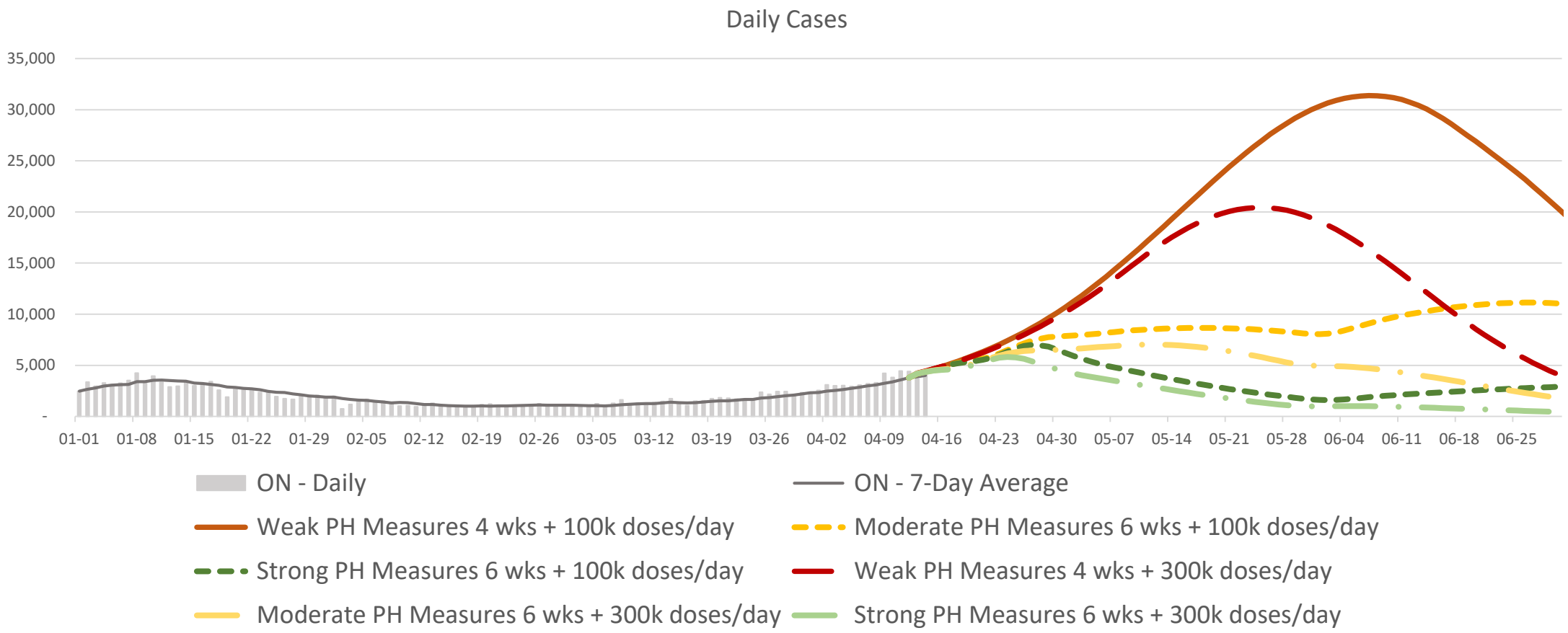
Vaccine assumptions:

- 60% effective in preventing infection
- 100,000 doses/day
- Administered at random

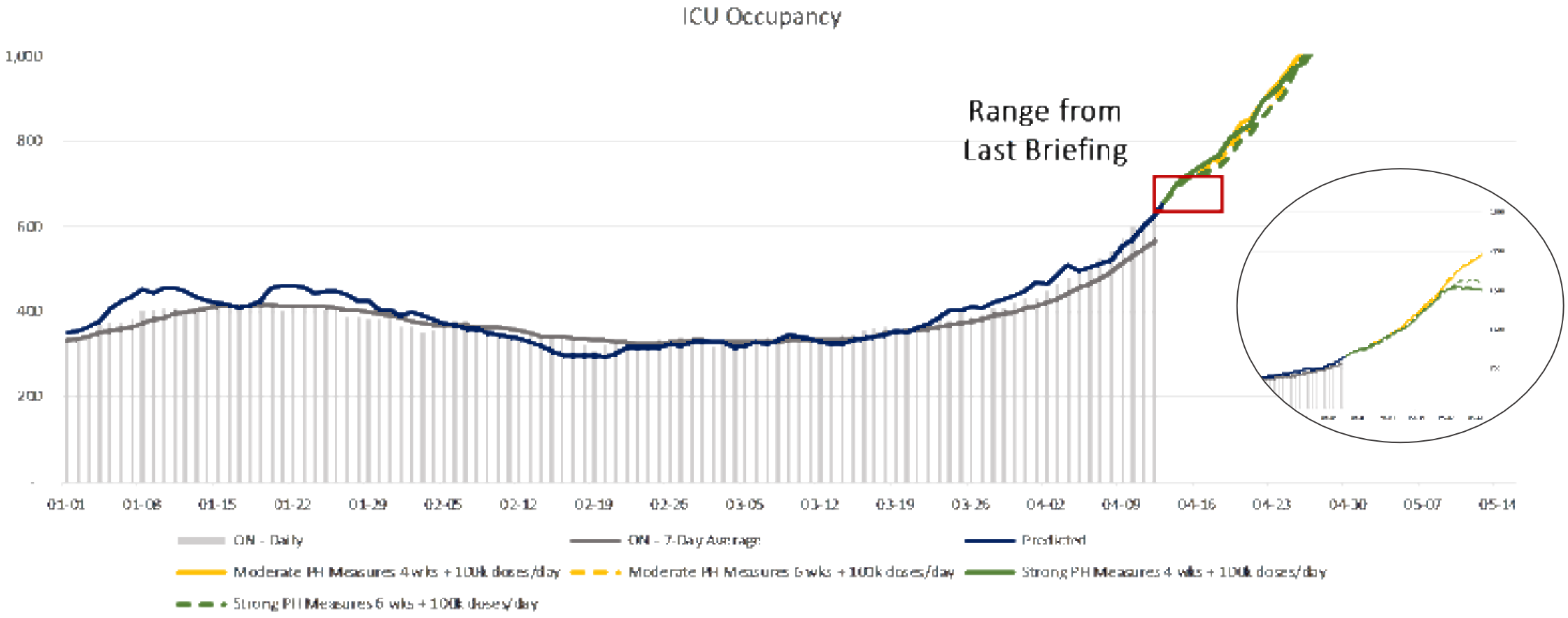


Predictions informed by modeling from COVID-19 ModCollab, Fields Institute, McMasterU, PHO, YorkU
Data (Observed Cases): covid-19.ontario.ca

Under every scenario, more vaccines mean a faster resolution in the long-run

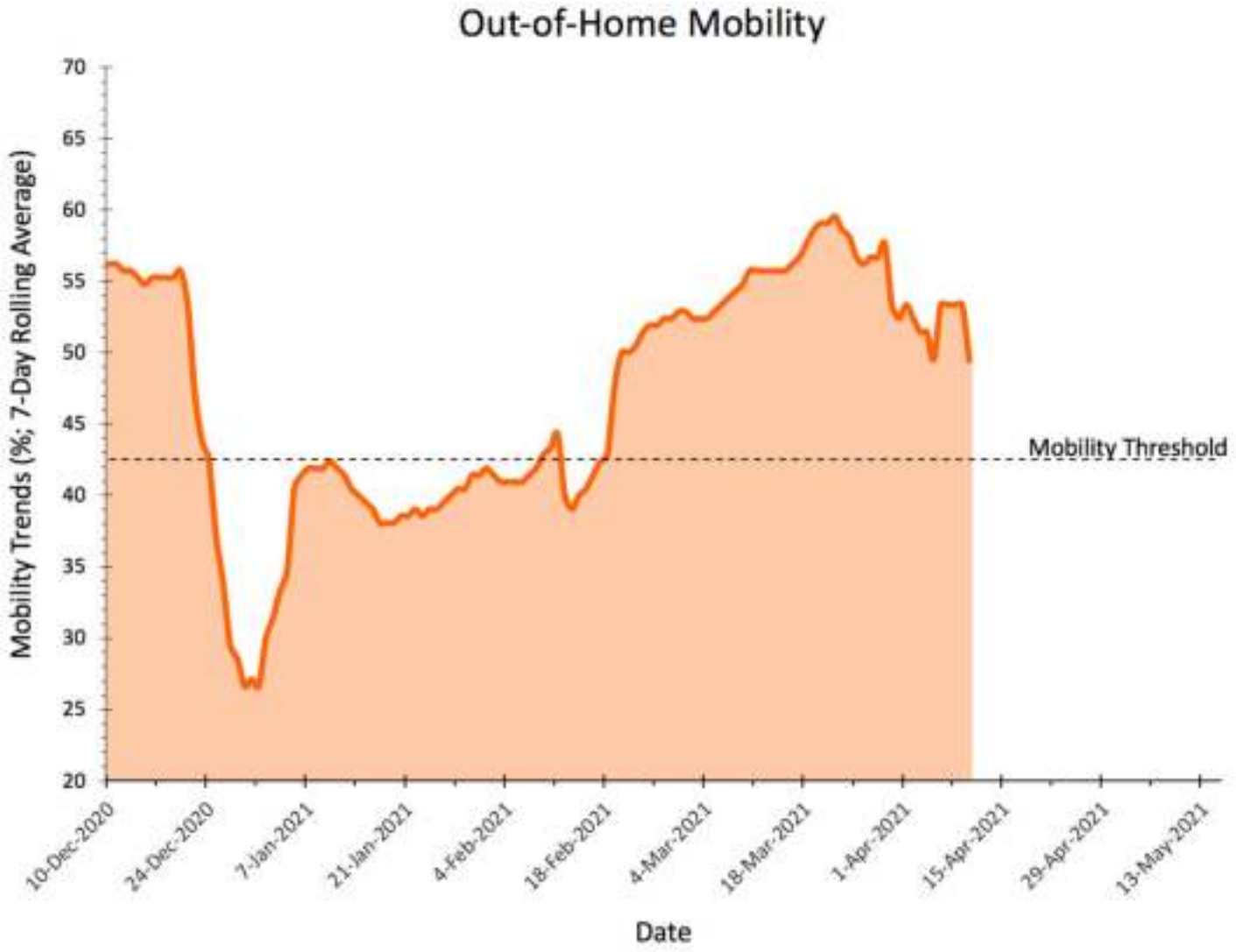


As predicted, ICU occupancy is rising dramatically. System-level public health measures will help blunt some of the impact.



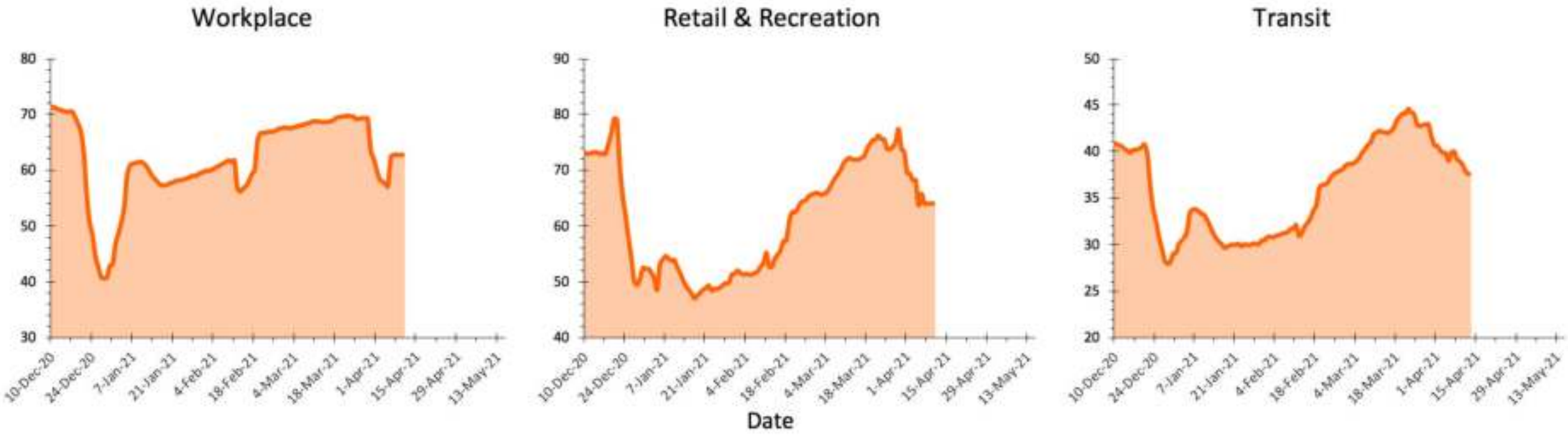
Predictions: COVID-19 ModCollab.
Data (Observed ICU Occupancy): CCSO

Mobility has declined slightly but not enough to bring current growth under control.



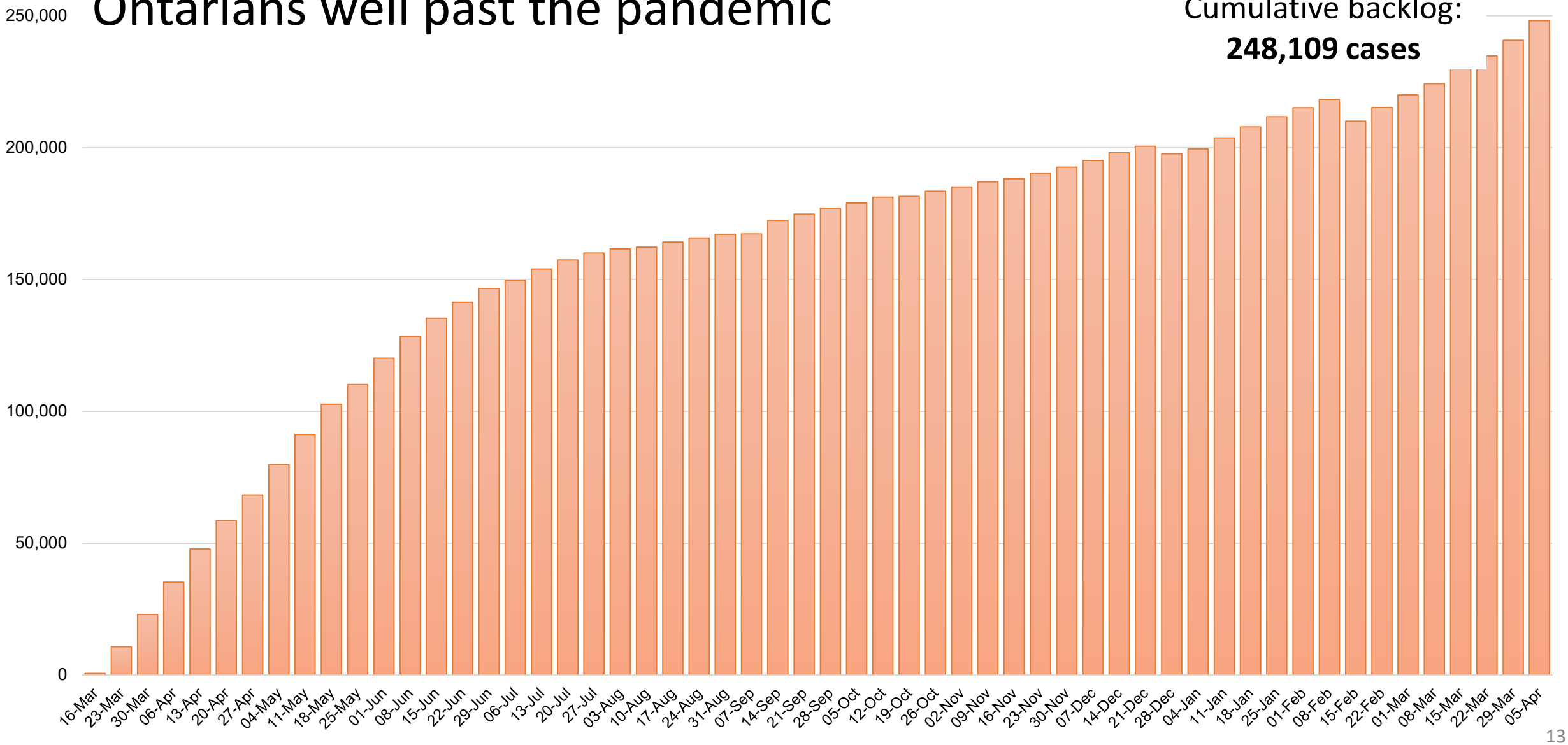
Predictions: COVID-19 SAT.
Data Google and Apple Mobility data

Mobility has declined slightly across settings. Further reducing mobility and always wearing a mask and distancing is how Ontarians help reduce cases.



Predictions: COVID-19 SAT.
Data Google and Apple Mobility data

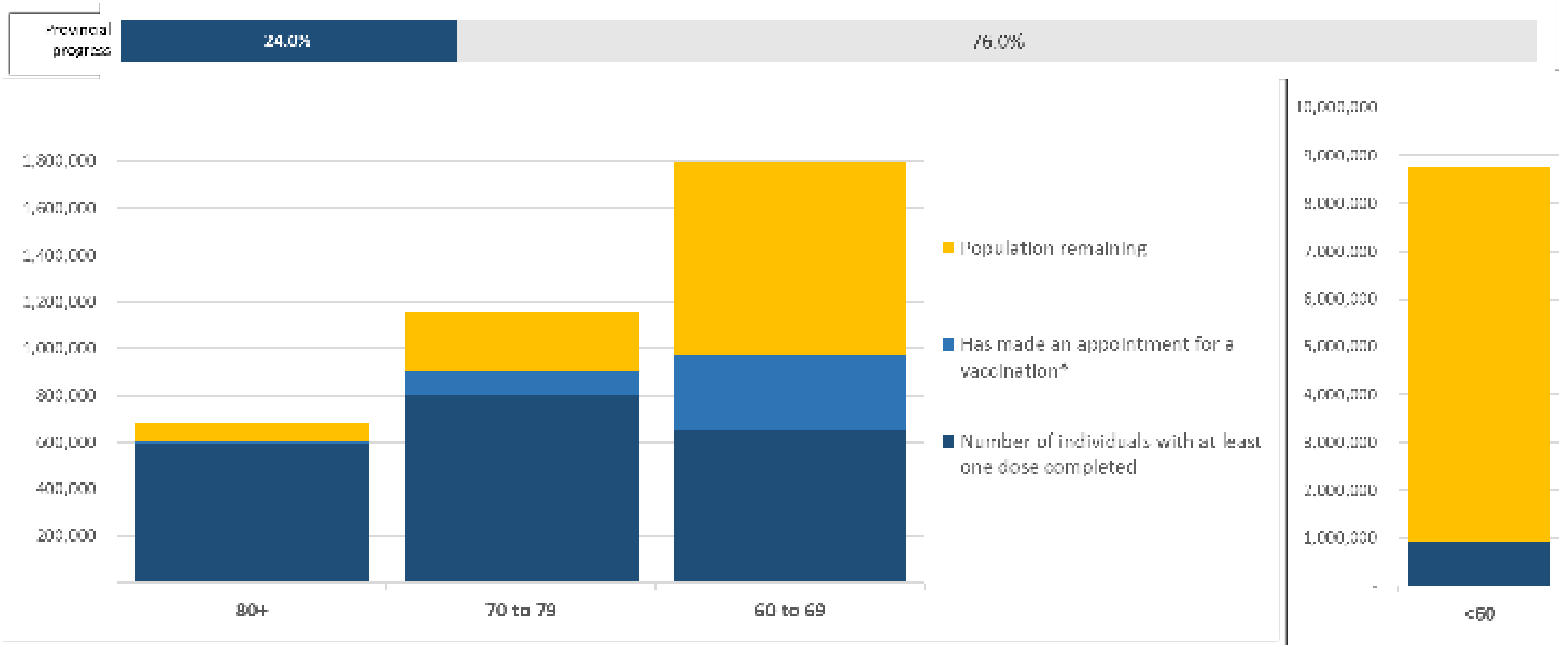
The access to care deficit is building which will be felt by Ontarians well past the pandemic



Data Source: Wait Times Information System. Backlog estimated based on comparison of 2020/21 with 2019/20 surgical volumes

First dose vaccine coverage expanding but remains incomplete

More than 3m doses administered

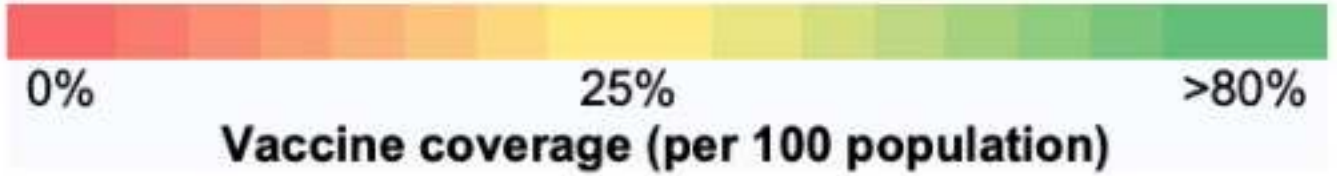


Data Sources
MOF Population Projections
COVAX analytical file, extracted, 8:00 pm Apr 12 2021, CPAD, MOH
COVAX Skedulo, extracted 6:00pm Apr 12 2021

Vaccination by risk is improving but remains a key to controlling spread

Figure excludes long-term care vaccination – at least 1 dose as of April 12, 2021

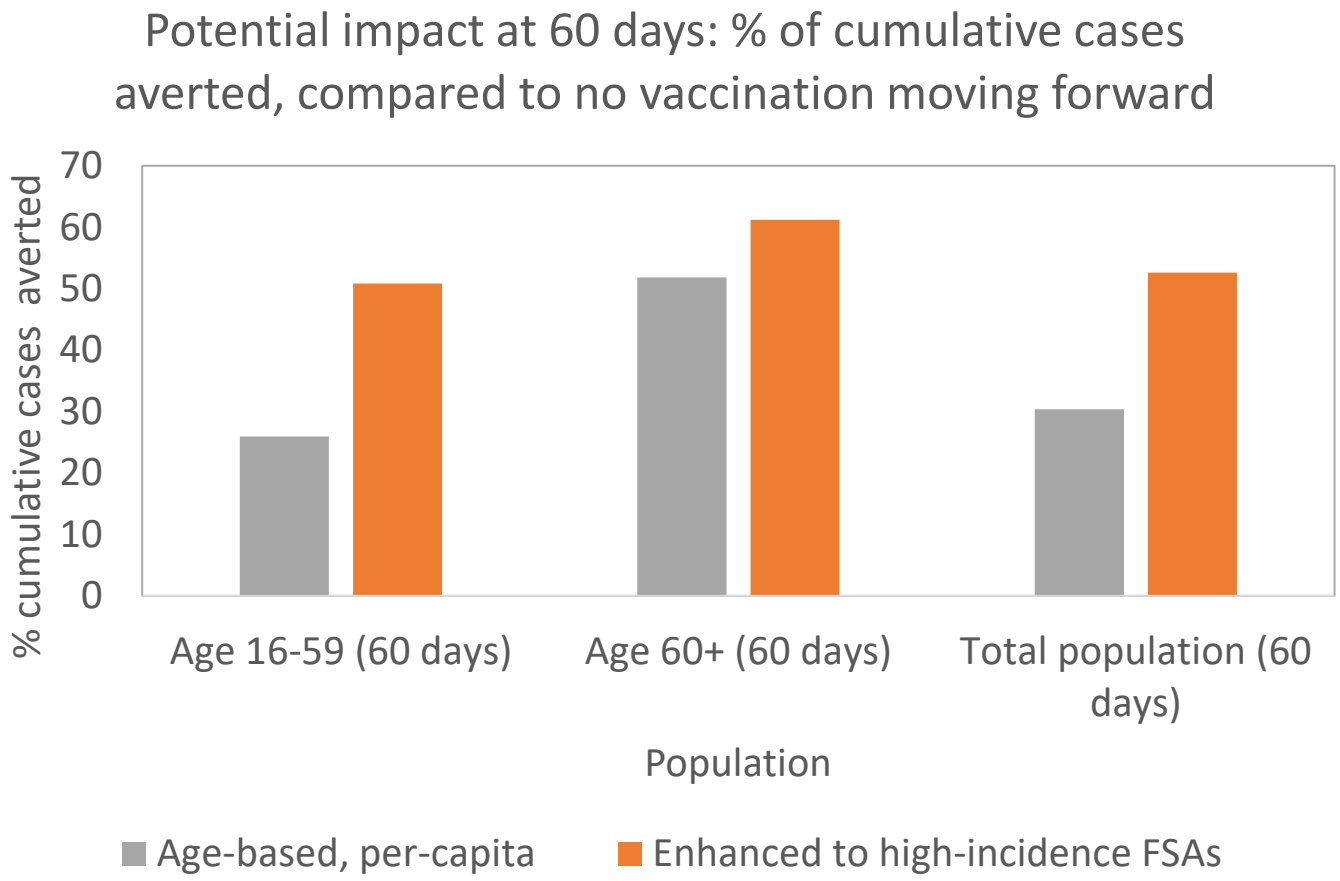
	Neighbourhood Risk‡										
	1 = high incidence of COVID-19 infections → **10 =** low incidence of COVID-19 infections										
Age group	1	2	3	4	5	6	7	8	9	10	**Overall**
80+	65%	68%	70%	75%	77%	77%	79%	81%	82%	82%	**76%**
75-79	63%	68%	70%	73%	75%	74%	75%	77%	74%	71%	**72%**
70-74	57%	64%	62%	66%	65%	64%	63%	62%	51%	39%	**58%**
65-69	42%	48%	44%	39%	41%	38%	36%	34%	22%	19%	**35%**
60-64	40%	42%	38%	36%	35%	34%	30%	27%	23%	27%	**33%**
55-59	20%	25%	21%	20%	21%	22%	20%	20%	17%	17%	**20%**
50-54	14%	18%	13%	13%	13%	13%	13%	13%	13%	14%	**14%**
45-49	9%	14%	9%	11%	11%	11%	11%	11%	13%	14%	**11%**
40-44	7%	9%	9%	10%	10%	11%	10%	11%	12%	13%	**10%**
16-39	5%	7%	6%	8%	8%	8%	8%	8%	10%	10%	**8%**
Overall	**15%**	**20%**	**18%**	**19%**	**20%**	**20%**	**19%**	**19%**	**20%**	**20%**	**23%**



Source: ICES

What happens if we vaccinate 3 million adults over the next 30 days?

100,000 vaccinations per day, top 20% highest incidence neighbourhoods



Number vaccines per case averted

Analysis: COVID Heterogeneity Research Group, COVID-19 ModCollab, PHO.
Data: CCM

Key Findings

- COVID-19 cases, hospitalizations and ICU occupancy are **at their highest levels since March 2020** and variant cases continue to rise sharply.
- ICU occupancy is **compromising care for all patients.**
- Ontarians can help themselves and others by limiting mobility to truly necessary trips and **always wearing a mask and keeping 6 feet distant** when in contact with anyone outside their household.
- Although improving, vaccination is not reaching people at high-risk fast enough to overcome the level of serious illness in our communities and our hospitals.
- Without stronger system-level measures and immediate support for essential workers and high-risk communities, **high case rates will persist through the summer.**

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* Chairs of Scientific Advisory, Evidence Synthesis, and Modelling Consensus Tables

For table membership and profiles, please visit the About and Partners pages on the Science Advisory Table website.

This is **Exhibit "U"** referred to
in the Affidavit of DR. DAVID McKEOWN,
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Ryan Cookson

A Commissioner for the Taking of Affidavits

COVID cases in ICU and ICU occupancy*

Hospitals' ability to maintain scheduled surgeries is at risk as there are more than 150 COVID+ patients in ICU in Ontario.

Table 4: COVID-19 cases in ICU (+/- daily change) and available adult baseline beds – April 18

Total CRCI patients in ICU	# CRCI patients in ICU with mechanical ventilation	# CRCI patients in ICU not on mechanical ventilation	Total suspected COVID-19 patients in ICU	# suspected COVID-19 patients in ICU with mechanical ventilation	# suspected COVID-19 patients in ICU not on mechanical ventilation	# available baseline adult ICU beds in the system
755 (+14)	516 (+10)	239 (+4)	322 (+14)	110 (-6)	212 (+20)	400 (+3)

Table 5: ICU occupancy (adult baseline beds and adult vented beds), province and region – April 18

Region	Number of patients in ICU	Number of ICU beds	ICU occupancy	Number of vented patients	Number of vented beds	Vented occupancy
1 -West	563	675	83.4%	235	431	54.5%
2 -Central	424	490	86.5%	217	372	58.3%
3 -Toronto	385	437	88.1%	205	312	65.7%
4 -East	446	559	79.8%	228	364	62.6%
5 -North	87	144	60.4%	23	81	28.4%
ONTARIO	**1905 (+5)**	**2305 (+8)**	**82.6% (-0.1%)**	**908 (+9)**	**1560 (+8)**	**58.2% (+0.3%)**

Data source: Critical Care Information System (CCIS), CritiCALL based on patient counts April 18, 2021 at 11:59 pm; COVID status as of 6 am April 19, 2021.
Data quality notes and caveats: Incremental beds that were readily available in the case of a surge in ICU admissions have returned to their previous function in the hospital (e.g., acute beds), and have been removed from the above table as of October 14. CRCI includes patients in ICU currently testing positive for COVID and patients who remain in ICU due to COVID but are currently testing negative.

Ontario

This is **Exhibit "V"** referred to
in the Affidavit of DR. DAVID McKEOWN,
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Ryan Cookson

A Commissioner for the Taking of Affidavits

NEWS RELEASE

Ontario Releases Three-Step Roadmap to Safely Reopen the Province

Province Safely Reopening Outdoor Recreational Amenities Prior to End of Stay-at-Home Order

May 20, 2021
Office of the Premier

TORONTO — The Ontario government, in consultation with the Chief Medical Officer of Health, has released its Roadmap to Reopen, a three-step plan to safely and cautiously reopen the province and gradually lift public health measures based on the provincewide vaccination rate and improvements in key public health and health care indicators. In response to recent improvements to these indicators, Ontario will allow more outdoor recreational amenities to reopen, with restrictions in place, effective May 22, 2021 at 12:01 a.m.

"As a result of the strict public health measures we introduced to stop the spread of COVID-19 variants, we are seeing a steady improvement in our situation as ICU and hospital numbers begin to stabilize," said Premier Doug Ford. "While we must remain conscious of the continued threat the virus poses, with millions of Ontarians having received at least their first dose of vaccine we can now begin the process of a slow and cautious re-opening of the province in full consultation with our public health professionals."

Roadmap to Reopen outlines three steps to easing public health measures, guided by the following principles:

- **Step One** An initial focus on resuming outdoor activities with smaller crowds where the risk of transmission is lower, and permitting retail with restrictions. This includes allowing outdoor gatherings of up to 10 people, outdoor dining with up to four people per table and non-essential retail at 15 per cent capacity.
- **Step Two** Further expanding outdoor activities and resuming limited indoor services with small numbers of people where face coverings are worn. This includes outdoor gatherings of up to 25 people, outdoor sports and leagues, overnight camps, personal care services where face coverings can be worn and with capacity limits, as well as indoor religious services, rites or ceremony gatherings at 15 per cent capacity.
- **Step Three** Expanding access to indoor settings, with restrictions, including where there are larger numbers of people and where face coverings can't always be worn. This includes indoor sports and recreational fitness; indoor dining, museums, art galleries and libraries, and casinos and bingo halls, with capacity limits.

The province will remain in each step for at least 21 days to evaluate any impacts on key public health and health system indicators. If at the end of the 21 days, the following vaccination thresholds have been met, along with positive trends in other key public health and health system indicators, then the province will move to the next step:

- **Step 1:** 60 per cent of adults vaccinated with one dose.
- **Step 2:** 70 per cent of adults vaccinated with one dose and 20 per cent vaccinated with two doses.
- **Step 3:** 70 to 80 per cent of adults vaccinated with one dose and 25 per cent vaccinated with two doses.

Based on current trends in key health indicators, including the provincial vaccination rate, the government expects to enter Step One of the Roadmap the week of June 14, 2021. The province will confirm closer to the expected start of Step One.

"While we know that now is not yet the moment to reopen, Ontarians deserve to know the path forward on what we will carefully reopen and when, starting with the settings we know are safest," said Christine Elliott, Deputy Premier and Minister of Health. "Brighter days are ahead and we believe this Roadmap represents a path out of the pandemic and will encourage Ontarians to get vaccinated and to continue following public health advice."

The provincewide emergency brake restrictions remain in effect while the province assesses when it will be moving to Step One of the roadmap with the Stay at Home order expiring on June 2, 2021. During this time, the government will continue to work with stakeholders on reopening plans to ensure full awareness of when and how they can begin to safely reopen.

Due to the continuing success of Ontario's vaccine rollout and the collective efforts of Ontarians in following public health and workplace safety measures to date, effective May 22, 2021 at 12:01 a.m. the province will reopen outdoor recreational amenities with restrictions in place, such as the need to maintain physical distancing. These amenities include but are not limited to golf courses and driving ranges, soccer and other sports fields, tennis and basketball courts, splash and spray pads and skate parks. No outdoor sports or recreational classes are permitted. Outdoor limits for social gatherings and organized public events will be expanded to five people, which will allow these amenities to be used for up to five people, including with members of different households. All other public health and workplace safety measures under the provincewide emergency brake will remain in effect.

At this time, publicly funded and private elementary and secondary schools in the province will continue to operate under teacher-led remote learning. Data will be assessed on an ongoing basis and medical experts, including the Chief Medical Officer of Health, and other health officials will be consulted to determine if it may be safe to resume in-person learning.

"Due to the stringent efforts of Ontarians following public health and workplace safety measures, we have reached the point where we can begin preparing to exit the provincewide emergency brake and lift the Stay-at-Home order," said Dr. David Williams, Chief Medical Officer of Health. "We must remain vigilant however, as the fight against COVID-19 is not over and our case counts, ICU capacity and hospitalizations are still concerning. It remains critical that all Ontarians continue to follow all public health and workplace safety measures currently in place to help further reduce transmission and save lives."

The government will continue to work with the Public Health Measures Table, Public Health Ontario, and other public health and scientific experts to determine public health guidance for Ontarians to follow, including protocols for masking and outdoor/indoor gatherings, after being fully vaccinated.

Quick Facts

- Based on the latest modelling data COVID-19 case, positivity and hospitalization rates are decreasing, and control of the pandemic is improving. Maintaining the current rate of vaccination and public health and workplace safety measures will help to ensure Ontario starts to safely and gradually reopen.
- Ontario has administered first doses of the COVID-19 vaccines to over 58.5 per cent of Ontarians aged 18 and over. Over two million doses of the COVID-19 vaccine have been administered in Ontario since the start of May, and the province remains on track to have administered first doses to 65 per cent of Ontarians aged 18 and over by the end of May.
- The government has extended the provincewide Stay-at-Home Order until June 2, 2021, and has maintained all public health and workplace safety measures under the provincewide emergency brake to help to stop the rapid transmission of COVID-19 variants in communities, protect hospital capacity and save lives.
- The Stay-at-Home order currently in effect requires everyone to remain at home except for specified purposes, such as going to the grocery store or pharmacy, accessing health care services (including getting vaccinated), for outdoor exercise, or for work that cannot be done remotely.
- If passed by the Legislature, powers under the Reopening Ontario (A Flexible Response to COVID-19) Act, 2020 (ROA) will be extended to December 1, 2021 to ensure public health measures currently in place can be extended and adjusted as necessary, to deal with the impacts of COVID-19 and support a gradual re-opening of the province. There are currently 29 orders in effect under the ROA. Orders can be extended for up to 30 days at a time under the ROA, and the government must report on all order extensions to the Select Committee on Emergency Management Oversight.
- As of 8:00 a.m. on Tuesday, May 18, 2021, individuals aged 18 and over in 2021 across Ontario are eligible to book a COVID-19 vaccine appointment through the provincial booking system and call centre, or directly through public health units that use their own booking system.

Additional Resources

- Roadmap to Reopen
- Ontario Extending Stay-at-Home Order Until June 2
- COVID-19 Vaccine Booking Expanding to Ontarians 18+ Ahead of Schedule
- Visit Ontario's COVID-19 communications resources web page for resources in multiple languages to help local communication efforts.
- Visit Ontario's website to find out if you are eligible to receive a COVID-19 vaccine at this time.
- Eligible groups can use Ontario's vaccine booking system to find out how to schedule an appointment, or can call the Provincial Vaccine Booking Line number at 1-833-943-3900. For general inquiries, individuals can call the Provincial Vaccine Information Line number at 1-888-999-6488 or TTY service is also available by calling 1-866-797-0007.
- Visit Ontario's COVID-19 vaccine web page to view the latest provincial data and information on COVID-19 vaccines.

- Visit Ontario's COVID-19 information website to learn more about how the province continues to protect the people of Ontario from the virus.
- For public inquiries call ServiceOntario, INFOline at 1-866-532-3161 (Toll-free in Ontario only).

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This is **Exhibit "W"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

Public Health Ontario | Santé publique Ontario

EVIDENCE BRIEF

Considerations for Public Health Measures for Individuals with Partial Vaccination for SARS-CoV-2

Date: 04/15/2021

Key Messages

- Effectiveness of the first dose of a two-dose vaccination schedule of vaccines available in Canada to prevent symptomatic or asymptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection ranges between 60-80% at approximately 21-28 days after first dose; however, data indicate that the current viral vector vaccine in Canada (i.e., AstraZeneca) has less first-dose effectiveness than mRNA vaccines (i.e., Pfizer-BioNTech and Moderna).

- Clear messaging is required for the public to understand that the protective effects of the first dose of the vaccines takes weeks to develop and is neither immediate nor the same as being fully vaccinated. Further, an individual's risk factors for severe SARS-CoV-2 infection (e.g., age, immunocompromise) can impact vaccine effectiveness. Nonetheless, widespread coverage with a first dose would be sufficient to lower case rates in the population thereby allowing reductions in population level measures rather than individual level measures.

- No jurisdictions with total population vaccination programs using vaccines approved in Canada have indicated that societal public health measures can be relaxed for partially vaccinated individuals.

- Relaxing public health measures for partially vaccinated individuals is not advisable; current public health measures should remain for partially vaccinated individuals. Focus should be turned to rapidly deploying vaccine to have high first-dose coverage in the population, including reducing health inequities related to accessing first dose vaccination in the communities with the highest rates of SARS-CoV-2 that are also more likely to be of low socioeconomic status.

Issue and Research Question

This evidence brief explores whether or not it would be advisable to loosen public health measures recommended for individuals after a single dose of a two-dose vaccination schedule (also termed partially vaccinated individuals or series initiation) for SARS-CoV-2. This evidence brief does not address recommendations that are specific to health care workers who are partially vaccinated, or case/contact measures for individuals who are partially vaccinated.

Currently in Ontario, there is a low proportion of partially and fully vaccinated individuals.[1] Incentives to receive the first dose of a vaccine given the long period between vaccine doses will be called upon by the public. However, any incentives must be based on available evidence and expert opinion such that the pandemic is controlled and moves towards a return to a new normal with respect to public health measures. Moreover, at this time there are no recommendations for public health measures affecting fully vaccinated individuals in the general community in Ontario at this time.

Methods

The National Advisory Committee on Immunization (NACI) has released a summary and review of vaccine intervals in Canada in the context of limited vaccine supply.[2] The review is recent to late March 2021. The NACI report has been reviewed and briefly summarized alongside evidence from previous reports from Public Health Ontario (PHO), with a focus on the points relevant to considerations for public health measures for individuals who have been partially vaccinated (received the first of a two-dose vaccination schedule) against SARS-CoV-2.[3]

Main Findings

Vaccine Effectiveness after a First Dose of Vaccine

Vaccine efficacy to prevent symptomatic disease from clinical trial data with Pfizer-BioNTech and Moderna 14 days after the first dose and up until the second dose (typically either 21 or 28 days post-first dose) is estimated to be 92%.[2] For AstraZeneca, the efficacy to prevent symptomatic disease from clinical trial data between 22 and 90 days after the first dose was reported to be 76%.[2]

Real-world vaccine effectiveness (VE) data are predominantly from non-peer reviewed preprint publications using different study designs, dose intervals, study populations, outcomes measured (e.g., laboratory confirmed versus hospitalizations or deaths), and outcome dates (e.g., date of symptom onset, specimen collection). Results reported for each vaccine, mostly pertaining to mRNA vaccines, varied considerably.

The following summary of real-world VE is for vaccines intended to be given as a 2-dose regimen that have been approved by Health Canada as of April 8, 2021 (Pfizer-BioNTech COVID-19 vaccine [BNT162b2], Moderna COVID-19 vaccine [mRNA-1273], Oxford University/AstraZeneca [AZD1222/ChAdOx1-S]) and is based on the PHO's *COVID-19 Real-World Vaccine Effectiveness – What We Know So Far* document and the NACI Statement on Extended dose intervals for COVID-19 vaccines.[2,4] There is currently limited VE data on specific populations who are at increased risk of severe outcomes from COVID-19 and who may have a suboptimal immune response. While emerging data has helped to identify special populations (e.g., transplant patients, individuals with malignant hematological disorders or solid tumors on active therapy) as potentially having a lower response to a first dose of vaccine, a comprehensive list of other groups that may experience decreased response from a single dose has not yet been identified due to lack of data.[5] Therefore, it is important to note that the following summary of VE after a first dose of vaccine pertains to the general, community-dwelling population.

Recognizing differences between specific vaccines and populations studied, overall VE is good 21-28 days after the first dose of vaccine. Real-world studies have reported VE of 60 to 80% for preventing SARS-CoV-2 infection (asymptomatic and symptomatic COVID-19 disease) 3-4 weeks after receiving a single dose of Pfizer, Moderna or AstraZeneca vaccine; this increases to greater than 85% after a second

dose.[6-9] The VE for preventing severe disease and COVID-19-related hospitalization is 70 to 90% after the first dose of vaccine and the VE for reducing deaths attributable to COVID-19 is 70 to 85% after the first dose.[9-11] After a second dose, VE for prevention of severe disease and hospitalization increases with most estimates of VE being greater than 90%.[6,12] Please see COVID-19 Real-World Vaccine Effectiveness – What We Know So Far for further detail including study characteristics.[4]

The VE for preventing asymptomatic infection is particularly important given the challenges of preventing asymptomatic transmission with other public health measures. Data from Israel indicate that VE for preventing asymptomatic infection is 29%, 14 to 20 days after the first dose, and 52%, 21 to 27 days, after the first dose, increasing to 90%, 7 days after the second dose which is likely a first dose effect given timing. However it is important to note that this was in the context of a rapid decline in cases amidst deployment of a national vaccine campaign and in the absence of systematic asymptomatic testing.[6] A US retrospective cohort study of asymptomatic patients undergoing screening before surgical and medical procedures found a VE of 79% more than 10 days after the first dose (before the second dose) and a VE of 80% after the second dose. However the VE after the second dose was estimated starting at 0 days after the second dose, which also likely represents a first dose effect.[13]

Emerging data demonstrates that vaccination is associated with reduced spread in individuals and populations, regions, or facilities with higher rates of vaccination or those that were vaccinated earlier than others. However, these estimates are for individuals receiving *at least one dose* of vaccine and includes individuals that have received 2 doses.

- In an observational study in Israel, breakthrough infections occurring 12-37 days after individuals received the first dose of the Pfizer vaccine had significantly reduced viral loads at the time of testing, potentially decreasing viral shedding and contagiousness of the disease.[14]

- An analysis of early statewide vaccination efforts in the US found that vaccination was effective in reducing daily COVID-19 case growth rates by 0.124, 0.347, 0.345, 0.464, 0.490, and 0.756 percentage point declines, respectively, in the 1-5, 6-10, 11-15, 16-20, 21-25, and 26 or more days after the start of vaccination (i.e., administration date of first COVID-19 vaccine dose).[15]

- A separate analysis of vaccination rates and COVID-19 incidence found that the cumulative county-level vaccination rate in the US (percentage of the county population who have received at least one dose) was significantly associated with a corresponding decline in COVID-19 incidence; that is, higher vaccination rates translated to a decreased county-level COVID-19 incidence.[16]

- In Israel, where COVID-19 cases and hospitalizations started to decline after implementation of a national vaccine campaign that prioritized vaccination of older individuals, an analysis between early-vaccinated cities and late-vaccinated cities found a larger and earlier decrease in the number of COVID-19 cases and hospitalizations of older individuals (> 60 years) in earlier compared to later-vaccinated cities. While a concurrent lockdown could have also influenced results, the study authors noted that these same downward trends in older individuals were not observed during previous lockdowns in which measures of clinical outcomes had similar dynamics across age groups. At the time of the study, 68.7% of individuals over 16 years had received the first dose and 48% had received the second dose of vaccine.[17]

Extended Dose Intervals for COVID-19 Vaccines in Canada

The NACI recommendation to allow for an extended interval between first and second doses of vaccine aims to minimize death and disease at a population level by immunizing as many individuals, as quickly as possible in the context of a limited supply.[18] This recommendation was informed by modelling developed by the Public Health Agency of Canada (PHAC) which compared the impact of different vaccination strategies under real-world effectiveness conditions.[19] Results showed that longer intervals of up to 6 months between the first and second dose prevented more hospitalizations and deaths. Conditions under which extended dose intervals led to worse outcomes included VE of less than 65% for preventing death after the first dose or protection waning to 0% by month 3 before the scheduled second dose at 6 months. Achieving the benefits of the extended dose interval strategy greatly depends on accelerated, widespread first dose vaccine coverage in individuals 20-74 years old since older adults were prioritized for early vaccination.[19]

Jurisdictional Responses to Public Health Measures Based on the Two-dose Vaccination Schedule for SARS-CoV-2

In brief, Canada, England, Scotland, Denmark, United States, and Israel all do not have public health measures specific to individuals who are partially vaccinated (i.e., single dose in a two-dose vaccine schedule) even though some of these countries have high vaccine coverage.[3,20-29]

Discussion and Conclusions

Vaccination, including after the first dose of a two-dose vaccine schedule, provides significant protection from symptomatic disease and severe outcomes such as hospitalization and death compared to not being vaccinated against SARS-CoV-2. Therefore, it is expected that widespread coverage of the population with the first dose of vaccine will lower case rates in the population. However, there is no evidence whether a single dose of a two-dose vaccine schedule will either increase or decrease the emergence of VOC.[2]

Those countries that are leading in total population vaccination coverage have not opted to reduce observed public health measure recommendations to partially vaccinated individuals. The rationale for not having different public health measures for partially vaccinated individuals has not been described by the jurisdictions reviewed, although we note that some jurisdictions (i.e., Israel) chose to provide both doses of a two-dose regimen within a shorter interval than Ontario. A literature review on the topic was not performed for this evidence brief.

Implications for Practice

Public health messaging regarding vaccination needs to be transparent about decision-making reasons in order to avoid unintended negative impacts such as public mistrust impacting vaccination uptake or willingness to follow public health measures. Ontario's vaccine coverage, including proportion of the population having received a first dose, lags behind countries that have been able to follow recommended vaccination schedules and sufficient procurement. At this time, with low proportions of partially vaccinated and fully vaccinated individuals in the Ontario population,[1] and in the context of high disease incidence including VOC, it is not advisable to reduce public health measures for partially vaccinated individuals despite data demonstrating decreased incidence in asymptomatic and symptomatic disease, and data is still needed regarding risk of transmission to others after receiving the

first dose of a vaccine available in Canada. Moreover, VOC for which reduced vaccine efficacy for in vitro studies and effectiveness is documented, will continue to pose a higher risk to the community until there is low circulation of SARS-CoV-2 overall.

Valuable data for vaccines available in Canada that are still needed to better inform decisions regarding public health measures for partially vaccinated individuals includes: real world data of implications from countries with more comprehensive vaccination coverage enacting public health measures for partially vaccinated individuals, effectiveness of partially vaccinated versus fully vaccinated individuals including a time to event analysis (e.g., hazard analysis), what individual level factors influence first-dose vaccine effectiveness, risk of spread from partially vaccinated individuals to unvaccinated individuals, duration of immunity from single dose vaccination, effectiveness of single dose vaccination in subgroups that have not been studied, and what influence that changes to public health measures for partially vaccinated and/or fully vaccinated individuals may have on vaccine uptake for one dose and both doses.

Current data from Forward Sortation Area (first three digits of the postal code) analyses in Toronto show that the areas with the highest burden of disease have the lowest vaccine coverage rates.[30] News reports have stated that the analyses indicates higher socioeconomic status neighbourhoods in Toronto, based on postal code and census data, have higher vaccine coverage than low socioeconomic neighbourhoods where rates of SARS-CoV-2 and severe outcomes of COVID-19 are higher.[31,32] Hot spot communities are known to often have higher concentrations of populations who are disproportionately affected by COVID-19 in Ontario due to a number of intersecting equity factors and factors related to the determinants of health. These populations include Black, racialized, lower income and materially deprived communities.[33] Focusing strategies to vaccinate these populations at risk is already proposed in Phase 2 of Ontario's vaccination plan.[33,34]

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Ryan Cookson

A Commissioner for the Taking of Affidavits

NEWS RELEASE

Ontario Maintains COVID-19 Restrictions as Stay-at-Home Order is Set to Expire

Measures address ongoing risks as province prepares to safely and cautiously reopen

June 01, 2021
Solicitor General

TORONTO — As was previously announced, Ontario's Stay-at-Home order will expire on June 2, 2021. When it does, all other public health and workplace measures will remain in place provincewide until Ontario enters Step One of the Roadmap to Reopen, at which point some restrictions will ease with an initial focus on outdoor settings.

"We've seen great progress in our fight against COVID-19 in recent weeks, but now is not the time to let our guard down," said Solicitor General Sylvia Jones. "With the Stay-At-Home order set to expire, we need to provide people with certainty so that they can continue to follow public health guidance. Doing so will help us to meet our goal of starting to gradually lift some restrictions when we enter Step One of the Roadmap when it is safe to do so."

On April 7, 2021, in response to the rapid increase in COVID-19 transmission driven by new, more contagious variants, the Ontario government declared a provincial emergency and issued a Stay-at-Home order as well as enhanced public health measures. In a concentrated effort to reduce mobility and opportunities for transmission, the Stay-At-Home order required Ontarians to remain at home except for the purposes set out in the order, such as exercise, going to the grocery store or pharmacy, or accessing health care services. Once the Stay-at-Home order expires on June 2, these restrictions will no longer be in effect.

However, all other existing measures will remain in place provincewide, including restrictions on gatherings, businesses, services and activities. This includes limiting indoor gatherings to households only and outdoor gatherings to up to five people, subject to limited exceptions, maintaining a cap of 25 per cent capacity for essential retail where only certain goods are permitted to be sold, restricting non-essential retail to curbside pickup and delivery only, as well as limiting short-term rentals to individuals in need of housing and allowing Ontario Parks and campgrounds on public lands to be used for day-use only, subject to limited exceptions.

Ontarians will be able to leave home to travel within the province to a secondary residence for any reason, however, they are not be permitted to host members of another household indoors except for a person from another household who lives alone or a caregiver.

A simple, easy-to-understand summary of restrictions can be found on the province's "Reopening Ontario" webpage, which provides details on what public health measures are in place before the province enters Step One of the Roadmap to Reopen. As always, anyone who may have been exposed to COVID-19 or who may be exhibiting symptoms of the virus should use the province's self-assessment tool to determine what they should do next, including getting a test and isolating if necessary.

"As we continue to accelerate second doses of the COVID-19 vaccine for Ontarians, maintaining public health measures will ensure we continue to protect our hospital capacity and help stop the spread of COVID-19 variants," said Christine Elliott, Deputy Premier and Minister of Health. "As we look towards Step One of Ontario's Roadmap and begin to gradually lift public health measures, it remains critical that all Ontarians continue to follow public health advice and roll up their sleeves to receive the vaccine. Every dose administered means we are one step closer to the end of the pandemic."

With the expiry of the Stay-at-Home order, emergency order O. Reg 266/21 (Residential Evictions) will also expire on June 2, 2021. Emergency orders currently in effect under the *Emergency Management and Civil Protection Act* have been extended until June 16, 2021:

- O. Reg. 8/21 Enforcement of COVID-19 Measures
- O. Reg. 55/21 Compliance Orders for Retirement Homes
- O. Reg. 271/21 Work Redeployment for Local Health Integration Networks and Ontario Health
- O. Reg. 272/21 Transfer of Hospital Patients

- O. Reg. 288/21 Closure of Public Lands for Recreational Camping
- O. Reg. 293/21 Persons Entering Ontario From Manitoba or Quebec
- O. Reg. 304/21 Work Redeployment for Independent Health Facilities
- O. Reg. 305/21 Regulated Health Professionals
- O. Reg. 317/21 Agreements Between Health Service Providers and Retirement Homes

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Additional Resources

- Ontario Releases Three-Step Roadmap to Safely Reopen the Province
- For up-to-date information on the province's vaccine rollout and instructions on how to book an appointment, visit Ontario's vaccine webpage.
- For resources in multiple languages to help local communication efforts in responding to COVID-19, visit Ontario's COVID-19 communication resources webpage.
- Visit Ontario's website to learn more about how the province continues to protect the people of Ontario from COVID-19.

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This is **Exhibit "Y"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

Update on COVID-19 Projections

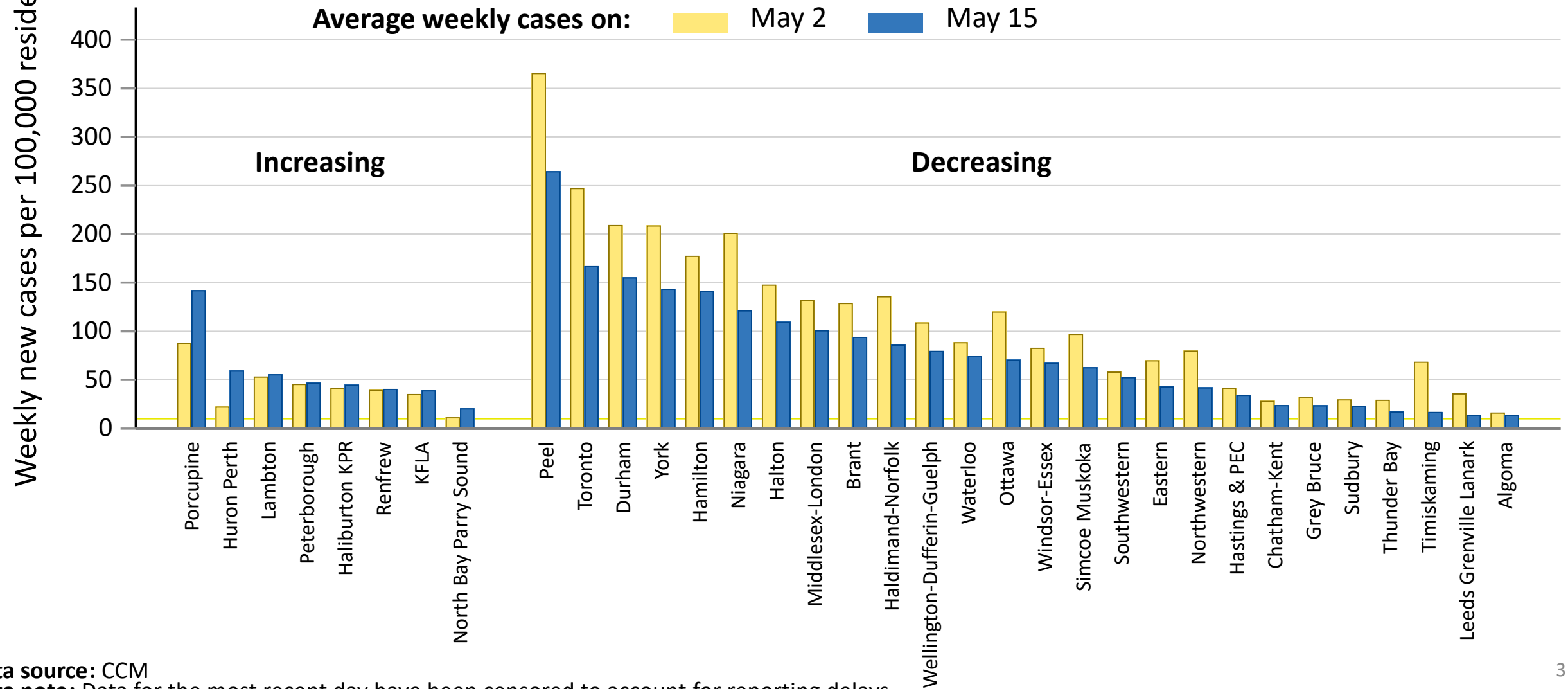
Science Advisory and Modelling Consensus Tables

May 20, 2021

Key Findings

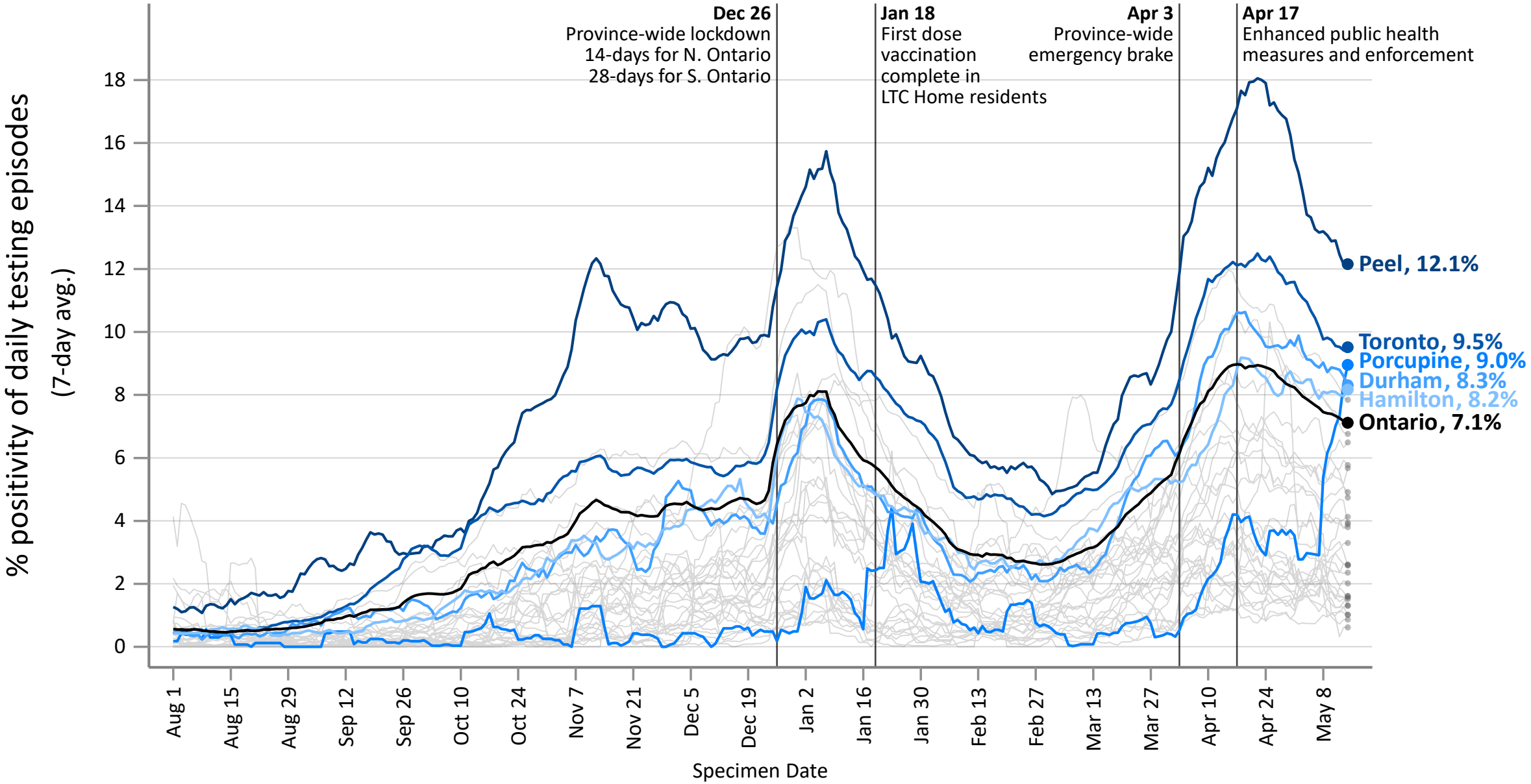
- Cases, positivity and hospitalization rates are decreasing. **Control of the pandemic is improving** due to current public health measures and the efforts of Ontarians.
- The access to care deficit continues but high-priority surgeries are being performed at higher rates.
- **Maintaining progress on vaccinations and maintaining some public health measures** until mid-June can help ensure a good summer:
  - School re-opening will create an increase in cases, but this may be manageable.
  - **Outdoor activities are much safer** than indoor activities and should be encouraged.

Cases are decreasing in most Public Health Units, with the greatest progress made in hotspot areas



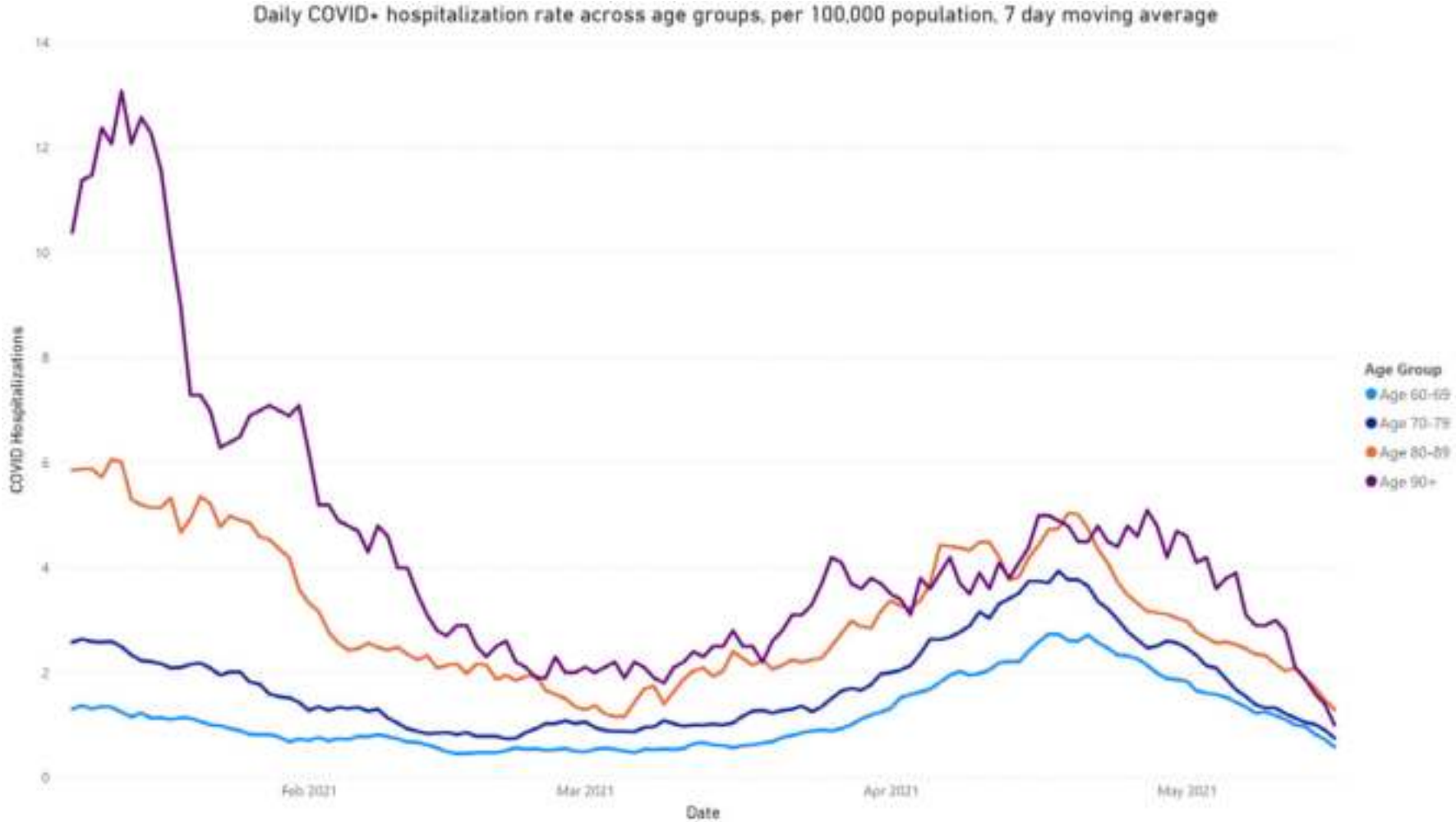
Data source: CCM
Data note: Data for the most recent day have been censored to account for reporting delays

% positivity is declining across Ontario

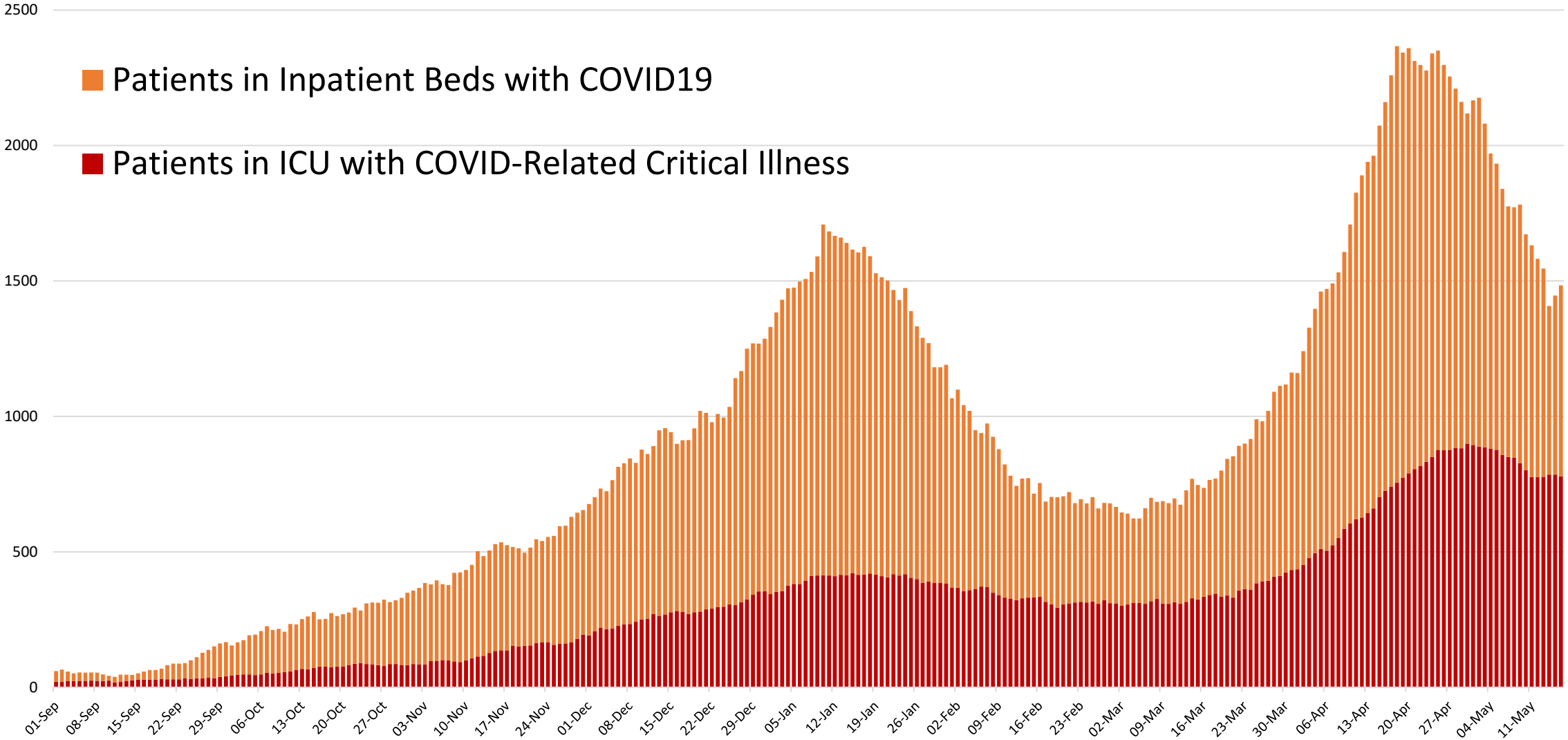


Data source: Ontario Laboratory Information System (OLIS), data up to May 14

Higher vaccination coverage is starting to control hospitalizations in older age groups



Hospitalization rates are down, ICU occupancy has dropped slightly



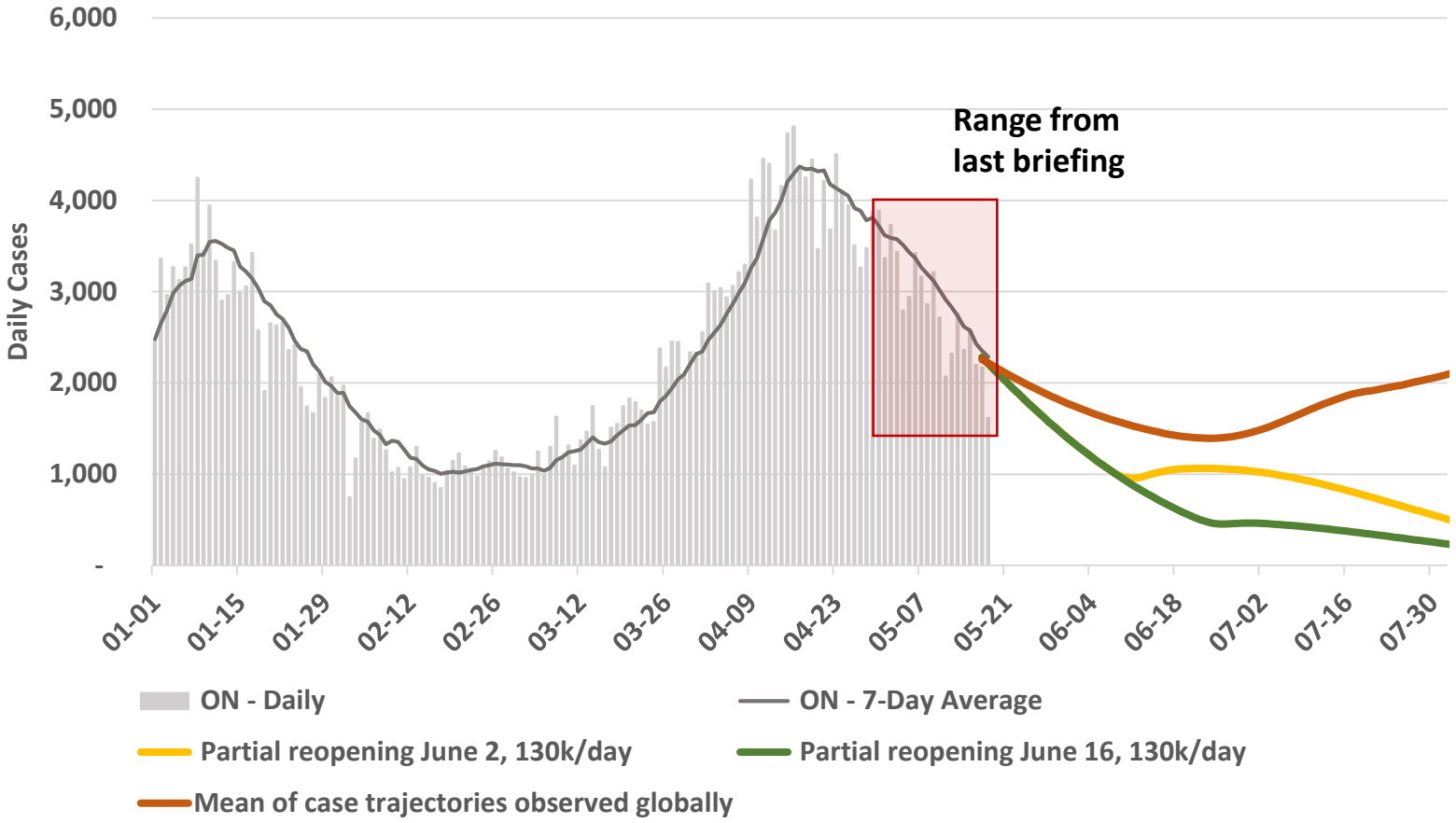
Data Sources: MOH COVID Inpatient Census and Critical Care Information System

Continued efforts to control spread of COVID-19 can help limit the impact of all variants of the virus

Figure shows predictions based on 5 models.

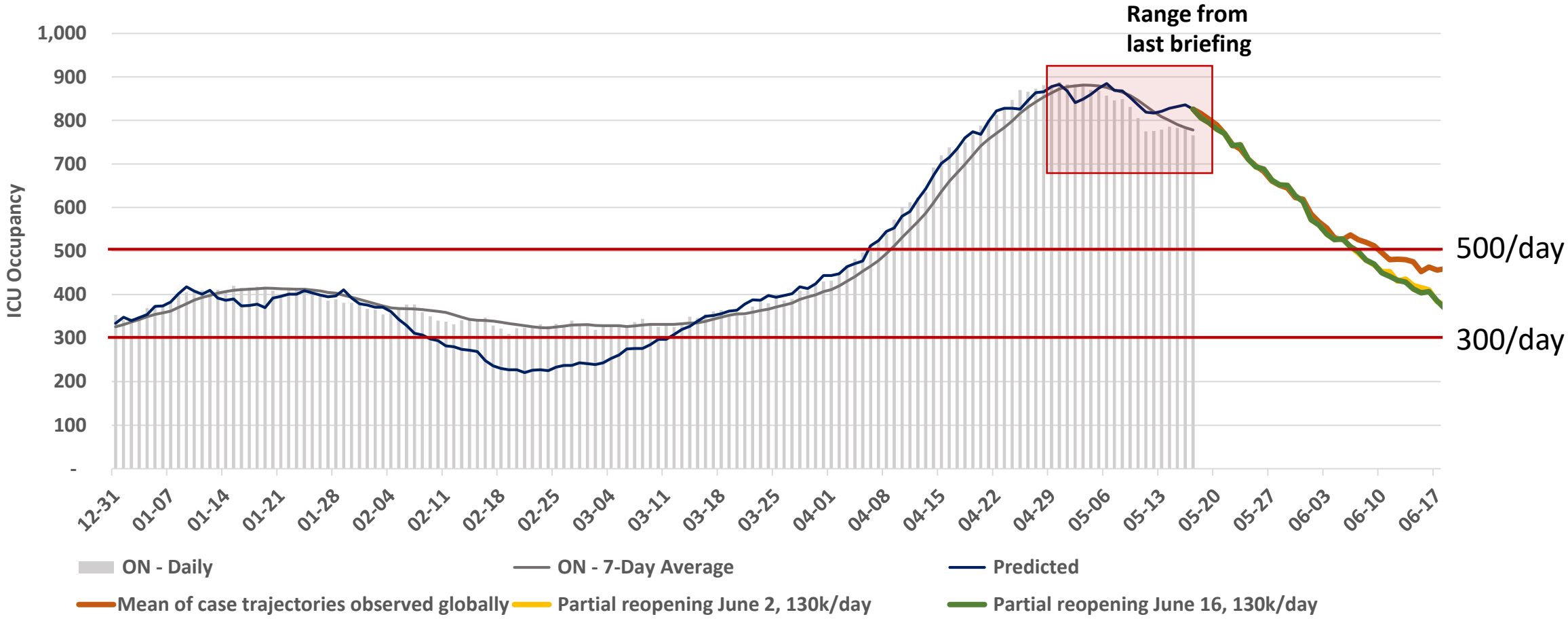
- Partial reopening June 2 or 16
- Vaccinating 100k-150k/day
- New VOC not explicitly considered

Not shown: 2 models looked at school opening June 2: School opening associated with a 6-11% increase in new daily cases



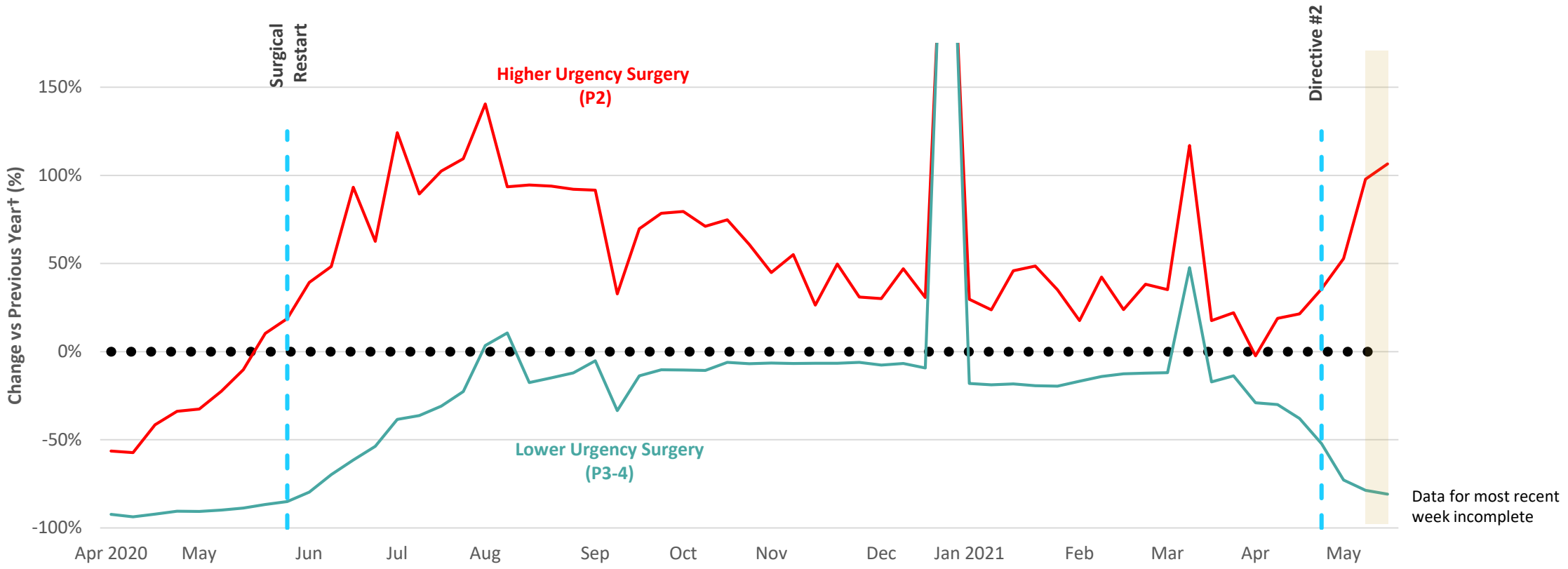
Predictions informed by modeling from COVID-19 ModCollab, Fields Institute, McMasterU, PHO, YorkU
Data (Observed Cases): covid-19.ontario.ca

ICU occupancy continues to decrease slowly, with potentially fewer than 500 patients with COVID-19 in ICUs by mid-June



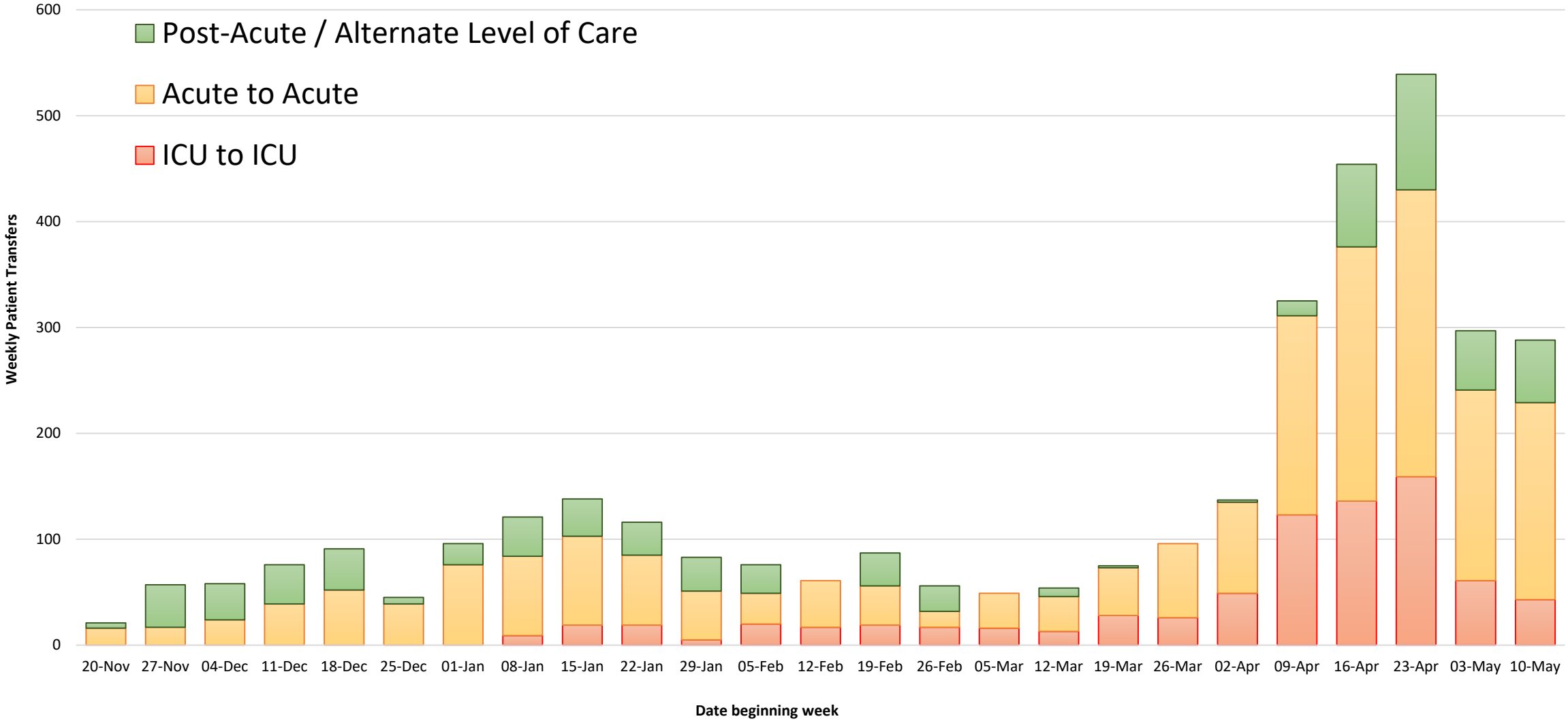
Predictions: COVID-19 ModCollab.
Data (Observed ICU Occupancy): CCSO

Higher priority procedures were more likely to be completed throughout the pandemic



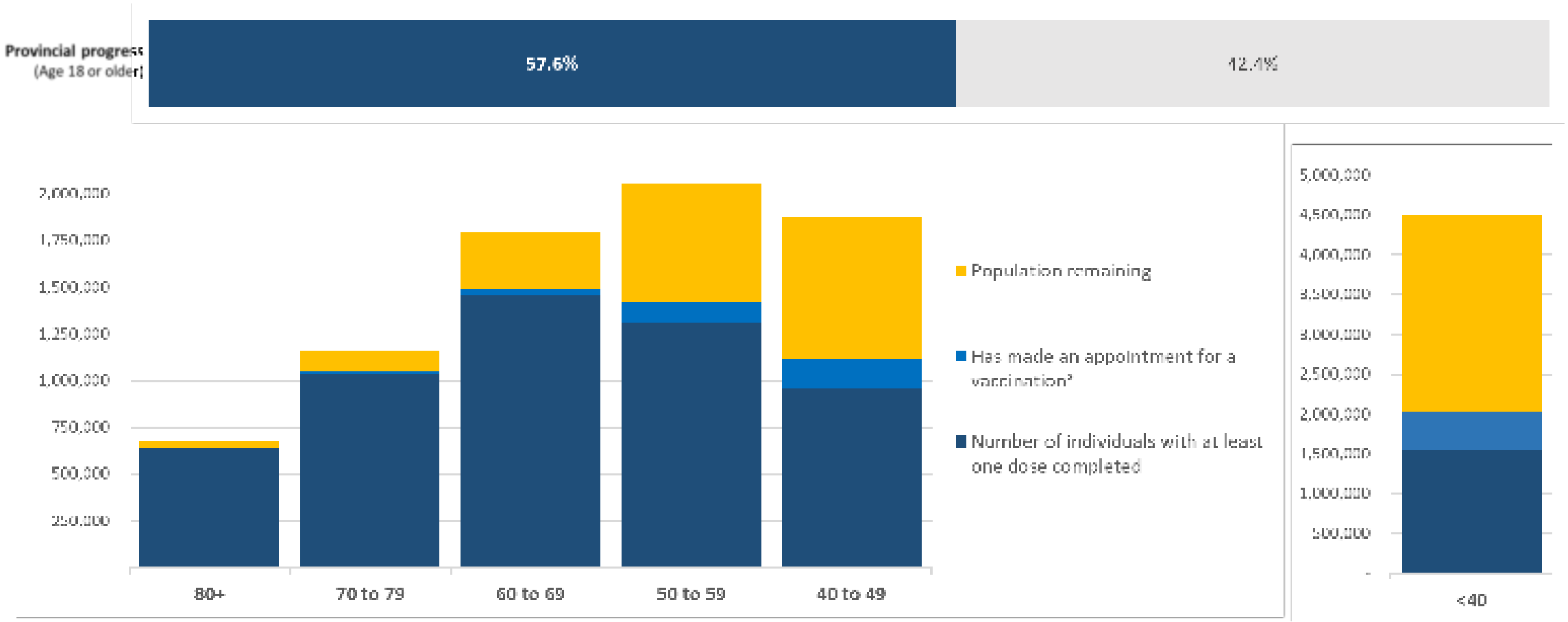
† As of the week of March 8, 2021, the comparator year was rolled back to 2019 to ensure the baseline for comparison continues to be pre-pandemic data

While the situation is improving, a high volume of patient transfers continues due to system capacity pressures



Data Sources: GTA IMS Transport Tracking, Ontario Health

Vaccination coverage continues to increase



* Note that this is just *Pending Appointments*. Anyone that has made an appointment and received a vaccine will be counted under "Individuals with at least one dose". Data for Appointments reflect 21 PHUs that are captured through the provincial booking system. Appointments made through other systems (e.g., local PHU booking systems, pharmacies, primary care) are not included.
Age is based on year of birth. Age <40 includes those age 18-39. Figure for age <40 is shown separately because of the difference in scale of the overall population size.

Data Sources
MOF 2020 Population Projections
COVAX analytical file, extracted, 8:00 pm May 18 2021, CPAD, MOH
COVAX Skedulo, extracted 6:00pm May 18 2021

The hotspot strategy is working. Continued efforts are key to a good summer.

Figure excludes long-term care vaccination – at least 1 dose as of May 17, 2021

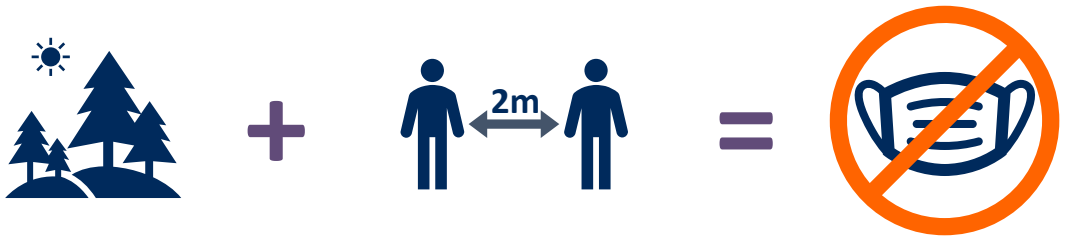
	Neighbourhood Risk‡ **1** = high incidence of COVID-19 infections → **10** = low incidence of COVID-19 infections										
Age group	1	2	3	4	5	6	7	8	9	10	**Overall**
80+	73%	75%	78%	80%	81%	83%	84%	86%	87%	87%	**82%**
75-79	75%	78%	80%	82%	83%	84%	85%	86%	87%	85%	**83%**
70-74	75%	79%	79%	81%	82%	83%	84%	85%	85%	82%	**82%**
65-69	75%	77%	77%	77%	79%	80%	81%	81%	81%	76%	**79%**
60-64	74%	76%	75%	74%	76%	77%	78%	77%	77%	70%	**75%**
55-59	70%	72%	68%	65%	66%	67%	67%	67%	65%	54%	**66%**
50-54	68%	68%	62%	57%	57%	56%	55%	54%	50%	41%	**57%**
45-49	61%	62%	56%	51%	51%	49%	49%	47%	41%	36%	**51%**
40-44	52%	55%	50%	46%	48%	46%	46%	43%	38%	33%	**46%**
16-39	41%	44%	38%	32%	31%	29%	29%	25%	21%	21%	**32%**
Overall (16+)	**57%**	**60%**	**55%**	**52%**	**53%**	**53%**	**53%**	**51%**	**51%**	**49%**	**54%**

Source: ICES

Outdoor activities can be much safer

Two-out-of-three rule for outdoor activities

Outdoors + Distance = No Masks Needed



Outdoors + No Distance = Masks Needed

Always wear masks and distance indoors

Byproducts to avoid when engaging in outdoor activities

Dining indoors, dining with others, sharing food or drinks

Crowding and going to crowded places

Carpooling with others

Travel between regions

Sharing overnight accommodation with others

Locker rooms and shared amenities

Marr L, Virginia Tech 2021

Select examples of safer outdoor activities

Camping

- Local camping with your own household is safer
- Camping elsewhere with your own household is not safer
- Camping with people outside your household is not safer

Basketball

- Basketball with masks is safer

Tennis

- Single tennis is safer
- Doubles tennis with masks is safer

Singing and playing music

- Singing outside where there is social distancing is safer

Note: Indoor facilities associated with outdoor recreation (e.g., change rooms and clubhouses) present a greater risk and should remain closed at this time

Key Findings

- Cases, positivity and hospitalization rates are decreasing. **Control of the pandemic is improving** due to current public health measures and the efforts of Ontarians.
- The access to care deficit continues but high-priority surgeries are being performed at higher rates.
- **Maintaining progress on vaccinations and maintaining some public health measures** until mid-June can help ensure a good summer:
  - School re-opening will create an increase in cases, but this may be manageable.
  - **Outdoor activities are much safer** than indoor activities and should be encouraged.

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* Chairs of Scientific Advisory, Evidence Synthesis, and Modelling Consensus Tables

For table membership and profiles, please visit the About and Partners pages on the Science Advisory Table website.

This is **Exhibit "Z"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

INSTRUCTIONS FROM THE MEDICAL OFFICER OF HEALTH

DATE: Thursday June 10, 2021 **EFFECTIVE:** Friday, June 11, 2021 at 12:01 a.m.

TO: All persons responsible for a business or organization **(workplace)** in the Porcupine Health Unit **(PHU)** region, where workers (including employees, those hired under third party agencies, contractors, vendors, volunteers or students and any other such persons) are present at the workplace or the public are regularly present.

First of all, I would like to thank you for your ongoing efforts to comply with public health requirements that aim to protect your staff, patrons and other members of our community. I would like to thank you for your strong commitment to encourage workers to receive their vaccinations against COVID-19.

As much as we have achieved by working together in the face of this pandemic, at this time, I must ask for your continued patience and support in the interests of protecting the health of our community.

While our vaccination rates are strong and growing daily, other trends in public health and health system indicators are very concerning:

- Our data reflects that Porcupine Health Unit has one of the highest rates of COVID-19 transmission in the province, with approximately 300 cases per 100,000 for the past 3 weeks;
- There have been multiple COVID-19 outbreaks across the region, including in workplaces and remote communities with limited access to health care services;
- The surge in cases in our community has affected health care and public health capacity, requiring additional support from other health units as well as the Ontario Ministry of Health's Provincial Work Force;
- We have clear evidence that the Delta variant – significantly more transmissible than the B.1.1.7 variant – is circulating in our region - with cases confirmed so far in Timmins. The Province has identified Porcupine as one of the seven health unit regions where the delta variant is of concern.

These trends are worrisome and require extreme caution as we move to lift public health measures. Some municipalities and First Nation communities have already responded to these developments by declaring a state of emergency.

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Web site: www.porcupinehu.on.ca

Branch Offices: Cochrane, Hearst, Hornepayne, Iroquois Falls, Kapuskasing, Matheson,
Moosonee, Smooth Rock Falls

With strong support from Ontario's Chief Medical Officer of Health, who recognizes the need for an approach tailored to the Porcupine Health Unit's unique circumstances, we will therefore be taking more gradual approach to reopening starting on June 11, 2021 at 12:01 a.m.

While operating under some of the new provincial Step 1 Rules immediately, we must maintain some Shutdown-level restrictions to minimize the person-to-person interactions that are fueling uncontrolled transmission of COVID-19 within our communities.

I anticipate these continued Shutdown-level restrictions will remain necessary for no longer than the next two weeks, remaining in place until June 25, 2021 at 12:01 a.m. I will regularly assess our progress against key public health and health system indicators and will report publicly on our progress.

Ontario's new Step 1 Rule continue to require persons responsible for a business or organization that is open to operate the business or organization in compliance with the instructions of public health officials. This includes the following instructions issued by me in this document.

These instructions will be enforced by provincial offences officers and public health officials under one or more of the *Health Protection and Promotion Act*, *Reopening Ontario (A Flexible Response to COVID-19) Act, 2020* and/or the *Emergency Management and Civil Protection Act*. Failure to comply is a provincial offence. Among enforcement actions that may be taken, you may be charged, and penalties imposed including fines, imprisonment and/or closure of premises.

Should you have any questions, please do not hesitate to contact the Porcupine Health Unit at 1-800-461-1818 or visit our website: https://www.porcupinehu.on.ca/en/your-health/infectious-diseases/novel-coronavirus/covid-orders/covid-moh-instructions/.

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These instructions remain in effect until amended or rescinded by me.

ENSURE STRICT COMPLIANCE WITH ALL STEP 1 RULES AND INSTRUCTIONS THAT APPLY

1. You must familiarize yourself with all Step 1 Rules and instructions that apply to your workplace and ensure strict compliance with them, at all times, by workers and members of the public present at the workplace.

2. Ontario's Step 1 Rules are contained at Schedules 6 through 10 of Ontario Regulation 82/20 and may be accessed at: https://www.ontario.ca/page/emergency-information. The Shutdown Rules are contained at Schedules 1 through 5 of this same regulation.

3. Until more positive trends in key public health and health system indicators are demonstrated in the PHU region, the instructions set out in paragraphs 5 to 39 below continue some Shutdown-level requirements, maintaining a higher level of restriction than the Step 1 Rules. For greater certainty, nothing in the Step 1 Rules or in these instructions precludes any business or organization from:

    a) providing goods by mail or other forms of delivery or making goods available for pick-up; and
    b) providing services online, by telephone or by other remote means.[1]

[1] See Step 1 Rules, section 1(7), Schedule 6, O. Reg. 82/20

4. **Physical distancing and masks or face coverings in lines, etc.** In addition to the requirements of section 5, Schedule 6, O. Reg. 82/20, the person responsible for a business or place that is open must not permit patrons to line up or congregate outside of the business or place, unless they are both,

    a) maintaining a physical distance of at least two metres from other groups of persons; and
    b) wearing a mask or face covering in a manner that covers their mouth, nose and chin, unless they are entitled to any of the exceptions set out in subsection 2(5) Schedule 6, O. Reg. 82/20.[2]

5. **Sale and service of liquor.**

    a) The person responsible for a business or place that is open and in which liquor is sold or served under a licence or a special occasion permit shall ensure that,
        i. liquor is sold or served only between 9 a.m. and 9 p.m.; and
        ii. no consumption of liquor is permitted in the business or place between the hours of 10 p.m. and 9 a.m.
    b) The conditions set out in subsection a) do not apply with respect to businesses and places in airports.
    c) The conditions set out in subsection a) do not apply with respect to,
        i. the sale of liquor for removal from licensed premises in accordance with section 56.1 of Regulation 719 (Licences to Sell Liquor) made under the Liquor Licence Act; and
        ii. the sale of liquor for delivery in accordance with section 56.2 of Regulation 719 (Licences to Sell Liquor) made under the *Liquor Licence Act*.

6. **Discount and big box retailers selling groceries.** In addition to the requirements of section 2, Schedule 7, O. Reg. 82/20, discount and big box retailers that engage in retail sales to the public must meet the following conditions:

    a) The discount or big box retailer sells groceries to the public.
    b) In-store shopping must only be available for grocery items, pet care supplies, household cleaning supplies, pharmaceutical items, health care items, school supplies, household safety supplies and personal care items.
    c) No other goods or services may be sold to the public unless the discount or big box retailer complies with any conditions that are applicable with respect to the sale of those goods or services by other retail establishments under the Step 1 Rules as modified by these instructions (e.g., to exclude in-store shopping for non-essential retail etc.).[3]

7. **Safety supply stores.** In addition to the requirements of section 2, Schedule 7, O. Reg. 82/20, safety supply stores must meet the following conditions:

    a) They must only permit members of the public to enter the business premises by appointment.
    b) They must open no earlier than 7:00 a.m. and close no later than 8:00 p.m. and must not deliver goods to patrons outside of the hours of 6:00 a.m. to 9:00 p.m.[4]

[2] See Shutdown Rules, section 4, Schedule 1, O. Reg. 82/20
[3] See Shutdown Rules, section 3(1), Schedule 2, O. Reg. 82/20
[4] See Shutdown Rules, section 4(2), Schedule 2, O. Reg. 82/20

8. **Businesses that primarily sell, rent or repair assistive devices, aids or supplies, mobility devices, aids or supplies or medical devices, aids or supplies.** In addition to the requirements of section 2, Schedule 7, O. Reg. 82/20, these businesses must meet the following conditions:

    a) They must only permit members of the public to enter the business premises by appointment.
    b) They must open no earlier than 7:00 a.m. and close no later than 8:00 p.m. and must not deliver goods to patrons outside of the hours of 6:00 a.m. to 9:00 p.m.[5]

9. **Optical stores that sell prescription eyewear to the public.** In addition to the requirements of section 2, Schedule 7, O. Reg. 82/20, these stores must meet the following conditions:

    a) They must only permit members of the public to enter the business premises by appointment.
    b) They must open no earlier than 7:00 a.m. and close no later than 8:00 p.m. and must not deliver goods to patrons outside of the hours of 6:00 a.m. to 9:00 p.m.[6]

10. **Retail stores operated by telecommunications providers.** In addition to the requirements of sections 2 and 30, Schedule 7, O. Reg. 82/20, these stores must meet the following conditions:

    a) They must only permit members of the public to enter the premises by appointment and only for the purchase of cell phones, for repairs or for technical support.
    b) They must open no earlier than 7:00 a.m. and close no later than 8:00 p.m. and must not deliver goods to patrons outside of the hours of 6:00 a.m. to 9:00 p.m.[7]

11. **Stores, other than establishments described in section 3, Schedule 7, O. Reg. 82/20, that sell liquor, including beer, wine and spirits.** In addition to the requirements of section 2, Schedule 7, O. Reg. 82/20, these stores must meet the following condition:

    a) They must open no earlier than 7:00 a.m. and close no later than 8 p.m. and must not deliver goods to patrons outside of the hours of 6:00 a.m. to 9:00 p.m.[8]

12. **Outdoor garden centres and plant nurseries.** In addition to the requirements of section 2, Schedule 7, O. Reg. 82/20, outdoor garden centres and plant nurseries must meet the following condition:

    a) They must open no earlier than 7:00 a.m. and close no later than 8:00 p.m. and must not deliver goods to patrons outside of the hours of 6:00 a.m. to 9:00 p.m.[9]

13. **Indoor greenhouses.** In addition to the requirements of section 2, Schedule 7, O. Reg. 82/20, indoor greenhouses must meet the following condition:

    a) They must open no earlier than 7:00 a.m. and close no later than 8:00 p.m. and must not deliver goods to patrons outside of the hours of 6:00 a.m. to 9:00 p.m.[10]

[5] See Shutdown Rules, section 4(2), Schedule 2, O. Reg. 82/20
[6] See Shutdown Rules, section 4(2), Schedule 2, O. Reg. 82/20
[7] See Shutdown Rules, section 33, Schedule 2, O. Reg. 82/20
[8] See Shutdown Rules, section 5, Schedule 2, O. Reg. 82/20
[9] See Shutdown Rules, section 9.1, Schedule 2, O. Reg. 82/20
[10] See Shutdown Rules, section 9.2, Schedule 2, O. Reg. 82/20

14. **Restaurants, bars, food trucks, concession stands and other food or drink establishments.** In addition to the requirements of section 3, Schedule 7, O. Reg. 82/20, establishments other than those described in subsection (3) may open only for the purpose of providing take-out, drive-through or delivery service.[11]

15. **Nightclubs and strip clubs that open solely as food or drink establishments.** In addition to the requirements of section 4, Schedule 7, O. Reg. 82/20, these nightclubs and strip clubs may open only for the purpose of providing take-out, drive-through or delivery service.[12]

16. **Shopping malls.** In addition to the requirements of section 5, Schedule 7, O. Reg. 82/20, shopping malls must meet the following conditions:

    a) Members of the public must only be permitted to enter the shopping mall for the purpose of accessing a business or place that is permitted to be open under the Step 1 Rules as modified by these instructions.
    b) Subject to subparagraph c), the shopping mall must open no earlier than 7:00 a.m. and close no later than 8:00 p.m. and must not deliver goods to patrons outside of the hours of 6:00 a.m. to 9:00 p.m.
    c) A shopping mall may open outside of the hours described in subparagraph b) only for the purpose of providing access for members of the public to a business or place that,
        i. is permitted to open during those hours under the Step 1 Rules as modified by these instructions; and
        ii. only has public entrances that open into the interior of the shopping mall.
    d) For greater certainty, section 8(2) paragraph 5 of Schedule 7, O. Reg. 82/20 does not prevent a restaurant, bar or other food or drink establishment within a shopping mall from opening and operating in compliance with section 3 of Schedule 7 as modified by these instructions.[13]

17. **Fitting rooms in a business.** Fitting rooms in a business may open if patrons are not permitted to occupy adjacent fitting room stalls at any one time.[14]

18. **Businesses that sell motor vehicles etc.** These requirements apply to businesses that sell:

    - Motor vehicles, including cars, trucks and motorcycles;
    - Recreational vehicles, including motor homes;
    - Trailers and travel trailers;
    - Boats and other watercraft; or
    - Other motorized vehicles, including power-assisted bicycles, golf carts, scooters, snowmobiles and all-terrain vehicles.

    In addition to the requirements of section 5.2, Schedule 7, O. Reg. 82/20, these businesses must meet the following conditions:

    a) Members of the public must only be permitted to enter the premises by appointment.

    b) They must open no earlier than 7:00 a.m. and close no later than 8:00 p.m. and must not deliver goods to patrons outside of the hours of 6:00 a.m. to 9:00 p.m.

[11] See Shutdown Rules, section 6, Schedule 2, O. Reg. 82/20
[12] See Shutdown Rules, section 6, Schedule 2, O. Reg. 82/20
[13] See Shutdown Rules, section 8, Schedule 2, O. Reg. 82/20
[14] See Shutdown Rules, section 8.1, Schedule 2, O. Reg. 82/20

c) They must limit the number of persons in the place of business so that the total number of persons in the place of business at any one time does not exceed 25 per cent capacity, as determined in accordance with subsection 3(3) of Schedule 6.[15]

19. **Outdoor markets, including farmer's markets and holiday markets.** In addition to the requirements of section 6, Schedule 7, O. Reg. 82/20, these markets must meet the following conditions:

    a) Products must only be provided to patrons,
        i. in a manner that allows members of the public to remain in an outdoor area at all times, or
        ii. through an alternative method of sale that does not require patrons to enter the indoor area, such as curbside pick-up or delivery.
    b) The outdoor market must open no earlier than 7:00 a.m. and close no later than 8:00 p.m. and must not deliver goods to patrons outside of the hours of 6:00 a.m. to 9:00 p.m.[16]

20. **Other businesses engaging in retail sales to the public.** In addition to the requirements of section 7, Schedule 7, O. Reg. 82/20, these businesses must meet the following conditions:

    a) Sales must be exclusively made using an alternative method of sale that does not require patrons to enter the indoor area of the business, including curbside pick-up or delivery.
    b) If the business allows patrons to pick up items, it must,
        i. have a public entrance that opens onto a street or exterior sidewalk, or
        ii. in the case of a business in a shopping mall, permit patrons to pick up the items at a designated location established by the shopping mall under subsection 8 (3) or (4).
    c) An item may only be provided for pick-up if the patron ordered the item before arriving at the business premises.
    d) Patrons may only pick up orders by making a prior appointment.
    e) They must open no earlier than 7:00 a.m. and close no later than 8:00 p.m. and must not deliver goods to patrons outside of the hours of 6:00 a.m. to 9:00 p.m.
    f) Despite anything else in the Step 1 Rules, any business that engages in retail sales to the public and that is not already described in sections 1 to 6 of Schedule 7, must comply with the conditions set out in subsection 7(1) as modified by these instructions.
    g) Cannabis retail stores operating under the authority of a retail store authorization issued under the *Cannabis Licence Act, 2018* may open if they comply with the conditions set out in subsection 7(1) as modified by these instructions.[17]

21. **Rental and leasing services.** Further to section 8, Schedule 7, O. Reg. 82/20, rental and leasing services including automobile, commercial and light industrial machinery and equipment rental must meet the following conditions:

    a) They only permit members of the public to enter the business premises by appointment.
    b) They limit the number of persons in the place of business so that the total number of persons in the place of business at any one time does not exceed 25 per cent capacity, as determined in accordance with subsection 3 (3) of Schedule 6.

[15] See Shutdown Rules, section 9, Schedule 2, O. Reg. 82/20
[16] See Shutdown Rules, section 10, Schedule 2, O. Reg. 82/20
[17] See Shutdown Rules, section 10.1, Schedule 2, O. Reg. 82/20

c) They must open no earlier than 7:00 a.m. and close no later than 8:00 p.m. and must not deliver goods to patrons outside of the hours of 6:00 a.m. to 9:00 p.m.[18]

22. **Vehicle and equipment repair, essential maintenance etc.** Further to section 15, Schedule 7, O. Reg. 82/20, vehicle and equipment repair and essential maintenance and vehicle and equipment rental services must meet the following conditions:

    a) They only permit members of the public to enter the business premises by appointment.
    b) They limit the number of persons in the place of business so that the total number of persons in the place of business at any one time does not exceed 25 per cent capacity, as determined in accordance with subsection 3 (3) of Schedule 6.
    c) They must open no earlier than 7:00 a.m. and close no later than 8:00 p.m. and must not deliver goods to patrons outside of the hours of 6:00 a.m. to 9:00 p.m.[19]

23. **Child care providers.** For greater certainty further to section 21, Schedule 7, O. Reg. 82/20, the term "child care providers" includes but is not limited to operators and providers of the following:

    a) Child care centres that meet the conditions set out in subsection 21(2) of Schedule 7.
    b) Home child care at a person's dwelling.
    c) Child care described in paragraph 2 of subsection 6 (3) of the *Child Care and Early Years Act, 2014* that is provided at a person's dwelling.
    d) Authorized recreational and skill building programs that meet the conditions set out in subsection 21(3) of Schedule 7.[20]

24. **Businesses providing short term rental accommodation.** In addition to the requirements of section 21.1, Schedule 7, O. Reg. 82/20, businesses providing short term rental accommodation (including cabins and cottages but excluding hotels, motels, lodges, resorts and other shared rental accommodation including student residences) shall ensure that any rentals are only provided to individuals who are in need of housing.[21]

25. **Campgrounds.** In addition to the requirements of section 23, Schedule 7, O. Reg. 82/20, campgrounds must meet the following conditions:

    a) Campsites must be made available only for trailers and recreational vehicles that,
        i. are used by individuals who are in need of housing, or
        ii. are permitted to be there by the terms of a full season contract.
    b) Only campsites with electricity, water service and facilities for sewage disposal may be provided for use.
    c) All recreational facilities in the campground and all other shared facilities in the campground, other than washrooms and showers, must be closed.
    d) Other areas of the seasonal campground must be closed to the general public and must only be opened for the purpose of preparing the seasonal campground for reopening.[22]

[18] See Shutdown Rules, section 11, Schedule 2, O. Reg. 82/20
[19] See Shutdown Rules, section 18, Schedule 2, O. Reg. 82/20
[20] See Shutdown Rules, section 24, Schedule 2, O. Reg. 82/20
[21] See Shutdown Rules, section 6, Schedule 2, O. Reg. 82/20
[22] See Shutdown Rules, section 26, Schedule 2, O. Reg. 82/20

26. **Day camps for children.** Further to section 15, Schedule 7, O. Reg. 82/20, day camps for children must not provide in-person activities or services.[23]

27. **Construction.** Further to section 40, Schedule 7, O. Reg. 82/20, construction activities or projects and related services, including land surveying and demolition services continue to be restricted to those that:

    a) are associated with the health care sector or long-term care, including new facilities, expansions, renovations and conversion of spaces that could be repurposed for health care space;
    b) ensure safe and reliable operations of, or provide new capacity in,
        i. municipal infrastructure, or
        ii. provincial infrastructure, including but not limited to, the transit, transportation, resource, energy and justice sectors;
    c) support the operations of, or provide new capacity in, electricity generation, transmission, distribution and storage, natural gas distribution, transmission and storage or in the supply of resources;
    d) support the operations of, or provide new capacity in, schools, colleges, universities or child care centres within the meaning of the Child Care and Early Years Act, 2014;
    e) are required for,
        i. the maintenance and operations of petrochemical plants and refineries,
        ii. significant industrial petrochemical projects where preliminary work commenced before April 17, 2021, or
        iii. industrial construction and modifications to existing industrial structures limited solely to work necessary for the production, maintenance or enhancement of personal protective equipment, medical devices such as ventilators and other identified products directly related to combatting the COVID-19 pandemic;
    f) would provide additional capacity in the production, processing, manufacturing or distribution of food, beverages or agricultural products;
    g) were commenced before April 17, 2021 and that would,
        i. provide additional capacity for businesses that provide logistical support, distribution services, warehousing, storage or shipping and delivery services,
        ii. provide additional capacity in the operation and delivery of Information Technology (IT) services or telecommunications services, or
        iii. provide additional capacity to, or enhance the efficiency or operations of, businesses that extract, manufacture, process and distribute goods, products, equipment and materials;
    h) support the operations of broadband internet and cellular technologies and services;
    i) are residential construction activities or projects and related services;
    j) prepare a site for an institutional, commercial, industrial or residential development, including any necessary excavation, grading, roads or utilities infrastructure;
    k) are necessary to temporarily close construction sites that have paused, or that are not active, to ensure ongoing public safety;
    l) are funded in whole or in part by,
        i. the Crown in right of Canada or in right of Ontario,
        ii. an agency of the Crown in right of Canada or in right of Ontario, or

[23] See Shutdown Rules, Schedule 2, O. Reg. 82/20

iii. a municipality;

m) are,

i. intended to provide shelter or supports for vulnerable persons or affordable housing, and

ii. being funded in whole or in part by, or are being undertaken by,
(A) the Crown in right of Canada or in right of Ontario,
(B) an agency of the Crown in right of Canada or in right of Ontario,
(C) a municipality,
(D) a service manager as defined the *Housing Services Act, 2011*,
(E) a registered charity within the meaning of the *Income Tax Act* (Canada), or
(F) a not-for-profit corporation; or

n) support the operations of, or provide new capacity for, veterinary facilities within the meaning of the *Veterinarians Act*.[24]

28. **Facilities for indoor or outdoor sports and recreational fitness activities.** In addition to the requirements of section 45, Schedule 7, O. Reg. 82/20, indoor or outdoor sports and recreational activities at indoor or outdoor sports and recreational fitness are restricted to those that meet the conditions set out in subsections 45(2), (3), (4) and (5) only. For greater certainty, no indoor or outdoor sports or recreational classes are permitted at any indoor or outdoor sport and recreational facilities.[25] See also paragraph 37 of these instructions, below.

29. **Personal physical fitness, etc.** Further to section 45.1, Schedule 7, O. Reg. 82/20, personal fitness and sports trainers must not provide in-person services.[26]

30. **Teaching and instruction.** Further to section 57.1, Schedule 7, O. Reg. 82/20, must not provide in-person services.[27]

31. **Commercial film and television production.** In addition to the requirements of section 63, Schedule 7, O. Reg. 82/20, commercial film and television production, including all supporting activities, must meet the following condition:

    a) Singers and players of brass or wind instruments must be separated from any other performers by plexiglass or some other impermeable barrier.[28]

32. **Commercial and industrial photography.** Further to section 63.1, Schedule 7, O. Reg. 82/20, retail photo studios must not provide in-person services.[29]

33. **Concert venues, theatres and cinemas.** Further to section 65, Schedule 7, O. Reg. 82/20, concert venues, theatres and cinemas must not engage in in-person activities for the purpose of rehearsing or performing a recorded or broadcasted concert, artistic event, theatrical performance or other performance. For

[24] See Shutdown Rules, section 43, Schedule 2, O. Reg. 82/20
[25] See Shutdown Rules, section 48, Schedule 2, O. Reg. 82/20
[26] See Shutdown Rules, Schedule 2, O. Reg. 82/20
[27] See Shutdown Rules, Schedule 2, O. Reg. 82/20
[28] See Shutdown Rules, section 63, Schedule 2, O. Reg. 82/20
[29] See Shutdown Rules, section 66, Schedule 2, O. Reg. 82/20

greater certainty, drive-in or drive-through format movies, concerts, artistic events, theatrical performances or other performances are not permitted.[30]

34. **Outdoor tour and guide services.** Further to section 66, Schedule 7, O. Reg. 82/20, outdoor tour and guide services are not permitted to provide in-person services.[31]

35. **Public libraries.** In addition to the requirements of section 1, Schedule 8, O. Reg. 82/20, public libraries must meet the following condition:

    a) Circulating materials returned to the library must be disinfected or quarantined for an appropriate period of time before they are recirculated.[32]

36. **Schools and private schools.** In addition to the requirements of section 3, Schedule 8, O. Reg. 82/20, schools and private schools within the meaning of the *Education Act* must meet the following condition:

    a) the in-person activities addressed in subsection 3(5) are not permitted.[33]

37. **Indoor and outdoor recreational amenities.** In addition to the requirements of section 4, Schedule 8, O. Reg. 82/20, an outdoor recreational amenity described in subsection 4(2) must meet the following conditions:

    a) Team sports must not be practised or played within the amenity.
    b) Any locker rooms, change rooms, showers, clubhouses, restaurants, pools, meeting rooms, fitness centres or other recreational facilities on the premises must remain closed, except to the extent they provide access to equipment storage, a washroom or a portion of the amenity that is used to provide first aid.[34]

38. **Museums etc.** Further to section 5, Schedule 8, O. Reg. 82/20, museums, galleries, aquariums, zoos, science centres, landmarks, historic sites, botanical gardens and similar attractions must not provide in-person services.[35]

39. **Organized public events, gatherings.** In addition to the requirements of section 1, Schedule 9, O. Reg. 82/20, all businesses and organizations that are open are subject to the following conditions:

    a) They must not host, organize or otherwise participate in an organized public event or social gathering that is held indoors, including a public event or social gathering associated with a wedding, a funeral or a religious service, rite or ceremony even if it is held at a private dwelling.
    b) They must not host, organize or otherwise participate in an organized public event or social gathering of more than 5 people that is held outdoors, including a public event or social gathering associated with a wedding, a funeral or a religious service, rite or ceremony even if it is held at a private dwelling.

[30] See Shutdown Rules, Schedule 2, O. Reg. 82/20
[31] See Shutdown Rules, Schedule 2, O. Reg. 82/20
[32] See Shutdown Rules, s.1, Schedule 3, O. Reg. 82/20
[33] See Shutdown Rules, s.3, Schedule 3, O. Reg. 82/20
[34] See Shutdown Rules, s.4, Schedule 3, O. Reg. 82/20
[35] See Shutdown Rules, s.5, Schedule 3, O. Reg. 82/20

c) They must not host, organize or otherwise participate in an indoor or outdoor gathering of more than 10 people for the purposes of a wedding, a funeral or a religious service, rite or ceremony even if it is held at a private dwelling.[36]

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Lianne Catton, MD, CCFP-EM, MPH
Medical Officer of Health and Chief Executive Officer
Porcupine Health Unit
Postal Bag 2012
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Timmins, ON P4N 8B7

These instructions shall be posted at: https://www.porcupinehu.on.ca/en/your-health/infectious-diseases/novel-coronavirus/covid-orders/covid-moh-instructions/.
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[36] See Shutdown Rules, s.1, Schedule 4, O. Reg. 82/20

Instructions from the Medical Officer of Health for Businesses and Workplaces (Moosonee): 2021-06-25

DATE: Wednesday June 23, 2021

EFFECTIVE: Friday, June 25, 2021 at 12:01 a.m.

TO:

All persons responsible for a business or organization **(workplace)** in the Town of Moosonee within the Porcupine Health Unit **(PHU)** region, where workers (including employees, those hired under third party agencies, contractors, vendors, volunteers or students and any other such persons) are present at the workplace or the public are regularly present.

Once again, I thank you for your ongoing efforts to comply with public health requirements that aim to protect your staff, patrons and other members of our community. I also thank you for your strong commitment to encourage workers to receive their vaccinations against COVID-19.

As much as we have achieved by working together in the face of this pandemic, however, I must ask for your continued support in the interests of protecting the health of our community. While our vaccination rates are strong and growing daily, other trends in public health and health system indicators are very concerning:

- A total of 1,353 confirmed COVID-19 cases have been reported between May 1st and June 21, 2021. Of these, 437 cases were reported in the James and Hudson Bay region.
- In May, 72 cases were reported from the James and Hudson Bay region (average of 2.3 cases per day) and 155 cases were reported between June 11th and June 17th (average of 22.1 cases per day) and 41 cases were reported between June 18th and June 22nd (average of 8.2 cases per day).
- PHU's overall infection rate increased by 278% from 93.5 per 100,000 on May 1 to a high of 353.5 per 100,000 on May 25. Since then, the rate has decreased but remains high at 101.9 per 100,000 on June 21, 2021.
- More cases have been confirmed for the Delta variant. As of June 22, 2021, a total of 30 Delta VOCs has been detected to date in the PHU area.
  - Of these 30 Delta VOCs, 28 were from the Timmins area, 1 from Iroquois Falls and 1 from Smooth Rock Falls.
  - These 30 Delta variants likely reflect only a tip of the iceberg. Because it is highly transmissible, more cases are expected as further results from tests in progress are received.
- A total of 63 confirmed COVID-19 cases in the PHU area have been hospitalized in the period since May 1.

- Thirty-three outbreaks have been declared in different settings since March 27, 2021, twenty of which are in workplaces resulting in 238 cases and 786 close contacts.

These trends are worrisome and require extreme caution and enhanced diligence with the public health measures as we move to lift the current restrictions.

Ontario's new Step 1 Rules that apply in the PHU Region continue to require persons responsible for a business or organization that is open to operate the business or organization in compliance with the instructions of public health officials. This includes the following instructions issued by me in this document.

Ontario's Chief Medical Officer of Health has recognized the need for an approach tailored to the PHU's unique circumstances, requiring a more gradual approach to reopening beginning on June 11, 2021. The Town of Moosonee, in particular, faces special challenges given its important role and connections with many remote communities – including but not limited to Moose Factory and 6 unique First Nation communities.

With strong support from leadership within the town of Moosonee and region I have therefore determined that some continued restrictions – set out in the instructions below – are needed for Moosonee as we move to reopen under Ontario's Step 1 Rules.

These instructions will be enforced by provincial offences officers and public health officials under one or more of the *Health Protection and Promotion Act, Reopening Ontario (A Flexible Response to COVID-19) Act, 2020 and/or the Emergency Management and Civil Protection Act.* Failure to comply is a provincial offence. Among enforcement actions that may be taken, you may be charged and penalties imposed including fines, imprisonment and/or closure of premises.

Should you have any questions, please do not hesitate to contact the Porcupine Health Unit at 1-800-461-1818 or visit our website: www.porcupinehu.on.ca.

These instructions remain in effect

until amended or rescinded by me.

ENSURE STRICT COMPLIANCE WITH ALL STEP 1 RULES AND INSTRUCTIONS

1. You must familiarize yourself with all Step 1 Rules that apply to your workplace and ensure strict compliance with them, at all times, by workers and members of the public present at the workplace.
   Ontario's Step 1 Rules are contained at Schedules 6 through 10 of Ontario Regulation 82/20.[1] They may be accessed at: https://www.ontario.ca/page/emergency-information.

2. You must also familiarize yourself with all instructions issued by me that apply to your workplace and ensure strict compliance with their requirements.To date, these instructions include:

   a. The instructions set out in this document; and

b. The instructions for all workplaces across the PHU, also issued by me on June 23, 2021 and effective June 25, 2021 at 12:01 a.m. These may be accessed on the PHU website at phu.fyi/covid-step1.

3. Nothing in the Step 1 Rules or in these instructions prevents any business or organization from:
   a. providing goods by mail or other forms of delivery or making goods available for pick-up, e.g., “curbside”; and
   b. providing services online, by telephone or by other remote means.[2]

4. The following instructions are in addition to all relevant requirements of the Step 1 Rules.
5. The following businesses that engage in retail sales to the public must operate at no greater than 25% capacity:
   a. Supermarkets, grocery stores, convenience stores, indoor farmers’ markets and other stores that primarily sell food (other than restaurants, bars, food trucks, concession stands and other food or drink establishments); and
   b. Stores that sell liquor, including beer, wine and spirits (again, other than restaurants, bars, food trucks, concession stands and other food or drink establishments).
   c. All other businesses that engage in retail sales to the public must limit the number of patrons in the place of business to one person at a time.
6. All other businesses that engage in retail sales to the public must limit the number of patrons in the place of business to one person at a time.

7. Restaurants, bars, food trucks, concession stands and other food or drink establishments may open only for the purpose of providing take-out, drive-through or delivery.

8. No indoor or outdoor sports or recreational classes are permitted at any indoor or outdoor sport and recreational facilities *other than*those permitted by subsections 45(2), (3), (4) and (5) of the Step 1 Rules (e.g., for identified sports teams, child care providers, mental health/addictions support services, social services or persons with disabilities).

Lianne Catton, MD, CCFP-EM, MPH
Medical Officer of Health and Chief Executive Officer
Porcupine Health Unit
Postal Bag 2012
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Timmins, ON P4N 8B7

[1] Formerly under the Emergency Management and Civil Protection Act and continued under the Reopening Ontario (A Flexible Response to COVID-19) Act, 2020.

[2] See Step 1 Rules, section 1(7), Schedule 6, O. Reg. 82/20.

Letter rescinding Medical Officer of Health instructions to persons responsible for businesses and organizations in Moosonee

DATE: June 29, 2021

EFFECTIVE: June 30, 2021 at 12:01 a.m.

TO:

All persons responsible for a business or organization **(workplace)** in the Town of Moosonee within the Porcupine Health Unit **(PHU)** region, where workers (including employees, those hired under third party agencies, contractors, vendors, volunteers or students and any other such persons) are present at the workplace or the public are regularly present.

Thanks to the efforts of our community members and strong support from leadership within the town of Moosonee and region, we have witnessed a steady downward trend of new COVID-19 cases, a decrease in new and active outbreaks, and a decrease in rates of hospitalizations in the Porcupine Health Unit (PHU) region including the town of Moosonee. There also continues to be good uptake of first and second doses of COVID-19 vaccines.

Effective June 30, 2021, at 12:01 a.m., I will therefore be rescinding my instructions issued June 23, 2021, and effective June 25, 2021, at 12:01 a.m. that required enhanced public health measures and restrictions in Moosonee.

While this is good news, we must not let our guard down and remember to stay committed to the public health measures to get us to the end of this pandemic.

I acknowledge and thank you for complying with provincial and local rules and requirements to protect your staff, patrons and the community at large as these have changed through the course of the pandemic and ask for your continued vigilance and commitment as we move forward.

Lianne Catton, MD, CCFP-EM, MPH
Medical Officer of Health and Chief Executive Officer
Porcupine Health Unit
Postal Bag 2012
(169 Pine Street South)
Timmins, ON P4N 8B7

Instructions from the Medical Officer of Health for Businesses and Workplaces (PHU): 2021-06-30

Date: **Tuesday, June 29, 2021**

Effective: **Wednesday, June 30, 2021 at 12:01 a.m.**

To:

All persons responsible for a business or organization **(workplace)** in the Porcupine Health Unit **(PHU)** region, where employees, those hired under third party agencies, contractors, vendors, volunteers or students and any other such persons **(workers)** are present at the workplace or the public are regularly present, with the exception of:

- A licensed child care program that is in compliance with guidance issued by the Ministry of Education;
- Health care providers and health care entities as defined in Section 77.7 of the Health Protection and Promotion Act (HPPA) who are subject to the Chief Medical Officer of Health's Directives issued under the HPPA, other than the portion of premises used for the sale of goods that are neither medication nor health related supplies in pharmacies;
- Schools and school boards licensed under the Education Act; and
- Schools and private schools within the meaning of the Education Act, that are operated in accordance with a return to school direction issued by the Ministry of Education and approved by the Office of the Chief Medical Officer of Health.

First of all, I would like to thank you for your ongoing efforts to comply with public health requirements that aim to protect your staff, patrons and other members of our community. I would also like to thank you for your continued strong commitment to encourage workers to receive their vaccinations against COVID-19.

As much as we have achieved by working together in the face of this pandemic, however, I must ask for your continued patience and support in the interests of protecting the health of our community. While our vaccination rates are strong and growing daily, continued diligence will limit the risk for all as the region moves forward.

With our enhanced measures in the PHU region, the cases, outbreaks and hospital admissions have stabilized. However confirmation of the continued presence of the Delta VOC requires continued caution and enhanced diligence as we move to lift further restrictions.

Ontario's rules for reopening under the Reopening Ontario (A Flexible Response to COVID-19) Act, 2020 that apply in the Porcupine region continue to require persons responsible for a business or organization that is open to operate the business or organization in compliance with the instructions of public health officials. This includes the following instructions issued by me in this document.

The only amendments to these instructions as originally issued effective June 25, 2021, at 12:01 a.m., is to replace references to the Step 1 Rules with more general references to Ontario's rules under the Reopening Ontario (A Flexible Response to COVID-19) Act, 2020 as these may change from time to time as we complete the steps to move to full reopening in Ontario and the Porcupine region.

Please note that these amended instructions, and the continued restrictions they impose, are temporary. They have been issued in response to the very high rates of COVID-19 transmission within the Porcupine region in this recent wave, reflecting the highly transmissible VOCs. Their sole intent is to protect the public in our communities – including workers – from the very real and ongoing threat of COVID-19 and from its related impacts on our health system. These instructions will be rescinded as soon as conditions in our region permit.

These instructions will be enforced by provincial offences officers and public health officials under one or more of the Health Protection and Promotion Act, Reopening Ontario (A Flexible Response to COVID-19) Act, 2020 and/or the Emergency Management and Civil Protection Act. Failure to comply is a provincial offence. Among enforcement actions that may be taken, you may be charged, and penalties imposed including fines, imprisonment and/or closure of premises.

Should you have any questions, please do not hesitate to contact the Porcupine Health Unit at 1-800-461-1818 or visit our website: www.porcupinehu.on.ca.

THESE INSTRUCTIONS REMAIN IN EFFECT
UNTIL AMENDED OR RESCINDED BY ME

1. **ENSURE STRICT COMPLIANCE WITH ALL STEP 1 RULES AND INSTRUCTIONS:**
    1. You must familiarize yourself with all rules under the *Reopening Ontario (A Flexible Response to COVID-19) Act, 2020* **(ROA Rules)** and instructions that apply to your workplace and ensure strict compliance with them, at all times, by workers and members of the public present at the workplace.
    2. Ontario's ROA Rules, which may change from time to time, may be accessed at: https://www.ontario.ca/page/emergency-information.
    3. Effective June 30, 2021 at 12:01 a.m., and until rescinded by me, all workplaces in the PHU region must also comply with these amended instructions issued to strengthen the implementation and monitoring of public health measures in the workplace. These additional measures are specific to the PHU region's unique circumstances, which are aimed at limiting the further spread of COVID-19 as we reopen. These additional instructions may be accessed at: phu.fyi/covid-orders
2. **PROTECT ALL YOUR WORKERS FROM COVID-19:**
    1. You must continue to implement all COVID-19 prevention measures for your sector outlined in provincial guidelines and PHU guidance (see section 2.6 below), including but not limited to screening, physical distancing, wearing of masks and eye protection, hand hygiene, infection prevention and control and a safety plan.

2. Without limiting the generality of section 2.1 above, these prevention measures must include policies and procedures implemented to ensure the following:
    i. Active verification of completed screening prior to arrival on site, equivalent to the Ontario COVID-19 self-assessment (https://covid-19.ontario.ca/screening/worker/) and immediate exclusion of all workers whose screening results require self-isolation and or testing for COVID-19;
    ii. Occupancy of the premises must be limited to only as many persons as can be accommodated such that 2m distancing between persons can be maintained;
    iii. Physical distancing of 2m between persons must be maintained in all work areas, lunchrooms, change rooms, washrooms, subject only to para iv. below;
    iv. If work arrangements or the workplace environment cannot be altered to allow the required 2m distancing at all times, the workers must be provided with appropriate personal protective equipment including procedural and medical-grade masks (3-ply) and eye protection;
    v. Signage regarding COVID-19 safety measures available from the PHU or other relevant authorities must be posted throughout the workplace premises;
    vi. Masks (and eye protection and other personal protective equipment (PPE) as appropriate) must be used correctly and consistently inside the workplace premises by all workers and visitors at all times;
    vii. Eye protection must be worn when work requires contact closer than 2m;
    viii. If workplace or some work activities are outside, ensure distancing 2m at all times when possible; masks and eye protection must be worn when within 2 metres of others;
    ix. If work involves car pooling or shared vehicles, people must sit as far apart as possible and windows should be opened for increased ventilation; masks must be worn and eye protection (where safe to do so) is recommended where distancing of 2m cannot be maintained;
    x. Train all workers, and monitor to ensure, proper donning and doffing of masks, eye protection and other PPE used in the workplace;
    xi. Availability of adequate hand hygiene supplies and;
    xii. Appropriate cleaning and disinfection of workspaces with the focus on high-touch surfaces;
3. You must support self-isolation for all workers diagnosed with COVID-19, with COVID-19 symptoms, and who are close contacts of a person with COVID-19 as determined by the PHU or another public health agency.
4. You must:
    i. Maintain current and complete records for all workers so as to be able to provide a log of all workers present at the workplace during the period directed by the PHU (including first name, last name, phone number, date and location worked and, if possible, email address);
    ii. Make this log available immediately upon request by the PHU for case and contact management purposes; and

iii. This log must be retained for a minimum of 30 days.

5. Implement workplace policies and procedures to ensure the following:
   i. Symptomatic workers should get tested as soon as possible from the date of onset of symptoms;
   ii. Workers who test positive for COVID-19 shall notify their employer immediately; and
   iii. Asymptomatic workers are encouraged to seek testing.
6. Comply with all relevant directives and guidance including those from:
   i. Porcupine Health Unit:
      - Class Order - Section 22
      - Instructions from the Medical Officer of Health
      - PHU Resources to prevent COVID-19 in the workplace
   ii. Ministry of Health
      - Sector-specific guidelines
   iii. Ministry of Labour, Training and Skills Development
      - Resources to prevent COVID-19 in the workplace
7. These requirements apply to all workplaces, including those not open to the public such as construction sites and private dwellings.

3. **COMMUNICATE TO ALL WORKERS:**
   1. That every worker symptomatic for COVID-19 should be tested as soon as possible from the date of onset of symptoms at an assessment centre approved for diagnostic testing, not at a workplace screening site; and
   2. That every worker who is COVID-19 positive, is or becomes symptomatic for COVID-19, or has been identified as a close contact (meaning high risk contact) for COVID-19 as determined by the PHU or another public health agency, is required to self-isolate by the s.22 class order issued by me under the HPPA on February 26, 2021 ("Class Order"); and
   3. Provide each worker with a copy of the Class Order.
4. **IMMEDIATELY EXCLUDE FROM THE WORKPLACE EVERY PERSON IDENTIFIED AS:**
   a. diagnosed with COVID-19; or
   b. having the signs and symptoms of COVID-19 and having been tested for COVID-19 and awaiting the results of their test; or
   c. otherwise having reasonable grounds to believe they have symptoms of COVID-19; or
   d. a close contact for COVID-19 as determined by the PHU or another public health agency.
5. **FOR EVERY PERSON IDENTIFIED IN 4. ABOVE:**
   1. Immediately reiterate the information set out in Part 3 above. The Class Order requires these persons to confine themselves to their home or isolation facility (i.e., to self-isolate) until they have fully complied with all requirements of the Class Order.
   2. The Class Order provides that persons who are advised by the PHU that they are permitted to leave their home/isolation facility or who require emergency medical attention may do so but only if and as required for those limited purposes.

3. Immediately send home the worker with COVID-19 if they are at work (workers must avoid public transportation) and support them to stay off work while they are self-isolating.
4. Clean and disinfect any surfaces the worker may have touched.
5. If the worker is already at home, direct them not to enter the workplace. The worker will be contacted by public health and will be advised when it is safe for them to return to work.

6. **IF YOU BECOME AWARE OF TWO OR MORE WORKERS WITH COVID-19 AT YOUR WORKPLACE WITHIN A 14-DAY INTERVAL:**
   1. Immediately notify the PHU at 1-800-461-1818.
7. **IF YOU BECOME AWARE OF TWO OR MORE WORKERS WITH COVID-19 AT YOUR WORKPLACE WITHIN A 14-DAY INTERVAL, OR UPON NOTIFICATION BY THE PHU:**
   1. Ensure that the following steps are taken immediately:
      i. Notify:
         - the Ontario Ministry of Labour, Training and Skills Development;
         - the workplace's joint health and safety committee or health and safety representative;
         - the worker's trade union (if applicable); and
         - any other relevant governmental or other bodies (for example, you must report any occupationally acquired illnesses to the Workplace Safety and Insurance Board within 3 days of receiving notification of the illness).
      ii. Provide contact details of the most responsible decision-maker at the workplace premises and ensure that person is immediately available to the PHU;
      iii. Be readily available for contact by the PHU to implement any additional measures immediately as required by the PHU;
      iv. Cooperate with infection prevention and control personnel and any other personnel from the PHU including allowing entry into the workplace premises for inspection and to support enhanced infection prevention and control and any other measures for public health management of the outbreak;
      v. Follow all PHU directions pertaining to case and contact management and identifying workers who need to isolate, including that all directions as specified by the PHU are communicated to workers; and
      vi. Workers of a closed workplace premises shall not work in another workplace during their period of isolation.
   2. Immediately communicate to all workers:
      i. Advise workers that two or more cases of COVID-19 at your workplace and that the PHU has been notified of the situation; include further information if and as directed by the PHU (including whether an outbreak has been declared); and
      ii. Reiterate the information set out in Part 3 above.
8. **IF YOU WISH TO IMPLEMENT WORKPLACE ANTIGEN POINT-OF-CARE TESTING FOR COVID-19:**
   1. Before initiating COVID-19 antigen point-of-care testing (antigen POCT), you must:

i. Review and familiarize yourself with the Ministry of Health's COVID-19 Guidance: Considerations for Antigen Point-of-Care Testing, as current, to ensure compliance with this document subject to para ii. below;
ii. Comply with all additional requirements set out in these instructions; and
iii. Advise the PHU of your intention to initiate antigen POCT at 1-800-461-1818.

2. Antigen POCT is no more than an additional screening tool. It must be used for screening purposes only:
   i. Antigen POCT does not prevent a person from getting COVID-19.
   ii. Antigen POCT does not replace public health measures such as vaccination, symptom screening, physical distancing, appropriate PPE (e.g., masking and eye protection) and hand hygiene. Antigen POCT is no more than an additional screening tool.
3. Antigen POCT must NOT be used for any persons (including but not limited to workers):
   i. With symptoms;
   ii. Who are close contact for COVID-19 as determined by PHU or other public health agency;
   iii. Who have previously been infected with and recovered from COVID-19;
   iv. To diagnose COVID-19 infection; or
   v. To investigate a workplace outbreak.
4. Specimen collection for all antigen POCT must be conducted in an appropriate room with adherence to all appropriate public health measures and infection prevention and control requirements including PPE.
5. All workplaces initiating antigen POCT testing must implement policies and procedures to:
   i. Inform each tested person of their results; and
   ii. Establish a process to follow if the person tests positive that includes communicating information to direct and enable the person to book a confirmatory PCR test at the local assessment centre and return-to-work requirements (for workers).
6. All positive antigen POCT test results for any person tested must be immediately reported by fax to the PHU at705-360-7324 (confidential fax number)
7. Every person who receives a positive antigen POCT result must:
   i. Self-isolate immediately;
   ii. Inform their family and household members to self-isolate immediately;
   iii. Inform their employer, if the employer is not aware of the positive result;
   iv. Immediately book an appointment at the local assessment centre to obtain laboratory-based PCR testing within 24 hours of the positive antigen POCT result;
   v. Remain in self-isolation until they receive their PCR test result:
      - Those who test negative with a PCR test obtained within 24 hours of the positive antigen POCT result and asymptomatic may come out of self-isolation and return to work;
      - Those who test negative with a PCR test obtained within 24 hours of the positive antigen POCT result but have symptoms (even mild symptoms) of COVID-19 must remain in

self-isolation in accordance with the Class Order described in section 3.2 above and follow any other public health guidance from the PHU; and

- Those who test positive with a PCR test must remain in self-isolation in accordance with the Class Order described in section 3.2 above and follow any other public health guidance from the PHU.

8. Anyone with a positive antigen POCT result who either refuses laboratory-based PCR testing, or who does not obtain testing laboratory-based PCR testing within 48 hours of the positive antigen POCT result, must not return to work and must self-isolate for 10 days from the date of the positive antigen test.

Lianne Catton, MD, CCFP-EM, MPH
Medical Officer of Health and Chief Executive Officer
Porcupine Health Unit
Postal Bag 2012
(169 Pine Street South)
Timmins, ON P4N 8B7

These instructions shall be posted on the PHU website at https://phu.fyi/covid-orders.

This is **Exhibit "AA"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

INSTRUCTIONS FROM THE MEDICAL OFFICER OF HEALTH

DATE: June 29, 2021 **EFFECTIVE DATE:** June 30, 2021 at 12:01 a.m.

TO: All persons responsible for a business, organization or facility in the Region of Waterloo (ROW)

First of all, I would like to thank you for your ongoing efforts to comply with public health requirements that aim to protect your staff, patrons and other members of our community. I would like to thank you for your strong commitment to encourage workers to receive their vaccinations against COVID-19 and your efforts in facilitating their ability to do so.

We have achieved much by working together in the face of this pandemic; however, at this time I must ask for your continued patience and support in the interests of protecting the health of our community, and to give us the best chance to re-open and successfully stay open.

With strong support from Ontario's Chief Medical Officer of Health and local health care leadership including all hospital CEOs, we will be taking a more gradual approach to reopening.

We must maintain Step 1 - level restrictions for approximately two weeks to minimize increased person-to-person interactions that would grow significantly with a move to Step 2 for our community at this time.

While our vaccination rates are growing daily, other trends in public health and health system indicators are concerning:

- Our data shows that ROW has had one of the highest rates of COVID-19 transmission in the province in the month of June 2021. As of June 28, 2021, our weekly case rate per 100,000 residents is over 5 times the provincial rate;
- We have seen COVID-19 spread in multiple, different types of settings in Waterloo Region, and rising infection rates in the younger age groups, including those under 20. There are multiple COVID-19 outbreaks in workplaces across the ROW. In essence, the variant is prevalent throughout the region and is not limited to one demographic;
- The surge in cases in our community has significantly affected our local hospitals. As of June 25, 2021, 60 individuals considered infectious for COVID-19 were hospitalized (this does not count those who are no longer infectious but still require hospital care), with 27 in the intensive-care unit, and our local hospitals had begun to transfer patients out of region for care;
- We have evidence that the Delta variant, significantly more transmissible than the Alpha variant (the variant driving Ontario's third wave), is the predominant

circulating strain in RoW. Public Health Ontario has estimated that the percentage of N501Y- and E484K- cases (a proxy for the Delta variant) was 81.4% in ROW from June 8, 2021 to June 14, 2021, and 93.9% in ROW from June 15, 2021 to June 21, 2021 (https://www.publichealthontario.ca/-/media/documents/ncov/epi/covid-19-prevalence-growth-voc-mutation-epi-summary.pdf). The Province has identified the ROW as one of the delta variant hotspots in Ontario.

These trends are worrisome and require a more cautious approaching to lifting public health restrictions at this time.

At this time, I anticipate these continued Step 1 - level restrictions will remain necessary for two additional weeks after most of Ontario moves to Step 2 on June 30, 2021, remaining in place until approximately mid-July, 2021. I will regularly assess our progress against key public health and health system indicators and will report publicly on our progress.

Ontario's new Step 2 Rule continues to require persons responsible for a business or organization to operate the business or organization in compliance with the instructions of public health officials. This includes the following instructions issued by me in this document pursuant to Regulation 263/20, as amended, under the Reopening Ontario (A Flexible Response to COVID-19) Act, 2020.

These instructions will be enforced by provincial offences officers and public health officials under one or more of the *Health Protection and Promotion Act*, *Reopening Ontario (A Flexible Response to COVID-19) Act, 2020* and/or the *Emergency Management and Civil Protection Act*. Failure to comply is a provincial offence. Among enforcement actions that may be taken, you may be charged, and penalties imposed including fines, and/or closure of premises.

Should you have any questions, please do not hesitate to contact Region of Waterloo Public Health at 519-575-4400 or visit our website: www.regionofwaterloo.ca/Instructions

For additional resources for workplaces please visit our website at: https://www.regionofwaterloo.ca/en/health-and-wellness/coronavirus-resources-for-workplaces.aspx

These instructions remain in effect until amended or rescinded by me.

1. You must comply with the requirements and restrictions as set out in Appendix A herein - which are the Step 1 requirements and restrictions as set out in Ontario Regulation 82/20, Schedules 6, 7, 8, 9 and 10 - as applicable to your business, organization or facility and to the extent that they are more strict than the Step 2 requirements and restrictions as set out in Ontario Regulation 263/20, as amended.

2. (1) Without limiting section 1 and subject to sections 3 to 6 herein, no person who operates a business, organization or facility shall allow persons to attend any of the following at their business, organization or facility,

(a) an organized public event that is held indoors;

(b) a social gathering that is held indoors, including a social gathering associated with a gathering described in clause (d);

(c) an organized public event or social gathering of more than 10 people that is held outdoors, including a social gathering associated with a wedding, funeral or a religious service, rite or ceremony, but not including the wedding, funeral or a religious service, rite or ceremony itself;

(d) an indoor gathering for the purposes of a wedding, a funeral or a religious service, rite or ceremony where the number of persons occupying any particular room in a building or structure while attending the gathering exceeds 15 per cent of the capacity of the room; or

(e) an outdoor gathering for the purposes of a wedding, a funeral or a religious service, rite or ceremony where the number of persons attending the gathering exceeds the number that can maintain a physical distance of at least two metres from every other person in the space where the gathering is held.

(2) A person attending an organized public event, social gathering or a gathering for the purposes of a wedding, a funeral or a religious service, rite or ceremony shall comply with public health guidance on physical distancing.

(3) For greater certainty, subsections (1) and (2) apply with respect to an organized public event, social gathering or a gathering for the purposes of a wedding, a funeral or a religious service, rite or ceremony, even if it is held at a private dwelling.

(4) For greater certainty, the limits in clauses (1) (b) and (c) apply to a social gathering associated with a wedding, a funeral or a religious service, rite or ceremony, such as a wedding reception, while the limits that apply to the wedding, funeral or religious service, rite or ceremony itself are set out in clauses (1) (d) and (e).

(5) Clause (1) (c) does not apply with respect to an outdoor end-of-school-year celebration ceremony held by a school or private school within the meaning of the *Education Act* that is in compliance with a direction issued by the Ministry of Education and approved by the Office of the Chief Medical Officer of Health.

3. Section 2 does not apply with respect to,

(a) a gathering of members of a single household;

(b) a gathering that includes members of a household and one other person from another household who lives alone; or

(c) a gathering that includes persons described in clause (a) or (b), and a caregiver for any of those persons.

4. Section 2 does not apply with respect to a gathering in a retirement home within the meaning of the *Retirement Homes Act, 2010* if it is in compliance with the policies or guidance, if any, issued by the Retirement Homes Regulatory Authority.

5. The prohibitions on attendance at an organized public event in subsection 2 (1) do not apply with respect to attendance at a business for a purpose related to providing or receiving the goods or services provided by the business if the business is not required to close.

6. (1) This section applies with respect to gatherings for the purposes of a wedding, funeral, religious service, rite or ceremony if the persons attending the gathering, other than those conducting the service, rite or ceremony, do so in a motor vehicle.

   (2) Clause 2 (1) (e) does not apply to a gathering to which this section applies if the person follows all of the following precautions that apply:

   1. Each person attending the gathering, other than the persons conducting the service, rite or ceremony, must remain within a motor vehicle that is designed to be closed to the elements, except,
      i. where necessary to use a washroom, or
      ii. as may otherwise be necessary for the purposes of health and safety.
   2. The driver of a motor vehicle must ensure that it is positioned at least two metres away from other motor vehicles.
   3. A person who ordinarily uses a non-motorized vehicle because of their religious belief and who attends the gathering must remain within their non-motorized vehicle except where necessary to use a washroom or as may otherwise be required for the purposes of health and safety, and paragraph 2 applies with necessary modifications.

Dr. Hsiu-Li Wang, MD, FRCPC
Commissioner & Medical Officer of Health
Region of Waterloo Public Health & Emergency Services

These instructions shall be posted at:
https://www.regionofwaterloo.ca/en/health-and-wellness/orders-and-instructions.aspx

APPENDIX A TO INSTRUCTIONS ISSUED BY THE MEDICAL OFFICER OF HEALTH FOR THE REGIONAL MUNICIPALITY OF WATERLOO ON JUNE 29, 2021

STEP 1

SCHEDULE 6
GENERAL RULES AT STEP 1

Closures

1. (1) Each person responsible for a business, or a part of a business, that is not listed in Schedule 7 or 8 shall ensure that the business, or part of the business, is closed.

(2) Each person responsible for a business, or part of a business, that is listed in Schedule 7 or 8 subject to conditions shall ensure that the business, or part of the business, either meets those conditions or is closed.

(3) Each person responsible for a place, or a part of a place, that is required to be closed by Schedule 8 shall ensure that the place, or part of the place, is closed in accordance with that Schedule.

(4) Each person responsible for a place, or a part of a place, that is listed in Schedule 8 subject to conditions shall ensure that the place, or part of a place, either meets those conditions or is closed.

(5) Each person responsible for a business or place, or part of a business or place, that does not comply with sections 2 to 11 of this Schedule shall ensure that it is closed.

(6) Despite subsections (1) to (5), temporary access to a business or place, or part of a business or place, that is required to be closed is authorized, unless otherwise prohibited by any applicable law, for the purposes of,

(a) performing work at the business or place in order to comply with any applicable law;

(b) preparing the business or place to be reopened;

(c) allowing for inspections, maintenance or repairs to be carried out at the business or place;

(d) allowing for security services to be provided at the business or place; and

(e) attending at the business or place temporarily,

(i) to deal with other critical matters relating to the closure of the business or place, if the critical matters cannot be attended to remotely, or

(ii) to access materials, goods or supplies that may be necessary for the business or place to be operated remotely.

(7) Nothing in this Order precludes a business or organization from operating remotely for the purpose of,

(a) providing goods by mail or other forms of delivery or making goods available for pick-up; and

(b) providing services online, by telephone or by other remote means.

(8) Nothing in this Order precludes a business or place from providing access to an outdoor recreational amenity that is permitted to open under section 4 of Schedule 8, including by opening such limited areas of the business or place as are necessary to enable access.

(9) Nothing in this Order precludes operations or delivery of services by the following in Ontario:

1. Any government.
2. Any person or publicly-funded agency or organization that delivers or supports government operations and services, including operations and services of the health care sector.

General compliance

2. (1) The person responsible for a business or organization that is open shall ensure that the business or organization operates in accordance with all applicable laws, including the *Accessibility for Ontarians with Disabilities Act, 2005* and the *Occupational Health and Safety Act* and the regulations made under them.

(2) The person responsible for a business or organization that is open shall operate the business or organization in compliance with the advice, recommendations and instructions of public health officials, including any advice, recommendations or instructions on physical distancing, cleaning or disinfecting.

(3) The person responsible for a business or organization that is open shall operate the business or organization in compliance with any advice, recommendations and instructions issued by the Office of the Chief Medical Officer of Health or another public health official on screening individuals by, among other things,

(a) posting signs at all entrances to the premises of the business or organization, in a conspicuous location visible to the public, that inform individuals on how to screen themselves for COVID-19 prior to entering the premises; and

(b) actively screening every person who works at the business or organization before they enter the premises of the business or organization.

(4) REVOKED: O. Reg. 440/21, s. 10 (3).

(5) The person responsible for a business or organization that is open shall ensure that any person in the indoor area of the premises of the business or organization, or in a vehicle that is operating as part of the business or organization, wears a mask or face covering in a manner that covers their mouth, nose and chin during any period when they are in the indoor area unless the person in the indoor area,

(a) is a child who is younger than two years of age;

(b) is attending a school or private school within the meaning of the *Education Act* that is operated in accordance with a return to school direction issued by the Ministry of Education and approved by the Office of the Chief Medical Officer of Health;

(c) is attending a child care program at a place that is in compliance with the child care re-opening guidance issued by the Ministry of Education;

(c.1) is attending a day camp for children that is in compliance with section 24 of Schedule 7;

(d) is receiving residential services and supports in a residence listed in the definition of "residential services and supports" in subsection 4 (2) of the *Services and Supports to Promote the Social Inclusion of Persons with Developmental Disabilities Act, 2008*;

(e) is in a correctional institution or in a custody and detention program for young persons in conflict with the law;

(f) is performing or rehearsing in a film or television production or in a concert, artistic event, theatrical performance or other performance;

(g) has a medical condition that inhibits their ability to wear a mask or face covering;

(h) is unable to put on or remove their mask or face covering without the assistance of another person;

(i) needs to temporarily remove their mask or face covering while in the indoor area,

(i) to receive services that require the removal of their mask or face covering,

(ii) to engage in an athletic or fitness activity,

(iii) to consume food or drink, or

(iv) as may be necessary for the purposes of health and safety;

(j) is being accommodated in accordance with the *Accessibility for Ontarians with Disabilities Act, 2005*;

(k) is being reasonably accommodated in accordance with the *Human Rights Code*; or

(l) performs work for the business or organization, is in an area that is not accessible to members of the public and is able to maintain a physical distance of at least two metres from every other person while in the indoor area.

(6) Subsection (5) does not apply with respect to premises that are used as a dwelling if the person responsible for the business or organization ensures that persons in the premises who are not entitled to an exception set out in subsection (5) wear a mask or face covering in a manner that covers their mouth, nose and chin in any common areas of the premises in which persons are unable to maintain a physical distance of at least two metres from other persons.

(6.1) The person responsible for a business or organization shall ensure that every person who performs work for the business or organization and whose mask or face covering is temporarily removed to consume food or drink under subclause (5) (i) (iii) is separated from every other person by,

(a) a distance of at least two metres; or

(b) plexiglass or some other impermeable barrier.

(7) For greater certainty, it is not necessary for a person to present evidence to the person responsible for a business or place that they are entitled to any of the exceptions set out in subsection (5).

(8) A person shall wear appropriate personal protective equipment that provides protection of the person's eyes, nose and mouth if, in the course of providing services, the person,

(a) is required to come within two metres of another person who is not wearing a mask or face covering in a manner that covers that person's mouth, nose and chin during any period when that person is in an indoor area; and

(b) is not separated by plexiglass or some other impermeable barrier from a person described in clause (a).

Work from home except where necessary

2.1 (1) Each person responsible for a business or organization that is open shall ensure that any person who performs work for the business or organization conducts their work remotely, unless the nature of their work requires them to be on-site at the workplace.

(2) Subsection (1) does not apply to a business or organization described in subsection 1 (9).

Capacity limits for businesses or facilities open to the public

3. (1) Subject to any other provisions set out in this Order, the person responsible for a place of business or facility that is open to the public shall limit the number of members of the public in the place of business or facility so that,

(a) the members of the public are able to maintain a physical distance of at least two metres from every other person in the business or facility; and

(b) the total number of members of the public in the business or facility at any one time does not exceed 50 per cent capacity, as determined in accordance with subsection (2).

(2) For the purposes of this Order, the maximum number of members of the public permitted in a business or facility that is operating at 50 per cent capacity is determined by taking the total square metres of floor area accessible to the public in the business or facility, not including shelving and store fixtures, dividing that number by 8 and rounding the result down to the nearest whole number.

(3) For the purposes of this Order, the maximum number of members of the public permitted in a business or facility that is operating at 25 per cent capacity is determined by taking the total square metres of floor area accessible to the public in the business or facility, not including shelving and store fixtures, dividing that number by 16 and rounding the result down to the nearest whole number.

(3.1) For the purposes of this Order, the maximum number of members of the public permitted in a business or facility that is operating at 15 per cent capacity is determined by taking the total square metres of floor area accessible to the public in the business or facility, not including shelving and store fixtures, dividing that number by 26.67 and rounding the result down to the nearest whole number.

(4) For greater certainty, subsection (1) does not require persons who are in compliance with public health guidance on households to maintain a physical distance of at least two metres from each other while in a place of business or facility.

(5) The person responsible for a place of business or facility that engages in retail sales to the public must post a sign in a conspicuous location visible to the public that states the maximum capacity they are permitted to operate under.

(6) Subsection (1) does not apply to schools and private schools within the meaning of the *Education Act* that are,

(a) operating in accordance with a return to school direction issued by the Ministry of Education and approved by the Office of the Chief Medical Officer of Health; or

(b) operated by,

(i) a band, a council of a band or the Crown in right of Canada,

(ii) an education authority that is authorized by a band, a council of a band or the Crown in right of Canada, or

(iii) an entity that participates in the Anishinabek Education System.

Requirements that apply to individuals

4. (1) Every person on the premises of a business or organization that is open shall wear a mask or face covering in a manner that covers their mouth, nose and chin during any period in which they are in an indoor area of the premises.

(2) Every person shall wear a mask or face covering in a manner that covers their mouth, nose and chin during any period in which they are,

(a) in attendance at an organized public event or gathering permitted by this Order; and

(b) within two metres of another individual who is not part of their household.

(3) Subsections (1) and (2) do not require a person to wear a mask or face covering if they are subject to an exception set out in subsection 2 (5).

(4) Every member of the public in a place of business or facility that is open to the public, and every person in attendance at an organized public event or gathering permitted by this Order, shall maintain a physical distance of at least two metres from every other person, except from their caregiver or from members of the person's household.

(5) The physical distancing described in subsection (4) is not required,

(a) where necessary to complete a transaction or to receive a service, if the member of the public wears a mask or face covering in a manner that covers

their mouth, nose and chin or is subject to an exception set out in subsection 2 (5);

(a.1) when attending a day camp for children that is in compliance with section 24 of Schedule 7;

(b) when passing one another in a confined location, such as in a hallway or aisle, if the member of the public wears a mask or face covering in a manner that covers their mouth, nose and chin or is subject to an exception set out in subsection 2 (5); and

(c) in situations where another provision of this Order expressly authorizes persons to be closer than two metres from each other.

(6) For greater certainty, nothing in subsection (5) affects the obligation of persons who provide services to comply with subsection 2 (8).

(7) No person shall use an indoor or outdoor recreational amenity that is required to close under this Order.

Physical distancing and masks or face coverings in lines, etc.

5. (1) The person responsible for a business or place that is open must not permit patrons to line up or congregate outside of the business or place unless they are maintaining a physical distance of at least two metres from other groups of persons.

(2) The person responsible for a business or place that is open must not permit patrons to line up inside the business or place unless they are,

(a) maintaining a physical distance of at least two metres from other groups of persons; and

(b) wearing a mask or face covering in a manner that covers their mouth, nose and chin, unless they are entitled to any of the exceptions set out in subsection 2 (5).

(3) This section does not apply with respect to day camps for children that are in compliance with section 24 of Schedule 7.

Safety plan

6. (1) The person responsible for a business that is open shall prepare and make available a safety plan in accordance with this section, or ensure that one is prepared and made available.

(2) The safety plan shall describe the measures and procedures which have been implemented or will be implemented in the business to reduce the transmission risk of COVID-19.

(3) Without limiting the generality of subsection (2), the safety plan shall describe how the requirements of this Order will be implemented in the location including by screening, physical distancing, masks or face coverings, cleaning and disinfecting of surfaces and objects, and the wearing of personal protective equipment.

(4) The safety plan shall be in writing and shall be made available to any person for review on request.

(5) The person responsible for the business shall ensure that a copy of the safety plan is posted in a conspicuous place where it is most likely to come to the attention of individuals working in or attending the business.

7. REVOKED: O. Reg. 440/21, s. 10 (8).

Meeting or event space

8. (1) The person responsible for a business or place that is open may only rent out meeting or event space if the meeting or event space is only rented out,

(a) for a day camp for children described in section 24 of Schedule 7;

(b) to a provider of child care within the meaning of the *Child Care and Early Years Act, 2014*;

(c) for the purpose of the provision of social services;

(d) for the purpose of collective bargaining, so long as no more than ten people are permitted to occupy the rented space;

(e) for the purpose of delivering or supporting the delivery of court services;

(f) for operations by or on behalf of a government;

(g) for the purpose of delivering or supporting the delivery of government services;

(h) for the purpose of delivering or supporting mental health support services or addictions support services, so long as no more than ten people are permitted to occupy the rented space; or

(i) for the purpose of conducting in-person examinations for the registration, licensing or accreditation of persons in any of the fields or occupations described in subsection 2 (2) of Schedule 8, so long as no more than 50 students are permitted to occupy the rented space.

(1.1) The person responsible for a business or place that rents out meeting or event space must ensure that the business or place actively screens individuals in accordance with the advice, recommendations and instructions of the Office of the Chief Medical Officer of Health before they enter the indoor premises of the business or place.

(2) The person responsible for a business or place that is open shall,

(a) record the name and contact information of every member of the public who attends a meeting or event;

(b) maintain the records for a period of at least one month; and

(c) only disclose the records to a medical officer of health or an inspector under the *Health Protection and Promotion Act* on request for a purpose specified in section 2 of that Act or as otherwise required by law.

(3) Subsection (2) does not apply to the rental of meeting or event space for the purpose of delivering or supporting the delivery of court services.

9. REVOKED: O. Reg. 440/21, s. 10 (9).

Driving instruction

10. (1) The person responsible for a business or place shall ensure that no in-person driving instruction is provided by or at the business or place.

(2) Subsection (1) does not apply to in-person driving instruction for drivers of commercial motor vehicles,

(a) where the instruction is part of the Ontario Driver Certification Program administered by the Ministry of Transportation and involves the operation of motor vehicles for which,

(i) a class of driver's licence other than Class G, G1, G2, M, M1 or M2 is required, or

(ii) an air brake endorsement is required; or

(b) that is provided by a private career college that is in compliance with section 2 of Schedule 8.

(3) In this section,

"commercial motor vehicle" has the same meaning as in subsection 1 (1) of the *Highway Traffic Act*.

Cleaning requirements

11. (1) The person responsible for a business or place that is open shall ensure that,

(a) any washrooms, locker rooms, change rooms, showers or similar amenities made available to the public are cleaned and disinfected as frequently as is necessary to maintain a sanitary condition; and

(b) any equipment that is rented to, provided to or provided for the use of members of the public must be cleaned and disinfected as frequently as is necessary to maintain a sanitary condition.

(2) For greater certainty, clause (1) (b) applies to computers, electronics and other machines or devices that members of the public are permitted to operate.

Professional and elite amateur sports

12. (1) In this section,

"Framework" means the document titled "Return-to-Play Framework for Professional and Elite Amateur Sport Leagues and Events" approved by the Office of the Chief Medical Officer of Health under subsection (2), as amended from time to time; ("cadre")

"International Single Sport Event" means an international single sport event hosted by a national sport organization that is either funded by Sport Canada or recognized by the Canadian Olympic Committee or the Canadian Paralympic Committee; ("Manifestation internationale unisport")

"participant" means a person who is a member of a specified participant group in a return-to-play plan; ("participant")

"return-to-play plan" means a return-to-play plan for,

(a) a sport league or association listed in the Tables to subsection (3), or

(b) an International Single Sport Event. ("plan de retour au jeu")

(2) The Office of the Chief Medical Officer of Health may approve the Framework.

(3) The person responsible for a sport league or association in the Tables to this subsection shall ensure that a return-to-play plan that is consistent with the Framework has been established before that sport league or association can, in accordance with this section, return to play the sport referred to in Column 3:

TABLE 1
PROFESSIONAL SPORT LEAGUES OR ASSOCIATIONS

Column 1	Column 2 Professional Sport Leagues or Associations	Column 3 Sport
1.	American Hockey League	Hockey

2.	Canadian Elite Basketball League	Basketball
3.	Canadian Football League	Football
4.	Canadian Premier League	Soccer
5.	Major League Baseball	Baseball
6.	Major League Soccer	Soccer
7.	NBA G League	Basketball
8.	National Basketball Association	Basketball
9.	National Hockey League	Hockey
10.	National Lacrosse League	Lacrosse
11.	National Women's Hockey League	Hockey
12.	Professional Women's Hockey Players Association	Hockey
13.	USL League 1	Soccer

Column 1	Column 2 Elite Amateur Sport Leagues or Associations	Column 3 Sport
1.	Canadian Hockey League	Hockey
2.	Elite Baseball League of Ontario U 18 Division	Baseball
3.	League 1 Ontario	Soccer
4.	Ontario Junior "A" Lacrosse League	Lacrosse
5.	Ontario Scholastic Basketball Association	Basketball
6.	Ontario Women's Field Lacrosse U 19 "A" League	Lacrosse
7.	Provincial Women's Hockey League	Hockey

TABLE 2
ELITE AMATEUR SPORT LEAGUES OR ASSOCIATIONS

(4) Before an International Single Sport Event can return to play in accordance with this section, the person responsible for that International Single Sport Event must ensure that a return-to-play plan has been established that is,

(a) consistent with the Framework; and

(b) approved by a national sport organization that is either funded by Sport Canada or recognized by the Canadian Olympic Committee or the Canadian Paralympic Committee.

(5) The person responsible for an International Single Sport Event or a sport league or association listed in the Tables to subsection (3) must provide notice of its intent to return to play to the local Medical Officer of Health for each Public Health Unit region in which the International Single Sport Event or the sport league or association, as the case may be, intends to operate before returning to play.

(6) The return-to-play plan shall,

(a) list the businesses and places that may be used by the participants, which may include,

(i) hotels,

(ii) facilities for indoor or outdoor sports and recreational fitness activities,

(iii) businesses or places that are in hotels or facilities mentioned in subclause (i) or (ii), and

(iv) restaurants or bars;

(b) list specified groups of persons who are participants; and

(c) describe the measures and procedures which have been implemented or will be implemented in the businesses or places referred to in clause (a) to reduce the transmission risk of COVID-19.

(7) A business or place that is listed in the return-to-play plan as being available for the use of participants may open for use by participants if the business or place complies with the following conditions:

1. The business or place must operate in accordance with the return-to-play plan.
2. No spectators may be permitted at the business or place.
3. The business or place must ensure that any other conditions or requirements set out in this section are complied with on the premises of the business or place.

(8) The return-to-play plan shall be in writing and shall be made available by the person responsible for the International Single Sport Event or the sport league or association listed in the Tables to subsection (3), as the case may be, to any provincial offences officer upon request.

(9) The following provisions do not apply to the provision of goods or services to a participant by a business or place listed, in accordance with clause (6) (a), in the return-to-play plan when they are provided in accordance with the return-to-play plan:

1. Subsection 2 (5) of this Schedule, but only in respect of players and coaches in an International Single Sport Event or a sport league or association listed in the Tables to subsection (3).

2. Sections 3, 6 and 8 of this Schedule.
3. Section 45 of Schedule 7.
4. Clauses 1 (1) (a) and (b) of Schedule 9.

(10) Businesses and places listed in the return-to-play plan may provide in-person dining for participants if they meet the following conditions:

1. Participants must be seated at all times in any area of the establishment in which food or drink is permitted except,

i. while entering the area and while moving to their table,

ii. while placing or picking up an order,

iii. while paying for an order,

iv. while exiting the area,

v. while going to or returning from a washroom,

vi. while lining up to do anything described in subparagraphs i to v, or

vii. where necessary for the purposes of health and safety.

2. The person responsible for the establishment must,

i. record the name and contact information of every participant that enters an area of the establishment, unless the participant temporarily enters the area to place, pick up or pay for a takeout order,

ii. maintain the records for a period of at least one month, and

iii. only disclose the records to a medical officer of health or an inspector under the *Health Protection and Promotion Act* on request for a purpose specified in section 2 of that Act or as otherwise required by law.

3. No participant may be permitted to line up or congregate outside of the establishment unless they are maintaining a physical distance of at least two metres from other groups of persons inside or outside the establishment.
4. No participant may be permitted to line up or congregate inside the establishment unless they are,

i. maintaining a physical distance of at least two metres from other groups of persons inside or outside the establishment, and

ii. wearing a mask or face covering in a manner that covers their mouth, nose and chin, unless they are entitled to any of the exceptions set out in subsection 2 (5) of Schedule 6.

5. No participant shall dance, sing or perform music at the establishment.

(11) Hotels listed in the return-to-play plan may open meeting and event spaces and indoor pools, indoor fitness centres or other indoor recreational facilities that are part of the operation of the hotels, other than communal steam rooms, saunas and whirlpools, if the following conditions are met:

1. The hotels must ensure that the facilities are open only for the use of participants.
2. The hotels must ensure that the facilities are used in accordance with the return-to-play plan.

(12) Therapists referred to in the return-to-play plan may open for the sole purpose of providing services to players in an International Single Sport Event or in a sport league or association listed in the Tables to subsection (3), as the case may be, and shall provide such services in accordance with the return-to-play plan.

(13) Television productions relating to an International Single Sport Event or a game of a sport league or association listed in the Tables to subsection (3), as the case may be, that are in compliance with the return-to-play plan may open, and the conditions set out in paragraphs 1 to 5 of subsection 60 (1) of Schedule 7 do not apply to such television productions.

13. REVOKED: O. Reg. 440/21, s. 10 (10).

O. Reg. 96/21, s. 10; O. Reg. 117/21, s. 2; O. Reg. 126/21, s. 3; O. Reg. 144/21, s. 3; O. Reg. 162/21, s. 3; O. Reg. 216/21, s. 2; O. Reg. 313/21, s. 1; O. Reg. 440/21, s. 10; O. Reg. 482/21, s. 1; O. Reg. 489/21, s. 1.

SCHEDULE 7
BUSINESSES THAT MAY OPEN AT STEP 1

Supply chains

1. Businesses that supply businesses or places that are permitted to open within Ontario, or that supply businesses or services that have been declared essential in a jurisdiction outside of Ontario, with the support, products, supplies, systems, or services, including processing, packaging, warehousing, distribution, delivery, and maintenance necessary to operate.

Retailers

2. (1) The following businesses that engage in retail sales to the public and that meet the conditions set out in subsection (2):

1. Supermarkets, grocery stores, convenience stores, indoor farmers' markets and other stores that primarily sell food, other than establishments described in section 3.
2. Pharmacies.
3. Discount and big box retailers selling groceries.
4. Safety supply stores.
5. Businesses that primarily sell, rent or repair assistive devices, aids or supplies, mobility devices, aids or supplies or medical devices, aids or supplies.
6. Optical stores that sell prescription eyewear to the public.
7. Retail stores operated by telecommunications providers.
8. Stores, other than establishments described in section 3, that sell liquor, including beer, wine and spirits.
9. Outdoor garden centres and plant nurseries.
10. Indoor greenhouses.

(2) The business must comply with the following conditions:

1. They must limit the total number of members of the public in the place of business so that the total number of members of the public in the place of business at any one time does not exceed 25 per cent capacity, as determined in accordance with subsection 3 (3) of Schedule 6.
2. They must ensure that any music played at the place of business is not at a decibel level that exceeds the level at which normal conversation is possible.

(3) For greater certainty, paragraph 1 of subsection (1) includes stores that predominately sell one category of food.

(4) Nothing in this section permits a business located within an indoor farmer's market to exceed 15 per cent capacity for in-store shopping unless it is a business that primarily sells food.

3. (1) Restaurants, bars, food trucks, concession stands and other food or drink establishments that meet the conditions set out in subsection (2).

(2) A business described in subsection (1) may open only if it complies with the following conditions:

1. No indoor dining or buffet-style service may be provided.

2. Patrons must be seated at all times in any outdoor dining area of the establishment except,

i. while entering the area and while moving to their table,

ii. while placing or picking up an order,

iii. while paying for an order,

iv. while exiting the area,

v. while going to or returning from a washroom,

vi. while lining up to do anything described in subparagraphs i to v, or

vii. where necessary for the purposes of health and safety.

3. The outdoor dining area must be configured so that patrons seated at different tables are separated by,

i. a distance of at least two metres, or

ii. plexiglass or some other impermeable barrier.

4. The person responsible for the establishment must,

i. record the name and contact information of every patron that enters an area of the establishment, unless the patron temporarily enters the area to place, pick up or pay for a takeout order,

ii. maintain the records for a period of at least one month, and

iii. only disclose the records to a medical officer of health or an inspector under the *Health Protection and Promotion Act* on request for a purpose specified in section 2 of that Act or as otherwise required by law.

5. REVOKED: O. Reg. 440/21, s. 11 (3).

6. No patron may be permitted to line up or congregate outside of the establishment unless they are maintaining a physical distance of at least two metres from other groups of persons inside or outside the establishment.

6.1 No patron may be permitted to line up inside the establishment unless they are,

i. maintaining a physical distance of at least two metres from other groups of persons inside or outside the establishment, and

ii. wearing a mask or face covering in a manner that covers their mouth, nose and chin, unless they are entitled to any of the exceptions set out in subsection 2 (5) of Schedule 6.

7. No more than four people may be seated together at an outdoor table at the establishment unless everyone seated at the table is,

i. a member of the same household,

ii. a member of up to one other household who lives alone, or

iii. a caregiver for any member of either household.

8. The total number of patrons permitted to be seated outdoors at the establishment must be limited to the number that can maintain a physical distance of at least two metres from every other person at the establishment.
9. The person responsible for the establishment must post a sign in a conspicuous location visible to the public that states the maximum capacity they are permitted to operate under.
10. Music must not be played at a decibel level that exceeds the level at which normal conversation is possible.
11. No person shall dance, sing or perform music at the establishment.
12. If an outdoor dining area at the establishment is covered by a roof, canopy, tent, awning or other element, at least two full sides of the entire outdoor dining area must be open to the outdoors and must not be substantially blocked by any walls or other impermeable physical barriers.
13. If an outdoor dining area at the establishment is equipped with a retractable roof and the roof is retracted, at least one full side of the outdoor dining area must be open to the outdoors and must not be substantially blocked by any walls or other impermeable physical barriers.
14. The establishment must actively screen any dine-in patrons in accordance with the advice, recommendations and instructions of the Office of the Chief Medical Officer of Health before they enter the premises of the establishment.

(3) Despite subsection (2), the following establishments may provide indoor dining if they meet the conditions set out in paragraphs 1, 2, 3, 4, 6, 8.1, 9, 10, 12, and 13 of subsection 1 (1) of Schedule 2 to Ontario Regulation 263/20 made under the Act:

1. Establishments on hospital premises.
2. Establishments in airports.

3. Establishments located within a business or place where the only patrons permitted at the establishment are persons who perform work for the business or place in which the establishment is located.

(4) The physical distancing described in subsections 3 (1) and 4 (4) of Schedule 6 is not required when patrons are seated together at a table in an establishment.

(5) The capacity limits set out in clause 3 (1) (b) of Schedule 6 do not apply to outdoor dining areas in an establishment.

4. Nightclubs and strip clubs that open solely as food or drink establishments and that comply with the conditions set out in section 3.

5. (1) Shopping malls that comply with the following conditions:

1. Despite section 7, the only businesses in the shopping mall that may open for in-person retail sales to the public are,

i. businesses described in section 2, and

ii. any other businesses that have a public entrance that opens onto a street or exterior sidewalk.

2. Members of the public must only be permitted to enter the shopping mall,

i. for the purpose of accessing a business or place that is permitted to be open under this Order,

ii. for the purpose of accessing a designated location described in subsection (4) or (5),

iii. for the purpose of delivering or supporting the delivery of court services,

iv. for operations by or on behalf of a government, or

v. for the purpose of delivering or supporting the delivery of government services.

3. Members of the public who enter the shopping mall for a reason described in paragraph 2 must not be permitted to loiter in any area of the shopping mall that is not related to the purpose of their visit.

4. If a business or place in the shopping mall has a public entrance that opens onto a street or exterior sidewalk,

i. members of the public may only be permitted to enter and exit the business or place through a public entrance that opens onto a street or exterior sidewalk, and

ii. members of the public must be prohibited from entering or exiting the business or place through any entrance that opens directly into the shopping mall.

5. Any interior dining spaces inside the shopping mall, including any tables and seating in food courts, must be closed.
6. The shopping mall must ensure that any music played at the shopping mall is not at a decibel level that exceeds the level at which normal conversation is possible.
7. If the shopping mall is an indoor shopping mall, the shopping mall must actively screen individuals in accordance with the advice, recommendations and instructions of the Office of the Chief Medical Officer of Health before they enter the indoor premises of the mall.

(2) Any business in the shopping mall that is not permitted to open for in-person retail sales to the public may open for the purpose of,

(a) making sales using an alternative method of sale that does not require patrons to enter the shopping mall, including curbside pick-up or delivery; or

(b) permitting patrons to pick up items at a designated location established by the shopping mall under subsection (4) or (5).

(3) For greater certainty, paragraph 5 of subsection (1) does not prevent a restaurant, bar or other food or drink establishment within a shopping mall from opening and operating in compliance with section 3.

(4) A shopping mall may establish a single designated location inside the shopping mall for the purpose of allowing patrons to pick up an order from a business or place inside the shopping mall. Patrons may only pick up orders from the indoor designated location by making a prior appointment, and an item may only be provided for pick-up if the patron ordered the item before arriving at the business premises.

(5) A shopping mall may establish any number of designated locations outside the shopping mall for the purpose of allowing patrons to pick up an order from a business or place inside the shopping mall. Patrons may only pick up orders from the outdoor designated location by making a prior appointment, and an item may only be provided for pick-up if the patron ordered the item before arriving at the business premises.

5.1 REVOKED: O. Reg. 440/21, s. 11 (8).

5.2 (1) Businesses that meet the conditions set out in subsection (2) and that sell,

(a) motor vehicles, including cars, trucks and motorcycles;

(b) recreational vehicles, including motor homes;

(c) trailers and travel trailers;

(d) boats and other watercraft; or

(e) other motorized vehicles, including power-assisted bicycles, golf carts, scooters, snowmobiles and all-terrain vehicles.

(2) A business described in subsection (1) may only open if they meet the following conditions:

1. Members of the public must not be permitted in areas where the products described in subsection (1) are neither sold nor displayed for sale.
2. If members of the public are permitted to test drive any of the vehicles, boats or watercraft,

i. the test drive must be limited to no more than 10 minutes,

ii. a maximum of two people, including up to one sales representative, may be present in the vehicle, boat or watercraft during the test drive, and

iii. if two people who are not members of the same household are present in the vehicle during the test drive, any windows in the vehicle, boat or watercraft must be opened at all times.

6. Outdoor markets, including farmer's markets and holiday markets, that meet the following conditions:

1. They primarily sell food to the public.
2. If an area at the market is covered by a roof, canopy, tent, awning or other element, at least two full sides of the entire area must be open to the outdoors and must not be substantially blocked by any walls or other impermeable physical barriers.
3. If an area at the market is equipped with a retractable roof and the roof is retracted, at least one full side of the area must be open to the outdoors and must not be substantially blocked by any walls or other impermeable physical barriers.
4. The market must limit the number of members of the public in the place of business so that the total number of members of the public in the place of business at any one time does not exceed 25 per cent capacity, as determined in accordance with subsection 3 (3) of Schedule 6.

7. (1) Businesses not already described in sections 2 to 6 that engage in retail sales to the public and that comply with the following conditions:

1. They must limit the number of members of the public in the place of business so that the total number of members of the public in the place of business at any

one time does not exceed 15 per cent capacity, as determined in accordance with subsection 3 (3.1) of Schedule 6.

2. They must ensure that any music played at the place of business is not at a decibel level that exceeds the level at which normal conversation is possible.

(2) Despite anything else in this Order, any business that engages in retail sales to the public and that is not already described in sections 1 to 6 must comply with the conditions set out in subsection (1).

(3) Cannabis retail stores operating under the authority of a retail store authorization issued under the *Cannabis Licence Act, 2018* may open if they comply with the conditions set out in subsection (1) and provide products to patrons through in-person sales or through an alternative method of sale, such as curbside pick-up or delivery.

(4) A business that, as of December 26, 2020, was permitted to be open only in accordance with the conditions described in subsection (1) as it read on that date may only continue to be open in accordance with the conditions under that subsection as amended whether or not, after that date, it modified its operations or the type of products it sells.

(5) Despite subsection 32 (2) of Ontario Regulation 268/18 (General) made under the *Smoke-Free Ontario Act, 2017*, a person responsible for a specialty vape store as defined in that Regulation that is permitted to be open in accordance with the conditions described in subsection (1) shall not permit an electronic cigarette to be used for the purpose of sampling a vapour product in the specialty vape store.

Services

8. Rental and leasing services, including automobile, commercial and light industrial machinery and equipment rental.

9. Gas stations and other fuel suppliers.

10. Automated and self-service car washes.

11. Laundromats and drycleaners.

12. Lawn care services, snow clearing and landscaping services.

13. Security services for residences, businesses and other properties.

14. Domestic services that support children, seniors or vulnerable persons, including housekeeping, cooking, indoor and outdoor cleaning and maintenance services.

15. Vehicle and equipment repair and essential maintenance and vehicle and equipment rental services.

16. Courier, postal, shipping, moving and delivery services.

17. Funeral and related services.

18. Staffing services including providing temporary help.

19. (1) Veterinary services and other businesses that provide for the health and welfare of animals, including farms, boarding kennels, stables, animal shelters, and research facilities.

(2) For greater certainty, nothing in this Order precludes a person responsible for a boarding kennel or stable from allowing an animal's owner or their representative to visit the animal, assist in the care or feeding of the animal or, as applicable, ride the animal.

20. Businesses that provide pet services, including pet grooming services, pet sitting services, pet walking services and pet training services, including services for the training and provision of service animals.

21. (1) Child care providers, subject to subsections (2) and (3).

(2) A child care centre may open if it meets the following conditions:

1. The centre shall not operate a before or after school program on any school day for a child unless the child's school is permitted under this Order to provide in-person teaching or instruction to the child on that day.
2. The centre shall not provide child care on school days during typical school hours for a child whose school is not permitted under this Order to provide in-person teaching or instruction to the child on that day and who, immediately before April 12, 2021,

i. was enrolled in school, and

ii. was not registered to attend the centre on those days and during those hours.

3. If the Minister of Education designates a child care centre as an emergency child care centre that provides care for children of individuals listed in Schedule 10, paragraph 2 does not apply with respect to the provision of child care by the centre to the children of those individuals.

(3) A provider of authorized recreational and skill building programs shall not provide such a program to a child on a school day unless the child is enrolled in a school that is permitted under this Order to provide in-person teaching or instruction on that day.

(4) In this section,

"authorized recreational and skill building programs", "child care", "child care centre" and "child care provider" have the same meaning as in the *Child Care and Early Years Act, 2014*; ("programme autorisé de loisirs et de développement des compétences", "garde d'enfants", "centre de garde", "fournisseur de services de garde")

"school day" has the same meaning as in the *Education Act*. ("jour d'école")

21.1 Businesses providing short term rental accommodation that meet the following condition:

1. Any indoor pools, communal steam rooms, saunas or indoor whirlpools, indoor fitness centres, or other indoor recreational facilities that are part of the operation of these businesses, are closed.

22. Hotels, motels, lodges, cabins, cottages, resorts and other shared rental accommodation, including student residences, that meet the following condition:

1. Any indoor pools, communal steam rooms, saunas or indoor whirlpools, indoor fitness centres, or other indoor recreational facilities that are part of the operation of these businesses, are closed.

22.1 (1) Establishments that operate for the purposes of providing access to sensory deprivation pods that are being used for a therapeutic purpose prescribed by, or administered by, a regulated health professional and that comply with the following conditions:

1. Persons who provide services in the business must wear appropriate personal protective equipment.
2. No member of the public may be permitted to enter the premises except by appointment.
3. No member of the public may be permitted to be in the premises except for the period of time during which they are receiving sensory deprivation pod services.
4. The total number of patrons permitted indoors in the establishment must be limited to the number that can maintain a physical distance of at least two metres from every other person in the establishment, and in any event cannot exceed the lesser of,

i. five patrons, and

ii. 25 per cent capacity as determined in accordance with subsection 3 (3) of Schedule 6.

(2) Paragraph 3 of subsection (1) does not apply to a single caregiver accompanying an individual receiving the sensory deprivation pod service or to a single child of such individual.

23. Campgrounds that meet the following condition:

1. Any restaurant, indoor pool, communal steam room, sauna or indoor whirlpool, meeting room, indoor fitness centre or other indoor recreational facility on the premises must be closed to the public, except for any portion of those areas that,

i. is used to provide first aid services,

ii. is used to provide take-out or delivery service or outdoor dining in accordance with section 3,

iii. contains a washroom, or

iv. provides access to an area described in subparagraph i, ii or iii.

24. (1) Day camps for children that are operated in a manner consistent with the safety guidelines for COVID-19 for day camps produced by the Office of the Chief Medical Officer of Health.

(2) REVOKED: 345/21, s. 1 (1).

24.1 REVOKED: O. Reg. 440/21, s. 11 (17).

25. (1) Community centres and multi-purpose facilities that open to provide space for any, some or all of the following and that meet the requirements set out in subsection (2):

1. A day camp for children described in section 24.
2. A provider of child care within the meaning of the *Child Care and Early Years Act, 2014*.
3. Mental health support services or addictions support services, so long as no more than ten people are permitted to occupy the space.
4. The provision of social services.

(2) The person responsible for a community centre or multi-purpose facility that is open shall,

(a) record the name and contact information of every member of the public who attends the community centre or multi-purpose facility;

(b) maintain the records for a period of at least one month; and

(c) only disclose the records to a medical officer of health or an inspector under the *Health Protection and Promotion Act* on request for a purpose specified in section 2 of that Act or as otherwise required by law.

26. Cheque cashing services.

Financial services

27. Businesses that provide the following financial services:

1. Capital markets and related securities trading and advisory services.
2. Banking/credit union activities including credit intermediation.
3. Insurance.
4. Land registration services.
5. Pension and benefits payment services.
6. Financial services including payroll and payment processing and accounting and tax services.

28. (1) Real estate agent services that do not host, provide or support any open house events.

(2) Nothing in subsection (1) prevents a real estate agency from showing a property by appointment.

Telecommunications and IT infrastructure/service providers

29. Information Technology (IT) services, including online services, software products and the facilities necessary for their operation and delivery.

30. (1) Telecommunications providers and services (phone, internet, radio, cell phones etc.) and facilities necessary for their operation and delivery.

(2) For greater certainty, retail stores operated by telecommunications providers are required to comply with the rules set out in section 2.

31. Newspapers, radio and television broadcasting.

Maintenance

32. Maintenance, repair and property management services that manage and maintain the safety, security, sanitation and operation of institutional, commercial, industrial and residential properties and buildings.

Transportation services

33. Businesses and facilities that provide transportation services, including,

(a) transportation services provided by air, water, road and rail, including taxis and other private transportation providers; and

(b) support services for transportation services, including,

(i) logistical support, distribution services, warehousing and storage, truck stops and tow operators, and

(ii) services that support the operations and safety of transportation systems including maintenance and repairs.

34. (1) Marinas, boating clubs and other organizations that maintain docking facilities for members or patrons that meet the following condition:

1. Any clubhouse, restaurant, indoor pool, communal steam room, sauna or indoor whirlpool, meeting room, indoor fitness centre or other indoor recreational facility on the premises must be closed to the public, except for any portion of those areas that,

i. is used to provide first aid services,

ii. is used to provide take-out or delivery service or outdoor dining in accordance with section 3,

iii. contains a washroom, or

iv. provides access to an area described in subparagraph i, ii or iii.

(2) For greater certainty, nothing in this Order precludes a person responsible for a marina, boating club or other organization that maintains docking facilities for members or patrons from operating a grocery or convenience store on the premises or from providing fuel supply, watercraft repair and servicing, watercraft docking and watercraft launching services.

35. Businesses that provide and support online retail, including by providing warehousing, storage and distribution of goods that are ordered online.

Manufacturing

36. Businesses that extract, manufacture, process and distribute goods, products, equipment and materials, including businesses that manufacture inputs to other manufacturers (e.g. primary metal/steel, blow molding, component manufacturers, chemicals, etc. that feed the end-product manufacturer), regardless of whether those other manufacturers are inside or outside of Ontario, together with businesses that support and facilitate the movement of goods within integrated North American and global supply chains.

Agriculture and food production

37. Businesses that produce food and beverages, and agricultural products including plants, including by farming, harvesting, aquaculture, hunting and fishing.

38. Businesses that process, manufacture or distribute food, beverages, crops, agricultural products, animal products and by-products.

39. Businesses that support the food or agricultural products supply chains and the health and safety of food, animals and plants.

Construction

40. Construction activities or projects and related services that support construction activities or projects, including demolition services.

41. Land surveyors.

Resources and energy

42. Businesses that provide and ensure the domestic and global continuity of supply of resources, including, resource exploration, mining, forestry, aggregates, petroleum, petroleum by-products and chemicals.

43. Electricity generation, transmission, distribution and storage and natural gas distribution, transmission and storage.

Community services

44. Businesses that deliver or support the delivery of community services including,

(a) sewage treatment and disposal;

(b) collecting, transporting, storing, processing, disposing or recycling of any type of waste;

(c) potable drinking water;

(d) critical infrastructure repair and maintenance including roads, dams, bridges, etc.;

(e) environmental rehabilitation, management and monitoring, and spill clean-up and response;

(f) administrative authorities that regulate and inspect businesses;

(g) professional and social services that support the legal and justice system;

(h) government services including but not limited to policing and law enforcement, fire and emergency services, paramedics, coroner and pathology services, corrections and court services, licences and permits; and

(i) allotment gardens or community gardens.

Facilities for indoor or outdoor sports and recreational fitness activities

45. (1) Facilities for indoor or outdoor sports and recreational fitness activities that meet the conditions set out in subsection (2), (3), (4) or (7), as applicable.

(2) A facility for indoor or outdoor sports and recreational fitness activities may open if it meets the following conditions:

1. The facility is,

i. operated by, or for the sole use of, persons who are athletes, coaches or officials training or competing to be a part of Team Canada at the next summer or winter Olympic Games or Paralympic Games, if the persons are,

A. identified by a national sport organization that is either funded by Sport Canada or recognized by the Canadian Olympic Committee or the Canadian Paralympic Committee, and

B. permitted to train, compete, coach or officiate under the safety protocols put in place by a national sport organization mentioned in sub-subparagraph A, or

ii. REVOKED: O. Reg. 489/21, s. 2 (1).

2. REVOKED: O. Reg. 489/21, s. 2 (2).

If the facility is operated by a sports team, the team's league must have established a health and safety protocol for the use of training facilities, and the facility must be operated in compliance with the health and safety protocol.

3. The only persons permitted to enter and use the facility must be,

i. players, athletes, coaches or officials who are using the facility for the purposes of training or conditioning, and

ii. such staff as are strictly necessary to operate the facility and support the training or conditioning of the players.

(3) A facility for indoor or outdoor sports and recreational fitness activities may open if it meets the following conditions:

1. The facility must open solely for the purpose of providing space for any, some or all of the following:

i. A day camp for children described in section 24.

ii. A provider of child care within the meaning of the *Child Care and Early Years Act, 2014*.

iii. Mental health support services or addictions support services, so long as no more than ten people are permitted to occupy the space.

iv. The provision of social services.

2. The person responsible for the facility must,

i. record the name and contact information of every member of the public who attends the space described in paragraph 1,

ii. maintain the records for a period of at least one month, and

iii. only disclose the records to a medical officer of health or an inspector under the *Health Protection and Promotion Act* on request for a purpose specified in section 2 of that Act or as otherwise required by law.

(4) A facility for indoor or outdoor sports and recreational fitness activities may, but is not required to, open if it meets the following conditions:

1. The facility must be open solely for the purpose of allowing use of the facility by,

i. persons with a disability, within the meaning of the *Accessibility for Ontarians with Disabilities Act, 2005*, who,

A. have received a written instruction for physical therapy from a regulated health professional who is qualified to provide the instruction, and

B. are not able to engage in the physical therapy elsewhere,

ii. such staff as are strictly necessary to operate the facility and support the provision of the physical therapy, and

iii. such support persons or service animals as may be necessary for the person with a disability.

2. The facility must have established a health and safety protocol for the use of the facility that is consistent with sections 2, 3, 4, 5, 6 and 11 of Schedule 6, and the facility must be operated in compliance with the health and safety protocol.
3. The person responsible for the facility must,

i. record the name and contact information of every person described in paragraph 1 who enters and uses the facility,

ii. maintain the records for a period of at least one month, and

iii. only disclose the records to a medical officer of health or an inspector under the *Health Protection and Promotion Act* on request for a purpose specified in section 2 of that Act or as otherwise required by law.

(5) Despite paragraph 1 of subsection (3) and paragraph 1 of subsection (4), a facility may be open for both purposes described subsections (3) and (4) if the facility meets the conditions in both subsections.

(6) For greater certainty, no indoor or outdoor sports or recreational classes are permitted at any indoor or outdoor sport and recreational facilities, except as permitted under subsection (7).

(7) A facility for outdoor sports and recreational fitness activities, including a facility for indoor sports and recreational fitness activities that has such outdoor facilities, may be open if it complies with the following conditions:

1. The only activities permitted on the premises are outdoor fitness classes, personal training and training for team and individual sports.
2. No patrons are permitted to be in the indoor areas of the facility, except as may be necessary,

i. to access a washroom,

ii. to access an outdoor area that can only be accessed through an indoor route, or

iii. as may be necessary for the purposes of health and safety.

3. No more than 10 patrons may participate,

i. in an outdoor fitness class at any one time, or

ii. as a group in personal training or in training for team or individual sports.

4. No spectators are permitted to be at the facility. However, a person under the age of 18 years who is engaged in activities in the facility may be accompanied by one parent or guardian.
5. Any person who enters or uses the facility must maintain a physical distance of at least three metres from any other person who is using the facility.
6. For greater certainty, team sports must not be practised or played at the facility, with the exception of training sessions for members of a sports team that do not include games or scrimmage games.
7. Activities that are likely to result in individuals coming within three metres of each other must not be practised or played at the facility.
8. The person responsible for the facility must,

i. record the name and contact information of every member of the public who enters the facility,

ii. maintain the records for a period of at least one month, and

iii. only disclose the records to a medical officer of health or an inspector under the *Health Protection and Promotion Act* on request for a purpose specified in section 2 of that Act or as otherwise required by law.

9. The facility must actively screen individuals in accordance with the advice, recommendations and instructions of the Office of the Chief Medical Officer of Health before they enter the facility.

(8) Despite paragraph 1 of subsection (2) , paragraph 1 of subsection (3) and paragraph 1 of subsection (4), a facility may be open for both a purpose described in subsection (2), (3) or (4) as applicable and a purpose described in subsection (7) if the facility meets the conditions in both subsections.

(9) REVOKED: O. Reg. 440/21, s. 11 (21).

Personal physical fitness, etc.

45.1 Personal physical fitness and sports trainers that meet the following conditions:

1. Any services must be provided outside.
2. Services may not be provided to more than 10 patrons at one time.

3. No spectators are permitted. However, a person under the age of 18 years who is engaged in physical fitness or sports training activities may be accompanied by one parent or guardian.
4. Any person who is engaged in physical fitness or sports training activities must maintain a physical distance of at least three metres from any other person.
5. Training sessions for members of a sports team cannot include games or scrimmage games.
6. Activities that are likely to result in individuals coming within three metres of each other must not be practised or played.
7. The personal trainer or sports trainer must,

i. record the name and contact information of every member of the public who they are providing services to,

ii. maintain the records for a period of at least one month, and

iii. only disclose the records to a medical officer of health or an inspector under the *Health Protection and Promotion Act* on request for a purpose specified in section 2 of that Act or as otherwise required by law.

8. The personal trainer or sports trainer must actively screen individuals in accordance with the advice, recommendations and instructions of the Office of the Chief Medical Officer of Health before they engage in personal physical fitness or sports training activities.

Recreation

46. (1) Subject to subsection (2), businesses whose primary purpose is to operate an outdoor recreational amenity that is permitted to open under section 4 of Schedule 8.

(2) Amusement parks and water parks must be closed.

47. Outdoor horse racing tracks, car racing tracks and other similar venues may open for training and races if they comply with the following conditions:

1. No members of the public are permitted at the venue.
2. Only persons who are essential to the training, race or operation of the venue are permitted to be on the premises of the venue.

Research

48. Businesses and organizations that maintain research facilities and engage in research, including medical research and other research and development activities.

Health care and social services

49. Organizations and providers that deliver home care services or personal support services to seniors and persons with disabilities.

50. Regulated health professionals.

50.1 Osteopathic manual practitioners.

51. Professionals or organizations that provide in-person counselling services.

52. Organizations that provide health care including retirement homes, hospitals, clinics, long-term care facilities, independent health facilities and mental health and addictions counselling supports.

53. Laboratories and specimen collection centres.

54. Manufacturers, wholesalers, distributors and retailers of pharmaceutical products and medical supplies, including medications, medical isotopes, vaccines and antivirals, medical devices and medical supplies.

55. Manufacturers, distributors and businesses that provide logistical support of or for products and/or services that support the delivery of health care in all locations.

56. Organizations that provide critical personal support services in home or residential services for individuals with physical disabilities.

57. Organizations that support the provision of food, shelter, safety or protection, and/or social services and other necessities of life to economically disadvantaged and other vulnerable individuals.

Teaching and instruction

57.1 Businesses that open to provide in-person teaching and instruction and that meet the following conditions:

1. The instructional space for the in-person teaching and instruction must be outdoors.
2. The students must maintain a physical distance of at least two metres from every other person in the instructional space, except where necessary for teaching and instruction that cannot be effectively provided if physical distancing is maintained.
3. The total number of students permitted to be in each instructional space at any one time must be limited to 10 persons.

4. If the in-person teaching or instruction involves singing or the playing of brass or wind instruments,

i. every person who is singing or playing must be separated from every other person by plexiglass or some other impermeable barrier, or

ii. every person in the instructional space must remain at least three metres apart from every other person in the instructional space.

5. Students must be actively screened in accordance with the advice, recommendations and instructions of the Office of the Chief Medical Officer of Health before they enter the business.

6. The person responsible for the business shall,

i. record the name and contact information of every student who attends the in-person teaching and instruction,

ii. maintain the records for a period of at least one month, and

iii. only disclose the records to a medical officer of health or an inspector under the *Health Protection and Promotion Act* on request for a purpose specified in section 2 of that Act or as otherwise required by law.

58. Businesses that are primarily engaged in the provision of health and safety training and that meet the following conditions:

1. The instructional space for any in-person training must be operated to enable students to maintain a physical distance of at least two metres from every other person in the instructional space, except where necessary for teaching and instruction that cannot be effectively provided if physical distancing is maintained.
2. The total number of students permitted to be in each instructional space at any one time must be limited to the number that can maintain a physical distance of at least two metres from every other person in the business or place, and in any event cannot exceed 10 persons.

Media industries

59. Sound recording, production, publishing and distribution businesses.

60. (1) Commercial film and television production, including all supporting activities such as hair, makeup and wardrobe, that meet the following conditions:

1. No studio audiences may be permitted to be on the film or television set.

1.1 No more than 50 performers may be permitted to be on the film or television set.

2. The set must be configured and operated in such a way as to enable persons on the set to maintain a physical distance of at least two metres from other persons, except where necessary for the filming of the film or television production.
3. Persons who provide hair or makeup services must wear appropriate personal protective equipment.
4. REVOKED: O. Reg. 440/21, s. 11 (28).
5. The person responsible for the film or television production must ensure that the production operates in accordance with the guidance document titled "Film and television industry health and safety during COVID-19" issued by the Film and Television Health and Safety Advisory Committee of the Ministry of Labour, Training and Skills Development, as amended from time to time.

(2) For greater certainty, for the purposes of this section, the film or television set may be located in any business or place, including any business or place that is otherwise required to be closed under this Order.

61. Film and television post-production, visual effects and animation studios.

62. Book and periodical production, publishing and distribution businesses.

63. Commercial and industrial photography.

63.1 Photography studios and services that meet the following conditions:

1. Photography may only be provided by appointment.
2. Any in-person services provided to patrons, including the taking of photographs, must be provided outdoors.
3. Patrons must be actively screened in accordance with the advice, recommendations and instructions of the Office of the Chief Medical Officer of Health before photography is provided.

64. Interactive digital media businesses, including,

(a) computer system software or application developers and publishers; and

(b) video game developers and publishers.

Entertainment

65. (1) Concert venues, theatres and cinemas that meet the conditions set out in subsection (2) or (3).

(2) Concert venues, theatres and cinemas may open for the purpose of rehearsing or performing a recorded or broadcasted concert, artistic event, theatrical performance or other performance on outdoor premises if they comply with the following conditions:

1. No spectators may be permitted anywhere on the premises.
2. Only persons who are essential to the rehearsal or performance are permitted anywhere on the premises.
3. No more than 10 performers may be permitted to participate in the rehearsal or performance.
4. Every performer and other person who performs work for the concert venue, theatre or cinema must maintain a physical distance of at least three metres from every other person.
5. No performer or other person who performs work for the concert venue, theatre or cinema may be permitted in an indoor area of the concert venue, theatre or cinema, except,

i. where necessary to use a washroom,

ii. where necessary to access an outdoor area that can only be accessed through an indoor route, or

iii. as may otherwise be required for the purposes of health and safety.

6. The person responsible for the concert venue, theatre or cinema must,

i. record the name and contact information of every performer or other person who is present at the rehearsal or performance,

ii. maintain the records for a period of at least one month, and

iii. only disclose the records to a medical officer of health or an inspector under the *Health Protection and Promotion Act* on request for a purpose specified in section 2 of that Act or as otherwise required by law.

7. The person responsible for the concert venue, theatre or cinema must ensure that individuals are actively screened in accordance with the advice, recommendations and instructions of the Office of the Chief Medical Officer of Health before they enter the premises.

(3) Concert venues, theatres and cinemas may open if they comply with the following conditions:

1. The movie, concert, artistic event, theatrical performance or other performance must be provided in a drive-in or drive-through format.
2. Each person in attendance at the drive-in cinema or the drive-in or drive-through concert, event or performance, other than persons who perform work for the drive-in cinema or the drive-in or drive-through concert, event or performance, must remain within a motor vehicle designed to be closed to the elements except,

i. where necessary to purchase admission,

ii. where necessary to use a washroom, or

iii. as may otherwise be required for the purposes of health and safety.

3. Every motor vehicle at the drive-in cinema or the drive-in or drive-through concert, event or performance may only contain members of a single household plus a maximum of one additional person from outside that household who lives alone.
4. The driver of a motor vehicle at the drive-in cinema or the drive-in or drive-through concert, event or performance must ensure that it is positioned at least two metres away from other motor vehicles.

66. Businesses that provide outdoor tour and guide services, including guided fishing and hunting trips, tastings and tours for wineries, breweries and distilleries, trail riding tours, walking tours and bicycle tours, but not motor vehicle tours or boat tours other than boat tours for guided fishing trips, may open if they comply with the following conditions:

1. The tour must be operated to enable every person on the tour, including tour guides, to maintain a physical distance of at least two metres from every other person, except where necessary,

i. to facilitate payment, or

ii. for the purposes of health and safety.

2. Every person on the tour must wear a mask or face covering in a manner that covers their mouth, nose and chin during any period in which they come within two metres of another person, unless they are entitled to any of the exceptions set out in subsection 2 (5) of Schedule 6.
3. The number of members of the public on the tour must not exceed the number of persons that would permit compliance with paragraph 1 while on the tour, and in any event cannot exceed 10 persons.

4. Every member of the public who intends to participate in the tour must be actively screened in accordance with the advice, recommendations and instructions of the Office of the Chief Medical Officer of Health before they participate in the tour.
5. The persons on the tour must remain outdoors at all times, except where necessary to use a washroom or as may otherwise be required for the purposes of health and safety.
6. The tour or guide service must,

i. record the name and contact information of every patron that participates in the tour,

ii. maintain the records for a period of at least one month, and

iii. only disclose the records to a medical officer of health or an inspector under the *Health Protection and Promotion Act* on request for a purpose specified in section 2 of that Act or as otherwise required by law.

O. Reg. 96/21, s. 10; O. Reg. 103/21, s. 2; O. Reg. 126/21, s. 4; O. Reg. 144/21, s. 4; O. Reg. 162/21, s. 4; O. Reg. 216/21, s. 3; O. Reg. 221/21, s. 5; O. Reg. 239/21, s. 4; O. Reg. 345/21, s. 1; O. Reg. 440/21, s. 11; O. Reg. 481/21, s. 1; O. Reg. 489/21, s. 2.

SCHEDULE 8
PLACES THAT MUST CLOSE OR THAT ARE SUBJECT TO CONDITIONS AT STEP 1

Public libraries

1. (1) Public libraries may only open if they comply with the following conditions:

1. Circulating materials must be reserved over the telephone or online.
2. Circulating materials may only be exchanged with members of the public through contactless drop-off, pick-up or delivery.
3. Patrons must only be permitted to enter the premises to facilitate contactless drop-off and pick-up or to access computers, photocopiers or similar services.
4. Patrons must not be permitted to be in the book stacks, or to handle circulating materials that are shelved, or in other areas of library storage.
5. REVOKED: O. Reg. 440/21, s. 12 (2).
6. The person responsible for the public library must comply with subsection (3), if applicable.

(2) The conditions set out in paragraphs 3 and 4 of subsection (1) do not apply with respect to any space the library provides for,

(a) a day camp for children described in section 24 of Schedule 7;

(b) a provider of child care within the meaning of the *Child Care and Early Years Act, 2014*;

(c) mental health support services or addictions support services, so long as no more than ten people are permitted to occupy the space; or

(d) the provision of social services.

(3) The person responsible for a public library shall,

(a) record the name and contact information of every member of the public who attends the space described in subsection (2);

(b) maintain the records for a period of at least one month; and

(c) only disclose the records to a medical officer of health or an inspector under the *Health Protection and Promotion Act* on request for a purpose specified in section 2 of that Act or as otherwise required by law.

Post-secondary institutions

2. (1) Post-secondary institutions may only open if they meet the following conditions:

1. In-person teaching or instruction may only be provided if the following conditions are met:

i. The subject matter of the teaching or instruction requires that it be taught in-person, such as clinical training or training related to a trade.

ii. The instructional space must be operated to enable students to maintain a physical distance of at least two metres from every other person in the instructional space, except where necessary for teaching and instruction that cannot be effectively provided if physical distancing is maintained.

iii. The total number of students permitted to be in each instructional space at the institution at any one time must be limited to the number that can maintain a physical distance of at least two metres from every other person in the business or place, and in any event cannot exceed,

A. 50 persons, in the case of an instructional program described in subsection (2), and

B. 10 persons, in any other case.

2. If in-person teaching or instruction at the institution involves singing or the playing of brass or wind instruments,

i. every person who is singing or playing must be separated from every other person by plexiglass or some other impermeable barrier, or

ii. every person in the instructional space must remain at least three metres apart from every other person in the instructional space.

3. Any in-person examinations must be provided in accordance with the following rules:

i. Every person in the examination room must remain at least two metres apart from every other person in the examination room.

ii. The total number of persons who may take the examination in the same room at the same time cannot exceed,

A. 50 persons, in the case of an examination for an instructional program described in subsection (2), and

B. 10 persons, in any other case.

(2) An instructional program referred to in sub-subparagraphs 1 iii A and 3 ii A of subsection (1) is an instructional program in any of the following fields or an instructional program to train an individual for any of the following occupations, as the case may be:

0.1 Dental hygiene.

0.2 Dentistry.

1. Diagnostic cardiac sonography.
2. Diagnostic medical sonography.
3. Diagnostic ultrasound.
4. Medical imaging.
5. Medical laboratory assistant.
6. Medical laboratory technician.

6.1 Medical laboratory technologist.

7. Medical radiation technology.
8. Medicine.
9. Mental health and addictions services, including psychology services, social work services and counselling services.

9.1 Midwifery.

10. Nursing.

10.1 Optometry.

11. Paramedic.

12. Personal support worker, supportive care worker, home care worker or a similar occupation.

13. Pharmacy/pharmacy technician.

13.1 Physician assistant.

14. Public health inspector, if the program is accredited by the Canadian Institute of Public Health Inspectors.

15. Rehabilitation sciences (nutrition, speech language pathology, occupational science, and physiotherapy).

16. Respiratory therapy.

17. Veterinary medicine.

(3) In this section,

"post-secondary institution" means,

(a) a university,

(b) a college of applied arts and technology,

(c) a private career college,

(d) an Indigenous Institute prescribed for the purposes of section 6 of the *Indigenous Institutes Act, 2017*,

(e) an institution that is authorized to grant a degree by an act of the Legislature,

(f) a person who is delivering in-person teaching or instruction in accordance with a consent given under section 4 of the *Post-secondary Education Choice and Excellence Act, 2000*,

(g) a person approved to provide training for apprenticeship programs under paragraph 5 of section 64 of the *Ontario College of Trades and Apprenticeship Act, 2009*, or

(h) any other institution that is a designated learning institution within the meaning of section 211.1 of the *Immigration and Refugee Protection Regulations* (Canada), other than a school or private school within the meaning of the *Education Act*.

Schools and private schools

3. (1) Schools and private schools within the meaning of the *Education Act* shall not provide in-person teaching or instruction.

(2) Despite subsection (1), schools and private schools within the meaning of the *Education Act* may open,

(a) to the extent necessary to facilitate the operation of a child care centre within the meaning of the *Child Care and Early Years Act, 2014*;

(b) if approved by the Minister of Education, to the extent necessary to facilitate the operation of an extended day program, as defined in the *Education Act*, for the provision of emergency child care for the children of individuals listed in Schedule 10 during the period when schools are not permitted to provide in-person teaching or instruction;

(c) to allow staff of the school or private school to provide remote teaching, instruction or support to pupils, so long as the school or private school operates in accordance with a return to school direction issued by the Ministry of Education and approved by the Office of the Chief Medical Officer of Health;

(d) to the extent necessary to provide in-person instruction to pupils with special education needs who cannot be accommodated through remote learning and who wish to attend a school or their private school for in-person instruction, so long as the school or private school operates in accordance with a return to school direction issued by the Ministry of Education and approved by the Office of the Chief Medical Officer of Health; or

(e) to facilitate the operation of a day camp for children described in section 24 of Schedule 7.

(3) Subsections (1) and (2) do not apply to schools that meet the condition set out in subsection (4) and that are operated by,

(a) a band, a council of a band or the Crown in right of Canada;

(b) an education authority that is authorized by a band, a council of a band or the Crown in right of Canada; or

(c) an entity that participates in the Anishinabek Education System.

(4) A school described in subsection (3) may open if it meets the following condition:

1. If a person who holds a study permit issued under the *Immigration and Refugee Protection Act* (Canada) and who entered Canada on or after November 17, 2020 attends the school, in-person teaching or instruction may only be provided to that person if the school or private school,

i. has a plan respecting COVID-19 that has been approved by the Minister of Education, and

ii. operates in accordance with the approved plan.

(5) A school or private school may allow persons, other than persons allowed to be at the school or private school under subsection (2), to enter the school or private school temporarily, as necessary,

(a) to prepare for an end-of-school-year celebration ceremony described in subsection 1 (5) of Schedule 9, if the person is a staff member or student at the school or private school and is required to be indoors for such preparation;

(b) to use a washroom or as may otherwise be required for the purposes of health and safety while attending the end-of-school-year celebration; or

(c) to return goods or supplies or retrieve personal belongings.

Recreational amenities

4. (1) Each person responsible for an indoor or outdoor recreational amenity that is not in compliance with this section, and that is not a facility for indoor or outdoor sports and recreational fitness activities that is permitted to open under section 45 of Schedule 7, must ensure that it is closed.

(2) The following outdoor recreational amenities may open if they are in compliance with subsection (3):

1. Parks and recreational areas.
2. Baseball diamonds.
3. Batting cages.
4. Soccer, football and sports fields.
5. Tennis, platform tennis, table tennis and pickleball courts.
6. Basketball courts.
7. BMX parks.
8. Skate parks.
9. Golf courses and driving ranges.
10. Frisbee golf locations.
11. Cycling tracks.
12. Trails.
13. Horse riding facilities.
14. Shooting ranges, including those operated by rod and gun clubs.
15. Playgrounds.
16. Portions of parks or recreational areas containing outdoor fitness equipment.

17. Archery ranges.
18. Boat and watercraft launches.
19. Lawn game courts, including lawn bowling, bocce and croquet courts.
20. Horseshoe pits.
21. Outdoor pools, splash pads, spray pads, whirlpools, wading pools and water slides.

(3) An outdoor recreational amenity described in subsection (2) may only open if the following conditions are met:

1. Subject to paragraph 2, any person who enters or uses the amenity must maintain a physical distance of at least two metres from any other person who is using the amenity.
2. Any person who engages in physical exercise in the amenity, including by engaging in a training session, sport or game, must maintain a physical distance of at least three metres from any other person who is using the amenity.
3. Team sports must not be practised or played within the amenity, with the exception of training sessions for members of a sports team that do not include games or scrimmage games.
4. Other sports or games that are likely to result in individuals coming within three metres of each other must not be played within the amenity.
5. Clubhouses on the premises must be closed, except to the extent that they,

i. are used in conjunction with an outdoor pool, splash pad, spray pad, whirlpool, wading pool or water slide, or

ii. provide access to equipment storage, a washroom or a portion of the amenity that is used to provide first aid.

(4) Paragraphs 1 and 2 of subsection (3) do not apply in respect of the following persons who enter or use an outdoor recreational amenity:

1. Parasport participants and their attendants or guides.
2. Members of a single household.

(5) Paragraphs 1 to 4 of subsection (3) do not apply with respect to an amenity, or a particular area of an amenity, during periods when the amenity or the particular area is exclusively being used by persons who are athletes, coaches and officials training or competing to be a part of Team Canada at the next summer or winter Olympic Games or Paralympic Games if the persons are,

(a) identified by a national sport organization that is either funded by Sport Canada or recognized by the Canadian Olympic Committee or the Canadian Paralympic Committee; and

(b) permitted to train, compete, coach or officiate under the safety protocols put in place by a national sport organization mentioned in clause (a).

(6) Each person responsible for a boat or watercraft shall ensure that if a group of persons uses that boat or watercraft together for recreational purposes, the members of the group are all members of the same household or one other person from outside that household who lives alone or a caregiver for any member of the household.

Museums, etc.

5. (1) Subject to subsections (2) and (3), museums, galleries, aquariums, zoos, science centres, landmarks, historic sites, botanical gardens and similar attractions must be closed to members of the public.

(2) An attraction described in subsection (1) may open to provide drive-in or drive-through access to the public if it complies with the conditions set out in section 65 of Schedule 7, subject to any necessary modifications.

(3) An outdoor attraction described in subsection (1) may open if it complies with the following conditions:

1. The number of members of the public in the attraction must be limited so that the total number of members of the public in the outdoor ticketed area of the attraction at any one time does not exceed 15 per cent capacity, determined by taking the total square metres of outdoor ticketed area accessible to the public in the attraction, dividing that number by 26.67 and rounding the result down to the nearest whole number.
2. The person responsible for the attraction must post a sign in a conspicuous location visible to the public that states the maximum capacity they are permitted to operate under.
3. No member of the public may enter a ticketed area of the attraction unless they have made a reservation to do so.
4. No member of the public may be permitted access to interactive exhibits or exhibits that would create a high risk of personal contact.
5. No member of the public may be permitted to enter any indoor area of the premises, except,

i. to access a washroom,

ii. to access an outdoor area that can only be accessed through an indoor route, or

iii. as may be necessary for the purposes of health and safety.

6. No amusement rides or tour vehicles may be operated by the attraction.

O. Reg. 96/21, s. 10; O. Reg. 348/21, s. 2; O. Reg. 440/21, s. 12.

SCHEDULE 9
ORGANIZED PUBLIC EVENTS, CERTAIN GATHERINGS AT STEP 1

Gatherings

1. (1) Subject to sections 2 to 4, no person shall attend,

(a) an organized public event that is held indoors;

(b) a social gathering that is held indoors, including a social gathering associated with a gathering described in clause (d);

(c) an organized public event or social gathering of more than 10 people that is held outdoors, including a social gathering associated with a wedding, funeral or a religious service, rite or ceremony, but not including the wedding, funeral or a religious service, rite or ceremony itself;

(d) an indoor gathering for the purposes of a wedding, a funeral or a religious service, rite or ceremony where the number of persons occupying any particular room in a building or structure while attending the gathering exceeds 15 per cent of the capacity of the room; or

(e) an outdoor gathering for the purposes of a wedding, a funeral or a religious service, rite or ceremony where the number of persons attending the gathering exceeds the number that can maintain a physical distance of at least two metres from every other person in the space where the gathering is held.

(2) A person attending an organized public event, social gathering or a gathering for the purposes of a wedding, a funeral or a religious service, rite or ceremony shall comply with public health guidance on physical distancing.

(3) For greater certainty, subsections (1) and (2) apply with respect to an organized public event, social gathering or a gathering for the purposes of a wedding, a funeral or a religious service, rite or ceremony, even if it is held at a private dwelling.

(4) For greater certainty, the limits in clauses (1) (b) and (c) apply to a social gathering associated with a wedding, a funeral or a religious service, rite or ceremony, such as a wedding reception, while the limits that apply to the wedding, funeral or religious service, rite or ceremony itself are set out in clauses (1) (d) and (e).

(5) Clause (1) (c) does not apply with respect to an outdoor end-of-school-year celebration ceremony held by a school or private school within the meaning of

the *Education Act* that is in compliance with a direction issued by the Ministry of Education and approved by the Office of the Chief Medical Officer of Health.

(6) All persons participating in an end-of-school-year celebration ceremony described in subsection (5) must remain outdoors at all times, except as permitted under subsection 3 (5) of Schedule 8.

(7) Clauses 1 (a) and (c) do not apply with respect to day camps for children that are in compliance with section 24 of Schedule 7.

Exception, single household, etc.

2. Section 1 does not apply with respect to,

(a) a gathering of members of a single household;

(b) a gathering that includes members of a household and one other person from another household who lives alone; or

(c) a gathering that includes persons described in clause (a) or (b), and a caregiver for any of those persons.

Exception, retirement homes

2.1 Section 1 does not apply with respect to a gathering in a retirement home within the meaning of the *Retirement Homes Act, 2010* if it is in compliance with the policies or guidance, if any, issued by the Retirement Homes Regulatory Authority.

Exception, attendance at business

3. The prohibitions on attendance at an organized public event in subsection 1 (1) do not apply with respect to attendance at a business for a purpose related to providing or receiving the goods or services provided by the business if the business is not required to close under this Order.

Gathering in motor vehicles for religious service, rite or ceremony

4. (1) This section applies with respect to gatherings for the purposes of a wedding, funeral, religious service, rite or ceremony if the persons attending the gathering, other than those conducting the service, rite or ceremony, do so in a motor vehicle.

(2) Clause 1 (1) (e) does not apply to a person who attends a gathering to which this section applies if the person follows all of the following precautions that apply to the person:

1. Each person attending the gathering, other than the persons conducting the service, rite or ceremony, must remain within a motor vehicle that is designed to be closed to the elements, except,

i. where necessary to use a washroom, or

ii. as may otherwise be necessary for the purposes of health and safety.

2. The driver of a motor vehicle must ensure that it is positioned at least two metres away from other motor vehicles.

3. A person who ordinarily uses a non-motorized vehicle because of their religious belief and who attends the gathering must remain within their non-motorized vehicle except where necessary to use a washroom or as may otherwise be required for the purposes of health and safety, and paragraph 2 applies with necessary modifications.

O. Reg. 96/21, s. 10; O. Reg. 189/21, s. 1; O. Reg. 221/21, s. 6; O. Reg. 440/21, s. 13; O. Reg. 482/21, s. 2.

This is **Exhibit "BB"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

Public Health Ontario | Santé publique Ontario

SYNTHESIS

12/01/2020

COVID-19 Routes of Transmission – What We Know So Far

Introduction

Public Health Ontario (PHO) is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19). "What We Know So Far" documents provide a rapid review of the evidence related to a specific aspect or emerging issue related to COVID-19.

The development of these documents includes a systematic search of the published literature as well as scientific grey literature (e.g., ProMED, CIDRAP, Johns Hopkins Situation Reports) and media reports, where appropriate. Relevant results are reviewed and data extracted for synthesis. All "What We Know So Far" documents are reviewed by PHO subject matter experts before posting.

As the COVID-19 outbreak continues to evolve and the scientific evidence rapidly expands, the information provided in these documents is only current as of the date of posting.

See Appendix A for Glossary of Terms for COVID-19 Routes of Transmission.

Updates in Latest Version

Since the last version (July 16, 2020), multiple new studies and systematic reviews have been published with evidence on the potential for transmission via several routes including respiratory droplet and close-contact, vertical, conjunctival and fomite transmission. There was more evidence against several modes of transmission, including sexual and transmission through breast milk.

Importantly, there are now experimental studies and outbreak case studies that support severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission through small particle respiratory droplets or aerosols during prolonged exposure in a poorly ventilated space. The primary mode of SARS-CoV-2 transmission; however, remains through respiratory droplets and unprotected close contact.

New modes of transmission addressed in this update include potential transmission from wastewater, food, urine and zoonotic transmission (through animals).

Key Points

- Overall, the evidence for various transmission routes relies heavily on the detection of viral RNA in clinical and environmental samples, rather than the detection of viable, infectious virus. Further, the quantity of viral RNA that is representative of an infectious dose is unclear.

- Transmission of SARS-CoV-2 occurs predominantly through close (<2 m), unprotected contact with an infected individual(s). Based on the epidemiology of COVID-19, transmission predominantly occurs via respiratory droplets from symptomatic, presymptomatic or less commonly, asymptomatic individuals.
- Transmission over longer distances (>2 m) is less common, but possible under certain conditions such as prolonged exposure in a poorly ventilated space. Under these conditions, inhalation of small particle respiratory droplets and aerosols can occur. SARS-CoV-2 is likely an *opportunistic* airborne pathogen, as non-airborne transmission is most common, but aerosols may result in transmission under favourable conditions.
- Relatively uncommon routes of transmission of SARS-CoV-2 include conjunctival, vertical (intrauterine), fecal-oral, fomite and zoonotic. While these routes of transmission are possible, their contribution to the epidemiology of COVID-19 is unclear.
- Routes of transmission that are theoretically possible due to the detection of viral RNA, but that are very unlikely, are sexual transmission (via semen and vaginal secretions); bloodborne transmission (blood products, organ transplant); transmission through breast milk; transmission through urine; food-borne transmission; and transmission through contaminated wastewater.

Background

The purpose of this document is to outline the evidence for various SARS-CoV-2 transmission routes, based on a review of the scientific literature. SARS-CoV-2 is genetically similar to other coronaviruses and shares a high degree of genetic similarity (79%) with the coronavirus (SARS-CoV-1) responsible for Severe Acute Respiratory Syndrome (SARS).[1] Therefore, in instances of limited evidence for COVID-19, we have extrapolated existing data from other coronaviruses, in particular SARS-CoV-1.

During the COVID-19 pandemic, evidence for and against potential routes of transmission has evolved. In some instances, there is no consensus on the contribution from certain modes of transmission. A number of reports postulate transmission routes; however, in many it is challenging to determine the precise mode of transmission where there are multiple opportunities for transmission to occur (i.e. through direct contact, fomites, or inhalation). In addition, the strength of evidence by transmission route has changed. In contrast to the July 16, 2020 version of this document, there have been several systematic reviews published on the subject that are included. The systematic reviews contribute to bringing the evidence base closer to a consensus. Within this document, we underpin our findings with systematic reviews and meta-analyses where available, supporting findings with case series and cohort studies.

Methods

In considering feasibility, scope and the need for responsiveness, a rapid review was chosen as an appropriate approach to determining the routes of transmission for SARS-CoV-2. A rapid review is a type of knowledge synthesis wherein certain steps of the systematic review process are compromised in order to be timely.[2]

PHO is actively monitoring, reviewing and assessing relevant information related to COVID-19. This document provides a rapid review of the evidence related to transmission routes of SARS-CoV-2.

On October 14, 2020, PHO Library Services developed and conducted a search in MEDLINE (Appendix B). English language peer-reviewed and grey literature records that describe transmission of SARS-CoV-2

were included. We did not restrict year of publication. We reviewed references of included studies for additional articles.

Two reviewers screened titles and abstracts, and the senior author reviewed the application of the eligibility criteria. The senior author synthesized relevant data. We did not perform a critical appraisal of the methodological quality of studies due to time constraints. PHO subject matter experts reviewed this rapid review before posting.

Results

Droplet and Contact Transmission

Current evidence suggests that the primary mode of transmission of COVID-19 is through direct contact from respiratory droplets that have the potential to be propelled for varying distances.[3-5]

Household secondary attack rates are indicative of predominantly droplet and close-contact transmission:

In household settings, people are in close proximity to one another, thereby increasing the risk of infection. The consensus among systematic reviews is that most infections are occurring in household settings where physical distancing is not feasible and household secondary attack rates are higher than in casual-contact settings (e.g., shopping).

In a systematic review and meta-analysis, Lei et al. reported the secondary attack rate in households was 27% (95% confidence interval [CI]: 21−32); the risk of secondary infection was 10 times higher in households compared to non-household settings (odds ration [OR]: 10.72; 95% CI: 5.70–20.17; p<0.001).[7] In another systematic review and meta-analysis by Madewell et al., the household secondary attack rate was 18.8% (95% CI: 15.4–22.2).[8] Koh et al, in a meta-analysis, reported that the household secondary attack rate was 18.1% (95% CI: 15.7–20.6), much higher than the secondary attack rate in health care settings (0.7%; 95% CI: 0.4–1.0).[9] Further, these findings do not support predominant airborne transmission. If SARS-CoV-2 was predominantly and efficiently spread through an airborne route (i.e., through aerosols), household secondary attack rates would be expected to be substantially higher (e.g., >90% in measles).[6]

Contact tracing studies also show higher secondary attack rates in households, compared to other settings. The limited transmission to contacts outside the household setting suggests that the mode of SARS-CoV-2 transmission is predominantly from close contact. Luo et al. studied 3,410 close contacts of 391 index cases in Guangzhou, China and found that the secondary attack rate was lower when people were exposed in health care settings (1.0%; OR: 0.09; 95% CI: 0.04–0.20) and on public transportation (0.1%; OR: 0.01; 95% CI: 0.00–0.08), compared to the household secondary attack rate (10.3%).[10] In a retrospective cohort study in Guangzhou, China, Jing et al. reported the household secondary attack rate (among close relatives) was 12.4% (95% CI: 9.8–15.4).[11] In most studies, non-household close contacts have secondary attack rates less than 1% (Bi et al., Chaw et al., Cheng et al., Li et al.).[12-15]

Evidence for SARS-CoV-2 droplet and contact transmission:

The majority of COVID-19 cases have been linked to person-to-person transmission through close, direct contact with symptomatic patients,[16-18] or through close contact with a pre-symptomatic patient.[19-21] In addition, high viral loads have been identified in individuals who were asymptomatic or pre-

symptomatic .[22-24] In a case-control study of patients 18 years old and older in the United States (US), Fisher et al. reported that close contact with a person with COVID-19 was reported more often among cases (42%) than controls (14%).[25] A study modelling the transmission risk from epidemiological data among train passengers revealed that travellers directly adjacent to the index patient had a much higher infection risk (relative risk [RR]: 18.0; 95% CI: 13.9–23.4), and the attack rate decreased with increasing distance.[26] Furthermore, the attack rate increased by 0.15% (p=0.005) per hour of co-travel time.

Using whole-genome sequencing of SARS-CoV-2 clinical samples during a nosocomial outbreak of COVID-19 in Dublin, Ireland, Lucey et al. reported that the majority of infections were among patients who required extensive and prolonged care by health care providers.[27] The authors concluded that the likely mode of transmission from health care workers to patients was through respiratory droplets and close contact, rather than airborne transmission.

The reproductive number (R_0) is less suggestive of airborne spread, as airborne infections tend to have a higher R_0. For example, in a systematic review by Guerra et al., the R_0 for measles in the pre-vaccine era was 6.1–27.0;[28] compared to the range of R_0 (2–3) reported for COVID-19.[29]

Evidence for distance travelled by respiratory droplets:

Researchers have demonstrated the propulsion of respiratory droplets up to 2 m, and in a study by Guo et al., respiratory droplets were found on the floor up to 4 m away from a patient.[30] A systematic review of studies assessing the horizontal distance travelled by respiratory droplets found that droplets could travel up to 8 m.[31]

Airborne Transmission

Respiratory virus transmission occurs on a spectrum from larger droplets that spread at close range to smaller droplets (or aerosols) that have the potential to be infectious over longer distances (i.e. >2 m) and may be suspended for longer periods of time (typically hours). As summarized above, current evidence supports that SARS-CoV-2 transmission is predominantly through close, unprotected contact, which supports larger droplet spread. However, under conditions of poor ventilation or with recirculation of unfiltered and untreated air, aerosols may accumulate in sufficient quantities to become infectious and transmission via inhalation is plausible based on the emerging literature.[32] Further evidence regarding the quantity of viral particles required to cause infection is needed. There is no evidence at this time of transmission over long distances through the air (such as through air ducts). The term “airborne transmission” has special meaning in public health, for infection prevention and control purposes, and in health care settings. This term is typically reserved to describe infections efficiently transmitted by small droplets and particles suspended in the air over long distances and persisting in the air for long periods (see Appendix for size designations). Airborne pathogens typically require specialized engineering controls to prevent spread (e.g. negative-pressure isolation rooms and specific personal protective equipment (PPE) such as respirators). However, the historical dichotomy of airborne vs non-airborne pathogens used in health care settings is likely imprecise. Infectious pathogens can be considered on a spectrum of efficiency for airborne transmission classified as *obligate* (infection only occurs via aerosols), *preferential* (aerosols predominate), or *opportunistic* (non-airborne transmission is most common but aerosols may transmit under favorable conditions). Current evidence supports SARS-CoV-2 as an *opportunistic* airborne pathogen.[33]

A commentary by Morawska and Milton appealed to the medical community to recognize the potential for airborne transmission, based on experimental evidence that small respiratory droplets (or aerosols)

could be inhaled.[34] Another commentary by Klompas et al. discussed how the balance of currently available evidence does not support long-range aerosol transmission as the dominant mode of COVID-19 transmission. While aerosols are reported by Stadnytskyi et al. to be produced during activities such as speaking, breathing and coughing,[35] it is not clear what role aerosols have in transmission for distances greater than 2 m, as viable SARS-CoV-2 has only once been detected during air sampling. The role of these aerosols has been suggested in a modelling study by Chen et al. to be most important for transmission in close proximity (<2 m).[36]

As discussed in the Droplet and Contact Transmission section, household secondary attack rates are more consistent with primary transmission through respiratory droplets when people are in close contact with one another, rather than airborne transmission. There is emerging evidence that *opportunistic* aerosol transmission occurs under the right combination of conditions (i.e. poorly ventilated space with sufficient quantity of infectious virus produced). However, as discussed above, this appears to be less frequent, and less efficient, when compared with direct close contact.

Environmental exposures, such as sunlight, may have significant effects on viability of SARS-CoV-2. Using a rotating drum experiment similar to other studies for viability of SARS-CoV-2, simulated sunlight (UVA/UVB) was applied to aerosolized virus through a window on the drum.[37] Results indicated 90% inactivation of virus within 20 minutes.

Experimental evidence of aerosol generation of SARS-CoV-2:

In a study comparing SARS-CoV-2 and SARS-CoV-1, van Doremalen et al. reported that SARS-CoV-2 could be artificially aerosolized with a jet nebulizer and detectable for up to 3 h in a rotating metal drum.[38] The half-lives of SARS-CoV-2 and SARS-CoV-1 were similar in aerosols with median estimates of the half-life of 1.1–1.2 h. While the van Doremalen et al. study concluded that aerosol transmission was possible, they did not demonstrate that it occurred (refer to the PHO Synopsis on this study for further details). Fears et al. drew similar conclusions through conducting a similar experiment.[39]

Lee modelled the minimum sizes of aerosols emitted from an infected individual that could be expected to contain viral particles.[40] Under certain assumptions, Lee estimated that the minimum sizes theoretically ranged from 0.4–42 μm; by using experimental data of virus in oral fluid, they estimated a range of 4.7–32 μm. Studies discussed by Lee detected virus by polymerase chain reaction (PCR) in much smaller aerosol sizes (<0.25–4 μm). The author reconciled differences in the modelled sizes and air-sampled sizes by acknowledging that aerosols evaporate to smaller sizes (which may take only seconds) and/or the possible range of virus in oral fluid can be higher than reported by the previous experiment used to inform this model. Lee also noted that the virus particles captured in those experiments may not be viable.

Studies have not consistently detected viable SARS-CoV-2 in air samples:

Multiple air sampling studies performed in proximity to confirmed COVID-19 cases were unable to detect any virus by PCR.[41-47] Santarpia et al. was unable to culture virus from air samples collected outside of patient rooms.[48] Similarly, Binder et al. reported that 3 PCR-positive air samples, collected at distances of 1–3.2 m from patients, were culture negative.[49] Cheng V et al. sampled air at a high flow rate 10 cm from the chin of symptomatic and asymptomatic patients (n=6), with no viable virus detected by culture from collected air samples.[44] One PCR-positive air sample was obtained during an endotracheal intubation within 10 cm of the patient's head in a naturally ventilated room (window open

with fan attached); eleven other air samples near patients and 17 samples outside patient rooms and at nursing stations were PCR-negative.[50]

Lednicky et al. used a prototype and commercial version of an air sampler and custom PCR probes for detection of SARS-CoV-2 in a patient room with two patients. One patient was discharged soon after sampling periods began and after receiving a negative PCR test.[51] The remaining patient began experiencing respiratory illness two days prior to admission to the room. The results of the study include PCR-positive air samples following 3 h of sampling as well attempting viral cultures. Researchers positioned samplers 2–4.8 m from the recently symptomatic patient's head. The ventilation unit provided 6 air changes/h, filtering air and treating air with UV irradiation before recycling the air. Estimates of virus per volume of air ranged from 6–74 tissue culture infective dose $(TCID)_{50}$ units/L of air. More studies quantifying viable virus, with details of the type of ventilation and patient characteristics as reported in this study, are needed to inform the gaps in understanding aerosol transmission.

Another study detected SARS-CoV-2 by PCR in 38.7% (14/31) of air samples from a London hospital in the United Kingdom (UK) during the first peak of their epidemic. However, Zhou et al. did not detect virus by culture, suggesting there may not be adequate virus present in air samples to cause transmission.[52] Another study by Guo et al. detected SARS-CoV-2 by PCR in 35% (14/40) of air samples in an intensive care unit (ICU) and 12.5% (2/16) of air samples in the general ward that manages patients with COVID-19. 15 of 16 PCR-positive air samples were from within 2 m of patients, with 1/8 samples positive at 4 m away.[30] Ben-Shmuel et al. conducted limited sampling (generally one air sample per area) in rooms with ventilated and non-ventilated patients, at a nursing station, and in private and public areas of a quarantine hotel.[53] Positive air samples were detected in a room with a ventilated patient (n=1/1), at a nursing station (n=1/1), and in a quarantine hotel room (n=1/1). However, there were no positive air samples in rooms of non-ventilated patients (n=0/3), a doffing area (n=0/1), and a public area of a quarantine hotel (n=0/1).

Kenarkoohi et al. detected SARS-CoV-2 in 1/5 samples from a ward containing intubated, severely ill patients, but did not find any positive air samples in other areas of the hospital such as wards with suspected, confirmed and mild patients.[54] In a series of distinct room types (two airborne infection isolation rooms [AIIR] with 15+ air changes per hour, an isolation room without negative pressure, and a shared cohort room) for patients admitted within 7 days of symptom onset, Kim et al. reported that 32 air samples were negative and 20 air samples from anterooms were also negative.[55]

Chia et al., in an extended study of Ong et al., detected SARS-CoV-2 RNA by PCR in air samples collected within 1 m of patients in two of three AIIRs.[56] Lei et al. reported limited detection of SARS-CoV-2 virus by air sampling in open wards, private isolation rooms and bathrooms.[57]

Further research is needed to reconcile differences in viral RNA detection and viral viability in air samples, despite positive samples found on the surfaces of ventilation units. Differences may be due to several factors, including: 1) air sampling devices were potentially not capable of maintaining viability of captured virus; 2) timing of air sampling varies by time since onset of symptoms, severity of disease, or viral load; and, 3) the conditions of ventilation (engineering controls) reducing concentrations of viral aerosols to undetectable levels.[49,51,53]

Evidence for long distance spread of SARS-CoV-2 is uncommon:

There were few reports that have identified long distance transmission of SARS-CoV-2. The minimal transmission to fellow passengers seated near individuals with COVID-19 on airplanes does not support an airborne transmission route.[58-60] The airflows in an airplane cabin were modelled in a study

demonstrating how risk of infection may be restricted to certain areas in front and behind an infected passenger.[61]

In one case study, worshippers who were not wearing masks were exposed to a presymptomatic index patient for 100 minutes while on a bus.[62] Twenty-four of 67 worshippers became infected, including several passengers seated beyond 2 m distance. Seven of 172 other worshippers attending the same event were positive for SARS-CoV-2. The bus containing the index patient was heated and air was recirculated without filtration. Infections occurred in individuals at either end of the bus and the index case was located roughly in the middle. Risk of infection was only moderately higher for individuals sitting closer to the index patient. The authors of this study postulate that the poor ventilation in the bus supports aerosols in this large transmission cluster; however, other routes of transmission such as close contact from movement within the bus or fomites could not be excluded.

An investigation by Lu et al. into a COVID-19 outbreak in a restaurant in Guangzhou, China involving three families sitting in close proximity for more than 1 hour concluded that the air conditioning (AC) ventilation likely contributed to transmission.[63] In this scenario, there was between 53–73 min of contact between the presymptomatic index case and secondary cases. The location of a consistently running AC unit (the outlet and exhaust flanked the table of the index case) was in the airflow path of the secondary cases and was in an enclosed environment. No secondary cases occurred at adjacent tables that were outside of the likely "air column." The furthest distance between index and secondary cases was approximately 3 m.

Recent outbreaks with detailed reporting are less likely to be explained completely by droplet or contact routes (Miller et al., Brlek et al.).[64,65] In a choir group, 53 of 60 individuals (excluding the index patient) were confirmed or strongly suspected to have been infected during a 2.5 hour rehearsal in a main hall. Individuals who moved to another area of the building from the index case to practice for 45 min were less likely to have become infected than those who remained in the main hall for the full duration of the rehearsal.[64,65] In another study, infection was documented from exposure in a squash court used by patrons after a recently symptomatic index patient had played for 1 hour. Two sets of patrons using the court after the index patient were also infected (up to 90 min later). Aerosol persistence in a poorly ventilated squash court, re-aerosolization of virus from the squash court floor due to rapid movement of players, or fomite transmission were possible routes of transmission. However, this case investigation strongly supports indirect transmission of SARS-CoV-2, most likely through persistence of aerosols in a poorly ventilated space.

In an outbreak in a nursing home, de Man et al. reported that the outbreak involved 81% (n=17) of residents and 50% (n=17) of health care workers. The authors concluded that AC units and a ventilation system that did not provide adequate air exchanges contributed to the outbreak.[66] However, it should be noted that health care workers did not wear masks during non-patient care activities and the mobility and interaction between residents was not considered.

In a call center in South Korea, half of one floor of the office building experienced an outbreak in 94/216 employees.[67] The outbreak description is limited in providing further detail because the index patient was not known, ventilation parameters were not reported (especially whether air circulation was shared on both sides of the building), and daily mingling habits were not described. A handful of infected individuals were detected on two other floors, but no outbreaks occurred in those areas and the infected individuals could not be linked to the outbreak.

The importance of ventilation is described in a modeling study by Jones, who suggested that exposure to inhalable particles are mostly (80%) experienced within close proximity to the patient.[68] Even in rooms with high air exchanges, Tang et al.'s review of SARS-CoV-2 aerosols indicates that viral RNA copies can still be detected in air samples from patient rooms (1.8–3.4 viral RNA copies/m^3), toilet rooms (19 copies/m^3), and PPE doffing rooms (18–42 copies/m^3).[69]

Airborne Transmission during AGMPs

There were no documented cases of airborne transmission of SARS-CoV-2 during AGMPs in the peer-reviewed literature we examined. We note the lack of transmission in these settings may be due to the appropriate use PPE during AGMPs, with few unprotected close-contact exposures.

Evidence for transmission of SARS-CoV-2 during AGMPs:

There is little evidence demonstrating AGMPs as a contributor to health care worker transmission. In a case-control study involving health care workers, Lentz et al. reported that while AGMPs were not associated with an increased risk of SARS-CoV-2 infection, respirator use during AGMPs lowered the risk of infection (adjusted OR: 0.4; 95% CI: 0.2–0.8; p=0.005).[70]

While airborne transmission does not appear to be the predominant mode of transmission (i.e., such as in households and in routine patient care), medical procedures that generate aerosols may be associated with an increased risk of transmission.[71] During the SARS outbreak in 2003, infections disproportionately occurred among healthcare workers, with those involved in AGMPs and manipulation of the airway (i.e., at the time of intubation) at greatest risk.[72] An investigation into a nosocomial outbreak of SARS in Toronto concluded that the epidemiological links described in their investigation support the hypothesis that SARS-CoV-1 was transmitted primarily through respiratory droplets and direct contact, noting that transmission occurred during high-risk procedures (i.e. intubation) when only a surgical mask was utilized, in the absence of protective eyewear.[73] Infected healthcare workers were no less likely to contract SARS-CoV-1 while wearing an N95 respirator (vs. surgical mask), suggesting that it may have been doffing (taking off) of PPE where transmission occurred.[74] AGMPs do not appear to be a significant risk factor for SARS-CoV-2 transmission among health care workers, potentially related to improved health care worker precautions for AGMPs and/or the lower infectiousness of SARS-CoV-2 in the second week of illness (in contrast to SARS-CoV-1).[70,75-78]

Fecal-oral (Feces, Wastewater) Transmission

While fecal-oral transmission of SARS-CoV-2 is possible, it is unclear the extent to which this transmission route plays in the epidemiology of COVID-19. The evidence supporting fecal-oral transmission was limited.

Researchers have documented angiotensin-converting enzyme 2 (ACE-2; proposed receptor used by SARS-CoV-2 to enter cells) receptor expression in gastrointestinal epithelial cells; SARS-CoV-2 infects these glandular cells, as evidenced by RNA detection and intracellular staining of viral nucleocapsid protein in gastric, duodenal and rectal epithelia.[79] Gastrointestinal symptoms occur in about 9.5% of adults and children with COVID-19.[80] Tissues in the oral cavity express ACE-2 receptors.[81] SARS-CoV-2 RNA and live virus have been detected in the stool of patients with COVID-19. Given detection of infectious virus in stool and that virus can infect via the oral mucosa, fecal-oral transmission is possible.

Evidence for SARS-CoV-2 RNA detection and shedding in feces:

In systematic reviews, the mean prevalence of SARS-CoV-2-RNA-positive stool in patients with COVID-19 ranged from approximately 40% to 50% and viral RNA shedding in stool lasted longer than in nasopharyngeal (NP) swabs. In a systematic review and meta-analysis of 4,243 patients, Cheung et al. reported the prevalence of viral RNA in stool was 48.1% (95% CI: 38.3–57.9).[82] In a meta-analysis by van Doorn et al., the pooled prevalence of viral RNA in stool or anal swabs was 51.8% (95% CI: 43.8%–59.7%); and fecal samples remained positive for a mean duration of 12.5 days after negative NP swabs in 282/433 (64%) of patients who had serial test results for both respiratory and GI specimens.[83] A systematic review by Gupta et al. noted that 53.9% (291/540) of COVID-19 patients had viral RNA-positive fecal samples; duration of fecal shedding ranged from 1 to 33 days after negative NP swabs.[84] Parasa et al. reported on a meta-analysis of 407 patients with COVID-19, where the prevalence of viral RNA-positive stool was 40.5% (95% CI: 27.4–55.1).[85] In a meta-analysis, Wong MC et al. reported a pooled detection rate of viral RNA in fecal samples among patients was 43.7% (95% CI: 32.6–55.0).[86]

In studies detecting viral RNA in various clinical samples other than NP swabs, researchers more commonly detect viral RNA in stool of patients with COVID-19. In a systematic review of 569 patients by Roshandel et al., prevalence of viral RNA was higher in stool (39.5%) than blood (21.3%) and urine (8%).[87] In another systematic review, Morone et al. reported the prevalence of viral RNA-positive stool (48.8%) was higher than positive blood (17.5%) and urine (16.4%) samples; median duration of viral shedding in stool was significantly longer than shedding in respiratory samples (19 days vs. 14 days; $p<0.001$).[88] Comparing viral RNA detection in serum, urine and stool in 74 patients, Kim et al. reported a detection rate of 2.8% (9/323 samples), 0.8% (2/247) and 10.1% (13/129), respectively.[89] The mean viral load was 1,210 ± 1,861, 79 ± 30 and 3,176 ± 7,208 copies/µL, respectively, and no viable virus was detected in cell cultures. In a review, Jones et al. noted that the abundance of viral RNA in urine (10^2–10^5 genome copies [gc]/ml) and feces (10^2–10^7 gc/ml) was lower than in NP swabs (10^5–10^{11} gc/ml).[90]

In a study of 69 children, 86% had viral RNA-positive stool/rectal/anal swabs and the mean duration of viral shedding was 23.6 ± 8.8 days from symptom-onset.[91] In a study of 69 patients with COVID-19, patients with positive fecal samples were significantly younger compared to patients with negative fecal samples (mean age: 43 vs. 52 years; $p=0.003$).[92] Viral shedding in stool persisted for over 3 weeks since symptom-onset and the severity of COVID-19 was not associated with duration of viral shedding in stool.[93,94]

Kang et al. reported on an outbreak of COVID-19 in a high-rise apartment building in Guangzhou, China, where the proposed mode of transmission was through fecal aerosols via the pipes in the building.[95] However, the authors did not demonstrate the exact mode of transmission; i.e., through direct contact or indirectly through inhalation of aerosolized virus or touching contaminated surfaces.

Environmental sampling in health care and non-health care settings detected viral RNA on toilets and other bathroom surfaces.[43,55,96-99] While readily detected, it is not clear if the source of viral RNA in bathrooms was the result of respiratory droplets or from fecal contamination.

Evidence for live SARS-CoV-2 detection in feces:

Live virus has been cultured in stool samples of patients with COVID-19.[100,101] In a systematic review, viable virus was detected in the stool of six out of 17 patients, where culturing of virus was attempted.[83] It is important to note that the authors did not define positive and negative controls in these studies. While researchers detect live virus in feces, the extent of fecal-oral transmission in COVID-19 epidemiology is unclear.

Evidence for SARS-CoV-2 RNA in wastewater:

Viral RNA detection in wastewater systems in areas experiencing outbreaks; however, the risk of transmission through contaminated wastewater is low.[102,103] In a study of treated and raw sewage in Germany, the authors detected viral RNA, but not viable virus.[104] Where wastewater contaminates recreational or drinking water (especially in resource-limited countries), there is a theoretical risk of transmission; however, there is no documented transmission in these settings.[105]

In a study of eight patients with COVID-19 in a densely populated area of Guangzhou, China, the postulated mode of transmission was through the fecal-oral route, initiated from contaminated sewage in street puddles (viral RNA-positive).[106] In this study, there was an increased risk of infection when patients worked as cleaners/waste pickers, wore outdoor shoes inside their homes and cleaned dirty shoes. The authors did not confirm transmission via sewage in this study, as the authors did not detect viable virus from samples and they did not rule out other modes of transmission.

Conjunctival Transmission

To date, there is a low risk of COVID-19 infection through the conjunctiva.

Transmission through the ocular surface is a possible route of transmission of SARS-CoV-2 based on the detection of viral RNA in ocular samples of patients with COVID-19 and indirect evidence that eye protection decreases the risk of infection.[107] The risk of tears or ocular secretions acting as a source of infection is low, given that only one study has successfully cultured viable virus in these samples.

Several studies have demonstrated the expression of ACE-2 and transmembrane serine protease 2 (TMPRSS2) receptors in the eye's surface epithelium (i.e., conjunctiva, limbus and cornea) and corneal endothelium, indicating a potential entry point for SARS-CoV-2.[108-111] The conjunctiva has been proposed as a possible site of initial infection, where it can spread to the upper respiratory tract via the nasolacrimal system.[112] Deng et al. demonstrated that rhesus macaques developed mild disease after inoculation of the conjunctiva, providing further animal-study evidence of conjunctival transmission.[113]

Evidence for conjunctival transmission:

In a case report, Lu et al. described a healthcare worker who became infected after caring for a patient with COVID-19; the health care worker was wearing an N95 respirator, but no eye protection.[114] The health care worker developed eye redness and then pneumonia.

In a study of an ophthalmologist with COVID-19, 142 patients were exposed; however, only a single patient developed symptoms (but PCR negative), indicating the use of face shields, masks and performing hand hygiene prevented infection.[115] In the meta-analysis by Chu et al., eye protection provided significant protection against coronavirus infections (unadjusted RR: 0.34; 95% CI: 0.22–0.52), suggesting that transmission through the conjunctiva was possible.[116]

Fomite (Surfaces, Objects, Food) Transmission

SARS-CoV-2 can survive on a variety of surfaces, potentially leading to transmission via fomites; however, the evidence supporting fomite transmission of COVID-19 was limited and based primarily on studies of virus stability under laboratory-controlled conditions.

Evidence for fomite transmission of SARS-CoV-2:

From a detailed investigation, including whole genome sequencing, into an inter-facility outbreak of up to 135 nosocomial COVID-19 cases (including 88 staff and 47 patients) in South Africa, Lessells et al. concluded that a patient in the emergency department likely spread the infection to at least five hospital units, a local nursing home and an outpatient dialysis unit on campus.[117] Based on the pattern of transmissions, the authors concluded that indirect contact and fomite transmission were the predominant modes of transmission, facilitated by frequent patient movement between wards.

In an epidemiological and environmental study of two family clusters (n=5 patients) of COVID-19 in Guangzhou, China, Xie et al. reported potential transmission via contaminated surfaces.[118] In this case, the proposed link between the two families was through nasal secretions, in which a patient had touched a contaminated elevator button. In this study, other modes of transmission cannot be ruled out and no viable virus was detected on surfaces (only viral RNA detection).

As mentioned previously, transmission in a squash court occurred in players that used the space after it was occupied by the index case for one hour.[65] In this case, there is a possibility of aerosol persistence; however, transmission via fomites is possible (e.g., on high-touch surfaces).

Evidence for SARS-CoV-2 RNA detection on surfaces:

In health care settings, studies documented the presence of viral RNA on high-touch surfaces in the environment of symptomatic and asymptomatic patients with COVID-19 (especially medical equipment, phones, bed rails, door handles and toilets).[41,42,46,47,56,96,119-121] In a hospital in Wuhan, China, Ye et al. reported that the most contaminated surfaces were self-service printers for patient use, keyboards and doorknobs.[122] In Italy, researchers detected viral RNA on the external surface of Continuous Positive Airway Pressure (CPAP) helmets worn by COVID-19 patients; however, samples did not grow in viral culture.[123] A study reported viral RNA on surfaces (keyboards, telephones and scanners) in a clinical microbiology laboratory testing COVID-19-patient respiratory samples.[124] In a multicenter study in South Korea, contamination of surfaces was common, especially in places not adequately sanitized.[55]

Cheng et al. reported that the median load of viral RNA on surfaces was 9.2×10^2 copies/mL (range: 1.1×10^2 to 9.4×10^4 copies/mL) and positivity rates on surfaces increased with increasing viral loads in clinical samples.[96]

In non-healthcare settings (patient homes, work places), viral RNA has also been detected on surfaces (especially in bathrooms and bedrooms).[95,98,125] In a study of 39 patients and 259 environmental samples from their homes (Guangzhou, China), surfaces most commonly contaminated with viral RNA were in the bathroom on high touch surfaces (toilets, door knobs, faucets).[43]

Evidence for the detection of live SARS-CoV-2 on surfaces:

In most of the studies we examined, researchers failed to detect viable virus on surfaces or detection of viable virus was inconsistent.[41,49] Ben-Shmuel et al. investigated the viability of SARS-CoV-2 from 97 samples from surfaces of patients.[53] None of the samples grew in viral culture. In controlled experiments, virus viability on plastic and metal ceased after 4 days at ambient temperature (22°C) and decreases in virus viability negatively correlated with increasing temperature. Nonetheless, some studies indicate that under ideal conditions, SARS-CoV-2 remains viable on surfaces for several days.

Van Doremalen et al. compared surface stability of SARS-CoV-2 and SARS-CoV-1.[38] The authors noted an exponential decay in virus titre for both viruses in all experimental conditions. At 40% relative humidity and 21°C–23°C, both SARS-CoV-2 and SARS-CoV-1 were detectable for up to 24 h on cardboard and up to 2–3 d on plastic and stainless steel. On copper, the authors did not find live SARS-CoV-2 and SARS-CoV-1 after 4 h and 8 h, respectively. The estimated median half-lives for SARS-CoV-2 on these surfaces were 0.7 h for copper, 3.5 h for cardboard, 5.6 h for stainless steel, and 6.8 h for plastic. While the van Doremalen et al. study concluded that fomite transmission is possible given detection of SARS-CoV-2 on a number of surfaces, they did not demonstrate that it occurs.

Riddell et al. tested the stability of SARS-CoV-2 under controlled conditions on seven surface types (stainless steel, plastic, paper bank notes, polymer bank notes, vinyl, cotton and glass).[126] The authors concluded that infectious virus survived on non-porous surfaces for at least 28 d at 20°C and 50% relative humidity in the dark. In addition, virus titres decreased by 90% by 10 d post-inoculation at 20°C on all surfaces.

Chan et al. reported that at room temperature (20°C–25°C), SARS-CoV-2 in dried form or solution remained viable 3–5 d and 7 d, respectively; virus remained viable in solution or dried for 14 d at 4°C and about 1 d at 37°C.[127] SARS-CoV-2 was detected at pH 4 to pH 11 for several days.

Chin et al. investigated the surface stability of SARS-CoV-2 at 22°C and 65% relative humidity.[128] the authors did not detect infectious virus on printing and tissue paper 3 h after inoculation. Infectious virus was no longer present on glass or paper money by day 4 and on day 7 for plastic and stainless steel. The authors state, “The virus is highly stable at 4°C, but sensitive to heat. At 4°C, there was about a 0.7 log-unit reduction of infectious titre on day 14. With the incubation temperature increased to 70°C, the time for virus inactivation was reduced to 5 min. SARS-CoV-2 can be highly stable in favourable environments, but it is also susceptible to standard disinfection methods.”

Evidence for food-borne transmission of SARS-CoV-2:

To date, there is no evidence for food-borne transmission of SARS-CoV-2. No peer-reviewed studies investigated SARS-CoV-2 survival or detection on food and no peer-reviewed studies reported on infection through eating contaminated food. There is likely a risk of transmission from droplet or close contact during eating (from an infectious person); in addition, there is a possibility of fecal-oral transmission during eating with contaminated utensils.

Several studies have identified viral RNA on food preparation surfaces and utensils, which could potentially be a source of infection through the oral mucosa; however, the contribution of this mode of transmission is unknown. In a study of surfaces in health care settings, researchers have detected viral RNA on food preparation areas.[129] Liu et al. reported the detection of viral RNA on wooden chopsticks handled by asymptomatic and presymptomatic patients with COVID-19.[130]

Vertical (Intrauterine) Transmission

To date, there is growing evidence supporting vertical transmission, specifically intrauterine transmission, of SARS-CoV-2; however, the degree to which this mode of transmission occurs is unclear.

In a commentary, Schwartz et al. proposed that confirming vertical, intrauterine transmission requires detection of SARS-CoV-2 in chorionic villous cells using immunohistochemistry or *in situ* hybridization.[131] Early onset of COVID-19 or detection of viral RNA soon after birth in neonates, along with immunological response in neonates and RNA-positive swabs of whole placenta are not sufficient to confirm

intrauterine transmission. In addition, vertical transmission would require the detection of viral RNA in umbilical cord tissue or blood.

Evidence against vertical transmission of SARS-CoV-2:

In five systematic reviews and meta-analyses, ranging from 87 to 1,316 births, there were SARS-CoV-2 RNA-positive newborns but no evidence of vertical transmission.[132-136] In a systematic review of 1,125 mothers and 1,141 newborns, Dhir et al. concluded that the majority of infections in newborns occurred in the post-partum period (41/45; 4 infections were reported as congenital).[137]

In a multicenter observational cohort study of 242 pregnant women in Spain, Marin Gabriel et al. found no evidence of vertical transmission in newborns.[138] Yan et al. reported no vertical transmission in a series of 99 mothers with COVID-19, in which no children (n=100) tested positive.[139] Liu et al. reported no vertical transmission after delivery in 19 mothers with COVID-19; neonates tested negative by PCR (throat swab, urine, feces); amniotic fluid and breast milk also tested negative by PCR.[140]

Evidence for post-partum infection (SARS-CoV-2 RNA not detected in placenta or umbilical cord):

There are several studies where newborns tested positive (viral RNA, antibodies) soon after birth under strict infection control and prevention precautions; however, testing of chorionic villous cells or umbilical cord were negative or not performed.[141-148] In a systematic review of 275 pregnant women with COVID-19 and 246 neonates, the testing of additional samples for viral RNA did not produce positive samples (cord blood, n=30; amniotic fluid, n=24; cervical/vaginal fluids, n=7; placenta, n=6).[149]

Kirtsman et al. reported a case of probable vertical transmission of SARS-CoV-2 in a neonate born to a mother who tested positive for viral RNA by PCR on NP swab and put on airborne, droplet and contact precautions.[150] The baby was born by semi-urgent Caesarean section and placed in a resuscitator 2 m away from the mother. The NP swab was positive for viral RNA at birth and on day 2 and 7. Neonatal plasma was viral RNA-positive on day 4 and on day 7 in stool. However, viral RNA was not detected by PCR on the umbilical cord tissue and cord blood was not available for testing.

Knight et al. report the results from a prospective national population-based cohort study using the UK Obstetric Surveillance System, which included 427 pregnant women admitted to hospital with COVID-19.[151] Twelve (5%) of 265 infants tested positive by PCR for viral RNA, six within 12 h of birth. The authors did not attempt viral detection on the umbilical cord blood, placenta or vaginal secretions and did not describe infection prevention and control practices after birth.

Evidence for vertical transmission of SARS-CoV-2:

Using immunofluorescence, Taglauer et al. examined the location of SARS-CoV-2 spike glycoprotein (CoV2 SP) and two viral entry proteins (ACE-2, TMPRSS2) in placentas of 15 COVID-19-positive mothers and 10 COVID-19-negative mothers.[152] CoV2 SP and ACE-2 were localized in the outer syncytiotrophoblast layer placental villi. However, several other studies report that the expression of ACE-2 and TMPRSSR in the placenta is low.[153,154]

In a systematic review and meta-analysis of 122 neonates, Raschetti et al. reported that 5.7% of infections were confirmed as congenital, 4.9% were probable congenital infections and 1.6% were possible congenital infections.[155]

Patanè et al. found viral RNA on the fetal side of the placenta in two mothers infected with COVID-19.[156] Both children were also positive by PCR from NP swabs taken at birth. Hosier et al. analyzed the

placenta from a woman in her second trimester with symptomatic COVID-19 infection, complicated by preeclampsia and placental abruption.[157] Hosier et al. detected viral RNA predominantly in the syncytiotrophoblast cells at the maternal-fetal interface of the placenta. Additionally, Zhang et al. reported virus in syncytiotrophoblast cells, atrophic endometrial glandular epithelium and subchorionic plate (Langhan's fibrinoid) through *in situ* hybridization (2/53 placentas).[158]

Breastfeeding (Breast Milk) Transmission

Currently, there is no evidence to support mother-to-child transmission of COVID-19 through breast milk. Researchers inconsistently detect SARS-CoV-2 RNA in breast milk, with no evidence of live virus in breast milk. There have been no documented cases where breast milk is the suggested mode of transmission to an infant.

During breastfeeding, an infected mother can transmit COVID-19 to the child through respiratory droplets and close-contact transmission. In a systematic review and meta-analysis, Raschetti et al. reported that close contact of mother and child in the first 72 hours of life increased the risk of infection in the child (aOR: 6.6; 95% CI: 2.6–16.0; p<0.0001), while breastfeeding did not (aOR: 2.2; 95% CI: 0.09–1.18; p=0.15).[155]

In experiments that inoculated breast milk with live SARS-CoV-2, Holder pasteurization inactivated the virus; therefore, suggesting donated breast milk that is pasteurized may be safe for recipient children and care providers.[159]

Evidence for SARS-CoV-2 RNA detection in breast milk:

The majority of the literature agrees that there is no transmission of SARS-CoV-2 through breast milk and the benefits of breastfeeding newborns far outweigh any risks of infection.[160-163] In most studies of mothers with COVID-19, breast milk was negative for viral RNA by PCR.[140,144,164,165] While uncommon, there are case reports of mothers with viral RNA-positive breast milk; however, there were no detections of viable virus from breast milk.[166-168] In a living systematic review, Centeno-Tablante et al. reported that 9 of 68 breast milk samples were viral RNA-positive, but concluded that COVID-19 transmission did not occur through breast milk.[169]

A case report detected viral RNA in the breast milk of a breastfeeding mother with COVID-19.[170] The breastfed child developed symptoms one day after his mother, at which time he tested positive by NP swab. The transmission route in this case could not be established.

Groß et al. report on a study of two women who tested positive for viral RNA by PCR after birth and were breastfeeding.[171] Breast milk was viral RNA-positive in one of the two women at 10–13 days after birth. The authors did not attempt to culture the virus. Both infants tested positive for viral RNA (at day 8 and 11), but it is unknown if breastfeeding led to the infection in one of the infants, as the two women and infants had shared a room for some time after delivery.

Evidence for SARS-CoV-2 antibodies in breast milk:

Antibodies to SARS-CoV-2 have been detected from breast milk. In a study of 14 mothers with COVID-19, Gao et al. did not detect viral RNA in breast milk; however, three out of four mothers had breast milk with IgG and IgM antibodies.[172] In another immunological study of 18 women with COVID-19, both IgG and IgA were detected in all 37 of breast milk samples.[173]

Bloodborne (Blood, Blood Products, Organs) Transmission

While SARS-CoV-2 RNA has been detected in the blood of patients with COVID-19, all systematic reviews and studies indicated that the risk of bloodborne or organ transplant transmission is exceedingly low. Compared to upper respiratory samples, the detection of viral RNA in blood and blood products is relatively uncommon and, to our knowledge, there has been no detection of viable virus from these sources.

Evidence for SARS-CoV-2 RNA detection in blood:

Several studies have reported detection of viral RNA, in either the plasma or serum of patients with COVID-19.[18,93,100,174] In Germany, viral RNA was not detected in whole blood or serum of 18 asymptomatic and symptomatic patients; however, viral RNA (low-level RNA: 179 copies/mL) was detected in the plasma of one patient.[175] In a systematic review including 1,348 recovered patients, 17.5% of blood samples were positive for viral RNA; however, no viable virus was cultured.[88]

Evidence against blood-borne transmission:

Several case reports and case series indicate the risk of SARS-CoV-2 transmission in blood products is exceedingly low.[176,177] In a review, Kiely et al. noted that bloodborne transmission is only a theoretical possibility and that a blood phase for COVID-19 infection is brief, uncommon and usually associated with severe disease.[178] In an immunocompromised child, COVID-19 did not develop after platelet transfusion from an asymptomatic donor with COVID-19.[179] In France, low levels of viral RNA were detected in three blood products (pathogen-reduced platelet concentrate, plasma, red blood cell units) from asymptomatic COVID-19-positive donors; none of the four recipients developed disease even though they all had immune system compromise.[180] In the French study, positive plasma samples did not grow virus in culture attempts. Dres et al. reported no transmission of SARS-CoV-2 through extracorporeal membrane oxygenation and dialysis membranes.[181]

No studies have documented transmission of SARS-CoV-2 through organ transplantation. While research has not demonstrated permanent damage to non-lung organs, the consensus is that active COVID-19 infection in donors (living or deceased) is a contraindication for organ donation.[182,183] Hong et al. reported a possible infection in a liver donor recipient, in which the donor was infected at time of donation; however, transmission may have been through direct close contact.[184]

Sexual (Semen, Vaginal Secretions, Urine) Transmission

Sexual transmission may occur through direct contact and through respiratory droplets. The risk of transmission via semen or vaginal secretions is low and the evidence supporting transmission via semen or vaginal secretions was limited.

Based on viral detection in feces, some have proposed possible transmission of SARS-CoV-2 through certain sexual behaviours involving oral-anal contact.[185] In addition, the detection of viral RNA and live virus detected in the saliva of COVID-19 patients represents a potential mode of transmission during sex or intimate contact.[186,187] Jing et al. reviewed the literature on ACE-2 expression in the female reproductive system and noted expression of ACE-2 receptors in the vagina.[188] ACE-2 receptors are also present in testes (i.e., spermatogonia, Leydig and Sertoli cells).[189] While receptors for SARS-CoV-2 are present in reproductive organs, currently there is no evidence for sexual transmission. There was no evidence for the detection of live virus in semen or vaginal secretions.

Evidence for SARS-CoV-2 RNA detection in semen and vaginal secretions:

To date, most studies have failed to detect viral RNA in semen or vaginal secretions in patients with COVID-19 patients.[166,172,190] In a study of 23 male patients with active infection or recovering from infection, Guo et al. did not detect viral RNA in semen samples.[191] Similarly, a study of nine males recovering from mild COVID-19 infection did not show evidence of viral shedding in semen.[192]

Li et al. reported that 15.8% (6/38) of male COVID-19 patients had viral RNA present in their semen. The authors collected semen samples from two clinically recovered patients and four patients at the acute stage of infection.[193] In the Li et al. study, the authors detected viral RNA up to 16 d after the onset of symptoms. Massarotti et al. hypothesized that viral RNA detections in semen are due to viral RNA-contamination by patient urine.[194]

Evidence for SARS-CoV-2 RNA detection in urine:

Researchers report detection of viral RNA in urine; however, the risk of transmission via urine is low. We are only aware of one instance where infectious virus was isolated from the urine of a patient with COVID-19.[195]

In a systematic review and meta-analysis, Roshandel et al. reported that 8.1% of (46/569; see Table 3 in paper) patients showed viral RNA shedding in urine (compared to 42.1% [210/499] for stool and 21.3% [100/469] for stool; see Figure 2 in paper) and viral RNA shedding in urine increases with disease severity.[87] In a systematic review, 16.4% (60/366) of patients were positive for viral RNA in urine.[88] In another systematic review of 549 patients, 6.9% showed evidence of viral RNA in their urine; however, culturing attempts were not successful.[196] In a study of 74 patients hospitalized with COVID-19, Kim et al. found that 0.8% (2/247) of urine samples were positive for viral RNA (viral load: 79 ± 30 copy/µL; compared to 3,176 ± 7,208 copy/µL in stool); however, no viable virus was cultured.[197]

Zoonotic transmission

Evidence for zoonotic transmission from companion, domestic and wild animals to humans was limited. Most of the evidence to date indicated that non-human animals are more at risk of infection from humans, especially companion and domestic animals.[198] Further research is needed to identify potential reservoirs of SARS-CoV-2 and what risk they pose to humans and animals.

Early research revealed SARS-CoV-2 is a close relative of SARS-CoV-1 and MERS-CoV, and all are βCoVs that originated from bats (*Rhinolophus* species).[199,200] Natural infection of animals with SARS-CoV-2, were all exposed to symptomatic humans. Infected animals include companion animals (domestic dogs [*Canis lupus*], domestic cats [*Felis catus*], farmed animals (American mink [*Neovison vison*], and zoo animals (lions [*Panthera leo*], tigers [*Panthera tigris*]).[201-203]

Evidence for animal-to-human and animal-to-animal transmission:

Currently, the intermediate source of the initial COVID-19 infections in humans is unknown and the risk of transmission from animals to humans is low.

Malayan pangolins (*Manis javanica*) have been postulated as the intermediate host based on the presence of viruses closely related to SARS-CoV-2; however, this hypothesis has not been confirmed.[204-206] Recently, Freuling et al. reported that raccoon dogs (*Nyctereutes procyonoides*) are susceptible to SARS-CoV-2 infection and may represent an important intermediate and reservoir host.[207] Authors in

this study infected raccoon dogs through the intranasal route, which led to animal-to-animal transmission through direct contact, with high-level viral shedding with mild disease. Raccoon dogs are widespread in China and raised for their fur. It is important to note that there are no reports of SARS-CoV-2 natural infection in raccoon dogs.

In the Netherlands, there was evidence that COVID-19 transmission occurred from an infectious American mink to human.[208] It should be noted that in most circumstances, transmission of SARS-CoV-2 involving animals is human-to-animal or animal-to-animal.[203] In a laboratory experiment, ferrets can transmit the virus to other ferrets through respiratory droplets and direct contact,[209] and potentially via small aerosols.[210]

In a laboratory experiment, dogs and cats were susceptible to COVID-19; however, neither developed clinical disease.[203,211] Cats transmitted the virus to other cats through close contact. Cats shed virus for 5 days post infection; however, there was no viral shedding in dogs. Authors noted oral and nasal viral shedding 7 days after exposure in two in-contact cats. Therefore, there is a possibility that transmission could occur from cats to humans. In addition, Shi et al. reported that experimental exposure in cats resulted in subclinical and symptomatic infections, and juvenile cats were at a higher risk of severe infection or death.[212]

Evidence for human-to-animal transmission (reverse zoonosis):

The first documented instance of human-to-animal transmission occurred between an infected person in Hong Kong and their companion dog, soon after there was a report of human-to-cat transmission in Hong Kong.[205] There is evidence that human-to-dog transmission may be limited due to cross-reaction of SARS-CoV-2 and canine respiratory coronavirus (CRCoV), providing some immunological cross-protection.[213] The most commonly reported human-to-animal transmission has involved domestic cats, where most cats have a reported close contact with a confirmed human case of COVID-19.[203,214] In Wuhan, China, 14.7% (15/102) of cats seroconverted to SARS-CoV-2 early during the pandemic.[215]

Several researchers have highlighted the need to monitor wild animals, to ensure that reverse zoonosis does not occur (human-to-animal transmission). Olival et al. reported that there is a risk of immunologically naïve North American bats acquiring SARS-CoV-2.[216] Researchers also demonstrated that deer mice (*Peromyscus maniculatus*) are susceptible to infection and are potential reservoirs of SARS-CoV-2 in North America.[217]

To date, laboratory studies indicate that domestic ducks (*Anas platyrhynchos domesticus*), chickens (*Gallus gallus domesticus*) and pigs (*Sus scrofa*) were not susceptible to SARS-CoV-2.[212,218]

Other susceptible animals, used in laboratory experiments or as animal models, include ferrets (*Mustela putorius*), fruit bats (*Rousettus aegyptiacus*), rhesus monkeys (*Macaca mulatta*) and Syrian hamsters (*Mesocricetus auratus*).[212,219]

Conclusions

Transmission of SARS-CoV-2 occurs predominantly through respiratory droplets during close (<2 m), unprotected contact. Airborne transmission over longer distances (>2 m) through the inhalation of small respiratory droplets or aerosols is less common, but possible under certain conditions such as prolonged exposure in a poorly ventilated space.

Relatively uncommon routes of transmission of SARS-CoV-2 include conjunctival, vertical, fecal-oral, fomite and zoonotic. These routes of transmission are possible; however, their contribution to COVID-19 epidemiology is unclear. While modes of transmission such as through semen, breast milk or urine are theoretically possible, the probability of these occurring is exceedingly low.

PHO will continue to monitor the scientific evidence on transmission routes of COVID-19, updating this document as necessary.

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Appendix A. Glossary of Terms for COVID-19 Routes of Transmission

Advisory

The glossary below contains definitions that may be changing with the understanding of evidence. Definitions may be different from how the same terms are used in other contexts or even seen as controversial due to different use within the same context by different organizations. Therefore, these definitions are provided to support the understanding of the COVID-19 – What We Know So Far About… Routes of Transmission document. This glossary is not exhaustive and may be updated with new terms or revised at any time.

Key Terms

Airborne transmission: Transmission of infection occurring due to the inhalation of aerosols that have remained suspended for a long period of time or have been suspended on air currents over long distances.

Air sampling for virus: Collection of volumes of air by a device to determine if aerosols may contain virus. Collection can vary by aerodynamic size captured, duration of collection, volume per second collected, and media on which samples deposit. Air samples can then be tested by molecular methods and/or viral culture.

Aerosol: Aerosols are defined by National Institute for Occupational Safety and Health (NIOSH) as a suspension of particles (solids) or droplets (liquids) in the air.[1] The diameter of microorganism-containing aerosols relevant to inhalation ranges from 0.01 to 100 µm. Discussion of respiratory infections focus on droplets rather than particles because the sources of infectious aerosols are assumed to be from respiratory mucosa or epithelium, which will be droplets (liquids) that contain infectious biological material. Droplets >100um are too large to be suspended in the air, and are therefore not considered aerosols.[2] Droplets generally lose mass while suspended in air as aerosols due to evaporation of volatile components or water. The droplets that result from the process of evaporation are often referred to as droplet nuclei. The final size of a droplet will depend on a variety of environmental factors.

Aerosol generating medical procedures: Aerosol generating medical procedures (AGMPs) are defined as medical procedures that result in the production of aerosols that create the potential for airborne transmission of infections that may otherwise only be transmissible by the droplet route, and are epidemiologically associated with an increased risk of acquisition of infection.[3]

Contact transmission: Transmission of infection through direct contact.

Direct transmission: Transmission of infection through contact or droplet transmission.

Droplet transmission: Transmission of infection occurring due to impaction of large droplets (usually >100 um) that are too large to be suspended in air for long durations. Infection may follow by direct impaction onto mucosal surfaces (mouth, eyes, nose), or contaminate a person's body/clothing which then makes direct or indirect contact with susceptible surfaces (e.g., mucosal surfaces for COVID-19).

Indirect transmission: Includes any mode of transmission where direct contact or droplet transmission is not involved (e.g., fomite transmission, airborne transmission, and vectors).

Fomite/Fomite transmission: Objects that may become contaminated with microorganisms and serve as vehicles of transmission.[4]

Polymerase Chain Reaction (PCR): A molecular method used to amplify nucleic acids. If nucleic acids of the microorganism of interest is present in a sample, then PCR can be used for the identification of that microorganism. This method cannot determine whether or not the microorganisms detected are viable.

Viral culture: Viral culture is used to determine whether a sample containing virus is capable of replication. Replication is a surrogate measure for inducing infection. Other methods to detect virus in a sample such as PCR cannot determine the viability of the organism in the sample. A sample is applied to a susceptible culture of cells and incubated up to a few weeks to detect morphological changes such as plaques that would indicate the presence of a viable virus.

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Appendix B. MEDLINE Search Strategy

Search results reporting

DATABASES SEARCHED

Database	Date searched	Records	Duplicates removed by database	Remaining
MEDLINE	10/14/2020	2641	330	2311

RECORDS TOTALS

Records source	Records
Records identified through database searching	2641
Duplicates removed by database	330
Duplicates removed by bibliographic management software	11
Total records after duplicates removed	2300

Search strategies

MEDLINE

Ovid MEDLINE(R) ALL <1946 to May 29, 2020>

#	Searches	Results	Concept
1	("2019 corona virus" or "2019 coronavirus" or "2019 ncov" or "corona virus 19" or "corona virus 2019" or "corona virus 2019" or "corona virus disease 19" or "corona virus disease 2019" or "corona virus epidemic*" or "corona virus outbreak*" or "corona virus pandemic*" or "coronavirus 19" or "coronavirus 2019" or "coronavirus 2019" or "coronavirus disease 19" or "coronavirus disease 2019" or "coronavirus epidemic*" or "coronavirus outbreak*" or "coronavirus pandemic*" or "covid 19" or "covid 2019" or "new corona virus" or "new coronavirus" or "novel corona virus" or "novel coronavirus" or "novel human coronavirus" or "sars coronavirus 2" or "sars cov 2" or "sars cov2" or "sars like coronavirus" or "severe acute respiratory syndrome corona virus 2" or "severe acute respiratory syndrome coronavirus 2" or "severe specific contagious pneumonia" or "wuhan corona virus" or "wuhan coronavirus" or 2019ncov or covid19 or covid2019 or ncov or sarscov2 or ((novel or Wuhan or China or Chinese or "seafood	69649	COVID-19

#	Searches	Results	Concept
	market" or "2019" or outbreak* or epidemic* or pandemic*) adj5 (coronavirus* or "corona virus*" or betacoronavirus* or "beta coronavirus*" or "beta corona virus*" or pneumonia* or SARS or "severe acute respiratory syndrome")) or ((coronavirus* or "corona virus*" or betacoronavirus* or "beta coronavirus*" or "beta corona virus*" or SARS or "severe acute respiratory syndrome") adj5 pneumonia*) or "coronavirus response" or "corona virus response").kf,kw,ti.		
2	Disease Transmission, Infectious/ or Virus Shedding/ or tm.fs. or (transmi* or spread* or infectivity or (infect* adj3 route*) or excret* or shed*).kf,kw,ti. or (transmi* or spread* or infectivity or (infect* adj3 route*) or excret* or shed*).ab. /freq=2	493440	Transmission
3	(route* or mode or modes or "non-respiratory" or nonrespiratory or (transmission adj3 (dynamics or risk or potential))).kf,kw,ti.	92893	Route
4	Bodily Secretions/ or Body Fluids/ or Sneezing/ or Cough/ or (droplet* or ((body or bodies or lung* or mouth* or nose*) adj3 (fluid* or secretion* or secrete or discharge*)) or cough* or sneez*).kf,kw,ti.	74516	Droplet
5	exp Parents/ or Family/ or Grandparents/ or Housing/ or Public Housing/ or Siblings/ or Spouses/ or ("close contact*" or "communal living" or "direct contact*" or "flat mate*" or "personal residence*" or "physical contact*" or accommodation* or apartment* or brother* or cohabit* or "co-habit*" or coliving or "co-living" or commune or communes or condo* or contacts or domicile* or dwelling* or familial or family or families or father* or flatmate* or grandparent* or ((home or homes) not "stay at home order*") or hous* or husband* or intrafamilial or mother* or parent or parents or relatives or roommate* or "room mate*" or sibling* or sister* or spouse* or wife or wives).kf,kw,ti.	688458	Contact
6	Conjunctiva/ or Conjunctivitis, Viral/ or Conjunctivitis/ or Eye/ or Tears/ or (conjunctiv* or eye or eyes or ocular or tear or tears).kf,kw,ti.	212437	Conjunctiva
7	Air/ or Air Microbiology/ or Air Pollution, Indoor/ or Inhalation Exposure/ or Exhalation/ or Air Ambulances/ or Aircraft/ or Ventilation/ or (air or airborne* or aircraft* or airplane* or ((building* or room* or office*) adj3 circulat*) or exhal* or flight or flights or HVAC or inhal* or plane or planes or vent or vents or "ventilation system*" or duct*).kf,kw,ti.	282916	Airborne
8	Aerosols/ or ((Disease Transmission, Infectious/ or Coronavirus Infections/tm or Pneumonia, Viral/tm) and (Intubation/ or Intubation, Intratracheal/ or Cardiopulmonary Resuscitation/ or Suction/ or Bronchoscopy/ or exp Surgical Procedures, Operative/ or surgery.fs. or Autopsy/ or Sputum/ or exp Positive-Pressure Respiration/ or Oxygen Inhalation Therapy/)) or aerosol*.kf,kw,ti. or ((transmi* or spread* or infect*) and (nebuliz* or nebulis* or intubat* or ((cardiopulmonary or "cardio-pulmonary") adj3	59726	Aerosol-Generating Procedures

#	Searches	Results	Concept
	resuscitation) or bronchoscopy or surgery or surgical or autops* or (sputum adj3 induc*) or (high adj3 oxygen adj3 therapy) or "positive pressure ventilation" or "positive pressure respiration")).kf,kw,ti.		
9	Fomites/ or Health Facility Environment/ or Patients' Rooms/ or Disease Reservoirs/ or exp Textiles/ or Clothing/ or Glass/ or Plastics/ or Metals/ or Cell Phone/ or Computers, Handheld/ or Smartphone/ or fomite*.kf,kw,ti. or (surface or surfaces).ti. or ((clean* or colonis* or coloniz* or contamina* or decay* or decontaminat* or detect* or disinfect* or distribut* or expos* or grow* or harbor* or harbour* or inactivat* or "infection control" or persist* or sanit* or stabilit* or surviv* or viab*) adj15 (bathroom* or bed* or carpet* or chair* or cloth* or counter or counters or curtain* or "door handle*" or "door knob*" or doorknob* or environment* or equipment or fabric* or faucet* or fixture* or floor* or furnish* or furniture* or glass* or gown* or handrail* or "hand rail*" or ipad* or iphone* or keyboard* or keypad* or "key pad*" or "light switch*" or linen* or material* or mattress* or metal* or phone* or plastic* or railing or railings or reservoir* or sink* or smartphone* or surface or surfaces or telephone* or textile* or tile* or toilet* or "touch screen*" or upholster* or wall* or washroom*)).kf,kw,ti.	400853	Fomites
10	Feces/ or Diarrhea/ or exp Gastrointestinal Diseases/ or (fecal or faecal or feces or stool or stools or diarrhea or diarrhoea or enterocolitis or gastrointestin* or gastroenter*).kf,kw,ti.	1125779	Fecal-Oral
11	Blood-Borne Pathogens/ or Blood Safety/ or bl.fs. or (bloodborne or blood or BBI).kf,kw,ti.	2190148	Bloodborne
12	Sexually Transmitted Diseases/ or Sexually Transmitted Diseases, Viral/ or Semen/ or Semen Analysis/ or Vaginal Discharge/ or Vaginal Smears/ or (sexual* or semen or vagina*).kf,kw,ti.	213704	Sexual Transmission
13	Amniotic Fluid/ or Breast Feeding/ or exp Delivery, Obstetric/ or exp Parturition/ or exp Pregnancy/ or Fetal Blood/ or Fetus/ or Infant, Newborn/ or Infectious Disease Transmission, Vertical/ or Maternal Exposure/ or Maternal-Fetal Exchange/ or Milk, Human/ or Peripartum Period/ or Postpartum Period/ or Pregnancy Complications, Infectious/ or Pregnancy Complications/ or Pregnancy Outcome/ or Pregnancy, High-Risk/ or Pregnant Women/ or ("amniotic fluid" or "breast feeding" or "breast milk" or "cord blood" or "fetal blood" or "human milk" or "in utero" or ((infant* or baby or babies) and mother*) or birth* or breastfeeding or breastmilk or fetal or fetus or foetal or foetus or gestation* or gestation* or infant* or intrapartum or intrauterine or maternal* or mother* or natal* or neonat* or newborn* or obstetric* or parturition or perinatal* or placenta* or placenta* or postnatal* or postpartum* or pregnan* or prenatal* or puerperal*	1928571	Vertical Transmission

#	Searches	Results	Concept
	or reproductive or transplacental or trans-placental or transuterine or trans-uterine or uter* or vertical).kf,kw,ti.		
14	1 and 2 and 3	296	
15	1 and 2 and 4	165	
16	1 and 2 and 5	356	
17	1 and 2 and 6	123	
18	1 and 2 and 7	318	
19	1 and 2 and 8	886	
20	1 and 9	550	
21	1 and 2 and 10	285	
22	1 and 2 and 11	141	
23	1 and 2 and 12	60	
24	1 and 2 and 13	590	
25	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	3063	
26	("2019 corona virus" or "2019 coronavirus" or "2019 ncov" or "corona virus 19" or "corona virus 2019" or "corona virus 2019" or "corona virus disease 19" or "corona virus disease 2019" or "corona virus epidemic*" or "corona virus outbreak*" or "corona virus pandemic*" or "coronavirus 19" or "coronavirus 2019" or "coronavirus 2019" or "coronavirus disease 19" or "coronavirus disease 2019" or "coronavirus epidemic*" or "coronavirus outbreak*" or "coronavirus pandemic*" or "covid 19" or "covid 2019" or "new corona virus" or "new coronavirus" or "novel corona virus" or "novel coronavirus" or "novel human coronavirus" or "sars coronavirus 2" or "sars cov 2" or "sars cov2" or "sars like coronavirus" or "severe acute respiratory syndrome corona virus 2" or "severe acute respiratory syndrome coronavirus 2" or "severe specific contagious pneumonia" or "wuhan corona virus" or "wuhan coronavirus" or 2019ncov or covid19 or covid2019 or ncov or sarscov2 or ((novel or Wuhan or China or Chinese or "seafood market" or "2019" or outbreak* or epidemic* or pandemic*) adj5 (coronavirus* or "corona virus*" or betacoronavirus* or "beta coronavirus*" or "beta corona virus*" or pneumonia* or SARS or "severe acute respiratory syndrome")) or ((coronavirus* or "corona virus*" or betacoronavirus* or "beta coronavirus*" or "beta corona virus*" or SARS or "severe acute respiratory syndrome") adj5 pneumonia*) or "coronavirus response" or "corona virus response").ti.	66947	COVID-19 (focused, title only)
27	*Disease Transmission, Infectious/ or *Virus Shedding/ or *Coronavirus Infections/tm or *Pneumonia, Viral/tm or (transmi* or spread* or (infect* and route*) or excret* or shed*).ti.	183017	Transmission (focused, title only)
28	26 and 27	2994	
29	25 or 28	4832	
30	limit 29 to yr="2020 -Current"	4642	
31	limit 30 to English	4539	
32	(202006* or 202007* or 202008* or 202009* or 202010*).ez.	585088	

#	Searches	Results	Concept
33	31 and 32	2802	
34	limit 33 to (comment or editorial or news)	161	
35	33 not 34	2641	
36	remove duplicates from 35	2311	

Citation

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Ontario

This is **Exhibit "CC"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

Public Health Ontario | Santé publique Ontario

SYNTHESIS

20/05/21

COVID-19 Transmission Through Large Respiratory Droplets and Aerosols… What We Know So Far

Introduction

Public Health Ontario (PHO) is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19). "What We Know So Far" documents provide a rapid review of the evidence on a specific aspect or emerging issue related to COVID-19. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is transmitted in different ways; however, this document will focus on transmission by respiratory droplets and aerosols.

Key Findings

- The historical dichotomy of droplet versus airborne transmission, while useful in implementing infection prevention and control (IPAC) strategies, does not accurately recognize the complexity of viral respiratory transmission, including for SARS-CoV-2.
- SARS-CoV-2 is transmitted most frequently and easily at short range through exposure to respiratory particles that range in size from large droplets which fall quickly to the ground to smaller droplets, known as aerosols, which can remain suspended in the air.
- There is evidence to suggest long-range transmission can occur under the right set of favourable conditions, implicating aerosols in transmission.
- The relative role of large respiratory droplets versus smaller droplet particles in short-range transmission is challenging to quantify. Their contributions to a specific case-contact interaction vary based on contextual factors including source/receptor characteristics (e.g., forceful expulsions such as singing, coughing, sneezing; viral load) and pathway characteristics (e.g., duration of exposure; environmental conditions such as ventilation, temperature, humidity, ultraviolet light; source control; and use of personal protective equipment).
- Translation of this summary into control measures needs to take into consideration other information, such as evidence around the effectiveness of control measures to date. Several control measures applied together in a layered approach are likely to be effective irrespective of the relative contribution of droplets or aerosols, including achieving high vaccination coverage and avoiding the "3 C's" (closed spaces, crowded places and close contact).

Background

The diameter of microorganism-containing respiratory particles relevant for respiratory infections ranges from approximately 0.01 micrometres (µm) to greater than 100 µm.[1] Particles larger than about 100 µm play a role in respiratory infection transmission by impacting on mucosal surfaces, such as the nostrils, mouth and eyes. Particles smaller than 100 µm can be inhaled or impact on mucosal surfaces. Some particles are small enough that they can be suspended in the air for various periods of time (known as aerosols).[2] Environmental factors such as local air currents and humidity affect these particles, e.g., how they move, evaporate, and how long they remain in air.[3] Therefore, the mode of transmission is influenced by three key elements: the source, the pathway, and the receptor. Depending on the unique characteristics of each element, certain modes may be more likely than others.

Traditionally, respiratory particles >5 or 10 µm have been termed droplets and were thought to impact directly on mucous membranes, while smaller particles were thought to be inhaled. This dichotomy of transmission routes has been applied to infection prevention controls within health care settings worldwide. However, these transmission routes are not mutually exclusive as droplets well over 5 µm are capable of remaining suspended in air for some time and can be inhaled. At short range within about 2 metres (m), infection can occur from inhaled aerosols as well as droplets landing on mucous membranes (short-range transmission). Herein, we refer to what was traditionally called airborne transmission via inhalation of aerosols that have remained suspended over long distances and periods of time[4,5] as long-range transmission.

We describe transmission through epidemiological studies, experimental or simulation of transmission studies, and statistical or mathematical modelling. Modelling shows what is possible, experimental studies what is plausible, and epidemiologic studies observe what is actually occurring, and each type of evidence is subject to limitations. However, exact routes of SARS-CoV-2 transmission in real-life scenarios can only be inferred based on the available data.

The purpose of this rapid review is to outline the evidence for droplets and aerosols in SARS-CoV-2 transmission. We have summarized the evidence as either short-range transmission from large respiratory droplets and small droplets or aerosols, or long-range transmission from aerosols.

Methods and Scope

In considering feasibility, scope and timelines, we undertook a rapid review to update our summary of SARS-CoV-2 transmission from large respiratory droplets and aerosols. A rapid review is a knowledge synthesis where certain steps of the systematic review process are omitted in order to be timely (e.g., duplicate screening).[6]

We conducted literature searches in MEDLINE (April 22, 2021) and National Institutes of Health COVID-19 Portfolio (Preprints) (April 27, 2021), search strategies are available upon request. We searched PubMed and Google Scholar on April 28, 2021 for additional articles of interest.

English-language peer-reviewed and non-peer-reviewed records that described large respiratory droplet and aerosol routes of transmission of COVID-19 were included. We restricted the search to articles published after January 1, 2020. This rapid review concentrated on evidence from systematic reviews and meta-analyses, supplemented by primary literature where appropriate. We reviewed citations from included articles to identify additional research.

Prior to publishing, PHO subject-matter experts review all What We Know So Far documents. As the scientific evidence is expanding rapidly, the information provided in this document is only current as of the date of respective literature searches.

Out-of-scope for this document was a review of IPAC practices appropriate for individual transmission scenarios and settings. Application of a hierarchy of control measures for non-health care settings is briefly discussed in the conclusions. For additional information related to IPAC in health care settings, please see PHO's technical briefing *IPAC Recommendations for Use of Personal Protective Equipment for Care of Individuals with Suspect or Confirmed COVID-19* and *Interim Guidance for Infection Prevention and Control of SARS-CoV-2 Variants of Concern for Health Care Settings*.[7,8] Please note that the *Ministry of Health's Directive 1* is the provincial baseline standard for provision of personal protective equipment for hospitals, long-term care homes and retirement homes and that the *Ministry of Health's Directive 5* provides agency to health care workers to make professional decisions regarding the appropriate personal protective equipment when dealing with suspected, probable or confirmed COVID-19 patients or residents.[9,10] Evidence for contact/fomite transmission, and virus and host (source/receptor) factors were not reviewed in this document, but are acknowledged as contributors to short- and long-range transmission. Other routes of transmission are reviewed in PHO's synthesis *COVID-19 Routes of Transmission – What We Know So Far*.[11]

Short-range Transmission

Main Findings

SARS-CoV-2 is transmitted most frequently and easily at short range. Short-range transmission generally occurs within 2 m of an infectious individual (e.g., during a conversation with inadequate distancing, no barriers, no personal protective equipment). Theoretically, short-range transmission may occur due to droplets or aerosols, but the relative contribution of either is specific to each case-contact interaction which varies based on contextual factors including source/receptor and pathway characteristics.

Environmental Factors Affecting Short-range Droplets and Aerosols

In addition to virus and host factors, environmental factors are associated with short-range viral transmission. The distance travelled by large respiratory droplets is generally <2 m, although it can reach up to 8 m in certain circumstances. In a study by Guo et al. (2020), SARS-CoV-2 virus was detected on the floor up to 4 m away from a patient.[12] In a systematic review of studies assessing the horizontal distance travelled by respiratory droplets, Bahl et al. (2020) reported that droplets could travel up to 8 m.[13] In a mathematical model, Chen et al. (2021) reported that respiratory droplets >100 µm in diameter are only important in transmission at a distance of less than 0.2 m when the infector is talking, or within 0.5 m when the infector is coughing.[14] Modelling by Wang et al. (2021) (preprint) suggested droplets >100 µm would most often not travel past 1.75 m (most droplets >100 µm diameter settle before 1.25 m).[15]

In a review of respiratory virus transmission, Leung (2021) reported that environmental factors affecting transmission include temperature, relative humidity, ventilation, airflow and ultraviolet (UV) light.[16] Ventilation, airflow and forceful expulsion (sneezing or coughing) can make respiratory particles travel further than 2 m through momentum.[14,17] High temperature and low humidity contributes to shrinking of droplets such that they may remain suspended in air for longer periods of time.[18]

Even at short-range distances, ventilation may affect transmission. De Oliveira et al. (2021) modelled infection risk in ventilated (10 air changes per hour [ACH]) and unventilated spaces without respiratory protection during a 1-hour exposure at 2-m distance.[19] The impact of decreasing concentration of virus in the air through ventilation was notable. Estimates of infection risk were reduced by at least three times based on the parameters and assumptions of their model. The authors also commented that the direction of airflow can have a significant impact – upward air streams can maintain aerosols at face height significantly increasing infectious risk.

Indoor settings are a predominant risk factor for transmission. In a systematic review of 5 studies, Bulfone et al. (2020) reported that the odds of indoor transmission were 18.7 times (95% confidence interval [CI]: 6.0–57.9) higher than outdoor settings, and less than 10% of infections occurred outdoors.[20] Very few superspreading events have been described from exclusively outdoor exposures. The explanation for this observation is likely multifactorial which includes important differences in ventilation, UV light, humidity, as well as possible differences in behaviour.

Epidemiological and Modelling Studies Describing Short-range Transmission

The following section reviews the epidemiologic and modelling evidence supporting short-range transmission of COVID-19. It reviews the reproductive number and summarizes the epidemiological and modelling studies by setting, including transportation, health care and sports.

The reproductive number (R_0) of SARS-CoV-2 is less suggestive of long-range transmission commonly occurring, as viruses where long-range transmission commonly occurs tend to have a higher R_0.[16] For example, in a systematic review by Guerra et al. (2017), the R_0 for the measles virus in the pre-vaccine era was 6.1–27.0,[21] compared to the median range of R_0 (2.7–3.3) reported for SARS-CoV-2.[22] It is important to note that R_0 is not a direct measure or indication of transmission route, as R_0 can be setting and population-specific, and be impacted by factors such human behaviours. The R_0 for SARS-CoV-2 also displays overdispersion, where the overall R_0 is lower than pathogens that commonly transmit through aerosols at long-range, but a small proportion of cases are associated with reproductive numbers in the range typical of viruses that commonly transmit through aerosols at long-range (i.e., superspreader events).[23] Such cases illustrate the potential variability in COVID-19 transmission, depending on differences in source/receptor characteristics and environment.

Short-range transmission was favoured in a retrospective cohort study of 18 short-to-medium haul flights (median flight time 115 minutes) to England from the beginning of the pandemic.[24] The attack rate was 0.2% (95% confidence interval [CI]: 0.1–0.5) for all aircraft-acquired cases, and was higher at 3.8% (95% CI: 1.3–10.6) if a subgroup analysis was performed only on contacts within a two-seat radius. It was assumed that no masks were worn given that it was early in the pandemic.

Family gatherings for meals are high-risk scenarios for transmission. Lo Menzo et al. (2021) reported transmission of lineage B.1.1.7 variant of concern to 8 of 9 family members during a dinner gathering.[25] The only uninfected family member was presumed to have immunity acquired from a previous infection (high antibody titres and polymerase chain reaction (PCR) negative result). Contact and fomite transmission cannot be excluded from this type of event.

In a case-control study of 154 patients 18 years and older in the United States (US), Fisher et al. (2020) reported that close contact with a person with COVID-19 was reported more often among cases (42.2%) than controls (14.5%) ($p<0.01$).[26]

Short-range transmission has been documented in school settings. Four student-to-student and one student-to-teacher transmission events were reported in Salt Lake County, Utah.[27] For four transmission events, unprotected, short-range exposures were noted. There was a lack of transmission to other students that were a median of 1 m away during class, but adhered to control measures implemented in the school. However, when household transmission associated with the secondary cases was evaluated, transmission was high for 3 of the 5 households of secondary patients. In these three households, 6 of 8 household members were also infected and may be related to challenges with physical distancing, masking, and shared surfaces in the household.

Using whole genome sequencing of SARS-CoV-2 clinical samples (n=50) in Dublin, Ireland, Lucey et al. (2020) investigated cases of hospital-acquired COVID-19 and reported that the majority of infections were among patients who required extensive and prolonged care by health care providers.[28] The authors concluded that the likely mode of transmission from health care workers to patients was through short-range transmission and close contact, rather than long-range transmission. Notably, the use of masks by health care providers was not universal and patients were not wearing masks either.

Three short-range health care-associated transmission events have been reported where large respiratory droplet transmission was less likely because masks were worn by either the source or the contact and in two of three events, the contact was also wearing eye protection.[29] In case 1, an asymptomatic, unmasked patient transmitted infection to two health care workers who wore medical masks and face shields, following multiple hours of exposure in a room with 6 ACH. A second case occurred where a presymptomatic masked health care worker transmitted infection to an unmasked patient in a room with 6 ACH. A third case involved a presymptomatic masked patient transmitting infection to a health care worker who was wearing a mask and goggles during a 45 minute face-to-face discussion at 1 m. Notably in the third case, the patient's mask was removed temporarily for oropharynx inspection. While each case was verified by whole genome sequencing, there was a lack of detail about the specific encounters (e.g., distance, duration, if direct contact occurred, if doffing errors occurred), and no airflow studies were conducted.

An analysis of SARS-CoV-2 infections in an outdoor rugby league, including video evaluation of close contact due to tackling inherent in the game, indicated that no cases among players in the league could be linked to close-contact during the outdoor rugby games.[30] Instead, transmissions were linked to other indoor short-range transmission events. While this study demonstrates examples where outdoor close-contact transmission did not occur, there were not enough close-contacts documented to provide evidence that close-contact transmission could not have occurred in the context of outdoor rugby.

In a modelling study, Zhang and Wang (2020) reported that the median infection risk via long-range aerosol transmission (10^{-6}–10^{-4}) was significantly lower than the risk via close contact (10^{-1}).[31] The model was based on a 1-hour exposure in a room with an area of 10–400 m^2, with one infected individual and a ventilation rate of 0.1–2.0 ACH. In a modelling study by Hu et al. (2020), the transmission risk from epidemiological data among train passengers as 0%–10.3% (95% CI: 5.3%–19.0%).[32] Travellers directly adjacent to the index patient had a much higher infection risk (relative risk [RR]: 18.0; 95% CI: 13.9–23.4), and the attack rate decreased with increasing distance.

Household and Non-Household Secondary Attack Rates

The consensus among systematic reviews is that household settings, where physical distancing, consistent source control mask-wearing, and disinfection of shared surfaces are potentially not feasible, are associated with a higher risk of infection compared to casual-contact settings (17%–27% compared

to 0%–7%). However, the secondary household attack rates are not as high as would be expected if SARS-CoV-2 easily spread through long-range transmission (e.g., >90% in measles).[16,33]

In a systematic review and meta-analysis of 54 studies and 77,758 patients, Madewell et al. (2020) reported that the household secondary attack rate was 16.6% (95% CI: 14.0–19.3).[34] In a systematic review and meta-analysis of 45 studies, Thompson et al. (2021) estimated the household secondary attack rate as 21.1% (95% CI: 17.4–24.8; 29 studies).[35] Non-household settings had lower secondary attack rates: 1) social settings with family and friends (5.9%; 95% CI: 0.3–9.8; 7 studies); 2) travel (5.0%; 95% CI: 0.3–9.8; 5 studies); 3) health care facilities (3.6%; 95% CI: 1.0–6.9; 10 studies); workplaces (1.9%; 95% CI: 0.0–3.9; 7 studies); and casual social contacts with strangers (1.2%; 95% CI: 0.3–2.1; 7 studies). Koh et al. (2020), in a meta-analysis of 43 studies, reported that the household secondary attack rate was 18.1% (95% CI: 15.7–20.6; 43 studies), much higher than the secondary attack rate in health care settings (0.7%; 95% CI: 0.4–1.0; 18 studies).[36] In a systematic review and meta-analysis of 24 studies, Lei et al. (2020) reported that the secondary attack rate in households was 27% (95% CI: 21−32); the risk of secondary infection was 10 times higher in households compared to non-household settings (odds ratio [OR]: 10.7; 95% CI: 5.7–20.2; p<0.001).[37] Tian and Huo (2020), in a meta-analysis of 18 studies, reported that the household secondary attack rate was 20% (95% CI: 15–28; 15 studies; n=3,861 patients), followed by social gatherings at 6% (95% CI: 3–10; 5 studies; n=2,154 patients) and health care settings at 1% (95% CI: 1–2; 4 studies; n=1,320 patients).[38]

Long-range Transmission

Main Findings

Transmission of SARS-CoV-2 over longer distances (generally >2 m) and time occurs through inhalation of aerosols under favourable circumstances, such as prolonged exposure in an inadequately ventilated space. Current evidence supports long-range transmission of SARS-CoV-2 occurring “opportunistically”, in that long-range transmission can occur under some circumstances, but inconsistently, and is not the predominant situation in which transmission occurs. Epidemiological and modelling studies support that long-range transmission via aerosols occurs. All of these examples include combinations of favourable source/receptor and pathway conditions such as inadequate ventilation, prolonged exposure time, high viral load, with certain activities (singing, exercising, yelling, etc.), and lack of masking for source control by the index case.

Environmental Factors Affecting Long-range Aerosols

In experimental models, researchers have demonstrated the potential for long-range transmission. In a series of experiments, simulations and modelling, Wang et al. (2021) (preprint) reported that aerosols could remain suspended for a longer period than historically predicted.[15] In general, viral copies/millilitre (ml) or concentration decreased as distance from source increased. The work showed that the evaporation time for large respiratory droplets is longer than predicted, especially at higher relative humidity (90%). In a sneeze plume, the largest respiratory droplets (>100 µm) are centrally located within the plume, with smaller respiratory droplets and aerosols at the periphery. The largest droplets contain more virus copies but are less abundant as they settle quickly to the ground, while smaller droplets carry fewer virus copies but are more abundant and remain in the air. The authors conclude that while aerosol transmission is important past 1 m from the source, aerosol transmission is likely even more important at shorter ranges.

Modelling studies have also highlighted the potential for aerosol transmission at varying distances. Xu et al. (2021) analysed the data of 197 symptomatic COVID-19 cases in the Diamond Princess cruise ship outbreak and concluded that long-range transmission did not occur between cabins based on the random distribution of symptomatic cases on all decks and the lack of spatial clusters of close contact (within cabin) infection.[39] The authors inferred that most transmission had occurred in public areas before the quarantine, possibly due to crowding and insufficient ventilation in those spaces. The authors also inferred that there was no transmission between passenger rooms during the quarantine period, and suggested that the ship's central heating, ventilation, and air conditioning (HVAC) system did not play a role in SARS-CoV-2 transmission. However, the authors noted that the lack of data on 109 of the 306 symptomatic individuals and on the 328 asymptomatic individuals may alter their estimation. In addition, their estimation did not take into consideration possible transmission between crew and passengers. Another model of the same outbreak estimated that the contribution of short-range transmission (from large droplets or aerosols) accounted for a median of 36% (mean: 35%) of transmission events, fomite (median: 21%; mean: 30%) and long-range (median: 41%; mean: 35%) contributing to the remainder.[40]

A study of aerosol particles (<5 μm diameter) by Dobramysl et al. (2021) (preprint) reported that time to infection increases approximately linearly as distance from source increases, the most important parameter for time to infection.[41] Exposure to a person breathing normally (simulating an asymptomatic individual) at a distance of 1 m led to infection after 90 minutes; however, coughing every 5 minutes led to infection in 15 minutes. Mask use and even minimal ventilation increased time to infection at a given distance. The importance of ventilation is also described in a modelling study by Jones (2020) which suggested that exposure to inhalable particles mostly (80%) occurs within close proximity to the patient.[42] In still air, aerosols will rise above head-level; however, turbulent air can change the trajectory of virus-laden aerosols, bringing aerosols closer to the head.[43-45] A modelling study by Sen (2021) found that when the ceiling-mounted elevator fan was off, about 11% of the droplets expelled by coughing fell to the ground while 89% evaporated and became smaller.[46] After travelling downward in cough-induced turbulence for approximately 6 seconds, droplets about 50 μm tended to move up and spread in the upper part of the elevator. If the cough happened at 30° to another rider, up to 40% of the droplets may fall on the face of another elevator rider. However, when the fan is operating, up to 50% of the droplets were dragged down to the floor in less than 3 seconds.

The basement of a large wholesale market was investigated as the source of a major outbreak in Beijing, China.[47] Many factors contributed to spread across multiple possible modes of transmission including long-range transmission. A field study of the area using fluorescent powders and microspheres as tracers allowed authors to conclude that while air was circulated, the air was unfiltered and there was very little fresh air, there was high humidity, low temperature, inadequate hand sanitization supplies in washrooms, and significant contamination of surfaces possibly due in part to resuspension of droplets from wet floors.

Given that persistence of aerosols over time is a factor in long-range transmission, the viability of SARS-CoV-2 in aerosols is important to consider. The half-life of SARS-CoV-2 in aerosols is approximately 1 hour.[48,49] Humidity seems to have less of an effect on SARS-CoV-2 viability in aerosols compared to the effect of sunlight or temperature.[50,51] Increasing temperature is associated with a reduction in the half-life of SARS-CoV-2 in aerosols.[52-54] Using a rotating drum experiment similar to other studies for viability of SARS-CoV-2, simulated sunlight (UVA/UVB) was applied to aerosolized virus through a window on the drum.[51] Results indicated 90% inactivation of virus within 20 minutes.

Inadequate ventilation can contribute to spread of aerosols, where the buildup of infectious aerosols is inversely proportional to the number of air exchanges.[55-57] In a modelling study, Schijven et al. (2021) assessed the risk of aerosol transmission of SARS-CoV-2 at a distance beyond 1.5 m from continuous breathing, speaking, or singing, or from one cough or one sneeze, in an indoor environment of 100 m^3.[58] Where there was no ventilation, the mean risk of transmission (derived from dose-response data for human coronavirus 229E) after 20 minutes of exposure to a person with 10^7 RNA copies/ml of mucous was estimated at 0.1%, except for sneezing with high aerosol volume (40,000 picolitres/sneeze). The mean risk of transmission increased to above 30% for sneezing with high aerosol volume and above 10% for singing after an exposure of 2 hours to a person with mucous RNA concentration above 10^8 copies/ml. Ventilation at 1 ACH reduced the risk by approximately half and at 6 ACH, the risk of transmission was reduced by a factor of 8–13 for sneezing and coughing, and by a factor of 4–9 for singing, speaking and breathing.

Estimates for minimum infectious dose, amount of viable virus in aerosols and quantified exposure rates are lacking. One preprint study assessed superspreading events related to long-range transmission in order to determine a minimum infectious dose for transmission.[59] The model used rate of aerosolized virion shedding based on data from other coronaviruses and a destabilization rate measured for SARS-CoV-2. They reported a critical exposure threshold for aerosol transmission of 50 virions. A computational characterization of inhaled droplets by Basu (2021) reported an estimated inhaled infectious dose around 300 virions, which was similar to estimates of 500 virions for ferrets.[60] The author acknowledged that this estimate could vary widely depending on environmental and individual biological factors.

Epidemiological and Modelling Studies Describing Long-range Transmission

Epidemiological case studies have reported long-range transmission of SARS-CoV-2, exclusively in indoor settings (e.g., bus, church, restaurant, concert halls, apartment building, office building).[61-67] In most of these case studies, long-range transmission was inferred as the dominant route of transmission, given that infectees were usually further than 2 m away from index cases. In addition, in these case studies, susceptible people were exposed to index cases for prolonged periods (>50 minutes) in indoor environments with inadequate ventilation and, in some instances, with increased respirations (e.g., singing, yelling, or exercising) and/or no face mask use (by case and/or contact). As with most epidemiological studies on transmission events, it was difficult to exclude other contributing routes of transmission. We summarize a few of these case studies, highlighting settings and contributing contextual factors to long-range transmission.

Stagnant indoor conditions can contribute to aerosol transmission. One example is a series of transmissions linked to an individual who developed symptoms around the time they were playing squash in an unventilated squash court.[68] Players who arrived hours after the index case and played in the same squash court were later identified as positive cases, though the role of other potential routes (e.g. unidentified staff contacts, shared surfaces) may have contributed as well and the source of transmission could not be confirmed. In contrast, a post-operative analysis of susceptible patients (no previous SARS-CoV-2 infection or vaccination) in a surgical suite within 48 hours following the use of the suite by SARS-CoV-2 positive patients indicated that there were no transmission events. The event rate was lower than the number of events in a control group (0% vs. 1.9%).[69] Ventilation was likely a significant factor that prevented transmission in the surgical suite.

In a study of six indoor singing events (five with transmission) in the Netherlands, Shah et al. (2021) (preprint) reported that long-range transmission was the likely route of transmission (short-range transmission possibly contributing to transmission at three of these events and indirect contact transmission possibly contributing to transmission at one of the events).[62] The authors assigned transmission likelihood as either less likely or possible; however, the authors do not state how these were defined. Attack rates at these events ranged from 25%–74% (9–21 people aged 20–79 years attended the events) and authors hypothesize that singing led to transmission. The authors note that they cannot quantify the contribution of each route of transmission. Genomic sequencing was not performed to help rule out other sources of SARS-CoV-2.

In a choir group (Washington, US), 53 of 60 individuals (excluding the index patient) were confirmed or strongly suspected to have been infected during a 2.5 hour rehearsal in a main hall.[64] Individuals who moved to another area of the building from the index case to practice for 45 minutes were less likely to become infected than those who remained in the main hall for the full duration of the rehearsal.

Twelve secondary cases of SARS-CoV-2 were linked to an index case, an 18-year-old chorister with high viral load who sang at four 1-hour services.[70] The index case was seated at a piano raised approximately 3 m from the ground floor and facing away from the secondary cases. Secondary cases sat between 1–15 m (horizontal distance) from the index case. Use of masks was not in place and there was minimal ventilation during the service (ventilation system was off, fans were off and doors and windows were largely closed). Interestingly, no new cases were linked to exposure that occurred the day of respiratory symptom-onset, and no explanation could be provided for why only a certain section near the chorister was affected and other sections (including those directly in front of the index case) were not.

In a case study by Shen et al. (2020), passengers who were not wearing masks were exposed to a presymptomatic index patient for 100 minutes while on a bus in eastern China.[61] Twenty-four of 67 passengers became infected, including several passengers seated beyond 2 m distance. The bus containing the index patient was heated and air was recirculated without filtration. Infections occurred in individuals at either end of the bus and the index case was located roughly in the middle. Risk of infection was only moderately higher for individuals sitting closer to the index patient. In contrast, seven of 172 other people attending the same religious event were positive for SARS-CoV-2. Some of the cases became positive after 14 days from exposure; thus, transmission likely did not occur on the bus for these case. The authors of this study postulate that the poor ventilation in the bus supports aerosol transmission in this cluster; however, other routes of transmission such as close contact from movement within the bus or fomites could not be excluded.

Vehicles are also potential environments for short-range and long-range transmission. A patient transport van was implicated in long-range aerosol transmission despite physical distancing observed by the infected drivers in two distinct transmission events.[71] One driver did not wear a mask, but all passengers wore a single-layer mask. The passengers were exposed for 2 hours during both events. Transmission was confirmed by whole genome sequencing. Fans were on medium speed and windows were closed. Airflow experiments were conducted with different size aerosols demonstrating plausibility of spread from the driver.

An epidemiological investigation of a chain of transmissions was reported beginning with a flight from India to New Zealand, a bus ride to a quarantine facility, a stay at a quarantine facility, a bus ride to the airport, and subsequent household transmissions.[72] Based on positivity test dates, genome sequencing, flight positions and hotel room placement the transmission events were ascribed to both short-range and long-range transmission on flights, within the quarantine facility, and within households. Masks

were required on flights and bus rides. One of the transmission events occurred between two adjacent hotel rooms in the quarantine facility. The authors used recorded video and observed >20 hours between any shared items and no direct contact. The authors concluded that fomite transmission was unlikely and attributed transmission to aerosols in the corridor outside of the hotel rooms wherein the space was enclosed and unventilated. Notably, the hotel rooms themselves, based on a review of the ventilation system, exerted positive pressure relative to the corridor.

An investigation by Lin et al. (2021) into an outbreak of nine COVID-19 cases from three families living in vertically-aligned units of an apartment building in Wuhan, China supported the possibility of long-range transmission.[66] Phylogenetic analysis of respiratory samples showed that all cases were infected by the same strain of SARS-CoV-2. Epidemiological investigation revealed that 4/5 cases of the index family in apartment 15-b had a travelling history to Wuhan, while the other four cases in apartments 25-b and 27-b had neither a travelling history to Wuhan nor close contact with any COVID-19 cases prior to their infection. Transmission through close contact in the elevators was considered unlikely as video records in the elevator did not show any close contact between the index family and the cases from units 25-b and 27-b. However, there was an incident where one unmasked occupant of unit 27-b took the elevator 8 minutes after two unmasked occupants from the index family had left the elevator. Epidemiologically, the infection rate for residents in units b was significantly higher ($p<0.05$) than that in units a and c. Testing of wind speed at the bathtub drain and floor drain found that the airflow produced by toilet flushing on one storey can influence the entire building as the drain pipes for toilets and the sewage pipes connected with floor drains were connected with the exhaust pipe. An experiment with a tracer gas indicated that gas could spread from one storey to another via the drainage and vent systems, especially as the seals in U-shaped traps in the floor drains were dried out in some units and the use of exhaust fans could create a negative pressure in the pipeline system. A similar situation was reported involving air ducts in a naturally ventilated apartment complex in Seoul, South Korea.[67] There were no valves blocking air from entering the bathrooms from the shared natural ventilation shafts (not for building or apartment unit ventilation). Limitations of this outbreak investigation included no genome sequencing or air sampling. Direct applicability to Canadian contexts may be limited by different building construction standards and practices.

Independent of ventilation, movement of air from an infected individual to others nearby can be an important factor in long-range transmission. Direct airflow was deemed responsible for a long-range transmission event in a restaurant in Korea.[73] The suspected index case sat 4.8 m and 6.5 m away and directly upwind of the airflow from two secondary cases at different tables. Nine other visitors in the restaurant did not test positive for SARS-CoV-2 even though at least two were closer to the index case for longer but not in the direct path of airflow originating from the index case. Notably the transmission in one case was suspected to have occurred from an exposure as short as five minutes, and three patrons sitting with the secondary cases but facing away from the index cases were not infected.

An investigation by Lu et al. (2020) into a COVID-19 outbreak in a restaurant in Guangzhou, China involving three families sitting at three tables in close proximity for about 1 hour concluded that the air conditioning (AC) system likely contributed to transmission.[63] In this scenario, a presymptomatic index case and secondary cases were present in the same area for 53–73 minutes. The location of a consistently running AC unit was in the airflow path of the secondary cases and was in an enclosed environment. No secondary cases occurred in staff or at adjacent tables that were outside of the likely "air column". The furthest distance between index and secondary cases was approximately 3 m. Additional investigation indicated that the exhaust fans had been closed due to cold outside temperatures.[74] The airflow assessment indicated that air was recirculating in a defined area, which exposed the three families.

A report involving group exercise at three facilities in Hawaii, US calculated attack rates of 25%–100%.[75] There was no fresh air ventilation and exposure occurred over a duration of 1 hour. Extended close contact and lack of masks in some cases were concluded as contributing to the transmission.

An outbreak in a multi-bed hospital room occurred wherein three patients and six health care workers became infected despite the use of masks and presence of ventilation of 3–4 ACH.[76] The presymptomatic index case was a parent located in a chair beside their child's bed who constantly wore a surgical mask, near the entrance to the room. Notably the air conditioning unit appeared to be located on the ceiling and no details were given about how it operated (e.g., constant versus timed/triggered) and what amount of fresh air circulation it provided. There were no exhaust vents indicated on the room diagram. Exposures for health care workers were in the range of 10–15 minutes, most at distances further than 2 m from the index patient. The report noted that masks were worn as personal protective equipment by health care workers. Transmission was based on the epidemiology of the outbreak without corroboration by genomic analysis of infections.

Detection of SARS-CoV-2 in Air Samples

Air sampling for virus refers to the process of collecting volumes of air by a device to determine if aerosols may contain virus. Collection can vary by aerodynamic size captured, duration of collection, volume per second collected, and media on which samples deposit. Air samples can then be tested by molecular methods such as reverse transcription PCR (RT-PCR) to amplify viral nucleic acids and/or viral culture. RT-PCR cannot determine whether the microorganisms detected are viable. Viral culture is used to determine whether a sample containing the virus is capable of replication. While there are several factors that contribute to the probability of infection, replication is a surrogate measure for inducing infection. To detect viability, researchers apply a sample to a susceptible cell culture and incubate up to a few weeks to detect morphological changes.

Detection of SARS-CoV-2 RNA in air samples has been inconsistent.[77] Multiple air sampling studies performed in proximity to confirmed COVID-19 cases were unable to detect any virus by RT-PCR.[78-86] Kenarkoohi et al. detected SARS-CoV-2 RNA by RT-PCR in 1/5 samples from a ward containing intubated, severely ill patients, but did not find any positive air samples in other areas of the hospital such as wards with suspected, confirmed and mild patients (culturing of virus was not attempted in this study).[87] Chia et al. (2020), in an extended study of Ong et al. (2020), detected SARS-CoV-2 RNA by RT-PCR in air samples collected within 1 m of patients in two of three airborne infection isolation rooms (AIIRs) (no culture of virus attempted).[88] Lei et al. (2020) reported limited detection of SARS-CoV-2 RNA virus by air sampling in open wards, private isolation rooms and bathrooms.[85] One PCR-positive air sample was obtained during an endotracheal intubation within 10 cm of the patient's head in a naturally ventilated room (window open with fan attached), eleven other air samples near patients and 17 samples outside patient rooms and at nursing stations were PCR-negative.[89] The stage of infection and level of infectiousness of the patient populations sampled were not reported.

In a study of SARS-CoV-2 RNA in air samples collected from a variety of settings, Liu et al. (2020) reported that the highest concentration of viral RNA was reported from patient and staff areas of hospitals, compared to public areas.[90] Gharehchahi et al. (2021) (preprint) found SARS-CoV-2 RNA in 7/17 (41.2%) of air samples in a hospital for COVID-19 patients, including a mechanically-ventilated temporary waste storage area, two naturally-ventilated offices (one in the admission and discharge area, the other in an administrative department), and within 2 m of patients' beds in two intensive care units (ICUs), a negative pressure room, and an accident and emergency ward that are mechanically-ventilated with or without natural ventilation.[91] SARS-CoV-2 RNA was not detected from the four

samples at nursing stations 2–5 m from patients' beds. The authors speculated that the detection of RNA in non-clinical areas could be due to inadequate ventilation and the occasional presence of infected health care workers.

Stern et al. (2021) sampled air in locations outside of patient care areas in an acute care hospital and found 8/90 (9%) of the samples positive for SARS-CoV-2 RNA, with concentrations ranging from 5–51 copies/m^3.[92] The size of the RNA-positive samples ranged from ≤2.5 to ≥10 μm. Locations adjacent to negative-pressured wards designated for COVID-19 patients did not appear to increase the likelihood of detecting viral RNA, having higher viral concentration, or finding particles of specific sizes in air samples. However, a significant positive association was observed between the average number of COVID-19 patients staying in the hospital during each sampling period, and the likelihood of an air sample testing positive for SARS-CoV-2 RNA. Furthermore, areas where staff congregated during times of high community rates of COVID-19 were associated with positive air samples. Of note, one RNA-positive air sample was taken when the unit was closed for cleaning and not under negative pressure, and the unit doors were left open for cleaning staff who had to pass by the air sampler to access the area for cleaning.

When air samples were RT-PCR-positive, culturing attempts were infrequently successful. In a systematic review and meta-analysis of 24 studies, Birgand et al. (2020) reported that 17.4% (82/471) of air samples from patient environments were RNA-positive (there was no difference in positivity at ≤1 m [2.5%] or 1–5 m [5.5%]; p=0.22), while culturing produced viable virus in 8.6% (7/81; 2 out of 5 studies) of samples.[93] A study by Guo et al. (2020) detected SARS-CoV-2 by RT-PCR in 35% (14/40) of air samples in an ICU and 12.5% (2/16) of air samples in the general ward that managed patients with COVID-19. Fifteen of 16 RT-PCR-positive air samples were from within 2 m of patients, with 1/8 samples positive at 4 m away.[12] Ben-Shmuel et al. (2020) conducted limited sampling (generally one air sample per area) in rooms with ventilated and non-ventilated patients, at a nursing station, and in private and public areas of a quarantine hotel.[94] RT-PCR-positive air samples were detected in a room with a ventilated patient (distance from patient was not reported) (n=1/1), at a nursing station (n=1/1), and in a quarantine hotel room (n=1/1). However, there were no positive air samples in rooms of non-ventilated patients (n=0/3), a doffing area (n=0/1), and a public area of a quarantine hotel (n=0/1). The authors attempted viral culturing; however, no samples were positive.

At this time, only three studies, two from the same research group and one preprint from July 2020, have successfully cultured viable virus from the air. The preprint and one published study were already referred to above in the summary of Birgand et al. (2020). Sampling techniques and equipment may have caused the lack of culture viability despite RT-PCR detection in other studies. Future studies should aim to replicate the use of equipment and culture methods as these studies.

Lednicky et al. (2021) used a prototype and commercial version of an air sampler and custom RT-PCR probes for detection of SARS-CoV-2 in a patient room with two patients. One patient was discharged soon after sampling periods began and after receiving a negative RT-PCR test.[95] The remaining patient began experiencing respiratory illness two days prior to admission to the room. The study detected RT-PCR-positive air samples following 3 hours of sampling as well as positive viral cultures. Researchers positioned samplers 2–4.8 m from the recently symptomatic patient's head. The ventilation unit provided 6 ACH, filtering air and treating air with UV irradiation before recycling the air. Estimates of virus per volume of air ranged from 6–74 tissue culture infective dose $(TCID)_{50}$ units/L of air. Recently, a second study by Lednicky et al. was performed to detect viable SARS-CoV-2 virus from the front passenger seat area of a car driven by a SARS-CoV-2-positive patient without cough symptoms.[96] This study involved a sampler affixed to the sun visor in the passenger seat collecting particles sizes in ranges

of <0.25 µm, 0.25–0.50 µm, 0.50–1.0 µm, 1.0–2.5 µm and >2.5 µm. The patient drove for 15 minutes with the windows up and air conditioner on. The sampler was turned off 2 hour after the patient completed the 15 minute drive. Viable virus was cultured only from the 0.25–0.5 µm fraction, which also had the highest quantity of detectable copies of viral RNA.

Further research is needed to reconcile differences in viral RNA detection and virus viability in air samples, despite RT-PCR-positive samples found on the surfaces of ventilation units.[97] Differences may be due to several factors, including: 1) air sampling devices are potentially not capable of maintaining viability of captured virus; 2) timing of air sampling varies by time since onset of symptoms, severity of disease or viral load; and 3) the conditions of ventilation (engineering controls) reducing concentrations of viral aerosols to undetectable levels. Even in rooms with high air exchanges, Tang et al.'s review of SARS-CoV-2 aerosols indicates that viral RNA copies can still be detected in air samples from patient rooms (1.8–3.4 viral RNA copies/m^3), toilet rooms (19 copies/m^3), and personal protective equipment doffing rooms (18–42 copies/m^3).[98] In a series of distinct room types (two AIIR with 15+ ACH, an isolation room without negative pressure and a shared cohort room) for patients admitted within 7 days of symptom-onset, Kim et al. reported that 32 air samples were negative and 20 air samples from anterooms were also negative.[86] Culturing viruses is technically challenging; therefore, the lack of positive cultures does not necessarily indicate an absence of infectious virus. On the other hand, the detection of SARS-CoV-2 viral RNA on surfaces that are rarely touched suggests that the virus may be transported through the air to those no-touch surfaces.[99]

Conclusions

Respiratory virus transmission occurs on a spectrum, from larger droplets that spread at short range, to aerosols that are present at short ranges but may also contribute to long-range transmission. As a result, categorizing SARS-CoV-2 transmission as either droplet or airborne does not accurately reflect this spectrum. Other respiratory viruses, like influenza, have similarly been described to demonstrate a spectrum of droplet sizes contributing to transmission.[100,101]

The highest risk of SARS-CoV-2 transmission likely occurs via close (<2 m), unprotected exposure (lacking multiple prevention measures) to an infectious individual. While there is a lower risk of transmission at longer distances with unprotected exposure, this kind of transmission has only been documented to occur under certain conditions, usually involving inadequate ventilation or with recirculation of unfiltered or untreated air in combination with activities involving increased exhalation/expulsion (e.g., shouting, singing, exercising), and often with a lack of source control masking.[102] Defining measures or cutoffs for inadequate ventilation was not possible based on the available descriptions of the contexts in which inadequate ventilation was reported to contribute to transmission. However, they included situations where air is circulated without filtration or exchange with fresh air, where there is no ventilation (e.g., windowless rooms without a ventilation system), and where the size of the room and ventilation rate relative to the quantity of infectious aerosols generated exceeds an unknown threshold of risk for infection. VOCs may be more effectively transmitted across all modes of transmission; however, there is no evidence that any VOCs transmit by fundamentally different routes.[103-105]

The delineation of relative contributions of short-range large respiratory droplets and aerosols and long-range aerosols to overall transmission patterns is complicated by the variable confluence of dynamic source/receptor factors and pathway factors. For example, each infector/infectee interaction is affected by source activities and amount of source viral load (e.g., forceful expulsion of droplets during coughing or singing, and timing in the course of illness), source/receptor adherence to preventative measures in place (e.g., hand hygiene, physical distancing, surface disinfection, mask-wearing and ventilation), and

pathway factors that include airflow, UV, temperature, and humidity in indoor or outdoor environments.[16] It is likely that the relative contribution of respiratory particle size to transmission will depend on these combination of factors.

A large body of evidence is emerging related to SARS-CoV-2. Studies related to identification of a specific mode of transmission are generally low quality. Moreover, data from different fields (e.g., epidemiology versus modelling) can be at odds with respect to conclusions drawn about the role of different sized droplets in short-range transmission and relative importance of long-range transmission events. Ongoing study is needed for further evidence regarding the quantity of viral particles required to cause infection. Additional assessment of SARS-CoV-2 viability in aerosols is needed. Lastly, elucidation of setting-specific risk factors for transmission (e.g., differences between source/receptor and pathway factors in health care settings, residential buildings, schools, warehouses, transportation) may provide further insight into mechanisms for transmission.

The COVID-19 pandemic has identified the importance of interdisciplinary collaboration towards understanding and having a common lexicon for describing virus transmission. When the analysis and interpretation of data is challenged by variable terminology used between and within public health, clinicians, aerosol scientists and the public, this can limit progress towards identification and application of appropriate mitigation measures.[106]

Implications for Practice

This document summarizes the evolving evidence on transmission through respiratory particles and acknowledges the role for both larger droplets and aerosols in transmission. While our understanding of how transmission occurs has evolved and the relative contribution of droplets and aerosols continues to be studied, this may not necessitate a change in infection control measures, but highlights the importance of incorporating multiple infection control layers to mitigate transmission. Translation of this information into recommendations for control measures also needs to take into consideration evidence not reviewed in this document on the overall effectiveness of control measures to date: 1) effectiveness of measures in isolation and in combination as layered mitigation; 2) effectiveness in the community vs. health care settings; and 3) effectiveness and the impact of implementation fidelity.

A detailed assessment of the evidence for infection prevention and control measures was out of scope for this document and thus limits discussion of recommendations for specific measures in different contexts. Of note, vaccination against SARS-CoV-2 is a relatively recent measure that is very effective at reducing transmission regardless of the mode of transmission and should be the priority control measure both in health care and community settings.[107]

In health care settings, recommendations for IPAC measures are described in *IPAC Recommendations for Use of Personal Protective Equipment for Care of Individuals with Suspect or Confirmed COVID-19* and *Interim Guidance for Infection Prevention and Control of SARS-CoV-2 Variants of Concern for Health Care Settings*.[7,8] These documents integrate the existing evidence around droplet, aerosol and contact transmission with jurisdictional experience with control measures and outbreak management to date, and recommends the use of the hierarchy of hazard controls to reduce the risk of transmission.

The bulk of disease transmission occurs in the community and in workplaces, not in health care settings. As SARS-CoV-2 transmits early in the course of infection, most commonly in the asymptomatic or presymptomatic period[108-111] and within the first two days of symptom-onset, cases may not seek health care during their most transmissible phase. In all settings it is necessary to utilize multiple control

measures to mitigate the dynamic transmission factors and address potential routes of transmission. Infection prevention controls should also be context-dependent and take into account vaccination status/coverage, the ability to physically distance and avoid crowding, the feasibility of proper wearing of appropriate personal protective and source control equipment, training and education on the appropriate use of personal protective equipment, hand hygiene, surface disinfection, indoor ventilation, and early identification and isolation of infectious persons. Finally, application of measures should also be in the context of overall rates of community transmission and risk of exposure.

Several resources exist for community guidance (e.g., non-health care workplaces, public and private spaces) on how to reduce the risk of SARS-CoV-2 transmission through a layered approach of multiple public health measures designed to mitigate short-range and long-range transmission.[112-114] In general these involve avoiding the "3 C's": closed spaces, crowded places, and close contact. The degree to which various mitigation layers are necessary or possible will depend on the setting and risk context. Transmission can be mitigated through:

- Getting vaccinated[115,116] (higher vaccine coverage in the population can reduce risk for individuals unable to receive a vaccine)
- Staying home when sick[117,118] (e.g., active and passive screening prior to entry into public settings)
- Limiting the number and duration of contacts with individuals outside your household
- Physical distancing[114] and avoiding crowded spaces
- Consistently and appropriately using a well-fitted, well-constructed (2-3-layer) mask for source control and personal protective equipment.[119-122]
- Ensuring that ventilation systems[123] are well-maintained and optimized with the support of professionals according to relevant recommendations (e.g., from American Society of Heating, Refrigerating and Air-Conditioning Engineers) and/or using outdoor environments whenever possible.
- Performing hand hygiene, respiratory etiquette, and environmental cleaning[124]

The above measures are effective means of reducing risk of transmission irrespective of the relative contribution of larger droplets or aerosols to transmission. Some controls will be more effective than others and it is the combination and consistent application of these controls that is most effective for reducing disease spread.

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Ontario

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This is **Exhibit "DD"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

Public Health Ontario | Santé publique Ontario

SYNOPSIS

05/22/2020

COVID-19 – What We Know So Far About… Asymptomatic Infection and Asymptomatic Transmission

Introduction

PHO is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19). "What We Know So Far" documents are intended to provide a rapid review of the evidence related to a specific aspect or emerging issue related to COVID-19.

The development of these documents includes a systematic search of the published literature as well as scientific grey literature (e.g., ProMED, CIDRAP, Johns Hopkins Situation Reports) and media reports, where appropriate. Relevant results are reviewed and data extracted for synthesis. All "What We Know So Far" documents are reviewed by PHO subject-matter experts before posting.

As the COVID-19 outbreak continues to evolve and the scientific evidence rapidly expands, the information provided in these documents is only current as of the date of posting.

Key Points

This document summarizes the evidence regarding asymptomatic infection and transmission of SARS-CoV-2, the virus that causes COVID-19, by individuals who are asymptomatic. For clarity, in this document we will use the term COVID-19 to refer to both the virus and the disease.

Asymptomatic infection:

- **There is clear evidence of asymptomatic infection with COVID-19**. Estimates of the proportion of laboratory-confirmed cases who are asymptomatic may vary by age group, study setting and study methodology, ranging from 8.2% (infants under 1 year of age),[1] 18.2% (contact tracing in a conference outbreak),[2] 36.7% (travellers),[3] 43.2% (universal screening in a town),[4] up to 87.8% (outbreak investigation in a homeless shelter)[5] (see Asymptomatic Infection). The method of detection of asymptomatic cases (i.e., mass screening or testing contacts of cases), and the duration of follow-up to ensure asymptomatic individuals do not subsequently develop symptoms may influence the proportion of cases who are reported to be asymptomatic.

Asymptomatic transmission:

- There is some epidemiological and virological evidence of transmission from people who are asymptomatic and never develop symptoms. On the other hand, there is **more epidemiological and virological evidence as well as inferences from modelling and statistically analyses, that**

transmission can occur from presymptomatic COVID-19 patients (where transmission takes place during their incubation period). In particular, epidemiological investigations and virological findings have suggested that **transmission can occur as early as six days before symptom onset** and possibly even earlier, although alternative unrecognized sources of infection cannot be ruled out. Other studies have estimated the serial interval (time from onset of symptoms in one case to the onset of symptoms in the person they infect) and found that it is shorter than the length of the incubation period, suggesting transmission during the incubation period (see Modelling and Statistical Analysis below).

Background

Asymptomatic infection occurs when an individual is infected but experiences no symptoms, while asymptomatic transmission occurs when an infected individual without symptoms transmits the virus to another person. There are two mechanisms by which asymptomatic transmission can potentially occur:

1. Transmission from an individual who never develops symptoms—if the infected person is asymptomatic throughout his/her infection but nevertheless is infectious.

2. Transmission from an individual during their incubation period—if the infected person is infectious before he/she develops symptoms.

Asymptomatic Infection

Evidence of asymptomatic COVID-19 infection has been reported in studies that report on contact tracing activities, as well as in outbreak investigations and surveillance data. Asymptomatic infections have been reported in all age groups, occurring in various proportions of confirmed cases in different settings. Several studies reported that a substantial portion of COVID-19 patients remained asymptomatic at the end of their isolation period.

Asymptomatic Infections by Settings

The following highlights the proportion of asymptomatic COVID-19 cases from contact tracing activities, outbreak investigations and surveillance activities in various settings.

HEALTH CARE SETTING

A number of studies reported rates of asymptomatic infections after a period of isolation:

- Among the 138 cases detected in Brunei from March 5 to April 24, 2020, all were hospitalized and followed until viral clearance; 42 (30%) were presymptomatic at the time of diagnosis but later developed symptoms and **16/138 (12%) remained asymptomatic until viral clearance**.[3]

- 13/23 (57%) resident cases identified at a point-prevalence screening in a long-term care skilled nursing facility in Washington, United States with a COVID-19 outbreak were asymptomatic; only **3/23 (13.0%) remained asymptomatic at rescreening one week later**.[6]

- 14/19 (74%) resident cases and 4/8 (50%) staff cases identified at multiple point-prevalence screenings in a long-term care skilled nursing facility in California, United States with a COVID-19 outbreak were asymptomatic; **6/19 (31.6%) resident cases remained asymptomatic after at least 17 days of observation**.[7]

- 29/33 (87.9%) pregnant women who tested positive for SARS-CoV-2 at two New York obstetric centres were asymptomatic when screened at delivery; **26/33 (78.8%) remained asymptomatic until discharge**.[8] In another report from about a week before to a week after universal screening was started at these same two centres, 14/43 (32.6%) SARS-CoV-2–positive pregnant women were found to be asymptomatic on admission (two because they later developed symptoms and 12 by screening); 4/43 (9.3%) were asymptomatic throughout their postpartum courses.[9]

- **28/131 (21.4%)** COVID-19 confirmed hemodialysis patients from 65 centres in Wuhan, China remained **asymptomatic throughout** the course of their infection.[10]

- 30/1,012 (3%) patients admitted during February 7-12 to a make-shift hospital for non-critically ill COVID-19 patients in Wuhan, China were asymptomatic on admission. **14/1,012 (1.4%) patients remained asymptomatic after a median duration of 24 days** from exposure (interquartile range: IQR: 22-27).[11]

- Of 31 patients who were asymptomatic on admission to a hospital in Guangzhou, China, **9/31 (29.0%) remained symptom-free during hospitalization**. The viral load was higher in those who subsequently developed symptoms than in those who remained symptom-free.[12]

- 13/328 (4.0%) adult **patients admitted** to a public health centre in Shanghai, China were asymptomatic; **10/328 (3.0%) remained asymptomatic from 5 to 21 days after admission**, although all but one patient had radiologic abnormalities on chest CT.[13]

- **13/71 (18.3%) admitted patients** at a hospital in South Korea were **asymptomatic on admission. 10/71 (14.1%) remained asymptomatic for the entire quarantine period**, and the other 3 cases developed symptoms within 2 days of admission.[14]

CONGREGATE LIVING SETTINGS

High prevalence of asymptomatic infections at the time of testing have been reported in a few congregate settings:

- 87.8% of 147 adult COVID-19 cases identified through screening at a homeless shelter in Boston.[5]

- More than 350 of 615 (>57%) COVID-19 cases on the Theodore Roosevelt aircraft carrier.[15]

- 3 of the 4 resident cases identified at a senior independent and assisted living community in Seattle, Washington reported feeling well between the 14 days prior to and 14-21 days after testing.[16]

- 410/696 (58.9%) confirmed passenger and crew COVID-19 cases in the Diamond Princess cruise ship outbreak.[17] Adjusting for the possible future development of symptoms (right censoring) using a statistical model, Mizumoto et al. estimated the asymptomatic proportion to be 17.9% (95% credible interval (CrI): 15.5 to 20.2%).[18]

COMMERCIAL PREMISES

Two outbreak reports identified cases that remained asymptomatic through the follow-up period:

- In a call centre outbreak in Seoul, 4/97 (4.1%) confirmed COVID-19 cases were presymptomatic and another **4/97 (4.1%) remained asymptomatic throughout a 14-day isolation period**.[19]

- In a conference outbreak in Munich, Germany, **2/12 (17%)** infected attendees **remained asymptomatic after weeks of follow-up**.[2]

COMMUNITY

There are regional and national surveillance reports on the presence of asymptomatic infection in the community:

- A national surveillance report by the Chinese Center for Disease Control and Prevention reported 889/45,561 (2%) of laboratory-confirmed cases as asymptomatic at the time testing as of February 11.[20]

- 94/728 (12.9%) laboratory-confirmed children reported to the Chinese Center for Disease Control and Prevention during January 16-February 8, 2020 were asymptomatic (from 8.2% in children <1 year of age [7/85] to 17.6% for those 6-10 years of age [30/170]).[1]

- Integrated surveillance of COVID-19 in Italy reported 28.6% of the 33,189 cases with clinical data were asymptomatic as of May 20.[21]

- Analysis of regional surveillance data from one day in Lombardy, Italy found 17/380 (4.5%) cases as asymptomatic.[22]

- 35/81 (43.2%) cases identified in two point-prevalence surveys of all inhabitants of the municipality of Vò, Italy were asymptomatic at the time of testing.[4]

- 30/112 (26.8%) cases in a cluster of fitness dance classes in South Korea were asymptomatic at the time of testing.[23]

There are also studies reporting community-based infections that remained asymptomatic after a period of time:

- **50/1,015 (4.9%) confirmed cases** (41 adults and 9 children) in Huangshi, China were **asymptomatic throughout a quarantine period of at least 14 days**, according to publicly available disease databases of Hubei Provincial Health Committee up to March 27, 2020.[24]

- **5/48 (10.4%) secondary cases** among close contacts in Zhuhai, China **remained asymptomatic through a 21-day follow-up**.[25]

- Wan R et al. described 2 close contacts of confirmed patients. Case 1 was exposed at work to a COVID-19 patient and diagnosed 16 days later by reverse transcription polymerase chain reaction (RT-PCR). He **remained asymptomatic up to the end of the isolation period 25 days after exposure**; two chest radiographs taken during his isolation period were negative. Case 2 was the adult son of a COVID-19 patient. Case 2 was isolated the day after the parent's diagnosis and he **remained asymptomatic throughout 26 days of isolation**. Two chest radiographs taken during his isolation were also negative.[26]

TRAVELLERS

A few countries that tested their repatriated passengers or travellers from countries at high-risk of COVID-19 also reported asymptomatic infections:

- 40/783 (5.1%) repatriated passengers to Greece during March 20-25, 2020 who tested positive for SARS-CoV-2 reported no general or respiratory symptoms.[27]
- 2/114 (1.8%) repatriated passengers to Germany on February 1 were asymptomatically infected and remained afebrile 7 days after diagnosis, although one patient developed a faint rash and minimal pharyngitis.[28]
- Out of the 30 arrivals to Brunei who tested positive for SARS-CoV-2 between March 21 and April 24, 11 (36.7%) were presymptomatic and 3 (10%) were asymptomatic.[3]
- In a cluster of 6 travellers and 6 secondary cases in Vietnam, 1/12 cases (8.3%) remained asymptomatic but viral RNA was detected by RT-PCR throughout the 9-day follow-up period.[29]

Abnormal Chest Imaging

Asymptomatically infected individuals can have abnormal chest imaging.

- Hu Z et al. showed that 12/19 asymptomatic adults and children had abnormal chest CT scans.[30]
- Chan JF et al. described an abnormal chest CT in a 10-year old asymptomatic child.[31]
- Wang Y et al. noted pneumonia in CT findings in 37/55 of asymptomatic cases on admission. Note that all 55 cases developed symptoms during hospitalization: 14 had mild infection, 39 had ordinary symptoms and 2 had severe COVID-19.[32]
- Zhou X et al. reported that 9/10 asymptomatic patients hospitalized at a public health centre had signs of pneumonia on their chest CT scans.[13]
- Zhou R et al. noted bilateral abnormalities in chest CT scans typical of pneumonia in 4/9 patients who remained asymptomatic throughout hospitalization.[12]
- Inui S et al. reported that chest CT findings consistent with pneumonia were seen in 41/76 (54%) asymptomatic passengers on Diamond Princess cruise ship.[33]

Asymptomatic Transmission

There is some **evidence of transmission from people who are asymptomatic and never develop symptoms**, and **more evidence of transmission from people who are in their incubation period** (i.e. people who transmit infection while asymptomatic, but prior to their development of symptoms).

Transmission From People who Never Developed Symptoms

Findings from epidemiological and virological investigation have been published to support the observation that transmission can occur from people who never developed symptoms after their infection.

EPIDEMIOLOGICAL EVIDENCE FOR ASYMPTOMATIC TRANSMISSION

Several authors reported clusters of infections in China where epidemiological findings suggest the possibility of transmission by asymptomatic patients.

- Zhou J et al. reported two transmission events by asymptomatic patients in ZhuZhou, China.[34]

    - A 37-year-old woman was isolated for observation after returning from Wuhan on January 22, 2020. Viral RNA was only detected in the 5th specimen taken on February 15, and she remained asymptomatic up to March 2 when her test turned negative and showed no pulmonary imaging changes. Meanwhile, her father was diagnosed of COVID-19 on February 12, 3 days before viral RNA was detected in the woman's specimen.

    - An asymptomatic patient who returned from Wuhan appears to have infected her mother-in-law and father-in-law.

    Zhou et al. conclude that asymptomatic SARS-CoV-2 carriers can spread the virus before viral RNA was detected. It should be noted that they did not provide any information on potential alternate sources of infection or on the reliability of the testing done.

- Zhang J et al. reported a family cluster of 5 in Beijing. The index case was the only one in the cluster who had been to Wuhan; he returned to Beijing in January and invited his nephew (M/32) for dinner that day. This nephew became ill 3 days later and was diagnosed 2 days after symptom onset. Around that time, the index patient's wife (F/45) had a fever and they heard of a relative in Wuhan having COVID-19. As a result, the index patient and family visited a hospital to be assessed and the index and 4 family members (including the nephew and wife) were diagnosed with COVID-19. Both the index patient and a family member remained asymptomatic throughout the observation up to the end of February. The index patient's chest radiograph showed ground glass opacities but that of the other asymptomatic family member was normal. The authors believe the index patient passed the infection on to his family despite having no symptoms himself. However, details of other family members' contact history were not given to rule out potential alternate sources of infection.[35]

- A study by Bai Y et al. reported on an asymptomatic individual who transmitted COVID-19 to five family members in Anyang. She tested positive 18 days after her presumed exposure, with a negative test on day 16 and two negative tests on days 26 and 29. Although the authors argue that the asymptomatic individual was the source of infection for the family members, the family visited a hospital as well. Although the hospital reported no COVID-19 cases at that time, this is a potential alternative source of exposure.[36]

- Hu Z et al. reported on an asymptomatic case who appears to have acquired his infection in Hubei province and transmitted his infection to his wife, son and daughter-in-law who lived with him in Nanjing. His family members denied any other known exposures to confirmed or suspect COVID-19 patients.[30]

- Lavezzo E et al. reported on 3 cases who appeared to have acquired their infection based on contact with asymptomatic individuals. The cases were identified on the second of two point-prevalence surveys that took place at the end of a two-week lockdown of the municipality of Vò, Italy: case 1 had exposure to 4 infected relatives who did not have any symptoms at the time of contact; case 2 had a meeting with an asymptomatic case before the lockdown; case 3 shared

the same flat with two asymptomatic relatives. The authors noted that all the asymptomatic individuals never developed symptoms during the two-week lockdown.[4]

VIROLOGICAL EVIDENCE FOR ASYMPTOMATIC TRANSMISSION

Several studies reported high viral loads in asymptomatic individuals as measured by real-time RT-PCR.

- Arons MM et al.[37] cultured the real time RT-PCR-positive specimens from two point-prevalence surveys in a skilled nursing facility as part of an outbreak investigation, as described in Kimball A et al.[6] above. Viral growth was observed for 13/20 symptomatic residents, 17/24 presymptomatic residents, 1/3 asymptomatic residents. **Viable virus was isolated from 6 days before to 9 days after symptom onset**. In addition, **high viral RNA loads were detected in all groups with median cycle threshold values at 24.8 in those with typical symptoms and 25.5 for those who were asymptomatic**. This suggests the potential for substantial viral shedding in asymptomatic cases. No correlation was observed between cycle threshold values and time from symptom onset.[37]

- Zou L et al. noted that an asymptomatic individual had similar viral loads from nasal and throat swabs compared to 17 symptomatic individuals.[38]

- Roxby AC et al. noted that the viral load in 3 generally asymptomatic residents (one developed a mild cough) of an independent living community were similar to those reported among ill hospitalized patients.[16]

- Kam K et al. noted a high viral load in a nasopharyngeal specimen from a generally well baby. Nasopharyngeal specimens were positive for 16 days and one stool specimen was also positive.[39]

- Hoehl S et al. observed COVID-19 virus in cell culture in throat specimens from two repatriated passengers who tested positive by RT-PCR. One patient developed slight rash and minimal pharyngitis the day after testing but both persons remained well and afebrile during the 7 days after hospital isolation.[28]

- Cereda D et al. noted that the median viral RNA levels in nasal swabs were not statistically different between 295 symptomatic and 17 asymptomatic obstetric cases:
5.0 $\log_{10}$ RNA copies/mL (range 1.7-10.1) vs 4.7 $\log_{10}$ copies/mL (range 2.1-7.1), (P=.51).[22]

Transmission During the Incubation Period

There is both epidemiological and virological evidence, as well as inferences from modelling and statistical analysis, that point to transmission from people prior to their symptom onset.

EPIDEMIOLOGICAL EVIDENCE FOR PRESYMPTOMATIC TRANSMISSION

Several studies describe potential transmission prior to symptom onset, i.e., in the incubation period. In most instances, the contacts who acquired the infection reported no other known sources of exposure other than a case who was in their incubation or early symptomatic period.

- Hijnen D et al. reported an outbreak amongst at least 11/13 attendees (one attendee was not tested) from seven countries at a 2-day conference in Munich, Germany in February, when under 20 cases of COVID-19 had been diagnosed in the country. The **index patient** (a physician

was believed to have been infected when examining a patient in Italy two days before the start of the conference) **developed symptoms only after he had left the conference**.[2]

- Rothe C et al. reported an outbreak in Germany resulting from a business meeting in late January.[40] Böhmer MM et al. reconstructed the transmission events with epidemiological findings and whole genome sequencing of 13 of the 16 subsequent cases.[41] The index case was a Chinese resident from Shanghai who had had contact with her parents from Wuhan before visiting Germany in January for work reasons. Presymptomatic transmission likely occurred from patient 4 (symptom onset on January 24) to patient 5, as patient 5 did not meet the index case but had encounters with patient 4 on January 22 when they sat back to back in the canteen and patient 5 turned to ask patient 4 to borrow the salt shaker from their table. Böhmer MM et al. noted that **presymptomatic transmission is strongly supported by virus sequence analysis**. In addition, presymptomatic transmission could possibly have occurred for 5 more cases.[41]

- Jang S et al. reported on the active surveillance results of a COVID-19 cluster associated with fitness dance classes. On February 15, 2020, a 4-hour workshop for 27 fitness instructors took place in Cheonan, South Korea (approximately 200 km from Daegu where an outbreak was emerging). After discovering cases in Cheonan linked to fitness dance classes, the workshop was investigated. Eight of the 27 instructors at the workshop were found to be infected with SARS-CoV-2. One of these instructors was from Daegu, and therefore was the presumed source case for the outbreak, and developed symptoms on February 18, 2020, three days after the workshop.[23]

- Cheng HY et al. conducted a prospective study that enrolled all the initial 100 confirmed cases in Taiwan from January 15 to March 18, 2020 and their 2,761 close contacts. All close contacts were quarantined at home for 14 days after their last exposure to the index case, and any typical symptoms triggered testing. High-risk contacts (e.g., household and hospital contacts) were tested regardless of symptoms. No secondary clinical cases were detected from all 91 close contacts of the 9 asymptomatic patients. Cheng et al. identified 22 secondary cases, 18 of whom had symptoms. They determined a secondary clinical infection risk of 0.7% (95% confidence interval (CI): 0.4% - 1.0%) among 2,761 close contacts. **For the 299 contacts with exclusive presymptomatic exposures to the index case, the secondary clinical attack rate was 0.7% (95% CI, 0.2%-2.4%)**. The authors noted that the actual contribution of early transmission could be greater as they did not completely identify contacts before symptom onset of the index cases.[42]

- Wei WE et al. reviewed the clinical and epidemiological records of all 243 cases in Singapore to determine whether presymptomatic transmission might have occurred. Of these cases, **157 were locally acquired with 10 (6.4%) attributed to presymptomatic transmission within 7 clusters**, where investigation did not identify any other potential sources of infection. The authors noted that although an unknown source might have caused some of these infections, given that COVID-19 prevalence was very low during the period under investigation and strong surveillance systems were in place, presymptomatic transmission was deemed the most likely mode of transmission. The authors also note that recall bias related the onset date of symptoms might add uncertainty to the duration of the presymptomatic period.[43]

Multiple authors also reported clusters of infections in China where the transmission histories suggest the occurrence of presymptomatic transmission. It should be noted that due to circulation of COVID-19 in China during that time, it is possible that there was another unrecognized source of infection, in addition to the cases reported.

- Gao Y et al. reported a 15-person cluster with 4 generations of transmission and 6 asymptomatic cases in Wuxi. Except the index case, none of the other 14 cases had any history of suspicious exposure except for contact with the previous generation case(s). In this cluster, infections are believed to have spread to the next generation before onset in the previous generation as follows: 2-7 days before onset (1st to 2nd generation), 6-7 days before onset (2nd to 3rd generation), and 3-8 days and 9 days before onset (3rd to 4th generation). The authors noted that generation 2 might also have been infected from other sources while touring in Japan. However, the transmission history of the other generations support the idea of presymptomatic transmission.[44]

- Luo SH et al. reported a cluster of 4 adults in Anqing. Epidemiological evidence suggests that one patient was infected by her husband during the presymptomatic stage of his infection. Neither the wife nor husband had travelled to Wuhan or adjacent areas or had recent exposure to wild animals. However, the husband likely acquired his infection from a relative while the relative was symptomatic.[45]

- Huang L et al. reported a cluster of 8 teenagers and young adults aged 16-23 years in Hefei, originating from a 22-year-old male returning from Wuhan. Six secondary cases became infected after contact of several hours duration with the index case one day before his symptom onset; another secondary case was likely exposed 3 days before the index case's symptom onset. None of the secondary cases had visited Wuhan or had any exposure to wet markets, wild animals, or medical institutes within the previous 3 months.[46]

- Li C et al. described transmission in a familial and hospital settings in Xuzhou. The source case is believed to have acquired his infection on January 14, 2020 during a 6-hour transfer in a train station in Wuhan when travelling to Xuzhou and developed symptoms on January 19, 2020. While caring for his son-in-law in hospital he interacted with another patient and that patient's son from January 15 to 18 (1 to 4 days before the source patient's onset of symptoms); both the other patient and his son became infected. The source case also infected several members of his family whom he was with both before and after the onset of symptoms. Other source(s) of infection, particularly in the hospital setting may also be possible, although were not mentioned by the authors.[47]

- Li P et al. describe a familial cluster of 4 in Zhoushan, who had close contact with a presymptomatic family member 4 to 7 days before the index case's symptom onset. Other than the index case, the family reported no contact with people with fever or respiratory symptoms in Wuhan or other areas with persistent local COVID-19 transmission in the 14 days prior to their symptom onset, and no history of contact with wild animals or poultry.[48]

- Ye F et al. reported a cluster of 5 people from 2 families in Luzhou. The three members of Family 1 traveled from Wuhan to Luzhou on January 22, and met with the two members of Family 2 between January 23 and 25 and on January 30. Family 2 had not left Luzhou and their only contact with anyone from Wuhan was Family 1. The first and last contact between Family 1 and 2 was 13 and 6 days before the first case in Family 1 developed symptoms on February 5. All five family members developed symptoms and the symptoms in the first case in Family 2 started on February 1, 2020, 4 day before the symptoms in Family 1.[49]

- Yu P et al. described an 88-year-old man from Shanghai who developed symptoms 5 days after the arrival of two visitors from Wuhan. The two visitors developed symptoms after the man,

with the earliest symptom onset among the two visitors occurring 11 hours after the man's first symptoms. This suggests that at least one of the visitors had spread infection in their incubation period. Assuming the visitor with the earliest symptom onset transmitted infection to the man, **the earliest the infection could have occurred is from 5 days before onset of illness in that visitor**, based on the date of the visitors' arrival.[50]

- Huang R et al. described a patient from near Wuhan who visited her family in Nanjing and did not develop symptoms until 4 days after leaving Nanjing. She infected six family members, some of whom she lived with and some with whom she attended one or more dinners with, including one on the day before her departure. Two family members, who appear to have been infected at the family dinner with the visiting woman the day before her departure, attended another family dinner with three different relatives. This occurred on the day after the dinner with the visiting woman, and 3 and 4 days before the onset of symptoms. The three relatives subsequently developed symptoms and were found to be infected with COVID-19. **This suggests that transmission can occur at least 5 days before symptom onset and that transmission may occur as early as 1 day following exposure**.[51]

- Tong ZD et al. reported a case of COVID-19 from Wuhan who attended a conference in Zhoushan three days before illness onset. Two colleagues from Zhoushan also attended the conference and dined with the case the following day (2 days before illness onset), sharing the same serving plates. The two colleagues were subsequently confirmed to be infected. **This suggests that the source patient likely infected his two colleagues at least 2 days prior to symptom onset**.[52]

VIROLOGICAL EVIDENCE FOR PRESYMPTOMATIC TRANSMISSION

In addition to epidemiological reports that attribute the source of infection to presymptomatic COVID-19 patients, we found an article that reports on finding viable COVID-19 virus in specimens from patients prior to their symptom onset. Another two studies reported high viral loads in presymptomatic individuals as measured by real-time RT-PCR.

- Arons MM et al. cultured the real time RT-PCR-positive specimens from two point-prevalence surveys in a skilled nursing facility as part of an outbreak investigation (see also Virological Evidence for Asymptomatic Transmission). **Viable virus was isolated from 6 days before to 9 days after symptom onset**. In addition, **high viral RNA loads were detected in all groups with median cycle threshold values at 24.8 in those with typical symptoms and 23.1 for the presymptomatic**. This suggests the potential for substantial viral shedding in presymptomatic cases. No correlation was observed between cycle threshold values and time from symptom onset.[37]

- Kim SE et al. noted very high viral loads (cycle threshold values <20) in specimens from 2 presymptomatic patients two days before symptom onset.[14]

- Zhou R et al. noted significantly higher viral load in nasopharyngeal specimens from presymptomatic patients (median cycle threshold value: 34.5 [IQR 32.2-37.0]) than those from asymptomatic patients (median cycle threshold value: 39.0 [IQR 37.5-39.5]).[12]

MODELLING AND STATISTICAL ANALYSIS

We found a modelling study which estimated that **infectiousness started from 2.3 days (95% CI: 0.8-3.0 days) before symptom onset and peaked at 0.7 days** (95% CI: 2.0 days before symptom onset to 0.2 days after onset). In addition, a number of authors have compared the incubation period with the serial interval of COVID-19. The serial interval is the time from onset of symptoms in one case to the time of symptom onset in the case(s) they infect. When the serial interval is shorter than the incubation period, some transmission is likely to have occurred in the incubation period.

- He X et al. assessed viral RNA load from 414 throat swabs of 94 patients from symptom onset up to 32 days after onset. Viral load based on RT-PCR was observed to be high soon after symptom onset and then declined. The authors then identified 77 transmission pairs from publicly available international sources. Using a mean incubation period of 5.2 days, the serial interval was estimated to have a median of 5.2 days (95% CI: 4.1-6.4 days), with 7.6% having negative serial intervals (which occur when the secondary case's symptom onset precedes that of the primary case). The estimated proportion of presymptomatic transmission was 44% (95% CI: 25-69%).[53]

- From 22 transmission pairs out of 100 confirmed cases in Taiwan, Cheng HY et al. estimated a median incubation period of 4.1 days (95% credible interval, 0.4-15.8) and a median serial interval of 4.1 days (95% credible interval, 0.1-27.8).[42]

- Analyzing published data of 18 transmission pairs with onset dates clearly defined in published articles, Nishiura H et al. estimated a median serial interval of 4.6 days (95% CrI: 3.5-5.9), which was shorter than a mean incubation of approximately 5 days from other published sources.[54]

- Analyzing 16 cases in four transmission generations, Böhmer MM et al. estimated a median incubation period of 4.0 days (IQR 2.3-4.3) and a median serial interval of 4.0 days (IQR 3.0-5.0).[41]

- Assuming a single source of infection for each household, Wu J et al. analyzed 48 secondary cases from index cases in 35 households in Zhuhai, China and estimated a median incubation period of 4.3 days (95% CI: 3.4-5.3) and a serial interval of 5.1 days (95% CI: 4.3-6.2).[25]

- From a cluster of seven people (1 teenager, 6 young adults) infected by a 22 year-old in Hefei, China, Huang L et al. estimated a median incubation period of 2 days (range 1-4) and a median serial interval of 1 day (range 0-4).[46]

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Ontario

This is **Exhibit "EE"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

Public Health Ontario | Santé publique Ontario

SYNTHESIS

09/14/2020

Wearing Masks in Public and COVID-19 – What We Know So Far

Introduction

"What We Know So Far" documents are intended to provide an overview of some of the published and unpublished reports related to emerging issues with respect to Coronavirus Disease 2019 (COVID-19). The reports are found through ongoing scanning of the published literature and scientific grey literature (e.g., ProMed, CIDRAP, Johns Hopkins Situation Reports), as well as media reports. For this report, library information specialists at Public Health Ontario searched Ovid MEDLINE, Embase, PsycINFO, EBSCOhost, CINAHL, and Scopus from January 1, 2000 to August 31, 2020 (search strategy available upon request). It is recognized that there may be additional information not captured in this document. As this is a rapidly evolving outbreak, the information will only be current as of the date the document was written.

Key Points

- Public mask-wearing is **likely beneficial as source control** when worn by persons shedding infectious SARS-CoV-2 virus.
- **Mandatory public mask policies** have been associated with a decrease in new COVID-19 cases compared to regions without such policies.
- **Studies evaluating masking in children are limited and have demonstrated variable results** with respect to their effectiveness for source control. However, studies have consistently shown lower adherence, especially in younger children.
- Masking to **protect the wearer is unlikely to be effective in non-healthcare settings**. Existing evidence demonstrates that wearing a mask within households after an illness begins is not effective at preventing secondary respiratory infections.
- There is variability in the effectiveness of homemade and cloth masks. Some materials adequately filter the expulsion of viral droplets from the wearer making them theoretically suitable for **source control**.
- There are theoretical risks of harms from public mask use including self-contamination from improper use and facial dermatitis or discomfort. Children may experience more discomfort from wearing a mask compared to adults. Though there are studies that observe subtle physiologic changes caused by N95 use, there is currently **no evidence that surgical or cloth masks exacerbate respiratory diseases**.

Background

Masks have two potential functions. They may protect the wearer of the mask from exposure (personal protective equipment), or protect individuals from exposure to respiratory aerosols/droplets from the mask wearer, referred to as source control. The use of masks for the general public has been recommended as one of several COVID-19 pandemic mitigation strategies. The Canadian and Ontario governments are currently recommending non-medical face masks or homemade face coverings to be worn by the public when physical distancing cannot be maintained.[1,2] The World Health Organization revised their guidance on June 5, 2020 that "governments should encourage the general public to wear masks in specific situations and settings as part of a comprehensive approach to suppress SARS-CoV-2 transmission".[3,4] These recommendations have been made largely due to the increasing recognition of the importance of pre-symptomatic and asymptomatic transmission and the potential benefit for source control.[5,6] As part of Ontario's school re-opening plans, masks are recommended for children in junior kindergarten (JK) to grade 3 and mandatory for grades 4-12.[7] This *What We Know So Far* was updated on September 8, 2020 and reviews the available evidence for wearing a mask to prevent respiratory viral infections in non-healthcare settings including evidence surrounding homemade masks and evidence specific to children.

Mask-wearing in Non-Healthcare Settings - COVID-19 Studies

No randomized trials have been published so far on mask use by the public during the COVID-19 pandemic. However, observational and ecological studies suggest that mask-wearing provides source control and public mask-wearing mandates have led to reduced daily COVID-19 growth rates.[8-11]

- An ecological report from Germany released in June 2020 utilized Synthetic Control Methodology (SCM) to evaluate the impact of mandatory mask use on public transportation and in sales shops in the city of Jena.[10] On March 30th, the local government in Jena announced that masks would be mandatory starting April 6th, 2020. Masks became mandatory in the rest of Germany between April 20 and 29th, 2020. SCM involves identifying synthetic control groups which were following the same COVID-19 trend as Jena prior to April 6th. The weighted average of this synthetic control group of regions where masks did not become mandatory on April 6th were used as a counterfactual to evaluate the causal effect of mandatory masking. The authors concluded that mandatory masking reduced the daily growth rate of COVID-19 in Jena by 40%. It is not known from this ecological analysis the extent and quality of uptake of mask wearing, the type of masks worn, and if the demonstrated benefit is related to source control, protecting the wearer, or a combination thereof. It is possible there were other public health measures taken in Jena at this time that confound this finding (i.e. physical distancing), and the impact of behavioural change due to mandatory masking was not addressed. However, the authors do note that the timing of the introduction of face masks was not affected by other overlapping public health measures as a general "lock down" had been in place for two weeks. This report has not been peer-reviewed.[10]
- Lyu et al. 2020 performed an observational event analysis, similar to a difference-in-differences design, which provides evidence that states in the United States (US) mandating face mask use in public had a greater decline in daily COVID-19 cases compared to states that did not issue mandates.[11] Sixteen regions issued mask mandates between April 8th and May 15th. Compared to states without mandates, daily COVID-19 growth rates significantly declined by 0.9%, 1.1%,

1.4%, 1.7%, and 2.0% at 1-5, 6-10, 11-15, 16-20, and 21 or more days following the state mandate, respectively. In another analysis, the authors evaluated the impact of employee-only mandates (no public community requirement) and did not find a significant impact from those more targeted mask mandates. While the authors attempted to adjust for other public health measures in their models, residual confounding is possible. This study was unable to assess masking adherence by the public, but provides supporting evidence that state-level mask mandates may have been effective in reducing COVID-19 case numbers.[11]

- Xu et al. 2020 conducted an interrupted time series evaluating trends in new COVID-19 cases and deaths in the US.[12] The authors report slope changes which they attribute to stay-at-home orders on March 23rd (slope change: -0.18, 95% CI: -0.22 to -0.14) and face mask recommendations by the US Centers for Disease Control and Prevention (CDC) on April 3rd (slope change: -0.10, 95% CI: -0.18 to -0.08). Two delayed slope changes were also identified in new deaths on April 9th (slope change: -0.17, 95% CI: -0.21 to -0.14) and April 19th (slope change: -0.13, 95% CI: -0.25 to -0.07). There is a high risk of residual confounding in this study. The attribution of the initial slope change to these two policy interventions is very close together and it is unlikely that the CDC recommendation on April 3rd would result in an immediate change in incidence of new cases. Furthermore, this observational study was unable to account for the multiple simultaneous public health interventions occurring.[12]
- Cheng et al. 2020 report COVID-19 data from Hong Kong with 11 clusters (113 cases) from "mask-off" settings (dining, karaoke, fitness clubs) compared to 3 clusters (11 cases) from "mask-on" settings in workplaces (p=0.036).[13] However, this study cannot differentiate if the differences are related to masks versus physical distancing and increased expulsion of droplets (i.e., singing, exercising) in these settings. They also describe COVID-19 epidemiology in Hong Kong, which had a daily mask compliance of >95%, compared to representative countries in North America, Europe, and Asia and describe significantly lower COVID-19 incidence in Hong Kong. These findings also have potential confounding from broad public health measures of strict quarantine and physical distancing guidance early on in the pandemic in Hong Kong.[13]
- Wang et al. 2020 conducted a retrospective cohort study of household contacts of COVID-19 cases for predictors of secondary transmission in Beijing, China.[9] The overall secondary attack rate was 23% and they found that if it was reported that one or more family members (primary case or family contacts) wore face masks **prior to the development of symptoms**, then there was a 79% reduction in transmission (OR=0.21, 95%CI: 0.06-0.79). Of note in this study was no protective effect of mask-wearing by household contacts if initiated after symptom-onset in the primary case. The findings are associated with the inherent limitations with telephone interview including recall bias.[9]
- Hong et al. 2020 conducted contact tracing of 197 residents in Taizhou, China exposed to 41 presymptomatic COVID-19 positive cases who returned from Wuhan in January 2020.[8] The secondary attack rates from 28 mask-wearing presymptomatic cases was 8.1% (10/123) compared to 19.0% (14/74) from 13 non-mask-wearing presymptomatic cases (p<0.001).[8]
- A contact investigation of two hairstylists with respiratory symptoms and confirmed COVID-19 who wore cloth face masks during close contact with 139 clients did not result in any secondary transmissions (67 of whom tested negative for SARS-CoV-2 by RT-PCR).[14]
- Two case reports describe no in-flight transmission aboard an airplane with symptomatic COVID-19 cases who wore masks during the flight.[15,16]
- Chou et al. 2020 are conducting a living rapid systematic review on the effectiveness of mask use in both healthcare and community settings.[17] As of their most recent update on September

1st, 2020, they have identified one study by Wang et al., discussed above. Updates are expected every 1-2 months.[17]

Mask-wearing as Source Control – Non-COVID-19 Studies

Studies to date have found that the use of medical masks may reduce the amount of aerosol/droplet shedding of some bacteria and viruses from symptomatic individuals, but have inconsistently demonstrated a reduction in secondary cases in household or other close contact studies.

- MacIntyre et al. 2020 re-analyzed data from a previous clinical trial using only seasonal coronavirus data.[18] They identified 10 index cases in the mask group and 9 controls. There was no secondary transmission in either group, although 5/9 control index cases reported wearing a mask.[18]
- Barasheed et al. 2014 conducted a pilot study randomizing tents at the Hajj to 'supervised mask use' (mask use 76%) or 'no supervised mask use' (mask use 12%) for both individuals with influenza-like illness (ILI) and their contacts who slept within 2 meters.[19] They found less ILI among contacts in the mask group (31% versus 53%, p=0.04); however, there were no differences in laboratory-confirmed respiratory virus detections.[19]
- MacIntyre et al. 2016 performed a cluster randomized controlled trial (RCT) of surgical masks for patients with ILI (n=123) compared to controls (n=122) evaluating the risk of secondary cases in household contacts.[20] There were no statistically significant differences in clinical respiratory illness (relative risk (RR) 0.61, 95% CI 0.18 to 2.13), ILI (RR 0.32, 95% CI 0.03 to 3.13) or laboratory-confirmed viral infections (RR 0.97, 95% CI 0.06 to 15.54). As one third of controls wore masks, the authors conducted a post-hoc per protocol analysis and there was a statistically significant protective effect in clinical respiratory infections (RR 0.22, 95% CI 0.06 to 0.86), but not laboratory-confirmed respiratory infections.[20]
- Stockwell et al. 2018 found that mask-wearing significantly reduced the release of *Pseudomonas aeruginosa* aerosols during coughing in people with cystic fibrosis compared to uncovered coughing.[21] The results were similar for surgical masks and N95 respirators.[21]
- Milton et al. 2013 examined exhaled breath samples from symptomatic people infected with seasonal influenza viruses and found that surgical masks reduced the amount of viral aerosol shedding by 3.4 fold overall, ranging from 2.8 to 25 fold depending on particle size.[22]
- Dharmadhikari et al. 2012 studied patients with multidrug-resistant tuberculosis and demonstrated that surgical mask-wearing significantly reduced transmission in experimental conditions.[23]
- Leung et al. 2020 studied surgical mask-wearing in 246 symptomatic individuals with influenza, rhinovirus, and seasonal coronaviruses.[24] They found a significant reduction in virus by polymerase chain reaction testing of exhaled breath droplets and aerosols in the 124 individuals randomized to wearing masks (4/10 versus 0/11, p=0.04). This study did not confirm if the quantity of virus was infectious.[24]

Evidence for Mask Use in Children

There have been no studies evaluating mask use for COVID-19 source control in children. However, there have been 4 cluster RCTs evaluating mask use for influenza prevention in the community that included children as the index cases. Two studies found a possible protective effect for masking and hand hygiene (HH) together, particularly if the intervention was implemented within 36 hours of symptom-onset in the index case,[25,26] while two studies found no apparent protective effect.[27,28]

However, in all studies, mask-adherence when reported was generally poor and the effects may have been related to adults in the study wearing masks, children wearing masks for source control, or a combination thereof. The one study which evaluated masking alone for source control (33% of the index cases were children) did not demonstrate any benefit.[27] One observational study in Japan found a small reduction in influenza infections from self-reported mask-wearing in schools.[29]

- Canini et al. 2010 performed a cluster RCT of masking the index patient for five days after testing positive for influenza on a rapid test to prevent secondary household transmission. ILI was reported in 16.2% of contacts where the index case was masked, and 15.8% when the index case was not masked; there were no significant differences between surgical mask and control groups. This study included 35 (33%) children <15 years as the index case. The analysis was not stratified by age; however, children were significantly more likely to report mask discomfort (i.e., reported feeling pain), compared to adults (3/12 [25%] vs. 1/39 [2.6%], p=0.036).[27]
- Suess et al. 2012 conducted a cluster RCT comparing masking, masking + HH, or control in 84 households, including index cases, with influenza infection in the 2009/10 and 2010/11 seasons.[25] There was no significant effect from either intervention in the primary analysis. Almost all index cases were children <14 years (81/84 [96%]). The average daily adherence to masking by index patients ranged from 40-60% and decreased over time. There was a potential effect observed in the subgroup that implemented masking + HH within 36 hours of symptom-onset of the index case (adjusted odds ratio (OR): 0.16, 95% CI: 0.03-0.92).[25]
- Simmerman et al. 2011 performed a cluster RCT of 442 households in Thailand during the influenza H1N1 pandemic comparing HH, HH + masking with surgical masks, or control to prevent influenza transmission in households with an influenza-positive child.[28] 50% (221/442) of the index patients were <6 years of age. There were no differences in clinical or laboratory-confirmed influenza in either intervention arm (HH + mask compared to control; OR: 1.16; 95% CI: 0.74-1.82). Adults wore their masks for a median of 153 (IQR: 40-411) minutes per day compared to 35 (IQR: 4-197) minutes in the child index cases.[28]
- Larson et al. 2010 conducted a cluster RCT in 509 households and 2,788 individuals (47.3% children ≤ 17 years) comparing health education (HE), HE + HH, or HE + HH + masking with surgical masks on incidence and secondary transmission of upper respiratory tract infections and influenza.[26] There was a significant decrease in secondary respiratory infections in the HE + HH + mask group compared to HE alone (OR: 0.82, 95% CI: 0.70-0.97). This study did not evaluate a masking-only group and while index cases were encouraged to wear masks in the masking group, adherence to mask use was reported as poor by the authors.[26]
- Uchida et al. 2017 conducted an observational questionnaire-based study with 10,524 school-aged children in Japan, of whom 5,474 (52.0%) reported wearing masks.[29] In the multivariable logistic regression model, wearing a mask was associated with reduced risk of influenza infection (OR: 0.86; 95% CI: 0.78-0.95). 21.5% of non-mask-wearing children in grades 4-6 were diagnosed with influenza compared to 18.9% of mask-wearing children (relative effectiveness 12.0%, absolute risk reduction 2.6%). 21.3% of non-mask-wearing children in grades 1-3 were diagnosed with influenza, compared to 20.2% of mask-wearing children (relative effectiveness 5.3%, absolute risk reduction 1.1%). No statistical analysis was performed on the subgroups by age.[29]
- Chen et al. 2020 conducted a survey of 3,649 school-aged children 6-13 years of age about mask use.[30] 51.6% reported good mask-wearing behaviour, with older children (grades 5-6 compared to grades 1-2; OR 1.21, 95% CI; 1.03-1.43), and parental educational level, being associated with better reported mask-wearing behaviour.[30]

- Allison et al. 2010 conducted a survey of teachers after distributing masks to both teachers and students for 4 weeks.[31] Teachers reported that 39% of them thought mask use was not disruptive and 35% reported they would use masks again the following winter. However, 97% reported they would use masks during a pandemic. By direct observation only 30% of students wore masks in week 1 of the study, which decreased to 15% in week 2.[31]
- Stebbins et al. 2009 conducted a parent and teacher survey on nonpharmaceutical interventions to prevent influenza in schools.[32] Student mask-wearing was among the lowest acceptable interventions by both parents and teachers.[32]
- Van der Sande et al. 2008, discussed further in the next section, compared homemade tea cloth masks, surgical masks, and FFP-2 (European equivalent of N95 respirators) in 28 healthy adult volunteers and 11 children between the ages of 5-11 years performing various physical maneuvers and measured quantitative differences in particles with a Portacount®.[33] There were no differences in median protection factors between adults and children.[33]

Protective Effects to the Mask-wearer in Non-Healthcare Settings - Non-COVID-19 Viral Respiratory Infections

Randomized Trials

There have been several cluster randomized studies on the use of medical masks outside of the hospital setting. These studies have evaluated the effectiveness of masking household members and individuals in other confined spaces (e.g. university residences, airplanes) to prevent acquisition of respiratory infections. In the majority of studies, no significant benefit from wearing masks was identified. Studies that demonstrated a benefit were associated with enhanced hand hygiene measures. No RCTs evaluating the effectiveness of mask use by the public to decrease COVID-19 infections have been completed, however there is a trial in Denmark under way (NCT04337541).[34]

- Dugre et al. 2020 performed an umbrella systematic review of masks in healthcare workers and the public.[35] They identified 11 systematic reviews, with 18 RCTs, of which 12 were in the community. In their meta-analysis, mask-wearing by the public did not reduce clinical respiratory infection (RR=1.06, 95% CI; 0.82-1.36; I^2=0%) or confirmed influenza or other viral respiratory infection.[35] The authors pooled the two studies below by Aiello from 2010 and 2012 and identified a significant protective effect on mask-wearing in university dormitories for ILI (RR=0.83, 95% CI; 0.69-0.99; I^2=0%; NNT=24).[36,37]
- Aggarwal et al. 2020 pooled controlled trials and did not identify a significant effect for either mask use alone versus control (5 studies, pooled effect size (pES) -0.17, 95%CI -0.43 to 0.10) or mask use with HH versus control (6 studies, pES -0.09, 95%CI -0.58 to 0.40), in reducing ILI in household and university settings.[38]
- Aiello et al. 2012 conducted a cluster RCT in university residents comparing three arms: HH + masking, masking alone, or control. They found no effect in the primary analysis of ILI or laboratory-confirmed respiratory infections. However, there was a significant effect on ILI in weeks 3-6 of the study in the mask + HH arm (RR = 0.25, 95% CI, 0.07 to 0.87), but not in the mask-only arm, suggesting the effect may have been due to HH.[37]
- Aiello et al. 2010 performed a cluster RCT in university residence halls with 3 arms; masking with surgical masks, masking + HH, or no intervention. In the primary adjusted analysis there were no

significant differences in the mask only group (relative risk (RR) 0.90, 95% confidence interval (CI) 0.77-1.05) or mask + HH group (RR 0.87, 95% CI 0.73-1.02).[36]

- Cowling et al. 2009 performed a cluster RCT of 259 households with confirmed influenza patients.[39] Households (≥3 people) were randomized to either HE (control), HH, or HH + masking with surgical masks. The study included 189 (73%) index cases <16 years. There was no statistically significant difference in either laboratory-confirmed or clinical influenza infection between the 3 groups. In a post-hoc analysis limited to those that applied the intervention within 36 hours of symptom-onset in the index case, mask + HH reduced laboratory-confirmed influenza infections (OR: 0.33, 95% CI; 0.13-0.87), but not clinically-defined influenza. Self-reported mask adherence + HH for index cases and contacts was 49% and 26%, respectively. The authors conclude that if applied early, masks + HH for household contacts of influenza-infected individuals may be effective.[39]
- MacIntyre et al. 2009 performed a cluster RCT of adult household members masking after a child was diagnosed with a respiratory illness. They compared surgical mask, N95 respirator, or control. There were no significant differences between either type of mask and control; however, mask adherence was low.[40]

Non-randomized Studies

Systematic reviews and meta-analyses of observational studies for non-COVID infections have found protective effects from mask-wearing. In contrast to the largely negative randomized trials above, the results of these studies should be interpreted cautiously considering the substantial biases present from the original studies used in these meta-analyses.

- Liang et al. 2020 performed a systematic review and meta-analysis of mask effectiveness. Of the 21 identified studies for inclusion, 8 were in non-healthcare workers.[41] The pooled results of these 8 studies published from 2004-2014 showed a significant protective effect from mask-wearing (OR: 0.53; 95% CI; 0.36-0.79, I^2=45%). However, a number of trials were not included and the observed effect was predominately driven by observational studies (not RCTs).[41]
- Chu et al performed a systematic review and meta-analysis utilizing observational data from Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and COVID-19 health-care and non-health care studies to evaluate the protective effects of physical distancing, mask use, and eye protection.[42] Overall, mask use (non-medical, medical or respirator) was effective (unadjusted studies OR 0.34, 95%CI 0.26-0.45; adjusted studies OR 0.15, 95%CI 0.07-0.34); however, from the three included non-healthcare settings (all patients with SARS) masks were significantly less protective compared to healthcare settings (OR 0.56, 95%CI 0.40-0.79, $p_{intereraction}$=0.049). The applicability of these studies to non-healthcare transmission of COVID-19 are questionable.[42]
- Saunders-Hastings et al. 2017 conducted a systematic review and meta-analysis on the effect of personal protective measures on pandemic influenza transmission.[43] The meta-analysis found regular HH provided a significant protective effect against pandemic viral transmission (OR = 0.62; 95% CI 0.52–0.73), but the effect of facemask use was not statistically significant (OR = 0.53; 95% CI 0.16–1.71).[43]
- There is a body of literature on wearing masks at mass gatherings (e.g. Hajj). Barasheed et al. 2016 performed a systematic review of 25 studies.[44] The studies were heterogeneous and generally of poor quality; however, the authors pooled results from 13 studies of masking involving 7,652 participants and found a small but significant protective effect against respiratory infections (RR 0.89 95% CI 0.84-0.94).[44]

- Zhang et al. 2013 conducted an observational study that evaluated the risk of influenza pH1N1 on two flights, after several passengers developed infections.[45] They found that on one flight from New York to Hong Kong there were 9 infections in passengers compared to 32 asymptomatic controls. None of the infected passengers wore masks compared to 15 (47%) of the controls who did wear masks. The index case was never identified. The authors concluded that wearing a mask on this flight was potentially protective.[45]

Homemade and Cloth Masks

Given the challenges in maintaining personal protective equipment supply during the COVID-19 pandemic, the use of homemade and/or cloth masks is the recommended mask type for use in non-healthcare settings. Broadly speaking, there are two types of studies on the effectiveness of cloth masks: studies that evaluate filter efficiency in a laboratory setting, and studies that evaluate infection risk to the wearer and those around them. There are more of the former studies which generally agree that at least some filtration occurs under certain conditions; the latter have observed some evidence for reduction of viral respiratory transmission at the population level, although have not proven such masks effective at an individual level. Overall, the evidence suggests there is variability in the effectiveness of cloth masks and that they are generally inferior to medical masks. One study in a healthcare setting demonstrated that cloth masks were associated with an increased risk of infection and they should not be used to protect healthcare workers.[46] However, the body of evidence supports that certain cloth materials provide sufficient filtration to be a suitable option for source control in non-healthcare settings. With respect to the materials used in cloth masks, a few studies looked at filtration efficiency in a lab setting, and generally agreed that cotton materials with high thread count were more efficient than other materials. There was some variability in findings of filtration efficiency with respect to layered designs and combining materials. Adding electrostatic charge was also noted to improve filtration efficiency.

- Ho et al. 2020 compared a 3-layer 100% cotton mask versus surgical mask and found 86.4% and 99.9% filtration efficiency, respectively.[47] They recruited 211 infected adult volunteers (205 influenza, 6 suspected COVID-19) and compared particle concentrations without masks, with medical masks, and with cotton masks. Both surgical and cotton masks significantly reduced ($p=0.03$) filtered particles, compared to no mask, with no significant differences between mask types.[47]
- Ma et al. 2020 conducted an experiment, using an avian influenza virus, on the comparable efficiency between N95, surgical masks, and homemade masks (made from 4 layers of “kitchen paper” plus 1 layer of polyester cloth) to block nebulizer-produced aerosols.[48] They found that the masks blocked 99.9%, 97.1%, and 95.2% of aerosols, respectively.[48]
- Davies et al. 2013 in an experimental study found that masks made from 100% cotton t-shirts had about 50% the median-fit factor of surgical masks.[49] Both masks blocked microorganisms expelled; however, surgical masks were three times more effective.[49]
- Dato et al. 2006 fashioned a nine-ply (one outer layer and eight inner layers) face mask out of heavy-weight 100% cotton T-shirt material, and achieved a maximum fit factor of 67 using quantitative measurements (a Portacount Fit Tester), with minimal discomfort or difficulty breathing reported in the three test subjects.[50] Note that National Institute for Occupational Safety and Health (NIOSH)-approved N95 respirators are required to have a fit factor of 100.[50]
- Rengasamy et al. 2010 similarly found in experimental conditions that cloth masks and various fabric materials were much less efficient than N95 respirators at filtering various size aerosols.[51] Sodium chloride (NaCl) aerosol penetration tests were run at face velocities of 5.5 and 16.5 cm/s

flow rates, using a NIOSH particulate respirator certification method for polydisperse (various size) NaCl aerosol and a TSI 3160 Fractional Efficiency Tester for monodisperse (specific size) NaCl aerosol. Percentage penetration (ratio of downstream to upstream concentration) for cloth masks and fabric ranged from 40-90% for polydisperse aerosols, compared to N95 penetrations of 0.12% and <5% at the lower and higher velocities, respectively. For monodisperse aerosols, penetration varied by particle size and fabric type in the 20-1000 nm range. Certain fabrics (e.g., towels and scarves) had slightly lower penetration (around 20-80% for towels, increasing with particle diameter), which was noted by the authors to be comparable to other studies of surgical mask penetration levels (measured in cited studies ranging from 51-89%). They conclude that fabric materials provide minimal respiratory protection to the wearer from aerosol-sized particles, but that "the use of improvised fabric materials may be of some value compared to no protection at all when respirators are not available."[51]

- MacIntyre et al. 2015 conducted a cluster RCT (N=1,607) on the effectiveness of cloth or surgical masks, compared to routine practices (personal protective equipment as needed), in hospital healthcare workers.[46] The primary outcomes were rates of ILI or laboratory-confirmed respiratory viral infection. Infection rates were highest in the cloth mask group, with an RR for ILI of 13 compared to the medical mask arm, an RR for ILI of 6.6 compared to the control arm, and an RR for laboratory-confirmed virus of 1.7 compared to the medical mask group. Penetration of particles in cloth masks was 97%, compared to 44% in the medical masks.[46]
- Van der Sande et al. 2008 compared homemade tea cloth masks, surgical masks, and FFP-2 (European equivalent of N95 respirators) in healthy volunteers performing various physical maneuvers and measured quantitative differences in particles with a Portacount®.[33] They calculated median protection factors (or PFs, the ratio of particle concentrations sized 0.02-1 µm outside to inside the mask) of 2.2-3.2 for cloth masks, 4.1-5.3 for surgical masks, and 66-113 for FFP-2 respirators among the adult volunteers. Marginal protection was seen for all mask types when testing for reduction in outgoing transmission of respiratory particles.[33]
- Konda et al. 2020 evaluated filtration efficiency for particle sizes in the 10nm to 10µm range for 15 different cloth types (e.g. cotton, silk, flannel, etc.).[52] These were evaluated in different configurations (e.g. layers, combinations, and with simulated "gaps" in seal as may be expected in real-world use), and compared to N95 and surgical masks, using an aerosol generator. They observed that combinations of materials (e.g. high threads-per-inch cotton along with silk, chiffon, or flannel) filtered particles across the tested size spectrum (<300nm-6um), and that was likely due to the combined effects of electrostatic and physical filtering, with efficiencies that were generally >80%. They also noted a significant drop in filter efficiency with simulated gaps, 60% drop in the >300 nm range, and this was observed for all materials including N95 and surgical masks.[52]
- Zhao et al. 2020 evaluated filtration efficiency for various common household materials (e.g. cotton, silk, nylon), as well as materials used in N95 and surgical masks (i.e. polypropylene).[53] Filtration efficiency for polypropylene in N95 masks was >95%, whereas for most other materials (including polypropylene from surgical masks) ranged from 5-30%. The authors noted that the testing did not account for leakage that would be expected in real-world settings, which would reduce efficiency further.[53]
- Lustig et al. 2020 evaluated filtration efficiency using simulated cough/sneeze-generated aerosols comprised of fluorescent aqueous droplets (intended to simulate viruses), testing over 70 different common fabric combinations.[54] Combinations of materials with hydrophilic, hydrophobic, and absorbent layers were most efficient, and were comparable to materials in N95 respirators in this laboratory setting.[54]

- Zangmeister et al. 2020 evaluated 32 different cloth materials and combinations of materials using NaCl aerosols of diameters of 50-825nm, and found that 3 of 5 top performing materials were high thread-count cottons.[55]

Risks Associated with Wearing Masks

Mask use by the general public could be associated with a theoretical elevated risk of COVID-19 through decreased physical distancing and self-contamination. The external surface of the mask may become contaminated and touching one's face is a common practice.[56] Continuous mask use may be associated with facial skin lesions, irritant dermatitis, impaired vision in those wearing glasses, or worsening acne.[4,57,58] One study observed physiologic respiratory changes from the use of N95 respirators in healthcare workers (with prolonged use), these finding were subtle and not considered clinically relevant.[59] Another study in healthcare workers reported various subjective complaints (e.g. headache, impaired cognition); however, only skin effects (e.g. irritation, acne) were consistently noted.[60] The Canadian Thoracic Society position statement on mask use for the public states, "There is NO evidence that wearing a face mask will exacerbate (cause a 'flare up' of) an underlying lung condition."[61] Studies in children have identified low adherence to proper use in school settings.[30-32] No study has evaluated the impact of mask use on children's education quality. Further studies are needed on optimal methods for optimizing mask use in children.

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Ontario

This is **Exhibit "FF"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

Public Health Ontario | Santé publique Ontario

SYNOPSIS

02/02/2021

Review of "Rapid review on the characteristics of effective non-medical face masks in reducing the risk of SARS-CoV-2 transmission"

Article citation: Young K, Otten A. Rapid review on the characteristics of effective non-medical face masks in reducing the risk of SARS-CoV-2 transmission [Internet]. Ottawa, ON: Public Health Agency of Canada; 2021 [cited 2021 Jan 27]. Available upon request from: https://www.nccmt.ca/covid-19/covid-19-evidence-reviews/261

One-Minute Summary

- This rapid review examined the evidence on the characteristics and efficacy of non-medical masks in reducing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission.
- **Primary findings of the rapid review:**
  - Experimental simulation studies have found that non-medical masks were more effective for source control (i.e., preventing the spread of SARS-CoV-2 if worn by an infectious person) than preventing infections in the person wearing the mask.
  - Non-medical masks reduced the distance respiratory droplets travelled during indoor talking, coughing and sneezing.
  - The filtration efficiency of non-medical face masks (with variable designs and fabrics) ranged from less than 10% to more than 95% in 42 studies.
  - The efficacy of non-medical masks depended on: 1) filtration efficiency, 2) breathability, and 3) fit.
    - When non-medical masks were made from high quality fabrics consisting of multiple layers and snug fit, they reduced the expulsion of respiratory droplets, although to a lesser extent than medical masks.
- **The characteristics of non-medical masks that reduced the risk of spreading or contracting SARS-CoV-2 included:**
  - Tight-fitting, double-layer masks with different material types (e.g., combed cotton and polyester) or masks made from one type of material but with greater than 2 layers exhibited similar source reduction efficiencies as medical masks (>90%). Loose-fitting non-medical masks reduced filtration effectiveness by more than 50% in some studies.
  - Multiple-layer non-medical masks improved filtration efficiency, but masks with more than three layers reduced breathability.
  - Fabrics should be of high-quality and tightly woven, including hydrophobic fabrics (e.g., polyester, spunbound polypropylene, polyaramid); fabrics that can capture charged particles (e.g., polyester, silk); or fabrics with hydrophilic properties that increase comfort

and longevity (e.g., cotton). The filtration efficiencies of most household fabrics were higher for larger, low-velocity respiratory droplets.
    - A triple-layered mask made of a hydrophobic exterior, blended non-woven fabric middle, and hydrophilic interior was the ideal combination for source reduction and potential infection prevention.
- The authors stated that "The existing research on how effective non-medical masks are is of low quality and results will likely change with additional research".

Additional Information

- The authors included 54 primary research articles in their rapid review. Twenty-two studies investigated non-medical masks as source control and 37 studies investigated how non-medical masks can prevent infection. Studies used human volunteers (n=15), manikins (n=15), filter-holders (n=34) and animal models (n=1). Of note, filter holder studies use fabric samples mounted in place by a filter holder and do not take fit of a human face into account.
- Non-medical masks, whether homemade or manufactured, are not considered personal protective equipment since they do not undergo standardized testing. Non-medical masks are not recommended for use by healthcare professionals and those with an increased risk of infection where physical distancing cannot be maintained.
- **Fabrics and designs to avoid in non-medical face masks:**
    - Avoid using vacuum cleaner bags as fabric, as they may contain harmful ingredients and fibers.
    - Avoid loosely-folded face masks, bandana-style face masks, and single-layered neck gaiters, as they do not effectively block respiratory droplets.
    - Avoid respirators with an exhalation valve, as these masks are not effective for source control.
- **Limitations:**
    - The majority of included studies were experimental and used non-human models. None of the studies identified how effective specific types of non-medical masks are in real-world settings.
    - The types and composition of non-medical masks used in the included studies, along with variability in fit and methodologies, made comparisons among studies difficult.
    - Studies that examined filtration efficiency used a variety of methods that targeted a wide variety of droplet sizes (<1 to >5 µm in diameter) using artificial materials. This variability made it difficult to compare filtration efficiencies between studies.

PHO Reviewer's Comments

- The evidence comparing non-medical masks to medical grade masks is limited to experimental studies evaluating filtering efficiency and is not based on clinical or real-world settings. The clinical data on public mask-wearing has been reviewed separately.[1]
- The body of evidence supports mask-wearing in public as effective for source control with possible synergistic effects for infection prevention if both the source and contact are appropriately wearing well-fitted non-medical masks.
- Experimental data supports higher quality masks, such as 3-layer non-medical masks or medical grade masks, as providing superior filtering efficiency. By inference, this may reduce the potential for transmission.

- Variants of Concern (VOC) have emerged in Ontario which have been associated with increased transmissibility. At the time of posting no studies have evaluated the relative effectiveness of different mask types in mitigating transmission from SARS-CoV-2 VOCs.[2]

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1. Ontario Agency for Health Protection and Promotion (Public Health Ontario). Wearing masks in public and COVID-19 – what we know so far [Internet]. Toronto, ON: Queen's Printer for Ontario; 2020 [cited 2021 Feb 02]. Available from: https://www.publichealthontario.ca/-/media/documents/ncov/covid-wwksf/what-we-know-public-masks-apr-7-2020.pdf?la=en

2. Ontario Agency for Health Protection and Promotion (Public Health Ontario). COVID-19 UK variant VOC-202012/01 – what we know so far [Internet]. Toronto, ON: Queen's Printer for Ontario; 2020 [cited 2021 Feb 02]. Available from: https://www.publichealthontario.ca/-/media/documents/ncov/covid-wwksf/2020/12/what-we-know-uk-variant.pdf?la=en

Citation

Ontario Agency for Health Protection and Promotion (Public Health Ontario). Review of "Rapid review on the characteristics of effective non-medical face masks in reducing the risk of SARS-CoV-2 transmission". Toronto, ON: Queen's Printer for Ontario; 2021.

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Ontario

This is **Exhibit "GG"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

Mask use in the context of COVID-19

Interim guidance

1 December 2020

World Health Organization

This document, which is an update of the guidance published on 5 June 2020, includes new scientific evidence relevant to the use of masks for reducing the spread of SARS-CoV-2, the virus that causes COVID-19, and practical considerations. It contains updated evidence and guidance on the following:

- mask management;
- SARS-CoV-2 transmission;
- masking in health facilities in areas with community, cluster and sporadic transmission;
- mask use by the public in areas with community and cluster transmission;
- alternatives to non-medical masks for the public;
- exhalation valves on respirators and non-medical masks;
- mask use during vigorous intensity physical activity;
- essential parameters to be considered when manufacturing non-medical masks (Annex).

Key points

- The World Health Organization (WHO) advises the use of masks as part of a comprehensive package of prevention and control measures to limit the spread of SARS-CoV-2, the virus that causes COVID-19. A mask alone, even when it is used correctly, is insufficient to provide adequate protection or source control. Other infection prevention and control (IPC) measures include hand hygiene, physical distancing of at least 1 metre, avoidance of touching one's face, respiratory etiquette, adequate ventilation in indoor settings, testing, contact tracing, quarantine and isolation. Together these measures are critical to prevent human-to-human transmission of SARS-CoV-2.
- Depending on the type, masks can be used either for protection of healthy persons or to prevent onward transmission (source control).
- WHO continues to advise that anyone suspected or confirmed of having COVID-19 or awaiting viral laboratory test results should wear a medical mask when in the presence of others (this does not apply to those awaiting a test prior to travel).
- For any mask type, appropriate use, storage and cleaning or disposal are essential to ensure that they are as effective as possible and to avoid an increased transmission risk.

<u>Mask use in health care settings</u>

- WHO continues to recommend that health workers (1) providing care to suspected or confirmed COVID-19 patients wear the following types of mask/respirator in addition to other personal protective equipment that are part of standard, droplet and contact precautions:
  - medical mask in the absence of aerosol generating procedures (AGPs)
  - respirator, N95 or FFP2 or FFP3 standards, or equivalent in care settings for COVID-19 patients where AGPs are performed; these may be used by health workers when providing care to COVID-19 patients in other settings if they are widely available and if costs is not an issue.
- In areas of known or suspected community or cluster SARS-CoV-2 transmission WHO advises the following:
  - universal masking for all persons (staff, patients, visitors, service providers and others) within the health facility (including primary, secondary and tertiary care levels; outpatient care; and long-term care facilities)
  - wearing of masks by inpatients when physical distancing of at least 1 metre cannot be maintained or when patients are outside of their care areas.
- In areas of known or suspected sporadic SARS-CoV-2 transmission, health workers working in clinical areas where patients are present should continuously wear a medical mask. This is known as targeted continuous medical masking for health workers in clinical areas;
- Exhalation valves on respirators are discouraged as they bypass the filtration function for exhaled air by the wearer.

<u>Mask use in community settings</u>

- Decision makers should apply a risk-based approach when considering the use of masks for the general public.
- In areas of known or suspected community or cluster SARS-CoV-2 transmission:
  - WHO advises that the general public should wear a non-medical mask in indoor (e.g. shops, shared workplaces, schools - see Table 2 for details) or outdoor settings where physical distancing of at least 1 metre cannot be maintained.
  - If indoors, unless ventilation has been be assessed to be adequate[1], WHO advises that the general public should wear a non-medical mask, regardless of whether physical distancing of at least 1 metre can be maintained.

[1] For adequate ventilation refer to regional or national institutions or heating, refrigerating and air-conditioning societies enacting ventilation requirements. If not available or applicable, a recommended ventilation rate of 10 l/s/person should be met (except healthcare facilities which have specific requirements). For more information consult "Coronavirus (COVID-19) response

  - Individuals/people with higher risk of severe complications from COVID-19 (individuals ≥ 60 years old and those with underlying conditions such as cardiovascular disease or diabetes mellitus, chronic lung disease, cancer, cerebrovascular disease or immunosuppression) should wear medical masks when physical distancing of at least 1 metre cannot be maintained.
- In any transmission scenarios:
  - Caregivers or those sharing living space with people with suspected or confirmed COVID-19, regardless of symptoms, should wear a medical mask when in the same room.

Mask use in children (2)

- Children aged up to five years should not wear masks for source control.
- For children between six and 11 years of age, a risk-based approach should be applied to the decision to use a mask; factors to be considered in the risk-based approach include intensity of SARS-CoV-2 transmission, child's capacity to comply with the appropriate use of masks and availability of appropriate adult supervision, local social and cultural environment, and specific settings such as households with elderly relatives, or schools.
- Mask use in children and adolescents 12 years or older should follow the same principles as for adults.
- Special considerations are required for immunocompromised children or for paediatric patients with cystic fibrosis or certain other diseases (e.g., cancer), as well as for children of any age with developmental disorders, disabilities or other specific health conditions that might interfere with mask wearing.

Manufacturing of non-medical (fabric) masks (Annex)

- Homemade fabric masks of three-layer structure (based on the fabric used) are advised, with each layer providing a function: 1) an innermost layer of a hydrophilic material 2) an outermost layer made of hydrophobic material 3) a middle hydrophobic layer which has been shown to enhance filtration or retain droplets.
- Factory-made fabric masks should meet the minimum thresholds related to three essential parameters: filtration, breathability and fit.
- Exhalation valves are discouraged because they bypass the filtration function of the fabric mask rendering it unserviceable for source control.

Methodology for developing the guidance

Guidance and recommendations included in this document are based on published WHO guidelines (in particular the WHO Guidelines on infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care) (2) and ongoing evaluations of all available scientific evidence by the WHO ad hoc COVID-19 Infection Prevention and Control Guidance Development Group (COVID-19 IPC GDG) (see acknowledgement section for list of GDG members). During emergencies WHO publishes interim guidance, the development of which follows a transparent and robust process of evaluation of the available evidence on benefits and harms. This evidence is evaluated through expedited systematic reviews and expert consensus-building through weekly GDG consultations, facilitated by a methodologist and, when necessary, followed up by surveys. This process also considers, as much as possible, potential resource implications, values and preferences, feasibility, equity, and ethics. Draft guidance documents are reviewed by an external review panel of experts prior to publication.

Purpose of the guidance

This document provides guidance for decision makers, public health and IPC professionals, health care managers and health workers in health care settings (including long-term care and residential), for the public and for manufactures of non-medical masks (Annex). It will be revised as new evidence emerges.

WHO has also developed comprehensive guidance on IPC strategies for health care settings (3), long-term care facilities (LTCF) (4), and home care (5).

Background

The use of masks is part of a comprehensive package of prevention and control measures that can limit the spread of certain respiratory viral diseases, including COVID-19. Masks can be used for protection of healthy persons (worn to protect oneself when in contact with an infected individual) or for source control (worn by an infected individual to prevent onward transmission) or both.

However, the use of a mask alone, even when correctly used (see below), is insufficient to provide an adequate level of protection for an uninfected individual or prevent onward transmission from an infected individual (source control). Hand hygiene, physical distancing of at least 1 metre, respiratory etiquette, adequate ventilation in indoor settings, testing, contact tracing, quarantine, isolation and other infection prevention and control (IPC) measures are critical to prevent human-to-human transmission of SARS-CoV-2, whether or not masks are used (6).

Mask management

For any type of mask, appropriate use, storage and cleaning, or disposal are essential to ensure that they are as effective as possible and to avoid any increased risk of transmission. Adherence to correct mask management practices varies, reinforcing the need for appropriate messaging (7).

WHO provides the following guidance on the correct use of masks:

- Perform hand hygiene before putting on the mask.
- Inspect the mask for tears or holes, and do not use a damaged mask.
- Place the mask carefully, ensuring it covers the mouth and nose, adjust to the nose bridge and tie it securely to minimize any gaps between the face and the mask. If using ear loops, ensure these do not cross over as this widens the gap between the face and the mask.

resources from ASHRAE and others''
https://www.ashrae.org/technical-resources/resources

- Avoid touching the mask while wearing it. If the mask is accidently touched, perform hand hygiene.
- Remove the mask using the appropriate technique. Do not touch the front of the mask, but rather untie it from behind.
- Replace the mask as soon as it becomes damp with a new clean, dry mask.
- Either discard the mask or place it in a clean plastic resealable bag where it is kept until it can be washed and cleaned. Do not store the mask around the arm or wrist or pull it down to rest around the chin or neck.
- Perform hand hygiene immediately afterward discarding a mask.
- Do not re-use single-use mask.
- Discard single-use masks after each use and properly dispose of them immediately upon removal.
- Do not remove the mask to speak.
- Do not share your mask with others.
- Wash fabric masks in soap or detergent and preferably hot water (at least 60° Centigrade/140° Fahrenheit) at least once a day. If it is not possible to wash the masks in hot water, then wash the mask in soap/detergent and room temperature water, followed by boiling the mask for 1 minute.

Scientific evidence

Transmission of the SARS-CoV-2 virus

Knowledge about transmission of the SARS-CoV-2 virus is evolving continuously as new evidence accumulates. COVID-19 is primarily a respiratory disease, and the clinical spectrum can range from no symptoms to severe acute respiratory illness, sepsis with organ dysfunction and death.

According to available evidence, SARS-CoV-2 mainly spreads between people when an infected person is in close contact with another person. Transmissibility of the virus depends on the amount of viable virus being shed and expelled by a person, the type of contact they have with others, the setting and what IPC measures are in place. The virus can spread from an infected person's mouth or nose in small liquid particles when the person coughs, sneezes, sings, breathes heavily or talks. These liquid particles are different sizes, ranging from larger 'respiratory droplets' to smaller 'aerosols.' Close-range contact (typically within 1 metre) can result in inhalation of, or inoculation with, the virus through the mouth, nose or eyes (8-13).

There is limited evidence of transmission through fomites (objects or materials that may be contaminated with viable virus, such as utensils and furniture or in health care settings a stethoscope or thermometer) in the immediate environment around the infected person (14-17). Nonetheless, fomite transmission is considered a possible mode of transmission for SARS-CoV-2, given consistent finding of environmental contamination in the vicinity of people infected with SARS-CoV-2 and the fact that other coronaviruses and respiratory viruses can be transmitted this way (12).

Aerosol transmission can occur in specific situations in which procedures that generate aerosols are performed. The scientific community has been actively researching whether the SARS-CoV-2 virus might also spread through aerosol transmission in the absence of aerosol generating procedures (AGPs) (18, 19). Some studies that performed air sampling in clinical settings where AGPs were not performed found virus RNA, but others did not. The presence of viral RNA is not the same as replication- and infection-competent (viable) virus that could be transmissible and capable of sufficient inoculum to initiate invasive infection. A limited number of studies have isolated viable SARS-CoV-2 from air samples in the vicinity of COVID-19 patients (20, 21).

Outside of medical facilities, in addition to droplet and fomite transmission, aerosol transmission can occur in specific settings and circumstances, particularly in indoor, crowded and inadequately ventilated spaces, where infected persons spend long periods of time with others. Studies have suggested these can include restaurants, choir practices, fitness classes, nightclubs, offices and places of worship (12).

High quality research is required to address the knowledge gaps related to modes of transmission, infectious dose and settings in which transmission can be amplified. Currently, studies are underway to better understand the conditions in which aerosol transmission or superspreading events may occur.

Current evidence suggests that people infected with SARS-CoV-2 can transmit the virus whether they have symptoms or not. However, data from viral shedding studies suggest that infected individuals have highest viral loads just before or around the time they develop symptoms and during the first 5-7 days of illness (12). Among symptomatic patients, the duration of infectious virus shedding has been estimated at 8 days from the onset of symptoms (22-24) for patients with mild disease, and longer for severely ill patients (12). The period of infectiousness is shorter than the duration of detectable RNA shedding, which can last many weeks (17).

The incubation period for COVID-19, which is the time between exposure to the virus and symptom onset, is on average 5-6 days, but can be as long as 14 days (25, 26).

Pre-symptomatic transmission – from people who are infected and shedding virus but have not yet developed symptoms – can occur. Available data suggest that some people who have been exposed to the virus can test positive for SARS-CoV-2 via polymerase chain reaction (PCR) testing 1-3 days before they develop symptoms (27). People who develop symptoms appear to have high viral loads on or just prior to the day of symptom onset, relative to later on in their infection (28).

Asymptomatic transmission – transmission from people infected with SARS-CoV-2 who never develop symptoms – can occur. One systematic review of 79 studies found that 20% (17–25%) of people remained asymptomatic throughout the course of infection. (28). Another systematic review, which included 13 studies considered to be at low risk of bias, estimated that 17% of cases remain asymptomatic (14%–20%) (30). Viable virus has been isolated from specimens of pre-symptomatic and asymptomatic individuals, suggesting that people who do not have symptoms may be able to transmit the virus to others. (25, 29-37)

Studies suggest that asymptomatically infected individuals are less likely to transmit the virus than those who develop symptoms (29). A systematic review concluded that individuals who are asymptomatic are responsible for transmitting fewer infections than symptomatic and pre-symptomatic cases (38). One meta-analysis estimated that there is a 42% lower relative risk of asymptomatic transmission compared to symptomatic transmission (30).

Guidance on mask use in health care settings

Masks for use in health care settings

Medical masks are defined as surgical or procedure masks that are flat or pleated. They are affixed to the head with straps that go around the ears or head or both. Their performance characteristics are tested according to a set of standardized test methods (ASTM F2100, EN 14683, or equivalent) that aim to balance high filtration, adequate breathability and optionally, fluid penetration resistance (39, 40).

Filtering facepiece respirators (FFR), or respirators, offer a balance of filtration and breathability. However, whereas medical masks filter 3 micrometre droplets, respirators must filter more challenging 0.075 micrometre solid particles. European FFRs, according to standard EN 149, at FFP2 performance there is filtration of at least 94% solid NaCl particles and oil droplets. US N95 FFRs, according to NIOSH 42 CFR Part 84, filter at least 95% NaCl particles. Certified FFRs must also ensure unhindered breathing with maximum resistance during inhalation and exhalation. Another important difference between FFRs and other masks is the way filtration is tested. Medical mask filtration tests are performed on a cross-section of the masks, whereas FFRs are tested for filtration across the entire surface. Therefore, the layers of the filtration material and the FFR shape, which ensure the outer edges of the FFR seal around wearer's face, result in guaranteed filtration as claimed. Medical masks, by contrast, have an open shape and potentially leaking structure. Other FFR performance requirements include being within specified parameters for maximum CO_2 build up, total inward leakage and tensile strength of straps (41, 42).

A. Guidance on the use of medical masks and respirators to provide care to suspected or confirmed COVID-19 cases

Evidence on the use of mask in health care settings

Systematic reviews have reported that the use of N95/P2 respirators compared with the use of medical masks (see mask definitions, above) is not associated with statistically significant differences for the outcomes of health workers acquiring clinical respiratory illness, influenza-like illness (risk ratio 0.83, 95%CI 0.63-1.08) or laboratory-confirmed influenza (risk ratio 1.02, 95%CI 0.73-1.43); harms were poorly reported and limited to discomfort associated with lower compliance (43, 44). In many settings, preserving the supply of N95 respirators for high-risk, aerosol-generating procedures is an important consideration (45).

A systematic review of observational studies on the betacoronaviruses that cause severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and COVID-19 found that the use of face protection (including respirators and medical masks) is associated with reduced risk of infection among health workers. These studies suggested that N95 or similar respirators might be associated with greater reduction in risk than medical or 12–16-layer cotton masks. However, these studies had important limitations (recall bias, limited information about the situations when respirators were used and limited ability to measure exposures), and very few studies included in the review evaluated the transmission risk of COVID-19 (46). Most of the studies were conducted in settings in which AGPs were performed or other high-risk settings (e.g., intensive care units or where there was exposure to infected patients and health workers were not wearing adequate PPE).

WHO continues to evaluate the evidence on the effectiveness of the use of different masks and their potential harms, risks and disadvantages, as well as their combination with hand hygiene, physical distancing of at least 1 metre and other IPC measures.

Guidance

WHO's guidance on the type of respiratory protection to be worn by health workers providing care to COVID-19 patients is based on 1) WHO recommendations on IPC for epidemic- and pandemic-prone acute respiratory infections in health care (47); 2) updated systematic reviews of randomized controlled trials on the effectiveness of medical masks compared to that of respirators for reducing the risk of clinical respiratory illness, influenza-like illness (ILI) and laboratory-confirmed influenza or viral infections. WHO guidance in this area is aligned with guidelines of other professional organizations, including the European Society of Intensive Care Medicine and the Society of Critical Care Medicine, and the Infectious Diseases Society of America (48, 49).

The WHO COVID-19 IPC GDG considered all available evidence on the modes of transmission of SARS-CoV-2 and on the effectiveness of medical mask versus respirator use to protect health workers from infection and the potential for harms such as skin conditions or breathing difficulties.

Other considerations included availability of medical masks versus respirators, cost and procurement implications and equity of access by health workers across different settings.

The majority (71%) of the GDG members confirmed their support for previous recommendations issued by WHO on 5 June 2020:

1. In the absence of aerosol generating procedures (AGPs)[2], WHO recommends that health workers providing care to patients with suspected or confirmed COVID-19 should wear a medical mask (in addition to other PPE that are part of droplet and contact precautions).
2. In care settings for COVID-19 patients where AGPs are performed, WHO recommends that health workers should wear a respirator (N95 or FFP2 or FFP3 standard, or equivalent) in addition to other PPE that are part of airborne and contact precautions.

In general, health workers have strong preferences about having the highest perceived protection possible to prevent COVID-19 infection and therefore may place high value on the potential benefits of respirators in settings without AGPs. WHO recommends respirators primarily for settings where AGPs are performed; however, if health workers prefer them and they are sufficiently available and cost is not an issue, they could also be used during care for COVID-19 patients in other settings. For additional guidance on PPE, including PPE

[2] The WHO list of AGPs includes tracheal intubation, non-invasive ventilation, tracheotomy, cardiopulmonary resuscitation, manual ventilation before intubation, bronchoscopy, sputum induction using nebulized hypertonic saline, and dentistry and autopsy procedures.

beyond mask use by health workers, see WHO IPC guidance during health care when COVID-19 infection is suspected (3) and also WHO guidance on the rational use of PPE (45).

Exhalation valves on respirators are discouraged as they bypass the filtration function for exhaled air.

B. Guidance on the use of mask by health workers, caregivers and others based on transmission scenario

Definitions

Universal masking in health facilities is defined as the requirement for all persons (staff, patients, visitors, service providers and others) to wear a mask at all times except for when eating or drinking.

Targeted continuous medical mask use is defined as the practice of wearing a medical mask by all health workers and caregivers working in clinical areas during all routine activities throughout the entire shift.

Health workers are all people primarily engaged in actions with the primary intent of enhancing health. Examples are: nursing and midwifery professionals, doctors, cleaners, other staff who work in health facilities, social workers, and community health workers.

Evidence on universal masking in health care settings

In areas where there is community transmission or large-scale outbreaks of COVID-19, universal masking has been adopted in many hospitals to reduce the potential of transmission by health workers to patients, to other staff and anyone else entering the facility (50).

Two studies found that implementation of a universal masking policy in hospital systems was associated with decreased risk of healthcare-acquired SARS-CoV-2 infection. However, these studies had serious limitations: both were before-after studies describing a single example of a phenomenon before and after an event of interest, with no concurrent control group, and other infection control measures were not controlled for (51, 52). In addition, observed decreases in health worker infections occurred too quickly to be attributable to the universal masking policy.

Guidance

Although more research on universal masking in heath settings is needed, it is the expert opinion of the majority (79%) of WHO COVID-19 IPC GDG members that universal masking is advisable in geographic settings where there is known or suspected community or cluster transmission of the SARS-CoV-2 virus.

1. In areas of known or suspected community or cluster SARS-CoV-2 transmission, universal masking should be advised in all health facilities (see Table 1).

- All health workers, including community health workers and caregivers, should wear a medical mask at all times, for any activity (care of COVID-19 or non-COVID-19 patients) and in any common area (e.g., cafeteria, staff rooms).
- Other staff, visitors, outpatients and service providers should also wear a mask (medical or non-medical) at all times
- Inpatients are not required to wear a mask (medical or non-medical) unless physical distancing of at least 1 metre cannot be maintained (e.g., when being examined or visited at the bedside) or when outside of their care area (e.g., when being transported).
- Masks should be changed when they become soiled, wet or damaged or if the health worker/caregiver removes the mask (e.g., for eating or drinking or caring for a patient who requires droplet/contact precautions for reasons other than COVID-19).

2. In the context of known or suspected sporadic SARS-CoV-2 virus transmission, WHO provides the following guidance:

- Health workers, including community health workers and caregivers who work in clinical areas, should continuously wear a medical mask during routine activities throughout the entire shift, apart from when eating and drinking and changing their medical masks after caring for a patient who requires droplet/contact precautions for other reasons. In all cases, medical masks must be changed when wet, soiled, or damaged; used medical masks should be properly disposed of at the end of the shift; and new clean ones should be used for the next shift or when medical masks are changed.
- It is particularly important to adopt the continuous use of masks in potentially high transmission risk settings including triage, family physician/general practitioner offices; outpatient departments; emergency rooms; COVID-19 designated units; haematology, oncology and transplant units; and long-term health and residential facilities.
- Staff who do not work in clinical areas (e.g., administrative staff) do not need to wear a medical mask during routine activities if they have no exposure to patients.

Whether using masks for universal masking within health facilities or targeted continuous medical mask use throughout the entire shift, health workers should ensure the following:

- Medical mask use should be combined with other measures including frequent hand hygiene and physical distancing among health workers in shared and crowded places such as cafeterias, break rooms, and dressing rooms.
- The medical mask should be changed when wet, soiled, or damaged.
- The medical mask should not be touched to adjust it or if displaced from the face for any reason. If this happens, the mask should be safely removed and replaced, and hand hygiene performed.
- The medical mask (as well as other personal protective equipment) should be discarded and changed after caring for any patient who requires contact/droplet precautions for other pathogens, followed by hand hygiene.
- Under no circumstances should medical masks be shared between health workers or between others wearing them. Masks should be appropriately disposed of whenever removed and not reused.

- A particulate respirator at least as protective as a United States of America (US) National Institute for Occupational Safety and Health-certified N95, N99, US Food and Drug Administration surgical N95, European Union standard FFP2 or FFP3, or equivalent, should be worn in settings for COVID-19 patients where AGPs are performed (see WHO recommendations below). In these settings, this includes continuous use by health workers throughout the entire shift, when this policy is implemented.

Note: Decision makers may consider the transmission intensity in the catchment area of the health facility or community setting and the feasibility of implementing a universal masking policy compared to a policy based on assessed or presumed exposure risk. Decisions need to take into account procurement, sustainability and costs of the policy. When planning masks for all health workers, long-term availability of adequate medical masks (and when applicable, respirators) for all workers should be ensured, in particular for those providing care for patients with confirmed or suspected COVID-19. Proper use and adequate waste management should be ensured.

The potential harms and risks of mask and respirator use in the health facility setting include:

- contamination of the mask due to its manipulation by contaminated hands (53, 54);
- potential self-contamination that can occur if medical masks are not changed when wet, soiled or damaged; or by frequent touching/adjusting when worn for prolonged periods (55);
- possible development of facial skin lesions, irritant dermatitis or worsening acne, when used frequently for long hours (56-58);
- discomfort, facial temperature changes and headaches from mask wearing (44, 59, 60);
- false sense of security leading potentially to reduced adherence to well recognized preventive measures such as physical distancing and hand hygiene; and risk-taking behaviours (61-64);
- difficulty wearing a mask in hot and humid environments
- possible risk of stock depletion due to widespread use in the context of universal masking and targeted continuous mask use and consequent scarcity or unavailability for health workers caring for COVID 19 patients and during health care interactions with non-COVID-19 patients where medical masks or respirators might be required.

Alternatives to medical masks in health care settings

The WHO's disease commodity package (DCP) for COVID-19 recommends medical masks for health workers to be type II or higher (65). Type II medical masks provide a physical barrier to fluids and particulate materials and have bacterial filtration efficiency of ≥98% compared to Type I mask, which has bacterial filtration efficiency of ≥95% and lower fluid resistance (66) In case of stock outs of type II or higher medical masks, health workers should use a type I medical mask as an alternative. Other alternatives such as face shields or fabric masks should be carefully evaluated.

Face shields are designed to provide protection from splashes of biological fluid (particularly respiratory secretions), chemical agents and debris (67, 68) into the eyes. In the context of protection from SARS-CoV-2 transmission through respiratory droplets, face shields are used by health workers as personal protective equipment (PPE) for eye protection in combination with a medical mask or a respirator (69, 70) While a face shield may confer partial protection of the facial area against respiratory droplets, these and smaller droplets may come into contact with mucous membranes or with the eyes from the open gaps between the visor and the face (71,67).

Fabric masks are not regulated as protective masks or part of the PPE directive. They vary in quality and are not subject to mandatory testing or common standards and as such are not considered an appropriate alternative to medical masks for protection of health workers. One study that evaluated the use of cloth masks in a health care facility found that health care workers using 2 ply cotton cloth masks (a type of fabric mask) were at increased risk of influenza-like illness compared with those who wore medical masks (72).

In the context of severe medical mask shortage, face shields alone or in combination with fabric mask may be considered as a last resort (73). Ensure proper design of face shields to cover the sides of the face and below the chin.

As for other PPE items, if production of fabric masks for use in health care settings is proposed locally in situations of shortage or stock out, a local authority should assess the product according to specific minimum performance standards and required technical specifications (see Annex).

Additional considerations for community care settings

Like other health workers, community health workers should apply standard precautions for all patients at all times, with particular emphasis regarding hand and respiratory hygiene, surface and environmental cleaning and disinfection and the appropriate use of PPE. When a patient is suspected or confirmed of having COVID-19, community health workers should always apply contact and droplet precautions. These include the use of a medical mask, gown, gloves and eye protection (74).

IPC measures that are needed will depend on the local COVID-19 transmission dynamics and the type of contact required by the health care activity (see Table 1). The community health workforce should ensure that patients and workforce members apply precautionary measures such as respiratory hygiene and physical distancing of at least 1 metre (3.3 feet). They also may support set-up and maintenance of hand hygiene stations and community education (74). In the context of known or suspected community or cluster transmission, community health workers should wear a medical mask when providing essential routine services (see Table 1).

Table 1. Mask use in health care settings depending on transmission scenario, target population, setting, activity and type*

Transmission scenario	Target population (who)	Setting (where)	Activity (what)	Mask type (which one) *
Known or suspected community or cluster transmission of SARS-CoV-2	Health workers and caregivers	Health facility (including primary, secondary, tertiary care levels, outpatient care, and long-term care facilities)	For any activity in patient-care areas (COVID-19 or non-COVID-19 patients) or in any common areas (e.g., cafeteria, staff rooms)	Medical mask (or respirator if aerosol generating procedures performed)
	Other staff, patients, visitors, service suppliers		For any activity or in any common area	Medical or fabric mask
	Inpatients	In single or multiple-bed rooms	When physical distance of at least 1 metre cannot be maintained	
	Health workers and caregivers	Home visit (for example, for antenatal or postnatal care, or for a chronic condition)	When in direct contact with a patient or when a distance of at least 1 metre cannot be maintained.	Medical mask
		Community	Community outreach programmes/essential routine services	
Known or suspected sporadic transmission of SARS-CoV-2 cases	Health workers and caregivers	Health facility (including primary, secondary, tertiary care levels, outpatient care, and long-term care facilities)	In patient care area- irrespective of whether patients have suspected/confirmed COVID-19	Medical mask
	Other staff, patients, visitors, service suppliers and all others		No routine activities in patient areas	Medical mask not required. Medical mask should be worn if in contact or within 1 metre of patients, or according to local risk assessment
	Health workers and caregivers	Home visit (for example, for antenatal or postnatal care, or for a chronic condition)	When in direct contact or when a distance of at least 1metre cannot be maintained.	Medical mask
		Community	Community outreach programs (e.g., bed net distribution)	
No documented SARS-CoV-2 transmission	Health workers and caregivers	Health facility (including primary, secondary, tertiary care levels, outpatient care, and long-term care facilities)	Providing any patient care	Medical mask use according to standard and transmission-based precautions
		Community	Community outreach programs	
Any transmission scenario	Health workers	Health care facility (including primary, secondary, tertiary care levels, outpatient care, and long-term care facilities), in settings where aerosol generating procedures (AGP) are performed	Performing an AGP on a suspected or confirmed COVID-19 patient or providing care in a setting where AGPs are in place for COVID-19 patients	Respirator (N95 or N99 or FFP2 or FFP3)

**This table refers only to the use of medical masks and respirators. The use of medical masks and respirators may need to be combined with other personal protective equipment and other measures as appropriate, and always with hand hygiene.*

Guidance on mask use in community settings

Evidence on the protective effect of mask use in community settings

At present there is only limited and inconsistent scientific evidence to support the effectiveness of masking of healthy people in the community to prevent infection with respiratory viruses, including SARS-CoV-2 (75). A large randomized community-based trial in which 4862 healthy participants were divided into a group wearing medical/surgical masks and a control group found no difference in infection with SARS-CoV-2 (76). A recent systematic review found nine trials (of which eight were cluster-randomized controlled trials in which clusters of people, versus individuals, were randomized) comparing medical/surgical masks versus no masks to prevent the spread of viral respiratory illness. Two trials were with healthcare workers and seven in the community. The review concluded that wearing a mask may make little or no difference to the prevention of influenza-like illness (ILI) (RR 0.99, 95%CI 0.82 to 1.18) or laboratory confirmed illness (LCI) (RR 0.91, 95%CI 0.66-1.26) (44); the certainty of the evidence was low for ILI, moderate for LCI.

By contrast, a small retrospective cohort study from Beijing found that mask use by entire families before the first family member developed COVID-19 symptoms was 79% effective in reducing transmission (OR 0.21, 0.06-0.79) (77). A case-control study from Thailand found that wearing a medical or non-medical mask all the time during contact with a COVID-19 patient was associated with a 77% lower risk of infection (aOR 0.23; 95% CI 0.09–0.60) (78). Several small observational studies with epidemiological data have reported an association between mask use by an infected person and prevention of onward transmission of SARS-CoV-2 infection in public settings. (8, 79-81).

A number of studies, some peer reviewed (82-86) but most published as pre-prints (87-104), reported a decline in the COVID-19 cases associated with face mask usage by the public, using country- or region-level data. One study reported an association between community mask wearing policy adoption and increased movement (less time at home, increased visits to commercial locations) (105). These studies differed in setting, data sources and statistical methods and have important limitations to consider (106), notably the lack of information about actual exposure risk among individuals, adherence to mask wearing and the enforcement of other preventive measures (107, 108).

Studies of influenza, influenza-like illness and human coronaviruses (not including COVID-19) provide evidence that the use of a medical mask can prevent the spread of infectious droplets from a symptomatic infected person to someone else and potential contamination of the environment by these droplets (75). There is limited evidence that wearing a medical mask may be beneficial for preventing transmission between healthy individuals sharing households with a sick person or among attendees of mass gatherings (44, 109-114).

A meta-analysis of observational studies on infections due to betacoronaviruses, with the intrinsic biases of observational data, showed that the use of either disposable medical masks or reusable 12–16-layer cotton masks was associated with protection of healthy individuals within households and among contacts of cases (46). This could be considered to be indirect evidence for the use of masks (medical or other) by healthy individuals in the wider community; however, these studies suggest that such individuals would need to be in close proximity to an infected person in a household or at a mass gathering where physical distancing cannot be achieved to become infected with the virus. Results from cluster randomized controlled trials on the use of masks among young adults living in university residences in the United States of America indicate that face masks may reduce the rate of influenza-like illness but showed no impact on risk of laboratory-confirmed influenza (115, 116).

Guidance

The WHO COVID-19 IPC GDG considered all available evidence on the use of masks by the general public including effectiveness, level of certainty and other potential benefits and harms, with respect to transmission scenarios, indoor versus outdoor settings, physical distancing and ventilation. Despite the limited evidence of protective efficacy of mask wearing in community settings, in addition to all other recommended preventive measures, the GDG advised mask wearing in the following settings:

1. In areas with known or suspected community or cluster transmission of SARS-CoV-2, WHO advises mask use by the public in the following situations (see Table 2):

   Indoor settings:

- in public indoor settings where ventilation is known to be poor regardless of physical distancing: limited or no opening of windows and doors for natural ventilation; ventilation system is not properly functioning or maintained; or cannot be assessed;
- in public indoor settings that have adequate[3] ventilation if physical distancing of at least 1 metre cannot be maintained;
- in household indoor settings: when there is a visitor who is not a household member and ventilation is known to be poor, with limited opening of windows and doors for natural ventilation, or the ventilation system cannot be assessed or is not properly functioning, regardless of whether physical distancing of at least 1 metre can be maintained;
- in household indoor settings that have adequate ventilation if physical distancing of at least 1 metre cannot be maintained.

[3] For adequate ventilation refer to regional or national institutions or heating, refrigerating and air-conditioning societies enacting ventilation requirements. If not available or applicable, a recommended ventilation rate of 10 l/s/person should be met (except healthcare facilities which have specific requirements). For more information consult "Coronavirus (COVID-19) response resources from ASHRAE and others'' https://www.ashrae.org/technical-resources/resources

Table 2. Mask use in community settings depending on transmission scenario, setting, target population, purpose and type*

Transmission scenario	Situations/settings (where)	Target Population (who)	Purpose of mask use (why)	Mask type (which one)
Known or suspected community or cluster transmission of SARS-CoV-2	Indoor settings, where ventilation is known to be poor or cannot be assessed or the ventilation system is not properly maintained, regardless of whether physical distancing of at least 1 meter can be maintained	General population in public* settings such as shops, shared workplaces, schools, churches, restaurants, gyms, etc. or in enclosed settings such as public transportation. For households, in indoor settings, when there is a visitor who is not a member of the household	Potential benefit for source control	Fabric mask
	Indoor settings that have adequate [4] ventilation if physical distancing of at least 1 metre cannot be maintained			
	Outdoor settings where physical distancing cannot be maintained	General population in settings such as crowded open-air markets, lining up outside a building, during demonstrations, etc.		
	Settings where physical distancing cannot be maintained, and the individual is at increased risk of infection and/or negative outcomes	Individuals/people with higher risk of severe complications from COVID-19: • People aged ≥60 years • People with underlying comorbidities, such as cardiovascular disease or diabetes mellitus, chronic lung disease, cancer, cerebrovascular disease, immunosuppression, obesity, asthma	Protection	Medical mask
Known or suspected sporadic transmission, or no documented SARS-CoV-2 transmission	Risk-based approach	General population	Potential benefit for source control and/or protection	Depends on purpose (see details in the guidance content)
Any transmission scenario	Any setting in the community	Anyone suspected or confirmed of having COVID-19, regardless of whether they have symptoms or not, or anyone awaiting viral test results, when in the presence of others	Source control	Medical mask

**Public indoor setting includes any indoor setting outside of the household*

[4] For adequate ventilation refer to regional or national institutions or heating, refrigerating and air-conditioning societies enacting ventilation requirements. If not available or applicable, a recommended ventilation rate of 10l/s/person should be met (except healthcare facilities which have specific requirements).). For more information consult "Coronavirus (COVID-19) response resources from ASHRAE and others'' https://www.ashrae.org/technical-resources/resources

In outdoor settings:

- where physical distancing of at least 1 metre cannot be maintained;
- individuals/people with higher risk of severe complications from COVID-19 (individuals ≥ 60 years old and those with underlying conditions such as cardiovascular disease or diabetes mellitus, chronic lung disease, cancer, cerebrovascular disease or immunosuppression) should wear medical masks in any setting where physical distance cannot be maintained.

2. In areas with known or suspected sporadic transmission or no documented transmission, as in all transmission scenarios, WHO continues to advise that decision makers should apply a risk-based approach focusing on the following criteria when considering the use of masks for the public:

- **Purpose of mask use**. Is the intention source control (preventing an infected person from transmitting the virus to others) or protection (preventing a healthy wearer from the infection)?
- **Risk of exposure to SARS-CoV-2**. Based on the epidemiology and intensity of transmission in the population, is there transmission and limited or no capacity to implement other containment measures such as contact tracing, ability to carry out testing and isolate and care for suspected and confirmed cases? Is there risk to individuals working in close contact with the public (e.g., social workers, personal support workers, teachers, cashiers)?
- **Vulnerability of the mask wearer/population**. Is the mask wearer at risk of severe complications from COVID-19? Medical masks should be used by older people (≥ 60 years old), immunocompromised patients and people with comorbidities, such as cardiovascular disease or diabetes mellitus, chronic lung disease, cancer and cerebrovascular disease (117).
- **Setting in which the population lives**. Is there high population density (such as in refugee camps, camp-like settings, and among people living in cramped conditions) and settings where individuals are unable to keep a physical distance of at least 1 metre (for example, on public transportation)?
- **Feasibility**. Are masks available at an affordable cost? Do people have access to clean water to wash fabric masks, and can the targeted population tolerate possible adverse effects of wearing a mask?
- **Type of mask**. Does the use of medical masks in the community divert this critical resource from the health workers and others who need them the most? In settings where medical masks are in short supply, **stocks should be prioritized for health workers and at-risk individuals.**

The decision of governments and local jurisdictions whether to recommend or make mandatory the use of masks should be based on the above assessment as well as the local context, culture, availability of masks and resources required.

3. In any transmission scenario:

- Persons with any symptoms suggestive of COVID-19 should wear a medical mask and (5) additionally:
  - self-isolate and seek medical advice as soon as they start to feel unwell with potential symptoms of COVID-19, even if symptoms are mild);
  - follow instructions on how to put on, take off, and dispose of medical masks and perform hand hygiene (118);
  - follow all additional measures, in particular respiratory hygiene, frequent hand hygiene and maintaining physical distance of at least 1 metre from other persons (46). If a medical mask is not available for individuals with suspected or confirmed COVID-19, a fabric mask meeting the specifications in the Annex of this document should be worn by patients as a source control measure, pending access to a medical mask. The use of a non-medical mask can minimize the projection of respiratory droplets from the user (119, 120).
  - Asymptomatic persons who test positive for SARS-CoV-2, should wear a medical mask when with others for a period of 10 days after testing positive.

Potential benefits/harms

The potential advantages of mask use by healthy people in the general public include:

- reduced spread of respiratory droplets containing infectious viral particles, including from infected persons before they develop symptoms (121);
- reduced potential for stigmatization and greater of acceptance of mask wearing, whether to prevent infecting others or by people caring for COVID-19 patients in non-clinical settings (122);
- making people feel they can play a role in contributing to stopping spread of the virus;
- encouraging concurrent transmission prevention behaviours such as hand hygiene and not touching the eyes, nose and mouth (123-125);
- preventing transmission of other respiratory illnesses like tuberculosis and influenza and reducing the burden of those diseases during the pandemic (126).

The potential disadvantages of mask use by healthy people in the general public include:

- headache and/or breathing difficulties, depending on type of mask used (55);
- development of facial skin lesions, irritant dermatitis or worsening acne, when used frequently for long hours (58, 59, 127);
- difficulty with communicating clearly, especially for persons who are deaf or have poor hearing or use lip reading (128, 129);
- discomfort (44, 55, 59)
- a false sense of security leading to potentially lower adherence to other critical preventive measures such as physical distancing and hand hygiene (105);
- poor compliance with mask wearing, in particular by young children (111, 130-132);
- waste management issues; improper mask disposal leading to increased litter in public places and environmental hazards (133);
- disadvantages for or difficulty wearing masks, especially for children, developmentally challenged persons, those with mental illness, persons with cognitive impairment, those with asthma or chronic respiratory or breathing problems, those who have had facial trauma or recent oral maxillofacial surgery and those living in hot and humid environments (55, 130).

Considerations for implementation

When implementing mask policies for the public, decision-makers should:

- clearly communicate the purpose of wearing a mask, including when, where, how and what type of mask should be worn; explain what wearing a mask may achieve and what it will not achieve; and communicate clearly that this is one part of a package of measures along with hand hygiene, physical distancing, respiratory etiquette, adequate ventilation in indoor settings and other measures that are all necessary and all reinforce each other;
- inform/train people on when and how to use masks appropriately and safely (see mask management and maintenance sections);
- consider the feasibility of use, supply/access issues (cleaning, storage), waste management, sustainability, social and psychological acceptance (of both wearing and not wearing different types of masks in different contexts);
- continue gathering scientific data and evidence on the effectiveness of mask use (including different types of masks) in non-health care settings;
- evaluate the impact (positive, neutral or negative) of using masks in the general population (including behavioural and social sciences) through good quality research.

Mask use during physical activity

Evidence

There are limited studies on the benefits and harms of wearing medical masks, respirators and non-medical masks while exercising. Several studies have demonstrated statistically significant deleterious effects on various cardiopulmonary physiologic parameters during mild to moderate exercise in healthy subjects and in those with underlying respiratory diseases (134-140). The most significant impacts have been consistently associated with the use of respirators and in persons with underlying obstructive airway pulmonary diseases such as asthma and chronic obstructive pulmonary disease (COPD), especially when the condition is moderate to severe (136). Facial microclimate changes with increased temperature, humidity and perceptions of dyspnoea were also reported in some studies on the use of masks during exercise (134, 141). A recent review found negligeable evidence of negative effects of mask use during exercise but noted concern for individuals with severe cardiopulmonary disease (142).

Guidance

WHO advises that people should not wear masks during vigorous intensity physical activity (143) because masks may reduce the ability to breathe comfortably. The most important preventive measure is to maintain physical distancing of at least 1 meter and ensure good ventilation when exercising.

If the activity takes place indoors, adequate ventilation should be ensured at all times through natural ventilation or a properly functioning or maintained ventilation system (144). Particular attention should be paid to cleaning and disinfection of the environment, especially high-touch surfaces. If all the above measures cannot be ensured, consider temporary closure of public indoor exercise facilities (e.g., gyms).

Face shields for the general public

At present, face shields are considered to provide a level of eye protection only and should not be considered as an equivalent to masks with respect to respiratory droplet protection and/or source control. Current laboratory testing standards only assess face shields for their ability to provide eye protection from chemical splashes (145).

In the context of non-availability or difficulties wearing a non-medical mask (in persons with cognitive, respiratory or hearing impairments, for example), face shields may be considered as an alternative, noting that they are inferior to masks with respect to droplet transmission and prevention. If face shields are to be used, ensure proper design to cover the sides of the face and below the chin.

Medical masks for the care of COVID-19 patients at home

WHO provides guidance on how to care for patients with confirmed and suspected COVID-19 at home when care in a health facility or other residential setting is not possible (5).

- Persons with suspected COVID-19 or mild COVID-19 symptoms should wear a medical mask as much as possible, especially when there is no alternative to being in the same room with other people. The mask should be changed at least once daily. Persons who cannot tolerate a medical mask should rigorously apply respiratory hygiene (i.e., cover mouth and nose with a disposable paper tissue when coughing or sneezing and dispose of it immediately after use or use a bent elbow procedure and then perform hand hygiene).
- Caregivers of or those sharing living space with people with suspected COVID-19 or with mild COVID-19 symptoms should wear a medical mask when in the same room as the affected person.

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Acknowledgments

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WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance document will expire 1 year after the date of publication.

Annex: Updated guidance on non-medical (fabric) masks

Background

A non-medical mask, also called fabric mask, community mask or face covering, is neither a medical device nor personal protective equipment. Non-medical masks are aimed at the general population, primarily for protecting others from exhaled virus-containing droplets emitted by the mask wearer. They are not regulated by local health authorities or occupational health associations, nor is it required for manufacturers to comply with guidelines established by standards organizations. Non-medical masks may be homemade or manufactured. The essential performance parameters include good breathability, filtration of droplets originating from the wearer, and a snug fit covering the nose and mouth. Exhalation valves on masks are discouraged as they bypass the filtration function of the mask.

Non-medical masks are made from a variety of woven and non-woven fabrics, such as woven cotton, cotton/synthetic blends, polyesters and breathable spunbond polypropylene, for example. They may be made of different combinations of fabrics, layering sequences and available in diverse shapes. Currently, more is known about common household fabrics and combinations to make non-medical masks with target filtration efficiency and breathability (119, 146-150). Few of these fabrics and combinations have been systematically evaluated and there is no single design, choice of material, layering or shape among available non-medical masks that are considered optimal. While studies have focussed on single fabrics and combinations, few have looked at the shape and universal fit to the wearer. The unlimited combination of available fabrics and materials results in variable filtration and breathability.

In the context of the global shortage of medical masks and PPE, encouraging the public to create their own fabric masks may promote individual enterprise and community integration. Moreover, the production of non-medical masks may offer a source of income for those able to manufacture masks within their communities. Fabric masks can also be a form of cultural expression, encouraging public acceptance of protection measures in general. The safe re-use of fabric masks will also reduce costs and waste and contribute to sustainability (151-156).

This Annex is destined intended for two types of readers: homemade mask makers and factory-made masks manufacturers. Decision makers and managers (national/sub-national level) advising on a type of non-medical mask are also the focus of this guidance and should take into consideration the following features of non-medical masks: breathability, filtration efficiency (FE), or filtration, number and combination of fabric layers material used, shape, coating and maintenance.

Evidence on the effectiveness of non-medical (fabric) masks

A number of reviews have been identified on the effectiveness of non-medical masks (151-156). One systematic review (155) identified 12 studies and evaluated study quality. Ten were laboratory studies (157-166), and two reports were from a single randomized trial (72, 167). The majority of studies were conducted before COVID-19 emerged or used laboratory generated particles to assess filtration efficacy. Overall, the reviews concluded that cloth face masks have limited efficacy in combating viral infection transmission.

Homemade non-medical masks

Homemade non-medical masks made of household fabrics (e.g., cotton, cotton blends and polyesters) should ideally have a three-layer structure, with each layer providing a function (see Figure 1) (168). It should include:

1. an innermost layer (that will be in contact with the face) of a hydrophilic material (e.g., cotton or cotton blends of terry cloth towel, quilting cotton and flannel) that is non-irritating against the skin and can contain droplets (148)
2. a middle hydrophobic layer of synthetic breathable non-woven material (spunbond polypropylene, polyester and polyaramid), which may enhance filtration, prevent permeation of droplets or retain droplets (148, 150)
3. an outermost layer made of hydrophobic material (e.g. spunbond polypropylene, polyester or their blends), which may limit external contamination from penetrating through the layers to the wearer's nose and mouth and maintains and prevents water accumulation from blocking the pores of the fabric (148).

Although a minimum of three layers is recommended for non-medical masks for the most common fabric used, single, double or other layer combinations of advanced materials may be used if they meet performance requirements. It is important to note that with more tightly woven materials, breathability may be reduced as the number of layers increases. A quick check may be performed by attempting to breathe, through the mouth, through the multiple layers.

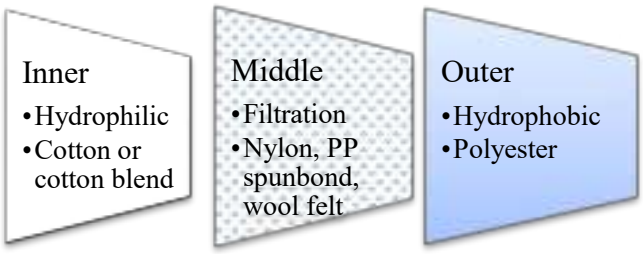

Figure 1. Non-medical mask construction using breathable fabrics such as cotton, cotton blends, polyesters, nylon and polypropylene spunbond that are breathable may impart adequate filtration performance when layered. Single- or double-layer combinations of advanced materials may be used if they meet performance requirements (72).

Assumptions regarding homemade masks are that individual makers only have access to common household fabrics and do not have access to test equipment to confirm target performance (filtration and breathability). Figure 1 illustrates a multi-layer mask construction with examples of fabric options. Very porous materials, such as gauze, even with multiple layers, may provide very low filtration efficiency (147). Higher thread count fabrics offer improved filtration performance (169). Coffee filters, vacuum bags and materials not meant for clothing should be avoided as they may contain injurious content when breathed in. Microporous films such as Gore-Tex are not recommended (170).

Factory-made non-medical masks: general considerations for manufacturers

The non-medical mask, including all components and packaging, must be non-hazardous, non-toxic and child-friendly (no exposed sharp edges, protruding hardware or rough materials). Factory-made non-medical masks must be made using a process that is certified to a quality management system (e.g., ISO 9001). Social accountability standards (e.g., SAI SA8000) for multiple aspects of fair labour practices, health and safety of the work force and adherence to UNICEF's Children's Rights and Business Principles are strongly encouraged.

Standards organizations' performance criteria

Manufacturers producing masks with consistent standardized performance can adhere to published, freely available guidance from several organizations including those from: the French Standardization Association (AFNOR Group), The European Committee for Standardization (CEN), Swiss National COVID-19 Task Force, the American Association of Textile Chemists and Colorists (AATCC), the South Korean Ministry of Food and Drug Safety (MFDS), the Italian Standardization Body (UNI) and the Government of Bangladesh.

Essential parameters

The essential parameters presented in this section are the synthesis of the abovementioned regional and national guidance. They include filtration, breathability and fit. Good performance is achieved when the three essential parameters are optimized at the preferred threshold (Figure 2).

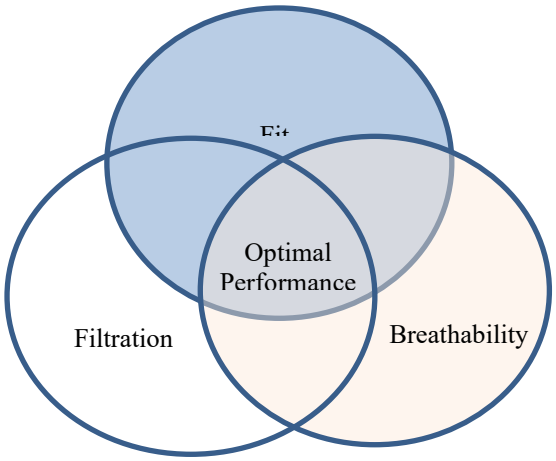

Figure 2. Illustration of the three essential parameters of filtration, breathability and fit.

The summary of the three essential parameters can be found in Table 1 and the additional performance considerations in Table 2. The minimum threshold is the minimum acceptable parameter, while the preferred threshold is the optimum.

Filtration and breathability

Filtration depends on the filtration efficiency (in %), the type of challenge particle (oils, solids, droplets containing bacteria) and the particle size (see Table 1). Depending on the fabrics used, filtration and breathability can complement or work against one another. The selection of material for droplet filtration (barrier) is as important as breathability. Filtration is dependent on the tightness of the weave, fibre or thread diameter. Non-woven materials used for disposable masks are manufactured using processes to create polymer fibres that are thinner than natural fibres such as cotton and that are held together by partial melting.

Breathability is the difference in pressure across the mask and is typically reported in millibars (mbar) or Pascals (Pa) or, normalized to the cm^2 in $mbar/cm^2$ or Pa/cm^2. Acceptable breathability of a medical mask should be below 49 Pa/cm^2. For non-medical masks, an acceptable pressure difference, over the whole mask, should be below 60 Pa/cm^2, with lower values indicating better breathability.

Non-medical fabric masks consisting of two layers of polypropylene spunbond and two layers of cotton have been shown to meet the minimum requirements for droplet filtration and breathability of the CEN CWA 17553 guidance. It is preferable not to select elastic material to make masks as the mask material may be stretched over the face, resulting in increased pore size and lower filtration through multiple usage. Additionally, elastic fabrics are sensitive to washing at high temperatures thus may degrade over time.

Coating the fabric with compounds like wax may increase the barrier and render the mask fluid resistant; however, such coatings may inadvertently completely block the pores and make the mask difficult to breathe through. In addition to decreased breathability unfiltered air may more likely escape the sides of the mask on exhalation. Coating is therefore not recommended.

Valves that let unfiltered air escape the mask are discouraged and are an inappropriate feature for masks used for the purpose of preventing transmission.

Table 1. Essential parameters (minimum and preferred thresholds) for manufactured non-medical mask

Essential Parameters	Minimum threshold	Preferred threshold
1. Filtration*		
1.1. filtration efficiency	70% @ 3 micron	> 70%, without compromising breathability
1.2. Challenge particle	Solid: sodium chloride (NaCl), Talcum powder, Holi powder, dolomite, Polystyrene Latex spheres Liquid: DEHS Di-Ethyl-Hexyl-Sebacat, paraffin oil	Based on availability
1.3. Particle size	Choose either sizes: 3 µm, 1 µm, or smaller	Range of particle sizes
2. Breathability		
2.1. Breathing resistance**	≤60 Pa/cm^2	Adult: ≤ 40 Pa/cm^2 Paediatric: ≤ 20 Pa/cm^2
2.2 Exhalation valves	Not recommended	N/A
3. Fit		
3.1. Coverage	Full coverage of nose and mouth, consistent, snug perimeter fit at the nose bridge, cheeks, chin and lateral sides of the face; adequate surface area to minimize breathing resistance and minimize side leakage	Same as current requirements
3.2 Face seal	Not currently required	Seal as good as FFR (respirator): Fit factor of 100 for N95 Maximum Total Inward Leakage of 25% (FFP1 requirement)
3.2. Sizing	Adult and child	Should cover from the bridge of the nose to below the chin and cheeks on either side of the mouth Sizing for adults and children (3-5, 6-9, 10-12, >12)
3.3Strap strength		> 44.5 N

* Smaller particle may result in lower filtration.
** High resistance can cause bypass of the mask. Unfiltered air will leak out the sides or around the nose if that is the easier path.

Fit: shape and sizing

Fit is the third essential parameter, and takes into consideration coverage, seal, sizing, and strap strength. Fit of masks currently is not defined by any standard except for the anthropometric considerations of facial dimensions (ISO/TS 16976-2) or simplified to height mask (South Korean standard for KF-AD). It is important to ensure that the mask can be held in place comfortably with as little adjustment of the elastic bands or ties as possible.

Mask shapes typically include flat-fold or duckbill and are designed to fit closely over the nose, cheeks and chin of the wearer. Snug fitting designs are suggested as they limit leaks of unfiltered air escaping from the mask (148). Ideally the mask should not have contact with the lips, unless hydrophobic fabrics are used in at least one layer of the mask (148). Leaks where unfiltered air moves in and out of the mask may be attributed to the size and shape of the mask (171).

Additional considerations

Optional parameters to consider in addition to the essential performance parameters include if reusable, biodegradability for disposal masks, antimicrobial performance where applicable and chemical safety (see Table 2).

Non-medical masks intended to be reusable should include instructions for washing and must be washed a minimum of five cycles, implying initial performance is maintained after each wash cycle.

Advanced fabrics may be biodegradable or compostable at the end of service life, according to a recognized standard process (e.g., UNI EN 13432, UNI EN 14995 and UNI / PdR 79).

Manufacturers sometimes claim their NM masks have antimicrobial performance. Antimicrobial performance may be due to coatings or additives to the fabric fibres. Treated fabrics must not come into direct contact with mucous membranes; the innermost fabric should not be treated with antimicrobial additives, only the outermost layer. In addition, antimicrobial fabric standards (e.g., ISO 18184, ISO 20743, AATCC TM100, AATCC 100) are generally slow acting. The inhibition on microbial growth may take full effect after 2- or 24-hour contact time depending on the standard. The standards have generally been used for athletic apparel and substantiate claims of odour control performance. These standards are not appropriate for non-medical cloth masks and may provide a false sense of protection from infectious agents. If claims are maid, manufacturers should specify which standard supports antimicrobial performance, the challenge organism and the contact time.

Volatile additives are discouraged as these may pose a health risk when inhaled repeatedly during wear. Certification according to organizations including OEKO-TEX (Europe) or SEK (Japan), and additives complying with REACH (Europe) or the Environmental Protection Agency (EPA, United States of America) indicate that textile additives are safe and added at safe levels.

Table 2. Additional parameters for manufactured non-medical masks

Additional parameters	Minimum thresholds
If reusable, number of wash cycles	5 cycles
Disposal	Reusable If biodegradable (CFC-BIO), according to UNI EN 13432, UNI EN 14995
Antimicrobial (bacteria, virus, fungus) performance	ISO 18184 (virus) ISO 20743 (bacteria) ISO 13629 (fungus) AATCC TM100 (bacteria)
Chemical safety	Comply with REACH regulation, including inhalation safety

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WHO reference number: WHO/2019-nCoV/IPC_Masks/2020.5

This is **Exhibit "HH"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

Public Health Ontario | Santé publique Ontario

FACT SHEET

Comparing SARS-CoV-2 Variants of Concern (VOCs)* as of May 31, 2021

This table compares characteristics of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Variants of Concern (VOCs). This table is current as of May 31, 2021 and will be updated as more information becomes available.

	B.1.1.7	B.1.351	B.1.617[†]	P.1
Public Health England name	VOC-20DEC-01	VOC-20DEC-02	VOC-21APR-02	VOC-21JAN-02
Nextstrain clade	20I/S:501Y.V1	20H/S:501Y.V2	21A/S:154K (for B.1.617.1) 21A/S:478K (for B.1.617.2)	20J/S:501Y.V3
World Health Organization label	Alpha	Beta	Delta (for B.1.617.2)	Gamma
Location first detected	United Kingdom (Kent)	South Africa (Eastern Cape)	India	Brazil (Manaus)
Detected in multiple countries?	Yes	Yes	Yes	Yes
Detected in Ontario?	Yes	Yes	Yes	Yes
Increased transmissibility?	Yes +55%[‡]	Yes +58%[‡]	Yes	Yes +58%[‡]
Increased disease severity?	Yes	Unknown[§]	Unknown[§]	Unknown[§]
Impact on molecular tests?	Yes[¶]	No	No	No
Impact on antigen tests?	No	No	Unknown[§] (but unlikely)	No

	B.1.1.7	B.1.351	B.1.617[†]	P.1
Impact on serological tests?	Unknown[§]	Unknown[§]	Unknown[§]	Unknown[§]
Immune escape?	No	Yes	Potential[#]	Yes
Impact on vaccine effectiveness?	No	Yes[**,††]	Potential impact[††]	Potential impact[††]
Notable mutations (key mutations in bold) [‡‡]	**Δ69-70[¶], N501Y[§§]** D614G, P681H/R	L18F, **K417N, E484K, N501Y,** D614G, A701V	**L452R**, D614G, G142D **P681R**, **E484Q**	L18F, **K417T, E484K, N501Y,** D614G

Abbreviations: Δ, deletion; VOC, variant of concern

For additional information on VOCs and interpreting this table, please refer to PHO's *Companion Guide to Variants of Concern (VOCs)*[1]

* VOCs are classified according to the national definitions for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) variants established by the Canadian SARS-CoV-2 Variant Surveillance Group.[2]

† B.1.617 contains three sub-lineages (B.1.617.1; B.1.617.2; B.1.617.3) which differ by few potentially relevant mutations in the spike protein and their global prevalence of detection.[3] Designation of the sublineages in Canada may change as evidence on their attributes are being reviewed by the Canadian SARS-CoV-2 Variant Surveillance Group.[2]

‡ Based on the odds ratio of secondary household transmission using a household study of VOC transmission in Ontario (forthcoming). For methods, see (https://doi.org/10.1093/cid/ciab186).[4]

§ Unknown indicates that it is under investigation or there is currently no data for assessment.

¶ Spike (S) gene target failure (SGTF) is observed for variants with the Δ69-70 mutation using some SARS-CoV-2 molecular assays that target this region of the S gene. These are multiple gene target assays that will still detect SARS-CoV-2 via the additional targets.

Laboratory evidence suggests resistance to certain therapeutic monoclonal antibodies and/or slightly reduced neutralization by convalescent sera.

** Reduced effectiveness to AstraZeneca and Johnson & Johnson.

†† Laboratory evidence to suggest reduced effectiveness by AstraZeneca, Moderna mRNA-1273, and Pfizer-BioNTech vaccines.

‡‡ Mutations in other genes are not represented in this table.

§§ A small subset of B.1.1.7 variants have been found to have the E484K mutation.

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Ontario

This is **Exhibit "II"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

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SYNTHESIS

05/26/2021

COVID-19 B.1.617 Variant of Concern – What We Know So Far

Introduction

Public Health Ontario (PHO) is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19). "What We Know So Far" documents provide a rapid review of the evidence related to a specific aspect or emerging issue related to COVID-19.

Key Findings

- Lineage B.1.617 is a new variant of concern (VOC) of Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) and is associated with the notable mutations L452R and E484Q, which have the potential for greater transmissibility and reduced vaccine effectiveness.
- B.1.617 was first reported in India in late March 2021 and has spread to over 40 other countries around the world in less than two months' time. However, its geographic distribution and incidence trends are not fully understood due to inconsistent testing and sequencing in different regions of the world.
- Field evidence from the United Kingdom (UK), where most B.1.617.2 sequences outside of India have been reported, suggest higher transmissibility for this lineage. Data to date are insufficient to determine if B.1.617 causes more severe disease.
- Preliminary in-vitro studies suggest that B.1.617 has reduced neutralization by vaccine-induced sera and convalescent sera, while an observational study suggests a possible small reduction in effectiveness after full vaccination.

Background

On March 24, 2021, the Ministry of Health and Family Welfare of India reported a new variant that contains two mutations in the Spike gene of SARS-CoV-2: E484Q and L452R.[1] The discovery of this "double mutant" generated concern in India as it took place when the incidence of Coronavirus Disease 2019 (COVID-19) surged rapidly after a long decline from late September 2020 to mid-February 2021.

In less than a month's time, this variant was detected in several other countries including the UK, Singapore, Australia and the United States (US), and was named B.1.617.[2] Public health scientists internationally have noted that the E484Q and L452R mutations may enable B.1.617 to transmit more easily and render vaccines less effective.[3,4]

In the UK, sublineage B.1.617.1 was designated as a Variant Under Investigation (VUI-21APR-01) on April 1, 2021, given its mutation profile and increasing incidence in England, while sublineages B.1.617.2 (with

a different mutation profile) and B.1.617.3 (rapid spread not apparent) were under surveillance.[5] On May 6, 2021, sublineage B.1.617.2 was escalated in its designation to VOC (VOC-21APR-02) when its transmissibility was assessed to be at least equivalent to that of the VOC B.1.1.7. Meanwhile, B.1.617.3 became a VUI (VUI-21APR-03) as of April 27, 2021.[6]

On May 10, 2021, the World Health Organization characterized B.1.617 as a VOC lineage which contains three sublineages: B.1.617.1, B.1.617.2 and B.1.617.3. The designation was based on early evidence of rapid increases in prevalence observed in multiple countries (for B.1.617.1 and B.1.617.2), preliminary laboratory findings of reduced effectiveness of monoclonal therapeutic antibody Bamlanivimab, and potentially slight reduction in neutralization abilities of vaccinee sera.[7]

On May 14, 2021, the Canadian SARS-CoV-2 Variant Surveillance Group classified B.1.617 as a VOC, noting that the designation of the sublineages may change as evidence on their attributes is reviewed (See Appendix A for the Canadian definitions of variant of concern).[8]

Methods

From January 17 to May 26, 2021, PHO Library Services conducted daily searches of primary and preprint literature using the MEDLINE database (search strategies available upon request). In addition, we performed grey literature searches daily using news feeds in the Shared Library Services Partnership. English-language peer-reviewed and non-peer-reviewed (preprint) records that described "double mutant" or B.1.617 were included.

Prior to posting, PHO subject-matter experts reviewed the content of this document.

As the COVID-19 outbreak continues to evolve and the scientific evidence rapidly expands, the information provided in this document is only current as of the date of respective literature searches.

Jurisdictional scan of involving data from England involved keyword searches conducted on May 17 and 18, 2021 in the Google search engine for literature related to COVID-19 epidemiology, vaccination programs, and public health measures in England. A formal database search was not conducted due to time constraints; thus, some relevant articles may not be included.

Epidemiology

- The first B.1.617 genome noted in the global database (GISAID) dates back to October 5, 2020. It was first detected in the UK on February 22, 2021 and in the US on February 23, 2021.[9] As of May 17, 2021, the three sublineages of B.1.617 (B.1.617.1, B.1.617.2 and B.1.617.3) have been reported in 50 countries from Asia, Europe, North America and Australia.[5,9,10] The relative frequency of B.1.617 and the sublineages in different countries is unknown due to the different sequencing capacities and strategies.

- B.1.617 was first detected in India where the majority of this lineage (412 reports as of April 22, 2021) was reported.[10,11] On March 24, 2021, the Indian SARS-CoV-2 Consortium on Genomics reported that about 15%–20% of samples from Maharashtra carry the E484Q and L452R mutations, and there was an increase in the percentage of samples carrying these two mutations since December 2020. Subsequently, B.1.617 was classified as a VOC in India.[1] B.1.617 was found in 61% of 361 cases sequenced between January and March, 2021 in Maharashtra, India. However, the scale of testing was too small to conclude if this lineage was driving the surge in COVID-19 cases in Maharashtra.[9,12]

- In the UK, B.1.617.1 was first detected in mid-February 2021. Its daily incidence rose quickly in April to peak at 15 cases in mid-April, then declined quickly in late April to <4 cases as of early May 2021.[13] B.1.617.3 was first detected in late March 2021 and its daily incidence has remained low, peaking at 3 cases a day in mid-April and dropping to a case occasionally.[13] On the other hand, the daily incidence of B.1.617.2 had remained low from first detection in mid-March 2021 before slowly increasing in early April, after which it rose quickly to 235 cases a day in early May 2021.[13] The proportion of specimens belonging to the B.1.617.2 sublineage among all variants sequenced in the UK increased from 1% in the first week of April 2021, to 26% in the first week of May 2021, and reached 58% by the week of May 16, 2021.[14] (See What's Happening in England? for further epidemiological context and response measures).

- In the US, B.1.617.1 comprised 0.2% (95% confidence interval [CI]: 0.1%–0.2%) of VOCs and variants of interest (VOIs) sequences collected through the Centers for Disease Control and Prevention's national genomic surveillance; B.1.617.2 0.5% (95% CI: 0.3%–0.7%); and <10 observations of B.1.617.3 between April 11 and 24, 2021.[15]

- In Canada, B.1.617 and the sublineages have been reported in one territory and all provinces.[16] The first patient identified in Quebec was reported to have been vaccinated against COVID-19 two months prior.[17]

Genomic Features

B.1.617 contains three sublineages: B.1.617.1; B.1.617.2 and B.1.617.3 with different mutation profiles (see Appendix B). Common spike gene mutations of concern across the sublineages are L452R, P681R and D614G. In addition, B.1.617.1 and B.1.617.3 carry the amino acid mutations E484Q and G142D[7] (the latter may also be found in some B.1.617.2 sequences[18]).

- L452R: this amino acid mutation occurs in the receptor-binding domain and has been associated with **immune escape** from therapeutically relevant monoclonal antibodies and convalescent sera,[9,19,20] and **enhanced receptor binding affinity and transmissibility**.[5] A preprint by Jacobson et al. reported on the detection of L452R in **breakthrough infections** by SARS-CoV-2 after vaccination; however, the risk ratios were not elevated for this mutation when community prevalence was taken into consideration.[21] It is also found in other variants including B.1.427 and B.1.429 (both first detected in California and are estimated to have increased transmissibility by up to 24%),[18,22] and B.1.526.1 (first detected in New York).[18]

- P681R: this mutation occurs near the furin cleavage site and is similar to P681H. The P681R/H mutation is also found in B.1.1.7 and has been shown to optimise spike cleavage by furin with **potentially enhanced transmissibility**.[19]

- D614G: this mutation occurs in the receptor-binding domain and is **linked to increased transmissibility, infectivity and viral loads**.[23-26]

- E484Q: this amino acid mutation has **not been associated with any change in receptor-binding avidity**,[19] unlike mutation E484K which is found in VOCs B.1.351 and P.1, and which have been linked to immune escape and potentially decreased vaccine effectiveness.[27] Findings of a preprint by Chen et al. suggest that **clinical effectiveness of some monoclonal antibodies may be compromised** by the E484Q mutation.[28] Another preprint by Ranjan et al. finds lower binding energy against antibody (CR3022) and higher binding affinity for angiotensin-converting enzyme 2 (ACE2) receptor by the E484Q and L452R mutations, compared to wild-type (not defined), and suggests **reduced vaccine efficacy**.[29]

- G142D: this mutation is associated with **immune escape from some monoclonal antibodies** but further studies are required to determine the impact on the effectiveness of vaccine and convalescent serum.[19]

Potential Public Health Impacts

Data on potential public health impacts are mostly for B.1.617.1 and B.1.617.2; there have been very few cases of B.1.617.3 globally.

Transmissibility

Epidemiological data from India and the UK, as well as two modelling studies from the UK, indicate that **B.1.617.1 and B.1.617.2 may be more easily transmitted** than non-variant strains of SARS-CoV-2.

B.1.617.1

- In India, the **proportion of B.1.617.1** among the sequenced viruses uploaded to GISAID **has increased to about 50% in late March 2021** before starting to decline in April 2021.[30]

B.1.617.2

- In India, the **proportion of B.1.617.2** among the sequenced viruses uploaded to GISAID **has been increasing since early March to become the dominant variant reported in mid-April 2021**.[30]

- In the UK, the Scientific Advisory Group for Emergencies (SAGE) reported on May 13, 2021 with high confidence that **B.1.617.2 can be up to 50% more transmissible than the VOC B.1.1.7**.[31] This is based on an observed rise in the number of sequenced cases of B.1.617.2 and of the proportion of spike-gene (S-gene)–positives being B.1.617.2 in a small number of areas.[32] S-gene–positives are specimens with cycle threshold values ≤ 30 in all S, N and ORF1ab gene targets of a specific 3-target assay (TaqPath assay) used in some laboratories. The proportion of B.1.617.2 in S-gene–positives rose from 72.2% (570/754) in the second half of April to 93% (368/397) in early May of 2021,[32] and to 97.3% in the week of May 11, 2021.[33] This happened when the proportion of B.1.1.7 among all VOCs and VOIs was declining, so local contact and behaviour patterns alone could not account for the rapid rise in B.1.617.2. However, many of these increases were detected in a small number of local regions, some of which had a higher proportion of specimens tested in laboratories using the TaqPath assay. The B.1.617.2 sublineage may also have been overrepresented as a result of targeted contact tracing in outbreak settings.[32]

- A modelling study by the Centre for Mathematical Modelling of Infectious Diseases COVID-19 Working Group **estimated the reproduction number (R) of B.1.617.2 as 1.64 (95% CI: 1.61–1.67)**. The working group used data on imported and local cases between February 1 and April 27, 2021 and assumed the same generation interval for B.1.617.2 and other strains. Imported cases of B.1.617.2 were estimated from three data sources: reported cases in India, proportion of sequenced cases that were B.1.617.2, and reported imported cases into the UK from India. The authors noted that the estimates may not generalize to other areas in the UK.[34]

- Another modelling study by the Joint Universities Pandemic and Epidemiological Research Consortium using S-gene–positives as proxy of B.1.617.2 **estimated that B.1.617.2 may have a transmission advantage of >1.4 compared to S-gene negatives**. The authors used primarily community-based COVID-19 testing data and there were significant delays in sequencing results. The authors also noted that the conclusion of increased transmissibility of B.1.617.2 could not be made due to the following factors: S-gene positives may contain other VOCs, wild-type, even

some B.1.1.7; different population and behavioural patterns and superspreading events could not be ruled out; travelling status of cases were not available; uneven geographic distribution of laboratories that test for S-gene positives.[35]

- A cluster analysis by Public Health England found that the size of COVID-19 **clusters initiated by travellers from India** tended to be larger if the index cases were infected with B.1.617.2 vs. B.1.1.7. However, the **difference in cluster sizes was not statistically significant (P=0.19)** after adjusting for the number of travellers at the origin of each cluster.[33]

SECONDARY ATTACK RATES

Data from the UK between March 29 and May 4, 2021 estimate **higher secondary attack rates for contacts of individuals infected with B.1.617.2 than those infected with B.1.1.7 or B.1.617.1**.[33]

- For contacts of cases with travel history:
    - B.1.617.2: 2.9% (174/5,908); 95% CI: 2.5%–3.4%
    - B.1.617.1: 2.2% (56/2,509); 95% CI: 1.7%–2.9%
    - B.1.1.7: 1.7% (452/26,934); 95% CI: 1.5%–1.8%
- For contacts of cases with no or unknown travel history:
    - B.1.617.2: 13.5% (537/3,977); 95% CI: 12.5%–14.6%
    - B.1.617.1: 11.0% (33/301); 95% CI: 7.9%–15.0%
    - B.1.1.7: 8.1% (5,587/68,713); 95% CI: 7.9%–8.3%

UK contact tracing data between March 29 and May 4, 2021 estimate **higher secondary attack rates among household and non-household contacts of the 1,446 cases with B.1.617.2 compared to those of cases with B.1.1.7 and with no or unknown travel history**.[33]

- For household contacts of cases with no or unknown travel history:
    - B.1.617.2: 15.0% (490/3,274); 95% CI: 13.8%–16.2%
    - B.1.1.7: 8.9% (5,019/56,374); 95% CI: 8.7%–9.1%
- For non-household contacts of cases with no or unknown travel history:
    - B.1.617.2: 6.7% (47/703); 95% CI: 5.1%–8.8%
    - B.1.1.7: 4.6% (568/12,339); 95% CI: 4.2%–5.0%

Serial Interval and Incubation Period

Contact tracing data from the UK between March 29 and May 5, 2021 estimate that the median serial interval (time between symptom-onset or testing date of index cases and symptom-onset household contacts) is 4 days for both B.1.617.2 (n=618; range 2–10 days) and B.1.1.7 (n=5,376; range 2–12 days). For non-household contacts, the median incubation period (time between exposure and symptom-onset) is 5 days for B.1.617.2 (n=160; range 2–7 days) and 4 days for B.1.1.7 (n=888; range 2–10 days).[33] In progress are longitudinal sampling studies to provide a clearer picture by overcoming some of the challenges in recall error.

Disease Severity

In India, anecdotal evidence from clinicians suggests that B.1.617 is less virulent (most patients do not require hospitalization).[12] However, a sharp rise in death rates was observed at the time of increasing incidence of B.1.617, but patient-level data are not available to determine if the increase death rates was due to higher transmission and/or suboptimal access to health care services.[30]

In the UK, there have been 12 deaths out of 5,599 cases due to B.1.617.2 as of May 25, 2021, with a case fatality rate of 0.2% (95% CI: 0.1%–0.4%), compared to 2.0% (95% CI: 1.9%–2.0%) for B.1.1.7. The actual case fatality rate may change as a high proportion of recent cases have not completed a follow up of 28 days. Meanwhile, there have been no deaths reported out of 406 cases of B.1.617.1 and 14 cases of B.1.617.3.[33]

From February 1 to May 25, 2021, 0.8% (34/5,599) of the patients with B.1.617.2 who presented to emergency departments were admitted, compared to 1.5% (2,079/136,048) of those with B.1.1.7 and 0.5% (2/406) of those with B.1.617.1.[33] There is insufficient information to date to determine if any sublineages of B.1.617 would result in more severe infections, as most cases were very recent.[36]

Impact on Testing

There is no evidence to date that indicates reduced effectiveness of molecular tests in use for diagnosing B.1.617.[30] While the detection capability of antigen tests for B.1.617 detection has not been assessed, it is unlikely that their performance would be affected. However, it is unclear at this time if B.1.617 and the sublineages may impact on serological tests.

Immunity and Reinfection

As of 25 May, 2021, 2 cases of re-infection with B.1.617.1 and 54 cases of re-infection with B.1.617.2 have been reported in the UK, as expected with any prevalent variant.[33] Also, the SARS-CoV-2 Immunity and Reinfection Evaluation (The SIREN study), which monitors COVID-19 infections among National Health Service health care workers in the UK, reported only one reinfection (VOC status not reported) between April 22 and May 21, 2021.[14]

On the other hand, SAGE speculates on some **potential reduction in protection offered by natural infection or vaccine due to the observed antigenic distance between B.1.617.2 and wild-type virus**, which is less than that for B.1.351, similar to that for B.1.617.1; greater than that for B.1.1.7.[37] Four preprints of in vitro neutralization experiments also report on **reduced neutralization of B.1.617 or the sublineages B.1.617.1 and B.1.617.2 by convalescent sera**.

- Edara et al. reported that 19/24 (79%) of convalescent sera were able to neutralize live virus of B.1.617.1 despite a significant 6.8-fold reduction in neutralization titre, compared to that against the WA1/2020 wild-type.[38]
- Planas et al. reported 6-fold reduction in neutralization titres against live virus of B.1.617.2 compared to B.1.1.7 by convalescent sera of a cohort of unvaccinated individuals (n=56) at 6 months post-infection.[39]
- Hoffmann et al. reported an approximately 2-fold reduction in neutralization titre against pseudovirus bearing B.1.617 S protein by convalescent sera (n=15), compared to the Wuhan-1 wild-type. The authors suggest that B.1.617 might evade with moderate efficiency humoral immunity in convalescent patients.[40]

- Tada et al. reported approximately 2-fold reduction in neutralization titre against pseudovirus bearing L452R/E4384Q/P681R S protein by convalescent sera (n=8), compared to the wild-type with D614G mutation.[41]

Vaccine Effectiveness

REAL-WORLD EXPERIENCE FROM THE UK: B.1.617.2

Lopez Bernal et al. compared the vaccine effectiveness against symptomatic COVID-19 in individuals tested for COVID-19 in the UK up to May 16, 2021. The authors reported that **after only one dose, vaccine effectiveness against symptomatic COVID-19 with B.1.617.2 was reduced by approximately 20% compared to that for B.1.1.7**: 33.2% (95% CI: 8.3%–51.4%) vs. 49.2% (95% CI: 42.6%–55.0%) for the Pfizer vaccine, 32.9% (95% CI: 19.3%–44.3%) vs. 51.4% (95% CI: 47.3%–55.2%) for the ChAdOx1 (i.e., AstraZeneca) vaccine. However, the **reduction in vaccine effectiveness after two doses of vaccine was very small**: 87.9% (78.2%–93.2%) vs. 93.4% (95% CI: 90.4%–95.5%) for the Pfizer vaccine; 59.8% (95% CI: 28.9%–77.3%) vs. 66.1% (95% CI: 54.0%–75.0%) for the ChAdOx1 vaccine. The study included 12,675 sequenced COVID-19 variant cases (11,621 cases with B.1.1.7 and 1,054 cases with B.1.617.2). The authors noted that shorter follow-up time after two doses of ChAdOx1 (i.e., AstraZeneca) vaccine may explain the lower vaccine effectiveness.[42]

Experience from Bolton, UK (where clusters of B.1.617.2 are have been detected) **suggests that COVID-19 vaccines are effective against B.1.617.2**, as nearly 90% of the 25 people hospitalized with COVID-19 as of May 19, 2021 were not fully vaccinated.[43] (COVID-19 vaccines used in the UK include Pfizer BNT162b2 mRNA, Moderna mRNA-1273, and Oxford/AstraZeneca.)[44]

IN VITRO NEUTRALIZATION ASSAYS

Findings from seven preprints and one peer-reviewed study, however, **suggest potential slight to moderate reduction in effectiveness** of four COVID-19 vaccines (Pfizer-BioNTech BNT162b2 mRNA, Moderna mRNA-1273, AstraZeneca, and Covaxin) compared to the wild-type or the B.1.1.7 strains. Three of the studies looked at B.1.617 while the other four focused on sublineage B.1.617.1.

B.1.617

- Hoffmann et al. reported approximately **3-fold reduction in neutralization ability by sera from fully-vaccinated Pfizer vaccinees** (n=15) against pseudovirus with B.1.617 S protein, compared to the Wuhan-1 wild-type.[40]

- Yadav et al. reported a **2-fold reduction in neutralization ability by sera from Covaxin vaccinees** (n=28; vaccination status not reported) against live virus of B.1.617, compared to the B.1 (D614G) prototype and VOC B.1.1.7.[45]

- Tada et al. reported approximately **4-fold reduction in neutralization ability by sera from Pfizer vaccinees** (n=6; vaccination status not reported) **and Moderna vaccinees** (n=3; vaccination status not reported) against pseudovirus with L452R, E484Q and P681R spike mutations, compared to the wild-type with D614G mutation.[41]

B.1.617.1

- Ferreira et al. reported **significant reduction in neutralization ability** (actual titre not reported) compared to the Wuhan-1 D614G wild-type, when pseudovirus bearing spike mutations in L452R and E484Q (proxy of B.1.617.1) were tested with sera from Pfizer vaccinees (n=9; vaccination status not reported).[46]

- Edara et al. reported that **all sera from Moderna fully-vaccinated vaccinees (n=15) and Pfizer fully-vaccinated vaccinees (n=10) were able to neutralize live virus** of B.1.617.1 despite a **significant 6.8-fold reduction in neutralization ability** compared to that against the WA1/2020 wild-type.[38]

- Yadav et al. reported that 22/43 (51%) of sera from fully-vaccinated Covishield vaccinees without prior COVID-19 infection did not show any neutralizing antibodies against B.1.617.1. A **significant 2-fold reduction in neutralization ability** against B.1.617.1 was observed compared to the B.1 (D614G) prototype. With a geometric mean titre of 21.92 ± 4.42 (95% CI: 24.4–62.64) against B.1.617.1, the authors speculate that the vaccine are likely to protect against severe infection and death from that sublineage.[47]

- Shi et al. reported that **all sera from Pfizer fully-vaccinated vaccinees (n=20) were able to neutralize pseudovirus** bearing mutations in G142D, E154K, L452R, E484Q, D614G, P618R, Q1071H, H1101D and D111 as proxy of B.1.617.1, despite a 0.26 times reduction in plaque reduction neutralization testing ($PRNT_{50}$) compared to that of the wild-type WA1/2020.[48]

B.1.617.2

- Planas et al. reported that 94% of sera (n=16) at 8 weeks after two doses of **Pfizer** vaccine were **able to neutralize live virus of B.1.617.2, despite a 3-fold reduction in neutralization titres compared to that for B.1.1.7**. Even at 16 weeks after vaccination, neutralization ability was retained by 85% of the sera. On the other hand, **only 8% of sera (n=12) from vaccinees with one dose of AstraZeneca vaccine were able to neutralize the virus**. However, even one dose of vaccine (9 with Pfizer, 9 with AstraZeneca, 3 with Moderna) was observed to increase the median neutralizing titres in convalescent sera (n=23) by 130-fold against both B.1.1.7 and B.1.617.2 even at 12 months after infection, suggesting a **single dose of vaccine could boost cross-neutralizing antibody responses**.[39]

What's Happening in England?

Epidemiological Context

- The 7-day rolling average daily cases of COVID-19 rose slowly from late February 2020 to plateau around 4,500 to 4,800 in April 2020, then declined to stay below 700 during late-June to late-July 2020. Daily cases started to climb in September 2020 and plateaued around 21,000 and 24,600 from mid-October to mid-November 2020, dipped quickly to around 14,500 in late November before shooting to the peak of 61,239 in early January 2021. Since then, daily cases have been declining rapidly to around 12,000 in mid-February, then slowly to a low of 1,847 at the end of April 2021, and hovering around 1,900 to 2,100 for the first week of May. As of May 15, 2021, the 7-day rolling average number of daily new COVID-19 cases in England was 1,563 (22 cases per 100,000). As of May 14, 2021, the cumulative number of cases in England was 4.4 million.[49]

- The 7-day average daily admission to hospitals due to COVID-19 rose sharply from late March 2020 to a peak at 3,116 in early April 2020, then dropped slowly to a low of 97 in late August 2020. Daily admission then rose to a high of 1,777 in mid-November 2020 and peaked at 4,232 in mid-January 2021. Daily admission was at 234 at the start of April and hovered around 100 and 120 for the first week of May in 2021.[50]

- In the past 7 days (as of May 17, 2021) the areas with the greatest rates of cases per 100,000 were the Yorkshire and The Humber regions (2151 cases or 39.1 per 100,000) and the North West region (2764 cases or 37.7 per 100,000)[51]

- On April 9, 2021, B.1.617.2 made up 0.1% of COVID-19 cases in England, and by May 7, 2021, the lineage made up 19.6% of cases.[52] UK experts expect B.1.617.2 to become the dominant lineage by the end of the week of May 18, 2021, if not already.[53] As of May 17, 2021, there were 2,323 confirmed cases of B.1.617 in the UK, which represents a 77% increase from just five days earlier.[54]

- North West and South Central England have the highest proportions of B.1.617.2 cases, but cases are being reported across the country.[54]

- In Blackburn and Bolton (North West England) where the B.1.617 variant are spreading the fastest,[55] the number of cases among those under 60 years of age has increased significantly more than among those over 60 (who are more likely to be vaccinated) suggesting the effectiveness of vaccines.[56] The majority of the cases in Bolton were individuals in their teens, 20s and 30s, most of whom had not been vaccinated against Covid-19.[57]

Vaccine Context

- As of May 18, 2021, 57.9 million doses of the COVID-19 vaccine had been administered; 70.2% of the population had received at least one dose of the COVID-19 vaccine and 39.6% were fully vaccinated.[58]

- As of May 13, 2021, the vaccine is currently being offered to: individuals aged 36 and over and individuals who will turn 36 before July 1, 2021, individuals at high risk from COVID-19 (clinically extremely vulnerable), individuals who live or work in care homes, health and social care workers, individuals with a condition that puts them at higher risk (clinically vulnerable), individuals with a learning disability, and individuals who are a main carer for someone at high risk from COVID-19.[44]

- To address the rising cases of B.1.617.2, the government announced on May 14, 2021 that it would shorten the interval for second doses from 12 weeks to 8 weeks for the country's top 9 priority groups.[59] England is also accelerating COVID-19 vaccinations in regions with a high proportion of B1.617.2 cases.

Public Health Measures

- As of May 17, 2021, the English government started loosening restrictions for a variety of public health measures, including indoor settings such as hospitality and organized sports.[55]

- The government recommends that particular caution be used in certain areas of England (i.e., Bolton Metropolitan Borough and Blackburn with Darwen Borough) where variants are spreading the fastest.[55]

- In a press conference on May 14, 2021, the prime minister stated that if the B.1.617 variant turns out to be only marginally more transmissible, the country can continue to move forwards with their re-opening plan; however, if it is significantly more transmissible the roadmap to re-opening may have to be delayed or adapted (particular Step 4 in June[60] which involves removing all legal limits on social contact[61]).

Actions Taken to Control the Spread of Variants

- A press release from May 13, 2021 stated that due to the recent surge in B.1.617.2 cases in select regions, "a new Surge Rapid Response Team is being deployed in Bolton, additional surge testing will shortly launch in areas such as Formby, and enhanced contact tracing is in place across England".[62] Additionally, in areas where clusters of cases have been identified additional contact tracing, increased genomic sequencing of positive cases, increased community engagement and support for individual to get tested and self-isolate, and ensure access to vaccination and encourage uptake.

- England has also accelerated genomic sequencing, enhanced contact tracing and implemented surge testing in the North West in efforts to rapidly break chains of B.1.617.2 transmission.[63]

Ontario Context

- Currently, all positive SARS-CoV-2 specimens in Ontario with a cycle threshold (Ct) value ≤35 are tested for presence of the N501Y and E484K mutations, and only specimens positive for E484K mutation with Ct value ≤30 will be sequenced.[64] It is unclear at this time whether the current E484K assay will detect the E484Q mutation associated with B.1.617.

- Approximately 90%–95% of positive specimens that undergo VOC testing in Ontario have either N501Y and/or E484K mutations.[65] As these mutations are not associated with the B.1.617 lineage, the vast majority of specimens in Ontario are highly unlikely to be B.1.617. A proportion of non-VOC specimens are routinely sent for sequencing, in addition to all travel-related positive specimens, as part of Ontario's ongoing surveillance for emerging variants.

- As of May 19, 2021, there have been 260 cases with B.1.617 detected in Ontario (an increase from 45 as of May 12). Of the 260 cases, 203 were tested by the National Microbiology Laboratory as part of international travel arrival quarantine procedures, while 57 were detected by PHO, most of whom were associated with out-of-country travel.[66]

Risk Assessment and Practice Implications

Overall risk assessment: The risk of B.1.617 transmission in Ontario is moderate to high and depends on the number of existing B.1.617 cases and continued introductions into the province. Given the rapid emergence of B.1.617, PHO's level of confidence in the existing primary literature, preprint literature and grey literature is low but building up quickly with emergence of new evidence. This overall risk assessment may change as new evidence emerges.

- **Transmissibility:** The risk of increased transmissibility by B.1.617 is high, with a relatively low degree of uncertainty.

- **Disease severity:** The risk of B.1.617 causing severe disease is unknown.

- **Immunity and re-infection:** The risk of re-infection with B.1.617 in convalescent patients is low, with a high degree of uncertainty.

- **Vaccine effectiveness:** The risk of B.1.617 causing lowered vaccine effectiveness is moderate, with a moderate degree of uncertainty.

- **Surveillance:** The risk of B.1.617 cases not being detected in Ontario's surveillance program is moderate, with a moderate degree of uncertainty.

Surveillance testing (including genomic sequencing of a sufficient sample of positive cases) will help us better understand the epidemiology of B.1.617. Currently, there is no indication that individual or societal public health measures such as case and contact management, vaccination rollout and non-pharmaceutical interventions such as physical distancing in Ontario need to be changed. However, ongoing monitoring of single-dose vaccine effectiveness and the impact of England's shortened second-dose schedule will help to inform Ontario's second-dose roll-out. Heightened surveillance, close monitoring of case rate indicators, and local assessment of transmissibility are also needed to inform public health measures and Ontario's new recovery plan.[67]

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Appendix A

For the purposes of this document, the definition of variants of interest (VOI) and variants of concern (VOC) as proposed by the Canadian SARS-CoV-2 Variants Expert Working Group (CSVEWG) are used.[8]

Variant of Interest (VOI)

A SARS-CoV-2 variant is a variant of interest (VOI) if it:

- has a genome with mutations associated with changes in epidemiology, antigenicity, or virulence, or changes that potentially have a negative impact on available diagnostics, vaccines, therapeutics or public health measures; AND is known to cause community transmission/multiple COVID-19 cases/clusters in Canada or has been detected in multiple countries; OR
- is otherwise assessed to be a VOI by WHO; OR
- is otherwise assessed to be a VOI by the CSVEWG.

Variant of Concern (VOC)

A variant is a VOC if, through a comparative assessment, it:

- has been demonstrated to be associated with one or more of the following:
    - increased transmissibility or detrimental change in COVID-19 epidemiology;
    - increased virulence or change in clinical disease presentation;
    - decreased effectiveness of available diagnostics, vaccines, therapeutics or public health measures; OR
- is otherwise assessed to be a VOC by WHO; OR
- is otherwise assessed to be a VOC by the CSVEWG.

Appendix B

Notable mutations in the spike protein (non-synonymous) found in the B.1.617 sublineages[§7]

Amino acid substitution or deletion	B.1.617.1	B.1.617.2	B.1.617.3
D614G	**Yes**	**Yes**	**Yes**
D950N	No	**Yes**	**Yes**
E484Q	**Yes**	No	**Yes**
G142D	**Yes**	**Yes**	No
E154K	**Yes**	No	No
L452R	**Yes**	**Yes**	**Yes**
P681R	**Yes**	**Yes**	**Yes**
Q1071H	**Yes**	No	No
T19R	No	**Yes**	**Yes**
T478K	No	**Yes**	No
Δ157/158	No	**Yes**	No

§ Characteristic spike mutations detected in more than 60% of sequences.[7]

Citation

Ontario Agency for Health Protection and Promotion (Public Health Ontario). COVID-19 B.1.617 variant of concern – what we know so far. Toronto, ON: Queen's Printer for Ontario; 2021.

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This is **Exhibit "JJ"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

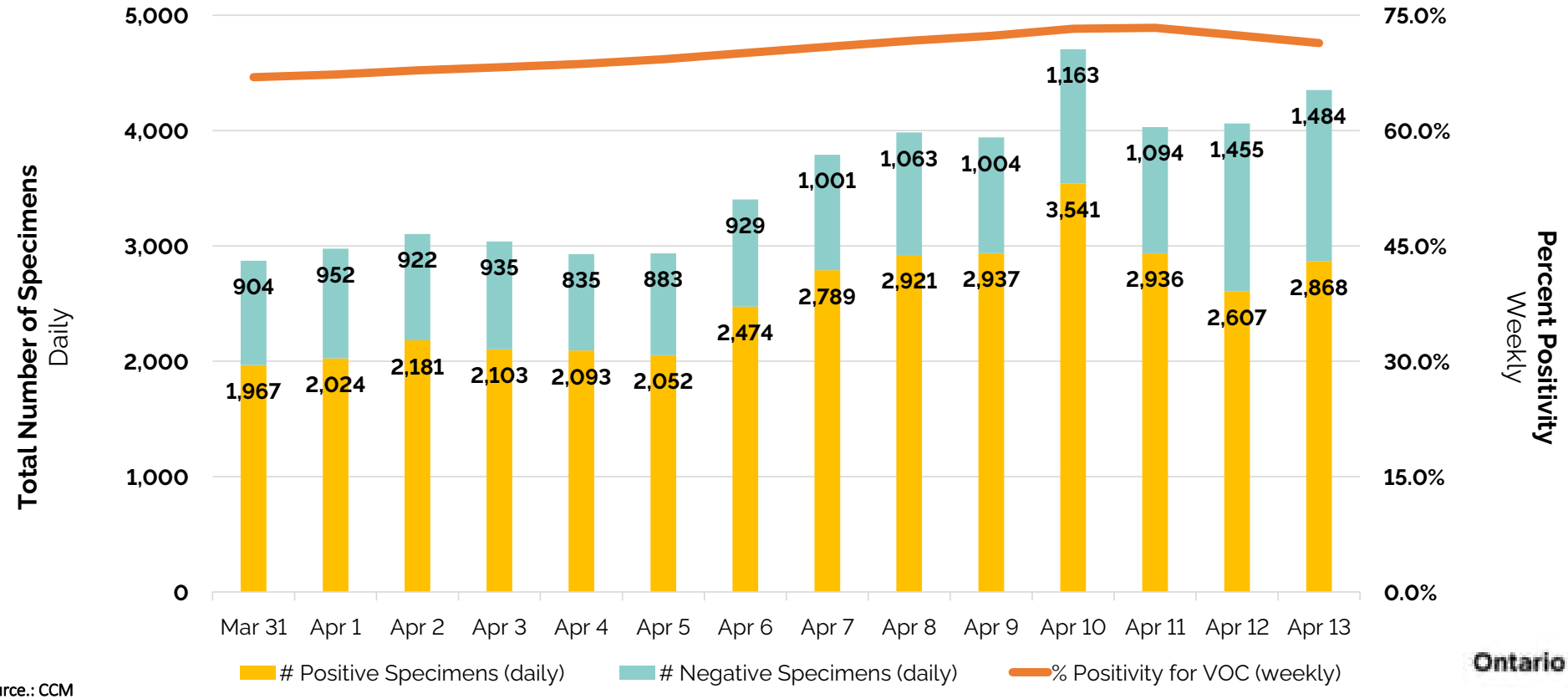
Variant COVID-19 Cases

As of April 19, 2021

The % positivity for VOCs (weekly) is leveling out around 70%.

64,643
cases with a mutation or VOC detected

71.4% Weekly Percent Positivity (April 13)
70.1 % Previous week (April 6)



Source.: CCM

This is **Exhibit "KK"** referred to
in the Affidavit of DR. DAVID McKEOWN,
affirmed this 5th day of July, 2021.

Ryan Cookson

A Commissioner for the Taking of Affidavits

Public Health Ontario | Santé publique Ontario

DAILY EPIDEMIOLOGICAL SUMMARY

COVID-19 in Ontario: January 15, 2020 to July 3, 2021

This report includes the most current information available from CCM as of **July 3, 2021**.

Please visit the interactive Ontario COVID-19 Data Tool to explore recent COVID-19 data by public health unit, age group, sex, and trends over time.

A weekly summary report is available with additional information to complement the daily report.

This **daily** report provides an epidemiologic summary of recent COVID-19 activity in Ontario. The change in cases is determined by taking the cumulative difference between the current day and the previous day.

Highlights

- There are a total of 545,803 confirmed cases of COVID-19 in Ontario reported to date.
- Compared to the previous day, this represents:
    - An increase of 213 confirmed cases (percent change of +1.9%)
    - An increase of 9 deaths (percent change of 0.0%)
    - An increase of 286 resolved cases (percent change of +9.2%)

In this document, the term 'change in cases' refers to cases publicly reported by the province for a given day. Data corrections or updates can result in case records being removed and or updated from past reports and may result in subset totals for updated case counts (i.e., age group, gender) differing from the overall updated case counts.

The term public health unit reported date in this document refers to the date local public health units were first notified of the case.

Case Characteristics

Table 1a. Summary of recent confirmed cases of COVID-19: Ontario

	Change in cases July 2, 2021	Change in cases July 3, 2021	Percentage change July 3, 2021 compared to July 2, 2021	Cumulative case count as of July 3, 2021
Total number of cases	209	213	+1.9%	545,803
Number of deaths	9	9	0.0%	9,214
Number resolved	262	286	+9.2%	534,558

Note: The number of cases publicly reported by the province each day may not align with case counts reported to public health on a given day; public health unit reported date refers to the date local public health was first notified of the case. Data corrections or updates can result in case records being removed and or updated from past reports.
Data Source: CCM

Table 1b. Summary of recent confirmed cases of COVID-19 by age group and gender: Ontario

	Change in cases July 2, 2021	Change in cases July 3, 2021	Cumulative case count as of July 3, 2021
Gender: Male	109	111	271,959
Gender: Female	96	95	270,054
Ages: 19 and under	57	51	87,920
Ages: 20-39	83	64	204,406
Ages: 40-59	42	53	155,746
Ages: 60-79	19	37	72,521
Ages: 80 and over	7	8	25,110

Note: Not all cases have a reported age or gender reported. Data corrections or updates can result in case records being removed and or updated from past reports and may result in subset totals (i.e., age group, gender) differing from past publicly reported case counts.
Data Source: CCM

Table 2. Summary of recent confirmed cases of COVID-19 in school aged children by age group, August 30, 2020 to July 3, 2021: Ontario

	Change in cases July 2, 2021	Change in cases July 3, 2021	Cumulative case count from August 30, 2020 to July 3, 2021
Ages: 4 to 8	18	11	16,260
Ages: 9 to 13	8	14	20,360
Ages: 14 to 17	8	10	20,720

Note: Includes all confirmed cases of COVID-19 for specified ages, regardless of school attendance. Data corrections or updates can result in case records being removed and or updated from past reports and may result in subset totals (i.e., age group) differing from past publicly reported case counts.
Data Source: CCM

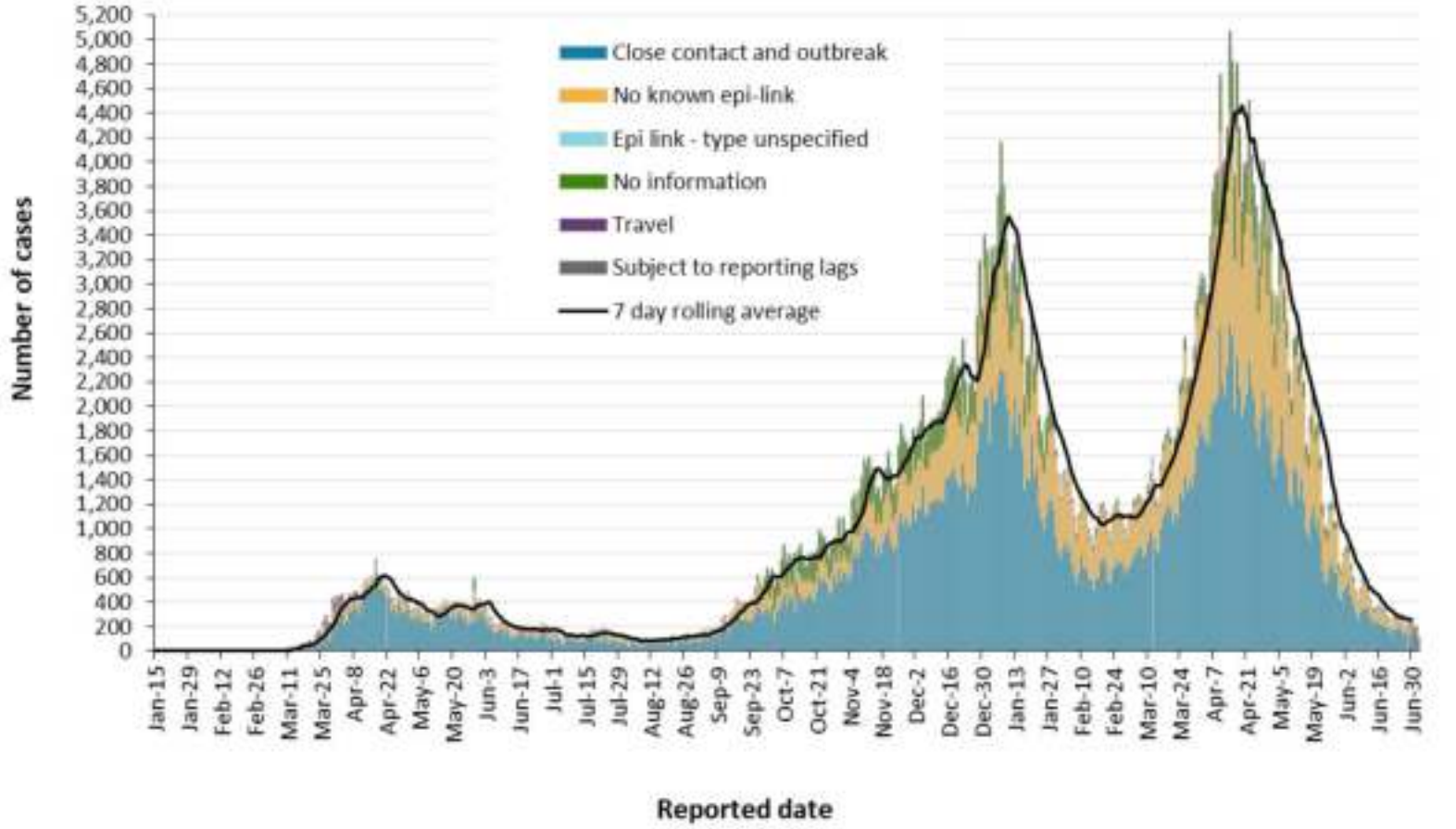
Table 3. Summary of recent confirmed cases of COVID-19 in long-term care homes: Ontario

Long-term care home cases	Change in cases July 2, 2021	Change in cases July 3, 2021	Cumulative case count as of July 3, 2021
Residents	1	1	15,400
Health care workers	1	0	7,195
Deaths among residents	0	1	3,971
Deaths among health care workers	0	0	10

Note: Information on how long-term care home residents and health care workers are identified is available in the technical notes. Also, the change in cases in these categories may represent existing case records that have been updated.
Data Source: CCM

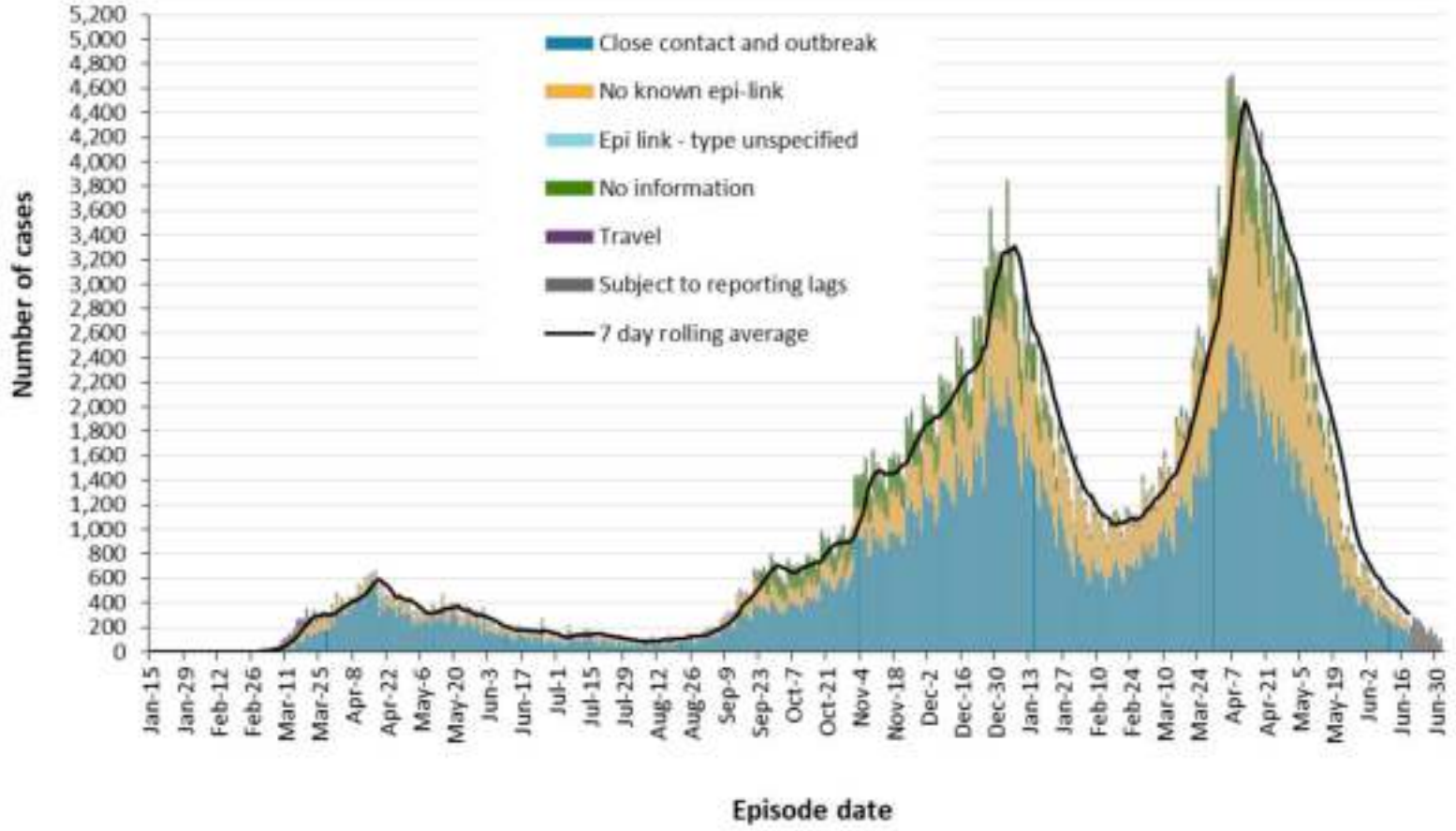
Time

Figure 1. Confirmed cases of COVID-19 by likely acquisition and public health unit reported date: Ontario, January 15, 2020 to July 3, 2021



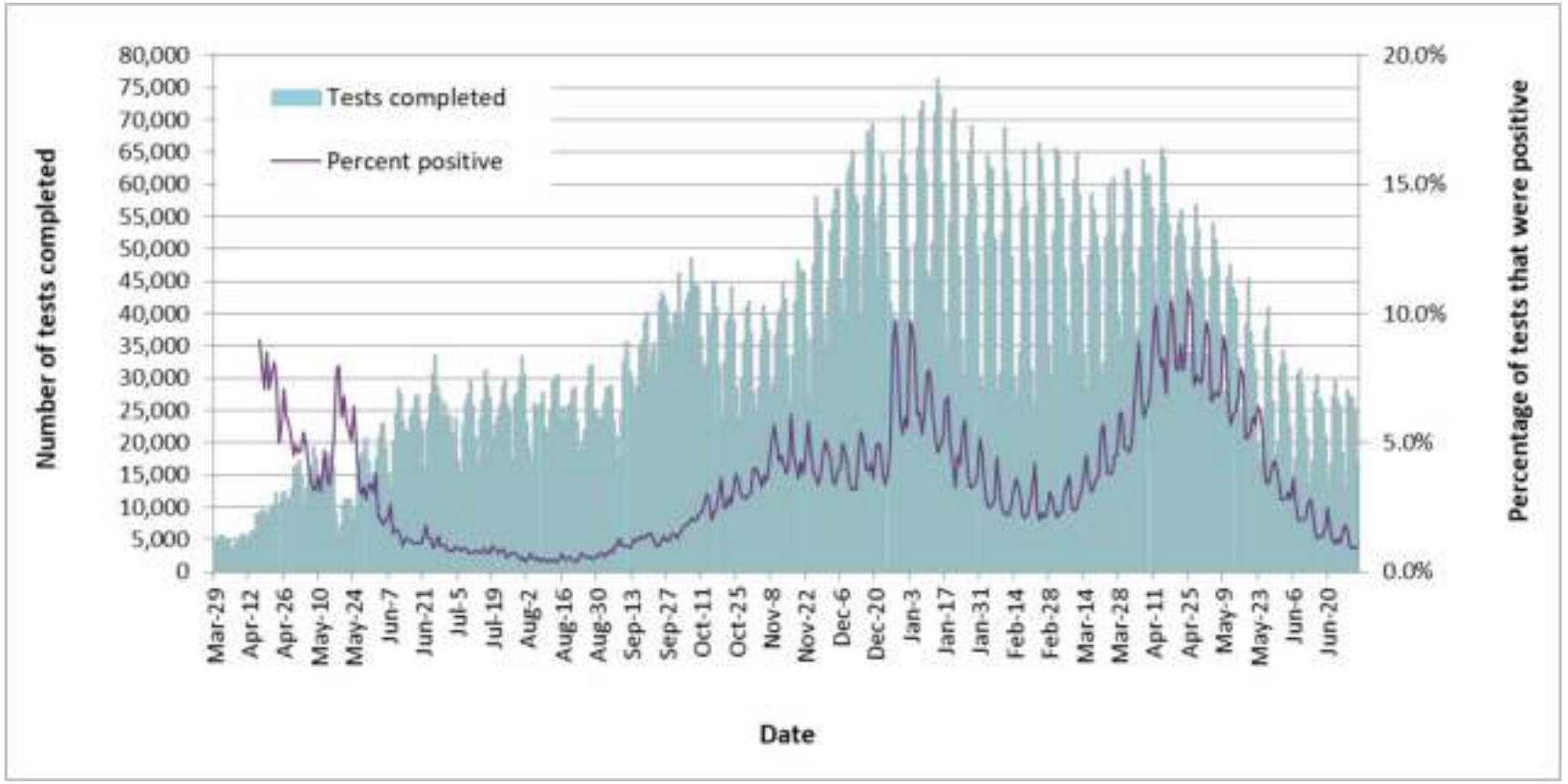
Data Source: CCM

Figure 2. Confirmed cases of COVID-19 by likely acquisition and approximation of symptom onset date: Ontario, January 15, 2020 to July 3, 2021



Note: Not all cases may have an episode date and those without one are not included in the figure. Episode date is defined and available in the technical notes.
Data Source: CCM

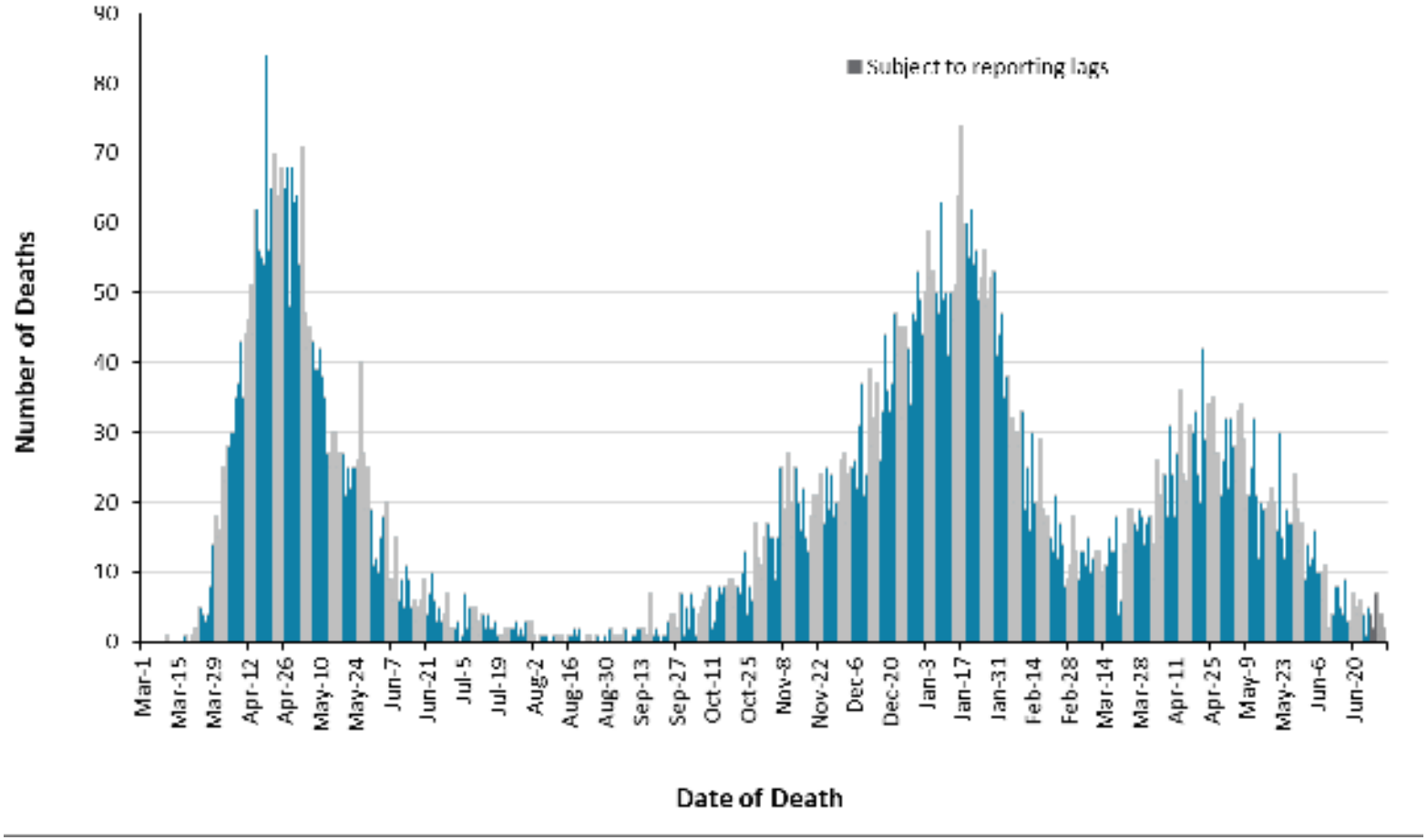
Figure 3. Number of COVID-19 tests completed and percent positivity: Ontario, March 29, 2020 to July 2, 2021



Note: The number of tests performed does not reflect the number of specimens or persons tested. More than one test may be performed per specimen or per person. As such, the percentage of tests that were positive does not necessarily translate to the number of specimens or persons testing positive.
Data Source: The Provincial COVID-19 Diagnostics Network, data reported by member microbiology laboratories.

Severity

Figure 4. Confirmed deaths among COVID-19 cases by date of death: Ontario, March 1, 2020 to July 3, 2021



Note: Cases without a death date are not included in the figure.
Data Source: CCM

Table 4. Confirmed cases of COVID-19 by severity: Ontario

	Cumulative case count as of July 3, 2021	Percentage of all cases
Cumulative deaths reported (please note there may be a reporting delay for deaths)	9,214	1.7%
Deaths reported in ages: 19 and under	4	<0.1%
Deaths reported in ages: 20-39	82	<0.1%
Deaths reported in ages: 40-59	581	0.4%
Deaths reported in ages: 60-79	2,937	4.0%
Deaths reported in ages: 80 and over	5,609	22.3%
Ever in ICU	5,378	1.0%
Ever hospitalized	27,962	5.1%

Note: Not all cases have an age reported. Data corrections or updates can result in case records being removed and/or updated and may result in totals differing from past publicly reported case counts.
Data Source: CCM

Geography

Table 5. Summary of recent confirmed cases of COVID-19 by public health unit and region: Ontario

Public Health Unit Name	Change in cases July 2, 2021	Change in cases July 3, 2021	Cumulative case count	Cumulative rate per 100,000 population
Northwestern Health Unit	0	0	1,091	1,244.4
Thunder Bay District Health Unit	-2	0	3,337	2,225.3
TOTAL NORTH WEST	-2	0	4,428	1,863.4
Algoma Public Health	0	0	400	349.5
North Bay Parry Sound District Health Unit	1	1	607	467.8
Porcupine Health Unit	5	6	2,080	2,492.8
Public Health Sudbury & Districts	2	2	2,150	1,080.3
Timiskaming Health Unit	0	0	208	636.3
TOTAL NORTH EAST	8	9	5,445	973.5
Ottawa Public Health	11	9	27,682	2,624.7
Eastern Ontario Health Unit	-7	0	4,610	2,208.8
Hastings Prince Edward Public Health	0	0	1,133	672.4
Kingston, Frontenac and Lennox & Addington Public Health	-1	2	1,551	729.1
Leeds, Grenville & Lanark District Health Unit	0	0	1,752	1,011.7
Renfrew County and District Health Unit	1	0	744	684.9
TOTAL EASTERN	4	11	37,472	1,945.2

Public Health Unit Name	Change in cases July 2, 2021	Change in cases July 3, 2021	Cumulative case count	Cumulative rate per 100,000 population
Durham Region Health Department	6	6	25,237	3,542.5
Haliburton, Kawartha, Pine Ridge District Health Unit	5	1	2,171	1,149.1
Peel Public Health	12	17	109,517	6,819.4
Peterborough Public Health	1	1	1,593	1,076.5
Simcoe Muskoka District Health Unit	6	3	12,384	2,065.4
York Region Public Health	4	4	52,625	4,293.1
TOTAL CENTRAL EAST	34	32	203,527	4,542.4
Toronto Public Health	20	42	165,100	5,291.1
TOTAL TORONTO	20	42	165,100	5,291.1
Chatham-Kent Public Health	0	0	1,884	1,772.1
Grey Bruce Health Unit	20	25	1,658	976.0
Huron Perth Public Health	2	5	1,936	1,385.3
Lambton Public Health	3	0	3,605	2,752.7
Middlesex-London Health Unit	2	9	12,585	2,479.7
Southwestern Public Health	1	1	3,884	1,836.4
Windsor-Essex County Health Unit	11	-4	16,862	3,969.1
TOTAL SOUTH WEST	39	36	42,414	2,508.6
Brant County Health Unit	-1	0	3,854	2,483.2
City of Hamilton Public Health Services	8	10	21,284	3,594.3
Haldimand-Norfolk Health Unit	1	1	2,681	2,350.1

Public Health Unit Name	Change in cases July 2, 2021	Change in cases July 3, 2021	Cumulative case count	Cumulative rate per 100,000 population
Halton Region Public Health	22	12	17,421	2,814.0
Niagara Region Public Health	20	6	16,247	3,438.6
Region of Waterloo Public Health and Emergency Services	47	49	17,726	3,033.4
Wellington-Dufferin-Guelph Public Health	9	5	8,204	2,630.3
TOTAL CENTRAL WEST	106	83	87,417	3,068.0
TOTAL ONTARIO	**209**	**213**	**545,803**	**3,671.9**

Notes: Health units with data corrections or updates could result in records being removed from totals, leading to negative or zero counts.
Data Source: CCM

Outbreaks

Table 6. Summary of recent confirmed COVID-19 outbreaks reported in long-term care homes, retirement homes and hospitals by status: Ontario

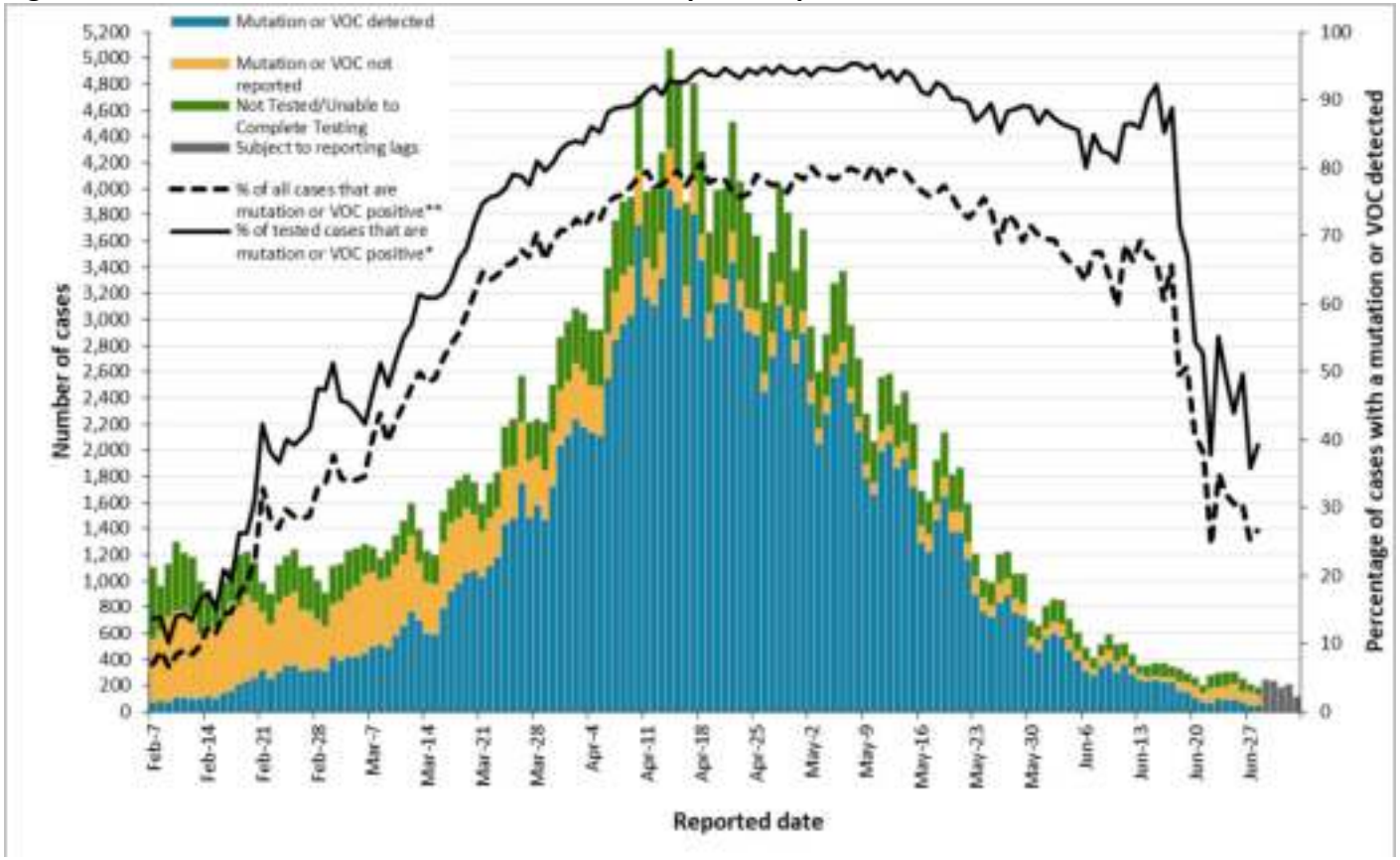
Institution type	Change in outbreaks July 2, 2021	Change in outbreaks July 3, 2021	Number of ongoing outbreaks	Cumulative number of outbreaks reported
Long-term care homes	0	1	4	1,486
Retirement homes	0	0	3	871
Hospitals	2	0	7	575

Note: Ongoing outbreaks include all outbreaks that are 'Open' in CCM without a 'Declared Over Date' recorded, or where the outbreak started more than five months ago, even for outbreaks where the Outbreak Status value selected in CCM is 'OPEN'. The start of the outbreak is determined by the onset date of first case, or if missing the outbreak reported date, or else if that is also missing, then the outbreak created date.
Data Source: CCM

Variant COVID-19 Cases

The laboratory detection of a variant of concern (VOC) is a multi-step process. Samples that test positive for SARS-CoV-2 and have a cycle threshold (Ct) value ≤ 35 can be tested for mutations common to variants of concern. If positive for the mutation of interest with a Ct value of ≤ 30, these samples may then undergo genomic analyses to identify the VOC lineage. VOC lineages may still be confirmed using genomic analysis despite specific S gene mutation(s) being documented as 'unable to complete' due to poor sequence quality at the genome position. For more information about whole genome sequencing, please see the SARS CoV-2 Whole Genome Sequencing in Ontario report.

Figure 5. Number of confirmed COVID-19 cases and percent positive for mutations or VOCs: Ontario, February 7, 2021 to July 3, 2021



Note: Data used to calculate the number of cases tested for mutations common to VOCs or lineages using genomic analyses are obtained using information from the Laboratory object in CCM in addition to the data from the Investigation Subtype field. Therefore, comparisons to counts using only information from the Investigation Subtype field may not align. The percent of cases due to a VOC may be higher than described in this report.
*The denominator includes only confirmed COVID-19 cases that were able to be tested for VOCs (e.g. those identified as 'Detected' or 'Not Detected'). Mutations tested for routinely are the N501Y and E484K mutations. Mutations common to the B.1.617.2 lineage are not included in the current VOC mutation test. However, cases identified as B.1.617.2 after whole genome sequencing is completed are included in the VOC detected category.
**The denominator includes all confirmed COVID-19 cases, including those that were unable to be tested for VOCs (e.g. those identified as 'Detected', 'Not Detected' and 'Not Tested/Unable to Complete Testing').
Data Source: CCM

Table 7. Summary of confirmed COVID-19 cases with a mutation or VOC detected: Ontario

	Change in cases July 2, 2021	Change in cases July 3, 2021	Cumulative case count up to July 3, 2021
Variant of Concern			
Lineage B.1.1.7 (Alpha)*	34	32	143,899
Lineage B.1.351 (Beta)**	0	0	1,415
Lineage P.1 (Gamma) ***	3	0	4,631
Lineage B.1.617.2 (Delta)†	32	14	2,041
Mutations			
N501Y and E484K	-1	4	4,709
N501Y (E484K unknown)‡	-4	3	13,957
E484K (N501Y negative)	5	3	5,810
E484K (N501Y unknown)	-3	-4	452
Mutation not detected§	19	7	11,693

Note: Interpret the VOC and mutation trends with caution due to the varying time required to complete VOC testing and/or genomic analysis following the initial positive test for SARS-CoV-2. Due to the nature of the genomic analysis, test results may be completed in batches. Data corrections or updates can result in case records being removed and/or updated and may result in totals differing from past publicly reported case counts. Data for calculating the change in cases and the cumulative case counts uses data from the Investigation Subtype field only. Changes to the VOC testing algorithm may impact counts and trends. Further details can be found in the data caveats section.

*Includes all confirmed COVID-19 cases where lineage B.1.1.7 was identified by genomic analysis and those presumed to be B.1.1.7 based on positive N501Y and negative E484K mutation in the Investigation Subtype field

**Includes B.1.351 cases identified by genomic analysis and those presumed to be B.1.351 based on 'Mutation K417N+ and N501Y+ and E484K+' in the Investigation Subtype field

***Includes P.1 cases identified by genomic analysis and those presumed to be P.1 based on 'Mutation K417T+ and N501Y+ and E484K+' in the Investigation Subtype field

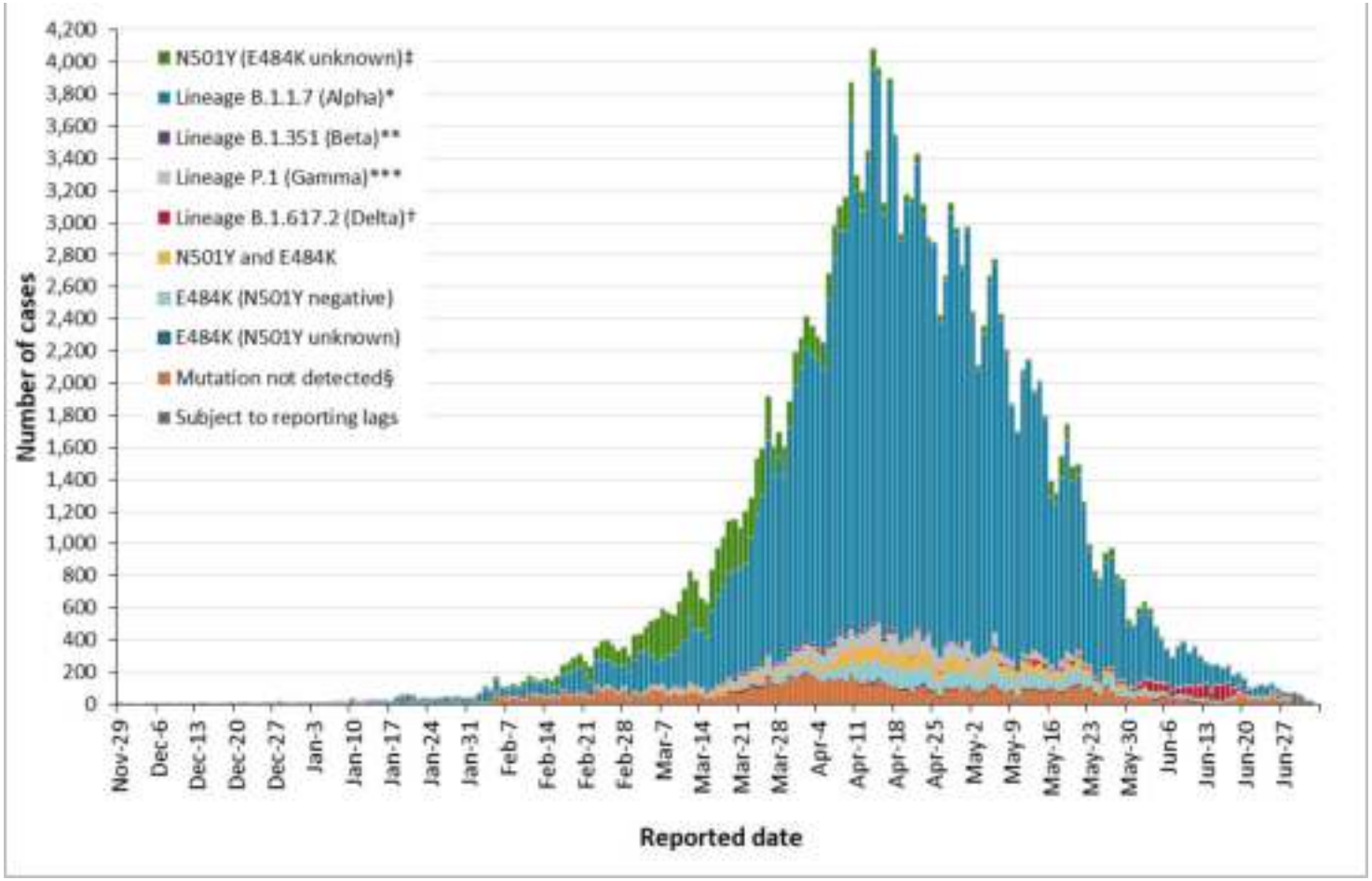
†Includes B.1.617.2 cases identified by genomic analysis. Mutations common to B.1.617.2 are not included in the current VOC mutation test.

‡The category 'N501Y (E484K unknown)' mainly consists of results from before the introduction of the E484K test. Counts will shift from this category into a VOC lineage category as E484K tests or genomic analysis are completed.

§Includes cases identified as 'Mutation not detected' or 'Mutation N501Y- and E484K-' in the Investigation Subtype field only.

Data Source: CCM

Figure 6. Confirmed COVID-19 cases with a mutation or VOC detected by public health unit reported date: Ontario, November 29, 2020 to July 3, 2021



Note: Reported date is based on the date the case was reported, not the date that the VOC or mutation was identified. Further details on testing for variants of concern can be found in the technical notes. Interpret the VOC and mutation trends with caution due to the varying time required to complete testing and/or genomic analysis following the initial positive test for SARS-CoV-2. Data for calculating the change in cases and the cumulative case count uses data from the Investigation Subtype field only. Data for cases with a B.1.1.7, B.1.351, P.1 and B.1.617.2 lineage detected or any of the mutations listed above are determined using the

Investigation Subtype field only. Changes to the VOC testing algorithm may impact counts and trends. Further details can be found in the data caveats section. As of March 22, 2021, positive specimens with a Ct ≤ 35 are tested for both the N501Y and E484K mutation, with all E484K positive specimens with a Ct ≤ 30 forwarded for further genomic analysis. If found to be positive for the N501Y mutation only, no further genomic analysis are performed as these are presumed to be B.1.1.7. As of May 26, 2021, cases where an E484K mutation is detected will no longer be reflexed for sequencing as VOC testing labs switched to a representative sampling method where only a proportion of all positives with a Ct ≤ 30 are forwarded for further genomic analysis.

*Includes all confirmed COVID-19 cases where lineage B.1.1.7 was identified by genomic analysis and those presumed to be B.1.1.7 based on positive N501Y and negative E484K mutation in the Investigation Subtype field

**Includes B.1.351 cases identified by genomic analysis and those presumed to be B.1.351 based on 'Mutation K417N+ and N501Y+ and E484K+' in the Investigation Subtype field

***Includes P.1 cases identified by genomic analysis and those presumed to be P.1 based on 'Mutation K417T+ and N501Y+ and E484K+' in the Investigation Subtype field

†Includes B.1.617.2 cases identified by genomic analysis. Mutations common to B.1.617.2 are not included in the current VOC mutation test.

‡The category 'N501Y (E484K unknown)' mainly consists of results from before the introduction of the E484K test. Counts will shift from this category into a VOC lineage category as E484K tests or genomic analysis are completed.

§Includes cases identified as 'Mutation not detected' or 'Mutation N501Y- and E484K-' in the Investigation Subtype field only.

Data Source: CCM

Technical Notes

Data Sources

- The data for this report were based on information successfully extracted from the Public Health Case and Contact Management Solution (CCM) for all PHUs by PHO as of **July 3, 2021 at 1 p.m**. for cases reported from February 1, 2021 onwards and as of **July 2, 2021 at 9 a.m.** for cases reported up to January 31, 2021.

- VOC data for this report were based on information successfully extracted from CCM for all PHUs by PHO as of **July 3, 2021 at 1 p.m.** for cases reported from April 1, 2021 onwards and as of **July 2, 2021 at 9 a.m.** for cases reported up to March 31, 2021.

- CCM is a dynamic disease reporting system, which allows ongoing updates to data previously entered. As a result, data extracted from CCM represent a snapshot at the time of extraction and may differ from previous or subsequent reports.

- Ontario population projection data for 2020 were sourced from Ministry, IntelliHEALTH Ontario. Data were extracted on November 26, 2019.

- COVID-19 test data were based on information from The Provincial COVID-19 Diagnostics Network, reported by member microbiology laboratories.

Data Caveats

- The data only represent cases reported to public health units and recorded in CCM. As a result, all counts will be subject to varying degrees of underreporting due to a variety of factors, such as disease awareness and medical care seeking behaviours, which may depend on severity of illness, clinical practice, changes in laboratory testing, and reporting behaviours.

- Data cleaning for older cases is incorporated on Mondays and may impact the case count published on Tuesdays

- Lags in CCM data entry due to weekend staffing may result in lower case counts than would otherwise be recorded.

- Only cases meeting the confirmed case classification as listed in the MOH Case Definition – Coronavirus Disease (COVID-19) document are included in the report counts from CCM

- Cases of confirmed reinfection, as defined in the provincial case definitions, are counted as unique investigations.

- Case classification information may be updated for individuals with a positive result issued from a point-of-care assays.

- The number of tests performed does not reflect the number of specimens or persons tested. More than one test may be performed per specimen or per person. As such, the percentage of tests that were positive does not necessarily translate to the number of specimens or persons testing positive.

- Reported date is the date the case was reported to the public health unit.

- Case episode date represents an estimate of disease onset. This date is calculated based on the earliest date of symptom onset, specimen collection/test date, or the date reported to the public health unit.

- Resolved cases are determined only for COVID-19 cases that have not died. Cases that have died are considered fatal and not resolved. The following cases are classified as resolved:

    - Cases that are reported as 'recovered' in CCM

    - Cases that are not hospitalized and are 14 days past their episode date

    - Cases that are currently hospitalized (no hospital end date entered) and have a status of 'closed' in CCM (indicating public health unit follow-up is complete) and are 14 days past their symptom onset date or specimen collection date

- Hospitalization includes all cases for which a hospital admission date was reported or hospitalization/ICU was reported as 'Yes' at the time of data extraction. It includes cases that have been discharged from hospital as well as cases that are currently hospitalized. Emergency room visits are not included in the number of reported hospitalizations.

- ICU admission includes all cases for which an ICU admission date was reported at the time of data extraction. It is a subset of the count of hospitalized cases. It includes cases that have been treated or that are currently being treated in an ICU.

- Orientation of case counts by geography is based on the diagnosing health unit (DHU). DHU refers to the case's public health unit of residence at the time of illness onset and not necessarily the location of exposure. Cases for which the DHU was reported as MOH-PHO (to signify a case that is not a resident of Ontario) have been excluded from the analyses.

- Likely source of acquisition is determined by examining the epidemiologic link and epidemiologic link status fields in CCM. If no epidemiologic link is identified in those fields the risk factor fields are examined to determine whether a case travelled, was associated with a confirmed outbreak, was a contact of a case, had no known epidemiological link (sporadic community transmission) or was reported to have an unknown source/no information was reported. Some cases may have no information reported if the case is untraceable, was lost to follow-up or referred to FNIHB. Cases with multiple risk factors were assigned to a single likely acquisition source group which was determined hierarchically in the following order:

    - For cases with an episode date *on or after* April 1, 2020: Outbreak-associated > close contact of a confirmed case > travel > no known epidemiological link > information missing or unknown

    - For cases with an episode date *before* April 1, 2020: Travel > outbreak-associated > close contact of a confirmed case > no known epidemiological link > information missing or unknown

- Deaths are determined by using the outcome field in CCM. Any case marked 'Fatal' is included in the deaths data. The CCM field Type of Death is not used to further categorize the data.

    - The date of death is determined using the outcome date field for cases marked as 'Fatal' in the outcome field.

- COVID-19 cases from CCM for which the Classification and/or Disposition was reported as ENTERED IN ERROR, DOES NOT MEET DEFINITION, IGNORE, DUPLICATE or any variation on these values have been excluded. The provincial case count for COVID-19 may include some duplicate records, if these records were not identified and resolved.

- Ongoing outbreaks include all outbreaks that are 'Open' in CCM without a 'Declared Over Date' recorded, or where the outbreak started more than five months ago, even for outbreaks where the Outbreak Status value selected in CCM is 'OPEN'. The start of the outbreak is determined by the onset date of first case, or if missing the outbreak reported date, or else if that is also missing, then the outbreak created date.

- 'Long-term care home residents' includes cases that reported 'Yes' to the risk factor 'Resident of a long-term care home'; or 'Yes' to the risk factor 'Resident of nursing home or other chronic care facility' and reported to be part of an outbreak assigned as a long-term care home (via the Outbreak number or case comments field); or were reported to be part of an outbreak assigned as a long-term care home (via the outbreak number or case comments field) with an age over 70 years and did not report 'No' to the risk factors 'Resident of long-term care home' or 'Resident of nursing home or other chronic care facility'. 'Long-term care home residents' excludes cases that reported 'Yes' to any of the health care worker occupational risk factors.

- The 'health care workers' variable includes cases that reported 'Yes' to any of the occupation of health care worker, doctor, nurse, dentist, dental hygienist, midwife, other medical technicians, personal support worker, respiratory therapist, first responder.

- 'Health care workers associated with long-term care outbreaks' includes 'health care workers' reported to be part of an outbreak assigned as a long-term care home (via the outbreak number or case comments field). Excludes cases that reported 'Yes' to risk factors 'Resident of long-term care home' or 'Resident of nursing home or other chronic care facility' and 'Yes' to the calculated 'health care workers' variable.

- Percent change is calculated by taking the difference between the current period (i.e., daily count or sum of the daily count over a 7-day period) and previous period (i.e., daily count or sum of the daily count over a 7-day period), divided by the previous period.

- Public Health Ontario conducts testing and genomic analyses for SARS-CoV-2 positive specimens using the criteria outlined here: https://www.publichealthontario.ca/en/laboratory-services/test-information-index/covid-19-voc

- Lineage nomenclature is dynamic. PANGO lineage naming and assignment may change as more samples are sequenced and analyzed.

- Variant status may be updated based on scientific evidence. Variants designated as a VOC in Canada is available on the Public Health Agency of Canada's SARS-CoV-2 Variants webpage.

- Changes to the VOC testing algorithm may occur over time and trends should be interpreted with caution. Since February 3, 2021 all PCR positive SARS-Co-V-2 specimens with Ct values ≤ 35 are tested for a N501Y mutation. As of March 22, 2021, positive specimens with a Ct ≤ 35 are tested for both the N501Y and E484K mutation, with all E484K positive specimens with a Ct ≤ 30 forwarded for further genomic analysis. If found to be positive for the N501Y mutation only, no further genomic analysis are performed as these are presumed to be B.1.1.7. As of May 26, 2021, cases where a E484K mutation is detected will no longer be reflexed for sequencing as

VOC testing labs switched to a representative sampling method where only a proportion of all positives with a Ct ≤ 30 are forwarded for further genomic analysis.

- The laboratory detection of a variant of concern is a multi-step process. Samples that test positive for SARS-CoV-2 and have a cycle threshold (Ct) value ≤ 35 can be tested for mutations common to variants of concern. If positive for the mutation of interest with a Ct value of ≤30, these samples may then undergo genomic analyses to identify the VOC lineage. VOC lineages may still be confirmed using genomic analysis despite specific S gene mutation(s) being documented as 'unable to complete' due to poor sequence quality at the genome position.

- VOC testing data are analyzed for cases with a reported date on or after February 07, 2021. VOC testing data are based on CCM information reported within the laboratory object for select Logical Observation Identifiers Names and Codes (LOINC) and supplemented with information from the Investigation Subtype field. A confirmed Case Investigation is assigned a VOC test value (e.g., VOC test detected, VOC test not detected) based on the following hierarchy:

    - If multiple laboratory results are identified, a VOC test value is assigned based on the following hierarchy: Detected > Not Detected > Unable to complete

    - If a laboratory result is 'Not Detected' or 'Unable to complete', but data on the Investigation Subtype field is listed as a lineage or mutation common to a VOC, then the VOC test value is set to 'Detected'

- If a VOC is identified through genomic analysis cases initially classified as a mutation may be updated and moved to the appropriate lineage (B.1.1.7, B.1.351, P.1 and B.1.617.2)

- LOINCs are a set of internationally used result description codes. In the absence of a standard LOINC, Ontario Health can create local result codes, which are identified with an 'XON' prefix. LOINCs incorporate details of the result value (e.g. test method, target detected - such as IgG, DNA, isolate etc.) and are unique to each result.

- VOC testing data in this report are assigned on a per case basis. Multiple laboratory results may be associated to a single case investigation, but for analysis purposes are only counted once.

    - The percent of cases that test VOC positive is calculated by taking the number of VOC test positive, divided by the total number of confirmed COVID-19 cases for a given reported date.

- The VOC percent positive may be higher than described in this report. As testing algorithms change, the VOC percent positivity may not be reflective of the exact number of COVID-19 cases due to VOCs

- Only CCM case investigations with a CONFIRMED classification have their laboratory records with VOC testing information included in the percent positivity calculations

Appendix A

Table A1. Weekly rates of confirmed COVID-19 cases per 100,000 population over recent rolling 7-day periods, by reported date and public health unit: Ontario, June 18 to June 30, 2021

Public Health Unit Name	June 18 to June 24	June 19 to June 25	June 20 to June 26	June 21 to June 27	June 22 to June 28	June 23 to June 29	June 24 to June 30	% change from June 18 – June 24 to June 24 - June 30
NORTH WEST								
Northwestern Health Unit	8.0	6.8	6.8	9.1	8.0	8.0	5.7	-28.8%
Thunder Bay District Health Unit	4.7	4.7	4.7	4.7	4.7	4.0	2.0	-57.4%
NORTH EAST								
Algoma Public Health	1.7	0.9	0.9	0.9	0.0	0.0	0.0	-100.0%
North Bay Parry Sound District Health Unit	43.9	43.2	47.0	45.5	37.8	32.4	30.8	-29.8%
Porcupine Health Unit	91.1	98.3	87.5	87.5	91.1	95.9	82.7	-9.2%
Public Health Sudbury & Districts	15.6	17.1	12.1	10.6	9.5	9.0	4.0	-74.4%
Timiskaming Health Unit	0.0	0.0	0.0	0.0	0.0	0.0	0.0	N/A
EASTERN								
Ottawa Public Health	9.8	8.0	7.1	7.2	6.1	5.6	4.6	-53.1%
Eastern Ontario Health Unit	2.4	1.4	1.9	1.9	1.9	1.9	1.0	-58.3%
Hastings Prince Edward Public Health	0.6	0.6	0.6	1.2	1.2	1.8	1.8	+200.0%
Kingston, Frontenac and Lennox & Addington Public Health	4.7	3.8	1.4	1.4	0.9	0.9	1.4	-70.2%

Public Health Unit Name	June 18 to June 24	June 19 to June 25	June 20 to June 26	June 21 to June 27	June 22 to June 28	June 23 to June 29	June 24 to June 30	% change from June 18 – June 24 to June 24 - June 30
Leeds, Grenville & Lanark District Health Unit	1.2	1.7	1.7	2.3	2.3	2.9	3.5	+191.7%
Renfrew County and District Health Unit	2.8	3.7	3.7	2.8	3.7	3.7	2.8	0.0%
CENTRAL EAST								
Durham Region Health Department	10.0	8.7	8.1	8.3	9.4	8.7	8.0	-20.0%
Haliburton, Kawartha, Pine Ridge District Health Unit	7.4	6.4	6.9	4.8	5.3	5.3	4.8	-35.1%
Peel Public Health	13.9	12.8	11.8	10.2	10.2	10.3	9.5	-31.7%
Peterborough Public Health	8.1	7.4	6.1	4.1	2.7	4.1	6.1	-24.7%
Simcoe Muskoka District Health Unit	6.7	6.2	6.0	6.3	6.2	6.7	6.2	-7.5%
York Region Public Health	6.9	6.3	5.7	5.1	4.9	4.4	4.2	-39.1%
TORONTO								
Toronto Public Health	10.2	10.3	10.1	9.6	9.3	8.5	8.5	-16.7%
SOUTH WEST								
Chatham-Kent Public Health	1.9	1.9	2.8	3.8	3.8	4.7	5.6	+194.7%
Grey Bruce Health Unit	46.5	71.2	77.1	82.4	84.8	97.1	106.5	+129.0%
Huron Perth Public Health	7.9	7.2	7.9	7.2	6.4	9.3	8.6	+8.9%
Lambton Public Health	29.0	32.1	30.5	27.5	26.0	24.4	17.6	-39.3%
Middlesex-London Health Unit	6.5	5.9	6.5	6.9	8.3	8.9	9.7	+49.2%

Public Health Unit Name	June 18 to June 24	June 19 to June 25	June 20 to June 26	June 21 to June 27	June 22 to June 28	June 23 to June 29	June 24 to June 30	% change from June 18 – June 24 to June 24 - June 30
Southwestern Public Health	7.6	8.0	5.7	7.1	5.2	5.7	6.6	-13.2%
Windsor-Essex County Health Unit	10.1	8.7	8.7	9.7	9.2	8.0	8.0	-20.8%
CENTRAL WEST								
Brant County Health Unit	7.1	7.7	9.0	7.7	7.7	7.7	7.1	0.0%
City of Hamilton Public Health Services	18.6	16.4	16.7	16.0	18.2	16.5	15.4	-17.2%
Haldimand-Norfolk Health Unit	7.0	7.0	7.0	7.0	7.9	9.6	7.0	0.0%
Halton Region Public Health	7.4	7.8	7.6	7.3	6.6	7.3	9.7	+31.1%
Niagara Region Public Health	14.4	15.0	14.0	14.2	14.4	12.5	12.9	-10.4%
Region of Waterloo Public Health and Emergency Services	66.1	64.2	66.1	65.5	65.4	63.8	61.3	-7.3%
Wellington-Dufferin-Guelph Public Health	12.8	14.4	16.0	15.7	17.0	18.0	18.3	+43.0%
TOTAL ONTARIO	**13.2**	**13.0**	**12.7**	**12.4**	**12.3**	**12.1**	**11.7**	**-11.4%**

Note: Rates are based on the sum of the daily case counts during the date ranges specified in each column.
Data Source: CCM

Table A2. Summary of confirmed COVID-19 cases with a mutation or VOC by public health unit: Ontario as of July 3, 2021

Public Health Unit Name	Cumulative count for Lineage B.1.1.7 (Alpha)*	Cumulative count for Lineage B.1.351 (Beta)**	Cumulative count for Lineage P.1 (Gamma)***	Cumulative count for Lineage B.1.617.2 (Delta)†	Cumulative count for mutations‡
Algoma Public Health	68	0	12	2	28
Brant County Health Unit	665	2	88	28	495
Chatham-Kent Public Health	113	5	14	0	110
City of Hamilton Public Health Services	4,964	65	101	66	2,100
Durham Region Health Department	9,500	65	261	56	1,207
Eastern Ontario Health Unit	648	44	17	2	273
Grey Bruce Health Unit	306	0	5	52	56
Haldimand-Norfolk Health Unit	368	3	22	8	402
Haliburton, Kawartha, Pine Ridge District Health Unit	443	0	17	33	313
Halton Region Public Health	5,075	29	159	72	606
Hastings Prince Edward Public Health	77	0	8	2	406
Huron Perth Public Health	234	0	11	17	67
Kingston, Frontenac and Lennox & Addington Public Health	439	2	35	3	129
Lambton Public Health	433	0	17	13	129
Leeds, Grenville & Lanark District Health Unit	293	18	0	0	42
Middlesex-London Health Unit	3,358	2	96	20	187

Public Health Unit Name	Cumulative count for Lineage B.1.1.7 (Alpha)*	Cumulative count for Lineage B.1.351 (Beta)**	Cumulative count for Lineage P.1 (Gamma)***	Cumulative count for Lineage B.1.617.2 (Delta)†	Cumulative count for mutations‡
Niagara Region Public Health	4,233	4	17	17	1,084
North Bay Parry Sound District Health Unit	230	28	2	7	13
Northwestern Health Unit	56	0	1	0	16
Ottawa Public Health	6,647	488	50	21	478
Peel Public Health	30,574	132	1,405	504	3,580
Peterborough Public Health	613	4	7	8	161
Porcupine Health Unit	1,065	2	0	35	8
Public Health Sudbury & Districts	615	11	5	1	341
Region of Waterloo Public Health and Emergency Services	3,094	11	71	437	302
Renfrew County and District Health Unit	224	8	6	1	12
Simcoe Muskoka District Health Unit	3,848	31	159	61	831
Southwestern Public Health	659	2	14	15	165
Thunder Bay District Health Unit	104	0	2	5	74
Timiskaming Health Unit	83	1	0	0	0
Toronto Public Health	45,108	373	1,483	429	8,296
Wellington-Dufferin-Guelph Public Health	2,074	1	61	53	192
Windsor-Essex County Health Unit	1,826	5	17	3	130

Public Health Unit Name	Cumulative count for Lineage B.1.1.7 (Alpha)*	Cumulative count for Lineage B.1.351 (Beta)**	Cumulative count for Lineage P.1 (Gamma)***	Cumulative count for Lineage B.1.617.2 (Delta)†	Cumulative count for mutations‡
York Region Public Health	15,862	79	468	70	2,695
TOTAL ONTARIO	**143,899**	**1,415**	**4,631**	**2,041**	**24,928**

Note: Interpret the VOC and mutation trends with caution due to the varying time required to complete VOC testing and/or genomic analysis following the initial positive test for SARS-CoV-2. Due to the nature of the genomic analysis, test results may be completed in batches. Data corrections or updates can result in case records being removed and/or updated and may result in totals differing from past publicly reported case counts. Data for calculating the change in cases and the cumulative case count uses data from the Investigation Subtype field only. Changes to the VOC testing algorithm may impact counts and trends. Further details can be found in the data caveats section.

*Includes all confirmed COVID-19 cases where lineage B.1.1.7 was identified by genomic analysis and those presumed to be B.1.1.7 based on positive N501Y and negative E484K mutation.

**Includes B.1.351 cases identified by genomic analysis and those presumed to be B.1.351 based on 'Mutation K417N+ and N501Y+ and E484K+' in the Investigation Subtype field

***Includes P.1 cases identified by genomic analysis and those presumed to be P.1 based on 'Mutation K417T+ and N501Y+ and E484K+' in the Investigation Subtype field

†Includes B.1.617.2 cases identified by genomic analysis. Mutations common to B.1.617.2 are not included in the current VOC mutation test.

‡Mutations includes all confirmed COVID-19 cases with the following mutations detected, reported from the Investigation Subtype field: N501Y and E484K, N501Y (E484K unknown), E484K (N501Y negative), E484K (N501Y unknown).

If a VOC is identified through genomic analysis, the change in cases and/or cumulative case counts for mutations will fluctuate as the case is moved to one of the listed lineages.

Data Source: CCM

Table A3. Weekly percent positivity for cases positive for mutations or VOCs over recent rolling 7-day periods using all confirmed cases as the denominator, by reported date and public health unit: Ontario, June 16 to June 28, 2021

Public Health Unit Name	June 16 to June 22	June 17 to June 23	June 18 to June 24	June 19 to June 25	June 20 to June 26	June 21 to June 27	June 22 to June 28
Algoma Public Health	50.0	50.0	50.0	100.0	100.0	100.0	0.0
Brant County Health Unit	91.7	85.7	63.6	66.7	42.9	41.7	33.3
Chatham-Kent Public Health	0.0	0.0	0.0	0.0	33.3	25.0	25.0
City of Hamilton Public Health Services	36.8	36.3	29.1	26.8	26.3	23.2	23.1
Durham Region Health Department	63.9	59.5	52.1	50.0	39.7	42.4	35.8
Eastern Ontario Health Unit	50.0	60.0	60.0	66.7	50.0	50.0	50.0
Grey Bruce Health Unit	20.0	12.1	11.4	13.2	21.4	20.7	19.4
Haldimand-Norfolk Health Unit	42.9	62.5	37.5	50.0	50.0	62.5	55.6
Haliburton, Kawartha, Pine Ridge District Health Unit	46.7	71.4	57.1	50.0	30.8	33.3	40.0
Halton Region Public Health	54.5	50.9	50.0	47.9	36.2	33.3	26.8
Hastings Prince Edward Public Health	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Huron Perth Public Health	57.1	44.4	36.4	30.0	18.2	20.0	22.2
Kingston, Frontenac and Lennox & Addington Public Health	70.0	63.6	70.0	75.0	66.7	33.3	0.0
Lambton Public Health	36.8	33.3	26.3	28.6	30.0	27.8	26.5

Public Health Unit Name	June 16 to June 22	June 17 to June 23	June 18 to June 24	June 19 to June 25	June 20 to June 26	June 21 to June 27	June 22 to June 28
Leeds, Grenville & Lanark District Health Unit	100.0	100.0	100.0	66.7	66.7	75.0	75.0
Middlesex-London Health Unit	65.9	59.4	48.5	36.7	36.4	34.3	38.1
Niagara Region Public Health	18.1	13.8	5.9	7.0	4.5	4.5	5.9
North Bay Parry Sound District Health Unit	73.7	73.3	77.2	76.8	73.8	71.2	69.4
Northwestern Health Unit	16.7	14.3	14.3	0.0	0.0	0.0	0.0
Ottawa Public Health	64.6	59.8	61.2	54.8	50.7	48.7	43.8
Peel Public Health	62.4	60.1	57.4	54.9	52.1	47.0	48.8
Peterborough Public Health	75.0	71.4	66.7	63.6	55.6	66.7	50.0
Porcupine Health Unit	61.6	59.5	56.6	52.4	46.6	47.9	48.7
Public Health Sudbury & Districts	81.8	90.0	90.3	88.2	83.3	81.0	78.9
Region of Waterloo Public Health and Emergency Services	24.2	15.0	5.2	2.7	3.1	3.4	3.7
Renfrew County and District Health Unit	66.7	33.3	33.3	25.0	25.0	0.0	25.0
Simcoe Muskoka District Health Unit	61.5	51.5	37.5	35.1	27.8	26.3	27.0
Southwestern Public Health	50.0	55.6	75.0	76.5	83.3	80.0	72.7
Thunder Bay District Health Unit	20.0	28.6	14.3	14.3	14.3	14.3	14.3
Timiskaming Health Unit	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Public Health Unit Name	June 16 to June 22	June 17 to June 23	June 18 to June 24	June 19 to June 25	June 20 to June 26	June 21 to June 27	June 22 to June 28
Toronto Public Health	61.2	59.1	55.5	52.6	52.2	48.2	47.8
Wellington-Dufferin-Guelph Public Health	23.7	14.3	15.0	17.8	16.0	16.3	15.1
Windsor-Essex County Health Unit	41.7	38.3	30.2	24.3	18.9	22.0	20.5
York Region Public Health	52.1	50.5	44.0	37.7	30.0	28.6	30.0
TOTAL ONTARIO	**48.9**	**44.7**	**39.0**	**35.8**	**32.8**	**30.8**	**29.6**

Note: Data for calculating the number of cases tested for mutations common to VOCs or lineages using genomic analyses are obtained using information from the Laboratory object in CCM in addition to the data from the Investigation subtype field. Therefore, comparisons to counts using only information from the Investigation Subtype field may not align. The percent of cases due to a VOC may be higher than described in this report. While all confirmed COVID-19 cases are included in the denominator, not all cases were able to be tested for VOCs. Percent positivity is based on the sum of the daily cases that test positive divided by the number of cases reported during the date ranges specified in each column.
Data Source: CCM

Table A4. Weekly percent positivity for cases positive for mutations or VOCs over recent rolling 7-day periods using cases tested for mutations or VOCs as the denominator, by reported date and public health unit: Ontario, June 16 to June 28, 2021

Public Health Unit Name	June 16 to June 22	June 17 to June 23	June 18 to June 24	June 19 to June 25	June 20 to June 26	June 21 to June 27	June 22 to June 28
Algoma Public Health	100.0	100.0	100.0	100.0	100.0	100.0	0.0
Brant County Health Unit	100.0	92.3	70.0	72.7	54.5	50.0	44.4
Chatham-Kent Public Health	0.0	0.0	0.0	0.0	50.0	33.3	33.3
City of Hamilton Public Health Services	61.4	62.1	53.3	54.2	52.0	46.8	41.7
Durham Region Health Department	86.8	83.0	74.0	72.1	65.7	64.1	57.1
Eastern Ontario Health Unit	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Grey Bruce Health Unit	21.4	13.5	13.0	15.5	25.7	24.8	23.3
Haldimand-Norfolk Health Unit	75.0	83.3	75.0	80.0	80.0	100.0	83.3
Haliburton, Kawartha, Pine Ridge District Health Unit	53.8	71.4	57.1	50.0	36.4	42.9	50.0
Halton Region Public Health	65.2	63.6	63.9	63.9	50.0	50.0	40.7
Hastings Prince Edward Public Health	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Huron Perth Public Health	80.0	66.7	50.0	42.9	33.3	33.3	40.0
Kingston, Frontenac and Lennox & Addington Public Health	87.5	77.8	77.8	85.7	66.7	50.0	0.0
Lambton Public Health	100.0	90.9	90.9	80.0	80.0	76.9	75.0

Public Health Unit Name	June 16 to June 22	June 17 to June 23	June 18 to June 24	June 19 to June 25	June 20 to June 26	June 21 to June 27	June 22 to June 28
Leeds, Grenville & Lanark District Health Unit	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Middlesex-London Health Unit	84.4	70.4	57.1	47.8	50.0	44.4	51.6
Niagara Region Public Health	68.4	60.0	28.6	29.4	23.1	23.1	26.7
North Bay Parry Sound District Health Unit	91.3	91.7	95.7	95.6	95.7	97.7	97.1
Northwestern Health Unit	50.0	50.0	50.0	0.0	0.0	0.0	0.0
Ottawa Public Health	93.6	92.8	94.0	90.2	88.4	84.1	84.8
Peel Public Health	84.3	79.9	75.7	73.4	71.7	68.1	67.8
Peterborough Public Health	85.7	83.3	80.0	77.8	62.5	66.7	50.0
Porcupine Health Unit	97.8	97.8	97.7	97.7	97.1	100.0	100.0
Public Health Sudbury & Districts	94.7	96.4	96.6	96.8	95.2	94.4	93.8
Region of Waterloo Public Health and Emergency Services	31.5	20.3	7.1	3.6	4.3	4.6	5.0
Renfrew County and District Health Unit	100.0	100.0	100.0	100.0	100.0	0.0	100.0
Simcoe Muskoka District Health Unit	70.6	58.6	45.5	41.9	38.5	37.0	41.7
Southwestern Public Health	61.1	66.7	80.0	81.3	90.9	85.7	80.0
Thunder Bay District Health Unit	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Timiskaming Health Unit	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Public Health Unit Name	June 16 to June 22	June 17 to June 23	June 18 to June 24	June 19 to June 25	June 20 to June 26	June 21 to June 27	June 22 to June 28
Toronto Public Health	81.9	78.8	74.9	69.8	68.9	64.7	65.4
Wellington-Dufferin-Guelph Public Health	31.0	20.0	22.2	22.9	20.5	22.2	21.1
Windsor-Essex County Health Unit	87.0	90.0	81.3	75.0	77.8	75.0	66.7
York Region Public Health	70.4	70.8	63.8	53.7	44.7	43.9	45.0
TOTAL ONTARIO	**68.1**	**63.2**	**56.3**	**51.7**	**48.8**	**46.3**	**44.8**

Note: Data for calculating the number of cases tested for mutations common to VOCs or lineages using genomic analyses are obtained using information from the Laboratory object in CCM in addition to the data from the Investigation subtype field. Therefore, comparisons to counts using only information from the Investigation Subtype field may not align. The percent of cases due to a VOC may be higher than described in this report.
Percent positivity is based on the sum of the daily cases that test positive divided by the number of cases that were tested for mutations common to VOCs or lineages (e.g. those identified as 'Detected' or 'Not Detected') during the date ranges specified in each column.
Data Source: CCM

Citation

Ontario Agency for Health Protection and Promotion (Public Health Ontario). Epidemiologic summary: COVID-19 in Ontario – January 15, 2020 to July 3, 2021. Toronto, ON: Queen's Printer for Ontario; 2021.

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For more information, cd@oahpp.ca.

Public Health Ontario

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Kitchener Court File No.: CV-21-00000095-0000
St. Thomas Court File No.: CV-21-08
Welland Court File No.: CV-21-00013361-0000

ONTARIO
SUPERIOR COURT OF JUSTICE

B E T W E E N:

THE ATTORNEY GENERAL OF ONTARIO

Applicant

-and-

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHUURMAN, DEAN WANDERS, RANDY FREY, HARVEY FREY, and DANIEL GORDON

Respondents

A N D B E T W E E N:

HER MAJESTY THE QUEEN IN ONTARIO

Applicant

-and-

THE CHURCH OF GOD (RESTORATION) AYLMER, HENRY HILDEBRANDT, ABRAM BERGEN, JACOB HIEBERT, PETER HILDEBRANDT, SUSAN MUTCH, ELVIRA TOVSTIGA, and TRUDY WIEBE

Respondents

A N D B E T W E E N:

WELLANDPORT UNITED REFORMED CHURCH

Applicant

-and-

HER MAJESTY THE QUEEN AS REPRESENTED BY THE ATTORNEY GENERAL OF ONTARIO

Respondent

A N D B E T W E E N:

STEPHEN RICHARDSON

Applicant

-and-

THE ATTORNEY GENERAL OF ONTARIO

Respondent

AFFIDAVIT OF MATTHEW HODGE
(Affirmed July 2, 2021)

I, MATTHEW HODGE, of the [redacted] in the Province of Ontario, **AFFIRM**:

I. BACKGROUND

1. I am a licensed medical practitioner who practices Public Health & Preventive Medicine ("**PHPM**") and Emergency Medicine in Ontario.[1] I joined Public Health Ontario ("**PHO**") in October 2020 and was the co-lead for Epidemiology & Surveillance activities within the Incident Management System ("**IMS**") structure of the Health Protection division of PHO from November, 2020 until April 9, 2021. The global COVID-19 pandemic (the "**Pandemic**") constitutes a public health emergency, so many organizations, including PHO, have established IMS structures to redeploy staff and prioritize activities. In my role within IMS, I was responsible for strategic input and work on data management, analyses and reporting. Currently, I work as a consultant with PHO. Throughout the pandemic, I have continued practicing emergency medicine at the Scarborough General site of the Scarborough Health Network. My work there includes caring for patients with COVID-19 infections over the past sixteen months.

2. I graduated with an MD (1996) and PhD (Epidemiology & Biostatistics, 1995) from McGill University and completed PHPM specialty training at the University of Toronto in 2000. Over the past twenty-one years, my practice has included multiple roles in public health, including Associate Medical Officer of Health, City of Hamilton (2005-2007), United Nations agencies (WHO: 1999-2001, UNICEF: 2001-2002, UNFPA: 2008-2010), Cancer Care Ontario (2010-2011), two positions with the Ontario Ministry of Health and Long-Term Care (2003-2004, 2015-2016), and a wide range of consulting work. I also completed Harvard's Masters in Health Care

[1] Public health and preventative medicine is a population or society focused discipline. This can be contrasted with infectious disease medicine which is focused on individual patients.

Management in 2011. I am also a peer reviewer for the Canadian Medical Association Journal and occasionally for the Canadian Journal of Public Health.

3. Following the province's declaration of an emergency in response to the Pandemic on March 17, 2020, I worked for six months assisting Peel Public Health's Pandemic response. My work there included guiding the implementation of the provincial Case & Contact Management system.

4. My *curriculum vitae* is attached to this affidavit as **Exhibit "A"**.

5. I have been asked to provide an expert opinion answering the questions relevant to this court proceeding that are set out below. My signed Acknowledgment of Expert's Duty is attached to this Affidavit as **Exhibit "B"**. Where I have relied on a document or data in forming my opinion, I have set out the citation to that document or data in the footnotes. Where I have relied on information provided to me by others, I have stated the source of that information and I believe it to be true.

II. OVERVIEW

6. I have been asked to answer the following questions in this expert affidavit:

   a. What are the harms caused by COVID-19 disease?

   b. How is COVID-19 disease transmitted?

   c. What are the risk factors for transmission?

   d. Why are measures to limit COVID-19 transmission needed in Ontario?

   e. Why do limits on religious gatherings contribute to reducing COVID-19 transmission and harms from COVID-19?

   f. Can the risk of transmission at indoor religious gatherings be adequately addressed by rules requiring physical distancing and face coverings or other personal protective equipment?

g. Do you agree or disagree with the affidavits of Dr. Warren dated April 6, 2021, Dr. Schabas and Dr. Kettner?

7. My answers are detailed below. I make three preliminary observations. First, my opinions are informed by the realities of public health practice in Ontario, including the need to prepare advice and make decisions with imperfect information, and the challenge of minimizing adverse effects of measures that establish limits on human behaviour. Ontario's Health Plan for an Influenza Pandemic, ("OHPIP"), cited by experts retained by the Applicant, explicitly recognizes this reality of incomplete information, noting that 'the OHPIP severity model includes an initial stage before severity is known when the limited availability of surveillance data does not allow for confident identification of severity. The severity may not be clearly known until after an influenza pandemic is over'.[2] For COVID-19, the rise of variants with increased transmissibility and, for some variants, increased severity of illness, adds additional uncertainty.

8. Second, public health measures in Ontario must take into account the precautionary principle. The OHPIP states 'The MOHLTC does not await scientific certainty before taking action to protect health'.[3] The application of the precautionary principle is particularly relevant during the early stages of a pandemic when scientific evidence on the severity of a novel virus is limited or, for COVID-19, as new variants are identified whose transmissibility and severity are incompletely understood at the time that government must make decisions to protect Ontarians from infection, illness and death.[4]

9. Third, my opinions are informed by the burden model, which recognizes that it is generally appropriate to implement more restrictive public health measures when an infectious disease

[2] See **Exhibit "C":** Ontario, Ministry of Health and Long-Term Care, Emergency Management Branch, *Ontario's Health Plan for an Influenza Pandemic* (March 2013) at p. 14, online: https://www.health.gov.on.ca/en/pro/programs/emb/pan_flu/docs/ch_01.pdf. See also pp. 10-13.
[3] See **Exhibit "C"**, *supra* note 2 at p. 11.
[4] For an example in the context of influenza, see **Exhibit "C"**, *supra* note 2 at p. 11.

imposes a higher burden. This notion of burden can be understood as a function of the prevalence of the disease (i.e. number of cases in a population), the exposure risk (i.e. the probability that one infected person will infect others), and the consequences of infection, such as hospitalization and death.

10. When Ontario enacted more stringent public health measures during each of the three waves of the pandemic to date, there was increasing community prevalence of COVID-19, growing numbers of new cases, and concerns about hospital and ICU occupancy. Accordingly, in my opinion it was a reasonable public health measure to restrict religious gatherings temporarily while community spread of COVID-19 posed this potential (wave 1) or real (waves 2 & 3) burden on Ontario's health care system. Furthermore, the emergence of variants of concern ("VOC"), with initial uncertainty about their transmissibility and severity, borne out by evidence of higher transmissibility (alpha & delta variants) and more severe illness (alpha variant) mandated a more stringent public health response. The pace of easing temporary limits on indoor religious gatherings is one of a suite of measures designed to keep Ontario from entering a fourth wave of the pandemic.

III. WHAT ARE THE HARMS CAUSED BY COVID-19?

11. COVID-19 illness is caused by a coronavirus that infects the respiratory system. Infection causes symptoms of upper respiratory tract infection including cough, fever and sore throat. COVID-19 infection also appears to cause a characteristic loss of taste and smell for many infected people. Based on Ontario's COVID-19 experience, 5% of people with COVID-19 will require hospital-based care, typically for oxygen at a minimum and often, ICU-level care. Complications leading to ICU admission or death may include respiratory failure, acute respiratory distress syndrome, sepsis and septic shock, thromboembolism, and/or multiorgan failure, including injury

of the heart, liver or kidneys.[5] As of June 24, 2021 in Ontario, 543,571 people have been diagnosed with COVID-19, and 9,101 (approximately 1.7%) have died.[6] The number of cumulative cases of COVID-19 in Ontario is likely higher than the number of recorded cases since some individuals who acquire COVID-19 are not tested and diagnosed. This was particularly the case during the early months of the COVID-19 pandemic.

12. The number of reported COVID-19 infections, hospitalizations, and deaths as of June 24, 2021 (Ontario), June 29, 2021 (Canada), or June 30, 2021 (global) are set out in the table below:

TABLE 1: Cases, hospitalizations, and deaths

	Cases	Hospitalizations	Deaths
Ontario[7]	543,571	27,643	9,101
Canada[8]	1,414,736	74,044	26,273
Global[9]	181,521,067	Unavailable	3,937,437

13. COVID variants are expected to arise due to high rates of viral transmission globally. Over the sixteen months of the pandemic, Ontario's context has evolved with increases in the prevalence of VOCs. As an example of the impact of VOCs in Ontario, the B117 variant (recently designated as the alpha variant) was reported to be more transmissible and cause more severe illness, contributing to an increased percentage of people with COVID-19 who need hospitalization and

[5] See **Exhibit "D":** World Health Organization, "Coronavirus disease (COVID-19)" (October 12, 2020), online: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/coronavirus-disease-covid-19>.
[6] See **Exhibit "E":** Public Health Ontario, "Ontario COVID-19 Data Tool", online: <https://www.publichealthontario.ca/en/data-and-analysis/infectious-disease/covid-19-data-surveillance/covid-19-data-tool?tab=summary> (accessed 24 June 2021).
[7] See **Exhibit "E"**, *supra* note 6.
[8] See **Exhibit "F":** Canada, "COVID-19 Daily Epidemiology Update" (June 29, 2021), online: <https://health-infobase.canada.ca/covid-19/epidemiological-summary-covid-19-cases.html?stat=num&measure=total&map=pt#a2>.
[9] **Exhibit "G"**: World Health Organization, "WHO Coronavirus (COVID-19) Dashboard" (June 30, 2021), online: <https://covid19.who.int/> .

ICU care, including younger people in their 40s and 50s.[10] The alpha variant that drove the third wave during early 2021 is currently being supplanted by the delta variant about which knowledge is rapidly evolving.[11]

14. The number of COVID-19 cases and hospitalizations in Ontario have increased with each of the three COVID 'waves', periods marked by rising case loads and concomitant rising pressures on Ontario's health system. Numbers of hospitalizations are relevant to COVID-19 decision-making because Ontario has the lowest rate of hospital beds per 1000 population (1.4) compared to the Canadian average (2.0). Overall, Canada's hospital capacity is among the lowest of the OECD countries, with 20% more in the USA (2.4/1000), 30% more in Italy (2.6/1000) and 55% more in France (3.1/1000).[12] Given that Canada has relatively few beds and Ontario has the fewest in Canada, the threshold above which the burden of COVID-19 infections and illness could push Ontario' acute care system past the point of being able to provide care to patients is logically lower than in other countries or even other Canadian provinces.

15. Ontario's response to COVID hospitalizations has, by virtue of this lower number of hospital beds compared to other comparable jurisdictions, involved moving substantial numbers of patients from the hospital at which they arrived to one with an available bed, often far from their community[13] and, at a societal level, implementing non-pharmaceutical interventions ("NPIs").

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[10] See **Exhibit "H":** Tuite AR, Fisman DN, Odutayo A, et al. "COVID-19 hospitalizations, ICU admissions and deaths associated with the new variants of concern" (2021) 1:18 *Science Briefs of the Ontario COVID-19 Science Advisory Table,* online: <https://covid19-sciencetable.ca/wp-content/uploads/2021/03/Science-Brief_VOC-Prognosis_20210329_published4.pdf>.

[11] See **Exhibit "I":** Public Health Ontario, "Weekly Epidemiological Summary: SARS-CoV-2 Whole Genome Sequencing in Ontario, June 23, 2021", online: <https://www.publichealthontario.ca/-/media/documents/ncov/epi/covid-19-sars-cov2-whole-genome-sequencing-epi-summary.pdf?la=en>.

[12] Ontario Hospital Association, "Ontario Hospitals – Leaders in Efficiency" (December 2019).

[13] Kelly Grant, "How COVID-19 exposed long-term health-care issues at Brampton hospital" (June 21, 2021) *The Global and Mail,* online: <https://www.theglobeandmail.com/canada/article-how-the-covid-19-pandemic-exposed-long-term-health-care-issues-at/>. Ontario Health data cited by the Globe and Mail note 3219 transfers between mid-November, 2020 and the end of May, 2021.

NPIs comprise a bundle of measures, including temporary restrictions on mobility and gatherings, designed to reduce COVID-19 transmission and thus hospitalization and death, both to mitigate threats to the integrity of health care and to 'minimize serious illness and overall deaths through appropriate management of Ontario's health system.'[14]

16. A health system in which every available bed is occupied by someone infected with COVID-19 has no way to respond to people with heart attacks, hip fractures or strokes, potentially adding to the elevated mortality attributable to COVID-19. Put simply, the harms caused by COVID-19 would be compounded with additional preventable deaths due to heart attacks, hip fractures and other health conditions if there are no beds and no staff available to care for patients with these conditions. Once overwhelmed, the acute care system would likely face a prolonged recovery period, hence the relevance of the precautionary principle to decision making aiming to ensure the integrity of the health system.

17. Given that different jurisdictions have applied a different mix of policy responses to the COVID-19 pandemic, and that there are real harms associated with the restrictive nature of the temporary public health measures implemented across dozens of countries, it may be instructive to examine these in comparative terms. At its simplest, a key question is 'what would have been the mortality from COVID-19 if Ontario had chosen less restrictive measures?'; the table below summarizes the results from three jurisdictions described as less restrictive by the Applicant's expert, Dr. Schabas, as compared to Ontario's mortality rate.

[14] See **Exhibit "C"**, *supra* note 2 at p. 10 (Objective #1).

TABLE 2

	Ontario	Sweden	Brazil	Florida
Population	14,000,000	10,159,183	213,956,756	21,600,000
COVID-19 Deaths	9,101[15]	14,619[16]	507,109[17]	37,772[18]
Crude Death Rate[19]	0.65/1000	1.44/1000	2.37/1000	1.75/1000
Projected Additional Deaths in Ontario[20]	NA (zero)	+11,060 (+122%)	+24,080 (+265%)	+15,400 (+169%)

IV. HOW IS THE VIRUS TRANSMITTED?

18. COVID-19 is caused by the SARS-CoV-2 virus and its variants (together, "**COVID-19**" or the "**Virus**"), which spreads between people, through respiratory particles of varying sizes, mainly when an infected person is in close contact with another person.[21]

19. COVID-19 can spread from an infected person's mouth or nose in small liquid particles when they cough, sneeze, speak, sing, or breathe heavily. These liquid particles are different sizes, ranging from larger respiratory droplets to smaller aerosols. While the science is still evolving, these particles travel further indoors than outdoors and their survival on surfaces appears to be

[15] See **Exhibit "E"**, *supra* note 6.
[16] World Health Organization, "Sweden: WHO Coronavirus Disease (COVID-19) Dashboard With Vaccination Data", online: <https://covid19.who.int/region/euro/country/se> (accessed 26 June 2021).
[17] World Health Organization, "Brazil: WHO Coronavirus Disease (COVID-19) Dashboard with Vaccination Data", online: <https://covid19.who.int/region/amro/country/br> (accessed 26 June 2021).
[18] "Tracking Coronvirus in Florida: Latest Map and Case Count", *The New York Times,* online: <https://www.nytimes.com/interactive/2021/us/florida-covid-cases.html> (accessed 26 June 2021).
[19] Number of reported cases/population; age-adjustment would yield slightly more accurate figures but the change due to age adjustment is insufficient to explain the greater than 2-fold variation.
[20] Calculated as (death rate in jurisdiction – death rate in Ontario)*population of Ontario.
[21] See **Exhibit "J":** Public Health Ontario, "Synthesis: COVID-19 Transmission Through Large Respiratory Droplets and Aerosols…What We Know So Far" (May 21, 2021), online: <https://www.publichealthontario.ca/-/media/documents/ncov/covid-wwksf/2021/05/wwksf-transmission-respiratory-aerosols.pdf?la=en>.

greater indoors than outdoors. Whether indoors or outdoors, people can contract COVID-19 when the Virus enters their mouth, nose, or eyes.[22]

20. Many people infected with COVID-19 show no symptoms (asymptomatic) or experience several days between when they are infected and when they develop symptoms (presymptomatic). This is particularly challenging as transmission risk seems to be highest prior to symptoms appearing, meaning that most infected people will unknowingly infect others before they themselves have symptoms.[23] Thus, to reduce COVID-19 transmission and the harms, including hospitalization and death that such transmission can cause, NPIs need to apply to people who do not exhibit COVID-19 symptoms in order to be effective.

V. WHAT ARE THE RISK FACTORS FOR TRANSMISSION?

21. Risk factors for virus transmission include being in close contact for prolonged periods, higher voice volume, being indoors, inconsistent use of face coverings (such as removing a face covering to talk or shout, eat or drink), improper use of face coverings (e.g. not covering the nose or wearing one that is too loosely fitted), and background infection rates in the community(s) from which a gathering's attendees are drawn.

22. The World Health Organization provides the '3C' framework for assessing risks of COVID-19 transmission: crowded places, close contact, confined spaces. Risks of Virus transmission are increased when two or more of these conditions occur together.[24] In addition, risks increase with increasing degrees of the 3Cs, including:

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[22] See **Exhibit "K":** World Health Organization, "Coronavirus disease (COVID-19): How is it transmitted?" (updated April 30, 202), online: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/coronavirus-disease-covid-19-how-is-it-transmitted>.

[23] *Ibid*.

[24] See attached **Exhibit "L"**: World Health Organization, "Avoid the Three Cs", online: <https://www.who.int/images/default-source/wpro/countries/malaysia/infographics/three-3cs/final-avoid-the-3-cs-poster.jpg?sfvrsn=638335c1_2>.

a. being in close contact for longer periods causes greater risk than shorter periods;[25]

b. higher voice volume likely increases both droplet production and projection;[26]

c. being indoors increases risk, as droplets persist in indoor environments longer than outdoors;[27] and

d. inconsistent or improper use of face coverings, such as removing a face covering to sing or consume food and beverages or leaving the nose uncovered, increases risk.

23. The risk from any particular setting is also determined by the likelihood that other persons present are infected with COVID-19. Community prevalence describes the percentage or rate of COVID-19 infection in a population. When community prevalence is elevated, even lower risk activities can contribute to pressures on the integrity of the health system as more infections lead to increased numbers of persons needing hospitalization.

24. After the first wave of COVID-19 in Ontario when COVID-19 spread widely within institutional settings such as long-term care homes ("LTCHs"), transmission risks now appear to be highest in non-institutional settings such as workplaces and households. Secondary attack rates (the number of cases among contacts of a case) within households have been estimated to be 5-10 fold higher than in non-institutional , non-household settings.[28] The transmissibility of COVID-19 within households is complex and determined by still poorly understood interactions of density (persons per room), social interaction patterns among household members, use of personal

[25] See **Exhibit "J"**, *supra* note 21.
[26] See **Exhibit "M"**: Valentyn Stadnytskyi et al, "The airborne lifetime of small speech droplets and their potential importance in SARS-CoV-2 transmission", (2020) 119:22 PNAS 11875-11877, online: <https://www.pnas.org/content/117/22/11875>.
[27] See **Exhibit "J"**, *supra* note 21.
[28] See **Exhibit "N":** Sarah A. Buchan et al., "Increased household secondary attack rates with Variant of Concern SARS-CoV-2 index cases" (March 31, 2021), *Public Health Ontario* (April 5, 2021 pre-print), online: <https://www.medrxiv.org/content/10.1101/2021.03.31.21254502v1> (accessed 26 June 2021).

protective equipment within the home, and social and cultural norms determining roles and behaviours within households. As these are not amenable to policy action on the time scale of COVID-19 transmission, the cornerstone of evidence-informed actions to reduce the burden of COVID-19 in Ontario is reducing risks of COVID-19 being introduced into households, thus reducing COVID-19 transmission and subsequent incidences of clinical illness, hospitalization and death.

25. At a population level, the overall risk of transmission is further increased when community prevalence of the Virus is higher, since any encounter carries a higher chance of involving a person infected with COVID-19. In addition, gatherings that draw individuals from different households together increase risks of transmission to more households, increasing the expected burden of COVID-19. High rates of household transmission, with entire families being hospitalized during the most recent period of heightened incidence, highlight the importance of implementing public health measures that reduce the chances of COVID-19 entering a household.

Risk of transmission at religious gatherings

26. As set out above, the risk of COVID-19 transmission at an event or gathering depends on a number of factors, including the number of people attending, adherence to physical distancing, mask wearing, duration of the event or gathering, ventilation, whether there is singing or high-volume talking, and background infection rates in the community(s) from which the gathering's attendees are drawn.

27. Religious gatherings often feature several heightened risk factors for COVID-19 transmission, including singing or high-volume speaking, chanting or preaching. The scientific basis for this is understood to be greater production of respiratory particles with increasing

volume.[29] While it is uncertain whether there is an independent increased risk from singing when compared to speech at the same volume, it appears reasonable that even if the singing effect is a pure volume effect, the reality that singing occurs at higher volumes than speaking confers increased risk of producing COVID-19-containing respiratory particles.

28. Ontario COVID-19 outbreak data suggest that when COVID-19 outbreaks occur in association with religious gatherings, more cases are identified than from outbreaks in other non-institutional settings. Through June 18, 2021, Ontario's 34 local public health units reported 59 outbreaks associated with places of worship with 526 associated cases, for an average of 8.9 cases per outbreak. While not diminishing the toll of COVID-19 in LTCHs and other institutional settings (4032 outbreaks, 49304 associated cases) and acknowledging that while places of worship may be workplaces (2616 outbreaks, 24000 associated cases) for some persons, appropriate comparable settings would be other indoor locations into which individuals from different households voluntarily enter, such as restaurants, retail establishments and recreational fitness establishments. This grouping of other settings comprises 979 outbreaks with 5283 associated cases, for an average of 5.4 cases per outbreak.

29. Taken together, these Ontario data on declared COVID-19 outbreaks in places of worship indicate that the number of cases per outbreak is 65% higher in places of worship than in comparable non-workplace settings (8.9 versus 5.4). From the point of view of reducing COVID-19 transmission, these data support temporary limits on religious gatherings as part of a bundle of measures designed to reduce COVID-19 transmission since outbreaks associated with places of

[29] See **Exhibit "O":** Sima Asadi et al., "Aerosol emission and superemission during human speech increase with voice loudness" (2019) 9:2348 *Nature,* online: <https://www.nature.com/articles/s41598-019-38808-z> (accessed 26 June 2021).

worship yield more identified infections than outbreaks in comparable non-institutional, non-workplace[30] settings.

D. WHY ARE MEASURES TO LIMIT COVID-19 TRANSMISSION NEEDED IN ONTARIO?

30. Seeking to protect persons from mortality and morbidity from COVID-19 and to reduce the likelihood the acute care system would be overwhelmed by persons requiring hospital care for COVID-19 infection, the government of Ontario has implemented a bundle of temporary public health measures, generally referred to as non-pharmacologic interventions ("NPIs"). NPIs seek to reduce close contact among persons from different households, and thus reduce COVID-19 transmission risk. NPIs implemented temporarily in Ontario are broadly similar to those implemented in most if not all OECD jurisdictions and include limits on occupancy of indoor spaces, mobility limits, limits on and prohibitions of gatherings and events, and school closures.

31. These policy interventions are complemented by individual-focused**,** evidence-based mitigation measures such as requirements for face covering and physical distancing. Together these measures, both individual and policy level, can reduce, but not eliminate, the risk of COVID-19 transmission. Vaccination, once high levels of population coverage are achieved, is expected to obviate the need for NPIs. Ontario's *Roadmap to Reopening* explicitly links the end of NPIs to increasing levels of vaccination among Ontarians. It is hoped that vaccinations will eventually render these NPIs unnecessary, however with only 30% of Ontario's adult population fully vaccinated as of June 29, 2021,[31] levels of vaccination coverage are as yet insufficient to cease all NPIs.

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[30] Data summarized by Public Health Ontario as of June 18, 2021.
[31] Noah Little, *COVID-19 Tracker Canada* (2020), online: <https://covid19tracker.ca/provincevac.html?p=ON> (accessed June 29, 2021).

E. WHY DO LIMITS ON RELIGIOUS GATHERINGS CONTRIBUTE TO REDUCING COVID-19 TRANSMISSION AND HARMS FROM COVID-19?

32. In a society as diverse as Ontario, religious gatherings encompass a wide range of practices which may include singing, preaching, close contact for the purposes of greetings or other verbal and/or physical exchanges, and the passing of religiously significant physical material from person to person.

33. From an epidemiologic perspective, all gatherings as a class pose risks that rise with the number of attendees, reflecting the declining probability that every person present will be COVID-free as the number of persons increases. Experts retained by the Applicants have attempted to estimate this risk. Acknowledging that any such model involves estimates and assumptions, the table below asks a more basic policy-relevant question: for gatherings of different numbers of people and with different proportions of COVID-19 infection in the community, what is the chance that at least one person who is infected with COVID-19 will be present and thus able to transmit COVID-19 to others?

34. The 1 case/500 people proportion column aligns with the Applicant's expert's (Dr. Kettner's) estimated incidence of 1 case/5000 people/day with correction for the epidemiologic reality that infected people can transmit COVID-19 to others for roughly 10 days. Furthermore, from a community perspective, effects are multiplicative, such that a community with 10 gatherings of 10 attendees where 1 out of every 500 attendees has COVID-19 has a greater than 18% chance of someone having COVID at at least one gathering. If ten gatherings are held once/week for 10 weeks, that risk of having at least one attendee with COVID-19 at any one of those 100 gatherings rises to greater than 86%. Put another way, over 10 weeks, 10-person gatherings for religious services in 10 locations within a community yields an 86% chance that at least one attendee at at least one service has COVID-19. While the gathering-specific transmission

risks would be determined by multiple factors including mask use, ventilation and distancing, the 86% chance of COVID-19 being present highlights the importance of temporary limits on gatherings, religious or otherwise.

TABLE 3

Table entries are % chance of at least one attendee with COVID-19, where higher numbers mean a greater chance of someone with COVID-19 attending a gathering[32]

Number of People Attending	1 of Every 100 Attendees Have COVID-19	1 of Every 500 Attendees Have COVID-19	1 of Every 1000 Attendees Have COVID-19
10	9.5%	2%	<1%
100	63%	18%	9.5%
1000	>99.9%	86%	63%

35. In addition, specific religious practices such as those listed above increase risks of transmission, notably when voice volume is increased, as with singing and preaching, and when people are in close contact. In addition, entry and egress into many places of worship will bring people into close contact due to the near-simultaneous arrival of attendees to points of entry and egress.

36. Data on outbreaks associated with places of worship gathered by Public Health Ontario summarized above in para. 28 highlight the greater transmission risks among identified outbreaks associated with places of worship when compared to comparable non-institutional, non-workplace settings.

37. Both Drs. Schabas & Kettner, experts retained by the Applicants, have noted that few deaths are directly attributable to transmission in places of worship, yet overlook the reality that

[32] Assuming independence of infection risk among attendees, prob (at least one attendee with COVID-19) = (1-(Prob that all are uninfected) = (1-% of attendees with COVID)^number of attendees.

many people who attend religious gatherings also work outside their homes, whether as essential workers in LTCHs or transit operators or dentists who, if infected at a place of worship can then transmit COVID-19 to those they care for, drive for or serve, in addition to transmitting COVID-19 to uninfected household members. As a transmission location cannot be identified for many of the thousands of cases of COVID-19 deemed to be community transmission, temporary restrictions have been imposed on a wide range of settings and gatherings. Given that reducing COVID-19 transmission (as the upstream cause of COVID-19 harms including illness, hospitalization and death) is a major policy focus of government action regarding COVID-19, temporary limits on gatherings are a reasonable element of the bundle of NPIs aiming to reduce COVID-19 transmission and subsequent harms.

38. The Applicants' experts make reference to 'safety plans' (Dr. Kettner) and provide an admonition that 'public health should work constructively with religious congregations to find ways to allow religious services to continue to function at an acceptable risk' (Dr. Schabas). Given the diversity of religious practices and the venues where religious gatherings occur, the policy rationale for diverting sparse public health resources to working with individual religious organizations seems based on the assertion that cooperation will be forthcoming from all groups, which experience (including the experience of some of the applicants in this case) teaches may not happen in practice.

39. It may be theoretically possible to argue that contact tracing would be a reasonable alternative, arguing that if an infection occurred, then attendees could be contacted and advised to self-isolate, be tested or follow other public health advice. However, contact tracing requires being able to identify by name people who may have been in contact with a confirmed case of COVID-19 so that these persons can be directed to testing and advised to self-isolate. This argument, if

valid, assumes three critical elements: that people are truthful and complete when asked about places they have been, that an accurate and complete list of attendees for each place of worship is maintained by every place of worship and that society has the resources to contact each identified person. Even if all three elements are present, the significant likelihood of asymptomatic or presymptomatic COVID-19 transmission means infection of others is expected to occur before the index case is confirmed which is the necessary step that would trigger contact tracing. Ontario's COVID-19 experience to date suggests that the theoretical impact of contact tracing has not been realized, due to both the biology of COVID-19 and the reality that any single case will likely have infected others before test results are available to initiate contact tracing.

40. In keeping with Ontario's commitment to reduce illness and mortality from pandemic infectious disease, and noting the far higher death rates seen in jurisdictions that opted for less restrictive measures than in Ontario, the Province of Ontario implemented temporary limits on gatherings, including those at places of worship and for religious observance. As discussed above, in addition to the risk associated with any gathering, COVID-19 outbreaks have been reported from places of worship and these have been more severe than outbreaks in other settings as demonstrated by the increased number of cases per outbreak.

41. Specific features of religious services including singing, preaching and close contact all increase risks of COVID-19 transmission. Furthermore, persons who attend places of worship may become infected and transmit to others in their households and workplaces. Taken together, these factors lead me to conclude that temporarily limiting religious gatherings is a public health measure which contributes to reducing COVID-19 transmission and thus harms from COVID-19. At such time as COVID-19 incidence rates decline significantly, reducing and eventually eliminating temporary limits on religious gatherings would be appropriate, as occurred when

regions moved into lower zones of Ontario's *Keeping Ontario Safe and Open Framework*, and as is already happening with the current *Roadmap to Reopening*.[33]

VI. CAN THE RISK OF TRANSMISSION AT INDOOR RELIGIOUS GATHERINGS BE ADEQUATELY ADDRESSED BY RULES REQUIRING PHYSICAL DISTANCING AND MASKS OR OTHER PERSONAL PROTECTIVE EQUIPMENT ("PPE")?

42. Evidence-based mitigation measures such as face covering and physical distancing can reduce, but not eliminate, the risk of Virus transmission. The ongoing global pandemic highlights the reality that adherence with these measures is imperfect, and the imposition of regulatory fines has not eliminated non-compliance.

43. At religious gatherings, rules requiring the use of face coverings and physical distancing are inadequate to prevent COVID-19 transmission when community transmission is heightened. First, individuals may refuse to comply with such rules and reactive measures (i.e. enforcement actions) such as penalties or other sanctions for non-compliance imposed after the fact will do nothing to stop a COVID-19 outbreak caused by transmission that has already occurred at a gathering. At the height of the third wave, given the high prevalence of COVID-19 variants and the pressures on Ontario's hospital and ICU capacity, even isolated incidents of non-compliance with physical distancing and face covering requirements at religious gatherings would have had grave public health implications.

44. Second, the risks associated with religious gatherings further include the risk that participants may acquire or spread COVID-19 when they travel to and from the place of worship. As noted above, these risks are increased when community prevalence of COVID-19 is heightened.

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[33] See **Exhibit "P":** Ontario, "Reopening Ontario", online: <https://www.ontario.ca/page/reopening-ontario#section-1> (accessed July 1 2021).

45. Although a religious leader, (e.g. Rabbi, Imam, Pastor, etc.) if present, may be able to ensure compliance with physical distancing and face covering requirements, the sense of community at religious gatherings may also prompt people to approach within two metres of each other to exchange greetings or sing at a high volume, particularly when such activities are an integral part of observance, increasing the risk of transmission. Further, a religious leader's ability to monitor and promote compliance risks being compromised in larger gatherings where it is more difficult to keep track of all participants. Even isolated incidents of non-compliance with physical distancing and face covering requirements at religious gatherings may lead to COVID-19 transmission, hospitalizations, and add to the significant pressures on Ontario's health care system.

VII. DO YOU AGREE OR DISAGREE WITH THE AFFIDAVITS OF DR. WARREN, DR. SCHABAS, AND DR. KETTNER?

i) Dr. Warren's affidavit

46. I have reviewed the affidavit of Dr. Warren.

47. With regard to Dr Warren's analogy of tuberculosis for COVID-19, the differing burden of each of these infectious diseases renders this analogy inapt. As discussed above, the notion of burden can be understood as a function of the prevalence of the disease (i.e., number of cases in a population), the exposure risk (i.e., the probability that one infected person will infect others), and the consequences of infection, such as hospitalization and death. To summarize, approximately 300 cases of tuberculosis are diagnosed in the City of Toronto each year.[34] Even if all 300 persons diagnosed with tuberculosis required hospitalization (which would be unheard of), 300 hospitalizations over a year is insignificant in comparison to the 25-35 hospitalizations/day from

[34] See **Exhibit "Q":** City of Toronto, "Programs & Services for Tuberculosis (TB)", online: <https://www.toronto.ca/community-people/health-wellness-care/health-programs-advice/tuberculosis-tb/programs-services-for-tuberculosis-tb/> (accessed April 22, 2021).

COVID-19 in April 2021 alone. For public health practice, higher burdens are an important motivator for more restrictive measures.

48. Similar considerations apply to Dr. Warren's reliance on influenza. While the prevalence of influenza is higher than tuberculosis, the consequences of acquiring influenza are generally less severe, with significantly lower mortality and hospitalization rates. Accordingly, seasonal outbreaks of influenza do not result in the same pressures on hospital and ICU capacity. It should also be pointed out that influenza has been thoroughly studied whereas COVID-19 is a new disease with even newer variants. The public health response to influenza has been finely tuned over the years – while obvious, it bears noting that there simply has not been the same lengthy period available for finely tuned public health measures to COVID-19.

49. In short, the important differences between COVID-19 and tuberculosis and influenza obligate public health officials to recommend a different public health response commensurate with the relative burdens of each infectious disease.

50. The limits on religious gatherings have been an important part of Ontario's broader public health response to the COVID-19 pandemic. If no limits were placed on religious gatherings, as Dr. Warren urges, this could be expected to push infection rates higher, increase the number of people hospitalized with COVID-19, and bring Ontario's health system nearer to the point where it would be unable to care not only for people infected with COVID-19 but also for others who need hospital based care.

51. Accordingly, I do not agree with Dr. Warren's statement that no limits should be placed on religious gatherings aside from physical distancing. The burden associated with COVID-19 in Ontario's health system, the higher risks of transmission associated with aspects of religious gatherings such as singing, and the greater number of cases per outbreak all support my opinion

that temporary limits on religious gatherings are a reasonable measure to protect Ontarians from COVID-19 and Ontario's health system from collapse due to COVID-19.

ii) Dr. Schabas' affidavit

52. I have reviewed the affidavit of Dr. Schabas. The affidavit makes repeated references to an undefined notion of 'lockdown'. It seems reasonable to assess Dr Schabas' assertions about lockdowns with regard to temporary limits on religious gatherings which is the matter at issue in this proceeding. Dr Schabas asserts the following points with my response set out below each point:

1. Temporary limits on religious gatherings have been arbitrary and capricious because they are not necessary or effective.

Temporary limits on religious gatherings are neither arbitrary nor capricious when considered in light of the evidence of elevated risks of COVID-19 transmission associated with elements of religious observance (e.g. singing) and Ontario's COVID-19 outbreak data showing 65% more cases from outbreaks associated with places of worship than with comparable non-institutional, non-workplace settings. Moreover, these temporary limits have been part of a bundle of NPIs which, when implemented with increasing stringency in each of the three waves to date, have been followed by decreases in the daily case count and growth rates.

2. Temporary limits on religious gatherings cause more harm (to mental health) than good (preventing COVID-19 related mortality and morbidity).

Dr. Schabas provides no evidence to support this assertion. Seeking the mental health benefits of attending religious gatherings, adherents to a wide range of diverse observances have established virtual gatherings, drive-in gatherings, and as conditions have improved, outdoor gatherings and larger indoor gatherings, suggesting that it is possible both to reap the health benefits of observance for adherents and to reduce risks of COVID-19 transmission in the wider population.

3. The initial temporary limits on religious gatherings in March 2020 were based on inaccurate models, including an overestimate of the Infection Fatality Rate ("IFR") by at least four times (especially outside of LTCs).

Dr. Schabas provides no details of the models which he describes as 'inaccurate'. The precautionary principle, coupled with the novelty of COVID-19 provides an adequate basis for implementing NPIs in line with Ontario's pandemic plan.

4. Temporary limits on religious gatherings have not been used in the past for respiratory contagions, including for influenza. Currently tobacco is more deadly than COVID-19.

My response regarding respiratory contagions, including influenza, is detailed in my response to Dr. Warren. Tobacco is not comparable as it is not a communicable disease and thus does not require restrictions on gatherings to reduce its transmission to others. Moreover, the government

of Ontario, as many other governments, has implemented significant permanent restrictions on the ability to smoke in places where second-hand smoke could cause harm to others (see e.g. *Smoke-free Ontario Act*).

5. COVID is a serious public health problem but affects mostly old people. The measure of years of life lost must be used to recognize this reality. Diarrheal illness in children has a greater impact than COVID-19.

Years of lives lost is just one measure of the deadliness of a virus. Since the matter at issue in this proceeding is actions taken by the government of Ontario, a more appropriate comparison would be years of life lost or deaths from diarrhea in Ontario.[35]

6. Public Health data shows that incidence of spread at religious gatherings is low. In any event, it is very low where there is no overcrowding, singing and well-ventilated.

Fifty-nine outbreaks have been identified at places of worship with an average of 8.9 cases per outbreak. While reducing or eliminating overcrowding and singing and improving ventilation would all contribute to lower risks of transmission, the role of the government in a pandemic emergency context is generally to establish rules for each sector rather than to inspect and create safety plans for each individual place of worship. If Dr. Schabas is of the view that such detailed plans should be created by the government, some evidence of precedent and/or operational consideration for how this would take place in thousands of places of worship would seem a reasonable expectation from an expert in public health.

7. VOCs are more transmissible – and therefore require stricter temporary limits on religious gatherings. It is not the right path to impose increasingly stricter measures.

The precautionary principle behooves government to be more cautious, not less cautious, when dealing with uncertainty. The biology of COVID-19 variants (notably alpha and delta), by being more transmissible than the variants they displaced, increases the risk of overwhelming the health system, suggesting that more stringent public health measures should be put in place, not less stringent measures. Dr. Schabas acknowledges that the science related to "many aspects of covid is uncertain" and recognizes that decisions on which public health measures to employ "are of necessity based on judgment as much as science."

iii) Dr. Kettner's affidavit

53. I have reviewed the affidavit of Dr. Kettner. In my opinion, Dr. Kettner provides a flawed modelling approach as the basis for his conclusions that the "probability of transmission of

[35] In fact, COVID-19 is more deadly than diarrhea. The CDC states that 2195 children die each day from diarrhea while the WHO reported deaths from COVID-19 amount to >7,000/day. UNICEF data indicate that approximately 2000 children under age 5 die each year in Canada and that diarrhea accounts for 8% of global child mortality. Applying this to Ontario suggests an upper limit of 64 deaths annually from diarrhea. Over the 16 months of the COVID-19 pandemic, this would amount to approximately 85 deaths from diarrhea compared to 9101 from COVID-19. UNICEF data available online: <https://data.unicef.org/resources/data_explorer/unicef_f/?ag=UNICEF&df=CME&ver=1.0&dq=CAN.CME_TMM0+CME_TMY0T4..&startPeriod=2016&endPeriod=2021>.

COVID-19 in church services with attendees from with (sic) current rates of infections similar to that of the Niagara health region" (para 95).

54. Dr. Kettner begins by choosing a municipality that is not the one in which the Wellandport church is located; Wellandport is a hamlet located in West Lincoln, Ontario, not within the municipality of Welland. Data provided by Public Health Ontario indicate that this is slightly to the advantage of his analysis as the cumulative incidence for West Lincoln is 30/100,000 while that for Welland is 38.3/100,000. Regardless of the incidence rate chosen, Dr. Kettner provides no evidence that all attendees are drawn from a single municipality whose incidence can then be used for the calculations that follow.

55. Dr. Kettner's modeling approach appears to overlook the reality that many individuals attending religious gatherings will do so as members of household groups. COVID-19 secondary attack rates within households are reported to be higher for asymptomatic and presymptomatic cases than for symptomatic cases and these rise further for VOCs, such that VOCs were determined to have a household secondary attack rate 1.31 times higher than non-VOC for symptomatic cases, 1.91 times higher for asymptomatic VOC cases, and 3.41 times higher for presymptomatic cases.[36] The non-independence of COVID-19 infection risk among members of a household, coupled with high secondary attack rates in the time of VOCs' emergence, undermines Dr. Kettner's model as a basis for prudent decision making.

56. Furthermore, Dr. Kettner's model assumes a constant (i.e. the same number of new cases every day) incidence rate over a period when incidence varied substantially in Niagara region.

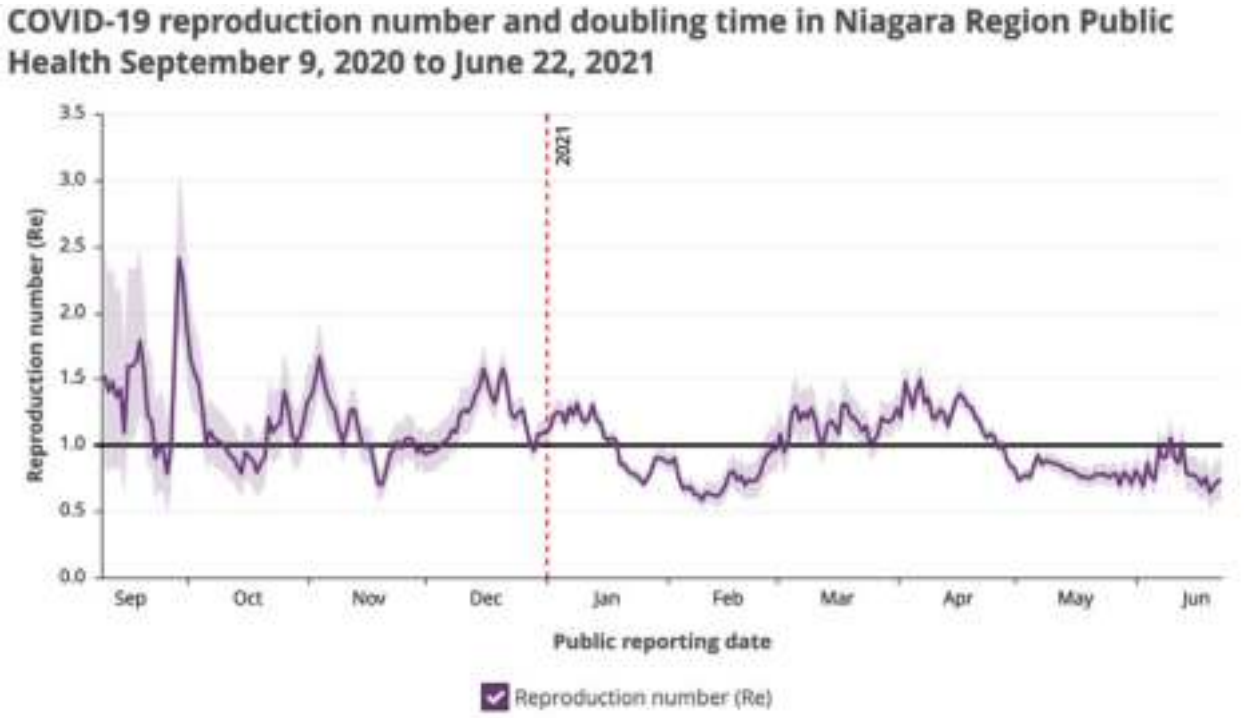
[36] See **Exhibit "N"**, *supra* note 28.

Using the day with the highest number of new cases, (200 cases, April 12, 2021), Kettner's 1/5000 estimate would more correctly be 1/1937, or 2.58 times greater.

57. Finally, Dr. Kettner's model fails to consider transmission dynamics over time. Using his rate of 1/5000 per day with the first infection on a Monday and services on Sunday, 7/5000 people will be infected by the first Sunday, 5 will be within Dr. Kettner's 10 days of infectiousness and 2 within Kettner's period of presymptomatic COVID (para 53). Using Dr. Kettner's 8% risk of transmission, the risk of infection from a symptomatic case on the first Sunday would be 5/5000*0.08 = 0.00008 (1 in 12500), but a week later the risk would have increased to 12/5000*0.08 = 0.000192 (1 in 5208), and that ignores the secondary cases, both within households and in the wider community. Dr. Kettner's model does not appear to account for the effective reproduction rate ("Re") during the period under consideration (March 14, 2020- April 29, 2021). Data provided by Public Health Ontario and shown in Figure 1 below indicate that the effective reproduction rate varied during this period and was greater than 1 for several weeks. Re greater than 1 means that exponential growth in the number of new cases is occurring yet Dr. Kettner's model picks 1/5000 as the constant correct rate and applies it across the entire time

period. This oversimplification fails to acknowledge the rapid growth rates of COVID-19 cases that occurred during the peaks of the second and third waves of COVID in Ontario.

FIGURE 1[37]



58. In summary, a model that uses the wrong geography, makes no account for household transmission dynamics, assumes a constant incidence over a period when incidence varied

[37] See **Exhibit "R":** Public Health Ontario, "Ontario COVID-19 Data Tool", online: <https://www.publichealthontario.ca/en/data-and-analysis/infectious-disease/covid-19-data-surveillance/covid-19-data-tool?tab=retd> (accessed 27 June 2021; configured to Niagara Region Public Health, 09 Sep 2020 – 22 Jun 2021).

significantly and included weeks with exponential growth (Re> 1), and which ignores the effects of time in transmission dynamics is not one to be recommended as a basis for policy decisions.

AFFIRMED by video conference by
MATTHEW HODGE of the [redacted]
in the Province of Ontario before me on this
2nd Day of July, 2021 in accordance with
O Reg 431/20, Administering Oath or
Declaration Remotely

Commissioner for the Taking of Affidavits

MATTHEW HODGE

This is "**Exhibit A**"
to the Affidavit of Matthew Hodge,
affirmed this 2nd day of July, 2021

A Commissioner, etc.

MATTHEW HODGE, MDCM, PhD, CCFP(EM), FRCPC

Informatics and metrics-savvy physician leader committed to quality improvement, developing people, value-for-money and reliable operational excellence supported by data and information systems. Results-focused physician executive with leadership experience in public health, health care delivery, and international health organizations; public health & preventive medicine specialist and practicing ER physician.

PROFESSIONAL EXPERIENCE & ACCOMPLISHMENTS

EMERGENCY DEPARTMENT PHYSICIAN, Toronto, ON **June 2011 - ongoing**
Providing clinical services in hospitals ranging from Rainy River to major academic centres in Toronto, currently at SRH, General & Birchmount sites and locum small hospital work in Grey-Bruce and NE Ontario.

CONSULTANT PHYSICIAN **June 2011 - ongoing**
Recent engagements include defining an analytic strategy to position a public health organization to focus its program efforts in early child development, redesigning public health inspection services, and ED operations consulting with Canadian startup Metricaid. Previous engagements have included LEAN-driven Emergency Department improvement projects, review and recommendations for restructuring and reorienting surveillance activities in a public health organization, and assessment of efficiency and provider mix in primary care. COVID work has included engagements with PHAC, PHO & Peel Region Public Health.

MEDICAL MANAGER, RMFCU. APFRB, MOHLTC, Toronto, ON **January 2016 – April 2017**
Providing clinical expertise to Risk Management & Fraud Control Unit (RMFCU) within the Corporate Services Division of the MOHLTC. Developed a strategic framework focused on deterrence, recovery and value to prioritize efforts and established analytic platform for post-payment review of expenditures.

CANCER CARE ONTARIO, Toronto, ON **March 2010 – June 2011**
Chief Medical Information Officer, & Director, Informatics
Led 140 informatics staff supporting cancer service management and Access-to-Care (Ontario-wide wait times for surgery, diagnostic imaging and Emergency Department care); represented CCO at provincial bodies including ER-ALC expert panel. Managed budget of CDN$16M.

Developed 'one informatics' plan to i) unify disparate informatics resources across the organization, ii) rationalize processes using LEAN and iii) engage and support hospitals and other health care delivery organizations directly in their performance improvement efforts; aligned enterprise architecture development, $2M electronic data warehouse project and business intelligence strategy around shared vision of the patient journey; led division with highest staff satisfaction scores.

UNITED NATIONS POPULATION FUND (UNFPA), New York, NY **January 2008 – February 2010**
Chief, Evaluation Branch, Division of Oversight Services
Led review and revision of evaluation program; subsequently promoted to Chief, Evaluation. Conducted or supervised 8 evaluations of country programmes with internal auditors; resulting tools established a shared audit & evaluation risk-based framework for evaluating relevance and strategic alignment of the Fund's country programmes, comprising $300M in annual expenditures. Reduced time from fieldwork to final report from over 360 days to 30 days. Led and participated in cross-functional audit/evaluation teams in the field in Africa and Asia. Contributed to the Fund's development of an evaluation policy.

CITY OF HAMILTON PUBLIC HEALTH SERVICES, Hamilton, ON **February 2005 – October 2007**
Associate Medical Officer of Health
Led epidemiology & evaluation within municipal public health department including responsibility for surveillance and emergency planning. Transformed $800K Public Health Research Education and Development (PHRED) program from unaccountable fund to competitive grants program; developed and implemented program evaluation cycle with self-assessment, epidemiologic best-evidence and peer review; led investigation, media and provincial liaison during legionella outbreak (2006) and provided ongoing medical expertise to communicable disease and environmental health investigations; represented Canada's

pubic health practitioners on Integration Working Group for Canada Health Infoway-funded communicable disease surveillance system (Panorama), 2006 - 2008

MCMASTER UNIVERSITY, Hamilton, ON **July 2005 - ongoing**

Associate Professor, Clinical Epidemiology & Biostatistics
Developed management education for Public Health & Preventive Medicine residents, course director 2012, 2013, 2014, 2016.

UNIVERSITY HEALTH NETWORK, Toronto, ON **January 2001 – April 2012**

Staff Physician, Emergency Department
Member, Practice Plan & Finance Committees

UNITED NATIONS CHILDREN'S EMERGENCY FUND (UNICEF) October 2003 – June 2004

Consultant, Evaluation Office
Completed thematic evaluations of midterm progress on Strategic Plan goals in immunization and HIV/AIDS; policy development for HIV/AIDS care and support and technical support to UNICEF-funded projects to prevent mother-to-child transmission of HIV infection in 11 countries.

MINISTRY OF HEALTH & LONG-TERM CARE, Toronto, ON **September 2002 – March 2003**

Senior Medical Consultant, Public Health Branch

Negotiated terms of MOHLTC pilot funding for colorectal cancer screening to be implemented by Cancer Care Ontario; SARS response.

UNITED NATIONS CHILDREN'S EMERGENCY FUND (UNICEF) September 2001 – September 2002

Senior Health Advisor, HIV/AIDS

WORLD HEALTH ORGANIZATION (WHO), Geneva, SUI **January 1999 – July 2001**

Medical Officer

EDUCATION AND PROFESSIONAL CERTIFICATIONS

MS, **Masters of Health Care Management, Harvard University**, 2011 (Mid-career physician management and leadership training program offered by Harvard School of Public Health)
MSIT, **Master of Science (Inf. Technology), Carnegie Mellon University,** 2008
MSc, **Development Finance, University of London**, 1999
MDCM, **McGill University**, 1996
PhD, **McGill University,** 1995 (MD-PhD Program, Thesis Title: Methods for Geographic Analyses of Health Services Use)
BA, **Economics, Yale University**, 1987
College of Physicians & Surgeons of Ontario (CPSO): Medical License #70425
Fellow, Royal College of Physicians and Surgeons of Canada, 2000
Public Health & Preventive Medicine
Diplomate, American Board of Preventive Medicine, 2007
Clinical Informatics Certification, American Board of Preventive Medicine, 2013
Certificate of Special Competence in Emergency Medicine, (CCFP(EM)), 2012

COMMUNITY CONTRIBUTIONS

Advisor, MARS Discovery District: providing advice to start-ups in the Health practice, 2014-ongoing
Public Health Physicians of Canada, formerly National Specialty Society for Community Medicine
President, 2009 – 2011; Treasurer, 2008 - 2009
Event Physician, Athletics Canada National Cross Country Championships, 2007 – 2010

PUBLICATIONS

Available upon request

This is "**Exhibit B**"
to the Affidavit of Matthew Hodge,
affirmed this 2nd day of July, 2021

A Commissioner, etc.

Kitchener Court File No.: CV-21-00000095-0000
St. Thomas Court File No.: CV-21-08
Welland Court File No.: CV-21-00013361-0000

ONTARIO
SUPERIOR COURT OF JUSTICE

BETWEEN:

THE ATTORNEY GENERAL OF ONTARIO

Applicant

-and-

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHUURMAN, DEAN WANDERS, RANDY FREY, HARVEY FREY, and DANIEL GORDON

Respondents

AND BETWEEN:

HER MAJESTY THE QUEEN IN ONTARIO

Applicant

-and-

THE CHURCH OF GOD (RESTORATION) AYLMER, HENRY HILDEBRANDT, ABRAM BERGEN, JACOB HIEBERT, PETER HILDEBRANDT, SUSAN MUTCH, ELVIRA TOVSTIGA, and TRUDY WIEBE

Respondents

AND BETWEEN:

WELLANDPORT UNITED REFORMED CHURCH

Applicant

-and-

HER MAJESTY THE QUEEN AS REPRESENTED BY THE ATTORNEY GENERAL OF ONTARIO

Respondent

AND BETWEEN:

STEPHEN RICHARDSON

Applicant

-and-

THE ATTORNEY GENERAL OF ONTARIO

Respondent

ACKNOWLEDGMENT OF EXPERT'S DUTY

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1. My name is Dr. Matthew Hodge. [redacted] in the Province of Ontario.

2. I have been engaged by the Attorney General of Ontario to provide evidence in relation to the above-noted court proceeding.

3. I acknowledge that it is my duty to provide evidence in relation to this proceeding as follows:

   (a) to provide opinion evidence that is fair, objective and non-partisan;

   (b) to provide opinion evidence that is related only to matters that are within my area of expertise; and

   (c) to provide such additional assistance as the court may reasonably require, to determine a matter in issue.

4. I acknowledge that the duty referred to above prevails over any obligation which I may owe to any party by whom or on whose behalf I am engaged.

Date: July 2nd, 2021

Dr. Matthew Hodge

This is "**Exhibit C**"
to the Affidavit of Matthew Hodge,
affirmed this 2nd day of July, 2021

A Commissioner, etc.

Ontario Health Plan for an Influenza Pandemic

Chapter 1: Introduction

March, 2013

Ontario

Ministry of Health and Long-Term Care
Emergency Management Branch
1075 Bay Street, Suite 810
Toronto, Ontario
Canada M5S 2B1
416-212-8022 (local); 1-866-212-2272 (long distance)
emergencymanagement.moh@ontario.ca

Ontario Health Plan for an Influenza Pandemic

Chapter 1: Introduction

Audience

- health sector employers, health care providers and other health workers, emergency planners, health administrators and other provincial health system partners

Chapter objectives

- to introduce and orient readers to the 2013 Ontario Health Plan for an Influenza Pandemic (OHPIP)

Introduction

The Ministry of Health and Long-Term Care (MOHLTC) leads the development of the OHPIP to support the provincial health system to prepare for and respond to an influenza pandemic.

Since the release of the first iteration of the plan in 2004, the OHPIP has been regularly updated to reflect new knowledge, information and best practices. This process is supported by the OHPIP Steering Committee – which consists of representatives from health associations, unions, regulatory bodies and government organizations – and a variety of workgroups (See Appendix A – OHPIP Steering Committee and workgroup members).

The OHPIP supported the provincial health system's response to the 2009 H1N1 influenza pandemic (pH1N1). Although a number of simulated scenarios have been held over the years to exercise components of the OHPIP, pH1N1 was the first opportunity to use the plan to guide the response to a pandemic.

The 2013 version of the OHPIP was updated to incorporate the priority lessons learned and best practices from pH1N1. More information about Ontario's evaluation of the response to pH1N1 can be found in Pandemic (H1N1) 2009: A Review of Ontario's Response and The H1N1 Pandemic – How Ontario Fared: A Report by Ontario's Chief Medical Officer of Health.

Previous versions of the OHPIP have used World Health Organization (WHO) and Public Health Agency of Canada (PHAC) response plans as a conceptual foundation. These pandemic response plans are in the process of being revised based on the lessons learned and best practices from pH1N1. Some concepts that were previously incorporated in the OHPIP aren't in the 2013 iteration as they haven't yet been updated by the WHO and PHAC. For example, the WHO's six-phase description of a pandemic featured in previous versions of the OHPIP and Canadian Pandemic Influenza Plan for the Health Sector (CPIP). An evaluation by an external review committee on the functioning of the International Health Regulations (2005) in relation to pH1N1 recommended that the WHO simplify the pandemic phase structure. As the WHO has not released an updated plan since the evaluation was released, the phase structure is not included in this version of the OHPIP.

This is the final iteration of the OHPIP. The Ontario Influenza Response Plan *(*OIRP) will eventually replace it. Through this new plan, the provincial health system's focus will shift from preparing for an influenza pandemic to creating and building effective seasonal influenza responses and escalating those measures during a pandemic. The OIRP will link to updated pandemic response plans from the WHO and PHAC, and it will also address the next steps documented in this version of the OHPIP and outstanding lessons learned and best practices from pH1N1. The OIRP will outline influenza responses for the entire health system, including government, primary health care, community care, hospitals and public health.

Roles and responsibilities

All health system partners have a role to play during the response to an influenza pandemic, from the WHO at the international level to health sector employers and health workers at the community level.

The MOHLTC leads the Government of Ontario's response to an influenza pandemic through health system coordination and direction.[1] Within the MOHLTC's emergency response structure, there are many individuals and groups who provide operational and/ or strategic direction to guide the response. For example, the Chief Medical Officer of Health (CMOH) has legislated responsibilities under the Health Protection and Promotion Act (HPPA) and is the MOHLTC's Executive Lead during the response to an influenza pandemic. This means that the CMOH provides strategic leadership for the MOHLTC's response.

In the OHPIP, references to the MOHLTC include the Minister, CMOH and other individuals/ groups in the MOHLTC (e.g., Deputy Minister, Ministry Action Group). Please see the Ministry Emergency Response Plan for more detail on the MOHLTC's emergency response structure and decision-making process.

Table 1 outlines general roles and responsibilities of health system partners during an influenza pandemic. Each OHPIP chapter includes more detailed roles and responsibilities relevant to the chapter topic.

[1] As per the Emergency Management and Civil Protection Act, the MOHLTC assumes the role of primary ministry for emergencies, declared and undeclared, when the primary Government of Ontario response falls under the ministry's emergency responsibilities of "human health, disease and epidemics" or "health services during an emergency" as assigned by Order in Council (OIC) 1157/2009. The MOHLTC responds to the impacts on the health of Ontarians and on the health system.

TABLE 1. GENERAL INFLUENZA PANDEMIC RESPONSE ROLES AND RESPONSIBILITIES[2]

Party	Roles and responsibilities
WHO	Coordinate international response activities under the International Health Regulations Perform international surveillance and provide an early assessment of pandemic severity in order to help countries determine the level of intervention needed in the response Declare an influenza pandemic Select the pandemic vaccine strain and determine the time to begin production of the pandemic vaccine
PHAC	Coordinate national pandemic influenza response activities, including nation-wide surveillance, international liaison and coordination of the vaccine response, as outlined in the CPIP

[2] The information in this table is intended to provide general information about roles and responsibilities of different parties during an influenza pandemic. It is not a comprehensive listing of roles or obligations of a party. Roles, responsibilities and obligations of a party vary in specific circumstances.

Party	Roles and responsibilities
MOHLTC (through the Ministry Emergency Operations Centre (MEOC))	Liaise with PHAC and other provinces and territories Collaborate with Public Health Ontario (PHO) to use surveillance information to determine severity Develop recommendations[3] and provincial response strategies[4] for the provincial health system, as well as others affected by public health measures Communicate with provincial health system partners through situation reports, Important Health Notices (IHNs), the Health Care Provider Hotline, the Health Stakeholder Teleconference, the MOHLTC website and other methods Develop and issue directives[5], orders and requests as per the HPPA, Long-Term Care Homes Act and other relevant provincial legislation[6] Communicate with the public through media briefings, the MOHLTC website and other methods Solicit and respond to feedback and input from provincial health system partners Deploy supplies & equipment from the MOHLTC stockpile to health workers and health sector employers Deploy antivirals from the MOHLTC stockpile to community-based pharmacies and other dispensing sites

[3] This term refers to best practices as well as guidance on the risk posed by the pandemic. Recommendations related to occupational health and safety (OHS) may be considered by health sector employers to be reasonable precautions in the application of the Occupational Health and Safety Act (OHSA).

[4] Provincial response strategies include the surveillance strategy, public health measures strategy, outpatient care & treatment strategy, antiviral distribution strategy, immunization strategy and supplies & equipment strategy

[5] Directives are sent from the CMOH to health care providers or other health entities as per the HPPA.

[6] The OHSA continues to apply during an influenza pandemic and prevails when there is a conflict between that act and any other legislation.

Party	Roles and responsibilities
Public Health Ontario (PHO) (through the MEOC)	Support the MOHLTC to use surveillance information to determine severity Lead and coordinate the provincial surveillance strategy Coordinate and provide provincial influenza laboratory testing Provide scientific and technical advice to the MOHLTC (e.g., advice on infection prevention and control measures) Generate knowledge translation tools and offer training opportunities to supplement the MOHLTC's recommendations, directives and response strategies
Ministry of Labour (MOL)	Provide OHS advice to the MOHLTC (through the MEOC) Enforce the OHSA and its regulations
Emergency Management Ontario	Coordinate the provincial response to an influenza pandemic, with an emphasis on coordinating responses to non-health system impacts and consequences as outlined in the Provincial Coordination Plan for an Influenza Pandemic
Local Health Integration Networks (LHINs)[7]	Liaise between transfer payment (TP) organizations and the MOHLTC Participate in the coordination of local care & treatment
Public health units (PHUs)[8]	Follow MOHLTC recommendations, directives, orders and requests Develop and issue orders[9] Lead local implementation of the surveillance strategy Lead local implementation of immunization Participate in the coordination of local care & treatment Lead local implementation of public health measures Continue to provide other public health services

[7] Other LHIN roles during an influenza pandemic are currently under development.

[8] Throughout the OHPIP, PHU includes boards of health, medical officers of health (MOHs) and other PHU health workers (e.g., public health inspectors, epidemiologists, public health nurses, etc.). See the HPPA and Ontario Public Health Standards for more information on the roles and responsibilities of various PHU parties.

[9] This refers to orders made by MOHs and public health inspectors as per the HPPA.

Party	Roles and responsibilities
Health liaison organizations (provincial associations, unions and regulatory bodies)	Liaise between members and the MOHLTC (see Chapter 2: Health Sector Communications) Share best practices among sector/ membership
Health workers and health sector employers[10]	Follow MOHLTC recommendations, directives, orders and requests Follow PHU orders Continue to provide safe and effective care Participate in the coordination of local care & treatment Participate in research and surveillance activities Practice and role model appropriate behaviour to protect clients/ patients/ residents (C/P/Rs) and prevent further spread of influenza (e.g., get immunized; practise respiratory etiquette and hand hygiene; stay home when sick)
Other employers	Implement public health measures Follow MOHLTC orders and requests Follow PHU orders Encourage immunization among employees Be immunized as soon as possible
Public	Follow public health measures such as staying home when symptomatic, performing hand hygiene and keeping commonly touched surfaces clean Follow MOHLTC and PHU orders Be immunized as soon as possible

Ontario's approach to an influenza pandemic

The 2013 OHPIP is a response document. As opposed to providing detailed planning guidance for provincial health system partners, it outlines anticipated response activities

[10] See Chapter 5: Occupational Health & Safety and Infection Prevention & Control and Chapter 9: Primary Health Care.

based on the severity of the pandemic virus. The actual response activities will be confirmed by the MOHLTC at the time of a pandemic based on the epidemiology of the virus (see Chapter 3: Surveillance), impacts on the provincial health system and behavioural responses of the public. Before these things are known, the MOHLTC considers the precautionary principle in making decisions. During the planning phase, provincial health system partners are encouraged to review the response activities outlined in the OHPIP and take steps to ensure they are able to perform their role during an influenza pandemic. Health system partners are also encouraged to have continuity of operations plans in place that enable them to respond to any type of business disruption, including an influenza pandemic.

The MOHLTC recognizes that planning to respond to an influenza pandemic is not enough.

To ensure an effective pandemic response, health workers and health sector employers need to appropriately respond to seasonal influenza each year – including consistently applying appropriate OHS & infection prevention & control (IPAC) measures; effectively promoting and administering influenza immunization programs for C/P/Rs, health workers and members of the public; implementing timely epidemiological and laboratory surveillance; engaging and tailoring interventions to the needs of vulnerable populations; and promoting appropriate public health measures

Preparedness tip

Health organizations should develop a continuity of operations plan to support their ability to respond to emergencies, such as an influenza pandemic. PHUs can use the Ontario Public Health Standards' Public Health Emergency Preparedness Protocol to guide their planning.

Ontario's influenza pandemic response objectives

The objectives of the MOHLTC's response to an influenza pandemic are consistent with those in the CPIP:

- first, to minimize serious illness and overall deaths through appropriate management of Ontario's health system
- second, to minimize societal disruption in Ontario as a result of an influenza pandemic

Guiding principles

The actions of the MOHLTC during a pandemic response are based on the following guiding principles. Many of these principles are useful in guiding the decision making of

other parties, including health sector employers, health workers, emergency planners and other public health leaders.

Evidence

The MOHLTC uses scientific and technical evidence to inform decision-making, including evidence on the risk posed by the pandemic. The MOHLTC partners closely with PHO to obtain, understand and communicate the evidence.

Legislation

The MOHLTC responds based on provincial legislative requirements and responsibilities.

Precautionary principle

The MOHLTC does not await scientific certainty before taking action to protect health. For example, the MOHLTC considers the precautionary principle when developing recommendations and directives related to OHS & IPAC measures, especially during the early stages of an influenza pandemic when scientific evidence on the severity of the novel virus is limited.[11]

See Chapter 5: Occupational Health & Safety and Infection Prevention & Control for more information on the application of the precautionary principle to OHS.

Ontario Public Service values

The MOHLTC uses the Ontario Public Service values to inform decision making during an influenza pandemic.

Work is underway federally to develop an ethical framework for the CPIP. Future versions of the OIRP will include an ethical framework that aligns with that in the CPIP.

Health equity

The MOHLTC considers the needs of vulnerable populations[12] when developing response and recovery measures.

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[11] As outlined in the HPPA, the CMOH must consider the precautionary principle when issuing a directive to a health care provider or health care entity related to health worker health and safety in the use of any protective clothing, equipment or device.

[12] The OHPIP defines vulnerable populations as a group of people who, because of the determinants of health, are more likely to be exposed to influenza, more likely to

To accomplish this, the MOHLTC may use the Health Equity Impact Assessment (HEIA), a decision support tool developed by the ministry to identify how a health program, service or policy impacts population groups in different ways. Work is underway at the MOHLTC to adapt the HEIA for a health emergency management context to ensure that provincial and local interventions do not exacerbate health disparities during an emergency.

Communication principles

The MOHLTC bases its communications with the provincial health system and the public on the following principles[13]:

- timeliness
- transparency
- accessibility
- credibility

Assumptions

The 2013 OHPIP is based on the following assumptions:

Origin and Timing

- The next pandemic could emerge anywhere in the world – including in Ontario.
- The next pandemic could emerge at any time of year.
- Ontario has little lead time between when a pandemic virus is first identified and when it arrives in the province.

Transmission

- The pandemic virus behaves like seasonal influenza viruses in significant ways, including the incubation period, period of communicability and methods of transmission.
- The pandemic strain is primarily community spread; that is, it is transmitted from person-to-person in the community as well as in institutional settings.

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experience a serious impact because of exposure, less likely to benefit from response and recovery measures and/ or who may be negatively affected by response and recovery measures.

[13] See Chapter 2: Health Sector Communications for more information on the application of these principles to the MOHLTC's two-way communications with the health system.

Pandemic Epidemiology

- An influenza pandemic consists of two or more waves – or intense periods – of viral transmission.
- The novel influenza virus displaces other circulating seasonal strains during the pandemic.

Clinical Features

- As with seasonal influenza, the severity of the pandemic cannot be predicted, may be partially determined by the effectiveness of interventions such as treatment with antivirals and is not easily determinable at the start of an outbreak. (See Severity of an influenza pandemic for more information on the scenarios used to guide the development of the 2013 OHPIP).
- As with seasonal influenza, the clinical severity of the illness experienced by Ontarians who are infected by the pandemic virus varies considerably: some individuals who are infected do not display any clinical symptoms, while others become quite ill and may require hospitalization and may even die.
- The groups at increased risk for severe disease and complications during an influenza pandemic are similar to those for seasonal influenza; however, there may be additional high-risk groups because of specific features of the pandemic virus.
- Vulnerable populations that typically experience a disproportionate burden of negative health outcomes, or are more vulnerable to these outcomes, because of the effects of the social determinants of health are more severely affected by the pandemic than other members of the community. This includes Ontarians with low incomes, who face language barriers, and who are homeless.

Interventions

- Vaccine is available in time to have an impact on the overall pandemic; however, it is not available for the first wave.
- The MOHLTC maintains an antiviral stockpile to provide treatment for individuals that meet its clinical recommendations.
- The efficacy and dose requirements of antivirals are not known until the pandemic begins and may differ from that of seasonal influenza; therefore, recommendations may change.

Severity of an influenza pandemic

Given that the severity of a pandemic cannot be known in advance, the anticipated response activities outlined in the 2013 OHPIP are based on a number of severity scenarios adapted from draft work undertaken by the Centers for Disease Control and Prevention. In this model, severity is measured along two dimensions – transmissibility of the virus and clinical severity of illness. There are four severity scenarios – ranging from a mild scenario that is similar to seasonal influenza (low transmissibility and low

clinical severity) to the most severe scenario with high transmission and high clinical severity rates.

As well, the OHPIP severity model includes an initial stage before severity is known when the limited availability of surveillance data does not allow for confident identification of severity. The severity may not be clearly known until after an influenza pandemic is over. The MOHLTC uses surveillance data to estimate severity (see Chapter 3: Surveillance).

This model has been used to provide information on the types of responses that may be used during an influenza pandemic. As more information about the severity of an influenza pandemic is available, the MOHLTC will establish and communicate the provincial response strategies such as the outpatient care & treatment strategy, immunization strategy, public health measures strategy, antiviral distribution strategy and surveillance strategy.

Figure 1 outlines the four severity scenarios used in the OHPIP. Table 2 outlines how various influenza pandemics and seasonal epidemics are categorized in this model and the major health system impacts.

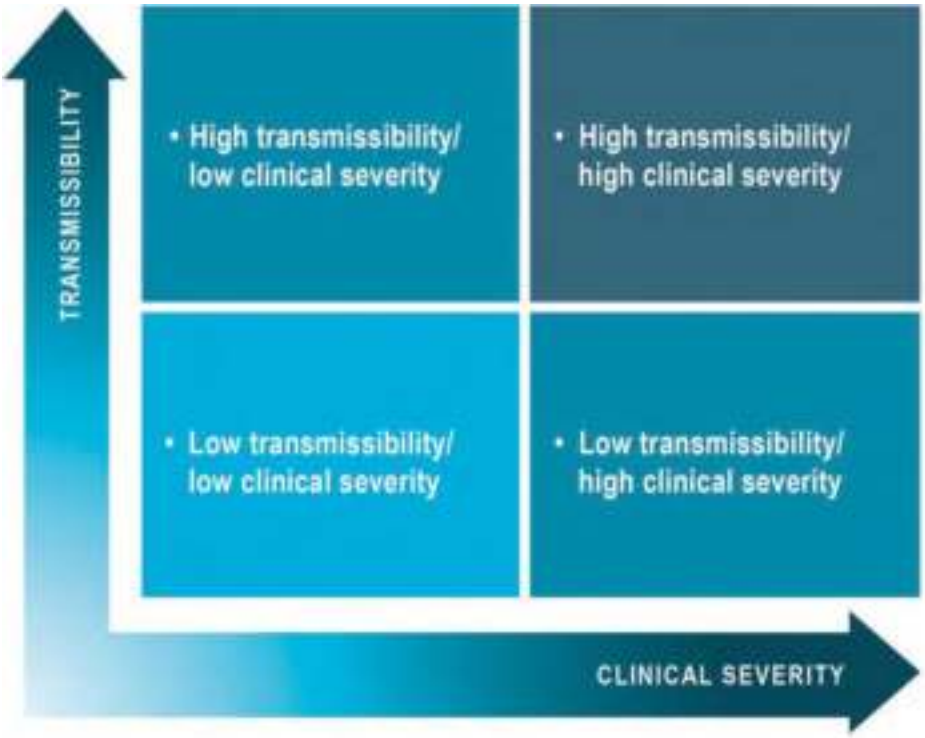

FIGURE 1. FOUR SEVERITY SCENARIOS USED IN THE OHPIP

TABLE 2. EXAMPLES AND IMPACT OF SEVERITY SCENARIOS

Overall severity	Characteristics	Examples	Impact on health system
Before severity is known	Limited surveillance data available	Either in the pre-pandemic phase or early in the pandemic, before there is enough information available to determine the severity of the pandemic	Unknown
Low transmissibility & low clinical severity	Cumulative attack rate[14]: < 21% R_0 (basic reproduction number)[15]: <1.6 Case Fatality Rate (CFR)[16]: <0.25%	Typical seasonal influenza epidemics 2009 influenza pandemic 1968 influenza pandemic	Comparable to seasonal influenza
High transmissibility & low clinical severity	Cumulative attack rate: ≥21% $R_0 \geq 1.6$ CFR: <0.25%	1927-28 seasonal influenza epidemic	Significant workplace absenteeism High burden on outpatient and acute services
Low transmissibility & high clinical severity	Cumulative attack rate: < 21% R_0: <1.6 CFR: ≥0.25%	1957 influenza pandemic	High burden on critical health care services

[14] The cumulative attack rate is the percentage of people who (are expected to) become symptomatic at some point during the influenza pandemic.

[15] The basic reproductive number is the number of secondary cases one case should produce in a completely susceptible population.

[16] The case fatality rate is the ratio of deaths within a designated population of cases over the course of a pandemic.

Overall severity	Characteristics	Examples	Impact on health system
High transmissibility & high clinical severity	Cumulative attack Rate: ≥21% R_0≥1.6 CFR: ≥0.25%	1918 influenza pandemic	Significant need for public health measures High burden on critical health care services

In addition to the characteristics of the virus, other factors – including the effectiveness of interventions, the behavioural response of Ontarians, the capacity of Ontario's health system and the social determinants of health – determine the impact of the pandemic.

Another consideration is that novel influenza viruses may differentially affect specific populations. For example, while the severity of a pandemic may be comparable to seasonal influenza (low transmissibility and low clinical severity), transmissibility or clinical severity could be significantly higher in specific population groups (e.g., children and youth). Therefore, the MOHLTC may need to develop recommendations and response strategies during an influenza pandemic to address specific population needs.

Next steps

In the development of the OIRP, the MOHLTC will work with its partners to:

- continue to clarify the role of LHINs in influenza pandemic response
- align the OIRP with the CPIP, including
  - the measurement of pandemic severity
  - ethical framework
- further develop strategies to support vulnerable populations, including adapting the HEIA for a health emergency management context

Appendix A – OHPIP Steering Committee and workgroup members

The MOHLTC is grateful to the following organizations and their members for their contributions to the 2012-13 OHPIP Steering Committee, workgroups and consultations:

- Aboriginal Affairs and Northern Development Canada
- Association of Family Health Teams of Ontario
- Association of Iroquois and Allied Indians
- Association of Local Public Health Agencies
- Association of Municipalities of Ontario
- Association of Ontario Health Centres
- Chiefs of Ontario
- Critical Care Services Ontario
- Emergency Management Ontario, Ministry of Community Safety and Correctional Services
- Emergency Nurses Association of Ontario
- Federation of Health Regulatory Colleges of Ontario
- First Nations and Inuit Health Branch, Ontario Region
- Independent First Nations
- Local Health Integration Networks
- Ministry of Children and Youth Services
- Ministry of Community and Social Services
- Ministry of Labour
- Nishnawbe Aski Nation
- Nurse Practitioners Association of Ontario
- Ontario Association for Non-Profit Homes and Services for Seniors
- Ontario Association of Community Care Access Centres
- Ontario Association of Medical Laboratories
- Ontario College of Family Physicians
- Ontario Community Support Association
- Ontario Home Care Association

- Ontario Hospital Association
- Ontario Long-Term Care Association
- Ontario Medical Association
- Ontario Nurses' Association
- Ontario Pharmacists' Association
- Ontario Public Services Employees Union
- Public Health Agency of Canada, Ontario and Nunavut Region
- Public Health Ontario
- Public Services Health & Safety Association
- Registered Nurses' Association of Ontario
- Union of Ontario Indians (Anishinabek Nation)

Appendix B – Glossary

Additional precautions

Additional precautions (i.e., contact precautions, droplet precautions and airborne precautions) that are necessary in addition to routine practices for certain pathogens or clinical presentations. These precautions are based on the method of transmission (e.g., contact, droplet, airborne). (Source: Provincial Infectious Disease Advisory Committee's Routine Practices and Additional Precautions in All Health Care Settings).

Adverse event

Adverse events are an unexpected and undesired incident directly associated with the care or services provided to the client/patient/resident (Source: Provincial Infectious Disease Advisory Committee's Best Practices for Infection Prevention and Control Programs in Ontario).

Aerosol-generating medical procedure

Aerosol-generating medical procedures are any procedure carried out on a client, patient or resident that can induce the production of aerosols as a result of manipulation of a person's airway. Examples of aerosol-generating medical procedures include intubation and related procedures (e.g., manual ventilation, open endotracheal suctioning); cardiopulmonary resuscitation; bronchoscopy; sputum induction; nebulized therapy; surgery and autopsy; and bi-level positive airway pressure (i.e., BiPAP) (Source: Canadian Pandemic Influenza Plan for the Health Sector).

Affiliated clients/ patients

Also known as rostered clients/ patients. Affiliated clients/ patients are formally enrolled with a primary health care organization, such as a family health team, community health centre or Aboriginal health access centre. Clients/ patients that are affiliated with a primary health care organization typically do not seek primary health care services in other locations.

Airborne precautions

Airborne precautions are used in addition to routine practices for clients/ patients/ residents known or suspected of having an illness transmitted by the airborne route (i.e., by small droplet nuclei that remain suspended in the air and may be inhaled by others)

(Source: Provincial Infectious Disease Advisory Committee's Routine Practices and Additional Precautions in all Health Care Settings).

Client/ patient/ resident

Any person receiving health care services within a health care setting (Source: Provincial Infectious Disease Advisory Committee's Best Practices for Infection Prevention and Control Programs in Ontario).

Client/ patient/ resident environment

The immediate space around a client/ patient/ resident that may be touched by the client/ patient/ resident and may also be touched by the health care provider when providing care. The client/ patient/ resident environment includes equipment, medical devices, furniture (e.g., bed, chair, bedside table), telephone, privacy curtains, personal belongings (e.g., clothes, books) and the bathroom that the client/ patient/ resident uses. In a multi-bed room, the client/ patient/ resident environment is the area inside the individual's curtain. In an ambulatory setting, the client/ patient/ resident environment is the area that may come into contact with the client/ patient/ resident within their cubicle. In a nursery/ neonatal setting, the patient environment is the isolette or bassinet and equipment outside the isolette/bassinet that is used for the infant. Source: Provincial Infectious Disease Advisory Committee's Routine Practices and Additional Precautions in all Health Care Settings).

Cohorting

The assignment of a geographic area such as a room or a care area to two or more clients/ patients/ residents who are either colonized or infected with the same microorganism, with staffing assignments restricted to the cohorted group of patients (Source: Provincial Infectious Disease Advisory Committee's Routine Practices and Additional Precautions in all Health Care Settings).

Contact tracing

The process of identifying relevant contacts of a person with an infectious disease and ensuring that they are aware of their exposure (Source: Provincial Infectious Disease Advisory Committee's Sexually Transmitted Infections Case Management and Contact Tracing Best Practice Recommendations).

Directives

Instructions that may be issued by the Chief Medical Officer of Health under the terms of the Health Protection and Promotion Act. A health care provider or health care entity that is served with a directive must comply with it.

Eye protection

A device that covers the eyes and is used by health care providers to protect the eyes when it is anticipated that a procedure or care activity is likely to generate splashes or sprays of blood, body fluids, secretions or excretions, or within two metres of a coughing client/patient/resident. Eye protection includes safety glasses, safety goggles, face shields and visors (Source: Provincial Infectious Disease Advisory Committee's Routine Practices and Additional Precautions in all Health Care Settings).

Fit-test

A qualitative or quantitative method to evaluate the fit of a specific make, model and size of respirator on an individual. Fit-testing is to be done periodically, at least every two years and whenever there is a change in respirator face piece or the user's physical condition that could affect the respirator fit (Source: Provincial Infectious Disease Advisory Committee's Routine Practices and Additional Precautions in all Health Care Settings).

Flu assessment centre

Temporary services during an influenza pandemic provided by primary health care organizations or emergency departments to provide influenza care & treatment services to community members who cannot rapidly access primary health care, with temporary financial and material support of the Ministry of Health and Long-Term Care.

Hand hygiene

A general term referring to any action of hand cleaning. Hand hygiene relates to the removal of visible soil and removal or killing of transient microorganisms from the hands. Hand hygiene may be accomplished using soap and running water or an alcohol-based hand rub. Hand hygiene also includes surgical hand antisepsis (Source: Provincial Infectious Disease Advisory Committee's Routine Practices and Additional Precautions in all Health Care Settings).

Health and safety representative

Workplaces with more than five workers and no joint health and safety committee must have a health and safety representative [section 8(1)]. Like joint health and safety committee members, the representative is committed to improving health and safety conditions in the workplace. (Source: Ministry of Labour's A Guide for Joint Health and Safety Committees and Representatives in the Workplace).

Health care-associated infection

A term relating to an infection that is acquired during the delivery of health care services (also known as '*nosocomial infection'*) (Source: Provincial Infectious Disease Advisory Committee's Routine Practices and Additional Precautions in all Health Care Settings).

Health care facility

A set of physical infrastructure elements supporting the delivery of health care services. A health care facility does not include a client's/ patient's home or physician offices where health care services may be provided (Source: Provincial Infectious Disease Advisory Committee's Routine Practices and Additional Precautions in all Health Care Settings).

Health care provider

Any person delivering health care services to a client/ patient/ resident. This includes, but is not limited to, the following: emergency service workers, physicians, dentists, nurses, respiratory therapists and other health professionals, personal support workers, clinical instructors, students and home health care workers. In some non-acute settings, volunteers might provide care and would be included as a health care provider. See also, *Staff* (Source: Provincial Infectious Disease Advisory Committee's Routine Practices and Additional Precautions in all Health Care Settings).

Health Care Provider Hotline

24/7 line for health care providers to contact the Ministry of Health and Long-Term Care's Emergency Management Branch (1-866-212-2272). This Hotline can be used by health system partners to reach the ministry during the response to an emergency. It is also operational during non-emergencies to enable health system partners to inform the ministry of a hazard or risk that has the potential to become an emergency.

Health care setting

Any location where health care services are provided, including settings where emergency care is provided, hospitals, complex continuing care, rehabilitation hospitals, long-term care homes, mental health facilities, outpatient clinics, community health centres and clinics, physician offices, dental offices, offices of allied health professionals and home health care (Source: Provincial Infectious Disease Advisory Committee's Routine Practices and Additional Precautions in all Health Care Settings).

Health care services

Direct client/ patient/ resident care, including diagnostic, treatment and care services.

Health Equity Impact Assessment

The Ministry of Health and Long-Term Care's Health Equity Impact Assessment is a decision support tool that walks users through the steps of identifying how a program, policy or similar initiative impacts population groups in different ways. The Health Equity Impact Assessment surfaces unintended potential impacts. The end goal is to maximize positive impacts and reduce negative impacts that could potentially widen health disparities between population groups — in short, more equitable delivery of the program, service or policy.

Health liaison organization

A provincial health association, union or regulatory body that liaises between its members and the Ministry of Health and Long-Term Care during an emergency. These organizations are a critical conduit for information collection, analysis and dissemination. Health liaison organizations typically participate in the Health Stakeholder Teleconference. See Chapter 2: Health Sector Communications for more information.

Health organization

An organization or agency that receive funding from the Ministry of Health and Long-Term Care to provide health services.

Health sector

Part of the economy dealing with health-related issues in society. (Source: WHO's Health System Performance Website)

Health sector employer

A person in a health setting who employs one of more workers or contracts for the services of one or more workers and includes a contractor or subcontractor who performs work or supplies services and a contractor or subcontractor who undertakes with an owner, constructor, contractor or subcontractor to perform work or supply services.(Source: Based on the Occupational Health and Safety Act)

Health services

Services delivered by the health system, including health promotion, disease prevention, diagnostic, treatment and care services.

Health setting

Organizations and agencies that receive funding through the Ministry of Health and Long-Term Care to provide health services.

Health system

The people, institutions and resources, arranged together in accordance with established policies, to improve the health of the population they serve, while responding to people's legitimate expectations and protecting them against the cost of ill-health through a variety of activities whose primary intent is to improve health. (Source: WHO's Health System Performance Website).

Health worker

A person who performs work or supplies services for monetary compensation in a health setting (Source: based on the Occupational Health and Safety Act)

High-risk group

Population with an increased likelihood of becoming ill and/ or suffering serious health outcomes as a consequence of pandemic influenza virus infection.

Infection

The entry and multiplication of an infectious agent in the tissues of the host. Asymptomatic or sub-clinical infection is an infectious process running a course similar to that of clinical disease but below the threshold of clinical symptoms. Symptomatic or clinical infection is on resulting in clinical signs and symptoms (disease) (Source: Provincial Infectious Disease Advisory Committee's Routine Practices and Additional Precautions in all Health Care Settings).

Infection prevention & control

Evidence-based practices and procedures that, when applied consistently in health care settings, can prevent or reduce the risk of transmission of microorganisms to health care providers, other clients/patients/residents and visitors (Source: Provincial Infectious Disease Advisory Committee's Routine Practices and Additional Precautions in all Health Care Settings).

Infection prevention & control professional(s)

Trained individuals responsible for a health care setting's infection prevention & control activities. In Ontario, an infection prevention & control professional must receive a minimum for 80 hours of instruction in a Community and Hospital Infection Control Association of Canada endorsed infection control program within six months of entering their role and must acquire and maintain Certification in Infection Control when eligible (Source: Provincial Infectious Disease Advisory Committee's Routine Practices and Additional Precautions in all Health Care Settings).

Infection prevention & control program

A health care facility or organization (e.g., hospital, long-term care, continuing complex care, home care) program responsible for meeting the recommended mandate to decrease infections in the client/ patient/ resident, health care providers and visitors. The program is coordinated by health care providers with expertise in infection prevention & control and epidemiology (Source: Provincial Infectious Disease Advisory Committee's Best Practices for Infection Prevention and Control Programs in Ontario).

Influenza

A highly contagious, febrile, acute respiratory infection of the nose, throat, bronchial tubes and lungs caused by the influenza virus. It is responsible for severe and potentially fatal clinical illness of epidemic and pandemic proportions (Source: Canadian Pandemic Influenza Plan for the Health Sector).

Influenza-like illness

A cluster of symptoms resembling and that could be caused by influenza, without laboratory confirmation. Case definitions for influenza-like illness vary, and are provided during an influenza pandemic by the Ministry of Health and Long-Term Care,

Integrated Public Health Information System

The information technology system used by public health units to report case information on all reportable communicable diseases that are outlined in the Health Protection and Promotion Act. Public health units are responsible for collecting case information on reportable communicable diseases occurring within their boundaries and entering this information into this system.

Isolation

Separation, for the period of communicability, of infected persons or animals from others in such places and under such conditions as to prevent or limit the direct or

indirect transmission or the infectious agent from those infected to those who are susceptible or who may spread the agent to others. (Source: Canadian Pandemic Influenza Plan for the Health Sector)

Joint health and safety committee

Committee composed of people who represent the workers and the employer, as described under the Occupational Health and Safety Act. Together, they are committed to improving health and safety conditions in the workplace. Committees identify potential health and safety problems and bring them to the employer's attention. As well, members must be kept informed of health and safety developments in the workplace. (Source: Ministry of Labour's A Guide for Joint Health and Safety Committees and Representatives in the Workplace).

Key population groups for immunization

The key population groups for immunization are those groups that are eligible to receive the pandemic vaccine. Given that vaccine availability will increase over time, the key population groups will expand during the course of the pandemic immunization program (i.e., additional population groups will be added as more vaccine becomes available).

Local Health Integration Network transfer payment agency

Also known as Local Health Integration Network Health Service Providers. Organizations that Local Health Integration Networks are responsible for, including hospitals, divested psychiatric hospitals, community care access centres, community support service organizations, community mental health and addictions agencies, community health centres and long-term care homes.

Long-term care

A broad range of personal care, support and health services provided to people who have limitations that prevention them from full participation in the activities of daily living. The people who use long-term care services are usually the elderly, people with disabilities and people who have a chronic or prolonged illness (Source: Provincial Infectious Disease Advisory Committee's Best Practices for Environmental Cleaning for Prevention and Control of Infections).

Mandatory public health measures

Extraordinary actions that are supported by the Health Protection and Promotion Act designed to address and counter specific public health threats.

Ministry Emergency Operations Centre

Site where the Ministry of Health and Long-Term Care coordinates its response to an emergency.

Ministry of Health and Long-Term Care

Throughout the Ontario Health Plan for an Influenza Pandemic, the Ministry of Health and Long-Term Care includes the Minister, Chief Medical Officer of Health and the rest of the Ministry of Health and Long-Term Care. For information on how emergency decisions are made in the MOHLTC, please see the Ministry Emergency Response Plan.

N95 respirator

A personal protective device that is worn on the face and covers the nose and mouth to reduce the wearer's risk of inhaling airborne particles. A National Institute for Occupational Safety and Health-certified N95 respirator filters particles one micron in size, has 95% filter efficiency and provides a tight facial seal with less than 10% leak (Source: Provincial Infectious Disease Advisory Committee's Routine Practices and Additional Precautions in All Health Care Settings).

Outpatient settings

Pertaining to a health care organization that provides influenza care & treatment services for clients/ patients who are not hospitalized or admitted to a long-term care home. It includes primary health care organizations, hospital emergency departments, community-based pharmacies and home care settings.

Pandemic

An epidemic disease of widespread prevalence around the globe (Source: Canadian Pandemic Influenza Plan for the Health Sector).

Pandemic Precautions

Occupational health & safety and infection prevention & control precautions recommended in health care settings during an influenza pandemic (e.g., use of N95 respirators for health workers at risk of exposure to a client/ patient/ resident with influenza-like illness or that client/ patient/ resident's environment)

Personal protective equipment

Clothing or equipment worn by health workers for protection against hazards (Source: Based on Provincial Infectious Disease Advisory Committee's Routine Practices and Additional Precautions in All Health Care Settings).

Point of care

The place where three elements occur together: the client/ patient/ resident, the health care provider, and care or treatment involving client/ patient/ resident contact (Source: Provincial Infectious Disease Advisory Committee's Best Practices for Infection Prevention and Control Programs in Ontario).

Precautions

Interventions to reduce the risk of transmission of microorganisms (e.g., client/ patient/ resident-to-client/ patient/ resident, client/ patient/ resident-to-worker, contact with the environment, contact with contaminated equipment). (Source: PIDAC's Best Practices for Environmental Cleaning for Prevention and Control of Infections)

Precautionary principle

A principle used by the Ministry of Health and Long-Term Care and Chief Medical Officer of Health to guide decision-making during an emergency. According to this principle, reasonable steps to reduce risk should not await scientific certainty (Source: Spring of Fear, Justice Archie Campbell).

Primary health care

Primary care (the provision of integrated, accessible health care services by clinicians who are accountable for addressing a large majority of personal health care needs, developing a sustained partnership with clients/ patients and practicing in the context of family and community), disease prevention, health promotion, population health and community development within a holistic framework, with the aim of providing essential community-focused health care (Sources: World Health Organization, Institute of Medicine). Primary health care organizations include family health teams, community health centres, Aboriginal health access centres, departments of family medicine, nurse practitioner-led clinics and solo practitioners such as family physicians, general practitioners and pediatricians.

Provincial Infectious Disease Advisory Committee

A multidisciplinary scientific advisory body that provides to the Chief Medical Officer of Health evidence-based advice regarding multiple aspects of infectious disease identification, prevention and control (Source: Provincial Infectious Disease Advisory Committee's Routine Practices and Additional Precautions in all Health Care Settings).

Public Health Agency of Canada

A national agency that promotes improvement in the health status of Canadians through public health action and the development of national guidelines (Source: Provincial Infectious Disease Advisory Committee's Best Practices for Environmental Cleaning for Prevention and Control of Infections).

Public health measures

Non-pharmaceutical interventions that help to slow the spread of disease in the community.

Public Health Ontario

Formerly known as the Ontario Agency for Health Protection and Promotion. An arm's-length government agency dedicated to protecting and promoting the health of all Ontarians and reducing inequities in health. Public Health Ontario was created by legislation in 2007 and began operations in July 2008 with a mandate to provide scientific and technical advice to those working to protect and promote the health of Ontarians. Its vision is to be an internationally recognized centre of expertise dedicated to protecting and promoting the health of all Ontarians through the application and advancement of science and knowledge (Source: Provincial Infectious Disease Advisory Committee's Best Practices for Infection Prevention and Control in Perinatology).

Recommendations from the Ministry of Health and Long-Term Care

This term refers clinical, occupational health & safety and infection prevention & control guidance. Recommendations related to occupational health & safety may be considered reasonable precautions in the application of the Occupational Health and Safety Act.

Regional Infection Control Networks

Networks that coordinate and integrate resources related to the prevention, surveillance and control of infectious diseases across all health care sectors and for all health care providers, promoting a common approach to infection prevention & control and utilization of best-practices within the region (Source: Provincial Infectious Disease Advisory Committee's Best Practices for Environmental Cleaning for Prevention and Control of Infections).

Respiratory etiquette

Personal practices that help prevent the spread of bacteria and viruses that cause acute respiratory infections (e.g., covering the mouth when coughing, care when disposing of tissues) (Source: Provincial Infectious Disease Advisory Committee's Routine Practices and Additional Precautions in all Health Care Settings).

Routine practices

The system of infection prevention & control practices recommended by the Public Health Agency of Canada to be used with all clients/ patients/ residents during all care activities to prevent and control transmission of microorganisms in all health care settings (Source: Provincial Infectious Disease Advisory Committee's Routine Practices and Additional Precautions in all Health Care Settings).

Seal-check

A procedure that the health care provider must perform each time an N95 respirator is worn to ensure it fits the wearer's face correctly to provide adequate respiratory protection (Source: Provincial Infectious Disease Advisory Committee's Routine Practices and Additional Precautions in all Health Care Settings).

Sentinel health care provider

A health care provider that participates in a sentinel surveillance system. In Ontario, sentinel health care providers participate in Public Health Agency of Canada's FluWatch Program or the national Sentinel Vaccine Effectiveness Study. Ideally, Ontario would have adequate numbers of sentinel health care providers, representative of the population of the province, so that the information gathered from FluWatch and the Sentinel Vaccine Effectiveness Study could be applied to the population as a whole.

Seroprevalance

The proportion of a population that is seropositive – i.e., has been exposed to the influenza virus.

Surgical mask

Also known as procedure mask. Surgical masks are used as physical barriers to protect users from hazards, such as splashes of large droplets of blood or body fluids. Surgical masks are used for several different purposes, including being placed on sick people to limit the spread of infectious respiratory secretions to others. (Source: Based on United States Department of Labor Occupational Safety and Health Administration Fact Sheet: Respiratory Infection Control).

Surveillance

The systematic ongoing collection, collation and analysis of data with timely dissemination of information to those who require it in order to take action (Source: Provincial Infectious Disease Advisory Committee's Best Practices for Infection Prevention and Control Programs in Ontario).

Syndromic surveillance

The detection of individual and population health indicators of illness (i.e., signs and symptoms of infectious disease) that are discernible before confirmed laboratory diagnoses are made (Source: Provincial Infectious Disease Advisory Committee's Best Practices for Infection Prevention and Control Programs in Ontario).

Vaccine delivery agent

Health care providers who administer immunization outside of a public health unit.

Visitor

An individual who does not have an established relationship with a health organization. Visitors may be household contacts and friends that accompany clients/ patients to outpatient settings or visit clients/ patients/ residents in inpatient settings.

Voluntary public health measures

The behaviours and the environmental supports that create the conditions that support good public health practices.

Vulnerable population

A group of people who, because of the determinants of health, are more likely to be exposed to influenza, more likely to experience a serious impact because of exposure,

less likely to benefit from response and recovery measures and/ or who may be negatively affected by response and recovery measures.

Appendix C – Acronyms

AHAC	Aboriginal health access centre
BAL	bronchoalveolar lavage
CAEFISS	Canadian Adverse Events Following Immunization Surveillance System
CCIS	Critical Care Information System
CDC	Centers for Disease Control and Prevention
CFR	case fatality rate
CHC	community health centre
CMOH	Chief Medical Officer of Health
C/P/R	client/ patient/ resident
CPIP	Canadian Pandemic Influenza Plan for the Health Sector
EDSS	Emergency Department Syndromic Surveillance
EMCPA	Emergency Management and Civil Protection Act
ETT	endotracheal tube
FAC	flu assessment centre
F/P/T	federal - provincial - territorial
FF100	first few hundred
FHT	family health team
HCRF	Health Care and Residential Facilities regulation
HEIA	Health Equity Impact Assessment
HNS	Health Network System
HPPA	Health Protection and Promotion Act
HSR	health and safety representative
IHN	Important Health Notice
ILI	influenza-like illness
IMPACT	Immunization Monitoring Program ACTive
IPAC	infection prevention & control
iPHIS	Integrated Public Health Information System
IRS	internal responsibility system
JHSC	joint health and safety committee
LHIN	Local Health Integration Network

LTCHA	Long-Term Care Homes Act
MEOC	Ministry Emergency Operations Centre
MOH	medical officer of health
MOHLTC	Ministry of Health and Long-Term Care
MOL	Ministry of Labour
MRSA	methicillin-resistant *S. aureus*
NACI	National Advisory Committee on Immunization
NML	National Microbiology Laboratory
NP	nasopharyngeal
OHIP	Ontario Health Insurance Plan
OHPIP	Ontario Health Plan for an Influenza Pandemic
OHS	occupational health & safety
OHSA	Occupational Health and Safety Act
PEOC	Provincial Emergency Operations Centre
PHAC	Public Health Agency of Canada
PHO	Public Health Ontario
PHOL	Public Health Ontario Laboratories
PHU	public health unit
PICB	Performance Improvement and Compliance Branch
PIDAC	Provincial Infectious Disease Advisory Committee
PPE	personal protective equipment
R_0	basic reproduction number
RACE	recognize the hazard, assess the risk, control the risk and evaluate the controls
RICN	Regional Infection Control Network
RIDT	rapid influenza diagnostic testing
RP/AP	routine practices and additional precautions (i.e., PIDAC's Routine Practices and Additional Precautions in All Health Care Settings)
SARS	Severe Acute Respiratory Syndrome
TP	transfer payment
UIIP	Universal Influenza Immunization Program
VDA	vaccine delivery agent
WHO	World Health Organization

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to the Affidavit of Matthew Hodge,
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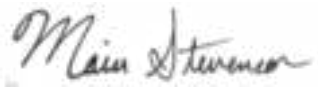

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World Health Organization

< Go back to all Coronavirus disease 2019 Q&As

Coronavirus disease (COVID-19)

12 October 2020 | Q&A

Latest update 13 May 2021 - WHO is continuously monitoring and responding to this pandemic. This Q&A will be updated as more is known about COVID-19, how it spreads and how it is affecting people worldwide. For more information, regularly check the WHO coronavirus pages. https://www.who.int/covid-19

What is COVID-19?

What are the symptoms of COVID-19?

What happens to people who get COVID-19?

Among those who develop symptoms, most (about 80%) recover from the disease without needing hospital treatment. About 15% become seriously ill and require oxygen and 5% become critically ill and need intensive care.

Complications leading to death may include respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multiorgan failure, including injury of the heart, liver or kidneys.

In rare situations, children can develop a severe inflammatory syndrome a few weeks after infection.

Who is most at risk of severe illness from COVID-19?

Are there long-term effects of COVID-19?

How can we protect others and ourselves if we don't know who is infected?

When should I get a test for COVID-19?

What test should I get to see if I have COVID-19?

What about rapid tests?

I want to find out if I had COVID-19 in the past, what test could I take?

What is the difference between isolation and quarantine?

What should I do if I have been exposed to someone who has COVID-19?

How long does it take to develop symptoms?

Is there a vaccine for COVID-19?

What should I do if I have COVID-19 symptoms?

Are there treatments for COVID-19?

Are antibiotics effective in preventing or treating COVID-19?

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WHO TEAM Emergencies Preparedness

Related

COVID-19 hub

Advice for the public

All COVID-19 Q&As

WHO Information Network on Epidemics (EPI-WIN)

Science in 5 series: WHO experts explain the science related to COVID-19

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Public Health Ontario | Santé publique Ontario

Ontario COVID-19 Data Tool

The Ontario COVID-19 Data Tool provides epidemiological information on COVID-19 activity in Ontario to-date. Explore the most recent COVID-19 data including: daily case counts, hospitalizations and deaths (Case trends), total or recent cases counts by age and sex, map by public health unit, source of COVID-19 infection (acquisition), outbreaks and laboratory testing.

Additions to the Ontario COVID-19 Data Tool as of May 28th, 2021:

- Vaccine uptake data on the Summary, Map and Vaccines sections
- COVID-19 reproduction number and doubling time

The COVID-19 Data Tool is updated Monday to Fridays at 11:30 a.m. except on statutory holidays. For weekend case counts see the **Daily Epidemiological Summary.**

For questions about the data, please contact **EPIR@oahpp.ca**.

Summary | Case trends | Age and sex | Map | Acquisition | Reproduction | Outbreaks | Lab tests | Vaccines | Technical notes | Glossary

Summary +

Date

24 Jun 2021

Confirmed COVID-19 cases in Ontario

As of June 24, 2021

Daily cases, rates, hospitalizations and deaths by public health unit can be found in **Case trends**.

Change in cases

256

Recent cases

5,469

reported in last 14 days
1.0% of cases

Total cases

543,571

3,656.9 per 100,000

Total hospitalized

27,643

186.0 per 100,000
5.1% of cases

Total deaths

9,101

61.2 per 100,000
1.7% of cases

COVID-19 cases in Ontario with a variant of concern detected

As of June 24, 2021

Find daily case counts of COVID-19 variants of concern by public health unit in **Case trends**.

Total case counts for B.1.1.7 include all confirmed COVID-19 cases where lineage B.1.1.7 was identified by genomic analysis and those presumed to be B.1.1.7 based on a positive N501Y and negative E484K mutation.

Total cases

B.1.1.7	**143,035**
B.1.351	**1,161**
P.1	**4,270**

Laboratory tests for COVID-19 in Ontario

As of June 24, 2021

See daily historical data in **Lab tests**.

New tests

26,561

178.7 tests per 100,000

Daily % positive

1.3

Total tests

15,805,892

106,333.7 tests per 100,000

COVID-19 vaccine uptake in Ontario

As of June 23, 2021 Vaccine data are updated weekly on Thursdays.

See the **Vaccine** and **Map** tabs for more vaccination data.

At least one dose

9,753,684

65.6% of population

Fully vaccinated

3,348,673

22.5% of population

Change in cases reflects new cases reported since the previous day.

Recent cases include cases reported within the past 14 days with a three day lag from the time of data extraction.

Rate is per 100,000 population.

Hospitalizations include all cases reported as ever being hospitalized during their infection.

Percent positive refers to the percentage of tests performed that were positive for COVID-19 and does not translate to the number of specimens or persons testing positive.

New tests refer to the number of tests performed and do not reflect the number of specimens or persons tested.

COVID-19 variants of concern (VOC) cases are confirmed COVID-19 cases where a designated VOC was identified by genomic analysis of their SARS-CoV-2 positive specimen. Lineage B.1.1.7 includes cases where lineage B.1.1.7 was identified by genomic analysis and those presumed to be B.1.1.7 based on positive N501Y and negative E484K mutation

- **PANGO lineage B.1.1.7** first detected in England.
- **PANGO lineage B.1.351** first detected in South Africa.
- **PANGO lineage P.1** first detected in Brazil.

Interpret the VOC and mutation case counts with caution. Daily counts may change due to the varying time required to complete VOC testing and/or genomic analysis following the initial positive test for SARS-CoV-2 and may result in totals differing from past publicly reported case counts. Additionally, changes to the VOC testing algorithm may occur over time. Refer to the Technical Notes for more information.

Vaccine series: the number of vaccine doses within a schedule that has been approved by Health Canada. COVID-19 vaccine

products available in Ontario have either a one-dose (i.e. Janssen) or two-dose (i.e. Moderna, Pfizer-BioNTech, AstraZeneca or COVISHIELD) schedule. Note: Janssen vaccines have not yet been distributed in Ontario.

At least one dose: refers to individuals that have received at least one dose of a COVID-19 vaccine. Reflects individuals that have received the first dose of a two-dose series, as well as those that have completed a COVID-19 vaccine series.

At least one dose coverage: the proportion of the total population of Ontario, or a public health unit, that has received at least one dose of a COVID-19 vaccine. Reflects individuals that have received the first dose of a two-dose series, as well as those that have completed a COVID-19 vaccine series

Fully vaccinated: refers to individuals that have received both doses of a two-dose COVID-19 vaccine series (i.e. dose two of two) or one dose of a one-dose COVID-19 vaccine series (i.e. dose one of one). Reflects individuals that have completed a COVID-19 vaccine series.

Fully vaccinated coverage: the proportion of the total population of Ontario, or a public health unit, that has received both doses of a two-dose COVID-19 vaccine series (i.e. dose two of two) or one dose of a one-dose COVID-19 vaccine series (i.e. dose one of one). Reflects individuals that have completed a COVID-19 vaccine series.

« Previous Next »

Related Information

Coronavirus Disease 2019 (COVID-19)

External Resources

COVID-19 case data: All Ontario - Government of Ontario

COVID-19 cases in schools and child care centres - Ministry of Education

COVID-19 Hospitalizations - Government of Ontario

COVID-19 Vaccines Status - Government of Ontario

Updated 30 June 2021

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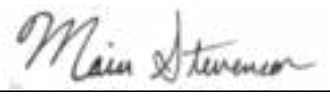

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Government of Canada | Gouvernement du Canada

COVID-19 daily epidemiology update

Updated: June 29, 2021, 7 pm EST

Summary of COVID-19 cases across Canada and over time. Contains detailed data about the spread of the virus over time and in different regions of the country. Includes breakdowns by age and sex or gender. Provides an overview of hospitalizations and deaths, testing, variants of concern and exposures.

Key updates as of June 29, 2021, 7 pm EST

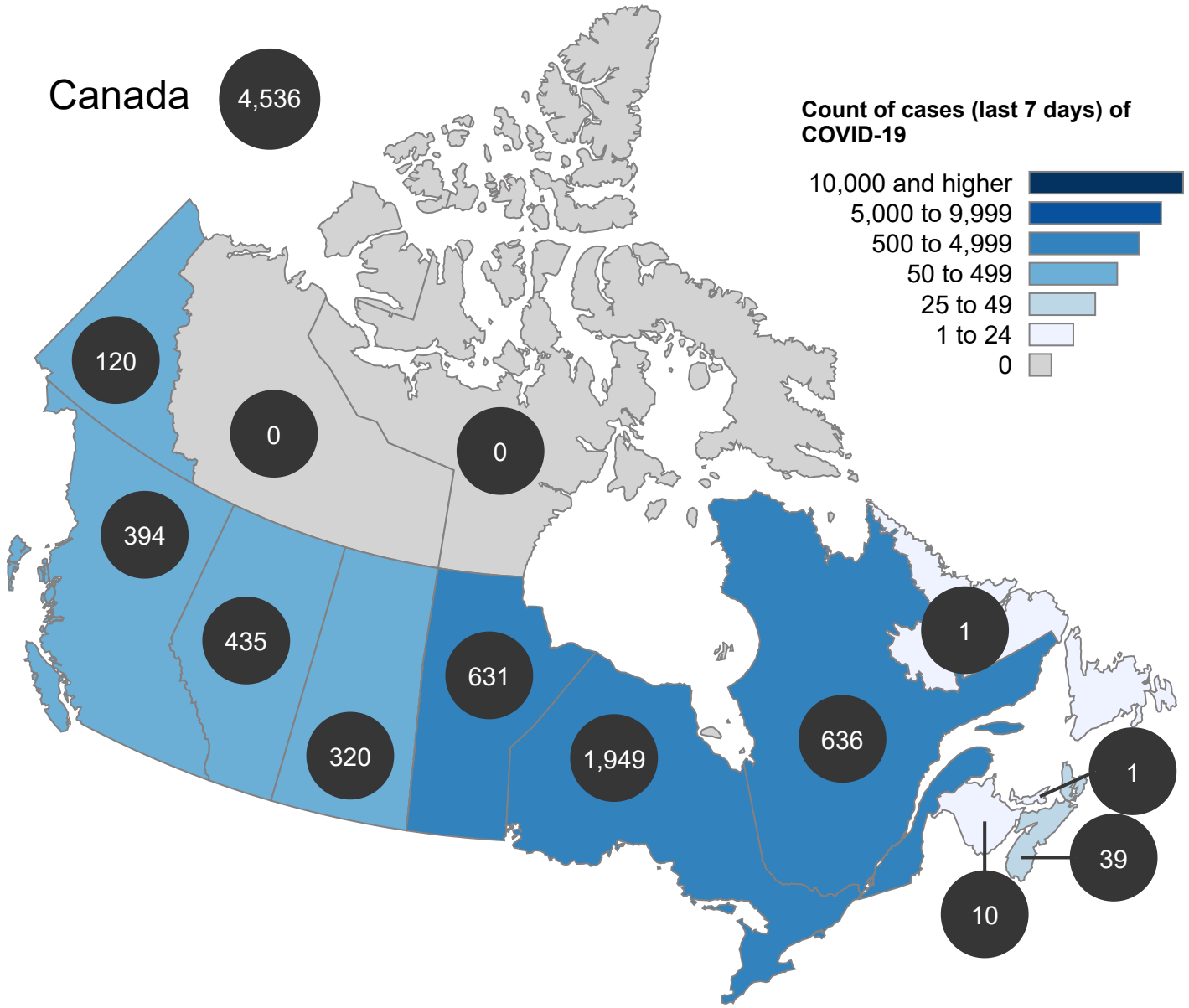
Cases today	Total cases	Active cases	Total resolved	Deaths today	Total deaths
602	1,414,736	7,447	1,381,016	35	26,273

Total tests performed	Daily percent positive (last 7 days)	Daily tests per 100,000 population (last 7 days)
36,705,571	1.2%	156

- We update these sections daily at 7:00 PM EST: Key updates, Current situation and National overview. Laboratory data represents specimens received by labs up to June 27, 2021 to allow time to process results.
- We update these sections every Friday: Epidemic curve, Demographics, How people were exposed, and Severe illness and outcomes.
- Most cases (65.0%) and deaths (77.5%) were reported by Ontario and Quebec.
- Of the 13 jurisdictions reporting updates, no new cases were reported in 3 provinces or territories in the past 24 hours.
- Of the 13 jurisdictions reporting updates, no new deaths were reported in 9 provinces or territories in the past 24 hours.

Current situation

Figure 1a. Count of cases (last 7 days) of COVID-19, by province/territory as of June 29, 2021



The count of cases (last 7 days) of COVID-19 in **Canada** was **4,536** as of June 29, 2021.

This information is based on data our provincial and territorial partners published on cases, deaths, and testing daily, and are current as of the day they are published. Today's numbers are current as of June 29, 2021. For the most up to date data for any province, territory or city, please visit their website. The number of cases or deaths reported on previous days may differ slightly from those on the provincial and territorial websites as these websites may update historic case and death counts as new information becomes available.

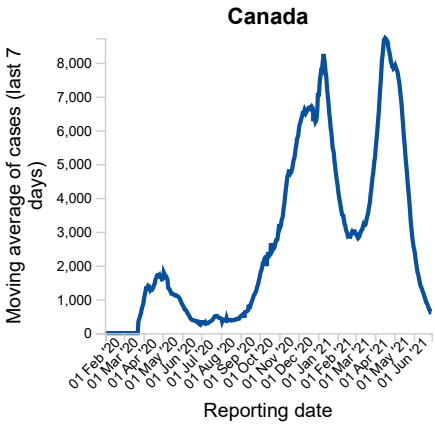
Areas in Canada with cases of COVID-19 as of June 29, 2021

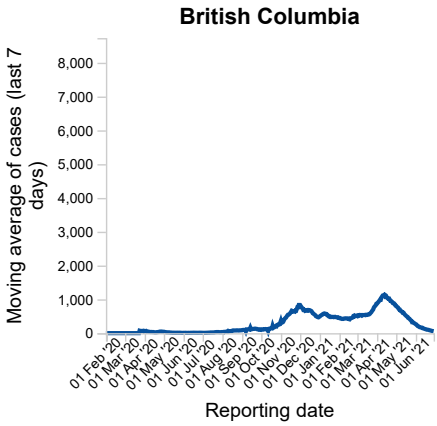
	Total cases		Cases last 7 days		Active cases		Resolved	Deaths		Deaths last 7 days		Total tests performed	Moving average tests performed last 7 days		Moving average positivity last 7 days
Location	Count	Rate*	Count	Rate*	Count	Rate*	Count	Count	Rate*	Count	Rate*	Count	Count	Rate*	Percent
Canada	**1,414,736**	**3,722**	**4,536**	**12**	**7,447**	**20**	**1,381,016**	**26,273**	**69**	**119**	**0**	**36,705,571**	**59,346**	**156**	**1.2%**
British Columbia	147,578	2,867	394	8	893	17	144,931	1,754	34	11	0	2,883,199	5,135	100	1.4%
Alberta	231,911	5,245	435	10	1,132	26	228,480	2,299	52	9	0	4,670,457	5,614	127	1.3%
Saskatchewan	48,823	4,142	320	27	464	39	47,791	568	48	4	0	910,196	1,579	134	3.2%
Manitoba	56,097	4,067	631	46	1,408	102	53,550	1,139	83	10	1	867,383	1,828	133	6.3%
Ontario	544,713	3,697	1,949	13	2,409	16	533,150	9,154	62	72	0	15,747,264	22,492	153	1.3%
Quebec	374,731	4,370	636	7	878	10	362,646	11,207	131	12	0	9,791,320	17,537	205	0.5%
Newfoundland and Labrador	1,385	265	1	0	9	2	1,369	7	1	0	0	300,841	702	135	0.1%
New Brunswick	2,329	298	10	1	26	3	2,258	45	6	0	0	373,609	594	76	0.2%
Nova Scotia	5,832	596	39	4	51	5	5,689	92	9	0	0	935,353	3,519	359	0.2%
Prince Edward Island	207	130	1	1	1	1	206	0	0	0	0	174,182	258	162	0.0%
Yukon	332	790	120	285	176	419	152	4	10	1	2	9,129	N/A	N/A	N/A
Northwest Territories	128	283	0	0	0	0	128	0	0	0	0	24,745	29	65	0.5%
Nunavut	657	1,670	0	0	0	0	653	4	10	0	0	17,817	58	147	0.0%

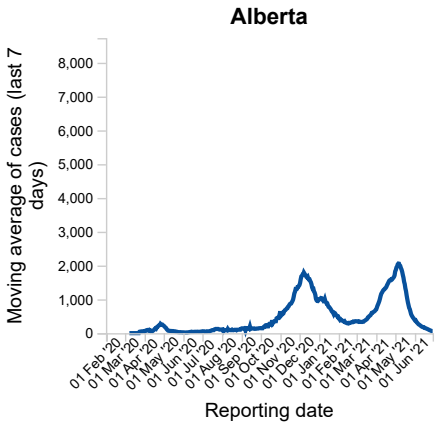
* Rate per 100,000 population

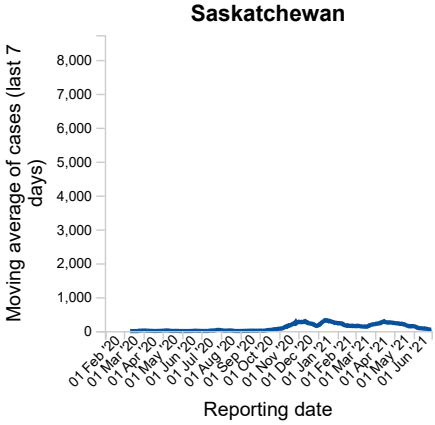
Figure 1b. Moving average of cases (last 7 days) of COVID-19 in Canada as of June 29, 2021, 7 pm EST

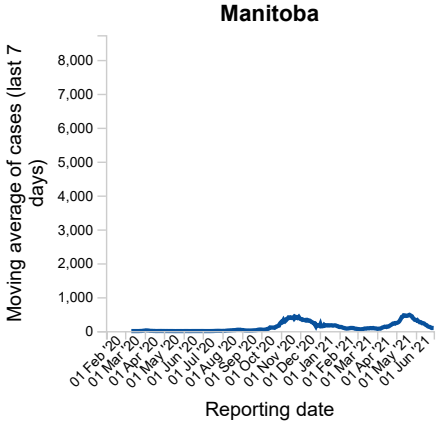
The figures below show cases over time. The range of dates (January 31st, 2020 - present date) is the same for each figure. This allows you to compare the provinces and territories on the same timescale.

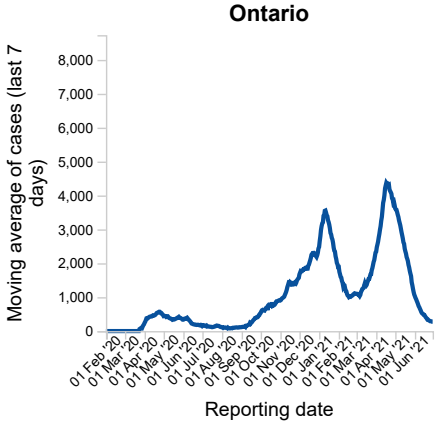


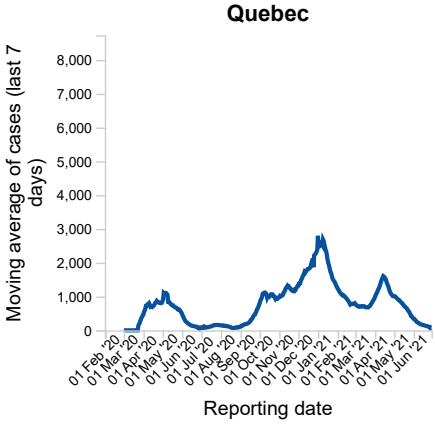


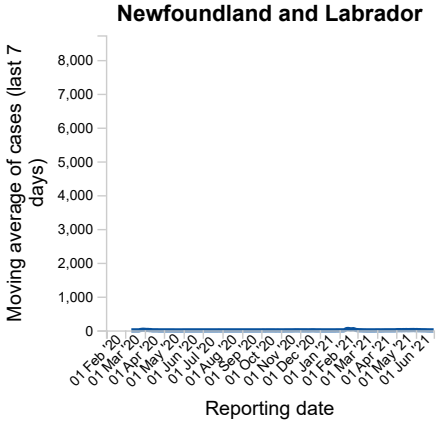


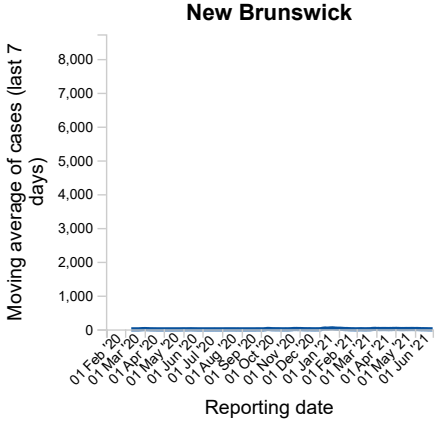


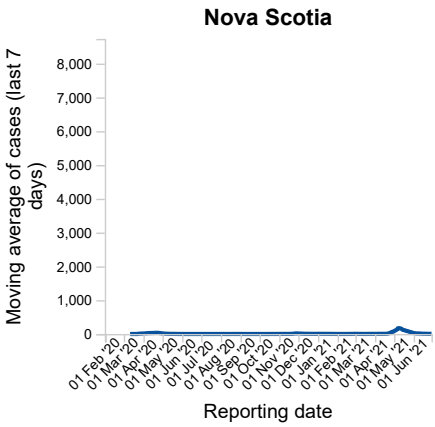


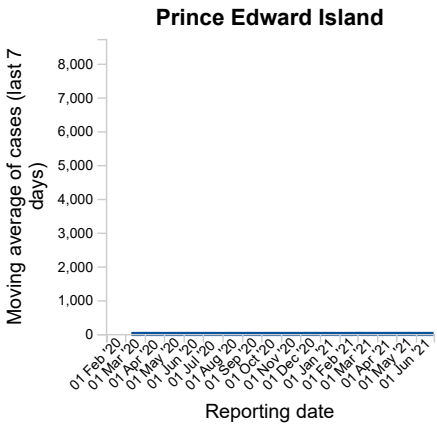


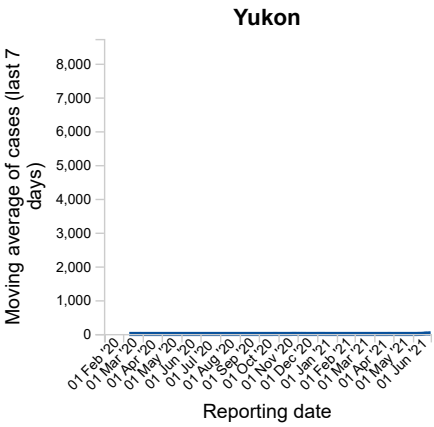


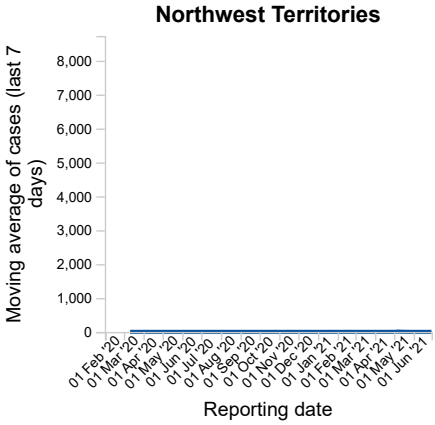


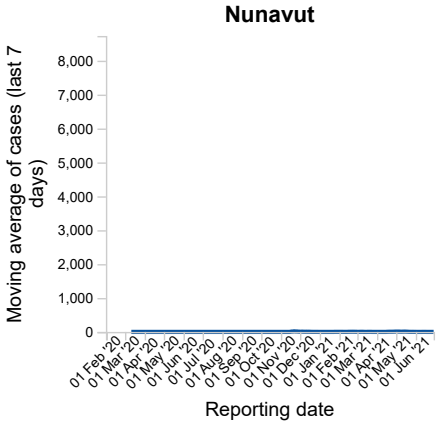












This information is based on data our provincial and territorial partners published on cases, deaths, and testing daily, and are current as of the day they are published. Today's numbers are current as of June 29, 2021. For the most up to date data for any province, territory or city, please visit their website. The number of cases or deaths reported on previous days may differ slightly from those on the provincial and territorial websites as these websites may update historic case and death counts as new information becomes available.

Downloadable data (in .csv format).

Note: Out of the total number of people tested, 76 were repatriated travellers, of which 13 were cases.

National overview

There have been over **36,705,571** COVID-19 tests performed in Canada or **965,803 tests per 1 million people**. Of these, **4.0%** were positive. For information about testing trends, please see the Detailed weekly epidemiological report (PDF).

Table 1. Daily* change in the number of cases, deaths and tests performed, by province or territory, as of June 29, 2021, 7 pm EST

Location	New cases	New deaths	Tests performed
Canada	**602**	**35**	**61,585**
British Columbia	29	0	3,664
Alberta	61	4	22,232
Saskatchewan	52	2	1,425
Manitoba	61	0	1,575
Ontario	299	25	13,071
Quebec	71	4	15,365
Newfoundland and Labrador	0	0	561
New Brunswick	3	0	401
Nova Scotia	1	0	3,077
Prince Edward Island	1	0	138
Yukon	24	0	N/A
Northwest Territories	0	0	13
Nunavut	0	0	63

* The new cases, deaths and tests reflect the difference between a province or territory's current report and their last report. Some provinces and territories do not update daily.

N/A means that no daily update was provided by the province or territory.

Variants of concern (VOC) in Canada

All viruses, including COVID-19, change or mutate over time. Not all mutations are of concern. However, some changes result in variants of concern (VOC). A VOC (Variants of concern) has changes that are significant to public health.

For example, they might:

- spread more easily
- cause more severe illness
- require different treatments, or
- not respond the same to current vaccines

The Public Health Agency of Canada (PHAC) updates VOC (Variants of concern) information from Sunday to Thursday at 7:00 PM EDT, using publicly reported information from the provinces and territories.

Table 2. Cumulative number of cases involving variants of concern (VOC) publicly reported, as of June 29, 2021

Location	B.1.1.7 variant	B.1.351 variant	P.1 variant
Canada	**221,763**	**2,149**	**17,974**
British Columbia	12,054	151	9,709
Alberta	45,508	159	2,752
Saskatchewan	6,634	10	322
Manitoba	6,630	72	205
Ontario	143,381	1,315	4,439
Quebec	6,989	420	511
Newfoundland and Labrador	187	6	1
New Brunswick	180	4	1
Nova Scotia	73	12	1
Prince Edward Island	26	0	0
Yukon	3	0	31
Northwest Territories	77	0	2
Nunavut	21	0	0

Note:

- The table reports publicly available information from the provinces and territories. In case of discrepancies, the provincial or territorial data should be considered current and correct.

- PHAC is in the process of replacing this table with a graphical view that is more representative of the mix of variants present in Canada in the coming weeks. This new graphical view will include all variants of concern including B.1.617 and variants of interest.

There are many variants being tracked internationally and across Canada. Most of these are similar to the original variants that emerged in 2020. VOCs (Variants of concern) now represent a majority of COVID-19 cases in Canada.

Four VOCs (Variants of concern) have been detected in most provinces and territories:

- B.1.1.7
- B.1.351
- P.1
- B.1.617

The **B.1.1.7 variant** continues to account for most VOCs (Variants of concern) classified to date in Canada.

The **B.1.617 variant** has only been recently identified and thus is less understood. Its 3 sub-lineages may have different properties. Early data from the U.K. indicate that the B.1.617.2 sub-lineage may be more transmissible overall, either similar to or perhaps more transmissible than the B.1.1.7 variant. However, laboratory data suggest that currently authorized vaccines are also effective against this sub-lineage. The B.1.617.1 and B.1.617.3 sub-lineages are less well-known, but may be less affected by vaccines. There are many variants being tracked internationally and across Canada, most of which are similar to the original variants that emerged in 2020.

The impact of the B.1.617 variant and its sub-lineages is still being assessed in Canada, where the variant has been identified in all 10 provinces and 1 territory. Genomic surveillance has also identified all 3 sub-lineages (B.1.617.1, B.1.617.2 and B.1.617.3).

Of these 3:

- B.1.617.1 accounted for most of the identified cases in March and April 2021
- B.1.617.2 accounted for most of the identified cases detected at the border
- B.1.617.3 accounts for a very small proportion (1%) of identified cases

Canada is collecting evidence to determine if each of these sub-lineages meets the definition for a variant of concern or a variant of interest.

New variants will continue to appear. It is crucial to remain vigilant and take all available measures to limit spread.

Detailed case information

The tables and figures below reflect detailed case information provided to the Public Health Agency of Canada (PHAC) by health authorities in the provinces and territories. This data is updated every week. It may change as we get more information about cases.

Updated: June 25, 2021, 7 pm EST

Epidemic curve

As of June 25, 2021, 7 pm EST, PHAC has received detailed case report data on 1,410,946 cases. Both exposure and symptom onset date were available for 1,254,652 (88.9%) cases [1].

The shaded area on the far right of Figure 2 represents lag time. This is the period of time (1 to 2 weeks) before the latest cases are reported to PHAC. This delay is a result of the time required to seek health care, get tested and receive results. It also takes time for public health authorities to gather information on cases. We update this information as it becomes available.

Figure 2. COVID-19 cases (n=1,411,021 [1]) in Canada by date of illness onset [2] as of June 25, 2021, 7 pm EST (total cases)

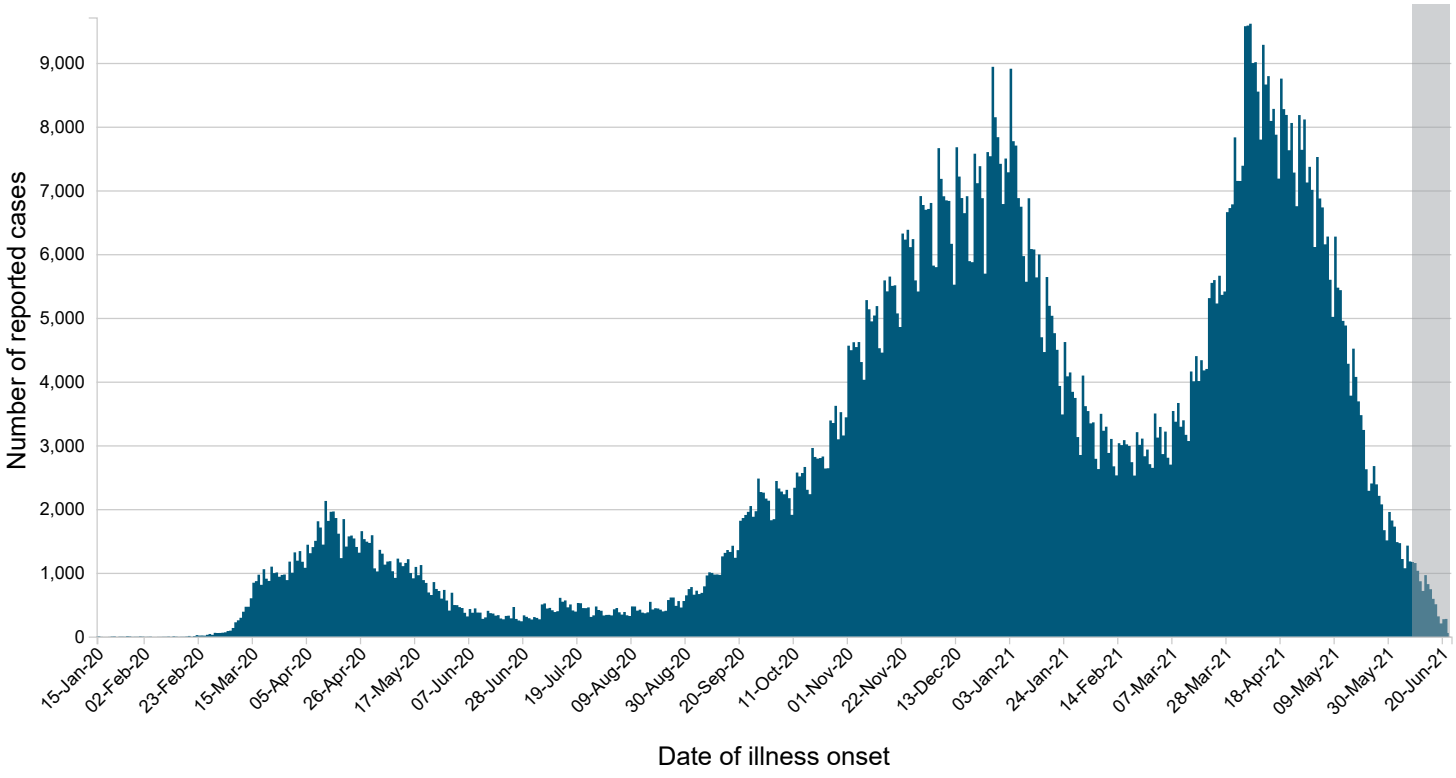


Figure 2. COVID-19 cases (n=1,254,652 [1]) in Canada by date of illness onset [2] as of June 25, 2021, 7 pm EST (by exposure)

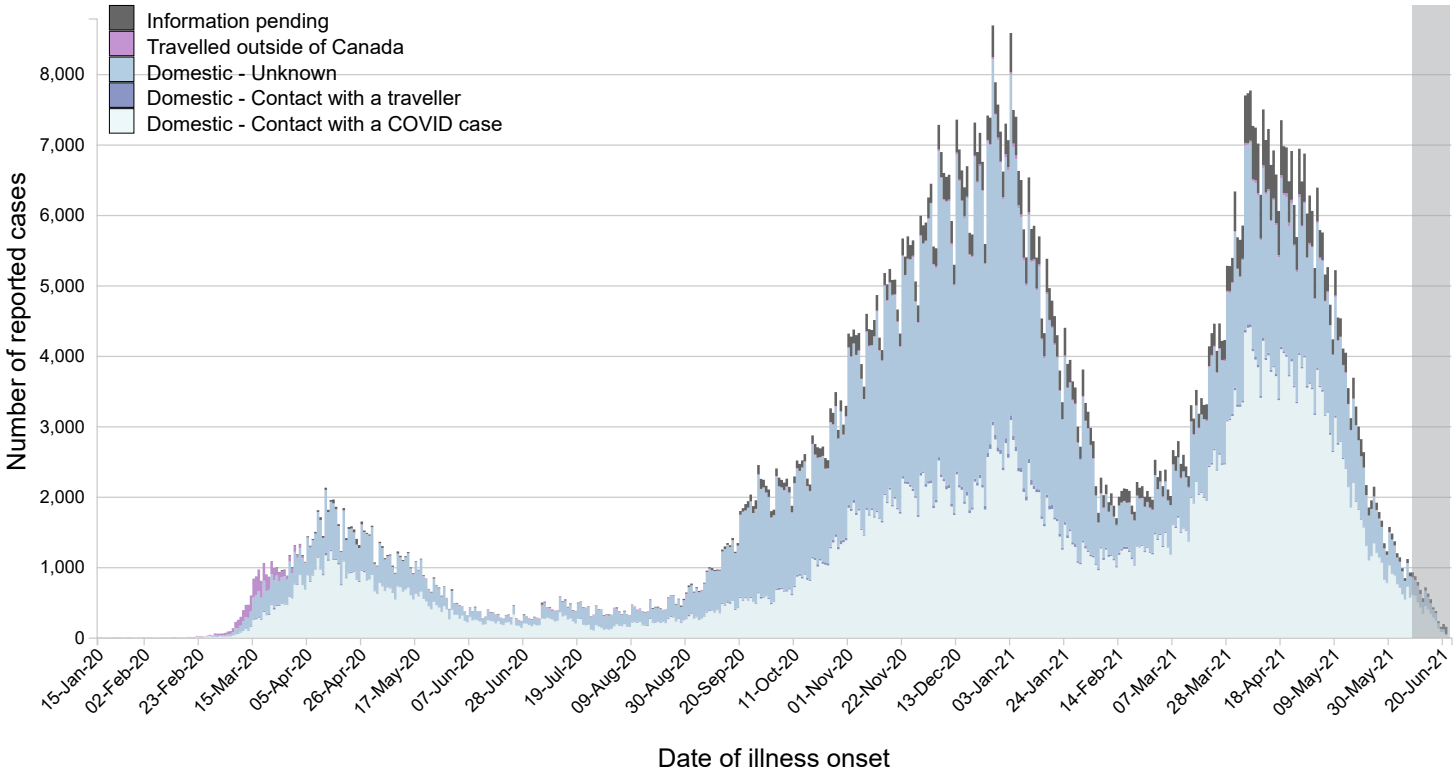


Figure 2. COVID-19 cases (n=1,410,571 [1]) in Canada by date of illness onset [2] as of June 25, 2021, 7 pm EST (by age - 10 year groups)

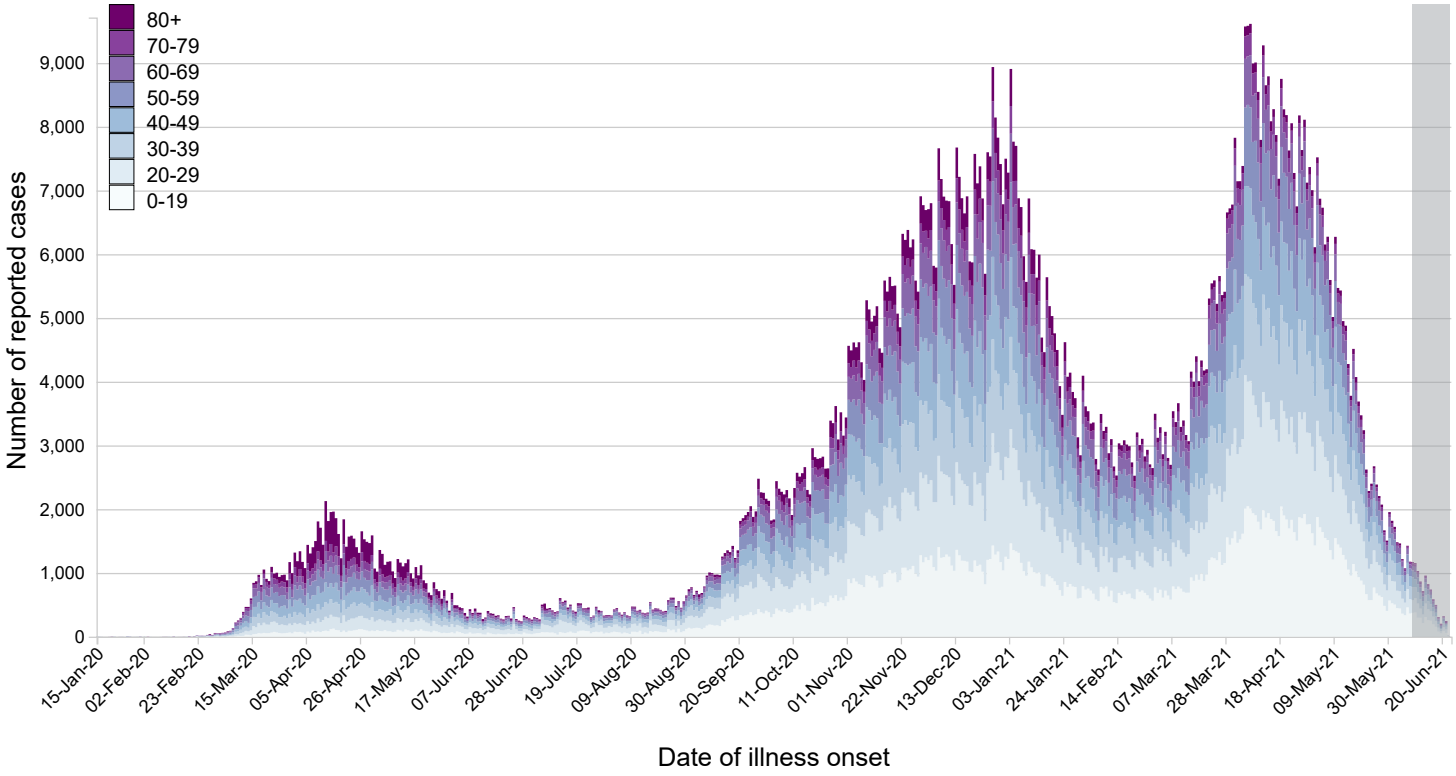
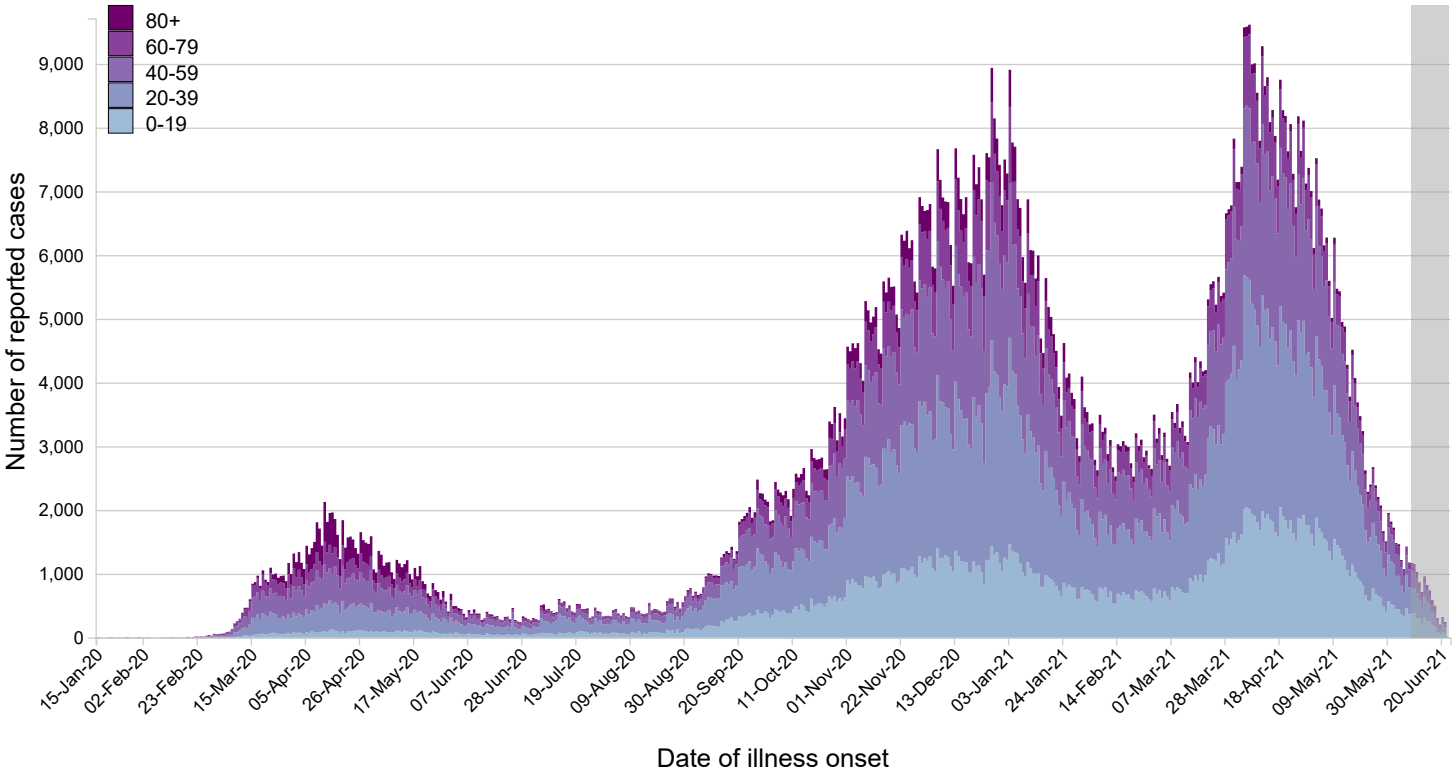


Figure 2. COVID-19 cases (n=1,410,571 [1]) in Canada by date of illness onset [2] as of June 25, 2021, 7 pm EST (by age - 20 year groups)



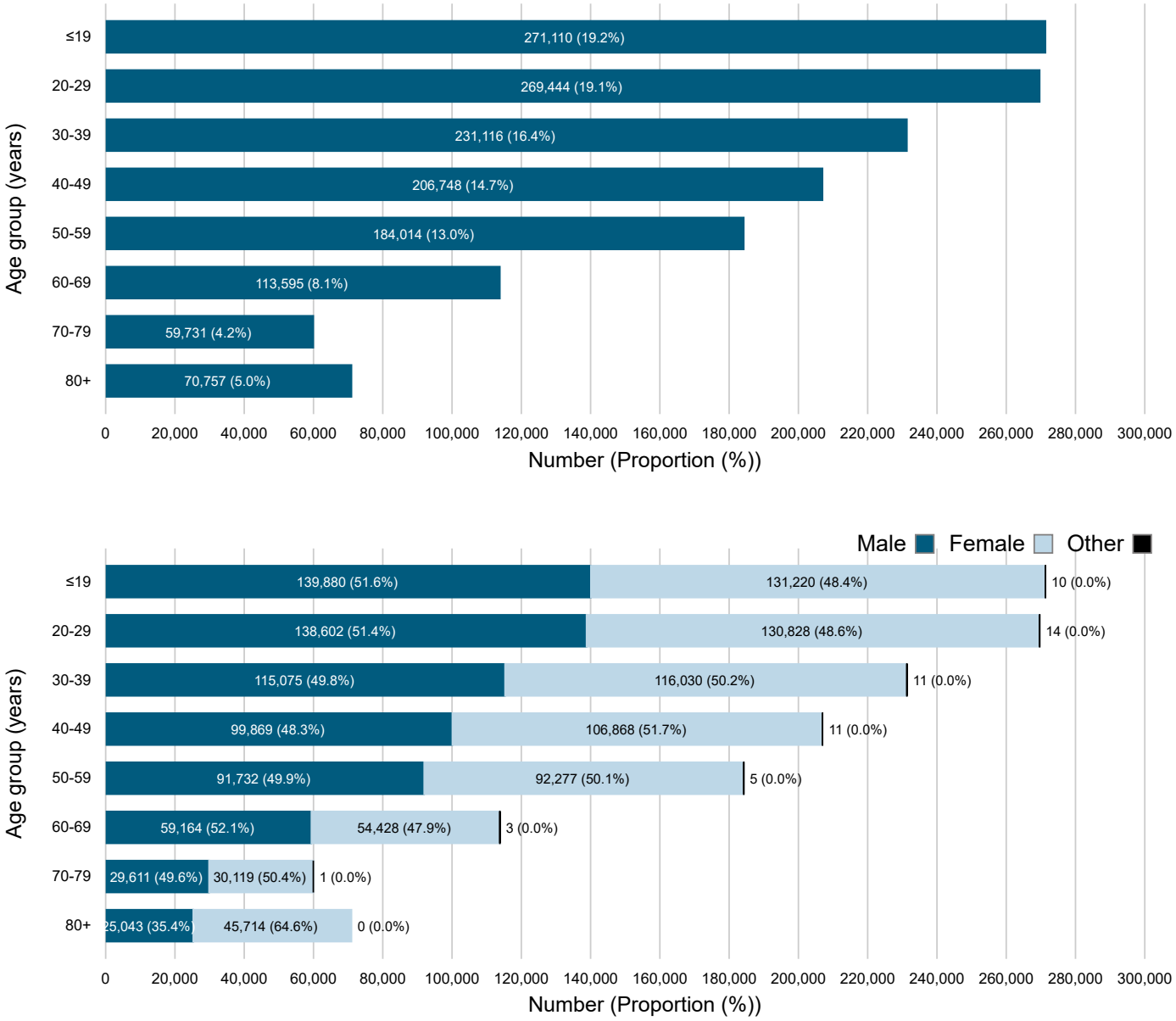
This figure may underestimate the total number of cases among returning travelers. Exposure history is not available for all cases and jurisdictions have not all consistently reported exposure history to PHAC throughout the pandemic.

Demographics

We have detailed case report data from 1,410,946 cases. We know the age of patients in 100.00% of cases, and both age and gender in 99.69% of cases.

Of the cases reported in Canada so far, 50.3% were female and 35.6% were between 20 and 39 years old (Figure 3).

Figure 3. Age distribution of COVID-19 cases (n=1,410,946 [1]) in Canada as of June 25, 2021, 7 pm EST [4]



Age by gender [4] distribution of COVID-19 cases (n=1,410,946 [1]) in Canada, June 25, 2021, 7 pm EST

Age group (years)	Number of cases with case reports (percentage)	Number of male cases (percentage)	Number of female cases (percentage)	Number of other cases (percentage)
≤19	271,110 (19.2%)	139,880 (20.0%)	131,220 (18.5%)	10 (18.2%)
20-29	269,444 (19.1%)	138,602 (19.8%)	130,828 (18.5%)	14 (25.5%)
30-39	231,116 (16.4%)	115,075 (16.5%)	116,030 (16.4%)	11 (20.0%)
40-49	206,748 (14.7%)	99,869 (14.3%)	106,868 (15.1%)	11 (20.0%)
50-59	184,014 (13.0%)	91,732 (13.1%)	92,277 (13.0%)	5 (9.1%)
60-69	113,595 (8.1%)	59,164 (8.5%)	54,428 (7.7%)	3 (5.5%)
70-79	59,731 (4.2%)	29,611 (4.2%)	30,119 (4.3%)	1 (1.8%)
80+	70,757 (5.0%)	25,043 (3.6%)	45,714 (6.5%)	0 (0.0%)
Total	1,406,515 (100%)	698,976 (100%)	707,484 (100%)	55 (100%)

How people were exposed [3]

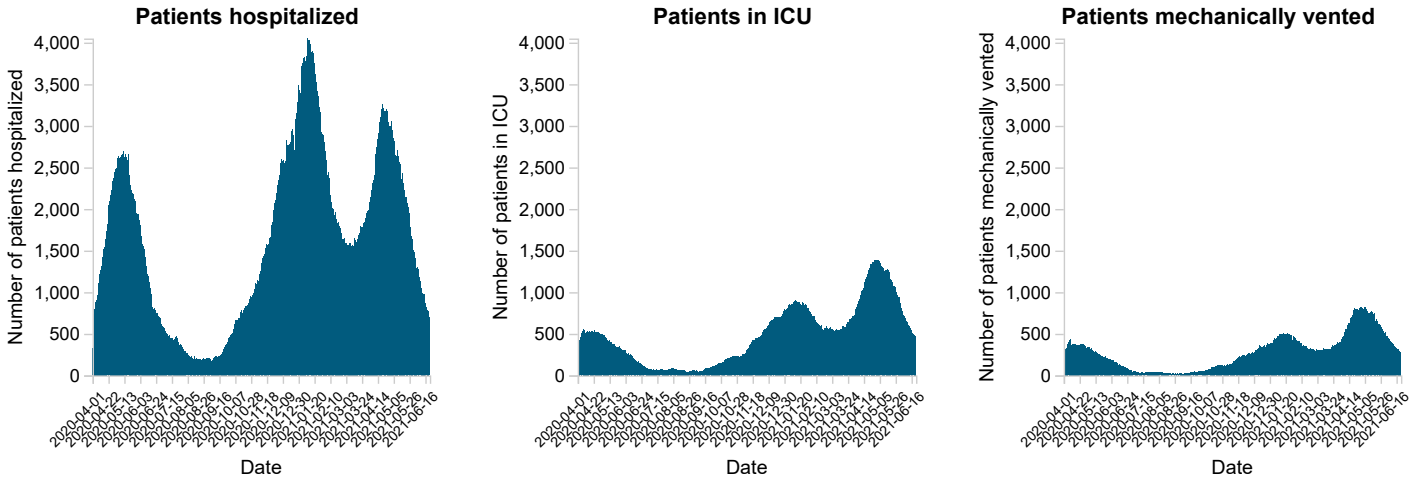
In Canada, detailed case report data were provided for 1,410,946 cases. We have exposure history for 1,254,652 (88.9%) cases. The probable exposure setting of these cases [1] are:

- any exposure that occurred in Canada: **1,167,909 (93.1%)**, including
  - from contact with a known COVID case: **583,505 (46.5%)**
  - from contact with a traveller: **8,451 (0.7%)**
  - from an unknown source: **575,953 (45.9%)**
- currently unknown (information pending): **77,135 (6.1%)**
- travelled outside of Canada: **9,608 (0.8%)**

Severe illness and outcomes

Hospital use

Figure 4. Daily number of hospital beds and ICU beds occupied by COVID-19 patients as of June 21, 2021



Between June 14, 2021 and June 21, 2021:

- the number of **hospital beds** occupied by COVID-19 patients **decreased** from **981** to **696** beds.
- the number of **ICU beds** occupied by COVID-19 patients **decreased** from **563** to **471** beds.
- the number of **COVID-19 patients who were mechanically vented decreased** from **337** to **282**.

Hospitalizations and deaths to date

We have detailed case report data on 1,410,946 cases, and hospitalization status for 988,451 (70.1%) of them:

- **74,044** cases **(7.5%)** were hospitalized, of whom:
  - **13,789 (18.6%)** were admitted to the ICU
  - **1,919 (2.6%)** needed mechanical ventilation

The provinces and territories provided detailed case report forms for **26,172** deaths related to COVID-19.

Figure 5a. Age and gender [4] distribution of COVID-19 cases hospitalized in Canada as of June 25, 2021, 7 pm EST (n=73,902 [1])

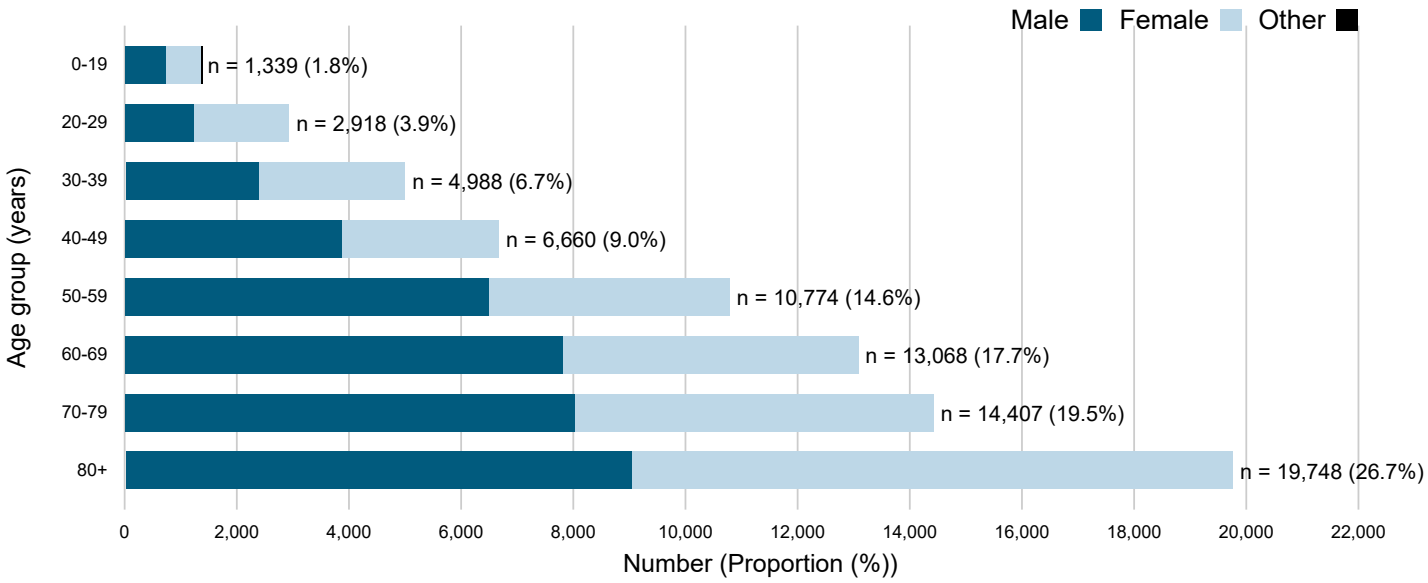


Figure 5b. Age and gender [4] distribution of COVID-19 cases admitted to ICU in Canada as of June 25, 2021, 7 pm EST (n=13,754 [1])

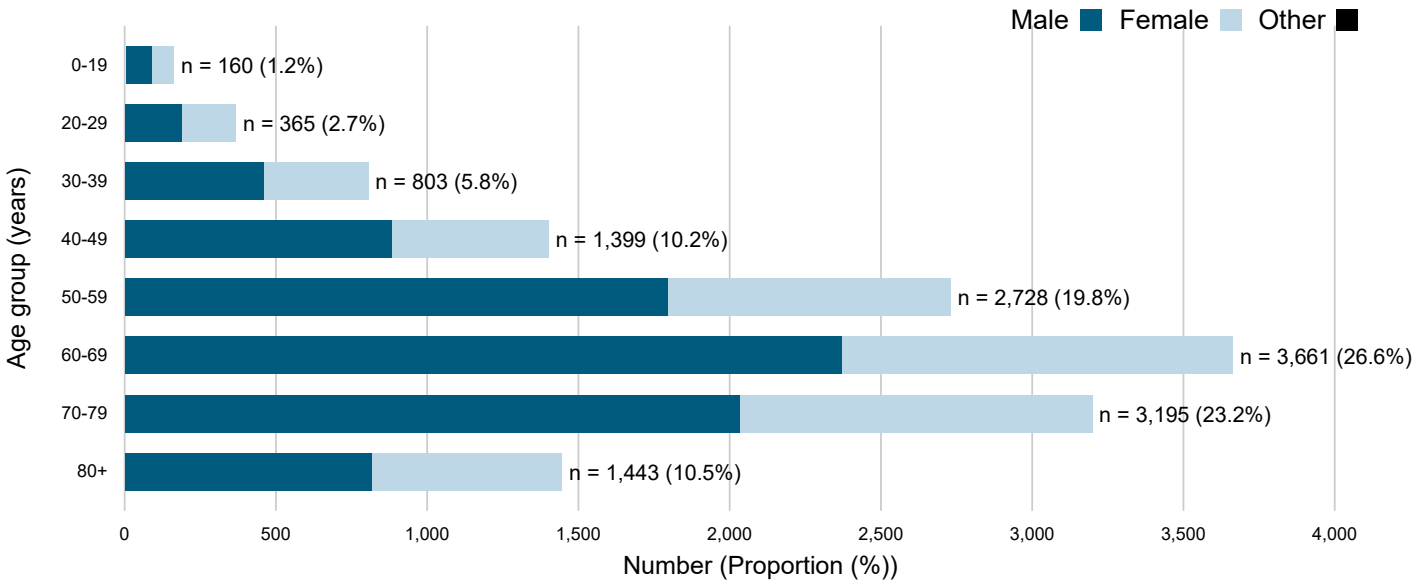
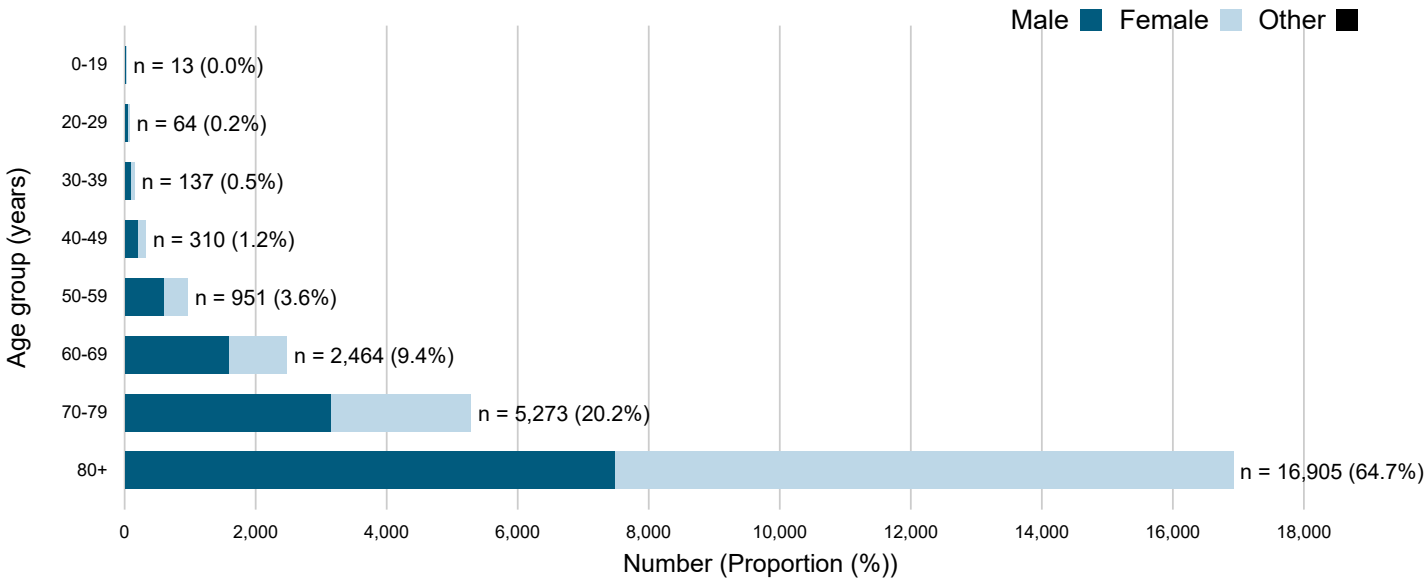


Figure 5c. Age and gender [4] distribution of COVID-19 cases deceased in Canada as of June 25, 2021, 7 pm EST (n=26,117 [1])



Data note: Figure 5 includes COVID-19 cases hospitalized, admitted to ICU, and deceased for which age and gender information were available. Therefore, some COVID-19 hospitalizations, ICU admissions, and deaths may not be included in Figure 5.

Age and gender [4] distribution of COVID-19 cases hospitalized in Canada as of June 25, 2021, 7 pm EST (n=73,902 [1])

Age group (years)	Number of cases with case reports (percentage)	Number of male cases (percentage)	Number of female cases (percentage)	Number of other cases (percentage)
0-19	1,339 (1.8%)	714 (1.0%)	624 (0.8%)	1 (0.0%)
20-29	2,918 (3.9%)	1,231 (1.7%)	1,687 (2.3%)	0 (0.0%)
30-39	4,988 (6.7%)	2,389 (3.2%)	2,599 (3.5%)	0 (0.0%)
40-49	6,660 (9.0%)	3,870 (5.2%)	2,790 (3.8%)	0 (0.0%)
50-59	10,774 (14.6%)	6,486 (8.8%)	4,288 (5.8%)	0 (0.0%)
60-69	13,068 (17.7%)	7,802 (10.6%)	5,266 (7.1%)	0 (0.0%)
70-79	14,407 (19.5%)	8,010 (10.8%)	6,397 (8.7%)	0 (0.0%)
80+	19,748 (26.7%)	9,040 (12.2%)	10,708 (14.5%)	0 (0.0%)

Age and gender [4] distribution of COVID-19 cases admitted to ICU in Canada as of June 25, 2021, 7 pm EST (n=13,754 [1])

Age group (years)	Number of cases with case reports (percentage)	Number of male cases (percentage)	Number of female cases (percentage)	Number of other cases (percentage)
0-19	160 (1.2%)	89 (0.6%)	71 (0.5%)	0 (0.0%)
20-29	365 (2.7%)	189 (1.4%)	176 (1.3%)	0 (0.0%)
30-39	803 (5.8%)	459 (3.3%)	344 (2.5%)	0 (0.0%)
40-49	1,399 (10.2%)	881 (6.4%)	518 (3.8%)	0 (0.0%)
50-59	2,728 (19.8%)	1,795 (13.1%)	933 (6.8%)	0 (0.0%)
60-69	3,661 (26.6%)	2,371 (17.2%)	1,290 (9.4%)	0 (0.0%)
70-79	3,195 (23.2%)	2,031 (14.8%)	1,164 (8.5%)	0 (0.0%)
80+	1,443 (10.5%)	817 (5.9%)	626 (4.6%)	0 (0.0%)

Age and gender [4] distribution of COVID-19 cases deceased in Canada as of June 25, 2021, 7 pm EST (n=26,117 [1])

Age group (years)	Number of cases with case reports (percentage)	Number of male cases (percentage)	Number of female cases (percentage)	Number of other cases (percentage)
0-19	13 (0.0%)	6 (0.0%)	7 (0.0%)	0 (0.0%)
20-29	64 (0.2%)	39 (0.1%)	25 (0.1%)	0 (0.0%)
30-39	137 (0.5%)	87 (0.3%)	50 (0.2%)	0 (0.0%)
40-49	310 (1.2%)	200 (0.8%)	110 (0.4%)	0 (0.0%)
50-59	951 (3.6%)	588 (2.3%)	363 (1.4%)	0 (0.0%)
60-69	2,464 (9.4%)	1,580 (6.0%)	884 (3.4%)	0 (0.0%)
70-79	5,273 (20.2%)	3,148 (12.1%)	2,125 (8.1%)	0 (0.0%)
80+	16,905 (64.7%)	7,470 (28.6%)	9,435 (36.1%)	0 (0)

Provincial, territorial and international reporting

For more information, please refer to provincial or territorial COVID-19 webpages:

- British Columbia
- Alberta
- Saskatchewan
- Manitoba
- Ontario
- Quebec
- Newfoundland and Labrador
- New Brunswick
- Nova Scotia
- Prince Edward Island
- Yukon
- Northwest Territories
- Nunavut
- World Health Organization
- Centers for Disease Control and Prevention
- European Centre for Disease Control and Prevention

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1 This figure is based on cases for which a case report form was received by the Public Health Agency of Canada from provincial or territorial partners.

2 The shaded area represents a period of time (lag time) where it is expected that cases have occurred but have not yet been reported nationally. The earliest of the following dates were used as an estimate: Onset date, Specimen Collection Date, Laboratory Testing Date, Date Reported to Province or Territory, or Date Reported to PHAC.

3 Exposure information may not be available for all cases. Some jurisdictions haven't consistently reported to PHAC how people were exposed throughout the pandemic. As a result, this may underestimate the total number of cases by different exposures, especially among returning travelers.

4 Where available, gender data was used; when gender data was unavailable, sex data was used. Reliable data on gender diverse respondents are unavailable due to small counts.

Date modified:
2021-06-29

This is "**Exhibit G**"
to the Affidavit of Matthew Hodge,
affirmed this 2nd day of July, 2021

A Commissioner, etc.

https://covid19.who.int

World Health Organization

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Covid-19 Response Fund

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WHO Coronavirus (COVID-19) Dashboard

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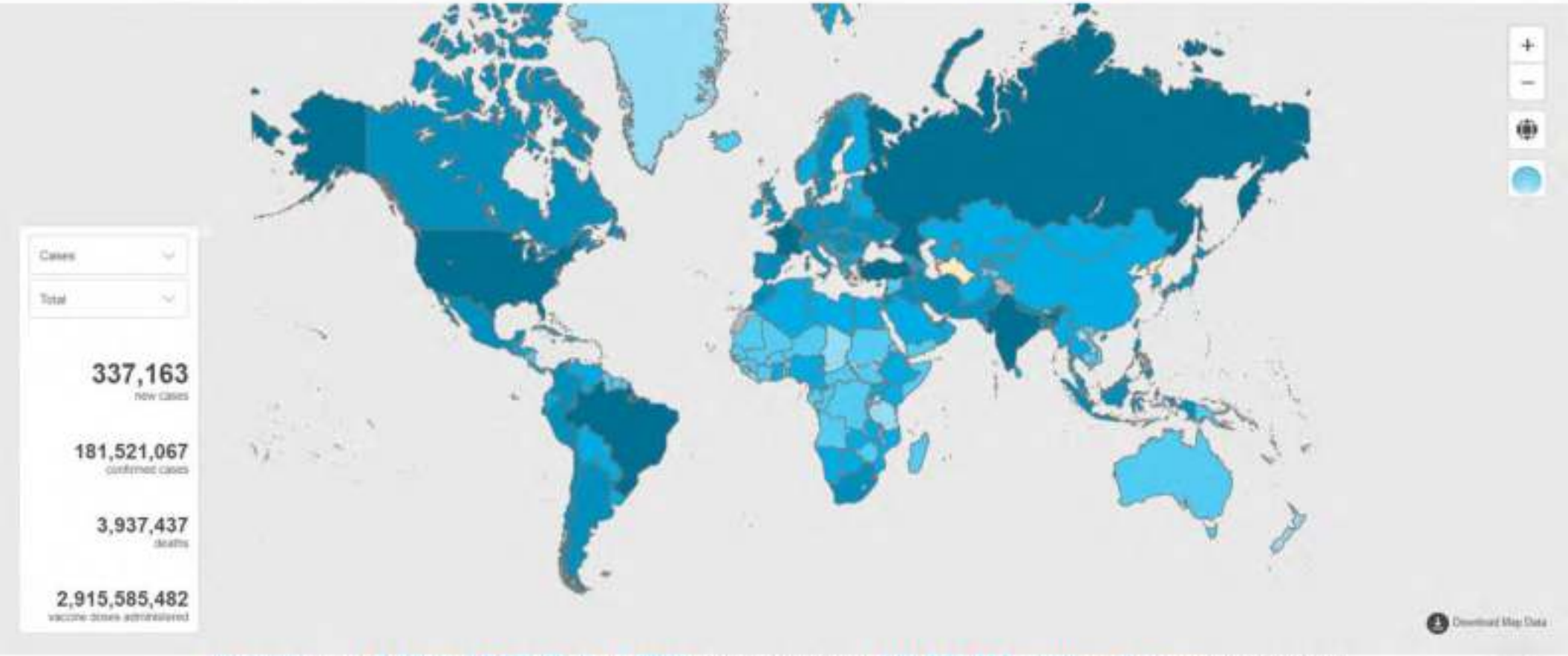
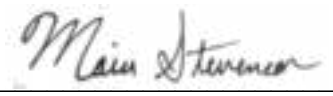


Globally, as of **6:09pm CEST, 30 June 2021**, there have been **181,521,067 confirmed cases** of COVID-19, including **3,937,437 deaths**, reported to WHO. As of **30 June 2021**, a total of **2,915,585,482 vaccine doses** have been administered.

This is "**Exhibit H**"
to the Affidavit of Matthew Hodge,
affirmed this 2nd day of July, 2021



A Commissioner, etc.

SCIENCE BRIEFS

COVID-19 Hospitalizations, ICU Admissions and Deaths Associated with the New Variants of Concern

Ashleigh R. Tuite, David N. Fisman, Ayodele Odutayo, Pavlos Bobos, Vanessa Allen, Isaac I. Bogoch, Adalsteinn D. Brown, Gerald A. Evans, Anna Greenberg, Jessica Hopkins, Antonina Maltsev, Douglas G. Manuel, Allison McGeer, Andrew M. Morris, Samira Mubareka, Laveena Munshi, V. Kumar Murty, Samir N. Patel, Fahad Razak, Robert J. Reid, Beate Sander, Michael Schull, Brian Schwartz, Arthur S. Slutsky, Nathan M. Stall, Peter Jüni on behalf of the Ontario COVID-19 Science Advisory Table

Version 1.0

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Author Affiliations: The affiliations of the members of the Ontario COVID-19 Science Advisory Table can be found at https://covid19-sciencetable.ca/.

Declarations of Interest: The declarations of interest of the members of the Ontario COVID-19 Science Advisory Table, its Working Groups, or its partners can be found at https://covid19-sciencetable.ca/.

About Us: The Ontario COVID-19 Science Advisory Table is a group of scientific experts and health system leaders who evaluate and report on emerging evidence relevant to the COVID-19 pandemic, to inform Ontario's response. Our mandate is to provide weekly summaries of relevant scientific evidence for the COVID-19 Health Coordination Table of the Province of Ontario, integrating information from existing scientific tables, Ontario's universities and agencies, and the best global evidence. The Science Table summarizes its findings for the Health Coordination Table and the public in Science Briefs.

Correspondence to: Secretariat of the Ontario COVID-19 Science Advisory Table (info@covid19-sciencetable.ca)

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The views and findings expressed in this Science Brief are those of the authors and do not necessarily reflect the views of all of the members of the Ontario COVID-19 Science Advisory Table, its Working Groups, and its partners.

Key Message

New variants of concern (VOCs) now account for 67% of all Ontario SARS-CoV-2 infections. Compared with early variants of SARS-CoV-2, VOCs are associated with a 63% increased risk of hospitalization, a 103% increased risk of intensive care unit (ICU) admission and a 56% increased risk of death due to COVID-19.

VOCs are having a substantial impact on Ontario's healthcare system. On March 28, 2021, the daily number of new SARS-CoV-2 infections in Ontario reached the daily number of cases observed near the height of the second wave, at the start of the province-wide lockdown, on December 26, 2020.

The number of people hospitalized with COVID-19 is now 21% higher than at the start of the province-wide lockdown, while ICU occupancy is 28% higher (Figure 1). The percentage of COVID-19 patients in ICUs who are younger than 60 years is about 50% higher now than it was prior to the start of the province-wide lockdown.

Because the increased risk of COVID-19 hospitalization, ICU admission and death with VOCs is most pronounced 14 to 28 days after diagnosis, there will be significant delays until the full burden to the health care system becomes apparent.

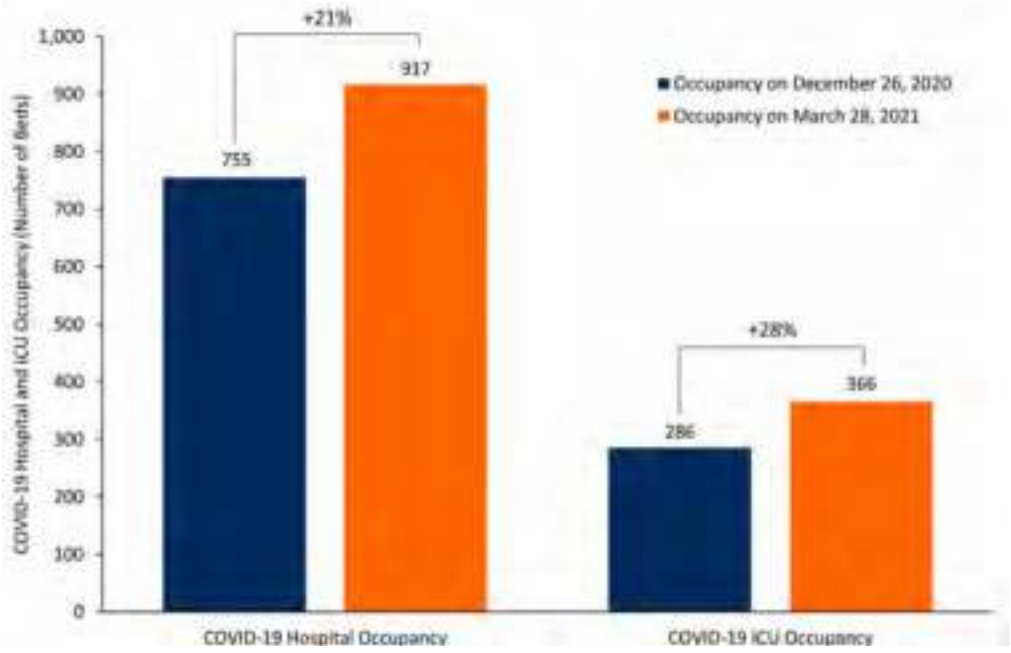

Figure 1. COVID-19 Hospital and ICU Occupancy on March 28, 2021 Compared with December 26, 2020
Bar graphs showing the COVID-19 hospital and ICU occupancy in Ontario. The relative increase between March 28,

2021 and December 26, 2020 is indicated above the corresponding bars for hospital and ICU occupancy. ICU, intensive care unit.

Summary

Background

As of March 28, 2021 new variants of concern (VOCs) account for 67% of all Ontario SARS-CoV-2 infections. The B.1.1.7 variant originally detected in Kent, United Kingdom accounts for more than 90% of all VOCs in Ontario, with emerging evidence that it is both more transmissible and virulent.

Questions

What are the risks of COVID-19 hospitalization, ICU admission and death caused by VOCs as compared with the early variants of SARS-CoV-2?

What is the early impact of new VOCs on Ontario's healthcare system?

Findings

A retrospective cohort study of 26,314 people in Ontario testing positive for SARS-CoV-2 between February 7 and March 11, 2021, showed that 9,395 people (35.7%) infected with VOCs had a 62% relative increase in COVID-19 hospitalizations (odds ratio [OR] 1.62, 95% confidence interval [CI] 1.41 to 1.87), a 114% relative increase in ICU admissions (OR 2.14, 95% CI 1.52 to 3.02), and a 40% relative increase in COVID-19 deaths (OR 1.40, 95% CI 1.01 to 1.94), after adjusting for age, sex and comorbidities.

A meta-analysis including the Ontario cohort study and additional cohort studies in the United Kingdom and Denmark showed that people infected with VOCs had a 63% higher risk of hospitalization (RR 1.63, 95% CI 1.44 to 1.83), a doubling of the risk of ICU admission (RR 2.03, 95% CI 1.69 to 2.45), and a 56% higher risk of all-cause death (RR 1.56, 95% CI 1.30 to 1.87). Estimates observed in different studies and regions were completely consistent, and the B.1.1.7 variant was dominant in all three jurisdictions over the study periods.

The number of people hospitalized with COVID-19 on March 28, 2021, is 21% higher than at the start of the province-wide lockdown during the second wave on December 26, 2020, while ICU occupancy is 28% higher.

Between December 14 to 20, 2020, there were 149 new admissions to ICU; people aged 59 years and younger accounted for 30% of admissions. Between March 15, 2021 and March 21, 2021, there were 157 new admissions to ICU; people aged 59 years and younger accounted for 46% of admissions.

Interpretation

The new VOCs will result in a considerably higher burden to Ontario's health care system during the third wave compared to the impact of early SARS-CoV-2 variants during Ontario's second wave.

Since the start of the third wave on March 1, 2021, the number of new cases of SARS-CoV-2 infection, and the COVID-19 hospital and ICU occupancies have surpassed prior thresholds at the start of the province-wide lockdown on December 26, 2020.

Background

Around March 1, 2021, Ontario entered the third wave of the COVID-19 pandemic, with the slope of the epidemic curve driven by the increasing number of VOCs since March 3, 2021 (Figure 2).[1] As of March 28, 2021, there were an estimated total of

107.1 new SARS-CoV-2 infections per 100,000 persons per week, with 35.7 new SARS-CoV-2 infections per 100,000 Ontarians per week caused by early variants of SARS-CoV-2 (non-VOCs), and 71.4 new SARS-CoV-2 infections per 100,000 Ontarians per week caused by new VOCs. The VOCs accounted for an estimated 67% of new cases of SARS-CoV-2 infections.[1] VOCs are now the dominant source of SARS-CoV-2 infection in Ontario.

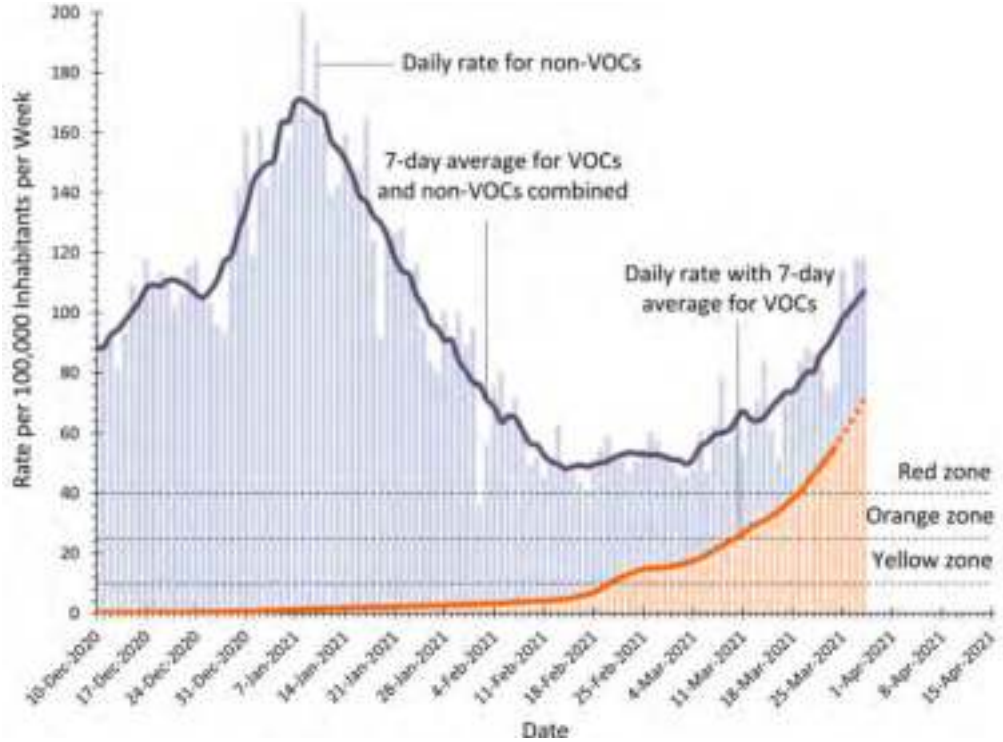

Figure 2. Rate of New SARS-CoV-2 Infections in Ontario

Seven-day moving averages of confirmed new SARS-CoV-2 infections overall in Ontario per 100,000 inhabitants per week (purple line), and infections caused by new VOCs in Ontario per 100,000 inhabitants per week (orange line). The daily rate per 100,000 inhabitants per week is represented by blue and orange bars. The incidence of new infections related to VOCs from March 24th 2021 and onwards is predicted (dashed orange line). The color-coded zones are the zones of public health measures established by Ontario's COVID-19 response framework: grey/red zone = weekly SARS-CoV-2 incidence of ≥40 per 100,000; orange zone = weekly incidence 25 to 39.9 per 100,000; and yellow zone = weekly incidence of 10 to 24.9 per 100,000. VOC, variant of concern. Graph adapted from Ontario COVID-19 Science Advisory Table.[1]

The B.1.1.7 variant, which was originally detected in Kent, United Kingdom, currently accounts for more than 90% of all VOCs in Ontario. The B.1.351 and P.1 variants originally detected in South Africa and Brazil, respectively, account for the remaining VOCs.[2] The B.1.1.7 variant which is dominant in Ontario, is at least 40% more transmissible than early variants of SARS-CoV-2,[3] and emerging evidence suggests it may be more virulent.[4]

Questions

What are the risks of COVID-19 hospitalization, ICU admission and death caused by VOCs as compared with the early variants of SARS-CoV-2?

What is the early impact of new VOCs on Ontario's healthcare system?

Findings

Table 1 presents the results of a retrospective cohort study of 26,314 people in Ontario who were PCR-positive for SARS-CoV-2 between February 7 and March 11, 2021, with 9,395 people (35.7%) having an infection caused by a VOC. After adjusting for age, sex and comorbidities, infections due to VOCs were associated

with a 62% relative increase in COVID-19 hospitalizations (odds ratio [OR] 1.62, 95% confidence interval [CI] 1.41 to 1.87), a 114% relative increase in ICU admissions (OR 2.14, 95% CI 1.52 to 3.02), and a 40% relative increase in COVID-19 deaths (OR 1.40, 95% CI 1.01 to 1.94). These risk elevations for COVID-19 hospitalization, ICU admission and death were consistent across all age groups.

	Adjusted odds ratio (95% CI)
COVID-19 Hospitalizations	1.62 (1.41 to 1.87)
COVID-19 ICU admissions	2.14 (1.52 to 3.02)
COVID-19 Deaths	1.40 (1.01 to 1.94)

Table 1. Risk of COVID-19 Hospitalization, Intensive Care Unit Admission and Death Associated with VOCs Compared to Early Variants in Ontario, Canada

Adjusted odds ratios and 95% confidence intervals for the risk of COVID-19 hospitalizations, intensive care unit admissions and deaths associated with new VOCs compared to early variants. VOC, variant of concern; CI, confidence interval; ICU, intensive care unit.

Figure 3 presents the results a meta-analysis of cohort studies in Ontario (Table 1, above), the United Kingdom[5,6] and Denmark[7] comparing new VOCs with early variants, again with the dominant VOC being B.1.1.7 in all three jurisdictions over the study periods.[3] Pooling adjusted estimates of relative risks (RRs), people infected with VOCs had a 63% higher risk of hospitalization (RR 1.63, 95% CI 1.44 to 1.83), a doubling of the risk of ICU admission (RR 2.03, 95% CI 1.69 to 2.45), and a 56% higher risk of all-cause death (RR 1.56, 95% CI 1.30 to 1.87). Estimates observed in different studies and regions were completely consistent.

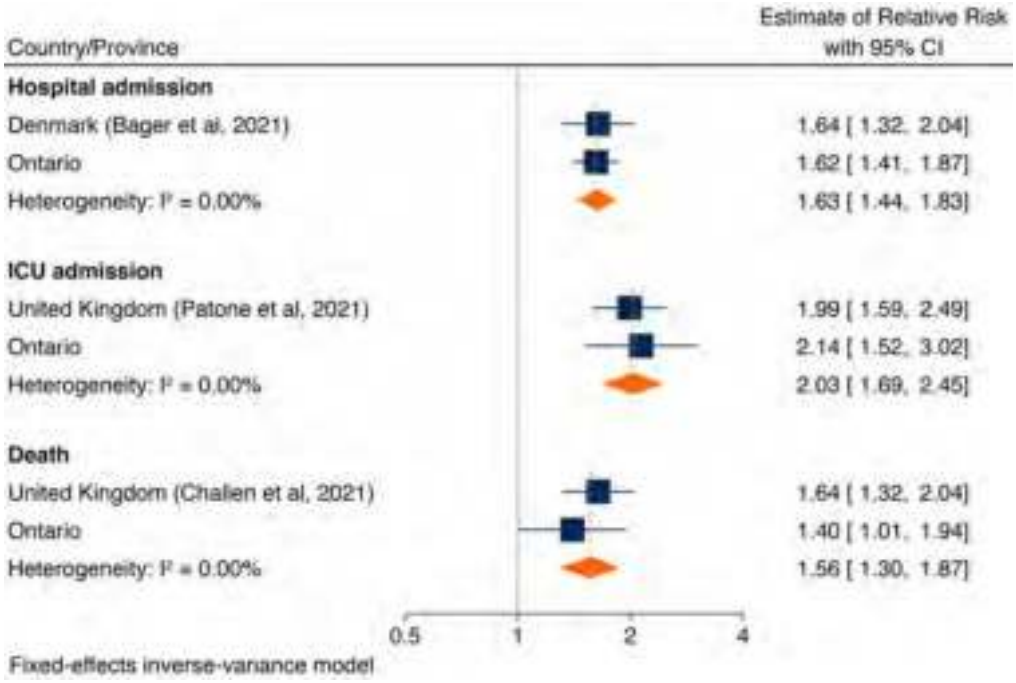

Figure 3. Meta-Analysis of the Risk of COVID-19 Hospitalization, Intensive Care Unit Admission and Death Associated with new VOCs Compared to Early Variants

Each square presents the results of an individual cohort study, with the size of the square being proportional to the weights used in the meta-analysis and the horizontal lines indicating the 95% confidence intervals. The solid vertical line at 1 indicates that there is no difference in prognosis between new VOCs and early variants. The diamond indicates the pooled estimate of the relative risk combining individual studies from different regions. Estimates for Ontario and Denmark are odds ratios; estimates for the United Kingdom are hazard ratios. The retrospective cohort study in Ontario included 26,314 participants in Ontario with PCR confirmed SARS-CoV-2 infection between February 7 and March 11, 2021, of whom 9,395 were infected with new VOCs. The retrospective cohort study by Bager et al. included 18,449 participants in Denmark with PCR confirmed SARS-CoV-2 infection between January 1 and February 9, 2021 with 2,155 infected with new VOCs.[7] Estimates were adjusted for age, sex, calendar period, region, and number of comorbidities during the past 5 years. The retrospective cohort study by Patone et al. included 198,420 individuals in the United Kingdom with PCR confirmed SARS-CoV-2 infection between November 1, 2020 and January 27, 2021, of whom 80,494 were infected with new VOCs. Relative risk estimates were adjusted for age, sex, region, socio-demographic factors and comorbidities, including asthma, chronic obstructive pulmonary disease, diabetes

and hypertension.[5] The retrospective cohort study by Challen et al. included 109,812 individuals in the United Kingdom with PCR confirmed SARS-CoV-2 infection between October 1, 2020 and January 29, 2021, with 54,906 participants with new VOCs matched to 54,906 participants with early variants.[6] Participants were matched on age, sex, date of specimen collection, ethnicity, geographical location, and index of multiple deprivation, which is a marker for socioeconomic status; estimates were subsequently adjusted for age. VOC, variant of concern; CI, confidence interval; ICU, intensive care unit.

Figure 4 shows the time to death observed in a retrospective cohort study by Challen et al. in the United Kingdom involving 109,812 participants with positive PCR tests for SARS-CoV-2 between October 1, 2020, to January 29, 2021, with 54,906 participants infected with new VOCs matched to 54,906 participants infected with the early variant.[6] The curves overlap until day 12 after diagnosis, at which point the curves start to separate, with a higher risk of death among participants infected with new VOCs compared with participants infected with early variants.

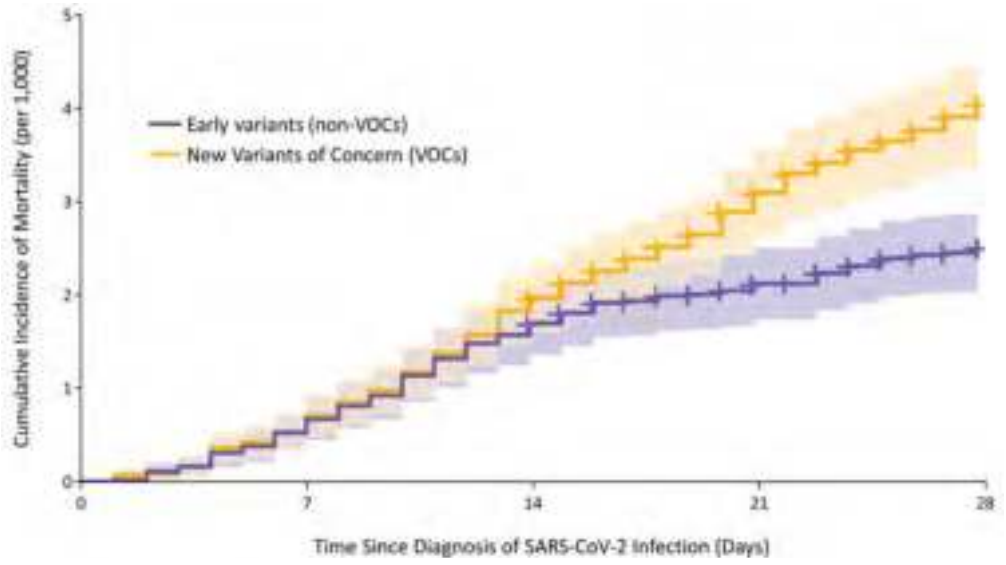

Figure 4. Time to Death Following SARS-CoV-2 Infection with New VOCs Compared with Early Variants
Curves describing the time to death from first PCR confirmation of SARS-CoV-2 infection among individuals in the United Kingdom infected with new VOCs versus early SARS-CoV-2 variants. Participants were matched on age, sex, date of specimen collection, ethnicity, geographical location, and index of multiple deprivation, which is a marker for socioeconomic status, and estimates were subsequently adjusted for age. Data from Challen et al.[6] VOC, variant of concern.

Figure 5 shows the risk of death associated with new VOCs compared with early SARS-CoV-2 variants from days 0 to 14 and days 15 to 28 after diagnosis of SARS-CoV-2 infection. Results are adapted from the aforementioned retrospective cohort study of people with PCR confirmed SARS-CoV-2 infection in the United Kingdom by Challen et al.[6] Between days 0 and 14 after diagnosis, there was only a minimal difference in the risk of death (RR 1.23, 95% CI 0.92 to 1.64) associated with the new VOCs compared with early variants. However, between days 15 and 28, the risk of death was more than doubled (RR 2.40, 95% CI 1.66 to 3.47).

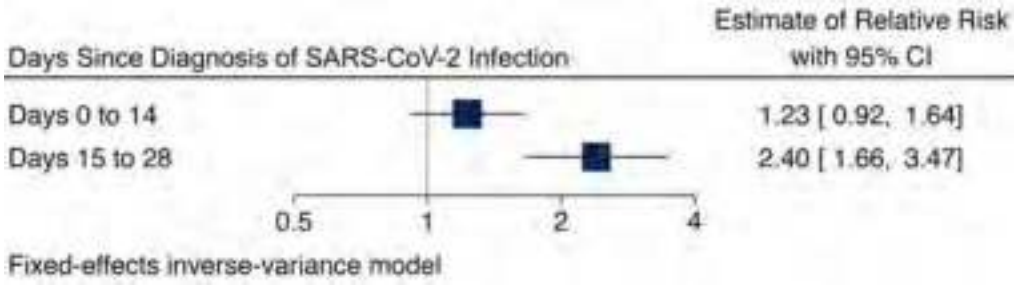

Figure 5. Risk of COVID-19 Death Associated with new VOCs Compared with Early Variants by Time Since Diagnosis of SARS-CoV-2 Infection
Adapted from a retrospective cohort study by Challen et al. which included 109,812 individuals in the United Kingdom with PCR-confirmed SARS-CoV-2 infection between October 2020 to 29 January 2021, with 54,906 individuals with new VOCs matched to 54,906 individuals with the early variant.[6] Individuals were matched on age, sex, date of specimen

collection, ethnicity, geographical location, and index of multiple deprivation, which is a marker for socioeconomic status. Each square presents the relative risk for death with the new VOCs versus early variants. The horizontal lines indicate the 95% confidence intervals. The solid vertical line at 1 indicates that there is no difference in prognosis between new VOCs and early SARS-CoV-2 variants. VOC, variant of concern; CI, confidence interval.

Figure 6 shows the risk of ICU admission associated with new VOCs versus early SARS-CoV-2 variants at days 1, 5, 10 and 15 after diagnosis of SARS-CoV-2 infection in a retrospective cohort study by Patone et al. The study involved 198,420 individuals in the United Kingdom with PCR-confirmed SARS-CoV-2 infection, of whom 80,494 were infected with new VOCs.[5] On day 1, there was a minimal difference in the risk of ICU admission between people infected with new VOCs and those infected with early variants (RR 1.20, 95% CI 0.58 to 2.48). Subsequently, there was a progressive, lagged increase in the risk of ICU admission associated with new VOCs, with a 58% increase at day 5 and a near fourfold increase at day 10.

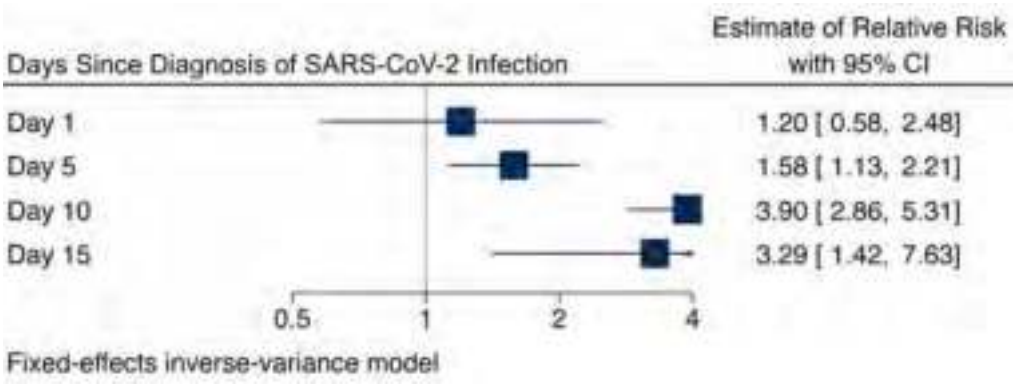

Figure 6. Risk of COVID-19 ICU Admission Associated with New VOCs Compared with Early Variants by Time Since Diagnosis of SARS-CoV-2 Infection

Adapted from a retrospective cohort study by Patone et al.[5] The study involved 198,420 individuals in the United Kingdom with PCR-confirmed SARS-CoV-2 infection, of whom 80,494 were infected with new VOCs. Relative risk estimated were adjusted for age, sex, region, socio-demographic factors and comorbidities including asthma, chronic obstructive pulmonary disease, diabetes and hypertension. Each square represents the relative risk for ICU admission with the new VOCs versus early variants. The horizontal lines indicate the 95% confidence intervals. The solid vertical line at 1 indicates that there is no difference in prognosis between new VOCs and early variants. VOC, variant of concern; CI, confidence interval.

Figure 7 shows the 7-day moving average of daily SARS-CoV-2 infections, and daily COVID-19 hospital and ICU occupancy in Ontario. At the time of the province-wide lockdown near the height of Ontario's second wave on December 26, 2020, there were 2,236 new infections per day, 755 people were hospitalized due to COVID-19, and 286 in ICU due to COVID-19.

Since the start of the third wave around March 1, 2021, the number of new cases, as well as hospital and ICU occupancy have surpassed prior thresholds seen at the start of the province-wide lockdown on December 26, 2020. The threshold of 286 COVID-19 cases in ICUs at the time of the lockdown on December 26, 2020, was reached on March 9, 2021. Likewise, COVID-19 hospital occupancy of 755 people was reached on March 16, 2021. Finally, the threshold of 2,236 new SARS-CoV-2 infections per day was reached on March 28, 2021.

We project a 2 to 4 week time lag between daily SARS-CoV-2 cases and COVID-19 hospitalizations and ICU admissions, with lagging risk increases due to the new VOCs (see Figures 3 to 5). Therefore, hospital and ICU occupancies due to COVID-19 will continue to increase considerably over time, and would so even if SARS-CoV-2 case numbers were to remain at the current level seen on March 28, 2021.

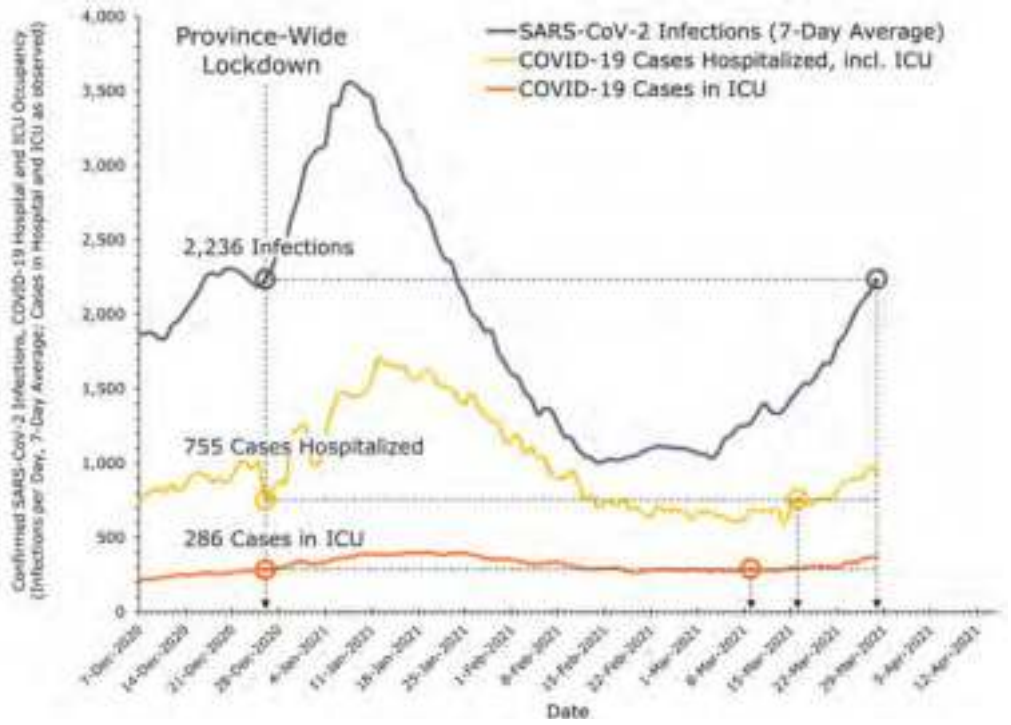

Figure 7. Number of New SARS-CoV-2 Infections, COVID-19 Hospital, and ICU Occupancy in Ontario
7-day moving averages of confirmed new SARS-CoV-2 infections in Ontario per week, number of people hospitalized with COVID-19, and number of ICU beds in Ontario occupied by COVID-19 patients. VOC, variant of concern; ICU, intensive care unit.

Table 2 presents a comparison of the number of new SARS-CoV-2 infections and COVID-19 hospital and ICU occupancy for key dates during the third wave compared with the start of the province-wide lockdown on December 26, 2020 during the second wave. As of March 28, 2021, the predicted 7-day average of SARS-CoV-2 infections during the third wave reached the 7-day midpoint average seen at the start of the province-wide lockdown on December 26, 2020.

Key	Date	SARS-CoV-2 Infections	Hospital Occupancy	ICU Occupancy
A	26-Dec-20	**2,236**	**755**	**286**
B	9-Mar-21	1,269	689	**290**
C	16-Mar-21	1,480	**761**	292
D	28-Mar-21	**2,236**	917	366

Table 2. Comparison of Key Dates During the Third Wave in Ontario with the Start of the Province-Wide Lockdown During the Second Wave on December 26, 2020
A, December 26, 2020, was the start date of the province-wide lockdown during the second wave; B, March 9, 2021 is the date when the COVID-19 ICU occupancy during the third wave reached COVID-19 ICU occupancy seen on December 26, 2020; C, March 16, 2021 is the date when COVID-19 hospital occupancy during the third wave reached COVID-19 hospital occupancy seen on December 26, 2020; D, March 28, 2021 is the date when the predicted 7-day average of SARS-CoV-2 infections during the third wave reached the 7-day midpoint average seen on December 26, 2020. ICU, intensive care unit. Second wave, September 1, 2020 to February 28, 2021. Third wave, March 1, 2020 to ongoing.

Figure 1 above presents a comparison of COVID-19 hospital occupancy and ICU occupancy in Ontario on March 28, 2021, compared with the start of the province-wide lockdown on December 26, 2020. The number of people hospitalized with COVID-19 on March 28, 2021, is 21% higher than on December 26, 2020, while ICU occupancy is 28% higher.

Figure 8 presents the percentage of COVID-19 ICU admissions in Ontario by age group in the week prior to the lockdown during the second wave (December 14 to 20, 2020) with the last available week of ICU admission data during the third wave (March 15 to 21, 2021). Between December 14 to 20, 2020, there were 149 new admissions to ICU; people aged 59 years and younger accounted for 30% of admissions. Between March 15, 2021 and March 21, 2021, there were 157 new admissions to ICU; people aged 59 years and younger accounted for 46% of admissions.

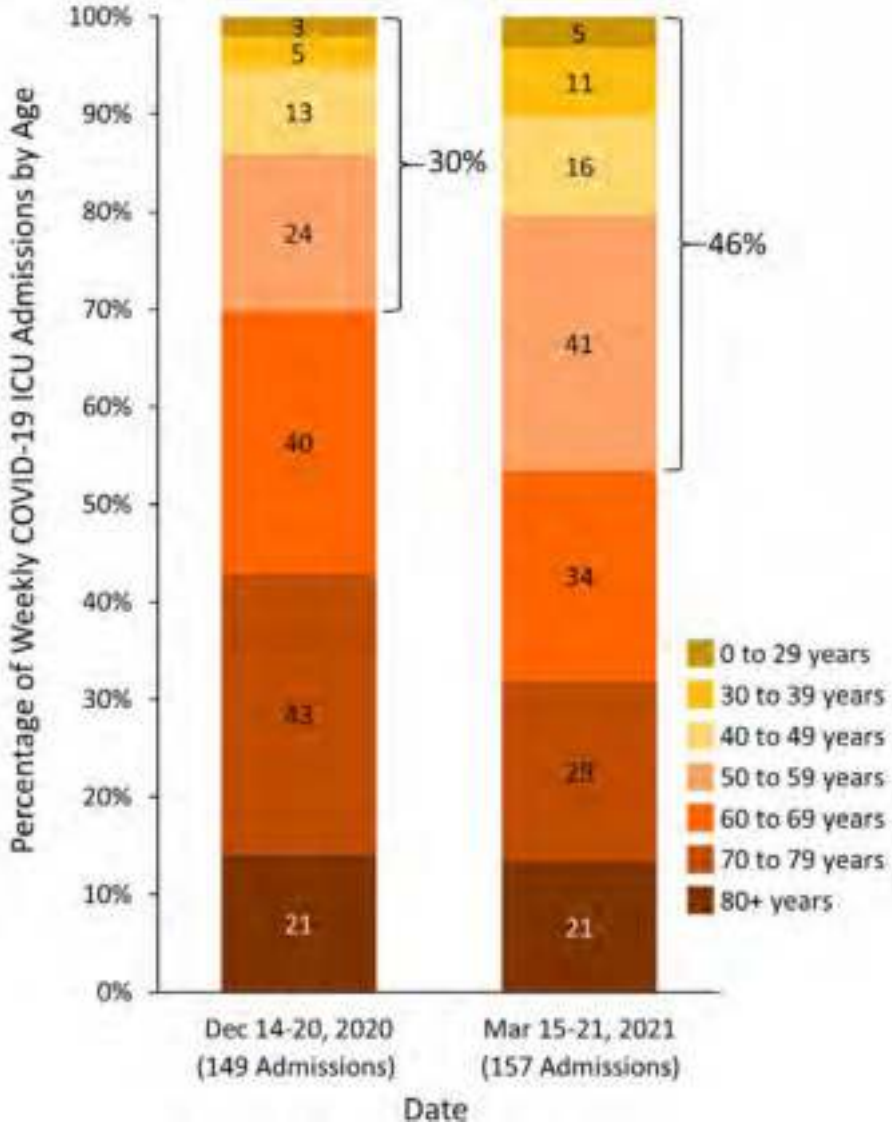

Figure 8. Weekly COVID-19 ICU Admissions in Ontario by Age
December 14 to 20, 2020 corresponds to the week prior to lockdown during the second wave, March 15 to 21, 2021 corresponds to the last available week of ICU admission data during the third wave. Data sourced from the Critical Care Information System (CCIS).

Interpretation

Compared with early variants of SARS-CoV-2, new VOCs are associated with a 103% increase in the risk of hospitalization, a 63% increase in the risk of ICU admission and a 56% increase in the risk of death due to COVID-19, which will result in a considerably higher burden to the health care system than observed with early variants during the second wave. The risk increase is particularly pronounced 14 to 28 days after a diagnosis of SARS-CoV-2 infection, which in turn will result in delays until the full burden to the health care system becomes apparent.

Since the start of the third wave around March 1, 2021, the number of new cases of SARS-CoV-2 infection, and the COVID-19 hospital and ICU occupancies have surpassed prior thresholds at the start of the province-wide lockdown on December 26, 2020. As of March 28, 2020, hospital occupancy was 21% higher and ICU occupancy 28% higher than at the start of the province-wide lockdown.

Currently, patients aged 59 years and younger make up 46% of new COVID-19 admissions to ICUs, compared with 30% in the week prior to the start of the province-wide lockdown on December 26, 2020.

Methods Used for This Science Brief

We conducted a retrospective cohort study using cases of SARS-CoV-2 infection reported in CCM/iPHIS with a case report date between Feb 7 and March 11, 2021. We restricted the analysis to cases that were tested for variants of concern. As Ontario's long-term care population was highly vaccinated with SARS-CoV-2 vaccines as of February 2021, and were unlikely to become critically ill and require intensive care, long term care residents were excluded from the analysis. A total of 26,314 individuals were included in the analysis, of whom 9,395 had a detected SARS-CoV-2 infection with a VOC. Associations between VOC SARS-CoV-2 infection and COVID-19 outcomes were evaluated by constructing logistic regression models with the following prespecified covariates: age (by 10-year age categories), sex, obesity, and any of the following medical comorbidities: asthma, immunocompromise, COPD, hematological disease, renal disease, neurological condition, diabetes, or liver disease. Time (date of case report) was included as a linear trend term. To account for geographic variability in the fraction of infections caused by VOCs, public health units were included as indicator variables. The analysis of the age distribution in Figure 8 is based on all cases, without exclusion of long-term care residents.

We searched PubMed, Google Scholar, the COVID-19 Rapid Evidence Reviews, the Joanna Briggs Institute's COVID-19 Special Collection, LitCovid in PubMed, the Oxford COVID-19 Evidence Service, the World Health Organization's Global Literature on Coronavirus Disease, and other COVID-19 specific resources listed by the Guidelines International Network and the McMaster Health Forum for studies on the prognosis associated with new VOCs compared with early variants. In addition, we retrieved reports citing relevant articles through Google Scholar and reviewed references from identified articles for additional studies. The search was last updated on March 26, 2021. For the United Kingdom, the analysis by Challen et al[6] was selected for extraction of mortality data rather than the analysis by Davies et al[4] since Challen et al.'s analysis was considered to have a lower risk of confounding.

We used an inverse-variance fixed-effects meta-analysis to combine adjusted estimates from individual studies. Analyses were done in R (R Foundation, Vienna, Austria) and STATA (StataCorp LLC, College Station, TX).

Author Contributions

PJ conceived the Science Brief. ART, AO and PJ wrote the first draft. ART, DNF, PB and PJ performed analyses. All authors revised the Science Brief critically for important intellectual content and approved the final version.

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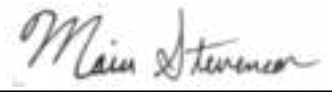
This is "**Exhibit I**"
to the Affidavit of Matthew Hodge,
affirmed this 2nd day of July, 2021



A Commissioner, etc.

Public Health Ontario | Santé publique Ontario

WEEKLY EPIDEMIOLOGICAL SUMMARY

SARS-CoV-2 Whole Genome Sequencing in Ontario, June 23, 2021

This report summarizes the results of SARS-CoV-2 whole genome sequencing completed by Public Health Ontario (PHO) as of June 17, 2021 and partner laboratories in the Ontario COVID-19 Genomics Network as of June 16, 2021. Not all data from the network laboratories were available to be included in this report. Results included in this report represent the number of samples tested and not the number of cases. More than one sample may be sequenced per person.

Background

The continued monitoring of global SARS-CoV-2 genomic data has identified changes in the genome as it spreads through populations. These random changes or mutations arise as a virus evolves over time. The accumulation of these mutations can result in a new lineage of the virus, which is a common occurrence. These new lineages will differ slightly in genome sequence and are termed variants. Although many variants will have no difference in the ability to spread or cause disease, some variants have mutations which may enhance virulence, transmissibility, and/or allow the virus to escape natural or vaccine-induced immunity.

The identification of variants and mutations occurs through whole genome sequencing (WGS) of select samples. Through global surveillance of SARS-CoV-2 genomes, a number of variants have been identified with evidence of clinical and/or public health significance, termed variants of concern (VOC). Current VOCs include B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma) and B.1.617.2 (Delta). WGS has also identified a number of variants of interest (VOI), which may share one or more mutations in common with a VOC, but do not have sufficient evidence at this time to be categorized as a VOC (i.e. evidence of increased transmissibility, disease severity, or immune escape). These variants are also characterized and monitored through genomic surveillance. A VOI may be re-classified as a VOC where there is sufficient scientific evidence to support this designation. Full definitions of VOC/VOI can be found on the Public Health Agency of Canada's SARS-CoV-2 Variants webpage.[1]

The Ontario COVID-19 Genomics Network performs WGS on select samples received for SARS-CoV-2 diagnostic testing or VOC PCR testing. Sequences are processed using bioinformatics analysis and assigned a Pango lineage[2] using the pangolin tool[3], allowing for the identification of VOC, VOI and other lineages.

Highlights

- From May 9 to June 5, 2021, there were 2,342 samples sequenced by the Ontario COVID-19 Genomics Network for representative surveillance. The majority were Pango lineage B.1.1.7 (Alpha; 71.6%), followed by B.1.617.2 (Delta; 17.1%), and P.1 (Gamma; 4.0%).
- The proportion that were B.1.617.2 (Delta) increased from 14.1% (May 23 to 29) to 22.2% (May 30 to June 5).
- The public health units with the highest proportion of B.1.617.2 (Delta) from May 30 to June 5, 2021 were: Peel Public Health (38.2%), Region of Waterloo Public Health and Emergency Services (34.9%), Porcupine Health Unit (29.4%), and Halton Region Public Health (26.7%); excluding public health units with fewer than 25 samples sequenced.
- From January 1 to June 5, 2021, the most commonly identified VOI was B.1.1.318, with a total of 1,513 samples.

The data in this report should be interpreted with caution. For representative surveillance, PHO began sequencing eligible samples prior to other laboratories. For cumulative whole genome sequencing (WGS) results, the selection of samples for WGS historically has been influenced by laboratory testing algorithms. This has created a sampling bias reflected in the distribution of lineage results.

The Ontario COVID-19 Genomics Network is in the process of implementing a representative surveillance strategy. This will allow for provincial estimates of the prevalence of VOC, VOI, and other lineages. On June 14, the network moved to sequencing 100% of eligible samples.

Representative Surveillance

Table 1. Number and percentage of samples by VOC/VOI Pango lineage and week, representative surveillance, Ontario, May 9, 2021 to June 5, 2021

Pango lineage (WHO label)	Week 19 (May 9-15)	Week 20 (May 16-22)	Week 21 (May 23-29)	Week 22 (May 30-June 5)	Total (May 9-June 5)
Variant of concern (VOC)					
B.1.1.7 (Alpha)	337 (77.3%)	252 (68.9%)	483 (75.6%)	605 (67.1%)	1,677 (71.6%)
B.1.351 (Beta)	1 (0.2%)	3 (0.8%)	4 (0.6%)	5 (0.6%)	13 (0.6%)
P.1 (Gamma)	25 (5.7%)	14 (3.8%)	18 (2.8%)	36 (4.0%)	93 (4.0%)
B.1.617.2 (Delta)	47 (10.8%)	64 (17.5%)	90 (14.1%)	200 (22.2%)	401 (17.1%)
Variant of interest (VOI)					
A.23.1	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
B.1.1.318	10 (2.3%)	8 (2.2%)	21 (3.3%)	19 (2.1%)	58 (2.5%)
B.1.427/B.1.429 (Epsilon)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.525 (Eta)	3 (0.7%)	4 (1.1%)	4 (0.6%)	14 (1.6%)	25 (1.1%)
B.1.526 (Iota)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.0%)
B.1.526.1	0 (0.0%)	1 (0.3%)	3 (0.5%)	1 (0.1%)	5 (0.2%)
B.1.526.2	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
B.1.526.3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.616	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.617.1 (Kappa)	1 (0.2%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	2 (0.1%)
B.1.617.3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
P.2 (Zeta)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
P.3 (Theta)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-VOC/VOI	12 (2.8%)	19 (5.2%)	14 (2.2%)	20 (2.2%)	65 (2.8%)
Total sequenced	**436 (100%)**	**366 (100%)**	**639 (100%)**	**901 (100%)**	**2,342 (100%)**

Note: Results may not be representative of Ontario overall. PHO began sequencing 10% of eligible samples on May 2 and 50% on May 30. Other VOC PCR testing laboratories were asked to submit 10% of eligible samples to the Ontario COVID-19 Genomics Network (OCGN) on May 26 and 50% on June 2. Results are included for four (of five) OCGN laboratories. Week was assigned based on earliest date available for the sample. Results for recent weeks are incomplete as not all sequencing and bioinformatics analysis were complete at the time of data extraction and will be included in subsequent reports.
Data source: PHO, The Hospital for Sick Children, Kingston Health Sciences Centre, Shared Hospital Laboratory

Table 2. Percentage of B.1.617.2 (Delta) samples identified (number identified/total sequenced) by public health unit (PHU), region, and week, representative surveillance, Ontario, May 9, 2021 to June 5, 2021

Public Health Unit	Week 19 (May 9-15)	Week 20 (May 16-22)	Week 21 (May 23-29)	Week 22 (May 30-June 5)	Total (May 9- June 5)
Northwestern Health Unit	0.0% (0/2)	0.0% (0/1)	0.0% (0/0)	0.0% (0/0)	0.0% (0/3)
Thunder Bay District Health Unit	0.0% (0/3)	0.0% (0/0)	0.0% (0/12)	0.0% (0/4)	0.0% (0/19)
TOTAL NORTH WEST	**0.0% (0/5)**	**0.0% (0/1)**	**0.0% (0/12)**	**0.0% (0/4)**	**0.0% (0/22)**
Algoma Public Health	50.0% (1/2)	0.0% (0/5)	0.0% (0/0)	0.0% (0/1)	12.5% (1/8)
North Bay Parry Sound District Health Unit	0.0% (0/3)	0.0% (0/0)	0.0% (0/1)	33.3% (1/3)	14.3% (1/7)
Porcupine Health Unit	0.0% (0/3)	12.5% (2/16)	7.1% (2/28)	29.4% (15/51)	19.4% (19/98)
Public Health Sudbury & Districts	0.0% (0/0)	0.0% (0/0)	33.3% (1/3)	0.0% (0/1)	25.0% (1/4)
Timiskaming Health Unit	0.0% (0/0)	0.0% (0/0)	0.0% (0/0)	0.0% (0/0)	0.0% (0/0)
TOTAL NORTH EAST	**12.5% (1/8)**	**9.5% (2/21)**	**9.4% (3/32)**	**28.6% (16/56)**	**18.8% (22/117)**
Ottawa Public Health	25.0% (1/4)	0.0% (0/3)	0.0% (0/27)	0.0% (0/13)	2.1% (1/47)
Eastern Ontario Health Unit	0.0% (0/3)	0.0% (0/1)	0.0% (0/2)	0.0% (0/0)	0.0% (0/6)
Hastings Prince Edward Public Health	100.0% (1/1)	0.0% (0/2)	0.0% (0/0)	0.0% (0/0)	33.3% (1/3)
Kingston, Frontenac and Lennox & Addington Public Health	0.0% (0/6)	0.0% (0/3)	0.0% (0/1)	0.0% (0/5)	0.0% (0/15)
Leeds, Grenville & Lanark District Health Unit	0.0% (0/0)	0.0% (0/0)	0.0% (0/0)	0.0% (0/0)	0.0% (0/0)
Renfrew County and District Health Unit	0.0% (0/0)	100.0% (1/1)	0.0% (0/1)	0.0% (0/0)	50.0% (1/2)
TOTAL EASTERN	**14.3% (2/14)**	**10.0% (1/10)**	**0.0% (0/31)**	**0.0% (0/18)**	**4.1% (3/73)**
Durham Region Health Department	0.0% (0/4)	0.0% (0/6)	0.0% (0/22)	12.0% (6/50)	7.3% (6/82)
Haliburton, Kawartha, Pine Ridge District Health Unit	0.0% (0/5)	0.0% (0/10)	0.0% (0/9)	60.0% (3/5)	10.3% (3/29)
Peel Public Health	13.9% (28/201)	21.2% (33/156)	19.0% (33/174)	38.2% (47/123)	21.6% (141/654)
Peterborough Public Health	0.0% (0/4)	0.0% (0/5)	0.0% (0/4)	50.0% (3/6)	15.8% (3/19)
Simcoe Muskoka District Health Unit	0.0% (0/1)	0.0% (0/1)	20.0% (4/20)	5.9% (2/34)	10.7% (6/56)
York Region Public Health	0.0% (0/6)	0.0% (0/6)	3.8% (1/26)	20.7% (12/58)	13.5% (13/96)
TOTAL CENTRAL EAST	**12.7% (28/221)**	**17.9% (33/184)**	**14.9% (38/255)**	**26.4% (73/276)**	**18.4% (172/936)**
Toronto Public Health	5.1% (5/98)	17.8% (13/73)	15.6% (27/173)	21.9% (78/356)	17.6% (123/700)
TOTAL TORONTO	**5.1% (5/98)**	**17.8% (13/73)**	**15.6% (27/173)**	**21.9% (78/356)**	**17.6% (123/700)**
Chatham-Kent Public Health	0.0% (0/1)	0.0% (0/0)	0.0% (0/0)	0.0% (0/3)	0.0% (0/4)
Grey Bruce Health Unit	0.0% (0/1)	0.0% (0/1)	0.0% (0/0)	100.0% (1/1)	33.3% (1/3)
Huron Perth Public Health	0.0% (0/0)	75.0% (3/4)	33.3% (1/3)	0.0% (0/2)	44.4% (4/9)

Public Health Unit	Week 19 (May 9-15)	Week 20 (May 16-22)	Week 21 (May 23-29)	Week 22 (May 30-June 5)	Total (May 9- June 5)
Lambton Public Health	0.0% (0/0)	0.0% (0/0)	0.0% (0/1)	0.0% (0/3)	0.0% (0/4)
Middlesex-London Health Unit	0.0% (0/4)	0.0% (0/0)	7.7% (1/13)	4.0% (1/25)	4.8% (2/42)
Southwestern Public Health	100.0% (1/1)	0.0% (0/0)	0.0% (0/3)	0.0% (0/4)	12.5% (1/8)
Windsor-Essex County Health Unit	0.0% (0/17)	0.0% (0/11)	0.0% (0/24)	0.0% (0/22)	0.0% (0/74)
TOTAL SOUTH WEST	**4.2% (1/24)**	**18.8% (3/16)**	**4.5% (2/44)**	**3.3% (2/60)**	**5.6% (8/144)**
Brant County Health Unit	0.0.0% (0/0)	0.0% (0/2)	0.0% (0/6)	0.0% (0/19)	0.0% (0/27)
City of Hamilton Public Health Services	0.0% (0/4)	0.0% (0/2)	100.0% (2/2)	50.0% (1/2)	30.0% (3/10)
Haldimand-Norfolk Health Unit	33.3% (1/3)	0.0% (0/2)	50.0% (2/4)	25.0% (1/4)	30.8% (4/13)
Halton Region Public Health	12.5% (1/8)	33.3% (2/6)	20.0% (3/15)	26.7% (8/30)	23.7% (14/59)
Niagara Region Public Health	0.0% (0/2)	0.0% (0/1)	0.0% (0/2)	0.0% (0/8)	0.0% (0/13)
Region of Waterloo Public Health and Emergency Services	10.8% (4/37)	12.9% (4/31)	26.7% (12/45)	34.9% (15/43)	22.4% (35/156)
Wellington-Dufferin-Guelph Public Health	33.3% (4/12)	35.3% (6/17)	6.7% (1/15)	23.8% (5/21)	24.6% (16/65)
TOTAL CENTRAL WEST	**15.2% (10/66)**	**19.7% (12/61)**	**22.5% (20/89)**	**23.6% (30/127)**	**21.0% (72/343)**
UNKNOWN	0.0% (0/0)	0.0% (0/0)	0.0% (0/3)	25.0% (1/4)	14.3% (1/7)
TOTAL ONTARIO	**10.8% (47/436)**	**17.5% (64/366)**	**14.1% (90/639)**	**22.2% (200/901)**	**17.1% (401/2,342)**

Note: Results may not be representative of public health units overall. PHO began sequencing 10% of eligible samples on May 2 and 50% on May 30. Other VOC PCR testing laboratories were asked to submit 10% of eligible samples to the Ontario COVID-19 Genomics Network (OCGN) on May 26 and 50% on June 2. Results are included for four (of five) OCGN laboratories. Week was assigned based on earliest date available for the sample. Results for recent weeks are incomplete as not all sequencing and bioinformatics analysis were complete at the time of data extraction and will be included in subsequent reports. Public health unit was assigned based on patient postal code. If unavailable, ordering provider postal code was used (13.8% of samples).
Data source: PHO, The Hospital for Sick Children, Kingston Health Sciences Centre, Shared Hospital Laboratory

Table 3a. Number and percentage of samples by VOC/VOI Pango lineage and public health unit (PHU), representative surveillance, North West Region, May 9, 2021 to June 5, 2021

Pango lineage (WHO label)	Northwestern Health Unit	Thunder Bay District Health Unit	Total
Variant of concern			
B.1.1.7 (Alpha)	0 (0.0%)	15 (78.9%)	15 (68.2%)
B.1.351 (Beta)	0 (0.0%)	0 (0.0%)	0 (0.0%)
P.1 (Gamma)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.617.2 (Delta)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Variant of interest			
A.23.1	1 (33.3%)	0 (0.0%)	1 (4.5%)
B.1.1.318	0 (0.0%)	4 (21.1%)	4 (18.2%)
B.1.427/B.1.429 (Epsilon)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.525 (Eta)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.526 (Iota)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.526.1	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.526.2	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.526.3	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.616	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.617.1 (Kappa)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.617.3	0 (0.0%)	0 (0.0%)	0 (0.0%)
P.2 (Zeta)	0 (0.0%)	0 (0.0%)	0 (0.0%)
P.3 (Theta)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-VOC/VOI	2 (66.7%)	0 (0.0%)	2 (9.1%)
Total sequenced	**3 (100%)**	**19 (100%)**	**22 (100%)**

Note: Results may not be representative of public health units overall. PHO began sequencing 10% of eligible samples on May 2 and 50% on May 30. Other VOC PCR testing laboratories were asked to submit 10% of eligible samples to the Ontario COVID-19 Genomics Network (OCGN) on May 26 and 50% on June 2. Results are included for four (of five) OCGN laboratories. Sample date is the earliest date available for the sample. Results for recent weeks are incomplete as not all sequencing and bioinformatics analysis were complete at the time of data extraction and will be included in subsequent reports. Public health unit was assigned based on patient postal code. If unavailable, ordering provider postal code was used.
Data source: PHO, The Hospital for Sick Children, Kingston Health Sciences Centre, Shared Hospital Laboratory

Table 3b. Number and percentage of samples by VOC/VOI Pango lineage and public health unit (PHU), representative surveillance, North East Region, May 9, 2021 to June 5, 2021

Pango lineage (WHO label)	Algoma Public Health	North Bay Parry Sound District Health Unit	Porcupine Health Unit	Public Health Sudbury & Districts	Timiskaming Health Unit	Total
Variant of concern						
B.1.1.7 (Alpha)	4 (50%)	6 (85.7%)	79 (80.6%)	3 (75.0%)	0 (0.0%)	92 (78.6%)
B.1.351 (Beta)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
P.1 (Gamma)	2 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.7%)
B.1.617.2 (Delta)	1 (12.5%)	1 (14.3%)	19 (19.4%)	1 (25.0%)	0 (0.0%)	22 (18.8%)
Variant of interest						
A.23.1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.1.318	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.427/B.1.429 (Epsilon)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.525 (Eta)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.526 (Iota)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.526.1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.526.2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.526.3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.616	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.617.1 (Kappa)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.617.3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
P.2 (Zeta)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
P.3 (Theta)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-VOC/VOI	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Total sequenced	**8 (100%)**	**7 (100%)**	**98 (100%)**	**4 (100%)**	**0 (0.0%)**	**117 (100%)**

Note: Results may not be representative of public health units overall. PHO began sequencing 10% of eligible samples on May 2 and 50% on May 30. Other VOC PCR testing laboratories were asked to submit 10% of eligible samples to the Ontario COVID-19 Genomics Network (OCGN) on May 26 and 50% on June 2. Results are included for four (of five) OCGN laboratories. Sample date is the earliest date available for the sample. Results for recent weeks are incomplete as not all sequencing and bioinformatics analysis were complete at the time of data extraction and will be included in subsequent reports. Public health unit was assigned based on patient postal code. If unavailable, ordering provider postal code was used.

Data source: PHO, The Hospital for Sick Children, Kingston Health Sciences Centre, Shared Hospital Laboratory

Table 3c. Number and percentage of samples by VOC/VOI Pango lineage and public health unit (PHU), representative surveillance, Eastern Region, May 9, 2021 to June 5, 2021

Pango lineage (WHO label)	Eastern Ontario Health Unit	Hastings Prince Edward Public Health	Kingston, Frontenac and Lennox & Addington Public Health	Leeds, Grenville & Lanark District Health Unit	Ottawa Public Health	Renfrew County and District Health Unit	Total
Variant of concern							
B.1.1.7 (Alpha)	6 (100%)	2 (66.7%)	14 (93.3%)	0 (0.0%)	42 (89.4%)	1 (50.0%)	65 (89.0%)
B.1.351 (Beta)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
P.1 (Gamma)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.1%)	0 (0.0%)	1 (1.4%)
B.1.617.2 (Delta)	0 (0.0%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	1 (2.1%)	1 (50.0%)	3 (4.1%)
Variant of interest							
A.23.1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.1.318	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
B.1.427/B.1.429 (Epsilon)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.525 (Eta)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.526 (Iota)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.526.1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.526.2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.526.3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.616	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.617.1 (Kappa)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.617.3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
P.2 (Zeta)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
P.3 (Theta)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-VOC/VOI	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (6.4%)	0 (0.0%)	3 (4.1%)
Total sequenced	**6 (100%)**	**3 (100%)**	**15 (100%)**	**0 (0.0%)**	**47 (100%)**	**2 (100%)**	**73 (100%)**

Note: Results may not be representative of public health units overall. PHO began sequencing 10% of eligible samples on May 2 and 50% on May 30. Other VOC PCR testing laboratories were asked to submit 10% of eligible samples to the Ontario COVID-19 Genomics Network (OCGN) on May 26 and 50% on June 2. Results are included for four (of five) OCGN laboratories. Sample date is the earliest date available for the sample. Results for recent weeks are incomplete as not all sequencing and bioinformatics analysis were complete at the time of data extraction and will be included in subsequent reports. Public health unit was assigned based on patient postal code. If unavailable, ordering provider postal code was used.
Data source: PHO, The Hospital for Sick Children, Kingston Health Sciences Centre, Shared Hospital Laboratory

Table 3d. Number and percentage of samples by VOC/VOI Pango lineage and public health unit (PHU), representative surveillance, Central East Region, May 9, 2021 to June 5, 2021

Pango lineage (WHO label)	Durham Region Health Department	Haliburton, Kawartha, Pine Ridge District Health Unit	Peel Public Health	Peterborough Public Health	Simcoe Muskoka District Health Unit	York Region Public Health	Total
Variant of concern							
B.1.1.7 (Alpha)	54 (65.9%)	14 (48.3%)	440 (67.3%)	15 (78.9%)	46 (82.1%)	65 (67.7%)	634 (67.7%)
B.1.351 (Beta)	0 (0.0%)	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	3 (0.3%)
P.1 (Gamma)	2 (2.4%)	0 (0.0%)	27 (4.1%)	0 (0.0%)	3 (5.4%)	12 (12.5%)	44 (4.7%)
B.1.617.2 (Delta)	6 (7.3%)	3 (10.3%)	141 (21.6%)	3 (15.8%)	6 (10.7%)	13 (13.5%)	172 (18.4%)
Variant of interest							
A.23.1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.1.318	4 (4.9%)	0 (0.0%)	17 (2.6%)	0 (0.0%)	1 (1.8%)	5 (5.2%)	27 (2.9%)
B.1.427/B.1.429 (Epsilon)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.525 (Eta)	16 (19.5%)	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (1.9%)
B.1.526 (Iota)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.526.1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.526.2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.526.3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.616	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.617.1 (Kappa)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
B.1.617.3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
P.2 (Zeta)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
P.3 (Theta)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-VOC/VOI	0 (0.0%)	12 (41.4%)	24 (3.7%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	37 (4.0%)
Total sequenced	**82 (100%)**	**29 (100%)**	**654 (100%)**	**19 (100%)**	**56 (100%)**	**96 (100%)**	**936 (100%)**

Note: Results may not be representative of public health units overall. PHO began sequencing 10% of eligible samples on May 2 and 50% on May 30. Other VOC PCR testing laboratories were asked to submit 10% of eligible samples to the Ontario COVID-19 Genomics Network (OCGN) on May 26 and 50% on June 2. Results are included for four (of five) OCGN laboratories. Sample date is the earliest date available for the sample. Results for recent weeks are incomplete as not all sequencing and bioinformatics analysis were complete at the time of data extraction and will be included in subsequent reports. Public health unit was assigned based on patient postal code. If unavailable, ordering provider postal code was used.

Data source: PHO, The Hospital for Sick Children, Kingston Health Sciences Centre, Shared Hospital Laboratory

Table 3e. Number and percentage of samples by VOC/VOI Pango lineage and public health unit (PHU), representative surveillance, Toronto Region, May 9, 2021 to June 5, 2021

Pango lineage (WHO label)	Toronto Public Health	Total
Variant of concern		
B.1.1.7 (Alpha)	503 (71.9%)	503 (71.9%)
B.1.351 (Beta)	4 (0.6%)	4 (0.6%)
P.1 (Gamma)	29 (4.1%)	29 (4.1%)
B.1.617.2 (Delta)	123 (17.6%)	123 (17.6%)
Variant of interest		
A.23.1	0 (0.0%)	0 (0.0%)
B.1.1.318	17 (2.4%)	17 (2.4%)
B.1.427/B.1.429 (Epsilon)	0 (0.0%)	0 (0.0%)
B.1.525 (Eta)	7 (1.0%)	7 (1.0%)
B.1.526 (Iota)	0 (0.0%)	0 (0.0%)
B.1.526.1	0 (0.0%)	0 (0.0%)
B.1.526.2	1 (0.1%)	1 (0.1%)
B.1.526.3	0 (0.0%)	0 (0.0%)
B.1.616	0 (0.0%)	0 (0.0%)
B.1.617.1 (Kappa)	0 (0.0%)	0 (0.0%)
B.1.617.3	0 (0.0%)	0 (0.0%)
P.2 (Zeta)	0 (0.0%)	0 (0.0%)
P.3 (Theta)	0 (0.0%)	0 (0.0%)
Non-VOC/VOI	16 (2.3%)	16 (2.3%)
Total sequenced	**700 (100%)**	**700 (100%)**

Note: Results may not be representative of public health units overall. PHO began sequencing 10% of eligible samples on May 2 and 50% on May 30. Other VOC PCR testing laboratories were asked to submit 10% of eligible samples to the Ontario COVID-19 Genomics Network (OCGN) on May 26 and 50% on June 2. Results are included for four (of five) OCGN laboratories. Sample date is the earliest date available for the sample. Results for recent weeks are incomplete as not all sequencing and bioinformatics analysis were complete at the time of data extraction and will be included in subsequent reports. Public health unit was assigned based on patient postal code. If unavailable, ordering provider postal code was used.
Data source: PHO, The Hospital for Sick Children, Kingston Health Sciences Centre, Shared Hospital Laboratory

Table 3f. Number and percentage of samples by VOC/VOI Pango lineage and public health unit (PHU), representative surveillance, South West Region, May 9, 2021 to June 5, 2021

Pango lineage (WHO label)	Chatham-Kent Public Health	Grey Bruce Health Unit	Huron Perth Public Health	Lambton Public Health	Middlesex-London Health Unit	Southwestern Public Health	Windsor-Essex County Health Unit	Total
Variant of concern								
B.1.1.7 (Alpha)	4 (100%)	1 (33.3%)	1 (11.1%)	4 (100%)	37 (88.1%)	6 (75.0%)	68 (91.9%)	121 (84.0%)
B.1.351 (Beta)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (0.7%)
P.1 (Gamma)	0 (0.0%)	0 (0.0%)	4 (44.4%)	0 (0.0%)	2 (4.8%)	0 (0.0%)	0 (0.0%)	6 (4.2%)
B.1.617.2 (Delta)	0 (0.0%)	1 (33.3%)	4 (44.4%)	0 (0.0%)	2 (4.8%)	1 (12.5%)	0 (0.0%)	8 (5.6%)
Variant of interest								
A.23.1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.1.318	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.427/B.1.429 (Epsilon)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.525 (Eta)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.526 (Iota)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
B.1.526.1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (6.8%)	5 (3.5%)
B.1.526.2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.526.3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.616	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.617.1 (Kappa)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.617.3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
P.2 (Zeta)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
P.3 (Theta)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-VOC/VOI	0 (0.0%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	2 (1.4%)
Total sequenced	**4 (100%)**	**3 (100%)**	**9 (100%)**	**4 (100%)**	**42 (100%)**	**8 (100%)**	**74 (100%)**	**144 (100%)**

Note: Results may not be representative of public health units overall. PHO began sequencing 10% of eligible samples on May 2 and 50% on May 30. Other VOC PCR testing laboratories were asked to submit 10% of eligible samples to the Ontario COVID-19 Genomics Network (OCGN) on May 26 and 50% on June 2. Results are included for four (of five) OCGN laboratories. Sample date is the earliest date available for the sample. Results for recent weeks are incomplete as not all sequencing and bioinformatics analysis were complete at the time of data extraction and will be included in subsequent reports. Public health unit was assigned based on patient postal code. If unavailable, ordering provider postal code was used.
Data source: PHO, The Hospital for Sick Children, Kingston Health Sciences Centre, Shared Hospital Laboratory

Table 3g. Number and percentage of samples by VOC/VOI Pango lineage and public health unit (PHU), representative surveillance, Central West Region, May 9, 2021 to June 5, 2021

Pango lineage (WHO label)	Brant County Health Unit	City of Hamilton Public Health Services	Haldimand -Norfolk Health Unit	Halton Region Public Health	Niagara Region Public Health	Region of Waterloo Public Health and Emergency Services	Wellington-Dufferin-Guelph Public Health	Total
Variant of concern								
B.1.1.7 (Alpha)	20 (74.1%)	6 (60.0%)	8 (61.5%)	39 (66.1%)	11 (84.6%)	110 (70.5%)	47 (72.3%)	241 (70.3%)
B.1.351 (Beta)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (3.2%)	0 (0.0%)	5 (1.5%)
P.1 (Gamma)	5 (18.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	5 (3.2%)	0 (0.0%)	11 (3.2%)
B.1.617.2 (Delta)	0 (0.0%)	3 (30.0%)	4 (30.8%)	14 (23.7%)	0 (0.0%)	35 (22.4%)	16 (24.6%)	72 (21.0%)
Variant of interest								
A.23.1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.1.318	2 (7.4%)	1 (10.0%)	1 (7.7%)	5 (8.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (2.6%)
B.1.427/B.1.429 (Epsilon)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.525 (Eta)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.526 (Iota)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.526.1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.526.2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.526.3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.616	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B.1.617.1 (Kappa)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.3%)
B.1.617.3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
P.2 (Zeta)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
P.3 (Theta)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-VOC/VOI	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	1 (7.7%)	0 (0.0%)	2 (3.1%)	4 (1.2%)
Total sequenced	**27 (100%)**	**10 (100%)**	**13 (100%)**	**59 (100%)**	**13 (100%)**	**156 (100%)**	**65 (100%)**	**343 (100%)**

Note: Results may not be representative of public health units overall. PHO began sequencing 10% of eligible samples on May 2 and 50% on May 30. Other VOC PCR testing laboratories were asked to submit 10% of eligible samples to the Ontario COVID-19 Genomics Network (OCGN) on May 26 and 50% on June 2. Results are included for four (of five) OCGN laboratories. Sample date is the earliest date available for the sample. Results for recent weeks are incomplete as not all sequencing and bioinformatics analysis were complete at the time of data extraction and will be included in subsequent reports. Public health unit was assigned based on patient postal code. If unavailable, ordering provider postal code was used.
Data source: PHO, The Hospital for Sick Children, Kingston Health Sciences Centre, Shared Hospital Laboratory

Cumulative Whole Genome Sequencing Results

Table 4. Number of samples by VOC/VOI Pango lineage, cumulative counts, Ontario, January 1, 2021 to June 5, 2021

Pango lineage (WHO label)	January 1 - May 8	May 9 - June 5	Total
Variant of concern (VOC)			
B.1.1.7 (Alpha)	6,767	2,107	8,874
B.1.351 (Beta)	1,093	39	1,132
P.1 (Gamma)	3,324	365	3,689
B.1.617.2 (Delta)	269	684	953
Variant of interest (VOI)			
A.23.1	83	1	84
B.1.1.318	1,187	326	1,513
B.1.427/B.1.429 (Epsilon)	16	0	16
B.1.525 (Eta)	306	50	356
B.1.526 (Iota)	95	3	98
B.1.526.1	2	5	7
B.1.526.2	4	1	5
B.1.526.3	7	0	7
B.1.616	0	0	0
B.1.617.1 (Kappa)	72	5	77
B.1.617.3	2	0	2
P.2 (Zeta)	46	0	46
P.3 (Theta)	1	0	1
Non-VOC/VOI	3,390	126	3,516
Total sequenced	**16,664**	**3,712**	**20,376**

Note: Includes results from PHO since January 1, 2021, The Hospital for Sick Children since April 21, 2021, Kingston Health Sciences Centre since January 1, 2021, Shared Hospital Laboratory since March 26, 2021, and Hamilton Regional Laboratory Medicine Program since April 11, 2021. Past testing algorithms have led to preferential sequencing of samples with N501Y and/or E484K mutations detected by PCR, which has biased the results toward lineages with these mutations. Results should be interpreted with caution as frequencies do not reflect prevalence. Sample date is the earliest date available for the sample.
Data source: PHO, The Hospital for Sick Children, Kingston Health Sciences Centre, Shared Hospital Laboratory, Hamilton Regional Laboratory Medicine Program

Technical Notes

Data Sources

- Public Health Ontario (PHO)
    - Data were extracted from the PHO Laboratory Information Management System on June 17 at approximately 5:00 a.m.
    - Data were extracted from the PHO SARS-CoV-2 Whole Genome Sequencing Database on June 17 at approximately 9:00 a.m.
- The Hospital for Sick Children (HSC)
    - Data were received by PHO on June 16, 2021 at approximately 11:45 a.m.
- Kingston Health Sciences Centre (KHSC)
    - Data were received by PHO on June 16, 2021 at approximately 4:00 p.m.
- Shared Hospital Laboratory (SHL)
    - Data were received by PHO on June 16, 2021 at approximately 5:45 p.m.
- Hamilton Regional Laboratory Medicine Program (HRLMP)
    - Data were received by PHO on June 17, 2021 at approximately 6:45 a.m.

Ontario SARS-CoV-2 Whole Genome Sequencing Strategy

- At the beginning of 2021, Ontario's whole genome sequencing strategy was to sequence samples with specific mutations identified from VOC PCR testing to confirm they were variants of concern. From February 3, 2021 this included sequencing samples with the N501Y mutation detected (initially associated with the B.1.1.7 [Alpha] lineage) and from March 22, 2021, samples with the E484K mutation detected (initially associated with the P.1 [Gamma] and B.1.351 [Beta] lineages).
- Ontario's strategy has recently shifted to representative surveillance with VOC PCR testing laboratories being asked to send 10% of eligible samples (Ct ≤ 30 and sufficient volume remaining) to Ontario COVID-19 Genomics Network (OCGN) sequencing laboratories. PHO began sequencing a 10% systematic sample of eligible samples on May 2; 50% on May 30; and 100% on June 14. Other VOC PCR testing laboratories were asked to begin submitting a 10% systematic or random sample of eligible samples to OCGN laboratories on May 26; 50% on June 2; and 100% on June 14.

Data Caveats and Methods

- Whole genome sequencing sample logistics are complex and require samples to be transferred across a large network of laboratories. Samples are initially sent to one of 73 diagnostic testing laboratories. If the diagnostic PCR cycle threshold is ≤ 35 and there is sufficient volume remaining, samples are submitted for testing at one of 11 VOC PCR testing laboratories. If the VOC PCR cycle threshold is ≤ 30 and there is sufficient volume remaining, VOC PCR testing laboratories have been asked to submit a proportion of their eligible samples to one of five OCGN laboratories for sequencing according to the surveillance strategy.

- Results included in this report are sample-based and not person-based. As such, it is possible that more than one sample was sequenced per individual.

- The dates associated with samples submitted by network laboratories vary due to sample logistics and different laboratory information systems. Dates associated with WGS samples were assigned based on a hierarchy: sample collection date > SARS-CoV-2 diagnostic received date > SARS-CoV-2 diagnostic reported date > VOC PCR received date > VOC PCR reported date > WGS received date > WGS reported date. Weeks were created to align with surveillance weeks used by the Public Health Agency of Canada for influenza reporting.

- Lineage nomenclature is dynamic. Pango lineage naming and assignment may change as more samples are sequenced and analyzed globally. Similarly, VOC and VOI classifications may change.

Data Caveats and Methods: Representative Surveillance

- Results may not be representative of Ontario overall. Samples selected include a proportion of eligible samples received by OCGN laboratories according to the whole genome sequencing strategy. Individual VOC PCR laboratories may have implemented the strategy and/or increased the proportion of samples selected from 10% to 50% on different dates.

- PHO is unable to confirm whether VOC PCR testing laboratories have submitted eligible samples.

- Results for recent weeks are incomplete as not all sequencing and bioinformatics analysis were complete at the time of data extraction.

- Public health unit was assigned based on patient postal code. If unavailable, ordering provider postal code was used (13.8% of samples).

Data Caveats and Methods: Whole Genome Sequencing Results

- The data included do not reflect all whole genome sequencing conducted in Ontario. Data from the OCGN laboratories cover different time periods: PHO since January 1, 2021, HSC since April 21, 2021, KHSC since January 1, 2021, SHL since March 26, 2021, and HRLMP since April 11, 2021.

- Past testing algorithms have led to preferential sequencing of samples with N501Y and/or E484K mutations detected by VOC PCR. This has created a sampling bias reflected in the distribution of lineage results. Data submitted to PHO from other laboratories in the OCGN have not been independently verified.

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Ontario

This is "**Exhibit J**"
to the Affidavit of Matthew Hodge,
affirmed this 2nd day of July, 2021

A Commissioner, etc.

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SYNTHESIS

20/05/21

COVID-19 Transmission Through Large Respiratory Droplets and Aerosols… What We Know So Far

Introduction

Public Health Ontario (PHO) is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19). "What We Know So Far" documents provide a rapid review of the evidence on a specific aspect or emerging issue related to COVID-19. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is transmitted in different ways; however, this document will focus on transmission by respiratory droplets and aerosols.

Key Findings

- The historical dichotomy of droplet versus airborne transmission, while useful in implementing infection prevention and control (IPAC) strategies, does not accurately recognize the complexity of viral respiratory transmission, including for SARS-CoV-2.
- SARS-CoV-2 is transmitted most frequently and easily at short range through exposure to respiratory particles that range in size from large droplets which fall quickly to the ground to smaller droplets, known as aerosols, which can remain suspended in the air.
- There is evidence to suggest long-range transmission can occur under the right set of favourable conditions, implicating aerosols in transmission.
- The relative role of large respiratory droplets versus smaller droplet particles in short-range transmission is challenging to quantify. Their contributions to a specific case-contact interaction vary based on contextual factors including source/receptor characteristics (e.g., forceful expulsions such as singing, coughing, sneezing; viral load) and pathway characteristics (e.g., duration of exposure; environmental conditions such as ventilation, temperature, humidity, ultraviolet light; source control; and use of personal protective equipment).
- Translation of this summary into control measures needs to take into consideration other information, such as evidence around the effectiveness of control measures to date. Several control measures applied together in a layered approach are likely to be effective irrespective of the relative contribution of droplets or aerosols, including achieving high vaccination coverage and avoiding the "3 C's" (closed spaces, crowded places and close contact).

Background

The diameter of microorganism-containing respiratory particles relevant for respiratory infections ranges from approximately 0.01 micrometres (µm) to greater than 100 µm.[1] Particles larger than about 100 µm play a role in respiratory infection transmission by impacting on mucosal surfaces, such as the nostrils, mouth and eyes. Particles smaller than 100 µm can be inhaled or impact on mucosal surfaces. Some particles are small enough that they can be suspended in the air for various periods of time (known as aerosols).[2] Environmental factors such as local air currents and humidity affect these particles, e.g., how they move, evaporate, and how long they remain in air.[3] Therefore, the mode of transmission is influenced by three key elements: the source, the pathway, and the receptor. Depending on the unique characteristics of each element, certain modes may be more likely than others.

Traditionally, respiratory particles >5 or 10 µm have been termed droplets and were thought to impact directly on mucous membranes, while smaller particles were thought to be inhaled. This dichotomy of transmission routes has been applied to infection prevention controls within health care settings worldwide. However, these transmission routes are not mutually exclusive as droplets well over 5 µm are capable of remaining suspended in air for some time and can be inhaled. At short range within about 2 metres (m), infection can occur from inhaled aerosols as well as droplets landing on mucous membranes (short-range transmission). Herein, we refer to what was traditionally called airborne transmission via inhalation of aerosols that have remained suspended over long distances and periods of time[4,5] as long-range transmission.

We describe transmission through epidemiological studies, experimental or simulation of transmission studies, and statistical or mathematical modelling. Modelling shows what is possible, experimental studies what is plausible, and epidemiologic studies observe what is actually occurring, and each type of evidence is subject to limitations. However, exact routes of SARS-CoV-2 transmission in real-life scenarios can only be inferred based on the available data.

The purpose of this rapid review is to outline the evidence for droplets and aerosols in SARS-CoV-2 transmission. We have summarized the evidence as either short-range transmission from large respiratory droplets and small droplets or aerosols, or long-range transmission from aerosols.

Methods and Scope

In considering feasibility, scope and timelines, we undertook a rapid review to update our summary of SARS-CoV-2 transmission from large respiratory droplets and aerosols. A rapid review is a knowledge synthesis where certain steps of the systematic review process are omitted in order to be timely (e.g., duplicate screening).[6]

We conducted literature searches in MEDLINE (April 22, 2021) and National Institutes of Health COVID-19 Portfolio (Preprints) (April 27, 2021), search strategies are available upon request. We searched PubMed and Google Scholar on April 28, 2021 for additional articles of interest.

English-language peer-reviewed and non-peer-reviewed records that described large respiratory droplet and aerosol routes of transmission of COVID-19 were included. We restricted the search to articles published after January 1, 2020. This rapid review concentrated on evidence from systematic reviews and meta-analyses, supplemented by primary literature where appropriate. We reviewed citations from included articles to identify additional research.

Prior to publishing, PHO subject-matter experts review all What We Know So Far documents. As the scientific evidence is expanding rapidly, the information provided in this document is only current as of the date of respective literature searches.

Out-of-scope for this document was a review of IPAC practices appropriate for individual transmission scenarios and settings. Application of a hierarchy of control measures for non-health care settings is briefly discussed in the conclusions. For additional information related to IPAC in health care settings, please see PHO's technical briefing *IPAC Recommendations for Use of Personal Protective Equipment for Care of Individuals with Suspect or Confirmed COVID-19* and *Interim Guidance for Infection Prevention and Control of SARS-CoV-2 Variants of Concern for Health Care Settings*.[7,8] Please note that the *Ministry of Health's Directive 1* is the provincial baseline standard for provision of personal protective equipment for hospitals, long-term care homes and retirement homes and that the *Ministry of Health's Directive 5* provides agency to health care workers to make professional decisions regarding the appropriate personal protective equipment when dealing with suspected, probable or confirmed COVID-19 patients or residents.[9,10] Evidence for contact/fomite transmission, and virus and host (source/receptor) factors were not reviewed in this document, but are acknowledged as contributors to short- and long-range transmission. Other routes of transmission are reviewed in PHO's synthesis *COVID-19 Routes of Transmission – What We Know So Far*.[11]

Short-range Transmission

Main Findings

SARS-CoV-2 is transmitted most frequently and easily at short range. Short-range transmission generally occurs within 2 m of an infectious individual (e.g., during a conversation with inadequate distancing, no barriers, no personal protective equipment). Theoretically, short-range transmission may occur due to droplets or aerosols, but the relative contribution of either is specific to each case-contact interaction which varies based on contextual factors including source/receptor and pathway characteristics.

Environmental Factors Affecting Short-range Droplets and Aerosols

In addition to virus and host factors, environmental factors are associated with short-range viral transmission. The distance travelled by large respiratory droplets is generally <2 m, although it can reach up to 8 m in certain circumstances. In a study by Guo et al. (2020), SARS-CoV-2 virus was detected on the floor up to 4 m away from a patient.[12] In a systematic review of studies assessing the horizontal distance travelled by respiratory droplets, Bahl et al. (2020) reported that droplets could travel up to 8 m.[13] In a mathematical model, Chen et al. (2021) reported that respiratory droplets >100 µm in diameter are only important in transmission at a distance of less than 0.2 m when the infector is talking, or within 0.5 m when the infector is coughing.[14] Modelling by Wang et al. (2021) (preprint) suggested droplets >100 µm would most often not travel past 1.75 m (most droplets >100 µm diameter settle before 1.25 m).[15]

In a review of respiratory virus transmission, Leung (2021) reported that environmental factors affecting transmission include temperature, relative humidity, ventilation, airflow and ultraviolet (UV) light.[16] Ventilation, airflow and forceful expulsion (sneezing or coughing) can make respiratory particles travel further than 2 m through momentum.[14,17] High temperature and low humidity contributes to shrinking of droplets such that they may remain suspended in air for longer periods of time.[18]

Even at short-range distances, ventilation may affect transmission. De Oliveira et al. (2021) modelled infection risk in ventilated (10 air changes per hour [ACH]) and unventilated spaces without respiratory protection during a 1-hour exposure at 2-m distance.[19] The impact of decreasing concentration of virus in the air through ventilation was notable. Estimates of infection risk were reduced by at least three times based on the parameters and assumptions of their model. The authors also commented that the direction of airflow can have a significant impact – upward air streams can maintain aerosols at face height significantly increasing infectious risk.

Indoor settings are a predominant risk factor for transmission. In a systematic review of 5 studies, Bulfone et al. (2020) reported that the odds of indoor transmission were 18.7 times (95% confidence interval [CI]: 6.0–57.9) higher than outdoor settings, and less than 10% of infections occurred outdoors.[20] Very few superspreading events have been described from exclusively outdoor exposures. The explanation for this observation is likely multifactorial which includes important differences in ventilation, UV light, humidity, as well as possible differences in behaviour.

Epidemiological and Modelling Studies Describing Short-range Transmission

The following section reviews the epidemiologic and modelling evidence supporting short-range transmission of COVID-19. It reviews the reproductive number and summarizes the epidemiological and modelling studies by setting, including transportation, health care and sports.

The reproductive number (R_0) of SARS-CoV-2 is less suggestive of long-range transmission commonly occurring, as viruses where long-range transmission commonly occurs tend to have a higher R_0.[16] For example, in a systematic review by Guerra et al. (2017), the R_0 for the measles virus in the pre-vaccine era was 6.1–27.0,[21] compared to the median range of R_0 (2.7–3.3) reported for SARS-CoV-2.[22] It is important to note that R_0 is not a direct measure or indication of transmission route, as R_0 can be setting and population-specific, and be impacted by factors such human behaviours. The R_0 for SARS-CoV-2 also displays overdispersion, where the overall R_0 is lower than pathogens that commonly transmit through aerosols at long-range, but a small proportion of cases are associated with reproductive numbers in the range typical of viruses that commonly transmit through aerosols at long-range (i.e., superspreader events).[23] Such cases illustrate the potential variability in COVID-19 transmission, depending on differences in source/receptor characteristics and environment.

Short-range transmission was favoured in a retrospective cohort study of 18 short-to-medium haul flights (median flight time 115 minutes) to England from the beginning of the pandemic.[24] The attack rate was 0.2% (95% confidence interval [CI]: 0.1–0.5) for all aircraft-acquired cases, and was higher at 3.8% (95% CI: 1.3–10.6) if a subgroup analysis was performed only on contacts within a two-seat radius. It was assumed that no masks were worn given that it was early in the pandemic.

Family gatherings for meals are high-risk scenarios for transmission. Lo Menzo et al. (2021) reported transmission of lineage B.1.1.7 variant of concern to 8 of 9 family members during a dinner gathering.[25] The only uninfected family member was presumed to have immunity acquired from a previous infection (high antibody titres and polymerase chain reaction (PCR) negative result). Contact and fomite transmission cannot be excluded from this type of event.

In a case-control study of 154 patients 18 years and older in the United States (US), Fisher et al. (2020) reported that close contact with a person with COVID-19 was reported more often among cases (42.2%) than controls (14.5%) ($p<0.01$).[26]

Short-range transmission has been documented in school settings. Four student-to-student and one student-to-teacher transmission events were reported in Salt Lake County, Utah.[27] For four transmission events, unprotected, short-range exposures were noted. There was a lack of transmission to other students that were a median of 1 m away during class, but adhered to control measures implemented in the school. However, when household transmission associated with the secondary cases was evaluated, transmission was high for 3 of the 5 households of secondary patients. In these three households, 6 of 8 household members were also infected and may be related to challenges with physical distancing, masking, and shared surfaces in the household.

Using whole genome sequencing of SARS-CoV-2 clinical samples (n=50) in Dublin, Ireland, Lucey et al. (2020) investigated cases of hospital-acquired COVID-19 and reported that the majority of infections were among patients who required extensive and prolonged care by health care providers.[28] The authors concluded that the likely mode of transmission from health care workers to patients was through short-range transmission and close contact, rather than long-range transmission. Notably, the use of masks by health care providers was not universal and patients were not wearing masks either.

Three short-range health care-associated transmission events have been reported where large respiratory droplet transmission was less likely because masks were worn by either the source or the contact and in two of three events, the contact was also wearing eye protection.[29] In case 1, an asymptomatic, unmasked patient transmitted infection to two health care workers who wore medical masks and face shields, following multiple hours of exposure in a room with 6 ACH. A second case occurred where a presymptomatic masked health care worker transmitted infection to an unmasked patient in a room with 6 ACH. A third case involved a presymptomatic masked patient transmitting infection to a health care worker who was wearing a mask and goggles during a 45 minute face-to-face discussion at 1 m. Notably in the third case, the patient's mask was removed temporarily for oropharynx inspection. While each case was verified by whole genome sequencing, there was a lack of detail about the specific encounters (e.g., distance, duration, if direct contact occurred, if doffing errors occurred), and no airflow studies were conducted.

An analysis of SARS-CoV-2 infections in an outdoor rugby league, including video evaluation of close contact due to tackling inherent in the game, indicated that no cases among players in the league could be linked to close-contact during the outdoor rugby games.[30] Instead, transmissions were linked to other indoor short-range transmission events. While this study demonstrates examples where outdoor close-contact transmission did not occur, there were not enough close-contacts documented to provide evidence that close-contact transmission could not have occurred in the context of outdoor rugby.

In a modelling study, Zhang and Wang (2020) reported that the median infection risk via long-range aerosol transmission (10^{-6}–10^{-4}) was significantly lower than the risk via close contact (10^{-1}).[31] The model was based on a 1-hour exposure in a room with an area of 10–400 m^2, with one infected individual and a ventilation rate of 0.1–2.0 ACH. In a modelling study by Hu et al. (2020), the transmission risk from epidemiological data among train passengers as 0%–10.3% (95% CI: 5.3%–19.0%).[32] Travellers directly adjacent to the index patient had a much higher infection risk (relative risk [RR]: 18.0; 95% CI: 13.9–23.4), and the attack rate decreased with increasing distance.

Household and Non-Household Secondary Attack Rates

The consensus among systematic reviews is that household settings, where physical distancing, consistent source control mask-wearing, and disinfection of shared surfaces are potentially not feasible, are associated with a higher risk of infection compared to casual-contact settings (17%–27% compared

to 0%–7%). However, the secondary household attack rates are not as high as would be expected if SARS-CoV-2 easily spread through long-range transmission (e.g., >90% in measles).[16,33]

In a systematic review and meta-analysis of 54 studies and 77,758 patients, Madewell et al. (2020) reported that the household secondary attack rate was 16.6% (95% CI: 14.0–19.3).[34] In a systematic review and meta-analysis of 45 studies, Thompson et al. (2021) estimated the household secondary attack rate as 21.1% (95% CI: 17.4–24.8; 29 studies).[35] Non-household settings had lower secondary attack rates: 1) social settings with family and friends (5.9%; 95% CI: 0.3–9.8; 7 studies); 2) travel (5.0%; 95% CI: 0.3–9.8; 5 studies); 3) health care facilities (3.6%; 95% CI: 1.0–6.9; 10 studies); workplaces (1.9%; 95% CI: 0.0–3.9; 7 studies); and casual social contacts with strangers (1.2%; 95% CI: 0.3–2.1; 7 studies). Koh et al. (2020), in a meta-analysis of 43 studies, reported that the household secondary attack rate was 18.1% (95% CI: 15.7–20.6; 43 studies), much higher than the secondary attack rate in health care settings (0.7%; 95% CI: 0.4–1.0; 18 studies).[36] In a systematic review and meta-analysis of 24 studies, Lei et al. (2020) reported that the secondary attack rate in households was 27% (95% CI: 21−32); the risk of secondary infection was 10 times higher in households compared to non-household settings (odds ratio [OR]: 10.7; 95% CI: 5.7–20.2; p<0.001).[37] Tian and Huo (2020), in a meta-analysis of 18 studies, reported that the household secondary attack rate was 20% (95% CI: 15–28; 15 studies; n=3,861 patients), followed by social gatherings at 6% (95% CI: 3–10; 5 studies; n=2,154 patients) and health care settings at 1% (95% CI: 1–2; 4 studies; n=1,320 patients).[38]

Long-range Transmission

Main Findings

Transmission of SARS-CoV-2 over longer distances (generally >2 m) and time occurs through inhalation of aerosols under favourable circumstances, such as prolonged exposure in an inadequately ventilated space. Current evidence supports long-range transmission of SARS-CoV-2 occurring “opportunistically”, in that long-range transmission can occur under some circumstances, but inconsistently, and is not the predominant situation in which transmission occurs. Epidemiological and modelling studies support that long-range transmission via aerosols occurs. All of these examples include combinations of favourable source/receptor and pathway conditions such as inadequate ventilation, prolonged exposure time, high viral load, with certain activities (singing, exercising, yelling, etc.), and lack of masking for source control by the index case.

Environmental Factors Affecting Long-range Aerosols

In experimental models, researchers have demonstrated the potential for long-range transmission. In a series of experiments, simulations and modelling, Wang et al. (2021) (preprint) reported that aerosols could remain suspended for a longer period than historically predicted.[15] In general, viral copies/millilitre (ml) or concentration decreased as distance from source increased. The work showed that the evaporation time for large respiratory droplets is longer than predicted, especially at higher relative humidity (90%). In a sneeze plume, the largest respiratory droplets (>100 µm) are centrally located within the plume, with smaller respiratory droplets and aerosols at the periphery. The largest droplets contain more virus copies but are less abundant as they settle quickly to the ground, while smaller droplets carry fewer virus copies but are more abundant and remain in the air. The authors conclude that while aerosol transmission is important past 1 m from the source, aerosol transmission is likely even more important at shorter ranges.

Modelling studies have also highlighted the potential for aerosol transmission at varying distances. Xu et al. (2021) analysed the data of 197 symptomatic COVID-19 cases in the Diamond Princess cruise ship outbreak and concluded that long-range transmission did not occur between cabins based on the random distribution of symptomatic cases on all decks and the lack of spatial clusters of close contact (within cabin) infection.[39] The authors inferred that most transmission had occurred in public areas before the quarantine, possibly due to crowding and insufficient ventilation in those spaces. The authors also inferred that there was no transmission between passenger rooms during the quarantine period, and suggested that the ship's central heating, ventilation, and air conditioning (HVAC) system did not play a role in SARS-CoV-2 transmission. However, the authors noted that the lack of data on 109 of the 306 symptomatic individuals and on the 328 asymptomatic individuals may alter their estimation. In addition, their estimation did not take into consideration possible transmission between crew and passengers. Another model of the same outbreak estimated that the contribution of short-range transmission (from large droplets or aerosols) accounted for a median of 36% (mean: 35%) of transmission events, fomite (median: 21%; mean: 30%) and long-range (median: 41%; mean: 35%) contributing to the remainder.[40]

A study of aerosol particles (<5 μm diameter) by Dobramysl et al. (2021) (preprint) reported that time to infection increases approximately linearly as distance from source increases, the most important parameter for time to infection.[41] Exposure to a person breathing normally (simulating an asymptomatic individual) at a distance of 1 m led to infection after 90 minutes; however, coughing every 5 minutes led to infection in 15 minutes. Mask use and even minimal ventilation increased time to infection at a given distance. The importance of ventilation is also described in a modelling study by Jones (2020) which suggested that exposure to inhalable particles mostly (80%) occurs within close proximity to the patient.[42] In still air, aerosols will rise above head-level; however, turbulent air can change the trajectory of virus-laden aerosols, bringing aerosols closer to the head.[43-45] A modelling study by Sen (2021) found that when the ceiling-mounted elevator fan was off, about 11% of the droplets expelled by coughing fell to the ground while 89% evaporated and became smaller.[46] After travelling downward in cough-induced turbulence for approximately 6 seconds, droplets about 50 μm tended to move up and spread in the upper part of the elevator. If the cough happened at 30° to another rider, up to 40% of the droplets may fall on the face of another elevator rider. However, when the fan is operating, up to 50% of the droplets were dragged down to the floor in less than 3 seconds.

The basement of a large wholesale market was investigated as the source of a major outbreak in Beijing, China.[47] Many factors contributed to spread across multiple possible modes of transmission including long-range transmission. A field study of the area using fluorescent powders and microspheres as tracers allowed authors to conclude that while air was circulated, the air was unfiltered and there was very little fresh air, there was high humidity, low temperature, inadequate hand sanitization supplies in washrooms, and significant contamination of surfaces possibly due in part to resuspension of droplets from wet floors.

Given that persistence of aerosols over time is a factor in long-range transmission, the viability of SARS-CoV-2 in aerosols is important to consider. The half-life of SARS-CoV-2 in aerosols is approximately 1 hour.[48,49] Humidity seems to have less of an effect on SARS-CoV-2 viability in aerosols compared to the effect of sunlight or temperature.[50,51] Increasing temperature is associated with a reduction in the half-life of SARS-CoV-2 in aerosols.[52-54] Using a rotating drum experiment similar to other studies for viability of SARS-CoV-2, simulated sunlight (UVA/UVB) was applied to aerosolized virus through a window on the drum.[51] Results indicated 90% inactivation of virus within 20 minutes.

Inadequate ventilation can contribute to spread of aerosols, where the buildup of infectious aerosols is inversely proportional to the number of air exchanges.[55-57] In a modelling study, Schijven et al. (2021) assessed the risk of aerosol transmission of SARS-CoV-2 at a distance beyond 1.5 m from continuous breathing, speaking, or singing, or from one cough or one sneeze, in an indoor environment of 100 m^3.[58] Where there was no ventilation, the mean risk of transmission (derived from dose-response data for human coronavirus 229E) after 20 minutes of exposure to a person with 10^7 RNA copies/ml of mucous was estimated at 0.1%, except for sneezing with high aerosol volume (40,000 picolitres/sneeze). The mean risk of transmission increased to above 30% for sneezing with high aerosol volume and above 10% for singing after an exposure of 2 hours to a person with mucous RNA concentration above 10^8 copies/ml. Ventilation at 1 ACH reduced the risk by approximately half and at 6 ACH, the risk of transmission was reduced by a factor of 8–13 for sneezing and coughing, and by a factor of 4–9 for singing, speaking and breathing.

Estimates for minimum infectious dose, amount of viable virus in aerosols and quantified exposure rates are lacking. One preprint study assessed superspreading events related to long-range transmission in order to determine a minimum infectious dose for transmission.[59] The model used rate of aerosolized virion shedding based on data from other coronaviruses and a destabilization rate measured for SARS-CoV-2. They reported a critical exposure threshold for aerosol transmission of 50 virions. A computational characterization of inhaled droplets by Basu (2021) reported an estimated inhaled infectious dose around 300 virions, which was similar to estimates of 500 virions for ferrets.[60] The author acknowledged that this estimate could vary widely depending on environmental and individual biological factors.

Epidemiological and Modelling Studies Describing Long-range Transmission

Epidemiological case studies have reported long-range transmission of SARS-CoV-2, exclusively in indoor settings (e.g., bus, church, restaurant, concert halls, apartment building, office building).[61-67] In most of these case studies, long-range transmission was inferred as the dominant route of transmission, given that infectees were usually further than 2 m away from index cases. In addition, in these case studies, susceptible people were exposed to index cases for prolonged periods (>50 minutes) in indoor environments with inadequate ventilation and, in some instances, with increased respirations (e.g., singing, yelling, or exercising) and/or no face mask use (by case and/or contact). As with most epidemiological studies on transmission events, it was difficult to exclude other contributing routes of transmission. We summarize a few of these case studies, highlighting settings and contributing contextual factors to long-range transmission.

Stagnant indoor conditions can contribute to aerosol transmission. One example is a series of transmissions linked to an individual who developed symptoms around the time they were playing squash in an unventilated squash court.[68] Players who arrived hours after the index case and played in the same squash court were later identified as positive cases, though the role of other potential routes (e.g. unidentified staff contacts, shared surfaces) may have contributed as well and the source of transmission could not be confirmed. In contrast, a post-operative analysis of susceptible patients (no previous SARS-CoV-2 infection or vaccination) in a surgical suite within 48 hours following the use of the suite by SARS-CoV-2 positive patients indicated that there were no transmission events. The event rate was lower than the number of events in a control group (0% vs. 1.9%).[69] Ventilation was likely a significant factor that prevented transmission in the surgical suite.

In a study of six indoor singing events (five with transmission) in the Netherlands, Shah et al. (2021) (preprint) reported that long-range transmission was the likely route of transmission (short-range transmission possibly contributing to transmission at three of these events and indirect contact transmission possibly contributing to transmission at one of the events).[62] The authors assigned transmission likelihood as either less likely or possible; however, the authors do not state how these were defined. Attack rates at these events ranged from 25%–74% (9–21 people aged 20–79 years attended the events) and authors hypothesize that singing led to transmission. The authors note that they cannot quantify the contribution of each route of transmission. Genomic sequencing was not performed to help rule out other sources of SARS-CoV-2.

In a choir group (Washington, US), 53 of 60 individuals (excluding the index patient) were confirmed or strongly suspected to have been infected during a 2.5 hour rehearsal in a main hall.[64] Individuals who moved to another area of the building from the index case to practice for 45 minutes were less likely to become infected than those who remained in the main hall for the full duration of the rehearsal.

Twelve secondary cases of SARS-CoV-2 were linked to an index case, an 18-year-old chorister with high viral load who sang at four 1-hour services.[70] The index case was seated at a piano raised approximately 3 m from the ground floor and facing away from the secondary cases. Secondary cases sat between 1–15 m (horizontal distance) from the index case. Use of masks was not in place and there was minimal ventilation during the service (ventilation system was off, fans were off and doors and windows were largely closed). Interestingly, no new cases were linked to exposure that occurred the day of respiratory symptom-onset, and no explanation could be provided for why only a certain section near the chorister was affected and other sections (including those directly in front of the index case) were not.

In a case study by Shen et al. (2020), passengers who were not wearing masks were exposed to a presymptomatic index patient for 100 minutes while on a bus in eastern China.[61] Twenty-four of 67 passengers became infected, including several passengers seated beyond 2 m distance. The bus containing the index patient was heated and air was recirculated without filtration. Infections occurred in individuals at either end of the bus and the index case was located roughly in the middle. Risk of infection was only moderately higher for individuals sitting closer to the index patient. In contrast, seven of 172 other people attending the same religious event were positive for SARS-CoV-2. Some of the cases became positive after 14 days from exposure; thus, transmission likely did not occur on the bus for these case. The authors of this study postulate that the poor ventilation in the bus supports aerosol transmission in this cluster; however, other routes of transmission such as close contact from movement within the bus or fomites could not be excluded.

Vehicles are also potential environments for short-range and long-range transmission. A patient transport van was implicated in long-range aerosol transmission despite physical distancing observed by the infected drivers in two distinct transmission events.[71] One driver did not wear a mask, but all passengers wore a single-layer mask. The passengers were exposed for 2 hours during both events. Transmission was confirmed by whole genome sequencing. Fans were on medium speed and windows were closed. Airflow experiments were conducted with different size aerosols demonstrating plausibility of spread from the driver.

An epidemiological investigation of a chain of transmissions was reported beginning with a flight from India to New Zealand, a bus ride to a quarantine facility, a stay at a quarantine facility, a bus ride to the airport, and subsequent household transmissions.[72] Based on positivity test dates, genome sequencing, flight positions and hotel room placement the transmission events were ascribed to both short-range and long-range transmission on flights, within the quarantine facility, and within households. Masks

were required on flights and bus rides. One of the transmission events occurred between two adjacent hotel rooms in the quarantine facility. The authors used recorded video and observed >20 hours between any shared items and no direct contact. The authors concluded that fomite transmission was unlikely and attributed transmission to aerosols in the corridor outside of the hotel rooms wherein the space was enclosed and unventilated. Notably, the hotel rooms themselves, based on a review of the ventilation system, exerted positive pressure relative to the corridor.

An investigation by Lin et al. (2021) into an outbreak of nine COVID-19 cases from three families living in vertically-aligned units of an apartment building in Wuhan, China supported the possibility of long-range transmission.[66] Phylogenetic analysis of respiratory samples showed that all cases were infected by the same strain of SARS-CoV-2. Epidemiological investigation revealed that 4/5 cases of the index family in apartment 15-b had a travelling history to Wuhan, while the other four cases in apartments 25-b and 27-b had neither a travelling history to Wuhan nor close contact with any COVID-19 cases prior to their infection. Transmission through close contact in the elevators was considered unlikely as video records in the elevator did not show any close contact between the index family and the cases from units 25-b and 27-b. However, there was an incident where one unmasked occupant of unit 27-b took the elevator 8 minutes after two unmasked occupants from the index family had left the elevator. Epidemiologically, the infection rate for residents in units b was significantly higher ($p<0.05$) than that in units a and c. Testing of wind speed at the bathtub drain and floor drain found that the airflow produced by toilet flushing on one storey can influence the entire building as the drain pipes for toilets and the sewage pipes connected with floor drains were connected with the exhaust pipe. An experiment with a tracer gas indicated that gas could spread from one storey to another via the drainage and vent systems, especially as the seals in U-shaped traps in the floor drains were dried out in some units and the use of exhaust fans could create a negative pressure in the pipeline system. A similar situation was reported involving air ducts in a naturally ventilated apartment complex in Seoul, South Korea.[67] There were no valves blocking air from entering the bathrooms from the shared natural ventilation shafts (not for building or apartment unit ventilation). Limitations of this outbreak investigation included no genome sequencing or air sampling. Direct applicability to Canadian contexts may be limited by different building construction standards and practices.

Independent of ventilation, movement of air from an infected individual to others nearby can be an important factor in long-range transmission. Direct airflow was deemed responsible for a long-range transmission event in a restaurant in Korea.[73] The suspected index case sat 4.8 m and 6.5 m away and directly upwind of the airflow from two secondary cases at different tables. Nine other visitors in the restaurant did not test positive for SARS-CoV-2 even though at least two were closer to the index case for longer but not in the direct path of airflow originating from the index case. Notably the transmission in one case was suspected to have occurred from an exposure as short as five minutes, and three patrons sitting with the secondary cases but facing away from the index cases were not infected.

An investigation by Lu et al. (2020) into a COVID-19 outbreak in a restaurant in Guangzhou, China involving three families sitting at three tables in close proximity for about 1 hour concluded that the air conditioning (AC) system likely contributed to transmission.[63] In this scenario, a presymptomatic index case and secondary cases were present in the same area for 53–73 minutes. The location of a consistently running AC unit was in the airflow path of the secondary cases and was in an enclosed environment. No secondary cases occurred in staff or at adjacent tables that were outside of the likely "air column". The furthest distance between index and secondary cases was approximately 3 m. Additional investigation indicated that the exhaust fans had been closed due to cold outside temperatures.[74] The airflow assessment indicated that air was recirculating in a defined area, which exposed the three families.

A report involving group exercise at three facilities in Hawaii, US calculated attack rates of 25%–100%.[75] There was no fresh air ventilation and exposure occurred over a duration of 1 hour. Extended close contact and lack of masks in some cases were concluded as contributing to the transmission.

An outbreak in a multi-bed hospital room occurred wherein three patients and six health care workers became infected despite the use of masks and presence of ventilation of 3–4 ACH.[76] The presymptomatic index case was a parent located in a chair beside their child's bed who constantly wore a surgical mask, near the entrance to the room. Notably the air conditioning unit appeared to be located on the ceiling and no details were given about how it operated (e.g., constant versus timed/triggered) and what amount of fresh air circulation it provided. There were no exhaust vents indicated on the room diagram. Exposures for health care workers were in the range of 10–15 minutes, most at distances further than 2 m from the index patient. The report noted that masks were worn as personal protective equipment by health care workers. Transmission was based on the epidemiology of the outbreak without corroboration by genomic analysis of infections.

Detection of SARS-CoV-2 in Air Samples

Air sampling for virus refers to the process of collecting volumes of air by a device to determine if aerosols may contain virus. Collection can vary by aerodynamic size captured, duration of collection, volume per second collected, and media on which samples deposit. Air samples can then be tested by molecular methods such as reverse transcription PCR (RT-PCR) to amplify viral nucleic acids and/or viral culture. RT-PCR cannot determine whether the microorganisms detected are viable. Viral culture is used to determine whether a sample containing the virus is capable of replication. While there are several factors that contribute to the probability of infection, replication is a surrogate measure for inducing infection. To detect viability, researchers apply a sample to a susceptible cell culture and incubate up to a few weeks to detect morphological changes.

Detection of SARS-CoV-2 RNA in air samples has been inconsistent.[77] Multiple air sampling studies performed in proximity to confirmed COVID-19 cases were unable to detect any virus by RT-PCR.[78-86] Kenarkoohi et al. detected SARS-CoV-2 RNA by RT-PCR in 1/5 samples from a ward containing intubated, severely ill patients, but did not find any positive air samples in other areas of the hospital such as wards with suspected, confirmed and mild patients (culturing of virus was not attempted in this study).[87] Chia et al. (2020), in an extended study of Ong et al. (2020), detected SARS-CoV-2 RNA by RT-PCR in air samples collected within 1 m of patients in two of three airborne infection isolation rooms (AIIRs) (no culture of virus attempted).[88] Lei et al. (2020) reported limited detection of SARS-CoV-2 RNA virus by air sampling in open wards, private isolation rooms and bathrooms.[85] One PCR-positive air sample was obtained during an endotracheal intubation within 10 cm of the patient's head in a naturally ventilated room (window open with fan attached), eleven other air samples near patients and 17 samples outside patient rooms and at nursing stations were PCR-negative.[89] The stage of infection and level of infectiousness of the patient populations sampled were not reported.

In a study of SARS-CoV-2 RNA in air samples collected from a variety of settings, Liu et al. (2020) reported that the highest concentration of viral RNA was reported from patient and staff areas of hospitals, compared to public areas.[90] Gharehchahi et al. (2021) (preprint) found SARS-CoV-2 RNA in 7/17 (41.2%) of air samples in a hospital for COVID-19 patients, including a mechanically-ventilated temporary waste storage area, two naturally-ventilated offices (one in the admission and discharge area, the other in an administrative department), and within 2 m of patients' beds in two intensive care units (ICUs), a negative pressure room, and an accident and emergency ward that are mechanically-ventilated with or without natural ventilation.[91] SARS-CoV-2 RNA was not detected from the four

samples at nursing stations 2–5 m from patients' beds. The authors speculated that the detection of RNA in non-clinical areas could be due to inadequate ventilation and the occasional presence of infected health care workers.

Stern et al. (2021) sampled air in locations outside of patient care areas in an acute care hospital and found 8/90 (9%) of the samples positive for SARS-CoV-2 RNA, with concentrations ranging from 5–51 copies/m^3.[92] The size of the RNA-positive samples ranged from ≤2.5 to ≥10 μm. Locations adjacent to negative-pressured wards designated for COVID-19 patients did not appear to increase the likelihood of detecting viral RNA, having higher viral concentration, or finding particles of specific sizes in air samples. However, a significant positive association was observed between the average number of COVID-19 patients staying in the hospital during each sampling period, and the likelihood of an air sample testing positive for SARS-CoV-2 RNA. Furthermore, areas where staff congregated during times of high community rates of COVID-19 were associated with positive air samples. Of note, one RNA-positive air sample was taken when the unit was closed for cleaning and not under negative pressure, and the unit doors were left open for cleaning staff who had to pass by the air sampler to access the area for cleaning.

When air samples were RT-PCR-positive, culturing attempts were infrequently successful. In a systematic review and meta-analysis of 24 studies, Birgand et al. (2020) reported that 17.4% (82/471) of air samples from patient environments were RNA-positive (there was no difference in positivity at ≤1 m [2.5%] or 1–5 m [5.5%]; p=0.22), while culturing produced viable virus in 8.6% (7/81; 2 out of 5 studies) of samples.[93] A study by Guo et al. (2020) detected SARS-CoV-2 by RT-PCR in 35% (14/40) of air samples in an ICU and 12.5% (2/16) of air samples in the general ward that managed patients with COVID-19. Fifteen of 16 RT-PCR-positive air samples were from within 2 m of patients, with 1/8 samples positive at 4 m away.[12] Ben-Shmuel et al. (2020) conducted limited sampling (generally one air sample per area) in rooms with ventilated and non-ventilated patients, at a nursing station, and in private and public areas of a quarantine hotel.[94] RT-PCR-positive air samples were detected in a room with a ventilated patient (distance from patient was not reported) (n=1/1), at a nursing station (n=1/1), and in a quarantine hotel room (n=1/1). However, there were no positive air samples in rooms of non-ventilated patients (n=0/3), a doffing area (n=0/1), and a public area of a quarantine hotel (n=0/1). The authors attempted viral culturing; however, no samples were positive.

At this time, only three studies, two from the same research group and one preprint from July 2020, have successfully cultured viable virus from the air. The preprint and one published study were already referred to above in the summary of Birgand et al. (2020). Sampling techniques and equipment may have caused the lack of culture viability despite RT-PCR detection in other studies. Future studies should aim to replicate the use of equipment and culture methods as these studies.

Lednicky et al. (2021) used a prototype and commercial version of an air sampler and custom RT-PCR probes for detection of SARS-CoV-2 in a patient room with two patients. One patient was discharged soon after sampling periods began and after receiving a negative RT-PCR test.[95] The remaining patient began experiencing respiratory illness two days prior to admission to the room. The study detected RT-PCR-positive air samples following 3 hours of sampling as well as positive viral cultures. Researchers positioned samplers 2–4.8 m from the recently symptomatic patient's head. The ventilation unit provided 6 ACH, filtering air and treating air with UV irradiation before recycling the air. Estimates of virus per volume of air ranged from 6–74 tissue culture infective dose $(TCID)_{50}$ units/L of air. Recently, a second study by Lednicky et al. was performed to detect viable SARS-CoV-2 virus from the front passenger seat area of a car driven by a SARS-CoV-2-positive patient without cough symptoms.[96] This study involved a sampler affixed to the sun visor in the passenger seat collecting particles sizes in ranges

of <0.25 µm, 0.25–0.50 µm, 0.50–1.0 µm, 1.0–2.5 µm and >2.5 µm. The patient drove for 15 minutes with the windows up and air conditioner on. The sampler was turned off 2 hour after the patient completed the 15 minute drive. Viable virus was cultured only from the 0.25–0.5 µm fraction, which also had the highest quantity of detectable copies of viral RNA.

Further research is needed to reconcile differences in viral RNA detection and virus viability in air samples, despite RT-PCR-positive samples found on the surfaces of ventilation units.[97] Differences may be due to several factors, including: 1) air sampling devices are potentially not capable of maintaining viability of captured virus; 2) timing of air sampling varies by time since onset of symptoms, severity of disease or viral load; and 3) the conditions of ventilation (engineering controls) reducing concentrations of viral aerosols to undetectable levels. Even in rooms with high air exchanges, Tang et al.'s review of SARS-CoV-2 aerosols indicates that viral RNA copies can still be detected in air samples from patient rooms (1.8–3.4 viral RNA copies/m^3), toilet rooms (19 copies/m^3), and personal protective equipment doffing rooms (18–42 copies/m^3).[98] In a series of distinct room types (two AIIR with 15+ ACH, an isolation room without negative pressure and a shared cohort room) for patients admitted within 7 days of symptom-onset, Kim et al. reported that 32 air samples were negative and 20 air samples from anterooms were also negative.[86] Culturing viruses is technically challenging; therefore, the lack of positive cultures does not necessarily indicate an absence of infectious virus. On the other hand, the detection of SARS-CoV-2 viral RNA on surfaces that are rarely touched suggests that the virus may be transported through the air to those no-touch surfaces.[99]

Conclusions

Respiratory virus transmission occurs on a spectrum, from larger droplets that spread at short range, to aerosols that are present at short ranges but may also contribute to long-range transmission. As a result, categorizing SARS-CoV-2 transmission as either droplet or airborne does not accurately reflect this spectrum. Other respiratory viruses, like influenza, have similarly been described to demonstrate a spectrum of droplet sizes contributing to transmission.[100,101]

The highest risk of SARS-CoV-2 transmission likely occurs via close (<2 m), unprotected exposure (lacking multiple prevention measures) to an infectious individual. While there is a lower risk of transmission at longer distances with unprotected exposure, this kind of transmission has only been documented to occur under certain conditions, usually involving inadequate ventilation or with recirculation of unfiltered or untreated air in combination with activities involving increased exhalation/expulsion (e.g., shouting, singing, exercising), and often with a lack of source control masking.[102] Defining measures or cutoffs for inadequate ventilation was not possible based on the available descriptions of the contexts in which inadequate ventilation was reported to contribute to transmission. However, they included situations where air is circulated without filtration or exchange with fresh air, where there is no ventilation (e.g., windowless rooms without a ventilation system), and where the size of the room and ventilation rate relative to the quantity of infectious aerosols generated exceeds an unknown threshold of risk for infection. VOCs may be more effectively transmitted across all modes of transmission; however, there is no evidence that any VOCs transmit by fundamentally different routes.[103-105]

The delineation of relative contributions of short-range large respiratory droplets and aerosols and long-range aerosols to overall transmission patterns is complicated by the variable confluence of dynamic source/receptor factors and pathway factors. For example, each infector/infectee interaction is affected by source activities and amount of source viral load (e.g., forceful expulsion of droplets during coughing or singing, and timing in the course of illness), source/receptor adherence to preventative measures in place (e.g., hand hygiene, physical distancing, surface disinfection, mask-wearing and ventilation), and

pathway factors that include airflow, UV, temperature, and humidity in indoor or outdoor environments.[16] It is likely that the relative contribution of respiratory particle size to transmission will depend on these combination of factors.

A large body of evidence is emerging related to SARS-CoV-2. Studies related to identification of a specific mode of transmission are generally low quality. Moreover, data from different fields (e.g., epidemiology versus modelling) can be at odds with respect to conclusions drawn about the role of different sized droplets in short-range transmission and relative importance of long-range transmission events. Ongoing study is needed for further evidence regarding the quantity of viral particles required to cause infection. Additional assessment of SARS-CoV-2 viability in aerosols is needed. Lastly, elucidation of setting-specific risk factors for transmission (e.g., differences between source/receptor and pathway factors in health care settings, residential buildings, schools, warehouses, transportation) may provide further insight into mechanisms for transmission.

The COVID-19 pandemic has identified the importance of interdisciplinary collaboration towards understanding and having a common lexicon for describing virus transmission. When the analysis and interpretation of data is challenged by variable terminology used between and within public health, clinicians, aerosol scientists and the public, this can limit progress towards identification and application of appropriate mitigation measures.[106]

Implications for Practice

This document summarizes the evolving evidence on transmission through respiratory particles and acknowledges the role for both larger droplets and aerosols in transmission. While our understanding of how transmission occurs has evolved and the relative contribution of droplets and aerosols continues to be studied, this may not necessitate a change in infection control measures, but highlights the importance of incorporating multiple infection control layers to mitigate transmission. Translation of this information into recommendations for control measures also needs to take into consideration evidence not reviewed in this document on the overall effectiveness of control measures to date: 1) effectiveness of measures in isolation and in combination as layered mitigation; 2) effectiveness in the community vs. health care settings; and 3) effectiveness and the impact of implementation fidelity.

A detailed assessment of the evidence for infection prevention and control measures was out of scope for this document and thus limits discussion of recommendations for specific measures in different contexts. Of note, vaccination against SARS-CoV-2 is a relatively recent measure that is very effective at reducing transmission regardless of the mode of transmission and should be the priority control measure both in health care and community settings.[107]

In health care settings, recommendations for IPAC measures are described in *IPAC Recommendations for Use of Personal Protective Equipment for Care of Individuals with Suspect or Confirmed COVID-19* and *Interim Guidance for Infection Prevention and Control of SARS-CoV-2 Variants of Concern for Health Care Settings*.[7,8] These documents integrate the existing evidence around droplet, aerosol and contact transmission with jurisdictional experience with control measures and outbreak management to date, and recommends the use of the hierarchy of hazard controls to reduce the risk of transmission.

The bulk of disease transmission occurs in the community and in workplaces, not in health care settings. As SARS-CoV-2 transmits early in the course of infection, most commonly in the asymptomatic or presymptomatic period[108-111] and within the first two days of symptom-onset, cases may not seek health care during their most transmissible phase. In all settings it is necessary to utilize multiple control

measures to mitigate the dynamic transmission factors and address potential routes of transmission. Infection prevention controls should also be context-dependent and take into account vaccination status/coverage, the ability to physically distance and avoid crowding, the feasibility of proper wearing of appropriate personal protective and source control equipment, training and education on the appropriate use of personal protective equipment, hand hygiene, surface disinfection, indoor ventilation, and early identification and isolation of infectious persons. Finally, application of measures should also be in the context of overall rates of community transmission and risk of exposure.

Several resources exist for community guidance (e.g., non-health care workplaces, public and private spaces) on how to reduce the risk of SARS-CoV-2 transmission through a layered approach of multiple public health measures designed to mitigate short-range and long-range transmission.[112-114] In general these involve avoiding the "3 C's": closed spaces, crowded places, and close contact. The degree to which various mitigation layers are necessary or possible will depend on the setting and risk context. Transmission can be mitigated through:

- Getting vaccinated[115,116] (higher vaccine coverage in the population can reduce risk for individuals unable to receive a vaccine)
- Staying home when sick[117,118] (e.g., active and passive screening prior to entry into public settings)
- Limiting the number and duration of contacts with individuals outside your household
- Physical distancing[114] and avoiding crowded spaces
- Consistently and appropriately using a well-fitted, well-constructed (2-3-layer) mask for source control and personal protective equipment.[119-122]
- Ensuring that ventilation systems[123] are well-maintained and optimized with the support of professionals according to relevant recommendations (e.g., from American Society of Heating, Refrigerating and Air-Conditioning Engineers) and/or using outdoor environments whenever possible.
- Performing hand hygiene, respiratory etiquette, and environmental cleaning[124]

The above measures are effective means of reducing risk of transmission irrespective of the relative contribution of larger droplets or aerosols to transmission. Some controls will be more effective than others and it is the combination and consistent application of these controls that is most effective for reducing disease spread.

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World Health Organization

< Go back to all Coronavirus disease 2019 Q&As

Coronavirus disease (COVID-19): How is it transmitted?

13 December 2020 | Q&A

The English version was updated on 30 April 2021.

How does COVID-19 spread between people?

We know that the disease is caused by the SARS-CoV-2 virus, which spreads between people in several different ways.

The virus can spread from an infected person's mouth or nose in small liquid particles when they cough, sneeze, speak, sing or breathe. These particles range from larger respiratory droplets to smaller aerosols.

- **Current evidence suggests that the virus spreads mainly between people who are in close contact with each other, typically within 1 metre (short-range). A person can be infected when aerosols or droplets containing the virus are inhaled or come directly into contact with the eyes, nose, or mouth.**
- **The virus can also spread in poorly ventilated and/or crowded indoor settings, where people tend to spend longer periods of time. This is because aerosols remain suspended in the air or travel farther than 1 metre (long-range).**

People may also become infected by touching surfaces that have been contaminated by the virus when touching their eyes, nose or mouth without cleaning their hands.

Further research is ongoing to better understand the spread of the virus and which settings are most risky and why. Research is also under way to study virus variants that are emerging and why some are more transmissible. For updated information on SARS-CoV-2 variants, please read the weekly epidemiologic updates.

When do infected people transmit the virus?

What is the difference between people who are asymptomatic or pre-symptomatic? Don't they both mean someone without symptoms?

Are there certain settings where COVID-19 can spread more easily?

How can I reduce my risk of getting COVID-19?

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Transmission of SARS-CoV-2: implications for infection prevention precautions

World Health Organization

< Go back to all Coronavirus disease 2019 Q&As

Coronavirus disease (COVID-19): How is it transmitted?

13 December 2020 | Q&A

The English version was updated on 30 April 2021.

How does COVID-19 spread between people?

When do infected people transmit the virus?

Whether or not they have symptoms, infected people can be contagious and the virus can spread from them to other people.

Laboratory data suggests that infected people appear to be most infectious just before they develop symptoms (namely 2 days before they develop symptoms) and early in their illness. People who develop severe disease can be infectious for longer.

While someone who never develops symptoms can pass the virus to others, it is still not clear how frequently this occurs and more research is needed in this area.

What is the difference between people who are asymptomatic or pre-symptomatic? Don't they both

What is the difference between people who are asymptomatic or pre-symptomatic? Don't they both mean someone without symptoms?

Are there certain settings where COVID-19 can spread more easily?

How can I reduce my risk of getting COVID-19?

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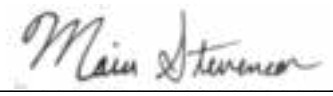

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Avoid the Three Cs

World Health Organization
Western Pacific Region

Be aware of different levels of risk in different settings.

There are certain places where COVID-19 spreads more easily:

1

Crowded places

with many people nearby

2

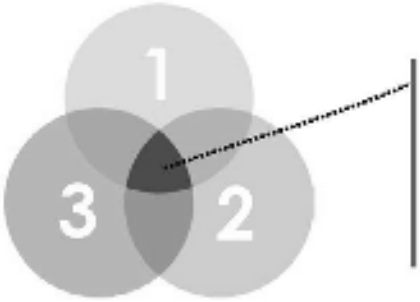
Close-contact settings

Especially where people have close-range conversations

3

Confined and enclosed spaces

with poor ventilation

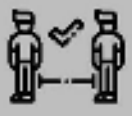


The risk is higher in places where these factors overlap.

Even as restrictions are lifted, consider where you are going and #StaySafe by avoiding the Three Cs.

WHAT SHOULD YOU DO?

Avoid crowded places and limit time in enclosed spaces



Maintain at least 1m distance from others

When possible, open windows and doors for ventilation

Keep hands clean and cover coughs and sneezes

Wear a mask if requested or if physical distancing is not possible

If you are unwell, stay home unless to seek urgent medical care.

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The airborne lifetime of small speech droplets and their potential importance in SARS-CoV-2 transmission

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Edited by Axel T. Brunger, Stanford University, Stanford, CA, and approved May 4, 2020 (received for review April 10, 2020)

Speech droplets generated by asymptomatic carriers of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are increasingly considered to be a likely mode of disease transmission. Highly sensitive laser light scattering observations have revealed that loud speech can emit thousands of oral fluid droplets per second. In a closed, stagnant air environment, they disappear from the window of view with time constants in the range of 8 to 14 min, which corresponds to droplet nuclei of *ca.* 4 μm diameter, or 12- to 21-μm droplets prior to dehydration. These observations confirm that there is a substantial probability that normal speaking causes airborne virus transmission in confined environments.

COVID-19 | speech droplet | independent action hypothesis | respiratory disease | disease transmission

It has long been recognized that respiratory viruses can be transmitted via droplets that are generated by coughing or sneezing. It is less widely known that normal speaking also produces thousands of oral fluid droplets with a broad size distribution (*ca.* 1 μm to 500 μm) (1, 2). Droplets can harbor a variety of respiratory pathogens, including measles (3) and influenza virus (4) as well as *Mycobacterium tuberculosis* (5). High viral loads of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been detected in oral fluids of coronavirus disease 2019 (COVID-19)–positive patients (6), including asymptomatic ones (7). However, the possible role of small speech droplet nuclei with diameters of less than 30 μm, which potentially could remain airborne for extended periods of time (1, 2, 8, 9), has not been widely appreciated.

In a recent report (10), we used an intense sheet of laser light to visualize bursts of speech droplets produced during repeated spoken phrases. This method revealed average droplet emission rates of *ca.* 1,000 s^{-1} with peak emission rates as high as 10,000 s^{-1}, with a total integrated volume far higher than in previous reports (1, 2, 8, 9). The high sensitivity of the light scattering method in observing medium-sized (10 μm to 100 μm) droplets, a fraction of which remain airborne for at least 30 s, likely accounts for the large increase in the number of observed droplets. Here, we derive quantitative estimates for both the number and size of the droplets that remain airborne. Larger droplets, which are also abundant but associated with close-proximity direct virus transfer or fomite transmission (11), or which can become resuspended in air at a later point in time (12), are not considered here.

According to Stokes' law, the terminal velocity of a falling droplet scales as the square of its diameter. Once airborne, speech-generated droplets rapidly dehydrate due to evaporation, thereby decreasing in size (13) and slowing their fall. The probability that a droplet contains one or more virions scales with its initial hydrated volume, that is, as the cube of its diameter, d. Therefore, the probability that speech droplets pass on an infection when emitted by a virus carrier must take into account how long droplet nuclei remain airborne (proportional to d^{-2}) and the probability that droplets encapsulate at least one virion (proportional to d^3), the product of which is proportional to d.

The amount by which a droplet shrinks upon dehydration depends on the fraction of nonvolatile matter in the oral fluid, which includes electrolytes, sugars, enzymes, DNA, and remnants of dehydrated epithelial and white blood cells. Whereas pure saliva contains 99.5% water when exiting the salivary glands, the weight fraction of nonvolatile matter in oral fluid falls in the 1 to 5% range. Presumably, this wide range results from differential degrees of dehydration of the oral cavity during normal breathing and speaking and from decreased salivary gland activity with age. Given a nonvolatile weight fraction in the 1 to 5% range and an assumed density of 1.3 $g{\cdot}mL^{-1}$ for that fraction, dehydration causes the diameter of an emitted droplet to shrink to about 20 to 34% of its original size, thereby slowing down the speed at which it falls (1, 13). For example, if a droplet with an initial diameter of 50 μm shrinks to 10 μm, the speed at which it falls decreases from 6.8 $cm{\cdot}s^{-1}$ to about 0.35 $cm{\cdot}s^{-1}$. The distance over which droplets travel laterally from the speaker's mouth during their downward trajectory is dominated by the total volume and flow velocity of exhaled air (8). The flow velocity varies with phonation (14), while the total volume and droplet count increase with loudness (9). Therefore, in an environment of stagnant air, droplet nuclei generated by speaking will persist as a slowly descending cloud emanating from the speaker's mouth, with the rate of descent determined by the diameter of the dehydrated speech droplet nuclei.

The independent action hypothesis (IAH) states that each virion has an equal, nonzero probability of causing an infection. Validity of IAH was demonstrated for infection of insect larvae by baculovirus (15), and of plants by Tobacco etch virus variants that carried green fluorescent protein markers (16). IAH applies to systems where the host is highly susceptible, but the extent to which IAH is valid for humans and SARS-CoV-2 has not yet been firmly established. For COVID-19, with an oral fluid average virus RNA load of 7×10^6 copies per milliliter (maximum of 2.35×10^9 copies per milliliter) (7), the probability that a 50-μm-diameter droplet, prior to dehydration, contains at least one virion is ∼37%. For a 10-μm droplet, this probability drops to 0.37%, and the probability that it contains more than one virion, if generated from a homogeneous distribution of oral fluid, is negligible. Therefore, airborne droplets pose a significant risk only if IAH applies to human virus transmission. Considering that frequent person-to-person transmission has been reported in community and health care settings, it appears likely that IAH

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The authors declare no competing interest.

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Data deposition: Movies that show the experimental setup and the full 85-minute observation of speech droplet nuclei have been deposited at Zenodo and can be accessed at https://doi.org/10.5281/zenodo.3770559.

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applies to COVID-19 and other highly contagious airborne respiratory diseases, such as influenza and measles.

Results and Discussion

The output from a green (532 nm) Coherent Verdi laser operating at 4-W optical power was transformed with spherical and cylindrical optics into a light sheet that is ~1 mm thick and 150 mm tall. This light sheet passed through slits centered on opposite sides of a cubic 226-L enclosure. When activated, a 40-mm, 12-V muffin fan inside the enclosure spatially homogenizes the distribution of particles in the enclosure. A movie showing the arrangement is available (17). Movie clips of speech droplet nuclei were recorded at a frame rate of 24 Hz with high-definition resolution (1,920 × 1,080 pixels). The camera lens provided a horizontal field of view of ~20 cm. Therefore, the volume intercepted by the light sheet and viewed by the camera is ~30 cm^3. The total number of particles in the enclosure can be approximated by multiplying the average number of particles detected in a single movie frame by the volume ratio of the enclosure to the visualized sheet, which is ~7,300. Slow convection currents, at speeds of a few centimeters per second, remained for the duration of the recording. These convection currents are attributed to a 0.5 °C temperature gradient in the enclosure (bottom to top) that presumably is due to heat dissipated by the iPhone11 camera, which was attached to the front side of the enclosure. Since the net air flux across any horizontal plane of the enclosure is zero, this convection does not impact the average rate at which droplet nuclei fall to the bottom of the enclosure.

With the internal circulation fan turned on, the enclosure was purged with HEPA-filtered air for several minutes. Then, the purge shutter was closed, the movie clip was started, the speaker port was opened, and the enclosure was "filled" with speech droplets by someone repeating the phrase "stay healthy" for 25 s. This phrase was chosen because the "th" phonation in the word "healthy" was found to be an efficient generator of oral fluid speech droplets. The internal fan was turned off 10 s after speech was terminated, and the camera continued recording for 80 min. The movie clip was analyzed frame by frame to determine the number of spots/streaks whose maximum single-pixel intensity exceeded a threshold value of 30. Fig. 1 charts the time-dependent decrease in the number of scattering particles detected. We are not yet able to quantitatively link the observed scattered light intensity to the size of the scattering particle because the light intensity varies across the sheet. However, the brightest 25% were found to decay more quickly than the dimmer fraction, with the two curves reasonably well described by exponential decay times of 8 and 14 min, respectively (Fig. 1*A*). These fits indicate that, near time 0, there were, on average, approximately nine droplet nuclei in the 30-cm^3 observation window, with the larger and brighter nuclei (on average) falling to the bottom of the enclosure at faster speeds than the smaller and dimmer ones.

With the assumption that the contents of the box are homogenized by the muffin fan at time 0, the average number of droplets found in a single frame near time 0 corresponds to *ca.* 66,000 small droplets emitted into the 226-L enclosure, or *ca.* 2,600 small droplet nuclei per second of speaking. If the particle size distribution were a delta function and the particles were uniformly distributed in the enclosure, the particle count would be expected to remain constant until particles from the top of the enclosure descend to the top of the light sheet, after which the particle count would decay linearly to background level. The observation that the decay profiles are approximately exponential points to a substantial heterogeneity in particle sizes, even after binning them into two separate groups.

The weighted average decay rate (0.085 min^{-1}) of the bright and dim fractions of particles (Fig. 1*A*) translates into a half-life in the enclosure of *ca.* 8 min. Assuming this half-life corresponds to the time required for a particle to fall 30 cm (half the height of the box), its terminal velocity is only 0.06 $cm{\cdot}s^{-1}$, which corresponds to a droplet nucleus diameter of ~4 μm. At the relative humidity (27%) and temperature (23 °C) of our experiment, we expect the droplets to dehydrate within a few seconds. A dehydrated particle of 4 μm corresponds to a hydrated droplet of *ca.* 12- to 21-μm diameter, or a total hydrated volume of ~60 nL to 320 nL for 25 s of loud speaking. At an average viral load of 7×10^6 per milliliter (7), we estimate that 1 min of loud speaking generates at least 1,000 virion-containing droplet nuclei that remain airborne for more than 8 min. These therefore could be inhaled by others and, according to IAH, trigger a new SARS-CoV-2 infection.

The longest decay constant observed by us corresponds to droplets with a hydrated diameter of ≥12 μm when exiting the mouth. The existence of even smaller droplets has been

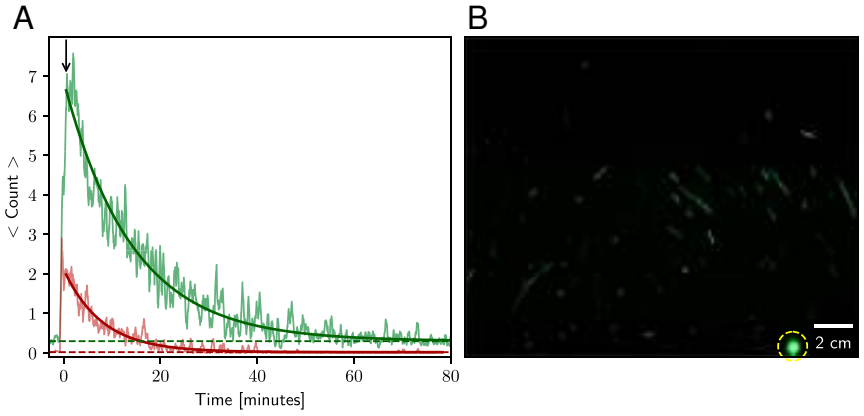

Fig. 1. Light scattering observation of airborne speech droplet nuclei, generated by a 25-s burst of repeatedly speaking the phrase "stay healthy" in a loud voice (maximum 85 dB_B at a distance of 30 cm; average 59 dB_B). (*A*) Chart of particle count per frame versus time (smoothed with a 24-s moving average), with the red curve representing the top 25% in scattering brightness and the green curve representing the rest. The bright fraction (red) decays with a time constant of 8 min, and the dimmer fraction (green) decays with a time constant of 14 min. Both exponential decay curves return to their respective background level of *ca.* 0 (red horizontal dashed line) and 0.4 (green dashed line) counts per frame. Time "0" corresponds to the time the stirring fan was turned off. The 25-s burst of speaking started 36 s before time 0. The black arrow (at 0.5 min) marks the start of the exponential fits. (*B*) Image of the sum of 144 consecutive frames (spanning 6 s) extracted shortly after the end of the 25-s burst of speaking. The dashed circle marks the needle tip used for focusing the camera. The full movie recording is available in ref. 17, with time "0" in the graph at time point 3:38 in the movie.

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established by aerodynamic particle sizer (APS) measurements (2). APS is widely used for detecting aerosol particulates and is best suited for particles in the 0.5- to 5-μm range. Morawska et al. (2) detected as many as 330 particles per second in the 0.8- to 5.5-μm range upon sustained "aah" vocalization. Considering the short travel time (0.7 s) between exiting the mouth and the APS detector, and the high relative humidity (59%) used in that study, droplet dehydration may have been incomplete. If it were 75% dehydrated at the detector, an observed 5.5-μm particle would have started as an 8.7-μm droplet when exiting the mouth, well outside the 12- to 21-μm range observed above by light scattering. This result suggests that APS and light scattering measurements form a perfect complement. However, we also note that, even while the smallest droplet nuclei effectively remain airborne indefinitely and have half-lives that are dominated by the ventilation rate, at a saliva viral load of 7×10^6 copies per milliliter, the probability that a 1-μm droplet nucleus (scaled back to its originally hydrated 3-μm size) contains a virion is only 0.01%.

Our current setup does not detect every small particle in each frame of the movie, and our reported values are therefore conservative lower limit estimates. We also note that the saliva viral load shows large patient-to-patient variation. Some patients have viral titers that exceed the average titer of Wölfel et al. by more than two orders of magnitude (7, 18), thereby increasing the number of virions in the emitted droplets to well over 100,000 per minute of speaking. The droplet nuclei observed in our present study and previously by APS (2, 9) are sufficiently small to reach the lower respiratory tract, which is associated with an increased adverse disease outcome (19, 20).

Our laser light scattering method not only provides real-time visual evidence for speech droplet emission, but also assesses their airborne lifetime. This direct visualization demonstrates how normal speech generates airborne droplets that can remain suspended for tens of minutes or longer and are eminently capable of transmitting disease in confined spaces.

Data Availability Statement. All raw data used for analysis are available in ref. 17.

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Title: Increased household secondary attacks rates with Variant of Concern SARS-CoV-2 index cases

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Abstract

IMPORTANCE: Higher secondary attack rates related to variant of concern (VOC) index cases have been reported, but have not been explored within households, which continue to be an important source of coronavirus disease 2019 (COVID-19) transmission

OBJECTIVE: To compare secondary attack rates in households with VOC versus non-VOC index cases.

DESIGN: A retrospective cohort study of household index cases reported from February 7 – 27, 2021. A propensity-score matched cohort was derived to calculate adjusted estimates.

SETTING: Ontario, Canada.

PARTICIPANTS: A population-based cohort of all private households with index cases. We excluded cases in congregate settings, as well as households with one individual or with >1 case with the same earliest symptom onset date.

EXPOSURE: VOC status, defined as either individuals confirmed as B.1.1.7 using whole genome sequencing or those that screened positive for the N501Y mutation using real-time PCR.

MAIN OUTCOME AND MEASURE: Household secondary attack rate, defined as the number of household secondary cases that occurred 1-14 days after the index case divided by the total number of household secondary contacts.

RESULTS: We included 1,259 index VOC and non-VOC cases in the propensity score-matched analysis. The secondary attack rate for VOC index cases in this matched cohort was 1.31 times higher than non-VOC index cases (RR=1.31, 95%CI 1.14-1.49), similar to the unadjusted estimate. In stratified analyses, the higher secondary attack rate for VOC compared to non-VOC index cases was accentuated for asymptomatic index cases (RR=1.91, 95% CI 0.96-3.80) and presymptomatic cases (RR=3.41, 95%CI 1.13-10.26)

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CONCLUSIONS AND RELEVANCE: This study provides strong evidence of increased transmissibility in households due to VOCs and suggests that asymptomatic and pre-symptomatic transmission may be of particular importance for VOCs. Our study suggests that more aggressive public health measures will be needed to control VOCs and that ongoing research is needed to understand mechanisms of VOC transmissibility to curb their associated morbidity and mortality.

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Introduction

The prevalence of variants having the N501Y mutation have rapidly increased globally,[1] including in Ontario, Canada, where this prevalence increased dramatically in February, 2021. These patterns of rapid strain replacement suggest increased transmissibility of variants with the N501Y mutation, which is present across variants of concern (VOC), including B.1.1.7, B.1.351, and P.1 lineages.[2] However the exact degree of increased transmissibility, and specific settings when increased transmissibility occurs, remains unclear. [1, 3,4,5] Higher secondary attack rates related to VOC index cases have been reported, [6] but have not been explored within households, which continue to be an important source of coronavirus disease 2019 (COVID-19) transmission.[7] The objective of this study was to compare secondary attack rates in households with VOC versus non-VOC index cases in Ontario, Canada.

Methods

We identified individuals with laboratory-confirmed COVID-19 reported in the Public Health Case and Contact Management Solution (CCM), Ontario's COVID-19 reporting system, and included households with index cases reported from February 7 to 27, 2021. VOC cases included either individuals confirmed as B.1.1.7 using whole genome sequencing or those that screened positive for the N501Y mutation using real-time PCR. B.1.1.7 accounted for 94% of confirmed VOC cases reported in Ontario until February 27, 2021.[8] All PCR-positive specimens in Ontario with cycle threshold ≤35 underwent screening for the N501Y mutation during the study period using real-time PCR. Non-VOC cases were those that screened negative for the N501Y mutation.

We grouped cases living in the same household based on residential address.[9] Index cases were defined as the first case in the household based on symptom onset date (or specimen collection date, if symptom onset date was not available) and secondary cases were included if they occurred 1-14 days after the index case. We excluded cases in congregate settings, as well as households with one individual or with >1 case with the same earliest symptom onset date. We used reported household size to calculate

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secondary attack rates by dividing the number of secondary cases by the total number of household secondary contacts (i.e., household size minus one). Cases with and without symptoms were classified based on symptom information and onset date reported in CCM.

Poisson regression was performed for the unadjusted and adjusted analyses, overall and by strata. The models were specified with the count of household secondary cases as the outcome, the logarithm of household size as the offset and VOC status as a binary exposure covariate. Clustering was accounted for with a random intercept for household to account for known overdispersion.

Our unadjusted risk ratios (RR) included the entire cohort of households with a VOC or non-VOC index case in Ontario. Adjusted RRs were based on a propensity score matched analysis. VOC index cases were 1:1 matched to non-VOC index cases based on gender and age group, and matched on the logit of the propensity score, using a caliper width of 0.2 times the standard deviation.[10] The propensity score was based on a logistic regression model of VOC status as a function of five covariates: reported date, time between symptom onset and testing, association with a reported outbreak, as well as the neighbourhood proportion of visible minority residents (non-white and non-Indigenous population) and household crowding as determined using 2016 Canadian Census data.[11] Regression estimates were reported using RRs and 95% confidence intervals (CI). Statistical analysis was performed in R version 4.0.4.[12]

This study was approved by Public Health Ontario's Research Ethics Board.

Results

We identified 5,617 index cases and 3,397 secondary cases across the study period. Amongst index cases, 1,318 were classified as VOC (151 B.1.1.7 and 1,167 N501Y) and 4,299 were classified as non-VOC. The overall secondary attack rate was higher for VOC index cases (25.9%) compared to non-VOC (20.5%, $p<0.01$) with consistently higher secondary attack rates for VOCs across individual characteristics of the index cases (Table 1). The secondary attack rate of VOC index cases was 1.28 times

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higher than that of non-VOC index cases (RR=1.28, 95% CI 1.16-1.42); a similar trend of increased secondary attack rate was observed across subgroups (Figure 1).

We included 1,259 index VOC and non-VOC cases in the propensity score-matched analysis. The secondary attack rate for VOC index cases in this matched cohort was 1.31 times higher than non-VOC index cases (RR=1.31, 95%CI 1.14-1.49), similar to the unadjusted estimate. In stratified analyses, the higher secondary attack rate for VOC compared to non-VOC index cases was accentuated for asymptomatic index cases (RR=1.91, 95% CI 0.96-3.80) and presymptomatic cases (RR=3.41, 95%CI 1.13-10.26)

Discussion

In our cohort, we estimated that the household secondary attack rate of VOC index cases was 31% higher than non-VOC index cases, providing evidence of increased transmissibility. This is consistent with previous VOC (i.e., B.1.1.7) secondary attack rate estimates from the United Kingdom (relative secondary attack rate (32%, 12.9% vs 9.7% among all contacts);[6] however, households are an important contributor to COVID-19 and provide a valuable setting in which to examine transmission.[7] Our estimates of increased transmission from asymptomatic and pre-symptomatic VOC index cases has not previously been reported and suggests an increased importance of prevention measures when individuals are not aware of their infection. The biological mechanism responsible for increased transmissibility has not been identified, but hypotheses include higher viral loads (i.e. increased transmission potential per contact), and prolonged viral shedding (i.e., longer infectious period).[3] The N501Y mutation has also been associated with enhanced binding affinity of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) to angiotensin-converting enzyme 2 (ACE2) receptors.[13,14]

Limitations of this study include potential misclassification of secondary cases as index cases and small sample sizes in some subgroups. We may have underestimated secondary attack rates as we only captured diagnosed secondary cases and we lacked testing data on all household contacts; however, we do not

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believe this would be differential by VOC status of the index case. Ontario implemented more stringent measures for close contacts of all cases (not just VOC cases) in early February in response to VOC introductions, including increased frequency of testing during quarantine and outbreaks.[15] If household contacts were more likely to test once VOC status was known, a similar increase in the risk ratio would be expected across symptom status, suggesting an independent effect of asymptomatic and presymptomatic VOC cases on transmission.

This study provides strong evidence of increased transmissibility in households due to VOCs and suggests that asymptomatic and pre-symptomatic transmission may be of particular importance for VOCs. Our study suggests that more aggressive public health measures will be needed to control VOCs. While measures effective for persons with unknown disease status such as physical distancing and masking may continue to be highly effective, measures focused on symptomatic individuals, such as public health contact tracing, may be increasingly ineffective unless extremely rapid. Ongoing research is needed to understand mechanisms of VOC transmissibility to curb their associated morbidity and mortality.

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Table 1. Characteristics of index cases by VOC status and household secondary attack rate

Index case characteristics	Non-variant		Variant of Concern	
	Index cases No. (%)	Secondary attack rate (%)	Index cases No. (%)	Secondary attack rate (%)
Total	4,299	20.5	1,318	25.9
Gender[a]				
Female	2,074 (48.2)	19.8	647 (49.1)	25.6
Male	2,214 (51.5)	21.1	660 (50.1)	26.2
Age group				
Median [IQR]	39 [27, 55]		37 [25, 52]	
0-9 years	195 (4.5)	17.0	55 (4.2)	23.0
10-19 years	351 (8.2)	17.0	114 (8.6)	20.1
20-29 years	783 (18.2)	15.8	319 (24.2)	21.8
30-39 years	837 (19.5)	20.8	225 (17.1)	25.2
40-49 years	681 (15.8)	20.4	233 (17.7)	26.3
50-59 years	711 (16.5)	25.9	186 (14.1)	34.9
60-69 years	457 (10.6)	25.3	126 (9.6)	32.5
70-79 years	188 (4.4)	22.1	45 (3.4)	24.3
≥80 years	96 (2.2)	21.9	15 (1.1)	47.8
Outbreak Related				
No	3,558 (82.8)	20.7	1,040 (78.9)	24.0
Yes	741 (17.2)	19.0	278 (21.1)	33.1
Testing delay[b]				
No symptoms	410 (9.7)	6.0	116 (8.9)	12.4
<0 days	159 (3.8)	6.3	71 (5.5)	16.0
0 days	431 (10.2)	13.9	137 (10.5)	15.5
1 day	769 (18.2)	21.6	258 (19.8)	28.7
2 days	672 (15.9)	21.9	207 (15.9)	33.2
3 days	498 (11.8)	23.9	138 (10.6)	24.5
4 days	335 (7.9)	23.6	86 (6.6)	31.4
≥5 days	960 (22.7)	26.2	288 (22.1)	30.1
Neighbourhood Characteristics				
Proportion of visible minorities[c]				
0-20%	1,128 (26.8)	19.7	229 (17.6)	24.0
21-40%	659 (15.7)	22.0	209 (16.1)	26.8
41-60%	649 (15.4)	22.4	224 (17.2)	21.7
61-80%	765 (18.2)	19.7	310 (23.9)	29.3
≥81%	1,001 (23.8)	20.3	327 (25.2)	26.3
Proportion of households with crowding[d]				
< 5%	2,381 (56.7)	21.5	640 (49.3)	27.4
≥ 5%	1,821 (43.3)	19.5	659 (50.7)	24.6

[a]This section does not include missing or other genders (22 index cases and 20 associated secondary cases and 73 household contacts).
[b]Testing delay: days between the index case symptom onset and specimen collection. Cases with no symptoms were defined as cases that were missing symptom onset date and did not have any COVID-19 symptoms flagged in CCM. Index cases with a testing delay of <0 days were those who were tested prior to the onset of their symptoms (i.e. presymptomatic). Those that did not report a symptom or did not report a symptom onset date and were not reported

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as asymptomatic, or did not report a specimen collection date, were excluded from this section (82 index cases and associated 59 secondary cases and 235 household contacts).

[c]Percentage of visible minorities (non-white and non-Indigenous population) in an Aggregate Dissemination Area having population between 5,000 to 15,000 based on the 2016 Census of Population in Canada. Households missing this measure were excluded from this section (116 index cases and associated 48 secondary cases and 311 household contacts).

[d]Percentage of households in an ADA which have more than 1 person per room. Households missing this measure were excluded from this section (116 index cases and associated 48 secondary cases and 311 household contacts).

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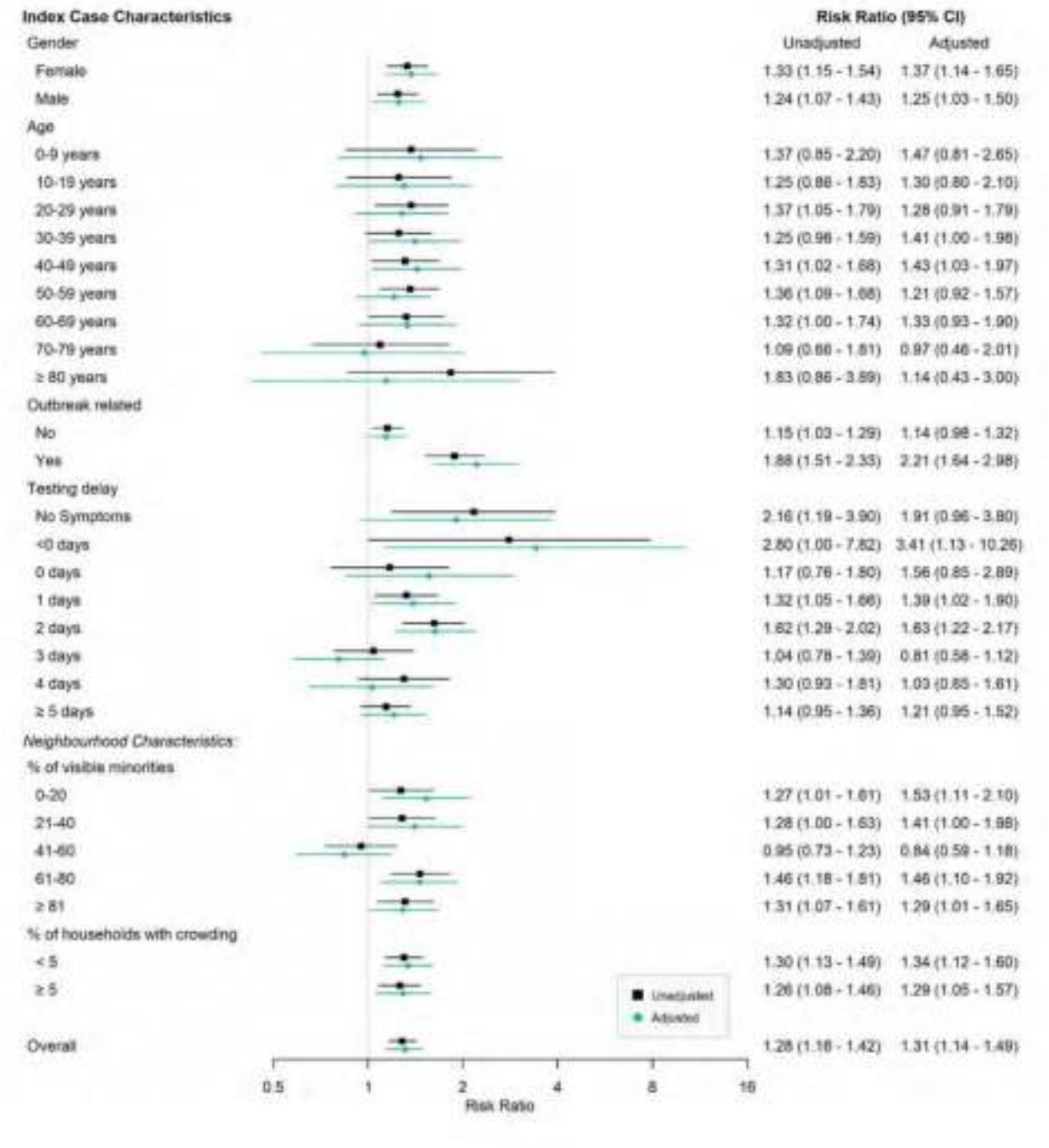
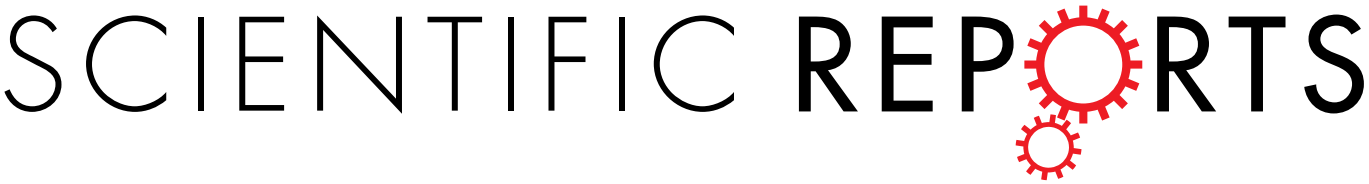
Figure 1. Risk ratio comparing household secondary attack rate associated with VOC vs. non-VOC index cases by characteristic of index case, unadjusted (black) and adjusted by 1:1 propensity-score matching (green) estimates



Note: Unadjusted risk ratio accounts for household clustering and includes the full cohort. Adjusted risk ratio refers to the propensity score-matched cohort.

This is "**Exhibit O**"
to the Affidavit of Matthew Hodge,
affirmed this 2nd day of July, 2021

A Commissioner, etc.



OPEN

Aerosol emission and superemission during human speech increase with voice loudness

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Mechanistic hypotheses about airborne infectious disease transmission have traditionally emphasized the role of coughing and sneezing, which are dramatic expiratory events that yield both easily visible droplets and large quantities of particles too small to see by eye. Nonetheless, it has long been known that normal speech also yields large quantities of particles that are too small to see by eye, but are large enough to carry a variety of communicable respiratory pathogens. Here we show that the rate of particle emission during normal human speech is positively correlated with the loudness (amplitude) of vocalization, ranging from approximately 1 to 50 particles per second (0.06 to 3 particles per cm^3) for low to high amplitudes, regardless of the language spoken (English, Spanish, Mandarin, or Arabic). Furthermore, a small fraction of individuals behaves as "speech superemitters," consistently releasing an order of magnitude more particles than their peers. Our data demonstrate that the phenomenon of speech superemission cannot be fully explained either by the phonic structures or the amplitude of the speech. These results suggest that other unknown physiological factors, varying dramatically among individuals, could affect the probability of respiratory infectious disease transmission, and also help explain the existence of superspreaders who are disproportionately responsible for outbreaks of airborne infectious disease.

It has long been recognized that particles expelled during human expiratory events, such as sneezing, coughing, talking, and breathing, serve as vehicles for respiratory pathogen transmission[1–6]. The relative contribution of each expiratory activity in transmitting infectious microorganisms, however, remains unclear[4]. Much previous research has focused on coughing[7–12] and sneezing[11,13,14] activities that yield relatively large droplets (approximately 50 μm or larger) easily visible to the naked eye. Less noticeable, but arguably more infectious for some diseases, are the smaller particles emitted during sneezing and coughing as well as during breathing[15–17] and talking[16,18,19]. These small particles are believed to be generated during breathing and talking from the mucosal layers coating the respiratory tract via a combination of a "fluid-film burst" mechanism within the bronchioles and from vocal folds adduction and vibration within the larynx[6,20,21]. The particles emitted during breathing and typical speech predominantly average only 1 μm in diameter[15–17] and are thus too small to see without specialized equipment; most people outside of the community of bioaerosol researchers are less aware of them.

Despite their small size, however, these micron-scale particles are sufficiently large to carry a variety of respiratory pathogens such as measles virus (50–500 nm)[22], influenza virus (100 nm–1 μm)[23], and *Mycobacterium tuberculosis* (1–3 μm)[24]. Indeed, recent work by Yan *et al.* has confirmed that significant amounts of influenza viral RNA are present in small particles (<5 μm) emitted by influenza-infected individuals during natural breathing, without coughing or sneezing[25]. These small particles are potentially more infectious than larger sneeze- or

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cough-generated droplets for several reasons. First, smaller particles persist in the air for longer time periods before setting by gravity, thus increasing the probability of inhalation by susceptible individuals[26]. Second, smaller particles have a larger probability of penetrating further into the respiratory tract of a susceptible individual to initiate a lower respiratory tract infection[4]. Third, and perhaps most importantly, speech can release dramatically larger numbers of particles compared to coughing. Early work by Papineni and Rosenthal[16] and Loudon and Roberts[19] reported that speaking (as exemplified by counting aloud) releases about 2–10 times as many total particles as a single cough. Similarly, Loudon and Roberts investigated the role of singing in the spread of tuberculosis and showed that the percentage of airborne droplet nuclei generated by singing is 6 times more than that emitted during normal talking and approximately equivalent to that released by coughing[27]. More recent work using advanced particle characterization techniques have yielded similar results[21,28–30]. Chao *et al.*[28] used an interferometric imaging technique to obtain the size distribution of particles larger than 2 μm and found that counting aloud from 1 to 100 releases at least 6 times as many particles as an individual cough. Likewise, Morawska and coworkers[21,29] reported that counting aloud for 10 seconds followed by 10 seconds of breathing, repeated over two minutes, releases half as many particles as 30 seconds of continual coughing, which in turn releases half as many particles as saying "aah" for 30 seconds. They also reported that more particles are released when speech is voiced, which involves vocal folds vibration, rather than whispered, which does not.

Despite the clear evidence that speech emits large quantities of potentially infectious particles, to date little is known about how particle emission is modulated by different types of speech. Notably, the above work measured neither the total duration nor the loudness of the vocalizations; it is also unclear whether counting aloud will have a distribution of phones (phonemes) that is representative of typical conversational speech. Many important questions remain unanswered. For example, does raising your voice cause an increase in particle emission, or alter the particle size distribution? Does it matter what language you speak? Do all individuals emit particles at similar rates?

To address these questions, we used an aerodynamic particle sizer (APS) placed in a laminar flow hood to characterize the number and size distribution of particles emitted by individual human volunteers while they performed various vocalizations and breathing activities. Using this approach, we find three key results:

(1) The particle emission rate during speech is linearly correlated with the amplitude (loudness) of vocalization, for four different languages tested.
(2) The particle size distribution is independent of vocalization loudness or language spoken.
(3) Some individuals emit particles at a rate more than an order of magnitude larger than their peers, i.e., they behave as "speech superemitters."

Taken together, the results strongly suggest that individual human speech patterns and speech-associated particle emissions are highly heterogeneous and thus might play a role in the transmission of some respiratory pathogens. Furthermore, the results suggest a new hypothesis: that speech superemitters might contribute to the phenomenon of superspreading, in which a relative few contagious individuals infect a disproportionately large number of secondary cases during infectious disease outbreaks[31].

Results

Four separate types of experiments were performed. In the first experiment, participants said /ɑ/ (the vowel sound in 'saw') for five seconds, followed by 15 seconds of nose breathing, repeated six times in succession. This procedure mimics previous experimental measurements of particle emission during vocalization[21], but here the participants also systematically repeated the experiment at different voice amplitudes. Representative raw data for a single participant performing a series of six successive /ɑ/ vocalizations, at approximately the same loudness, are shown in Fig. 1. The simultaneous microphone recording (Fig. 1A) and APS measurements (Fig. 1B) demonstrate that the dynamics of particle release are highly correlated with the vocalization. Prior to and between vocalizations, during nose breathing in which exhaled air is directed away from the APS, the particle count is negligible, as is expected for the HEPA filtered air inside the laminar flow hood. Shortly after the vocalization commences, the number of particles rapidly increases and peaks, then decreases back to zero as the participant resumes nose breathing; the process then repeats at the next five-second vocalization. The approximately two-second lag between onset of vocalization and the observed increase in particle count is due to the time necessary for the released particles to reach the sensor in the APS. We emphasize that by design an APS does not measure 100% of the particles drawn into it, so the particle emission rates reported here do not represent the absolute number of particles emitted by the participant; the emission rates are best understood in relative terms, or in terms of the equivalent instantaneous concentrations of particles sampled from the funnel. As shown in the secondary axis of Fig. 1B, the instantaneous concentration of particles for this particular experiment was approximately 2 per cm^3 of sampled air.

The six vocalizations shown in Fig. 1A were made, to the best of the participant's ability, at the same loudness. Each participant then repeated a similar series of /ɑ/ vocalizations at different self-regulated voice amplitudes. Representative results for a single participant (F4) show that the particle emission rate (N), defined as the total number of particles emitted during a single vocalization divided by the measured duration (in seconds) of that vocalization, also correlates with the root mean square amplitude (A_{rms}) of the vocalization (Fig. 2A). In our set-up $A_{rms} = 0.45$ corresponds to an extremely loud conversational voice, as loud as comfortable without yelling (~98 decibels measured 6.5 cm from the participant's mouth, measured over background noise of approximately 65 decibels), while $A_{rms} = 0.02$ corresponds to a quiet vocalization just above whispering (~70 decibels; cf. Supplementary Fig. S1). As shown in Fig. 2A, the particle emission rate is linearly correlated with A_{rms} over this entire range of vocalization amplitudes, with the particle emission rate increasing from 6 to 53 particles per second at the quietest and loudest vocalizations respectively.

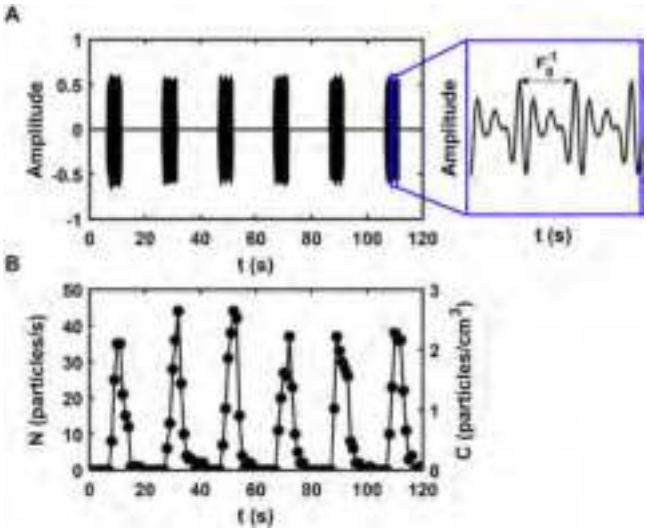

Figure 1. Representative raw data in which a participant (F4) said /ɑ/ for 5 seconds, followed by 15 seconds of nose breathing, repeated 6 times at approximately the same loudness. (**A**) The amplitude (arb. units) recorded by the microphone versus time. Magnification shows 13 ms of the waveform with fundamental frequency of F_0. (**B**) The corresponding number/concentration of particles measured by the APS versus time.

Although the particle emission rate increased with amplitude, the size distribution of the particles was not affected significantly (Fig. 2B), with the geometric mean particle diameter remaining near 1 μm regardless of voice amplitude (Supplementary Fig. S2A). Because the particle size remains similar regardless of amplitude, the increased particle counts shown in Fig. 2 indicate that the total volume of emitted respiratory fluid (i.e., the proteinaceous liquid droplets aerosolized from the serous and mucoid layers lining the respiratory tract) increases considerably with the vocalization loudness. Note that the characteristic time scale for evaporative drying of 1-micron diameter droplets is on the order of 100 milliseconds[26], which is much less than the time required for the particles to move from the participant's mouth into the detection module within the APS, suggesting that the particles measured here had fully dried into droplet nuclei prior to measurement (see methods and Supplementary Fig. S3).

Experiments with multiple participants indicated that these trends are conserved over a larger sample size (Fig. 2C). The particle emission rate increased approximately linearly with A_{rms} for each of the study participants, although the absolute magnitude varied between individuals. One participant (F3) released as many as 200 particles per second at higher amplitudes; another (F2) released as few as 1 particle per second at lower amplitudes. Notably, the data with this cohort of non-elderly adults reveal no obvious trends with gender or age (Supplementary Figs S4A, B). Similarly, no clear correlation was observed with the body mass index (BMI) of the participants (Supplementary Figs S4C, D).

To more closely represent normal conversational speech, the participants read aloud a short passage of text in English at varied loudness (quiet, intermediate, or loud). Representative raw data for a single participant (F4) indicate that the particle emission rate also correlates with voice amplitude for normal speech (Fig. 3A,B). To quantify the loudness, we take A_{rms} here as the average over the entire approximately two-minute duration of the vocalization, excluding pauses between words. Aggregated data for 10 participants confirms that the particle emission rate for normal English speech correlates linearly with A_{rms} (Fig. 3C); speaking loudly yielded on average a 10-fold increase in the emission rate compared to speaking the same series of words quietly. Again, the size distributions (Fig. 3D) and geometric mean diameter of particles (Supplementary Fig. S2B) were insensitive to voice amplitude. The reading experiment also was repeated in different languages to test whether choice of language matters; the results (Supplementary Fig. S5) confirmed the increasing trend between particle emission rate and amplitude, but exhibited no significant difference in the particle emission rate among the languages tested (Supplementary Fig. S6). Likewise, we measured the temperature and humidity during the experiments, and found no significant impact of temperature or humidity on either the particle emission rate or the mean particle size (Supplementary Figs S7 and S8).

A key recurring feature of the data is that some individual participants emitted many more particles than others. Because all participants spoke at slightly different amplitudes, we used linear regressions of the particle emission rate versus amplitude for each individual (cf. Fig. 2A) to calculate a normalized particle emission rate at the loudness amplitude of 0.1 (approximately 85 dB). Using this approach, the results for 40 people show that the particle emission rate for different individuals follows a long-tailed distribution for both vocalization of /ɑ/ (Fig. 4A) and reading of English text aloud (Fig. 4B). At this loudness, the normalized particle emission rates ranged from approximately 1 to 14 particles per second between different individuals, with an average of approximately 4 particles per second. Notably, the rates have a sizeable standard deviation well approximated by a lognormal fit (red curves in Fig. 4). In other words, although half of the participants emitted fewer than 3 particles per second, a small fraction of individuals (8 out of 40) emitted considerably more. These "speech superemitters,"

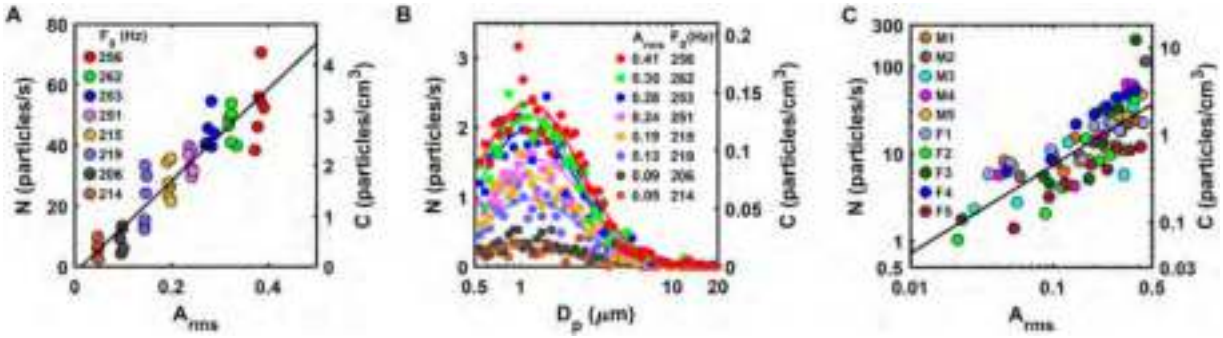

Figure 2. Particle emission rate/concentration while saying /ɑ/ at 8 different amplitudes, repeated 6 times at each amplitude. (**A**) Particle emission rate/concentration versus root mean square amplitude, A_{rms} (arb. units) for a representative participant (F4). Solid line is the best linear fit, with correlation coefficient $\rho = 0.932$ and Pearson's p value $= 5.9 \times 10^{-22}$. (**B**) Corresponding particle size distribution for the data presented in (**A**). (**C**) Aggregated particle emission rate/concentration versus root mean square amplitude, A_{rms} (arb. units) for 10 participants, 5 males (denoted as M1 to M5) and 5 females (denoted as F1 to F5). There are 8 data points for each participant, each representing the average of repeating /ɑ/ six times at approximately the same voice amplitude (cf. Fig. 1). Solid line is a power law fit with exponent 1.004, correlation coefficient $\rho = 0.774$ and Pearson's p value $= 3.8 \times 10^{-17}$.

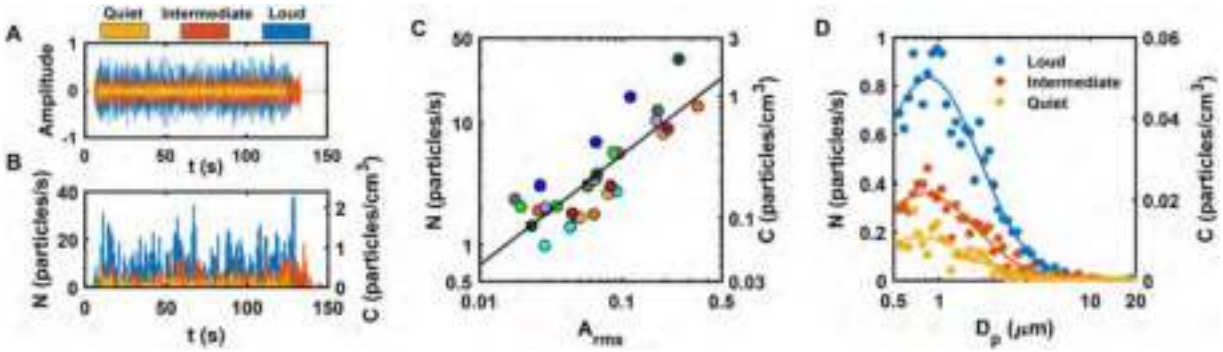

Figure 3. Particle emission rate/concentration while reading a passage of text aloud (the "Rainbow" passage), at three different loudness levels. (**A**) Superimposed representative recordings of amplitude (arb. units) for an individual (F4) reading the passage at three different voice amplitudes, and (**B**) the corresponding number/concentration of particles measured by the APS versus time. Color code same as in (**A**). (**C**) Particle emission rate/concentration as a function of root mean square amplitude, A_{rms}, for 10 participants. There are 3 points for each person, representing 3 voice amplitudes, color code same as Fig. 2C. Solid line is a power law fit with exponent 0.96, correlation coefficient $\rho = 0.865$ and Pearson's p value $= 6.8 \times 10^{-10}$. (**D**) Representative particle size distribution for the one individual (F4).

whose individual particle emission rate exceeded the group mean by one standard deviation or more, consistently released an order of magnitude more particles than their peers. For vocalizing /ɑ/, Fig. 4A shows that 15% of the participants emitted 32% of the total particles, while Fig. 4B shows that, for reading aloud in English, 12.5% of the participants emitted 40% of the total particles. Supplementary Fig. S9A shows that 4 out of these 8 individuals are superemitters for both saying /ɑ/ and passage reading activities, while 2 of them are only superemitters while saying /ɑ/, and 2 of them are superemitters while reading a text passage. We repeated the passage reading experiment for two of the participants (M5 and F4) on three different days separated by several months (Supplementary Fig. S9B), and the results show that the particle emission rates remained almost unchanged for at least these two individuals (F4, a superemitter, and M5, a non-superemitter) despite the long time period between measurements.

To help interpret our findings we also compared the particle emission rates of four different types of breathing with speech at three levels of loudness using the same experimental set-up. The breathing experiments included nose breathing, mouth breathing, a "deep-fast" mode, and a "fast-deep" mode (see methods for details). The results show that the particle emission rate for speech is significantly higher than all types of breathing tested here (Fig. 5A). Furthermore, the corresponding geometric mean diameters of the particles generated during speech are slightly larger on average than those generated during breathing (Fig. 5B), consistent with prior work and the hypothesis that vocalization activates laryngeal particle generation[21]. Note that in Fig. 5A the speech outliers correspond to a single participant who is a speech superemitter (F4), but this individual was not also responsible

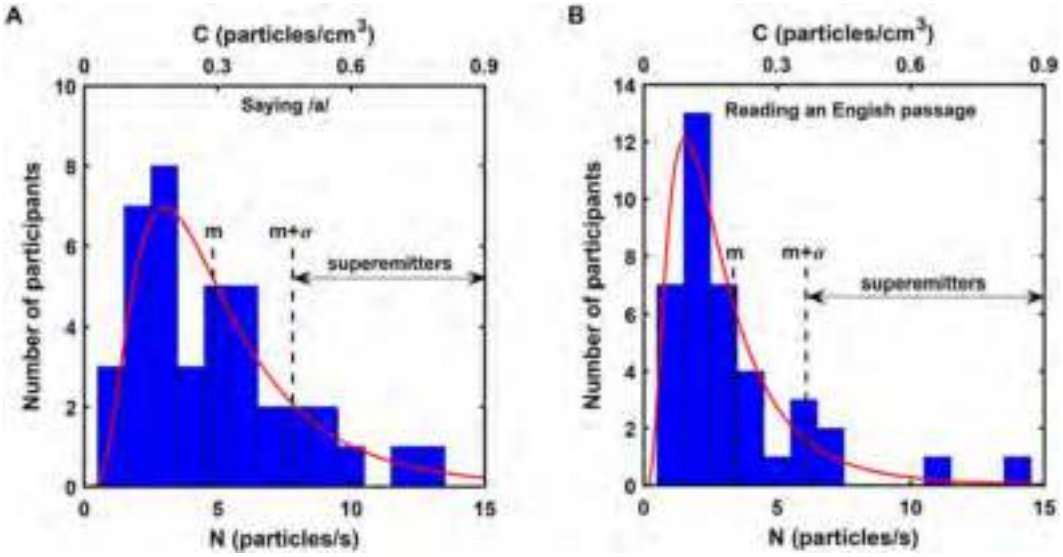

Figure 4. Histogram of particle emission rate/concentration at voice amplitude of 0.1 (approximately 85 dB). (**A**) For saying /ɑ/, with median of M = 4.3 particles/s, mean of m = 4.8 particles/s and standard deviation of σ = 3.0 particles/s. (**B**) For reading an English passage (10 people read the "Rainbow" passage and 30 people read chapter 24 of "The Little Prince") with median of M = 2.5 particles/s, mean of m = 3.4 particles/s and standard deviation of σ = 2.7 particles/s. Particle emission rates larger than m + σ are labeled superemitters. Red curves are lognormal fits found via nonlinear regression.

for the observed outliers of "fast-deep" and "nose" breathing activities. In other words, the "breathing high producers" as defined by Edwards *et al.*[15] are not necessarily also speech superemitters.

Discussion

Given that the results clearly indicate that particle emission rate is correlated with vocalization amplitude, a natural question is: why? The particles emitted during breathing and speech are hypothesized to be formed primarily by a "fluid-film burst" mechanism inside the small airways of the lungs and/or via vocal folds vibration and adduction at the larynx[6,20,21]. During exhalation the elastic walls of the respiratory bronchioles contract, and the mucosal fluid on the lumen surface forms a continuous film that can completely fill the airway. During the subsequent inhalation, the bronchioles expand and the film ruptures, yielding particles that are drawn into the alveoli and subsequently exhaled. A similar mechanism is believed to occur in the larynx, as the vocal folds repeatedly close and open during vocalization[21]; when the vocal folds come into contact during adduction, fluid films that form between them can then rupture during their subsequent abduction. Our direct comparison of particles emitted during various types of breathing versus speech demonstrates that even quiet speech yields significantly more particles than normal breathing (Fig. 5A). Coupled with the observation that the particles generated during speech on average are slightly larger (Fig. 5B), the results suggest that laryngeal particle generation, which presumably does not occur during normal breathing, is at least partially responsible for the observed larger rates of particle emission. Indeed, the fundamental frequency or "pitch" of vocalization (i.e., the frequency at which the vocal folds open and close) increases slightly with amplitude (cf. Supplementary Fig. S11 and Gramming *et al.*[32]), so the increased amplitude could reflect an increased opportunity for particles to form at the larynx.

Complicating matters, however, vocalization at a larger voice amplitude requires a larger exhalation flow rate[33,34]. A possible interpretation of our observations is that the underlying physical mechanism of particle release hinges on the combination of laryngeal particle generation rate and the time integral of the exhalation flow rate during vocalization[35]. If the volume of exhaled air is larger when the voice amplitude is higher, a larger fraction of particles formed in bronchiolar film rupture may escape from the lungs, with consequently more emitted particles, thus increasing the particle concentration in the exhaled air. Since our measurements only gauge the particle emission rate (and equivalent concentration), it is difficult to decouple the relative contributions of these two mechanisms. Fitting our particle size distributions to constrained bimodal lognormal distributions provides some evidence consistent with the interpretation presented by Johnson *et al.*[21] that there are two modes, presumably due to bronchiolar versus laryngeal generation, but we do not find any significant difference in particle emission rates for the two modes as a function of vocalization amplitude (Supplementary Fig. S10 and cf. Fig. 5B). Furthermore, it is less understood how particles originating in the respiratory tract might deposit in more proximal regions instead of being emitted during exhalation. Particle deposition efficiency during nasal exhalation is known to depend on exhalation flow rate in a convoluted fashion, with Brownian diffusion, sedimentation, and inertial impaction all playing roles at different length and time scales within the respiratory tract[36]. Nonetheless, our results strongly suggest that, in general, more particles escape the respiratory tract if the vocalization is louder.

Our results also clearly show that some participants release many more particles than others, for as-yet unclear reasons. It is known that the Rayleigh-Plateau instability that gives rise to small droplets during the "film burst" is

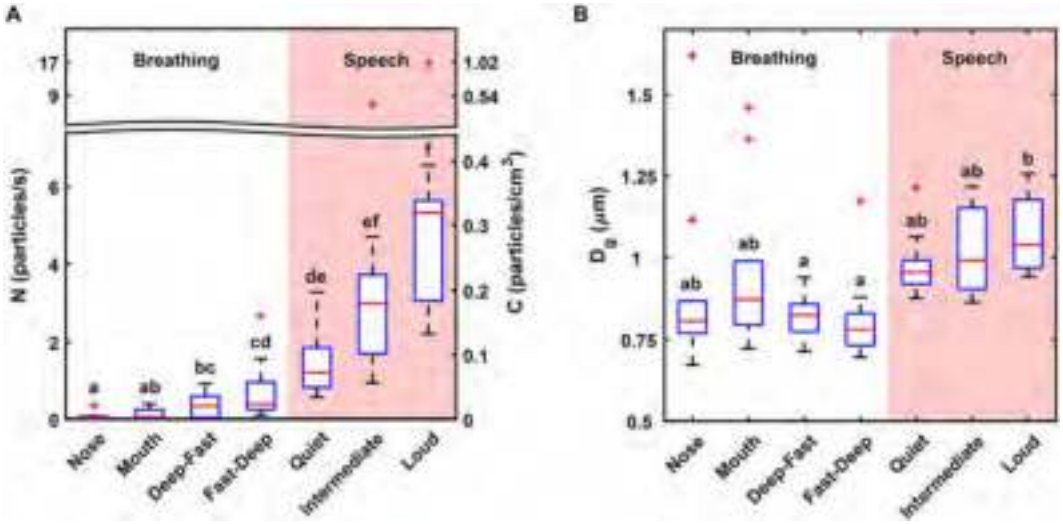

Figure 5. Comparison of (**A**) emission rate/concentration and (**B**) corresponding geometric mean diameters of particles emitted during various modes of breathing versus speech at different loudness levels. "Nose" denotes normal nasal breathing; "Mouth" denotes normal mouth breathing; "Deep-Fast" denotes deep, slow nasal inhalation followed by fast mouth exhalation; "Fast-Deep" denotes fast nasal inhalation followed by deep (i.e., slow and prolonged) mouth exhalation. "Quiet", "Intermediate", and "Loud" denote loudness levels while reading aloud a passage of text ("Rainbow" passage) at respective amplitudes. Red lines indicate medians, while bottom and top of blue boxes indicate the 25th and 75th percentiles respectively; sample size is n = 10. Outliers (defined as values that exceed 2.7 standard deviations) are indicated with red plus signs. Note that the 2 outliers for speech in (**A**) are a different individual (F4) than the two outliers observed for nose and fast-deep breathing (M24 and M5 respectively). Scheffe groups are indicated with letters; groups with no common letter are considered significantly different with $p < 0.05$, cf. Supplementary Table S1. Note that (**A**) has different scales above and below the break.

sensitive to the interfacial tension, density, and viscosity of the fluid[37], so one possible explanation is that the mucosal fluids in different people have different material properties and correspondingly generate more or fewer drops. Notably, different disease states are known to alter the physicochemical properties of the mucosal fluid lining the respiratory tract[38], so it is possible that infected individuals might generate markedly different quantities of particles than those emitted by the healthy individuals tested here. Intriguingly, Edwards *et al.*[15] found that delivering nebulized isotonic saline to individuals decreased the number of particles exhaled during normal breathing for a few hours after inhalation of the saline; further tests are warranted with speech. Alternatively, it is possible that individual manners of articulation affect the amount of internal deposition of the particles before they manage to escape the mouth. Our tests of different languages yielded no significant differences, at odds with previous speculation that language spoken might have played a role in the epidemiology of SARS coronavirus transmission[39], and suggesting that some as yet unknown physiological factor causes the dramatic variation among individuals.

Regardless of the underlying physical mechanism, from an epidemiological perspective the existence of speech superemitters motivates consideration of a new hypothesis: that speech superemitters contribute to "superspreading" of infectious diseases transmitted by emitted airborne particles. A superspreader is a contagious individual who infects a disproportionately large number of susceptible contacts[31,40,41]. To date, several airborne superspreading events have been documented, such as the MERS-CoV outbreak in South Korea in 2015 and the SARS-CoV outbreak in 2003, the latter being initiated in Hong Kong and spreading to Canada, Vietnam, and Singapore through travel[40–43]. In the case of respiratory infectious diseases in particular, the underlying physiological and immunological factors that contribute to heterogeneity in individual infectiousness remain poorly understood, despite the epidemiological importance of respiratory superspreaders. Quantifying infectious pathogen loads in exhaled air is technically challenging, relative to other contagious substances like blood, urine, and feces. Many factors presumably affect the secondary attack rate attributable to any infectious individual, including the herd immunity status of others in proximity. Nonetheless, our results suggest that, for respiratory infections transmitted from person to person via airborne particles, the existence of speech superemitters might help explain the existence of superspreaders. A similar hypothesis was advanced by Edwards *et al.*[15] in response to their observation of variability between individuals in the number of particles emitted during mouth breathing. Interestingly, our data show that speech superemitters are not necessarily breathing superemitters as well (Fig. 5A), suggesting that respiratory superemission during vocalized speech has a different underlying physiology than superemission during tidal breathing.

Our results indicate that speech is potentially of much greater concern than breathing for two reasons: the particles on average are larger, and thus could potentially carry a larger number of pathogens, and much greater quantities of particles are emitted compared to breathing, thus increasing the odds of infecting nearby susceptible individuals. Laryngeal particle generation during speech is also potentially important since some studies suggest that human influenza viruses attach more abundantly to the large airways of the upper respiratory tract than to

the bronchiolar and alveolar cells in the lower respiratory tract, while MERS-CoV and avian influenza viruses mainly cause lower respiratory tract infections due to the greater presence of these virus receptors deeper within the lung[44–47]; likewise there is evidence that laryngeal tuberculosis is potentially more contagious than typical pulmonary tuberculosis[48].

A second key epidemiological implication of our results is that simply talking in a loud voice would increase the rate at which an infected individual releases pathogen-laden particles into the air, which in turn would increase the probability of transmission to susceptible individuals nearby[49]. For example, an airborne infectious disease might spread more efficiently in a school cafeteria than a library, or in a noisy hospital waiting room than a quiet ward. Moreover, our data suggest a related hypothesis, that infected individuals could be transmitting significant numbers of respiratory pathogens via speech in the absence of overt clinical signs of illness like coughing or sneezing. More research is needed; however, the presence of asymptomatic or paucisymptomatic superspreaders would have important public health implications in the surveillance for and mitigation of infectious disease epidemics that are spread by airborne respiratory particles. The data presented here strongly suggest that further efforts to test these hypotheses are warranted.

Methods

Human subjects. The University of California Davis Institutional Review Board approved this study and all research was performed in accordance with relevant guidelines and regulations of the Institutional Review Board. We recruited 48 healthy volunteers (26 males and 22 females, ranging in age from 18 to 45 years old) by posting flyers at the University of California Davis campus over the time period May 2016 to March 2018. Informed consent was obtained from all participants prior to study participation. All participants completed a brief questionnaire including age, gender, weight, height, general health status, and smoking history. Only participants who self-reported as healthy non-smokers were included in the study. The subject in Supplementary Fig. S12 provided her written informed consent for the publication of identifying information/images in an online open-access publication.

Experimental set-up. A photograph of the experimental set-up is provided as Supplementary Fig. S12. An aerodynamic particle sizer (APS, TSI model 3321) operating at a total flow rate of 5 L/min (sheath flow rate $\cong$ 4 L/min, sample flow rate $\cong$ 1 L/min) was placed inside a HEPA filtered laminar flow hood that provided class 10 air. A plastic funnel (diameter = 10 cm) was connected to the APS sampling inlet via a conductive silicon tube (distance between funnel hole to APS inlet = 7.5 cm, tube inner diameter = 1.2 cm). During each experiment, participants sat at the laminar flow hood, in front of the APS, and spoke into the funnel. For the majority of speaking and breathing experiments, a nose rest across the funnel opening was used to position participants' mouths approximately 7.5 cm away from the funnel inlet (hole) and also to divert nasal exhalations away from the APS. During "nose-breathing" experiments, the nose rest was removed to allow nasal exhalations to be drawn into the APS. Note that participants' faces did not touch the funnel, so that air was free to move around the side of their faces; in this sense the cone was a semi-confined environment and not all expired particles were necessarily sampled by the APS. Also note that the sheath flow inside of an APS is filtered, so the particle emission rates sampled by the APS automatically remove 80% of the particles sampled from the funnel. Equivalent concentrations reported on the secondary axes in Figs 1 through 5 are determined from the raw particle counts using the sample flow rate, i.e., $C = \frac{\text{particles}}{\text{s}} \times \frac{\text{s}}{\text{cm}^3} = \frac{\text{particles}}{\text{cm}^3}$. Also note that the APS measures the size distribution of particles larger than 0.5 µm, but only detects the presence of particles between 0.37 µm and 0.5 µm without providing precise size measurements. For this reason Figs 1–5 exclude the counts of particles smaller than 0.5 µm; including them has little impact on the results since the vast majority of particles were larger than 0.5 microns.

A microphone (audio-technica PRO 37) and a decibel meter (Extech, 407760) were placed immediately on either side of the funnel to record the vocalizations. A computer screen with word prompts and a timer was placed behind the APS to guide participants in making requested vocalizations for the specified duration. The timing, duration, repetition, and order of vocalization and breathing experiments were coordinated by customized code written in LabVIEW (National Instruments). A digital hygrometer was used to measure the ambient temperature and relative humidity inside the laminar flow hood during all experiments. The participants were not allowed to drink or eat during the experiment, but they were free to rest between experiments for a few minutes as needed; data from each individual participant was gathered over an approximately 1-hour time period. We performed the experiments in an indoor (controlled) environment, so the ambient temperature varied only from approximately 20 to 25 °C, while the ambient relative humidity measured inside the laminar flow hood varied from a low of approximately 45% to a high of 80%. Control experiments indicate that the particle size distribution was independent of whether the particles were expired early or late during a sustained vocalization (Supplementary Fig. S3), indicating that transient fluctuations in the humidity inside the funnel due to exhalation had no impact on the final measured size distribution. Particles with initial diameter of less than 20 µm dry to approximately half of their initial diameter in less than 1 second[49,50]. Different correction factors have been suggested in the literature that one can use to estimate the initial size of the particles[49,51]; here we focus on the final size distribution because epidemiologically it is the final size distribution governs the deposition efficiency of the particles in the respiratory tract of nearby susceptible individuals[52].

Vocalization experiments. *"/ɑ/" experiments.* Participants (n = 10, 5 males, M1 to M5, and 5 females, F1 to F5) voiced /ɑ/ (the vowel sound in 'saw') for five seconds, followed by 15 seconds of nose breathing, repeated six times in succession. The participant repeated the series of six /ɑ/ vocalizations, to the best of the participant's ability, at the same amplitude. Each participant completed eight sets of /ɑ/ experiments, each set performed at different, self-regulated voice amplitude. Timed prompts with directions for the requested vocalization appeared on the computer screen, which displayed a timer and an amplitude (loudness) gauge to help the participants regulate their voice amplitude. The requested amplitudes were presented to participants in a random order.

"Rainbow passage" experiments. Participants (n = 10, 5 males, M1 to M5, and 5 females, F1 to F5) read aloud a 330-word excerpt of text in English, known in linguistics research as the Rainbow passage[53]. Participants were asked to read the Rainbow passage aloud three times, at a comfortable pace, over approximately 2 minutes per reading. Each of the three readings was performed at a different self-regulated amplitude: quiet, intermediate, and loud. Quiet was defined for participants as "just louder than a whisper," intermediate as a "normal conversational voice," and loud as "giving a loud lecture".

"The Little Prince" experiments. Bilingual participants (n = 30) fluent in both English and either Spanish (n = 10, 5 males, M6 to M10, and 5 females, F6 to F10), Mandarin (n = 10, 5 males, M11 to M15, and 5 females, F11 to F15), or Arabic (n = 10, 6 males, M16 to M21, and 4 females, F16 to F19) read Chapter 24 of "The Little Prince[54]" aloud six times, three times in English translation, each time at a different amplitude (quiet, intermediate, and loud) and three times in their respective language, again at three loudness levels.

Breathing/speaking experiments. Participants (n = 10, 6 males, M5 and M22 to M26, and 4 females, F4 and F20 to F22) alternated four silent breathing patterns with vocalized speech at three amplitudes. For breathing measurements, the breathing patterns were designated as "nose" (both inhalation and exhalation through the nose), "mouth" (both inhalation and exhalation through the mouth), "deep-fast" (deep, slow inhalation for ~3 seconds through the nose, holding it for ~1 second, followed by fast exhalation through the mouth (~1 second)), and "fast-deep" (rapid inhalation through the nose (~1 second), holding it for ~1 second, followed by slow exhalation through the mouth for ~3 seconds). Each breathing experiment was performed over 2 minutes, and at a comfortable pace for the participants. Between performing different breathing patterns, participants were asked to read the Rainbow passage in a "quiet," "intermediate," or "loud" voice, as prompted by the computer in random order.

Statistical analysis. Data analysis was performed in MATLAB (MathWorks), with data fits performed as noted in figure legends. Pearson's linear correlation coefficients and p values were calculated for linear fits. Lognormal fits were made via nonlinear regression, and median, mean, and standard deviation were calculated. Box-and-whisker plots show the median (red line), interquartile range (blue box), and range (black whiskers). To analyze the breathing/speaking experiments data presented in Fig. 5, Stata/SE 15.1 was used to perform general linear mixed model (GLMM) analysis to account for person-level correlations, and post hoc pairwise comparisons were performed and adjusted for multiple comparisons using Scheffe's method.

Data Availability

All relevant data are available from the corresponding authors upon request.

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Author Contributions

S.A., A.S.W., C.D.C., S. B., N.M.B. and W.D.R. designed research; S.A. performed experiments; S.A. and W.D.R. analysed the data; S.A. and W.D.R. wrote the manuscript, and all co-authors reviewed the manuscript.

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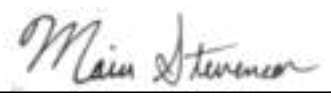
This is "**Exhibit P**"
to the Affidavit of Matthew Hodge,
affirmed this 2nd day of July, 2021



A Commissioner, etc.

Ontario is now in Step 2 of the Roadmap to Reopen. Follow the restrictions and public health measures.

Ontario

Reopening Ontario

Learn about the Roadmap to Reopen, the province's three-step plan to safely and gradually lift public health measures based on ongoing progress of provincewide vaccination rates and improvements of key public health and health care indicators.

Ontario is in Step 2 of the Roadmap to Reopen as of **June 30 at 12:01 a.m.**

Overview

The Roadmap to Reopen is a three-step plan to safely and cautiously reopen the province and gradually lift public health measures.

The plan is based on:

- the provincewide vaccination rate
- improvements in key public health and health care indicators

In Step 2 of the roadmap, we must all continue to follow the public health measures, advice and restrictions (https://covid-19.ontario.ca/public-health-measures) .

Guiding principles

Step 1: An initial focus on resuming outdoor activities with smaller crowds where the risk of transmission is lower, and permitting limited indoor settings with restrictions.

Step 2: Further expanding outdoor activities and resuming limited indoor services with small numbers of people and with face coverings being worn.

Step 3: Expanding access to indoor settings, with restrictions, including where there are larger numbers of people and where face coverings can't always be worn.

Moving through the steps

The province will remain at each step for **at least 21 days** to evaluate any impacts on key public health and health system indicators. It can take up to two weeks for COVID-19 vaccinations to offer protection against the virus.

The province will remain in Step 1 for at least 21 days to evaluate any impacts on key public health and health system indicators.

If at the end of the 21 days the province has met the following vaccination thresholds, and there are continued improvements in other key public health and health system indicators, the province may move to the next step of the

roadmap:

- **Step 1:** 60% of adults vaccinated with one dose
- **Step 2:** 70% of adults vaccinated with one dose and 20% vaccinated with two doses
- **Step 3:** 70 to 80% of adults vaccinated with one dose and 25% vaccinated with two doses

Roadmap to reopen – key highlights

Vaccination rate
plus key public health and health care indicators

Step 1

60%

Adults with one dose

Permit with restrictions

Outdoor spaces begin reopening, limited indoor settings with restrictions

- Outdoor social gatherings and organized public events for up to 10 people
- Outdoor dining for up to 4 people per table
- Essential retail capacity at 25%
- Non-essential retail capacity at 15%
- Religious services, rites and ceremonies indoors at 15% capacity and outdoors with capacity limited to permit physical distancing of 2 metres
- Outdoor sports training (no games or practices), fitness classes and personal training up to 10 people
- Day camps
- Overnight camping at campgrounds and campsites, including Ontario Parks and short-term rentals
- Outdoor horse racing and motor speedways without spectators
- Outdoor pools and wading pools

+21 days before next stage

Vaccination rate
plus key public health and health care indicators

Step 2

70%

Adults with one dose
20% Fully vaccinated

Permit with restrictions

Open indoors with small numbers and face coverings and expand outdoors

- Outdoor social gatherings and organized public events for up to 25 people
- Indoor social gatherings and organized public events for up to 5 people
- Outdoor dining for up to 6 people per table
- Essential and other select retail permitted at 50% capacity
- Non-essential retail capacity at 25%
- Stores in shopping malls open, with restrictions
- Larger indoor religious services, rites, or ceremonies, including wedding services and funeral services at 25% capacity
- Outdoor religious services, rites, or ceremonies, including wedding services and funeral services, capped at the number of people that can maintain a physical distance of two metres
- Overnight camps
- Personal care services where face coverings can be worn at all times at 25% capacity
- Outdoor fitness classes are capped at the number of people who can maintain 3 metres of distance
- Public libraries permitted at 25% capacity
- Outdoor meeting and event spaces at 25% capacity
- Outdoor amusement and water parks at 25% capacity
- Outdoor sports games, leagues and events at 25% capacity
- Outdoor cinemas, performing arts, live music events and attractions at 25% capacity
- Outdoor horse racing and motor speedways at 25% capacity

+21 days before next stage
Vaccination rate
plus key public health and health care indicators

Step 3

70-80%

Adults with one dose
25% Fully vaccinated

Permit with restrictions

Expand indoors where face coverings can’t always be worn

- Larger indoor and outdoor social gatherings and organized public events
- Indoor dining
- Essential and non-essential retail with limited capacity
- Larger indoor religious services, rites or ceremonies, including wedding services and funeral services with capacity limits
- Indoor meeting and event spaces
- Indoor sports and recreational facilities

- Indoor seated events
- Indoor attractions and cultural amenities
- Casino and bingo halls
- Other outdoor activities from Step 2 permitted to operate indoors

Roadmap to reopen at a glance

This is a high-level overview of what can reopen in each step.

Read our public health measures, advice and restrictions (https://covid-19.ontario.ca/public-health-measures) for a more detailed summary or refer to *O. Reg. 263/20 (https://www.ontario.ca/laws/regulation/200263)* for a complete list of public health and workplace safety measures and restrictions for Step 2.

Gatherings

Step 1

Maximum 10 people for outdoor gatherings

Outdoor end-of-school-year celebration ceremonies held by a school or private school are exempt from outdoor gathering limits, with restrictions

Retirement homes are exempt from gathering limits

Step 2

Maximum 25 people for outdoor gatherings

Maximum 5 people for indoor gatherings

Step 3

Larger indoor and outdoor gatherings with size limits

Religious services, rites or ceremonies, including wedding services and funeral services (does not apply to receptions)

Step 1

15% capacity indoors of the room

Outdoor permitted with capacity limited to permit physical distancing of 2 metres

Step 2

Indoor permitted at 25% capacity of the room

Outdoor permitted with capacity limited to permit physical distancing of 2 metres

Step 3

Larger indoor religious services, rites and ceremonies

Outdoor permitted with capacity limited to permit physical distancing of 2 metres

---

Retail

Step 1

Essential and select retail at 25% capacity and can sell all goods (including discount and big box)

Non-essential retail at 15% capacity

Retail stores in malls closed unless the stores have a street facing entrance

Restrictions on shopping malls

Step 2

Essential retail at 50% capacity

Non-essential retail at 25% capacity

Stores in shopping malls open

Step 3

Essential and non-essential retail open with capacity limited to permit physical distancing of 2 metres

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Liquor stores

Step 1

Open at 25% capacity

Step 2

Open at 50% capacity

Step 3

Open with capacity limited to permit physical distancing of 2 metres

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Restaurants and bars

Step 1

Outdoor dining with 4 people per table from different households and other restrictions

Step 2

Outdoor dining with 6 people per table and other restrictions

Karaoke permitted with restrictions (outdoor only)

Step 3

Indoor dining with capacity and other restrictions

Outdoor dining with capacity limited to permit physical distancing of 2 metres

Buffets permitted

Karaoke permitted with restrictions

Personal care services

Step 1

Closed

Sensory deprivation pods permitted when prescribed or administered by a regulated health professional, with restrictions

Step 2

Open at 25% capacity

Appointment required

Services that require the removal of a face covering not permitted

Step 3

Open with capacity limited to permit physical distancing of 2 metres and other restrictions

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Sports and recreational fitness facilities

Step 1

Outdoor fitness classes, outdoor sports training (no games or practices) and outdoor personal training, with 10 patrons maximum

Closed for indoor use except for high-performance athletes and day camps

Step 2

Outdoor sports leagues open

Training for professional or amateur athletes and/or competitions

Closed for indoor use except for high-performance athletes and day or overnight camps

Step 3

Indoor open, with restrictions

Outdoor open, with restrictions

Personal fitness and training

Step 1

Outdoor fitness classes – 10 people maximum, 3 metres distance

Outdoor personal training – 10 people maximum, 3 metres distance

Outdoor sports training only – 10 people maximum, 3 metres distance (no games or practices)

Step 2

Outdoor fitness classes and personal training – with limit on the number of patrons, 3 metres distance

Step 3

Outdoor and indoor fitness classes and personal training permitted, with restrictions

---

Outdoor recreational amenities

Step 1

Open with restrictions

Step 2

Open with restrictions

Step 3

Open

Water features

Step 1

Outdoor pools, splash pads, spray pads, whirlpools, wading pools and water slides open

Step 2

Outdoor pools, splash pads, spray pads, whirlpools, wading pools and water slides open

Step 3

Indoor and outdoor pools, splash pads, spray pads, whirlpools, wading pools and water slides open

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Meeting and event spaces

Step 1

Closed with exceptions for certain purposes including social services, government operations, court services, in-person examinations for select professions (subject to conditions)

Step 2

Outdoor spaces open at 25% capacity and other restrictions

Indoor meeting and event spaces closed, with exceptions for certain purposes, including for viewing for potential booking of a future event

Step 3

Indoor spaces open with capacity and other restrictions, including for tradeshows, conferences and exhibitions

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Day camps

Step 1

Open based on guidance from the Chief Medical Officer of Health (PDF) (https://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/2019_summer_day_camps_guidance.pdf)

Step 2

Open based on guidance from the Chief Medical Officer of Health (PDF) (https://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/2019_summer_day_camps_guidance.pdf)

Step 3

Open based on guidance from the Chief Medical Officer of Health (PDF) (https://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/2019_summer_day_camps_guidance.pdf)

Overnight camps

Step 1

Closed

Step 2

Open based on guidance from the Chief Medical Officer of Health

Step 3

Open based on guidance from the Chief Medical Officer of Health

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Commercial film and TV production

Step 1

Open with no audience, no more than 50 performers on set, and other restrictions

Step 2

Open with no audience, and other restrictions

Step 3

Open with capacity restrictions for studio audiences, and other restrictions

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Performing arts

Step 1

Outdoor open for rehearsing or performing a recorded or broadcasted event – 10 people maximum, spectators not permitted

Step 2

Indoor closed, permitted only for the purpose of rehearsing or performing a recorded or broadcasted event – spectators not permitted

Outdoor open, including live music, with spectator capacity at 25% and other restrictions

Step 3

Indoor open, including live music, with spectator capacity and other restrictions

Outdoor open, including live music, with spectator capacity and other restrictions

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Cinemas

Step 1

Drive-in open

Step 2

Indoor closed

Outdoor open with spectator capacity at 25% and other restrictions

Step 3

Indoor open with spectator capacity and other restrictions

Outdoor open with spectator capacity and other restrictions

Casino, bingo halls and gaming establishments

Step 1

Closed

Step 2

Closed

Step 3

Open with capacity and other restrictions

Horse racing

Step 1

Outdoor with capacity and crew restrictions

No spectators

Step 2

Outdoor open with spectator capacity at 25% and other restrictions

Step 3

Open with spectator capacity and other restrictions

Motorsports and speedways

Step 1

Outdoor with capacity and crew restrictions

No spectators

Step 2

Outdoor open with spectator capacity at 25% and other restrictions

Step 3

Open with spectator capacity and other restrictions

Short-term rentals (does not include hotels, motels, lodges or resorts, but does apply to cabins and cottages)

Step 1

Open

Indoor pools, communal steam rooms, saunas or indoor whirlpools, indoor fitness centres, or other indoor recreational facilities closed

Step 2

Open

Indoor pools, communal steam rooms, saunas or indoor whirlpools, indoor fitness centres, or other indoor recreational facilities closed

Step 3

Open

Indoor pools, communal steam rooms, saunas or indoor whirlpools, indoor fitness centres, or other indoor recreational facilities open with some restrictions

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Hotels, motels, lodges, resorts and other shared rental accommodation

Step 1

Open. Indoor pools, communal steam rooms, saunas or indoor whirlpools, indoor fitness centres, or other indoor recreational facilities closed

Step 2

Open. Indoor pools, communal steam rooms, saunas or indoor whirlpools, indoor fitness centres, or other indoor recreational facilities closed

Step 3

Open. Indoor pools, communal steam rooms, saunas or whirlpools, indoor fitness centres, or other indoor recreational facilities open with some restrictions

---

Public libraries

Step 1

Curbside pickup for materials

Access to computers, photocopiers, and similar services permitted

Step 2

Open with 25% capacity and other restrictions

Step 3

Open, with capacity limited to permit physical distancing of 2 metres and other restrictions

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Museums and attractions

Step 1

Outdoor zoos, landmarks, historic sites, botanical gardens, and similar outdoor attractions open with capacity limited to 15% for ticketed areas and other restrictions

Step 2

Outdoor waterparks open with 25% capacity and other restrictions

Outdoor amusement parks open with 25% capacity and other restrictions, including on rides

Step 3

Indoor museums and art galleries, Zoos and aquariums, waterparks, and amusement parks open with capacity restrictions

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Fairs and rural exhibitions

Step 1

Closed

Step 2

Outdoor open at 25% capacity and other restrictions

Step 3

Indoor and outdoor open at reduced capacity and other restrictions

---

Teaching and instruction (for example, recreational classes and lessons)

Step 1

Outdoor open, 10 patrons maximum, 2 metres physical distancing and other restrictions

Step 2

Outdoor open, with distancing and other restrictions

Step 3

Indoor and outdoor open with distancing and other restrictions

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Tour and guide services

Step 1

Outdoor open, 10 patrons maximum, 2 metres physical distancing and other restrictions

Boat tours and motor vehicle tours not permitted

Step 2

Outdoor open, with capacity at 25% and other restrictions

Step 3

Indoor and outdoor open with capacity and other restrictions

Construction

Step 1

All construction open

Step 2

All construction open

Step 3

All construction open

Driving instruction

Step 1

Not permitted, except for drivers of commercial vehicles

Step 2

Driving instruction permitted with restrictions

Step 3

Driving instruction permitted with restrictions

Ontario Parks and campgrounds

Step 1

Open

Step 2

Open

Step 3

Open

Marinas and boating clubs

Step 1

Permitted with clubhouses, and other indoor amenities closed

Recreational boating permitted but only members of a household can gather on a boat

Step 2

Permitted with clubhouses, and other indoor amenities closed

Step 3

Open with restrictions

Strip clubs

Step 1

Permitted to operate as a restaurant in alignment with restaurant restrictions

Step 2

Permitted to operate as a restaurant in alignment with restaurant restrictions

Step 3

Permitted to operate as a strip club in alignment with restaurant and performance restrictions

---

Domestic services

Step 1

Open to support children, seniors or vulnerable persons

Step 2

Open

Step 3

Open

Photography studios and services

Step 1

Outdoor open and by appointment only, with restrictions

Step 2

Outdoor and limited indoor open with restrictions

Step 3

Outdoor and indoor open with restrictions

Community centres and multi-purpose facilities

Step 1

Open for social services, child care and day camps, mental health support services or addictions support services, and permitted indoor and outdoors activities and services, with restrictions

Step 2

Open for social services, child care and day and overnight camps, mental health support services or addictions support services, and permitted indoor activities and services, with restrictions

Step 3

Open with restrictions

Real estate open houses

Step 1

Showings by appointment only

Step 2

Showings by appointment only

Step 3

Open

Drive-in and drive through events

Step 1

Open with restrictions

Step 2

Open with restrictions

Step 3

Open with restrictions

Health and safety training

Step 1

Indoor: 10 person limit

Outdoor: 10 person limit

Physical distance of at least two metres from every other person in the instructional space, except where necessary for teaching and instruction that cannot be effectively provided if physical distancing is maintained

Step 2

Indoor: 10 person limit

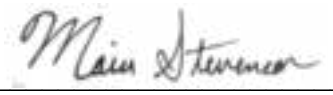
Outdoor open, with capacity and other restrictions

Step 3

Indoor and outdoor open with capacity and other restrictions

Updated: June 30, 2021
Published: April 27, 2020

This is "**Exhibit Q**"
to the Affidavit of Matthew Hodge,
affirmed this 2nd day of July, 2021



A Commissioner, etc.

TORONTO

COVID-19

Toronto is in Step Two of the Province's Roadmap to Reopen. Get health updates and information about COVID-19 vaccines at toronto.ca/covid19 (https://www.toronto.ca/home/covid-19).

Programs & Services for Tuberculosis (TB)

It is estimated that one in three people worldwide is infected with the TB bacteria. In Toronto, about 300 people become sick with **tuberculosis (https://www.toronto.ca/?page_id=28540)** every year. Treatment for TB disease involves taking medication every day for six months or longer. Although treatment can take a long time, a person can be cured of TB once treatment is complete.

Different specialty teams in the TB program work together to provide support for individuals with TB as well as their families and to help prevent the spread of TB in Toronto.

Expand All | Collapse All

Case Management Teams

- Provide case management services for people with active TB
- Ensure adequate TB treatment is received and completed
- Follow-up of individuals exposed to TB
- Educate clients and contacts
- Order TB medication for clients with TB disease and contacts with TB infection

Directly Observed Therapy

Directly Observed Therapy (https://www.toronto.ca/community-people/health-wellness-care/health-programs-advice/tuberculosis-tb/programs-services-for-tuberculosis-tb/directly-observed-therapy-dot-in-tuberculosis-tb/)

- Ensure clients take medication correctly
- Monitor for side effects
- Prevent/Reduce drug resistance caused by interrupted drug therapy
- Collaborates with Case Management Teams regarding client care

Homeless and Corrections Team

- Manage TB disease and infection in the **homeless/underhoused and corrections populations (https://www.toronto.ca/community-people/health-wellness-care/health-programs-advice/tuberculosis-tb/tuberculosis-tb-and-homeless-service-settings/)**
- Ensure adequate TB treatment is received and completed
- Follow-up of individuals exposed to TB
- Educate shelters, drop-in centers, clients, contacts and within correctional facilities
- Coordinate TB follow-up upon discharge from correctional facilities
- Liaise with Ministry of Community Safety and Correctional Services and other Toronto Public Health programs

Medical Surveillance and Drug Order Team

Medical Surveillance (https://www.toronto.ca/community-people/health-wellness-care/health-programs-advice/tuberculosis-tb/programs-services-for-tuberculosis-tb/tuberculosis-tb-medical-surveillance/) and Drug Order Team

- Immigrants, refugees, visitors, visa students/workers identified through immigration surveillance are monitored for TB disease
- Monitor clients with TB infection identified through routine surveillance
- Order TB medication for clients with TB infection on immigration and routine surveillance
- Order TB medication for Toronto clinicians whose clients live outside of Toronto

Prevention Team

Provide free educational materials, presentations, and consultation to clients, community agencies and health professionals

- Health promotion and community development
- Outreach to populations at higher risk for TB disease and health professionals
- Create and develop multi-language resource materials for clients and health professionals
- Partner with community agencies to increase TB awareness

Social Work for TB Clients

- .Provide assessment, counselling and referral
- Focus on income and housing
- Provide internal and external consultation

TB STOP Drop-in

TB STOP (https://www.toronto.ca/community-people/health-wellness-care/health-programs-advice/tuberculosis-tb/tuberculosis-tb-and-homeless-service-settings/?accordion=tb-stop-drop-in) provides drop-in services for people who are homeless and under-housed as well as for service providers to the homeless in Toronto:

- Symptom screening
- Sputum collection
- Referrals to other health professionals as appropriate
- TB skin testing

Contact Information

Tuberculosis Program
Toronto Public Health
Monday to Friday
8:30 a.m. - 4:30 p.m.

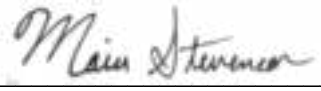
Ask to speak to someone in the TB Program.
Telephone: 416-338-7600
Email: targettb@toronto.ca (mailto:targettb@toronto.ca)

Related Information

Tuberculosis (TB) & Homeless Service Settings (https://www.toronto.ca/community-people/health-wellness-care/health-programs-advice/tuberculosis-tb/tuberculosis-tb-and-homeless-service-settings/)

Tuberculosis (TB) Information for Health Professionals (https://www.toronto.ca/community-people/health-wellness-care/information-for-healthcare-professionals/communicable-disease-info-for-health-professionals/tuberculosis-information-for-health-professionals/)

This is "**Exhibit R**"
to the Affidavit of Matthew Hodge,
affirmed this 2nd day of July, 2021



A Commissioner, etc.

Public Health Ontario | Santé publique Ontario

Ontario COVID-19 Data Tool

The Ontario COVID-19 Data Tool provides epidemiological information on COVID-19 activity in Ontario to-date. Explore the most recent COVID-19 data including: daily case counts, hospitalizations and deaths (Case trends), total or recent cases counts by age and sex, map by public health unit, source of COVID-19 infection (acquisition), outbreaks and laboratory testing.

Additions to the Ontario COVID-19 Data Tool as of May 28th, 2021:

- Vaccine uptake data on the Summary, Map and Vaccines sections
- COVID-19 reproduction number and doubling time

The COVID-19 Data Tool is updated Monday to Fridays at 11:30 a.m. except on statutory holidays. For weekend case counts see the **Daily Epidemiological Summary.**

For questions about the data, please contact **EPIR@oahpp.ca**.

Public health unit

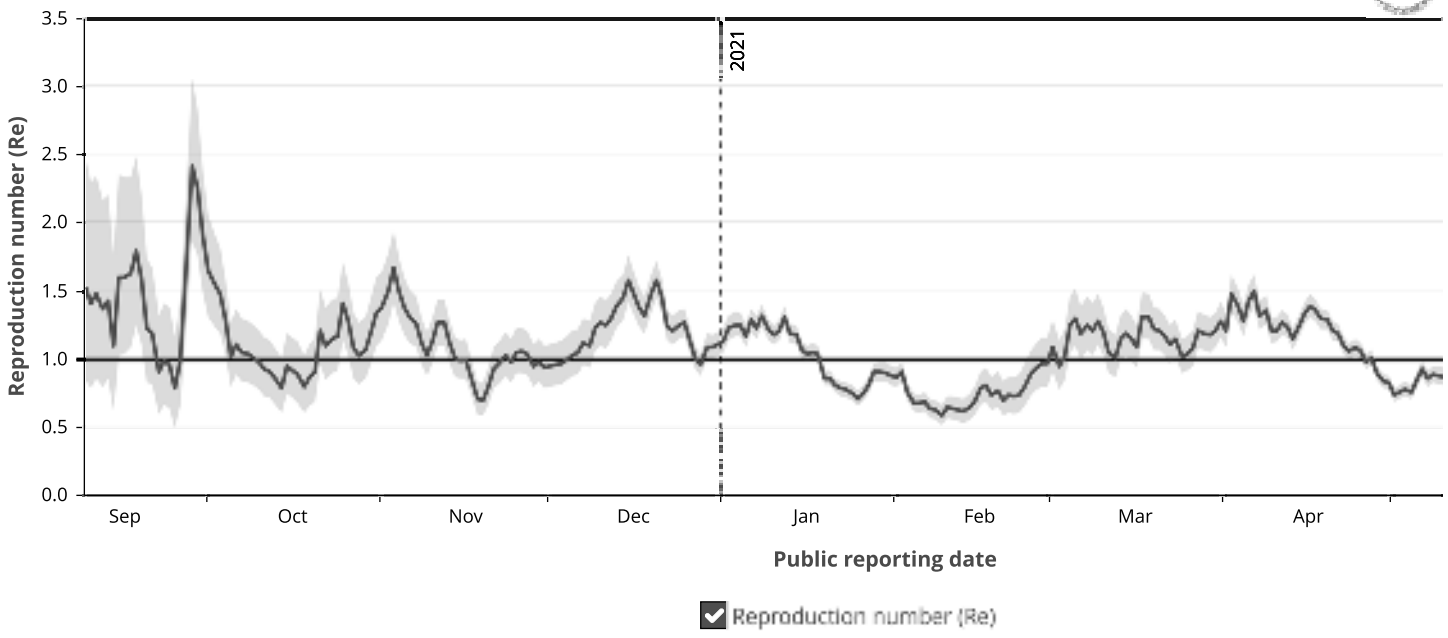
Niagara Region Public Health

09 Sep 2020 — 22 Jun 2021

doubling time in Niagara Region Public Health

September 9, 2020 to June 22, 2021

Reproduction data are updated weekly on Tuesdays. Scroll over the data line to view doubling time estimates. An Re greater than 1 means that the overall number of new cases is increasing, while an Re less than 1 means the overall number of new cases is decreasing. An Re equal to 1 means the overall number of new cases will remain stable.



The Re is not shown when there are fewer than 12 cases in the last 7 days for a local public health unit.

95% Credible Interval (CI): There is a 95% probability that the true estimate lies within this interval based on the observed data. This interval is highlighted in light purple on the graph.

Doubling time (Td) is an estimate of the number of days it will take for the number of daily COVID-19 cases to double given the current trends in incidence. When this estimate is greater than 100 days, it is reported as >100.

Public reporting date is the date the public health unit reported the case to Public Health Ontario plus one day to account for the delay in public reporting.

Reproduction number (Re) is the average number of secondary cases of infection generated by each person infected with COVID-19. An Re greater than 1 means that the overall number of new cases is growing in a region. An Re equal to 1 means the overall number of new cases will remain stable. An Re less than 1 means the overall number of new cases is decreasing and suggests that COVID-19 is coming under control in a region.

« Previous Next »

Related Information

Coronavirus Disease 2019 (COVID-19)

External Resources

COVID-19 case data: All Ontario - Government of Ontario

COVID-19 cases in schools and child care centres - Ministry of Education

COVID-19 Hospitalizations - Government of Ontario

COVID-19 Vaccines Status - Government of Ontario

Updated 30 June 2021

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Kitchener Court File No.: CV-21-00000095-0000
St. Thomas Court File No.: CV-21-08
Welland Court File No.: CV-21-00013361-0000

TRINITY BIBLE CHAPEL ET AL., CHURCH OF GOD (RESTORATION) AYLMER ET AL., WELLANDPORT UNITED REFORMED CHURCH, and STEPHEN RICHARDSON

Applicants/Respondents

-and -

THE ATTORNEY GENERAL OF ONTARIO

Respondent/Applicant

ONTARIO
SUPERIOR COURT OF JUSTICE

(ST. THOMAS)

AFFIDAVIT OF MATTHEW HODGE

THE ATTORNEY GENERAL OF ONTARIO

[redacted]

Joshua Hunter

[redacted]

Daniel Guttman

[redacted]

Ryan Cookson

[redacted]

Maia Stevenson

[redacted]

Counsel for the Respondent

Kitchener Court File No.: CV-21-00000095-0000
St. Thomas Court File No.: CV-21-08
Welland Court File No.: CV-21-00013361-0000

ONTARIO
SUPERIOR COURT OF JUSTICE

B E T W E E N:

THE ATTORNEY GENERAL OF ONTARIO

Applicant

-and-

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHUURMAN, DEAN WANDERS, RANDY FREY, HARVEY FREY, and DANIEL GORDON

Respondents

A N D B E T W E E N:

HER MAJESTY THE QUEEN IN ONTARIO

Applicant

-and-

THE CHURCH OF GOD (RESTORATION) AYLMER, HENRY HILDEBRANDT, ABRAM BERGEN, JACOB HIEBERT, PETER HILDEBRANDT, SUSAN MUTCH, ELVIRA TOVSTIGA, and TRUDY WIEBE

Respondents

A N D B E T W E E N:

WELLANDPORT UNITED REFORMED CHURCH

Applicant

-and-

HER MAJESTY THE QUEEN AS REPRESENTED BY THE ATTORNEY GENERAL OF ONTARIO

Respondent

A N D B E T W E E N:

STEPHEN RICHARDSON

Applicant

-and-

THE ATTORNEY GENERAL OF ONTARIO

Respondent

AFFIDAVIT OF DRS. KARIM ALI and ZAIN CHAGLA
(Affirmed July 5, 2021)

I, DR. KARIM ALI of the [redacted] in the Province of Ontario, and I, DR. ZAIN CHAGLA of the [redacted] in the Province of Ontario, **AFFIRM**:

1. Dr. Ali's work address is 1200, Fourth Ave, St Catharines, ON L2S 0A9.
2. Dr. Chagla's work address is 300-25 Charlton Ave. East, Hamilton ON, L5G 3l2.
3. At the request of counsel for the Attorney General of Ontario, we have provided an expert report regarding COVID-19 risk factors, transmission and public health measures. Our expert report is attached to this affidavit as **Exhibit "A".** It details the specific questions counsel for the Respondent asked us to address within the report, our relevant expertise and the sources of our information.
4. We make this affidavit to provide our expert opinion and for no improper purpose. To this end, attached as **Exhibits "B"** and **"C"** are signed copies of our Acknowledgement of Expert's Duty. Attached as **Exhibits "D"** and **"E"** are the CVs of Drs. Ali and Chagla, respectively.

AFFIRMED by video conference by DR. KARIM ALI of the [redacted] in [redacted] before me at the City of Toronto on this 5th Day of July, 2021 in accordance with O Reg 431/20, Administering Oath or Declaration Remotely

A Commissioner for the Taking of Affidavits

DR. KARIM ALI

AFFIRMED by video conference by DR. ZAIN CHAGLA of the [redacted] before me at the City of Toronto on this 5th Day of July, 2021 in accordance with O Reg 431/20, Administering Oath or Declaration Remotely

A Commissioner for the Taking of Affidavits

DR. ZAIN CHAGLA

Kitchener Court File No.: CV-21-00000095-0000
St. Thomas Court File No.: CV-21-08
Welland Court File No.: CV-21-00013361-0000

TRINITY BIBLE CHAPEL ET AL., CHURCH OF GOD (RESTORATION) AYLMER ET AL., WELLANDPORT UNITED REFORMED CHURCH, and STEPHEN RICHARDSON

Applicants/Respondents

-and -

THE ATTORNEY GENERAL OF ONTARIO

Respondent/Applicant

ONTARIO
SUPERIOR COURT OF JUSTICE

(ST. THOMAS)

AFFIDAVIT OF DRS. KARIM ALI and ZAIN CHAGLA

THE ATTORNEY GENERAL OF ONTARIO

[redacted]

Joshua Hunter

[redacted]

Daniel Guttman

[redacted]

Ryan Cookson

[redacted]

Maia Stevenson

[redacted]

Counsel for the Respondent

This is "**Exhibit A**"
to the Affidavit of Drs. Karim Ali and Zain Chagla,
affirmed this 5th day of July, 2021

_____

A Commissioner, etc.

1) Generation of Report

a) The following report was generated by Dr. Karim Ali and Dr. Zain Chagla and represent the opinions of the authors alone, and clinical evidence to support these.

b) Both Dr. Ali and Dr. Chagla have experience in COVID-19 first hand, in the prevention and management of COVID-19 transmission, both from a patient and staff standpoint in their respective healthcare systems, as well as assisting with outbreak management in other congregate settings.

c) The questions asked of this report are:
   i) What is your background and expertise related to COVID-19 and its transmission?
   ii) What are the dangers of COVID-19, including dangers of variants?
   iii) What are the modes of transmission of COVID-19 and the risk factors for COVID-19 transmission?
   iv) How does the public health risk of permitting places of worship to open compare to the public health risks of permitting other indoor establishments or activities like retail, stores, bars, and film/TV production to open?

d) Materials reviewed include the submissions by Dr. Schabas, Dr. Kettner, and Dr. Warren.

2.1) Your background and expertise related to COVID-19 and its transmission - Dr. Zain Chagla

a) Dr. Chagla did his B.Sc and MD at Queen's University in Kingston. He completed a residency in Internal Medicine at Western University. He completed a fellowship in Infectious Diseases at McMaster University.

b) Dr. Chagla also completed a M.Sc in Infectious Diseases through the London School of Hygiene and Tropical Medicine. He also completed a diploma in Tropical medicine through the same institute, which was done in East Africa.

c) Dr. Chagla has tenure at McMaster University as an Associate Professor.

d) Dr. Chagla practices as an Infectious Diseases Physician at St. Joseph's Healthcare in Hamilton, with interests in General Infectious Diseases, Renal Transplantation, and Complex Respiratory Infections.

e) Dr. Chagla serves as Co-Medical Director of Infection Control at St. Joseph's Healthcare, Niagara Health System.

f) Dr. Chagla is a Consultant Infection Control physician at Woodstock General Hospital.

g) Dr. Chagla is Section Chair for Infectious Diseases for the Ontario Medical Association.

h) During the pandemic, Dr. Chagla has provided pandemic planning, contact tracing, outbreak management, data modelling, clinical care and support, and advisory services for St. Joseph's Healthcare Hamilton, Hamilton Public Health, Niagara Health Systems, and Woodstock General Hospital.

i) This included a significant amount of work around the transmission and management of COVID-19 in congregate settings, which provided experience on the spread of COVID-19 in indoor settings, and the management of transmission events from both staff and patients. There was also experience preventing transmission across healthcare institutions with over 4000 employees.

j) Dr. Chagla has worked on provincial guidelines for COVID-19 through Ontario Health on personal protective equipment, procedures and surgical guidelines, and operating assessment clinics.

k) Dr. Chagla has served on federal committees with relation to foreign travel, as well as ventilation.

l) Dr. Chagla has co-authored 16 peer reviewed papers on COVID-19 over the past 16 months, including epidemiology, testing, serological analysis, therapeutics, infection control, and vaccine efficacy.

m) Dr. Chagla has co-authored 12 editorials in national newspapers, and had over 100 media interviews over Canadian, American, and global networks relating to COVID-19.

n) Dr. Chagla has also served as a mentor for global COVID-19 responses in India, Afghanistan, and Nepal.

2.2) Your background and expertise related to COVID-19 and its transmission - Dr. Karim Ali

a) Dr Ali completed his MBBS from Ziauddin Medical University in Karachi, Pakistan.

b) Dr. Ali completed his Internal Medicine Residency at Hennepin County Medical Center in Minneapolis, MN. He completed his Infectious Diseases fellowship at Creighton University Medical Center and University of Nebraska Medical Center.

c) Dr. Ali joined Niagara Health in 2012.

d) Dr. Ali established the Division of Infectious Diseases at Niagara Health.

e) Dr.Ali was instrumental in establishing a system wide Antimicrobial Stewardship program at Niagara Health.

f) Dr Ali currently serves as the Director, Division of Infectious Diseases and Antimicrobial Stewardship Program at Niagara Health.

g) Dr. Ali is also the pandemic preparedness lead for Niagara Health at this time. In this role, he has been advising Niagara Health on COVID-19 since January 2020.

h) Dr. Ali has provided support with contact tracing, management of outbreaks, pandemic planning and clinical care of COVID 19 patients.

i) Together with Dr Chagla, Dr. Ali has been part of the outbreak management and response team at Niagara Health.

j) Dr. Ali is an Assistant Clinical Professor (Adjunct) at McMaster University.

k) Dr. Ali is involved in multiple national and international clinical trials for COVID-19 therapeutics.

l) Dr. Ali has done numerous local and national media interviews with regards to COVID transmission, treatment, epidemiology and vaccines.

3) Background information on COVID-19 and the dangers it poses, including dangers of variants

a) SARS-CoV-2 is a novel coronavirus that was first identified in the human population in Dec. 2019. This virus is responsible for the disease COVID-19. There are numerous other coronaviruses that circulate in the human population. After initial spread in 2019, SARS-CoV-2 rapidly spread across the globe and led to sustained human to human transmission. This led to the World Health Organization declaring it a pandemic in March 2020. Thus far this is the only known pandemic due to a coronavirus in human history.

b) A novel virus poses a significant threat, as there is no immunity to this virus at the population level. Time and again we saw health care systems being overwhelmed by a large number of people becoming sick with COVID-19 in a short period of time, overrunning the health care systems. This was seen in New York, Los Angeles, Italy, Brazil and is currently unfolding in India and other parts of the world.

c) While other coronaviruses do show a seasonal pattern, given the novel nature of SARS-CoV-2, it is too early to make sound inferences about seasonality. For example, the Middle East Respiratory Syndrome Coronavirus (MERS CoV), does not show a clear seasonality pattern (16).

d) Like other respiratory viruses, SARS-CoV-2 undergoes genetic mutations as it replicates. We saw this in March 2020 with the D614G variant which likely arose in the People's Republic of China and then spread throughout the world. With a significant amount of disease burden across the world, it was expected that other variants would emerge. This is due to the fact that genetic mutations do occur with every individual infected, and any mutation that gives the virus an advantage to infect large populations would cause that variant to predominate as more people became infected. Furthermore, as there is an increase in spread, infections in immunocompromised individuals, who have chronic infections, may then lead to the generation of further variants.

e) The first such variant of concern (VOC) was identified in Kent, UK around Sept. 2020. This VOC was known as B.1.1.7 and has recently been renamed SARS-CoV-2

variant Alpha. It is not only approximately 60% more transmissible, it also carries a higher likelihood of hospitalization, ICU admission and death (1).

f) SARS-CoV-2 variant Alpha rapidly spread across the globe and became the predominant strain.

g) By February 2021, SARS-CoV-2 variant Alpha had become the predominant strain in Ontario and has been largely responsible for the third wave in Ontario. Although, one must acknowledge that vaccinations would have mitigated much of this, unfortunately the federal government was unable to secure a sufficient supply of vaccines at the time.

h) A study of 26,314 people in Ontario testing positive for SARS-CoV-2 between February 7 and March 11, 2021 showed that 9,395 people (35.7%) infected with VOCs had a 62% relative increase in COVID-19 hospitalizations, a 114% relative increase in ICU admissions and a 40% relative increase in COVID-19 deaths compared to prior circulating COVID-19 strains (2, 15).

i) In recent weeks, another VOC, SARS-CoV-2 variant Delta, was identified in India and has now spread to over 80 countries across the globe. SARS-CoV-2 variant Delta is relatively more transmissible, with some estimates at a 40-60% increase in infectivity over the Alpha variant (3).

j) SARS-CoV-2 variant Delta also has an increased risk of hospitalizations especially amongst people who are not vaccinated, or have been vaccinated with just one dose at this time (3). It is projected that SARS-Cov-2 variant Delta will be the predominant strain in Ontario by July 2021. The best defence against this is to have our populations fully vaccinated. Until that objective can be achieved, the next-best defence is to drive down transmission by Non-Pharmaceutical Interventions ("NPI") (e.g, limiting the number of people who can attend indoor gatherings or religious services etc.)

4) Modes of transmission of COVID-19 and risk factors

a) Respiratory viruses in general are transmitted by inhalation of respiratory particles, or contamination of surfaces and subsequent inoculation by contact with mucous membranes. Viruses can enter through either the respiratory tract (nasal and oral cavities), or through direct contact with mucous membranes such as the eye.

b) The fomite (contact) based transmission route of SARS-COV-2 has likely not played a large role in ongoing transmission globally. Although studies have suggested initial viability of SARS-COV-2 on surfaces (4), more recent analysis of high burden areas such as intensive care units show very little viral seeding of the environment (5). Based on this, the CDC has updated guidance identifying this as low risk (6).

c) With regards to respiratory transmission, SARS-COV-2 is generally transmitted by small respiratory droplets[1], leading to transmission typically within close contacts of an infected case (7). In most settings, transmission occurs within close contacts, particularly in close proximity (<2 meters). This has led to many of the precautions

[1] In limited circumstances, SARS-COV-2 is transmitted by aerosols. See para d) *infra*.

we see in day to day life including physical distancing, which is used to mitigate that risk. The use of masking, particularly in indoor settings, is meant to block the flow of respiratory droplets from the source, particularly in the context of individuals who are infectious prior to their symptom onset (presymptomatic) or people without symptoms.

d) In poorly ventilated spaces, particularly with long interactions, and with behaviours that generate increasing respiratory particles such as coughing, singing, talking, yelling, or breathing heavily, there has been aerosol based transmission of the virus. Such events have led to spread over increased distance over 2 meters, as well as to large degrees of people becoming infected in one setting.

e) The initial Skagit choir in Washington was a noted occurrence where 50-80% of individuals at the event were infected in a single event, likely worsened by high aerosol generation and ventilation (8).

f) A choir singer in an Australian church likely infected 12 individuals as far as 15 meters away from the source (9).

g) Other long range occurrences have been noted in a restaurant (10) and a bus (11), supporting longer range transmission in particular settings, with higher than normal attack rates.

h) Dr. Shabas notes in his materials that large indoor gatherings can contribute to the spread of COVID-19, but then also notes that evidence-based policies are lacking, and the larger impact of COVID-19 transmission is unknown. This would be contrary to the wealth of experience of superspreading events, such as the Skagit choir (8).

i) While mitigation measures such as masking and physical distancing do offer a pathway to minimize risk, they are fallible, and can still lead to transmission. In Ontario to date, there have been 213 outbreaks occurring in settings categorized as "other recreational" which includes religious congregations, each one involving several cases. With secondary transmission of the variants of concern being up to 12% for household members (3), and increasing social nodes of contact due to loosening restrictions, there likely have been further secondary cases generated from each of these known cases.

j) On top of the risks of transmission within a facility due to masking and physical distancing, the amount of COVID cases in the community also affect the risk of transmission. If there are increasing cases in the community, there is an increased risk of an individual entering a facility while asymptomatic or presymptomatic.

k) Even with this case data in mind, we also recognize that these numbers vastly underestimate risk, as many cases are not diagnosed due to minimal symptoms or a lack of access to testing, and appropriate contact tracing is not initiated unless outbreaks are recognized. Finally, even the mitigation measures such as masks and physical distancing are not perfect, as individuals may not wear well-fitting masks, ventilation may be suboptimal, and screening for active COVID-19 symptoms may miss people who are still infectious or who minimize their symptoms.

l) Dr. Warren's report notes that Canadian and Ontario COVID-19 data shows a small absolute number of cases associated with religious services. However, that data was collected during periods when there were regional controls in place to minimize the spread of COVID-19 in many provinces, many of which included restrictions on the size of religious gatherings. The paradox in public health is as cases are controlled and reduced through public health interventions, they are not accounted for as they are effectively prevented, and data is drawn from the "tip of the iceberg" of the cases that broke through. It is difficult to model the impact of not having public health measures against mechanisms of transmission.

m) Dr. Warren points to a paper on a randomized clinical trial of mask use for example (18) but this study was not used to assess the use of universal masking as a source control (i.e. as a method to reduce the user's shedding of aerosols and droplets to the environment), rather, the study only looked at the use of masking as personal protective equipment (i.e as a method to block aerosols and droplets from being inhaled by the user), which significantly underestimates the effect of masking on the overall reduction of transmission.

n) A randomized control trial would be ideal in this setting as Dr. Warren recognizes, however, the practicality of this within the context of a global pandemic is difficult. However, larger natural history studies comparing non-pharmaceutical interventions in the first wave showed cancellation of large and small gatherings, and minimization of gatherings to < 10 had significant impacts on reproductive rates (12, 13), which likely did have larger effects in pandemic prevention.

o) Dr. Kettner tries to approximate risk of infectivity by describing the local context of COVID-19, and approximating that to the risk of an individual being asymptomatic or presymptomatic on the day of attending a congregation. However, this approach underestimates the fact that a) many cases are undiagnosed, b) individuals are not truthful with screening, and c) presymptomatic transmission is a significant risk factor for spread. Finally, Dr. Kettner approximates his numbers from outbreaks in Ontario at the time, but only recognizes outbreaks where multiple cases acquired COVID-19 from a common link. There are still a significant number of cases in Ontario where no link is identified, and it is highly variable if contact tracing would identify these links in the community. This is due to the fact that contact tracing relies on self-reported data, and overwhelmed public health units may not trace individuals outside of very high risk facilities (eg hospitals, long term care, and workplaces), and the pattern of a common link between a number of cases is not easily recognized. In these circumstances, one could have acquired COVID-19 at a congregate facility like a church, but not attributed transmission to the church given the lack of contact tracing.

p) Adding to this underestimation of risk is the impact of overdispersed transmission. In large contact tracing studies, 20% of cases account for the bulk of transmission, particularly in superspreader events. This is magnified by the variants of concern. In the right environment with poor physical distancing, and high aerosol production, superspreader events can occur. The Skagat choir example had a 50-80% attack rate with a single exposure including deaths (8). Cumulatively these cases can also go back and infect community members, thereby worsening an outbreak.

5) How does the public health risk of permitting places of worship to open compare to other indoor establishments or activities like retail, stores, bars, and film/TV protection to open?

a) Prior to assessing risk, the major component of what can remain open relates to the ability to care for patients in acute care. When hospitals are overwhelmed with COVID-19, the ability to care for patients, both with COVID-19 and with other medical issues becomes compromised.

b) For example, at the peak of the 3rd wave in Ontario there were 891 people in Intensive care units. This required the halting of elective surgery, redeployment of healthcare staff into critical care units, transferring patients throughout the province to balance out hospitals dealing with surges, and the potential invocation of a triage protocol to limit access to intensive care units for those with the best prognosis.

c) During this interval, any pressures on the community leading to further transmission would have been devastating for providing healthcare to the community.

d) More generally, assessing risk in an individual setting requires an examination of the hierarchy of controls, which is a core principle of infection prevention and control (14).

e) Elimination is the most important element, and in the context of high transmission, may include closure of higher risk settings. While screening may offer the ability to eliminate symptomatic cases, presymptomatic cases often present the highest viral loads, and hence, may not be eliminated by a symptom screen.

f) Substitution Controls involve replacing the hazard. Engineering Controls involve isolating people from the hazard, and Administrative Controls involve changing the way people work. These types of control broadly encompass measures to prevent the spread of COVID-19 in environments, such as physical distancing, ventilation, prioritizing outdoor settings, minimizing capacity limits, cleaning and hand hygiene. These are important but less effective than Elimination in preventing the spread of infectious pathogens.

g) Personal protective equipment, such as the use of well fitted masks, may decrease the acquisition of COVID-19, as well as reduce the shedding of the user if they are unknowingly infected. While this has been an important measure, the effectiveness may be less than the measures above. For example, a meta-analysis showed masked use reduced the odds of infection by 85% with mask use, but 90-95% lower with physical distancing (17).

h) The decision to close or keep open across the province varied, but did have commonalities amongst settings with risk. For example, outdoor settings were considered much safer than indoors due to better ventilation. Capacity limits were used to mitigate transmission in retail settings.

i) Indoor settings often had a gradient of risk based on capacity, ventilation, controls, the ability to mask, and the production of aerosols through singing, talking, or heavy breathing.

j) In periods of harder "lockdowns", measures were put in place to limit the spread of COVID-19, using the risk profile above, and evaluating the essentialness of particular environments. It is outside of the scope of this report to determine what is considered essential, recognizing that the provision of food, essential goods, and medical care are very high on the list.

k) Ultimately, safety in settings opened during periods of high case transmission was related to the hierarchy of controls, particularly in the ability to operate safely while physical distancing, masking, having appropriate ventilation, screening, provide case and contact management, and the essential nature of work. These were the factors used by public health units, along with the health systems capacity, and the ability to contact trace cases effectively to determine what restrictions to impose.

l) Ultimately, settings such as restaurants and bars, had to either mitigate risk (such as by the use of patios, curbside pickup, and delivery), implement significant capacity restrictions or face closure during the highest periods of transmission.

m) Some businesses, such as film and TV used personal protective measures and serial testing in order to operate workplaces effectively. I have read the affidavit of Justin Cutler. As a result of COVID-19 health and safety measures in the last four months of 2020, 25 major MPA productions in Ontario administered more than 132, 938 PCR tests, with an overall positivity rate of 0.06%. This positivity rate was significantly less than the test positivity rate of between 0.6 and 9.7% for the general population at that time. Every positive test has been identified through testing without any further spread in the workplace.

n) While Dr. Warren asserts that there is no evidence for lockdown measures prior to COVID-19, a number of studies comparing non-pharmaceutical interventions do show differences between lockdowns, business closures, and low capacity limits for reductions of the community reproductive rate.

o) While Dr. Schabas compares the ability to keep a liquor store open and a church closed, it is important to remember that members of the public face lower risk in a liquor store or other retail setting given the transient nature of the gathering in those locations compared to religious gatherings.

6. Conclusion

a) Thank you for the opportunity to provide this report.

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This is "**Exhibit B**"
to the Affidavit of Drs. Karim Ali and Zain Chagla,
affirmed this 5th day of July, 2021

_____

A Commissioner, etc.

Kitchener Court File No.: CV-21-00000095-0000
St. Thomas Court File No.: CV-21-08
Welland Court File No.: CV-21-00013361-0000

ONTARIO
SUPERIOR COURT OF JUSTICE

B E T W E E N:

THE ATTORNEY GENERAL OF ONTARIO

Applicant

-and-

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHUURMAN, DEAN WANDERS, RANDY FREY, HARVEY FREY, and DANIEL GORDON

Respondents

A N D B E T W E E N:

HER MAJESTY THE QUEEN IN ONTARIO

Applicant

-and-

THE CHURCH OF GOD (RESTORATION) AYLMER, HENRY HILDEBRANDT, ABRAM BERGEN, JACOB HIEBERT, PETER HILDEBRANDT, SUSAN MUTCH, ELVIRA TOVSTIGA, and TRUDY WIEBE

Respondents

A N D B E T W E E N:

WELLANDPORT UNITED REFORMED CHURCH

Applicant

-and-

HER MAJESTY THE QUEEN AS REPRESENTED BY THE ATTORNEY GENERAL OF ONTARIO

Respondent

A N D B E T W E E N:

STEPHEN RICHARDSON

Applicant

-and-

THE ATTORNEY GENERAL OF ONTARIO

Respondent

ACKNOWLEDGMENT OF EXPERT'S DUTY

---

1. My name is Dr. Karim Ali. [redacted] in the Province of Ontario.

2. I have been engaged by the Attorney General of Ontario to provide evidence in relation to the above-noted court proceeding.

3. I acknowledge that it is my duty to provide evidence in relation to this proceeding as follows:

   (a) to provide opinion evidence that is fair, objective and non-partisan;

   (b) to provide opinion evidence that is related only to matters that are within my area of expertise; and

   (c) to provide such additional assistance as the court may reasonably require, to determine a matter in issue.

4. I acknowledge that the duty referred to above prevails over any obligation which I may owe to any party by whom or on whose behalf I am engaged.

Date: July 5th, 2021

Dr. Karim Ali

This is "**Exhibit C**"
to the Affidavit of Drs. Karim Ali and Zain Chagla,
affirmed this 5th day of July, 2021

_____

A Commissioner, etc.

Kitchener Court File No.: CV-21-00000095-0000
St. Thomas Court File No.: CV-21-08
Welland Court File No.: CV-21-00013361-0000

ONTARIO
SUPERIOR COURT OF JUSTICE

BETWEEN:

THE ATTORNEY GENERAL OF ONTARIO

Applicant

-and-

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHEURMAN, DEAN WANDERS, RANDY FREY, HARVEY FREY, and DANIEL GORDON

Respondents

AND BETWEEN:

HER MAJESTY THE QUEEN IN ONTARIO

Applicant

-and-

THE CHURCH OF GOD (RESTORATION) AYLMER, HENRY HILDEBRANDT, ABRAM BERGEN, JACOB HIEBERT, PETER HILDEBRANDT, SUSAN MUTCH, ELVIRA TOYSTIGA, and TRUDY WIEBE

Respondents

AND BETWEEN:

WELLANDPORT UNITED REFORMED CHURCH

Applicant

-and-

HER MAJESTY THE QUEEN AS REPRESENTED BY THE ATTORNEY GENERAL OF ONTARIO

Respondent

AND BETWEEN:

STEPHEN RICHARDSON

Applicant

-and-

THE ATTORNEY GENERAL OF ONTARIO

Respondent

ACKNOWLEDGMENT OF EXPERT'S DUTY

1. My name is Dr. Zain Chagla, [redacted] in the Province of Ontario.

2. I have been engaged by the Attorney General of Ontario to provide evidence in relation to the above-noted court proceeding.

3. I acknowledge that it is my duty to provide evidence in relation to this proceeding as follows:

(a) to provide opinion evidence that is fair, objective and non-partisan;

(b) to provide opinion evidence that is related only to matters that are within my area of expertise; and

(c) to provide such additional assistance as the court may reasonably require, to determine a matter in issue.

4. I acknowledge that the duty referred to above prevails over any obligation which I may owe to any party by whom or on whose behalf I am engaged.

Date: 2021/12/15

Dr. Zain Chagla

This is "**Exhibit D**"
to the Affidavit of Drs. Karim Ali and Zain Chagla,
affirmed this 5th day of July, 2021

_____

A Commissioner, etc.

Dr. Karim Firdous Ali
[redacted]

PROFILE
Infectious Diseases and Internal Medicine Physician with experience in general infectious diseases, antimicrobial stewardship & pandemic preparedness.

APPOINTMENTS
Staff Physician, Division of Infectious Diseases & Internal Medicine, Niagara Health - **2012- present**

Director, Division of Infectious Diseases Niagara Health - **2014- present**

Director Antimicrobial Stewardship Program, Niagara Health - **2014-present**

Pandemic Preparedness Lead, Niagara Health- **January 2020-present**

ACADEMIC APPOINTMENT
Assistant Clinical Professor of Infectious Diseases (Adjunct)
McMaster University DeGroote School of Medicine - **2014-present**

EDUCATION
MB, BS Ziauddin Medical University, Karachi, Pakistan - **2004**

POSTGRADUATE TRAINING
Internal medicine residency, Hennepin County Medical Center, Minneapolis, Minnesota - **2007-2010**
Infectious diseases fellowship. Creighton University-University of Nebraska Medical Center, Omaha, Nebraska - **2010-2012**

MEDICAL CERTIFICATION AND LICENSURE
United States Medical Licensing Examination. #06738363 - **2006**
Educational Commission for Foreign Medical Graduates. #06738363 - **2006**
Advanced Cardiac Life Support, American Heart Association - **2020**
Diplomate, Internal Medicine. American Board of Internal Medicine. #309784 - **2010**
Independent License College of Physicians and Surgeons of Ontario. # 99307 - **2012**
Diplomate, Infectious Diseases, American Board of Internal Medicine - **2013**

HONORS
Graduated medical school with honors - **2004**

PROFESSIONAL EXPERIENCE
Observer, Department of Hematology-Oncology, Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, Pakistan - **2005**
Observer, Infectious diseases service, Jackson Park Hospital, Chicago, Illinois - **2005 -2006**

PROFESSIONAL SOCIETY MEMBERSHIPS
Infectious Disease Society of America, Member
Ontario Medical Association
Canadian Medical Association
Association of Medical Microbiology and Infectious Diseases, Canada, Member

REVIEWER
Journal of Pakistan Medical Association, student editor - **2002-2004**

PROFESSIONAL COMMUNICATIONS AND PUBLICATIONS
Ali KF, Fawad A. Complications of TURP: Do Comorbidities Have a Role? **2003**. Pakistan Association of Urological Surgeons, Yearly Meeting, Karachi, Pakistan

Ali KF, Rausch D. Intramedullary Buffet: A Case of Hemophagocytic Lymphohistiocytosis. **2007**. American College of Physicians, Minnesota Chapter meeting, Minneapolis, Minnesota

Wirt J, Ali KF, Rausch D. Case of Clear Cell Sarcoma in an HIV Positive Patient. **2008**. American College of Physicians, Minnesota Chapter meeting, Minneapolis, Minnesota

Ali KF. Transplant Infections, 3rd Edition (Book Review), **2010**. Doody Enterprises

Ali KF, Preheim LC, Neemann K. A Disturbing Case of Diplopia. **Feb. 16, 2011**. Creighton University Internal Medicine Grand Rounds, Omaha, Nebraska

Fleming, D, Ali, KF et al. When Antimicrobial Stewardship Isn't Watching: The Educational Impact of Critical Care Prospective Audit and Feedback. Open Forum Infectious Diseases, Volume 3, Issue 3, **Summer 2016**

RESEARCH
Resident Research Project. Effects of bortezomib on NK cell functions. **2008**. Laboratory of Dr.Jeffrey Miller, University of Minnesota.

Third-year Resident Project. Isolation of Echinococcus granulosus DNA from hydatid cyst. **2010**. Project supervisor Glen T. Hansen, Hennepin County Medical Center

Principle Investigator, Niagara Health, Medical Masks vs N95 Respirators to prevent 2019 Novel Coronavirus Disease (COVID-19) in Health Care Workers: A Randomized Controlled Trial. **August 2020- Present**

Co Principle Investigator, St Catharines Site, BALANCE (Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness) Trial. This is a multinational trial looking at length of treatment and outcomes in patients with bacteremia. **2018- Ongoing**

Co Principle Investigator, LOVIT-COVID (Lessening Organ Dysfunction with Vitamin C- COVID) **Oct 2020-Present**

Co Principle Investigator, Niagara Health, CATCO (Canadian Trials for COVID), Part of WHO Solidarity trial **July 2020-Present**

Co Principle Investigator, Niagara Health, VIRTUES (COVID 19 Virtual Care at Home) **Oct 2020- Present**

Co Principle Investigator, Niagara Health CONCOR-1 (A randomized open label trial of Convalescent Plasma for Hospitalized Adults with Acute COVID-19 Respitatory Illness) **September 2020- Present**

VOLUNTEERING

Positive living Niagara in their Streetworks? Harm Reduction program **August 2019- Present**

Deputy Pandemic Response and Public Health, The Aga Khan Health Board for Canada. **May 2020-Present**

This is "**Exhibit E**"
to the Affidavit of Drs. Karim Ali and Zain Chagla,
affirmed this 5th day of July, 2021

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A Commissioner, etc.

Dr. Zain Chagla

[redacted]

PROFILE

Infectious Diseases Physician with clinical, research, education, and leadership experience

APPOINTMENTS

Associate Professor, Department of Medicine, McMaster University — 2014-present
Prior Assistant Professor 2014-2019

Chair of Assessments, McMaster University — 2018 - 2020
Postgraduate Internal Medicine Program

Infectious Diseases and Internal Medicine Consultant, St. Josephs Healthcare and Hamilton Health Sciences — 2014-present
Specialization in general infectious diseases, transplantation, and global health

Medical Director, Infection Control, St. Joseph's Healthcare Hamilton - 2016-present
Consultative services, outbreak management, and policy planning for local and regional infection control strategy.

President, Medical Staff Association, St. Joseph's Healthcare Hamilton - 2021

COVID-19 Response 2020-2021
Co-Chair, Regional Subject Matter Expert Committee
Co-Chair, Metrics Evidence and Surveillance Committee, City of Hamilton
Consultant, St. Joseph's Hospital IMS, Pandemic Operations, Vaccination Committee
Consultant, Ontario Health Guidelines for PPE, Surgical Infection Control, Assessment Centers, Clinical Treatments
Consultant, CADTH Guidelines on Ventilation
Consultant, Canadian Parliamentary Hearing on Airline Travel in the Pandemic

Medical Director, Infection Control, Niagara Health System - 2019-present
Consultative services, outbreak management, and policy planning for local and regional infection control strategy.

Consultant, Infection Control, Woodstock General Hospital – 2019-Present
Consultative services, outbreak management, and policy planning for local and regional infection control strategy.

Invited Lecturer, University of Namibia - 2014-present
Undergraduate lectures, curriculum and examination development, planning and policy for postgraduate medical education.

Lecturer, McMaster Masters of Global Health Program 2015-present

Member, McMaster Institute for Infectious Diseases Research 2020-present

Locum Hospitalist, Thunder Bay Regional Health Sciences Centre — 2013-2020

Consultant, Hamilton Public Health Sexual Health Program —2013-2016

EDUCATION

Fellowship, Infectious Diseases, McMaster University — 2014
FRCPC Infectious Diseases

M.Sc Infectious Diseases, London School of Hygiene and Tropical Medicine — 2012

Diploma, Tropical Medicine and Hygiene, London School of Hygiene and Tropical Medicine (East Africa Program – Tanzania/Uganda) — 2013

Residency, Internal Medicine, Western University — 2012
FRCPC Internal Medicine

Medical Doctor, Queen's University — 2009

B.Sc in Life Sciences, Queen's University — 2005

Healthcare Leadership for Physicians Certificat, McMaster CME – 2019

MEMBERSHIPS

Ontario Medical Association
Chair – Section of Infectious Diseases

Infection Prevention and Control Canada

AMMI Canada

GRANTS

W. Watson Buchanan AFP Clinician Educator Award, Grant, McMaster University, Education Research

PUBLICATIONS

The BNT162b2 (BioNTech/Pfizer) vaccine had 95% efficacy against COVID-19 ≥7 days after the 2nd dose. Chagla, Z. Ann Intern Med. 2021 Feb 2

The efficacy and safety of hydroxychloroquine for COVID-19 prophylaxis: A systematic review and meta-analysis of randomized trials. PLoS ONE. 2021 Jan 6;16(1)

Canadian consensus of COVID-19 policy and management aspects. Tsang K, Mertz D, Chagla Z, Smaill F, Khan S. OFID. 2020 Dec 31;7:S312–3.

Desperate times call for evidence-based measures: Prioritizing science during the COVID-19 pandemic. Chagla Z, Laupland KB, Schwartz IS. Official Journal of the Association of Medical Microbiology and Infectious Disease Canada. 2020 Oct;5(3):127–9.

Tocilizumab versus the Covid19 tempest: All's well that ends well or much ado about nothing? Lee TC, Butler-Laporte G, Chagla Z, McDonald EG. Clinical Microbiology and Infection. 2020 Sep;

International Hospital and Community Epidemiology Group. Re: It Is Time to Address Airborne Transmission of COVID-19. Chagla Z, Hota S, Khan S, Mertz D. Clinical Infectious Diseases. 2020 Aug 11.

A regional Canadian expert consensus on recommendations for restoring exercise and pulmonary function testing in low and moderate-to-high community prevalence coronavirus disease 2019 (COVID-19) settings. Khan S, Tsang KK, Mertz D, Dolovich M, Tunks M, Chagla Z, et al. Infect Control Hosp Epidemiol. 2020 Nov 20;1–3.

Novel coronavirus COVID-19: current evidence and evolving strategies. C Vannabouathong, T Devji, Z Chagla, et al. The Journal of bone and joint surgery. 102 (9). 723. 2020.

Utility of asymptomatic inpatient testing for COVID-19 in a low-prevalence setting: A multicenter point-prevalence study. Bai AD, Li XX, Alsalem M, Khan S, Smieja M, Mertz D, Chagla, Z. Infect Control Hosp Epidemiol. 2020 Jul 22;1–3.

Safety of Hydroxychloroquine among Outpatient Clinical Trial Participants for COVID-19. S Lofgran, M Nichol, Z Chagla, et al. OFID. 7(11):Nov 2020

Development of a serological assay to identify SARS-CoV-2 antibodies in COVID-19 patients [Internet]. Infectious Diseases (except HIV/AIDS); Huynh A, Arnold DM, Kelton JG, Smith JW, Moore JC, Chagla Z, et al. medrxiv. 2020 Sep

Cryptococcemia presenting as an opportunistic infection due to chronic visceral leishmaniasis. K Gregory Miller, Z Chagla, D Yamamura, P El-Helou. JAMMI. 4(3). 44-48. 2019.

Distribution of hepatitis B virus infection in Namibia. P Mhata, TW Rennie, LF Small, PM Nyarang'o, Z Chagla, CJ Hunter. SAMJ: South African Medical Journal 107 (10), 882-886. 2017.

Successful use of intrathecal colistin in the treatment of Pseudomonas aeruginosa ventriculitis. JAMMI. D Whellams, Z Chagla, N Irfan. 2(1),93-96. Sep 2017.

Z Chagla, D Siegal, P El-Helou, W Lim, J Rudkowski. Severe Acute Cytomegalovirus Infection Complicated by Disseminated Intravascular Coagulation and Pneumonitis in a Healthy Female. Canadian Journal of General Internal Medicine 10 (4). 2016.

F AlMutawa, D Leto, Z Chagla. Disseminated Cryptococcal disease in non-HIV, nontransplant patient. Case reports in infectious diseases. 2016.

L Jiao, Z Chagla, RM Kaki, G Gohla, M Smieja. Case report of necrotizing fasciitis associated with Streptococcus Pneumoniae. Canadian Journal of Infectious Diseases and Medical Microbiology (2016).

Z Chagla, AK Boggild, S Chakrabarti. A venomous visitor from the tropics. Canadian Journal of Infectious Diseases and Medical Microbiology. 26(5):243-244. 2015.

Z Chagla, N Aleksova, J Quirt, J Emery, C Kraeker, S Haider. Melioidosis in a returned traveller. Canadian Journal of Infectious Diseases and Medical Microbiology.. 25(4):225-226. 2014.

Z Chagla, J Quirt, K Woodward, J Neary, C Rutherford. Chronic norovirus infection in a transplant patient successfully treated with enterally administered immune globulin. Journal of Clinical Virology. 58(1):306-8. Sep 2013.

Z Chagla, M Salvadori, J M Sontrop, M John, Z Hussain, Y Chagla, B Warshawsky, C Achiam, B Thompson. Genetically typed community-acquired methicillin-resistant Staphylococcus aureus in a Canadian hospital. Canadian Journal of Infectious Diseases and Medical Microbiology. 20(3):E113-114. 2009.

TEXTBOOK CHAPTERS

McMaster Textbook of Internal Medicine – CNS Infections, Mediastinitis, COVID-19. Published 2020.

McMaster COVID-19 Survival Guide, 2020

Kitchener Court File No. CV-21-00000095-0000
St. Thomas Court File No. CV-21-08

ONTARIO
SUPERIOR COURT OF JUSTICE

MH/as

B E T W E E N:

THE ATTORNEY GENERAL OF ONTARIO

Applicant (Responding Party)

- and -

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHUURMAN, DEAN WANDERS, RANDY FREY, HARVEY FREY and DANIEL GORDON

Respondents (Moving Parties)

A N D B E T W E E N:

HER MAJESTY THE QUEEN IN ONTARIO

Applicant (Responding Party)

- and -

THE CHURCH OF GOD (RESTORATION) AYLMER, HENRY HILDEBRANDT, ABRAM BERGEN, JACOB HIEBERT, PETER HILDEBRANDT, SUSAN MUTCH, ELVIRA TOVSTIGA, and TRUDY WIEBE

Respondents (Moving Parties)

- - - - - - - - - -

This is the Cross-Examination of DR. DAVID McKEOWN, on his Affidavit sworn the 5th day of July, 2021, taken via videoconference at the offices of VICTORY VERBATIM REPORTING SERVICES INC., 222 Bay Street, Suite 900, Toronto-Dominion Centre, Toronto, Ontario, on the 19th day of November, 2021.

- - - - - - - - - -

A P P E A R A N C E S:

JOSHUA HUNTER	-- for the Applicant
RYAN COOKSON	
MAIA STEVENSON	
KINSEY BOWEN	
DANIEL GUTTMAN	
ROB KITTREDGE	-- for the Respondents

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--- upon convening at 10:00 a.m.

--- upon commencing at 10:01 a.m.

DR. DAVID McKEOWN, affirmed

CROSS-EXAMINATION BY MR. KITTREDGE:

1. Q. Good morning, Dr. McKeown.

A. Good morning.

2. Q. I represent the moving parties on this motion and I will be asking you a series of questions today. I understand you provided some evidence in this matter by way of an affidavit you affirmed on July 5th, 2021; is that correct?

A. Yes.

3. Q. Do you have a copy of your affidavit in front of you?

A. I do.

4. Q. At the time you affirmed your affidavit, you were the associate chief medical officer of health for Ontario; is that correct?

A. Correct.

5. Q. You say in paragraph 1 of your affidavit that you have held that position since early 2020. Can you be a little more precise about your start date?

A. March 30th, 2020.

6. Q. March 30, right. I understand that you have held the post of associate chief medical officer of health in the past, and, unless I specify otherwise, when I refer to your term as associate chief medical officer of health in my questioning, I mean your current term which began in 2020. Were you appointed associate chief medical officer of health permanently or temporarily?

A. I'm not sure what the human resources term would be for it for the government, but it was intended to be temporary.

7. Q. Right. Was it for a specified length of time?

A. Yes, it was, and that time has been extended several times.

8. Q. Right. In your role as associate chief medical officer of health, you were part of the office of the chief medical officer of health; is that correct?

A. Correct.

9. Q. And you reported directly to the chief medical officer of health?

A. Yes.

10. Q. And the chief medical officer of

health reports directly to the deputy minister of health?

A. Yes.

11. Q. Are you the only associate chief medical officer of health?

A. No.

12. Q. How many are there?

A. At the time that I joined in 2020, there were two others.

13. Q. And currently?

A. Currently, there are one, two, three, four, five others.

14. Q. And that increase, is that due to the...is that in response to the COVID-19 pandemic?

A. I believe those positions existed, but were vacant prior to the pandemic.

15. Q. And were you brought in as associate chief medical officer of health primarily in response to the COVID-19 pandemic?

A. Yes.

16. Q. Is it fair to say that since early 2020, your primary focus, and the primary focus of your office, has been on COVID-19 and the threat it may pose to public health?

A. Yes.

17. Q. At paragraph 2 of your affidavit, you say that your responsibilities in your role included monitoring the spread of COVID-19 in Ontario and advising on the Ontario government's policy response to the pandemic. Were these your primary responsibilities?

A. Yes.

18. Q. Apparently...approximately what percentage of your time was spent on COVID-related work?

A. It would be close to 100 percent.

19. Q. I understand that during your term, you were also a member of the Ontario COVID-19 Science Advisory Table?

A. For part of that term, yes.

20. Q. Okay, and you are no longer a member of that Table; is that correct?

A. Correct.

21. Q. And the Science Advisory Table is an independent group of scientific experts and health system leaders tasked with evaluating and reporting on emerging scientific evidence relevant to the COVID-19 pandemic. Is that an accurate description?

A. I think so.

22. Q. The Science Table provides weekly summary reports to Ontario's Health Coordination Table, formerly known as the Health Command Table; is that correct?

A. I don't think the reports were necessarily weekly throughout the full pandemic, but they were...

23. Q. No?

A. ...frequent.

24. Q. All right, thank you. Is the chief medical officer of health a member of the Health Coordination Table?

A. Yes, I believe so.

25. Q. And were you?

A. No.

26. Q. Among other things, the office of the chief medical officer of health set public policy and provincial public health control measures, communicates health guidance to Ontarians, and determines how the province will respond to urgent emergency public health situations?

MR. HUNTER: Can we just break... there's a number of items there,

Counsel. Can we just go one by one?

27. MR. KITTREDGE: Sure, I'm, essentially, reading off the description from the Public Health Ontario website, but I suppose...I can just move right on to my next question, then. I'll pass on that one.

BY MR. KITTREDGE:

28. Q. The office of the chief medical officer of health has the authority to direct local jurisdictions within Ontario to implement public health measures, when necessary, in response to a public health risk or emergency; correct?

A. Yes, that authority exists, but usually local public health officials act without needing to refer to that authority.

29. Q. Okay. In the context of the COVID-19 pandemic, the office of the CMOH...I'll just say "CMOH" rather than chief medical officer of health, because it's getting a little repetitive. In response to the...in the context of the COVID-19 pandemic, the office of the CMOH sets directives and guidelines around screening,

testing, triage, precautions and reporting; correct?

A. Yes.

30. Q. During the pandemic, the office of the CMOH has determined which businesses, services, products, and events are considered to be essential; is that correct?

A. No, the chief medical officer of health would provide advice to government. The government would make those decisions.

31. Q. Right, and has the government typically followed the advice of the chief medical officer of health?

MR. HUNTER: Don't answer that. The question what cabinet has or hasn't done, and what advice was given, is public-interest immunity. /R

BY MR. KITTREDGE:

32. Q. The office of the CMOH determines the definition used by the province for COVID probable cases and COVID confirmed cases; is that correct?

A. I have to confirm that. Certainly advice is provided on that. I'm not

sure what the final decision is.

33. Q. All right, can we get an undertaking to provide an answer to that question?

MR. HUNTER: I just want to clarify your question. You're asking about the definitions used by the province, not necessarily other public health units; correct?

34. MR. KITTREDGE: Yes.

MR. HUNTER: Okay, we'll make an undertaking to make inquiries to determine who sets that definition, if there is a standardized definition. U/T

BY MR. KITTREDGE:

35. Q. All right. In your affidavit, Dr. McKeown, where you use the term "case" without any additional qualifier, are you referring to a "probable case" or a "confirmed case"?

A. It might depend on the context, but, in general, when I use the word "case", I would mean a confirmed case.

36. Q. All right. The province's

definition of “probable case” may capture some instances where a person is not actually infected with COVID-19; is that correct?

A. I believe that’s why it’s called a “probable case”, yes.

37. Q. Right, and is it also true that the province’s definition of “confirmed case” may capture some instances where a person is not actually infected with COVID-19?

A. The “case” definition is intended to not have that happen.

38. Q. Right, but...all right, I understand that a person who has received a positive PCR test result would meet the province’s definition of a “confirmed case”; is that correct?

A. That is correct.

39. Q. A PCR test is typically done by taking a sample from a patient with a nasal swab; is that correct?

A. Well, it depends. Earlier on, the samples were usually taken with a much higher nasopharyngeal swab, but there are some tests, now, that can be done with a nasal swab.

40. Q. All right, but either way, you

are taking a sample of material from inside of the nose of a patient, in layman's term?

A. Correct.

41. Q. All right, and the result of the PCR test will be positive if any fragment of the SARS-CoV-2 virus is found in the sample; is that correct?

A. This is outside my expertise in terms of the details of the laboratory tests and how they work. So I...

42. Q. Okay.

A. ...can't speak to that.

43. Q. All right. SARS-CoV-2 is the virus that causes the disease COVID-19; is that correct?

A. Yes.

44. Q. So I may have to rephrase this based on the last one. A positive PCR test result indicates whether the SARS-CoV-2 virus was found in a sample taken from a patient; is that correct?

A. Yes.

45. Q. But it does not indicate, with certainty, whether that patient is infected with the disease COVID-19; is that correct?

A. I'm not sure I understand the distinction. Can you clarify the question?

46. Q. So the PCR test will return positive if some amount of the SARS-CoV-2 virus is found in a sample taken from a patient; that is correct, right?

A. Yes.

47. Q. All right, but it may or may not be that that patient has an active COVID-19 infection, as in he has the disease that's...he or she has the disease that is referred to as "COVID-19"; is that correct?

A. My understanding is that the presence of the virus does indicate an active infection. Whether or not the person is symptomatic is a different question.

48. Q. Could a positive PCR test indicate that a fragment of inactive or dead SARS-CoV-2 virus was found in a sample taken from an uninfected patient?

A. Again, you would have to consult someone who is more familiar with the technology of the test as to what its sensitivity for detecting different fragments of virus. I'm not a microbiologist, so I can't speak to that.

49. Q. Okay. All right, so you are not aware of whether a positive PCR test result could be a false positive in the sense that it detected inactive SARS-CoV-2 virus in a patient who was not infected with COVID-19?

A. No, I can't speak to that.

50. Q. Okay, would it be reasonable to assume that some of the PCR tests performed in Ontario produced false positive results?

A. I believe all tests can have false positive results.

51. Q. Okay, and that would include the PCR tests performed to detect SARS-CoV-2 virus?

A. Yes.

52. Q. All right. Have there been any known instances, or are you aware of any known instances, of false positive PCR test results in Ontario?

A. I'm not aware of specific false positive tests, but I'm aware that there have been false positive tests.

53. Q. Okay, so you agree that not everybody who tests positive on a PCR test is infectious or has the disease COVID-19?

A. Yes, to the extent that there are

false positives, that would be a true statement.

54. Q. Okay. Do you agree that, therefore, the province's counts of confirmed cases include at least some instances where a PCR test was a false positive?

A. Yes, unless there is an investigation to determine whether or not a positive test is a false positive, then, yes, there would be instances like that.

55. Q. And in the public health context, PCR tests are used for other viruses, as well; is that correct?

A. Yes.

56. Q. I understand that the idea that someone can test positive on a PCR test for a virus, but not become infected, or contract the disease that is associated with that virus, I understand that this occurs with other viruses, as well, as with the SARS-CoV-2 virus?

A. Could you repeat that, please?

57. Q. Sure, I'm a little confused myself. And I understand that the idea that someone can test positive on a PCR test for a virus, but not be infected by the disease associated with that virus, occurs with viruses

other than SARS-CoV-2 and COVID-19?

A. Okay, well, if you find the virus in an individual, whether they are...that implies that there is an infection. The infection is the presence of the virus in the individual's body. Whether or not they have a disease, depends on whether the virus produces any symptoms, and we do know that the COVID-19 can infect people without producing symptoms.

58. Q. Is it possible for a fragment of a virus, or a single virus, if that's the proper term, to be found in the nose of an individual where that fragment of virus, or individual virus, whatever the proper term is, was inactive at the time that it came into contact with the individual?

A. I don't know the answer to that.

59. Q. Okay, so you can't speak to whether it's possible that a positive finding on a PCR test might have happened because an inactive fragment of virus was...sorry, I'll just skip that. I think I have the answer to the question, and I'm having trouble rephrasing it myself.

When you use the term "testing" or

"test" in your affidavit, you are referring to PCR testing; correct?

A. In most cases, yes, because that was the dominant form of testing for most of the pandemic.

60. Q. All right, well, you just answered my next question. Of the people who do become infected with COVID-19, would you agree that the majority experienced mild or no symptoms, and go onto a full recovery?

A. Taken as a whole population, including all ages and all states of health, yes, the majority would recover. But there's a potential minority that experience severe illness.

61. Q. Those who do experience severe illness and severe outcomes, including hospitalization and death, have been primarily among those people over the age of 60; is that correct?

A. There's certainly a higher rate of hospitalization and severe illness amongst those who are older, but it also affects people who have other medical conditions which make them more vulnerable to disease.

62. Q. Right, but, by far, the majority of severe outcomes are in individuals over the age of 60; is that correct?

A. There are more severe outcomes in older people, yes.

63. Q. And higher numbers of severe outcomes in older people?

A. Well, you have...in order to say, you have to look at the number of older people there are. There's a higher rate, a higher likelihood of severe illness in people who are older. How they contribute to the overall numbers of cases in the population depends on the underlying denominator; how many older people are there, how many middle age, how many young people, and so forth.

64. Q. Right. All right, well, fair enough. And I understand that the overwhelming majority of COVID-19 deaths have occurred among persons over 60 years of age?

A. That's true.

65. Q. And the cohorts who are most at risk of severe outcomes or death have been relatively well understood since quite early in the pandemic; is that correct?

A. Yes, it's particularly the age distribution of severity...

66. Q. Right.

A. ...that has been understood since early on.

67. Q. And a higher likelihood of severe outcomes in people who comorbidities, or chronic illnesses, has been understood since early on, as well?

A. Yes, although I think our understanding of that has evolved. But, yes, the fundamentals were understood early on.

68. Q. Sure. Okay, thank you. The office of the chief medical officer of health designed the public health measures that the province has taken during the COVID pandemic; is that correct?

A. The chief medical officer of health made recommendations to the government about public health measures, yes.

69. Q. Right. Generally speaking, has the office of the chief medical officer of health been satisfied with the public health measures that the province has actually taken during the COVID-19 pandemic after receiving advice from the

CMOH; is that correct?

A. I'm not sure I know what you mean by "satisfy".

70. Q. The office of the chief medical officer of health felt that the public health measures taken by the province were effective in combating the COVID-19 pandemic; is that correct?

A. I can't speak for the chief MOH, himself...

71. Q. Oh, sorry, the office there.

A. ...but I would say that the measures taken were effective in reducing transmission of COVID-19.

72. Q. And when giving advice to the province on which public health measures should be taken, the office of the CMOH has provided advice...I'm backing myself into a corner here. I'll pass onto the next question.

The regulations that you reference in paragraphs 4 to 45 of your affidavit, in the second section, it's titled "Ontario's Policy Response to the COVID-19 Pandemic", are, in essence, embodiments of the recommendations of the office of the chief medical officer of health; is that correct?

A. Well, they reflect decisions made by the government following receiving advice from the chief MOH, yes.

73. Q. Right. In section number 3 of your affidavit, titled “The Impact of Ontario’s Public Health Measures”, which begins at paragraph 55, on page 23 of your affidavit, when you say “Public Health Measures” in the title of this section, you mean the regulations, legislation, and frameworks that you described in section 2 of your affidavit?

A. Yes, but it would also include actions that are advised by the chief MOH and the government, to the public, which are not framed in regulation. So there have been times when the government and the chief MOH have advised the public to, for example, wear a mask, where that is not required by regulation. The combination of regulatory interventions and public advice.

74. Q. All right, could you please read paragraph 55 of your affidavit for the record?

A. "...The public health measures implemented by Ontario had a significant impact on decreasing the transmission of COVID-19 across the province and

reducing the strain on the healthcare system. Among other things, the implementation of public health measures during the second and third states of emergency were shortly followed by a substantial decrease in the number of COVID-19 cases and hospitalizations..."

75. Q. On the following page, you provide two graphs showing the number of COVID daily case counts over time, from September 1st, 2020 to June 17th, 2021, as well as the daily hospitalization counts for the same time period; is that correct?

A. Yes.

76. Q. Are you aware of the maxim, "...Correlation does not imply causation..."

A. I'm familiar with it.

77. Q. What do you understand that phrase to mean?

A. That means that things that happen at the same time are not necessarily causally related.

78. Q. The charts you provided and your comments in paragraphs 55 to 57 of your affidavit

show a correlation between the timing of the second and third states of emergency and a drop in case counts and hospitalizations; would you agree?

A. Yes, they do.

79. Q. Does that correlation demonstrate with certainty that the restrictive public health measures in place during the second and third states of emergency caused those drops in case counts and hospitalizations?

A. I think, based on my experience with epidemics of different kinds, tracking this kind of data, I would say it’s very likely that there is a causal relationship.

80. Q. But it doesn’t demonstrate with certainty that there is a causal relationship?

A. No, I don’t think we can say “certainty”, but I think there’s a...

81. Q. Right.

A. ...high degree of likelihood.

82. Q. At paragraph 58 of your affidavit, you quote a statement from the Science Table’s May 20th, 2021 public update, to whit,

"...Control of the pandemic is improving due to current public health

measures..."

Is that correct?

A. Yes.

83. Q. Would you agree that this statement is, essentially, a restatement of your assertion at paragraph 55 that the public health measures implemented by Ontario had a significant impact on decreasing the transmission of COVID-19 across the province and reducing the strain on the healthcare system?

A. Yes, I think the members of the Science Table drew the same conclusion.

84. Q. Right, but it's, essentially, another way of saying the same thing?

A. I think...yes, I think the Science Table was in agreement with the statement that was made in the earlier paragraph, that's right.

85. Q. Did the Science Table read your affidavit before it made this statement that you quote in paragraph 55?

A. No...well, if I'm not mistaken, the statement preceded my comment.

86. Q. Yes. So the Science Table couldn't have been in agreement with a statement

that they had never read; is that correct?

A. Oh, I see what you are saying. I'm saying that they agreed with the content of the statement. I wasn't suggesting that they had reviewed the statement and evaluated it for their agreement.

87. Q. Right, so it is, essentially, another way of making the same statement that you made in paragraph 55?

A. I think it's more accurate to say that I and the Science Table came to the same conclusion looking at the data.

88. Q. And the data that you and the Science Table were looking at was a correlation between the timing of the second and third states of emergency and the decreases in COVID-19 case counts and hospitalizations that are shown on the charts in the following...in the paragraphs following paragraph 55?

A. I think that's part of it. I'm sure that the Science Table, as we did, was aware of similar relationships in other jurisdiction, which had implemented public health measures, was aware of the most current knowledge that we have about how COVID-19 is transmitted, and what

measures would be likely to interrupt that transmission, based on that understanding. So I can't speak for the Science Table, but I'm assuming that they would have been aware of all of that information when they made their statement.

89. Q. So is it fair to say that the section of the affidavit that we are reading right now, which is titled "The Impact of Ontario's Public Health Measures", is a statement of the...a summary of the evidence that is available to support your claim that the public health measures had a significant impact on decreasing the transmission of COVID-19 and lowering case counts and hospitalizations?

A. As I mentioned, there were other bits of evidence I think that underpin that conclusion rather than just the epidemiologic trends in Ontario, but yes.

90. Q. Are you aware that the motion you are speaking to today involves a challenge to the constitutionality of the public health measures taken by the province?

A. I'm not a lawyer, so I'm not sure that I understand that in the way that you would.

91. Q. Right, but have...but you are aware that this is a challenge of some kind to the public health measures taken by the province?

A. Yes.

92. Q. And that one of the consequences, if our challenge is successful, may be that certain of the public health measures taken would be struck down or deemed invalid?

A. Yes, I'm not familiar with the remedies that are available to the court, but I do understand that this is about the public health measures.

93. Q. So without asking you to draw any conclusions about what remedies are available to the court, you at least understand that it's important for the government to prevail in this matter?

MR. HUNTER: Mr. Kittredge, what's the relevance of the impact of a legal challenge on the evidence the witness has given?

94. MR. KITTREDGE: Well, I'm just trying to understand...

MR. HUNTER: I'm sure your clients also feel strongly that their

evidence...they would like to prevail on their case.

95. MR. KITTREDGE: It's true, it's true, but...

BY MR. KITTREDGE:

96. ...well, I could just move on to where I'm going with it, basically, which is that, did you put...in your affidavit, and particularly in this section of your affidavit, did you put forward the best evidence available to support your claim that the public health measures implemented by Ontario had a significant impact on decreasing the transmission of COVID-19 across the province?

A. The evidence that is in the affidavit, I think, does support that conclusion. There could have been a much more extensive body of evidence included...

97. Q. Right, so let's...

A. ...but this is the most appropriate and relevant to Ontario.

98. Q. Right, so reviewing what is contained in this section of the affidavit, you make, at paragraph 55, a statement to the effect

that the public health measures were effective, and that...in support of that statement, you offer that,

> "...among other things, the implementation of public health measures during the second and third states of emergency were shortly followed by a substantial decrease in the number of COVID-19 cases and hospitalizations..."

A. Yes, that's correct.

99. Q. You didn't specify what these "other things" were.

A. No, they are not specified in this part of the affidavit, that's correct.

100. Q. And at paragraph 56, you describe the chart that is attached at that paragraph, and provide further support for your claim that the public health measures were effective. That support constitutes nothing more than a statement to the effect that the case counts dropped after the states of emergency were implemented; is that correct?

A. Yes, that's what the graphs show.

101. Q. Right, so at paragraph 55, you offer that statement, in other words. At

paragraph 56, you offer pretty much the identical statement in a description of the graph below; is that correct?

A. No, I don't think it's an identical statement. The fact that there was a relationship between the trends, the epidemiologic trends, and the implementation of public health measures does support the statement in paragraph 55. It's not a restatement of it...

102. Q. I'm sorry...

A. ...it's evidence in support of, I would say.

103. Q. Sorry, can you repeat that? I missed what the additional evidence was.

A. I think you were asking me if paragraphs 55 and 56, basically, said the same thing, and I was pointing out that paragraph 56 summarizes the evidence of the statement in 55, or, at least, some of the evidence.

104. Q. And that "evidence" being the drops...the leveling off and drop in case counts that are shown in the chart below that paragraph; is that correct?

A. Yes, I'm pointing to that as evidence that supports the statement about the

effectiveness of public health measures, along with other things.

105. Q. Pardon me, I didn’t catch the last bit of that.

A. I just said...

106. Q. “Along with other”...

A. ...along with other evidence, but what is in the affidavit...

107. Q. But you’re not referring to the other evidence in paragraph 56; are you?

A. No, it’s not listed in paragraph 56, that’s correct.

108. Q. All right. And in paragraph 57, you describe the chart that appears below paragraph 57, a chart showing numbers of daily new hospitalizations for the same time period as the chart above?

A. Correct.

109. Q. And you note that it follows a similar trend as in the hospitalization counts drop at around the same time that the state of emergencies were implemented; is that correct?

A. Yes.

110. Q. And you don’t provide any further evidence in support of the effectiveness of the

public health measures in this paragraph; do you?

A. No, that's correct.

111. Q. And in paragraph 58, you describe the statement of the COVID-19 Science Table taken from its May 20th, 2021 update, and that statement, once again, was,

"...Control of the pandemic is improving due to current public health measures..."

Is that correct?

A. Yes.

112. Q. And you follow that up by pointing out that the Science Table noted that,

"...The percentage of individuals testing positive for COVID-19 decreased following the implementation of the province-wide lockdown and provincial emergency brake..."

In other words, the measures taken around the time of the state of emergency; is that correct?

A. Yes.

113. Q. And you could describe the chart that you have attached at paragraph 56 above as showing that the percentage of individuals testing positive for COVID-19 decreased around

the time of the two states of emergency; is that correct?

A. I'm sorry, could you repeat that?

114. Q. The Science Table's description of the evidence supporting its...sorry, your description of the Science Table's evidence, in support of the Science Table's statement to the effect that the public health measures caused the improvement in control of the pandemic...the evidence that you...that they offered was that the percentage of individuals testing positive for COVID-19 decreased following the implementation of the lockdowns and the emergency brake, in other words, the two states of emergency?

A. Yes, that's what the Science Table said, or noted, at that time.

115. Q. And you could just as easily have used that exact same phrasing to describe your chart at paragraph 56; is that true?

A. Well, they're two different types of data. They happen to support the same conclusion, but one of them is a track of daily case counts, that's reported cases. The percentage positivity is a different measure. We

use both to track...

116. Q. Oh, right.

A. ...the progress of the outbreak.

117. Q. So the percentage of individuals testing positive for COVID-19 might decrease if more tests were administered; is that the case?

A. Yes, it might.

118. Q. Does the fact that the percentage of individuals testing positive for COVID-19 decrease following the states of emergency, does that prove, with certainty, that the states of emergency caused that decrease?

A. No, once again, it’s a supportive piece of data, which supports the same conclusion, but, like all the other data, in and of itself, isn’t sufficient. You’re looking a number of different measures that allow you to draw a conclusion about what is happening.

119. Q. Right, and so far, the...

A. So what...the measures that we have typically looked at throughout the pandemic include case incidence reports, percent positivity of testing, hospitalization rates, the R-effective measure of transmissibility, all of these things are looked at together to help build

an accurate picture of what is happening in the pandemic.

120. Q. But you don't mention any of these things in this section of your affidavit; do you?

A. Not specifically. I mean, we'll see the Science Table statement is preceded by the words "Among other things". So it acknowledges that there are other factors that the Science Table is looking at in reaching its conclusion. But you are right, they are not enumerated in this affidavit.

121. Q. So, in short, there is nothing in paragraph 58 that proves a causal link between the public health measures and a decrease in COVID case counts, or hospitalizations, or percentage of people testing positive?

A. In my view, those facts all support the conclusion that the introduction of public health measures did cause a reduction in transmission of COVID-19, and the Science Table came to the same conclusion looking at the same information.

122. Q. Right, but it seems that what has been outlined in this section of your affidavit

is simply a correlation and not a causal relationship. Is that correct?

A. The conclusion that I draw from looking at this information based on my experience and expertise is that there is, in fact, a causal correlation...sorry, a causal relationship.

123. Q. And you put forward your best evidence for that in your affidavit; is that correct?

A. I put forward some of the evidence for it, yes.

124. Q. And what we have here is evidence of a correlation; is that correct?

A. There is a correlation, but some correlations reflect a causal relationship, and I would conclude that that's what is happening here.

125. Q. All right, and you would conclude that based on the correlation between the drop in case counts and the drop in hospitalizations, and the drop in percentage of individuals testing positive, the correlation between those measures and the timing of the two states of emergency?

A. Yes, I think the states of

emergency reflect the implementation of public health measures. So, yes, those things all factor into the conclusion that I draw, along with...and this is...remember, this is all Ontario data. There are a number of other jurisdictions around the world in which similar relationships have been seen as public health measures have been introduced and withdrawn, and it also entirely consistent with what we understand about the way in which COVID-19 is transmitted.

126. Q. All right. In paragraph 59, you acknowledge that there are many factors that contribute to the transmission of COVID-19; is that correct?

A. Yes.

127. Q. And rather than saying that the data, meaning the key public health indicators that you just mentioned, the drops in case counts, the drops in hospitalization, and the drops in percentage of individuals testing positive, you say that those suggest that the public health measures decrease the spread of COVID-19 in this paragraph; don't you?

A. Yes, that's the language that is

used here...that I've used.

128. Q. You didn't use the word "show" or the word "prove", or even that you "conclude" that Ontario's public health measures decreased the spread of COVID-19; is that correct?

A. Yes, I think...I think I could have just as easily used some of those words. I wouldn't have used the word "prove", but I could easily have used the word "I conclude" or "in my opinion, this is"...

129. Q. Do you think the word "suggests" has, essentially, the same meaning as "leads to the conclusion"?

A. I'm just saying that the choice of that word doesn't reflect on the strength of my view on this matter.

130. Q. But, nonetheless, you chose that word?

A. M'hmm.

131. Q. Isn't it possible that these decreases in case counts, hospitalizations, and percentage of individuals testing positive, could have been caused by factors other than the province's restrictive public health measures?

A. Well, as I say in that paragraph

of the affidavit that said, “there are many factors that contribute”...so, yes, there...undoubtedly, there are some other factors which have a bearing on the trends in transmission rates of COVID-19 in the population.

However, I think the evidence can fairly be interpreted as saying that the public health measures were responsible...one of the main factors responsible for these changes. As I said, I haven’t claimed that they are the only factors.

132. Q. Is it conceivable that the correlation is a coincidence?

A. In my opinion, I don’t believe that’s a reasonable conclusion to draw, no.

133. Q. So you believe that the correlation between the drops and the key public health measures is valid evidence to support the conclusion that the public health measures caused those drops?

A. Yes, taken together with other pieces of evidence that we’ve spoken about in the past few minutes.

134. Q. Could vaccination have contributed to these drops in case counts and

hospitalizations in Ontario?

A. Well, the timing of significant numbers of Ontarians becoming vaccinated came quite late in terms of these graphs, so I think the trends that are represented here can't reasonably be explained by vaccination.

If you were to follow the same indicators forward in time to the present day, then, yes, we currently have high levels of vaccination which are making a difference in the occurrence of COVID-19, but over the period covered by these graphs, that's not a factor.

135. Q. Would you agree that May 20th, 2021 falls within the time period covered by these graphs?

A. It's towards the very end, as I read it.

136. Q. Right...

A. It's after...

137. Q. ...can I take you to Exhibit Y of your affidavit? And we'll be coming back to these charts in a moment, so don't lose that spot, either. Exhibit Y is the May 20th, 2021 update on COVID-19 projections from Science Advisory Table.

A. Yes, hang on, I think I might have it. Sorry, you said the May 20th, 2021 update?

138. Q. Yes, it's at page...I have it marked as page 177...

A. Okay, well, my figure doesn't have any page numbers, unfortunately.

139. Q. ...if that helps. Okay, I'm...

A. I think I've got the one you mean.

140. Q. Okay, so this is...so the first page of it, after the Exhibit Y marking, is titled "Update on COVID-19 projections, dated May 20th, 2021"; is that correct?

A. That's what I've got.

141. Q. All right, so if we go one, two, three, four, five, six, seven, eight, nine, ten pages to a page marked page 11 in this exhibit, it's titled "Vaccination coverage continues to increase".

A. Got it.

142. Q. What does this tell you about the percentage of the populations who has received at least one dose of the COVID-19 vaccine?

A. It's not very well marked, this

particular page. I'm not sure. The only percentages I see are the ones at the top, as listed as "Provincial Progress", but it's not labeled in terms of what those numbers represent.

143. Q. As of May 20th, 2021, what is your understanding of the vaccination status in the province? What percentage of individuals in the province had received at least one dose of the vaccine?

A. I'm sorry, I don't have that in front of me, although this graph may show that. But, as I say, it's not labeled properly. What I recall, without reference to documents, is that vaccination was starting to ramp up at that point, and significant numbers were starting to occur towards the end of that third wave.

144. Q. And so if we look back at this page 11, once again, titled "Vaccination coverage continues to increase"...

A. Right.

145. Q. ...we have several charts divided up by age, at the bottom of the...or in the lower ...in the centre of the page. Is that correct?

A. I'm looking at the same page as you are, yes.

146. Q. Right, and the blue portion of the bars that appear on that chart on the left-hand side...

A. Right.

147. Q. ...represent the number of individuals with at least one dose completed?

A. Yes, the dark blue?

148. Q. Yes.

A. Yes.

149. Q. And then there is a much smaller number of individuals, marked in a lighter blue, who have made an appointment for a vaccination?

A. Right.

150. Q. And at the top of the bar, there’s yellow marking that represents the remaining population has not yet received a vaccine; is that correct?

A. That’s what it looks like.

151. Q. All right, and if you were to assume that that was true, would this reflect your understanding of the vaccination status of Ontarians aged 40 and up, at this time?

A. That’s what it looks like, yes.

152. Q. Right. So you were the associate chief medical officer of health, at this time,

dealing with COVID matters, primarily, and you have no...you don't have a sufficient recollection of the vaccination status of Ontarians, especially older Ontarians, at the end of this wave, a very significant moment in the pandemic? You don't have the recollection to go any further than to say "That's what this chart looks like"?

A. I'm trying to be accurate in my responses to your questions. What I recall is that the vaccination program, as I said, was ramping up and we were starting to get significant numbers of people vaccinated towards the end of that wave.

Where we started this question was about how the trend changed at the time public health measures were implemented. For most of that decline, I believe public health measures were responsible, rather than vaccination, for the decline that was happening.

The decline certainly happened before there was significant number of people vaccinated. Towards the end of that curve as it was coming down, undoubtedly vaccination was playing a role, particularly amongst the elderly

because they were given priority in terms of access to vaccines.

153. Q. Right, and we agreed earlier on that the vast majority of hospitalizations were among elderly people?

A. Yes, the hospitalization rates were much higher among elderly people.

154. Q. Right, and from looking at this chart, it appears that the vast majority of people, let’s say, older than 70 years old, had received at least one vaccination shot; is that correct?

A. Yes, I think that’s what this data looks like, yes.

155. Q. Right, and quite a large majority of individuals, aged 60 to 69, had also received one dose of the vaccine; is that correct...or does that look accurate to you?

A. Yes. Yes, it looks...again, these are not percentages, but it does look like it, yes.

156. Q. Sure. And perhaps about two-thirds to three-quarters of individuals, 50 to 59, had received one dose of the vaccine; does that look like a fair description to you?

A. Yes, I would say it does.

157. Q. And about half of the individuals, 40 to 49, had received at least once dose of the vaccine?

A. It does look that way.

158. Q. So the age groups we have covered here would include certainly the people most at risk of severe...or with the exception of younger people with comorbidities or chronic health conditions, what we see in this chart represents most of the people who are at risk of severe outcomes and hospitalization; is that true?

A. Yes, deliberately so, because they were given priority in vaccination.

159. Q. Right.

A. Also, I think I should point out that interpretation of this data...the blue, the dark blue, is one dose, which doesn't...

160. Q. Yes.

A. ...give us much protection. So these are people who are not considered fully immunized.

161. Q. True, but one dose of the vaccine does give...

A. Does give some protection.

162. Q. ...some protection?

A. Yes, yes.

163. Q. All right, and it would be expected that when a population that is most likely to become hospitalized receives a vaccination, hospitalizations will drop; would you agree with that?

A. Yes, and that fact is what has happened if you were to project the data forward, beyond this point.

164. Q. Right. So would you say that vaccination may have had an impact on the decrease in hospitalization rates as shown in the charts at your...on your page 24?

A. I would say, as I said before, just towards the end when...after the rates of both hospitalization and case numbers had already come down, I'm sure that the vaccination that was ramping up, at that point, to significant levels, did have some impact on pushing that curve lower.

165. Q. When did Ontario begin vaccinating people over 80 years old?

A. I don't have that date.

166. Q. Approximate.

A. I don't have that date in my

head, I'm afraid.

167. Q. Do you have an approximate date in your head?

A. I wouldn't want to...it's an easy enough number to find, but I wouldn't want to get it wrong. I don't have it in my head, though.

168. Q. Do you know what month the province started vaccinating 80-year-old people and older?

A. Yes, I'm afraid I don't have that in my head. Just to explain, I was not involved with the vaccination program very closely, so...

169. Q. Right.

A. But we could easily find out.

170. Q. Sure. Okay, well, I think we can move back up to your page 24, again.

A. M'hmm.

171. Q. You mentioned earlier that in your monitoring of the COVID-19 pandemic situation, you kept an eye on jurisdictions around the world, and that you had noticed that some of the...you had noticed that some jurisdictions saw drops in hospitalizations and drops in case counts at around the same time that the drops...or that the two...the second and

third states of emergency were imposed and in effect in Ontario; is that correct?

A. I don't think so. Could you repeat the question?

172. Q. You said that...well, correct me if I'm understanding you incorrectly, but I thought you said that one of the pieces of evidence that you had relied on in support of your conclusion, or the suggestion, that public health measures in Ontario had been effective in dropping case counts and hospitalizations, was seeing similar drops in other jurisdictions at around the same time; is that correct?

A. Okay, no, let me correct you. It wasn't that they were happening at the same time. It was that other jurisdictions saw reductions in hospitalization and case counts at the time that they implemented their public health measures.

So, in other words, we were seeing, in other jurisdictions, a similar relationship between the implementation of public health measures and the epidemiologic trends as were seen in Ontario; not that jurisdictions were experiencing at the same time as each other.

173. Q. Are you aware of any other

jurisdictions that experienced peaks and drops at around the same time that the Province of Ontario implemented its second and third states of emergency?

A. Again, I think the way you've stated it doesn't reflect what I said. It wasn't those...

174. Q. No, I'm just...I'm asking if you are aware of any, not...

A. It's not something we would have looked at. What we were looking for was the relationship between the implementation of measures and the outcomes, in terms of trends in the pandemic, not whether other jurisdictions were experiencing things at the same time as we were. I'm sure there were some, but that wasn't, primarily, what we were looking at.

175. Q. Did you follow the progress of the COVID-19 pandemic in Florida?

A. Yes, over the course of the pandemic, we looked at many other jurisdictions, many times. So Florida was, certainly, something that we looked at at different times.

176. Q. And what was remarkable or of note about...or, sorry, I'll rephrase that.

Florida was well known to have not imposed lockdowns, or public health measures, anywhere near as stringent as those imposed in Ontario; is that correct?

A. From memory, I believe that's correct.

177. Q. Were you following the progress of the COVID-19 pandemic in Sweden?

A. I think we did look at it at one point. I wouldn't be able to tell you much about it at this stage, but I think it was one of the jurisdictions we may have looked at.

178. Q. And Sweden was another jurisdiction that was well known for not having imposed public health measures anywhere near as strict as those imposed in Ontario, as well; is that correct?

A. I don't recall that. I can't comment on it.

179. Q. You don't recall hearing anything about Sweden taking a more laissez-faire approach to the COVID-19 pandemic than other jurisdictions?

A. No, I don't recall that.

180. Q. You don't recall hearing anything

about Sweden's approach to the COVID-19 pandemic?

A. I remember Sweden was one of many jurisdictions we looked at. I don't remember the specifics of what we saw in Sweden.

181. Q. So you have no recollection...

MR. HUNTER: Counsel, you have asked the question three times.

182. MR. KITTREDGE: Okay, sure, fair enough. All right, I would like to show you a couple of images or webpages. And I'll apologize at the outset of this because we may be heading for a minute or two of me figuring out exactly how to do this, but...so I have a second Zoom connection here that is called "Rob Kittredge Chat" and something else. So let me just open up this document. I hope I don't share something mortifying instead of the document I'm hoping to share.

All right, and what I suppose I will do here, Counsel, is I will share a screen capture that I have taken of the webpage that I would like to show your client, or your witness, and in the

event that you would prefer, I could share a live view of the webpage, itself. So, I suppose, just because of the nature of the proceedings, I'll take whichever approach you prefer, or both. So I'll leave it up to you. But why don't we start with the image and then if you have any preferences, just make them known and I'll behave accordingly.

MR. HUNTER: That's fine.

BY MR. KITTREDGE:

183. Q. So, Dr. McKeown...it strikes me that there's a risk of sharing some privileged documents at this point, so I'll be careful, and I'll apologize for the time it's going to take here, but I believe I'm not doing something terrible. All right, Dr. McKeown, can you see the document that I've just shared?

A. Yes, I'm seeing something.

184. Q. Sure. Does that document look familiar to you at all? It's a screen capture from a website.

A. I don't recognize it, but that doesn't mean I haven't seen it at some point.

185. Q. Right. Do you recognize the logo in the top-left corner?

A. Yes, WHO.

186. Q. Right. Do you recognize this as a screen capture from the WHO website?

A. I wouldn't be able to...apart from the logo, I wouldn't be able to comment on that...

187. Q. Would it be of any assistance if I shared a live view of the page where I captured this image? Or, alternately, would it be of any assistance if I sent you a link to the page where I captured this image?

A. "Of assistance" in what way? Are you asking me to...

188. Q. In recognizing this...

A. ...validate the source of the page?

189. Q. ...yes, and recognizing this document.

A. I don't think it would make a difference to my recognition. I mean, if you tell me that this came from the WHO website, I have no reason to doubt you.

190. Q. Right. Well, are you willing to

accept that this is a screen capture from the WHO website?

A. Sure. As I say, I have no reason to think it's not.

191. Q. All right.

A. If that's where you say you got it.

192. Q. Sure. All right, would you agree that this chart shows confirmed cases, over the course of time, from the beginning of the COVID pandemic to somewhere around the present day?

A. It does look that way. It looks like it's a bar graph for weekly case counts is the way I'm interpreting it.

193. Q. Right. Do you notice two peaks in this weekly bar graph of weekly case counts?

A. Yes. Well, two large peaks, anyway. There are other peaks, as well, but two large ones.

194. Q. Right, two prominent peaks...

A. Yes.

195. Q. ...the two most prominent peaks. And when would you estimate that those two most prominent peaks occurred?

A. Well, looking...

196. Q. I'm sorry, I'll rephrase that. When would you estimate that the first of the two most prominent peaks occurred?

A. I would only be able to estimate based on the x-axis, which is a time axis.

197. Q. Right.

A. It looks like late December.

198. Q. Right, and would you agree that the peaks that are shown on your charts, on page 24 of your affidavit, the first of the two prominent peaks on your charts also occurred around late December?

A. If you are referring to the third wave, yes, that's approximately right. I'm assuming this is 2021, but...

199. Q. The second state of emergency is the date that I'm looking at, the peak that I'm looking at.

A. Yes.

200. Q. So you would agree that that peak, the second state of emergency peak, in your chart corresponds, roughly, to the same time period as the first peak on this chart of weekly case counts in Sweden?

A. Yes, it looks roughly.

201. Q. And turning to the second peak, when would you estimate that took place? I'm sorry, the second peak in the Sweden chart.

A. In the Sweden...yes, well, again, you have to eyeball it, so it may not be accurate, but sometime early May/late April.

202. Q. Right. I mean, don't you see...do you see the date "April 1st" directly below two prominent...two of the highest weekly case counts?

A. I'm sorry, I misspoke. Yes, so early April.

203. Q. Right.

A. Yes.

204. Q. And would you agree that that corresponds, approximately, to the time of the third state of emergency...that the third state of emergency was imposed in Ontario?

A. Roughly, yes. Very roughly.

205. Q. And this peak corresponds to the peak...this peak, timewise, corresponds to the timing of the peak in the charts that...of the second peak in the charts that you provided at your page 24; is that correct?

A. Yes, very roughly, yes.

206. Q. Right, and after these two peaks on the Sweden chart, the cases dropped off and became lower?

A. That's correct.

207. Q. I mean, there's a substantial similarity in the shape of these two peaks and the timing of these two peaks and the two peaks and the timing of the two peaks in the charts that you provide at page 24; do you agree?

A. Yes, the timing of the highest level, yes.

208. MR. KITTREDGE: Sure. All right, well, I would like to mark this as Exhibit A to this cross-examination.

MR. HUNTER: I'm fine with marking it as an exhibit. Of course, we're not admitting the truth of any of the contents of it.

209. MR. KITTREDGE: Absolutely, okay. Thank you.

--- EXHIBIT A: Chart of Swedish weekly COVID cases

BY MR. KITTREDGE:

210. Q. And I would like to show you one other document, and I will probably...a strong possibility I'm going to accidentally close this window. I apologize for the delay here. Okay, all right, do you see the second document that I'm showing you now on my shared screen?

A. Yes.

211. Q. And do you recognize this? It's another captured webpage from the internet.

A. From the CDC website, I assume?

212. Q. Yes. Are you willing to accept that this is a capture from the CDC website, subject, of course, to not admitting the truth of its contents?

A. Yes, it appears to be that way from what I can see.

213. Q. All right, and can you describe the chart that you see in the centre of this or towards the bottom part of this image, right here?

A. Yes, it's labeled as "Daily Trends in Cases and Cumulative Incidence Rates in Florida as reported to CDC, per 100,000". It's a graph of cases over time with a number of peaks.

214. Q. And do you note that...and this

is a chart for the state of Florida, a chart of cases and cumulative incidence rates of cases in Florida?

A. Yes.

215. Q. Do you note that there's a peak around late December of 2020?

A. Yes, I can see that.

216. Q. And it's quite a prominent peak?

A. Yes.

217. Q. And would you say that the timing of that peak corresponds, roughly, to the timing of the imposition of the second state of emergency in Ontario, in late December?

A. Yes, very roughly, yes.

218. Q. Right, and after that peak, on the Florida chart, the cases drop off?

A. Yes.

219. Q. And do you notice another smaller peak around April of 2021 on this Florida chart?

A. Yes.

220. Q. And does that peak correspond, roughly, to the timing of the imposition of the third state of emergency in Ontario?

A. Again, very roughly.

221. Q. And after that peak, the case

counts drop off, as well; don't they?

A. Yes. Although interestingly, they...the thing that really strikes me about these curves is the high, high rates of case incidence that they have with...and the peak you've just been talking about, 15,000 cases a day, and even...

222. Q. Right.

A. ...at the low point, you're seeing, you know, not many fewer cases than Ontario saw at its highest.

223. Q. Right, so when you take that into consideration this peak in April, on the Florida chart, is actually...reflects a larger number of case counts than Ontario's peak at the same time; is that correct?

A. It appears that way, yes. You would have to...in terms of absolute numbers, that's true, you would have to do a bit of a rate. I can't recall the population of Florida, but, yes, it certainly represents a high rate of transmission.

224. Q. So there's a striking similarity both in shape and size to this peak and the rise in case counts leading up to it, and the falling

case counts after it, and the chart that we see at page 24 of your affidavit...both charts that we see at page 24 of your affidavit; is that correct?

A. Well, I think you can see peaks at roughly the same time. I'm not sure what conclusion one can draw from that. You know, you would have to have a lot more information about what's going on in Sweden and Florida and Ontario.

225. Q. So these happen at roughly the same time as the imposition of the states of emergency in Ontario, both of these peaks, the second and third states of emergency in Ontario?

A. Roughly, as we've said, yes.

226. Q. So there's a correlation between these peaks, and the peaks in Sweden, and the period of time during which the state of emergency was declared in Ontario; would you agree?

A. Well, I would go so far as to say that the peaks were happening at the same time.

227. Q. Sure, but you wouldn't say that that's a correlation?

A. No...yes...I'm not sure. Since

they're different jurisdictions, which don't have any...there's no reason to believe that they would be linked in terms of the timing of the pandemic, so I'm not sure that "correlation" is the right word.

228. Q. In Ontario, the correlation that you noted between the imposition of the public health measures and the drops in case counts was rooted in the fact that they occurred at around the same time, essentially; was it not?

A. Well, the alignment in time is a significant observation when the measures are being applied to the same...to the population with the intent of actually causing that reaction.

So, you know, you're looking for that trend to go in the way in which it did. You know, if we hadn't implemented public health measures, then you wouldn't have expected to see any impact of public health measures because they weren't implemented.

So I think the relationship between the two things is significant when it's in the same population, and when you are intending to have that outcome. I'm not sure how to think about

the relationship between trends and a different population in another continent.

229. Q. So am I to understand that you find a correlation because you are looking for it?

A. No, I don't think that's the reason you find a correlation. I think you are looking for an impact of measures which are taken intending to produce a particular outcome, and in that context, the finding of that impact is significant.

230. Q. So the evidence to support your conclusion that the Ontario public health measures were effective was essentially that those health measures happened at the same time as a drop of cases in Ontario; is that correct?

A. Well, the drop in cases is what would have been expected if the public health measures were effective, and that was, in fact, what we saw.

231. Q. Right, so...

A. I think it's entirely reasonable to conclude a causal relationship in that context.

232. Q. So if the public health measures

taken in Ontario were effective at causing a drop in case rates in Florida, then why would you not come to the same conclusion about the...why would you not see a correlation there, when you see one in Ontario?

A. It's not on the face of it a reasonable conclusion that Ontario's public policy would have an impact on rates in Florida. You know, I think...I think if you look around the world, there are many, many jurisdictions. I'm sure it's possible to find a number of jurisdictions in which there is a similar timing of the trends in the COVID pandemic.

There probably are lots of jurisdictions in which there are very different trends because of factors in those jurisdictions, and differences in the timing of implementation of public health measures, and other factors. You can...as I say, here, you picked and presented a couple of jurisdictions in which the timing aligns.

I don't think that means that there is a relationship between Ontario's public policy and what is happening in other jurisdictions. It's not a reasonable conclusion to draw. I think

it's a very reasonable conclusion to draw that public health measures in Ontario, which were implemented in order to produce the impact that we see, had, in fact...we had, in fact, observed the impact that we would expect if the measures were effective.

233. Q. To a certain extent, that presupposes that the measures were effective, though; doesn't it?

A. Well, the measures were implemented because we anticipated that they likely would be effective, partly because of what we've seen in some other jurisdictions, which had implemented them earlier, and partly because of our understanding of how the virus is transmitted. If you take measures which reduce contact between individuals, you would expect to see less transmission and that is, in fact, what we saw.

234. Q. All right, so here, despite the fact that these peaks and drops in Florida occurred at more or less the same time as the imposition of the states of emergency in Ontario, you view this as a coincidence?

A. I don't view them as a causal

relationship, certainly. It's not reasonable to think actions in Ontario could cause changes in Florida in this way. So, no, I don't know whether I'd call it a "coincidence", but... because there may be some overarching, global factors in transmission that affect all jurisdictions similarly. So...but, beyond that, no, I don't think these trends reflect an impact of Ontario's measures in Florida.

235. Q. All right, similarly, do you view the similarity in timing between the peaks and the following drops in cases in Sweden...sorry, I'm going to rephrase that. Do you view the fact that there were two similar peaks and two following drops in the chart that I showed you relating to Sweden, the fact that those peaks correspond, roughly, with the timing of these peaks, and they correspond, roughly, with the timing of the peaks and the imposition of the states of emergency in Ontario, do you view that as a coincidence?

A. You would have to look at what was going on in Sweden at the time, what was happening with vaccination, with public health measures. And it is possible that Sweden

implemented similar measures at the same time. I can't recall from our information gathering, but I think those are the more relevant factors. The fact that there were some peaks at similar times between jurisdictions in different parts of the world, I don't think is something that we can really understand in the way that you are suggesting.

236. Q. So in the case of Ontario, you view it as evidence of a causal relationship that these...that the Ontario peaks happened at the same time as the states of emergency, but the same...

A. Yes, I do. I do, because that's a reasonable conclusion to draw given that you are dealing with the application of the measures to the population, which had the trends that you would expect if the measures were effective. I think, you know, there are...I'm sure you could find a number of events around the world, events that had nothing to do with COVID, which happened to coincide in timing with the trends in COVID in Ontario. I don't think it's reasonable to conclude that there's a causal...or even any kind of a relationship between them.

237. Q. Do you agree that you could find a number of events relating to COVID case counts in Ontario that correspond with public health measures taken in Ontario, and yet were a mere coincidence?

A. Yes, I think, as we discussed before, it's always possible that events happen for a coincidence. If you...if someone...if I'm a doctor and someone comes to me with an illness, I give them medication, which I have reason to believe will cure their symptoms, and the symptoms go away, I don't immediately think it was a coincidence. Because in that particular context, it's entirely reasonable to believe that the medication that was intended to have the desired effect, in fact, had the desired effect. That doesn't rule out the possibility that the person could have gotten better on their own without any impact from the medication. But that wouldn't be the most likely explanation.

238. Q. But in that circumstance, your mind is open to the possibility that the recovery was a coincidence?

A. Well, I think we have to be open to the possibility in all circumstances. I'm

just saying that being open to that possibility, I come to the same conclusion, that the public health measures were likely responsible for the improvements in COVID transmission and hospitalization that we saw.

239. MR. KITTREDGE: All right, well, thank you. I'm going to close this...oh, I would like to mark this image as Exhibit B to my cross-examination.

MR. HUNTER: That's fine, same...

240. MR. KITTREDGE: Right, agreed.

--- EXHIBIT B: Daily Trends in Number of Cases and Cumulative Incidence Rate of COVID-19 Cases in Florida reported to CDC, per 100,000 population

241. MR. KITTREDGE: And I'll close this window.

BY MR. KITTREDGE:

242. Q. And if I can take you back up to, yet again, the charts at page 24 of your

affidavit. And are you at page 24 of your affidavit, Dr. McKeown?

A. I am.

243. Q. Would you agree that the charts shown on page 24 of your affidavit show a downward trend in case counts and hospitalizations only during the second and third states of emergency?

A. Yes, in terms of what is on the graph, yes, that's true.

244. Q. But both charts show an upward trend during the period between September 2020 and the imposition of the second state of emergency, and another upward trend during the period between the second and third provincial states of emergency; is that correct?

A. Yes.

245. Q. So while they may show a correlation between the public health measures in place during the second and third states of emergency and falling case and hospitalization counts, these charts also show a correlation between rising case counts and the public health measures in place at other times; would you agree?

A. No. I think the rising case counts occurred in a context in which public health measures were largely being withdrawn, or adjusted to be minimal.

246. Q. So you described a number of public health measures, some of which were in place during these periods of upward trend shown on these charts; wouldn't you agree with that?

A. Yes, there were public health measures in place, but as the affidavit points out, the intensity of those measures, and the strictness of them, varied quite a bit over the course of the pandemic.

The states of emergency coincided with times when the public health measures were made more strict for a period of time, and the other times there were some public health measures in place, but they were generally...the government was, generally, reducing them over time.

247. Q. But there were public health measures in place at all times shown on this chart, nonetheless; am I correct?

A. Yes, but...yes, with different levels of restrictiveness and different levels of intensity.

248. Q. But they were public health measures?

A. Yes, I'm just trying to point out that although you...saying that they are public health measures means very different things at different times in the pandemic, depending on what the policy was at the time.

249. Q. Right. At paragraph 55 of your affidavit, at the start of this "Impact of Ontario's Public Health Measures" section, you say that,

"...The public health measures implemented by Ontario had a significant impact on decreasing the transmission of COVID-19 across the province..."

Is that correct?

A. Yes, that's what it says.

250. Q. Do you mean only the public health measures that were in place while case counts were falling?

A. No, I think...I think even when fewer public health measures were in place, they were likely having some effect. The most effective public health measures were the ones that were the most restrictive, and which were

implemented during the states of emergency, and I think that reflects the graphs that you're talking about.

251. Q. Do you think the evidence that you have provided, in this section 3, supports the proposition that public health measures that were in place during periods of a rising trend, rising case counts and rising hospitalizations... do you think that the evidence that you provided in this section 3 supports the proposition that those public health measures were effective in controlling COVID-19?

A. It's, obviously, more difficult to tell in that case. The...undoubtedly, there was increases in transmission despite the measures that were in place, at the time, which were, during those times, less restrictive than at times when we saw decreases.

I think that's part of the relationship which supports the effectiveness of the measures ...is when you make the measures more strict, case rates go down, when you make them less strict, case rates can rise.

252. Q. Can you point to the evidence that you provide, in this section 3, to support

the proposition that public health measures in place during periods of rising trend were effective in controlling the transmission of COVID-19?

A. I'm sorry, can you repeat the question?

253. Q. Can you point to any evidence in this section 3 of your affidavit that supports the proposition that public health measures in place during periods of rising trend were effective in controlling the transmission of COVID-19?

A. I think I would say that they were less effective than the more strict measures that were put in place. It's difficult to...you can compare the impact of strict measures versus less strict measures. It's difficult to compare the impact of less strict measures with no measures, okay, unless we actually do that, which we haven't done.

254. Q. But it's possible...it's possible to evaluate the effectiveness of less strict measures; is that correct?

A. If you can compare them with a scenario with no measures at all, yes.

255. Q. In other words, if you had some evidence to support that analysis?

A. Yes. I'll concede that it's more difficult to judge the effectiveness of the less strict public health measures in the context of rising case rates; I think that's true.

256. Q. Would you agree that there is no evidence, whatsoever, in this section 3 to support the proposition that the public health measures in place during periods of rising trend were effective?

A. I think you would have to look at...if you look at some of these periods of rising effectiveness, different measures were in place in different parts of the province. And, again, that's not presented in the affidavit, but my recollection is that, where we saw measures particularly under one of the frameworks which explicitly applied different public health measures based on local epidemiology in different parts of the province, where we saw that, you could...

257. Q. I'm not sure...excuse me for interrupting, but I'm not sure that's a particularly responsive answer. I'm asking if

you would agree that there is no evidence presented in this section 3 of your affidavit to support the proposition that the public health measures in place during periods of rising trend were effective?

A. Yes, I can agree with that.

258. Q. All right, thank you. The "Keeping Ontario Safe and Open Framework" was released on November 3rd, 2020; is that correct?

A. November 3rd? Yes.

259. Q. One goal of the framework...I'll call it the "framework", was to keep Ontario safe from the COVID-19 pandemic; correct?

A. I think that's an absolute statement. I can't recall what the objectives were phrased as, but I don't think...I don't think that absolute safety was an objective of any of the framework.

260. Q. The framework is called "Keeping Ontario Safe" and "Keeping Ontario Open"...

A. Yes...

261. Q. ...but nonetheless, I'll move on.

A. Yes.

262. Q. During the period of time between the enactment of the framework in early November

and the end of 2020, did the case counts and hospitalization charts on page 24 of your affidavit show an upward trend or a downward trend?

A. Yes, provincially, there was an upward trend during that period.

263. Q. Right, the province shut down and declared its second state of emergency on January 12th, 2021, just over two months after the "Keeping Ontario Safe and Open Framework" was enacted. Do you agree that between early November 2020 and January 12th, 2021, the framework did not succeed in keeping Ontario safe and open?

A. Well, the framework succeeded in opening Ontario, because it was designed, in part, to reduce public health measures and their impact on the province. Again, we've talked earlier about how it's difficult to assess the impact of public health measures in the face of rising case counts, but it certainly was less effective, overall, than the subsequent frameworks, which applied stricter public health measures.

264. Q. Well, I asked...the question that

I asked was whether the framework, during the period of time that I mentioned, succeeded in keeping Ontario safe and open. And you mentioned that it may have opened Ontario, somewhat, although I would argue that it had the opposite effect as it was followed immediately by a state of emergency and a lockdown.

But I don't think you really addressed the part of my question which asked whether it succeeded in keeping Ontario safe. And would you agree that it didn't succeed in keeping Ontario both safe and open during the period of time that I referred to?

A. Let me try and do a better job with your question. As the title said, it attempted to do two different things. It was attempting to open Ontario, as much as possible, to reduce the impact of public health measures and control COVID transmission, and, I think, those are difficult things to achieve at the same time.

As you pointed out, during the time that that framework was in place, Ontario was more open, but we were also seeing rising rates of infection. So I would say that it's difficult to

achieve both objectives, and it was not entirely successful in meeting both objectives at the same time.

265. Q. All right. I would like you to compare the charts that we've been discussing on page 24 of your affidavit, with some other pages in your affidavit. Do you have a paper copy of your affidavit in front of you? Are you able to...

A. I do.

266. Q. ...look at two pages at the same time?

A. I should be able to.

267. Q. All right, can you hold on to the charts on page 24 and look at the tables that you provide at...on pages 36 and 37 of your affidavit, and that is paragraphs 91 and 92, I believe.

A. Right.

268. Q. All right. So let's start with the table on page 36, which is paragraph 91, which summarizes the restrictions imposed on my clients, The Church of God, and other churches in the southwestern PHU. Is that a fair description of that table?

A. Yes, I think so.

269. Q. The first row of this table discusses restrictions applicable from July 13th, 2020 to December 25th, 2020; is that correct?

A. I think that's what it says, yes.

270. Q. During that time period, limits were placed on the right of people in the PHU to freely assemble and practise their religion; would you agree with that?

A. I'm sorry, I was reading it while you were speaking. Could you please repeat?

271. Q. During that time period, limits were places by the province on the right of people in the PHU to freely assemble and practise their religion; is that correct?

MR. HUNTER: Counsel, he can talk about the whether or not limits were placed on assembling and worship. Leave it to the judge whether rights were limited.

272. MR. KITTREDGE: Sure. Okay, fair enough. I'll rephrase the question.

BY MR. KITTREDGE:

273. Q. During that time period, limits

were placed on people's ability to freely assemble and worship; is that correct?

A. Yes, certainly, restrictions were placed on people's ability to assemble, for sure.

274. Q. And to practise their religion in the manner to which they are accustomed; is that correct?

A. I'm not going to disagree with you, but I'm not...I can't judge...I don't have the information to judge people's ability to practise their religion as they choose to, just because I'm not that familiar with all of the faiths and what their practices are.

275. Q. Okay, so can you tell me what the restriction on outdoor services was, for example, during this time period?

A. During this time period, no more than 100 people were permitted to gather outdoors.

276. Q. So to the extent that a group of...that a religious group was accustomed to gathering in numbers greater than 100, would you agree that they were...their ability to practise their religion in the manner to which they are accustomed was limited?

A. Yes.

277. Q. What were the limits that the province imposed on indoor services?

A. During that time period?

278. Q. During that time period, I'm sorry.

A. Yes, equated as thirty percent of room capacity was the indoor services limit.

279. Q. Right. Now, please take a look at the first row of the table on page 37, which summarizes the restrictions applicable to my client's Trinity Bible Chapel, and other churches in the Waterloo PHU.

A. M'hmm.

280. Q. Are the indoor and outdoor capacity limits the same as in the southwestern PHU for approximately the same period?

A. It looks like it. Outdoor, 100 people, indoor, 30 percent.

281. Q. Right. Now, please consult the case count and hospitalization charts on page 24. Do the charts show an upward trend or a downward trend, generally speaking, during that time period?

A. Hang on. So we're talking about

July...mid-July to December. It looks like increase in case counts.

282. Q. Yes, it does. And now, if you could turn back to page 36, paragraph 91, and the southwestern PHU chart, and if you can take a look at the third row, February 16th, 2021 to March 28th, 2021, and can you tell me what the restrictions on indoor and outdoor services were during that time period, in this PHU?

A. It looks like 100 people outdoors, 30 percent indoors.

283. Q. Right, and if you can turn to the next page, paragraph 92, look at the third row of that table, and are the restrictions, essentially...are the restrictions identical during the identical time period?

A. It looks like it.

284. Q. Now, if you can turn back to page 24 and take a look at the two charts there. Look at the time period between February 16th, 2021 and March 28th, 2021, the time period we were looking at on the other charts, and tell me whether there is a, generally speaking, upward or downward trend in case counts and hospitalizations at that time?

A. It looks like it was increasingly upward towards the end of that period.

285. Q. Right, and if we can turn back to page 91...or, sorry, paragraph 91, again, the southwestern PHU chart...table, and look at the fourth row, which covers the time period March 29th, 2021 to April 2nd, 2021. And could you tell me what the capacity limits were on indoor and outdoor services in the southwestern PHU during that time period?

A. Outdoor, no limit as long as people could physically distance. Indoor, 30 percent.

286. Q. All right, and can you turn to the next page and confirm that the restrictions were the same for that time period?

A. Yes, it looks like they were.

287. Q. And can we go back to the charts on page 24, and can you tell me whether that time period had a, generally speaking, upward trend or a downward trend?

A. It looks like upward.

288. Q. Right. So during...all of these periods of time that we just discussed, restrictions were imposed, but case counts

continued to climb; would you agree with that?

A. Yes.

289. Q. Now, turning back to the restrictions summary table at paragraph 92, on page 37. This is the Waterloo PHU page. Are you looking at it?

A. Yes, I am, sorry.

290. Q. All of the headcount capacity limits listed in this table are multiples of 10...

A. M'hmm.

291. Q. ...10 or 100 people are the capacity limits. And all of the room capacity percentage limits are multiples of 15, 15 and 30 percent; is that correct?

A. Yes.

292. Q. I find this to be an interesting coincidence; do you?

A. I don't know what you mean.

293. Q. Well, you say, at paragraph 88 of your affidavit, that these restrictions are informed by key indicators, such as weekly incidence of COVID-19, test positivity rate, the effective reproduction number, and the evidence of recent outbreaks; correct?

A. Yes.

294. Q. And these key indicators are assessed objectively in every case?

A. I think based on the best available information and expert opinion, yes.

295. Q. And capacity limits and restrictive PHU...or public health measures are designed with a view to minimally impair the right...the freedoms of Canadians and Ontarians; would you agree with that?

A. Well, as we've discussed, the framework in place, at that time, tried to achieve a balance between COVID control and the adverse impacts of the control measures.

296. Q. And that balance, after objective consideration of those key indicators, in every one of the relevant time periods in which they were assessed, led the province to determine that capacity limits of 10, 100, 15 percent and 30 percent struck that perfect balance that you described?

A. If you are asking about why the numbers were the way they were...

297. Q. I'm asking...you just said that the province, in setting these capacity numbers,

they set them because it struck a perfect balance between minimal impairment of freedoms and control of COVID transmission; didn't you?

A. I don't think I used the phrase "perfect balance". I think I may have said something...

298. Q. Well, you said...

A. ...like "try to strike a balance", yes.

299. Q. Right.

A. To try and achieve both objectives at the same time.

300. Q. I mean, wouldn't a capacity limit of 99 on religious gatherings have been at least as effective as a limit of 100 in controlling the spread of COVID?

A. I don't think it's possible to...I don't think we can distinguish between 100 and 99.

301. Q. How about 190?

A. Well, I think...I think the numbers were chosen for a couple of reasons. Sort of best...

302. Q. I'm not really asking...

A. ...best judgement...oh, sorry, go

back...

MR. HUNTER: Counsel, let the witness answer the question.

THE DEPONENT: All right. I think that the numbers that were in the, sort of, staged implementation of measures where there were different levels of restriction, were chosen to be different enough that we believed that it would make a difference, but also, you know, a number that's reasonable for people to work with.

I don't think 99 has any advantages in terms of a number versus 100. So we picked 100 because it was different from 30, and 50, and so forth. So the numbers were picked for ease of implementation, in part.

BY MR. KITTREDGE:

303. Q. So it struck a perfect balance between...or it struck a balance between minimal impairment of freedoms and control of COVID transmission, and ease of implementation, then; correct?

A. Well, ease of implementation is...yes, ease of implementation played a role in the final levels of the restrictions that were chosen, but the overall plan was to try to minimize the impact of COVID restrictions on society and the economy, at the same time as controlling COVID.

And if you remember that framework, that was very much a geographic framework, where different measures were put in place in different parts of the province. So if a part of the province was having very low rates of COVID, fewer restrictions were placed because it wasn't necessary, and areas of the province with very high rates of COVID had higher restrictions, more restrictive public health measures, in order to achieve control. So the idea was to have as few restrictions as were necessary to try to reduce transmission of the virus.

304. Q. But that was balanced with a desire for ease of implementation. So, presumably, when you're striking a balance between two numbers...I mean, if you take, as an example, the idea of taking the average of two numbers...

MR. HUNTER: Counsel, I think you are misinterpreting the witness's answer. He said when talking about 99 versus 100, they picked a number that was easy to implement.

305. MR. KITTREDGE: I think you're answering the question for your witness here.

MR. HUNTER: I'm just saying what he said, so if you want to...

306. MR. KITTREDGE: I don't...

MR. HUNTER: ...ask some follow-up questions, feel free, but the question you...and we can have it read back if you like, the question you asked was, why not 99 over 100, and the witness answered a question about ease of implementation. He did not give a general answer about all possible spread of numbers. But feel free to ask your question...

307. MR. KITTREDGE: I think...well, I guess, rather than...I mean, there's no point...no need to repeat it. It will be in the transcript if it's there. I

believe it is, but...and, you know, to the extent that it is, it's there and I don't need it again, so...and if it isn't, perhaps you are correct, but I believe it is.

So I guess we're at five minutes to noon here, do we want to take a bit of a break?

MR. HUNTER: Do you have...I'm, obviously, not going to hold you to it, but do you have an estimate about how much longer you expect to be?

308. MR. KITTREDGE: Probably, it wouldn't be too much longer. I would expect less than an hour.

MR. HUNTER: Okay, so do you want to take a lunch break or...

309. MR. KITTREDGE: I wouldn't mind taking a lunch break. Do you want to reconvene in...I don't know, an hour?

MR. HUNTER: So 1:00, just to make it a round number?

310. MR. KITTREDGE: Yes, there you go. Sounds good. Ease of implementation. All right.

--- upon recessing at 11:57 a.m.

--- A LUNCHEON RECESS

--- upon resuming at 1:00 p.m.

DR. DAVID McKEOWN, resumed

CONTINUED CROSS-EXAMINATION BY MR. KITTREDGE:

311. Q. All right, Dr. McKeown, I don't have too many more questions for you, but I'll take you, now, to paragraph 82 of your affidavit, at page 32, where you list the number of risks that you feel are specific to religious gatherings. Is that a fair description of the contents of this section? Do we have audio from Dr. McKeown?

A. Sorry, I was muted for a second. Tell me the paragraph number, again, please?

312. Q. Paragraph 82 on page 32, and it's section 5...

A. Got it.

313. Q. ..."The Risks of COVID Transmission at Religious Gatherings".

A. Yes, got it.

314. Q. You outline a number of concerns in this section that you feel are specific to

religious gatherings and why you feel that religious gatherings pose a particular risk with regard to COVID-19 transmission; is that correct?

A. Yes.

315. Q. One of the concerns that you had is that you felt that religious gatherings often last for more than an hour; is that correct?

A. Yes, a concern about situations in which people from different households are near each other for an extended period of time.

316. Q. Right, but religious gatherings aren't the only sorts of gatherings where people might be together in the same space for more than an hour?

A. No, they're not.

317. Q. I mean, in a grocery store, people are together in the same space. Sometimes, people shop for more than an hour; is that correct?

A. I don't think they're together in the same sense. I think a better comparison would be a movie theatre, or a concert performance, where people are seated next to each other for an extended period. When I go grocery shopping, I'm wandering around the store, and I

don’t have very prolonged contact with any one other shopper.

318. Q. Right. Did you consider restricting religious gatherings in terms of their duration, in addition to, or instead of, restricting their capacity?

A. I don’t recall that specific suggestion coming up, no.

319. Q. Did you consider restricting the seating arrangements at religious gatherings such that people from different households are separated by a larger distance than they would otherwise be?

A. Well, that is one of the public health measures. At different points in the pandemic, religious services were required to limit members to the number who could be socially distanced, or physically distanced, at two metres, so that’s an example of, I think, what you are talking about.

320. Q. But members of the same household wouldn’t...there wouldn’t be much benefit to members of the same household observing that distance from each other; would there?

A. No, that’s true. And one church

that I'm familiar with arranges seating so that household members sit together, and non-household members don't, wherever possible.

321. Q. Sure, and did you consider making a recommendation to the effect that churches, across the province, should take those kinds of measures?

A. I think they were implicit in the requirement for social distancing.

322. Q. Did the requirement for social distancing exempt members of the same household, while they were at church, from those requirements?

A. I can't recall the exact wording, but in many...many times when we've talked about social distancing, it has been about people who are not in the same household.

323. Q. Right, but in most of the announcements for...like, where social distancing is required in public settings, can you...would you agree that most of the announcements where social distancing is required in public settings, do not make any mention of exempting members of the same household from those requirements?

A. I recall...I recall statements

which do mention that. As far as the regulations and how they apply to religious organizations, I would have to check the regulation for the details.

324. Q. Right. In the set of restrictions that you outline in the tables at pages 90, 91, 92, there's no mention of allowing members of the same family where social distancing is required, for example, in the outdoor services from March 29th, 2021 to April 2nd, 2021...there's no mention that capacity could be...you know, that social distancing guidelines wouldn't apply to members of the same family and...would you agree with that?

A. Yes, I agree it's not mentioned here. This is, sort of, a short form, so that's why I would want to check the actual regulation to make sure it's there or not.

325. Q. Right. Where there's a limit of 10 people, that wouldn't...that number wouldn't increase? Like, for example, between December 26th, 2020 and February 15th, 2021, that number wouldn't increase if, say, four of the members of the congregation of 10 were members of the same household; would it?

A. No, that's true, the 10 people did not take that into account. The 10 people was intended to allow a service to be delivered virtually. We weren't really anticipating that the convenor and the video operators, and so forth, would be family members, but I suppose it's possible.

326. Q. And if they were, there wouldn't be much of an impact to allowing them to gather more closely together than they would with members of other households, would there, in terms of transmission of COVID-19?

A. No, that's true. None of the public health measures were intended to separate members of the same household because we recognize that members of the same household are going to interact and have transmission opportunities, which are, essentially, unavoidable, you know, shared sleeping, shared bathroom, and kitchen arrangements. So all of the social distancing has, generally, been for non-household members.

327. Q. But in the restrictions on capacity of religious services that are calculated by headcount, where it's...as we noted

earlier on in your cross-examination, it's either 100 or 10 people in these charts, there's no effort to increase that number by allowing members of the same household, or members of several households, to gather more closely together than they would with the rest of the members of that congregation, thereby, perhaps, increasing the number from 100 to 120, or something like that?

A. Well, you could say that if we hadn't factored that in, we would have said 50 people. So, you know, I think 100 people could easily be said to be taking into account household members being part of the 100.

328. Q. So you mentioned that you were contemplating, in the setting of the limit of 10 participants in religious services, that part of the reasoning there was for assistance to the officiant, you know, people producing video recordings of the service, and disseminating it. I think you say, at one point, that you expected that, of the 10 people, several of them...oh, here it is,

"...Among other things, the higher capacity limits allowed a small number

of people, who may not be in the same household, to produce and disseminate virtual religious services to a wider community..."

It doesn't really sound like that number 10 was drafted, or designed, with the idea in mind of having a number of those people be members of the same household, from what I'm seeing here; would you agree?

A. Yes, I don't think we anticipated that those...that that small group would be members of same household, that's correct.

329. Q. But it would have minimally impaired the ability of Ontarians to gather... more minimally impaired the ability of Ontarians to gather...

MR. HUNTER: Counsel.

330. MR. KITTREDGE: ...and worship...yes?

MR. HUNTER: Minimal impairment is a legal concept, so I'm not going to let the witness opine on...

331. MR. KITTREDGE: I mean, it's also an English concept, but it's a...in the straightforward English sense, it's a term that people understand, wouldn't

you agree? No? All right.

MR. HUNTER: If you rephrase, I'm happy to consider letting the witness answer.

332. MR. KITTREDGE: Sure. No, I will.

BY MR. KITTREDGE:

333. Q. So wouldn't you agree that if the capacity limits allowed, for example, 15 people, where five of those people were members of the same household, that people in Ontario would be more free to gather and worship as they choose?

A. I can't speak to the impact on worship, but, yes, if household members had been taken into account, then there could have been slightly larger numbers in some religious settings.

334. Q. All right. Going back to paragraph...where were we...80...82, you seem to be concerned, at the end of paragraph 82, that physical distancing and mask-wearing won't be...guidance on mask-wearing and physical distancing won't be followed by people who attend religious services. Is there something specific about people who attend religious services that

makes you think that they would not follow guidance on these things, or not be concerned about their health?

A. No, I don't have any reason to believe that the compliance would be lower. I think it's a factor in all venues when we know that compliance is never 100 percent.

335. Q. Right. So there's nothing in particular about religious gatherings that makes you think that people in attendance would be more...or would be less likely to wear masks or less likely to physical distance?

A. I can't think of one.

336. Q. All right. You mention that services indoors in poorly ventilated areas are a concern. Why is that...is that a particular concern of yours with regard to religious gatherings?

A. No, I think, again, this is something which is a concern in many different venues. It's a concern in schools, it's a concern in movie theatres. Any place which has very poor ventilation, and which also contains, you know, large numbers of people in close proximity, poses a transmission risk.

337. Q. Right. You mentioned that you are concerned that people at religious services would sing, chant, and pray loudly. Did you consider imposing restrictions on singing...

A. We did...

338. Q. ...at religious services?

A. Yes, we did, in fact, at different points in the pandemic, limitations on singing, or separation between singers and other participants, those were part of the public health measures at different times.

339. Q. Right. You, also, appear to be concerned that people at religious services will be tempted to socialize. Isn't it true that most people are tempted to socialize?

A. I think socialization is common in many venues, maybe less so in some venues. You know, when I go to a movie theatre, I'm not really interested in...I don't know any of the other people who are there in the movie, other than the people I came with.

But, certainly, I think...it has been my experience, and others, that religious communities do have a sense of community, and many of the members, or the participants in

congregations, do know each other very well, and so, yes, I think it's a slightly higher risk in that setting than for other settings where people don't even know each other.

340. Q. You also mention that when prevalence of COVID-19 is high in community, risks at religious gatherings are proportionately higher. Isn't that the case for any gathering, or any setting at all?

A. Yes, that's true. Yes, some of these factors that are listed here that apply to religious gatherings, also apply to some other settings.

341. Q. Many of them, apparently. Would you agree?

A. I haven't made a count to see.

342. Q. All right. Activities which take place outdoors involving small numbers of people, say, five people or fewer, where social distancing can and does take place, are not considered to be a significant risk for COVID transmission; is that accurate?

A. I think that's accurate.

343. Q. Is outdoor-only golfing, where participants don't go into a clubhouse at any

point, but just do all of their golfing activities outside on a golf course, would that be a significant vector for COVID transmission, in your opinion?

A. No, I would say that would be a low risk situation.

344. Q. Have any COVID outbreaks been linked to outdoor-only golfing in Ontario?

A. I haven't looked, but not that I'm aware of.

345. Q. How about camping on Crown land, is that a significant vector for COVID transmission?

A. I wouldn't expect so, as long as the camping is small groups of people and not large gatherings.

346. Q. Has camping on Crown land been linked to any COVID outbreaks in Ontario?

A. Again, I don't recall any instances of that being reported. The tracking of venues for outbreaks is not exhaustive in its listing. So there may be some settings that aren't tracked in the data system, but I wouldn't expect to see a lot of outbreaks in that situation, no.

347. Q. Right, and camping in provincial parks, has that been linked to any COVID outbreaks in Ontario?

A. Again, not that I recall.

348. Q. Would you consider that to be a significant vector for COVID transmission?

A. No, outdoor activities, in general, are much lower risk than indoor activities, and that has been reflected at various times...sometimes, very explicitly, in the province’s policies.

349. Q. Right, and back country camping, camping in areas of provincial parks that are only accessible by long hikes or canoe trips, or things of that nature, do you consider that to be a significant vector for COVID transmission?

A. Again, as an outdoor activity with small numbers of people, I would not expect it to be a high-risk activity, no.

350. Q. And am I correct to assume that that has not been linked to any COVID outbreaks in Ontario, either?

A. Again, not that I know of, but it’s possible that there may be a small number, but I’m not aware of any.

351. Q. You think it's possible that back country camping led to a small number of outbreaks of COVID in Ontario?

A. I don't think it's likely.

352. Q. Right.

A. I wouldn't rule it out. Outdoor...

353. Q. Would you say it was...

A. ...activities are not risk free, they're just lower risk than indoor activities.

354. Q. Right. Would you say that back country camping, where the camp sites are only accessible by a long hike or a long canoe trip, is likely to be linked to any...sorry, is unlikely to be linked to any COVID outbreaks in Ontario?

A. I think it is unlikely.

355. Q. Would you say that it's highly unlikely?

A. I'm not sure what the quantitative equivalent of that is, but I would say it's pretty unlikely.

356. Q. All right, and, yet, at various points during the COVID pandemic, outdoor golfing, camping on Crown land and provincial

parks, and back country camping in provincial parks, have all been prohibited under the public health measures; isn't that the case?

MR. HUNTER: I fail to see the relevance of why other measures are or are not justified. This is a challenge to specific measures that apply to your client.

357. MR. KITTREDGE: Well, it's a challenge to whether the measures are...I mean, first of all, these regulations are referenced in the affidavit. They are public health measures. They're said to have been effective in...I think we were looking at page 24, around those charts, for most of the morning. So I think they're addressed in a number of places in the affidavit, and I think they are fair game.

MR. HUNTER: This is not a global challenge to every public health measure Ontario has taken. I have led you quite a bit of leeway, but we're not...you know, if you want to tie it into how

it's relevant to churches, I'm happy to let...consider letting the witness answer, but we're not going to go through every single measure and how...you know, whether there was an outbreak and whether that justified.

Quite frankly, if that wasn't justified, fine, let someone who is subject to that bring a challenge. If it was justified, great. This is a question about whether the measures that your clients were subject to, which were all about religious gatherings were justified, and the risk that they pose to the public health.

358. MR. KITTREDGE: All right, I'll move on.

BY MR. KITTREDGE:

359. Q. Liquor stores, and cannabis stores, and beer stores, have been open throughout the pandemic; have they not?

A. Yes, they have been at different times.

360. Q. And liquor stores, and beer

stores, and cannabis stores may have poor ventilation?

A. Yes, they may.

361. Q. People may talk loudly in a cannabis store, or a liquor store, or a beer store?

A. Not frequently, but it’s possible.

362. Q. People may socialize in a cannabis store, a liquor store, or a beer store?

A. Perhaps.

363. Q. When prevalence in the community is high, risks at a cannabis store, or a liquor store, or a beer store, are similarly high; would you agree with that?

A. Well, I would say...

364. Q. Proportionately.

A. Yes, as the rate in the community goes up, the rate in any...the likelihood that someone who is infected is going to be in a particular venue, including the ones you mentioned, would be higher, yes.

365. Q. When people show up at a retail store, or grocery store, do they always run in quickly just to pick up a few items?

A. No, sometimes it’s longer.

366. Q. Sometimes, people at a grocery store...

A. But people have to do it...

367. Q. Oh, sorry.

A. I think what’s important to transmission is the nature of the interaction between the shoppers, and between the shoppers and employees, which is usually not a long period of being close together.

368. Q. Right, but people, sometimes, do spend long periods of time in a store?

A. Oh, yes.

369. Q. And sometimes more than an hour?

A. That’s possible, yes.

370. Q. And people shopping in stores in neighbourhoods where they live or work might encounter friends, colleagues, or neighbours there; is that correct?

A. Indeed, they might.

371. Q. And they might be tempted to greet them?

A. Yes.

372. Q. And they might be tempted to socialize?

A. Yes, and they would be subject to the general advice that was given when those stores were open. With or without capacity limits, the advice was always to wear a mask and keep your distance. So we would hope that people would follow that advice in settings like retail stores, which remained open.

373. MR. KITTREDGE: Right. Well, I think that brings me to the end of my questions, so thank you very much for your time today, and I will pass it over to my friend.

MR. HUNTER: Thank you.

-- upon recessing at 1:21 p.m.

--- A BRIEF RECESS

--- upon resuming at 1:31 p.m.

DR. DAVID McKEOWN, resumed

RE-EXAMINATION BY MR. HUNTER:

374. Q. Dr. McKeown, you were asked a number of questions about presence of viral load in the nose versus having COVID-19 disease; do you remember those questions?

A. Yes.

375. Q. Now, is there any public health impact of people who have a viral load present in their nose or pharynx, such that they would test positive on a test, but are not showing signs of COVID-19 disease?

A. Well, first of all, there's a bit of confusion. "Viral load" is a different concept. The case definition for a confirmed case of COVID-19 is the detection of the virus in the specimen, in a person. So that's what gives people...makes someone a case.

Your question about, "Is there any implications?", yes. If someone is infected with the virus and has the virus in their body, even though they do not have symptoms, or do not yet have symptoms, still pose a risk of transmission to other people.

376. Q. You were asked some questions about, you know, the predominance of serious outcomes from COVID-19 in different age groups; do you remember those?

A. Yes.

377. Q. And you were asked about the predominance of those severe outcomes in older people, or people with underlying conditions.

What, if any...I guess, are there such outcomes in younger, healthy people, without underlying conditions?

A. Yes, there can be, just at a lower rate. But there certainly can be. In fact, there have been deaths from COVID-19 in Ontario in youth. Not very many, but some.

378. Q. And you were asked questions about, you know, whether most people recover fully. Is that the case for all young, healthy people who contract COVID-19?

A. No, most people recover fully. There is something called “long COVID”, which is a chronic condition that we are learning quite a bit about, which affects a proportion of people who were infected and may leave them with long-term symptoms.

379. Q. And even for those who, you know, either don’t develop symptoms, or do recover quickly, is there any public health impact of young, healthy people contracting COVID-19?

A. Well, certainly, they are unable to attend school, they can’t work for a period of time, there’s the possibility that they will transmit to other people who are more vulnerable

and may have a more severe illness. So, yes, there are lots of implications. I don't think we should think of infections in young people, even if they are mild, as having no implications for the population as a whole.

380. Q. Now, you were asked, at one point, about comorbidities, and you said, "Our understanding of comorbidities has evolved". How has it evolved?

A. I think we've just gotten more experienced. As COVID has spread, and more and more people have become infected, we've had more examples of people who have comorbidities who have acquired COVID, and we've seen that they can have a more severe outcome.

So, I mean, COVID is, essentially, a viral respiratory disease. So people who have pre-existing respiratory conditions, for example, are more likely to wind up in hospital, or intensive care, or to die, and we've seen...we've just had more experience with that over the months that the pandemic has happened.

381. Q. And, you know, obviously, it's a technical/medical term, "comorbidities". Can you just explain, like, what that term means, and

what are some examples of things that might have an impact on COVID-19?

A. Well, because COVID-19 is an infectious disease, anything which...any condition which renders the person's immune system less effective at responding to an infection is going to be a problem.

So, for example, people who are on immune suppressant therapy for transplant, or for drug...for...sorry, for cancer treatment, may have a more severe infection because their immune system doesn't respond as well. Another example would be the one I gave. People who have chronic illnesses, which affect the parts of the body which are most impaired by COVID, such as the lungs, may have poorer outcomes and more likely to be ill and end up in intensive care, or to die.

382. Q. Now, you were asked a number of questions about the two graphs that are in your affidavit, and the paragraphs about them, and you said, at one point, that you believed that there's a high degree of likelihood public health measures caused the drops in case counts and hospitalizations, as opposed to just being

correlated with them. Why do you think that?

A. Because these are the outcomes which we have been tracking, which we believe to be strongly related to the impact that COVID is having on the population. Things like hospitalization rates, case incidence, test positivity, these are all the things which are, we believe, valid indicators of the level of activity of the virus in the population.

And so, when we see those changing, we believe that that's a real phenomenon that is happening, when a transmission is less frequent, and the consequences of that transmission are less frequent. So when that happens in relationship to measures which are being taken which we expect would have a positive impact, I think it's reasonable to conclude that that's what's happened.

383. Q. And why did you expect those measures to have that positive impact?

A. Well, there's a few reasons. It has been recognized for some time that those types of measures can be useful in responding and reducing transmission of a respiratory virus. They've been part of plans that have been made

for epidemics or pandemics of respiratory viruses.

From what we understand about how the virus is transmitted through small and large particles, droplets that are expelled when people cough, or talk, or sing, or speak, we would expect, then, that the wearing of a mask, or keeping people separated, not having people gather, you would expect them to have that effect of limiting transmission. And so it appears that they do.

And over the course of the pandemic, quite a lot of research has been done, and there are individual studies, studies of outbreaks, studies of household transmission, which do show that the kinds of contact the public health measures limit is what is responsible for transmission of the virus.

384. Q. Now, at paragraph 55 of your affidavit, if you have that in front of you. It's on page 23.

A. Yes.

385. Q. You were asked a number of questions about the last sentence of that paragraph, about whether the implementation of

public health measures during the second and third states of emergency were shortly followed by a substantial decrease in the number of COVID-19 cases and hospitalizations, and you mentioned "Among other things". That's also in your affidavit. What are some of those "other things"?

A. Well, as I said, in addition to this relationship that we see, both in time and, also, geographically...you know, the graphs don't show this, but there were many points in the pandemic in which rates were higher in some parts of the province than in other parts of the province, and then, when public health measures were implemented in those areas, the rates came down. So there's lots of examples of that.

But, in addition to that, as I said, our understanding of transmission, and how it works, and what kinds of measures would be expected based on our understanding of the transmission to limit viral transmission from person-to-person, those...that's what underlies the public health measures. And so it's not surprising, I think, to see that it actually works.

In addition, we have looked at the

experience of other jurisdictions to see how the relationship between the implementation of public health measures in those jurisdictions...what it leads to in terms of measures of transmission of the pandemic. So those are some of the things which, I think, are inputs into the conclusion that is listed in that paragraph.

386. Q. And you mentioned looking to experiences of some other jurisdictions. What did you learn from those other jurisdictions about what did or what did not have an impact?

A. Well, in general, there was, first of all, the observation that when public health measures were implemented, it had a favourable impact on transmission. Secondly, that when...if measures were implemented quickly once there was an increase in evidence of transmission, it was more likely to bring that transmission down.

And lastly, I would say that more restrictive, or more severe, public health measures had a bigger impact than less severe ones. And, finally, that if measures were put in place, that they should be put in place for long enough, you know, at least four to six weeks, to

make a real difference. Those were, sort of, conclusions that many people reached looking at the experience from different jurisdictions around the world.

387. Q. Now, you were asked the question, and agreed with it, that correlation does not necessarily equal causation. In your experience, can correlation be evidence of causation, and how do you tell when it is and when it isn't?

A. Well, certainly, correlation isn't always causation, but, when it is, and it often is, what you see is...there's a few things which help you distinguish between correlation. One of them is a gradient effect.

So if the intervention that you are putting in place, if as you put a bigger intervention, you get a bigger impact, then that's a good sign that you are looking at a causal relationship rather than a correlation relationship.

If there's a biological basis for believing that the intervention would lead to the outcome you are seeing, that makes it more likely that it's causal. That was why I didn't believe that the jurisdiction...the interjurisdictional

comparisons that happened to have peaks at the same time, should appropriately be identified as causal. And...well, I'll stop there. There are, sort of, theoretical lists that measure, but those are some of the prominent ones that help you distinguish a causal relationship from one which is not.

388. Q. And you were also asked about, you know, whether the data proved things, or certainty of things. Just how do those concepts of proof and certainty, how do they play into public health practice?

A. Well, I would say, in particular, during this pandemic, with a novel pathogen, there's always some uncertainty. So I would be hesitant to use words which implied 100 percent certainty when we're dealing with something which we haven't seen before. We've learned a great deal over the past 21 months about COVID and what causes it, what controls it, but I wouldn't say that our knowledge is perfect, yet, and so I think it's appropriate to have a bit of humility.

389. Q. You were taken to Exhibit Y of your affidavit, and, in particular, a chart of vaccination rates; do you recall that?

A. Yes.

390. Q. And so...and you were asked questions about, you know, whether public health measures were justified given those levels of vaccination that occurred by this point, in May 2021. Looking at the vaccination data in the chart, in your opinion, would there still be a need for public health measures to slow the spread of COVID-19 given this vaccination rate?

A. Yes, and I think...we didn't talk about variants of concern, but, over the course of the pandemic, of course, we've seen the evolution of the virus, and we've gone from the original virus to the Alpha becoming the predominant variant, to, now, Delta is the predominant variant.

Each of those have been accompanied by an increase in transmissibility, and the...for example, the original estimates that were made, and built into the roadmap to recovery, were based on, you know, 60, 70, 75 percent of vaccination coverage being sufficient to allow public health measures to be lifted. It has become clear that when it comes to Delta, because of its increased transmissibility, much higher

levels of vaccination would be required to be effective at the population level.

So, now, as you probably know, our target is 90 percent fully vaccinated. And even with that, many people including the Science Table have said we will continue to need public health measures for some time.

391. MR. HUNTER: All right. Now, I'm going to take you to some of the questions you were asked about Florida, and then Sweden. So let's start with Florida. Now, Mr. Kittredge, I have prepared some screen shots of the same webpage you were using. I can take Dr. McKeown to the webpage live, and then we can just upload the screen shots, or I can go to the screen shots, whichever is easier. You are on mute.

MR. KITTREDGE: It's the same page that I was looking at? I mean...

392. MR. HUNTER: Some of the other tabs on the same page.

MR. KITTREDGE: Oh, okay, sure. I mean, you know, I'm fine with you marking whatever you want, but...

393. MR. HUNTER: So, for this one, since I was able to PDF them nicely, I will go to the screen shots. Of the WHO one, it doesn't PDF as nicely, so that one we may just have to do live. So let's start with the Florida one. Just a second.

BY MR. HUNTER:

394. Q. Okay, can you see this, Dr. McKeown?

A. Yes.

395. Q. Okay, so we're just showing... this is the same page. At the top, we have "Florida" and "Daily Cases".

A. Yes.

396. Q. Let's just scroll down to see the actual chart.

A. Right.

397. Q. And I understand...if you can just read off...in your view, what were the levels of daily cases per 100,000, at the various peaks, in this data?

A. I think I was...I commented on this in response to earlier questions. On the

daily case side, which is the lefthand side...but if you want to look at cases per 100,000, in the second major wave...we were in Florida, that is...was in the...about...it looks like about 9,500 per 100,000. Actually, I have a little trouble reading it because it's...

398. Q. I'll see if I can zoom in. Actually, I see...I think it's actually just talking about total cumulative cases per 100,000.

A. Yes, yes, so that's...it wasn't clear to me, but that's it. The other side is easier to understand because it's daily cases, so you can compare it with other jurisdictions.

399. Q. And how would those be comparable to Ontario's case counts at similar times?

A. You have to take into account the difference in the population, and I don't have Florida's population off the top of my head. But I remember, at the time, doing the calculation, and Florida's numbers and rates were very significantly higher than Ontario's, through this period, particularly in the most recent wave.

400. Q. I'm just going to show the...this is, now, the deaths, as opposed to just cases. Do you see that chart?

A. I can see. I see the chart, but I don't see the heading above it.

401. Q. Sorry, I'll go back up. It's just...

A. "Florida Daily Deaths", and it's showing a seven-day moving average. Okay, got it.

402. Q. And so, basically, the same question: Where does this peak in the number of daily deaths for the various waves?

A. Well, we're seeing, you know, 200 in the first couple of major waves, and then the third one that is shown here, they reach 400, which is astonishingly high, and much higher than Ontario's.

403. Q. Just on the cumulative, where did they end up on the cumulative cases per 100,000?

A. Cumulative? It looks like about 17,000 or 18,000.

404. Q. And how would that compare to Ontario?

A. Ontario has had less than 10,000.

405. Q. Sorry, is that total or per 100,000 for Ontario?

A. No, that's total cumulative.

406. Q. And this is total cases per 100,000; is it not?

A. Yes, it does look that way. So it would be 17,000 per 100,000. That doesn't sound right, Mr. Hunter.

407. Q. I've got one more that may...

A. I'm not sure how to interpret that side of the graph.

408. Q. Fair enough. We're all trying to guess how the CDC tracks its data, so perhaps this one will be helpful. This is the cumulative deaths and total cases per 100,000. So what do you interpret this graph as meaning, the cumulative death count...

A. Again...

409. Q. ...on the left axis?

A. Yes, so the left one is the one that's easier to understand. That's absolute numbers rather than rates. I'm not sure about the rates on the right. Absolute numbers, well, now, they're up to 60,000 deaths.

410. Q. And, sorry, what was the comparison for Ontario? Obviously, keep bearing in mind the populations are different.

A. Yes. We are a little under

10,000. So even taking into account a slightly larger population, it's a much higher cumulative death toll.

411. Q. And just for completeness...I don't think there's much more to ask, but just for completeness, I'm just going to show you the cumulative cases chart, just so we have all the comparative data. And what's the, I guess, cumulative case count of Florida to date?

A. Well, it looks like about 3.6 million.

412. Q. And what's the comparator for Ontario?

A. A little over 600,000.

413. MR. HUNTER: So can I have those marked as an exhibit? I can either do it as four separate exhibits, or one joint exhibit, whatever is easier for you, Mr. Kittredge.

MR. KITTREDGE: I really have no preference, so whatever you would like.

414. MR. HUNTER: So why don't we just mark them as one exhibit of screen shots from Centers for Disease Control and Prevention, COVID data tracker.

--- EXHIBIT C: Screen shots from Centers for Disease Control and Prevention, COVID data tracker

BY MR. HUNTER:

415. Q. I'll stop sharing that. I'm now going to show you this. And, unfortunately, I was not able to put it into nice screen shots, but we will do the live webpage. Can you see that, Dr. McKeown?

A. I don't have anything right now.

416. Q. Okay, it says it's sharing. Let's just...

A. Oh, hang on. Yes, now I've got it.

417. Q. Okay, so do you recognize this as the World Health Organization webpage Mr. Kittredge took you to earlier? I'll scroll down. It might make it easier to recognize the chart.

A. Yes, that I recognize, yes.

418. Q. So this was just talking about Sweden. I just want to direct your attention, at the top of the webpage, there's a map of, I guess, northern Europe, Scandinavia, in

particular.

A. M'hmm.

419. Q. And, unfortunately, it only pops up if I drag the mouse over the various maps, but if I put the mouse over Sweden, you see that there was 1,186,387 confirmed cases?

A. Yes, I see that.

420. Q. And 15,107 deaths?

A. Yes.

421. Q. And just if you look at...well, first of all, I guess we ask...if I just look at some of the neighbouring Scandinavian countries, which...I'm just going to go through them one by one. I'm going to read the data, and then I'll ask you the question, just because, unfortunately, I can't show them all at once. So in Norway, 232,826 confirmed cases, 995 deaths. In Finland, 173,632 confirmed cases, and 1,247 deaths. Just to finish off Scandinavia, Denmark, 434,798 confirmed cases and 2,786 deaths.

Now, obviously, we don't have the relative populations of those, but given there seems to be a significant difference in the number of cases, and number of deaths, are you aware of any public health reasons why those

might be different?

A. Again, you would have to look at the pattern of the underlying population and the pattern of implementation of both vaccination and public health measures. But I believe...my recollection is that Sweden has...Mr. Kittredge said was one of the jurisdictions which used fewer public health measures.

422. MR. HUNTER: I'll stop sharing that. Now, Mr. Kittredge, we're going to try...we might just take a break at the end to see if we can actually try and get that PDF that can be stamped as an exhibit. I'm just worried that the map does not PDF well, but we'll try that at the break just before we end, if that's all right with you.

MR. KITTREDGE: Sure. I mean, you know, I'm at your leisure, I suppose. But, yes, I mean, I have no objection to any of that, whatever you got to do. If you've got to poke around at it for a while, that's fine with me.

423. MR. HUNTER: Perfect. I'm almost done.

MR. KITTREDGE: If you needed to, you could screen shot it several times with the mouse over top of the various areas, if that's what you want to do.

424. MR. HUNTER: There's actually some technical problem with their website because they're upgrading it, or something, right now, so that's what is causing the trouble.

MR. KITTREDGE: Oh, really? Okay.

425. MR. HUNTER: Their website is too fancy for their own good, I think is the problem, but...

MR. KITTREDGE: Right, yes, for sure.

426. MR. HUNTER: Anyways, let's just wrap this up.

BY MR. HUNTER:

427. Q. Now, you were asked a number of questions about the impact of public health measures in between the states of emergency when cases were on an upward trajectory. Do you remember those questions?

A. Yes.

428. Q. What impact would you have

expected to see from public health measures, or would have expected to see if public health measures were not present?

A. Well, I think if public health measures...if sufficient public health measures were implemented, I think we would have expected to see a slowing of transmission and a decline in the number of cases.

The periods of time in which we didn't see that, when the cases were still rising despite the implementation of some public health measures, were, in general, times when the government backed off on public health measures, and was trying to give some relief to the institutions and businesses, and so forth, that were affected by the measures.

In my view, looking back on some of those times, particularly the one before the third wave in which there was a colour coded approach, was less successful in controlling COVID. And I think it was successful in opening up the province more, but in trying to achieve both objectives, I think, the one that was less successful was controlling COVID because the public health measures were not strongly enough

applied, in my view.

429. Q. And so you were asked some questions about the impact of public health measures on cases and hospitalization rates. You know, when you're looking at the data and you lift a measure or increase a measure, like, how do you see that track through into cases and hospitalization rates?

A. Well, first of all, there is a lag time, right? So the measure has to have an impact on people's behaviour and the degree of contact between individuals, and once it has that impact, then there's an incubation period.

Once you stop transmission, it...you know, the cases that would have occurred, don't occur, but one incubation period forward. So we normally, in implementing these, advise the government to wait four to eight weeks to see the impact of the public health measures because of that lag time.

430. Q. And you were asked some questions about members of a household, I think it was particularly in the church setting, and about whether they posed a risk to each other. Do you remember those questions?

A. Yes.

431. Q. Is the risk that members of a household pose to each other the only risk that would be relevant from a public health standpoint?

A. Well, first of all, let me say that household members do pose a risk to each other. If one member of a household is infected, there's actually a very high likelihood that other members will be affected. The trouble is it's not very amendable to public health measures. If people are sharing a household, sharing a kitchen, sharing a bathroom, sharing a bed, it's not practical for them to be separated in that way.

That's why we made allowances and applied public health measures differently to household members. Not because of the risk of transmission, which is, in fact, very high. So household members who do become infected, of course, can transmit the infection not only to other members of their household, but also to other people in the community. So, I mean, we are concerned about household members becoming infected for that reason.

432. Q. And does it make any difference when you are in a community, say, in a church setting, whether you have one member of a household or five members of a household there vis-a-vis capacity limits?

A. I don't understand your question, sorry.

433. Q. I guess my question is, you know, you were asked questions about why couldn't you allow a whole household. Does it make any difference whether you allow...I think you made the difference, we could have had 50 or 100. Does it make any difference if you count members of a household together or separately?

A. Well, no, I think...I think we have, in many settings during the pandemic, made allowances for household members. So we used... for example, the outside gathering limits were gathering limits for people who aren't members of the same household.

But that doesn't mean that there isn't going to be transmission in that setting. It just means that the transmission could also occur in the household, and it's not practical to keep people apart. But certainly, you know, the more

members of a household you have in any venue, the more likely you are to have transmission between household members and non-household members.

434. Q. And then you were asked about, you know, whether...wouldn't it make sense to put restrictions on other settings, and you talked about movie theatres and concerts that you said had similar risks. What, if any, public health measures were put on those settings, and were they the same or different than churches?

A. Well, I think the affidavit points this out. In almost all the times, through the measures that were used in the pandemic, the measures that were applicable to religious services, rites, and ceremonies, were less restrictive than for comparable settings. And when I say "comparable settings", I mean settings where you would have groups of people from different households gathered together, you know, sitting near each other for an extended period.

So when compared with those settings, which are, kind of, apples-to-apples comparisons, religious services had less strict restrictions, and I believe the reason the government made that

decision was in recognition of the importance of religious services to people's lives.

435. MR. HUNTER: Thank you. Those are my questions.

--- upon adjourning at 2:03 p.m.

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REPORTER'S NOTE:

Please be advised that any undertakings, objections, under advisements and refusals are provided as a service to all counsel, for their guidance only, and do not purport to be legally binding or necessarily accurate and are not binding upon Victory Verbatim Reporting Services Inc.

I hereby certify the foregoing to be a true and accurate transcription of the above-noted proceedings held before me via videoconference on the **19th DAY OF NOVEMBER, 2021**, and taken to the best of my skill, ability and understanding.

Certified Correct:

Maureen Hopman
Verbatim Reporter

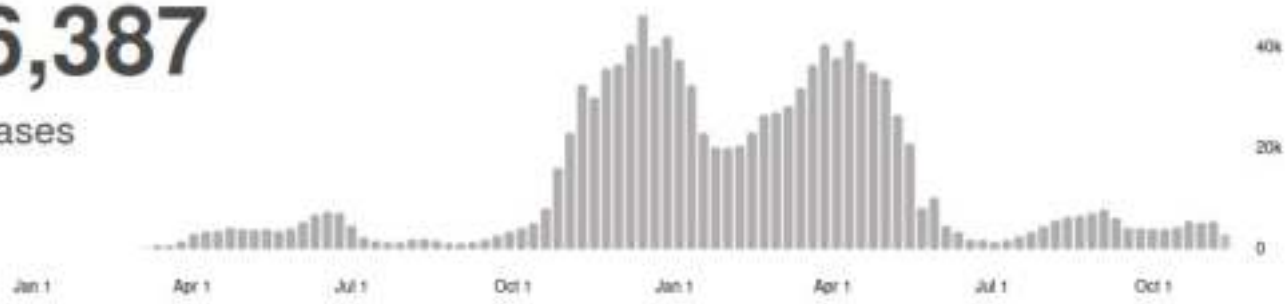
In **Sweden**, from **3 January 2020** to **4:27pm CET, 18 November 2021**, there have been **1,186,387 confirmed cases** of COVID-19 with **15,107 deaths**, reported to WHO. As of **14 November 2021**, a total of **14,236,091 vaccine doses** have been administered.

Sweden Situation

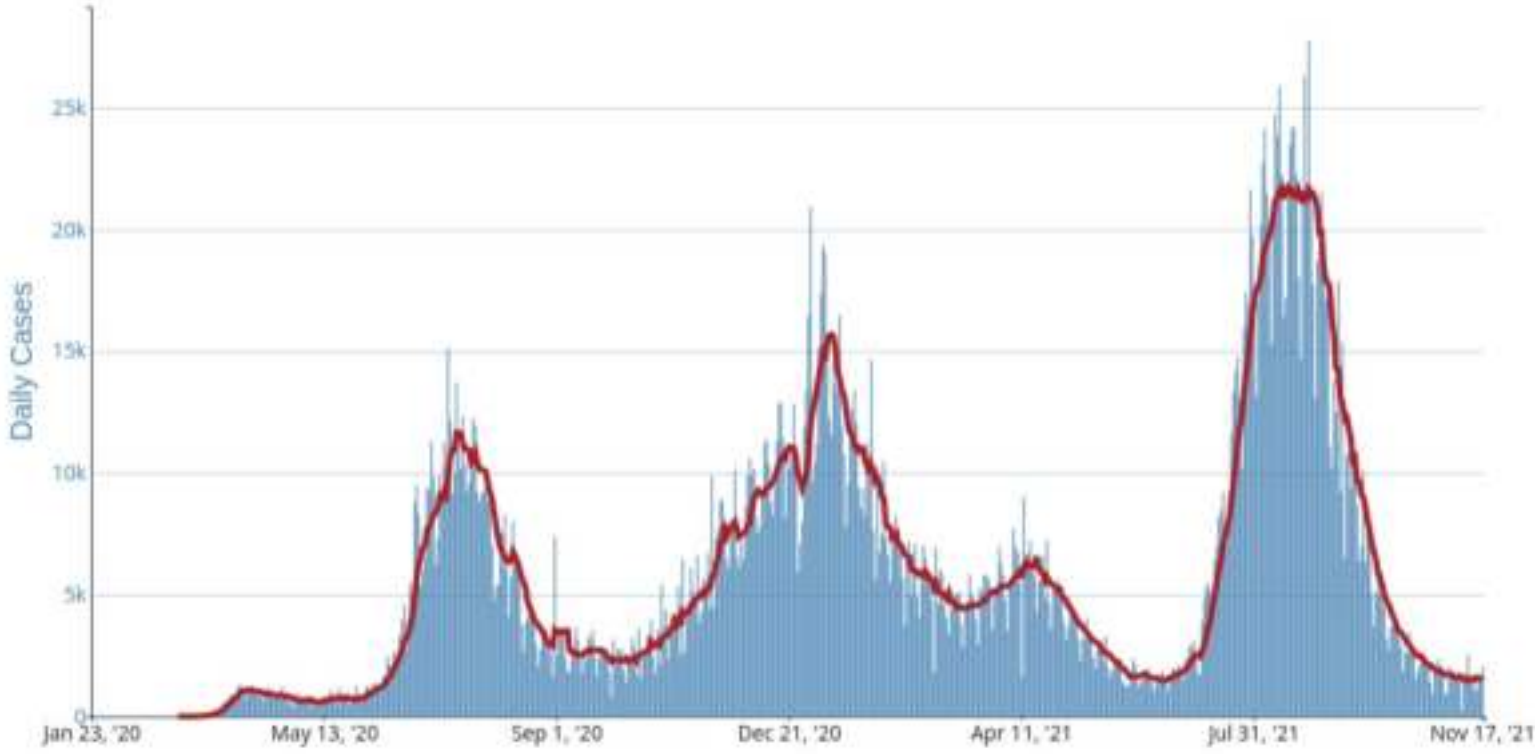
Daily Weekly

1,186,387

confirmed cases



Daily Trends in Number of COVID-19 Cases in Florida Reported to CDC



COVID Data Tracker

United States
At a Glance

Cases Total 47,352,367 — Last 30 Days
Deaths Total 764,473 — Last 30 Days
75.8% of People 12+ with At Least One Vaccination
Community Transmission: High

Data Tracker Home
COVID Data Tracker Weekly Review
Your Community
Health Equity Data
Pediatric Data
Pregnancy Data
Vaccination Delivery and Coverage
Vaccine Effectiveness and Breakthrough Surveillance
Cases, Deaths, and Testing
Cases, Deaths, and Testing
Daily and Total Trends
Compare Trends Across States and Regions
Global Counts and Rates
Global Percent Change
Global Trends
Demographic Trends
Health Care Settings

Trends in Number of COVID-19 Cases and Deaths in the US Reported to CDC, by State/Territory

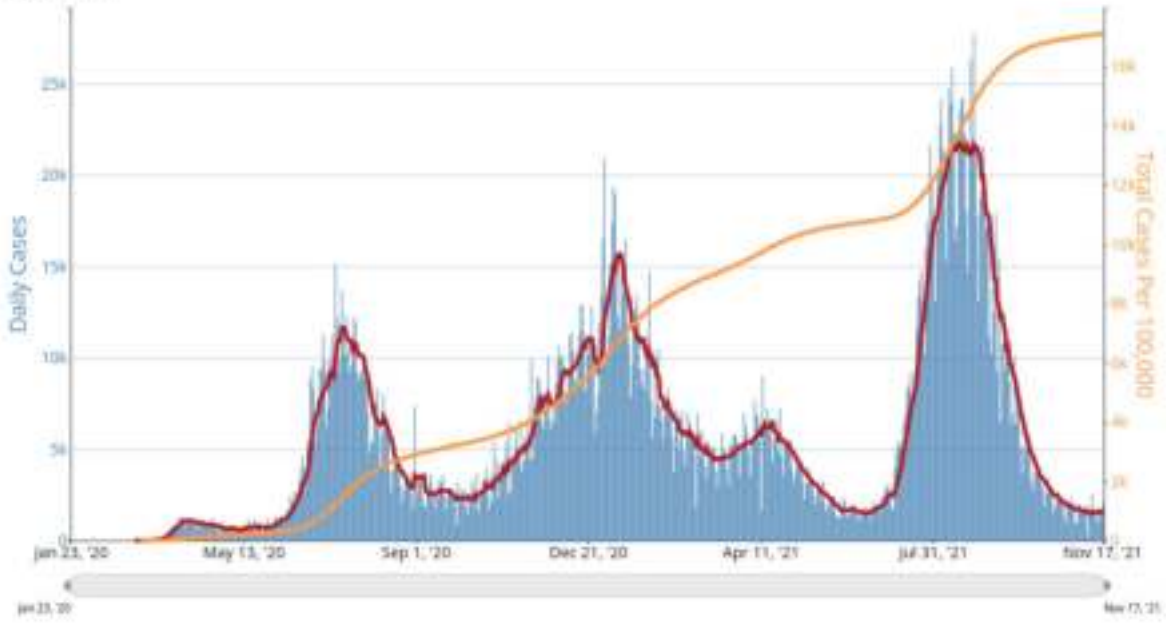
Reported to the CDC by State or Territory. Maps, charts, and data provided by CDC, updates Mon-Sat by 8 pm ET†

View Footnotes and Download Data

Select a state or territory: Florida
View(left axis): Daily Cases
Show: 7-Day moving average
View(right axis): Total Cases Per 100,000

The blue bars show daily cases. The red line is the 7-day moving average of cases. The orange line represents total cases per 100,000, allowing for comparisons between areas with different population sizes.

Daily Trends in Number of Cases and Cumulative Incidence Rate of COVID-19 Cases in Florida Reported to CDC, per 100,000 population.



Kitchener Court File No. CV-21-00000095-0000
St. Thomas Court File No.: CV-21-08

ONTARIO
SUPERIOR COURT OF JUSTICE

AA/ck

B E T W E E N:

THE ATTORNEY GENERAL OF ONTARIO

Applicant
(Responding Party)

- and -

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHUURMAN, DEAN WANDERS, RANDY FREY, HARVEY FREY and DANIEL GORDON

Respondents
(Moving Parties)

A N D B E T W E E N:

HER MAJESTY THE QUEEN IN ONTARIO

Applicant
(Responding Party)

- and -

THE CHURCH OF GOD (RESTORATION) AYLMER, HENRY HILDERBRANDT, ABRAM BERGEN, JACOB HIEBERT, PETER HILDEBRANDT, SUSAN MUTCH, ELVIRA TOVSTIGA, and TRUDY WIEBE

Respondents
(Moving Parties)

- - - - - - - - - -

This is the Cross-Examination of MATTHEW HODGE on his Affidavit sworn the 2nd day of July, 2021, taken via videoconference at the offices of VICTORY VERBATIM REPORTING SERVICES, Suite 900, 222 Bay Street, Toronto-Dominion Centre, Toronto, Ontario, on the 23rd day of November, 2021.

- - - - - - - - - -

APPEARANCES:

JOSHUA HUNTER	-- for the Applicants
RYAN COOKSON	
DANIEL GUTTMAN	
MAIA STEVENSON	
ROB KITTREDGE	-- for the Respondents

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--- upon convening at 1:00 p.m.

--- upon commencing at 1:00 p.m.

MATTHEW HODGE, affirmed

CROSS-EXAMINATION BY MR. KITTREDGE:

1. Q. I represent the moving parties in this matter, and I am going to ask you a series of questions today. I understand that you submitted some evidence in this matter by way of an affidavit that you affirmed on July 2, 2021. Do you have your affidavit in front of you now?

A. I do.

2. Q. Great. In your CV attached at Exhibit A of your affidavit, you mention that your COVID work has included engagements with PHAC during the pandemic, in addition to parking with Public Health Ontario and Peel Region Public Health. What does the acronym PHAC stand for?

A. Public Health Agency of Canada.

3. Q. Thank you. Other than in your affidavit, did you provide advice, comments, or recommendations relating to non-pharmaceutical COVID interventions to the Province or to the Government of Canada, at any point during the pandemic?

A. Sorry, could you restate the

question?

4. Q. Did you provide advice, comments, or recommendations relating to non-pharmaceutical COVID interventions to the Province or the Government of Canada, at any point during the pandemic?

A. My role with the Public Health Agency of Canada included comments on what might be described as, sort of, draft options for travel-related matters.

5. Q. All right. Were you involved...so, that answers my next question. Other than in your affidavit, did you provide any advice, comments, or recommendations related to the religious gathering restrictions that are in place...that were in place in Ontario during the pandemic?

A. No.

6. Q. All right, thank you. Let's start with a little bit of background on the nature of COVID-19. I understand that there is a distinction to be made between the virus and the disease that it causes. Am I correct to understand that SARS-CoV-2 is the name of the virus, and COVID is the name of the disease...the name given to the disease caused by the SARS-CoV-2 infection?

A. I think that would be an accurate

representation of common use, yes.

7. Q. So, the term "COVID-19" means a SARS-CoV-2 infection, essentially?

A. Generally, although, for practical purposes, it usually means a person with that infection, in the sense of having symptoms or having a risk of spreading it to others.

8. Q. Right, which brings me to the next question. A person whose SARS-CoV-2 infection is completely asymptomatic throughout its course, would that person be, nonetheless, considered to have COVID-19?

A. That is an open question. If they were tested, and they had a positive test, then they would be counted as a COVID-19 case, regardless of their symptoms. If they never sought testing, they would have...not show up in the statistics, in the data.

9. Q. I understand that viruses are fragments of genetic material, DNA or RNA, which are able to replicate themselves by infecting the cells of a host organism; is that accurate?

A. I think the viruses would argue they are not so much fragments, because they are intact organisms, but I am not here to represent the virus,

so...

10. Q. Right, fair enough.

A. ...if we think of it as a viral genome could be DNA or RNA, and contains all of the equipment, for lack of a better term, that a virus needs to replicate, typically, in the case of our conversation today, in a human host.

11. Q. So, what would the...if "fragment" isn't the right word, what is the right word to refer to, like, a single virus? "A virus"?

A. They are a viral particle.

12. Q. A viral particle, all right. And a virus is simply a collection of genetic code, which can't really be said to be alive; is that correct?

A. I think it's...it's dangerous to generalize across all viruses. There are literally, probably thousands of millions of viruses, some of which we have characterized, some of which we haven't. Viruses typically exist in relationship to a host, so they cannot survive...and that could be a human, it could be another...it could be a bacteria, it could be a tree, and they typically cannot survive for long periods of time without connection to that host.

13. Q. A viral particle can be damaged or

degraded, to the point where it is no longer capable of reproducing itself or infecting a host; is that correct?

A. You are asking me questions about virology, which is not my area of expertise. I would say that I am reasonably confident there are some viruses that proceed as you describe. I don't think that it would be...the science would not support a general statement about all viruses.

14. Q. Right. Well, in particular, the SARS-CoV-2 virus, it's possible to damage or degrade it, to the point where it is no longer capable of infecting an individual; is that correct?

A. Sure. I mean, if I cough into my hand, and then wash my hands, the virus particles that I coughed into my hand are generally rendered ineffective in infecting subsequent humans.

15. Q. Would it be fair to call such a damaged virus, damaged and non-infectious virus, a dead or inactive virus, and an infection virus, an active virus?

A. If you wish to classify it that way. I think it...our understanding of the virus is still evolving. And, so, what is not clear is how much damage a single viral particle can sustain before it

is unable to reproduce. It may reproduce at a much lower efficiency than a fully fledged particle, but if it can reproduce at all, and it finds a willing host, it can establish itself, and then, once it gets its mechanics going, I would expect it to be infectious.

16. Q. But I am, essentially, just creating some definitions here, that I am going to use later on. So, I am not looking for a...I don't need to get terribly in-depth about this, but it is possible to deactivate a SARS-CoV-2 virus, for example, by exposure to a sanitizer or a soap or sunlight or ultraviolet radiation, or something like that, to the point where it couldn't infect someone?

A. Yes, I mean, certainly the sanitizers are effective as antiviral agents. They render the virus incapable of reproduction.

17. Q. And they would leave a viral particle that could be called dead, in the sense that I described earlier?

A. That seems reasonable.

18. Q. All right. A person can't become infected by exposure to dead or inactive SARS-CoV-2 virus particles; is that correct?

A. If they are truly dead, dead, dead,

then...the issue is not whether they are dead or alive, it's their reproductive capability. So, if we agree that "dead" is unable to reproduce, then...they also...typically, the virus that is unable to reproduce, can't establish infection, because it can't hook onto the host cell and perform the gymnastics it needs to do to insert its genetic material into the host to begin the reproduction. So, think of...viruses are basically lazy. They have a genome, DNA or RNA, typically, and they use the host to make multiple copies. When those copies reach a certain point, the host cell typically explodes, and seeds virus. So, you have this phenomenon where the viral particle needs to both adhere to the host and have its own machinery to insert its genetic material into the host cell.

19. Q. Right. And in the event that an individual, a human, comes in contact with a dead or inactived SARS-CoV-2 virus particle, that human could not become infected by the virus?

A. As far as we know, yes.

20. Q. Right. So, a quick bit of background on the immune system, as well. I understand that antibodies are one of the most important lines of defence. We develop antibodies

to viruses and bacteria that our bodies have been exposed to in the past; is that generally correct?

A. I think that may be overly simplistic. The body's immune system, for simple human minds, is divided roughly into antibody mediated immunity and humoral mediated immunity. There is relatively few situations where the human host would defeat an invader, bacterial, viral, or parasitic, using only one of those sets of immune defences.

21. Q. All right, and, as far as a definition for infection, if a person is exposed to a virus, but that virus is killed by an immune process like the ones you have described, before it can reproduce, would that person be considered to have been infected?

A. No, I think that's...that's a question that's...if you ask six people, you will get 12 different opinions.

22. Q. Right.

A. And I think it depends on perspective. So, if we talk about, for example, tuberculosis, different...different organism, but we have clear...we have hundreds, if not decades, if not hundreds of years of understanding of TB and, in

the case of TB, individuals can be infected, they can have...they can never develop symptoms, and they can never transmit to somebody else. There is some suggestion that, with other organisms, you can be infected, transmitted to somebody else, but never get symptoms yourself. With COVID-19, it would seem that we have some people who are infected, transmitted to other people, and they themselves get symptoms, and some people where that doesn't seem to happen. And, depending on the population and how that is measured, there has been a range of estimates about what those proportions are, as I think one of your experts cited in their affidavit.

23. Q. Right. If an individual is exposed to, let's say, just for the sake of argument, a single virus particle, and that particle enters their respiratory system through their nose, something like that, and their immune system is able to deactivate, or kill the virus before it is able to attach to a cell and reproduce, first of all, is it possible for the immune system to kill a viral particle in that way?

A. I am afraid that is out of my area of expertise.

24. Q. Right, okay, fair enough. Thank

you. All right. At a number of points in your affidavit, including when you site various COVID-related statistics, you refer to numbers of cases of COVID-19, or numbers of people diagnosed with COVID-19. I would like to understand a bit more about what the terms "case" and "diagnosis" means. First, by "case", I imagine you mean confirmed case, rather than probable case; is that correct?

A. I would say, since probably May or June of 2020, that's reasonable. There was an early phase where access to testing was limited, and so there were clinical syndromic definitions used to define people as "probably cases". But, at this point, widespread testing availability means that caseness means you have a positive COVID test.

25. Q. So, a person with a case of COVID-19 has received a positive test for COVID-19 and, therefore, has been diagnosed with COVID-19?

A. So, I would say up until the point you said "diagnosed", yes, then there are certainly people out there who have...they would count in the case statistics, but they would never seek healthcare. So, they would...we can split hairs about whether diagnosis is a reserved act for

healthcare professionals or is done through testing. I think that the use of the term "case" is probably the safest one, in the sense of it is broadly agreeable that those are persons who have had a COVID positive...a test for COVID that was positive. Their motivations for testing mean that some of those people have symptoms, some don't have symptoms. Of those who don't have symptoms, some will develop them, some never will.

26. Q. Right. So, a positive test result...and when we say "test", we are typically referring to a PCR test; is that correct?

A. In Ontario, yes.

27. Q. A positive test result is required in order to diagnose a person with COVID-19 in Ontario?

A. I mean, I think, again, if we, sort of, move forward, past the first wave, that is a reasonable statement. If we take the totality of the pandemic experience, there certainly was a time when people were being clinically diagnosed with COVID-19, in the absence of test results.

28. Q. And, after that date in, what was it, May and June 2020, or after that early time frame, a positive result on a PCR test is sufficient

to diagnose a person with COVID-19 in Ontario. In other words, there are no other diagnostic criteria that must be met in order for a patient to be counted as a case of COVID-19?

A. Well, perhaps I wasn't clear about diagnosis versus caseness.

29. Q. Right, sorry.

30. Q. So, if you have a positive test...let's say you and I, we go to an assessment centre, bingo, we got positive tests, those results will be counted in the testing results for today, and published by Public Health Ontario. If we have no symptoms and/or we never seek healthcare, whether we are diagnosed or not, we are counted as a case and, depending on where it happens in Ontario, the local public health unit may or may not follow up to find out, "Do you have symptoms? Where were you exposed?", all those other questions. I think, in a clinical context, when people show up in the emergency department really short of breath, like, in the last week, and they are unvaccinated, and we test them, and they have a positive test, we also diagnose them with COVID-19 pneumonia, in this case.

31. Q. So, in short, I guess, a positive PCR test is sufficient to be counted amongst the

cases of COVID-19 but, to be diagnosed with COVID-19, they would have to visit a doctor?

A. I think that is a reasonable way to frame it. And, from a public health perspective, being a case, when it comes to an infection like COVID-19, is the basis for counting and decision-making, and all that follows. There are other respiratory infections, for example tuberculosis, where that would be quite different. So, it is important, perhaps, to specify that, with regard to COVID-19, a positive PCR test means that you are now considered a case, and you would show up in the daily case count.

32. Q. Right. So, we have talked a bit about PCR tests. I understand that PCR tests are conducted by taking a sample from a patient, typically from inside of their nose, and a positive result is returned if one or more SARS-CoV-2 virus particles are found in that sample; is that correct?

A. It's actually not looking for the particle. It is looking for a specific gene, or genetic sequence, that is found in intact virus. So, if you are familiar with the PCR testing, think of it as there are primers that are specific to the virus, they get mixed with the sample, there is a

series of amplifications, and then they look to see if those primers found their genetic counterparts. And the primers are not actually sequences, but they are the antisense sequence for what is in the viral genome.

33. Q. All right. So, we discussed the concept of a dead, or inactive, virus, that is to say a virus that has been damaged or degraded in such a way that it can no longer infect a host. If a dead virus particle is found in a PCR test sample, or if the genetic sequence is matched, the PCR test will return a positive result; correct?

A. Yes.

34. Q. And it is possible...when you say "intact virus"...you mentioned "intact virus" a moment ago. What does that mean?

A. So, the...I don't have the numbers at my fingertips, but the genetic material of the SARS-CoV-2 is some hundreds of amino...nucleic acids. And, so, an intact virus is one that has the complete set, and is more likely to be alive. To be alive, you have to have the complete set. You could be a dead virus and have the complete set, but much less likely, because the viral particle itself begins to degrade quite quickly.

35. Q. So, in short, if a dead virus particle is found in a PCR test sample, the PCR test will return a positive result, and the test can't distinguish between an infectious and non-infectious virus particle?

A. I mean, it doesn't distinguish in a, sort of, thumbs up/thumbs down way. The cycle thresholds have been used, which is the number of amplification cycles to distinguish between more likely live virus and more likely dead virus, with a higher cycle threshold number being used to be, "That's more likely dead virus".

36. Q. Right. The CT...was it a CT threshold you mentioned?

A. Yes.

37. Q. The CT threshold used in Ontario, is that standard across the province, for all PCR tests?

A. That is out of my area of expertise.

38. Q. All right.

A. My understanding is that Public Health Ontario has established expectations for laboratories that do COVID-19 testing and, in most cases, the appropriate way to do the test is fairly closely specified, so that if you test in North Bay,

and you have a biological condition of infection, you should get the same result as if you test in Windsor or Kingston.

39. Q. Right, but it is not unheard of for a PCR test in Ontario to return a positive result, when the virus particle that was located was, in fact, a dead virus particle, and not infectious?

A. I don't know what the frequency of those events are, but the way the test is designed, that is going to happen at some non-zero rate, yes.

40. Q. So, some...

A. And we see that with recovering patients, where they will have positive tests after their symptoms have resolved, and even after most experts would say they are no longer capable of transmitting infection, and we assume that is...or we understand that to be left over dead virus that the body is just getting around to cleaning up.

41. Q. So, in some cases, PCR test results are a false positive?

A. I think that it's probably...from my perspective, they are less false positives than they are...they have limitations. And, so... notwithstanding the esteemed efforts of the media to keep us up-to-date about how many hundred cases

there are every day. I mean, one of the things that, in practice, became a driver of Ontario's policy-making was hospitalizations. And, so, we can all...we could spend the rest of our time together, and months, haggling over the merits of PCR testing and what the rate of false...so-called false positives is, but I think relatively few people would haggle over the fact that a patient in a bed needs care, and all that follows from that. So, you know, if you think of it as there is a large number of people who are infected, some of them get tested, some of them have positive tests. From a health system point of view, we can use that to predict the expected number of hospitalizations, but it is actually the sick people who are driving many of the choices, and the goal of limiting the number of people who are sick, so that harms to them are reduced, and also that the health system doesn't fall off a cliff.

42. Q. Right. I think we can move forward, if we can agree to the proposition that some PCR test results are false positives.

A. So, I would say that, from my perspective, there are limitations of the test. And, so, from a policy-making framework, we want a

test that probably overcalls the positive slightly, rather than undercalls. If you wish to call them "false positives", I am not going to fight with you about it, but I think the presence...we can't know, at the point of testing, if this is dead virus or a live virus, and we also...there is an evolving understanding around how much...how dead the virus has to be, such that it is incapable of transmission to another host. So, there is certainly some unsettled science there, but, for practical purposes, why don't we agree to agree.

43. Q. And maybe I will just put it a slightly different way, that is maybe a little less controversial. It is possible for a person who was never infected with the SARS-CoV-2 virus to have a PCR test, and have that test return a positive result?

A. Oh, you have actually gone a completely different place. So, if I am never infected, if I understand your line of logic, then, by definition, I never had any SARS-CoV-2, so I can't have a positive test. It's much...the scenario that we were initially discussing was the virus is...it's living in my throat, but it's dead, it's not capable of making me sick or making anybody

else sick.

44. Q. But if a viral particle was introduced that was already dead, as we have defined that earlier on, like, say I, you know, inhaled a particle that, you know, for whatever reason, has been in the air too long and became inactive, or, you know, for whatever reason, is no longer infectious, that particle lodges in my nose, and a PCR test sample is taken that captures that individual piece of inactivated virus, the PCR test could return positive, despite the fact that I was never infected, and could not have been infected, because that viral particle was never active at the time when it was in my system; would you agree with that?

A. So, I think what I would say is that the probability, or likelihood of the scenario you describe, I cannot confidently say it is zero, but it is somewhere down there with getting struck by lightening three times in a week, or perhaps the Toronto Maple Leafs winning the Stanley Cup, I don't know. Because the amount of virus that is present, if it is a single viral particle, the probability of it being viable long enough between when it entered your nose and got on the swab and got to the lab, I

mean, we are talking about very low likelihood events that are multiplied together. So, I think the presence of virus in a human host is likely to be enough to yield a positive test. Some human hosts will have virus that is dead because they had an infection, they've cleared it, and they still have virus, and I am willing to concede that a small number of humans may have, in a very, sort of, simultaneous way, collected some dead virus, and it is hanging about long enough to get into the PCR test, but that is exceptionally rare.

45. Q. Fair enough. I think we can call that a day on the PCR aspect of things. So, when a person who has been diagnosed with an active case of COVID-19 dies, that...in other words, they have a positive PCR test result, and their case of COVID-19 isn't considered resolved, that death is recorded by the Province as a COVID-19 death; is that correct?

A. I mean, the coding of deaths is not so much by the Province. There is a series of steps that happens. So, typically, the attending physician would complete a death certificate. The fact of a COVID-19 infection may or may not be noted there. If the coroner is involved, there is typically a more complex death investigation, and

the writing on the death certificate may change. But, even before COVID-19, I mean, physicians, unfortunately, are notorious for screwing up death certificates, because there is typically an immediate cause, which is due to an antecedent cause, and then there are contributory causes. So, when we say it is attributed, there is an important, albeit, sort of, hair splitting thing about it, is it the immediate cause? Is it an antecedent cause, or is it a contributing cause.

46. Q. And for deaths that the Province reports, COVID-19 deaths, in every case, are those the...sorry, can you repeat the types of causes of death?

A. So, my recollection is that it's intermediate...sorry, immediate, antecedent, and contributing.

47. Q. So, is there a requirement in order for it to be recorded as a COVID-19 death for it to be the immediate cause of death?

A. I think the first requirement is it has to be recorded somewhere, and then I would have to defer to somebody with more knowledge of the death registration system. In clinical practice, the general tendency would be, if you were diagnosed

with a COVID-19 infection, admitted to hospital because you couldn't breath, and died on a ventilator, you died of COVID-19. If you had a hip fracture and, in the course of your pre-op workup, were found to be infected with COVID-19, and rolled off the operating table and died, I think it would depend on how the particular physician coded the death.

48. Q. All right. So, could you briefly explain what the term "infection fatality rate" means in the context of a disease like COVID-19?

A. I think it means different things to different people, and that's part of the challenge we are facing with this particular infection. So, the...it is a numerator, which would be the number of deaths over a denominator, which is typically the number of persons with infection. And, so, the fatalities, notwithstanding the conversation we just had, can be counted. The number of infections is much more challenging to count.

49. Q. Right. So, at paragraph 11 of your affidavit...and I will give you a moment to turn to that now. It is on page 5.

A. M'hmm.

50. Q. So, I believe it's the second

sentence reads:

"...Based on Ontario's COVID-19 experience, 5 percent of people with COVID-19 will require..."

I am sorry, I jumped to the wrong one. We are coming back to that one later. I will take you to the top of page 6. I am sorry about that. A little spoiler for where we are going next.

A. All right.

51. Q. So, still in paragraph 11, at the top of page 6 you say:

"...As of June 24, 2021, in Ontario, 543,571 people have been diagnosed with COVID-19, and 9,101, approximately 1.7 percent, have died..."

Do you see where you wrote that?

A. Yes, yes.

52. Q. In order to calculate that 1.7 percent number, you divided the number of confirmed cases of COVID in Ontario by the number of recorded COVID deaths in the province; is that correct?

A. Yes.

53. Q. That calculation is not an accurate method of determining the infection fatality rate of the virus, is it?

A. I think it is a practical...if you think of it as...the true IFR was probably not able to be known for a virus that is as ubiquitous as COVID-19, so we want to establish bounds, or a range within which it falls. So the number of cases that, in this case, are diagnosed in Ontario, and the number of deaths, is one part of establishing that range and, in this case, it's 1.7 percent, and...

54. Q. And if this number is part of a range, it's likely to be at the high end of the range?

A. So, I think that you are right, inasmuch as more people will have COVID-19 infection and not be diagnosed than will die of COVID-19 and not be found, but there is probably some variability in both numbers, a little bit more in the denominator, as you point out.

55. Q. Right. The true infection fatality rate of COVID-19 is much lower than 1.7 percent, isn't it?

A. What do you mean by "true"?

56. Q. Well, the actual number that is given, or the actual percentage that is given by taking the number of people who are actually infected, or have actually been infected with COVID-

19, and dividing that by the number of people who have actually died from COVID-19.

A. So, I think I would agree with you, it's less than 1.7 percent. I don't know whether it's 1.2, 0.8. And what we can reasonably say is that, if we apply a similar approach to other infectious diseases, we can establish a sense of how does this compare to other infectious diseases with which we are more familiar.

57. Q. Right. So, I am going to be going over some ground that you have already touched on, but just for the interest of setting down a record that I can take a succinct quote from, your calculation is based on the assumption that Ontario's cumulative case count was 543,571, as of June 24, 2021, but that number represents only confirmed cases, in other words, cases which had been confirmed by testing; wouldn't you agree with that?

A. Yes this is...so, this is persons with a positive test.

58. Q. And the actual number of cases in the general population was much higher, wasn't it?

A. I don't know what you mean by "much". So, it was...it was definitely higher, but

whether that is 5 percent, 10 percent, 50 percent, I think is open to conjecture.

59. Q. In your opinion, is it likely to be 5 percent?

A. I think it is more likely to be 5 to 10 percent than to be 50 to 100 percent.

60. Q. There is an inherent sampling bias in the cohorts of people who wind up having PCR tests done, isn't there?

A. Tell me more.

61. Q. In the sense that high risk populations, people who are experiencing severe symptoms, people who are, you know, concerned about their health, for one reason or another, but those people are going to be over-represented because they are going to be more likely to want to be tested; wouldn't you agree with that?

A. I mean, I think that that's...it's an open question, because we, as a society, haven't mandated testing. What is pretty clear is that there are people with clinical COVID illness who avoided going for testing, because they didn't want to know or because they were worried they couldn't go to work, and we know there are people with no evidence of COVID illness, certainly in the summer

of 2020, who were getting tested every week so they could go to cottages with different groups of friends. So, I think it...you know, the challenge with any sort of testing-based data is, unless testing is mandated, there will always be what you would call sampling bias, or what your expert is calling, perhaps, sampling bias. But the more important question is what is the likely magnitude of the bias in relation to the signal we have, and which direction do reasonable people think it would tend? And I think, in the case of COVID testing, we can make, particularly after the first wave, we can make an argument in both directions, that we had people who were sick, who were not getting tested, and we had people who were definitely not sick, who were getting a lot of tests.

62. Q. Would you agree that most asymptomatic cases would have gone undiagnosed? That is to say that most people infected with COVID-19, but who experienced no symptoms whatsoever, would you say that the majority of those people wouldn't have gone and been tested?

A. I don't know. I don't have any basis for having that...giving you a number on that.

63. Q. Right. But, in any event, the

Province's cumulative case count underestimates the actual number of cases?

A. So, I think it underestimates the actual number of people with symptomatic COVID-19 infection, and it probably does that less so than its underestimate of the total number of people who were infected, because, as you mentioned, there is some number unknown, the persons who get infected and never develop symptoms, so they would have no reason...they would have no way of knowing they had COVID-19, and they would have no particular motivation to be tested, unless their employer required serial testing.

64. Q. So, again, at paragraph 11, you note that the number of cumulative cases of COVID-19 in Ontario is likely higher than the number of recorded cases, since some individuals who acquire COVID-19 are not tested and diagnosed. You offered a few percentage ranges earlier on, but, based on your experience, can you give me an idea of what percentage, or approximately what percentage, or what range of percentages of, unrecorded cases would there be, you know, relative to the number of cases that have been recorded through PCR tests?

A. I mean, I think that I would be...I

would be guessing much the way you would, it's just I would guess as a physician and you would guess as a lawyer.

65. Q. Right.

A. I think, if we think of...one of the ways of, sort of, trying to narrow uncertainty in statistics is are we talking about 1 percent range, 10 percent, or 100 percent? I would propose that the 10 percent space is the most likely of those three. It's not a little bit. It's not, like, we missed the forest for a tree. But the...there are...other jurisdictions have made efforts to try to narrow that range using seroprevalence surveys. And certainly, when Ontario was doing that sort of work, we were not seeing evidence of widespread undetected infection. I believe that work came to an end in September 2020. So, I don't know what, if any, of that has continued.

66. Q. So, just to step back to the numbers there, for a second. When you say 10 percent may have gone undetected, that seems like a reasonable range to you? In other words, 90 percent of cases, of active cases of COVID, would have been detected by PCR testing, in Ontario?

A. I think that probably, based on what

I think clinically and what I saw as a public health person, most people who had COVID-19 were getting tested. They wanted to protect themselves, they wanted to protect others, they were directed by their employer, they were terrified of what they had heard about COVID.

67. Q. Right. So, if we are looking at a total of...sorry, whatever it was...550,000, essentially, cumulative cases of COVID, as of June 24, if...so, that would represent, in your estimation, 90 percent of the cases that had...to date, in Ontario, in total, including...or 90 percent of the total number of infections in Ontario, since the beginning of the pandemic?

A. Yes, so, if we go back to June, at that time, we had 543,000 cases, I would expect the true number of cases, if there were some higher force that could reveal that, to be somewhere around that, plus 10 percent. So, probably around 600,000.

68. Q. I am actually surprised that the number would be so high. So, when I see a case count, a daily case count, like, does that percentage carry over from the cumulative case count to the daily case counts that we see? So, in other words, if today there were 90 new COVID cases, you

would say that there would be another 10 that were undetected, and that would be a relatively reasonable estimate of how many total cases there were in the population?

A. I would actually add a caveat, because COVID now is very different from COVID even in June, and COVID in 2020. So, if we look at the COVID now, what we are seeing is high rates of cases among unvaccinated persons and, for many unvaccinated persons, they are unlikely to seek testing for COVID if they are of the view that COVID doesn't exist or COVID is fake news. So, there is also a regional and a rural/urban divide. Last night, I worked up in Markdale and, if you want a COVID test in Markdale, you have got to drive up to Owen Sound to get it, whereas, in Toronto, where I live, I mean, I could probably walk five minutes and have a couple of choices of how to get a COVID test. So, there is a lot of challenging to quantify factors that are going to affect that daily count. I think, from a practical...like, in the practice that I do as a public health physician point of view, we try to both acknowledge those, but also recognize that, if they are unmeasurable, we don't have the luxury of wringing our hands for six

months, trying to figure out how to measure them. We need to act based on the best information that is available.

69. Q. Right, but that best information would include, you know, models and estimates based on your experience and the experience of the people you are working with. You know, you are not going into this without even considering the prevalence of COVID in the general population, I imagine?

A. I mean, I think it...it probably turns on the specific question that is at hand. So, that undetected COVID burden is less important, provincially, if you are sitting...managing something for the Province than if you are in a particular region of Ontario with limited access to testing, as an example. So, it is probably important to be a little more specific about the decision and the geographic scope that is at state, because that is going to drive the...both the accuracy of the available information and how much energy people are going to put into making it more accurate or more complete.

70. Q. Right. Just...we are getting a little bit afield here, since, you know, we are talking about today rather than June 24, but this is

a bit of a matter of personal curiosity, so I am going to take advantage. How much do you think...you mentioned a few factors that would change your estimate of the percentage of undetected cases in the population, such as unvaccinated people being less likely to seek testing, for example, things like having to travel further for a COVID test, that sort of thing...if the number was...and again, I am not, you know, holding you to a specific number here, but if your estimate would have been 90 percent in June, how much would that have changed today?

A. You know, I think it depends on where you are sitting in the COVID pipeline. So, if I wear my emergency medicine hat, I've referred, I don't know, half a dozen patients for admission for COVID over the last month, not a single one of them had a positive test. So, their positive test is going to arrive when we do it in the emergency department and say, "Oh, yes, you clinically have COVID and, bingo, you have a positive test, and you were not vaccinated". So, from the hospital sector perspective, it's probably higher. The good news has been that the total number of people showing up who need a bed because of COVID has gone down

dramatically, to date, because of immunization.

I think, at a population level, you know, a number of people have attempted to use test positivity as a way to look for signal changes, in terms of which way is the case count moving, the thinking being that, as positivity goes up...I mean, it is kind of obvious, but it's worth saying anyway...as positivity goes up, all things being equal, that means there is more people with COVID walking around there, in whatever community that positivity is measured, and also that it may represent people coming in to testing, because there is a heightened level of concern. And that is probably a bit of wishful thinking and, to some degree, has been shown with other infectious diseases that as, sort of, the temperature goes up, people start to pay more attention. Some people pay attention when the temperature is very low, and then there is a, sort of, population gradient, and then we have some people who pay no attention at any time.

71. Q. All right. So, we were talking about infection fatality rates earlier, and your calculation that resulted in a 1.7 percent death rate. We discussed...we agreed that the actual

infection fatality rate, taking into account all cases in the general population, would be lower by some amount than 1.7 percent. That would be the fatality rate across the entire population, not accounting for age; is that correct?

A. Yes, this is what's called a crude rate. So, it's just the total number of deaths divided by the total number of cases.

72. Q. If we divide up the infection fatality rate by age cohort, isn't it true that, for people under the age of 65, the infection fatality rate for COVID-19 is quite significantly lower than 1.7 percent?

A. Yes, because we've had deaths clustered among the elderly.

73. Q. Right.

A. Which happens with virtually every cause of death, unfortunately.

74. Q. Sure. COVID's age distribution for death skews quite old though, doesn't it? Like, I mean, relative to other diseases?

A. Well, certainly compared to, say, HIV/AIDS, yes, but if you look at infectious disease, in general, if we exclude the childhood infectious diseases, which have, essentially, been

eliminated in Canada. We see a similar pattern with influenza. And, in fact, my understanding is that, in Canada, the death rates for COVID are much much higher than those for influenza in that, sort of, midlife age range of, sort of, 40 to 70, and then, in the 70 and over, influenza and COVID start to converge.

75. Q. All right. I would like to show you a document that I have sent to my friend, Mr. Hunter, to pass along to you. Could you pass that along to Dr. Hodge, please?

MR. HUNTER: We did.

BY MR. KITTREDGE:

76. Q. Great. That document is a PDF, and it's called, "Benatia et al, Estimates of COVID-19 Cases". Could you open that document and take a look at it?

A. Sure.

77. Q. And are you looking at it now?

A. Yes, it's just opening up.

78. Q. Sure.

A. Okay.

79. Q. Are you familiar with this document?

A. No.

80. Q. Can you describe what it appears to be to you?

A. It looks like either a preprint or a reprint of a journal article from Canadian Public Policy.

81. MR. KITTREDGE: Right. I would like to mark this document as Exhibit A to the cross-examination, and we can call it, let's say, estimates of COVID-19 cases across four Canadian provinces.

--- EXHIBIT A: Estimates of COVID-19 cases across four Canadian provinces

BY MR. KITTREDGE:

82. Q. And I am just going to very briefly direct your attention to page 2. The right-hand column, in the second paragraph. The first sentence of that paragraph reads:

"...Our results also suggest widespread undetected COVID-19 infection across Canadian provinces. We calculate that, for every diagnosed case, there were 12 population infections in mid-April..."

And this is referring to mid-April of 2020:

"...The ratio of population infection to diagnosis ranges from 8.6 in British Columbia to 14.8 in Ontario..."

Again, this refers to the period very early in the pandemic, in March and April of 2020. Do those ratios seem reasonable to you?

A. You know, I would need to review the...this is a modelling study, so it could be garbage in/garbage out. I can't give you an honest...an appropriate response, just being asked a question out of the blue.

83. Q. Right.

A. But I do note that these numbers would be not at all consistent with seroprevalence surveys that were done in Ontario, and...so that most public health people, rather than economists, would argue that that is a more accurate assessment. And, so, that's where people giving blood or getting tests for other medical conditions, their blood gets checked for antibodies to SARS-CoV-2.

84. Q. All right. So, would you estimate that the ratio of cases, COVID cases counted in this early period of the pandemic, to cases of COVID in the general population that were not counted, would remain something in the neighborhood of 90 percent

were detected and counted, and 10 percent went undetected and uncounted, or would that ratio be different at this point in the pandemic?

A. I mean, I think the...my way of thinking of it...and I am not an economist, so if I were asking questions about how to invest my savings or how to build an economy, I might ask an economist, but, as an epidemiologist, the event of hospitalization represents something by which there is relatively little debate. And, so, when I look at the proportion of persons...or proportion of COVID-19 cases that are hospitalized, that reaches a steady state, essentially, from the fall of 2020, over the last 12 months. And, so, I think that is a reasonable basis for saying that we are capturing a reasonably stable proportion of all COVID infections through testing.

85. Q. All right, can you please turn to the spoiler, page 5 of your affidavit, paragraph 11, again? Let me know when you are there.

A. Sure. Yes, I am there now.

86. Q. Great. So, once again, the second sentence here reads:

"...Based on Ontario's COVID-19 experience, 5 percent of people with COVID-19 will

require hospital-based care..."

Do you see where you wrote that?

A. Yes.

87. Q. That is not a true statement, is it?

A. That's quite a leading question, so maybe you could expand it a little for me.

88. Q. I am here to ask leading questions in the cross-examination. Well, that percentage, that 5 percent percentage was obtained by taking the total number of confirmed cases and dividing by the number of COVID hospitalizations; isn't it?

A. That's right.

89. Q. So, even if you take your estimate that...the number of confirmed cases...let me just do this calculation.

A. I think I can help you here. If I see where you are going, you want to add 10 percent to the case count...

90. Q. I do.

A. ...you get 600,000...

91. Q. And I want to see...

A. ...and you divide by the number of hospitalizations, it drops to, like, 4.7, 4.5.

92. Q. Fair enough. So, it is not precisely a true statement?

A. I think if it...it's not a matter of it's truth or not. It is a matter of, based on limitations of the data, that's where we end up.

93. Q. Right, but we know...

A. When we acknowledge those limitations, we can revise our estimate, but we are not moving from 5 percent to 1 percent, and we are not moving from 5 percent to 50 percent; right?

94. Q. But in the event that, you know, the actual number of undetected cases was something closer to 20 percent, the error in this would be more significant, obviously; would you agree?

A. Well, that is just arithmetic, but I haven't seen any basis to make it...to have a stronger argument for it to be 20 percent than roughly 10 percent.

95. Q. All right. At paragraph 28 of your affidavit...and I will give you a moment to turn there.

A. M'hmm. On page 13?

96. Q. Yes, I believe so. Yes. You note that:

"...By mid-June of 2021, 59 COVID outbreaks had been associated with places of worship, with 526 associated cases of COVID..."

Is that correct?

A. Yes.

97. Q. And Ontario's total case count, as of June 24, was 543,571, give or take 10 percent, according to your paragraph 12; is that correct?

A. M'hmm.

98. Q. So, slightly less than one in every 1,000 cases was associated with an outbreak at a place of worship; is that about right?

A. Well, in the available data, those associations were made for, yes, on the order of 1 in 1,000 cases, and then there is some notes that go with this, from Public Health Ontario, about the fact that they may not be able to associate all cases with any transmission event, and that, with any given outbreak, there may be...there is expected to be an undercounting of associated cases.

99. Q. Using your estimate that 5 percent of people infected with COVID will require hospitalization, which we have already established is somewhat low...or somewhat high, I am sorry, of those 526 associated with places of worship, perhaps 21 may require hospitalization; is that about right?

A. Well, that is arithmetic, but the good new is that, because of temporary restrictions

on attendance at places of worship, the number of outbreaks was substantially lower than it would have otherwise been. So, yes, there is a small number of people...small number of cases associated with outbreaks, but these outbreaks are all happening when attendance at religious gatherings has been limited by the public health measures that were put in place.

100. Q. Right, so, I am just going to ask the question again, and hope for a yes or no answer. Using your estimate that 5 percent of people infected with COVID will require hospitalization, which we have already established is somewhat high, of those 526 cases associated with places of worship, perhaps 21 might require hospitalization; would you say that is generally correct?

A. I agree with your arithmetic, yes.

101. Q. Thank you. Was there ever a time during the pandemic when an additional 21 cases requiring hospitalization would have overwhelmed the healthcare system?

A. Certainly if they were all in the same community they would have. There is no question about that. Let's imagine that that community, somewhere like St. Thomas, has a hospital

that has maybe 12 ICU beds. I mean, I think it's...part of the challenge, provincially, is that Ontario is a province of many provinces, if you think of it. You know, the thing that holds Canada together is people hate having to spend two days just to drive through Ontario to get on their cross-Canada trip. So, in a large centre like Toronto, there is much more healthcare capacity, in a smaller centre, like St. Thomas, much less. And the COVID infections have not been randomly, or uniformly distributed across the population. I think, in some ways, your focus on the 526 misses the point that substantial numbers of outbreaks were likely prevented by the limits that your clients are objecting to.

102. Q. Well, I mean...

MR. GUTTMAN: Mr. Kittredge, just for the record, I want to just correct the math. 5 percent of 526 is 26; is that what you were trying to say?

103. MR. KITTREDGE: Perhaps it was.

MR. GUTTMAN: You used the figure "21", and it should be 26.

THE DEPONENT: I will leave the arithmetic to the lawyers, and I will agree

with what you all settle on.

104. MR. KITTREDGE: All right, yes, I will agree with that. It was 26, so you are absolutely right. My apologies.

BY MR. KITTREDGE:

105. Q. So, you say, yourself, elsewhere in your affidavit, that due to Ontario's limitations, in terms of hospital capacity, much of Ontario's response included transferring patients between hospitals, as a matter of course, in order to move patients to hospitals with adequate capacity to handle them; isn't that correct?

A. There were movements of patients from heavily affected COVID hospitals to less affected COVID hospitals. There was also an almost complete cancellation of virtually every diagnostic and surgical procedure in order to accomplish that.

106. Q. Right, but the 26 cases that we were discussing, that might require hospitalization, it wouldn't have been impossible to accommodate 26 people, moving them around the province, and not all of these patients would be requiring, you know, ICU beds, or anything like that; wouldn't you agree with that?

A. I mean, I don't accept your initial premise that 500 cases is the basis for a planning process around outbreaks in places of worship. I would say that, if you look in the news, I believe, last week, the Sault area hospital was looking to transfer out patients because they were overwhelmed, and they had on the order of 20 COVID patients, and that is a fairly large sized hospital. It is an important regional centre. So, small numbers of patients can make a huge difference, particularly if hospitals are already full of patients with all the other reasons that people go to hospital, heart attacks, hip fractures, strokes.

107. Q. Right. Would you say that, at any point during the pandemic, Ontario's healthcare system lacked the capacity to accommodate an additional 26 patients?

A. You know, I don't have the visibility into Ontario's healthcare system. I can tell you that individual institutions certainly did. I can say that I think there is pretty clear evidence that it was incredibly disruptive for families to be told, "Oh, your sick uncle, father, or brother is being sent to Kingston. If he survives, we will tell you how to go visit him and

pick him up when he is ready to come home".

And I think the other piece which is important to note is that the capacity of the health system is a function of beds and equipment; that's the easy part. The humans to care for those patients is much more challenging. And, so, even if the hospital in Upper Armpit has 10 empty beds, if they've never had a sick COVID patient, it is not clear that their medical and nursing staff are going to be equipped to do what they need to do to take care of those people. So, it is a somewhat more complex question than the way you posed it.

108. Q. Well, I think you are making it more complex, to be fair. I mean, you do discuss, in a number of places in your affidavit, that one of the main concerns that you have, and one of the main justifications for restrictive non-pharmaceutical interventions in response to COVID is a concern that the healthcare system would be overwhelmed, and I am finding myself having a hard time pinning you down on what exactly that means. It seems to me that you should be able to answer the question in a more straightforward manner. Was there ever a point in the pandemic where Ontario's hospitals could not have accommodated 26 more COVID patients?

A. I think that I would say that it's unlikely that that question can be answered definitively, because Ontario's response was marked by a continuous process of adaptation and, essentially, punishing the rest of the population. So, 400,000 cancelled surgeries, 2.5 million postponed diagnostic procedures, like, that's the price of those 26 or 200 more, or whatever the number is, persons with COVID. So, the answer to your question is, "Yes and". Yes, those 26 people would be accommodated, and your uncle, who has a heart attack, "Sorry, he is not going to get anything", or your family member who has been waiting six months for cancer surgery, where that is going to affect their likelihood of survival, "Oh, they are going to wait another three months now". So, you know, it's not without its costs. I think that is...that is perhaps the difference in our perspective.

109. Q. I am going to circle back to that point a little bit later on. There is another point where it may flow with some other questions that I have for you, but I want to move ahead, now, on a few more questions about these outbreaks associated with places of worship. Let me just make a note of

where I am here. All right. So, we were discussing the outbreaks, the 59 COVID outbreaks that were reported as being associated with places of worship, and the 526 associated cases of COVID. Is it fair to assume that these outbreaks did not all occur at the same time?

A. That's right. They were over a period of, at the time this was done, approximately 15 months.

110. Q. At your paragraph 26, and elsewhere in your affidavit, you point out that probability of COVID transmission at a gathering depends on a number of factors, including the number of people attending and the background infection rates in the community; is that a fair summary?

A. Yes.

111. Q. Restrictions on attendance at religious gatherings were at their most restrictive, in other words, capacities were most limited, when background infection rates were at their highest in Ontario; is that accurate?

A. It varies slightly be region, because there was a period when, with the traffic light system, some regions had different restrictions than neighboring regions, but the

10-people limit in place from April through June and, similarly, from December through, generally, the end of February, depending where you were in Ontario, appears to have been the most restrictive, yes.

112. Q. So, those periods of restriction, capacity restriction to 10 people indoors, for example, would have coincided with the periods of time when background infection rates in Ontario were at their highest; would you agree with that?

A. Certainly the case counts in Ontario were at their highest, yes.

113. Q. Okay. And that, according to your estimate earlier on, likely accounts for 90 percent of the cases in the community. So, there would be an extra 10 percent of cases, or something in that neighborhood?

A. Yes, with some variability. Again, as we have discussed, basically, test-seeking behavior, and the people you represent, in one case, certainly are from a region of Ontario with relatively lower rates of testing in the population. So...

114. Q. Right, but, generally speaking...in any event, I have got enough of an answer there.

A. M'hmm.

115. Q. So, therefore, those outbreaks linked to places of worship, which occurred at times when background infection rates were high, would have resulted in fewer cases than at times...than outbreaks at times where the capacity limits were higher and the background infection rates were lower; would you agree with that?

A. I think that's really an "It depends". It would be professional misconduct for me to make such a broad generalization, because the identification of outbreaks in places of worship is not complete, the identification of cases associated with those is not complete, and I don't have the timeline from Public Health Ontario about where and when the outbreaks occurred.

116. Q. So, the average that you have given, the average number of cases per outbreak associated with these outbreaks at religious gatherings is apparently 8.9 cases per outbreak. Would capacity limits...does that number include the patient zero, the first...the person who brought the infection to the gathering?

A. My understanding is, no, it does not. So, those are all persons who were identified

as having had most likely their transmission event, where they received the virus, occur in a place of worship.

117. Q. So, to the extent that any of these outbreaks occurred when capacities were limited to 10 people indoors, would you agree that it is unlikely that each and every one of those would have...in a room full of 10 people, one of whom is patient zero, do you agree that it would be unlikely that, in every single case, that person would infect 8.9 of the remaining people? In other words, all of the remaining people, except for 10 percent, one of them...or, you know, do you agree that it is unlikely that, in a room full of 10 people, the average infection rate, case rate per outbreak, would be 8.9 cases?

A. I mean, in the abstract, you are absolutely correct. I think the important thing to bear in mind here is that we don't have the timeline in front of us. The outbreaks...some of these outbreaks occurred during the time periods of the greatest restrictions in places of worship where those restrictions were, shall we say, not being followed. So, the number 10, if all religious gatherings followed the rules, we could say, yes,

that is an accurate representation. I think that the other piece of it, some public health units had more and less energy to devote to tracking down people who may have attended a religious service, encouraged them to get tested, asked...some...there was variation among the 34 public health units as to the degree to which they even knew they should ask. For example, if you are living in Huron, and you drive to Waterloo to go to church, how do the people in Huron know there was an outbreak in Waterloo that they should ask you about? And then the final piece is that some religious organizations, as a matter of faith-adjacent belief refused to participate in contact tracing, or had very low rates of testing uptake. So, too many, what we would call confounding factors, in our business, whose magnitude is really impossible to estimate.

118. Q. So, where are you getting these numbers? What is the reporting on which you are basing this sentence here, that we are looking at?

A. This is in paragraph 28?

119. Q. Yes, it is.

A. About the number of outbreaks?

120. Q. Yes.

A. These are data that were provided

for the purpose of the affidavit by Public Health Ontario.

121. Q. Right. Is that data attached as an exhibit to your affidavit?

A. I believe it's footnote 30, data summarized by Public Health Ontario. Josh, if you can speak to whether it was...I don't believe it was an attachment explicitly...or there may have been a summary table. I didn't print out all the exhibits, I am afraid, for today's discussion.

122. Q. Since we are...I don't see it as an exhibit, and I am fairly certain it's not in there. I mean, there are many pages of exhibits, and I have been drowning in pages of exhibits over the last little while, but I am fairly certain I didn't see them in there. Assuming they are not, can I get an undertaking to produce that data?

MR. HUNTER: We will take that under advisement. I have to check whether there is any confidentiality concerns with Public Health Ontario.

U/A

123. MR. KITTREDGE: Sure. It just seems we are really getting in the weeds on the details of this, and if we are...you know, if I am to be expected to struggle my way

through that, I think I need the actual data.

MR. HUNTER: To be clear, we will make...advise what data is available to Public Health Ontario. We obviously don't have access to the underlying data that is kept by various public health units in Ontario, who aren't Ontario.

124. MR. KITTREDGE: Right. So, I am looking for the data on which this was based. Yes, okay.

BY MR. KITTREDGE:

125. Q. All right. So, a moment ago, we got in some other weeds while discussing whether an additional 26 patients would have posed a risk of overwhelming the healthcare system at any point during the pandemic. So, I will note, first of all, that you agreed that these outbreaks didn't occur at the same time. And, so, those...you know, if 5 percent of the associated cases required hospitalization, those 26 patients would have been spread across the course of the pandemic, and I would argue...I guess, would you agree with that?

A. Yes, the outbreaks were recorded

between March 2020 and June 18, 2021.

126. Q. Right. So, do you think that there would have been any real risk that spread out over the course of the entire pandemic, those 26 additional patients ran any risk of overwhelming the healthcare system?

A. Well, I would say that the question I think you are trying to ask me is, if there hadn't been the restrictive measures, how many more dozens or hundreds of outbreaks would there have been, and how many more dozens or hundreds of patients would we have had to spread out over the healthcare system?

127. Q. That is not precisely the question I am trying to ask you. I am asking...

A. I am struggling to follow your line of inquiry, so perhaps you could do me the favour of restating it?

128. Q. Sure. So, we have 526 cases associated with places of worship spread out through the course of the entire pandemic. Of those 526 cases, based on your estimate, 5 percent may need hospitalization. So, 21...26 people. And those 26 hospitalizations were spread across the entire course of the pandemic. Did the healthcare system,

at any point during the pandemic, reach a point where it was overwhelmed?

A. I think that it is reasonable to say that individual hospitals, essentially, had their backs to the wall. And, so, in the GTA, for example, mid-November of 2020, there was the overnight standing up of a GTA IMS structure to move patients around, because, certainly in Scarborough, we had a day where every emergency department bed, as I recall, was occupied by a COVID-infected person requiring hospital admission. So, the system...we, as citizens, may often imagine a system that is organized and all the pieces work together, and that is a helpful fiction. In reality, it is, sort of...it's more like baling twine and spit holding it together. So, there was a series of reactions to the evolving need for hospitalizations. The overall goal was to reduce the number of COVID infections in order to prevent the direct harms of COVID, people getting sick, people dying, and to preserve the healthcare system, whether it is your 526 patients you have identified here or a couple of thousand associated with sports practice. The challenge, from a policy framework, is, how do we put in place a set of measures that can be reasonably expected to

save the healthcare system from being pushed off a cliff, and reduce the harms directly to individuals? So, to pick out any one of those measures and say, "Well, what about these 500 people?" That's in the context of all the other 500s or 1,000s that were potentially also going to need care. Or, to flip it around, from a public health perspective, all the, ideally, hundreds to thousands of hospitalizations that we prevented, because Ontarions were willing to do the right thing and generally follow the measures that were put in place.

129. Q. So, a moment ago you used the phrase, "putting measures in place that would keep the healthcare system from being pushed off a cliff". Would you say that the measures put in place did, in fact, keep the healthcare system from being pushed off a cliff, in the manner that you used that phrase?

A. I mean, I think that we didn't end up like New York City, with people dying in the waiting room. So, if we define the cliff edge as people dying in the waiting room, okay, we did all right. The number of nurses who are leaving the practice of nursing in hospitals is staggering, to the point where, currently, where I work, we can't

staff a regular day in the emergency department. So, if we use that as our metric, we screwed up. We pushed too far, or we ran too close to the edge of that metaphorical cliff. I think that probably the millions of people whose diagnostic procedures were delayed, they might have a perspective that is somewhere between those two. I don't know.

I think that the...one of your experts chose a bed count approach to assessing healthcare capacity, and I think that that is table stakes. That's, like grade 4 level. But healthcare is functionally about people who deliver care to other people, and is about systems and processes, and I think we are going to find, in Ontario, we came...if we use New York as the standard, we didn't do as badly as New York, but we came perilously close, and that is a long-term outcome that will...if we are in this conversation in a few years, we will see who turned out to have the best sense of how bad that was.

130. Q. Well, you mentioned the bed count...what was in, a kindergarten approach?

A. Well, I will give him credit, grade 4.

131. Q. Grade 4, okay, fair enough. Well,

let's go through the exercise anyway. So, is it fair to say that Ontario had nearly 25,000 acute care hospital beds as of April 30, 2020?

A. I think that is an overestimate, based on...this was in the affidavit from Dr. Schabas, I believe.

132. Q. Yes, it was, the reply.

A. Point me to that paragraph, just because I have got...

133. Q. It was paragraph 6 in the reply affidavit, sworn on the 23rd.

A. Thank you. I think that, you know, Dr. Schabas' source for this is the government press release, which is perhaps generous of him to give it that much credence. The fundamental problem is the staffing. So, it's not...if you have nothing to do one evening, and you can slink into your local hospital, you will see that there are wards where there are physical beds, there's even linen on the beds, but there are no patients and no staff. And, so, for the purposes of, sort of, planning and thinking about how Ontario is going to navigate this, I think the OECD estimates and the OHA information that I cited in my affidavit are probably a more accurate basis for decision-making.

And, if we take the 1.4 number, we come up with a total that is about slightly shy of 20,000, which is somewhat lower than the one cited by your expert. That is in paragraph 14, page 7 of my affidavit.

134. Q. Okay, paragraph 14, page 7.

A. And part of my rationale for choosing this measure was to highlight why Ontario may have needed to move in a different way than other Canadian provinces or other jurisdictions. And, so, certainly the comparison with Alberta is an apt one, where Alberta's bed per population is approximately the same as the United States, which is almost double what it is in Ontario. So, the planning for best summer ever, I presume, included a recognition that they could tolerate higher levels of COVID than, say, Ontario could. Unfortunately, they may have overestimated.

135. Q. Well, all right. So, at no point in the pandemic have COVID patients occupied 10 percent of that 25,000 number. And let's just use that number, rather than your 20, for the sake of calculating 10 percent. So, at no point have there been more than 2,500 beds occupied by COVID patients in Ontario, have there?

A. That's correct, yes.

136. Q. Thank you. And the maximum count of COVID patients in Ontario was 2,360 on April 20,2021, was it not?

A. I would have to confirm that, but I will accept that as accurate, yes.

137. Q. Sure. And, in light of the COVID-19 pandemic, has the province increased hospital bed capacity since April of 2020?

A. Well, as your expert noted, they have certainly made media releases about announcing new beds. I am not aware that your expert or the government, have figured out how to manufacture nurses. So, there is a certain amount of smoke and mirrors when it comes to healthcare financing and, rather than get distracted by that, I would say that one of the things about...that COVID did for us in the health sector was that, initially, hospitals were emptied out and all procedures were cancelled, because we didn't know what to expect. That was wave one. Were we going to be Italy or were we going to be New York City? And Ontarions pretty much complied with the rules. We were fortunate that didn't happen. And then, people whose care had been delayed started to come to hospital. And, so, the census starts to rise, completely unrelated to

COVID, people who have congestive heart failure, people who have bad diabetes, people who need post-op care after hip fractures. So, the Ontario hospital system, as the OHA has pointed out, has the lowest number of beds in the OECD, which means that adding an additional 10 percent to the number of people who need a bed can be potentially catastrophic, compared to a system that is running along at 75 percent of capacity. Yes, you add another 10 percent, you go up to 85 percent. Ontario is running at, like, 105 percent. And, so, we already filled the cafeteria with people. Where are we going to put these extra people, and where are we going to find staff, even if we can find a place to put them?

138. Q. Okay. At paragraph 7 of your affidavit you state that your, "opinions are informed by, among other things, the challenge of minimizing adverse effects of measures that establish limits on human behavior"; correct?

A. M'hmm.

139. Q. But other than, insofar as you list and reject the intervention alternatives suggested by Dr. Kettner, Dr. Schabas and Dr. Warren, paragraph 7 is really the only time you make any

reference to the challenge of minimizing the impact of public health measures, is it not?

A. In general, yes.

140. Q. In fact, the Province could have implemented less restrictive interventions without significantly compromising the goal of controlling the spread of COVID; wouldn't you agree?

A. I think you'd need to specify what you mean when you say "less restrictive".

141. Q. So, for example, where an outdoor capacity limit was 10 people, it could easily have been 11 people, or 15 people, or 20 people, without bringing the healthcare system to its knees; wouldn't you agree?

A. I think the challenge for any policymaker is there is an arbitrariness to a number, and so a number must be chosen. I don't think that...my role as an expert is not to provide a recommendation as to whether it is 10 or 11. I think that my role is to provide a recommendation based on the burden model, saying, like, this looks like it is a pretty big deal and, therefore, we should consider these types of measures. And then, governments, in the process of iteration and contending perspectives decide how restrictive or

less restrictive they wish those measures to be.

142. Q. Non-pharmaceutical interventions can't be looked at in isolation. It would have been open to the Province to enact a less restrictive religious gathering restriction and make up for the resulting case count impact by imposing tighter restrictions in another sector, would it not?

A. I think you need to help me understand with an example what you have in mind.

143. Q. So, like, for example, if the Province set a capacity limit of 20 people in a religious gathering, and then made an according adjustment that would, you know, have a corresponding impact to, say, retail capacity. For example, they might have reduced capacity in beer stores, liquor stores and cannabis stores to offset the potential increase in cases from a larger religious capacity limit?

A. I mean, certainly, if public health were that simple, I wouldn't have had to spend all the years I did training. I think you are missing key features of religious gatherings that directly drive COVID risks of transmission that are profoundly different from retail establishments, a liquor store or beer store. And there is...

144. Q. Are you saying that there is no amount of...no restriction, no matter how restrictive, on retail, for example, dropping everything to online only and delivery only. You are saying that there is no adjustment that could be made that would make up for the difference in allowing an extra two people or five people or 10 people to attend a religious gathering?

A. I think you are asking me to opine on two, sort of, mixed up matters. So, maybe I can try to disentangle them. The first is, is there a mechanistic way we can say five more people in religious gatherings and X few people in a liquor store? And I would imagine that somebody, mechanistically, could come up with a model for that. There is a practical implementation aspect, which is that the restrictions were, in part, informed by, what is the risk of COVID transmission in a particular setting? And I would propose that, with regard to religious gatherings, despite there being higher risks than liquor stores or beer stores or, shall we say, other non-congregate living gatherings.

That is probably a better comparison. I mean, live music has been shut down for much much

longer, with much tighter restrictions, and live music and religious gatherings share, from a COVID transmission perspective, similar risk patters. So, the government appears to have deferred to the relatively greater importance of religion in the social context compared to live music performances in its choices. But the risk factors for transmission in a liquor store are profoundly different from those at a religious gathering.

So, the idea of somehow having a slider that you could move back and forth, it's a bit like trying to...you know, how many apples can I trade for a bicycle? Well, you have got to find a way of comparability between those two things. You might find somebody who is willing to trade bicycles for apples, but, as a society, we generally don't make those trade-offs.

145. Q. Well, you are always making those trade-offs in determining what interventions are going to be applied. I mean, there is nothing magic about the number 10 that instantly emerges as the correct capacity limit on a religious gathering, is there?

146. Q. I am not a religious person, myself. My understanding is that 10 was a recognition that

there are religious practices that require a gathering of persons who are of adherence to a particular faith. And so that 10 was a practical recognition of banning religious gatherings that was felt to be excessive, and there would be some, not zero, but minimized COVID risk if the limit was put at 10.

147. Q. But the limit could have been 12 just as easily?

A. I suppose. I wasn't at the table where these matters were discussed, so...

148. Q. Right.

A. I mean, my understanding is, in the Jewish tradition, the 10 is actually specified as the number that shall gather. There may be other religions that would have 12 as their minimum. I don't know.

149. Q. I mean, certainly a limit of 12 would accommodate a requirement for 10, would it not?

A. Yes.

150. Q. Thank you. The point being that any number of changes to the parameters of the interventions that were put in place would have been conceivable and possible, and there is no one set of

interventions that are absolutely known to be the right set; would you agree with that?

A. I think you are absolutely right that there is no perfect knowledge. I mean, as your experts, and I, have made the point, or attempted to, that knowledge is evolving about COVID and how to protect the population, and to strike a balance between the intended effects of those protections and the unavoidable harms of those protections. I think, if we look at non-congregate living voluntary gatherings as a class of exposure events, the restrictions for religious gatherings were less restrictive than other non-congregate living voluntary gatherings, despite having similar risk factors for COVID transmission. So, I take that to be an example of how governments sought to define that balance, and the number of times those restrictions changed reflect the desire to constantly...not constantly, but regularly rejig that balance between restriction and COVID risk.

151. Q. Can you point to anywhere in your affidavit where you make any comment that is critical of any of the NPIs imposed by the Province? And by "NPIs" I mean interventions, non-pharmaceutical interventions.

A. I mean, that was not my...whether they are...to criticize them was not the focus of the affidavit. I think that...

152. Q. So, is the answer to that question "No"?

A. Well, I think, if you turn to...let me just find the paragraph. So, if you look at paragraph 30, I think that I tried to provide some...my understanding of the, sort of, thinking process behind the NPIs:

> "...There is a bundle of temporary public health measures, referred to as NPIs. They seek to reduce close contact among persons from different households, and thus reduce COVID-19 risk. NPIs implemented temporarily in Ontario are broadly similar to those implemented in most, if not all, OECD jurisdictions, and include limits on occupancy of indoor spaces, mobility limits, limits on prohibitions of gatherings and events and school closures..."

153. Q. So, how would you say that that paragraph is critical of the NPIs imposed by the Province?

A. It's not been my...my affidavit sought to provide an explanation as to why the Government of Ontario chose the bundle of temporary measures.

154. Q. Right. So, the answer to the question is you can't find a point in your affidavit where you have made any comment that is critical of the NPIs imposed by the Province?

A. That is correct.

155. MR. KITTREDGE: All right, thank you. And thank you for your time. And, on a personal note, thank you for your work over the past two years, it is appreciated, and I am sure it has been challenging and tumultuous, and all that. And I have no further questions.

MR. HUNTER: And, so, why don't we just take a 10-minute break, and then we will come back and see if we have any re-exam?

156. MR. KITTREDGE: Sure.

THE DEPONENT: Okay, thank you.

--- upon recessing at 2:40 p.m.

--- A BRIEF RECESS

--- upon resuming at 2:50 p.m.

MATTHEW HODGE, resumed

RE-EXAMINATION BY MR. HUNTER:

157. Q. Thank you, Dr. Hodge. I just have a few questions arising out of the questions Mr. Kittredge asked you. First of all, you were asked some questions about dead viruses and live viruses and the possibility of transmission and, at one point, you talked about asymptomatic COVID-19 patients. First of all, could you just define what you mean by an "asymptomatic patient"?

A. So, that would be a person who, at the time of their assessment, has no symptoms of COVID-19 and, with the passage of time, they would either remain asymptomatic or they would be reclassified, after that moment, as, oh, they were actually pre-symptomatic, because, 48 hours later, they have a cough and a fever and they are short of breath.

158. Q. What relevance, if any, do those asymptomatic patients have to public health decisions?

A. Well, part of their relevance is that it's not clear if they are going to be pre-symptomatic...sorry, if they are, in fact, pre-symptomatic, but misclassified at that moment

and, therefore, are going to become sick. But the other, bigger, concern is that it's clear that persons can transmit COVID before they develop symptoms. So, some of those people who are asymptomatic at a moment in time may be, effectively, transmitting virus, and because they don't know that they have...if they don't know they have the virus, they may also be mixing more widely, not following the same measures to reduce those risks.

159. Q. You were asked some questions just about the way in which...if someone does die, and they had tested positive for COVID, that might be recorded, and you used a number of terms. I just want to make sure I understand those terms. So, you talked about "immediate", "contributing" and "antecedent" causes. Can you just give a short definition of what each of those terms mean, in your experience?

A. Sure. So, in the...there is an Ontario death certificate which is used for the recording of a death, and the first thing is the immediate cause, and then the next one is antecedent, as I recall, and the last one is contributing. So, for example, somebody who has

diabetes is at much higher risk of having coronary artery disease. So, they may come in and die of a heart attack, so myocardial infarction, the contributing cause would be diabetes. And there is a debate about whether it is an antecedent or a contributing, that is hair splitting, but the notion is that, for many deaths, particularly where there is not an injury or a trauma, there would be multiple factors that contribute to that final pathway out of this mortal life.

160. Q. And how would that play out in the case of a patient who had tested positive for COVID-19?

A. So, that depends on the clinical scenario. I think in our earlier discussion I used the example of two patients, one who is short of breath, has pneumonia, dies, they had a COVID-19 test. We would typically say their immediate cause of death was COVID-19 pneumonia, or pneumonia caused by COVID-19. Somebody who comes in because they fell and has a hip fracture, they get tested for COVID-19 as part of their preoperative screening, it turns up positive, they then fall off the operating table and sustain a catastrophic brain injury and die, they would be classified differently, to my

understanding.

161. Q. And what about if they, you know...say, someone, you know, an elderly patient had a stroke or a heart attack, and they had tested positive for COVID-19?

A. That would probably vary. COVID-19 appears to increase the risk of clotting events. So, certainly it's standard practice, when patients are admitted, we put them on medications to try to prevent clots. So, if the stroke appeared to be...for some physicians, they would link that to the COVID-19 infection, others might not. And there is some recoding of deaths that is done by...at the hospital level, so that there is a more standardized set of data that moves to vital statistics and to CIHI, but those are processes with which I am not familiar.

162. Q. Just for the record, CIHI?

A. Canadian Institute for Health Information.

163. Q. Thank you. You were asked a number of questions about, you know, infection fatality rates, and different numerators and denominators. First of all, just, you know, is an infection fatality rate a measure that is typically used in

public health practice and, if so, why and, if not, why not?

A. I would say, if we define "practice" to include people sitting around the table shooting the breeze, then, yes, it's widely used, but in practice practice terms, it's not, because it's mainly valuable, and it has been primarily used in relation to COVID, either for modelling purposes or to establish comparisons with other infectious diseases. So...

164. Q. And, so, from a practice practice point of view, making recommendations as to what measures should be taken, what measures would be used?

A. You know, I think...I was not at the tables where those recommendations were formulated. My understanding of the general process was to seek to find a set of measures that would have the effect of reducing risks of transmission into household, because, once it was inside a household, it was going to spread like wildfire, and the state has relatively few levers with which to interfere inside a household grouping, for disease control purposes. So, how do you prevent it getting into a household? And it is basically non-pharmacologic interventions

until we had vaccinations. So, for the first, say, 12 months, 15 months of COVID-19, it was only NPIs, and then...so, limit mobility, limit gatherings, facilitate distancing, mask mandates. The idea is, sort of, a multi-layer approach to protection, and trying to also recognize that people need to function in the world. So, for example, putting everybody under lockdown for two weeks, with inability to go to the doctor or get groceries probably isn't, on balance, going to be effective, because the population would be unable to tolerate it. It might be really good for COVID-19 control, but it is not practically implementable, so...

165. Q. And at one point you said that caseness, or being a case, is the basis for public health measures for COVID-19; why did you say that, or what do you mean by that, I should say?

A. Well, I mean that the testing data represent a way of taking...if I can use an analogy, taking the temperature of the pandemic in Ontario. We know that people get tested. We are reasonably confident in how to interpret the test results, and we have an accumulated body of experience that shows that, as test positivity goes in this direction, i.e. goes up, we see more people coming to hospital,

say, a week later. There is a number of those types of associations that have been learned over the course of the pandemic. So, while it would be...there are many theoretically better denominators to have. It would be great to have perfect knowledge and know exactly who is infected, and when they got infected, and how they got infected, but, absent that, it represents, like, kind of, the best we've got.

166. Q. So, you were asked, at one point, to compare the number of acute care beds in the Province, whether it was 25,000 or 20,000, and the number of COVID cases. In your view, is that a proper comparison to draw, for public health purposes?

A. I mean, it was the comparison that your esteemed colleague drew, and I tried to work with him to explain, from my perspective...the challenge is, if the system is at 105 percent of capacity...so, I am going to use the 20,000 number, because I can do the arithmetic on the fly...that means that there are 21,000 people in beds, but there are only 20,000 beds. So, there is a bunch of, sort of, Three-card Monte that is going on, whether it is beds in the cafeteria or people being

discharged sooner than would be optimal, in order to admit the next person, because they are sicker, and then you add another 2,500 people to that, I mean, that is just unfathomable. It would be different if we were, say, 20,000 or 25,000 beds, and only 70 percent occupancy. We could easily...more easily, let's say, accommodate another 10...2,500 patients.

And the other piece that is important to bear in mind on this, which I am happy to get into if you wish, is throughput. Many people with COVID stay in hospital for a relatively long time. So, if we look at bed days, that is probably a more accurate measure. The share of bed days attributable to COVID patients was far greater than 10 percent of bed capacity, because they were staying for longer than patients with CHF or patients with broken legs.

167. Q. Sorry, CHF?

A. Congestive heart failure.

168. Q. And, just so you know, those, I think it was, 2,000 or so COVID patients who needed hospitalization, would all of them only need an acute care bed, or would any of them need more than that?

A. So, I believe the number that Dr.

Schabas cited was the...all patients in hospital, of whom, at that point I would estimate probably between 400 and 800 were in ICU-level care. So, what had happened in many hospitals was that, as a matter of policy and practice, if you required certain interventions, you were in the ICU, and that's a physical location, and when that filled up, other places were designated as ICU beds. They didn't have all the whiz-bang equipment.

And the other piece of it is, generally, in the ICU, patients are staffed either one nurse per patient or one...sorry, one nurse per two patients, whereas, in a regular ward bed, it's one to four or one to five. So, in some cases, the designation of an ICU is also about the human resources that are available. So, patients weren't...it wasn't that they were, "Oh, we don't have an ICU bed. You just have to stay here and suffer". They would receive the care they needed, with everybody either working more or working faster, or changes in the staffing complement.

169. Q. So, you were also, at one point, taken to a...it was identified as an academic article, and you said it looked like it was a preprint or a reprint. What do those terms mean?

A. So, a reprint is simply a copy of an article that has appeared in a journal. And, so, that would be usually the PDF form. In the old days, it was a physical piece of paper that the author mailed you when you wrote and asked for it, now we just have PDFs of those. A preprint is a paper that is published on the internet, but has not been through a peer-review process. So, among printed articles, for which there would be reprints, there will be a very small number of retractions, or changes, down the road, typically related, unfortunately, to academic fraud, whereas, among preprints, because they haven't been through that review process, there is a fairly...a much higher proportion of preprints that never see it into a formal publication, whether because they were found to be methodologically unsound or because the author has retracted the paper, rather than have it go through the review process and be found to be not up to the standards of publication.

170. Q. Now, you were asked a number of questions about reports of cases and outbreaks in places of worship, and you said that both the cases...the number of outbreaks and the number of cases in an outbreak might be undercounted; why is

that?

A. So, part of the challenge for the people doing case-and-contact management is that some people will have exceptionally accurate recall of everywhere they have been and everywhere they have gone, and some people, at the other extreme, will actively not wish to participate. And, so, the art of case-and-contact management is trying to draw out, from the case individual, information that can help to establish where was the most likely transmission location where they received COVID, and where did they go that they might have given COVID to other people. So...and because of the way Ontario is structured, and people's lives are not centered within what the Province calls their public health unit, individuals may travel, for example, to attend what I called non-congregate living voluntary gatherings, such as live music or a religious gathering. And, so, when they return to their PHU of residence and are tested, it may not be known to the person doing the case investigation in, say, Durham Region that there is an outbreak at a church in Elgin, St. Thomas, or Southwest Public Health, that they should ask a direct question to the case person, "Did you attend a religious gathering at

this church, on this date, in the town of X, Y, Z?"

So, there is a lot of, if you think of it, missed connections there, because we don't have perfect knowledge, and it is humans who are doing case-and-contact management. Then, once two cases are identified associated with a location which would constitute an outbreak, there may be incomplete information about who else attended. So, most religious congregations do not record the names and contact information of persons attending. And, for some religious practices, my understanding is that they...part of the expression of their faith is to be open to all persons. So, they would actually explicitly not wish to record names and contact information, so there will be an incomplete census available to public health. It would be some of those people who won't answer the phone, some of them who aren't available, some of them who are informed but don't get tested. So, all of that contributes to the undercounting of the cases within the outbreak, and the underdetection is the piece I initially described. So, I hope I made that clear.

171. Q. And, just also, when you are talking about outbreaks at places of worship, if I understand your answer correctly, it was...you were

asked about the number of cases that are counted, and you said it wouldn't include patient zero, as it were, and it would include the cases contracted at the place of worship; is that right?

A. It would include cases where the most likely epidemiologic link, to use the jargon, is an exposure to the case at the place of worship. So, it's been rare in Ontario that we can use sequencing data to confirm that this virus is exactly the same as the virus that was in whatever the location was, but this notion of the most likely transmission location is one that is used and it is referred to as an "epidemiologic link".

172. Q. And would it include people...you know, if those people went home, and then gave it to their friends or co-workers or family members, would they be counted in the outbreak, those cases?

A. So, that's going to depend, again, on the local public health unit practice as to whether they think to make those associations, and then, you know, how the sausages are made, whether they link those cases within the IT system, so that they are seen as secondary cases from the outbreak.

173. Q. And you were asked, you know, some questions about comparing places of worship to

liquor stores or beer stores, and you said that was not an appropriate comparison, and other settings were. Why is that?

A. Well, I think it's for a number of reasons. Recognizing the diversity of religious practice, there is an inherent intentional social contact that's the basis of most religious gatherings, or many religious gatherings. I might go to the liquor store to meet my buddy, or I might run into a neighbour and say, "Hey, how's it going?", but I am not likely to be there with a large group of other people. I am not likely to be singing or speaking in high volume. I am not likely to engage in the passage of liquor or significant material in a way that may also increase the risk of infection, the way there is in some practices, religiously-significant materials are passed from person to person. So, there are a number of features of religious practice, broadly defined, which are associated with higher risks of COVID transmission, and those typically involve singing, speaking or singing at a loud volume, entry and exit into a space as a group. Religious services typically start at a designated time. People tend to show up, they are going to gather in those entry

and egress spaces. And then this notion of, sort of, the intentional social function, which is part of why many people value participation in those, may have the effect of reducing people's vigilance and adherence to masking and physical distancing.

174. Q. And the last question is, you were asked a number of questions about whether, I think it was, 526 cases and 26 hospitalizations would overwhelm the healthcare system, and you said, I think a couple of times, you disputed the premise of those questions; why is that?

A. Well, I think that the...I would say I looked at it from a couple of different perspectives, one was those 526 cases arose despite temporary restricted measures on religious gatherings. So, they represented some combination of bad luck, intentional non-compliance, and other factors. So, what that tells me is that it's not about 526 in religious gatherings, it's about...we had all these restrictions and we had 526 cases. So, without the restrictions, would that number have been 5,000, 50,000? I don't know.

And I think the related point to it is that the NPIs, as implemented in Ontario and in most OECD countries, tried to strike a balance, which I think

I would attribute to Michael Bloomberg, the former mayor of New York City. He introduced a housing policy, and everybody was opposed to it, and he was reported to have said, "I think I probably got it just about right, because I pissed off everybody". Inherent, or built into the notion of NPIs is we all have to sacrifice somewhat. And, so, to cherry pick out and say, "Well, like, let's just say we will treat...we will make it 12 people instead of 10" starts us down a path that...with no end, towards undermining the whole premise of NPIs, which is a broad set of measures that limit opportunities for virus transmission, and they do that by restricting mobility, by restricting opening hours, by restricting gatherings.

175. MR. HUNTER: Thank you. Those are my questions.

--- upon adjourning at 3:05 p.m.

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Estimates of COVID-19 Cases across Four Canadian Provinces

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Les auteurs estiment les taux d'infection par le coronavirus 2019 (COVID-19) de la population de quatre provinces canadiennes, de la fin de mars au début de mai 2020. Dans leur analyse, ils associent les données quotidiennes relatives au nombre de tests effectués et au nombre de cas diagnostiqués au moyen d'une méthodologie grâce à laquelle les données sont corrigées pour tenir compte du caractère non aléatoire des tests. Ils estiment la relation entre l'évolution quotidienne du nombre de tests effectués et de la proportion de cas positifs dans l'échantillon non aléatoire (généralement moins de 1 pour cent de la population) et utilisent ce gradient pour extrapoler une prédiction quant à la proportion de cas positifs qui seraient diagnostiqués si les tests étaient administrés à la population entière. Au cours de la période d'échantillonnage, les taux estimatifs d'infection de la population se situent dans les intervalles suivants : 1,7 à 2,6 pour cent au Québec, 0,7 à 1,4 pour cent en Ontario, 0,5 à 1,2 pour cent en Alberta et 0,2 à 0,4 pour cent en Colombie-Britannique. Dans chaque province, ces estimations se révèlent largement inférieures au taux moyen de cas positifs, ce qui s'explique par l'administration non aléatoire des tests aux populations qui présentent un risque plus élevé. Ces résultats indiquent également que les cas de COVID-19 non diagnostiqués sont largement répandus. Pour chaque cas diagnostiqué jusqu'à la mi-avril, les auteurs estiment à environ 12 le nombre de cas d'infection dans la population.

Mots clés : COVID 19, taux d'infection de la population, tests non aléatoires

This article estimates population infection rates from coronavirus disease 2019 (COVID-19) across four Canadian provinces from late March to early May 2020. The analysis combines daily data on the number of conducted tests and diagnosed cases with a methodology that corrects for non-random testing. We estimate the relationship between daily changes in the number of conducted tests and the fraction of positive cases in the non-random sample (typically less than 1 percent of the population) and apply this gradient to extrapolate the predicted fraction of positive cases if testing were expanded to the entire population. Over the sample period, the estimated population infection rates were 1.7–2.6 percent in Quebec, 0.7–1.4 percent in Ontario, 0.5–1.2 percent in Alberta, and 0.2–0.4 percent in British Columbia. In each province, these estimates are substantially below the average positive case rate, consistent with non-random testing of higher-risk populations. The results also imply widespread undiagnosed COVID-19 infection. For each identified case by mid-April, we estimate there were roughly 12 population infections.

Keywords: COVID-19, non-random testing, population infection rates

Introduction

The first cases of coronavirus disease 2019 (COVID-19) in Canada were documented in late January 2020, and by 5 May more than 63,000 cases had been reported (CSSE 2020). Because testing has been limited to a small fraction of the population and infected individuals with mild or

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no symptoms may not seek testing, however, the potential exists for widespread undocumented infections (see Bai et al. 2020; Dong et al. 2020; Hoehl et al. 2020; Lu et al. 2020; Pan et al. 2020).

In this article, we estimate population infection rates for COVID-19 across four Canadian provinces—Quebec, Ontario, Alberta, and British Columbia—from late March to early May. The analysis is based on the methodology developed in Benatia, Godefroy, and Lewis (2020) that corrects observed infection rates among tested individuals for non-random sampling to calculate infection rates in the overall population.[1] To implement the procedure, we estimate the relationship between the number of tests and the share of positive tests. This gradient is informative for the severity of selection bias. For example, a negative slope indicates positive selection bias, because individuals who are most frequently tested have the highest probability of infection. If the functional form of this relationship can be consistently estimated, we can compute the population infection rate as a combination of the observed sample infection rate and the estimated selection gradient, which corrects for non-random testing.

In practice, our approach faces two main empirical challenges. First, there is concern that the supply of testing may respond endogenously to underlying disease prevalence. For example, if policy-makers expand testing in response to increases in underlying disease prevalence, our estimation strategy would underestimate the selection bias gradient and thus overestimate total population infections. To address this concern, we focus on high-frequency day-to-day changes in the number of completed tests across US states and all Canadian provinces.[2] Because there is little scope for evolution in disease prevalence from one day to the next, daily changes in testing should be orthogonal to changes in population infection rates. To further validate this assumption, we estimate models that control for province and state fixed effects, thereby allowing for daily exponential growth in disease prevalence that is specific to each jurisdiction.

The second empirical challenge stems from uncertainty regarding the true functional relationship between the positive test rate and the size of the tested sample. In the empirical implementation, we specify a flexible functional relationship that appears to fit the data well. Nevertheless, the results ultimately depend on an untested assumption that the estimated relationship—based on data from the sample of tested individuals who typically make up less than 1 percent of the population—can be extrapolated to the rest of the population. Despite this limitation, we believe the approach offers significant advantages over existing methods used to estimate population infection rates (described later). In ongoing work, we hope to refine the estimation procedure to address this functional form concern.

We find wide cross-province differences in both the level of population infection rates and their trends. Average population infection rates over the sample period ranged from 0.3 percent in British Columbia to 3.0 percent in Quebec. Infection rates in British Columbia declined modestly over the sample period. In Ontario, infection rates rose from early to mid-April and subsequently declined. Meanwhile, Quebec and Alberta experienced increases in population infection rates over the month of April. These trends need not reflect increases in the number of newly infected individuals because our population infection rates capture both newly infected individuals and those with continued detectable viral load over the sample period.[3]

Our results also suggest widespread undetected COVID-19 infection across Canadian provinces. We calculate that for every diagnosed case, there were 12 population infections in mid-April. The ratio of population infection to diagnosis ranges from 8.6 in British Columbia to 14.8 in Ontario. These estimates are comparable to recent evidence on the rates of undetected infection in the United States and internationally (Ferguson et al. 2020; Johndrow, Lum, and Ball 2020; Perkins et al. 2020; Verity et al. 2020). For example, Aspelund et al. (2020) estimate that 80–90 percent of COVID-19 cases went undiagnosed in Iceland from late March to early April. Benatia et al. (2020) estimate a ratio of 12 population infections per diagnosed case in the United States by early April. More recently, the CDC (2020a) reported results based on seroprevalence that suggest that total infections were 10 times higher than the number of confirmed cases.

This article provides new evidence on overall population infection rates for COVID-19 in Canada. Our findings complement evidence for COVID-19 prevalence nationwide. Using survey results for COVID-19 symptoms, Reid (2020) finds that more than 100,000 households reported COVID-like symptoms after adjusting for seasonal influenza rates. The results do not account for potentially large numbers of asymptomatic infections. Meanwhile, Verity et al. (2020) combines assumptions regarding the age-adjusted case fatality rate with COVID-related deaths to estimate total population infections in Canada on 31 March. These estimates indicate that the case detection rate was just 5 percent through March. Our analysis provides the first provincial-level estimates. Given wide cross-province differences in per capita testing, official case counts may mask important geographic differences in the severity of the outbreak. Indeed, whereas the official case count in Quebec was 55 percent higher than in Ontario, our results show that gap in total cases was less than 20 percent.

Our empirical framework complements existing methods used to estimate population infection rates in the United States and internationally (Ferguson et al. 2020; Javan, Fox, and Meyers 2020; Johndrow et al. 2020; Li, Pei, et al. 2020; Perkins et al. 2020; Riou, Hauser, Counotte, and Althaus 2020; Verity et al. 2020). One approach has been

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based on the Susceptible Infectious Removed epidemiological model, which calibrates parameters to the specific characteristics of the severe acute respiratory syndrome coronavirus 2 pandemic to estimate current and future infections. A challenge for this approach is the large uncertainty regarding the relevant parameter values for the virus and the fact that the parameter values will evolve as societies take different measures to reduce transmission. Other research has relied on Bayesian modelling to infer past disease prevalence from observed COVID-19 deaths. Although these models require fewer assumptions regarding the underlying parameter values, because they scale up observed deaths to estimate population infections, small differences in the assumed case fatality will have substantial effects on the estimates. Given considerable uncertainty regarding the true case fatality, which may depend on local sociodemographic and environmental conditions, and the fact that COVID-19–related deaths may be undercounted during the course of the pandemic, these estimates may not capture the overall extent of population infection (see Clay, Lewis, and Severnini 2018, 2019; Clay et al. 2020; Han et al. 2020; Katz and Sanger-Katz 2020; Prakash and Hall 2020; Riou, Hauser, Counotte, Margossian, et al. 2020; Wu et al. 2020).

Most closely related to our article is Manski and Molinari (forthcoming), who use data on the total number of tests and the positive test rate to estimate ranges for population COVID-19 infection rates for Illinois, New York, and Italy in early April. Their approach requires only the imposition of weak monotonicity assumptions for identification. Their estimated bounds for infection rates are 0.1%–51.7% for Illinois, 0.8%–64.5% for New York, and 0.3%–51.0% for Italy. These are wide, model-free bounds. In this article, we estimate much narrower intervals, which are conditional on the accuracy of our model. Although we have developed our method for use during this crisis to employ the available information as fully as possible, policy-makers should be aware that bounds that include model uncertainty would be wider than ours by some unknown amount, which is not uncommon in econometric analyses. The model-free bounds of Manski and Molinari (forthcoming) serve as a remind of that issue.

Data

Our analysis draws on daily data on total test results (positive plus negative) and positive tests across Canadian provinces and US states for the period 31 March–5 May. Provincial data were obtained from the Epidemiological Data from the COVID-19 Outbreak in Canada project (Berry et al. 2020). This project is conducted by a team of researchers from the Universities of Toronto and Guelph and provides information on cases and testing across provinces based on publicly available information from government reports and news media. We exclude days on which there were identified changes in provincial reporting standards and days on which provincial health authorities did not release information on completed tests.[4] In addition, we use information on the number of positive tests by age group, which is available from provincial health departments, and provincial population estimates from Statistics Canada (2020). We supplement these data with information on total test results and positive cases across US states for the same time period from the COVID Tracking Project, a site launched by journalists from *The Atlantic* that publishes high-quality data on the outbreak across US states (Meyer, Kissane, and Madrigal 2020).

Figure 1 reports the daily tests and positive cases across the four provinces. Daily testing was fairly stable in Quebec throughout April. In contrast, daily testing substantially increased in both Ontario and Alberta and to a lesser extent in British Columbia.

Methodology

In this section, we present the theoretical framework developed in Benatia et al. (2020) to estimate COVID-19 prevalence. This framework motivates estimating Equation (6).

Theory

To evaluate population disease prevalence, we develop a simple selection model for COVID-19 testing and use the framework to link observed rates of positive tests to population disease prevalence. We consider a stable population, normalized to a population of one, and denote A and B as the number of sick and healthy individuals, respectively. Let p_n denote the probability that a sick person is tested and q_n the probability that a healthy person is tested, given a total number of tests, n. Thus, we have $n = p_nA + q_nB$, and assuming the test is accurate, the number of positive tests is $s = p_nA$.

This simple framework highlights how non-random testing will bias estimates of the population disease prevalence. Using Bayes's rule, we can write the relative probability of testing as

$$\frac{p_n}{q_n} = \frac{Pr(sick|\, tested, n) \,/\, Pr(healthy, tested, n)}{Pr(sick|\, n) \,/\, Pr(healthy, n)},$$

which is equal to one if tests are randomly allocated, $Pr(sick \setminus tested,n) = Pr(sick \setminus n)$. When testing is targeted to individuals who are more likely to be sick, we have $Pr(sick \setminus tested,n) > Pr(sick \setminus n)$, $Pr(sick \setminus tested,n) > Pr(sick \setminus n)$, and $Pr(healthy \setminus tested,n) < Pr(healthy \setminus n)$, so the ratio will be greater than one. In this scenario, the ratio of sick to healthy people in the sample, p_nA/q_nB, will exceed the ratio in the overall population, A/B.

We assume that the severity of selection bias can be expressed as a function of the number of tests,

$$\frac{p_n}{q_n} = f(n;\theta), \tag{1}$$

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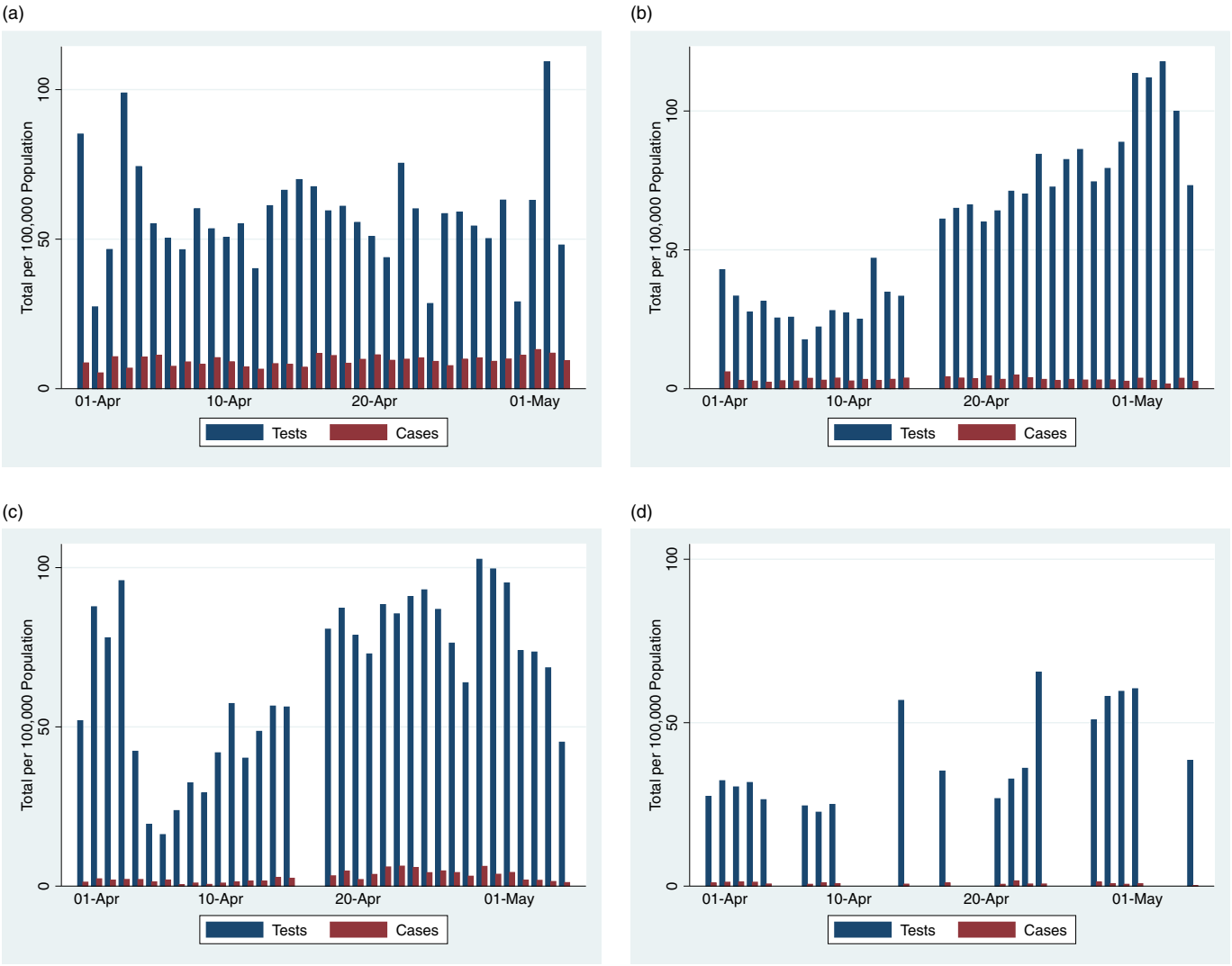

Figure 1: Daily Testing and New Cases across Provinces: (a) Quebec, (b) Ontario, (c) Alberta, and (d) British Columbia

Notes: This figure reports the total daily coronavirus tests and the number of new cases per 100,000 population by province. The trends are based on data from Berry et al. (2020). We exclude days for which there were identified changes in provincial reporting standards and days for which provincial health authorities did not release information on completed tests.

Source: Berry et al. (2020) and Statistics Canada (2020).

where n is number of conducted tests and θ is a vector of parameters to be estimated.

According to this setup, we can write the fraction of positive tests, s/n, as follows:

$$\frac{s}{n} = \frac{1}{1 + \frac{q_n}{p_n}\frac{B}{A}}. \tag{2}$$

Taking logs and using the fact that the latter term in the denominator is much larger than one, we can make the following approximation:[5]

$$\log\frac{s}{n} \approx \log\left(\frac{p_n}{q_n}\frac{A}{B}\right) = \log\left(\frac{p_n}{q_n}\right) + \log\left(\frac{A}{B}\right). \tag{3}$$

Equation (3) shows that the log share of positive tests in the sample can be approximated by the sum of the log ratio of the relative probability of testing, p_n/q_n, and the unobserved log ratio of sick to healthy people in the population, A/B.

From Theory to Estimation

To conduct the estimation, we adopt a first difference estimator, using as the dependent variable the difference $\log\frac{s_{i,t}}{n_{i,t}} - \log\frac{s_{i,t-1}}{n_{i,t-1}}$ on two consecutive days $t - 1$ and t in a given province/state i. Given the last equation, this first difference is equal to

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$$\log\frac{s_{i,t}}{n_{i,t}} - \log\frac{s_{i,t-1}}{n_{i,t-1}} = \log f\left(n_{i,t};\theta\right) - \log f\left(n_{i,t-1};\theta\right) + u_{i,t}, \quad (4)$$

where $u_{i,t} = \log\left(\frac{A_{i,t}}{B_{i,t}}\right) - \log\left(\frac{A_{i,t-1}}{B_{i,t-1}}\right) + \varepsilon_{i,t}$ is a mean zero error term that depends on the change in ratio of sick to healthy individuals in the population from $t-1$ to t and an idiosyncratic component, $\varepsilon_{i,t}$.

Equation (4) forms the basis of our empirical analysis. Our identifying assumption is strict exogeneity in the error term: $E(u_{i,t} \backslash n_{i,t}, n_{i,t-1})$. This assumption ensures that the errors are uncorrelated with any function of changes in the number of tests, $\Delta n_{i,t}$, and will be violated if changes in the population infection rate were systematically related to testing capacity. This assumption is supported by the short time interval in the daily first difference specification, which limits the scope for disease evolution. Also, in robustness tests, we control for province and state fixed effects, which allow for jurisdiction-specific exponential growth in underlying disease prevalence from one day to the next. These controls do not affect the main coefficient estimates.

Notice that by focusing on a daily first difference estimator, we are able to partial out the unobserved log ratio of sick to healthy people in the population, $A_{i,t}/B_{i,t}$. As a result, changes in the share of positive tests depend on the number of tests only through a selection channel.

How does this assumption enable us to estimate population infection rates? Using day-to-day changes in the share of positive tests and day-to-day changes in the number of tests, we can recover $\log f\left(n;\hat{\theta}\right)$ by estimating Equation (4). This term captures how changes in the share of positive tests are predicted to change with n. We can then use this prediction to recover population infection rates. Denote $\widehat{\frac{s_{pop}}{n_{pop}}}_{i,t}$ as the predicted fraction of positive tests if the entire population in province i was tested on date t, that is, $n_{i,t} = pop_i$. We can rewrite the first difference Equation (4) as

$$\log\widehat{\frac{s_{pop}}{n_{pop}}}_{i,t} = \log\frac{s_{i,t}}{n_{i,t}} + \log f\left(pop_i;\hat{\theta}\right) - \log f\left(n_{i,t};\hat{\theta}\right). \quad (5)$$

That is, the predicted log fraction of positive tests in the population is equal to the log fraction of positive tests in the sample plus an adjustment factor that corrects for non-random testing. One could also view our exercise as a reduced form estimation of the relationship between the fraction of individuals who test positive and the size of the tested population (holding constant the population share of those who are sick). Once this relationship has been consistently estimated, we can predict the share of positive tests for any value of n, including when $n = pop_i$.

Empirical Implementation

To implement the procedure described in the preceding section, we specify the following functional form for the selection process into testing, $f(n;\theta)$:

$$\frac{p_n}{q_n} = f\left(n;\theta\right) = 1 + e^{\gamma+\beta n}.$$

The term $e^{\gamma+\beta n} \geq 0$ reflects the fact that testing has been targeted toward higher-risk populations, with the intercept, γ, capturing the severity of selection bias when testing is limited. Meanwhile, the coefficient $\beta < 0$ identifies how selection bias decreases with n as the ratio p_n/q_n approaches one. Intuitively, as testing expands, the sample will become more representative of the overall population, and the selection bias will diminish.

We substitute this function into the first difference regression model, taking a third-order power series approximation of the log function, which yields the following estimating equation:[6]

$$\log\frac{s_{i,t}}{n_{i,t}} - \log\frac{s_{i,t-1}}{n_{i,t-1}} = \alpha_1\left[e^{\beta\frac{n_{i,t}}{pop_i}} - e^{\beta\frac{n_{i,t-1}}{pop_i}}\right] + \alpha_2\left[e^{2\beta\frac{n_{i,t}}{pop_i}} - e^{2\beta\frac{n_{i,t-1}}{pop_i}}\right] + \alpha_3\left[e^{3\beta\frac{n_{i,t}}{pop_i}} - e^{3\beta\frac{n_{i,t-1}}{pop_i}}\right] + \nu_{i,t}. \quad (6)$$

We estimate Equation (6) by non-linear least squares, allowing for heteroskedastic errors.[7] After estimation, we derive predicted values for population infection rates based on Equation (5), using the delta method to construct confidence intervals.

Before turning to the main results, several caveats should be highlighted. First, the estimates of population infection rates depend on a correctly specified functional relationship between the positive test rate and the size of the tested sample.[8] Although the model fits the data well (see Figure 2), an important assumption underlying our analysis is that this observed relationship in the tested sample—who typically make up less than 1 percent of the population—would continue to hold if testing were expanded out to the broader population. The accuracy of this extrapolation depends on a smoothness condition on the functional form and may be violated if, for example, some segments of the population can easily be tested and others cannot.

We also constrain the population coefficients (a_i, β) to be the same across jurisdictions. This assumption requires that decisions regarding how to prioritize tests were made similarly across provinces and US states. Although states had latitude to implement their own diagnostic testing procedures, the guidance laid out for testing prioritization by the CDC (2020b) was broadly similar to the policies implemented across Canadian provincial health departments. We also estimate the model for three distinct

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one-week intervals, 31 March–7 April 7, 14–21 April, and 28 April–5 May, to allow for the possibility that decisions about how to allocate tests across the population may have changed from late March to early May. Because policy decisions regarding testing of elderly populations may have differed across jurisdictions, we also report estimates based solely on cases among individuals aged younger than 70.

Finally, our analysis depends on the quality of diagnostic testing, and systematic false-negative test results may affect the population disease prevalence estimates (Ai et al. 2020; Liu et al. 2020; Yang et al. 2020). Because our analysis focuses on day-to-day variation, however, changes in the rates of misdiagnosis should not be systematically related to changes in the number of implemented tests.[9] As a result, these errors should not bias the coefficient estimates, but they may reduce precision through classical measurement error (Wooldridge 2002).

Results

Table 1, Panel A, reports the estimates for Equation (1) across three time periods: 31 March–7 April, 14–21 April, and 28 April–5 May. We estimate the model separately for all ages (Columns [1], [3], and [5]) and excluding cases among individuals aged older than 70 years (Columns [2], [4], and [6]). Consistent with the theoretical framework, we find large estimates of β ranging from –1,093 to –1,391, which implies that the sample selection in testing approaches zero as the number of tests approaches the total population size. We also find alternating signs on coefficient $\hat{\alpha}_1, \hat{\alpha}_2, \hat{\alpha}_3$, consistent with the estimates of the power series approximation developed in Benatia et al. (2020).

Figure 2 presents scatterplots of the relationship between daily changes in per capita testing and the share of positive tests across states and provinces for the three time periods. The downward-sloping relationships imply that

Table 1: Coefficient Estimates from Equation (6)

	Period 1, 31 March–7 April		Period 2, 14–21 April		Period 3, 28 April–5 May	
Coefficient	All Ages (1)	<70 y (2)	All Ages (3)	<70 y (4)	All Ages (5)	<70 y (6)
A: Baseline model						
α_1	11.570	11.704	10.004	10.347	8.199	8.159
	(2.090)	(2.157)	(1.564)	(1.625)	(1.640)	(1.679)
α_2	–23.975	–24.327	–20.765	–21.675	–16.026	–15.960
	(3.946)	(4.064)	(3.155)	(3.260)	(3.393)	(3.472)
α_3	17.545	17.781	15.628	16.230	12.255	12.225
	(2.230)	(2.292)	(1.929)	(1.984)	(2.096)	(2.139)
β	–1,390.815	–1,381.209	–1,608.010	–1,578.140	–1,107.816	–1,092.915
	(156.032)	(156.412)	(204.343)	(193.004)	(182.211)	(182.714)
σv	0.516	0.527	0.579	0.593	0.608	0.609
	(0.017)	(0.018)	(0.020)	(0.021)	(0.022)	(0.022)
No. of observations	443	443	410	408	399	399
B: Augmented model with province and state fixed effects						
α_1	11.313	11.422	10.045	10.333	8.026	7.994
	(1.512)	(1.561)	(1.115)	(1.153)	(1.155)	(1.181)
α_2	–23.469	–23.757	–20.818	–21.589	–15.540	–15.487
	(2.856)	(2.943)	(2.248)	(2.315)	(2.399)	(2.450)
α_3	17.261	17.454	15.649	16.162	11.866	11.844
	(1.614)	(1.660)	(1.378)	(1.414)	(1.491)	(1.518)
β	–1,405.202	–1,394.489	–1,596.620	–1,573.924	–1,111.405	–1,096.945
	(117.348)	(117.919)	(143.886)	(137.678)	(131.964)	(132.088)
σv	0.512	0.522	0.575	0.589	0.602	0.604
	(0.012)	(0.012)	(0.014)	(0.015)	(0.015)	(0.015)
No. of observations	443	443	410	408	399	399

Notes: This table reports the estimation of the coefficients from Equation (6). We estimate the model separately for each time period and for all ages versus cases among individuals aged younger than 70 y. Panel A reports the coefficient estimates from the baseline model. Panel B reports the estimates from augmented models that include province and state fixed effects. Heteroskedasticity robust standard errors are reported in parentheses.

Source: Authors' calculations.

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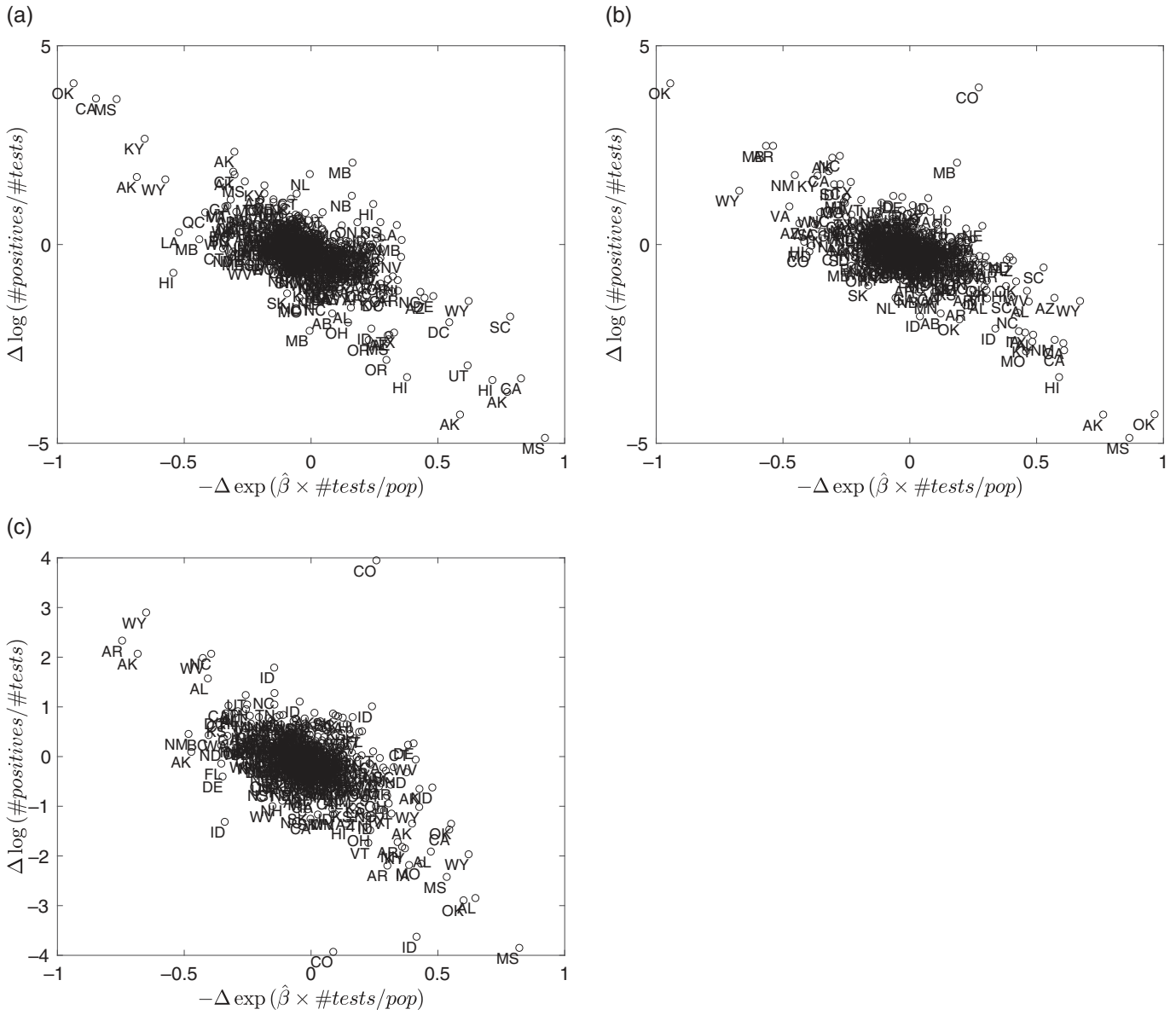

Figure 2: Daily Changes in Testing and the Share of Positive Cases: (a) Period 1, 31 March–April 7; (b) Period 2, 14–21 April; and (c) Period 3, 28 April–May 5

Notes: This figure reports the relationship between daily changes in the exponential of per capita testing and daily changes in the log share of positive tests for the three time periods. The relationship in each period is obtained using the estimated coefficient of β from the main estimates of Equation (6). See Table 1, Columns (1), (3), and (5).

Source: Authors' calculations.

larger day-to-day increases in the number of conducted tests are associated with decreases in the share of positive tests. A symptom of selection bias is that variables that have no structural relationship with the dependent variable may appear to be significant (Heckman 1979). So, these patterns strongly suggest non-random testing, because daily changes in testing should be unrelated to population disease prevalence except through a selection channel.

Table 2 reports the results for Quebec, Ontario, Alberta, and British Columbia that adjust observed COVID-19 case rates for non-random testing on the basis of the procedure described in the Methodology section. Column (2) reports the estimates for all-age population infection rates on 4 April, 18 April, and 2 May, along with heteroskedasticity robust 95 percent confidence intervals. Column (4) reports the average estimates for the three time periods 31 March–4 April, 14–18 April, and 28 April–2 May. These

Table 2: Estimated Population Infection Rates for COVID-19

Province	Positive Tests, % (1)	Estimated Population Prevalence, % All Ages (2)	Estimated Population Prevalence, % < 70 y (3)	Average Estimated Population Prevalence, % All Ages (4)	Average Estimated Population Prevalence, % < 70 y (5)
A: Early April					
	4 April	4 April		31 March–4 April	
Quebec	14.22	2.22 (1.03, 4.82)	1.95 (0.87, 4.35)	2.08	1.85
Ontario	7.31	0.86 (0.41, 1.79)	0.61 (0.29, 1.32)	1.23	0.96
Alberta	4.94	0.69 (0.33, 1.43)	0.63 (0.30, 1.34)	0.51	0.46
British Columbia	2.51	0.23 (0.11, 0.49)	0.12 (0.05, 0.26)	0.36	0.28
B: Mid-April					
	18 April	18 April		14–18 April	
Quebec	13.95	2.70 (1.52, 4.81)	2.56 (1.45, 4.53)	2.89	1.66
Ontario	5.93	1.21 (0.67, 2.18)	0.80 (0.44, 1.48)	1.42	0.70
Alberta	4.03	1.11 (0.59, 2.09)	1.05 (0.55, 2.00)	1.00	0.89
British Columbia	2.79	0.43 (0.24, 0.75)	0.36 (0.20, 0.63)	0.31	0.24
C: Early May					
	2 May	2 May		28 April–2 May	
Quebec	10.87	2.91 (1.51, 5.63)	1.98 (1.01, 3.90)	3.60	2.35
Ontario	2.69	0.76 (0.39, 1.47)	0.75 (0.38, 1.48)	0.86	0.76
Alberta	2.56	0.60 (0.32, 1.13)	0.57 (0.30, 1.10)	1.16	1.13
British Columbia	1.25	0.23 (0.13, 0.43)	0.24 (0.13, 0.45)	0.27	0.26

Notes: Column (1) reports the fraction of positive tests on the relevant day. Columns (2)–(3) report the coefficient estimates for population prevalence of COVID-19 based on the methodology described in the Methodology section. Heteroskedasticity robust 95% confidence intervals are reported in parentheses. We report the results for all age prevalence and prevalence among individuals aged younger than 70 y. Columns (4)–(5) report the average estimates for population prevalence of COVID-19 for the three time periods. COVID-19 = coronavirus disease 2019.

Source: Authors' calculations.

latter averages mitigate sampling error in the daily prevalence estimates, which depend on the observed share of positive tests on any particular day.

The results reveal widespread disparities in COVID-19 prevalence across provinces. Population infection rates range from more than 2.2 percent in Quebec to less than 0.4 percent in British Columbia Trends in infection rates differed significantly across provinces. Infection rates in British Columbia declined modestly over the sample period. In Ontario, infection rates rose from early to mid-April and subsequently declined. Meanwhile, Quebec and Alberta experienced steady increases in population infection rates over the sample period.

Columns (3) and (5) report the estimated population infection rates among individuals aged younger than 70 years.[10] These estimates will not be influenced by specific policies regarding the testing of the elderly population and residents of senior residential facilities that may have differed across provinces.[11] The results for Alberta and British Columbia are similar to the overall population prevalence. Meanwhile, the estimates are systematically lower in Ontario and Quebec, particularly in the latter

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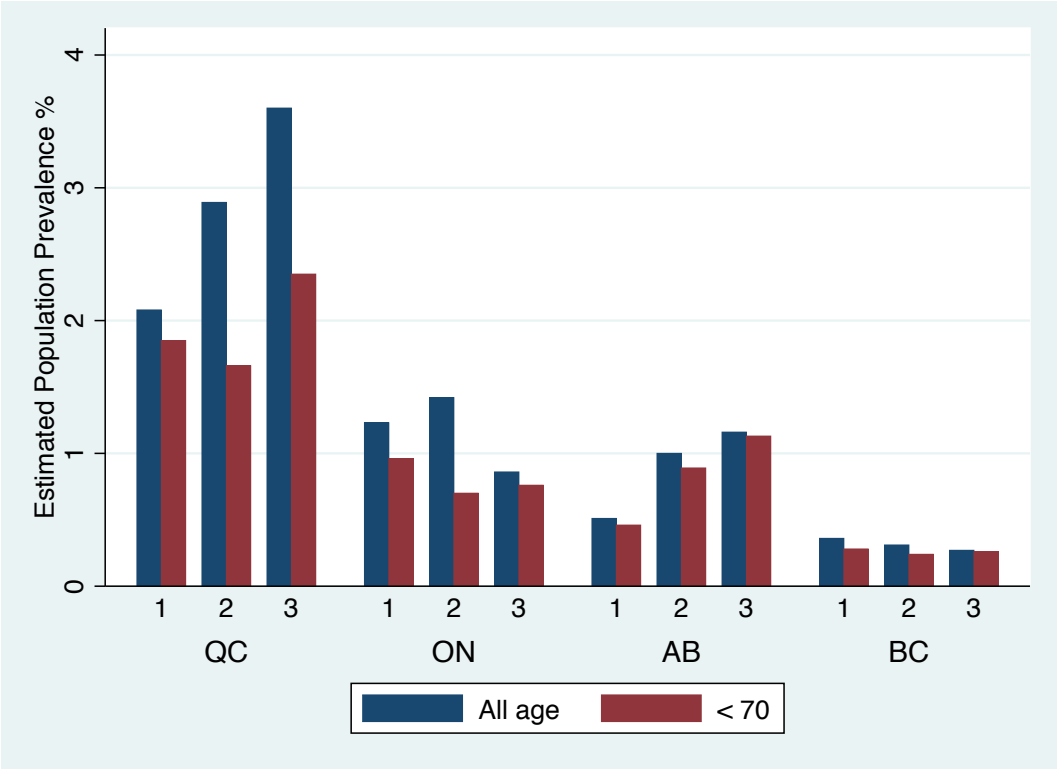

Figure 3: Population COVID-19 Infection Rates by Province and Period

Notes: This figure reports average population infection rates across provinces for three different time periods: (1) 31 March–4 April, (2) 14 April–18 April, and (3) 28 April–2 May. These average infection rates are obtained using the estimation procedure described in the Methodology section. All age population prevalence estimates are based on all cases and tests. To derive population prevalence for those aged younger than 70 y, we subtract the number of cases among elderly persons from the total daily cases and total tests across provinces. COVID-19 = coronavirus disease 2019.

Source: Authors' calculations.

periods. These results are consistent with the timing of the shift in testing in elderly facilities in these two provinces (Hinkson and Stevenson 2020; Jones 2020).

Table 3 explores the robustness of the main estimates to controls for province and state fixed effects. These controls allow for growth rates in underlying disease prevalence that are specific to each locality, to account for the fact that the true infection rate may evolve even within a 24-hour period. Because the intercepts are allowed to differ across each jurisdiction, they also account for variation in the daily evolution of the disease across states and provinces as a result of differing enforcement of social distancing or other location-based determinants of disease spread. The results (reported in the even-numbered columns) are virtually identical to the baseline estimates. Moreover, the augmented model tends to produce more precise confidence intervals, although as noted earlier we emphasize that these confidence intervals are conditional on our model.

To interpret the findings, we calculate the total population infections in mid-April and compare them with the number of diagnosed cases in each province. We multiply the average estimated prevalence from 14–18 April (Table 2, Panel B, Column [4]) by the total province population and compare it with the cumulative diagnosed cases by 23 April. The gap in the two periods captures the typical five-day incubation period to account for the fact that individuals may not seek testing until symptom onset (Lauer et al. 2020; Li, Guan, et al. 2020). In principal, these numbers capture two distinct measures of COVID-19 spread: current infections versus cumulative infections. Nevertheless, given limited COVID-19 infection before mid-March and the fact that viral presence is detectable by PCR testing three weeks after initial symptom onset (Cai et al. forthcoming; Zhou et al. 2020), population infection rates in mid-April are likely to be similar to cumulative infections since onset.

Table 4 presents the results. We find widespread undetected population infection. By 23 April, 41,371 cases had been identified across the four provinces; however, our estimates suggest that there were more than a half million infected individuals. In Quebec and Alberta, we find

Table 3: Robustness Exercises: Fixed-Effects Models

	Estimated Population Prevalence, %				Average Estimated Pop. Prevalence, %			
	All Ages		< 70 y		All Ages		< 70 y	
COVID-19 Prevalence in	Baseline (1)	Add Fixed Effects (2)	Baseline (3)	Add Fixed Effects (4)	Baseline (5)	Add Fixed Effects (6)	Baseline (7)	Add Fixed Effects (8)
A: Early April								
	4 April				31 March 31–4 April			
Quebec	2.22 (1.03, 4.82)	2.32 (1.33, 4.08)	1.95 (0.87, 4.35)	2.04 (1.14, 3.67)	2.08	2.17	1.85	1.93
Ontario	0.86 (0.41, 1.79)	0.89 (0.52, 1.52)	0.61 (0.29, 1.32)	0.64 (0.37, 1.11)	1.23	1.28	0.96	1.00
Alberta	0.69 (0.33, 1.43)	0.72 (0.42, 1.22)	0.63 (0.30, 1.34)	0.65 (0.38, 1.14)	0.51	0.54	0.46	0.48
British Columbia	0.23 (0.11, 0.49)	0.24 (0.14, 0.41)	0.12 (0.05, 0.26)	0.12 (0.07, 0.22)	0.36	0.38	0.28	0.29
B: Mid-April								
	18 April				14–18 April			
Quebec	2.70 (1.52, 4.81)	2.67 (1.77, 4.03)	2.56 (1.45, 4.53)	2.55 (1.70, 3.82)	2.89	2.85	1.66	1.66
Ontario	1.21 (0.67, 2.18)	1.19 (0.78, 1.82)	0.80 (0.44, 1.48)	0.80 (0.52, 1.24)	1.42	1.40	0.70	0.76
Alberta	1.11 (0.59, 2.09)	1.09 (0.70, 1.72)	1.05 (0.55, 2.00)	1.05 (0.66, 1.66)	1.00	0.98	0.89	0.89
British Columbia	0.43 (0.24, 0.75)	0.42 (0.28, 0.63)	0.36 (0.20, 0.63)	0.35 (0.23, 0.53)	0.31	0.31	0.24	0.23
C: Early May								
	2 May				28 April–2 May			
Quebec	2.91 (1.51, 5.63)	2.97 (1.87, 4.73)	1.98 (1.01, 3.90)	2.02 (1.25, 3.26)	3.60	3.66	2.35	2.39
Ontario	0.76 (0.39, 1.47)	0.77 (0.48, 1.24)	0.75 (0.38, 1.48)	0.78 (0.47, 1.24)	0.86	0.88	0.76	0.78
Alberta	0.60 (0.32, 1.13)	0.61 (0.39, 0.96)	0.57 (0.30, 1.10)	0.59 (0.37, 0.93)	1.16	1.18	1.13	1.16
British Columbia	0.23 (0.13, 0.43)	0.24 (0.15, 0.37)	0.24 (0.13, 0.45)	0.24 (0.16, 0.37)	0.27	0.27	0.26	0.26

Notes: This table explores the sensitivity of the findings to controls for province and state fixed effects. Columns (1)–(4) report the estimated population infection rates on the relevant date. Columns (5)–(8) report the average estimates for population prevalence of COVID-19 for the three time periods. Columns (1), (3), (5), and (7) report the baseline estimates, and Columns (2), (4), (6), and (8) report the estimates based on augmented models that include province and state fixed effects. Heteroskedasticity robust 95% confidence intervals are reported in parentheses.

Source: Authors' calculations.

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that there were 11–12 population infections per diagnosed case. In Ontario, there were 15 population infections per diagnosed case. These gaps align with differences in testing across provinces (Alberta and Quebec, 27 and 22 per 1,000, respectively, vs. Ontario, 13 per 1,000). Meanwhile, British Columbia had the smallest fraction of undetected cases, despite conducting just 14 tests per 1,000 population. This discrepancy can likely be attributed to the fact that the scope of the outbreak was substantially more limited in British Columbia, allowing officials to better identify clusters of cases.

Discussion

This article provides new evidence on the population prevalence of COVID-19 in Quebec, Ontario, Alberta, and British Columbia from late March to early May. Our analysis adapts a sample selection model approach developed in Benatia et al. (2020). We find widespread population

Table 4: Diagnosed Cases and Estimated Total Cases of COVID-19

Province	Positive COVID-19 Tests, by 23 April (1)	Estimated Total COVID-19 Cases (2)	Ratio of Total Cases to Positive Tests, (2)/(1) (3)	COVID-19 Tests per 1,000 Population (4)
Quebec	21,832	245,215	11.2	21.9
Ontario	13,995	206,845	14.8	13.4
Alberta	3,720	43,713	11.8	27.0
British Columbia	1,824	15,721	8.6	13.5

Notes: Column (1) reports the cumulative number of positive COVID-19 tests by 23 April. Column (2) reports the total number of COVID-19 cases implied by the average estimated population prevalence from 14–18 April (Table 2, Panel B, Column 4). Column (4) reports the cumulative number of COVID-19 tests by 23 April per 1,000 population. COVID-19 = coronavirus disease 2019.

Source: Berry et al. (2020); Statistics Canada (2020); authors' calculations.

infection that exceeds official reported cases by factors of 9 to 15 across provinces.

Our findings are comparable to recent prevalence estimates from the United States and countries in Western Europe. The estimated infection rates in Quebec are similar to those of the United Kingdom (2.7%) and several US states (Pennsylvania, 2.4%; Rhode Island, 2.4%; and Massachusetts, 3.4%). Meanwhile, the rates in Ontario are similar to those in Austria (1.1%), Denmark (1.1%), Vermont (1.4%), Virginia (1.4%), and Idaho (1.5%) in early April (see Benatia et al. 2020; Ferguson et al. 2020; Johndrow et al. 2020; Javan et al. 2020). Our results are also consistent with recent evidence from serological testing across several US jurisdictions that shows widespread undetected infection by mid-April (Bendavid et al. 2020; Conarck and Chang 2020; Goodman and Rothfeld 2020).

Our analysis provides a complement to existing methods used to estimate population infection rates. These approaches require either strong assumptions about unknown disease parameters or accurate measurement of COVID-related deaths, which may be undercounted over the course of the pandemic. Our estimation approach builds on standard econometric techniques. As high-frequency test data become more widely available at finer geographic units, this approach could be applied to estimate population infection rates at the city or district level. The current estimates depend on the accuracy of an extrapolation of the functional form relating the number of tests and the positive case rate to the large untested population. In ongoing work, we hope to refine the estimation procedure and explore the sensitivity of the results to various functional form assumptions.

As physical distancing policies continue to be relaxed, it will be essential that policy-makers have access to timely data on infection rates. Given the potential for widespread undiagnosed infection, the expansion of randomized population-based PCR testing may play a key role in identifying localized outbreaks. Meanwhile, widespread implementation of serological testing will help identify the large numbers of individuals with some level of immunity to the virus.

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Notes

1 A large body of research in economics is devoted to the issue of non-random sampling. See Blundell and Costa Dias (2002); Das, Newey, and Vella (2003); Heckman (1976, 1979); Heckman, Lalonde, and Smith (1999); and Newey (2009). Epidemiologists have also devoted considerable attention to the issue of sample representativeness (for a detailed discussion, see Davey Smith and Ebrahim 2013).

2 To improve the precision of the estimates, we include all Canadian provinces and US states to estimate the selection bias gradient. Once this gradient has been estimated, however, our estimates of underlying prevalence rely solely on the shares of positive cases across the four Canadian provinces we study.

3 There is an extended period over which individuals may test positive for COVID-19. Polymerase chain reaction (PCR) testing has identified cases days before symptom onset and detected continued viral RNA presence more than three weeks after symptom onset (Cai et al. 2020; Huang et al. 2020; Zhou et al. 2020). These positive cases often occur among individuals who are no longer symptomatic, and it is believed that they reflect lingering viral material that no longer poses a risk of transmission.

4 British Columbia has a large number of missing observations because daily testing results were not always released.

5 The median ratio of negative to positive tests, $\frac{q_n}{p_n}\frac{B}{A}$, across Canadian provinces was 21 during the sample period.

6 The first difference derivation is based on the following equation: $\log\frac{s}{n} \approx \log\left(1+e^{\gamma+\beta n}\right)+\log\frac{A}{B} \approx \sum_{k=1}^{M}\frac{(-1)^{k-1}e^{k\gamma}}{k}e^{k\beta n}+\log\frac{A}{B}$.

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The results are not sensitive to the inclusion of higher-order terms. Our baseline estimating equation does not include a constant, although we explore the robustness of the results to jurisdiction-specific intercepts.

7 Similar standard errors are found in models that allow for within-state/within-province serial correlation.

8 There is little guidance from theory about the functional form of relationship, and there are no individual-level survey data to shed light on who is tested.

9 To see why this is the case, let $\pi < 1$ denote the fixed probability that a test is positive if an individual is sick, so that some fraction of sick individuals may not be detected by testing. In this case, the researcher observes s/n, but the actual share of positive cases among the tested sample is $\frac{s}{\pi n}$. Provided that the rate of false negatives is constant over time, the term π drops out of the first difference Equation (4), so it will not affect the main estimates.

10 Figure 3 presents both all-age and aged-younger-than-70-years population infection rates.

11 To derive these estimates, we subtract the number of cases among elderly individuals from the total daily cases and total daily tests across provinces. Because we lack data on total tests by age group, negative tests among elderly individuals are included in the denominator, so these estimates should be interpreted as a lower-bound estimate for disease prevalence.

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The Attorney General of Ontario v. Trinity Bible Chapel et al.

RICHARD SCHABAS
on Friday, December 10, 2021

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Court File No. CV-21-00000095-0000

ONTARIO

SUPERIOR COURT OF JUSTICE

B E T W E E N:

THE ATTORNEY GENERAL OF ONTARIO

Applicant (Moving Party)

- and -

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHUURMAN, DEAN WANDERS, RANDY FREY, HARVEY FREY and DANIEL GORDON

Respondents (Responding Parties)

---This is the Cross-Examination of RICHARD SCHABAS, on his affidavit dated May 29, 2021, taken remotely through the offices of Neesons, A Veritext Company, Suite 2020, 77 King Street West, Toronto, Ontario, on the 10th day of December, 2021.

A P P E A R A N C E S:

Josh Hunter, Esq.	Counsel for the Applicant
Rob Kittredge, Esq.	Counsel for the Respondents

A L S O P R E S E N T:

Chandani Joshi, Court Reporter

TRANSCRIBED BY: Sandi Baxter, Transcriptionist

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The following list of undertakings, advisements and refusals is meant as a guide only for the assistance of counsel and no other purpose.

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NONE

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NONE

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NONE

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---Upon commencing at 1:07 p.m.

DR. RICHARD SCHABAS, SWORN

CROSS-EXAMINATION BY MR. JOSH HUNTER:

1. Q. Good afternoon, Dr. Schabas, or I suppose good morning where you are in British Columbia.

A. Yeah, thank you. Good morning, good afternoon.

2. Q. My name's John Hunter, I'm counsel with the Province of Ontario and I'm going to be asking you some questions today about an affidavit you swore in this proceeding. Do you have a copy of your affidavit with you with its exhibits?

A. I do. I don't -- I don't have all the exhibits, but I think I have them online, so I can access them if I need to.

3. Q. Great. If there's anything we really turn up we can go to it. The one I will ask you to have in front of you is do you have Exhibit A? That's your curriculum vitae?

A. I do.

4. Q. And before --

A. I should point out by the way, before we get into that, that there is a small error at the beginning of my affidavit. For some reason it

says I was Chief Medical Officer of Health from 1987 to 1998, that's not true. I -- I resigned in the -- towards the end of 1997, so just 10 years. I got a little time off for good behaviour I think.

5. Q. Fair enough. Actually, you anticipated my next question, was just was are there any corrections or amendments to your affidavit before we get started?

A. I think that's the only one, but -- but that one I'd like to correct, yeah.

6. Q. Well, let's turn to your CV then. And I just want to ask you a couple of questions about it. First of all, is this a up-to-date curriculum vitae?

A. I think so. I -- I -- I retired in -- in -- rather in 2016, at the end of 2016, and I haven't update it since then because I've been retired, so I guess there's nothing since then.

7. Q. Okay. And you're not currently licensed to practice medicine, right?

A. I am not.

8. Q. And you have not been since, I think it was March 2017?

A. I -- I don't -- my -- my licence in Ontario would have expired some time in 2017. I think

it was probably June, but somewhere around there, yeah.

9. Q. And you do not currently hold any academic appointments.

A. I do not.

10. Q. I think that last one you did was in 2016.

A. Yeah. I was -- I was at Queen's University. That was my last academic appointment, correct.

11. Q. Now, your CV says you've held a hospital appointment in Campbellford since 2005. Do you still hold that appointment?

A. No, I resigned that in 2016 when I retired.

12. Q. And you cite a number of academic papers on your CV. And if I'm reading it correctly, I think the most recent one was from 2012.

A. That could be. I -- I -- I -- without reviewing it I couldn't say, but probably. Probably the one on clostridium difficile, 2012. David Fisman of all people is the co-author.

13. Q. Yes, there was one. Clostridium difficile is the last one listed from the Canadian Journal of Infectious Diseases. Have you published

any more recent peer reviewed articles since 2012?

A. I don't -- I -- I don't recall any. I don't think so, but I -- I -- if they're not in my CV then I presume I haven't.

14. Q. But you have published some newspaper articles since then.

A. I have. I have, yes.

15. Q. I'd like to actually take you to one which you may recall. Let me just share my screen here. Just make sure it's working. Can you see the Globe and Mail article I'm sharing?

A. I see the beginning of it. I can't see the whole article.

16. Q. I'll maybe just zoom out a little.

A. Sure.

17. Q. It's an article, opinion article titled, "Strictly by the numbers, the coronavirus does not register as a dire global crisis," by a "Richard Schabas." It looks like it was published March 9th and updated March 11th of 2020. Do you remember writing that article?

A. I -- I wrote the article. I didn't write the headline of course.

18. Q. Fair enough.

A. You don't write your own headlines.

19. Q. If only you could. I just want to ask you a couple of questions about the views you expressed in that article.

A. Yes.

20. Q. Now, you state in the article that "COVID-19" was only, "A global crisis, for people who can't add"; is that right?

A. At that time, that's what I wrote, yes.

21. Q. And it was the:

"The Incredible Shrinking Pandemic."

A. At that time numbers were coming down, that's correct.

22. Q. And your opinion at that time, COVID-19 didn't seem, "Very transmissible among humans."

A. I -- I -- I said that. What I said actually is that -- is that most people don't transmit it, that it's transmitted by a relatively small number of people which turns out was a very pressing observation. I think I was probably the first person maybe to publish that observation anywhere in the world, and it turns out to be the over distributed nature of the infection, but indeed it's -- it was not

a highly infectious disease. And, yes, that's what I said at the time, correct.

23. Q. And you also said that, "The vast majority of infected" people:

"Spread the disease to precisely no one."

A. Correct, which I -- which I believed at the time and I still believe.

24. Q. And then so you concluded then, you know:

"Quarantine belongs back in the Middle Ages. Save your masks for robbing banks."

A. Correct. I did -- I concluded those and -- and by in large I still -- still maintain those views, yes.

MR. HUNTER: Can I have that marked as an exhibit, please? And objection, Mr. Kittredge?

MR. KITTREDGE: No objection.

MR. HUNTER: Thank you. That'll be Exhibit 1, Globe and Mail article by Richard Schabas, dated March 9th, 2020.

EXHIBIT NO. 1: Globe and Mail Article by Richard Schabas, dated March 9th, 2020.

BY MR. HUNTER:

25. Q. All right. Let's go into your affidavit then. Can I get you to turn -- we'll start at paragraph 7 of your affidavit.

A. Okay.

26. Q. And I think you'd agree with me that the science around COVID-19 has often been complex and uncertain?

A. That's what I said, yeah.

27. Q. That's a view you hold, right?

A. Yes.

28. Q. And that scientific understanding is constantly evolving?

A. Yes.

29. Q. Public health practitioners often don't have the luxury of waiting for science to solidify before they recommend action.

A. Absolutely true.

30. Q. And they have to act with the information that's available to them.

A. Absolutely true.

31. Q. And if public health measures are taken too slowly disease may spread and you may need even more stringent measures to regain control?

A. You may.

32. Q. And also, you know viruses themselves evolve.

A. We're seeing that happen before our eyes with COVID-19, yes.

33. Q. They can become more contagious.

A. Yes.

34. Q. They can spread more easily.

A. Well, become more contagious and spread more easily are pretty much the same thing, but, yes, they can certainly do that.

35. Q. They can cause more severe disease.

A. More or less severe disease, yeah.

36. Q. But sometimes they can cause more severe.

A. You know I think that's unusual. I -- I -- I -- that's a theoretical possibility. That's not what we normally see with the evolution of -- of -- of viruses. Generally speaking, there's evolutionary pressure on viruses to become more infections.

As the population immunity grows, there's evolutionary pressure on the -- on the virus to become more contagious, but here's no real evolutionary pressure on it to become more variant, in fact quite the opposite.

I think the -- the -- the general experience with infectious diseases or viruses is that over time they become less variant, so although that's possible, I wouldn't -- I wouldn't put that as being something that we would expect.

37. Q. And as you just mentioned, and we've seen it with COVID-19, we had the original variant and then we had the Alpha variant and now the Delta variant replacing each other as the dominant strains in Ontario.

A. That's correct.

38. Q. You know, and there's new variants like we're all now hearing in the news about Omicron variant and we're still learning about that.

A. Indeed.

39. Q. And you know, at least from what we know so far, it appears these variants have increased transmissibility and perhaps increased severity compared to the original generation of COVID.

A. Yeah, I think -- I think -- I certainly agree that they -- they have had fairly consistently greater infectivity. The issue of severity I think -- I think there's -- there's -- there's relatively little evidence to support that. It's possible. It's possible, but I'm -- I'm not

persuaded by that evidence.

40. Q. Now, are you aware that currently the spread of the Delta variant has led to increased cases in most Public Health Units in Ontario?

A. I'm aware of the fact that Ontario currently, as we speak now, is -- is starting to -- to see an increase in cases, and Delta's the dominant variant, yes.

41. Q. I'll just share my screen. And you're aware that Ontario has a COVID-19 science table?

A. I've -- I've -- I've read about it, yes.

42. Q. And you're aware that they provide advice and modeling to government?

A. I'm -- I'm aware of that, yes.

43. Q. And I'm just showing you an excerpt from their most recent publicly released advice which was on December 7th, so earlier this week. I'm just showing you now the chart of the various public health units and the weekly cases on November 15th and November 28th of this year.

A. Um-hmm.

44. Q. Would you agree that you know COVID cases are currently increasing in the majority of

Public Health Units in Ontario?

A. Well, certainly this graft shows cases increased from November 15th to November 28th. November 28th was what, two weeks ago. And there's about a two-week lag between when infections occur and cases get reported, so this tells us what happened about a month ago. I -- I very much suspect cases are continuing to increase, but I don't know that.

I certainly can't tell you that from this graft because as I say this is telling me -- this is giving me insight into what happened about a month ago in Ontario.

45. Q. Fair enough. So I'll have to get the more recent data to know what's happened since then. And do you understand what the concept of "test positivity" refers to?

A. Yes, I do.

46. Q. And how would you explain that?

A. Well, I presume you're talking about the percentage of test positivity. So one of the parameters that we measure is to what percentage -- the assumption is that if testing practice stays consistent as the percentage of positivities increase, so that's an indication of -- of -- of a true increase in disease, a true increase in cases. It's one of the

markers.

47. Q. And so I'm just going to show you two charts from the same data. The first actually is exactly that, testing rates. And you'll see the black line which represents the Ontario trend. And the title, as says, "Testing Rates Are Flat Since Mid July." Would that be your assessment of the data shown by the black line for all of Ontario?

A. The testing rates have been stable since July, yeah, it looks like it. It's a pretty flat line.

48. Q. And so given those unchanged testing rates, and given the next graft which shows the test positivity rates, would you agree that at least in several Public Health Units of Ontario would seem that as you say the disease is increasing?

A. I -- I couldn't hear that. There's a little plumbing up above that -- could you repeat that again? Sorry.

49. Q. Certainly, well, you just said that if you have consistent test rates, and you're seeing an increasing --

A. No, I -- I didn't say that. I said if you have consistent test practices as well as test rates. Has to be both.

50. Q. So therefore, assuming that nothing has changed in test practices which I take -- I'll accept is an assumption, if you were to see increasing test positivity rates as shown in this chart would that be evidence to you as a public health practitioner that disease rates were increasing?

A. Well, you asked me to comment on the -- on the testing rates from July, but in fact I see an increase in test positivity in the early part of September that was actually higher than what we're seeing now.

So, no, I'd make the observation -- if you want me to make the observation since July that in fact testing rates have been stable and percent positivity, although its fluctuated, has been fundamentally stable. Now, I don't know if rates are increasing in Ontario now, but that's what I see on this graft.

51. Q. Fair enough.

MR. KITTREDGE: Can I have that marked as an exhibit, please? That'll be Exhibit 2, Ontario science table projections.

MR. KITTREDGE: So no, no objection from me, although I'd note that Dr. Schabas hasn't had a chance to review that in any detail

EXHIBIT NO. 2: Ontario science table projections.

BY MR. HUNTER:

52. Q. Fair enough. All right. So in paragraph 7 of your affidavit, Dr. Schabas, you say that:

"Ontario has responded with a variety of restrictive measures."

That you generally characterize as a "lockdown." And so I just want to make sure I understand what exactly it is you mean when we're talking about a "lockdown." So in your view, when you use the term "lockdown," would that include reducing capacity in large indoor venues?

A. That's -- that's one component of it, yes.

53. Q. So if that was all we were doing was that a lockdown or was that just -- that's one indicia of --

A. No, no, no. I -- I think -- a lockdown, as I think you realized is a general term. And it's applied to a -- a whole variety of -- to a whole concept of approach to COVID, but -- but certainly restrictions on public gatherings is one part of that, yes.

54. Q. And so would prohibiting large organized public events be a lockdown?

A. It's part of a lockdown, yeah.

55. Q. And would reducing the number of people who can gather in person at a religious event be a lockdown?

A. It's part of a lockdown, yeah.

56. Q. Well, let's take a look actually at some of the measures that have been in place over the course of the pandemic in the areas of Ontario where Mr. Kittredge's clients are located. So let me just pull that up. Okay. It should be up now. Scroll, Niagara is no longer relevant.

So I'm going to go through -- we've got here charts for the three Public Health Units that were part of this case. One church is no longer a part of it. So I'm going to focus on Waterloo. They were similar for south-western, but some of the dates were a little different, so I'm just going to walk you through.

And what I'm going to do is I'm going to just quickly describe what the restrictions were at various times in the pandemic. I just want your view whether -- when you use the term "lockdown" are these the restrictions you're talking about? And so will

this be evidence that we were in a lockdown during these periods of time?

A. Oh, okay. So let -- let me -- let me just clarify to that, the -- the -- the fundamental difference in my opinion is between advice we give people about how to behave, about how to socially distance, about how to [indiscernible] themselves to reduce their risk of getting COVID-19 and transmitting COVID-19, and things that we -- things that public health has done that amount to orders.

And obviously the -- the -- the components of the orders vary from the sorts of things you're showing me here to things like stay-at-home orders and school closures, but it's all part and parcel of the same thing. Is there a difference between what we know in an advisory sense and what we do in terms of a kind of a statutory sense, how we order people to do.

So when we -- you know what -- what -- the whole -- the whole [indiscernible,] the whole package I think is part and parcel of a lockdown -- of a lockdown approach to the problem.

57. Q. And so I guess that's actually the example in your view. So in your view when we were -- for example, from July to December 2020, when

religious services could still have 100 people, indoor services could still have -- outdoors, 30 percent of room capacity indoors, drive-in services any capacity, or even say in March and April 2021 when there was no capacity limit outdoors, 30 percent indoors and drive-in services with no capacity limit, that would still be a lockdown in your view because the was capacity limits being imposed by orders?

A. Yeah. And indeed, putting restrictions on outdoor services, when the risk of COVID transmission outdoors is so trivial, is not only lockdown, it's absurd. In my opinion it's absurd.

58. Q. And so in your view we'd still be in a lockdown today when there's no capacity limit outdoors and no capacity limit indoors if you have proof of vaccination, if not it's just the number that can --

A. No.

59. Q. -- maintain physical distancing?

A. I didn't say that. I -- I said in my affidavit that Ontario has introduced a group of measures which can be generally described as "lockdown." I didn't say when you cross the threshold from restrictive measures into what was called "lockdown," and I don't know where you draw that line.

That -- that -- that's -- that's a work of art that I'm not sure I can do on a day-to-day basis or a restriction-by-restriction basis.

I can certainly say for the periods of time that Ontario was under stay-at-home orders and when there were travel bans, that that was a lockdown. Are we in lockdown now? It's certainly not the same as it was then, but it's also -- also there are significant restrictions on at least some activities, so I don't know when -- when we cross that line.

But I think we all know what I'm talking about when we talk about that as being an approach to COVID. It's -- it's a regulatory authoritative legal approach to limiting people's ability to do things to limit their -- their daily activities to greater or lessor degrees, which is fundamentally different as I said from simply advising them how they should behave.

60. Q. And so I notice in your affidavit you cite some articles that are talking about the harms of "lockdowns." And I think they draw a different distinction than you between lockdowns and restrictive public health measures.

For example, the Savaris article you cite, the whole point was taking a difference between

restrictive things like gathering limits and -- gathering limits, restrictions on capacity and stay-at-home lockdown, don't leave your house except to walk your dog, et cetera, kind of orders. Would you agree that's a fair characterization of the point of that study?

A. No, I'm not sure. Maybe you could point me to where they actually made that --

61. Q. Sure.

A. -- distinction?

62. Q. Let me actually bring that up.

A. I do not --

MR. KITTREDGE: Josh, can I just interject here and ask you to send me a link to this?

MR. HUNTER: These are the affidavits he -- these are the articles he cited --

MR. KITTREDGE: Oh, they are.

MR. HUNTER: -- piece of paper.

MR. KITTREDGE: Okay. Oh, yeah, I missed -- I was looking away when you started with this, sorry.

BY MR. HUNTER:

63. Q. And, sorry, I apologize, I actually had the wrong paper. It was the Chin (ph) paper I was asking about. I'll just find the passage.

A. Show me the paper.

64. Q. You cited two in the same footnote, but it was to Chin. I'll just take you to their conclusions in one second. So in that article they discuss two different models --

A. Um-hmm.

65. Q. -- that they were examining, and one was -- I'll just get the reading of it. Model one was doing a complete lockdown as they called it. And then their hope and their conclusion is that that didn't produce much benefit because they in fact had already had a number of significant measures under model two which had already --

A. Sorry, did you say -- did you say they said "complete lockdown"?

66. Q. They used the word "complete lockdown" --

A. Yeah, I -- I didn't use --

67. Q. -- or "total lockdown."

A. -- that term. I didn't use either of those words.

68. Q. Yeah, but that's what they -- that's what says and you're expanding was the impact of a total or a complete lockdown according to their own introduction.

A. Okay.

69. Q. So that was just my point is that when you're saying that's about lockdown, you're talking about a broader range, more colloquial use of lockdown to refer to not just the stay-at-home phase when you know you couldn't legally leave your home except for specified purposes, but the broader range of regulatory measures --

A. Yeah.

70. Q. -- that were used throughout the pandemic.

A. Yeah. I think that's what I said in my affidavit, yes.

71. Q. Okay.

MR. HUNTER: Oh, just before I move on, I'd just like to mark that chart as an exhibit. I'll stop sharing it. That'll be Exhibit 3, summary of COVID measures on religious gatherings.

MR. KITTREDGE: No particular objection from me, but if you can send that over to me after the examination that would be great? Thank you.

EXHIBIT NO. 3: Summary of COVID measures on religious gatherings.

MR. HUNTER: Yeah, we'll send all the exhibits over after.

BY MR. HUNTER:

72. Q. All right. Moving on in your affidavit, in paragraph 8 and 9 you state that:

"Ontario has rigidly applied the same rules to all public gatherings, regardless of the relative harm."

And I would suggest to you that in fact throughout most of the pandemic Ontario has applied less stringent rules to religious gatherings than it has to other social or organized public gatherings.

A. [Indiscernible] less stringent, yes. I believe -- I believe the percentages were a little higher for religious gatherings, but the spirit of the restriction was the same.

73. Q. But sometimes they were considerably higher. In fact, at times you know you still have 10 or 50 people for a social gather, you could have 100 or even just physical distancing for religious gathering.

A. Okay. Well, then if -- if -- that's -- that's fair enough.

74. Q. And you know if we just looked at the chart the severity of the rules, the capacity limits are in place, they varied over the course of the pandemic.

A. Yeah, but they were all entirely arbitrary, not based on good evidence. And they were -- there were limits.

75. Q. There were limits, but the limits were loosened when the situation permitted, when the situation improved.

A. The -- the -- the -- again, I'll stand by what I said, none of those -- none of those limits were -- were particularly evidenced-based. They were -- they were arbitrary. That doesn't mean they were wrong, and it doesn't -- but -- but they -- they were -- they were in and of themselves arbitrary and they were fixed limits.

76. Q. Although of course by "fixed," sometimes it was an actual fixed number and sometimes it was a percent of capacity.

A. Yeah. Those are still affixed.

77. Q. And sometimes it was just enough to maintain two metres social distancing.

A. Yeah. Fair enough.

78. Q. And you'd agree that that's the generally recommended distancing to decrease the --

A. Yeah, that's -- that's the recommendation. That's recommending to people about how they should conduct themselves prudently to reduce

their risk of -- of getting or transmitting COVID-19 which -- which is entirely reasonable, yeah, but that's July. I wouldn't -- I wouldn't characterize that as an arbitrary limit or as a measure of lockdown.

79. Q. And at times there were different rules in different parts of the province. I think actually we looked at chart, you know Waterloo. Local public health officers kept some restrictions in place a bit longer than the provincial limits.

A. It's quite possible. I don't know.

80. Q. Let's talk about some of those -- you say they increased the risk of contracting COVID-19. Would you agree with me that the prevalence of COVID-19 in the community affects the risk that you're going to contract COVID-19?

A. Yes.

81. Q. The level of vaccination in the community affects that risk?

A. Well, that's a more complicated question. Your own personal vaccine status will affect your risk of getting the disease, but the level of disease in the community is still -- is going to be what it is, so, no, the vaccination provides -- will reduce the overall amount of transmission in the

community and it will provide a substantial measure of individual protection.

82. Q. And so if a substantial number of those individuals are protected, and either don't have COVID or you know are symptomatic or capable of spread, they may not be symptomatic for a shorter period of time, there's going to be less people you're going to run into who are capable of giving you COVID; would that not be true?

A. If you were with people who are infected with COVID the less likely you are to run into somebody who's infected with COVID, that's true.

83. Q. I think you actually just mentioned this, but you have a higher risk of contracting COVID-19 indoors than outdoors?

A. Oh, yeah, there's very good evidence of that. The -- this goes way back to Wuhan. The risk of contracting COVID-19 outdoors is -- is -- is quite trivial. It's a disease like any respiratory virus that's primarily spread indoors.

84. Q. And of course, "trivial" is not zero, but it is much lower than indoors.

A. There are very few zeros in the natural world, so it's not zero.

85. Q. And so the more people who are

present in a given venue at one time the higher the risk of someone being there who has and can spread COVID?

A. Yes.

86. Q. And the more closely people are crowded together the higher the risk?

A. The -- the -- the risk of transmission of COVID, one of the determinants is -- is -- is -- is proximity and length of exposure. So you know close -- prolonged close contact, particularly with a symptomatic person indoors is -- is at least one of the -- one of the fundamental ways in which COVID is spread. It's not the only way because aerosol spread, which is a little different, is also important, but certainly those are important factors, yes.

87. Q. I think you anticipate my next question, which is if you're sitting next to someone for an hour or two it's more likely they're going to transmit COVID than if you just walk by them quickly?

A. Only if they're infected.

88. Q. But if they are --

A. If they are infected, and particularly if they are symptomatic then in fact there's a much -- then, yes, yes, it increases in

proportion, an inverse proportion to the distance of separation and in direct proportion to the time of contact, yeah.

89. Q. And would you agree that you know if you're singing or talking loudly that increases the risk you might spread COVID to those around you?

A. That certainly could increase droplet production, so if you are infected it may well indeed increase the risk of transmission to somebody else, yes.

90. Q. All right. So moving on to paragraph 14 of your affidavit --

A. Yeah, yeah.

91. Q. -- yeah, you suggest that perhaps rather than looking at Ontario and predictions, we should look at jurisdictions such as Sweden, Brazil and Florida that have used less restrictive public health measures.

A. No. What I said here is that the models which predicted -- which the models predicted much higher rates of disease even in -- in places that didn't use restrictive measures. We had -- going back to two years ago almost, the models had a range of projections, and one of them was what happens if you lock down, what happens if you -- if you don't lock

down, and they made projections for a variety of countries which were with huge rates of disease.

My point here is that even places that didn't embrace the kind of lockdown approach that Ontario embraced still had rates of disease that were far far lower than the models predicted. The models on which we based our initial response to COVID, and which to a great degree still influence our thinking about COVID were just fundamentally wrong.

They were wrong -- they -- they -- their predictions, projections were just -- were really just wildly wrong. And -- and that's not only true for places like Ontario, but it's true really everywhere in the world.

You may recall that the -- the -- the famous Imperil College model said there would be 40 million dead within the first five months. Well, we're now two years into it and it's five million dead. Now that's still a lot of deaths, but it's not 40 million deaths within five months.

Ontario, according to I believe the Fisman model from that time, or rather Canada, was going to have 330,000 deaths. Well, we have 30,000 deaths, but we don't have -- and two years later almost we don't have -- we don't have 330,000 deaths

by the mid summer of 2020, so those projections were just fundamentally wrong.

And the reasons that they were wrong, and I should say that these models, these modelers, that these models have a long track record of making bad predictions, so -- and it was like we -- we accepted them as being -- as -- as having good strong science, but if we look back at their projections for -- for bird flu, for H1N1, for SARS, they had a very bad track record of -- of -- of projections.

And the projections were wrong because they used the wrong parameters for infection fatality rate. I still think they used the wrong projections for -- for -- for are not, but the bottom line is -- and -- and because their models are very simplistic. They're very very simplistic. They don't [indiscernible] other factors that may influence it.

But the bottom line is that these models were -- were not -- not just wrong, not just wrong, they were -- they were wildly wrong.

92. Q. Well, now that we have the benefit of two years of actual data, I just want to ask you some questions about these three jurisdictions. You suggest them, so I just want to kind of compare their experience with here in Ontario.

I think we'd all agree that those three jurisdictions took a less restrictive approach to public health measures than Ontario did.

A. That's why I assigned them, yeah.

93. Q. Yeah. And they all have had significantly more cases per capita than Ontario has had.

A. Well, I think -- I think we need to be very careful with that. There -- there's a geographic distribution to COVID-19 that we don't begin to understand, so -- so indeed there are differences.

In Canada as a whole, for whatever reasons, has actually had relatively low rates of disease compared to many other countries, certainly compared to the United States and compared to western Europe, but there's no particular correlation between the -- the -- the lockdown measures and -- and rates of disease.

So that -- that indeed we can look at -- at -- looking just at Canada, for example, the -- the rate -- the population mortality rate from COVID-19 in Quebec is about twice as high as it was in Ontario, even though Quebec, if anything, took more restrictive measures than Ontario. And Ontario's

rate, population mortality rate is about twice as high as it is in British Columbia even though Ontario, if anything took substantially more restrictive measures than British Columbia, so it's not about the restrictions.

If we look at examples like Brazil, indeed Brazil took a more relaxed approach to COVID. It was -- it was the whipping boy for not taking an aggressive approach.

Argentina on the other hand, right next door, was the poster child for lockdown, but two years into the outbreak or a year and a half into the outbreak, when you look at their population mortality rate they were almost identical.

Sweden took a much more relaxed approach than many other European countries. It's now in the lower half of mortality rates for European countries, so, yeah, they had more than Ontario because western Europe had more than Ontario, Latin America had more than Ontario, and the United States had more than Ontario or more than Canada for reasons, again that -- that I don't think we truly understand, but which are certainly complex.

But to sort of attribute all of that to what we did or what we didn't do, I think -- I think

that's a fallacy. I think we have attributed far too much to human activity to the -- to the impact of what was done or wasn't done because we don't truly understand the dynamics of what has caused a geographic spread or lack of spread of this virus, but it cannot be attributed in my opinion simply to what -- what jurisdictions did or didn't do.

94. Q. You're the one who picked these three jurisdictions as examples of --

A. Yeah, but for a purpose.

95. Q. -- less restrictive measures.

A. But -- but I did that for a purpose, to show how the models were wrong. I didn't pick them as poster child's of what we should emulate. That's not what I said in the affidavit.

I used that as an example, because people say, oh, yeah, yeah, the models -- the models that we didn't achieve the levels of disease most because we locked down, because we did these things. I'm saying, no, that's not correct, because even jurisdictions that didn't do these things still had rates of disease far far lower than the model we projected.

It's to make the point that the models were wrong, not to hold these up as models for what we

should or should not have done.

96. Q. But the facts remained that -- I mean, obviously we can go through the math if that's helpful, but if you adjust for the different populations Sweden had about 11,000 more -- if we had had the same rates as those places --

A. Yeah, but you're -- you're completely misrepresenting my point. As I said again, I'm not suggesting that we should have emulated -- and that's another discussion, whether we should have emulated Sweden or Brazil or wherever. That's a totally different discussion.

That you want to reference paragraph 14, let's stick to the point I'm making in paragraph 14. It's to show that the -- that the exaggerated predictions of the models had nothing to do with whether people walked out or not, because even places that didn't had far lower rates of disease than the model projected. That's the point I'm making in that paragraph.

97. Q. So in paragraphs 15 to 17 you argue that we should have followed the Canadian Ontario pandemic influenza plans, and we'll come back to whether COVID-19 --

A. I don't think I said that. I don't

think I've said that. I -- I -- I said that we should have paid more attention to what was done that. That was our [indiscernible] that our fundamental basis for our starting point for how to handle COVID-19.

I'm well aware that there are differences between COVID-19 and influenza but that was the building block. We spent a lot of time for conceptualizing how to deal with a pandemic of a respiratory virus. And there were some fundamentals in the pandemic influenza plan that I think we would have been well advised to pay attention to.

98. Q. That's where I wanted to go, was ask you about some of those fundamentals.

A. Sure.

99. Q. So Canada's Pandemic Influenza Preparedness Plan, which you've attached as Exhibit C, recommends that:

"Jurisdictions in a moderate to severe pandemic."

And I'd assume you'd agree with me that COVID-19's at least equivalent to a moderate pandemic?

A. Um-hmm. Yeah.

100. Q. That:

"Jurisdictions consider social distancing matters or strategies to

minimize close contact among people in public places, for example, proactive school closures and cancellation or modification of public gatherings."

So I would suggest that cancelling and modifying public gatherings would be consistent with Canada's pandemic influenza plan.

A. It -- in -- in a moderate to severe pandemic, yes, with the caveat, with the caveat that -- that -- that -- that influenza outbreaks typically last about six weeks. So the expectation in handling an influenza outbreak, the feasibility of taking these measures in the context of influenza is that -- is the expectation that these will be short-term measures, that these will not be -- we're talking about a matter of a few weeks, not a matter of a few years.

101. Q. Pandemic influenza doesn't always last just a few weeks.

A. Yeah, outbreaks of pandemic influenza do actually last a few weeks. Influenza outbreaks are very typical. They -- they last between six and eight weeks in any one jurisdiction, so indeed they do.

102. Q. But there's often multiple waves of those infections if it's travelling around the world.

A. Generally speaking, a pandemic wave of -- of -- of -- the wave of a pandemic is usually just one wave. That was the case -- one -- one large wave. That was the case in 1957, 1968 and 2009. There were -- there were small waves before, but with very low rates of disease, so -- so, no, I don't agree with that statement.

103. Q. Going back to the Influenza Preparedness Plan, it does recommend looking at mathematical modeling as one of the ways of deciding which public health measures to use, correct?

A. Yeah, indeed.

104. Q. I'm sorry, now I'm turning actually to Ontario's Influenza Pandemic Plan, which is at Exhibit D. And it recognizes that:

> "As our understanding of a pandemic's severity evolves, orders may have to be made to close an organization or modify activities within organizations."

A. Okay.

105. Q. Do you agree that's part of Ontario's Influenza Pandemic Plan?

A. I -- I -- I -- you're reading in -- I'll take your word for it, yeah.

106. Q. All right. If you'd like to take a look it's on pages 10 --

A. With the caveat -- with the caveat that the difference is of course that these are short-term closures. By the nature of influenza these are short-term -- these are short-term measures.

107. Q. Let's switch to COVID then and planning for that. I'm showing you now interim guidance. It's issued by the World Health Organization:

"Considerations for implementing and adjusting public health and social measures in the context of COVID-19."

And it was last updated June 14th of 2021; do you see that?

A. I -- I see it, yeah. Um-hmm.

108. Q. I'm just going to take you to pages 7 and 8. So what this document recognizes is that there's different situational levels of SARS-CoV-2 virus, you know ranging from no known transmission to basic measures. Then you're getting into the levels two:

"Risk of community transmission behind clusters."

And then over on page 8 we have,

"Sustained community transmission," and then you know eventually level four, which hopefully we will never get to, the:

"Uncontrolled academic and the health system's falling apart."

But in level two which is:

"Low community instance or risk of community transmission."

It recommends -- this is the fourth bullet down, can you see that, starting, "Apply risk-based approach"?

A. Um-hmm.

109. Q. And it says:

"For public gatherings risk assessments should be undertaking by local and national public health authorities and event organizers with input from all relevant stakeholders. And this is to inform the decision to restrict, modify, postpone, cancel or proceed withholding any mass gatherings, including medium and small events."

So you would agree that the -- WHO is recommending that nation states consider, once you're getting into community transmission consider

restricting and modifying gatherings.

A. I'm sorry, you're showing me a complex technical document from the World Health Organization. You're showing me one paragraph and asking me to comment on the whole document. I'm not going to do that. If you want me to review the document I'll take the time to do it, but --

110. Q. I didn't ask you to comment on --

A. -- I can't do that.

111. Q. I mean, we're happy to --

MR. KITTREDGE: You're asking for a comment on what the WHO is recommending which I think it's fair to say that in order to understand that Dr. Schabas would have to have some time to review and understand the document itself.

MR. HUNTER: Sure. I'm happy to go off the record. And my question is actually quite simple, is just is the WHO recommending restrictions on mass gatherings be one of the measures that nation states consider.

MR. KITTREDGE: I mean, if you want to ask a specific question about the wording of that paragraph or something like that, I think I could accept that, but an opinion on what the WHO recommendation is overall would involve review of the

document.

BY MR. HUNTER:

112. Q. I mean, obviously if we need to take time we will, but I think my question was pretty simple, it's just is one of the measures that WHO recommends, and I'll give you a few minutes just to read this paragraph and the next one, you know what they call:

"Situational levels two and three."

That:

"Consider restricting, modifying, postponing, cancelling or proceeding with mass gatherings including medium and small events."

I'm not saying you have to cancel them all, but they're suggesting this is one of the measures that nation states consider at this level of risk.

MR. KITTREDGE: Why don't you ask him more specific --

THE WITNESS: Do you want me to read that paragraph? And which other paragraph do you want me to read?

BY MR. HUNTER:

113. Q. It's the same paragraph under, "Situational level three." It's the second from last bullet.

A. Okay. It simply says how you should approach any decision on that matter. It doesn't advise as to whether you should take that decision or not. That's what it says.

114. Q. But it suggests that you apply a risk-based approach to those decisions, correct?

A. That's what it says, yes.

MR. HUNTER: I'd like to mark that as an exhibit.

MR. KITTREDGE: All right. I mean, it's markable, but I -- and I think Dr. Schabas included enough caveats in his answer that I have no objection to it.

MR. HUNTER: Thank you. I think we're up to Exhibit 4 now, stop sharing.

EXHIBIT NO. 4: Document from World Health Organization.

BY MR. HUNTER:

115. Q. Now, at paragraph 23 of your affidavit --

A. Hang on. Yeah, okay.

116. Q. -- do you agree that COVID-19 is a

serious public health problem?

A. You say that, yes.

117. Q. Yeah. And at that time there were three million reported deaths. I think we're now, as you mentioned, we're over five million now.

A. Yeah.

118. Q. Yeah. And you make a comparison to children who unfortunately die from diarrheal illness.

A. Yes.

119. Q. Having a greater impact on premature mortality than COVID-19. Are you aware how many children in Canada die from diarrheal illness here?

A. Fortunately, very few. We're a developed country. No, this was a global statement, but indeed diarrheal illness is not an important cause of mortality in children in Canada, thank goodness.

120. Q. And that's both because, as you say we're a develop country with good sanitation, but also because childhood vaccinations have largely eliminated a number of those diseases in Canada?

A. No. It has -- it has very little to do with -- with immunization. It has to do with sanitation, generally good nutrition. There are a variety of what we would call the -- the -- the

determinants of health that really make a difference there.

121. Q. And now, in the next paragraph, paragraph 24, you focus on the deaths caused by COVID-19.

A. Correct.

122. Q. And you know I think we agree that obviously those two are very age stratified, but younger people can still have serious outcomes from contracting COVID-19, correct?

A. Yes.

123. Q. They can include death.

A. Yes.

124. Q. It can include long-term so called long COVID.

A. Yeah. I'm -- I'm a little cautious. Maybe you'd like to define what you mean by that if you want me to answer that question.

125. Q. I mean, they can have long-term respiratory, circulatory, kidney, liver, other damage from having the disease?

A. Yeah. I think -- I think those sorts of outcomes in healthy young people are -- are very unusual, but -- but indeed, yeah, if there are any -- COVID-19 has the capacity to cause serious

illness in younger people, but -- but it's - but it's -- it's -- it's -- the rates of -- of serious illness and -- and long-term consequences are very very much lower in -- in younger people.

In fact, fundamentally in people I put at the age of 60 the rates are very low. For people under the age of 60 the rates to that are -- are pretty comparable to what we see from influenza. And in fact, in children -- in children influenza appears to be more serious that COVID.

126. Q. And of course, people you know who contract COVID-19, and even if they recover they can sometimes require a period of time in the hospital or even in the ICU.

A. Yes.

127. Q. And of course --

A. It's a very serious illness, absolutely.

128. Q. Yeah.

A. Absolutely.

129. Q. When they're using that bed it's not available for someone else who might have had a heart attack or a car accident or anything else.

A. Yes, that -- they certainly use up -- we don't put two people in hospital beds, so when

somebody's in a bed, yeah, nobody else can use it, that's true.

130. Q. Now, in public health practice, when you're making recommendations to the public you want to make them easy for the public to understand, right?

A. You want to make them as easy as you can. You know sometimes the advice is complex. That's not -- that's not a rationale for oversimplifying. Indeed, you want to make it as comprehensible as possible, but -- but -- but sometimes advice is complex, and we have to recognize that.

131. Q. But as much as possible you want to make it -- like let me give you an example.

A. Sure.

132. Q. You know if you have -- you decide that the proper capacity limits should be 6.3 people in a room, might you round that down to five or if it's 9.8 you might round it up to 10 just because it's easier for people to work with round numbers?

A. I have absolutely no idea how you could come up with a number like 9.5 for -- for capacity limits, so I'm -- I'm sort of baffled by that, by that analogy.

133. Q. I just want to make the point that you know -- I believe Mr. Kittredge asked some of our witnesses, but why 10 people? Why not 11? Why not 9? And I'm just suggesting that --

A. Yeah. Well, it's -- it's kind of like we did with social distancing, because the actual evidence for social distancing, which was -- was that there was a benefit at one metre distance. And in fact, the WHO recommended social distancing of one metre. And a number of European countries adopted one metre.

The United States pretty much arbitrarily said, well, we'll go with six feet. Well, we didn't go with six feet in Canada because we're metric, so we went with two metres, so now we're out six and a half feet. It just -- yeah, that's -- sometimes simplification can -- can -- can lead you down that road, yeah.

134. Q. [Indiscernible] if you're going to tell -- you know you're going to make it businesses across the province would have to comply with something, giving them you know a number that's easier to calculate, divide your square footage by two rather than 1.5 or 1.7.

A. Fair enough, but -- but again, what

I -- what I -- yeah, okay. Yes.

135. Q. Now, at paragraph 28, I'm giving you this concept you call "arbitrarily," and I think by "arbitrarily" you mean just picking a bright line rule for all religious gatherings, is that what you mean when you say "arbitrarily" in that paragraph?

A. Well, all of the limits. None -- none of -- none of the limits, the percentage limits or the attendance limits where they posted a number, in my opinion are based on -- on -- on -- on strong science, so basically they -- somebody made a decision in their best judgment, but there's an arbitrariness to that decision, so it's not -- as I say not based on strong science.

136. Q. Are you aware of science that would allow a precise determination of exactly how large would be available?

A. No. No, I'm not. I'm not, but that doesn't make the decisions any less arbitrary.

137. Q. And you suggest that:

"Public health should work constructively with religious congregations to find ways to [indiscernible] risk."

And you give some examples. You

suggest that they could, for example, require a social distancing. Were you aware that Ontario in fact did require social distancing in a number of venues, including religious places of worship?

A. I'm certainly -- yeah, recommend social distancing, yeah. I think that -- I think that -- that in discussing with religious congregations that want to meet indoors the -- the -- these are the sorts of measures, social distancing, and the other things that I mentioned, are things that could mitigate the risk that could allow them to continue to practice their religion as they choose to by -- and mitigate the risk of transmission, yeah, but that does not --

138. Q. Are you aware that some of the rules are being challenged in this application include rules requiring social distancing?

A. Yeah. I'm not -- I'm not suggesting these would be rules. I don't say these should be rules. They -- they -- these -- these are examples of things that they could -- they could find ways with the congregation to mitigate the risk, to reduce the risk to allow that would be acceptable to the congregation rather than simply saying go ahead and -- and have your -- your -- your -- your religious

gathering, let's talking about things that we can reasonably do, but there's -- there's -- I'm not talking about imposing rules here.

139. Q. Okay. So you're saying that each religious -- you know you should have a conversation, but at the end of the day each congregation decides for itself?

A. No. I -- I think -- I think what I'm saying is that -- is that the -- the practice of religion is very fundamental to the public health of some people in the province. I make that point very strongly in my affidavit. We're not talking about -- we're not talking about retail stores or we're not talking about restaurants. We're not talking about hockey games or rock concerts.

We're talking about something that is -- is very fundamental to the -- the psychological and social wellbeing, which are two of the -- the pillars of people's health. So when we -- when we look at -- at the risk of COVID in that context we need to apply, I think a different standard than we do to hockey games and rock concerts and -- and retail stores because of the importance.

Not -- I'm not talking from a human rights perspective, that's not where my expertise is.

I'm talking about from a public health perspective. So indeed, I think that if there are people whose -- who the practice of religion, the -- the -- the ability to congregate to practice their religion in the way that they choose is so important to their own health that they are willing to face the risks of -- of COVID-19, even if it includes things like singing things that I would not recommend, then I think that that's something that we have to be respectful of, yes.

Yes, I think that -- that the people are able to make -- that people -- one of the -- one of the -- the -- the principles of public health as I always practiced is that people are allowed to make decisions about their own health. We don't think people should smoke, but we let them smoke.

I don't think people should go to a religious gathering and -- and -- and sing and -- and -- and be in close contact, but -- but if that's so important to them that they're -- that they're willing to face that risk I think we have to be respectful of that.

We have to at least document that -- that -- that it's causing a problem before we're taking measures to stop it. As I -- as I say in the

affidavit and make the point, and the Ontario data supports it, there's precious little avenues in the real world of Canada in the COVID outbreak that religious gatherings have been an important source of transmission, precious little evidence.

And yet we've taken these arbitrary measures and we've denied people something which for them, not for me, I'm not religious, this matters not to me at all, but I respect it for these people, practicing their religion is fundamental to their health.

140. Q. I'll come back to that in a minute, because I think that's the next paragraph. I just want to do one more thing before we move this paragraph. You mentioned that you could -- examples is that:

> "Public health could work to determine attendance limits based on the characteristics of the venue."

And I assume you mean each unique thing, correct?

A. Yeah, yeah.

141. Q. Are you aware of how many places of worship there are in Ontario?

A. I -- I don't. I don't have a

number. Do you have a number?

142. Q. I don't, but I would suggest it's at least in the tens of thousands, if not --

A. I would suspect there are. I would suspect there are tens of thousands, yes, indeed.

143. Q. And you know I would suggest that you know public health, with their many other responsibilities, especially during a pandemic, it would be very challenging for them to have those discussions with each and every place of worship to have an individualized discussion.

A. Yeah, I -- I find -- I find that a curious argument that when we're talking about something that's so fundamental to people's lives as the ability to practice their religion that the first -- that one of the lines of argument is that I'm sorry, we don't have no resources to take measure to -- I find that -- I find that on its face a very -- a very questionable argument.

I'd also say of course that -- that while there may well be tens of thousands of religious venues probably the great majority of them are not in fact going to -- going to -- going to want to go down this road. I suspect with all the fear that's been generated about COVID-19 the great majority of

religious -- of religious bodies are going to say, fine, we'll go with your recommended limits. We'll do as you say.

But even then, even then Ontario -- Ontario Public Health departments employ about 1,000 public health inspectors, trained public health inspectors who would be ideal people to do these kinds of assessments. And those people have been -- have been very -- have -- have -- important parts of their work in fact have disappeared with COVID-19 pandemic, restaurant closures, pool closures, all kinds of things that they would normally have to do.

So, no, I don't accept that we don't have the human resources to make at least a very good try at accommodating what I would think would be relatively few religious congregations that would want to go through this sort of assessment. So -- so, no, I don't think it's a daunting task at all. And I think it's quite shocking that Ontario hasn't even tried to do it.

144. Q. So your view you know those religious who want to stay open, they should just be able to decide that for themselves?

A. As I said I think -- I -- I've said -- this is -- this is -- this is a very nuanced area,

but the -- but what we've done is before there's been spread in religious congregations on any scale we've said you can't do this, but I would say, no, let's -- let's work with these bodies.

Let's make sure people are aware of their risk and then let's balance their freedoms, their freedom and their -- their need to practice their religion with the risk of COVID. And, yes, for some people it's going to mean a higher risk than we -- than I would think wise or you would think wise or Ontario Public Health would think wise, I agree with that.

And I wouldn't do it. I'm not going to go to a church and start singing in the choir. You're not going to find me there. But I respect that some people will make that decision that they will make the equation that the risk is -- you know the risk -- yes, COVID-19 can cause serious illness and death, but in fact the risk is -- for -- for many people, for most people it's actually quite small.

The risk of serious illness, hospitalization and death is really very small, even if they contract COVID-19. And that some reasonable people who put a very high premium on their ability to practice their religion they way they choose would

make a different decision. And I think we've made no effort to accommodate that, and I think that's wrong.

145. Q. And of course, they're not only taking those risks on for themselves.

A. Well, okay, so then we get into the issue indeed. It's an infectious disease, but we don't -- the contribution of churches are spread within religious gatherings, so the total burden of COVID-19 in Ontario has been trivial and almost certainly would be trivial.

And -- and so, yes, if we take the approach, which I must say I think has -- has -- has -- has poisoned a lot of the Ontario approach to COVID-19 that somehow we're going to stop this thing out, we're going to have zero COVID, we're going to get rid of the infection, yeah, if that's the priority, if that's in -- if that's in people's minds then in fact we can't do that.

But I think that's wrong. I think we have no capacity even with the vaccines to eliminate the disease. We have to accept there's a certain burden of illness, and in all other things we have to look at the balance here.

Where is the population level threat of these churches, the amount of spread in these churches

or other religious congregations. Is it so substantial that we are therefore -- that it's necessary for us to take these draconian or arbitrary measures? I'm not convinced of that.

MR. HUNTER: Can we just go off the record?

MR. KITTREDGE: Sure.

MR. HUNTER: Okay. So why don't we take let's say a 10-minute break to 2:20? I just want to talk to my team to see if there's anything else we want to --

MR. KITTREDGE: Okay. Sounds great.

MR. HUNTER: All right. So, Dr. Schabas, can you just turn your mic and -- your mic and screen off if you want? Obviously, I remind you you can't talk to Mr. Kittridge --

MR. KITTREDGE: Yeah.

THE WITNESS: You want to come back in 10 minutes?

MR. HUNTER: Yeah. So we're just going to take a 10 minute break. I'm going to talk to my team and then we'll see if we have any more questions for you.

THE WITNESS: Okay.

MR. KITTREDGE: And I'll keep my mic

and video off in the meantime.

MR. HUNTER: Great. We'll see you at 2:20.

---RECESS TAKEN AT UNKNOWN

---UPON RESUMING AT UNKNOWN

BY MR. HUNTER:

146. Q. All right. So, Dr. Schabas, just before the break we were just discussing you know your view that public health has overreacted, and at the end of the day we can't beat this virus. Would it be fair to say that public health officials in Ontario did not follow your recommendations?

A. What -- what --

147. Q. Your recommendations that we shouldn't be doing these lockdowns and strict rules we've just been talking about.

A. I'm sorry, when did I recommend that?

148. Q. Well, your whole affidavit states that we've overreacted by imposing restrictions on different gatherings.

A. That's one component of lockdown. You're -- you're characterizing that as we shouldn't have done any of these things, and that's not what I've said. I'm -- my affidavit relates specifically

to the issue of restrictions on religious practices, yeah, but yeah, I mean if what you're asking did Ontario Public Health introduce arbitrary measures on restriction of religious gatherings, yeah, that's true, they did.

149. Q. And in fact, public health authorities across Canada imposed restrictions on religious gatherings.

A. Yes, but I -- I -- I believe that's true, although I certainly know in British Columbia there was a lot less. I know when I wrote the affidavit I did a quick check of provinces and there were no restrictions at that time I believe in British Columbia, for example, so there's been variation.

150. Q. Just at that time they have certainly imposed restrictions --

A. Yeah, quite -- quite possibly. Quite possibly, yeah.

151. Q. And would it be fair to say that you would therefore be in the minority of Canadian public health practitioners vis-à-vis putting restrictions on congregate gatherings like religious --

A. I'm not taking a vote. I can't comment on that. I'll hold my opinions, you know.

Scientific matters are not decided by majority vote.

152. Q. Do you remember an interview you gave, when was it, back in March 2020 where you stated you were in the minority, a very small minority with your views?

A. Quite possibly. Was that -- so it's probably a fair statement, and certainly wasn't in March of 2020. I don't know what the situation is now. I hope -- I hope people are -- are -- are opening their minds up to the fact that maybe the things we've done have been without purpose and have caused great harm, but don't know that for a fact.

153. Q. Thank you.

MR. HUNTER: Those are all my questions.

MR. KITTREDGE: I just have a couple for re-examination. And I'm ready to go right now if you are.

MR. HUNTER: Yeah.

RE-EXAMINATION BY MR. KITTREDGE:

154. Q. Okay. Great. Thanks for your time today, Dr. Schabas. Early in his cross-examination Mr. Hunter showed you a Globe and Mail opinion piece that you wrote. Can you describe some of the ways that your approach to writing an opinion piece for a

newspaper differs from say authoring a paper for peer review?

A. Oh, sure. Opinion pieces in newspapers are -- are -- are short. They -- and they -- they -- they have to -- they're -- they're -- they're directed at a different audience, so I think there is a -- a need to hopefully not oversimplify, but to simplify and to make the -- make the piece punchy to get people to pay attention to what your key points are.

I think looking back at the -- at the Globe and Mail article, the -- the key point that -- that I was trying to make, and I'm not sure how well I made it, but that I was trying to make is it really related back to my experience with SARS. I was, as you -- you probably know through my CV, very intimately involved in the SARS outbreak in 2003.

And probably the most important lesson I took away from 2003 was that we've spent far too much time worrying about what we were afraid might happen and not enough time, not enough focus on what was actually happening. So in the -- in the Globe and Mail article I think what I said is let's look at the facts. Let's look at the data.

And I referred to the WHO webpage.

We've since started using things like world [indiscernible] and world data, but the idea is rather than speculate about the future and what might happen let's really focus on what -- on what -- what the data show.

And at the time the data showed that the case counts were -- were coming down. I said that's -- that's what it was. I also went on to say, but we've got to keep our minds open. We've got to keep any eye on the data, because what's happening, I mentioned in the -- in Korea at the time was worrying, and that this certainly could get -- get much worse, but I think that was my key message.

And I think the point I was trying to make is pay attention to the numbers, pay attention to the data. Let's deal with -- let's deal with the facts and not with the fears.

155. Q. Great. You were also asked several questions about hospitalization and the pressure that COVID puts on our healthcare system. Can you tell us a little about the capacity of Ontario's healthcare system and how it has coped during the COVID pandemic?

A. Sure. I think -- I think one of the kind of mantras that's developed is -- is this talk about the collapse of the healthcare system. We

have to prevent our healthcare system from collapsing. And -- and I think that's -- I think that is -- is -- is really very overdrawn.

The -- COVID-19 certainly has had the capacity to put pressure on ICU capacity. We've seen that, and we saw that initially in Italy where they made a whole bunch of serious errors, but -- but since then, even -- even in -- for example, in Ontario there's no question that it's put ICU capacity under some -- some strain, but ICU capacity is not the whole healthcare system.

The whole healthcare system is a much broader thing. And, no, our healthcare system has not brought to the -- to collapse or to the edge of collapse because there are pressures on -- on -- on ICU capacity.

Having said that -- having said that, even looking at Ontario, for example, and ICU capacity, we have roughly 2,000 ICU beds. And in April of 2020 Premier Ford announced that we had another 1,000-bed surge capacity, and that was right at the beginning.

And -- and -- and everyone knew, and I think should have known that in fact, the one -- the one -- the one pressure point in our healthcare system

was going to be ICU capacity, Canada went out and allegedly bought 40,000 ventilators. I have no idea what happened to them, but then like a year later, when we're in the midst of a COVID wave suddenly all we have are 2,000 beds.

What happened to the other 1,000 surge capacity beds? What happened? What have we been doing for the last year to try and build our capacity in the one place where there was going to be a problem?

I was the Chief of Staff at York Central Hospital in 2003 where we were one of four hospitals in -- in -- in North America that was hit by deal with SARS. And we were actually able overnight to double our ICU capacity.

We created a SARS unit that had -- had as many beds as -- as our ICU. Now, it was a stocket (ph) measure. We had to beg and borrow, but we weren't -- we weren't able for that period of the few weeks that we were dealt with with SARS, we weren't able to increase our capacity.

So, yeah, I don't -- I don't dismiss the pressures on our healthcare system, but remember, remember our healthcare system gets put under pressure every winter when there's an influenza outbreak. Go

back through the headlines in the Toronto Star for the last 10 years, and almost every Christmas time there are headlines about the pressure on our healthcare system from influenza.

There's nothing new or unique in this. The Ontario healthcare system is designed to be full. Our hospitals are designed to be full. Our ICUs are designed to be full. And -- and -- and what's happened with COVID is really not very -- very different.

So, no, I'm not dismissing the problem. Yes, it's an issue that we need to be aware of, but to use that as an excuse for the kinds of draconian measures that have been taken, I -- I don't accept that.

156. Q. Right. And so you probably answered this question, but at one point Mr. Hunter referenced a WHO level four scenario where hospitals are overrun and the nation's healthcare system collapses, how close do you think we've come to that scenario?

A. Well, in Canada not close at all. I mean, I don't think -- I said in my affidavit I think it's still true, I don't think Ontario's ever been over 10 percent of hospital beds occupied by

COVID patients. You know I don't think we've come remotely close to that.

I don't think any developed world jurisdiction, after Italy, and you can talk about what happened in Italy in March of 2020, but they made a whole series of -- of errors admitting people without symptoms at the hospital, poor infection control, and mistakes that haven't been repeated, so we learned that lesson.

So again, I think -- I think that's a fear that has been -- I think that's -- that -- that has been overblown and has been used as an excuse for measures, for justifying measures that -- that I don't think are necessary or appropriate.

157. Q. And you mentioned influenza. How comparable do you think COVID is to the severity of influenza in a given year?

A. Okay. Well, the -- the -- the COVID-19 outbreak, certainly in Canada, has been -- has been more severe than influenza, substantially more severe, but -- but maybe not as -- maybe not as much as -- as people think.

The -- typically -- and influenza occurs in a wave, and typically we get one wave of influenza, seasonal influenza every year, and we

expect somewhere in the neighbourhood of three to six-thousand influenza attributable deaths associated with that.

We've had four waves of COVID, and we've had about 30,000 deaths, so that's worse than we would have expected within influenza. And indeed, we've had more waves. We've had two waves a year, whereas we wouldn't expect that with influenza, so, yes, it's worse than influenza, but it's not so much worse. The idea that it's in a totally different ballpark, a totally different magnitude, I don't -- I don't think that's been true.

It's not true globally either. We expect in the neighbourhood of about a million deaths a year from influenza. And we've had two years with COVID and five million deaths. Yes, that's more. It absolutely is more. And I'm not suggesting that it hasn't been more severe.

But I think there's this notation that it's just a totally different thing. I -- in my affidavit I spoke about 1957, and that's -- I'm -- I'm -- I'm looking at Josh, and you're not young enough to remember, but you're -- you're -- you're too young to remember. I remember the Asian flu. You know I was six years old or whatever. I remember the Asian flu,

people talking about the Asian flu.

The Asian flu killed two to four million people globally in a world that had one-third of the population. And that was in the first year. That was in the first wave. And Asian flu, H2N2 came back every year as seasonal flu for the next 10 years proportionately to the disease burden of COVID.

It was a massively greater problem than we've seen. So we've been there before. It's -- I'm not -- I'm not -- I'm not minimizing it. I'm not saying it's not something we should respond to, and we should deal with, but the mindset we've gotten ourselves into that this is some sort of microbiological apocalypse is just not true.

And the level of -- the -- the degree of reaction, our panicked reaction, the way we've adopted measures of dubious effectiveness that come at huge costs, that we've used fear as an agent of public policy incurred -- public health, we've always always tried to give people a balanced view of things.

Fear is not a good strategy for public health, but public health has abandoned that and used fear as a strategy in this case. And maybe worst of all we've done it without any real idea of what it is we're trying to accomplish.

We don't really know where we're going with this, and that's why it's like a merry go round, and we're back where we started with Omicron. And we're just going round and round because we don't really know what we're trying to do. And -- and I've -- I -- I -- yeah, I -- I'm -- that's what I think.

158. Q. And you were asked a number of questions about mathematical modeling of the COVID pandemic and asked about how infection fatality rate estimates played a role in modelling. Can you tell us --

MR. HUNTER: I never asked that.

MR. KITTREDGE: Pardon me?

MR. HUNTER: I never asked that.

MR. KITTREDGE: You discussed the role --

MR. HUNTER: I merely said that the WHO recommended reliance on them. Dr. Schabas indicated he didn't really like mathematical modelling, had concerns about how they underestimated the results of certain countries. I never got into any of the details, so I don't think that's proper re-exam.

MR. KITTREDGE: Okay. I mean, you did mention infection fatality --

MR. HUNTER: No, I didn't

MR. KITTREDGE: Well, you just said that you did, but --

MR. HUNTER: No, I said I talked about mathematical modelling. I never talked about infection fatality rates or any other kind of fatality.

BY MR. KITTREDGE:

159. Q. Okay. Well, I mean, I don't have a transcript in front of me, but can you -- Dr. Schabas, can you tell us a little bit about the accuracy of the information that's fed into the mechanical modeling algorithms?

A. Yeah. No, I think I did make reference. I did talk about how the -- in my testimony I did -- I did make reference to the fact that they -- they -- they were wrong on their input parameters. And I specifically mentioned the infection fatality rate, you know the typical parameters were in the neighbourhood of one percent.

I know when David Fisman testified it was for the House of Commons, he -- he -- he used a number of 1.2 percent that he derived from Spain. You do the simple multiplication by 80 percent of the population, and you come up with these cataclysms of death -- death rates. So it's not only an inaccurate

input, it's a very very simplistic approach.

The WHO meta-analysis, which was conducted by John Ioannidis, and I think it's one of my references that came up with an estimate of, I think it was 2.3 percent based on seroprevalence studies. And Ioannidis himself was of the opinion that the real rate was substantially lower than that. That's around -- around -- I'm sorry, 2.3 percent. He thought it was more like about .15 percent.

And of course, now with -- with the use of immunization people who are immunized have a -- have a -- have a risk of death that's you know roughly an order of magnitude lower than that. So what that means of course is that -- is that -- is that people who -- who -- who are immunized have a -- have a -- have a very low risk of death.

The problem is you know we have to estimate infection fatality rates. And the reason for that is of course that we can't count all of the cases. In fact, as you -- you probably know, and I hope I'm not telling you something that -- that -- that you already know, but I presume you already know actually, that the -- that in fact we never -- we -- we count cases.

We measure cases, people with positive

PCR tests, but we know that that's just the tip of the iceberg of real infections. I think there was pretty good evidence in Canada from early on from the seroprevalence study in -- in British Columbia, for example, and other places that the ratio was -- was roughly 10 percent, maybe a little higher, maybe a little lower of -- of actual infections were detected by the PCR test.

I think that there's reason to think that those numbers have improved, but they're still -- we're still -- I'm very confident we're only catching a very -- a relatively small minority of cases we're testing, and that's inevitable with a disease of this kind where so many infections are either asymptomatic or have -- have very -- have very mild symptoms.

So -- so we -- we -- when we look at infection fatality rate we have to -- we have to estimate it because the case fatality rate of course is quite misleading because we're -- we're purportedly detecting a small portion of the cases.

160. Q. And what is the case fatality rate?

A. Well, the case fatality is the number of reported cases, the number of deaths divided by the number of reported cases, and that's -- that in Canada, I haven't looked at it recently, it's running

in the neighbourhood of one percent. We know that's way too high.

We know the infection fatality rate in Canada, particularly with immunization is -- is -- is maybe one-tenth that. So -- so we're still obviously, obviously dramatically under counting cases.

MR. KITTREDGE: All right. Well, I have no further questions. So thank for your time today.

THE WITNESS: Okay.

MR. KITTREDGE: Do you have anything?

MR. HUNTER: No.

MR. KITTREDGE: Great.

---Whereupon the proceedings concluded 2:46 p.m.

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Dated this 23rd day of December, 2021.

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PER: SANDI BAXTER,

Transcriber

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OPINION

Strictly by the numbers, the coronavirus does not register as a dire global crisis

RICHARD SCHABAS
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This article was published more than 1 year ago. Some information in it may no longer be current.

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Richard Schabas is a retired physician. He was Ontario's chief medical officer of health for 10 years, and was chief of staff at York Central Hospital during the SARS crisis in 2003.

In the three months or so since it started, the new coronavirus and its related COVID-19 disease – which emerged in the Chinese province of Hubei late in 2019 and now numbers more than 110,000 cases around the world – have caused more than 4,000 deaths, mostly in China. As the case numbers grow around the world, including in Canada, where there are now more than 70 cases, people have become concerned that a pandemic is inevitable.

But in the same three months, there have been about three million deaths in China from other causes, and about 14 million deaths worldwide. During the same three-month period, according to Health Canada, there have been almost 10,000 deaths in Canada from tobacco addiction, for instance – and just one from COVID-19.

Is COVID-19 a global crisis? Certainly for people who can't add.

I learned some powerful lessons from SARS in 2003. Maybe the most important one was how important it was to focus on what has happened rather than on what might happen. In other

words: “Just the facts, ma’am."

I pay close attention to the daily situation reports issued by the World Health Organization, particularly the new cases and the new deaths. I pay no attention to the various pundits and talking heads, because they are always wrong.

The information in the WHO reports is not perfect for many reasons, some technical and some political. Deaths are a more reliable measure, but deaths lag weeks behind the real outbreak. However, WHO is the best information we have, and it’s getting more complete and more reliable. And, as was the case with SARS, it paints a compelling picture.

The WHO started issuing daily situation reports on Jan. 21, six weeks ago. Initially, the numbers matched the perceptions: The new cases and new deaths, almost all from Hubei province, increased rapidly. Then, in the first week in February, the rate of new cases peaked at 4,083. Deaths peaked on Feb. 13, at 254. Then the number of daily cases dropped down quickly toward the end of February.

That’s because the Hubei outbreak peaked in late January. Indeed, it’s almost over.

Around the beginning of March, the number of new cases rose again because of outbreaks in South Korea, Italy and Iran. These outbreaks are smaller than the one that happened in Hubei. For the past week, the daily statistics have averaged fewer than 3,000 new cases and about 100 deaths worldwide.

Over the past month, the geography of COVID-19 has changed, but the global numbers have, if anything, become smaller. By the numbers, this is The Incredible Shrinking Pandemic. If we accept that testing capacity and vigilance have increased substantially in the past month, this observation is even more powerful.

A couple of important caveats: First, far more cases are out there than are being reported. This is because many cases have no symptoms and testing capacity has been limited. There have been about 100,000 cases reported to date, but, if we extrapolate from the number of reported deaths and a presumed case-fatality rate of 0.5 per cent, the real number is probably closer to two million – the vast majority mild or asymptomatic.

Likewise, the actual rate of new cases is probably at least 10,000 a day. If these numbers sound large, though, remember that the world is a very big place. From a global perspective, these numbers are very small.

Second, the Hubei outbreak – by far the largest, and a kind of worst-case scenario – appears to be winding down. How bad was it? Well, the number of deaths was comparable to an average influenza season. That's not nothing, but it's not catastrophic, either, and it isn't likely to overwhelm a competent health-care system. Not even close.

The only plausible explanation is that COVID-19 is just not very transmissible among humans. Thank goodness. When it comes to pandemic potential, transmissibility isn't the most important thing – it's the only thing.

When COVID-19 finds a sweet spot – a cruise ship, a South Korean church, an Italian hospital – it can spread efficiently. And the bug has a nasty bite. But these are the exceptions and not the rule. The vast majority of infected people spread the disease to precisely no one.

Could the situation change? Could COVID-19 become a true pandemic with millions of cases and tens of thousands of deaths every day? Of course. The current situation in Italy particularly is concerning. But as the days pass and the global patterns stay the same, this becomes less and less likely.

I am not preaching complacency. This disease is not going away any time soon; we should expect more cases and more local outbreaks. And COVID-19 still has the potential to become a major global health problem, with an overall burden comparable to that of influenza. We need to be vigilant in our surveillance.

Symptomatic travellers from areas with active disease should be tested, as should all patients hospitalized with atypical pneumonia. People infected with COVID-19 need to be isolated, and their close contacts should be monitored.

But we also need to be sensible. Quarantine belongs back in the Middle Ages. Save your masks for robbing banks. Stay calm and carry on. Let's not make our attempted cures worse than the disease.

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Phillip Crawley, Publisher

Update on COVID-19 Projections

Science Advisory and Modelling Consensus Tables

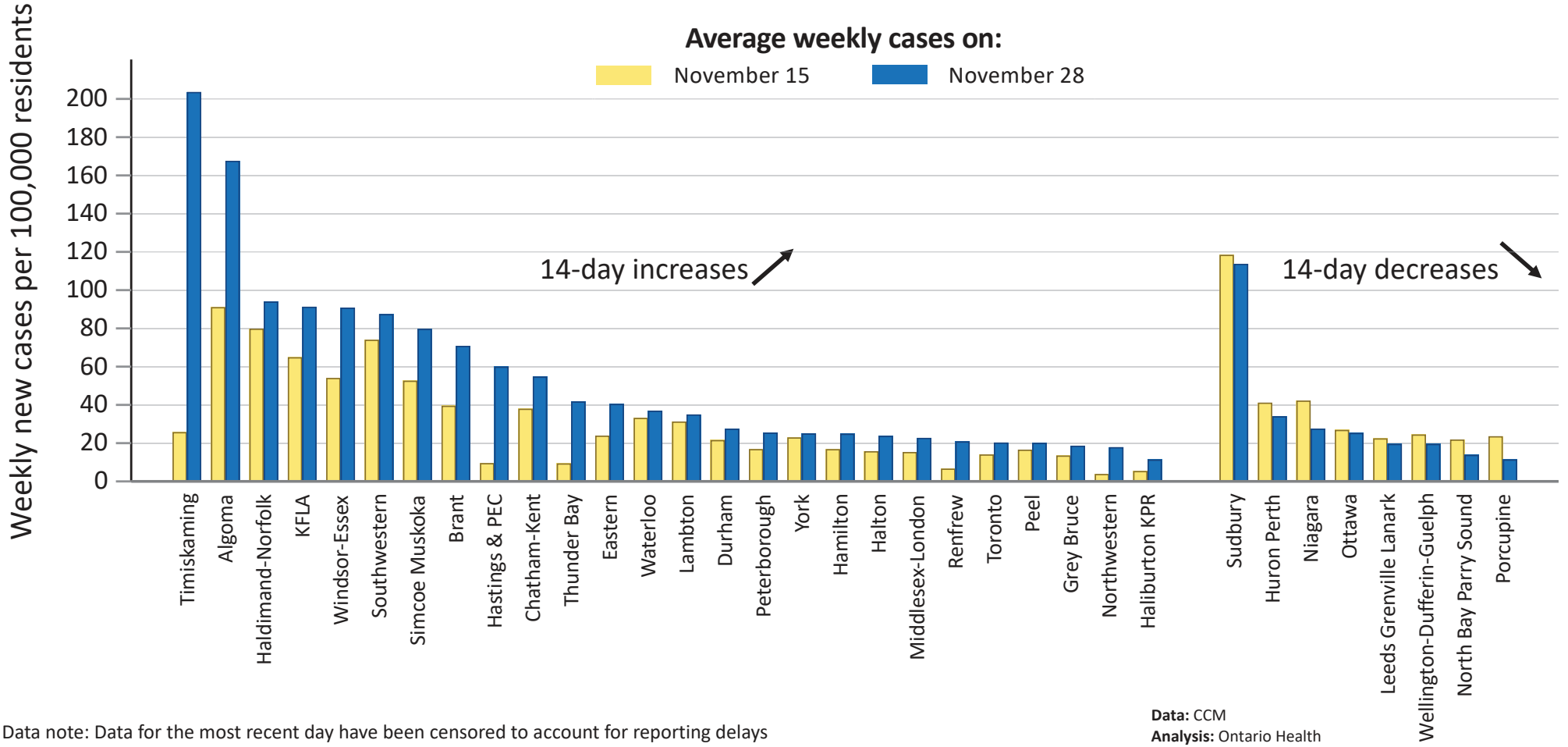
December 7, 2021

Key findings

- COVID-19 cases are rising in most Public Health Units due to the Delta variant. Testing has not increased, but positivity is rising. This is a real rise in cases.
- Vaccine effectiveness in Ontario remains very high but experience in other countries suggests we will need to boost immunity with third doses.
- Even without Omicron, ICU occupancy will likely grow to 250-400 beds in January, putting hospitals under strain again.
- To control cases and the impact on our health system, we need to **increase vaccination** (particularly 5-11 year-olds) and **continue to use public health measures** to reduce transmission now.

- Spread of the new Omicron variant will likely drive COVID-19 cases above current projections.
- In South African data, vaccination appears to protect against serious illness due to Omicron and most hospitalizations are in the unvaccinated. There is likely an increased risk of re-infection even amongst people those who have had COVID-19, emphasizing the importance of vaccination.
- Low global vaccine coverage means that we can expect new variants to arise.

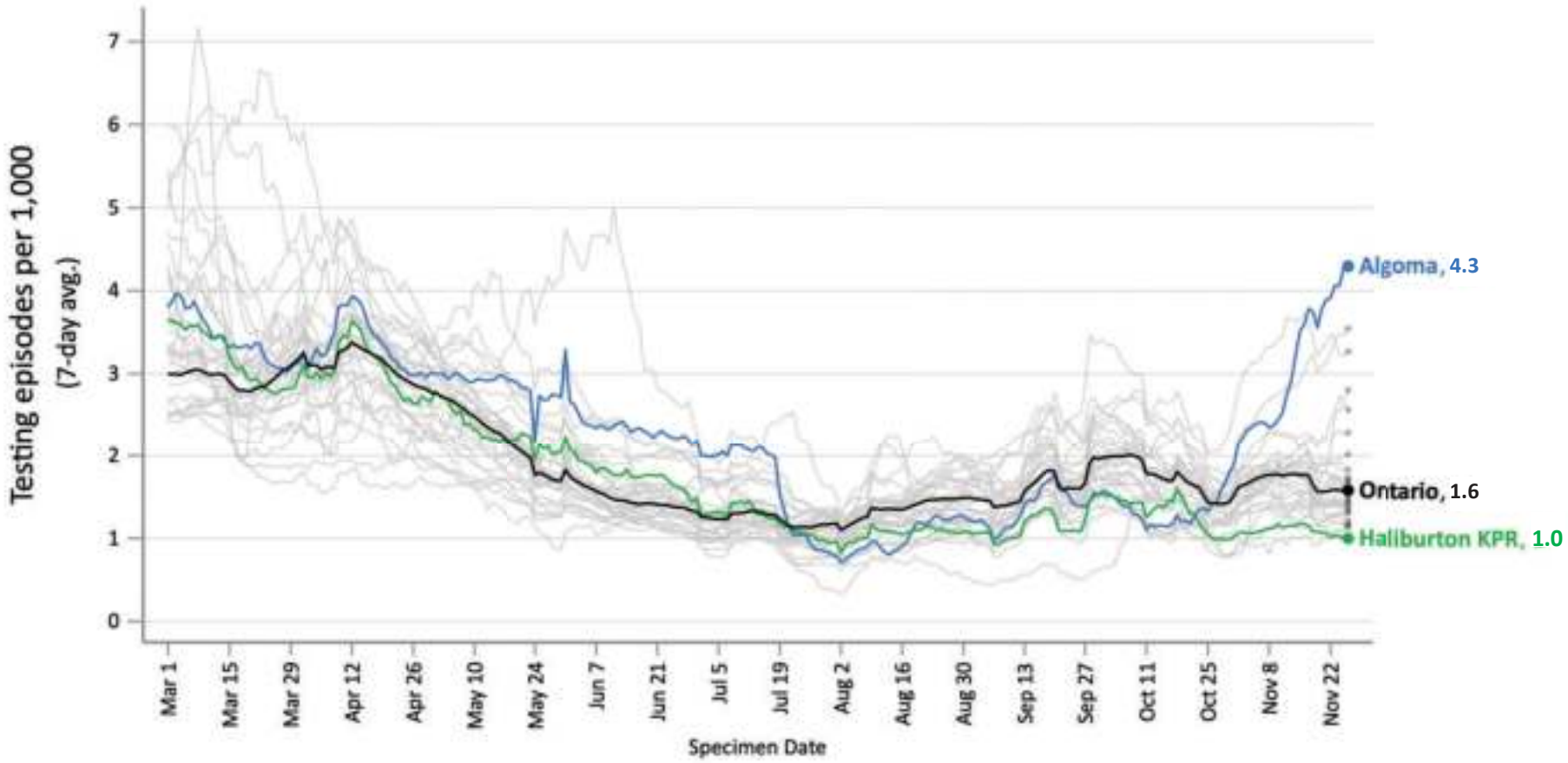
Cases are increasing in most public health units while Delta is the dominant variant



Data note: Data for the most recent day have been censored to account for reporting delays

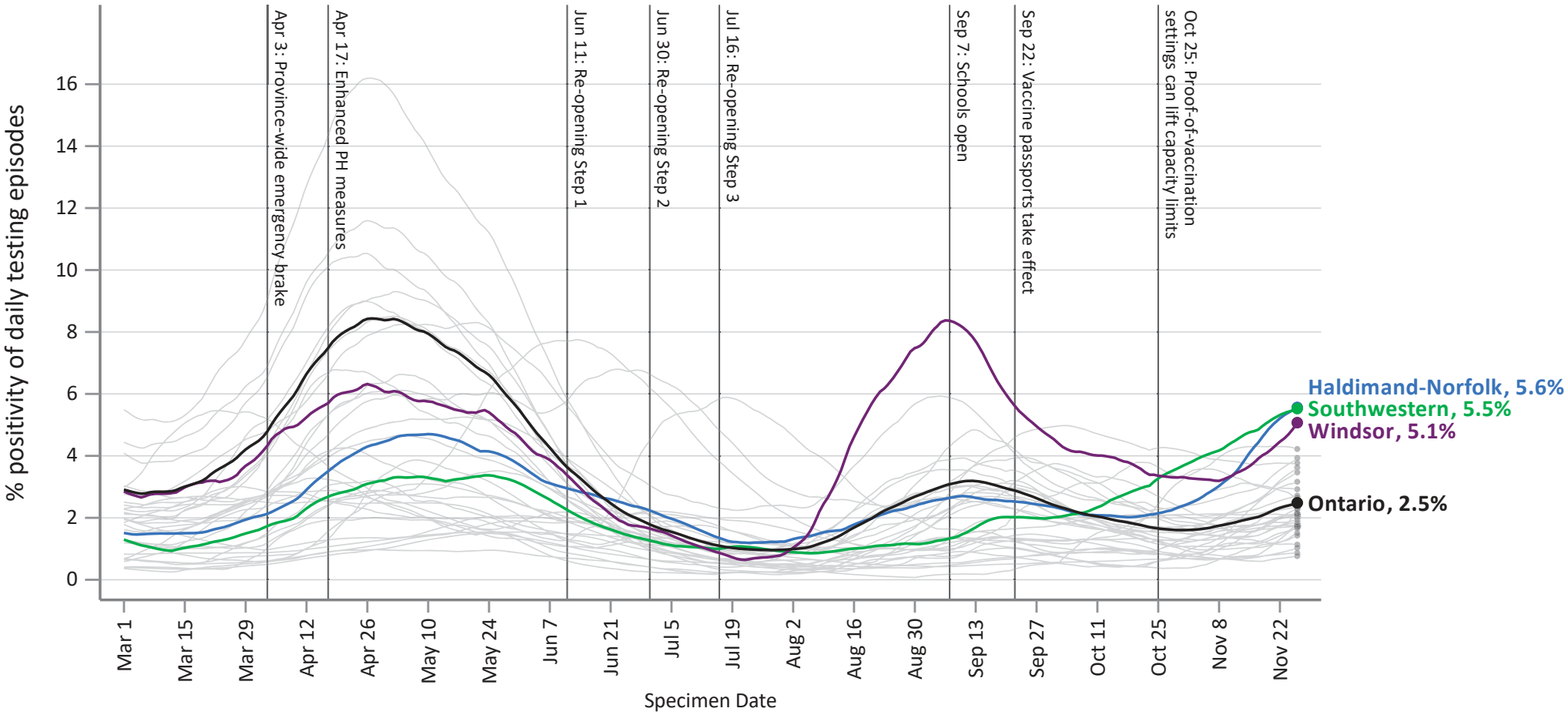
Data: CCM
Analysis: Ontario Health

Testing rates are flat since mid-July



Data: OLIS via SAS VA, data up to November 26
Analysis: Ontario Health

Even with unchanged testing rates, test positivity is rising

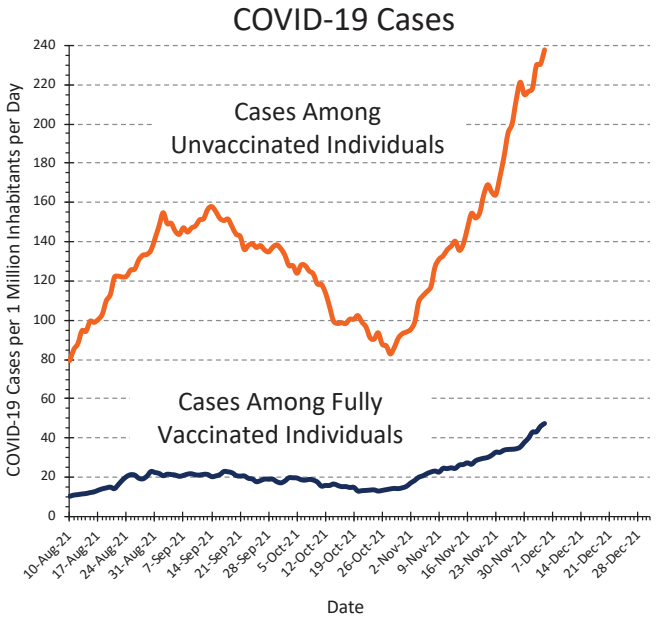


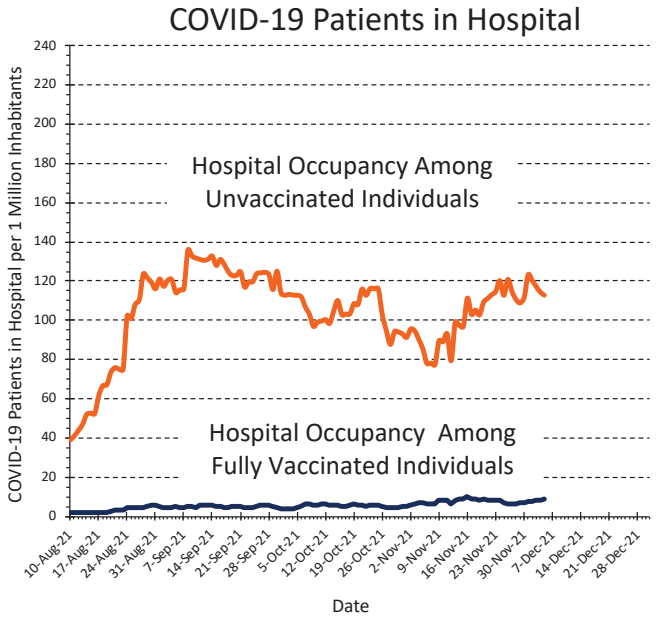
The most recent 3 days have been removed to account for incomplete data. Data are smoothed.

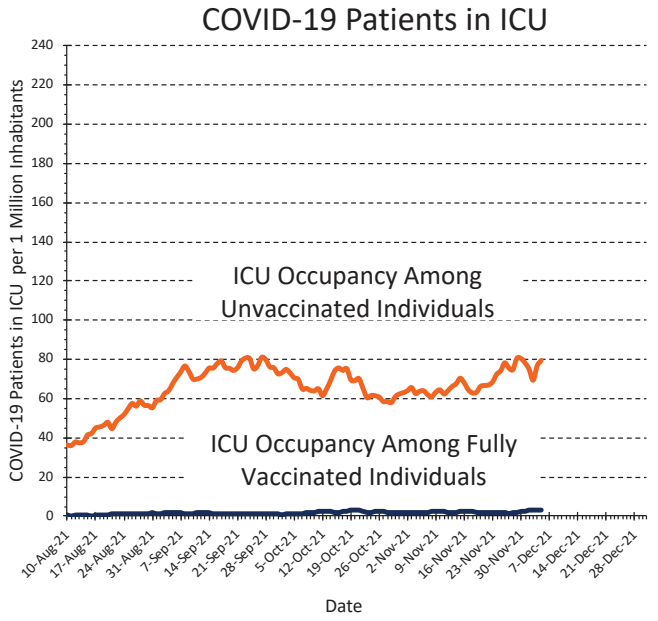
Data: OLIS via SAS VA, data up to November 26
Analysis: Ontario Health

Vaccination continues to be highly effective

Unvaccinated people have a 5-fold higher risk of symptomatic COVID-19 disease, a 13-fold higher risk of being in the hospital and 23-fold higher risk of being in the ICU compared to the fully vaccinated

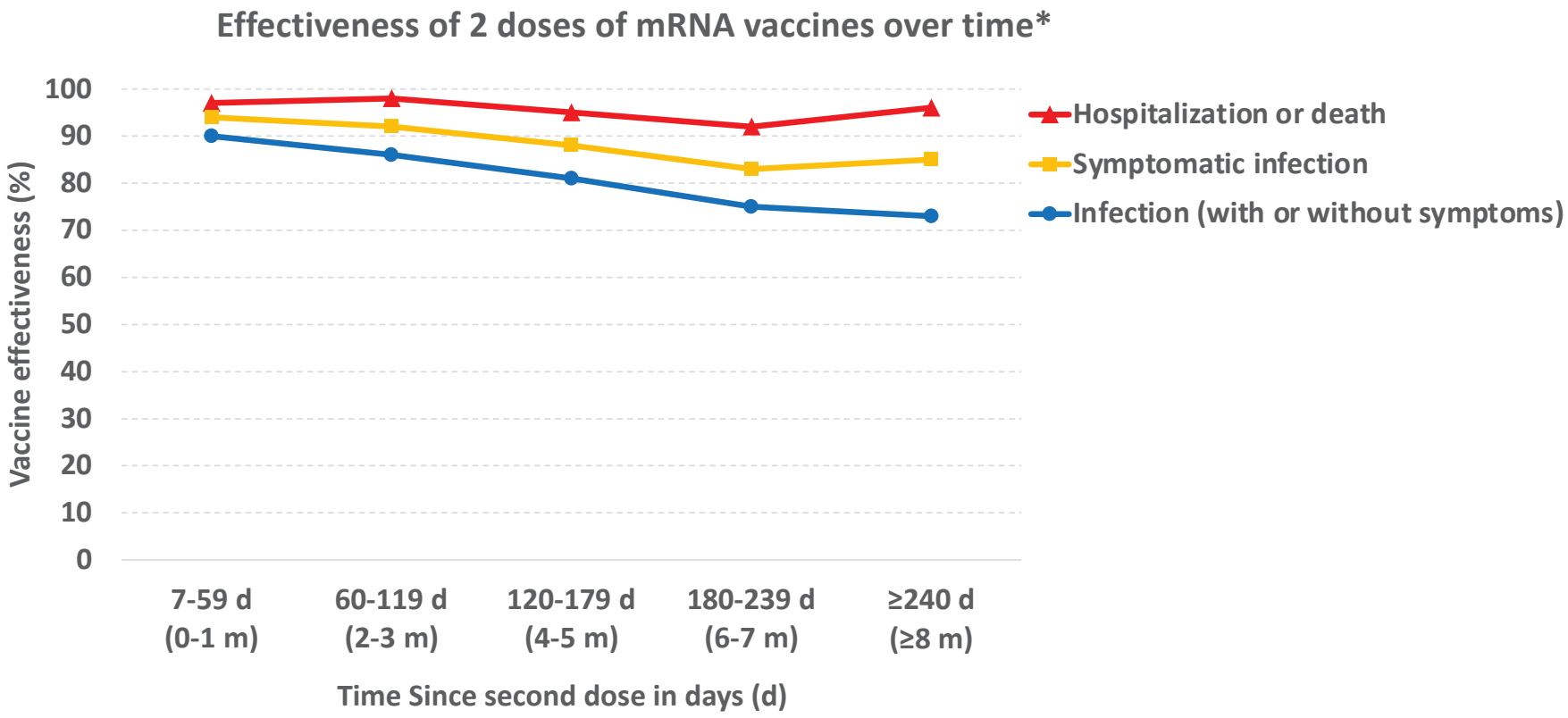






Data: https://data.ontario.ca/ and CCM plus; estimates of patients in hospital and ICU are age standardized
Analysis: Secretariat of the Science Advisory Table (https://covid19-sciencetable.ca/ontario-dashboard/)

Ontario data shows vaccines maintaining high effectiveness



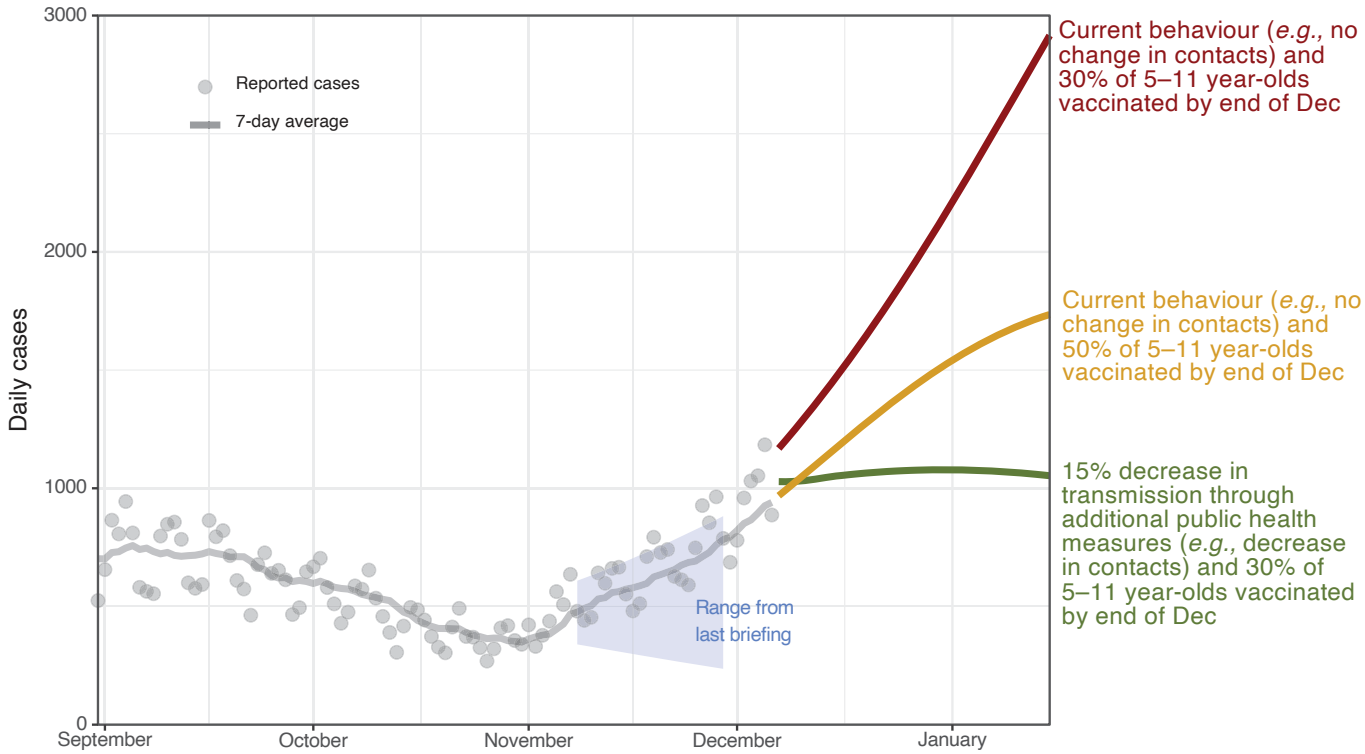
* Ontario, test-negative design, ≥16 years, any SARS-CoV-2 lineage, data to 1 Nov 2021

Data Source and Analysis: ICES

Cases continue to rise substantially, even without Omicron. To flatten the curve, we need to reduce transmission by increasing vaccination and public health measures.

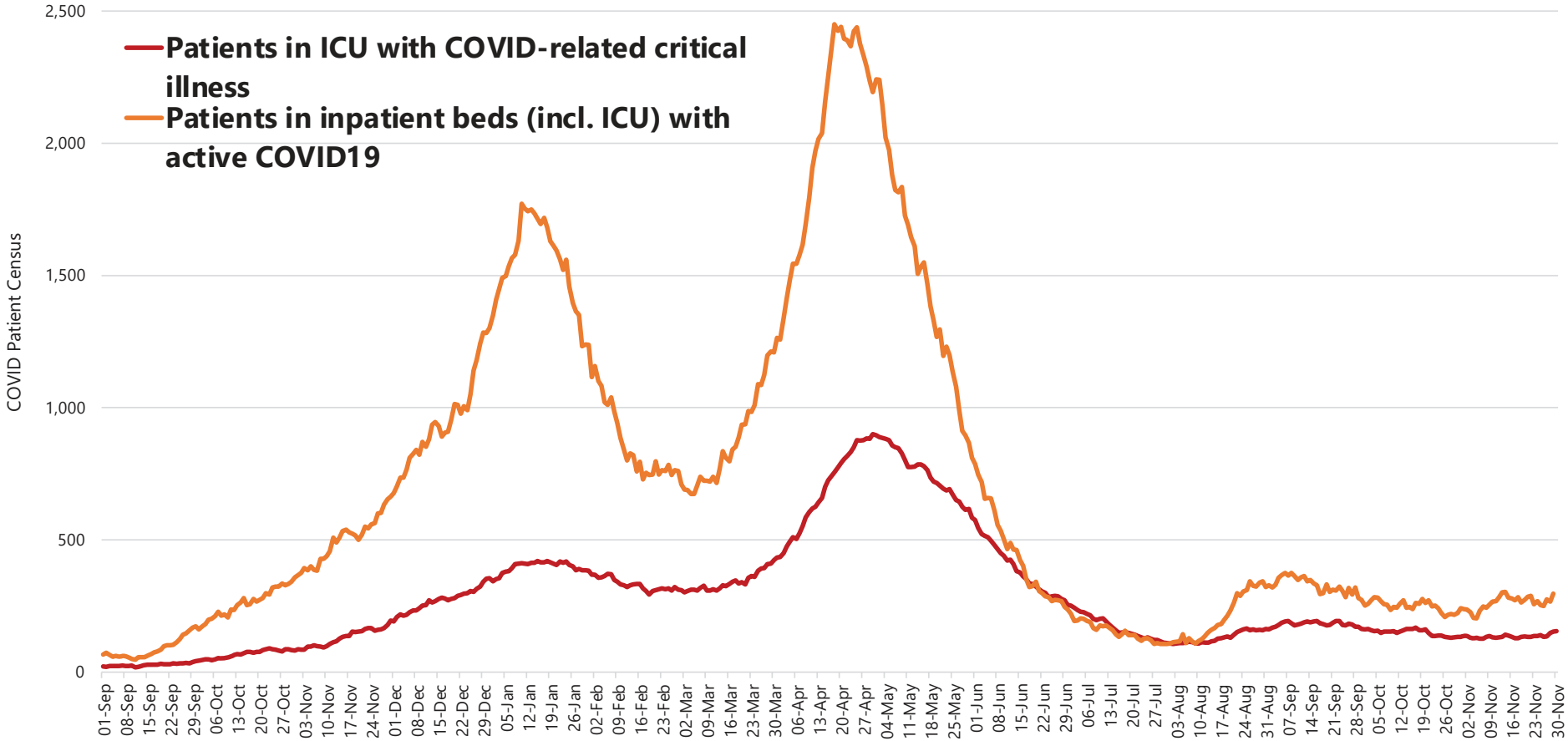
Figure shows predictions based on a consensus across models from 4 scientific teams.

- All scenarios assume continuing current public health measures.
- All scenarios include vaccinating kids 5-11 years of age, but differ on the proportion of kids vaccinated by end of December.
- Different models use different approaches and assumptions.
- Omicron not included in these scenarios, and would likely worsen these projections.



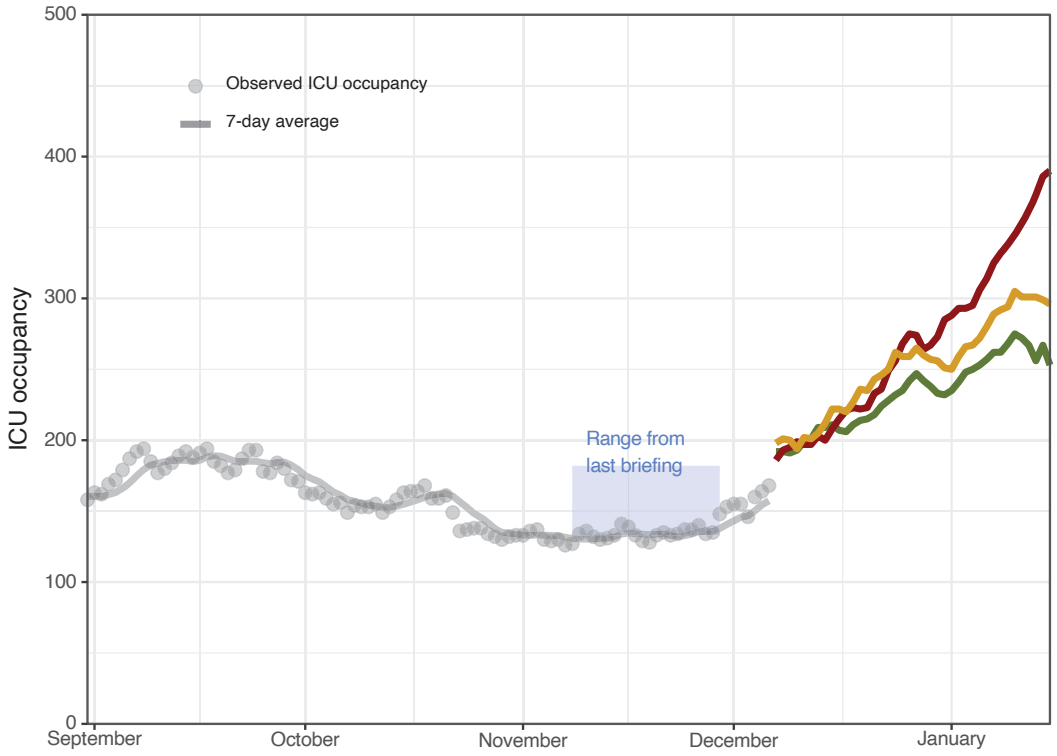
Predictions informed by modeling from McMasterU, PHO, WesternU, YorkU
Data (Observed Cases): covid-19.ontario.ca

COVID-19 hospitalizations and ICU admissions are stable for now



Analysis: Ontario Health

As cases increase, ICU occupancy will also increase, likely exceeding 250 by end of December without accounting for Omicron



Current behaviour (*e.g.*, no change in contacts) and 30% of 5–11 year-olds vaccinated by end of Dec

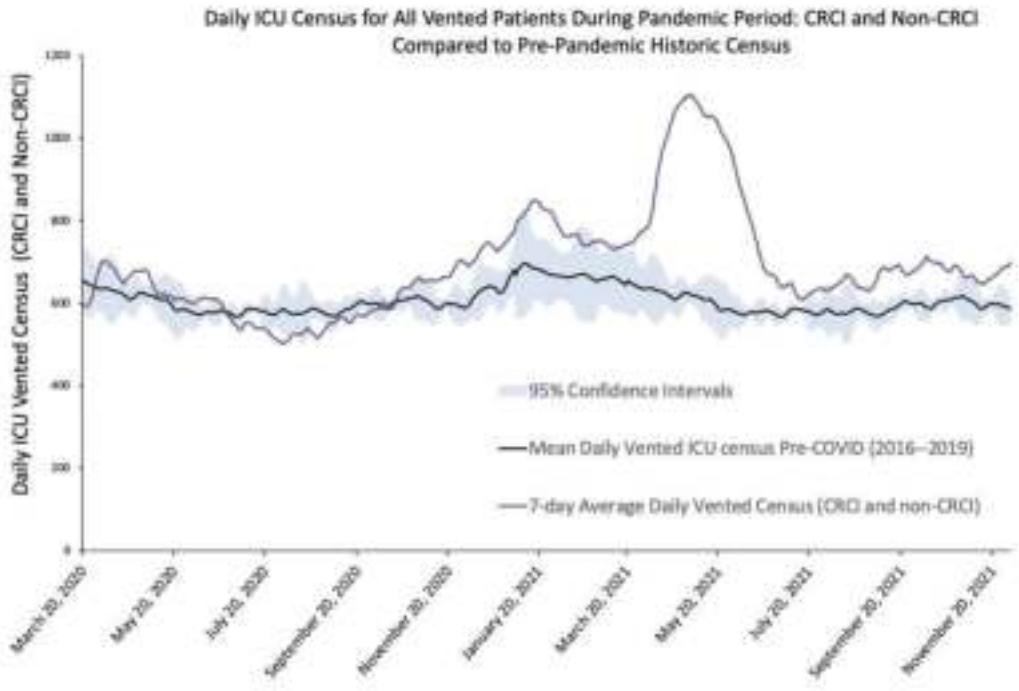
Current behaviour (*e.g.*, no change in contacts) and 50% of 5–11 year-olds vaccinated by end of Dec

15% decrease in transmission through additional public health measures (*e.g.*, decrease in contacts) and 30% of 5–11 year-olds vaccinated by end of Dec

Predictions: COVID-19 ModCollab based on case predictions in previous slide
Data (Observed ICU Occupancy): CCSO

Ontario ICUs have been under unprecedented pressure and will have trouble responding to another surge in patients

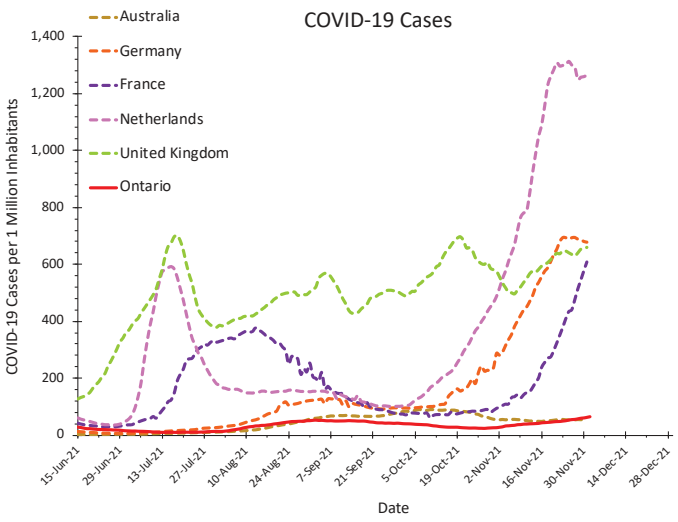
- Due to the need for urgent non-COVID-19 patient care, fewer staff are available to be redeployed and fewer staffed surge spaces are available
- Number of patients on ventilators has been above average for over a year; the pressure on ICUs has not let up
- There is a growing crisis in staffing for critical care patients with significant contribution from health care worker burnout
- Despite new beds and strong management, ICUs will be challenged in responding to any new surge in patients because of staffing constraints

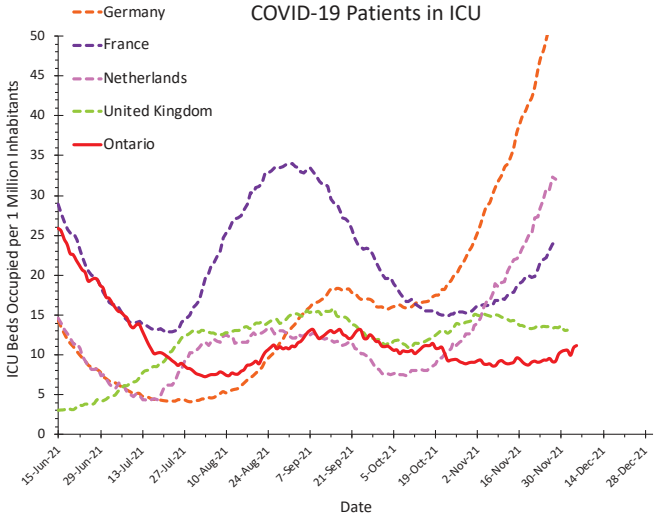


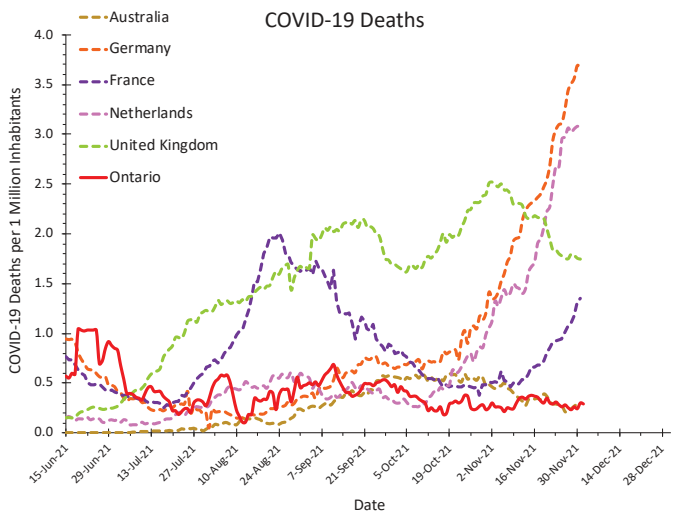
CRCI: COVID-19 related critical illness

Source: Science Briefs of the Ontario COVID-19 Science Advisory Table (https://doi.org/10.47326/ocsat.2021.02.51.1.0)

Rising cases, ICU occupancy, and deaths in European peer jurisdictions show potential risk



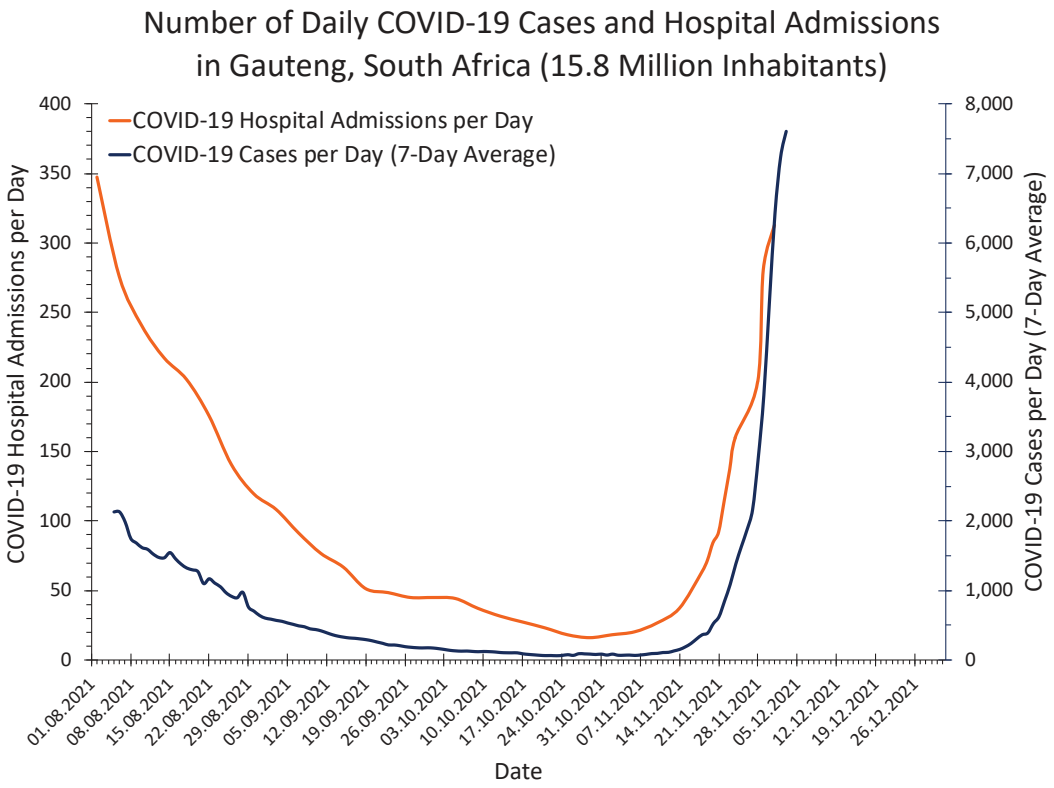




The Ontario Stringency Index (44) is similar to UK (47); the Netherlands are at 56, Australia, France and Germany are at ≥67.
Ontario vaccine coverage (77% of population fully vaccinated) similar to Netherlands and Australia (74%),
higher than remaining peer countries (~68%).

Data: https://data.ontario.ca/ and https://ourworldindata.org/explorers/coronavirus-data-explorer
Analysis: Secretariat of the Science Advisory Table (https://covid19-sciencetable.ca/ontario-dashboard/)

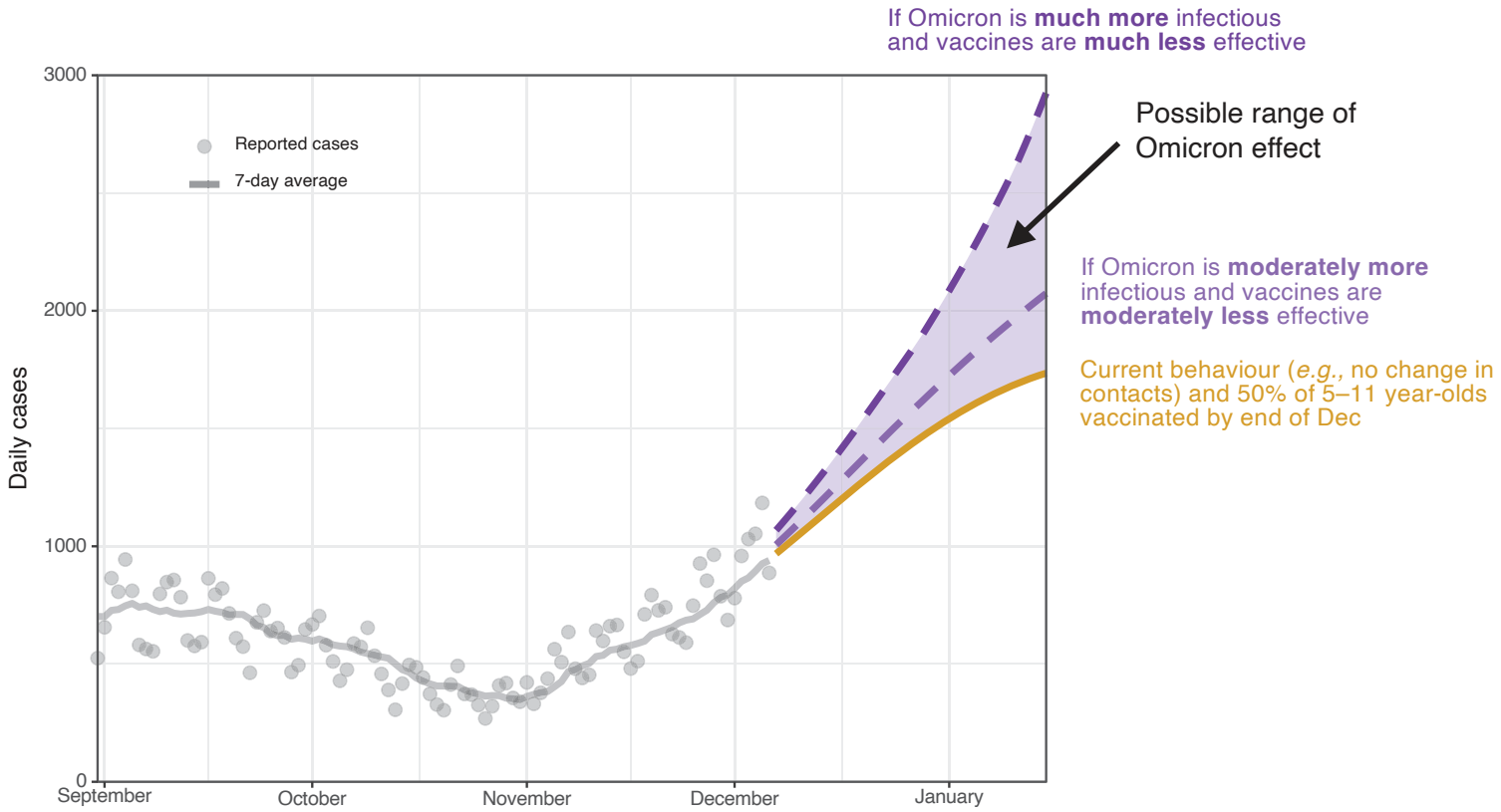
A new variant of concern called Omicron became rapidly dominant and caused a steep increase in cases in the province of Gauteng, South Africa



- Rapid increase in daily cases in Gauteng indicates that Omicron is more transmissible than Delta.
- Previously infected people have an increased risk of reinfection, suggesting partial evasion of immunity by Omicron.
- Hospital and ICU admissions are increasing because of steep increase in cases.
- Early data suggests vaccination protects against hospital admission caused by Omicron. Most patients admitted to hospital are unvaccinated.
- Omicron is transmitted exactly the same way as previous SARS-CoV-2 strains. Public health measures still work.

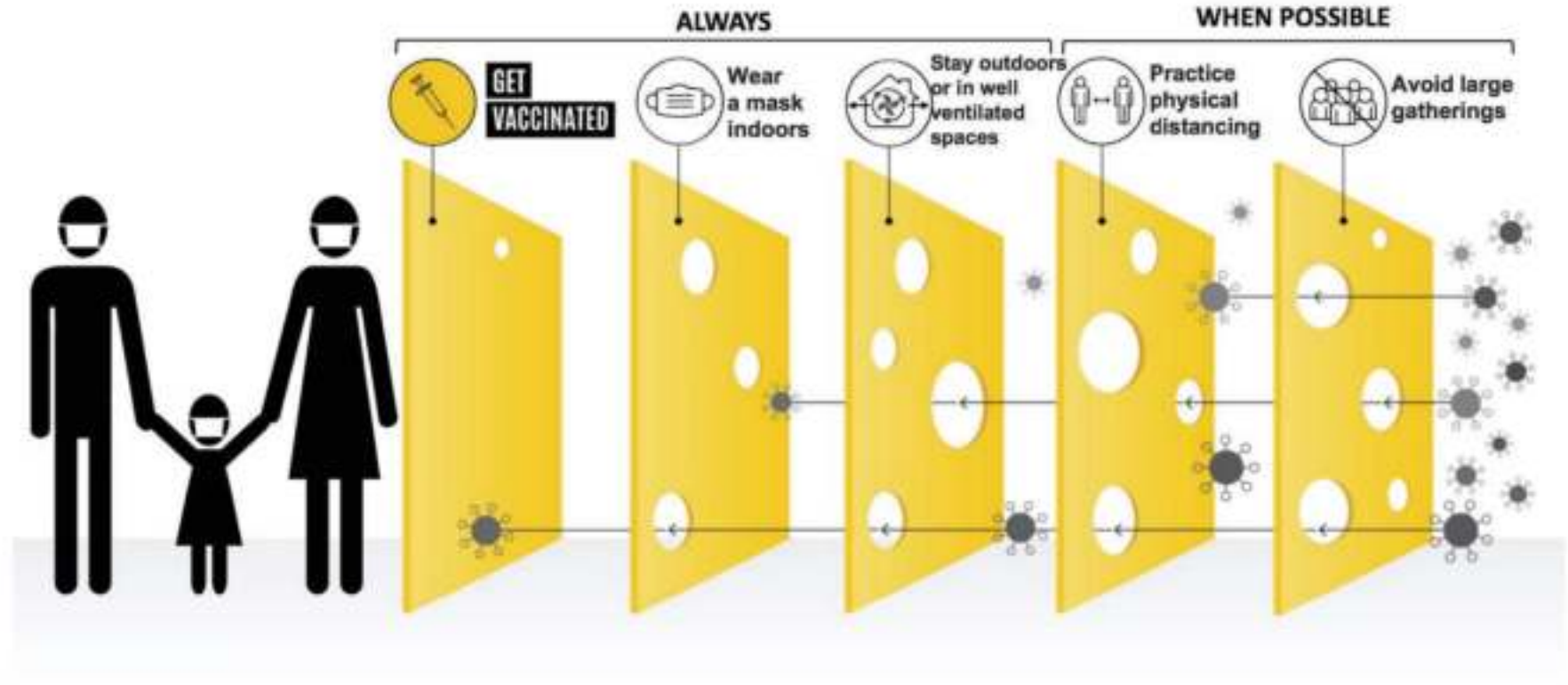
Data: https://www.sacmcepidemicexplorer.co.za/; https://www.nicd.ac.za/ and https://sacoronavirus.co.za/
Analysis: Secretariat of the Science Advisory Table (https://covid19-sciencetable.ca/)

The current situation is very uncertain, but the potential impact of Omicron on cases could be substantial



Predictions informed by modeling from McMasterU, WesternU

Current public health measures are effective against Omicron



Adapted from: https://uihc.org/health-topics/why-swiss-cheese-may-be-key-keeping-you-safe-covid-19

Key findings

- COVID-19 cases are rising in most Public Health Units due to the Delta variant. Testing has not increased, but positivity is rising. This is a real rise in cases.
- Vaccine effectiveness in Ontario remains very high but experience in other countries suggests we will need to boost immunity with third doses.
- Even without Omicron, ICU occupancy will likely grow to 250-400 beds in January, putting hospitals under strain again.
- To control cases and the impact on our health system, we need to **increase vaccination** (particularly 5-11 year-olds) and **continue to use public health measures** to reduce transmission now.

- Spread of the new Omicron variant will likely drive COVID-19 cases above current projections.
- In South African data, vaccination appears to protect against serious illness due to Omicron and most hospitalizations are in the unvaccinated. There is likely an increased risk of re-infection even amongst people those who have had COVID-19, emphasizing the importance of vaccination.
- Low global vaccine coverage means that we can expect new variants to arise.

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- **YorkU**: Jianhong Wu, Michael Glazer, Zack McCarthy

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*Chairs of Scientific Advisory, Evidence Synthesis, and Modelling Consensus Tables

For table membership and profiles, please visit the About and Partners pages on the Science Advisory Table website.

Capacity Limits for Religious Services, Rite or Ceremonies in the Niagara PHU

Date	Outdoor Services	Indoor Services	Drive-in Services
July 22, 2020 to December 25, 2020	100 people.	30% of room capacity.	Drive-in services permitted without any capacity limit.
December 26, 2020 to February 28, 2021	10 people.	10 people.	Drive-in services permitted without any capacity limit.
March 1, 2021 to March 28 , 2021	100 people.	30% of room capacity.	Drive-in services permitted without any capacity limit.
March 29, 2021 to April 2, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	30% of room capacity.	Drive-in services permitted without any capacity limit.
April 3, 2021 to April 18, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	15% of room capacity.	Drive-in services permitted without any capacity limit.
April 19, 2021 to June 10, 2021	10 people.	10 people.	Drive-in services permitted without any capacity limit.
June 11, 2021 to June 29, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	15% of room capacity.	Drive-in services permitted without any capacity limit.
June 30, 2021 to July 15, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	25% of room capacity.	Drive-in services permitted without any capacity limit.
July 16, 2021 to October 24, 2021	No capacity limit, provided participants comply with public health guidance on physical distancing.	The number occupying *any room* must be limited to the number that can maintain physical	Drive-in services permitted without any capacity limit

		distancing in the room.	
October 25, 2021 →	N/A. Capacity limit and physical distancing requirements *removed* from the regulation.	**No capacity limit and no physical distancing requirement *IF*** a location elects to require proof of vaccination (for the duration of the election). **If no election →** capacity *per room* limited to the number that can maintain physical distancing in the room. Participants must comply with public health guidance on physical distancing. Masking is always required indoors, whether an election re: proof of vaccination is made or not.	Drive-in services permitted without any capacity limit.

Capacity Limits for Religious Services, Rite or Ceremonies in the Southwestern PHU

Date	Outdoor Services	Indoor Services	Drive-in Services
July 13, 2020 to December 25, 2020	100 people.	30% of room capacity.	Drive-in services permitted without any capacity limit.
December 26, 2020 to February 15, 2021	10 people.	10 people.	Drive-in services permitted without any capacity limit.

Date	Outdoor Services	Indoor Services	Drive-in Services
February 16, 2021 to March 28, 2021	100 people.	30% of room capacity.	Drive-in services permitted without any capacity limit.
March 29, 2021 to April 2, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	30% of room capacity.	Drive-in services permitted without any capacity limit.
April 3, 2021 to April 18, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	15% of room capacity.	Drive-in services permitted without any capacity limit.
April 19, 2021 to June 10, 2021	10 people.	10 people.	Drive-in services permitted without any capacity limit.
June 11, 2021 to June 29, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	15% of room capacity.	Drive-in services permitted without any capacity limit.
June 30, 2021 to July 15, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	25% of room capacity.	Drive-in services permitted without any capacity limit.

Date	Outdoor Services	Indoor Services	Drive-in Services
July 16, 2021 to October 24, 2021	No capacity limit, provided participants comply with public health guidance on physical distancing.	The number occupying *any room* must be limited to the number that can maintain physical distancing in the room.	Drive-in services permitted without any capacity limit
October 25, 2021 →	N/A. Capacity limit and physical distancing requirements *removed* from the regulation.	**No capacity limit and no physical distancing requirement *IF*** a location elects to require proof of vaccination (for the duration of the election). **If no election →** capacity *per room* limited to the number that can maintain physical distancing in the room. Participants must comply with public health guidance on physical distancing. Masking is always required indoors, whether an election re: proof of vaccination is made or not.	Drive-in services permitted without any capacity limit.

Capacity Limits for Religious Services, Rite or Ceremonies in the Waterloo PHU

Date	Outdoor services	Indoor services	Drive-in services
July 17, 2020 to December 25, 2020	100 people.	30% of room capacity.	Drive-in services permitted without any capacity limit.
December 26, 2020 to February 15, 2021	10 people.	10 people.	Drive-in services permitted without any capacity limit.
February 16, 2021 to March 28 2021	100 people.	30% of room capacity.	Drive-in services permitted without any capacity limit.
March 29, 2021 to April 2, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	30% of room capacity.	Drive-in services permitted without any capacity limit.
April 3, 2021 to April 18, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	15% of room capacity.	Drive-in services permitted without any capacity limit.
April 19, 2021 to June 10, 2021	10 people.	10 people.	Drive-in services permitted without any capacity limit.
June 11, 2021 to June 29, 2021	No capacity limit, provided participants follow masking and	15% of room capacity.	Drive-in services permitted without any capacity limit.

Date	Outdoor services	Indoor services	Drive-in services
	physical distancing health guidance.		
June 30, 2021 to July 15, 2021	No capacity limit, provided participants follow masking and physical distancing health guidance.	15% of room capacity (pursuant to the section 22 order discussed at para. 54).	Drive-in services permitted without any capacity limit.
July 16, 2021 to October 24, 2021	No capacity limit, provided participants comply with public health guidance on physical distancing.	The number occupying *any room* must be limited to the number that can maintain physical distancing in the room.	Drive-in services permitted without any capacity limit
October 25, 2021 →	N/A. Capacity limit and physical distancing requirements *removed* from the regulation.	**No capacity limit and no physical distancing requirement *IF*** a location elects to require proof of vaccination (for the duration of the election). **If no election →** capacity *per room* limited to the number that can maintain physical distancing in the room. Participants must comply with public health guidance on physical distancing. Masking is always required	Drive-in services permitted without any capacity limit.

Date	Outdoor services	Indoor services	Drive-in services
		indoors, whether an election re: proof of vaccination is made or not.	

Considerations for implementing and adjusting public health and social measures in the context of COVID-19

Interim guidance

14 June 2021

World Health Organization

Key Messages

- Public health and social measures (PHSM) have proven critical to limiting transmission of COVID-19 and reducing deaths.
- The decision to introduce, adapt or lift PHSM should be based primarily on a situational assessment of the intensity of transmission and the capacity of the health system to respond, but must also be considered in light of the effects these measures may have on the general welfare of society and individuals.
- Indicators and suggested thresholds are provided to gauge both the intensity of transmission and the capacity of the health system to respond; taken together, these provide a basis for guiding the adjustment of PHSM. Measures are indicative and need to be tailored to local contexts.
- PHSM must be continuously adjusted to the intensity of transmission and capacity of the health system in a country and at sub-national levels.
- When PHSM are adjusted, communities should be fully consulted and engaged before changes are made.
- In settings where robust PHSMs are otherwise in place to control the spread of SARS-CoV-2, allowing the relaxation of some measures for individuals with natural or vaccine-induced immunity may contribute to limiting the economic and social hardship of control measures. Applying such individualized public health measures must take into account a number of ethical and technical considerations.

Introduction

Public health and social measures (PHSMs) are being implemented across the globe to suppress SARS-CoV-2 transmission and reduce mortality and morbidity from COVID-19.1 PHSMs include personal protective measures (e.g. physical distancing, avoiding crowded settings, hand hygiene, respiratory etiquette, mask-wearing); environmental measures (e.g. cleaning, disinfection, ventilation); surveillance and response measures (e.g. testing, genetic sequencing, contact tracing, isolation, and quarantine); physical distancing measures (e.g. regulating the number and flow of people attending gatherings, maintaining distance in public or workplaces, domestic movement restrictions); and international travel-related measures. In this context, it does not include medical countermeasures such as drug administration or vaccination. PHSMs act in concert, and a combination of measures is required to ensure adequate control. Measures should be implemented by the lowest administrative level for which situational assessment is possible and tailored to local settings and conditions.

Several important developments have occurred since the publication of the previous *Considerations for implementing and adjusting public health and social measures in the context of COVID-19*.[2] First, several COVID-19 vaccines have been approved by national regulatory authorities and through WHO Emergency Use Listing (EUL).[3] Vaccination has begun in most countries, bringing the prospect of significantly reducing severe disease and mortality further. Initial observational studies following rollout of vaccines suggest that vaccines may lead to protection against infection and a reduction in transmission,[4–6] which in addition to PHSMs will help control the spread of the virus. Second, four WHO-classified variants of concern (VOCs) have emerged since December 2020,[7,8] which are more transmissible and some of which may cause more severe disease[9] and/or lead to a degree of vaccine escape, requiring potential adjustments to response measures to account for their different characteristics, including their impact on vaccine effectiveness. Several other variants of interest (VOIs) are also being monitored. Finally, more evidence is now available on the effectiveness of a range of individual and community-level measures (outlined in Table 3 below).

Control of SARS-CoV-2 will depend on: i) the prevalence of infection and of circulating variants; ii) the rate of growth or decline in incidence; iii) the types, use of and adherence to control measures in place; iv) the speed with which vaccination occurs; v) the targeting and uptake of the vaccines among high-risk groups; and vi) vaccine effectiveness and natural immunity in the population.[10] National vaccination strategies should prioritize older individuals at highest risk of severe outcomes and health workers, to rapidly reduce mortality and the burden of disease and protect health care services. However, with successful COVID-19 vaccination of older populations following the prioritization of vulnerable groups, the virus may continue to spread among unvaccinated younger population groups.[11] After achieving high vaccination coverage of SAGE priority groups for stage

I and stage II (as outlined in the WHO SAGE Roadmap For Prioritizing Uses of COVID-19 Vaccines in the Context of Limited Supply)[12] across all countries, accelerating vaccination of other priority groups will be required to lower the infection rate, especially in areas of high population density.[13]

While vaccination is underway, PHSMs will need to continue to be implemented, in a tailored and agile way, particularly considering uncertainty in vaccine performance against known and potentially emerging VOCs and limited sequencing capacity to detect variants worldwide.[14] Moreover, significant inequities in global vaccine access mean that, globally, control of disease will continue to rely on PHSM for the foreseeable future, modulated by different levels of vaccination. Implementation of stricter PHSMs, however, needs to be balanced against their socio-economic impacts, especially in settings with high dependence on daily wages and informal economy. Decisions to tighten, loosen, or introduce PHSMs to control COVID-19 must be weighed against the positive and negative impacts these measures have on societies and individuals. Considerations include impacts on health, economy, security, mental health, and psychosocial wellbeing, human rights, food security, socioeconomic disparities, continuity of other public health programmes, treatment and management of medical conditions other than COVID-19 and gender-based violence. Other important considerations include vaccine acceptance and uptake, confidence, trust, motivational elements to get vaccinated and public sentiment and adherence to PHSMs. The overall health and wellbeing of communities should therefore be at the forefront of considerations when deciding on and adjusting PHSMs.

As the pandemic continues to evolve, PHSMs should be regularly reviewed and adjusted according to the local epidemiology. This requires agile decision-making based on ongoing situational assessments at the most local administrative level possible in a coherent and coordinated manner with neighbouring areas at the sub-national and national levels. Such assessments should be based on available data and take a risk/benefit approach considering the local epidemiology, the health system's capacity to respond and other contextual considerations (such as upcoming mass gathering events that may alter transmission or capacity). Epidemiological indicators and their thresholds will depend on a country's testing and surveillance strategies and capacities, data collection capacity, vaccination strategy and coverage and the overall COVID-19 response strategy. In settings where COVID-19 surveillance or testing capacities are limited, it is important to identify and utilize additional indicators on morbidity, mortality and pressure on the health system, such as bed occupancy for both regular hospital beds and ICU beds, to complement available epidemiological data

This document provides guidance to help Member States assess the situation at national and sub-national levels, as well as key recommendations about the implementation of PHSMs. It should be read in conjunction with WHO interim guidance documents on *Critical preparedness, readiness and response actions for COVID-19*[1] *and Considerations for implementing a risk-based approach to international travel in the context of COVID-19*[15,16], which address several other elements of preparedness, readiness and response for COVID-19 beyond PHSMs.

This guidance document is intended for public health and health services decision-makers at all levels at which decisions about tailored PHSMs are made and technical actors involved in relevant sectors (e.g. community engagement, education, social services) supporting or impacted by PHSMs.

The guidance will be updated as our knowledge evolves, in particular in relation to the impact of VOCs on vaccine-induced and natural immunity, the impact of various COVID-19 vaccines on transmission and the impact of PHSMs on VOCs.

Changes from the previous version

This updated guidance provides updates on the assessment framework that drives decision-making for PHSMs, particularly on the type of indicators and the thresholds in different epidemiological settings, and in the context of vaccine roll-out and circulation of VOCs.

It also contains a new section on considerations for individualized public health measures based on a person's SARS-CoV-2 immunity status following COVID-19 vaccination or past infection in the context of contact tracing, international travel, and private social gatherings.

Recently published WHO scientific briefs and guidance were reviewed and key findings were summarised in Table 3. For the evidence on COVID-19 natural immunity, the document is based on the latest WHO scientific brief on *COVID-19 natural immunity.* [17] For the evidence of vaccines effectiveness, the document relies on the following published work: *SAGE working groups Annexes to WHO interim recommendations for use of the COVID-19 vaccine BIBP: GRADE and Evidence to Recommendations*[18]; *Annexes to the interim recommendations for use of theChAdOx1-S [recombinant] vaccine against COVID-19 (AstraZeneca COVID-19 vaccine AZD1222, SII Covishield, SK Bioscience)*[19]; and *Background document on the mRNA-1273 vaccine (Moderna) against COVID-19.*[20]

Transmission scenarios

Knowing the level of transmission is key to assessing the overall COVID-19 situation in a given area and guiding decisions on response activities and tailoring epidemic control measures.[1]

The community transmission (CT) classification is divided into four levels, as shown below. These definitions are abbreviated; details about the transmission classifications can be found in the Annex to this guidance.

- No (active) cases
- Imported / Sporadic cases
- Clusters of cases
- CT1: Low incidence of locally acquired widely dispersed cases detected in the past 14 days
- CT2: Moderate incidence of locally acquired widely dispersed cases detected in the past 14 days
- CT3: High incidence of locally acquired widely dispersed cases in the past 14 days
- CT4: Very high incidence of locally acquired widely dispersed cases in the past 14 days.

The transmission level classification for a geographic area may improve or worsen over time, and different geographic areas within a country will likely experience different levels of transmission concurrently. In settings with limited surveillance and diagnostic capacities, additional indicators – such as influenza-like-illness (ILI) / severe acute respiratory infection (SARI), all-cause excess mortality trends and all-cause hospitalization rates – should be identified to complement information on COVID-19 cases and deaths. These indicators are meant to capture pressure on the health care system and outcomes from undiagnosed COVID-19 cases and can support assessment of local transmission levels when triangulated with COVID-19 epidemiological data.

The process for determining transmission classification is outlined in the Annex to this document.

Health system response capacity

In addition to assessing the level of transmission, it is also necessary to understand the health system response capacity. Depending on whether there is adequate, moderate or limited capacity, the same level of transmission can result in a drastically different situations and require a different degree of PHSMs. For the purpose of this document, 'response capacity' encompasses both health and public health services, including COVID-19 vaccination, and is measured in terms of both the actual ability to deliver services and the performance of those services.

Situational assessment using transmission level and response capacity

Whether or not vaccination has begun, countries should continue to monitor transmission level and take measures as needed.

Where there is a high level of vaccine-acquired immunity among prioritized groups, the epidemiology may start to change. A decoupling may occur between incidence and hospitalization and/or death rates because individuals most prone to hospitalization and death will have been immunized. In this situation, a greater proportion of cases will occur among younger, less vulnerable population groups. Here, recalibrating the incidence thresholds, focusing on hospitalization and ICU rates and analyzing incidence data by age group – as well as assessing the potential caseload of undiagnosed COVID-19 cases – are essential to guiding the adjustment of PHSMs.

As new variants of concern emerge, PHSMs may need to be adapted in the presence of variants that may be more transmissible, cause more severe disease and/or evade immunity induced by vaccination and/or natural infection. All epidemiological and health system indicators should be followed closely and PHSMs applied according to the prevailing epidemiological and health system situation. A greater disease transmissibility (as for all currently identified VOCs) may require keeping PHSMs in place for a longer period or may require intensifying the implementation of existing PHSMs to maintain effects on transmission.

Based on the joint assessment of the transmission scenario and the health system response capacity – which will inform whether and how to adjust PHSMs – a situational level should be assigned to a geographic area (see Table 1). The assessment should rigorously and comprehensively examine quantitative and qualitative information from multiple sources, which should be triangulated to provide an additional reality check on the assessed situational level. The resultant **situational levels should only be considered indicative,** because they may not correspond well to the response required in a specific context and to the COVID-19 control objectives of the country. For example, in a small country with limited capacity or remote areas with limited access to health services, stringent PHSMs may be warranted in the context of a relatively low level of transmission.

Table 1: Situational level assessment matrix using transmission level and response capacity indicators to guide adjustment of PHSMs

	Response capacity*		
Transmission level*	Adequate	Moderate	Limited
No cases	0	0	1
Imported/Sporadic cases	0	1	1
Clusters of cases	1	1	2
• Community - CT1	1	2	2
• Community - CT2	2	2	3
• Community - CT3	2	3	3
• Community - CT4	3	3	4

*Please refer to the Annex for transmission level definitions.

- **Situational Level 0** corresponds to a situation with no known transmission of SARS-CoV-2 in the preceding 28 days. The health system and public health authorities are ready to respond, but there are no significant domestic measures in place and thus no significant restrictions on daily activities.
- **Situational Level 1** is a situation where basic measures are in place to prevent transmission; or if cases are already present, the epidemic is being controlled through effective measures around the cases, with limited and transient localized disruption of social and economic life.
- **Situational Level 2** represents a situation with low community incidence or risk of community transmission beyond clusters. Additional measures may be required to control transmission; however, disruptions to social and economic activities can still be limited. In the context of vaccination, Situational Level 2 may also include areas with moderate levels of community transmission, but limited health service impact given adequate vaccination coverage in at-risk and older age groups.
- **Situational Level 3** is a situation of community transmission with limited additional capacity to respond and a risk of health services becoming overwhelmed. A larger combination of measures may need to be put in place to limit transmission, manage cases, and ensure epidemic control.
- **Situational Level 4** corresponds to an uncontrolled epidemic with limited or no additional health system response capacity available, thus requiring extensive measures to avoid overwhelming of health services and substantial excess morbidity and mortality.

Adjusting public health and social measures

Key principles

Decisions on which measures to implement, lift or strengthen, and the order in which these measures should be implemented, should be based on the following guiding principles:

- Measures with the highest level of acceptability and feasibility and proven effectiveness – and which minimize the negative consequences on health and wellbeing of all members of society and the economy and – should be adopted, using *the* COVID-19 Global Risk Communication and Community Engagement Strategy – interim guidance.21 Acceptability and feasibility should be determined through participatory approaches and shift away from directives and one-way communications. Engaging with the community for this assessment will help to maximize the likelihood of adherence. Effectiveness and potential negative effects of PHSMs should be evaluated through an evidence-based assessment (e.g. literature review, WHO guidance, etc.) and active monitoring of the impact of implemented PHSMs.
- Additional measures should be considered as soon as the situational level rises. Delays in implementation of measures will lead to increased morbidity and mortality and the need for more stringent measures to regain control. In particular, efforts should be made to prevent an intensification in transmission from 'clusters' to 'community transmission.
- When feasible, measures should be adjusted (implemented or lifted) in a controlled, stepwise manner to allow better understanding of the effects of each measure on transmission dynamics.
- Any decision to apply PHSMs must be weighed against the wider impact of the measures on health and well-being (lives lost in the short and long term compared to lives saved by applying PHSMs).

- Public health surveillance data and findings from case and cluster investigations may provide important information on conditions associated with transmission or severity. This is particularly important in the context of circulating VOCs, and potential new variants, since the lifting of PHSMs may provide a better understanding of the transmission and severity characteristics of these variants. Such information may help targeting application or intensification of certain PHSMs without imposing the measures universally on all settings (e.g. settings without these variants).
- Any available information on the level of immunity in the general population – either natural or vaccine-induced – must be taken into consideration when assessing the likely impact on SARS-CoV-2 transmission of lifting PHSMs.
- Protection of vulnerable populations,12 including those clinically at risk for severe disease should be central in the decision to implement, maintain or lift a measure. Vulnerable populations include people aged ≥60 years and/or with comorbidities that increase risk of serious COVID-19 disease; disadvantaged groups such as marginalized populations, vulnerable migrants and refugees; and those in high density/low resource settings and lower income groups. Vulnerable communities and disadvantaged individuals may face immediate challenges in meeting their basic life needs – such as income, shelter and food – when PHSMs are implemented and if implemented without adequate support.22 It is crucial that those essential needs be taken into account when designing different packages of PHSMs and addressed before these packages are implemented to avoid or minimize harm and improve effectiveness. It is critical to safeguard vulnerable and disadvantaged populations by implementing specific measures to support them, mobilizing resources and engaging all relevant sectors and communities to learn about their concerns and receive feedback. This includes ensuring access to health services (using community-based service delivery), which is especially challenging when transportation, clinics/hospitals and other government services are closed or have long waits. Other essential services include supplementary income or food provision; safe places for survivors of and/or those at risk of violence, including gender-based violence; and improvement of infrastructure and safety of public transport (which is used most by workers in vulnerable populations and essential workers) to make it compatible with PHSMs.
- The potential impact of lifting PHSMs on the health and public health systems capacities to rapidly respond to any new increase in cases should be considered. For example:
  - Adequate health system capacities should be in place to detect, test and manage new cases and their contacts.
  - The risk of outbreaks and/or severe disease in settings with vulnerable individuals should be minimized. This requires identifying all major drivers of SARS-CoV-2 transmission (e.g. various types of closed settings such as health care facilities and care homes) in the local context and understanding the vaccination coverage of priority populations in that context, with appropriate measures in place to maximize physical distancing and minimize the risk of outbreaks.
  - Key drivers of transmission in the area under assessment must be well understood using local surveillance data, and measures should be rapidly re-implemented should incidence increase. A particular focus should be on prevention and early detection of potential superspreading events.
- Basic risk mitigation measures aimed at reducing travel-associated exportation, importation and onward transmission of SARS-CoV-2 should always be maintained. For details, please refer to *Considerations for implementing a risk-based approach to international travel in the context of COVID-19*.[15,16]
  - In all cases, international travel should be prioritized for emergencies and humanitarian actions (such as emergency medical flights and medical evacuations); travel of essential personnel (such as emergency responders, providers of public health technical support, and critical personnel in the transport and security sectors such as seafarers); repatriations; and cargo transport for essential supplies such as food, medicines, and fuel.
  - Specific considerations are outlined in this document for the implementation of an individualized approach to quarantine and testing for international travellers with natural or vaccine-acquired immunity.

Community engagement and risk communication strategy

When PHSMs are adjusted, communities should be fully and regularly informed, engaged and enabled before changes are made, to allow them to take ownership of the selected PHSM.[23] It is critical to build and foster trust, especially in contexts where there is little or no involvement of the local population in decision-making. Clear, concise and transparent risk communication, including an evidence-based rationale for adjusting measures, should be developed with communities targeted for PHSM.

In particular:

- Communities should be given recognized roles to provide input and take ownership of when and how PHSMs will be implemented or lifted.
- Communities will be critical to implementing population-wide PHSMs and contributing to the mitigation of the social and economic impact of certain measures (e.g. disrupting availability of food and other needed supplies).
- Civil society organizations, faith-based organizations (FBOs) and volunteers play a critical role in fortifying community services (e.g. provision of food, medicines, mental health and other support services, tests and vaccinations) for those in need (e.g. people who are isolated or quarantined).

- Feedback mechanisms should be established to ensure that any societal impact of changes to PHSMs is quickly identified and reported for action. Communities should lead solutions to ensure adoption of measures that best meet local needs (for example by considering local cultural practices), which can increase the likelihood of adherence.
- Local community-level networks should be leveraged for sustained efforts by building capacity through training of local leaders.
- The infodemic[24] that has emerged from COVID-19 information overload and misinformation should be managed at all stages of the response by providing the right information at the right time to the right people through trusted channels (e.g. community and faith leaders, family doctors and other influential members of society). There should be a monitoring system in place to capture emerging trends (e.g. vaccine confidence and hesitancy, adherence to PHSM) to enable delivery of a targeted communication package.
- A communication and community engagement strategy should be developed before any changes to PHSMs are implemented or adjusted.[3] The strategy should be developed in consultation with relevant stakeholders from government, civil society, FBOs and community groups. Plans should include, at a minimum, behavioural objectives, target audiences, priority channels and a mix of strategies and activities to inform and engage the community.
- The key messages of such plans should cover information important to the community, such as the extent and estimated duration of the measures in place.
- Governments should regularly communicate epidemiological data to the public to further foster trust and increase acceptance and sustained adherence to PHSMs.

Adjustment of PHSMs based on situational assessment

Table 2 provides more detail on the types of domestic measures that may be implemented for each situational level. The measures at each level are only indicative, because some measures may be more or less feasible or appropriate in specific contexts and locations. Note that overall recommendations on international travel can be found in the interim guidance *Considerations for implementing a risk-based approach to international travel in the context of COVID-19*.[15,16]

Measures should be time-bound and regularly re-assessed, at least every two weeks, along with the situational level. The adherence to PHSMs should also be monitored, using sources such as mobility data, and this should be used to further inform future adjustment of PHSMs and the risk communications and community engagement strategy.

At all Situational Levels, individuals should apply personal protective measures such as hand hygiene, physical distancing, respiratory etiquette, staying home if unwell and wearing a mask where appropriate, and environmental measures (e.g. cleaning, disinfection, ventilation). Clear information should be provided to the public about what to do if unwell and whom to contact for advice, testing and/or treatment.

Table 2: Guidance on the implementation of domestic PHSMs for each Situational Level

Situational level	Considerations for implementation of PHSMs by situational level*
Situational level 0: No known transmission of SARS-CoV-2 in the preceding 28 days. The health system and public health authorities are ready to respond, but there are no significant restrictions on daily activities.	Surveillance should ensure that any new case can be detected and managed as early as possible, but there should be no restrictions on daily activities. Authorities may consider implementing the following measures: • Continue strengthening emergency preparedness, readiness and response actions,[1] ensuring adequate stockpiles of medicines and medical equipment and that sufficient staff have been recruited and trained to handle anticipated surges in cases. • Implement or maintain robust surveillance [25] to rapidly detect and investigate suspected SARS-CoV-2 cases and clusters[26] and ensure public health measures such as isolation and supported quarantine[27] are undertaken to reduce onward spread if cases are confirmed and contacts are identified, respectively. • Apply a risk-based approach based on the three steps of risk evaluation, risk mitigation and risk communication to inform the decision to restrict, modify, postpone, cancel or proceed with holding any mass gatherings, including medium and small events. For public gatherings, the risk assessment should be undertaken by local and national public health authorities and event organizers with input from all relevant stakeholders (emergency management, transport, safety and security, etc.). [28,29]
Situational level 1: Basic measures are in place to prevent transmission; or if cases are already present, the epidemic is being controlled through effective measures around the cases, with limited and transient localized disruption to social and economic life.	Specific measures should be taken around cases and/or clusters, and individual measures should be strengthened, with limited impact on social and economic activities. In addition to measures on emergency preparedness, readiness and response actions[1] and surveillance, personal protective measures and risk communications, authorities may consider implementing the following measures: • Emphasis should be placed on case and cluster detection, investigation, and tracing of contacts. • Promote avoidance of the '3 Cs' – Closed spaces, crowded places and close-contact settings. • Apply a risk-based approach based on the three steps of risk evaluation, risk mitigation and risk communication to inform the decision to restrict, modify, postpone, cancel or proceed with holding any mass gatherings, including medium and small events. For public gatherings the risk assessment should be undertaken by local and national public health authorities and event organizers with input from all relevant stakeholders (emergency management, transport, safety and security, etc.). [28,29] Daily activities and services, such as educational settings[30], businesses[31] and leisure/tourism can remain open with precautionary measures in place to limit the risk of spread. • Put in place measures to protect the most vulnerable, particularly ensuring that there are appropriate measures in place in long-term care[32] and other residential facilities.
Situational level 2: Low community incidence or a risk of community transmission beyond clusters. Additional measures with respect to Situational level 1 may be required to control transmission; however, disruptions to social and economic activities can still be limited	Measures should be applied to limit the number of physical encounters with others outside of the household, while ensuring services can remain open with precautionary measures in place. A wider range of PHSMs may be required to control transmission. In addition to measures on emergency preparedness and response and surveillance, personal protective measures and risk communications, authorities may consider implementing the following measures: • Education settings remain open with precautionary measures in place. • Businesses remain open, with precautionary measures in place, with teleworking encouraged as much as possible. • Improve local transport infrastructure to comply with PHSMs (improve availability, frequency, extension of schedules, etc.). • Apply a risk-based approach based on the three steps of risk evaluation, risk mitigation and risk communication to inform the decision to restrict, modify, postpone, cancel or proceed with holding any mass gatherings, including medium and small events. For public gatherings the risk assessment should be undertaken by local and national public health authorities and event organizers with input from all relevant stakeholders (emergency management, transport, safety and security, etc.) [28,29]. • If required, place further emphasis on protecting the most clinically vulnerable, through strict application of infection prevention and control measures, heightened surveillance and managing visits in long-term care and other residential facilities. • If contact tracing is overwhelmed, consider prioritization of contact tracing (see *Contact tracing in the context of COVID-19.*[33]).

Situational level	Considerations for implementation of PHSMs by situational level*
Situational level 3: Community transmission with limited additional capacity to respond and a risk of health services becoming overwhelmed. A larger combination of control measures may need to be put in place to limit transmission, manage cases, and ensure epidemic control.	Strengthening of all PHSMs is needed to avoid more stringent restrictions on movement and other related measures applied under level 4. All individuals should reduce their social contacts, and some activities may need to close while allowing for essential services, particularly schools, to remain open. In settings with high dependence on daily wages and informal economy, mitigation of the potential socio-economic costs of strengthening PHSMs needs to be planned properly in advance. In addition to measures on emergency preparedness and response and surveillance, personal protective measures and risk communications, authorities may consider implementing the following measures: • Adapt the functioning of businesses to minimize COVID-19 risk, including through remote working, modified service provision, or closure where necessary. • Improve local transport infrastructure to comply with PHSMs (improve availability, frequency, extension of schedules, etc.). • Consider limiting in-person university teaching, and institute e-learning. • Childcare services and primary and secondary schools should remain open with adequate safety and surveillance measures in place as long as the local context allows. Continuity of education for children for their overall well-being, health and safety should be at the forefront of all relevant considerations and decisions. • Due to risk of further transmission in an already high transmission level with limited healthcare resources, all PHSMs may be best applied without relaxing any measures according to individuals' immune status. See section below on "individualized public health measures". • Apply a risk-based approach based on the three steps of risk evaluation, risk mitigation and risk communication to inform the decision to restrict, modify, postpone, cancel or proceed with holding any mass gatherings, including medium and small events. For public gatherings the risk assessment should be undertaken by local and national public health authorities and event organizers with input from stakeholders (emergency management, transport, safety and security, etc.) [28,29]. • Quantify the needs in advance and provide the necessary socio-economic support for low-income individuals and households and those at risk of falling into poverty, ensuring no-one is left behind. Socioeconomic recovery for these vulnerable groups and the general population should also be prepared for in advance and resources secured to the extent possible.
Situational level 4: An uncontrolled epidemic with limited or no additional health system response capacity available, thus requiring extensive measures to avoid overwhelming of health services and substantial excess morbidity and mortality.	Reducing transmission in the community will be challenging, and stringent movement restrictions and related measures will need to be put in place to significantly reduce the number of in-person encounters. Such measures should be geographically limited to where they are needed and be time-bound and aimed to be as short as reasonably possible. In addition to measures on emergency preparedness and response and surveillance, personal protective measures and risk communications, authorities may consider implementing the following measures: • All individuals, including fully vaccinated, partially vaccinated and recovered individuals, should stay at home and limit physical contact with people outside the household. • Essential workers will need to continue activities, with maximum support and safety measures in place. Improve local transport infrastructure to comply with PHSMs (improve availability, frequency, extension of schedules, add private transport to public transport infrastructure, etc.). • Close non-essential businesses, and institute remote working. • Consider all options for continuity of in-person learning. If not possible, limit in-person contact. Options may include in-person or blended learning strategies that strictly limit the number of people physically on site (exceptions would include children of essential workers and their teachers) and remote learning. The closure of educational facilities should only be considered when there are no other alternatives. • All long-term care and other residential facilities should consider strict measures to limit the risk of infection, up to and including temporary suspension of in-person visits. • Cancel or postpone any mass gatherings. • Quantify needs (in advance) and provide necessary socio-economic support for low-income individuals and households and those at risk of falling into poverty, ensuring no-one is left behind. Carefully monitor the impact of strict PHSMs on the livelihoods and well-being of these vulnerable groups. Socio-economic recovery for these vulnerable groups and the general population should also be planned in advance and resources secured to the extent possible.

*The specific measures implemented at each level will need to be carefully considered based on the guiding principles outlined above. The measures at each level are only indicative, since some measures may be more or less feasible or appropriate in specific contexts and locations

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Considerations for the implementation of individualized public health measures

In settings where robust PHSMs are otherwise in place to control the spread of SARS-CoV-2, allowing the relaxation of some measures for some individuals may contribute to limiting the economic and social hardship of control measures. The differential "personal protective measures" for immune (fully vaccinated or recovered from infection) versus non-immune individuals will be referred to as **individualized public health measures**.

Applying **individualized public health measure** recommendations based on someone's immunity status must be carefully considered in the light of a number of aspects, including: the level of transmission of SARS-CoV-2; the evidence around the impact of various COVID-19 vaccines in preventing transmission; effectiveness against disease and duration of vaccine-induced immunity; the level and duration of protection conferred by natural immunity; the COVID-19 response strategy and risk tolerance of the implementing country; the potential circulation of immune-escape VOCs; and important ethical considerations, particularly given current limited availability of vaccines worldwide and existing inequities in vaccine availability across and within countries and population groups.

Ethical considerations

Details on the ethical considerations related to individualized public health measures in the context of COVID-19 are provided in other WHO publications.[17,34] Key considerations can be found below:

- **Proportionate and inclusive approach:** Before implementing individualized public health measures, governments or other competent authorities should, as much as possible, reduce barriers to vaccination; consider measures that least infringe of the rights and liberties of non-vaccinated individuals; and consider options for non-vaccinated individuals such as the results of reliable negative COVID-19 tests and making tests accessible to all (e.g. free testing once a week) or issuing immunity certificates for recovered individuals. This may help ensure that measures for non-vaccinated individuals are proportionate and as socially inclusive (defined here as removing or reducing barriers that prevent people from participating in civil, social and economic life) as possible.
- **Exemptions:** A system of recording and verifying exemptions from COVID-19 vaccination based on medical reasons, or other reasons provided for in law or relevant regulations, should be established if vaccination certificates are introduced to impose individualized public health measures on vaccinated and non-vaccinated individuals. Careful attention should be paid to ensuring that the collection, storage and use of such data are limited to scientifically and ethically justified purposes compatible with sustained public trust and confidence.

Technical considerations for individualized public health measures

Although vaccinated individuals or individuals with documented past infection may still be able to be (re-)infected and transmit the infection, growing evidence (see Table 3) suggests that the risk of infectiousness is substantially lowered. On this basis, countries may decide to relax quarantine requirements for individuals with evidence of immunity, since the burden of quarantine may outweigh the risk of transmission. However, if circulation of variant(s) able to evade established immunity becomes evident, such relaxation may not be advisable, because variants could still be transmitted efficiently.

The lower risk of infection following full COVID-19 vaccination likely varies by COVID-19 vaccine; given the paucity of data for all available COVID-19 vaccines, WHO recommends countries adopt a risk-based approach. This should also consider the local epidemiological context, and the context of the exposure (risk assessment of exposure), as some settings like health-care facilities may pose a higher risk, leading to classification of health-care workers as high-risk contacts.[5]

Table 3 below summarizes the main technical considerations around individualized public health measures in the context of vaccine-induced and natural immunity. The table was drafted based on evidence available as of 14 June 2021.

Table 3: Review of existing evidence on SARS-CoV-2 past infection, COVID-19 vaccines and variants of concern, and main technical considerations for individualized public health measures in the context of vaccine-induced and natural immunity

Element	Considerations
SARS-CoV-2 infection	• Natural immunity confers high levels of protection against reinfection, with estimates varying from around 81% to close to 100% protection in people younger than 65 years or among health workers during follow up of at least five to seven months.[6,35–37] Protection against reinfection appears to vary by age group and is lower (approximately 47%) among people aged 65 years and older.[35,38] • Evidence of immunity to SARS-CoV-2 is most commonly determined by measuring antibodies in sera. Within four weeks following infection, 90-99% of individuals infected with the SARS-CoV-2 virus develop detectable neutralizing antibodies.[14,39,40] • While correlates of protection are yet to be fully established, currently the presence of neutralizing antibodies is the best indication for protection against re-infection. How long protection lasts remains unclear and may differ depending on disease severity. Protection after infection with common cold coronaviruses, which often cause mild disease, is highly transient; and for SARS-CoV-2, there is evidence that immunological memory is 6-8 months.[41,42] • While protection is high, natural immunity does not provide 100% sterilizing immunity. Individuals who have natural immunity are still have a potential risk of reinfection and may be infectious.[43]
COVID-19 vaccination	• Different vaccine products may differ in their effectiveness, including against VOCs. The risk of onward transmission and duration of protection also may vary. Waning immunity and vaccine effectiveness over time will need to be documented as vaccination rollout progresses. • At the time of publication, in human clinical trials, all WHO Emergency Use Listed (EUL) vaccines have demonstrated efficacy (63% to 95%) against symptomatic, laboratory-confirmed COVID-19.[20,44–46] • In human clinical trials, all vaccines that currently have WHO EUL (as of the time of publication) have demonstrated high efficacy (over 89%) against severe COVID-19, indicating that the chance of developing severe disease in a fully vaccinated person is very low for younger and middle-aged adults and very low to moderate for older adults or other persons with underlying risk factors.[47,48] • Results from post-introduction observational studies have reported vaccine effectiveness estimates ranging from 64% to over 97%. The duration of protection remains unclear, because vaccine effectiveness has been measured only shortly after the introduction of the vaccines; but a recent eight-month follow up of recipients of one vaccine reported a durable response to the studied vaccine.[49] • One studied vaccine prevented infection for 70% of individuals at 21 days after a single dose and 85% of individuals at 7 days after two doses, providing real-world estimates of vaccine protection against infection.[50] • There is emerging evidence that vaccination substantially reduces the risk of onward transmission of SARS-CoV-2 to susceptible contacts.[51,52] • There is also emerging evidence that use of COVID-19 vaccines at the population level has a positive impact on the disease dynamics in the population.[53,54]
Variants of concern (VOCs) (as of the time of publication)	• Some SARS-CoV-2 variants, including all currently identified VOCs (i.e. Alpha [B.1.1.7], Beta [B.1.351], Gamma [P.1] and Delta [B.1.671.2], exhibit increased transmissibility as compared to previously/co-circulating variants.[8] This primarily influences transmission levels and the potential need to keep general PHSMs in place for longer or at a higher intensity, rather than specifically influencing considerations for individualized public health measures. • Evidence of increased resistance of some SARS-CoV-2 variants (including all four VOCs) to natural or vaccine-induced neutralizing antibodies has been reported, raising the concern that reinfection after natural infection or breakthrough infection after vaccination may increase in settings where such VOCs circulate widely.[8,55] • The convergent evolution of mutations thought to be associated with higher transmissibility or immune escape (e.g. N501Y, E484K) in VOCs highlights the fact that variants will likely continue to emerge under selective pressures such as population immunity.[56]

Note: references cited do not represent an exhaustive list of all relevant references on these topics

Implementation of individualized public health measures based on available evidence (as of 14 June 2021)

After taking into consideration ethical and technical considerations and transmission levels, countries may consider relaxing some measures for individuals meeting either of the following criteria:

- completion of full vaccination with one of the WHO EUL vaccines or approved by a stringent regulatory authority (and at least two weeks after completion of vaccination)
- SARS-CoV-2 infection confirmed by RT-PCR within the past 6 months and no longer infectious as per WHO's Criteria for releasing COVID-19 patients from isolation.[55]

Depending on the transmission level, below are some options for individualized measures in:

- waiving quarantine following close contact with a confirmed COVID-19 case
- waiving testing and/or quarantine requirements in the context of international travel
- allowing congregating in indoor private settings with other fully vaccinated or recovered individuals without wearing masks and without applying physical distancing.

Decision makers should apply a risk-based approach when considering the use of masks for the general public regardless of vaccination or natural immunity status. In areas of known or suspected community or cluster SARS-CoV-2 transmission: WHO advises that the general public should wear a non-medical mask in indoor (e.g. shops, shared workplaces, schools) or outdoor settings where physical distancing of at least 1 metre cannot be maintained. If indoors, unless ventilation has been be assessed to be adequate, WHO advises that the general public should wear a non-medical mask, regardless of whether physical distancing of at least 1 metre can be maintained.[56] As part of the risk-based approach, local authorities may consider allowing congregation of fully vaccinated or recovered individuals without wearing masks and without applying physical distancing in indoor **private** settings in regions with low SARS-CoV-2 incidence (<20/100000 population). **In community or health care settings, where measures such as mask wearing are recommended, they should continue to apply to everyone.**

Figure 1 provides guidance for a risk-based approach to individualized public health measures, which takes into consideration both risk to individuals and to the population. This figure, which is based on the evidence in Table 3, shows that as the transmission level increases (left column), the risk of infection for individuals and the overall risk of additional infections and onward transmissions increases (arrows in columns 2-5), as does the overall risk of additional cases of severe disease arrows in columns 6-9. The differing gradients of the arrows in columns 2-9 further show that the degree of increased risk varies according to an individuals' age and immunity status.

The resulting options are shown in the column labelled "options for individualized public health measures". At the lowest levels of transmission, individualized measures (waiving quarantine in the context of close contact, waiving quarantine and/or testing in the context of domestic and international travel, freely congregating in private settings with other fully vaccinated or recovered individuals without wearing masks or physical distancing) can be considered for all immune individuals. At the highest transmission levels, measures should be retained for all individuals, irrespective of immune status. At intermediate levels of transmission, there is a disproportionately high risk of transmission and severe disease in recovered individuals ≥60 and/or with underlying risk factors, and authorities may consequently wish to consider retaining measures for this group. Considerations may need to be further tailored to local contexts. For example, in situations with no known domestic circulation, a full quarantine may be required for all travellers, regardless of immunity status, to control the residual risk of importation. Further, in situations where healthcare capacity is extremely limited, measures may need to be retained at relatively lower levels of transmission to avoid overburdening the health care system with any additional cases.

Figure 1. Options for Individualized Public Health Measures

Exposure risk (transmission level)	Factors involved in informing options for individualized public health measures								Options for individualized public health measures	Factors that could increase the risk
	Fully vaccinated ≥60* and/or with underlying risk factors	Fully vaccinated <60	Recovered individuals ≥60 and/or with underlying risk factors	Recovered individuals < 60	Fully vaccinated ≥60 and/or with underlying risk factors	Fully vaccinated <60	Recovered individuals ≥60 and/or with underlying risk factors	Recovered individuals <60		
	Infection risk / Net transmission Risk				Net risk of severe disease					
Lower ↓ Higher	↓	↓	↓	↓	↓	↓	↓	↓	Relax measures for all immune individuals† ↓ Consider retaining measures for recovered individuals ≥60 and/or with underlying risk factors‡ ↓ Retain measures for all individuals§	Presence of immune escape variants

* Most transmission evidence uses an age category of 65 and older, while most severity evidence references persons 60 years and older; for consistency, the more conservative grouping of 60 years and older is retained in this table.

† Relaxing of restrictions and preventive measures (waiving quarantine in the context of close contact, waiving quarantine and/or testing in the context of and international travel, freely congregating with other fully vaccinated or recovered without wearing masks or physical distancing in private settings) for all immune individuals

‡ Due to increasing risk of severe disease and of transmission

§ Due to moderate to high risk of further transmission, all individuals should stay at home and limit physical contact with people outside the household.

The risk matrix presented above is informed by the scientific evidence on SARS-CoV-2 past infection, COVID-19 vaccines and SARS-CoV-2 variants of concern available at the time of this writing. *Infection risk* is a product of the *exposure risk* (which is proportionate to the level of transmission of the virus) and the *susceptibility to infection, if exposed*. The *net transmission risk* is the product of the *infection risk* and the *risk (if infected) of transmitting infection* to non-immune individuals. Given the lack of evidence to the contrary, for the purposes of this framework *the risk (if infected) of transmitting infection* by individuals with reinfection / vaccine-breakthrough infection is assumed to be equal to that seen in primary infection; thus, the *net transmission risk* is assumed to be proportionate to the *infection risk*. *Net risk of severe disease* is the product of the *infection risk* and the *risk (if infected) of severe disease*.

Considerations for quarantine

As per the evidence presented in Table 3, contacts who are fully vaccinated or contacts without risk factors who have recovered from COVID-19 could be considered lower-risk contacts, both in terms of the likelihood of becoming infected and the severity of disease if infected. Consequently, some countries may decide to exempt them from quarantine. However, these contacts should be advised to monitor their symptoms following their exposure; if symptoms develop, they should be tested for SARS-CoV-2, and isolated if they are found to be infected with SARS-CoV-2. Countries may also need to take into consideration the context of the exposure (risk assessment of nature of exposure), because some settings like health-care facilities may pose a higher risk, leading to classification of health-care workers as high-risk contacts. Tailored adjustment for key groups with low risk tolerance may be considered, such as for health care workers or staff of long-term care facilities for the elderly, to minimize risks of potential onward transmission.

As lower risk contacts may still pose some residual risk for onward transmission, countries may opt to quarantine lower-risk contacts if there are concerns about transmission of immune-escape variants, or if their goal is elimination of local transmission.

International travel risk-mitigation measures

At present, WHO does not support the introduction by national authorities or by conveyance operators of requirements for proof of vaccination or natural immunity against SARS-CoV-2, neither as a condition for exiting or entering a country, nor as a condition for traveling internationally.[57]

In the context of the COVID-19 pandemic, international travel should always be prioritized for emergencies and humanitarian actions; travel by essential personnel; repatriations; and cargo transport of essential supplies such as food, medicines and fuel.

At present, international travellers are not considered contacts of SARS-CoV-2 in principle unless a traveller meets the definition of a contact.[15,16] Furthermore, international travellers should not be categorized as suspected COVID-19 cases. Therefore, WHO does not recommend healthy travellers as a priority group for SARS-CoV-2 testing, in particular when resources are limited, to avoid diverting resources from settings and patients where testing can have a higher public health impact and drive action.[15,16]

In line with the individualized approach to public health measures outlined earlier in this guidance, countries may consider fully vaccinated or recovered individuals as lower-risk travellers and may consider waiving testing and/or quarantine of arriving international travellers. Such decisions should be based on a detailed risk assessment that takes into account the COVID-19 control objectives of the arrival country and the SARS-COV-2 incidence, and prevalence of VOCs, in the departure country. For more details, updated interim guidance: Considerations for implementing a risk-based approach to international travel in the context of COVID-19 is forthcoming.[15]

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Annex

Public health criteria to adjust public health and social measures in the context of COVID-19

Introduction

In response to the COVID-19 pandemic, countries around the globe have implemented public health and social measures (PHSM) for the control of SARS-CoV-2 transmission. As the local epidemiology of the disease changes, vaccines are rolled out and new variants of concern (VOCs) emerge, regular adjustment of such measures will be necessary.

This annex updates the annex to *Critical preparedness, readiness and response actions for COVID*-19 published on 4 November 2020 and outlines a process for decision-making on adapting PHSMs to the epidemiological situation, taking into account surveillance and testing capacities, the vaccination coverage in the target population and the health system's capacity for response. It should be read in conjunction with the main body of this document and the earlier interim guidance.[1]

This annex is intended for the public health divisions of national and sub-national authorities in locations that have introduced PHSMs and are considering adjusting them. Its guidance is restricted to the public health domain. Other documents published by WHO address different considerations that should enter into decision-making about introducing or loosening PHSM, including the welfare of a population.

How to use the guidance in this annex

The public health criteria in this annex are grouped into two dimensions that should be evaluated to address two main questions:

1. **Epidemiological situation/Transmission classification** – Is the epidemic controlled?
2. **Health system and public health services capacity and performance –** Is the health system able to detect and cope with COVID-19 cases while maintaining other essential health services?

These two dimensions should further be considered in the context of the national COVID-19 response strategy. Thresholds for action may depend on the country's overall strategy, and whether it is pursuing an elimination or control strategy.

The criteria are not prescriptive, and it may not be feasible to assess some of them, because of a lack of data, for example. Countries should focus on the criteria most relevant for them to inform decision making. In countries with limited surveillance data, vaccination coverage data among target groups can help steer decisions about PHSM, together with indicators from sentinel surveillance in health facilities or bed occupancy. The thresholds are indicative and may need to be revisited as further information about the epidemiology of COVID-19 and the impact of measures become available. It is recommended to systematically assess these criteria at least biweekly at the **lowest operational subnational administrative level** that is practical to inform tailored local responses.

This Annex also includes a third section presenting risk matrices for informing individualized public health measures.

1. Epidemiological situation/Transmission classification

Transmission classification categories can be used to determine the extent to which the epidemic can be considered controlled within each country/area and at sub-national levels. The transmission categories in one country, if published, are also useful to others when considering adjusting policies on trade and travel.

Defining transmission classification

The transmission classification developed in the last guidance has been maintained, with seven categories, as outlined in Table 1.

Annex Table 1: Definition of the categories for transmission classification

Category name	**Definition** *Countries/territories/areas with:*
No (active) cases	No new cases detected for at least 28 days (two times the maximum incubation period), in the presence of a robust* surveillance system. This implies a near-zero risk of infection for the general population.
Imported / Sporadic cases	Cases detected in the past 14 days are all imported, sporadic (e.g. laboratory acquired or zoonotic) or are all linked to imported/sporadic cases, and there are no clear signals of further locally acquired transmission. This implies minimal risk of infection for the general population.

Clusters of cases	Cases detected in the past 14 days are predominantly limited to well-defined clusters that are not directly linked to imported cases, but which are all linked by time, geographic location **and** common exposures. It is assumed that there are a number of unidentified cases in the area. This implies a low risk of infection to others in the wider community if exposure to these clusters is avoided.
Community transmission – level 1 (CT1)	**Low incidence** of locally acquired, widely dispersed cases detected in the past 14 days, with many of the cases not linked to specific clusters; transmission may be focused in certain population sub-groups. Low risk of infection for the general population.
Community transmission – level 2 (CT2)	**Moderate incidence** of locally acquired widely dispersed cases detected in the past 14 days; transmission less clearly focused in certain population sub-groups. Moderate risk of infection for the general population.
Community transmission – level 3 (CT3)	**High incidence** of locally acquired, widely dispersed cases in the past 14 days; transmission widespread and not focused in population sub-groups. High risk of infection for the general population.
Community transmission – level 4 (CT4)	**Very high incidence** of locally acquired widely dispersed cases in the past 14 days. Very high risk of infection for the general population.

* Note that in situations where COVID-19 surveillance is not robust, a lack of identified cases should not be interpreted as an absence of transmission; alternate indicators (see Table 5) should be examined to assess the possibility of undetected COVID-19 cases.

Primary indicators for assessing the level of community transmission

Four primary indicators to determine community transmission are proposed in Table 2. They are based on data that should be routinely collected during the pandemic. The relative importance of each available indicator will vary according to the local context (e.g. the reliability of the data for each indicator); and described limitations to interpreting each indicator should be taken into account. Indicators should be measured at the lowest administrative level of operations possible to inform targeted public health interventions. To develop transmission classification at a higher administrative level, a separate analysis should be conducted using indicators for that level, rather than attempting to aggregate lower-level transmission classifications.

These indicators should be used alongside other epidemiologic information available either routinely or through special studies or modelling estimates, as well as non-epidemiologic data and other considerations, for informing strategic and operational decisions.

It is recommended that these indicators be assessed biweekly, adopting the epidemiological week definition used in the country.

Ranges for the four indicators in Table 2 were developed through a review of existing data. They can be used to guide the application of the transmission classification at sub-national levels. These ranges are indicative and may require adjustment to local contexts and based on the performance (e.g. sensitivity, representativeness) of the local surveillance system and testing strategy and should be revisited periodically. Caution should be exercised when interpreting changes in indicators that occur in the context of changes to the surveillance system (e.g. an increase in testing rate or a change in the population under surveillance). Note that some indicators (e.g. overall incidence) may be higher in the presence of very large clusters, as in the case of superspreading events, than during community transmission.

It is helpful to monitor the testing rate as a measure of the coverage of surveillance. A minimum recommended rate is at least one person tested per 1000 population per week. Testing should not be limited to specific populations (e.g. only those in urban settings with high access to testing, or travellers). Denominator data must be available at the level of disaggregation being assessed (e.g. district, province). Some authorities may choose to specifically track these indicators among groups of individuals at greatest risk for severe disease and death.

After all available indicators are calculated, if the levels calculated based on each indicator are different, a qualitative review should be undertaken to determine the final transmission classification. It is recommended that if data are not available (or reliable) for all indicators, more weight should be given to the indicators considered more reliable in the local context. In many cases, indicators listed higher in Table 2 may be more reliable than those lower in the table.

In places where indicator values are not reliable, but the system is stable, trends can be used as an alternative assessment. One example would be a situation in which there is a very low testing rate, and many cases are likely missed, but the testing strategy is not changed.

Annex Table 2: Primary epidemiological indicators and proposed ranges to assess the level of COVID-19 transmission

Domain	Indicator	Description/Rationale	Major limitations	Level of community transmission			
				CT 1	CT 2	CT 3	CT 4
Hospitalization Rate	New COVID- 19 hospitalizations per 100 000 population per week*	A subset of all incident cases require hospitalization; thus, this is an indirect indicator of incidence. Unlikely to be subject to surveillance policy changes/differences.	May be influenced by hospitalization policy, e.g. if even mild cases are hospitalized for isolation purposes. Delayed measure of incidence.	<5	5 - <10	10 - <30	30+
Mortality	Number of COVID-19- attributed deaths per 100 000 population per week*	A subset of all incident cases are fatal, and thus this is an indirect indicator of incidence. Minimally influenced by surveillance policy if testing is comprehensive.	Delayed measure of incidence. At low levels and in small geographical regions, can be sensitive to minor fluctuations (e.g. one versus two deaths).	<1	1 - <2	2 - <5	5+
Case Incidence	New confirmed cases per 100 000 population per week*	Direct measure of incidence	Heavily influenced by surveillance system performance, testing policy and laboratory capacity. At low levels and in small geographical regions, can be sensitive to minor fluctuations in case counts, particularly due to batch reporting.	<20	20 - <50	50 - <150	150+
Testing	Test positivity rate per week (non-sentinel)*	This may be useful if there are limited sentinel sites. It may capture atypical cases better than sentinel surveillance.	Heavily influenced by testing strategy and capacity.	< 2%	2% - < 5%	5% - <20%	20%+

*Consider averaging over a two-week period to minimize the effect of random fluctuations.

Note: the thresholds in this table may be updated as additional data become available.

Additional indicators

Additional indicators that can provide further evidence to help classify the level of transmission are listed in Table 3. These indicators may not be readily available at the lowest administrative level of operations, however. They are therefore considered secondary to the primary four indicators listed in Table 2. Furthermore, they may not directly reflect transmission or force of infection of SARS- CoV-2 or may be more difficult to interpret and compare than those listed in Table 2. Thresholds are not presented for the secondary indicators, due to a lack of available data, high local variability or both.

As a last resort, where no indicator values are available, subjective assessment can be used, but this should be done over several weeks to avoid influences from transient or anecdotal observations.

Annex Table 3: Additional epidemiological indicators to assess level of COVID-19 community transmission*

Indicator	Description/Limitations
Intensive care unit (ICU) proportional occupancy	The proportion of new ICU admissions attributed to COVID-19, out of all ICU admissions for the same period (alternatively, proportion of current ICU beds occupied by patients with COVID-19, out of all occupied ICU beds)
Instantaneous reproduction number (Rt)	The instantaneous reproduction number is the average number of secondary cases each current case would produce if conditions remained the same. Rt should be estimated over successive weekly time windows and should be considered in combination with the number of cases at a given time. When there is a large volume of cases at a given time, Rt near 1.0 would sustain a high number of cases. While this is a widely used indicator of transmissibility, it requires familiarity with the various methods for calculation and sufficiently reliable and timely data on incidence. It also assumes a known serial interval distribution, which can in practice be hard to estimate for COVID-19 due to limited data on transmission chains.
Daily growth rate	The daily growth rate measures the epidemic growth or decline of an epidemic. It is approximately the percent of increase/decrease in daily case incidence.
Doubling time	The number of days required for the daily incidence to double. This is directly determined by the daily growth rate *r* and linked to Rt and the serial interval distribution. All else being equal, higher Rt will lead to shorter doubling times.
Proportion of unlinked cases among new cases	This is defined as the proportion of cases not previously listed as contacts (alternatively, the proportion not linked to known clusters/transmission chains). It is a measure of the spread in the community beyond known clusters. It is heavily influenced by case investigation and contact tracing capacity.
Test positivity proportion from sentinel sites averaged over a two- week period	Minimally influenced by testing strategy or capacity. Can provide a good, standardized way to monitor evolution over time if adequate number of samples are collected and sites are geographically representative. May not be representative of the general population if there are only limited sentinel sites.
Influenza-like-illness (ILI) or Severe Acute Respiratory Infection (SARI) trends	This is not directly indicative of COVID-19 cases, but sentinel surveillance for ILI and SARI can also capture a proportion of COVID-19 cases, and thus this is useful for monitoring trends for COVID-19. This measure may be helpful where COVID-19-specific surveillance is not robust.
Secondary attack rates (SAR)	This captures the probability that a contact person is infected following exposure to a confirmed case during their infectious period. Comparison of secondary attack rates in different contexts (e.g. vaccinated versus non-vaccinated individuals, different types of exposures, different variants) can shed light on risk factors for increased transmission.

All-cause hospitalization rate trends	This is not directly indicative of COVID-19 hospitalizations but, where COVID-19 cases make up a substantial proportion of hospitalizations, this can be useful for identifying trends in COVID-19 cases. These rates may decline due to restricted service provision and other public health measures. Trends must be analysed in the context of other potential causes of changes in hospitalization rates (e.g. concurrent influenza circulation). These trends may be helpful where COVID-19-specific surveillance is not robust.
All-cause (excess) mortality trends	This measure is not directly indicative of COVID-19 cases/deaths, but where COVID-19 deaths make up a substantial proportion of overall deaths, this can be useful for identifying trends in COVID-19 cases. Trends must be analysed in the context of other potential causes of changes in mortality rates (e.g. concurrent influenza circulation) and ideally compared with baseline data on mortality to identify excess above expected (e.g. seasonal) fluctuations. While this is a widely used indicator of transmission, it requires careful consideration of the inherent biases in mortality estimation methods.[3] This may also be a delayed indicator, depending on death and vital records system processes. These trends may be helpful where COVID-19-specific surveillance is not robust.
Cumulative vaccination uptake (by first dose or fully vaccinated)	Defined as the proportion of individuals who received a) the first dose, or b) the full recommended series of any COVID-19 vaccine, as percentages of the total population of a country or area. Cumulative vaccination uptake can provide a useful indication of population coverage†, especially in the short term. Over longer timeframes, using uptake data to infer vaccination coverage also needs to take into account changes in the population denominator (including by age group), especially mortality among targeted groups. Uptake and coverage data may provide an indication of population protection from COVID-19 disease during the months following vaccination. It is currently unknown whether such protection might wane over longer timeframes or whether new virus variants might affect vaccine efficacy and effectiveness. Evidence about the role of vaccination in preventing infection and preventing transmission is being assessed.

*This list should not be considered exhaustive. † For further information on COVID-19 vaccination uptake, rate, and coverage, please refer to *Monitoring COVID-19 Vaccination*, Page 5.[4]

Trends in transmission

In addition to calculating the category of transmission classification, it is also important to understand the direction of the trends of contributing indicators (stable, decreasing or increasing) over several weeks. This can assist in determining whether measures implemented are improving the epidemiological situation in the area, and for planning future changes, or putting in place anticipatory changes to public health measures based on a likely change in the transmission classification.

2. Health and public health services capacity and performance

The capacity to respond to the existing epidemiologic situation of COVID-19 (i.e., the transmission classification) is a key consideration in the decision to adapt PHSM. Clinical care and public health services are two key domains that reflect the ability of a country to adapt and respond to the requirements of both the COVID-19 caseload and the burden of disease more generally. Sufficient clinical care capacity is required to treat both inpatient and ambulatory cases of COVID-19 while ensuring that the health system is not overwhelmed and can continue to treat the regular caseload of patients with other conditions, particularly during seasonal peaks, such as the influenza season, and at times of rapid or large increases in SARS-CoV-2 transmission. The public health response relies on the capacity of the surveillance system to detect and respond to changes in SARS-CoV-2 transmission and focuses on key activities including case detection, diagnostic testing and contact tracing. Each of the two domains (health services and public health) is divided into two principal sub-domains, namely capacity (output indicators) and performance (outcome and impact indicators).

While this section is not aimed to be overly prescriptive, it provides quantitative thresholds (Table 4) to categorize response capacity and performance into three categories: adequate, moderate and limited. It is important to note that capacity needs to be assessed in the context of the current transmission classification. Response capacity that has been considered adequate may, under a higher incidence scenario, be reduced to moderate or limited response capacity.

Assessing the overall level of health system and public health services capacity and performance

To assess the overall capacity and performance of the health system and public health services, authorities should use the same approach as outlined for transmission classification. This includes:

- prioritizing those indicators that are available and reliable and adjusting thresholds to local contexts and reliability of the data
- interpreting changes to indicators in the context of changes to data collection mechanisms
- undertaking a qualitative review to determine the final health system capacity level if the levels calculated based on each indicator are different
- using trends instead of quantitative thresholds where data are not reliable, but denominators are stable
- using subjective assessment as a last resort if no data are available
- observing trends in indicators to anticipate future changes to the health system and public health services capacity and performance level.

Additional indicators that can be used for triangulation are provided in Table 5. Assessments should be updated biweekly.

Annex Table 4: Primary indicators and proposed ranges to assess level of COVID-19 health system and public health services capacity and performance

Domain	Indicator	Description/	Major limitations	Capacity to respond		
				Adequate	Moderate	Limited
Clinical care capacity	Proportion of occupied hospital beds	High morbidity and mortality will occur if there is insufficient capacity to hospitalize severe cases. Should count all hospitalizations, not only COVID-	May be influenced by hospitalization policy (e.g. if all cases are isolated in hospital), which does not indicate true saturation of hospital capacity.	<75%†	75-<90%†	90%+ †
Clinical care performance	Case fatality rate of resolved (i.e., outcome known) hospitalized cases	Overall impact indicator of adequate COVID-19 care.	Highly dependent on age and various biases.[3] Must take into account any changes in case detection or testing strategy.	Decreasing trend	Stable trend	Increasing trend

Public health response capacity	Number of persons tested per 1000 population per week, averaged over a two-week period	Without sufficient testing, it is difficult to appropriately isolate and treat cases.	Not all laboratories are able to report individuals tested; if possible, can count number of new rather than repeat tests; otherwise can count number of tests, but this may be misleading due to repeat testing. Laboratories not reporting location of cases may mask disparities in testing (e.g. among non-urban populations). If using rapid diagnostic tests, these should be used according to guidance, and thresholds may need to be raised.	4+	1 - < 4	<1
Public health response performance	Proportion of cases for which an investigation has been conducted within 24 hours of identification	This indicates the capacity to identify transmission risks and exposed contacts. Where investigation is not recorded directly, can be measured by proxy indicator - proportion of cases with contacts listed.	May be difficult to obtain timely data.	80%+	60 - <80%	<60%
Public health response performance	Support for / adherence to PHSMs (can be further subdivided into personal protective measures versus other measures)	Qualitative assessment based on observation, media monitoring, perception or behaviour surveys, hotlines, focus groups, etc. Analysis including forecasting of effectiveness of PHSM to be considered, it is important to identify not only the current status but any barriers or enablers to improvement.	May be highly variable between sub-groups and across individual PHSMs and over time.	High (nearly universal adherence to most PHSMs).	Moderate (modest adherence to most PHSMs, or variable adherence across individual PHSMs).	Low (minimal adherence to most PHSMs).

† Hospital occupancy routinely varies considerably between countries and health systems. Therefore, baseline (pre-COVID-19) occupancy must be taken into consideration.

** A significantly low hospital occupancy rate may also indicate barriers to access to hospital care, requiring investigation into the causes and remedial actions to be taken. In situations of community transmission, low hospital utilization may indicate large numbers of community deaths, which would potentially not be captured in facility-based mortality reports.

Annex Table 5: Additional indicators to assess level of COVID-19 health system and public health services capacity and performance*

Indicator	Description/Limitations
Number of trained ICU staff per 10 000 population	This indicates sufficient clinical capacity to respond to cases most likely to lead to mortality. This indicator may be more relevant when measured against a population of clinically vulnerable[i] persons, if data are available. This indicator is difficult to measure. It is a necessary but insufficient measure of ability to provide intensive care.
Number of ICU beds per 10 000 clinically vulnerable population[i]	Mortality from COVID-19 will be highest if capacity for intensive care is exceeded. Strictly counting the number of ICU beds does not guarantee successful care if there is inadequate staffing, equipment or supplies.
Proportion of occupied ICU beds	This indicator assesses sufficient clinical capacity to respond to cases most likely to lead to mortality. It may not be useful in countries with very few ICU beds (can be substituted with proportion of occupied hospital beds +/- oxygen in these situations). If this indicator is very low, overall health system capacity should be considered limited, regardless of adequate levels of other capacity indicators.
Proportion of occupied beds with access to oxygen supply	Oxygen is an important treatment for COVID-19, and sufficient capacity to provide oxygen can be useful even in the absence of ICU capacity. This indicator may be difficult to measure and may not be useful in countries with very low capacity.
Crude case fatality rate of COVID-19	This is an overall impact indicator of adequate COVID-19 care. It is highly dependent on age, other risk factors and various reporting biases.[3] Analysis of trends should consider any changes in case detection or testing strategy. Countries are advised to collect additional information on age, as this measure will be heavily affected by the age structure of the population.
Number of contact tracers per 100 000 population [alternatively per number of new cases in a week]	This indicates capacity to conduct sufficient contact tracing to interrupt transmission. It is an input indicator that may not correlate well with actual contact tracing outcomes. There is minimal evidence base for determining thresholds. This may be difficult to accurately measure where contact tracing is done by persons other than formally designated "contact tracers".
Number of points of entry surveillance officers per 100 000 daily travellers	This is a measure of the ability to successfully mitigate the risk of importation. It is a poor indicator of actual internal domestic capacity; is minimally relevant during widespread community transmission; and may be achieved when human resources are inappropriately diverted from internal domestic use.
Proportion of newly confirmed or probable cases interviewed for contact elicitation within 24 hours of identification	This indicator measures the timeliness of contact listing, which shortens exposure to potentially infected persons. A better metric of contact listing timeliness is the actual proportion of contacts identified and traced/quarantined within 48 hours.
Proportion of contacts of new cases who are monitored for 14 days (or locally specified period)	This indicates that contacts are monitored until no longer at risk for becoming secondary cases (linked to a particular source case). This indicator may be particularly important for assessment of public health system performance in the imported/sporadic and clusters transmission scenarios. It can be spuriously inflated by poor contact listing.
Proportion of identified cases isolated within 24 hours of positive test result (or determination as a probable case)	This indicates that investigation and isolation of new cases is sufficiently rapid to minimize the generation of secondary cases. This indicator may be particularly important for assessment of public health system performance in the imported/sporadic and clusters transmission scenarios.
Time from symptom onset to case confirmation	This measures the ability of the surveillance system to promptly detect, test and confirm symptomatic cases. Individual components (i.e., time from symptom onset to detection, detection to testing and test turnaround time) can also be measured independently.
Proportion of cases arising from contact lists	This describes the extent to which new cases are already captured by and known to the surveillance system through adequate case investigation. When this is low, it suggests widespread existence of "hidden" chains of transmission and/or poor-quality case investigation.
Number and proportion of samples sequenced	Wherever resources allow, laboratories could consider genomic sequencing of SARS-CoV-2 PCR-positive sentinel specimens.

*This list should not be considered exhaustive.

i 'Clinically vulnerable' in this context refers to individuals aged ≥ 60 years and/or with comorbidities that increase risk of serious COVID-19 disease, including heart disease, asthma and diabetes.

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WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance document will expire two years after the date of publication.

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ONTARIO
SUPERIOR COURT OF JUSTICE

BETWEEN:

THE ATTORNEY GENERAL OF ONTARIO,

APPLICANT (RESPONDING PARTY),

AND

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHUURMAN, DEAN WANDERS, RANDY FREY, HARVEY FREY, and DANIEL GORDON,

RESPONDENTS (MOVING PARTIES),

AND BETWEEN

HER MAJESTY THE QUEEN IN ONTARIO,

APPLICANT (RESPONDING PARTY)

AND

THE CHURCH OF GOD (RESTORATION) AYLMER, HENRY HILDEBRANDT, ABRAM BERGEN, JACOB HIEBERT, PETER HILDEBRANDT, SUSAN MUTCH, ELVIRA TOVSTIGA, and TRUDY WIEBE,

RESPONDENTS (MOVING PARTIES)

CROSS-EXAMINATION OF
DR. ZAIN CHAGLA

TUESDAY, DECEMBER 14, 2021
10:05 A.M.

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INDEX OF REFUSALS

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NOTE: The above-recorded indices are provided for ease of reference only and are not to be relied upon in any manner whatsoever by the parties hereto or any third party.

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CROSS-EXAMINATION OF DR. ZAIN CHAGLA

TUESDAY, DECEMBER 14, 2021

10:05 A.M.

THE REPORTER: Good morning, my name is Giles, on behalf of Professional Court Reporters. We're here to take the examination of Dr. Zain Chagla, in the matter of Her Majesty the Queen in Right of Ontario, vs. Church of God et al., and the Attorney General of Ontario vs. Trinity Bible Chapel et al.

The respective Court File Numbers are CV-21-95 and CV-21-08. Today is the 14th day of December 2021, the time is approximately five minutes past 10:00 a.m.

May I ask the witness to state his full name for the record, please?

THE DEPONENT: Zain Chagla.

THE REPORTER: Mr. Chagla, do you solemnly affirm that the evidence you are about to give today shall be the truth, the whole truth, and nothing but the truth?

THE DEPONENT: Yes.

THE REPORTER: Thank you. Counsel

Kittredge, could you identify yourself for the record, please, Sir?

MR. KITTREDGE: Sure. I am Rob Kittredge, K-I-T-T-R-E-D-G-E, and on the -- I am on for the moving parties in this matter.

THE REPORTER: Thank you. Counsel Hunter, could you identify yourself for the record please, Sir?

MR. HUNTER: Josh Hunter for Her Majesty and for the Attorney General.

THE REPORTER: Counsel Stevenson, could you identify yourself for the record please, Ma'am.

MS. STEVENSON: Yes, Maia Stevenson, Counsel for the Attorney General.

THE REPORTER: Thank you, Counsel Guttman, could you identify yourself for the record, please, Sir?

MR. GUTTMAN: Yes, Daniel Guttman, Counsel for Her Majesty the Queen, Right of Ontario.

THE REPORTER: Thank you. Also present is Sean Kissick and Ryan Cookson as observers.

Counsel, thank you very much. You may proceed with your examination.

DR. ZAIN CHAGLA, affirmed,

EXAMINATION BY MR. KITTREDGE:

1. Q. All right. Good morning, Dr. Chagla. My name is Rob Kittredge and I represent the moving parties in this matter. I'll be asking you a series of questions today.

I have a -- I have quite a few questions for you. But for the most part they're, yes or no, questions and we should be able to get through all of them relatively quickly.

Where possible, I'd like you to answer with a 'yes' or 'no', but if you feel that any -- any of my questions call for a more extensive answer, feel free to expand as required.

If you'd like to take a break at any point, just let me know, okay?

A. Sounds good.

2. Q. I understand you submitted some evidence in this matter in the form of an Affidavit dated July 5th, 2021, is that correct?

A. Yes.

3. Q. Do you have a copy of your Affidavit in front of you today?

A. I can pull it up here, one second.

4. Q. Great. And while you do that, to begin with, I'd like to talk a bit about how the Province of

Ontario tracks the progress and severity of the COVID-19 pandemic.

And I am going to awkwardly figure out how to share my screen and show you a document. Just one second. The benefits of virtual cross-examination are that you can do a cross in your underwear, but you have to figure out how to -- you have to overcome technical issues here. Just one second.

Okay, I'll make sure I am not sharing something mortifying. There it is. All right. So, can you see that document?

A. Yeah, I can.

5. Q. All right, does that document look familiar to you?

A. I believe this is the data site from Public Health Ontario, or the data tracker tool.

MR. KITTREDGE: Yes, that's what it was. I took a screenshot last night. I'd like to mark this document as Exhibit A to the cross examination.

Does the opposing Counsel have any objection?

MR. HUNTER: No.

MR. KITTREDGE: Let's call it Public Health Ontario, COVID Summary December 12th,

2021.

(WHEREUPON Exhibit A : Public Health Ontario COVID Summary December 12th, 2021.)

BY MR. KITTREDGE:

6. Q. Dr. Chagla, among other things, this document shows the number of -- the total number of confirmed cases of COVID-19 in Ontario since the beginning of the pandemic.

Can you read the number of total confirmed cases to date for the record?

A. 633,683.

7. Q. Does sound like an accurate number to you?

A. It's the number of confirmed cases. I would suspect it's not the number of total cases that have been through the pandemic.

8. Q. The Province of Ontario defines a confirmed case of COVID-19 as a person who is SARS-coV-2 infection has been confirmed by laboratory testing, is that correct?

A. Correct.

9. Q. So, all of the cases listed on this page have been confirmed by a laboratory test. And the PCR test is the most -- is the test most commonly used to confirm SARS-coV-2 infection, is that correct?

A. Correct.

10. Q. Confirmed cases counts are an important measure of the progress and severity of the COVID pandemic. And are a fundamental data point used to calculate other important statistical measures of the pandemic, is that correct?

A. Correct.

11. Q. For example, further down on this page we see the percentage of cases that resulted in hospitalization at five per cent. And the percentage of cases that resulted in death at 1.6 per cent. These percentages are calculated based on the confirmed case count; correct?

A. Correct.

12. Q. You note in your Affidavit that the confirmed case count, and you noted just a moment ago that the confirmed case count doesn't capture 100 per cent of the cases in the general population due to a lack of access to testing, for example, or because some people with asymptomatic infection may choose to get infect -- not to get tested.

That may have been the case at the beginning of the pandemic; but testing rates have increased significantly since then. Since at least January of 2021, the vast majority of infections in the general population have been confirmed via testing, and are

included in the provinces confirmed case count, isn't that true?

A. I would still say there's a large testing gap since January of 2021. And I can say even through clinical experiences we diagnose who are admitted to hospital, not testing in the community through a typical assessment centre. Which means that they have been riding out their symptoms without a test for some time.

13. Q. Isn't that a sort of minority opinion though? Like wouldn't -- wouldn't most epidemiologists and other experts agree that testing currently captures the overwhelming majority of cases circulating in the community?

A. No, I -- you know, if you look at seroprevalence data prevalence data, so looking for people who have antibodies in their blood. It often is markedly higher than -- than what has been described as total case counts.

And again, to be identified as a case you have to be someone that has, you know, decided to go get tested for whatever reason, and had a result -- and -- and been classified, right.

So, people who decide not to get tested, or people who have minor illnesses, or as you said people

that are asymptomatic could have COVID-19, but not be captured in these numbers.

14. Q. We have expert testimony in this case to the effect that 90 per cent of COVID-19 cases in Ontario are confirmed by testing and are included in the provinces confirmed case count.

In other words, daily confirmed case statistics at this point capture all but about ten per cent of the cases in the general population.

Do you disagree with that assessment?

A. I would disagree with that. I mean if you look at the seroprevalence data prevalence surveys, you know, across the region, we're talking about, you know, I think the last Canada seroprevalence data prevalence survey was ten to 15 per cent of the population that had described antibodies. And this is around wave 3 from what I recall.

So, you know, it would be less than what would be described here. And certainly, in my clinical experience, again, you know, there are people that are diagnosed with COVID-19, where there's a cluster at home that have it, that have not been diagnosed and -- and it's only because one has ended up in hospital that we've figured out that there's more cases behind them in that sense.

So, I would suspect, you know, there is a discrepancy well more than ten per cent here, in terms of the number of cases that have actually occurred in Ontario.

15. Q. And based on your experience what -- approximately what percentage of the total number of cases do you believe are captured by testing?

A. Yeah, I mean it varies based on where we are in the waves. If there's a lot of cases in the community, then it likely means there's a lot more people that are undiagnosed in the community in that sense. And if there's very little transmission in the community, there's more chance of capturing those cases.

But again, you know, somewhere between one to two, to one to three would probably be a rough estimate of the number of cases that are represented by positives as compared to what likely the burdens are in the community.

16. Q. So, you're saying that there's likely three cases that are not captured by testing for every one case that is?

A. Yeah, and that's considered pretty good in Ontario. I mean globally it's even worse than that. But having more access to testing, more people are --

can get testing in Ontario.

17. Q. So, you'd say rather than 90 per cent of cases being caught, you'd say 25 per cent of cases are caught.

A. Yes, I mean somewhere between 25 and 50 per cent. Again, it varies based on where we are. So, you know, for example at the worst of the third wave, we probably would suggest there were, you know, lots of people that were being captured because testing was hard to come by. And so, all of those measures would be there.

And, you know, at the best of our kind of post lockdown periods we're probably capturing, you know, in the 60, 70 per cent range. But it averages out, I think, to 25 to 50 per cent.

18. Q. Okay. So, that's a pretty big difference, 90 per cent to 25 per cent. Would you agree that understanding rates of testing versus overall rates of infection in the population, at least in approximate terms, is fundamental to understanding and assessing the severity of the COVID-19 pandemic?

A. Yeah, absolutely.

19. Q. Would you doubt that COVID expertise of an infectious disease doctor who believes that testing captures 90 per cent of cases?

A. Yeah, I mean, I think, again, from real world experience it's not -- we're not capturing every case. So, you're not even close to 90 per cent. You know, they're a lot of people who do not get tested. And it is the reality of the situation.

20. Q. Okay. Dr. Matthew Hodge was the expert who provided this testimony. Do you know Dr. Hodge?

A. Not personally.

21. Q. Dr. Hodge was the co-lead for epidemiology and surveillance activities within the incident management system structure of the health protection division of the PHO, from November 2020 until April 9th, 2021.

Does it seem possible to you that someone with Dr. Hodge's experience actually believes that testing captures 90 per cent of cases in the community?

A. Ah, I mean, I presume he looks at a data set that's different than what I have access to. Obviously, he may see different things than I do. But, you know, again as an on-the-ground clinician, you -- there are groups that I know that are uncaptured by testing. And we're seeing many of them every day.

22. Q. So, would you agree that claiming that 90

per cent of cases in the general population are captured by testing, is a false statement?

A. Yeah, I would -- I would suspect looking at seroprevalence data prevalence data it's much less than that.

23. Q. So, Dr. Hodge was -- was wrong on this point?

A. Again, for my opinion, I think we're not capturing as many people with testing as we think we are. And, again, the data from looking at blood donors, and that type of thing, would suggest that it's low -- I mean it's not -- there are more people identified in those types of surveys than we have in terms of cases.

24. Q. So, Dr. Hodge was wrong on this particular point?

A. I mean for my opinion, yeah, I don't we captured 90 per cent of cases. I don't think we -- under even 50 per cent.

25. Q. And not just a little bit wrong, but very wrong.

A. Yeah, and again, that -- that goes back to behaviour and testing. But, yes, I don't think we capture 90 per cent of cases by any means.

26. Q. Okay. I'd like to direct your attention

back to the image that I am sharing. The PHO Confirmed Case Summary. Let's look at that five per cent hospitalization percentage. This percentage was calculated based on the confirmed case count; correct?

A. Yes.

27. Q. And if the confirmed case count vastly underestimates the actual number of cases in the community, then the hospitalization percentage overstates the actual percentage of people with COVID who will require hospitalization. Is that correct?

A. Yes, although, again, I would not say -- how do I -- how do I say this? We test very aggressively when people end up in hospital. So, we will capture the COVID patients that are hospitalized. So, you know, it's less of that discrepancy from the community in that sense.

We're not going to let someone wander into the hospital with symptoms and not get tested in that sense. So, yeah, absolutely, the percentage is -- is probably lower, in the fact that denominator in the community is lower; but, you know, there is a skew to overly test in hospital to make sure that we capture the cases that we need to capture for the sake of making sure that they're isolated, they get appropriate treatment, that type of thing.

28. Q. And what -- what you mean by that -- like, I guess correct me if I am wrong, but it seems like what you mean by that, is that when somebody comes to the hospital with symptoms, or with, you know, where it appears to their physician that they may have COVID-19, they're tested for COVID-19?

A. Yeah, so ---

29. Q. So ---

A. Exactly.

30. Q. So, the number of hospitalizations is likely accurate?

A. Yeah.

31. Q. Like that number ---

A. Absolutely ---

32. Q. --- 38,331 is probably much more accurate than the number of confirmed cases, that is a representation of the number of actual cases?

A. Yeah, sorry, it's 31,689, I think, is the total hospitalized on there.

33. Q. Oh, sorry, I was looking at the new tests --

-

A. Yeah, yeah ---

34. Q. --- I'm sorry, thank you.

A. I agree, that's -- that's accurate. We rarely will miss people who are -- who are COVID

positive ending up in the hospital for the sake of, you know, it causes outbreaks. So, we're very, very keen on making sure that we capture everyone in that sense.

35. Q. Right. So, to the extent that the confirmed case count is off, as in it doesn't represent the actual number of cases in the community, the percentage -- the hospitalization percentage provided there will be overstated by a proportionate amount?

A. Yeah, yeah.

36. Q. All right. Looking at the deaths section, we see another percentage. 1.6 per cent of cases result in death. That, again, is calculated based on the -- the confirmed case count; isn't that correct?

A. Yeah, that's correct.

37. Q. But the risk of death to a person with COVID is actually much lower than 1.6 per cent, isn't it?

A. Yeah, if you look at an aggregate, and you made your denominator is higher, than -- than, yeah, absolutely, it would be lower.

38. Q. Okay. Let's talk a bit about PCR testing. PCR tests are not a hundred per cent accurate, are they?

A. No, absolutely. There are false positives and false negatives.

39. Q. All right, so, PCR tests fail to recognize infection in some cases, and fail to -- and find infection where it doesn't exist in other cases?

A. Yeah, absolutely.

40. Q. How often do false positive and false negative results occur?

A. False negatives are rare. There was a -- a series from Public Health Ontario where they looked at people who are tested again, who are at high suspicion of having COVID-19. And I think they saw one per cent difference amongst people who got tested again. You picked up one per cent more on that second test.

So, you know, it's not un -- that is a population that's at high risk, those are people that are being tested because a clinician thinks that person has COVID-19, and, you know, you see a flip over of that one per cent if you test them again.

False positives are a little trickier in the sense that it's not necessarily just biologic false positives, i.e., this person doesn't have COVID-19, but has a positive test. But it also -- because PCR is so sensitive for molecular evidence of COVID-19 that you capture people that have a positive test, you know, well after they had COVID-19.

41. Q. PCR tests are -- don't direct -- sorry, PCR

tests don't detect infection directly, do they?

A. No, they look for molecular -- the molecular signature of the -- of the pathogen basically. Or the -- the genetic material of the pathogen.

42. Q. Right. So, a sample is typically taken by -- from inside the nose of the patient and that is tested to find if a particular genetic sequence is found in the -- in the sample, is that generally speaking, correct?

A. Yeah, that would be in -- in -- yeah, exactly, genes for the Corona Virus would be found in that sample.

43. Q. Right. But the tests can't differentiate between an action -- active infectious virus particle and a dead non-infectious virus, or a fragment of a virus genome, is that correct?

A. Yeah, so, there is some caveat to that. That we can approximate how much virus there is. And we have data around viral culture. So, you know, what you're talking about to say if someone is truly infectious, actually growing the virus, and how -- what burden of virus on a -- on a PCR test would be in keeping with someone that would have a positive viral culture.

So, we set things like cycle thresholds,

which are, you know, how many times you have to do the PCR to figure out if there is genome that exits there or not. And that lower cycle thresholds it is much more indicative of someone that is actively infectious, as compared to higher cycle thresholds where it's less indicative of someone that's infectious to others.

44. Q. Would you agree that PCR tests for COVID have an estimated sensitivity between 75 per cent and 95 per cent?

A. It's a large rage, but, yes, that was the -- the original Chinese data was around 75 per cent. But I think as tests got more accurate and resolution got better, 90 to 95 per cent is pretty reasonable.

45. Q. Can you briefly explain what the sensitivity of a PCR test means? What it means when we're talking about the sensitivity of a PCR test?

A. Yeah, I mean it's -- it's the -- you know, the common association, it's the rule out value, right? So, if you have a negative test, how well does it rule out having COVID-19? Or, you know, another way of you saying is, you know, your -- your test positives will be your true positives. And -- so, you know, what is -- you know, if you get a positive result, what does that mean in that sense?

46. Q. So, if the range is between 75 per cent and 95 per cent, does that mean that between 5 per cent and 25 per cent of PCR test results are inaccurate?

A. It -- you -- it -- yeah, you do get false negative -- sorry, false positives 5 per cent or higher of the time. And again, the concept of a false positive here isn't necessarily that they -- the test is wrong, i.e., they picked up something that wasn't there. It also is inclusive of people that have had Corona Virus in the past; but had very low levels of nucleic acid that are a part of their assays basically.

47. Q. All right, would you agree that PCR tests are imperfect?

A. Absolutely, every test is imperfect. And, you know, this is where clinical medicine is a part of it. We apply testing to populations we -- we develop a pre-test probability for those populations. And then we interpret the test result in the context of what your pre-test probability was.

So, if someone walks into my emergency room with cough, fever, shortness of breath, and has a positive, you know, COVID-19 test, I am pretty sure that person has COVID-19.

If I am in the community, you know, testing

people before surgery, and they have a positive Corona Virus test, and they have seroprevalence data symptoms and have never had symptoms I am going to look at that result and say, well, my pre-test probability was low. What does this mean? And this is a false positive? Or being a true positive?

48. Q. Right, but regardless that case, if it was a false positive would be included in the provincial case counts, is that correct?

A. Not necessarily. So, the public health units do you have some leeway to retest people. And -- and classify cases as false positives or that type of thing.

And so, you know, these are -- you know, in real life these are the discussions that we have in -- with our local public health unit if we start seeing cases where they don't make sense, people are tested without symptoms, that, you know, public health units will often repeat the tests. That often gives a negative results, and those are considered, you know -- don't get included in the case counts. Or, again, cases get dropped off the case counts as they're resolved in that sense.

49. Q. Right. But -- but some of the cases included in the -- in the case counts are included

based on false positive PCR test results. Would you say that's a reasonable ---

A. Yeah, it's not a perfect system. It's up to public health units to capture them. So, yeah, there is some that -- that, you know, if they're not looking hard enough or if it's a bit of a suspect story, they'll always kind of favour it being a real test result as compared to a false positive.

50. Q. Right. And some smaller number of cases included in the case count are -- are not included in the case count, I'm sorry, because they were false negatives.

Would you agree that's fair?

A. Yeah, yeah, exactly. Like, you know, there are people where, you know, you can do multiple tests and they're negative. And only when you do things like serology, you can figure out that they've -- they've had COVID-19.

51. Q. Right. All right, so, moving on. I guess I will -- if I can figure how to stop sharing this thing. Oh, that's not helpful. Oh, there we go.

Okay, so, moving on, in your opinion COVID-19 is a serious threat to the lives and health of people in Ontario and around the world. Would that be fair to say?

A. Yeah, absolutely.

52. Q. And you're also concerned that uncontrolled spread of the disease could overwhelm Ontario's healthcare system. Is that fair?

A. Absolutely.

53. Q. And the provincial and federal governments appear to share these concerns, would you agree?

A. Yes.

54. Q. In fact, as you discuss in your Affidavit, the provincial and federal governments have taken some extraordinary steps in response to COVID, is that right?

A. Yes.

55. Q. Including implementing a variety of measures such as limiting the number of people who attend gatherings, ordering the closure of certain business, issuing stay-at-home orders, et cetera. What you describe in your Affidavit as non-pharmaceutical interventions or NPI's is that correct?

A. Yes.

56. Q. And the objective of these NPI's is to control the spread of COVID-19, right?

A. Yes.

57. Q. Many of these NPI's significantly limit the freedoms that we normally enjoy in Ontario, don't

they?

A. Yeah.

58. Q. For example, during the pandemic limits have been involved -- limits have been imposed on how, when, and where we can interact with our friends and family. Who we can invite into our homes, and even how physically close we're allowed to get to other people, is that correct?

A. Yes.

59. Q. Touching or hugging people outside of your household has been prohibited, right?

A. Ah, for much of the pandemic it has been discouraged.

60. Q. The Province of Ontario cancelled Halloween in 2020, is that right?

A. Yes.

61. Q. Limits have been placed on how people -- how many people are permitted to attend indoor and outdoor religious services, is that correct?

A. Yes.

62. Q. We haven't even been able to complete -- sorry, we haven't even been completely free to choose what we wear. Masks have been required in indoor public settings for most of the pandemic, is that correct?

A. Masks have been required, yes, since about, I think, May of 2020, they've been part of provincial legislation.

63. Q. And would you agree that these are pretty significant limitations on our freedoms?

A. Either there -- you know, these measures have not been used before in control of an infectious disease. So, they are certainly unprecedented in a -- in a -- in the -- in the pandemic, for sure.

64. Q. And most of these measures weren't even contemplated in the pandemic preparedness plan, prepared by Ontario in response to the -- in, I think it was 2012, is that correct?

A. Yeah, I think -- I believe that was in response to pandemic influenza. But, yeah, certainly, yeah. There -- there has not been a large publication of these measures prior to that point.

65. Q. From a public health perspective NPI's which help to control the spread of COVID19, protect public health, and ensure that the healthcare system is not overburdened to the point of collapse are justifiable and appropriate even if there are -- even if they are restrictive. Would you agree with that?

A. Correct.

66. Q. Would a restrictive NPI that does nothing to

control the spread of COVID protect public health, or protect the healthcare system be justified from a public health perspective?

A. No, I mean and this type of hypothetical -- I mean, again, we are trying to apply measures that work in reducing spread. So, if something were not to reduce spread, then one would not consider it a useful intervention.

67. Q. And you wouldn't consider it justifiable or appropriate from a public health perspective?

A. It -- if there is no benefit, then there shouldn't be a need to justify it. There should be a use to justify it, yeah.

68. Q. And the mere fact that an NPI has been imposed by government is no guarantee that it will be effective, would you agree with that?

A. Yes, although, I would say that many of the NPI's that we have instituted have had, you know, roots in what we think are effective in terms of reducing mixing in certain environments, and reducing risks of transmission based on certain outbreaks.

And so, there is usually a basis for these based on our prior clinical evidence. I am not saying every NPI has been, you know, well justified and brought out, but certainly the major ones that we've

used through the pandemic have had, you know, a justification through reduction in mixing, and trying to control respiratory spread.

69. Q. Right. It's possible to envision a potential NPI that would actually make the public health situation worse, isn't it?

A. Yeah, there -- there could be ones that, you know, have effects that are negative on the pandemic.

70. Q. Would an NPI (inaudible) of COVID-19 be justified and appropriate from a public health perspective?

A. Again, the whole point of NPI's is to reduce spread. So, if they -- if things are hypothetically increase spread, then we would definitely not want to use them.

71. Q. So, to sum that up COVID shouldn't be looked at as a blank cheque that justifies any restrictive order that a government might choose to impose; would you agree with that?

A. Yeah, I mean, again, there are risks and benefits. And we always have to weigh risks and benefits. But again, the NPI's (inaudible) COVID-19.

72. Q. And you've been quite critical of a number of NPI's imposed by the provincial and federal governments, isn't that a fair statement?

A. Yeah, correct.

73. Q. For example, in response to the recent emergence of the Omicron variant, Canada prohibited traveller from a number of African countries. And yet, the Omicron variant is now firmly established in Canada, isn't it?

A. Yeah, absolutely. I -- it's now probably going to be our dominant variant as of the end of this week.

74. Q. Right. And you've been pretty critical of this travel ban, haven't you?

A. Absolutely.

75. Q. Is this travel ban an effective way to control the spread of COVID-19?

A. If we were to know exactly where COVID, this Omicron variant emerged, the moment it emerged, it may have been an effective intervention.

But at the time the travel bans were announced, it was pretty clear that Omicron had been on everyone's soil, and they just had not discovered it at that point.

So, it didn't really make sense on why we would ban travel, rather than, again, trying to protect travel on the other side, on our side to mitigate the spread here in that sense.

76. Q. Right. So, would you consider the travel ban to be justified or appropriate from a public health perspective?

MR. HUNTER: Mr. Kittredge, I have allowed you a number of questions on this. But you do, of course, know that's a federal measure, right?

MR. KITTREDGE: Yes, I do. I do.

MR. HUNTER: I fail to see the relevance of a measure that's not one of the measures your clients are challenging in this proceeding.

MR. KITTREDGE: Well, it's just to establish the fact that not all NPI's are -- are reasonable measures. You know, just the fact that they exist, doesn't mean that they're effective or justifiable.

MR. HUNTER: The witness has already said that to you several times.

MR. KITTREDGE: Yes. Yes, well, that's what transcripts are for.

BY MR. KITTREDGE:

77. Q. So, moving on, can you briefly describe the concept of fomite transmission of respiratory viruses?

A. Yeah, I mean in simple terms it's, you know, the contamination of a surface which then leads to, you know, one touching a surface and then inoculating

a mucous membrane, so, eyes, nose, mouth, from then touching that surface. And then putting it in that mucous membrane and letting it replicate at that point.

78. Q. And fomite transmission doesn't play a significant role in the transmission of COVID-19, though; is that correct?

A. No, I think most international bodies suggest it might play a role in certain settings, but it is not by any means the predominant mode of transmission. And -- and can be mitigated quite easily by hand hygiene.

79. Q. And how early in the pandemic did -- was that fact generally known among experts?

A. I think many had early impressions that it was -- it was less of an issue. I mean there are respiratory viruses that have a significant fomite transmission mechanism. So, always being precautionary was important.

But I think towards July and August, as we started seeing A) our clinical experience, but B) you know, good studies that were sampling the environment, that showed very little fomites, and -- and even in that context, the ability for, you know, good hand hygiene and cleaning to really mitigate that risk. We

had suspected it was probably much less represented outside of very, very certain settings, where it's a bigger issue.

80. Q. All right, so, I am going to once again share my screen, and show you a document. And I have choice of one of about 25 windows that are open here. And I am not sure which one it is from these tiny little thumbnails. Where are we? Oh, here we go.

Okay, so, can you see that? Whoops -- what's going on there. How about that? I have just realized that if you move the window, you can see what's behind it. So, I'll have to be careful about that.

Do you recognize this image that I am showing to you?

A. Yeah, this is from my twitter interaction with Dr. David Fisman, from Toronto.

81. Q. Right, and what's the date on this tweet of yours here?

A. July 8th, 2020.

82. Q. And can you read it to us for the record?

A. Ah, so, Dr. -- do you want me to read the whole thing or just my statement?

83. Q. Just -- just yours.

A. My statement. Yeah, totally agree, not sure

why outdoor playgrounds were considered bad to begin with, especially once we realized this wasn't a fomite disease.

84. Q. So, would you agree that by July 8th, 2020, it was commonly known that COVID-19 isn't a fomite disease?

A. Yeah, that it didn't play a large role in transmission, especially in the community.

MR. KITTREDGE: So, I'll stop sharing that. And Josh, I am just going to mark all of these tweets that I am going to show at the end of the cross-examination. So, they'll come as a collection unless you have any objection to that?

MR. HUNTER: That's fine, unless of course there's any we find objectionable, which we'll let you know at the time.

MR. KITTREDGE: Sure, okay.

(WHEREUPON Exhibit B : Collection of tweets from Dr. Zain Chagla.)

BY MR. KITTREDGE:

85. Q. The SARS-coV-2 virus is generally transmitted by respiratory droplets and aerosols expelled by an infected person; is that correct?

A. Correct.

86. Q. And transmission is much, much more likely

indoors than outdoors, is that correct?

A. Correct.

87. Q. In fact, at least 99.9 per cent of cases are the result of indoor transmission, isn't that true?

A. Yeah, I -- I know there was one study out of Ireland that suggested that 1 in 100,000 was outdoors versus indoors.

88. Q. Right.

A. So ---

89. Q. Well, that's a ---

A. Yeah.

90. Q. That's a very small number. And why do you think that is?

A. Ah, I mean the outdoors has the -- you know, as we talk about ventilation as a particular mechanism for mitigating COVID spread, the more air that's exchanged, the more the air that's diluted basically means less of particularly those small aerosols that are hanging out in the air. And, you know, the outdoors is essentially pure air dilution, in the sense that you're exchanging air every second of the day basically.

91. Q. Right. I am going to -- I have sent a couple of documents to you via Josh.

A. Yeah.

92. Q. And I'd like you to open the document called Why we Need to Change the Narrative on Outdoor Transmission thestar.pdf.

A. Just give me one second here.

93. Q. Sure.

A. Let me -- sorry, literally every five seconds there's an email, so I have to ---

94. Q. I am familiar with the feeling.

A. Yeah, yeah, okay. So, this is an article that myself that Dr. Chakrabarti and Heidi Tworek wrote in April of 2021.

95. Q. Great. Can you read the date of the -- the date it was published for me, please?

A. Yeah, April 12th, 2021.

96. Q. All right. And can you read the first highlighted sentence fragment there?

A. Outdoor activity is generally safe whether there are ten cases a day or 10,000, even with variants of concern.

97. Q. And that was your opinion at the time you wrote this?

A. Yeah.

98. Q. And is that your opinion now?

A. Yeah, still with that mitigated outdoor transmission is safe in that sense.

99. Q. All right, and can you scroll down a little bit and read the second highlighted sentence fragment?

A. Being, ah -- being outdoors is much safer and may prevent transmission indoors.

100. Q. And when you say it may prevent transmission indoors, what do you mean by that?

A. Yeah, I mean I think the context of that article was in April when outdoor activity was largely being discouraged a little bit, or people were talking much more about the risk of outdoor transmission.

And, you know, counterfactual was, you know, if you're not giving people the ability to interact in a safe manner, and doing it outdoors versus indoors, you may be pushing them indoors. Which is the opposite of what we would want to do. We would want people to embrace, you know, mitigation outdoors as compared to indoors. And be able to use that appropriately.

101. Q. So, restrictions on outdoor gatherings could have the effect of increasing COVID transmission; would you agree with that?

A. Yeah, I mean especially in April when -- when things were so restricted. Again, the opinion of that article was really that, you know, we -- we should allow for outdoor activity a little bit more

freely to really use that as our mitigation technique.
102. Q. Some outdoor activities, like for example using playground equipment might be more risky if fomites were a significant COVID transmission factor, would you agree with that?
A. Yes. If it was a real, real concern, then certainly playgrounds would have been an issue. But clearly it wasn't with this.
103. Q. But as we discussed it's been well known that fomites weren't an issue since at least July of 2020; is that correct?
A. Absolutely. And again, outdoor equipment has other issue -- even viral infections on outdoor equipment, there's UV lights, there's temperature issues, and so it's not as simple even as saying -- even if there was fomite infect -- fomite issues that outdoor play equipment would be even then a significant cause.
104. Q. Right. Would you agree that NPI's which limited outdoor activities and gatherings did little or nothing to control the spread of COVID-19?
A. I think there may have some justification for ones that involved significant capacity. So, when you have lots of people that were enclosed is very small outdoor spaces, there may have still been a risk

of transmission there. But certainly, you know, outdoor activities where people could appropriately physical distance, probably were reasonable to do throughout the pandemic.

105. Q. Would you agree that NPI's which limited outdoor activities and gatherings may have, in fact, had the opposite effect, that is to say that might have contributed to the spread of COVID-19?

A. Yeah, I mean I think being liberal about the outdoors was -- was certainly a -- a messaging issue. And again, this is justification for that article. There were many jurisdictions that kept an outdoor facing presence and actually encouraged it.

And, yeah, it -- if people can be given the instructions on how to do an outdoor gathering appropriately, and be able to do it appropriately, you know, it -- it could certainly help with mitigating some of the human needs for, you know, a gathering or being with others.

106. Q. Right. And yet during the pandemic the province has issued quite a few public health orders which limited outdoor activities and gatherings, right?

A. Yeah, there have been capacity limits outdoors throughout the pandemic. There's been

certain activities that haven't been allowed. There's been the need for masking when people have been close contact outdoors. There's been shutdowns of outdoor facilities like ski, parks, that type of thing.

107. Q. And there have been limitations on attendance at outdoor religious services, isn't that correct?

A. Yes, there have been gathering limits, essentially for all outdoor activities, but including religious gatherings.

108. Q. Right. And in fact, in late April 2021, just about a week after the publication of this article, the province issued public health orders that severely limited outdoor gatherings and activities. Isn't that right?

A. I don't know exactly. My timelines are always a bit messed up. I know there was a -- a moment where they really limited things like playgrounds and that type of thing, in April, I don't know the exact dates, but I think it was around the time of this article.

109. Q. Right. And in -- in amongst those restrictions, a number of outdoor activities were banned, for example camping on Crown Land and in provincial parks was banned; is that correct?

A. I be -- yeah, I remember that, yes.
110. Q. Golf courses were closed?
A. Yeah, I remember that.
111. Q. Pickle -- pickleball courts, whatever they may be were closed ---
A. Closed, yes, exactly.
112. Q. Do you believe that these measures were effective ways to control the spread of COVID-19?
A. No, I mean I think we could have given people guidance in terms of what camping means in the COVID-19 pandemic, i.e., you shouldn't be in a tent together and you can distance yourself when you're hanging out together outdoors, and that would largely reduce the vast majority of risk.

And similarly, for, you know, a golf course what the expectations are that people stay outdoors for their golfing activity, that they distance while they're on the course, that type of thing. So, yeah, I -- I don't think, you know, large shutdowns of the outdoors without guidance were necessarily reasonable in that context.
113. Q. And do you think that these measures were justified from a public health perspective?
A. I think there could have been a lot more work. And we've seen in other jurisdictions that

outdoor gatherings were mitigated as compared to closed. And again, that they -- you know, as you said in that article, the worry was that if you start restricting the outdoors more that you may, unfortunately, push people indoors which is exactly what we don't want.

So, I think there was an opportunity there to try to enhance outdoors.

MR. KITTREDGE: Right, and I think I may have overlooked marking that Toronto Star article as an exhibit. Can I -- can the reporter confirm whether I did that or not?

THE REPORTER: Counsel, the -- I've listed your Exhibit A as a Public Health Ontario summary from December 12th, 2021. B I've just put loosely as collection of twitter screenshots, I am assuming there is more to come.

MR. KITTREDGE: Yes.

THE REPORTER: You did not mark -- list or suggest a listing of another exhibit after that.

MR. KITTREDGE: Great. Okay. Let's -- this document that we -- that we identifies as Toronto Star article by Dr. Chagla and others, published on April 12th, 2021, I'd like to make that

as Exhibit, what would that be C?

THE REPORTER: That would indeed be C, yes.

MR. KITTREDGE: All right, to the Affidavit. And let's call it Toronto Star, Why We Need to Change the Narrative on Outdoor Transmission.

Counsel, do you have any objection to that?

MR. HUNTER: No.

(WHEREUPON Exhibit C : Toronto Star article April 12th, 2021.)

BY MR. KITTREDGE:

114. Q. All right, sorry about that Dr. Chagla, a little absentmindedness on my part.

So, the orders that were put in place in April of this year, 2021, also limited attendance at outdoor religious gatherings to just ten people, didn't they?

A. Ah, I don't have the orders off the top of my head, but I believe there were gathering limits for outdoors for outdoor religious gatherings. I don't remember the exact numbers.

115. Q. Right. But does -- do you remember the limit being something in the neighbourhood of ten people. Does that sound ---

A. Yeah ---

116. Q. --- fair ---

A. --- I believe so. I believe so, yes.

117. Q. Yes. And that was on outdoor gatherings, just to be clear.

A. Yes.

118. Q. And that limit was in effect until sometime in June, wasn't it?

A. Yeah, I believe in June it was taken to 25. So, yeah, I guess that was the baseline.

119. Q. Right. Attending an outdoor religious service is generally safe whether there are ten COVID cases a day or 10,000, isn't it?

A. Yeah, as long as people use their mitigation techniques in terms of distancing appropriately, it could be considered safe. Not zero risk, but certainly much decreased risk from indoor gatherings for sure.

120. Q. But you would characterize it as safe?

A. Yeah, I would -- you know, the -- I think if you put all the mitigation techniques in there, then -- then it would be considered safe from -- from that standpoint.

121. Q. Okay. Do you think restricting attendance at outdoor religious gatherings was an effective way

to control the spread of COVID?

A. I would say that as numbers go up, of people at an event, the ability to make sure that mitigation techniques are appropriate and audited and enforced, gets harder and harder.

So, you know, if you could do it perfectly. You know, make sure everyone's distanced, no one's interacting. There's not much, you know, direct contact from person-to-person, then, you know, you could make those events work. But from a practical standpoint, the more people that are out there, the more chance that that you then breakdown some of those barriers that help mitigate outdoor transmission.

122. Q. Right. It's not very hard to find enough space to adequately distance ten people, is it?

A. No, I mean I think we can probably find that in a parking lot or a park, or something along those lines.

123. Q. I mean it's not very difficult for that matter to find space to adequate -- adequately distance 25 people or 50 people.

A. Yeah, no, I agree. Again, you just have to have the space. And you have to have the audits, and kind of the tools to make sure that people are doing appropriately and correct it, if not.

124. Q. Right. And those restrictions on attendance at outdoor religious gatherings may have actually contributed to the spread of COVID, wouldn't you agree?

A. I mean I obviously don't know what happened as people wanted to congregate religiously, whether or not they did it virtually or in their own homes, or otherwise. But certainly, you know, for things like social gatherings, I think, you know, there was always a worry for all of us that people didn't use the outdoors and then came indoors and kind of just didn't need their tools anymore, because they didn't find anyway to do them appropriately.

125. Q. So, it is possible that the religious gathering restrictions on outdoor gatherings contributed to the spread of COVID?

A. Yeah, if people came indoors to do their gatherings, you know, against the provincial rules, then -- then, you know, technically that would be a high-risk scenario.

126. Q. Right. I am once again going to share my screen with another in the series. Can you see that image?

A. Ah, yeah.

127. Q. And do you recognize that image?

A. Yeah, it's a tweet of mine from May 2020, May 31st, 2020.

128. Q. And can you read the tweet to us?

A. Protest is enshrined in universal human rights, for those of you who exercise your rights, please keep track of your symptoms, isolate, get tested in the coming days. I pray there is no transmission, but if there is, keeping others safe is paramount.

129. Q. And do you remember what this was in reference to?

A. I believe this was to the Black Lives Matter protests that were going on in May of 2020.

130. Q. And would you characterize those protests as large gatherings?

A. Yes, quite large.

131. Q. And would you say that proper social distancing was followed at all times during those protests?

A. No, they were chaotic. They were all over the place. And so, you know, I -- and -- and there was really no protocols for a lot of them; they were informally organized.

132. Q. And yet you're supportive of these protests on the basis ---

A. Ah ---

133. Q. --- presumably that protest is enshrined in universal human rights?

A. Yeah, I -- I didn't say that they were necessarily the best thing, but if people chose to do it, you know, these are the mitigation techniques for making sure that people had not acquired COVID-19 at these events.

134. Q. Would you agree that the right to practice one's religion as one chooses is also enshrined in universal human rights?

A. Yeah, but ---

MR. HUNTER: That's a legal question.

THE DEPONENT: Oh ---

MR. KITTREDGE: Well, I mean this is a -- a conclusion that he came to himself about protests. I am asking if he feels the same way about the right to practice religion.

MR. HUNTER: He can answer as to his own views. Obviously, he -- it will be for a Court to determine what if any ---

MR. KITTREDGE: Sure, I am not asking for him -- I am not asking for a legal conclusion.

MR. HUNTER: Yes.

MR. KITTREDGE: I am just asking for his own opinion.

THE DEPONENT: Then my own view that people, you know, should be able to -- to practice their religion.

BY MR. KITTREDGE:

135. Q. Right. You would say that that is also enshrined in universal human rights ---

A. Yeah, I ---

136. Q. --- in that sense that you ---

A. --- think the right to practice religion is -- is to me a fundamental piece of people's rights.

137. Q. All right. So, I would like you to open up another one of the documents that I sent over. And this one may be familiar. It's called Assessment of Burden on Essential Workers .pdf.

A. Yeah.

138. Q. Could you -- is this document familiar to you?

A. Yeah, this is paper, is a collaboration with myself, and a number of folks from Toronto that we wrote and published -- the pre-print was published, I think, in April or May of 2021, but this recently just go published in Jama Network Open I think about two

months ago.

139. Q. All right, can you briefly summarize the study for us and your findings?

A. Yeah, so, this is a study looking particularly as the variants of concern that were identified in December of 2020 started emerging in Canada. Ah, and looked at populations in Peel and Toronto based on income, and that was using census demographic data, and as well as essential work status. And again, breaking down by neighbourhoods.

And looked at these neighbourhoods from highest to lowest essential work, and highest to lowest income, in terms of where COVID cases grew, but also where these variants of concern emerged. And the whole purpose was to, you know, recognize that this was actually a nice time to kind of revisit the pandemic and track where COVID actually was transmitting at the highest burdens, and what mitigation techniques, you know, would be appropriate in that population.

140. Q. And the data is broken down by employment in essential work. How were you able to determine whether a given case was associated with essential work?

A. So, it was not necessarily individual cases

that were essential work. But it was the neighbourhoods that they were in that were represented by essential workers.

So, we couldn't get down to the granular data of does this person work in factory? It was, you know, is this a -- does this person live in a neighbourhood that has a high representation of people that work in factories? So, it's not -- it's an imperfect measure.

141. Q. Okay. What period did the study cover? In other words, when you talk about cases, when did those cases take place?

A. So, this was -- let me just pull them the exact -- but it was during the emergence -- so, February 3rd to March 10th of 2021.

142. Q. Okay. So, it covered about a month then?

A. Month and -- yeah, month and a half, yeah.

143. Q. All right. How many outbreaks involving essential workers occurred during that period?

A. There were several. In the GTA alone I think we heard about many, but there were a lot of workplace outbreaks. I don't know the exact number, but there were several for sure.

144. Q. And several, what do you mean by several? Like a ballpark number? Ten, 100, 1,000?

A. I would say probably in the hundreds given that they were the only things that were really opened at that point in the pandemic.

145. Q. All right, you've been quite critical of the governments failure to take action to support essential workers, haven't you?

A. Absolutely.

146. Q. What do you think the government should have done to support essential workers?

A. Yeah, I mean, I think there were a number of issues. One was the fact that income supports were difficult. And -- and so people's -- again, behaviours to go get tested even if they had minor symptoms, their ability to isolate, and take financial hardships for the sake of, you know, protecting their communities against COVID-19 put people in a very difficult choice.

And, you know, unfortunately, again, transmission in workplaces, led to transmission in-homes. And were overrepresented in terms of what that meant in our healthcare system, particularly in Peel and Toronto, where many other establishments were closed during the third wave. And so, you know, they were the people that were -- had to be out there that were getting infected at the highest quantity.

147. Q. Right, and how much of an impact do you think putting income supports and the other measures that you proposed in place would have had on essential worker COVID infections, hospitalizations, and/or deaths?

A. Yeah, I mean I ---

MR. HUNTER: So, I -- just -- sorry, hang on.

THE DEPONENT: Sorry.

MR. HUNTER: I fail to see the relevance of these questions to a challenge to gathering restrictions.

MR. KITTREDGE: Ah ---

MR. HUNTER: The government had a million different policy choices, and a million different things, with a million different people. What's the relevance?

MR. KITTREDGE: Well, we're getting there. Let me just see if I can just jump to something that's sort of -- should make it clear.

BY MR. KITTREDGE:

148. Q. Well, would you -- would you agree that there have been far more cases and far more outbreaks of COVID-19 associated with essential workers, than there have been -- than there have been cases and

outbreaks associates with religious gatherings?

A. Yes, and workplaces have had to be open throughout the pandemic. So, you know, it's kind of proportional in that sense that there's been a -- more people at risk in the sense that they've been workplaces in that sense.

149. Q. Right. Essential workers working indoors face greater COVID risks than people working outdoors, wouldn't you agree?

A. Yeah, yeah, the same science about outdoor transmission.

150. Q. Many workplaces have suboptimal ventilation, wouldn't you agree?

A. Yeah, absolutely.

151. Q. Essential workers would typically be at their workplaces for extended periods of time, shifts of eight hours, or more are common; wouldn't you agree?

A. Yeah.

152. Q. Coworkers are likely to socialize and talk with each other during their workday, would you agree?

A. Yeah.

153. Q. Yelling or talking loudly is pretty common in some workplaces, in particularly where loud background noise is an issue, right?

A. Yeah.
154. Q. People sometimes sing while they work, right?
A. I presume so. I don't think I have seen that. But sure.
155. Q. And people doing strenuous work may breathe heavily, right?
A. Yes. Yes.
156. Q. People often develop friendships with their coworkers, right?
A. Yeah.
157. Q. Close friendships sometimes?
A. Yeah.
158. Q. And it's not unheard of for people to hug their coworkers, is it?
A. Yeah. No, absolutely.
159. Q. Someone working as a cashier in a retail environment might have close to face-to-face interactions with hundreds of shoppers per day. Does that sound reasonable?
A. Yeah.
160. Q. And plexiglass barriers at checkout counters in retail stores have been a requirement for much of the pandemic, but people typically just stand at one end of the barrier or the other, don't they?

A. Yeah, they're not -- they're an imperfect method for preventing COVID transmission. They may help, but there are -- there are, you know, certainly human behavioural factors that make them imperfect.

161. Q. Right. And as you mentioned before due to financial pressure essential workers may be reluctant to get tested for COVID or to take time off work if they feel sick; is that right?

A. Yeah.

162. Q. Financial pressure may incentivize them not to be truthful with screening?

A. Yeah, absolutely.

163. Q. Infected essential workers who are undiagnosed, asymptomatic, or pre-symptomatic, could spread disease to their co-workers, is that correct?

A. Yeah.

164. Q. Essential workers may not always wear masks properly, may not have access to well fitted masks, and in some cases may not choose to wear masks at all, right?

A. Yeah.

165. Q. It seems that essential workers share a lot of characteristics with churchgoers, wouldn't you agree?

A. Ah, I am -- in what sense?

166. Q. Well, a lot of the characteristics that you point to in your Affidavit as transmission risk factors associated with religious gatherings, are also characteristics of many workplaces, wouldn't you agree?

A. Yeah, I mean the same features that cause COVID transmission indoors amongst people, you know, are there in workplaces.

And, yeah, they were the ones that we mention in the Affidavit around churches in terms of heavy breathing, singing, close contact, poor ventilation.

167. Q. Right. So, moving on to healthcare capacity. You expressed concerns in your Affidavit that Ontario's healthcare system could have been overwhelmed by COVID-19. You say at paragraph 5(b) that there were 891 people in intensive care units at the peak of the third wave. Were those all COVID patients?

A. There were 891 COVID related critical illnesses. So, those are patients who have active COVID-19, but also patients who are not infectious form their COVID19, but still sitting in the ICU.

168. Q. For reasons related to COVID-19.

A. Yeah.

169. Q. They're recovering ---

A. Yeah, yeah, they're still recovering from COVID-19 or not recovering from their COVID-19 in that sense.

170. Q. Right. Approximately how many intensive care beds are there in Ontario?

A. I actually don't know the answer to that question. I think there -- the -- the staffed beds are even 1,200, 1,300 range at the kind of crisis capacity. But -- but active functioning kind of day-to-day beds is much lower in that sense.

171. Q. Intensive care units are designed to run at or near 100 per cent capacity, are they not?

A. Yeah, I mean, I think we -- we all know our ICU's are pretty filled at baseline, for the, you know, regularly staffed beds.

172. Q. And that's the case pandemic or no pandemic, isn't that correct?

A. Yeah, hospital capacities have always been high pre-pandemic.

173. Q. Right. Prior to 2020 it wasn't uncommon for hospitals and ICU's to have occupancy rates of over 100 per cent, would you agree?

A. Yeah, absolutely.

174. Q. You go on to say that these 891 patients

required the potential indication of a triage protocol to limit access to intensive care units for those with the best prognosis.

Ontario hospitals never implemented such a protocol though, did they?

A. They did not. They did make preparations to invoke it. And I was involved in that. But -- but, yeah, they did not have to.

175. Q. You mention that these 891 patients required redeployment of healthcare staff and transferring patients to other hospitals. Pandemic or no pandemic, it's not at all uncommon for Ontario hospitals to redeploy healthcare staff or to transfer patients to other hospitals, isn't that correct?

A. Yes, but the magnitude of it was significantly more than had ever been seen before. You know, we -- it's not uncommon for small hospitals to send large hospitals patients. It is uncommon to see, you know, hundreds of patients going from one hospital to another hospital.

176. Q. You mentioned that these 891 patients caused elective surgeries to be cancelled. In May 2020, in response to the COVID pandemic, the Ontario Government imposed criteria that hospitals had to meet in order to perform non-emergency surgeries, isn't that true?

A. Yes.

177. Q. In order to perform non-emergency surgery a hospital's total occupancy rate had to be 85 per cent or lower; is that correct?

A. Yes, those were the guidelines after the first wave, I believe.

178. Q. Yes. And would you agree that that requirement handcuffed hospitals that were running well over 100 per cent capacity for years?

A. I mean it wasn't easy to impose as part of that. So, you know, certainly it's -- you know, the need to have a buffer was -- was part of us dealing with the surge. But it definitely had impacts on us being able to -- to scale up things like elective surgeries of have need for us to innovate elective surgeries to make sure that they were done, and people go out, you know, not admitted to hospital.

MR. KITTREDGE: All right, and I am just realizing I also forgot to mark the last exhibit.

I'd like to mark the Assessment of the Burden of SARS-coV-2 Variants of Concern Among Essential Workers in the Greater Toronto Area of Canada, Dr. Chagla's paper that I was referring to a moment ago, as Exhibit D, I believe to my -- to the

cross-examination.

THE REPORTER: That's correct. It's marked.

MR. KITTREDGE: Pardon me? It is marked?

THE REPORTER: I've just marked it, Counsel, as Exhibit D as requested.

MR. KITTREDGE: Okay, great. Do you have any objection, Counsel?

MR. HUNTER: No.

MR. KITTREDGE: Okay.

(WHEREUPON Exhibit D : Dr. Chagla's Burden of SARS-coV-2 paper.)

BY MR. KITTREDGE:

179. Q. Do you think the requirement, the criteria requiring hospitals to remain under 85 per cent capacity in order to perform non-elect -- or non-emergency surgery was justified from a public health perspective?

A. Ah, there were two sides of the coin. I think there was a need for us to have rapid surge capacity to deal with, you know, COVID was a transmission issue in the community, and us to have a buffer. But at the same time, you know, as we all know healthcare runs pretty ragged, and -- and there's

a lot of burden. And with all the slowdowns in healthcare there was a large degree of delayed care that required more hospitalization. So, it definitely put a drag on our ability to scale up as aggressively as possible.

MR. KITTREDGE: All right, and I guess at this point I would like to mark the collection of tweets that I've shown you as Exhibit E to the cross-examination. And let's call it collection of tweets. Counsel, do you have any ---

MR. HUNTER: You already have that as B.

MR. KITTREDGE: Pardon me?

MR. HUNTER: I think we already have that as B.

THE REPORTER: That's correct, Counsel.

MR. KITTREDGE: Oh right.

THE REPORTER: I've already marked it as B.

MR. HUNTER: And I have no objections.

MR. KITTREDGE: Okay, great.

All right, and I am going to turn over the questioning to my colleague Hatim Kheir.

Would you like to take a short break before that? I don't expect we'll be going on for all that much longer.

THE DEPONENT: No, I am good to keep going.

MR. KITTREDGE: Okay. Hatim, do you want to take over.

MR. KHEIR: Yes, thanks.

BY MR. KHEIR:

180. Q. Good morning, Dr. Chagla.

A. Good morning.

181. Q. So, I'll just have a few questions for you. So, just to begin, first I should add my names Hatim Kheir for the record.

In the course of my research, I found that since the start of the pandemic to now, there have been approximately 92,000 people hospitalized with COVID across Canada.

In your opinion, is that an accurate number?

A. Yeah, I don't have the number off the top of my head, but that seems appropriate for -- for what we've seen.

182. Q. So, I want to go through some comparisons of hospitalizations and deaths due to COVID and those due to the flu. Would you agree that using weights per

100,000 as opposed to absolute counts would be a reasonable way to compare those numbers?

A. Yeah, absolutely.

183. Q. So, you may want to pull up a calculator on your phone or computer as we go through some of the numbers.

But just as a preliminary point, would you agree that 38 million is a reasonable estimate of the population of Canada?

A. Yeah.

184. Q. Okay, so, if we wanted to find the rate of hospitalizations, we could take the number of hospitalizations, which we've agreed is approximately 92,000 and divide by the population being about 38 million. And then multiple it by 100,000. Would you agree that's a reasonable approach?

A. Yeah. Yeah.

185. Q. So, when I do that calculation, I get 242 hospitalizations due to COVID per 100,000 population. Is that what you get?

A. Correct, yeah.

186. Q. Okay. So, since the start of the pandemic to now there've been approximately 242 people hospitalized due to COVID for every 100,000 members of the population in Canada, right?

A. Yeah.

187. Q. Okay, I am going to show you a document, so just bear with me while I bring it up on my screen. Actually, first I will go to the top here. So, first of all do you see my screen? Did that work?

A. Yeah, it's a FluWatch from the public health agency of Canada.

188. Q. Okay. And are you -- are you familiar with these FluWatch documents?

A. Yeah, this is a lot of different surveillance networks that look at influenza rates across community, and self reported respiratory infection in the community.

189. Q. Okay. And so, I am just going to -- I am going to go down to page 8 here. And so, you here at the top there's a table where hospitalization rates per 100,000 for different age groups and different flu seasons, right?

A. Yeah.

190. Q. And so, it says for the 2018 to 2019 flu seasons, there were 45 hospitalizations per 100,000 for -- overall across the age groups, right?

A. Yeah.

191. Q. And looking at the previous years, would you agree it's comparable to previous years? It's not an

outlier?

A. No, no, I think that's the same across years.

192. Q. Okay. And in your experience would you agree that's a reasonable number in terms of trying to gauge the rate.

A. Yeah, again, FluWatch uses estimates. So, it's not perfect. You know, the COVID numbers are pretty precise numbers because they're literally the people that are being diagnosed with COVID that are being in the hospital. As compared to FluWatch which uses a bit of modelling to kind of get their numbers.

But, you know, they model based on sentinel networks. And so, would be, you know, accurate in that sense. They're -- they're just -- there is some error because it's not as perfect as saying x-number of cases, x-number of hospitalizations -- sorry, x-number of hospitalizations per 100,000.

193. Q. Right. In terms of trying to make comparisons, would you agree it's a reasonable number to work with?

A. Yeah, it's not unreasonable for sure. Again, this is their best estimate of flu activity in the community.

MR. KHEIR: Okay. I'd ask that

this exhibit be marked -- I believe it's exhibit F on the cross-examination.

MR. HUNTER: Fine. Fine.

MR. KHEIR: And we could call it FluWatch Report 2018 to 2019.

THE REPORTER: That will be Exhibit E. Counsel, yes, that's no problem.

MR. KHEIR: Okay. Thank you.

(WHEREUPON Exhibit E : FluWatch Report 2018 to 2019.)

BY MR. KHEIR:

194. Q. So, I am just going to take this down off my screen.

Okay, so, the number that we got for COVID, which was 242 hospitalizations per 100,000 it's about five times ---

A. Yeah ---

195. Q. --- the number we got for influenza, which was 45.

A. Yeah.

196. Q. Hospitalizations per 100,000.

Now, the number that we used for the rate of hospitalizations due to COVID that's based on two years of pandemic until now.

So, when we're comparing the numbers,

totalling one year of the flu, would you agree that to make a meaningful comparison it would make sense to compare it to two years of influenza?

A. The rate per 100,000 per year should be -- oh, I see what you mean. So, yeah, yeah, I see what you mean. So, yeah, a single year would be probably a better comparison if you're going to do absolute numbers for absolutely hospitalizations. Yes, I see what you mean.

197. Q. Okay. So, if we wanted to compare it to two years of the flu, we could double our rate for flue hospitalizations. So, we would get about 90 hospitalizations per 100,000?

A. Correct.

198. Q. So, when we -- when we compare those numbers then, the rate we calculated for COVID being 242 hospitalizations per 100,000, it's actually about two-and-a-half times the hospitalization rate we calculated for two years of influenza which was 90 hospitalizations per 100,000, right? Okay.

Are you aware of roughly how many people have died of COVID since the beginning of the pandemic across Canada?

A. I don't know the figure off the top of my head. I think we did pass 100,000 deaths at some

point, but I am not sure actually. I -- I don't know. I don't keep track of the numbers.

199. Q. Yes, that's fair. Here, I will show you -- I'll bring up the daily epidemiological reports. I'll just share my screen. Okay, you see that?

A. Yeah.

200. Q. Okay. So, can you identify this?

A. Ah, this is Canada epidemiologic update as of December 13th at 7:00 p.m. And total deaths of 29,941, including 15 deaths today.

201. Q. Okay. And as far as you're aware this is a -- this is an accurate number?

A. Yeah, this is the public health agency of Canada, so all provinces have to report to them.

MR. KHEIR: Okay. I'll just stop sharing my screen.

And before I forget, if we could have that marked as Exhibit F.

MR. HUNTER: Yes.

MR. KHEIR: This be -- be daily epidemiological summary for COVID-19.

(WHEREUPON Exhibit F : Daily Epidemiological Summary for COVID-19.)

BY MR. KHEIR:

202. Q. So, saying about 30,000 -- I think it was

29,000 and change, but about 30,000 in a population of 38 million. I get a rate of deaths of 79 deaths due to COVID per 100,000 population.

Is that what you get?

A. Yeah, I think so.

203. Q. I'll give you a moment if you want to just double check that.

A. Sorry, it's 29,000 deaths per 38 million population, times 100,000. I am 76; is that correct?

204. Q. Yes. So, I am going to -- and I apologize for bouncing around all these documents.

A. No ---

205. Q. But I am going to show you something else. Okay, so, do you see my screen?

A. Yes, this is the NASI Influenza Vaccine Statement from 2019, 2020.

206. Q. And I take it you may not have reviewed this particular document, but are you familiar with these -- these NASI statements?

A. Yeah, yeah, they put up statements for all different kinds of vaccines using the epidemiology and we see the vaccine information at the top.

207. Q. Okay. So, I am just going to scroll down to the first page here. And just that first paragraph in the introduction it -- it lists an estimate of 3,500

deaths related to influenza per year. Is that a reasonable estimate in your opinion?

A. Yeah, I think so. Yeah.

MR. KHEIR: Okay. And if we could have that marked Exhibit, I believe we're on G now. And we can -- we can call it the NASI Seasonal Influenza Vaccine Statement for 2019 to 2020.

MR. HUNTER: We can mark it, however I haven't seen a copy of that. So, if you could send me a copy before the re-exam that would be appreciated.

MR. KHEIR: Okay, will do.

(WHEREUPON Exhibit G : NASI Seasonal Influenza Vaccine Statement for 2019 to 2020.)

BY MR. KHEIR:

208. Q. So, if we're looking at an estimated 3,500 deaths due to flu every year in Canada, and we're looking at a population of about 38 million, I calculated that that would be about nine deaths due to flu per 100,000 population. Do you agree?

A. Sorry, I haven't calculated that. But I think that sounds about right. 3,500... yeah. Times 100,000. Yeah. Nine.

209. Q. Okay. So, the number that we calculated for the COVID death rate which was about 76 deaths to

COVID per 100,000 that's a -- it's about nine times the rate we got for influenza, which was nine deaths per 100,000, right?

A. Yeah.

210. Q. Okay. Now, just like with when we were comparing hospitalizations, we're looking at two years of COVID deaths. So, to make it a meaningful comparison we could compare it to two years of the flu. We could double our number to 18 deaths due to flu per 100,000, right?

A. Yeah.

211. Q. And so, in that case, the rate we calculated for COVID being 76 deaths per 100,000 it's actually about four-and-a-half times the rate we've calculated for two years of influenza being 18 deaths per 100,000, right?

A. Correct.

212. Q. Okay. Now, the numbers we've been looking at in terms of flu deaths and hospitalizations are associated with the seasonal influenza. But influenza, I understand, can also spread a pandemic, right?

A. Correct.

213. Q. And for example, there was an influenza pandemic in 1967 to '58, sometimes called the Asian

Flu.

A. Correct.

214. Q. Are aware of the death toll of the Asian Flu pandemic?

A. I am not sure.

215. Q. If I were to suggest to you it would be one to four million globally, would that be -- would that be a reasonable estimate?

A. I'd have to look at the actual estimates as reporting in the 1950's is, you know, largely not as great as it is in the digital era. So, point estimates are hard to -- to arrive in that sense as compared to -- you know, compared to 2021 data.

216. Q. That's fair. So, I am just going to show my screen again. Can you -- can you identify this document?

A. Yeah, World Health Organization Pandemic Influenza Management WHO interim guidance.

217. Q. And if I -- I am just going to go down to page 19 here. And there's a table in the middle of this page. It's titled characteristics of the past four influenza pandemics. Right?

A. Yeah.

218. Q. I'll zoom in. And now, specifically I -- I highlighted the row I was interested in. But it

suggests that the estimate attributable mortality worldwide for the Asian Flue was one to four million.

A. Yeah.

219. Q. In your opinion is that -- is that a reasonable estimate?

A. Again, presumably this is the World Health Organization, they've done their research. Again, these are estimated that are made from health records at the time and modelling. But it's probably the best estimate that could be made of it. I wouldn't say it's, you know, perfect, but it's probably as good as it's going to get in terms of a point estimate.

220. Q. Okay. So, I'll just stop sharing that again.

And so, if I were to suggest that the world population in around 1960 and 1957 was approximately 3 billion, do you accept that's a reasonable estimate?

A. I don't obviously know this off the top of my head. But I think that's what -- I presume we could look that up very quickly in terms of what the global population was at that point in time in history.

221. Q. So, if we -- if we want to calculate a population rate again for this mortality of the Asian Flu, and we're looking at -- we can look at first the

low end of the -- the estimate, it was one to four million. In a world population of about three billion I get about 33 deaths due to the Asian Flu per 100,000.

A. Yeah, okay. I am just trying to -- sorry, three one million. Lots of seroprevalence data, sorry. I don't think my calculator goes that high, but 33, yeah.

222. Q. Okay. And then on the high end of the rate being four million, I got 133 deaths per 100,000. Does that seem right to you, okay.

So, in that case the number that we came up with for COVID deaths per 100,000 which was 76 deaths, it falls within the range of estimated deaths. Or the estimated death rate, I should say, caused by the Asian Flu pandemic, right?

A. Yeah.

MR. KHEIR: Okay. And I suppose the -- the WHO Pandemic Influenza Risk Management Guide should be marked as Exhibit H.

THE REPORTER: That's correct, Counsel.

MR. KHEIR: Okay, thank you.

(WHEREUPON Exhibit H : WHO Pandemic Influenza Risk Management Guide.)

BY MR. KHEIR:

223. Q. Okay. And I am going to, once again, share my screen. Okay, do you see my screen?

A. Yeah.

224. Q. And I believe my colleague, Mr. Kittredge, already brought this document up. But can you just identify it for the record?

A. Ontario Health Plan for an Influenza Pandemic.

225. Q. Right. And it just says here it's Chapter 1, right?

A. M'hmm.

226. Q. And the document's dated March 2013?

A. Yeah.

227. Q. Okay. So, are you familiar with this document?

A. I have not read it, but I know this was generated, I think after 2009, after the H1N1 pandemic in terms of what to do for future pandemics.

228. Q. Okay. So, I am just going to take you to page 14 here. And well, you can see in the table and the text above it, that's providing context. They've essentially created or contemplated four different pandemic scenarios based on two -- two variables, right? The first variable is clinical severity.

A. M'hmm.

229. Q. And the second being transmissibility.

A. Yeah.

230. Q. Okay. And so, from that they generate four potential scenarios which, sorry, bear with me I'll just read for the record being low transmissibility, low clinical severity, high transmissibility, low clinical severity, low transmissibility, high clinical severity. And finally high transmissibility, high clinical severity, correct?

A. Yeah.

231. Q. Okay. And just going to the next page here. And they've essentially set out a table with those -- those four scenarios. One's -- it's on the next page, so if you need me to flip back and forth just ask.

And then they just included a fifth unknown category, right?

A. Right.

232. Q. Okay. And in this column here, you see they provide some examples of pandemics which would fall into the categories they've contemplated.

A. Right.

233. Q. Okay. And they -- they would place the 1957 influenza pandemic under the low transmissibility, high clinical severity, category?

A. Yes.

234. Q. Okay. And they also provide here in this table, characteristics that would place a pandemic into that category. And they -- they provided three -- three characteristics, right? Cumulative attack rate, the reproductive rate, and the case fatality rate. Right?

A. Yeah.

235. Q. And so, looking at these, these characteristics and the examples provided, and once again if you need me to -- to go the next screen just ask. But what category would you place the COVID pandemic in?

A. Ah, what was the -- can I see the last one there? So...

236. Q. Yes.

A. Ah, high transmissibility, high clinical severity. I am just trying to think of the case counts. Probably, I mean it -- it's hard right on the spot, but I would say either between high transmissibility, low clinical severity and high transmissibility, high clinical severity. But between one of the two.

237. Q. So, either -- sorry, high transmissibility, low clinical severity or ---

A. It ---

238. Q. --- high, high ---

A. --- high transmissible. High, high, yeah, exactly.

239. Q. Okay. Now, so, I just want to look at these -- these characteristics that are being presented.

And, you know, since -- since we're -- the rest of us here aren't medical experts, for our clarification, there's a footnote here explaining that cumulative attack rate. It refers to the percentage of people who are expected to become symptomatic at some point during the influenza pandemic, right?

A. Yeah.

240. Q. Now, to date, there have been about 1.8 million confirmed cases of COVID in Canada, right?

A. Correct.

241. Q. So, with a population of 38 million, that number would be far below that 21 per cent cut off. Right?

A. Yes, although, I would again with the earlier testimony was, you know, again is the confirmed -- the confirmed cases may not capture every symptomatic individual out there. And there may be a discrepancy here.

242. Q. So, given that you -- you've -- you've

testified you think that the -- the percentage of cases that we capture has -- has -- it has fluctuated throughout the pandemic.

A. M'hmm.

243. Q. Do you -- do you have an estimate in terms of this 1.8 million number, what that would compare to the actual number?

A. Yeah, I mean 1.8 on 3.33 38 million, there were some seroprevalence data-prevalence data, again, that suggested up to 15 per cent of the population was infected at any given time. So, -- or, sorry, at that kind of third wave.

So, I would suspect that would mean, I am just trying to do that, ah, 3.8 plus -- yeah, I mean 15 per cent as -- what I mean, that is 15 per cent. So, you know, I would say it has varied. But, you know, I would say somewhere between ten and 15 per cent. And, you know, the pandemic isn't over yet.

So, it's hard to kind of say at this point in time if that's going to be the end number as compared to these pandemics that have ended.

244. Q. Okay, but looking at, you know -- we're now two years in. It doesn't appear we've reached that 21 per cent benchmark, right?

A. Yeah, but I would not say that 21 per cent

is not reachable, even in the next few months with what's coming down the pipeline.

245. Q. Now, to fall into the low transmissibility, high severity category, it also states that the reproductive rate must be less than 1.6, correct?

A. Correct.

246. Q. Would you agree that the -- the reproductive rate for COVID is currently less than 1.6?

A. Yes. In Ontario I believe it sits at about 1.3 or 1.3 today. But, again, reproductive rates are hard to interpret just from a daily point estimate that's based on cases, which is based on the number of people that are diagnosed.

And, you know, these are baseline reproductive rates for a disease process in a susceptible population with no mitigation measures in place.

And so, you know, making direct comparisons to a 1.6, you know, if we were to let COVID run wild, basically, you know, the estimates for even the alpha variant, which was circulating I think in April were somewhere in the three to four range. And the delta variant in the six range. So, you may have a reproductive rate that is actually much higher.

247. Q. Now, the example provided for the high

transmissibility and high clinical severity rate is the 1918 Influenza Pandemic, right? The Spanish Flu.

A. M'hmm.

248. Q. So, given the examples and where we've talked about some of these characteristics fall, I am going to suggest that it would be -- it would be reasonable to place the COVID pandemic into either the high transmissibility, and low clinical severity, category as you indicated. Especially if we look at in terms of the cases capturing a wider -- or the actual case number being a much larger number than caught by the -- the deep laboratory confirmed case counts. Would that be reasonable?

A. Yeah, I -- again, the CFR .25 per cent, I am -- of the confirmed cases, and again -- again, this is where it gets difficult to -- to kind of tease out what the true CFR is. But if we were using, you know, 29,000 deaths, and I forget how many of the cases were confirmed in Canada now, you know, it would be -- yeah, again, I don't know the exact say far off the top of my head. So, I would have to kind of look it up based on current data.

249. Q. Would you agree that the pandemic certainly falls within the range of scenarios contemplated in 2013 when this document was issued?

A. Yeah, I think between -- again, the two that I have identified high transmissibility, low clinical severity, and high transmissibility and high clinical severity. And again, the big thing is -- is the case fatality rate, which -- which is the distinguishing between the two.

MR. KHEIR: Okay. At this point if we could take a 15-minute break.

MR. HUNTER: Yes.

OFF THE RECORD

(WHEREUPON A BRIEF RECESS WAS TAKEN)

ON THE RECORD

THE REPORTER: Back on the record at 11:53 a.m. Counsel.

DR. ZAIN CHAGLA, resumed,

CONTINUED EXAMINATION BY MR. KITTREDGE:

250. Q. Dr. Chagla, in preparing your Affidavit you've had the opportunity review the Affidavit of Dr. Kettner, didn't you?

A. Yes.

251. Q. And that Affidavit was prepared for a party that has since dropped out of this matter. But you address his Affidavit at paragraph, what is it, 4 (O) and 4 (P), I believe.

I am wondering if you can take me through

your reasoning here as you ---

MR. HUNTER: We'll just stop there for a second. As you've already stated that Affidavit -- Dr. Kettner's Affidavit was prepared for a different proceeding.

It is not in evidence in this proceeding. And in accordance with the Court Order that the matters be heard together, but not consolidated, Dr. Chagla and Ali (ph) prepared some paragraphs in response for use in that other proceeding.

Ontario is not relying on those paragraphs in this proceeding, because of course, Dr. Kettner's Affidavit is not in evidence. And therefore, I will refuse any questions related to Dr. Kettner's Affidavit.

MR. KITTREDGE: All right. I would just take -- I would take the position that the paragraphs dealing with Dr. Kettner's Affidavit are properly in evidence in the matter that we are continuing forward with. And that questions about Dr. Chagla's reasoning regarding his criticisms of Dr. Kettner's Affidavit are fair questions in this matter.

But am I to understand that you're going to refuse to allow me to ask any -- or instruct

your expert to -- not to answer any questions that I may ask about Dr. Kettner's Affidavit?

MR. HUNTER: That is correct.

(WHEREUPON Refusal NO. 1: To answer any questions asked regarding Dr. Kettner's Affidavit.)

MR. KITTREDGE: And if I was to show Dr. Chagla Dr. Kettner's Affidavit would you permit me to do that?

MR. HUNTER: No, because our view that would be an attempt to lead new evidence after cross examinations have commenced without leave of the Court.

MR. KITTREDGE: All right, well, I would take the position that it's proper for me to put any statement by any doctor in front of Dr. Chagla and ask him what he makes of it, whether that statement is in the form of an Affidavit prepared for the other party that was formally involved in this matter or not.

So ---

MR. HUNTER: You can put the statements to him, but I am not going to allow the -- I am not going to agree to allow the Affidavit in as evidence.

MR. KITTREDGE: Right ---

MR. HUNTER: If you want to put a statement to him, and ask him whether he agrees with it or not, by all means. But it is not evidence of Dr. Kettner that is in this proceeding.

MR. KITTREDGE: Right.

MR. HUNTER: Because he is not an expert that's been qualified in this proceeding.

MR. KITTREDGE: But you're not going to permit any questions asking Dr. Chagla to take me through his reasoning and his criticisms of Dr. Kettner's Affidavit as a whole?

MR. HUNTER: Well, the Affidavit is not there in the first place, so, what's the relevance of that?

MR. KITTREDGE: Well, if I show him the Affidavit, it would seem that ---

MR. HUNTER: I think you have my refusal.

MR. KITTREDGE: All right. In that case, I forwarded a copy of that Affidavit to pass along to Dr. Chagla.

Do you have any objections to marking it for identification?

MR. HUNTER: It can be marked as identification, yes. On the basis that it's been

refused in case there is any further arguments need to take place as a result of that.

MR. KITTREDGE: Okay, great.

(WHEREUPON Exhibit NO. I : Dr. Kettner's Affidavit.)

BY MR. KITTREDGE:

252. Q. Dr. Chagla, just before I go, I guess I'd like to say I have been following you on twitter since early in the pandemic, so it's been a pleasure to talk to you.

And thanks so much for your time today. As well as for everything you've done over the past two years with regards to COVID. It's appreciated.

A. Thanks. Thanks a lot.

MR. KITTREDGE: All right, and no further questions.

MR. HUNTER: We will have a few questions of re-examination. Can we just take a five-minute break.

MR. KITTREDGE: Sure.

MR. HUNTER: Come back, say at 12:05.

MR. KITTREDGE: Sounds good.

MR. HUNTER: So, a seven-minute break.

THE REPORTER: Very good, Counsel.

OFF THE RECORD

(WHEREUPON A BRIEF RECESS WAS TAKEN)

ON THE RECORD

THE REPORTER: Back on the record at 12:08 p.m., Counsel.

DR. ZAIN CHAGLA, resumed,

RE-EXAMINATION BY MR. HUNTER:

253. Q. Dr. Chagla, you were asked about some areas where you and Dr. Hodge had disagreed.

Do public health experts always agree on everything?

A. Clearly not. There's been a lot of discrepancy and it comes from different places of knowledge and different kind of clinical experiences. So, yeah, absolutely not -- not everyone agrees.

254. Q. And there's a wide range, often reasonable interpretations of even the same data, much less different data?

A. Yeah, absolutely. And again it's -- it's people's experience and what they see. And -- and how they interpret that data.

255. Q. And are you aware of what data Dr. Hodge used when he was giving his opinions in cross-examination?

A. I presumed it was the numbers that were

displayed, but I am not entirely sure.

256. Q. And you mentioned zero prevalence data prevalence data, first of all, can you just explain what zero prevalence data prevalence data is?

A. Sorry, seroprevalence data.

257. Q. Sero, sorry.

A. And this is -- yeah, this is using antibody data to describe, you know, better rates. It's not perfect, but it gives a sense of who has been infected over a set timeframe by using the antibodies in people's blood to get a sense.

So, it would pick up some of those people that would not have necessarily gotten tested, people that were asymptomatic, or very mildly symptomatic, had not noticed that they were infected. As compared to PCR tests which are kind of triggered by people to go get tested.

258. Q. And do you know if we have that data available for the whole province, throughout the whole pandemic?

A. There has been intermittent -- so, there has been a couple of studies done to -- provincial health laboratory through blood donors. And then there's been the Canada Immunity Taskforce, which has kind of had more national data looking at this.

259. Q. So, we don't have it for as many people as have PCR tests for?

A. No, no, as -- and again, it's not -- it's a lot of data where they've looked at things like blood donors or healthy volunteers and tried to get prevalence and model it out from there.

So, it's a -- you know, not like everyone has given a blood sample to be enrolled in this.

260. Q. And are we anywhere close to, or are we close, or are we getting close what so-called herd immunity based on the number of people who have been infected?

A. I mean, the fact that we have uncontrolled spread is probably telling in that sense that we haven't. You know, again, this disease is spreading. And especially with variants now that may evade immunity of it more, even having a set amount of immunity isn't necessarily a basis to stop things cold in the population as herd immunity would eventually do.

261. Q. And you were asked a number of questions about PCR testing.

A. M'hmm.

262. Q. Do we have better tools right now for determining if someone is capable of transmitting

COVID to others than a PCR test?

A. I mean, the gold standard we use in -- in studies is viral culture, but that's completely impractical and it's often just a reference standard for things like scientific testing. They're not really used in clinical practice. The reason being is, you know, growing the virus out needs special conditions, needs multiple days of incubation. So, they're pretty useless in a clinical context. We use them more for research or -- or to validate our PCR tests.

PCR is the gold standard and, you know, for other viral infections like Influenza and -- and other respiratory infections, other viral infections like hepatitis or HIV. You know, it's a -- it's used primarily as the gold standard diagnostic entity.

263. Q. I know you -- you had some questions about, you know, range of potential sensitivity or false positive rates. Has that changed throughout the pandemic?

A. Yeah, again, the initial data from China gave that 75 per cent PCR sensitivity. You know, PCR sensitivity is not only just the population you're testing, but is the assay itself. And so, how well it's been developed, and -- and you know some other

technical factors. So, you know, as assays have gotten better again, it's ranged higher rather than lower in terms of sensitivity.

264. Q. And so, just to be clear, so higher sensitivity, does that mean it's more accurate or less ---

A. Yeah, like, you know, again towards that 90 to 95 per cent range. The initial Chinese PCR's were a little bit off. But again, you know, with time it's -- repeating, find a better targets, that type of thing, you can -- you can get better assays as things progress.

265. Q. And so, you know, you were asked a lot of questions about percentages and such like. But I just want to understand the absolute numbers. You know, does thirty -- what if any impact, does 30,000 hospitalizations have on Ontario hospitals?

A. Yeah, I -- there are a lot. Right? I mean it took 891 ICU beds to cripple our healthcare system, to shutdown surgeries, to redeploy staff.

You know, 30,000 hospitalizations means people that are in hospital that need oxygen, that need care, that, you know, need clinical services to deal with them. Some of them need rehabilitation, some of them have secondary complications.

And so, you know, having zero of those would be fantastic. And we all realize that respiratory viruses lead to people being hospitalized. But the sheer number of people that have needed to be hospitalized from this virus in the last couple of years is -- is different than any other respiratory viruses in the past. And again that their healthcare bodies, they're real people that have to deal with them.

266. Q. And you were asked some questions about, you know, hospital and ICU capacity. You know, in your clinical practice, are you aware of any steps that have been taken to expand capacity during the pandemic?

A. I mean we've found beds. And we've bought ventilators, but we don't have the staff necessarily all the time for them. And so, you know, even to deal with kind of reinforcing our ICU's, we've had to retrain staff.

We've had to bring in agency staff, so third-party agencies rather than hiring them we've had to -- we've had to go through hiring fairs. We've really tried to blitz trying to get as many healthcare resources in, and particularly during the worst parts of our pandemic. Again, we had to shut down services

to just redeploy staff into the ICU, in order to offer more bodies.

267. Q. And are there any limits on our ability to do further or?

A. I mean it's not a secret that the healthcare human resources right now in the pandemic are probably one of the worse they've ever been for the fact that many staff are burnt out. Many nurses have left the profession. And so, you know, our ability to scale up even more is going to be difficult as time goes on.

268. Q. Now, you were asked a number of questions about whether different measures were, in your opinion justified on a public health basis.

Do public health practitioners always know with certainty, in advance, what's going to work?

A. No, and again, these -- these measures were made with transmission dynamics in mind. Some of them may not have been perfect, but -- but, you know, particularly the ones that targeted indoor measures were made to, you know, look at what would be the definable risks of COVID-19 in terms of people gathering, contacts, you know, the respiratory spread of the virus et cetera.

So, you know, no one -- we don't go in with randomized clinical trials to say this measure will

reduce COVID-19 by this much. We go in based on the assumptions that, you know, more people mixing, indoor spaces, poor ventilation, et cetera, increase the risk of transmission and -- and again, mitigating settings with those factors in mind, would likely decrease transmission and -- and lead to less -- less COVID cases.

269. Q. Now, you were askes a number of -- you were taken to an article you wrote in the Toronto Star about outdoor activity.

A. M'hmm.

270. Q. And you said outdoor activity is generally safe, and comparatively far safer. And then when you answered some questions, you spoke of mitigated outdoor activity, and outdoor activities being don appropriately.

So, what do you mean by those qualifiers?

A. Yeah, so, I mean again, you know, you're not going to get the benefits -- I mean, again, outdoor ventilation is appropriate, it does mitigate a lot of transmission. But, if for example, you're very, very close to each other, packed in a small space, if you're -- you know, we've seen kind of outdoor patios, for example, that have really been like three walls.

So, you know, it really is kind of a -- an

indoor space that looks like an outdoor space. Ah, ah -- you know, people are kind of, you know, very, very close to each other. If they're, you know, swapping drinks, or that type of thing, where there's saliva going back and forth. The outdoors isn't going to save you at that point, right?

You know, if you're -- if you're kind of breaking those barriers down, then -- then certainly, again, you know, the ventilation advantage of the outdoors is -- is turned off by the fact that you kind of broken down some of the barriers that lead to transmission.

271. Q. So, I'd like to talk to you a little bit now just about from what was put to you about COVID versus influenza.

A. M'hmm.

272. Q. First of all, you were asked some questions about the 1950's influenza pandemic. Do you know what, if any, public health measures were going on at that time to reduce the spread of influenza in the 50's?

A. I am not sure. I mean all I -- I was born and alive during the 2019 -- 2009 pandemic, but, yeah, I clearly don't know what life was like back in the 50's.

273. Q. And you also talked about influenza in 2019, 2020, so that would be the pandemic or at least before the pandemic in Canada. Were there significant public health measures in place to prevent influenza spread?

A. Outside of just encouraging people to get vaccinated, and stay home when sick, those are kind of the baseline measures, I think, for more respiratory viruses in the community.

274. Q. And do you know what impact, if any, the public health measures take into combat COVID-19 had on influenza after 2019, 2020?

A. We didn't have an influenza season in 2020, 2021. You know, it's just starting now because people are now engaging again it travels with them. But, yeah, from 2020 really that -- that influenza season shut down essentially when the lockdowns happened. And -- and really, you know, through last winter we didn't have an influenza season. There were just a handful of cases, nothing to declare a true influenza season.

275. Q. Okay. So, I am just going to take you to -- some of the exhibits my Friend took you to. I am going to start -- I am going to share my screen with the NACI advisory committee statement.

So, this is the exhibit my Friend took you

to. And he took you to that number about flu deaths.

A. M'hmm.

276. Q. Give me a second. And so, you notice there's a footnote 3, after that number he took you to?

A. Correct.

277. Q. And then if I just take you to the end notes, footnote 3 refers to a study by Schanzer, Sevenhuysen et al., about -- from estimating influenza deaths in Canada.

A. Correct.

278. Q. Let's actually go to that study. One second, I'll stop sharing. So, I'll just give you a minute to read the abstract of that study.

A. Okay.

279. Q. So, I am just going to suggest that this study was a regression modelling study, not an actual measuring of influenza positive patients.

A. Yes, again, as I think I mentioned in prior testimony a lot of our influenza data is -- is modelled. It's not -- it's not as accurate as COVID-19 data and we've been tracking every case in that sense.

280. Q. And also, this was data based from 1992 to 2009.

A. Correct.

MR. HUNTER: I'd like to mark the actual article as an exhibit.

MR. KITTREDGE: No objection.

(WHEREUPON Exhibit J : Schanzer and Sevenhuysen study estimating influenza data in Canada.)

BY MR. MR. HUNTER:

281. Q. And so, let's just -- one other thing on that point. If we go actually to the FluWatch study that my Friend's took you to. They took you to it about hospitalization rates. But they didn't mention what it said about death rates. Let me take a look at that. I'll share my screen.

Can you see the FluWatch study now?

A. Yeah, yeah, absolutely.

282. Q. And if you just look under the table you were taken to, how many ICU admissions and how many deaths related to flu did -- were reported for 2018/19?

A. A total 163 ICU admissions and 224 deaths were reported this season.

283. Q. I just want to say something, one other -- hang on one second, while Adobe decides to work for us. Can you see that now?

A. Yeah, yeah.

284. Q. Okay. So, just wanted to ask what they reported about the 2018, 19 influenza season. It's in the second bullet.

A. Ah, the 2019 -- 2018, 2019, influenza season was longer than previous five seasons, was characterized by two waves of influenza A activity, and influenza B situation, national season started week 43, October 21st, 27, 2018, and peaked in week 52 December 23rd to 29, 2018. And ended in week 21 May 19th to 25th, 2019.

285. Q. And do they say anything about the hospitalization rate? That's in the fifth bullet.

A. The annual season hospitalization rate was above average, compared to the previous five seasons. Adults 65 had the highest hospitalization, however the cumulative hospitalization rate shifted during the season, from children zero to four years of age, November to March. Adults 65plus of age, March onwards, likely due to the second wave of AH3N2.

286. Q. The last thing I want to take you to is the Ontario Health Plan that you were taken to. So, let's just put that up. Should be able to see that now. Just going to take you to the chart my Friend took you to.

So, here's the chart on pages 15 and 15 my

Friend took you to. I just want to make sure I understand some of the terms and how they're dealt with in public health practice.

So, first he asked you about the cumulative attack rate.

A. M'hmm.

287. Q. The percentage of people, it says in the note here, who are expected to become symptomatic at some point during the influenza pandemic.

Now, when you're trying to decide whether to impose various public health measures, do you look at the cumulative attack rate with those measures or the rate that you would have if you didn't take measures in deciding when you're higher or lower than this 21 per cent number?

A. Yeah, I mean I -- I think we take examples from what happens in the world, and we look at, you know, what the spread would look like. And again, we make proactive measures to deal with that.

So, again, you know, our -- our attack rate being, you know, less than 21 per cent is often -- the fact that we have less than 21 per cent is not necessarily the fact that this has not spread to 21 per cent of the population. It's the fact that public health measures have prevented it from spreading to

over 21 per cent of the population.

And, you know, that is the paradox of public health, when things actually work, they get reflected in lower numbers which is exactly what we want. And we don't necessarily measure what could have happened in that sense.

288. Q. And similarly with the other -- it's -- the other number were asked about, the reproductive number, R Num.

A. Yeah.

289. Q. Is there a different between this basic reproductive number that's referred to in this document for assessing the transmissibility of a disease, and the observed reproductive number in the community?

A. Yeah, absolutely. I mean, again, you know, the reproductive number right now in Ontario is very, very rough guide. And is in the context of a population that has 90 per cent immunity. When they talk about the basic reproductive number here, it is literally just you put the virus in the population, a pool that is completely susceptible and you look at, you know, the growth over time. And -- and again, you know, that is what the basic reproductive number is in that sense.

So, what our reproductive number for COVID-19 in the community, you know, again it's been less than 1.6 for sometime, thankfully, is not a reflection of COVID-19 having a reproductive number biologically on its own at less than 1.6. When you were to take COVID-19 put it in a pool, again, the estimates of the original COVID-19 strain are two to three. The estimate of the alpha strain is four. And the estimate of delta is six. And even Omicron we're not even sure yet what the estimate is.

So, you know, again it is much more than just, you know, what looking at daily case counts are and generating a model to say what the reproductive rate is. It is, you know, again a susceptible population in kind of letting it spread outwards in a uniform manner.

290. Q. Similarly, you talked about how the reproductive numbers change with the variants, has that affected the case fatality rate?

A. Ah, I mean more that get infected means that there is a bigger chance of dying. But it also means that more of the population has some protection through natural immunity as well as vaccine. So, yeah, absolutely.

I mean, again, what we've done has affected

the case fatality rate with therapeutics and other interventions that have gone on in the population if less people -- again, less high-risk people are infected. It -- it artificially lowers the case fatality rate. So, things like lockdowns, and vaccinations in nursing homes, for example, would take down the case fatality rate because you don't have your highest risk members of society dying in that sense.

291. Q. My question was actually just about the variants.

A. Oh.

292. Q. Alpha, Delta, and Omicron.

A. Yeah.

293. Q. Has that affected the case fatality at all?

A. Yeah, absolutely, absolutely. I mean I think Delta was an estimated -- sorry, Alpha was an estimated 1.5 times, I think it was in the Affidavit for -- based on the original Wuhan strain. Delta looks like it's much higher.

We're not sure about Omicron yet, because it's just so new. But the CFR has -- has increased with some of these variants of concern that have actually come out there. Especially Alpha and Delta as the big two.

MR. HUNTER: Thank you those are my questions. All right, are we off the record?

I hereby certify the foregoing to be the Cross Examination of DR. ZAIN CHAGLA, taken before me, via videoconference, on the 14th day of December, 2021.

CERTIFIED CORRECT: PROFESSIONAL COURT REPORTERS INC.

Giles Tingey

Court Reporter

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Date

12 Dec 2021

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Confirmed COVID-19 cases in Ontario

As of December 12, 2021

Daily cases, rates, hospitalizations and deaths by public health unit can be found in **Case trends**.

Change in cases	Recent cases	Total cases
1,536	14,206	633,683
	reported in last 14 days 2.2% of cases	4,300.8 per 100,000

Total hospitalized	Total deaths
31,689	10,079
215.1 per 100,000 5.0% of cases	68.4 per 100,000 1.6% of cases

Laboratory tests for COVID-19 in Ontario

As of December 12, 2021

See daily historical data in **Lab tests**.

New tests	Daily % positive	Total tests
38,331	5.5	20,221,300
260.2 tests per 100,000		137,242.3 tests per 100,000

COVID-19 vaccine uptake in Ontario

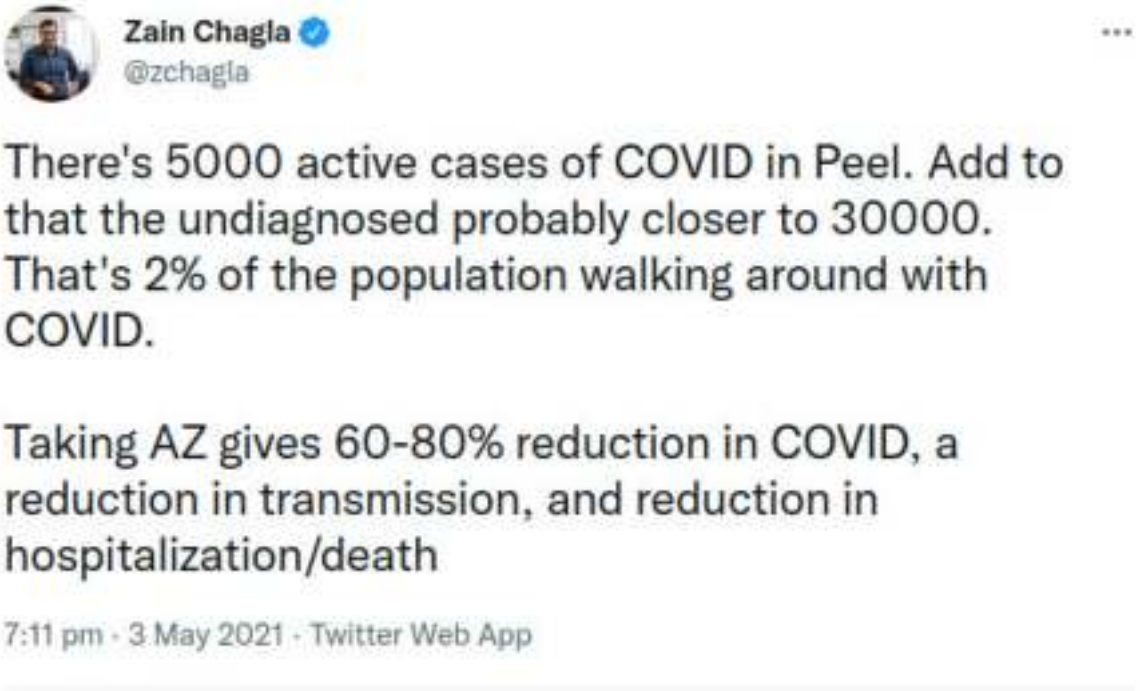
As of December 5, 2021

Vaccine data are updated weekly on Thursdays. See the **Vaccine** and **Map** tabs for more vaccination data.

At least one dose	Fully vaccinated
11,879,513	11,294,903
80.6% of Ontario population	76.7% of Ontario population

https://twitter.com/zchagla/status/1378491345199894529

https://twitter.com/zchagla/status/1389357032206180357



Zain Chagla
@zchagla

There's 5000 active cases of COVID in Peel. Add to that the undiagnosed probably closer to 30000. That's 2% of the population walking around with COVID.

Taking AZ gives 60-80% reduction in COVID, a reduction in transmission, and reduction in hospitalization/death

7:11 pm · 3 May 2021 · Twitter Web App

https://twitter.com/zchagla/status/1280868268979388416

https://twitter.com/zchagla/status/1267130466596982788

Zain Chagla
@zchagla

Protest is enshrined in universal human rights. For those of you who chose to exercise your rights, please keep track of your symptoms, isolate, and get tested in the coming days. I pray there is no transmission, but if there is keeping others safe is paramount

12:27 pm · 31 May 2020 · Twitter for iPhone

https://twitter.com/zchagla/status/1264336609127866371

Zain Chagla
@zchagla

@CBCQueensPark thanks for this! Setting arbitrary limits on capacity handcuffs hospitals that were running well over 100 percent for years, and now are holding on to even more alternate level of care patients cbc.ca/amp/1.5581177#...

7:25 pm · 23 May 2020 · Twitter for iPhone

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CANADA

Surge in patients forces Ontario hospitals to put beds in 'unconventional spaces'

By Theresa Boyle Health Reporter

Sun., April 16, 2017 | 17 min. read

Article was updated Apr. 27, 2017

It's been a rough few months for Ontario hospitals. Wait times for patients admitted through ERs have hit peak levels; more patients have been admitted than discharged; and a number of hospitals have simply run out of space.

Frazzled administrators, forced to get creative in accommodating the overflow, have coined the term "unconventional spaces" to describe their solution. They have converted into temporary accommodations patient lounges, staff classrooms, offices — and in some cases even storage rooms.

Overcrowded hospitals are nothing new to Ontario. They typically experience patient surges every January and February when flu season peaks and when there is a rebound effect after the Christmas lull. Hospitals struggle with overcrowded emergency rooms across Canada and in other countries, too.

But there has been something different about this year's surge in Ontario, according to numerous hospital CEOs interviewed by the Star — a handful on the record, but most off.

It was bigger than in years past and caught many by surprise. Patient capacity at about half of Ontario's 145 hospital corporations exceeded 100 per cent and reached as high as 130 per cent, according to figures requested by the Star from the Ontario Hospital Association (OHA).

Hardest hit have been large urban hospitals, regional facilities and some community hospitals. Even some rural hospitals have been overwhelmed. They include hospitals throughout the Greater Toronto Area, Hamilton, Ottawa, London, Kingston, Windsor, Sudbury and Cornwall.

Many have been over capacity for weeks, even months. While the surge has somewhat abated in recent weeks, it appears that some of the intensified demand for hospital services won't subside any time soon.

To accommodate the overflow, hospitals have been forced to open at least 1,100 "unfunded beds," more than 250 of them in unconventional spaces, according to the OHA. The organization said these are conservative estimates because not all hospitals participated in a survey on capacity.

An unfunded bed is one that a hospital did not budget for and therefore did not receive provincial funding to operate. To cover the cost, a hospital must dip into funds raised for capital projects, equipment and research through, for example, fees on parking, private rooms and food vendors.

The OHA is still surveying hospitals to determine exactly how severe the overcrowding problem has become, how many unfunded beds remain open and what the total cost of operating them has been. The cost of operating one such bed for a single day is $450, at the low end.

Some hospitals have incurred deficits to accommodate the extra patients.

There are three main causes of the growing pressures, health-care leaders agree: a population that is growing, aging and showing up in the ER sicker than ever; a health system that is not robust enough outside of hospitals, such as in the long-term-care and home-care sectors; and five years of austerity funding with minimal increases to operating budgets from the province. When inflation is factored in, hospitals budgets have actually fallen in real dollars.

The OHA has told the province that hospitals cannot go on at this rate without significantly compromising front-line care, the Star has learned. The organization has asked the province to put an end to the austerity and come to the rescue with a significant infusion of cash — $850 million — in the budget, to be tabled April 27.

A highly placed government source, who wasn't authorized to speak publicly, said the province is well aware of pressures on the sector, though questions whether they are really as severe as are being made out.

The source said the province may announce in the budget that it will loosen the purse strings to free up more hospital beds and create more capacity throughout the entire health system. Improving health care outside of hospitals is the key to relieving pressures inside them, he said.

Since October, Hamilton Health Sciences has been struggling to care for more patients than it has beds. Its capacity peaked in February at 114 per cent, but remains high today.

Last Sunday, it was at 111 per cent capacity. There were 70 more patients in beds than the hospital had budgeted for.

Senior administrators and physicians meet daily to pore over "bed maps" to figure out where they can accommodate the overflow. When there is no more space for gurneys in ER hallways, they look to unconventional spaces, which can include patient sunrooms and recovery rooms normally dedicated to short-term stay for patients who have just had surgery.

"The whole system is under stress and Hamilton Health Sciences is no exception," said president Rob MacIsaac. "We are constantly operating on the edge. There is no slack left in the system. Zero."

Among the hospital's 1,391 in-patients last Sunday were 168 who had completed their acute-care hospital treatment and no longer needed to be there. Mostly frail seniors, they are known as "alternate level of care" or ALC patients because what they really need is

care outside an acute-care hospital.

Alternatives can include long-term-care homes, their own homes with home-care support, palliative care, rehabilitation facilities and complex continuing care facilities.

But there are shortages in these sectors too, especially for patients who are both physically and cognitively impaired. The hardest to place have multiple chronic physical ailments, dementia, behavioural problems and/or mental health problems.

When ALC patients can't be discharged, there are fewer beds available for those admitted to hospital from the emergency department. That makes for a particularly bad combination when there is a big influx of patients on that end too. Last Sunday, there were 40 patients admitted through the ER at Hamilton Health Sciences, waiting for beds.

The hospital has seen a 3 per cent increase in emergency department visits over the last year. The average acuity of patients — or intensity of nursing care they require — jumped 5 per cent over the same period.

"Circumstances overwhelm anything we can do internally. Fundamentally, there is no making up for lack of capacity with better processes," MacIsaac said.

Staff are stressed, patient satisfaction is suffering and the facility's budget is stretched thin, he noted.

The hospital was forced in February and March to cancel and reschedule 26 surgeries though it "moves heaven and earth" not to do that, MacIsaac explained.

Cancelling surgeries compromises its regional role in providing treatment for cancer, trauma, burns, stroke, cardiac care and pediatrics. The hospital serves a population of 2.5 million and its catchment area stretches out to Burlington, Oakville, Milton Niagara, Branford, Haldimand-Norfork and Kitchener-Waterloo.

"We are waiting on tenterhooks to see what our funding is. We are beside ourselves trying to figure out how we are going to manage," MacIsaac exclaimed.

People are often surprised to learn Ontario has very low numbers of hospital beds, compared to countries in the Organization for Economic Co-operation and Development. The province has 2.3 beds per 1,000 people, fewer than 31 OECD counties. Only Mexico, Chile and New Zealand have fewer.

But provincial policy-makers don't see that as a bad thing. On the contrary, it's by design and it's a point of pride, proof of a highly efficient system.

Ontario has purposely shrunk its hospital system. In 1990, there were 33,403 acute-care hospital beds, according to the OHA; today there are 18,571.

During that same period, the province's population jumped 36 per cent to 14 million.

Additional figures from the OHA and Canadian Institute for Health Information requested by the Star show that:

- The number of visits to Ontario hospital emergency departments jumped by 5.6 per cent to 6.3 million from 2012-13 to 2015-16. These patients are older and sicker than ever before.
- Ontario spends $1,427 per capita on hospitals. Of the 10 provinces, only Quebec spends less.
- The average length of stay for Ontario hospital patients fell to 5.7 days in 2014-15 from 6.9 days in 1995-96. That is the lowest of all provinces.

Advances in technology have contributed to shorter patient stays. Surgeries are less invasive than they used to be, allowing for faster recoveries. More procedures are done on an outpatient basis and more followup care is provided through home care.

Groups such as the Ontario Health Coalition argue that the province has gone too far in cutting hospital beds and want to see the sector built back up.

But policy-makers and health-care leaders see it differently. In their view, patients wouldn't need to rely on hospitals as much if they were kept healthy in the first place and received more health-care services in the community, where it is less expensive.

This has long been the vision for Ontario's publicly funded health system, the way to keep it affordable and sustainable. But getting there has not gone as smoothly as planned.

Said one GTA hospital president, who spoke on the condition of anonymity: "Hospitals have maximized their efficiencies, but things have not evolved as they should have over the last five years outside of acute care. We need more resources in the community."

Said the government source: "So what part of the system is good and what part is disorganized? I would say our hospital systems are pretty good and we have the data to prove it. Outside hospitals we are disorganized."

The source said that the province's ongoing measures to transform the health system, an effort known as Patients First, will take pressure off hospitals by improving health care outside of them.

"That is why Patients First is so important ... to organize the primary care, home and community and mental health care that are currently disorganized," he said.

OHA president Anthony Dale had a feeling last year that hospitals were heading into a tough winter. He had been watching the provincial ALC rate, which the government has been trying for years to lower.

The proportion of acute-care hospital beds occupied by ALC patients had fallen from a high of 19.6 per cent in 2008 to a level hovering between 13 and 15 per cent between 2011 and 2015.

But in July 2015, the ALC rate started to rise again — sharply. It went from 13.9 per cent in July 2015 to 16.5 per cent in November 2016.

By January this year, there were 3,121 ALC patients waiting in acute-care beds. A third of them were waiting to get into long-term-care homes.

At the same time, pressure was building in ERs because of flu season. By February, ER waits hit their highest levels since the province began measuring wait times nine years ago. Nine out of 10 patients waiting to be admitted from the ER waited 32.4 hours or less. The target for admitting all complex patients is eight hours.

"What caught us by surprise was the intensity of the flu surge," Dale said.

ER waits are a barometer of how well the health system is functioning, he explained. If there is a problem somewhere, it inevitably manifests in the ER.

"(ER waits) are often a warning sign of a system under stress and at the moment, the warning is flashing bright red," he said.

In recognition of this, the provincial government last November provided an extra $140 million to the sector on top of the $345 million announced in last year's budget. It was a much welcome "lifeline," Dale said.

The sector has asked for and received very little in the way of extra funding over the last five years. Hospital base operating budgets were frozen for four of those years and last year increased by 1.5 per cent. When inflation is taken into account, hospitals have actually seen real-dollar budget cuts for nine years.

Hospitals agreed to take less funding so that other sectors with greater need — namely home, community and long-term care — could get more.

At the same time the provincial government has been trying to cut its deficit.

But hospitals say they can no longer take a back seat to other health sectors. They are hoping the budget will include a 4.9 per cent increase in total operating and capital funding.

"While hospitals have been understanding and supportive of the need to spend elsewhere in the system, the hospital sector is now at a critical turning point," the OHA budget submission states.

"We can no longer say that funding others is a greater priority," it continues, warning that inflationary pressures may require diverting a significant amount of funds from front-line care.

Toronto resident Julie Devaney was surprised to see how busy the ER at Mount Sinai Hospital was at 1 a.m. on Jan. 28. The woman who has Crohn's Disease was taken there by her partner because she was suffering from a bowel obstruction.

Throwing up, barely verbal and in agonizing pain, she was deemed ill enough to admit. But she waited 18 hours in the ER to get a bed.

Devaney, 37, spent the first part of her wait in a busy hallway where she was hooked up to IV fluids. She remembers the scene as being chaotic. There were lots of people walking back and forth, it was noisy and at one point a shouting match broke out. Police were on hand to break it up.

"It was pretty intense. I felt extremely vulnerable," she said, recalling how she had to use a plastic bag that she brought from home to vomit into.

She was eventually moved into an ER treatment room where she was given pain medication and spent the rest of her wait.

Despite the commotion and long wait, Devaney was impressed by the doctors and nurses: "Staff were amazing and very comforting."

NDP health critic France Gelinas got a taste of the growing hospital capacity problem back in Nov. 2015 when her now deceased 93-year-old mother-in-law ended up in the emergency department of Sudbury's Health Sciences North with an infected foot.

Because the ER was full, her mother-in-law was moved into a storage room. Half of the room had been cleared for patient use. A bed sheet covered cleaning supplies in the other half. There was no window, washroom or sink. The elderly woman stayed there for eight hours while she was treated with IV antibiotics.

"When they saw it was me, they profusely apologized," Gelinas said of hospital brass. "They were doing the best they could. There was nowhere else to go."

She and her party have been leading the charge at Queen's Park in calling for more hospital funding.

"Hospitals need money to rebuild surge capacity," she said, charging that a broken home-care system and inadequate primary care are placing undue pressure on the sector.

Dr. Denis-Richard Roy, president of Health Sciences North, said there were 25 patients in the ER, waiting for beds on a recent day when he was interviewed.

"I have never seen it this bad before. It seems like the new normal," he remarked.

Roy said the waiting patients were lying on gurneys in hallways and occupying ER treatment rooms, preventing other patients from being seen there.

The hospital has operated within budget for the last five years but is facing a $7 million deficit in this current fiscal year, he said. Much of that is from overtime wages paid to nurses.

"It's a terrible situation. It is not something HSN can manage on its own, it's a system problem," he said.

Dr. Howard Ovens, the province's lead for emergency medicine, acknowledges hospitals are under tremendous pressure. But looking at the problem from a historical context brings valuable perspective, he said.

Overcrowding was much worse 20 years ago when the government of the day made massive cuts to hospitals and to nursing staff, he said, recounting how two high-profile deaths related to poor ER access resulted in coroners' inquests.

"When people say the sky is falling right now, I say, 'You haven't seen a sky fall,'" remarks Ovens, who until last month served as the chief of emergency medicine at Mount Sinai.

Funding constraints in recent years have indeed resulted in more stress and less resilience in the system, he said.

But hospitals have responded much better than they did in the past because they've learned from mistakes and instituted new measures such as a "pay-for-results" incentive system, he explained. Hospitals get financial bonuses when they accommodate ER patients in a timely manner.

In Ovens' eyes, the use of unconventional spaces, while far from ideal, is smart.

"We didn't use sunrooms in the '90s. We didn't put patients in closets. We used to say there was nothing we could do and leave people out in the waiting room indefinitely and ultimately some would die out there," he said.

"The fact we now go to extraordinary lengths to create capacity is good thing."

Perhaps the hardest hit hospital in Ontario has been the Cornwall Community Hospital, which has reported occupancy rates as high as 138 per cent.

Since Christmas, it has been operating at more than 100 per cent capacity.

"Being overcapacity isn't anything new for us. What is different this year is the extreme levels of occupancy and the length of time we have been in this state," said president Jeanette Despatie.

The hospital is using not only ER hallways to accommodate the overflow, but hallways in the hospital's medical and surgical units as well. Former clinical space that had been turned into offices has also been converted back into patient rooms.

"It is a very challenging environment to work in. It has compromised our ability to ensure we are providing the quality and safety we want for our patients," Despatie said.

She is particularly worried that there is no "surge capacity" to deal with a large-scale emergency such as a pileup on Hwy. 401: "We would be hard pressed to meet the needs of an immediate surge."

ALC rates in Cornwall are up noticeably this year, at 19 per cent of total patient days compared to 15 per cent least year. Eight ALC patients have been waiting more than 100 days to get into long-term care and one has been waiting more than a year.

"These patients are tougher to place in appropriate settings because they have mental health or behavioural challenges," Despatie explained.

These ALC patients also include seniors who cannot afford to pay higher fees for private or semi-private rooms in long-term care homes and are waiting for subsidized, ward-style rooms to open up.

Despatie said there has also been an increase in ALC patients waiting to be discharged home with home-care support.

In the recent past, the hospital had more success in discharging patients home with help from the province's Homes First program, which allotted more home-care hours for frail, ailing seniors, she noted.

But now that same cohort of patients — older and sicker — is finding itself back in hospital, too sick to return home and waiting for long-term care.

The province needs to find alternatives to long-term care, said another hospital president, warning that it will go broke if most aging baby boomers plan to spend their final years there.

Dr. Alan Drummond is an ER doctor at the Great War Memorial Hospital in Perth where there are 50 beds and nine ER stretchers.

It's not uncommon for him to arrive at work in the morning to see up to five elderly patients, who had been admitted the night before, waiting on stretchers with no prospect of being transferred to the wards for hours or even occasionally days, he said.

"I sometimes examine them in the hallway or the triage area because there is no other space," said Drummond, former head of the Canadian Association of Emergency Physicians.

Every time a stretcher is occupied by an admitted patient, those in the waiting room are denied access to a treatment area and so they wait too, he explained.

"I have sometimes wandered the hospital, found an available stretcher and brought it down myself to the back of the ER hallway to give me a couple of spaces to see people," he said.

The crowding that urban hospitals began seeing in the mid-1990s didn't reach small rural hospitals like his until the last five or six years, Drummond said.

"Even in Perth now we have ambulances that cannot off-load their patients. Paramedics have to wait in the hallways with their patients. No place to off-load," he remarked.

It can be demoralizing and leaves ER nurses "constantly on the fringe of burnout," Drummond said.

Hospital officials across the province end up spending an excess amount of time trying to figure out patient flow. In Perth, doctors can no longer easily transfer their sickest to tertiary hospitals in Kingston and Ottawa because they are also full, Drummond said.

"Kingston is so bad that it's usually a wasted call. We then spend hours on the phone trying to find a bed elsewhere or try to maintain critically ill patients in our own facility," he said.

"The point is that it is now endemic and chronic and affects rural communities just as much ass city hospitals."

The government source questions the accuracy of hospitals' peak occupancy rates, noting they can vary widely depending on the time of day they are measured. For example, if measured during the middle of the day, it's possible for one bed to show two patients — one that has just been discharged and another that has just been admitted.

The most accurate time to take a patient census is midnight, he said, adding that the sector and government are currently working out a mutually agreed-upon measurement protocol.

This source also pointed out that the province does not fund hospital beds, per se, but rather patient activity. In a well-managed hospital, there should be some spare beds, say in an older section, that could be put to use in flu season and closed again when ER activity slows.

"Some hospitals will occasionally use unconventional spaces and that is not good and needs to be fixed," he said, acknowledging the sector is under pressure.

Both the OHA and the government accept that the average annual occupancy rates for Ontario hospitals hovered between 91 and 93 per cent between 2012 and 2016.

The oft-cited ideal capacity rate for hospitals is 85 per cent. Anything above that leads to long waits and increased risk of transmission of infectious disease. As well, it leaves little wiggle room in the event of a big emergency.

The government source said the budget may include extra money to relieve overcrowded hospitals. The funds would go to hospitals and to sectors such as home and community care, in an effort to lower ALC rates.

But the source also said that a lasting long-term solution rests with creating more forms of "congregate" living arrangements where personal support workers would be available to assist the growing senior population. In the past, cultural and religious organizations did more to support their seniors through the creation of assisted-living and supportive housing facilities, he explained.

Society needs to return to those models with the encouragement of government subsidies, he said, adding that the budget may make some movement in that direction.

The time to beef up services outside hospitals is running short, health-care leaders agree. The oldest of the baby boomers turns 71 this year. Age 75 is when people enter their high health-care consuming years.

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Research Letter | Public Health

Assessment of the Burden of SARS-CoV-2 Variants of Concern Among Essential Workers in the Greater Toronto Area, Canada

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Introduction

Variants of concern (VOC) of SARS-CoV-2 emerged toward the end of 2020. These resulted in documented replacement of wildtype SARS-CoV-2, with concerns of transmissibility, virulence, and immune escape, and were subsequently classified by an alphabetical system by the World Health Organization.[1] Prior to the emergence of VOC, across countries, SARS-CoV-2 transmission and COVID-19 were disproportionately concentrated in neighborhoods of low socioeconomic status, which are characterized by a larger proportion of frontline essential workers, and higher density contact networks.[2,3] We created a retrospective cohort of neighborhoods in the City of Toronto and Region of Peel, two of the most populous and most affected per capita regions of Ontario,[4] stratified by income and essential work status, and noted the emergence of VOC through this population.

Methods

This cohort study was approved by the University of Toronto Health Sciences Research Ethics Board and participant consent was waived because this was a secondary analysis of preexisting health administrative data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

We performed a retrospective cohort study on the burden of COVID-19 and VOC characterizing by essential work and income status, using Statistics Canada 2016 Census (self-reported) data for neighborhood-level characteristics, using dissemination areas of approximately 400 to 700 persons. Neighborhoods in the City of Toronto and Region of Peel were stratified into ascending tertiles 1, 2, and 3, which represent 33% of the population ranked by income (where tertile 1 is the lowest income), and essential work status (where tertile 1 is the highest proportion of essential work) represented in **Figure 1**. Essential work status included the proportion of the working population engaged in essential services (manufacturing, utilities, trades, transport, equipment, agriculture, sales, services, and health). We excluded cases among residents of long-term care homes because they represented a different outbreak setting from community-level outbreaks and transmissions.

We used a public health reportable disease database of person-level data among laboratory-confirmed COVID-19 cases between February 3 and March 10, 2021, and the Statistics Canada 2016 Census data for neighborhood-level characteristics. Polymerase chain reaction (PCR)–positive tests with a cycle threshold less than 35 underwent secondary PCR for the N501Y variation, and genetic sequencing for positive results by centralized laboratories,[5] representing VOC cases. Of the samples positive for the N501Y mutation, 93% were clade B.1.1.7.[5] Self-reported race-based data among individuals diagnosed with COVID-19 were collected after June 2021 but were not available for analyses in this study. During the observation period, both regions had closed nonessential businesses, restaurants, fitness centers, and had limits to only interact with one's household.[6] Tertiles were compared for case growth during the study period with descriptive analysis conducted in R version 4.0.2 (R Project for Statistical Computing) from February to April 2021.

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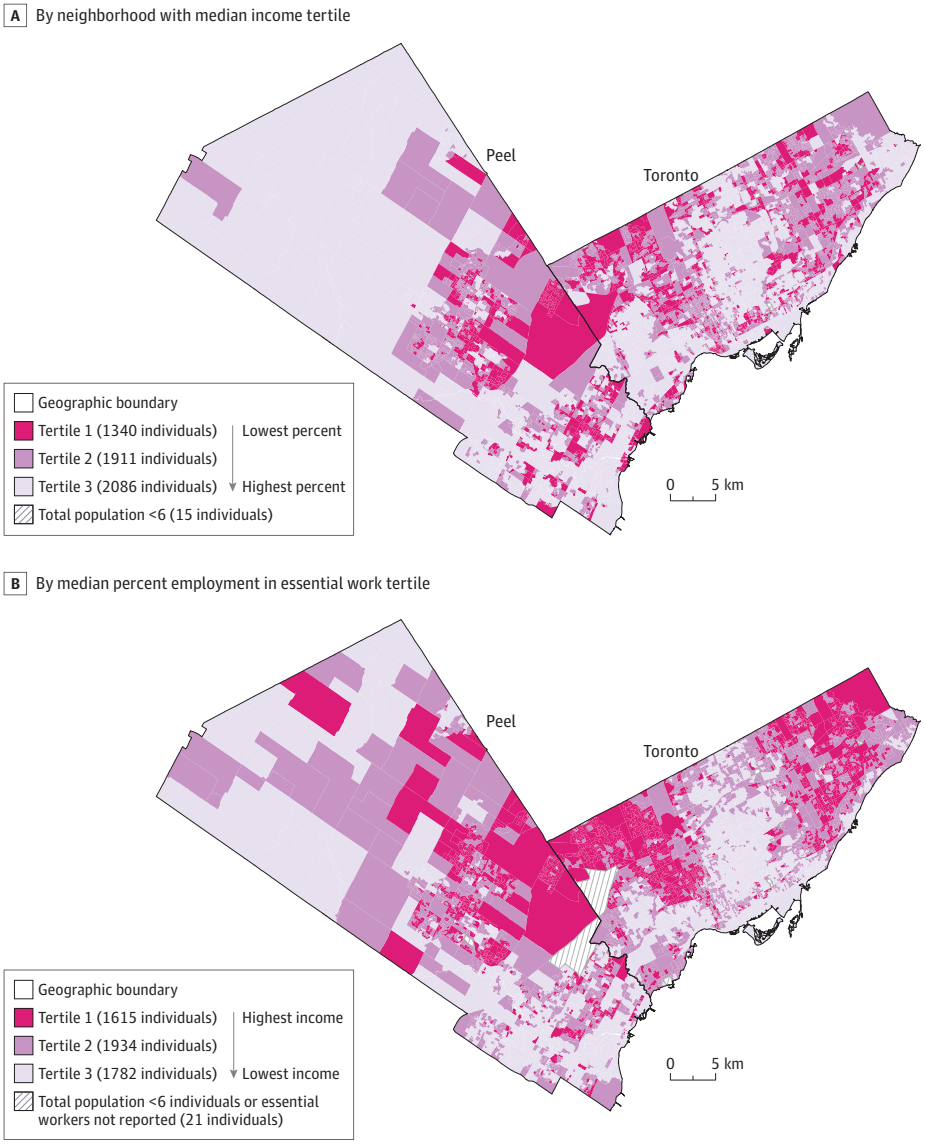
Results

A total of 19 912 COVID-19 cases were observed during the study period, of which 12 860 (64.6%) were screened for a VOC and 5084 (25.5%) screened positive. A similar pattern was observed with income tertiles. Of total cases within the study period, 8723 (43.8%) were in tertile 1, 7085 (35.6%) were in tertile 2, and 4104 (20.6%) were in tertile 3 (**Figure 2**A); whereas of VOC cases, 2228 (43.8%) were in tertile 1, 1757 (34.6%) were in tertile 2, and 1099 (21.6%) were in tertile 3 (Figure 2C).

When looking at essential work tertiles of total cases, 9597 (48.3%) were in tertile 1, 6504 (32.7%) were in tertile 2, and 3788 (19.0%) were in tertile 3 (Figure 2B). Among VOC cases in essential work tertiles, 2582 (50.8%) were in tertile 1, 1562 (30.8%) were in tertile 2, and 934 (18.4%) were in tertile 3 (Figure 2D).

Figure 1. Region of Peel and City of Toronto by Neighborhoods With Median Income Tertiles and Median Percentage Employment in Essential Work Tertiles



A, Median income tertiles were tertile 1: $33 819 (IQR, $29 337-37,054); tertile 2: $45 487 (IQR, $41 411-48,079); and tertile 3: $60 652 (IQR, $55 001-69,982). B, Median percentage employment in essential work tertiles were tertile 1: 63.2% (IQR, 59.4%-68.1%); tertile 2: 47.9% (IQR, 42.1%-52.0%); and tertile 3: 30.4% (IQR, 25.0%-35.3%).

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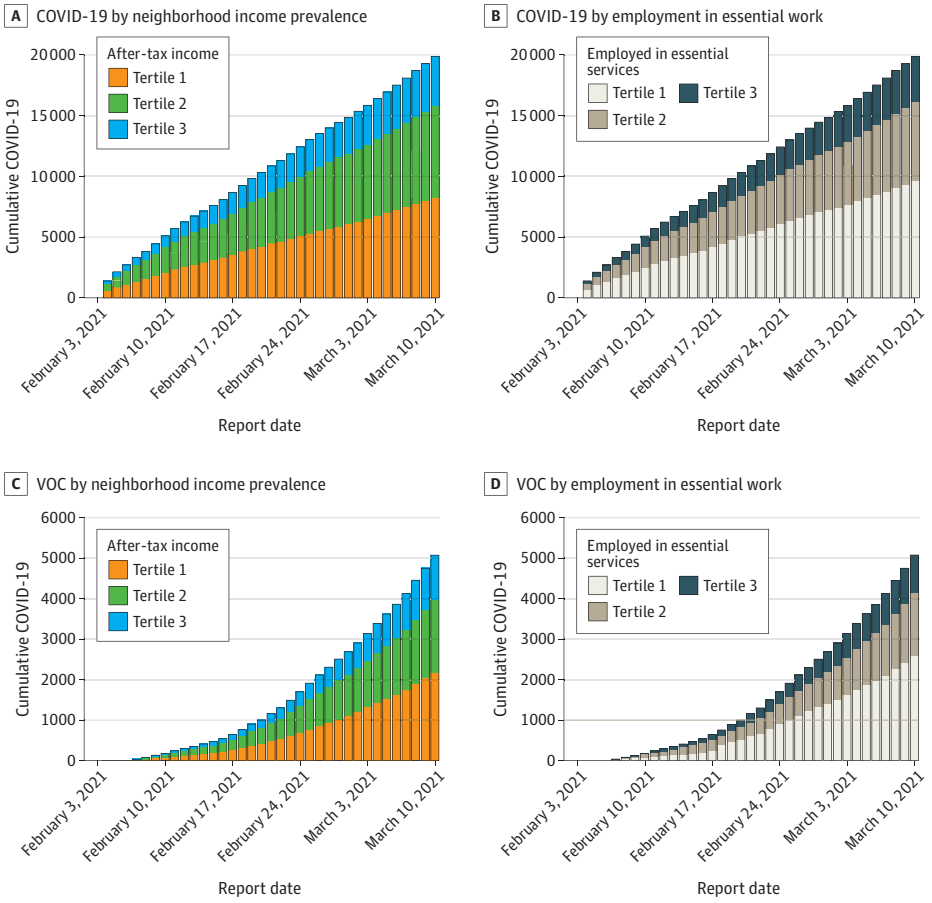
Figure 2. Cumulative COVID-19 Overall and Variants of Concern (VOC) Cases by Neighborhood-Level Prevalence of Income and by Essential Work in Toronto and Peel Regions, Canada



Discussion

These findings suggest that VOC of SARS-CoV-2, similar to wildtype SARS-CoV-2, are disproportionately associated with neighborhoods with lower income and a higher proportion of essential workers.[2] Notably, these analyses have some limitations. Use of ecological study design, rather than individual-level data on income and occupation for this analysis; and the potential for differential SARS-CoV-2 testing across tertiles, particularly less testing in low-income neighborhoods and essential work communities may result in underreporting both wildtype and VOC cases. Finally, not all samples were sent for VOC testing, and although testing was centralized, we cannot accurately ascertain if there were testing differences by region, with potential for a selection bias. Given the rapid mirroring of wildtype epidemics, these results suggest an association between essential work, income, and COVID-19 burden, which may be magnified by more transmissible variants. Reducing SARS-CoV-2 transmission and the associated morbidity and mortality necessitates tailored and equitable intervention strategies including vaccine prioritization and outreach services.

ARTICLE INFORMATION

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Acquisition, analysis, or interpretation of data: Ma, Sander, Baral, Moloney, Mishra.

Drafting of the manuscript: Chagla, Ma, Baral, Mishra.

Critical revision of the manuscript for important intellectual content: Chagla, Ma, Sander, Moloney, Mishra.

Statistical analysis: Chagla, Ma, Baral, Mishra.

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FluWatch

Public Health Agency of Canada | Agence de la santé publique du Canada

2018-19 Influenza Season (Aug 26, 2018 to Aug 24, 2019)

Overall Summary

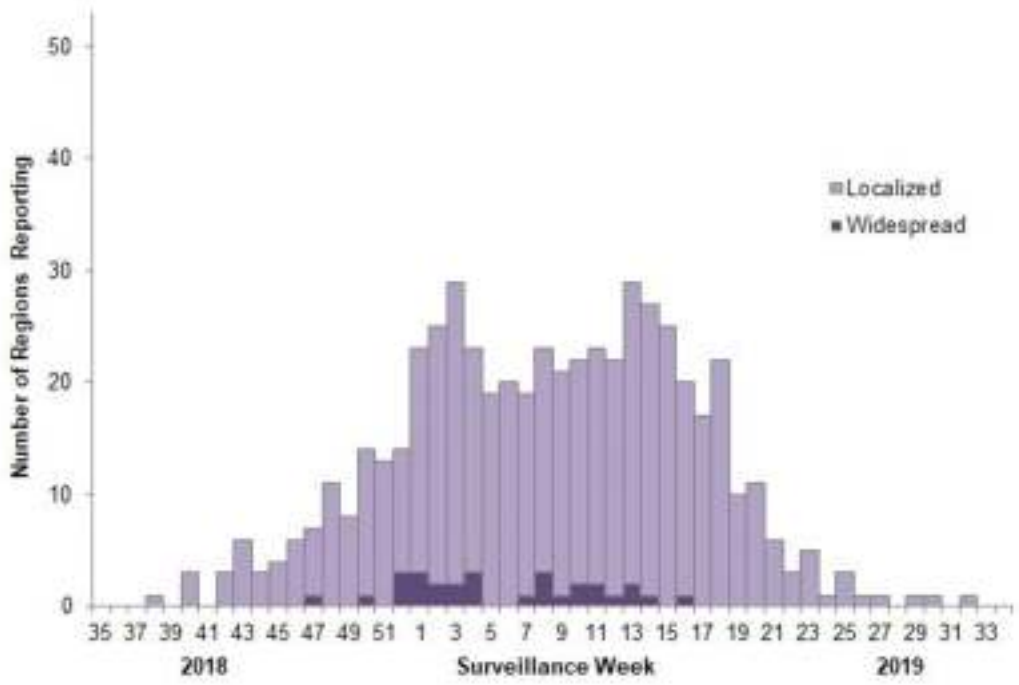
- During the influenza season, the FluWatch report is based on weekly data. This report is a summary of all of the data received for the 2018-19 influenza season and a comparison of these data to the previous five seasons.
- The 2018-19 influenza season in Canada was longer than the previous five seasons and was characterized by two waves of influenza A activity and very little influenza B circulation. The national season started in week 43 (October 21-27, 2018), peaked in week 52 (December 23-29, 2018) and ended in week 21 (May 19-25, 2019).
- A(H1N1) was predominant in the earlier part of the season (October to February) followed by a smaller wave of A(H3N2) circulation (March to April). Overall, A(H1N1) was the predominant strain nationally this season.
- Two waves of activity were observed in the number of reported outbreaks. The predominant subtype for typed outbreaks was A(H1N1) in the early part of the season (October to January), and A(H3N2) in the latter part of the season (Feburary onward).
- The annual seasonal hospitalization rate was above average compared to the previous five seasons. Adults 65 years of age and older had the highest overall hospitalization rate; however, the highest cumulative hospitalization rate shifted during the season from children 0-4 years of age (November to March) to adults 65 years of age and older (March onward), likely due to the second wave of A(H3N2).
- Overall, influenza vaccine coverage in the 2018-19 season (42%) was significantly higher than in the previous two seasons. Coverage was estimated at 34% for adults aged 18 to 64 years and 70% among seniors.
- Vaccine effectiveness studies in both the outpatient setting and adult inpatient setting observed good protection against A(H1N1) and little to no protection against A(H3N2) viruses relative to what is expected for influenza vaccine effectiveness.

Influenza/Influenza-like Illness (ILI) Activity (geographic spread)

Data on the geographic spread of influenza and influenza-like illness (ILI) are provided by all provinces and territories. All provinces and territories reported activity level data for each week of the 2018-19 influenza season.

- The number of surveillance regions reporting localized and widespread influenza activity peaked in week three and again in week 13 (Figure 1).
- Maps of the level of influenza activity reported by surveillance regions each week over the course of the season can be viewed here.

Figure 1 – Number of regions reporting widespread and localized influenza activity, Canada, weeks 2018-35 to 2019-34



Laboratory-Confirmed Influenza Detections

Data on laboratory-confirmed influenza detections are provided by 32 provincial, regional and some hospital laboratories. On average 99.6% of labs reported each week. During the 2018-19 season a total of 48,818 influenza detections were reported. Based on the seasonal thresholds for start and end of season (i.e. when the percentage of tests positive for influenza crossed 5%), the national influenza season started in week 43, peaked in week 52 and ended in week 21 (Figure 2).

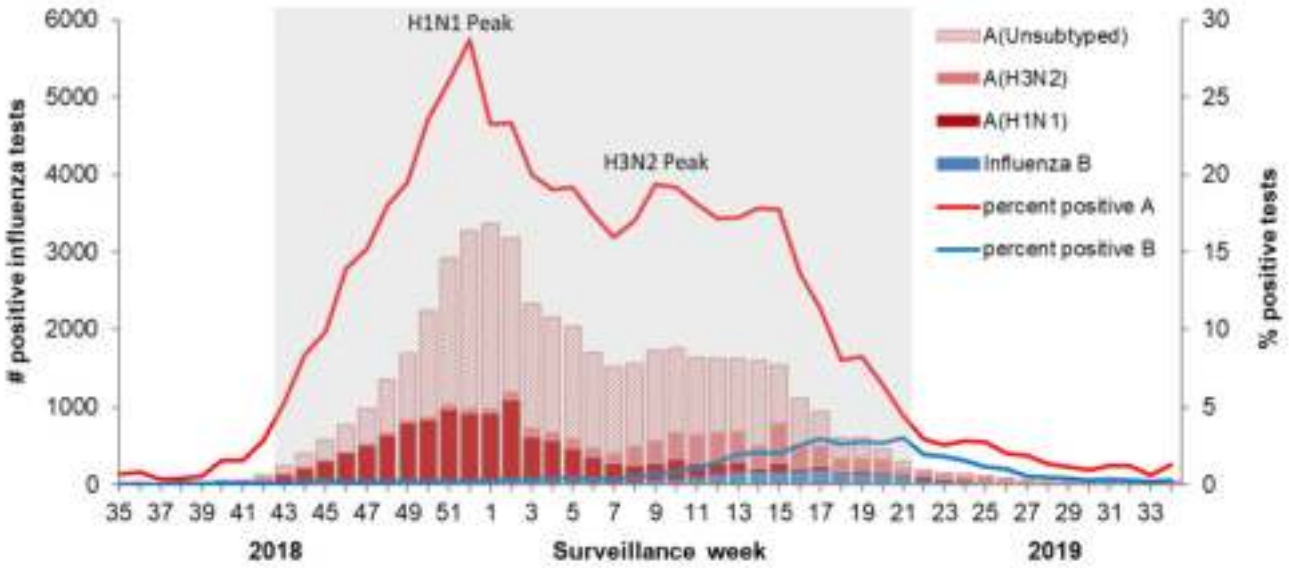
- Nearly all (95%) of influenza detections this season were influenza A. A(H1N1) was the predominant influenza strain and was the driver of the peak in percent positive detections in week 52. Among the 16,602 influenza A viruses that were subtyped this season, 69% were A(H1N1).
- The proportion of subtyped influenza A detections that were A(H3N2) began to increased markedly in mid-January (week three) and A(H3N2) became the predominant strain by week eight. This second more moderate wave of influenza A detections peaked in week nine and persisted near peak levels through to week 15.
- In the early part of the season (the A(H1N1) wave), influenza A activity was within the expected range; however, due to circulation of A(H3N2) in the latter part of the season, the overall proportion of detections of influenza A was higher compared to previous seasons.
- Compared to the last five seasons, the 2018-19 season started five weeks earlier than average; the number of weeks from the start of the season to the peak (10 weeks) was slightly longer than the average (nine weeks); and the length of the season (31 weeks) was six weeks longer than average (25 weeks).
- Canada observed the lowest cumulative total influenza B detections (5%) since the 2009 pandemic. Influenza B activity began to increase in week nine and peaked in week 17 but remained below previous seasonal values for the entire season.
- The distribution of influenza detections by type and subtype in provinces and territories was similar to the national distribution. The proportion of detections of influenza B was between zero and 5%. Among jurisdictions from which influenza A subtype information was provided, the proportion of A(H1N1) ranged from 62 to 100% of subtyped influenza A detections (Figure 3).

Detailed information on age and influenza type/subtype was received for 39,192 of laboratory-confirmed influenza cases. Among influenza A detections where subtype was identified (13,718), subtype distribution varied by age-group (Figure 4). A(H1N1) was the predominant subtype in all age groups except those 65 years of age and older, among

whom A(H3N2) was the predominant subtype (66%). Children less than five years of age had the highest proportion of A(H1N1) among subtyped influenza A detections (86%).

For more detailed weekly and cumulative influenza data, see the text descriptions for Figures 2 and 3 or the Respiratory Virus Detections in Canada Report.

Figure 2 – Number of positive influenza tests and percentage of positive tests, by type, subtype and report week, Canada, weeks 2018-35 to 2019-34



The shaded area indicates weeks where the positivity rate was at least 5% and a minimum of 15 positive tests were observed, signalling the period of seasonal influenza activity.

Data for week 14 excludes subtyping results from one jurisdiction due to batch reporting of subtype information. The results for week 14 should be interpreted with caution.

Figure 3 – Cumulative numbers of positive influenza specimens by type/subtype and province/territory, Canada, weeks 2018-35 to 2019-34

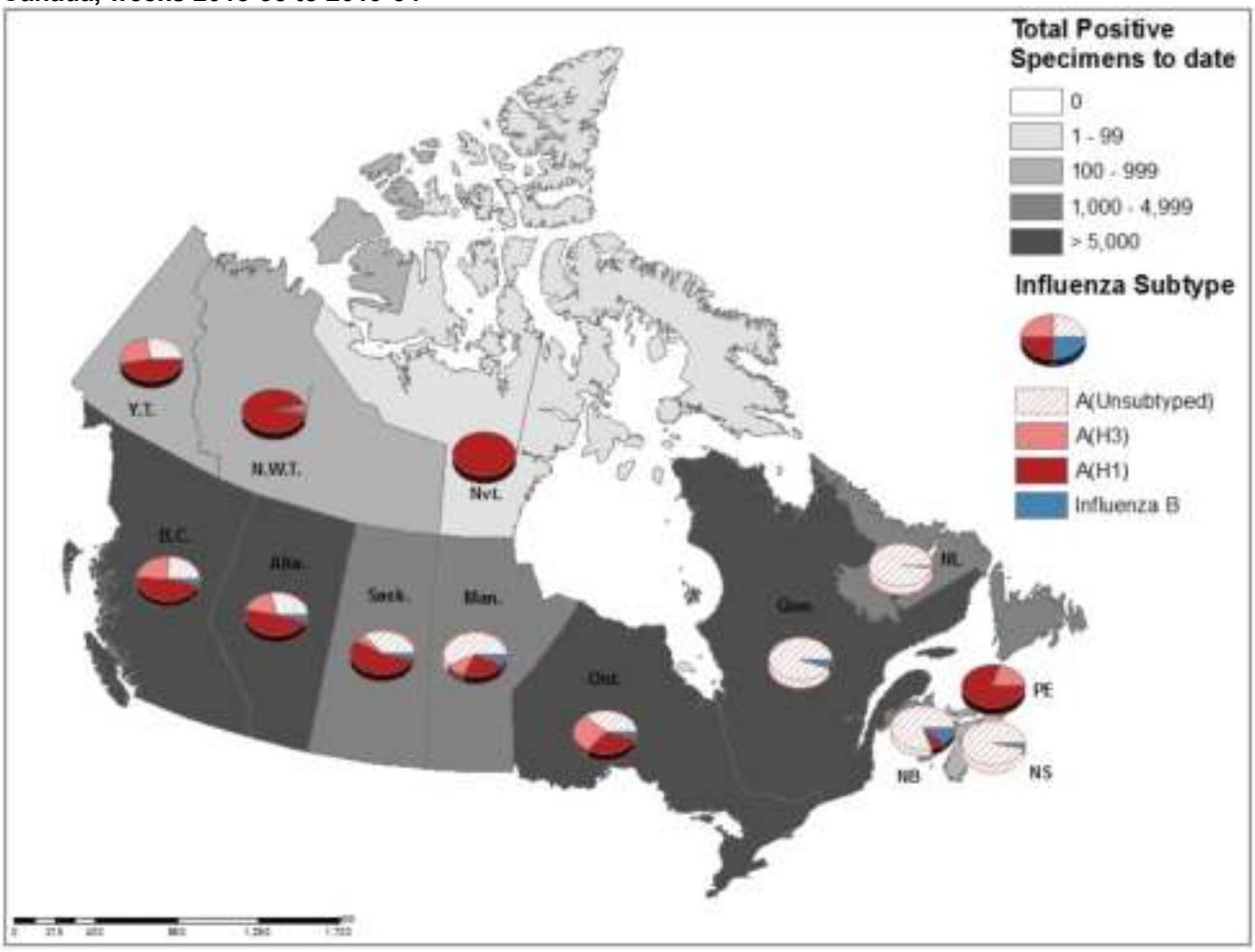
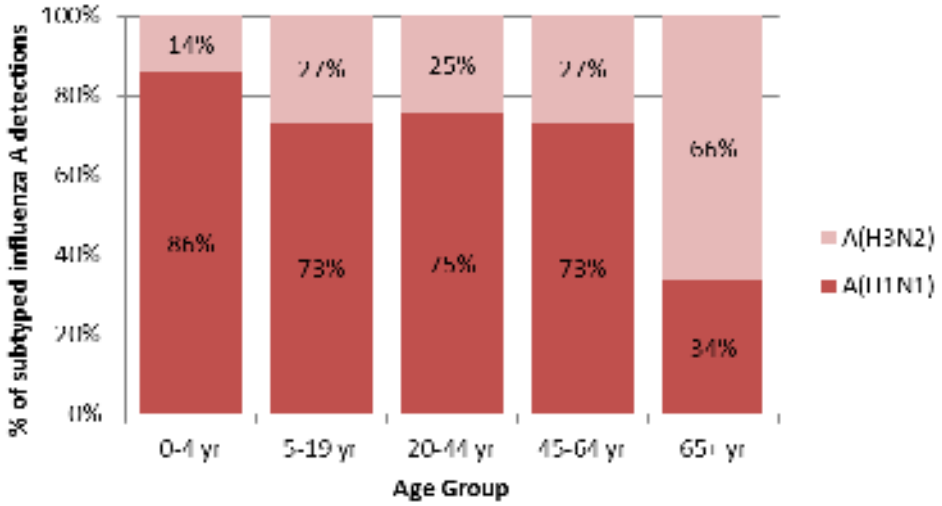


Figure 4 – Proportion of positive influenza A specimens by subtype and age-group reported through case-based laboratory reporting, Canada, weeks 2018-35 to 2019-34



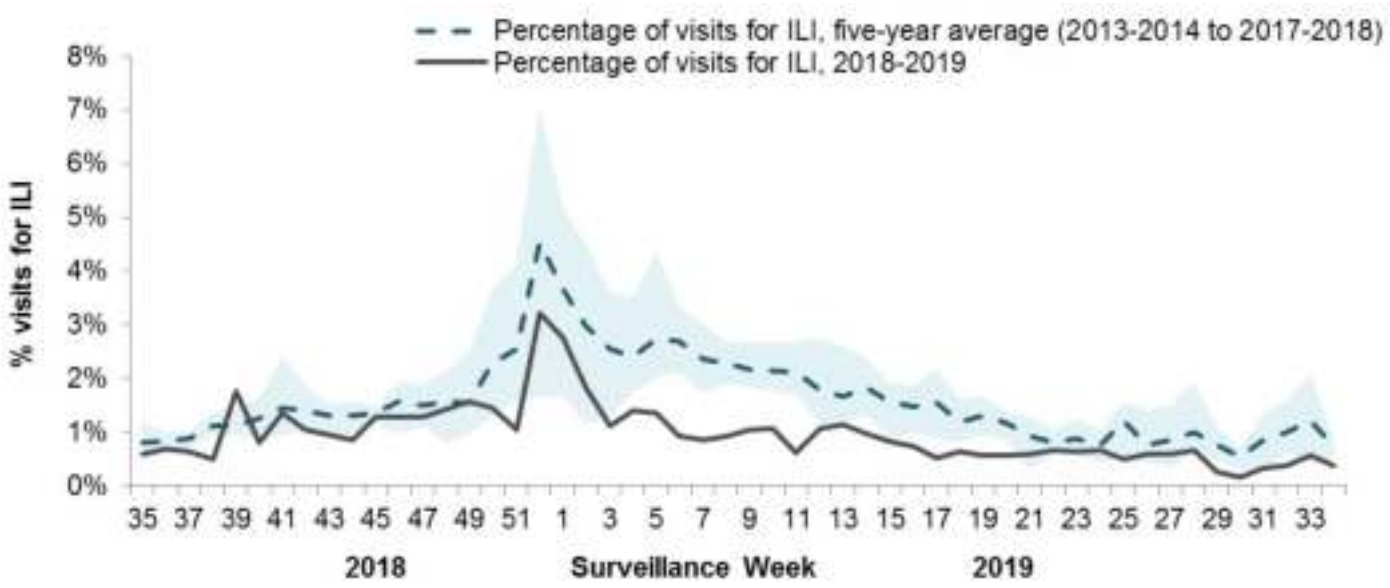
Syndromic / Influenza-like Illness Surveillance

Healthcare Practitioners Sentinel Syndromic Surveillance

On average, during the 2018-19 season, 106 healthcare practitioners across the country participated in influenza-like illness (ILI) surveillance for the FluWatch program. Each week these sentinel healthcare practioners report the proportion of patients in their practice who had ILI.

- Overall, ILI activity was below the five-year average for the majority of weeks this influenza season (range: 0.1% to 3.2%).
- 1.1% of all patient visits reported by sentinels were due to ILI this season (i.e. week 43 to week 21).
- The percentage of visitis for ILI reported by sentinels peaked in week 52 at 3.2%, consistent with the peak week of laboratory detections (Figure 5).
- For the majority of the season, the highest percentage of visits for ILI was reported among those less than 20 years of age. The lowest percentage of visits for ILI was reported among the 65+ year age group.

Figure 5 – Percentage of visits for ILI reported by sentinels by report week, Canada, weeks 2018-35 to 2019-34



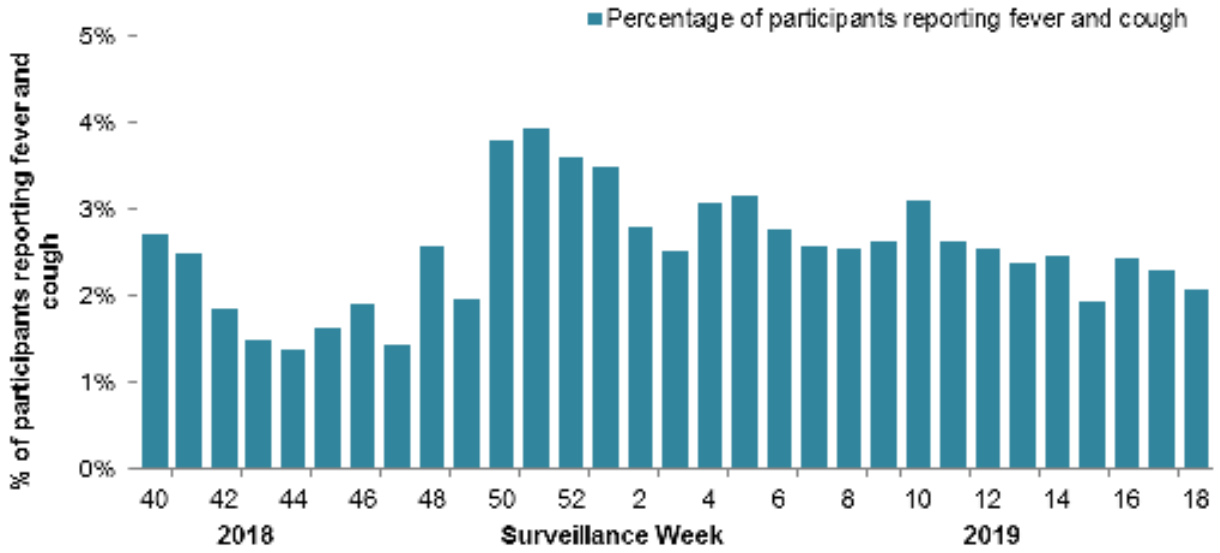
The shaded area represents the maximum and minimum percentage of visits for ILI reported by week from seasons 2013-2014 to 2017-2018

Participatory Syndromic Surveillance

FluWatchers are Canadians who report via a weekly online questionnaire if they have had symptoms of ILI in the preceding week. FluWatchers surveillance for the 2018-19 started in week 40 (October) and ended in week 18 (May). A total of 3,205 participants reported at least once this season, resulting in 64,728 completed questionnaires.

- The majority (75%) of FluWatchers particpants were adults 20-64 years of age. The age distribution of all FluWatchers participants this season was as follows:
  - 4% - 0 to 4 years of age
  - 15% - 5-19 years of age
  - 43% - 20 to 44 years of age
  - 33% - 45 to 64 years of age
  - 5% - 65 years of age and older
- 31% of FluWatchers reported experiencing cough and fever at least once this season.
- The percentage of FluWatchers reporting fever and cough peaked in week 51 with 3.9% of participants reporting cough and fever, consistent with the peak week of laboratory detections (Figure 6).
- A total of 1599 reports of cough and fever were reported by FluWatchers, of which 73% (1175) reported at least 24 hours off work or school, and 19% (306) reported a visit to a health care practitioner.
- A total of 46 tests for influenza and 15 positive tests were reported by FluWatchers.

Figure 6 – Percentage of FluWatchers participants reporting fever and cough, Canada, weeks 2018-40 to 2019-18



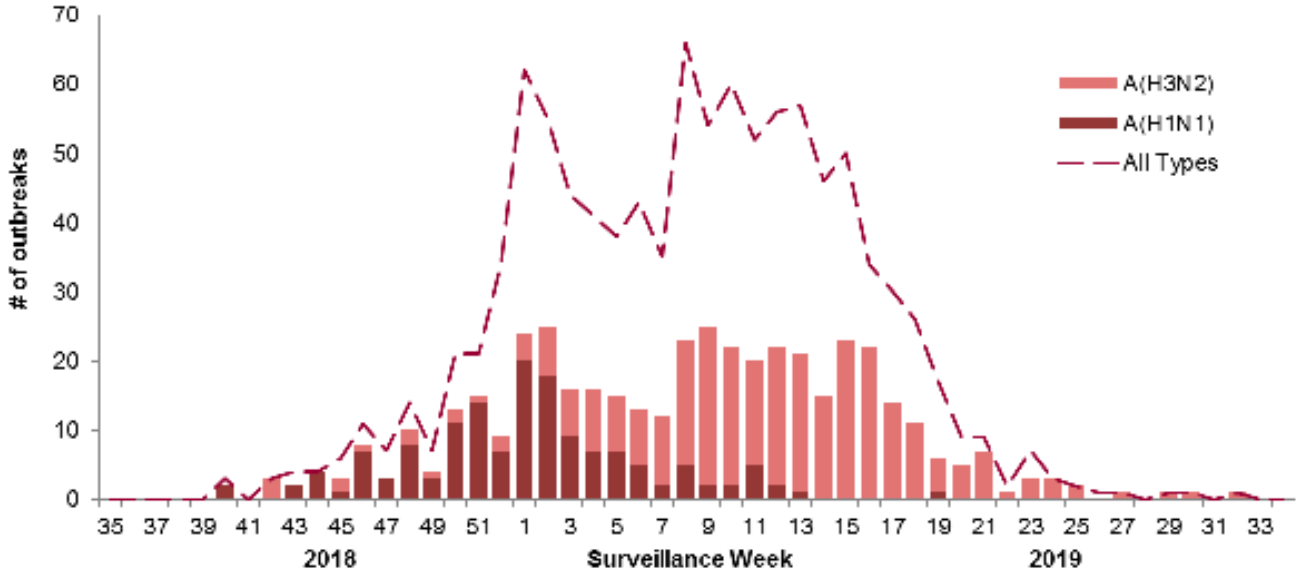
Influenza Outbreak Surveillance

Outbreak activity reports were provided by all provinces and territories each week this season. Not all provinces/territories conduct influenza outbreak surveillance in all the noted facilities. A total of 1038 laboratory-confirmed influenza outbreaks were reported (Figure 7).

- Two waves of activity were observed in the number of reported outbreaks.
- 62% (639) of reported outbreaks were in long-term care facilities (LTCF), 13% (138) were in acute care facilities, 3% (32) in schools and daycares and 22% (229) were in other settings (e.g. retirement homes, correctional facilities, etc.).
- Among the outbreaks for which influenza type (951) and subtype (446) were available, 98% (929) were associated with influenza A and 67% (298) were associated with influenza A(H3N2) respectively.
- Among the 220 outbreaks for which facility type was known and influenza A subtype was available:
    - 67% (173) of LTCF outbreaks were associated with influenza A(H3N2)
    - 65% (30) of acute care facility outbreaks were associated with influenza A(H3N2)
    - 85% (17) of school outbreaks were associatd with influenza A(H1N1).
- The predominant subtype for typed outbreaks was A(H1N1) from weeks 43 to two and A(H3N2) from weeks six to 29; between weeks three to five the number of A(H1N1) and A(H3N2) outbreaks was approximately equal.

In addition, a total of 180 outbreaks of influenza-like illness were reported; 112 occurred in LTCF, 62 in schools, five in acute care facilities, and one in a setting categorized as “other” (e.g. retirement homes, correctional facilities, etc.)

Figure 7 – Number of influenza outbreaks by report week (all types) and number of subtyped influenza A outbreaks by subtype and report week, Canada, weeks 2018-35 to 2019-34



Severe Outcomes Influenza Surveillance

Provincial/Territorial Influenza Hospitalizations and Deaths

Nine provinces and territories report influenza associated hospitalizations and deaths for all ages to FluWatch each week – Alberta, Manitoba, Saskatchewan, Newfoundland, Prince Edward Island, Nova Scotia, New Brunswick, Yukon and the Northwest Territories. The number of reporting provinces/territories varied over the course of the season. On average, seven provinces/territories reported each week.

A total of 3,657 influenza-associated hospitalizations were reported which corresponds to an annual seasonal hospitalization incidence of 45 hospitalizations per 100,000 population in the 2018-19 season (Table 1).

- 96% (3,525) were associated with influenza A.
- Among the 2,149 hospitalized cases for which the influenza subtype was available, the majority were associated with A(H1N1) (68%).
- Similar to the temporal pattern observed in laboratory detections, in the earlier part of the season (October to February) the majority (93%) of hospitalizations for which the influenza subtype was available were A(H1N1). In the latter part of the season (March to April) the majority (87%) of hospitalizations were A(H3N2).
- Overall, adults ≥ 65 years of age had the highest rate of hospitalizations (132 hospitalizations per 100,000 population); however, children 0-4 years of age had the highest cumulative hospitalization rate in the first part of the season from weeks 45 to 10, while adults ≥ 65 years of age had the highest cumulative rates in the second part of the season from weeks 10 to 29 which is likely due to the change in predominant subtype over time.
- This season's hospitalization rate (45 per 100,000 population) was slightly above the average compared to the previous five seasons (40 per 100,000 population), and notably higher than the annual seasonal hospitalization rates of the previous two A(H1N1) predominant seasons (25 and 34 per 100,000 population). The higher observed hospitalization rate relative to previous A(H1N1)-predominant seasons is likely due to the circulation of A(H3N2) in the latter part of the season.

Table 1 – Estimated annual seasonal incidence of influenza hospitalizations (per 100,000 population) by age group reported by participating provinces and territories[1], Canada, 2013/14 to 2018/19 influenza seasons

	Influenza Season (Predominant Influenza A Subtype)					
Age Groups (Years)	2013-14[2] (H1N1)	2014-15 (H3N2)	2015-16 (H1N1)	2016-17 (H3N2)	2017-18 (H3N2)	2018-19 (H1N1)
0-4	51	46	96	42	69	97
5-19	7	16	16	10	17	22
20-44	13	13	16	6	12	14
45-64	29	16	37	22	41	40
65+	41	207	68	143	268	132
Overall	25	45	34	34	64	45

1. Influenza-associated hospitalizations are reported by N.L., P.E.I, N.S., N.B., Man., Alb., Y.T. and N.W.T. Data provided by Sask is not included in these rates as only hospitalizations that require intensive medical care are reported by Sask. The annual seasonal hospitalization rate for a given season is calculated using the population by age-group in participating provinces and territories.
2. During the 2013-14 season N.B. did not report influenza-associated hospitalizations.
3. Highlighted boxes indicate the age group with the highest rate during the season.

A total of 613 ICU admissions and 224 deaths were reported this season.

- 97% (595) of reported ICU admissions and 98% (220) of reported deaths were associated with influenza A.
- Similar to the previous two A(H1N1)-predominant seasons, the highest proportion of ICU admissions was reported among adults 45-64 years of age (39%).
- The highest proportion of deaths was reported among adults ≥ 65 years of age (66%). This was approximately 20% higher than the number reported in the previous two A(H1N1)-predominant seasons and approximately 20% lower than the number reported in the previous three A(H3N2)-predominant seasons, likely as a result of the mixed A(H1N1) and A(H3N2) season.

Pediatric Influenza Hospitalizations and Deaths

Pediatric hospitalization data are provided by the Canadian Immunization Monitoring Program Active (IMPACT). IMPACT actively monitors pediatric influenza hospitalizations from 12 hospital sites in British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, Nova Scotia and Newfoundland.

A total of 1,352 pediatric hospitalized cases were reported this season. While the total number of hospitalized cases was above the five-year average (mean: 888; range: 593 to 1350) and the average of the last two A(H1N1)-predominant seasons (mean:1,032; range:714 to 1350), the number of hospitalized cases each week was within the expected range based on the minimum and maximum number of weekly cases observed in the previous five seasons.

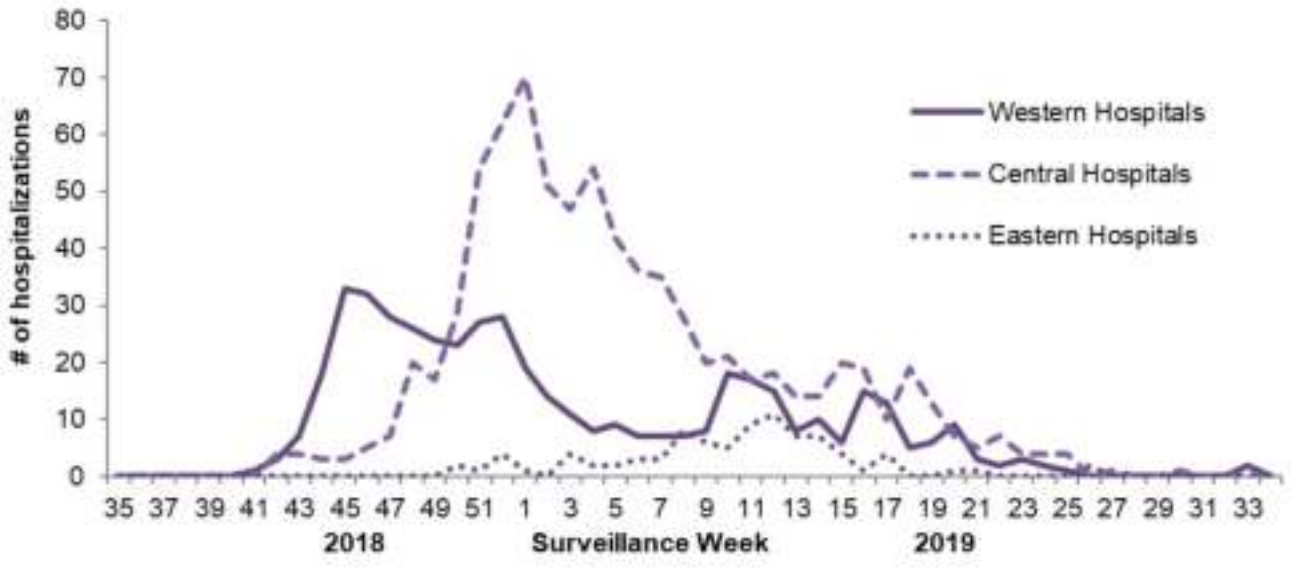
- Nationally, reports began earlier than previous seasons and peaked in week 52 consistent with the peak week of laboratory detections; however peaks varied by region, with an earlier peak in activity in sites in western Canada and a later peak of activity in sites in eastern Canada (Figure 8).
- More subtle peaks in activity can also be observed in western and central sites between weeks nine and 20 and in weeks 17 to 21 in eastern sites which may have resulted from the second wave of A(H3N2) activity and, along with this season's longer duration, may have contributed to the higher than average hospitalization counts.
- 91% (1,227) of pediatric hospitalized cases were associated with influenza A.
- Among the 402 pediatric hospitalized cases for which the influenza subtype was available, 80% (323) were associated with A(H1N1).
- 66% of pediatric hospitalized cases were among children under five years of age (Figure 9). This is consistent with the average proportion of hospitalized cases under five in the past five seasons (65%) and slightly less than the average of the two post-pandemic A(H1N1)-predominant seasons (71%) which were in 2013-14 and 2015-16.

Among the 1,352 pediatric hospitalized cases, a total of 271 (20%) ICU admissions and 10 (0.7%) deaths were reported. The proportion of hospitalized cases resulting in ICU admission was slightly above the average from the past five seasons (17%) and the last two A(H1N1)-predominant seasons (17%). The proportion of hospitalized cases

resulting in death was consistent with the average from the past five seasons (0.6%) and slightly above the average of the last two A(H1N1)-predominant seasons (0.4%).

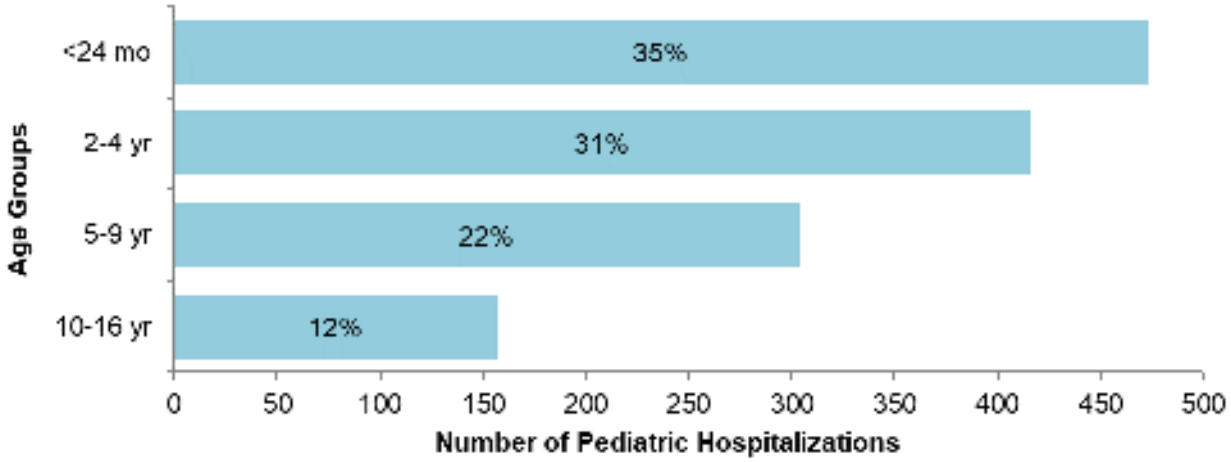
- 59% (161) of ICU admissions were among children under five years of age.
- 92% (248) of ICU admissions were associated with influenza A; 83% of the 111 cases for which the influenza A subtype was available were associated with A(H1N1).
- 80% (8) of deaths occurred in children two to four years of age.
- All deaths were associated with influenza A.

Figure 8 – Number of pediatric (≤16 years of age) hospitalizations reported by the IMPACT network, by region and by week of admission, Canada, weeks 2018-35 to 2019-34



Western hospitals consist of four sites in Vancouver, Calgary, Edmonton and Saskatoon. Central hospitals consist of 6 sites in Winnipeg, Toronto, Ottawa, Montreal and Quebec City. Eastern hospitals consist of 2 sites in Halifax & St. John's.

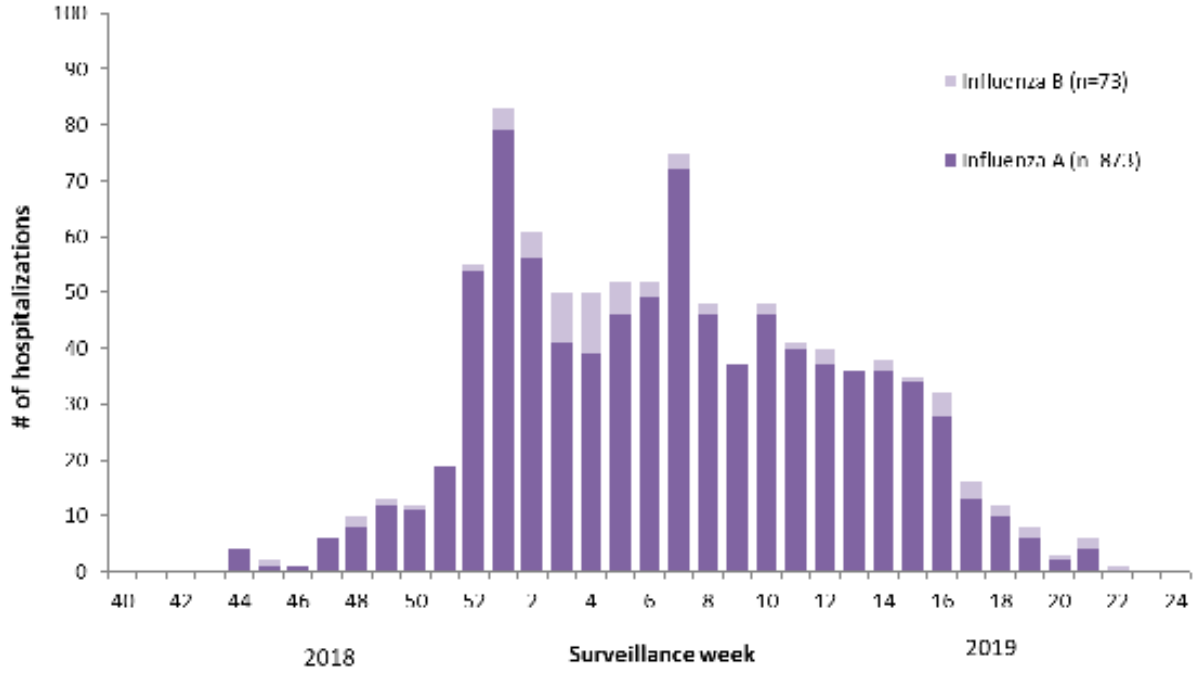
Figure 9 – Number and percentage of pediatric hospitalizations (≤16 years of age) with influenza by age-group reported by the IMPACT network, Canada, weeks 2018-35 to 2019-34



Adult Influenza Hospitalizations and Deaths

Surveillance of laboratory-confirmed influenza-associated adult (≥16 years of age) hospitalizations by the Canadian Immunization Research Network (CIRN) Serious Outcomes Surveillance (SOS) network began on November 1st (week 44) for the 2018-19 season and ended on June 1st (week 22). CIRN-SOS collects influenza hospitalization data from eight hospital sites in Ontario, Quebec, and Nova Scotia.

Figure 10 – Number of adult hospitalizations (≥16 years of age) with influenza reported by CIRN-SOS by surveillance week and influenza type, Canada, weeks 2018-44 to 2019-22



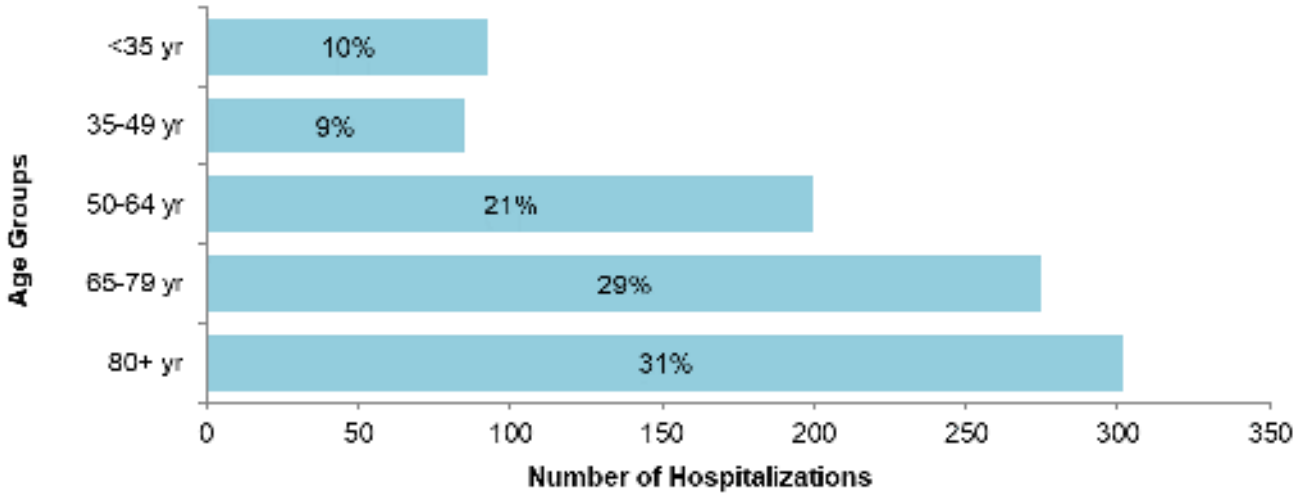
A total of 946 hospitalizations were reported by CIRN-SOS sentinels this season (age ≥16) (Figure 10):

- 92% (873) of hospitalizations were associated with influenza A.
- Among the 838 hospitalized cases for which the influenza subtype was available, 52% (439) were associated with A(H1N1).
- The highest proportion of hospitalized cases (31%) was among adults aged 80 years and over, followed by adults aged 65-79 years (29%) (Figure 11). The mean age of hospitalized cases was 67 years (range: 16 to 100).
- 89% of hospitalized cases reported at least one comorbid condition; vascular disorders were the most common comorbity (70% of all patients reporting a comorbidity) followed by cardiac disorders (43%).

A total of 137 (14%) ICU admissions and 65 (7%) deaths were reported.

- 95% (131) of ICU admissions were associated with influenza A.
- The majority of ICU admissions were among adults under the age of 65 (63%).
- The majority of deaths occurred among adults over the age of 65 (75%) with a mean age of 77 years.

Figure 11 – Number and percentage of adult hospitalizations (≥16 years of age) with influenza by age group reported by CIRN-SOS, Canada, 2018-19, weeks 2018-44 to 2019-22



Influenza Strain Characterizations

During the 2018-19 season, the National Microbiology Laboratory (NML) characterized 2,545 influenza viruses received from Canadian laboratories: 1,656 A(H1N1), 649 A(H3N2), 240 influenza B. Antigenic characterization is established by hemagglutination inhibition (HI) assay using cell-passaged vaccine reference viruses for A(H1N1) and influenza B, and the egg-passaged vaccine reference virus for A(H3N2). Over recent years, circulating strains of A(H3N2) have evolved, and are increasingly difficult to characterize by HI assay. Genetic characterization is established by sequencing the hemagglutinin gene of the influenza viruses to compare their genetic properties.

Influenza A(H3N2)

The influenza A(H3N2) component of the 2018-19 Northern Hemisphere influenza vaccine was an A/Singapore/INFIMH-16-0019/2016-like virus which belongs to the genetic group 3C.2a1.

All of the A(H3N2) viruses (649) were genetically characterized and 42% (378) of A(H3N2) viruses also grew to sufficient hemagglutination titer for antigenic characterization by HI assay (Table 2). Among all influenza A(H3N2) viruses genetically characterized, the most common subclade observed this season was 3C.2a1 (Figure 12). Of the A(H3N2) viruses characterized antigenically by HI assay (Figure 13-A):

- 56% (212) were characterized as A/Singapore/INFIMH-16-0019/2016-like by HI testing using antiserum raised against egg-propagated A/Singapore/INFIMH-16-0019/2016.
- 44% (166) of viruses showed reduced titer with ferret antisera raised against egg-propagated A/Singapore/INFIMH-16-0019/2016
- Among A(H3N2) viruses that showed reduced titer to A/Singapore/INFIMH-16-0019/2016, a greater proportion belonged to the genetic subclade 3C.3a. This is consistent with the genetic differences between subclades 3C.3a and 3C.2a1.

Table 2 – Genetic and antigenic characterization among characterized A(H3N2) viruses, Canada, weeks 2018-35 to 2019-34 (n=648)

Genetic clade	Genetic charaterization only	Antigenic characterization:		Total A(H3N2)
		Similar to A/Singapore/INFIMH-16-0019/2016	Reduced titer to A/Singapore/INFIMH-16-0019/2016	
Clade 3C.2a	20	17	3	40
Subclade 3C.2a1	242	132	16	390
Clade 3C.3a	8	63	147	218
Total	270	212	166	648

Influenza A(H1N1)

The influenza A(H1N1) component of the 2018-19 Northern Hemisphere influenza vaccine was an A/Michigan/45/2015-like virus.

Approximately 97% (1612) of the A(H1N1) viruses characterized were antigenically similar to A/Michigan/45/2015, while only 3% (44) of viruses showed reduced titer with ferret antisera raised against cell culture-propagated A/Michigan/45/2015 (Figure 13-B).

Influenza B

The recommended influenza B components for the 2018-19 Northern Hemisphere influenza vaccine were an B/Colorado/06/2017-like virus (Victoria lineage) and a B/Phuket/3073/2013-like virus (Yamagata lineage). The B/Colorado/06/2017-like virus was included in both the trivalent and quadrivalent vaccines. The B/Phuket/3073/2013-like virus was included in the quadrivalent influenza vaccine.

The majority of B viruses characterized, 70% (168), showed reduced titer with ferret antisera raised against cell culture-propagated B/Colorado/06/2017 (Figure 13-C). Sequence analysis showed that 96% (162) of viruses that showed reduced titer had a three amino acid deletion (162-164) in the hemagglutinin gene. Of the remaining B viruses characterized, 19% (46) were characterized as B/Colorado/06/2017-like (Victoria lineage) and 11% (26) were characterized as B/Phuket/3073/2013-like (Yamagata lineage).

Figure 12 – Distribution of genetic clades among characterized influenza A(H3N2) viruses, Canada, weeks 2018-35 to 2019-34

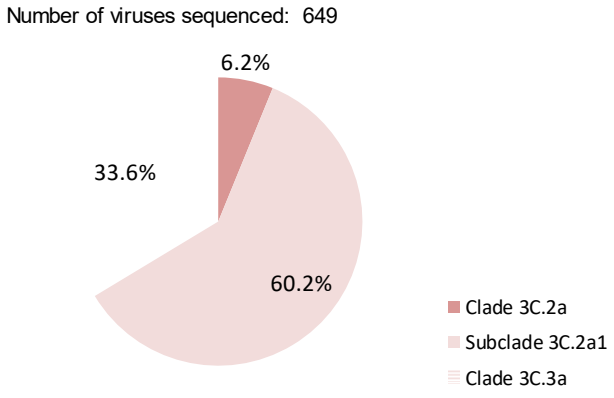
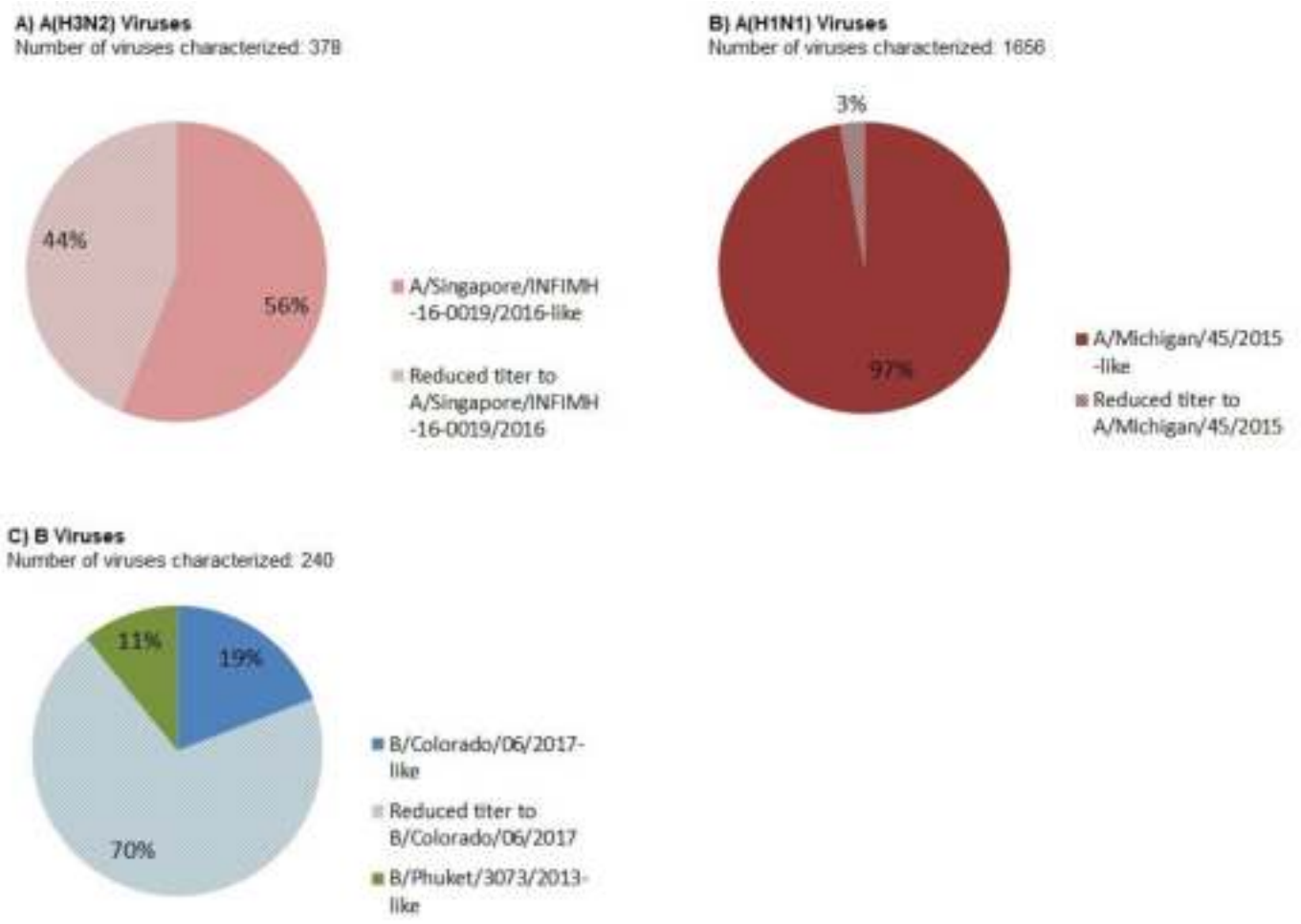


Figure 13 – Distribution of antigenic phenotypes among characterized influenza viruses, Canada, weeks 2018-35 to 2019-34



Antiviral Resistance

All influenza viruses characterized at the NML in the 2018-19 season were resistant to amantadine and sensitive to zanamivir. All influenza A(H3N2), all influenza B viruses, and all but four A(H1N1) viruses were sensitive to oseltamivir. The four A(H1N1) viruses resistant to oseltamivir had a H275Y mutation in the viral neuraminidase. The proportion of influenza viruses resistant to oseltamivir in 2018-19 is similar to recent seasons. Since the 2009 pandemic, nearly all circulating strains of influenza have been sensitive to oseltamivir and zanamivir. Widespread resistance to amantadine among influenza A viruses has been observed for more than 10 years.

Table 3 – Proportion of characterized influenza viruses resistant to antivirals by type and subtype, Canada, 2018-35 to 2019-34

Virus type and subtype	Oseltamivir		Zanamivir		Amantadine	
	# tested	# resistant (%)	# tested	# resistant (%)	# tested	# resistant (%)
A (H3N2)	222	0 (0%)	222	0 (0%)	135	135 (100%)
A (H1N1)	1084	4 (0.4%)	1082	0 (0%)	391	391 (100%)
B	142	0 (0%)	142	0 (0%)	NA[1]	NA[1]
TOTAL	1448	4 (0.3%)	1446	0 (0%)	526	526 (100%)

[1]NA: Not Applicable

Vaccine Monitoring

Vaccine monitoring refers to activities related to the monitoring of influenza vaccine coverage and effectiveness.

The quadrivalent vaccines used in the 2018-19 northern hemisphere influenza season contained:

- an A/Michigan/45/2015 (H1N1)pdm09-like virus;
- an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus;
- a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage); and
- a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage).

The B/Colorado/06/2017-like virus was included in both the trivalent and quadrivalent vaccines.

Vaccine Coverage

The Seasonal Influenza Immunization Coverage Survey is an annual telephone survey conducted between January and February that collects information from Canadians on whether they received the annual seasonal influenza vaccine that season. Vaccine coverage is measured as the percentage of people who received the influenza vaccine in a specific influenza season. More detail on the methodology used for the coverage survey can be viewed here.

Overall, influenza vaccination coverage in the 2018-2019 season (42%) was significantly higher than the 2017-2018 season (38%) and the 2016-2017 season (36%). The vaccination rate was lowest among adults 18-64 years of age without any chronic medical condition (31%); however, coverage increased mostly among this subgroup when compared to the previous two seasons. Among high-risk groups, vaccination coverage rates for adults 18-64 years of age with a chronic medical condition (43%) and seniors 65 years of age and older (70%) remained steady over the past three seasons.

Table 4 – Influenza vaccine coverage among adults (≥ 18 years of age) by age group, gender and chronic disease[1], Seasonal Influenza Vaccination Coverage Survey, Canada, September 2018-February 2019

	Male		Female		Combined	
Age group (years)	Total	Vaccine Coverage (%)	Total	Vaccine Coverage (%)	Total	Vaccine Coverage (%)
All adults (≥18)	1568	36.6	2150	46.8	3726	41.8
18-64	1252	28.6	1640	39.9	2898	34.3
without chronic diseases	948	25.8	1171	36.1	2124	30.8
with chronic diseases	304	36.3	465	48.5	770	42.8
≥65	316	69.0	510	70.9	828	69.9

[1]Excluded from stratified analysis: eight people who did not disclose their gender and four people (18-64 years old) who did not disclose whether they had any chronic diseases.

Vaccine Effectiveness

The Canadian Sentinel Practitioner Surveillance Network (SPSN) provides estimates of the effectiveness of the seasonal influenza vaccine in preventing primary care visits for laboratory confirmed influenza among Canadians of all ages but primarily those from 20-64 years of age.

Based on data collected between November 1, 2018 and April 30, 2019, VE against any influenza, foremost driven by A(H1N1) viruses, was 56% (95% CI: 47 to 64%), and for A(H1N1) alone was 67% (95% CI: 58 to 75%) (Table 5). This substantial protection against A(H1N1) was observed in all age groups. Conversely, the SPSN reported little or no vaccine protection against A(H3N2) viruses, with an overall VE against medically-attended outpatient A(H3N2) illness of 17% (95% CI: -13 to 39). Overall, the A(H3N2) VE estimate for 2018-19 was lower than expected generally for

A(H3N2) vaccines (~30%), and similar to that observed by SPSN in the 2017-18 A(H3N2)-dominant season where VE was estimated at 14% (95% CI: -8 to 31).

More information on the SPSN including study methodology and available publications can be viewed here.

The Serious Outcomes Surveillance (SOS) Network of the Canadian Immunization Research Network (CIRN-SOS) provides estimates of the effectiveness of the seasonal influenza vaccine in preventing hospitalization for laboratory-confirmed influenza in adults.

Based on data collected between November 1, 2018 and June 1, 2019 among adult (≥16 years of age) hospitalized cases of influenza, VE against any influenza was 43% (95% CI: 28 to 55%), and for A(H1N1) alone was 68% (95% CI: 52 to 79%). CIRN-SOS also reported little or no vaccine protection against A(H3N2) viruses, with an overall VE against hospitalized cases of influenza A(H3N2) of 19% (95% CI: -35 to 51). The number of influenza B hospitalized cases was too low to calculate an adjusted VE estimate.

More information on the CIRN-SOS Network including study methodology and available publications can be viewed here.

Table 5 – Vaccine effectiveness estimates against primary care visits (SPSN - November 1, 2018, to April 30, 2019) and hospitalizations (CIRN-SOS - November 1, 2018 to June 1, 2019)

	SPSN (Primay Care Visits)†		CIRN-SOS (Adult Hospitalizations)	
	VE(%) (CI)*	N	VE(%) (CI)**	N
All Influenza	56 (47, 64)	3034	43 (28, 55)	1350
Influenza A	55 (46, 63)	2992	58 (43, 69)	1105
Influenza A H1N1	67 (58, 75)	2630	68 (52, 79)	562
Influenza A H3N2	17 (-13, 39)	1993	19 (-35, 51)	409
Influenza B	72 (27, 89)	1703	n/a***	140

† SPSN 2018-19 estimates are published and available here and here
CI: 95% confidence interval
*adjusted for age, province, specimen collection interval and calendar time (natural cubic spline with 3 equally spaced knots)
** VE for All Influenza, Influenza A, Influenza A/H1, and Influenza A/H3 was adjusted for age, pregnancy and current or past smoker.
VE for 16-49 and 50-64 age groups was adjusted for age, body mass index categories, pregnancy and medications prior to admission.
VE for 65-75 and >75 age groups was adjusted for age, Frailty index prior to admission; and current or past smoker.
***Sample size was too small to calculate an adjusted estimate

Provincial and International Surveillance Links

- Alberta – Influenza Surveillance
- British Columbia – Influenza Surveillance; Vaccine Effectiveness Monitoring
- Manitoba - Seasonal Influenza Reports
- New Brunswick – Influenza Surveillance Reports
- Newfoundland and Labrador – Surveillance and Disease Reports
- Nova Scotia – Respiratory Watch Report
- Ontario – Ontario Respiratory Pathogen Bulletin
- Prince Edward Island – Influenza Summary
- Saskatchewan – Influenza Reports
- Québec – Système de surveillance de la grippe *(available in French only)*
- Australia – Influenza Surveillance Report and Activity Updates
- European Centre for Disease Prevention and Control – Surveillance reports and disease data on seasonal influenza
- New Zealand – Influenza Weekly Update
- United Kingdom -- Weekly Influenza Activity Reports
- Pan-American Health Organization – Influenza Situation Report
- United States Centres for Disease Control and Prevention – Weekly Influenza Summary Update
- World Health Organization – FluNet

Notes

To learn more about definitions, descriptions and the FluWatch program in general, see the Overview of influenza monitoring in Canada page. For more information on the flu, see our Flu (influenza) web page.

This report is available on the Government of Canada Influenza webpage.
Ce est disponible dans les deux langues officielles.

We would like to thank all the FluWatch surveillance partners who participated in the 2018-19 influenza surveillance program.

Government of Canada | Gouvernement du Canada

COVID-19 daily epidemiology update

Updated: December 13, 2021, 7 pm EST

Summary of COVID-19 cases across Canada and over time. Contains detailed data about the spread of the virus over time and in different regions of the country. Includes breakdowns by age and sex or gender. Provides an overview of hospitalizations and deaths, testing, variants of concern and exposures.

Key updates as of December 13, 2021, 7 pm EST

Cases today	Total cases
4,233	1,840,919

Active cases	Total resolved
36,844	1,774,134

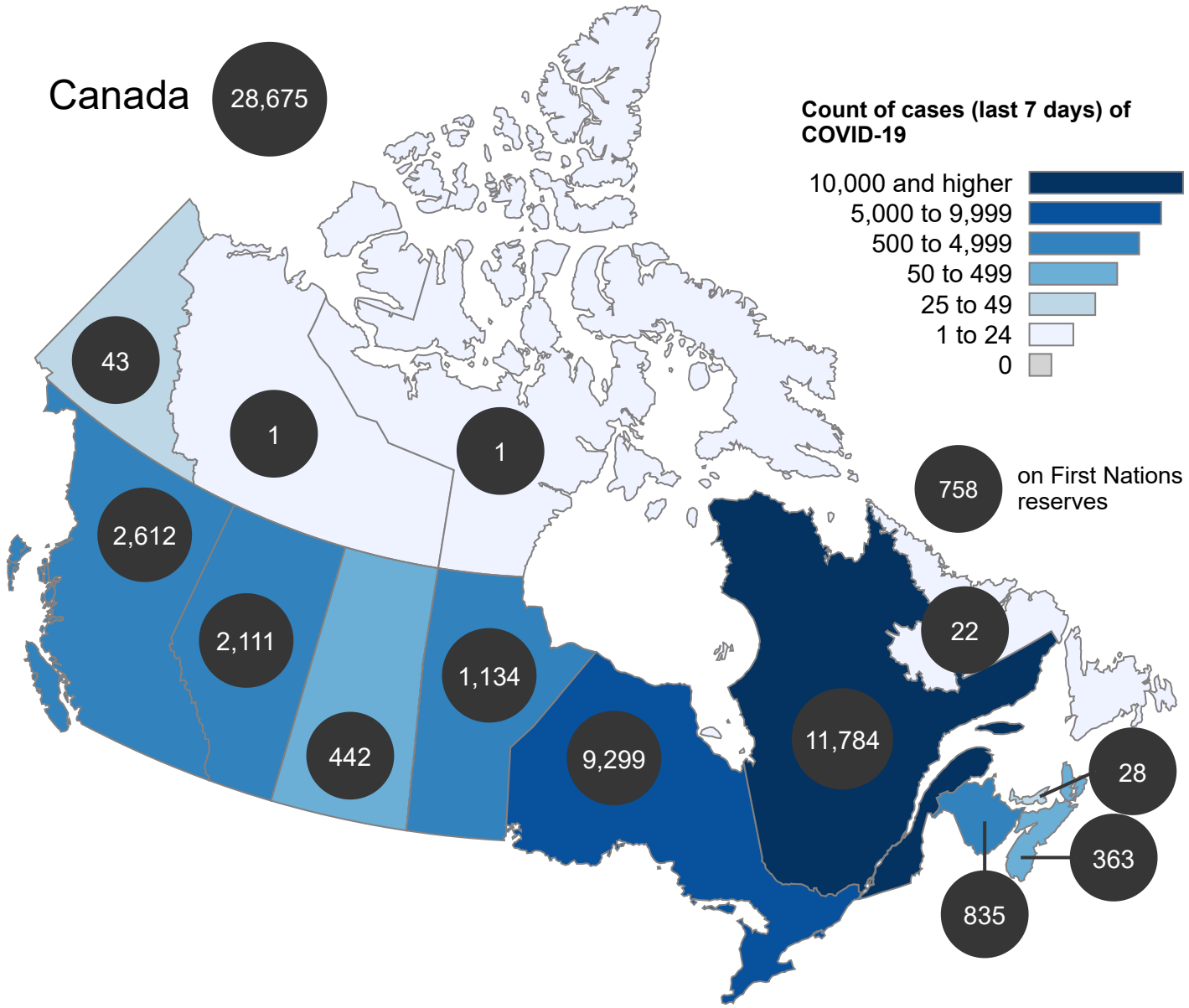
Deaths today	Total deaths
15	29,941

Total tests performed	Daily percent positive (last 7 days)	Daily tests per 100,000 population (last 7 days)
50,147,977	4.1%	269

- We update these sections Monday to Friday at 7:00 PM EST: Key updates, Current situation and National overview. Laboratory data represents specimens received by labs up to December 11, 2021 to allow time to process results.
- We update these sections every Friday: Epidemic curve, Demographics, How people were exposed, and Severe illness and outcomes.
- Of the 12 jurisdictions reporting updates, no new cases were reported in 2 provinces and territories in the past 24 hours.
- Of the 12 jurisdictions reporting updates, no new deaths were reported in 6 provinces and territories in the past 24 hours.

Current situation

Figure 1a. Count of cases (last 7 days) of COVID-19, by province/territory as of December 13, 2021



The count of cases (last 7 days) of COVID-19 in **Canada** was **28,675** as of December 13, 2021.

This information is based on data our provincial and territorial partners published on cases, deaths, and testing daily, and are current as of the day they are published. Today's numbers are current as of December 13, 2021, 2021, 7 PM EST. For the most up to date data for any province, territory or city, please visit their website. The number of cases or deaths reported on previous days may differ slightly from those on the provincial and territorial websites as these websites may update historic case and death counts as new information becomes available.

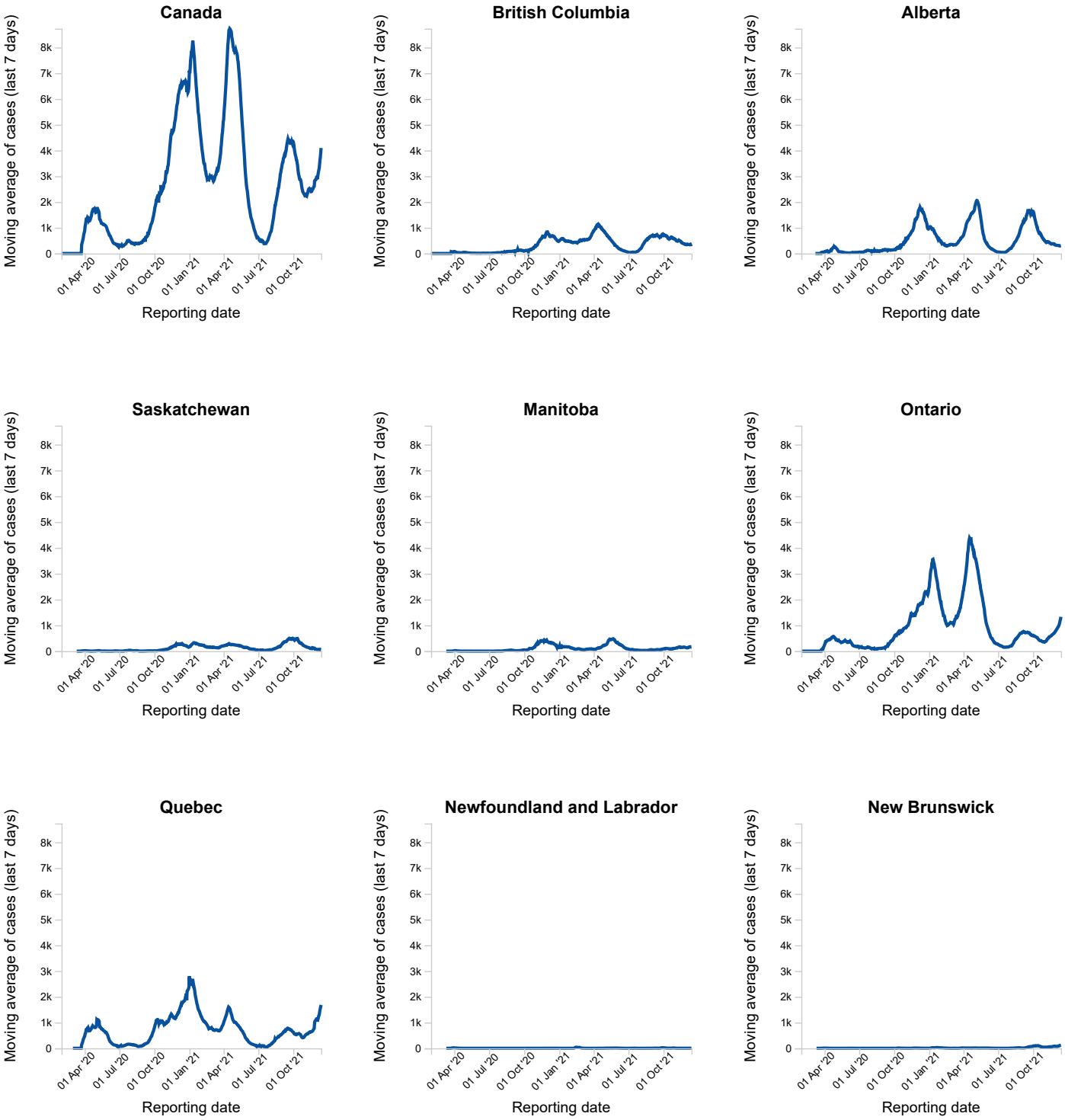
Areas in Canada with cases of COVID-19 as of December 13, 2021

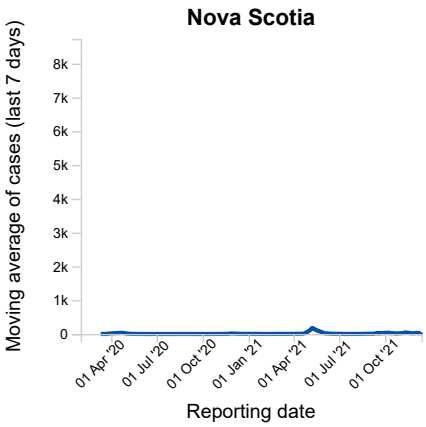
	Total cases		Cases last 7 days		Active cases		Resolved	Deaths		Deaths last 7 days		Total tests performed	Moving average tests performed last 7 days		Moving average positivity last 7 days
Location	**Count**	**Rate***	**Count**	**Rate***	**Count**	**Rate***	**Count**	**Count**	**Rate***	**Count**	**Rate***	**Count**	**Count**	**Rate***	**Percent**
British Columbia	223,142	4,279	2,612	50	3,051	59	217,705	2,386	46	24	0.5	4,768,196	12,424	238	3.0%
Alberta	339,291	7,637	2,111	48	4,182	94	331,834	3,275	74	12	0.3	6,193,592	8,099	182	3.6%
Saskatchewan	81,852	6,938	442	37	568	48	80,347	937	79	6	0.5	1,298,188	1,634	139	3.8%
Manitoba	69,979	5,057	1,134	82	1,700	123	66,926	1,353	98	19	1.4	1,257,958	2,896	209	6.3%
Ontario	633,683	4,274	9,299	63	11,538	78	612,066	10,079	68	52	0.3	20,081,389	35,926	242	4.1%
Quebec	467,609	5,434	11,784	137	14,251	166	441,747	11,611	135	22	0.3	13,793,358	35,047	407	4.6%
Newfoundland and Labrador	2,093	402	22	4	30	6	2,045	18	3	0	0.0	408,343	511	98	0.5%
New Brunswick	9,704	1,230	835	106	1,050	133	8,512	142	18	6	0.8	589,812	1,515	192	7.6%
Nova Scotia	8,790	886	363	37	379	38	8,301	110	11	0	0.0	1,446,626	3,847	388	2.1%
Prince Edward Island	420	256	28	17	37	23	383	0	0	0	0.0	241,584	903	550	0.7%
Yukon	1,597	3,715	43	100	46	107	1,537	14	33	0	0.0	9,129	N/A	N/A	N/A
Northwest Territories	2,070	4,549	1	2	10	22	2,048	12	26	0	0.0	36,655	38	83	1.1%
Nunavut	676	1,716	1	3	2	5	670	4	10	0	0.0	23,071	30	76	0.5%
Canada	**1,840,919**	**4,813**	**28,675**	**75**	**36,844**	**96**	**1,774,134**	**29,941**	**78**	**141**	**0.4**	**50,147,977**	**102,870**	**269**	**4.1%**

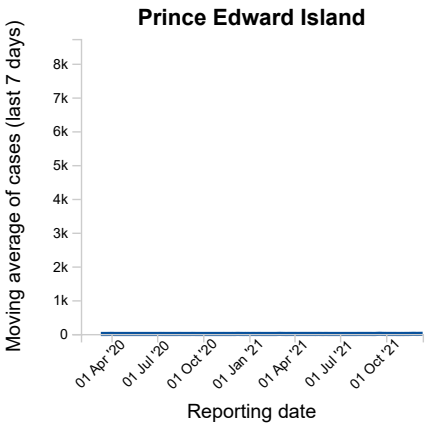
* Rate per 100,000 population

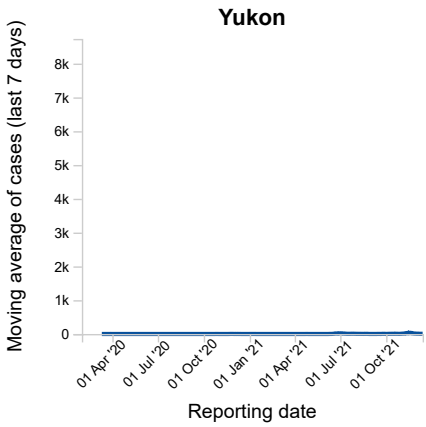
Figure 1b. Moving average of cases (last 7 days) of COVID-19 in Canada as of December 13, 2021, 7 pm EST

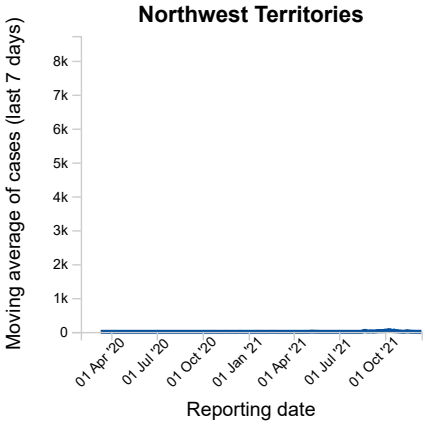
The figures below show cases over time. The range of dates (January 31st, 2020 - present date) is the same for each figure. This allows you to compare the provinces and territories on the same timescale.

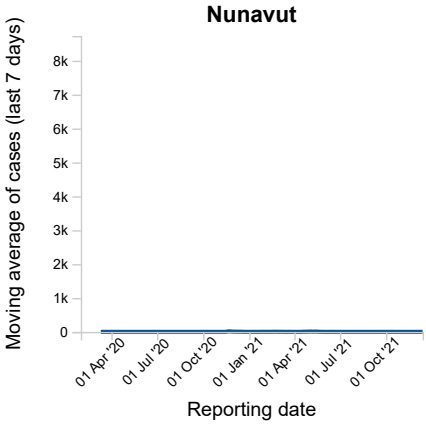












a. This information is based on data from our provincial and territorial partners. Data about cases was last updated on December 13, 2021. Laboratory data includes specimens received by labs up to December 11, 2021. For the most up to date data for any province, territory or city, please visit their web site.
b. The 7-day moving average is the total of the daily numbers for the previous 7 days (up to and including the day of the last update), divided by the number of days for which data is available. We go back and update the moving averages as provinces and territories submit more data. We calculate the national 7-day moving average by summing the 7-day moving average from the provinces and territories then dividing by the national population if a rate is calculated.

Downloadable data (in .csv format).

Note: Out of the total number of people tested, 76 were repatriated travellers, of which 13 were cases.

National overview

There have been over **50,147,977** COVID-19 tests performed in Canada or **1,311,192 tests per 1 million people**. For information about testing trends, please see the Detailed weekly epidemiological report (PDF).

Table 1. Daily* change in the number of cases, deaths and tests performed, by province or territory, as of December 13, 2021, 7 pm EST

Location	New cases	New deaths	Tests performed
British Columbia	349	5	12,412
Alberta	202	3	N/A
Saskatchewan	35	0	1,191
Manitoba	152	1	2,397
Ontario	1,536	1	38,477
Quebec	1,628	3	34,065
Newfoundland and Labrador	15	0	518
New Brunswick	100	2	1,474
Nova Scotia	199	0	4,766
Prince Edward Island	0	0	888
Yukon	17	0	N/A
Northwest Territories	N/A	N/A	24
Nunavut	0	0	11
Canada	**4,233**	**15**	**96,223**

* The new cases, deaths and tests reflect the difference between a province or territory's current report and their last report. Some provinces and territories do not update daily.

N/A means that no daily update was provided by the province or territory.

COVID-19 variants in Canada

All viruses, including COVID-19, change over time. These changes are called mutations, and result in variants of the virus. Not all mutations are of concern. Most do not cause more severe illness. However, some mutations result in variants of concern or variants of interest.

A variant of concern has mutations that are significant to public health. Before a variant of interest is considered one of concern, scientists and public health professionals must determine if the mutations result in an actual change in the behaviour of the virus. For example, it might:

- spread more easily
- cause more severe illness
- require different treatments, or
- reduce vaccine effectiveness

There are several variants of interest that have mutations similar to variants of concern, but we don't yet know if they pose a higher risk to public health.

The Public Health Agency of Canada (PHAC) works with provincial and territorial partners and the Canadian COVID-19 Genomics Network (CanCOGeN) to sequence a percentage of all positive COVID-19 test results. Sequencing reveals the genetic code of the virus, which tells us which variant is involved in a specific case of COVID-19. We report the proportion of COVID-19 variants in Canada every week.

We collect evidence to determine if new variants meet the definition for a variant of concern or a variant of interest. Many variants are being tracked across Canada and around the world. Variants of concern now represent a majority of COVID-19 cases in Canada.

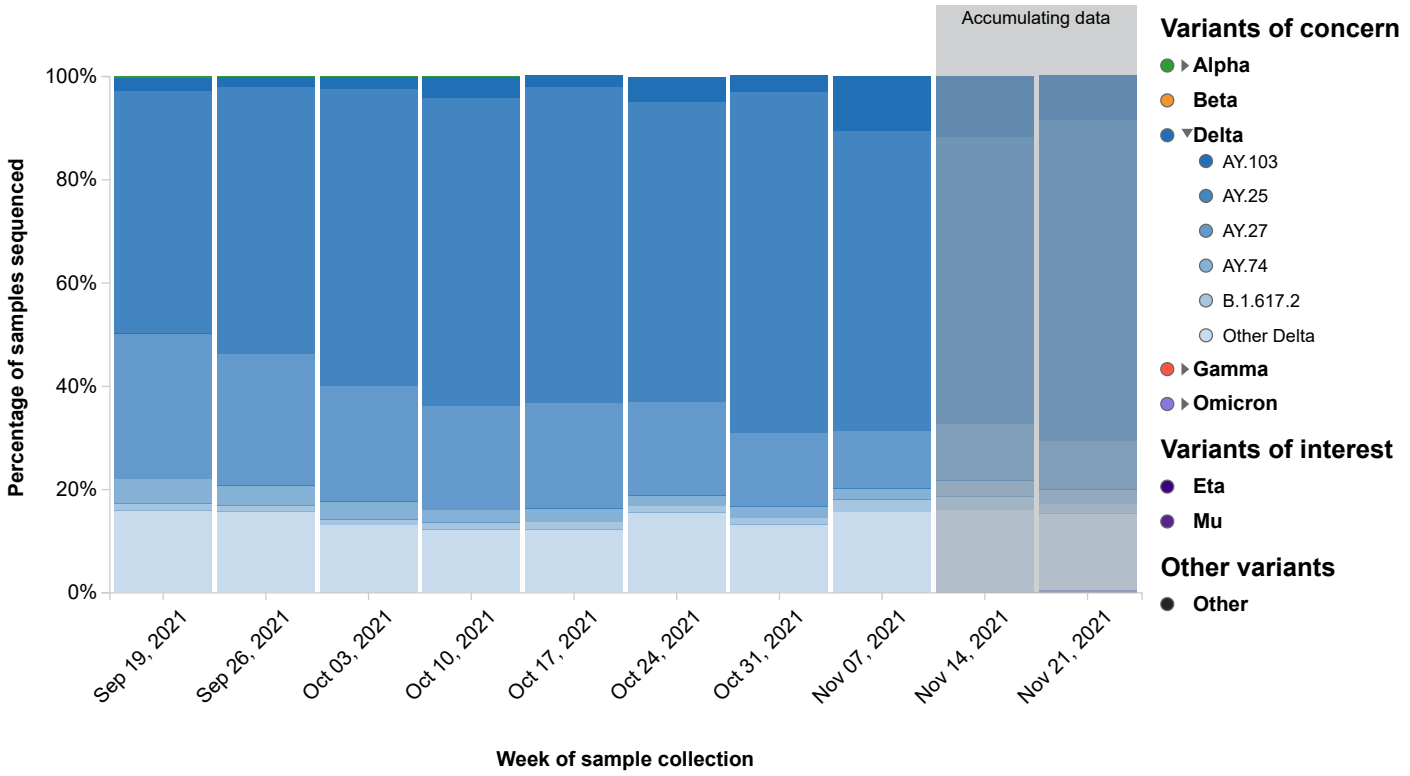
Current variants of concern in Canada include:

- Alpha (B.1.1.7)
- Beta (B.1.351)
- Gamma (P.1)
- Delta (B.1.617.2)
- Omicron (B.1.1.529)

New variants will continue to appear. We must remain vigilant and take all available measures to limit spread.

Figure 2. Weekly variant breakdown Updated: December 10, 2021, 4 pm EDT

The graphic shows the percentage mix of COVID-19 variants detected in Canada through whole genome sequencing, by week of sample collection. You can see the numbers for each date by hovering over, tabbing to, or long-pressing any of the bars. To see a specific variant or variant grouping, click or press return. Repeat to restore the complete graph. Sublineages or offshoots for some variants can be revealed or hidden by clicking on the name of the variant in the legend.



This information is based on whole genome sequencing from surveillance testing in all provinces and territories. In addition to sequencing done by the National Microbiology Laboratory in Winnipeg, data is included from provincial and territorial laboratories.

Sequencing takes from 1 to 3 weeks to complete, so the proportions for recent weeks may change as more data are added. Surveillance in each province or territory is organized and prioritized according to local needs and may change from time to time. Because of differences in local sampling and reporting, the percentages illustrate trends rather than precise measurements.

Weekly variant breakdown

Percentage of COVID-19 cases identified through whole genome sequencing, presented by variant and by week of sample collection.

Variant Grouping	Sep 19, 2021 (n=3,639)	Sep 26, 2021 (n=4,378)	Oct 03, 2021 (n=5,805)	Oct 10, 2021 (n=4,647)	Oct 17, 2021 (n=4,796)	Oct 24, 2021 (n=3,745)	Oct 31, 2021 (n=4,427)	Nov 07, 2021 (n=4,154)	Nov 14, 2021 (n=4,793)	Nov 2021 (n=4,
Variants of concern	**99.9%**	**100.0%**	**99.9%**	**99.9%**	**100.1%**	**99.7%**	**100.0%**	**99.9%**	**100.0%**	**100.**
Alpha	**0.3%**	**0.1%**	**0.1%**	**0.1%**	**-**	**0.0%**	**-**	**-**	**0.0%**	**-**
B.1.1.7	0.2%	0.1%	0.1%	0.1%	-	0.0%	-	-	0.0%	-
Q.8	0.1%	-	-	-	-	-	-	-	-	-
Beta	**-**	**-**	**-**	**-**	**-**	**0.0%**	**-**	**-**	**-**	**-**
B.1.351	-	-	-	-	-	0.0%	-	-	-	-
Delta	**99.6%**	**99.9%**	**99.8%**	**99.8%**	**100.1%**	**99.7%**	**100.0%**	**99.9%**	**100.0%**	**99.8**
AY.103	2.4%	2.0%	2.3%	4.1%	2.3%	4.7%	3.1%	10.6%	11.8%	8.6%
AY.25	47.1%	51.8%	57.5%	59.6%	61.1%	58.1%	66.0%	58.0%	55.6%	62.3%
AY.27	28.1%	25.4%	22.4%	20.1%	20.5%	18.2%	14.3%	11.2%	10.9%	9.4%
AY.74	4.8%	3.9%	3.5%	2.5%	2.6%	2.0%	2.3%	2.2%	3.1%	2.8%
B.1.617.2	1.4%	1.2%	1.1%	1.4%	1.5%	1.3%	1.2%	2.4%	2.7%	1.9%
Other Delta	15.8%	15.6%	13.0%	12.1%	12.1%	15.4%	13.1%	15.5%	15.9%	14.8%
Gamma	**0.0%**	**-**	**0.0%**	**-**	**0.0%**	**0.0%**	**-**	**-**	**-**	**-**
P.1	0.0%	-	-	-	-	0.0%	-	-	-	-
P.1.12	-	-	0.0%	-	0.0%	-	-	-	-	-
P.1.14	-	-	0.0%	-	-	-	-	-	-	-
Omicron	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**0.4%**
B.1.1.529	-	-	-	-	-	-	-	-	-	0.0%
BA.1	-	-	-	-	-	-	-	-	-	0.4%
Variants of interest	**-**	**-**	**-**	**0.0%**	**-**	**0.0%**	**-**	**-**	**-**	**-**
Eta	**-**	**-**	**-**	**-**	**-**	**0.0%**	**-**	**-**	**-**	**-**
B.1.525	-	-	-	-	-	0.0%	-	-	-	-

Variant Grouping	Sep 19, 2021 (n=3,639)	Sep 26, 2021 (n=4,378)	Oct 03, 2021 (n=5,805)	Oct 10, 2021 (n=4,647)	Oct 17, 2021 (n=4,796)	Oct 24, 2021 (n=3,745)	Oct 31, 2021 (n=4,427)	Nov 07, 2021 (n=4,154)	Nov 14, 2021 (n=4,793)	Nov 2021 (n=4,
Mu	**-**	**-**	**-**	**0.0%**	**-**	**-**	**-**	**-**	**-**	**-**
B.1.621	-	-	-	0.0%	-	-	-	-	-	-
Other variants	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**-**
Other	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**-**

Note: The shaded columns on the right represent a period of accumulating data.

Contributing laboratories:

- Saskatchewan - Roy Romanow Provincial Laboratory (RRPL)
- Public Health Ontario (PHO)
- Newfoundland and Labrador - Eastern Health
- New Brunswick – Vitalité Health Network
- Manitoba Cadham Provincial Laboratory
- Laboratoire de santé publique du Québec (LSPQ)
- BCCDC Public Health Laboratory
- Alberta Precision Labs - Edmonton (APL)
- National Microbiology Laboratory (NML) - supplemental sequencing for all provinces and territories

Detailed case information

The tables and figures below reflect detailed case information provided to the Public Health Agency of Canada (PHAC) by health authorities in the provinces and territories. This data is updated every week. It may change as we get more information about cases.

Updated: December 10, 2021, 7 pm EST

Epidemic curve

As of December 10, 2021, 7 pm EST, PHAC has received detailed case report data on 1,811,673 cases. Both exposure and symptom onset date were available for 1,338,828 (73.9%) cases [1].

The shaded area on the far right of Figure 3 represents a period of accumulating data. This is the period of time (1 to 2 weeks) before the latest cases are reported to PHAC. This delay is a result of the time required to seek health care, get tested and receive results. It also takes time for public health authorities to gather information on cases. We update this information as it becomes available.

Figure 3. COVID-19 cases (n=1,811,673 [1]) in Canada by date [2] as of December 10, 2021, 7 pm EST (total cases)

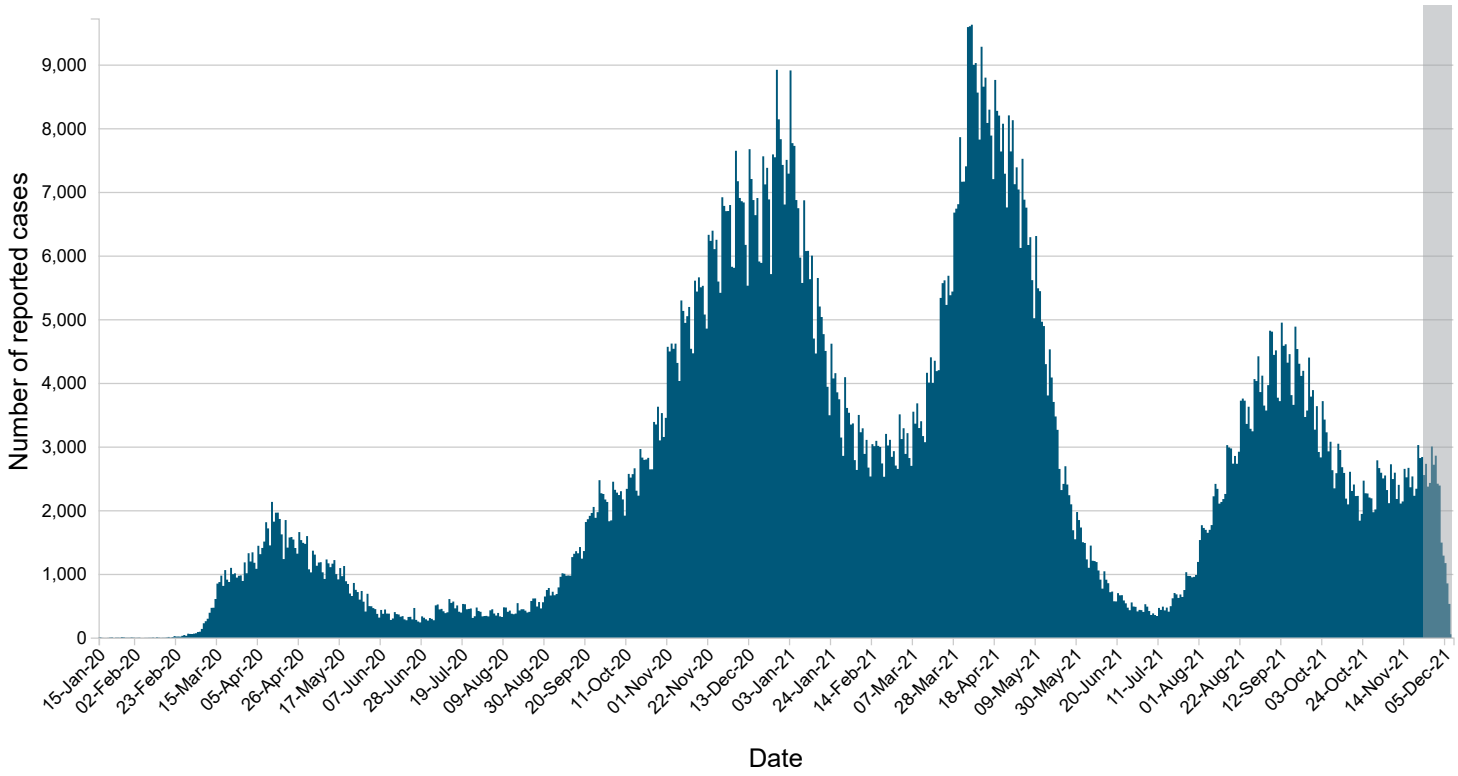


Figure 3. COVID-19 cases (n=1,338,828 [1]) in Canada by date [2] as of December 10, 2021, 7 pm EST (by exposure)

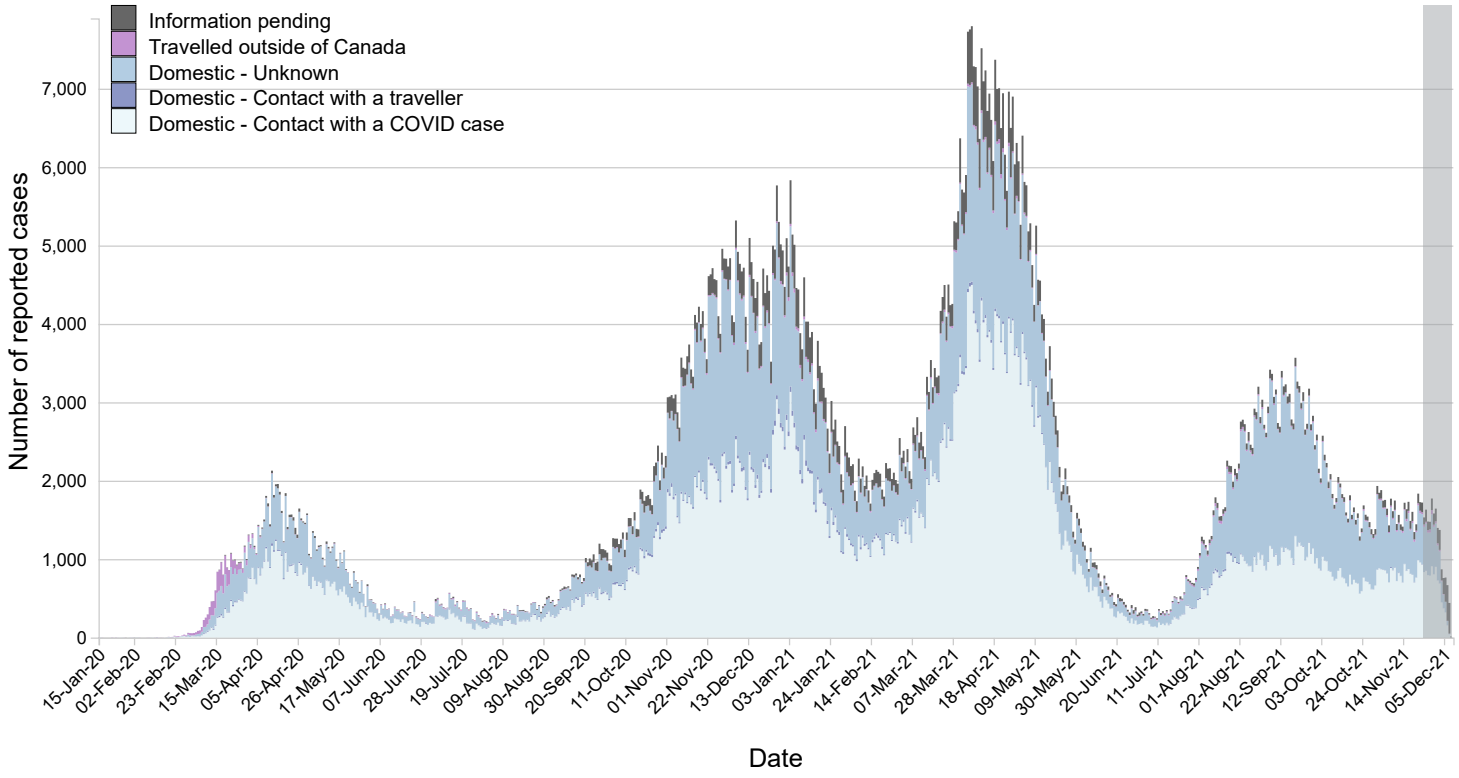


Figure 3. COVID-19 cases (n=1,748,330 [1]) in Canada by date [2] as of December 10, 2021, 7 pm EST (by age - 10 year groups)

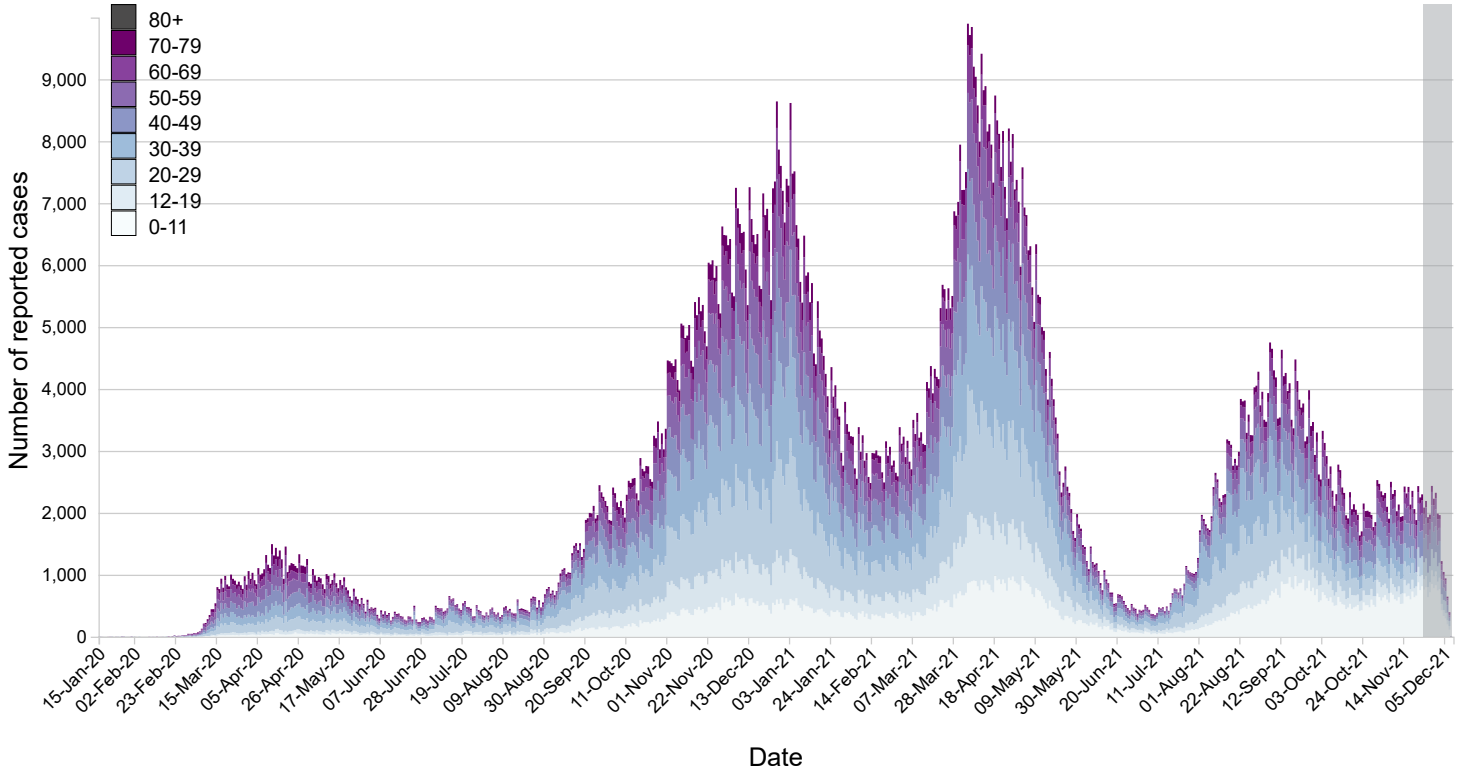
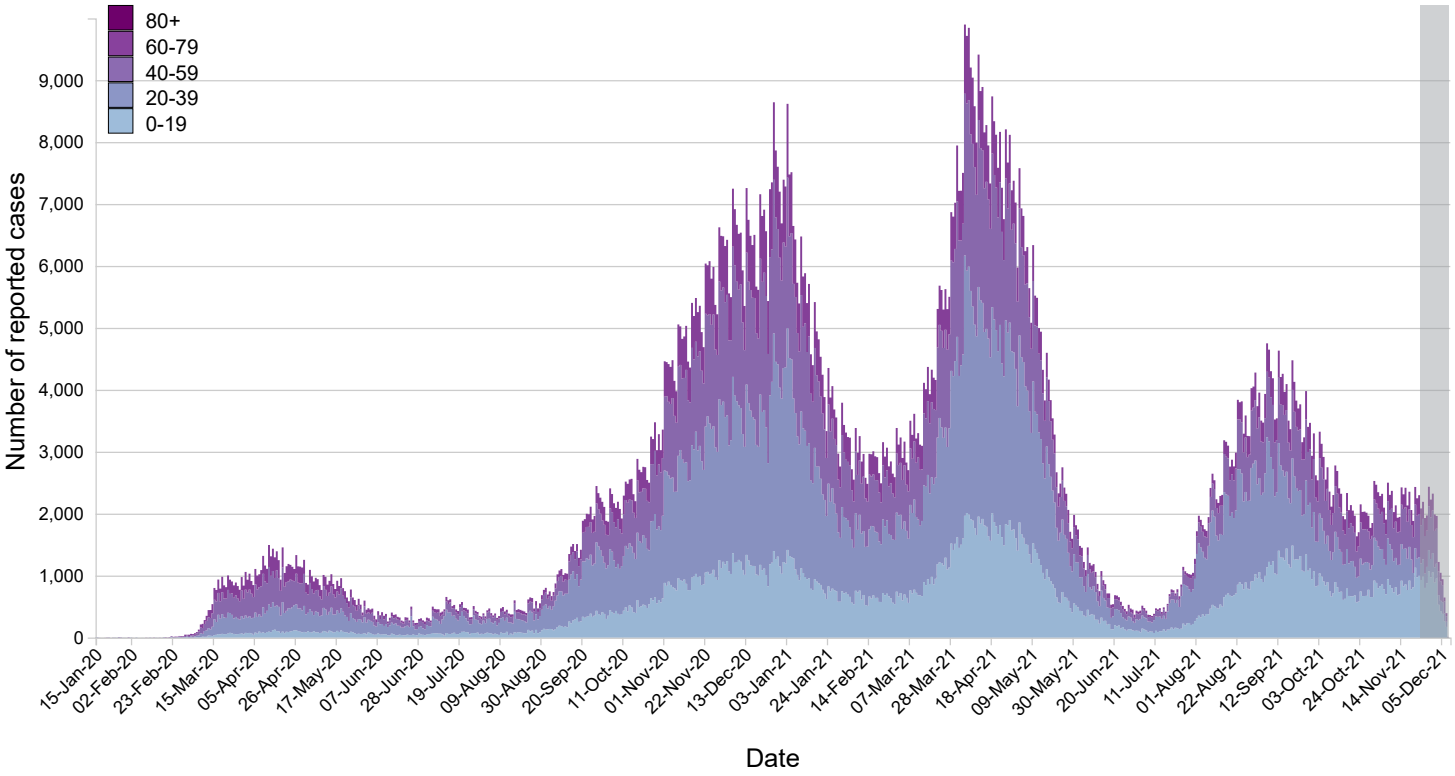


Figure 3. COVID-19 cases (n=1,748,330 [1]) in Canada by date [2] as of December 10, 2021, 7 pm EST (by age - 20 year groups)



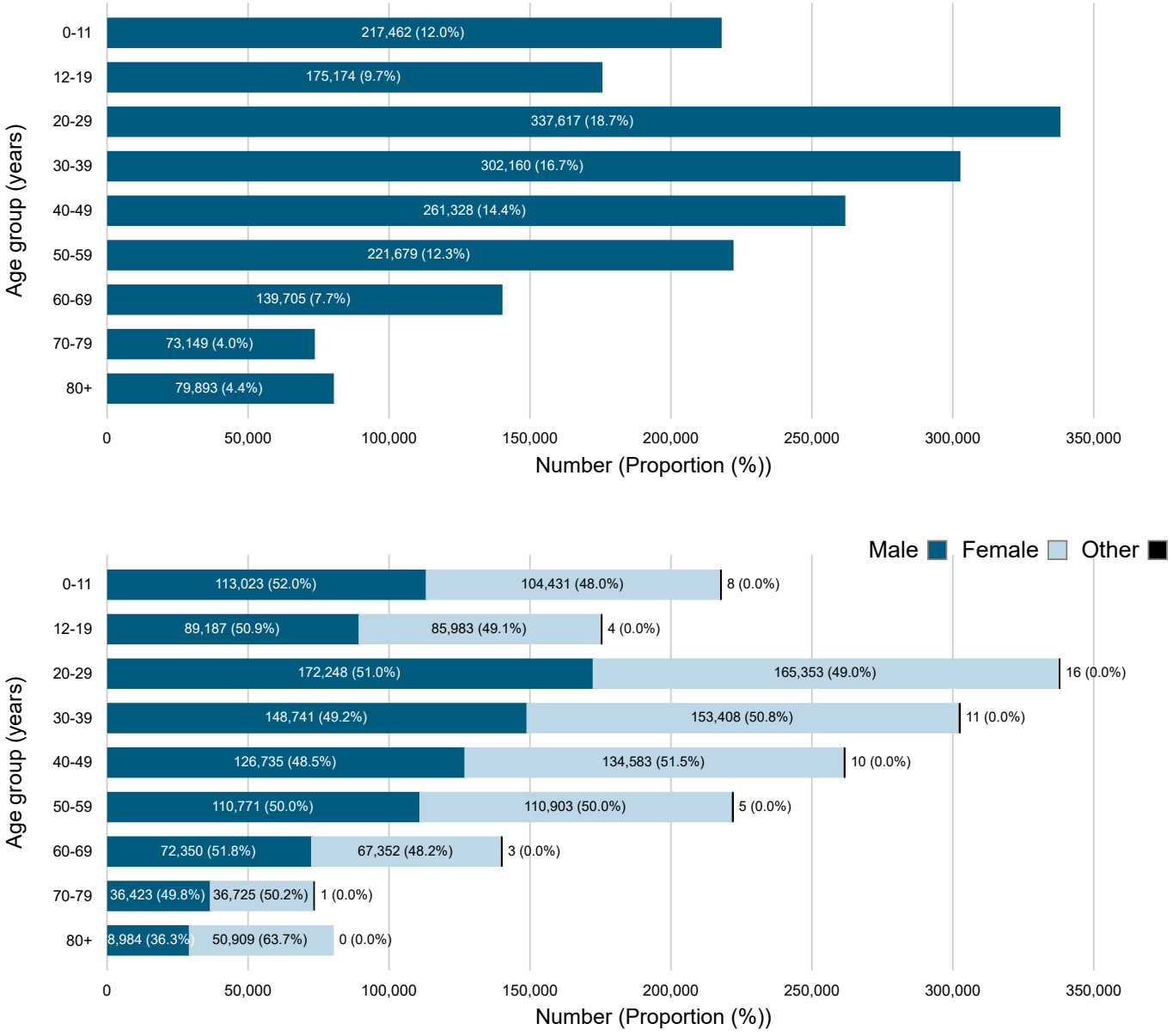
This figure may underestimate the total number of cases among returning travelers. Exposure history is not available for all cases and jurisdictions have not all consistently reported exposure history to PHAC throughout the pandemic.

Demographics

We have detailed case report data from 1,811,673 cases. We know the age of patients in 99.83% of cases, and both age and gender in 99.81% of cases.

Of the cases reported in Canada so far, 50.3% were female and 35.4% were between 20 and 39 years old (Figure 4).

Figure 4. Age distribution of COVID-19 cases (n=1,808,669 [1]) in Canada as of December 10, 2021, 7 pm EST [4]



Age by gender [4] distribution of COVID-19 cases (n=1,808,669 [1]) in Canada, December 10, 2021, 7 pm EST

Age group (years)	Number of cases with case reports (percentage)	Number of male cases (percentage)	Number of female cases (percentage)	Number of other cases (percentage)
0-11	217,462 (12.0%)	113,023 (12.6%)	104,431 (11.5%)	8 (13.8%)
12-19	175,174 (9.7%)	89,187 (9.9%)	85,983 (9.5%)	4 (6.9%)
20-29	337,617 (18.7%)	172,248 (19.2%)	165,353 (18.2%)	16 (27.6%)
30-39	302,160 (16.7%)	148,741 (16.6%)	153,408 (16.9%)	11 (19.0%)
40-49	261,328 (14.4%)	126,735 (14.1%)	134,583 (14.8%)	10 (17.2%)
50-59	221,679 (12.3%)	110,771 (12.3%)	110,903 (12.2%)	5 (8.6%)
60-69	139,705 (7.7%)	72,350 (8.1%)	67,352 (7.4%)	3 (5.2%)
70-79	73,149 (4.0%)	36,423 (4.1%)	36,725 (4.0%)	1 (1.7%)
80+	79,893 (4.4%)	28,984 (3.2%)	50,909 (5.6%)	0 (0.0%)
Total	1,808,167 (100%)	898,462 (100%)	909,647 (100%)	58 (100%)

How people were exposed [3]

In Canada, detailed case report data were provided for 1,811,673 cases. We have exposure history for 1,338,828 (73.9%) cases. The probable exposure setting of these cases [1] are:

- any exposure that occurred in Canada: **1,236,455 (92.4%)**, including
  - from contact with a known COVID case: **712,467 (53.2%)**
  - from contact with a traveller: **9,581 (0.7%)**
  - from an unknown source: **514,407 (38.4%)**
- currently unknown (information pending): **89,809 (6.7%)**
- travelled outside of Canada: **12,564 (0.9%)**

Cases following vaccination

Data extracted on December 03, 2021 for cases from December 14, 2020 up until November 20, 2021.

While the COVID-19 vaccines are effective, there is still a small percentage of the population who are vaccinated that will still be infected with COVID-19 if they are exposed to the virus that causes it. This means that even with high vaccine effectiveness, a small percentage of the population who are vaccinated against COVID-19 will still get sick and some may be hospitalized or even die as a result of their illness. It is also possible that a person could be infected just before or just after vaccination and still get sick. It typically takes about two weeks for the body to build protection after vaccination, so a person could get sick if the vaccine has not had enough time to provide protection.

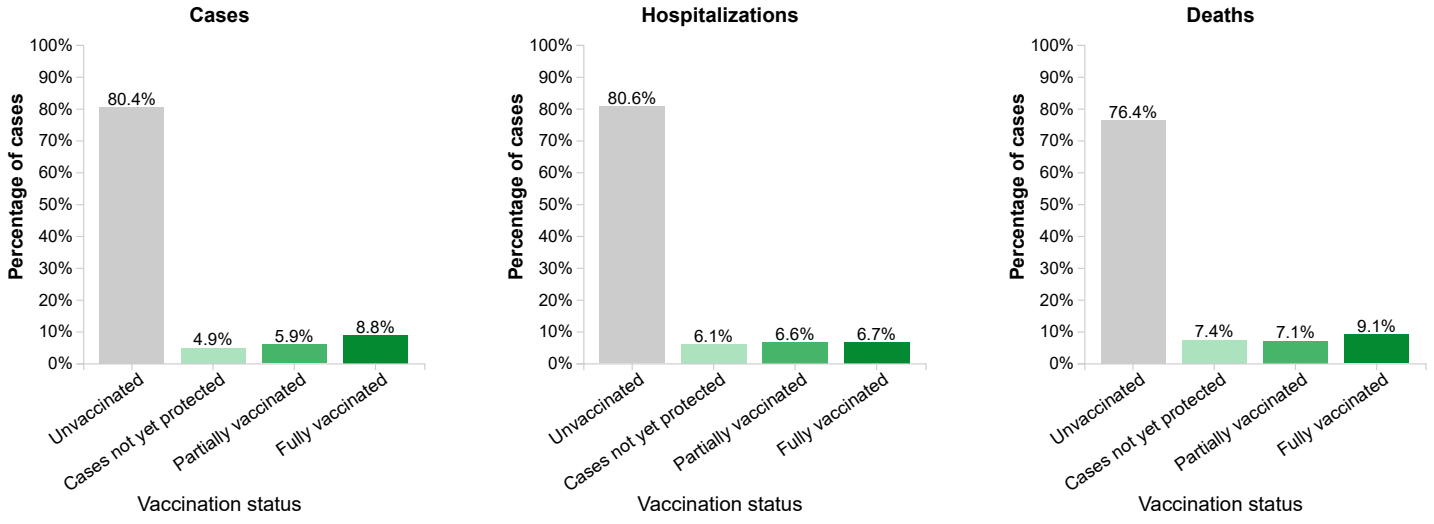
Cases reported since the start of the vaccination campaign, as of November 20, 2021

Since the start of the vaccination campaign on December 14, 2020, PHAC received case-level vaccine history data for 79.0% (n=873,512) of COVID-19 cases aged 12 years or older.

Of these cases:

- 702,434 (80.4%) were unvaccinated at the time of their episode date
- 42,876 (4.9%) were not yet protected by the vaccine, as their episode date occurred less than 14 days after their first dose
- 51,277 (5.9%) were only partially vaccinated, as their episode date occurred either 14 days or more after their first dose or less than 14 days after their second dose
- 76,925 (8.8%) were fully vaccinated, as their episode date occurred 14 days or more after their second dose

Figure 5. Distribution of confirmed COVID-19 cases reported to PHAC by vaccination status as of November 20, 2021



Characteristics and severe outcomes associated unvaccinated, partially vaccinated and fully vaccinated confirmed cases reported to PHAC, as of November 20, 2021

Status	Cases	Hospitalizations	Deaths
Unvaccinated	80.4%	80.6%	76.4%
Cases not yet protected	4.9%	6.1%	7.4%
Partially vaccinated	5.9%	6.6%	7.1%
Fully vaccinated	8.8%	6.7%	9.1%

Among the twelve jurisdictions that have reported case-level vaccine history data to PHAC, a total of 23.2 million people have received at least one dose of the COVID-19 vaccine as of November 20, 2021.

Of these people:

- 23.0 million achieved partial vaccination status, of which 51,277 (0.22%) were diagnosed with COVID-19 while partially vaccinated
- 21.9 million achieved full vaccination status, of which 76,925 (0.35%) were diagnosed with COVID-19 while fully vaccinated

Based on detailed case information reported to PHAC from provinces and territories, cases following vaccination were reported more frequently among females and those aged 60 years and older (Table 2). This may be the result of higher vaccination coverage in Canada among females and those aged 60 years and older due to the prioritization of older age groups and healthcare workers as part of the vaccine rollout.

Table 2. Characteristics and severe outcomes associated unvaccinated, partially vaccinated and fully vaccinated confirmed cases reported to PHAC, as of November 20, 2021

		Unvaccinated (n=702,434)	**Cases not yet protected** (n=42,876)	**Partially vaccinated** (n=51,277)	**Fully vaccinated** (n=76,925)	**Total cases** (n=873,512)
Gender*	Male	359,198 (82.1%)	20,629 (4.7%)	24,000 (5.5%)	33,890 (7.7%)	437,717 (100%)
	Female	341,713 (78.7%)	22,188 (5.1%)	27,208 (6.3%)	42,957 (9.9%)	434,066 (100%)
Hospitalizations		39,637 (80.6%)	2,977 (6.1%)	3,230 (6.6%)	3,310 (6.7%)	49,154 (100%)
Deaths		7,790 (76.4%)	751 (7.4%)	724 (7.1%)	933 (9.1%)	10,198 (100%)

Source: Detailed case information received by PHAC from provinces and territories, since December 14, 2020

Note:

- Twelve of thirteen provinces and territories have reported case-level vaccine history data to PHAC as part of the national COVID-19 dataset. Ten provinces and territories have reported case-level vaccine history data to PHAC since August 2021. A data cut-off of November 20, 2021 was used to account for routine reporting delays associated with vaccine history information.
- *Cases with missing gender were excluded. Where available, gender data was used; when gender data was unavailable, sex data was used. Reliable data on gender diverse respondents are unavailable due to small counts.

Fully vaccinated individuals diagnosed with COVID-19 were significantly protected from severe outcomes. Compared to unvaccinated cases, fully vaccinated cases were 80% less likely to be hospitalized and 68% less likely to die as a result of their illness (Table 3).

Table 3. Risk of severe outcomes among fully vaccinated cases compared to unvaccinated cases as of November 20, 2021

Severe Outcome	Adjusted* Odds Ratio (95% CI)
Hospitalizations	0.20 (0.19 - 0.21)
Deaths	0.32 (0.29 - 0.35)

*Adjusted for 10-year age groups and month of episode date

Source: Detailed case information received by PHAC from provinces and territories

Note: Due to the nature of the dataset (i.e. confirmed cases of COVID-19 in Canada), the odds of severe outcomes among cases following vaccination only considers vaccinated individuals that contracted COVID-19. It does not reflect the protection conferred by the vaccines to prevent COVID-19 infection.

Data for this analysis is extracted from the COVID-19 national data set, which contains detailed case-level information received by PHAC from all provinces and territories. Note that a data cut-off of November 20, 2021 was used to account for any reporting delays associated with vaccine history information. There are currently twelve jurisdictions reporting case-level vaccine history data to PHAC as part of the national COVID-19 dataset.

PHAC monitors cases following vaccination using the following categories:

Unvaccinated cases: include those who were unvaccinated at the time of their episode date.

Cases not yet protected from vaccination include those whose episode date occurred less than 14 days after their first dose of the vaccine.

Partially vaccinated cases include those whose episode date occurred 14 days or more after their first vaccine dose or less than 14 days after their second dose of the vaccine.

Fully vaccinated cases include those whose episode date occurred 14 days or more after their second dose of a two dose vaccine series or those whose episode date occurred 14 days or more after one dose of a one-dose vaccine.

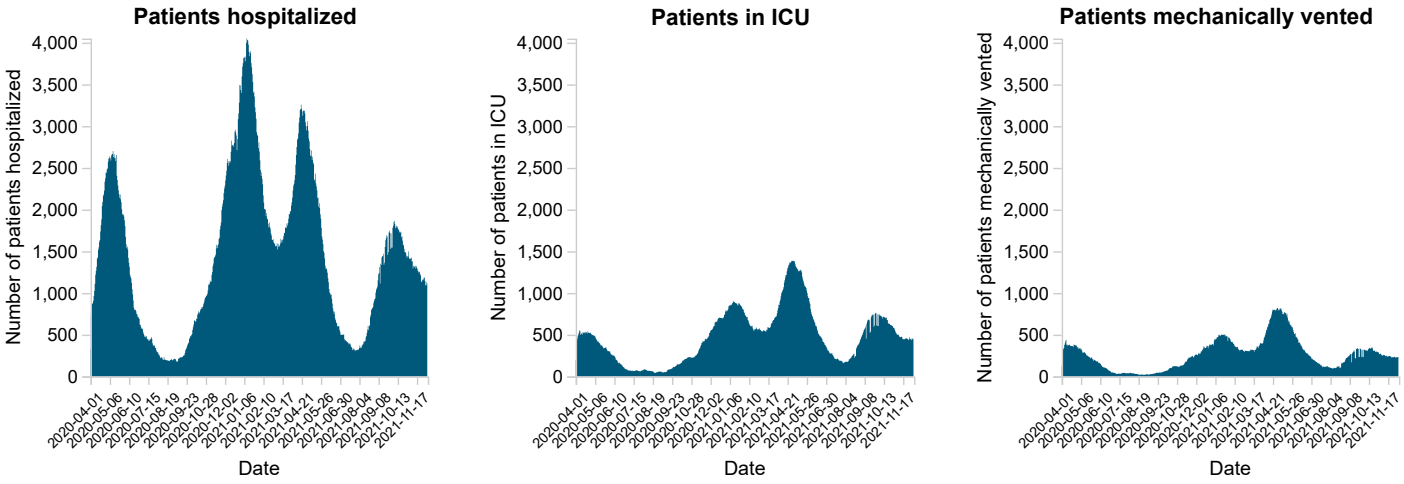
Note: When symptom onset date is unavailable or the case is asymptomatic, episode date uses the following dates as a proxy for classification: laboratory specimen collection date, or laboratory testing date.

For more information on cases following vaccination, please see the Weekly epidemiology report (PDF) available on the Government of Canada's COVID-19 data trends page.

Severe illness and outcomes

Hospital use

Figure 6. Daily number of hospital beds and ICU beds occupied by COVID-19 patients as of December 6, 2021



Between November 29, 2021 and December 6, 2021:

- the number of **hospital beds** occupied by COVID-19 patients **decreased** from **1,164** to **1,116** beds.
- the number of **ICU beds** occupied by COVID-19 patients **decreased** from **470** to **445** beds.
- the number of **COVID-19 patients who were mechanically vented decreased** from **238** to **228**.

Hospitalizations and deaths to date

We have detailed case report data on 1,811,673 cases, and hospitalization status for 1,318,820 (72.8%) of them:

- **93,472** cases **(7.1%)** were hospitalized, of whom:
  - **18,147 (19.4%)** were admitted to the ICU
  - **2,128 (2.3%)** needed mechanical ventilation

The provinces and territories provided detailed case report forms for **29,737** deaths related to COVID-19.

Figure 7a. Age and gender [4] distribution of COVID-19 cases hospitalized in Canada as of December 10, 2021, 7 pm EST (n=93,375 [1])

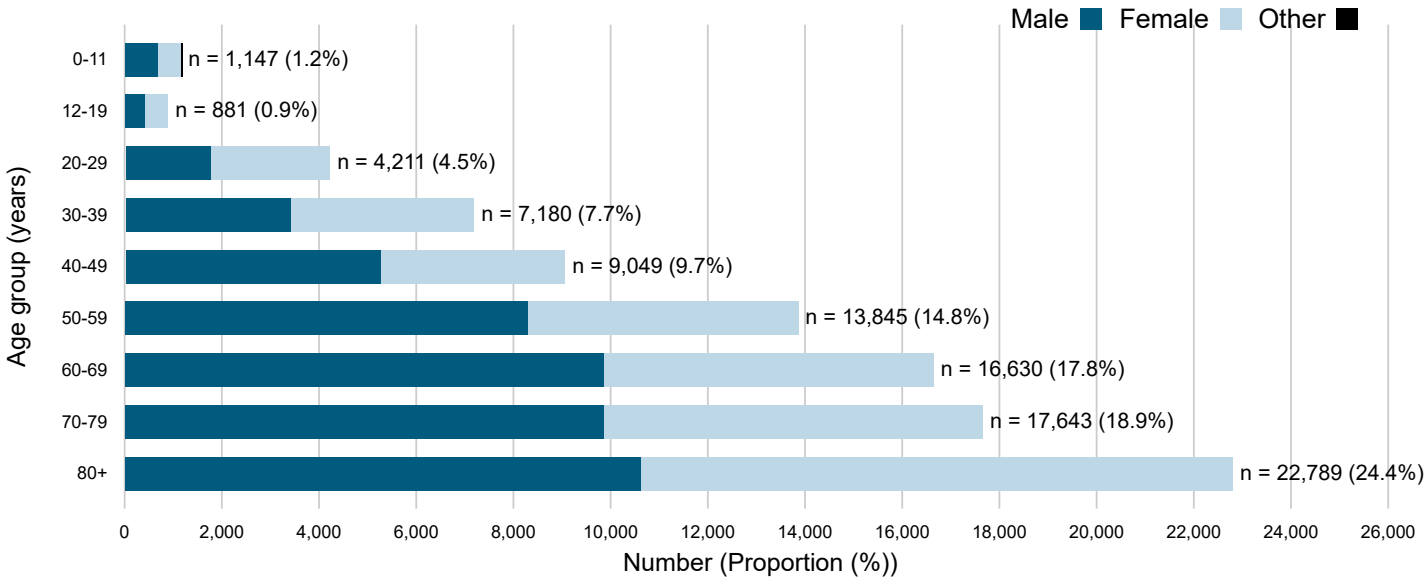


Figure 7b. Age and gender [4] distribution of COVID-19 cases admitted to ICU in Canada as of December 10, 2021, 7 pm EST (n=18,126 [1])

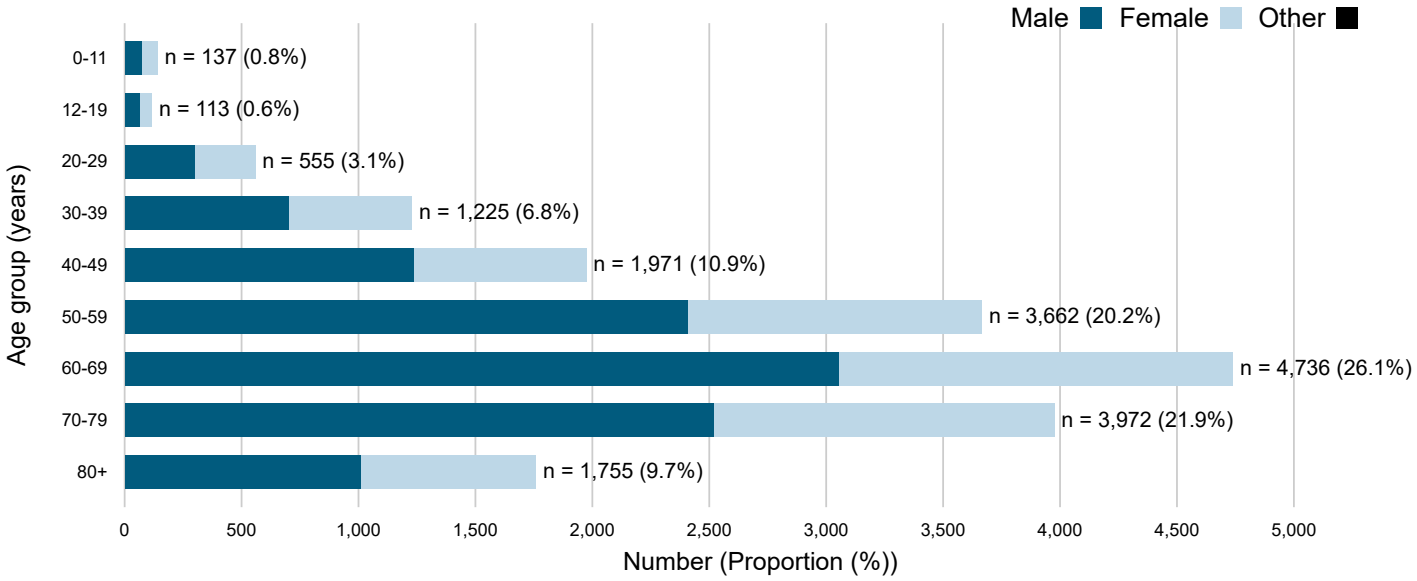
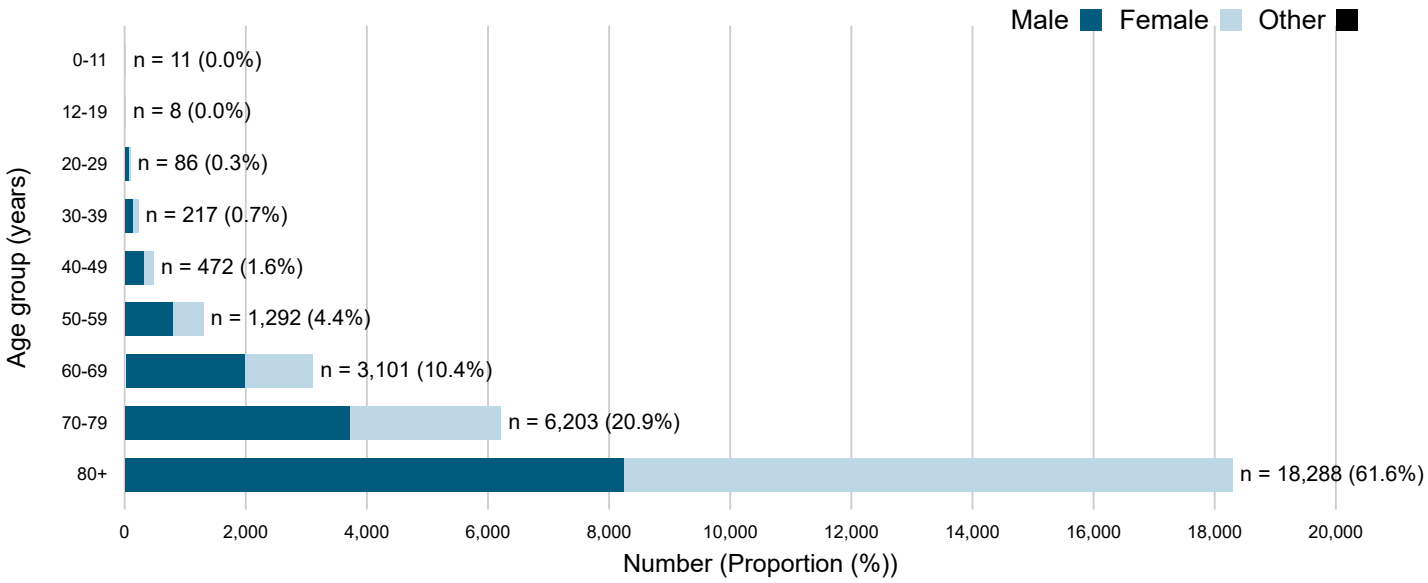


Figure 7c. Age and gender [4] distribution of COVID-19 cases deceased in Canada as of December 10, 2021, 7 pm EST (n=29,678 [1])



Data note: Figure 7 includes COVID-19 cases hospitalized, admitted to ICU, and deceased for which age and gender information were available. Therefore, some COVID-19 hospitalizations, ICU admissions, and deaths may not be included in Figure 7.

Age and gender [4] distribution of COVID-19 cases hospitalized in Canada as of December 10, 2021, 7 pm EST (n=93,375 [1])

Age group (years)	Number of cases with case reports (percentage)	Number of male cases (percentage)	Number of female cases (percentage)	Number of other cases (percentage)
0-11	1,147 (1.2%)	665 (0.7%)	481 (0.5%)	1 (0.0%)
12-19	881 (0.9%)	412 (0.4%)	469 (0.5%)	0 (0.0%)
20-29	4,211 (4.5%)	1,768 (1.9%)	2,443 (2.6%)	0 (0.0%)
30-39	7,180 (7.7%)	3,415 (3.7%)	3,765 (4.0%)	0 (0.0%)
40-49	9,049 (9.7%)	5,266 (5.6%)	3,783 (4.1%)	0 (0.0%)
50-59	13,845 (14.8%)	8,279 (8.9%)	5,566 (6.0%)	0 (0.0%)
60-69	16,630 (17.8%)	9,854 (10.6%)	6,776 (7.3%)	0 (0.0%)
70-79	17,643 (18.9%)	9,854 (10.6%)	7,789 (8.3%)	0 (0.0%)
80+	22,789 (24.4%)	10,623 (11.4%)	12,166 (13.0%)	0 (0.0%)

Age and gender [4] distribution of COVID-19 cases admitted to ICU in Canada as of December 10, 2021, 7 pm EST (n=18,126 [1])

Age group (years)	Number of cases with case reports (percentage)	Number of male cases (percentage)	Number of female cases (percentage)	Number of other cases (percentage)
0-11	137 (0.8%)	71 (0.4%)	66 (0.4%)	0 (0.0%)
12-19	113 (0.6%)	62 (0.3%)	51 (0.3%)	0 (0.0%)
20-29	555 (3.1%)	298 (1.6%)	257 (1.4%)	0 (0.0%)
30-39	1,225 (6.8%)	703 (3.9%)	522 (2.9%)	0 (0.0%)
40-49	1,971 (10.9%)	1,233 (6.8%)	738 (4.1%)	0 (0.0%)
50-59	3,662 (20.2%)	2,408 (13.3%)	1,254 (6.9%)	0 (0.0%)
60-69	4,736 (26.1%)	3,054 (16.8%)	1,682 (9.3%)	0 (0.0%)
70-79	3,972 (21.9%)	2,515 (13.9%)	1,457 (8.0%)	0 (0.0%)
80+	1,755 (9.7%)	1,007 (5.6%)	748 (4.1%)	0 (0.0%)

Age and gender [4] distribution of COVID-19 cases deceased in Canada as of December 10, 2021, 7 pm EST (n=29,678 [1])

Age group (years)	Number of cases with case reports (percentage)	Number of male cases (percentage)	Number of female cases (percentage)	Number of other cases (percentage)
0-11	11 (0.0%)	2 (0.0%)	9 (0.0%)	0 (0.0%)
12-19	8 (0.0%)	5 (0.0%)	3 (0.0%)	0 (0.0%)
20-29	86 (0.3%)	54 (0.2%)	32 (0.1%)	0 (0.0%)
30-39	217 (0.7%)	133 (0.4%)	84 (0.3%)	0 (0.0%)
40-49	472 (1.6%)	308 (1.0%)	164 (0.6%)	0 (0.0%)
50-59	1,292 (4.4%)	794 (2.7%)	498 (1.7%)	0 (0.0%)
60-69	3,101 (10.4%)	1,980 (6.7%)	1,121 (3.8%)	0 (0.0%)
70-79	6,203 (20.9%)	3,718 (12.5%)	2,485 (8.4%)	0 (0.0%)
80+	18,288 (61.6%)	8,243 (27.8%)	10,045 (33.8%)	0 (0.00%)

Provincial, territorial and international reporting

For more information, please refer to provincial or territorial COVID-19 webpages:

- British Columbia
- Alberta
- Saskatchewan
- Manitoba
- Ontario
- Quebec
- Newfoundland and Labrador
- New Brunswick
- Nova Scotia
- Prince Edward Island
- Yukon
- Northwest Territories
- Nunavut
- World Health Organization
- Centers for Disease Control and Prevention
- European Centre for Disease Control and Prevention

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1 This figure is based on cases for which a case report form was received by the Public Health Agency of Canada from provincial or territorial partners.

2 The shaded area represents a period of accumulating data where it is expected that cases have occurred but have not yet been reported nationally. The earliest of the following dates were used as an estimate: Onset date, Specimen Collection Date, Laboratory Testing Date, Date Reported to Province or Territory, or Date Reported to PHAC.

3 Exposure information may not be available for all cases. Some jurisdictions haven't consistently reported to PHAC how people were exposed throughout the pandemic. As a result, this may underestimate the total number of cases by different exposures, especially among returning travelers.

4 Where available, gender data was used; when gender data was unavailable, sex data was used. Reliable data on gender diverse respondents are unavailable due to small counts.

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2021-12-13

Summary of the NACI Seasonal Influenza Vaccine Statement for 2019–2020

L Zhao[1], K Young[1], I Gemmill[2,3] on behalf of the National Advisory Committee on Immunization (NACI)*

Abstract

Background: Many different influenza vaccines are authorized for use in Canada and new evidence on influenza and vaccines is continually emerging. The National Advisory Committee on Immunization (NACI) provides annual recommendations regarding the use of seasonal influenza vaccines to the Public Health Agency of Canada (PHAC) for the upcoming influenza season.

Objective: To summarize NACI recommendations regarding the use of seasonal influenza vaccines for the 2019–2020 influenza season, including conclusions from reviews of evidence on 1) a new split virus quadrivalent inactivated influenza vaccine and 2) the comparative effectiveness and immunogenicity of subunit and split virus inactivated influenza vaccines in adults 65 years of age and older.

Methods: For both topics, the NACI Influenza Working Group developed a predefined search strategy to identify all eligible studies, assessed their quality, summarized and analyzed the findings and, according to the NACI evidence-based process, proposed recommendations and identified the grade of evidence that supported them. In light of the evidence, the recommendations were then considered and approved by NACI.

Results: NACI concluded that the new split virus quadrivalent inactivated influenza vaccine has a safety and immunogenicity profile comparable to the quadrivalent inactivated influenza vaccines already authorized for adults and children 5 years of age and older (Grade B Evidence). Therefore, NACI recommended that this new vaccine may be considered among the quadrivalent inactivated influenza vaccines offered to adults and children five years of age and older (Discretionary NACI Recommendation). However, NACI concluded that the evidence is not sufficient (Grade I Evidence) to support specific recommendations on the differential use of subunit and split virus inactivated influenza vaccines in adults 65 years of age and older.

Conclusion: NACI continues to recommend that an age-appropriate influenza vaccine should be offered annually to anyone six months of age and older who does not have contraindications to the vaccine, with focus on the groups for whom influenza vaccination is particularly recommended. This includes people at high risk of influenza-related complications or hospitalization, people capable of transmitting influenza to those at high risk, people who provide essential community services and people in direct contact with poultry infected with avian influenza during culling operations.

Suggested citation: Zhao L, Young K, Gemmill I on behalf of the National Advisory Committee on Immunization (NACI). Summary of the NACI Seasonal Influenza Vaccine Statement for 2019–2020. Can Commun Dis Rep 2019;45(6):149–55. https://doi.org/10.14745/ccdr.v45i06a01

Keywords: National Advisory Committee on Immunization, NACI, influenza, influenza vaccine, guidance

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Introduction

Influenza, together with pneumonia, ranks among the top 10 leading causes of death in Canada (1). Although the burden of influenza can vary from year to year, it is estimated that there are an average of approximately 12,200 hospitalizations (2) and 3,500 deaths (3) related to influenza per year.

The National Advisory Committee on Immunization (NACI) provides annual recommendations regarding seasonal influenza vaccines to the Public Health Agency of Canada (PHAC). For the 2019–2020 influenza season, NACI updated the abbreviations it uses for the different types of influenza vaccines available in Canada. NACI also reviewed evidence from two literature reviews: one on studies relevant to a new split virus quadrivalent inactivated influenza vaccine (Afluria® Tetra, Seqirus) and one on the comparative effectiveness and immunogenicity of subunit and split virus inactivated influenza vaccines in adults 65 years of age and older. Complete details can be found in the *Statement on Seasonal Influenza Vaccine for 2019–2020* (4) and related publications.

The objective of this article is to summarize this annual seasonal influenza statement.

Updated influenza vaccine abbreviations

The abbreviations used by NACI have been updated to better describe the defining features of the various types of influenza vaccines. The new and corresponding former abbreviations are listed in **Table 1**.

Methods

To prepare the *Statement on Seasonal Influenza Vaccine for 2019–2020*, the Influenza Working Group identified two literature reviews and, following review and analysis of the information, proposed recommendations according to the NACI evidence-based process (5). NACI critically appraised the available evidence and approved the specific recommendations brought forward.

Use of Afluria Tetra influenza vaccine

The Influenza Working Group conducted a systematic review to inform the development of the NACI guidance on the use of Afluria Tetra in Canada. Five electronic databases (MEDLINE, Embase, Scopus, ProQuest Public Health Database and ClinicalTrials.gov) were searched from inception to

Table 1: New National Advisory Committee on Immunization (NACI) abbreviations for influenza vaccines

Influenza vaccine category	Formulation	Type	New NACI abbreviation[a]	Former NACI abbreviation
Inactivated influenza vaccine	-	-	IIV	IIV
	Trivalent	-	IIV3	TIV
		Standard dose[b], unadjuvanted, IM administered	IIV3-SD	Standard-dose TIV
		Adjuvanted[c], IM administered	IIV3-Adj	ATIV or adjuvanted TIV
		High dose[d], unadjuvanted, IM administered	IIV3-HD	High-dose TIV
	Quadrivalent	-	IIV4	QIV
		Standard dose[b], unadjuvanted, IM administered	IIV4-SD	Standard-dose QIV
Live attenuated influenza vaccine	-	-	LAIV	LAIV
	Trivalent	Nasal spray	LAIV3	Trivalent LAIV
	Quadrivalent	Nasal spray	LAIV4	Quadrivalent LAIV

Abbreviations: IIV, inactivated influenza vaccine; IIV3, trivalent inactivated influenza vaccine; IIV3-Adj, adjuvanted trivalent inactivated influenza vaccine; IIV3-HD, high-dose trivalent inactivated influenza vaccine; IIV3-SD, standard-dose trivalent inactivated influenza vaccine; IIV4, quadrivalent inactivated influenza vaccine; IIV4-SD, standard-dose quadrivalent inactivated influenza vaccine; TIV, trivalent inactivated influenza vaccine; QIV, quadrivalent inactivated influenza vaccine; -, not applicable
IM, intramuscular; LAIV, live attenuated influenza vaccine; LAIV3, trivalent live attenuated influenza vaccine; LAIV4, quadrivalent live attenuated influenza vaccine; -, not applicable
[a] The numeric suffix denotes the number of antigens contained in the vaccine ("3" refers to the trivalent formulation and "4" refers to the quadrivalent formulation). The hyphenated suffix "-SD" is used when referring to IIV products that do not have an adjuvant, contain 15 µg hemagglutinin (HA) per strain and are administered as a 0.5 mL dose by intramuscular injection; "-Adj" refers to an IIV with an adjuvant (e.g. IIV3-Adj for Fluad or Fluad Pediatric); and "-HD" refers to an IIV that contains higher antigen content than 15 µg HA per strain (e.g. IIV3-HD for Fluzone High-Dose)
[b] 15 µg HA per strain
[c] 7.5 µg (in 0.25 mL) or 15 µg (in 0.5 mL) HA per strain
[d] 60 µg HA per strain

August 22, 2017 to identify relevant literature on the efficacy, effectiveness, immunogenicity and safety of Afluria Tetra or the trivalent Afluria (1.5% sodium taurodeoxycholate [TDOC]) in adults and children aged six months and older. The use of 1.5% TDOC as a splitting agent was incorporated in the manufacturing process for Afluria and for the new Afluria Tetra after a safety signal in the 2010 Southern Hemisphere influenza season in Australia showed that Afluria made with less than 1.5% of TDOC was associated with an increased rate of fever and febrile seizures in children less than five years of age (6). Two reviewers independently screened the titles and abstracts of records retrieved from the search and eligible full-text articles for inclusion. Two reviewers extracted data from eligible studies and appraised the methodological quality of these studies using the criteria outlined by Harris et al. (7). A narrative synthesis of the extracted data was performed.

Comparative effectiveness and immunogenicity of subunit and split virus inactivated influenza vaccines in adults 65 years of age and older

A rapid review was performed to inform NACI on potentially important differences between subunit and split virus inactivated influenza vaccines in older adults. Three electronic databases (MEDLINE, Embase and ClinicalTrials.gov) were searched to identify relevant literature published between January 1, 2007 and October 13, 2017 on the effectiveness and immunogenicity of subunit and split virus inactivated influenza vaccines (unadjuvanted, standard dose) in adults 65 years of age and older. A manual search of the reference lists of included articles was performed because of the small number of records retrieved in the initial database search. A single reviewer screened the retrieved records and performed data extraction and quality appraisal of eligible studies. A narrative synthesis of the extracted data was performed.

Results

Use of Afluria Tetra influenza vaccine

Based upon a review of two randomized controlled trials of Afluria Tetra and two of Afluria (1.5% TDOC), NACI concluded that Afluria Tetra is safe and has immunogenicity non-inferior to comparable vaccines in adults and children five years of age and older. No direct evidence on the efficacy or effectiveness of Afluria Tetra was available. Furthermore, no evidence for any outcome was available on the use of Afluria Tetra for children less than five years of age, and Afluria Tetra is not authorized for use in this age group in Canada. Fever and febrile seizure were not identified as concerns for both Afluria Tetra and Afluria (1.5% TDOC) in two studies looking at children five years of age and older.

NACI recommends that Afluria Tetra may be considered among the quadrivalent inactivated influenza vaccines offered to adults and children five years of age and older (Discretionary NACI Recommendation, Grade B Evidence).

Complete details of the findings of literature review, and rationale and relevant considerations for the recommendation, can be found in the NACI *Supplemental Statement on Afluria Tetra* (6).

Comparative effectiveness and immunogenicity of subunit and split virus inactivated influenza vaccines in adults 65 years of age and older

Eight studies that assessed either vaccine effectiveness or immunogenicity of subunit compared with split virus inactivated influenza vaccines were identified. These studies did not show statistically significant differences in vaccine effectiveness or immunogenicity. Furthermore, the quality of the included studies was a concern. Based upon a review of these studies, NACI concluded that the evidence is not sufficient (Grade I Evidence) to support specific recommendations on the differential use of subunit and split virus inactivated influenza vaccines in adults 65 years of age and older.

The detailed findings of this review can be found in the *NACI Literature Review on the Comparative Effectiveness and Immunogenicity of Subunit and Split Virus Inactivated Influenza Vaccines in Adults 65 Years of Age and Older* (8).

Summary of NACI recommendations for the use of influenza vaccines for the 2019–2020 influenza season

NACI continues to recommend influenza vaccination to anyone six months and older who does not have contraindications to the vaccine. Vaccination should be offered as a priority to people at high risk of influenza-related complications or hospitalization, people capable of transmitting influenza to those at high risk of complications, and others as indicated in **Table 2**.

Recommended influenza vaccine options by age group and by dosage and route of administration by age are summarized in **Tables 3** and **4**, respectively.

Table 2: Groups for whom influenza vaccination is particularly recommended (4)

People at high risk of influenza-related complications or hospitalization:

- All pregnant women[a]
- Adults and children with the following chronic health conditions:
  - cardiac or pulmonary disorders (includes bronchopulmonary dysplasia, cystic fibrosis, and asthma)
  - diabetes mellitus and other metabolic diseases
  - cancer, immune compromising conditions (due to underlying disease, therapy or both)
  - renal disease
  - anemia or hemoglobinopathy
  - neurologic or neurodevelopmental conditions (includes neuromuscular, neurovascular, neurodegenerative and neurodevelopmental conditions and seizure disorders [for children, includes febrile seizures and isolated developmental delay], but excludes migraines and psychiatric conditions without neurological conditions)
  - morbid obesity (body mass index [BMI] of 40 and over)
  - children 6 months to 18 years of age undergoing treatment for long periods with acetylsalicylic acid, because of the potential increase of Reye's syndrome associated with influenza
- People of any age who are residents of nursing homes and other chronic care facilities
- Adults 65 years of age and older
- All children 6–59 months of age
- Indigenous peoples

People capable of transmitting influenza to those at high risk:

- Health care and other care providers in facilities and community settings who, through their activities, are capable of transmitting influenza to those at high risk
- Household contacts, both adults and children, of individuals at high risk, whether or not the individual at high risk has been vaccinated:
  - household contacts of individuals at high risk
  - household contacts of infants less than six months of age, as these infants are at high risk but cannot receive influenza vaccine
  - members of a household expecting a newborn during the influenza season
- Those providing regular child care to children 6–59 months of age, whether in or out of the home
- Those who provide services within closed or relatively closed settings to people at high risk (e.g. crew on a ship)

Others:

- People who provide essential community services
- People who are in direct contact with poultry infected with avian influenza during culling operations

[a] The risk of influenza-related hospitalization increases with length of gestation (i.e. it is higher in the third than in the second trimester)

Table 3: Recommendations on choice of influenza vaccine type for individual-level decision making[a] by age group (4)

Recipient by age group	Vaccine types available for use	Recommendations on choice of influenza vaccine
6–23 months	• IIV3-SD • IIV3-Adj • IIV4-SD	• Quadrivalent influenza vaccine should be used, given the burden of influenza B disease in this age group and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine • If a quadrivalent vaccine is not available, any of the available trivalent vaccines should be used
2–17 years	• IIV3-SD • IIV4-SD • LAIV4	• Either IIV4-SD or LAIV4 should be used for children without contraindications, including those with non-immune compromising chronic health conditions, given the burden of influenza B disease in this age group and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine • If IIV4-SD or LAIV4 is not available, IIV3-SD should be used • IIV4-SD should be used for children for whom LAIV is contraindicated, such as in children with: - severe asthma - medically attended wheezing in the seven days prior to vaccination - current receipt of Aspirin or Aspirin-containing therapy - immune compromising conditions • LAIV4 may be given to children with: - stable, non-severe asthma - cystic fibrosis who are not being treated with immunosuppressive drugs (e.g. prolonged systemic corticosteroids)
18–59 years	• IIV3-SD • IIV4-SD • LAIV4	• Any of the available influenza vaccines should be used in adults without contraindications • IIV should be used for adults for whom LAIV is contraindicated, such as in: - pregnant women - adults with any of the chronic health conditions identified in Table 2, including immune compromising conditions - HCWs
60–64 years	• IIV3-SD • IIV4-SD	• Any of the available influenza vaccines should be used
65 years and older[b]	• IIV3-SD • IIV3-Adj • IIV3-HD • IIV4-SD	• When available, IIV3-HD should be used over IIV3-SD, given the burden of influenza A (H3N2) disease and the evidence for better efficacy compared with IIV3-SD in this age group • There is insufficient evidence to make comparative individual-level recommendations on the use of IIV3-Adj or IIV4-SD over IIV3-SD or between IIV3-Adj, IIV3-HD and IIV4-SD

Abbreviations: HCW, health care worker; IIV, inactivated influenza vaccine; IIV3-Adj, adjuvanted trivalent inactivated influenza vaccine; IIV3-HD, high-dose trivalent inactivated influenza vaccine; IIV3-SD, standard-dose trivalent inactivated influenza vaccine; IIV4-SD, standard-dose quadrivalent inactivated influenza vaccine; LAIV4, quadrivalent live attenuated influenza vaccine

[a] Recommendations for individual-level decision making are intended for individuals wishing to protect themselves from influenza, or vaccine providers wishing to advise individual patients about preventing influenza

[b] The recommendations on influenza vaccine for individuals 65 years of age and older presented here are for individual-level decision making. For public health program–level decision making (i.e. provinces/territories making decisions for publicly funded immunization programs), NACI recommends that any of the available influenza vaccines be used, as there is insufficient evidence (cost-effectiveness assessments have not been performed) to make comparative public health program–level recommendations on the use of the available vaccines

Table 4: Recommended dose and route of administration, by age, for influenza vaccine types available for the 2019–2020 influenza season (4)

Age group	Influenza vaccine type (route of administration)				Number of doses required
	IIV3-SD[a] or IIV4-SD[b] (Intramuscular)	IIV3-Adj[c] (Intramuscular)	IIV3-HD[d] (Intramuscular)	LAIV4[e] (intranasal)	
6–23 months	0.5 mL[f]	0.25 mL	–	-	1 or 2[g]
2–8 years	0.5 mL	–	–	0.2 mL (0.1 mL per nostril)	1 or 2[g]
9–17 years	0.5 mL	–	–	0.2 mL (0.1 mL per nostril)	1
18–59 years	0.5 mL	–	–	0.2 mL (0.1 mL per nostril)	1
60–64 years	0.5 mL	–	–	–	1
65 years and older	0.5 mL	0.5 mL	0.5 mL	–	1

Abbreviations: IIV3-Adj, adjuvanted trivalent inactivated influenza vaccine; IIV3-HD, high-dose trivalent inactivated influenza vaccine; IIV3-SD, standard-dose trivalent inactivated influenza vaccine; IIV4-SD, standard-dose quadrivalent inactivated influenza vaccine; LAIV4, quadrivalent live attenuated influenza vaccine; - , not applicable

[a] Agriflu (six months and older), Fluviral (six months and older), Influvac (three years and older)

[b] Afluria Tetra (five years and older), Flulaval Tetra (six months and older), Fluzone Quadrivalent (six months and older)

[c] Fluad Pediatric (6–23 months) or Fluad (65 years and older)

[d] Fluzone High-Dose (65 years and older)

[e] FluMist Quadrivalent (2–59 years)

[f] Evidence suggests moderate improvement in antibody response in infants, without an increase in reactogenicity, with the use of full vaccine doses (0.5 mL) for unadjuvanted inactivated influenza vaccines (9,10). This moderate improvement in antibody response without an increase in reactogenicity is the basis for the full dose recommendation for unadjuvanted inactivated vaccine for all ages. For more information, refer to *Statement on Seasonal Influenza Vaccine for 2011–2012* (11)

[g] Children six months to less than nine years of age receiving seasonal influenza vaccine for the first time in their life should be given two doses of influenza vaccine, with a minimum interval of four weeks between doses. Children six months to less than nine years of age who have been properly vaccinated with one or more doses of seasonal influenza vaccine in the past should receive one dose of influenza vaccine per season thereafter

Conclusion

NACI continues to recommend annual influenza vaccination for all individuals aged six months and older (noting product-specific age indications and contraindications), with particular focus on people at high risk of influenza-related complications or hospitalization. This includes all pregnant women; people capable of transmitting influenza to those at high risk; people who provide essential community services; and people in direct contact during culling operations with poultry infected with avian influenza. For the 2019–2020 influenza season, NACI recommends that the new Afluria Tetra influenza vaccine may be considered among the quadrivalent inactivated influenza vaccines offered to adults and children five years of age and older. NACI concluded that there is insufficient evidence at this time to support specific recommendations on the differential use of subunit and split virus inactivated influenza vaccines in adults 65 years and older.

Authors' statement

LZ — Writing – original draft, writing – review and editing
KY — Writing – original draft, writing – review and editing
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Conflict of interest

None.

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Pandemic Influenza Risk Management

WHO Interim Guidance

WHO/HSE/HEA/HSP/2013.3

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Abbreviations

CAR	Clinical attack rate
CFR	Case-fatality ratio
ERMH	Emergency Risk Management for Health
GAP	Global Action Plan for Influenza Vaccines
GISRS	Global Influenza Surveillance and Response System
GOARN	Global Outbreak Alert and Response Network
IHR (2005)	International Health Regulations (2005)
PHEIC	Public Health Emergency of International Concern
PIP Framework	Pandemic Influenza Preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits
SAGE	Strategic Advisory Group of Experts on Immunization
UN	United Nations

Executive summary

Influenza pandemics are unpredictable but recurring events that can have consequences on human health and economic well-being worldwide. Advance planning and preparedness are critical to help mitigate the impact of a pandemic. This WHO guidance document, *Pandemic Influenza Risk Management*, updates and replaces *Pandemic influenza preparedness and response: a WHO guidance document*, which was published in 2009. This revision of the guidance takes account of lessons learnt from the influenza A(H1N1) 2009 pandemic and of other relevant developments.

The influenza A(H1N1) 2009 pandemic was both the first of the 21st century and the first since WHO had produced pandemic preparedness guidance. The experience of Member States during the pandemic varied, yet several common factors emerged. Member States had prepared for a pandemic of high severity and appeared unable to adapt their national and subnational responses adequately to a more moderate event. Communications were also demonstrated to be of immense importance: the need to provide clear risk assessments to decision-makers placed significant strain on ministries of health; and effective communication with the public was challenging. These, and other areas with improvement potential, were identified by the Review Committee on the Functioning of the International Health Regulations (2005) in relation to Pandemic (H1N1) 2009.

The influenza A(H1N1) 2009 pandemic provided a wealth of additional information to the established and growing body of knowledge on influenza viruses at the human–animal ecosystem interface. Other notable developments since the publication of the 2009 guidance include the adoption by the Sixty-fourth World Health Assembly of the Pandemic Influenza Preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits. In addition, risk management of acute public health events that have the potential to cross borders and threaten people worldwide continues to improve as a result of the International Health Regulations (2005) and States Parties' obligations on capacity strengthening.

This guidance can be used to inform and harmonize national and international pandemic preparedness and response. Countries should consider reviewing and/or updating national influenza preparedness and response plans to reflect the approach taken in this guidance. The roles and responsibilities of WHO relevant to pandemic preparedness, in terms of global leadership and support to Member States, are also articulated. This document is not intended to replace national plans, which should be developed by each country.

New in the 2013 guidance

Emergency Risk Management for Health

The approach taken in this 2013 guidance applies the principles of all-hazards emergency risk management for health (ERMH) to pandemic influenza risk management. The objectives of emergency risk management for health are to: strengthen capacities to manage the health risks from all hazards; embed comprehensive emergency risk management in the health sector; and enable and promote multisectoral linkage and integration across the whole-of-government and the whole-of-society. This guidance therefore aligns more closely with the disaster risk management structures already in place in many countries and underscores the need for appropriate and timely risk assessment for evidence-based decision-making at national, subnational and local levels.

Risk-based approach

This guidance introduces a risk-based approach to pandemic influenza risk management and encourages Member States to develop flexible plans, based on national risk assessment, taking account of the global risk assessment conducted by WHO. To support implementation, content on the application of assessments of risk and severity have been strengthened.

Approach to global phases and uncoupling global phases from national actions

In response to lessons learnt from the influenza A(H1N1) 2009 pandemic, a revised approach to global phases is introduced in this guidance. The phases, which are based on virological, epidemiological and clinical data, are to be used for describing the spread of a new influenza subtype, taking account of the disease it causes, around the world. The global phases have been clearly uncoupled from risk management decisions and actions at the country level. Thus, Member States are encouraged as far as possible to use national risk assessments to inform management decisions for the benefit of their country's specific situation and needs.

PIP Framework

The Pandemic Influenza Preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits, commonly known as the PIP Framework, brings together Member States, industry, other stakeholders and WHO to implement a global approach to pandemic influenza preparedness and response. Its key goals include:

- to improve and strengthen the sharing of influenza viruses with human pandemic potential; and
- to achieve, *inter alia*, more predictable, efficient and equitable access for countries in need of life-saving vaccines and medicines during future pandemics.

The Framework was developed by Member States and became effective on 24 May 2011, when it was adopted by the Sixty-fourth World Health Assembly.

1. Introduction

The influenza A(H1N1) 2009 pandemic was the first to occur since WHO had produced preparedness guidance. Guidance had been published in 1999, revised in 2005 and again in 2009 following advances in the development of antivirals and experiences with influenza A(H5N1) infections in poultry and humans. The emergence of the influenza A(H1N1)pdm09 virus provided further understanding of influenza pandemics and requirements for pandemic preparedness and response. The report of the Review Committee on the Functioning of the International Health Regulations (2005) in relation to Pandemic (H1N1) 2009 concluded: "The world is ill-prepared to respond to a severe influenza pandemic or to any similarly global, sustained and threatening public-health emergency" (*1*).

The Review Committee recommended that WHO should revise its pandemic preparedness guidance to support further efforts at the national and subnational level. Revisions recommended included: simplification of the pandemic phases structure; emphasis on a risk-based approach to enable a more flexible response to different scenarios; reliance on multisectoral participation; utilization of lessons learnt at the country, regional and global level; and further guidance on risk assessment. The Review Committee's report reflected the broad experiences of Member States during the influenza A(H1N1) 2009 pandemic – and the key point that previous pandemic planning guidance was overly rigid. Member States had prepared for a pandemic of high severity and appeared unable to adapt their responses adequately to a more moderate event. Communications also proved to be of immense importance during the influenza A(H1N1) 2009 pandemic, within the health and non-health sectors and to the public. Provision of clear risk assessments to decision-makers placed significant strain on ministries of health, and effective communication with the public was challenging.

This 2013 guidance is based on the principles of all-hazards emergency risk management for health (ERMH), thereby aligning pandemic risk management with the strategic approach adopted by WHO, in accordance with World Health Assembly resolution 64.10.[1] Commensurate with this approach, this guidance promotes building on existing capacities – in particular those under the International Health Regulations (2005) (*2*) (IHR [2005]) core capacities, in order to manage risks from pandemic influenza. Certain aspects of implementation of ERMH for national pandemic preparedness may therefore be linked with the core capacity strengthening activities required by the IHR (2005). This guidance can therefore be used as a model to illustrate how the mechanisms required for response to and recovery from pandemic influenza can be applied, as appropriate, to the management of all relevant health emergencies.

A risk-based approach to pandemic influenza management is emphasized and Member States are encouraged to develop flexible plans, based on national risk assessments. This guidance also places pandemic planning in the whole-of-society context. This 2013 revision therefore (1) reflects the approach taken at national level where pandemic influenza planning often rests with national disaster management authorities and (2) introduces or promotes all-hazards ERMH at Ministry of Health level, including mechanisms for wider national engagement.

This guidance also summarizes the roles and responsibilities of WHO relevant to pandemic preparedness, in terms of global leadership and support to Member States.

[1] WHA Resolution 64.10 in 2011, urges Member States to (1) integrate all-hazards health emergency and disaster risk management programmes (including disaster risk reduction) into national or subnational health plans; and (2) institutionalize capacities for coordinated health and multisectoral action to assess risks, proactively reduce risks, and prepare for, respond to, and recover from, emergencies, disasters and other crises.

2. WHO global leadership

WHO is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to Member States and monitoring and assessing health trends. WHO promotes health as a shared responsibility, involving equitable access to essential care and collective defence against transnational threats.

As the directing and coordinating authority for health within the United Nations (UN) system, WHO has a mandate for global pandemic influenza risk management, (*3*, *4*) which is reflected at all levels of the Organization. Key mechanisms by which WHO fulfils this obligation are summarized below.

2.1 Coordination under the International Health Regulations (2005)

The IHR (2005) are binding upon 196 States Parties[2] and provide a global legal framework to prevent, control or respond to public health risks that may spread between countries.

Convening of an Emergency Committee, declaration of a Public Health Emergency of International Concern and issuance of IHR (2005) temporary recommendations

The IHR (2005) provide the regulatory framework for the timely and effective management of international public health risks. In addition, the Regulations provide a basis for collective global action for certain rare events of particular importance. Such serious events that endanger global public health are specified by the Regulations as public health emergencies of international concern. The term Public Health Emergency of International Concern (PHEIC) is defined in the IHR (2005) as "an extraordinary event which is determined to constitute a public health risk to other States through the international spread of disease and to potentially require a coordinated international response". This definition implies a situation that: is serious, sudden, unusual or unexpected; carries implications for public health beyond the affected State's national border; and may require immediate international action.[3]

---

[2] Non-Member States of WHO can notify the Director-General of their acceptance of the IHR (2005) which enters into force for them three months after the said notification. Two non-Member States have made such notifications.

[3] Article 12 Determination of a public health emergency of international concern

1. The Director-General shall determine, on the basis of the information received, in particular from the State Party within whose territory an event is occurring, whether an event constitutes a public health emergency of international concern in accordance with the criteria and the procedure set out in these Regulations.
2. If the Director-General considers, based on an assessment under these Regulations, that a public health emergency of international concern is occurring, the Director-General shall consult with the State Party in whose territory the event arises regarding this preliminary determination. If the Director-General and the State Party are in agreement regarding this determination, the Director-General shall, in accordance with the procedure set forth in Article 49, seek the views of the Committee established under Article 48 (hereinafter the "Emergency Committee") on appropriate temporary recommendations.
3. If, following the consultation in paragraph 2 above, the Director-General and the State Party in whose territory the event arises do not come to a consensus within 48 hours on whether the event constitutes a public health emergency of international concern, a determination shall be made in accordance with the procedure set forth in Article 49.
4. In determining whether an event constitutes a public health emergency of international concern, the Director-General shall consider:

The responsibility of determining whether an event is within this category lies with the WHO Director-General and requires the subsequent convening of a committee of health experts – the IHR Emergency Committee. This committee advises the Director General on the recommended measures to be promulgated on an emergency basis, known as temporary recommendations. Temporary recommendations include health measures to be implemented by the State Party experiencing the PHEIC, or by other States Parties, to prevent or reduce the international spread of disease and avoid unnecessary interference with international traffic.

The Emergency Committee also gives advice on the determination of the event as a PHEIC in circumstances where there is inconsistency in the assessment of the event between the Director-General and the affected country/countries. The Emergency Committee continues to provide advice to the Director-General throughout the duration of the PHEIC, including any necessary changes to the recommended measures for control and on the determination of PHEIC termination. WHO maintains an IHR roster of experts and the members of an IHR Emergency Committee are selected from this roster and/or WHO expert advisory panels and committees. At least one member of the Emergency Committee should be an expert nominated by a State Party within whose territory the event arises, and such States Parties are invited to present their views to the Emergency Committee.

Provision of information and support to affected States Parties

The IHR (2005) also provide a mandate to WHO to perform public health surveillance, risk assessment, support States Parties and coordinate the international response to significant international public health risks. After preliminary assessment, WHO is obliged by the IHR (2005) to obtain verification of event reports from States Parties.[4] If verification is sought, including in the context of potential pandemic influenza, States Parties are required to respond to WHO within a prescribed time period and include available relevant public health information. The regulatory requirement to respond to requests for verification by WHO aims to provide early identification of any public health event that may constitute a PHEIC. WHO

(a) information provided by the State Party;
(b) the decision instrument contained in Annex 2;
(c) the advice of the Emergency Committee;
(d) scientific principles as well as the available scientific evidence and other relevant information; and
(e) an assessment of the risk to human health, of the risk of international spread of disease and of the risk of interference with international traffic.

5. If the Director-General, following consultations with the State Party within whose territory the public health emergency of international concern has occurred, considers that a public health emergency of international concern has ended, the Director-General shall take a decision in accordance with the procedure set out in Article 49.

[4] IHR Article 10 – Verification

1. WHO shall request, in accordance with Article 9, verification from a State Party of reports from sources other than notifications or consultations of events which may constitute a public health emergency of international concern allegedly occurring in the State's territory. In such cases, WHO shall inform the State Party concerned regarding the reports it is seeking to verify.
2. Pursuant to the foregoing paragraph and to Article 9, each State Party, when requested by WHO, shall verify and provide:
   (a) within 24 hours, an initial reply to, or acknowledgement of, the request from WHO;
   (b) within 24 hours, available public health information on the status of events referred to in WHO's request; and
   (c) information to WHO in the context of an assessment under Article 6, including relevant information as described in that Article.
3. When WHO receives information of an event that may constitute a public health emergency of international concern, it shall offer to collaborate with the State Party concerned in assessing the potential for international disease spread, possible interference with international traffic and the adequacy of control measures. Such activities may include collaboration with other standard-setting organizations and the offer to mobilize international assistance in order to support the national authorities in conducting and coordinating on-site assessments. When requested by the State Party, WHO shall provide information supporting such an offer.
4. If the State Party does not accept the offer of collaboration, WHO may, when justified by the magnitude of the public health risk, share with other States Parties the information available to it, whilst encouraging the State Party to accept the offer of collaboration by WHO, taking into account the views of the State Party concerned.

is also obligated to provide event information to States Parties regarding public health risks, whenever that information is necessary for them to protect their populations.

When WHO intends to make information available to other States Parties, it has an obligation to consult with the country experiencing the event. WHO may also make information related to an arising influenza pandemic available to the public, if other information about the event is already in the public domain, and if a need exists for public availability of information that is authoritative and independent. Under the IHR (2005), WHO must offer assistance to States Parties in assessing or controlling public health events occurring within their territories. This support can be in the form of technical advice and guidelines, specialized materials, deployment of international teams to affected areas, and coordination of international support from various sources.

Measures adopted by States Parties in relation to travel or trade

The IHR (2005) seek to limit the public health measures taken in response to disease spread to those "that are commensurate with and restricted to public health risks, and which avoid unnecessary interference with international traffic and trade". To achieve this objective, WHO regularly issues advice on trade and travel measures related to public health events where such measures are likely or relevant. While the IHR (2005) do not prevent States Parties from implementing specific trade and travel related measures, they do require States Parties to inform WHO of these measures and the justification for their introduction when they will result in significant interference, defined in the IHR (2005) as resulting in delays to movement of international travellers, baggage, cargo, containers, conveyances, goods, and the like, of greater than 24 hours. In addition to providing other States Parties with information on these measures, WHO can request the implementing State Party to reconsider their application.

2.2 Pandemic phases

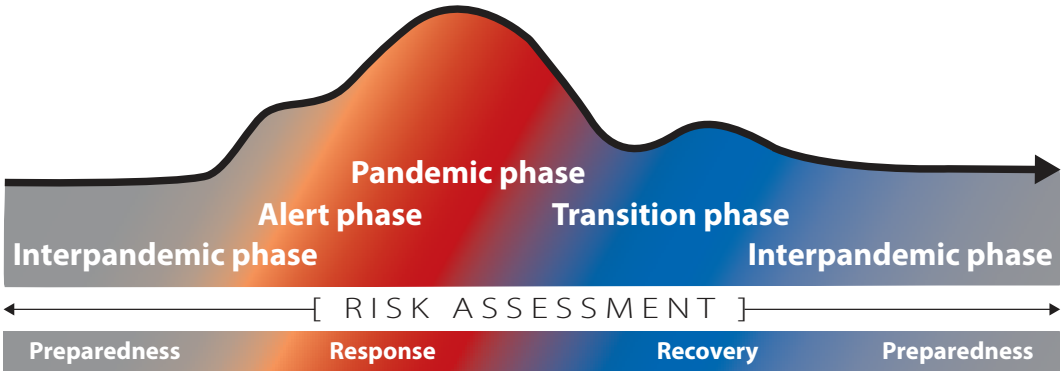
The pandemic influenza phases reflect WHO's risk assessment of the global situation regarding each influenza virus with pandemic potential that is infecting humans. These assessments are made initially when such viruses are identified and are updated based on evolving virological, epidemiological and clinical data. The phases provide a high-level, global view of the evolving picture.

The global phases – interpandemic, alert, pandemic and transition – describe the spread of the new influenza subtype, taking account of the disease it causes, around the world. As pandemic viruses emerge, countries and regions face different risks at different times. For that reason, countries are strongly advised to develop their own national risk assessments based on local circumstances, taking into consideration the information provided by the global assessments produced by WHO. Risk management decisions by countries are therefore expected to be informed by global risk assessments, but based on local risk assessments.

The risk-based approach to pandemic influenza phases is represented in **Figure 1** as a continuum, which also shows the phases in the context of preparedness, response and recovery, as part of an all-hazards approach to emergency risk management. Both WHO guidance and international standards exist that describe formats and conduct of such risk assessment (see **Section 4.2**). One of the underlying principles of this guidance is to acknowledge that emergency risk management at country level needs to be sufficiently flexible to accommodate different consequences within individual countries, for example, different severities and different numbers of waves of illness.

The global phases will be used by WHO to communicate the global situation. They will be incorporated into IHR (2005) related communications to National IHR Focal Points, in Disease Outbreak News releases and various other public and media interactions, including through social media channels.

Figure 1. The continuum of pandemic phases[a]



[a] This continuum is according to a "global average" of cases, over time, based on continued risk assessment and consistent with the broader emergency risk management continuum.

Interpandemic phase: This is the period between influenza pandemics.

Alert phase: This is the phase when influenza caused by a new subtype has been identified in humans.[5] Increased vigilance and careful risk assessment, at local, national and global levels, are characteristic of this phase. If the risk assessments indicate that the new virus is not developing into a pandemic strain, a de-escalation of activities towards those in the interpandemic phase may occur.

Pandemic phase: This is the period of global spread of human influenza caused by a new subtype. Movement between the interpandemic, alert and pandemic phases may occur quickly or gradually as indicated by the global risk assessment, principally based on virological, epidemiological and clinical data.

Transition phase: As the assessed global risk reduces, de-escalation of global actions may occur, and reduction in response activities or movement towards recovery actions by countries may be appropriate, according to their own risk assessments.

The global phases and their application in risk management are distinct from (1) the determination of a PHEIC under the IHR (2005) and (2) the declaration of a pandemic. These are based upon specific assessments and can be used for communication of the need for collective global action, or by regulatory bodies and/or for legal or contractual agreements, should they be based on a determination of a PHEIC or on a pandemic declaration.

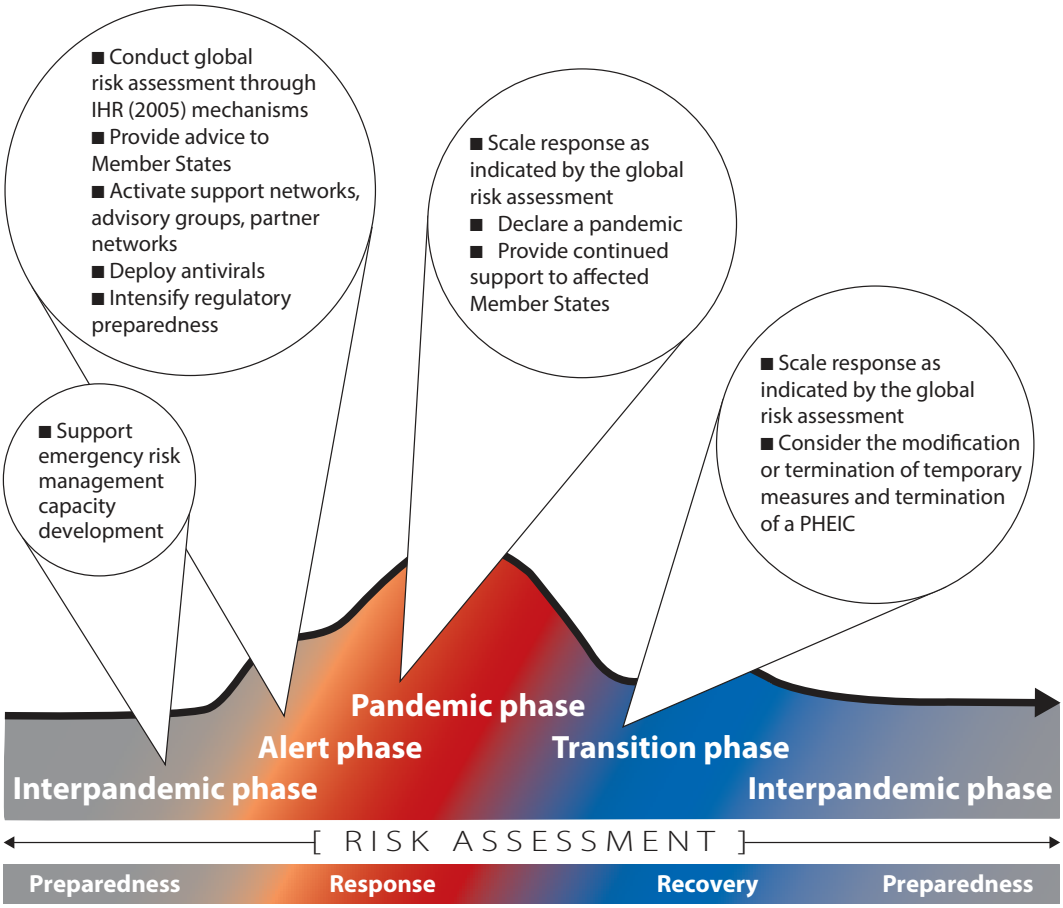
Determination of a PHEIC: The responsibility of determining a PHEIC lies with the WHO Director-General under Article 12 of the IHR (2005). The determination leads to the communication of temporary recommendations, see **Section 2.1**.

Declaration of a pandemic: During the period of spread of human influenza caused by a new subtype, and appropriate to the situation, the WHO Director-General may make a declaration of a pandemic.

While the determination of a PHEIC and/or declaration of a pandemic may trigger certain regulatory actions by WHO and Member States, actions at national level should be based on national/local risk assessments and be commensurate with risk.

[5] The IHR (2005) Annex 2 includes "human influenza caused by a new subtype" among the four specified diseases for which a case is necessarily considered "unusual or unexpected and may have serious public health impact, and thus shall be notified" in all circumstances to WHO.

Figure 2. The continuum of pandemic phases with indicative WHO actions



Actions by WHO occur throughout the phases continuum; their nature and scale at any point in time will be in line with the global risk assessment. Indicative actions by the Organization are illustrated in **Figure 2**. For further examples of WHO actions, see **Section 3.2**.

National actions: The nature and scale of national actions at any point in time will be in line with the current national risk assessments, taking into consideration the global risk assessment. The uncoupling of national actions from global phases is necessary since the global risk assessment, by definition, will not represent the situation in individual Member States. For further information on suggested national actions, see **Section 5**.

2.3 Pandemic Influenza Preparedness Framework

The Pandemic Influenza Preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits – widely known as the PIP Framework – brings together Member States, industry, other key stakeholders and WHO to implement a global, Member State-developed approach to pandemic influenza preparedness and response (*5*). The Framework aims to improve the sharing of influenza viruses with pandemic potential and to achieve, *inter alia*, more predictable, efficient and equitable access for countries in need of life-saving vaccines and medicines during future pandemics. The PIP Framework became effective on 24 May 2011, when it was adopted by the Sixty-fourth World Health Assembly. The Framework has three core components, described below.

Virus sharing

Member States share PIP biological materials[6] to ensure ongoing global monitoring and risk assessment and the development of safe and effective influenza vaccines. Standard Material Transfer Agreement 1 establishes the rights and obligations of Global Influenza Surveillance and Response System (GISRS)[7] laboratories when transferring PIP biological materials within GISRS and to parties outside GISRS.

Benefit sharing

Member States and WHO aim to ensure that benefits arising from the sharing of PIP biological materials are made more accessible and available to countries based on public health risk and need. Various key points are as follows:

- Standard Material Transfer Agreement 2 are binding contracts between WHO and all recipients of PIP biological materials outside of GISRS, which include: influenza vaccine, diagnostic and pharmaceutical manufacturers; biotechnology firms; and research and academic institutions. Non-GISRS recipients must assess benefits they can commit, or consider committing, to the PIP benefit-sharing system based on their nature and capacity.
- Partnership contribution: An annual contribution to WHO by influenza vaccine, diagnostic and pharmaceutical manufacturers who use WHO GISRS. The Framework specifies that the contribution will be used to improve global pandemic influenza preparedness and response.
- Other benefits: As listed under Section 6 of the PIP Framework, other benefits include laboratory and surveillance capacity building; regulatory capacity building; and the establishment of antiviral and interpandemic vaccine stockpiles.

Governance and review

The Framework puts in place an oversight mechanism with three pillars.

- The World Health Assembly to oversee implementation of the PIP Framework.
- The WHO Director-General to promote implementation.
- The Advisory Group to provide guidance to the Director-General, monitor PIP Framework implementation and report thereon annually to the Director-General.

WHO acts as the secretariat for implementing the PIP Framework and works with private and public partners to facilitate achieving results as efficiently as possible.

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[6] For the purposes of the PIP Framework and its annexed Standard Material Transfer Agreements and terms of reference and the Influenza Virus Tracking Mechanism, "PIP biological materials" include human clinical specimens; virus isolates of wild-type human H5N1 and other influenza viruses with human pandemic potential; and modified viruses prepared from H5N1 and/or other influenza viruses with human pandemic potential developed by WHO GISRS laboratories, these being candidate vaccine viruses generated by reverse genetics and/or high growth reassortment. Also included in "PIP biological materials" are RNA extracted from wild-type H5N1 and other human influenza viruses with human pandemic potential and cDNA that encompass the entire coding region of one or more viral genes.

[7] GISRS monitors which influenza viruses are circulating in humans around the world throughout the year. GISRS comprises WHO Collaborating Centres; National Influenza Centres; H5 Reference Laboratories; and Essential Regulatory Laboratories. The major technical roles of GISRS are to: monitor human influenza disease burden; monitor antigenic drift and other changes (such as antiviral drug resistance) in seasonal influenza viruses; obtain suitable virus isolates for updating of influenza vaccines; and detect and obtain isolates of new influenza viruses infecting humans, especially those with pandemic potential. WHO also develops logistics management capacity to ensure that public health laboratories have access to protocols, tests and diagnostic reagents necessary to identify non-seasonal influenza virus infections. (See http://www.who.int/influenza/gisrs_laboratory/en/index.html, accessed April 2013.)

Member States' responsibilities

Under the Framework, Member States are responsible for (1) ensuring the timely sharing of influenza viruses with human pandemic potential with GISRS; (2) contributing to the pandemic influenza benefit-sharing system, including by working with relevant public and private institutions, organizations and entities so they make appropriate contributions to this system; and (3) continuing the support of GISRS.

2.4 Pandemic vaccine production

WHO issues biannual recommendations on the composition of seasonal influenza vaccines. Since 2004, WHO has also been reviewing vaccine candidate viruses for A(H5N1) and other influenza subtypes with pandemic potential. This process is undertaken in consultation with WHO Collaborating Centres for Influenza, National Influenza Centres, WHO H5 Reference Laboratories and key national regulatory reference laboratories. It is based on surveillance conducted by GISRS. The recommendations and availability of vaccine viruses are announced in a public meeting and simultaneously on the WHO web site (*6*). They are also communicated to influenza vaccine manufacturers via the International Federation of Pharmaceutical Manufacturers and Associations and the Developing Country Vaccine Manufacturers Network.

A critical action of WHO during an emerging pandemic is the selection of the pandemic vaccine strain and determination of when to move from seasonal to pandemic vaccine production. As soon as there is credible evidence to suggest that an influenza virus with pandemic potential has acquired the ability to sustain human-to-human transmission, WHO will expedite the process of review, selection, development and distribution of vaccine viruses for pandemic vaccine production, as well as vaccine potency testing reagents and preparations, involving all stakeholders as necessary. The efficiency of this process depends on the timely sharing of viruses and clinical specimens with WHO via GISRS and the WHO Collaborating Centres for Influenza.

The decision to recommend a move to pandemic vaccine production will be taken in collaboration and consultation with relevant technical advisory bodies including the Strategic Advisory Group of Experts on Immunization (SAGE) and GISRS, with due consideration to applicable requirements under the IHR (2005), including advice from an IHR Emergency Committee, should one be convened. WHO will then announce its recommendations on whether and when to move production to pandemic vaccine and the virus strain that should be used in the pandemic vaccine.

The decision to revert to seasonal vaccine production will be based on the formal recommendation for the composition of influenza vaccines, which is based on the virological and epidemiological information provided by GISRS and on the advice of relevant technical advisory bodies.

3. Emergency risk management for health

3.1 Principles of Emergency Risk Management for Health

Health and the systems that support it are vulnerable to loss and disruption from a variety of acute hazards including: (1) health events, such as pandemic influenza, chemical spills and nuclear contamination; (2) hazards secondary to emergencies and disasters, such as cholera outbreaks following floods; as well as (3) system destabilizers, such as earthquakes or acute energy shortages. Management of the risk associated with such hazards is central to the protection and promotion of public health.

To a varying extent, risk is managed within existing health systems and via programmes focused on specific hazards. However, some functional components of hazard-specific preparedness and response systems are common to all hazards and can therefore be consolidated into a comprehensive system of emergency risk management for health (ERMH). The objectives of ERMH are to:

- strengthen country and community capacities to manage the health risks from all types of hazards (7).
- ensure that the essential components required in a comprehensive emergency risk management programme are in place in the health sector.
- link and integrate these components into (1) health systems, (2) multisectoral disaster management systems, and (3) other mechanisms across the whole of society, including relevant risk management within non-health sectors.
- enable the health sector to advocate for and strengthen the health aspects of national and international policies and frameworks related to emergency and disaster risk management, particularly in the reduction of risk and health impact from all hazards.

The emergency risk management for health continuum describes the range of measures to manage risks through prevention and mitigation, and preparing for, responding to and recovering from emergencies.[8] Risk management measures for any health emergency, including pandemic influenza should be made on the basis of national and local risk assessment, taking account of the global assessment produced by WHO as appropriate.

Emergency risk management for health is based on the principles listed below.

Comprehensive risk management: A focus on assessment and management of risks of emergencies rather than events.

All-hazards approach: Use, development and strengthening of elements and systems that are common to the management of risks of emergencies from all sources.

Multisectoral approach: Recognition that all elements of government, business and civil society have capacities relevant to ERMH.

[8] For the purposes of risk management for pandemic influenza, three main groups of measures are used – preparedness, response and recovery. Prevention and mitigation are important in the context of comprehensive ERMH. They are reflected in both preparedness and response activities to be considered in national Pandemic Influenza Risk Management, Section 5.

Multidisciplinary approach: Recognition of the roles of many disciplines in health required to manage the health risks of emergencies through risk assessment, mitigation, prevention, preparedness, response, recovery and capacity strengthening.

Community resilience: Utilization of capacities at community level for risk assessment, reporting, providing basic services, risk communication for disease prevention and long-term community care and rehabilitation.

Sustainable development: Recognition that development of country and community capacities in health and other sectors requires a long-term approach to protect health and build resilience.

Ethical basis: Consideration of ethical principles throughout health emergency risk management activities.

3.1.1 Ensuring ethical Emergency Risk Management for Health

Management of an influenza pandemic, as with any urgent public health situation, requires certain decisions that balance potentially conflicting individual and community interests. For example, during the influenza A(H1N1) 2009 pandemic, countries experienced pressures on critical services that required prioritization (*8*) and impacted at the individual level. In addition, questions about social distancing measures, forced isolation and quarantine arose, together with debates on mandatory vaccination of health-care workers.

Ethics do not provide a prescribed set of policies; rather, ethical considerations will be shaped by the local context and cultural values. Nevertheless, it is important that any emergency measures that limit individual rights and civil liberties are necessary, reasonable, proportional, equitable, non-discriminatory and in full compliance with national and international laws (**Annex 3**) (*9*).

3.1.2 Emergency Risk Management for Health throughout the whole-of-society

A pandemic will affect the whole of society. No single agency or organization can effectively prepare for a pandemic in isolation, and uncoordinated preparedness of interdependent public and private organizations will reduce the ability of the health sector to respond. A comprehensive, coordinated, whole-of-government, whole-of-society approach to pandemic preparedness is required (**Annex 4**).

In the absence of effective planning, the effects of a pandemic at country level could possibly lead to social and economic disruption, threats to the continuity of essential services, lower productivity, distribution difficulties and shortages of supplies and human resources. It is therefore essential that all organizations – private and public – plan for the potential disruptions that a pandemic may cause. Business continuity planning should be considered for all essential service providers (**Annex 5**).

3.2 Emergency Risk Management for Health: essential components

The six categories of ERMH essential components are: policies and resource management; planning and coordination; information and knowledge management; health infrastructure and logistics; health and related services; and community emergency risk management capacities. A summary of the essential components in each of the categories is provided in **Table 2**.

WHO has been mandated by a series of World Health Assembly resolutions to provide Member States with guidance and technical support regarding pandemic influenza (*3*, *4*). Some of these obligations are specific to pandemic influenza and others overlap with the Organization's responsibilities in all health emergencies. Examples of the various functions, which are fulfilled at all levels of WHO, are provided for each category of essential component.

Table 2. Essential components in each category

Categories	Essential components
Policies and Resource Management	• Policies and legislation
	• Capacity development strategies
	• Monitoring, evaluation and reporting
	• Financing
	• Human resources
Planning and Coordination	• Coordination mechanisms
	• ERMH units in Ministry of Health
	• Prevention and mitigation planning and coordination
	• Preparedness and response planning and coordination
	• Recovery planning and coordination
	• Business continuity management
	• Exercise management
Information and Knowledge Management	• Risk assessments
	• Early warning and surveillance
	• Research for ERMH
	• Knowledge management
	• Information management
	• Public communications
Health infrastructure and logistics	• Logistics and supplies
	• Safer, prepared, and resilient health facilities
Health and related services	• Health-care services
	• Public health measures
	• Specialized services for specific hazards
Community ERMH capacities	• Local health workforce capacities and community-centred planning and action

3.2.1 Policies and resource management

Appropriate policies, plans, strategies and legislation form the basis of effective governance of ERMH. Policies and legislation should use an all-hazards approach, i.e. one that recognizes that risk management measures for hazard-specific emergencies have common elements and should cover the ERMH continuum through prevention and mitigation, preparedness, response and recovery.

Legislation should clearly articulate procedures for declaring and terminating a national public health emergency, based on national risk assessment. It should also define emergency management structures across the government national emergency/disaster management authority and should articulate the precise roles, rights and obligations of different organizations during a health emergency, based on an ethical framework to govern policy development and implementation. National legislation should be consistent with legally binding international agreements and conventions. Policies specific to the health sector should be compatible with legislation and should include defined roles and responsibilities, procedures and standards of implementation of ERMH. Policies and mechanisms to finance all ERMH activities need to be considered.

This category of essential components also includes the management of human and material resources. A human resource plan should be developed and should contain the staffing requirements for the management of health emergencies and define the competencies needed.

These plans should also specify the roles, responsibilities and authorities of the responders with written terms of reference for each specific function.

Capacity development is central to ensure that the health workforce is well equipped to implement ERMH. These efforts should be systematic and start with a thorough capacity assessment and analysis of training available for different target groups. Based on these analyses, training programmes that are appropriate, effective and efficient should be developed and instigated within educational institutions and as continuing professional development for the workforce.

Role of WHO in supporting policies and resource management

- Provide support to assess, strengthen and maintain core capacities in order to meet IHR (2005) obligations (*10*).
- Provide technical support to document the disease burden and economic impact of seasonal influenza and develop a national vaccine policy, if indicated.
- Advise on ethical frameworks to govern policies.
- Provide support and guidance to strengthen workforce capacities, e.g. health-care worker training.
- Strengthen GISRS and other laboratories to increase influenza diagnostic and surveillance capabilities and provide technical support, capacity building and technology transfer for influenza vaccines and diagnostics.
- Promote the increase of global production capacity for pandemic vaccines in developing countries, though the Global Action Plan for Influenza Vaccines (GAP) (*11*).

3.2.2 Planning and coordination

The health sector should be properly represented at all levels of government in any emergency/disaster risk management coordination forum to ensure that health needs are identified and technical advice provided to other sectors. One of the roles of these fora will be to develop and strengthen appropriate command and control systems across the national disaster management authority, within each government ministry and at subnational levels. Another important role of these fora is to ensure that the most current evidence is available to inform policy decisions.

In addition, an operational entity within the Ministry of Health or related institution should be responsible for coordinating and supervising emergency risk management implementation throughout the health sector, with stakeholder involvement. Similar entities should be in place at all subnational and local administrative levels.

Prevention and mitigation actions for any risk should be determined following a detailed risk assessment and be included in ERMH programmes at the national and subnational levels. The implementation of prevention, mitigation and preparedness measures should be coordinated with relevant technical departments inside the Ministry of Health and with the whole of government, business and civil society (**Annex 4**).

Effective coordination should be integral to all aspects of the response, starting with the initial risk assessment and including: the development of short- and long-term action plans; the assignment of resources to priority needs; and the provision of urgent community care and support. Incident management systems may be considered to facilitate the coordination under a common management structure. ERMH processes should be well documented in contingency plans and should include standard operational procedures that are appropriately disseminated, regularly updated and exercised.

Recovery needs to be an integral part of response planning and should be done in parallel with other risk management actions, i.e. well in advance of an emergency. Sufficient attention should be given to recovery planning for the health sector.

Role of WHO in planning and coordination

- Consistent with the whole-of-society, whole-of-government approach required for robust risk management for pandemic influenza, advocate collaboration and coordinate prioritized activities with organizations of the UN system, bilateral development agencies, nongovernmental organizations, the private sector and stakeholders in non-health sectors.
- Establish joint initiatives for closer collaboration with national and international partners in (1) early detection, reporting and investigation of influenza outbreaks of pandemic potential and (2) coordination of research on the human–animal ecosystem interface.
- Collaborate with the animal health sector, e.g. the Food and Agriculture Organization of the United Nations and the World Organisation for Animal Health, on preparedness, prevention, risk assessment and risk reduction mechanisms to decrease exposure of humans to influenza viruses at the human–animal ecosystem interface.
- Promote agreements for international technical assistance, resource mobilization and fair sharing of influenza products such as through the UN prequalification programme, Essential Medicines List and the PIP Framework (*5*, *12*, *13*).
- Provide guidance and/or technical support to Member States in the preparation of pandemic influenza risk management plans and in identifying priority needs and response strategies and assessing preparedness.
- Facilitate regional/cross-border collaborations.

3.2.3 Information and knowledge management

Information and knowledge management encompasses technical guidance for risk management, communications and early warning and surveillance, which are highlighted below, as well as risk assessment, (see **Section 4.1**) research for emergency risk management and information management.

3.2.3.1 Technical guidance

Practitioners should be provided with practical technical guidance on all aspects of ERMH. These guidelines should include clinical and operational aspects of the event. Continuity of health-care provision strategies should be periodically updated, as well, to reflect new research findings and lessons learnt from past health emergency events.

3.2.3.2 Communication

Effective and efficient communication is critical throughout the ERMH continuum and include information dissemination within the health sector, between health and other sectors and, crucially, with the public.

In risk communication, national and local government authorities provide information to the public in an understandable, timely, transparent and coordinated manner before, during and after a health emergency. The objectives are to develop and maintain public trust in local and national health systems and to convey realistic expectations about capacities for health emergency risk management. Risk communication also promotes the effective exchange of information and opinion among science, public health and veterinary experts, which facilitates assessment, implementation and coordination of risk management activities.

A communications strategy involves processes to collect, develop and distribute information in a timely manner and procedures to ensure that formats are appropriate to the target audiences. The strategy should take into account behavioural aspects of how people react to and act on advice and information they receive, not only from authorities but also from sources such as mass and social media. Public understanding of hazards and risks is complex, context-dependent and culturally mediated, thus communications strategy development may benefit from community participation (*14*).

ERMH plans and activities across all hazards should use the principles of risk communication to build the capacity to understand and anticipate public concerns and develop effective and responsive dialogue mechanisms. This can be achieved through an emergency communications committee that has developed and tested standard operating procedures to ensure streamlined, expedited dissemination of information for decision-making and public communication.

3.2.3.3 Early warning and surveillance

Accurate, timely information is one of the most valuable commodities during a health emergency or disaster. This information serves as the evidence base for critical decisions at all levels of administration and defines the messaging for public communication and education. An effective system, with minimal data sets of information required throughout the management of an emergency, should be developed and tested in preparation for a response.

The systems required for early warning and surveillance should be robust and enable the capture of data required for assessment of severity, the implementation of protocols for operational research, including efficacy studies on interventions applied, and assessments of national impact based on criteria such as workplace and school absenteeism, regions affected, groups most affected and essential worker availability.

Role of WHO in information and knowledge management

- Provide guidance and/or technical support to Member States on identifying priority needs and response strategies to inform preparedness planning.
- Facilitate development of national guidelines for relevant activities such as targeted vaccination campaigns, laboratory biosafety and safe specimen handling/shipping.
- Promote public health research priorities relevant to all resource settings for pandemic, non-seasonal and seasonal epidemic influenza over the medium- to long-term period via the WHO Public Health Research Agenda for Influenza.[9]
- Provide support and guidance on capacity building for health systems (*15*), infection prevention and control in health-care settings (*16*), surge capacity and national vaccine deployment (*17*).
- Assess and monitor the type and pathogenicity of circulating influenza viruses through information provided through GISRS.
- Provide technical guidance and advice to support Member States to develop effective and responsive pandemic communications, including risk communication and behavioural interventions messaging (*18*, *19*).
- Provide guidance, technical support and tools for detection, investigation, rapid risk assessment and reporting (*20*).

[9] The WHO Public Health Research Agenda for influenza has five thematic streams: (1) reducing the risk of emergence of pandemic influenza; (2) limiting the spread of pandemic, non-seasonal and seasonal epidemic influenza; (3) minimizing the impact of pandemic, non-seasonal and seasonal epidemic influenza; (4) optimizing the treatment of patients; and (5) promoting the development and application of modern public health tools. The research agenda also aims to facilitate discussion and coordination among researchers, donors and public health experts. See http://www.who.int/influenza/resources/research/about/en/index.html, accessed February 2013.

- Provide technical support and information to national authorities:
  - to enhance surveillance and collection of clinical, virological and epidemiological data to facilitate assessment of the extent of human-to human transmission and the epidemiological situation;
  - on risk assessment of clusters of influenza-like illness; and
  - on interventions to reduce the spread of influenza disease.
- Define standards for initial case investigations and for routine sentinel surveillance.
- Establish and refine global case definitions for reporting by countries of human cases of influenza caused by viruses with pandemic potential.
- Coordinate and disseminate relevant public health messages through channels such as the WHO web site, published materials, press conferences and the media.
- Provide regular and timely feedback on the results of the analysis of data reported by Member States to WHO.
- Periodically reassess and modify recommended interventions in consultation with appropriate partners, including those outside the health-care sector, on the acceptability, effectiveness and feasibility of interventions.
- Provide principles and update guidance for appropriate: infection prevention and control; laboratory biosafety; clinical management in health-care facilities and home-based care; use of antivirals; and use of seasonal and pandemic vaccines.

3.2.4 Logistics and infrastructure

Effective management of health emergencies requires access to and management of adequate infrastructure and logistics, the most important of which involve transportation, telecommunications, stockpiling and distribution of medicines and supplies, and establishment of temporary health facilities. To ensure that logistic support will be available during health emergencies, the Ministry of Health should consider making advance arrangements with government departments responsible for transport, communications, public works and the armed forces together with external agencies, such as nongovernmental organizations, UN agencies and private companies. The type and quantity of supplies and medicines will be determined by the nature of the hazard. The most critical supplies for pandemic influenza are those needed to prevent and treat the disease and its complications while maintaining critical non-influenza health services.

The Ministry of Health or the central coordinating body could also consider identifying, supporting, training and deploying operational and logistics response teams.

Role of WHO in supporting health infrastructure and logistics

- Manage the WHO strategic global stockpile of antivirals and vaccines and develop standard operating procedures to ensure rapid deployment of the WHO global "stockpile" of pandemic vaccines, based on existing pandemic vaccine deployment guidelines.
- Develop logistics management capacity to ensure that public health laboratories have access to protocols, tests and diagnostic reagents to be able to identify non-seasonal influenza virus infections (*21*).

3.2.5 Health and related services

Regardless of the nature of a health emergency challenge faced, health and related services will need to be provided to the affected population to save lives, manage public health, prevent secondary effects and maintain essential non-hazard-related emergency services. While many

of these health services do not differ from services provided in non-emergency situations, their organization and delivery may change significantly during a health emergency. This will require thoughtful planning beforehand. Health services related to triage, emergency care and maintenance of non-influenza acute care are among the many specified services requiring effective planning for implementation during a pandemic. Examples include activating contingency plans for health and laboratory facilities to deal with potential staff shortages, adjust triage systems as required and implementing mortuary management procedures as necessary.

In addition to service provision and public health measures, this essential component also includes identifying priorities and response strategies for public and private health-care systems triage and surge capacity. Surge capacity should be planned in advance for different scenarios with predetermined procedures for mobilizing staff on short notice. Mechanisms for ensuring adequate human resources for long-term events, such as an influenza pandemic should be considered, including planning for staffing of alternative care facilities for cohorting influenza patients, based on national plans. It is also important to consider ensuring that health-care workers have the opportunity for rest and recuperation.

Role of WHO in supporting health and related services

- Provide advice and technical guidance on organization and delivery of health and related services, e.g. laboratory services, blood services, non-pharmaceutical measures and mass casualty management systems.
- Utilize existing clinical networks to review clinical information and effectiveness and safety of clinical interventions.
- Provide advice on measures for controlling international disease spread through temporary recommendations issued under IHR (2005).
- Support health system capacity assessments for emergency risk management (*22*).

3.2.6 Community capacities

Community capacities are a vital component of ERMH. The community-based health workforce is a crucial front line for ERMH activities and has the language and cultural skills to implement effective local ERMH activities, including social mobilization. This workforce may include appropriately trained and accredited community health workers, trained volunteers, community-based organizations that promote health, health education and social mobilization, and those from key sectors (water, sanitation, hygiene, agriculture, food security, shelter and education) that contribute to promoting health. Developing local action plans based on national plans for any hazard is also an important consideration for strengthening community capacities.

Role of WHO in supporting community capacities

- Promote the role played by the community-based health workforce in emergency risk management and advocate for scale-up of this vital resource (*23*).
- Advise on strengthening community-based health workforce programmes, including recruitment, training, supervision, evaluation, deployment and retention (*24*).
- Provide guidance on training community health workers (*25*).
- Provide advice and guidance on community capacity building activities during pandemic influenza (*15*).

4. National pandemic influenza risk assessment

4.1 Influenza viruses and pandemics

Influenza, a viral respiratory disease, can cause high morbidity and mortality in humans and is known to affect some animal species. Clinical disease can range from mild to severe and in some cases result in death. While influenza B remains a human disease, influenza A viruses are found in human, avian and some mammalian species. An influenza pandemic occurs when an influenza A virus to which most humans have little or no existing immunity acquires the ability to cause sustained human-to-human transmission leading to community-wide outbreaks. Such a virus has the potential to spread rapidly worldwide, causing a pandemic.

At the genetic level, pandemic influenza viruses may arise through: (1) genetic reassortment: a process in which genes from animal and human influenza viruses mix together to create a human–animal influenza reassortant virus; (2) genetic mutation: a process in which genes in an animal influenza virus change allowing the virus to infect and transmit easily in humans.

Influenza pandemics are unpredictable but recurring events that can have significant global consequences. Since the 16th century, influenza pandemics have been described at intervals ranging between 10 and 50 years with varying severity and impact. Characteristics of the past four pandemics are summarized in **Table 3**.

Table 3. Characteristics of the past four influenza pandemics (*26*)

Pandemic year of emergence and common name	Area of origin	Influenza A virus sub-type (type of animal genetic introduction/ recombination event)	Estimated reproductive number (*27*, *28*)	Estimated case fatality	Estimated attributable excess mortality worldwide	Age groups most affected (*29*)
1918 "Spanish flu"	Unclear	H1N1 (unknown)	1.2–3.0	2–3% (*30*)	20–50 million	Young adults
1957–1958 "Asian flu"	Southern China	H2N2 (avian)	1.5	<0.2%	1–4 million	All age groups
1968–1969 "Hong Kong flu"	Southern China	H3N2 (avian)	1.3–1.6	<0.2%	1–4 million	All age groups
2009–2010 "influenza A(H1N1) 2009"	North America	H1N1 (swine)	1.1–1.8 (*31*)	0.02% (*32*)	100 000–400 000 (*33*)	Children and young adults

In June 2009, WHO declared the first influenza pandemic of the 21st century after the emergence of the new A(H1N1)pdm09 virus subtype. This virus was first isolated from humans in Mexico and the United States of America in April 2009. Within a few weeks, the virus had spread rapidly, and there was sustained human-to-human transmission worldwide. The triple-reassortant virus contained a unique combination of gene segments from avian, swine and human influenza viruses. Risk factors for severe influenza A(H1N1)pdm09 disease were similar to those for seasonal influenza, e.g. pregnancy and many chronic medical illnesses, although younger age groups were more affected than usual.

Prior to 2009, much of the focus on influenza viruses with pandemic potential was on the avian influenza subtype A(H5N1). A human outbreak of avian influenza A(H5N1) was detected

in 1997 in Hong Kong SAR, China. This was the first recognized instance in which a highly pathogenic avian influenza virus had been transmitted to humans and resulted in serious illness. Since its widespread re-emergence in 2003–2004, this avian virus has resulted in millions of poultry infections and over 600 human cases. On rare occasions, human-to-human transmission of influenza A(H5N1) has occurred – most often to a family or other household member acting as a caregiver. However, none of these events has so far resulted in sustained community-level transmission.

Most animal influenza viruses do not cause disease in humans. However, viruses circulating in animals or derived from viruses circulating in animals have caused infections in humans, including avian and swine viruses and reassortants, notably of the H1, H3, H5, H7 and H9 subtypes. Most of these human infections have been mild and the viruses have not spread further to other people. In contrast, the influenza A(H1N1)pdm09 virus, which is thought to have originated in swine, would be an example of a swine influenza virus that was able to spread easily among people and cause disease.

Humans generally acquire these infections through direct contact or close exposure to infected animals or contaminated environments. Control of influenza among animals is therefore essential both to reduce the risk of human infection and the potential for pandemic strains to evolve and to prevent or reduce the economic consequences. Successfully meeting this challenge requires long-term commitment from countries and strong coordination between animal and human health authorities and practitioners.

Experience with the emergence of such a variety of different influenza strains that transmit from animals to humans illustrates the highly unpredictable nature of influenza viruses such that assumptions about where the next influenza virus with pandemic potential will emerge, or what its characteristics will be, cannot easily be made. This uncertainty underscores that planning should not focus only on avian influenza but should be based on broad and robust surveillance and evidence-based risk assessment.

4.2 National risk assessments

Risk assessment is a sy*stematic process for gathering, assessing and documenting information to assign a level of risk (20*). Risk assessment aims to determine the likelihood and consequences of events that impact public health at global, national, subnational and local levels. It provides the basis for taking action to manage and reduce the negative consequences of risks to public health.

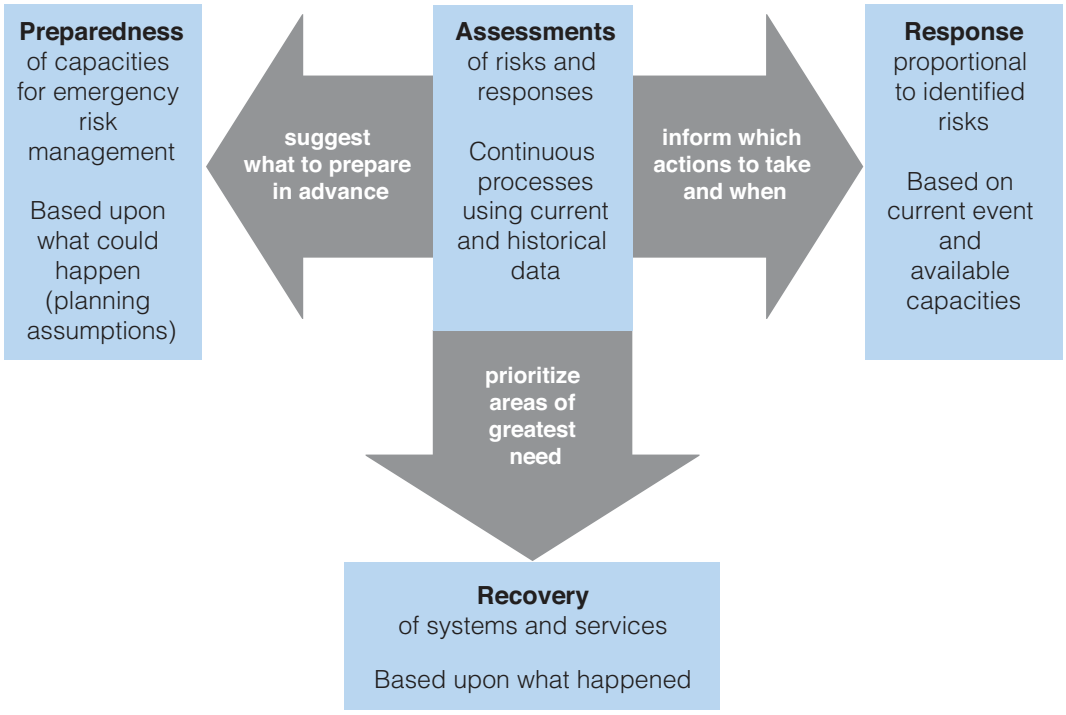
Use of risk assessment (*35*) promotes an understanding of the risks and attendant uncertainties of pandemic influenza and their potential influence on sustained health and other development objectives. It also facilitates the communication of risks and uncertainties. Risk assessment allows the provision of evidence-based information for policy-makers.

In an all-hazards approach, risk assessments can be performed to identify and prioritize preparedness, including mitigation and prevention, activities, response and recovery programmes, as illustrated in **Figure 3**.

For each influenza virus with pandemic potential, WHO will conduct global risk assessments in collaboration with the affected Member State(s), to inform decision-making for risk management (*36*). While WHO will communicate these global assessments and the uncertainties that surrounds them throughout the event, each Member State is strongly advised to assess national risk related to pandemic influenza in the context of their local experience, resources and vulnerabilities. Member States are also encouraged to share their risk assessments through networks or multilateral arrangements and to utilize regional resources for risk assessment.

At any point in a pandemic, one or many Member States may be responding to a national-level epidemic, while other Member States may not be affected for some months to come.

Figure 3. Pivotal role of risk assessment in preparedness, response and recovery actions



Consequently, each Member State is encouraged to conduct its own risk assessments, which will determine the timing, scale, emphasis, intensity and urgency of the actions required at their national and local levels. More information on suggested national actions is provided in **Section 5**.

National pandemic influenza risk assessment should involve a multidisciplinary team representative of the whole of government, together with stakeholders, and linked to relevant decision-makers. Since pandemic risk assessment has similar components across the whole of society, it should be conducted collaboratively with stakeholders at national, subnational and local levels.

A risk assessment considers hazard, exposure and context coupled with risk characterization. A hazard assessment relevant to pandemic influenza includes: identifying influenza viruses of concern; reviewing key virological and clinical information about each influenza virus; and ranking them by pandemic potential and possible consequences.

An exposure assessment seeks to define the groups of individuals known to have been, or likely to be, exposed to an influenza virus of concern and to delineate the susceptibility of these groups in terms of immunity and disease severity. This process incorporates epidemiological and susceptibility factors such as travel history, incubation period and estimation of potential for transmission.

These two assessments are then complemented by a context assessment. A context assessment is an evaluation of the environment in which the event takes place. It examines factors that affect risk, including: social; technological and scientific; economic; ethical; and policy and political factors, see **Table 4**.

Table 4. Factors to consider in context assessments

Factor	Examples
Social	• population size and characteristics such as distribution of high-risk groups
	• behaviours
	• impact of seasonal influenza
	• impact on lifestyle, e.g. acceptability and applicability of any social distancing recommendations
Technical and scientific	• ability to implement surveillance and mitigation activities
	• the likelihood that all suspect cases can be identified
	• the availability of mechanisms to reach specific high risk groups
	• the availability and acceptability of effective preventive measures and of treatment or supportive therapies
Economic	• direct and indirect financial costs including:
	• household income
	• hospitalization costs
	• potential impacts on tourism and trade
Ethical	• privacy issues
	• use of unlicensed products
	• transparency
	• unequal risk burden
	• potential requirements for the protection of critical infrastructure
Policy and political	• likely response of key stakeholders and media
	• government capacity to participate in risk management efforts
	• the country's recent experience with influenza
	• past and ongoing emergencies with implications for future hazards, vulnerabilities and capacities.

Once the hazard, exposure and context assessments are conducted, the risk can be characterized. Risk characterization seeks to organize the assessments into a determination of likelihood and impact of each risk. In the context of pandemic influenza, risk characterization employs these assessments to evaluate whether a particular influenza virus has pandemic potential and the degree to which such an event will impact on society, and, consequently, the urgency and scale of risk management actions to be implemented.

Throughout the risk assessment process, the uncertainty for each part of the assessment should be recorded and shared by the evaluating team. This documentation should include an overview of the basis for each assessment to ensure ongoing consistency in risk assessment processes.

Risk assessment is a continuous process throughout the risk management continuum. Member States are encouraged to conduct risk assessments at the national, subnational and local levels, in order to prioritize the development of risk management programmes tailored to the hazards present.

4.3 Assessment of pandemic severity

Gauging the severity of an influenza pandemic – a critical component of overall pandemic risk assessment – is an important consideration for WHO and Member States in planning for and responding to a pandemic. Early information about severity can help support decision-making at global and country levels. As a pandemic spreads from country to country, data derived from existing influenza disease and virological surveillance, coupled with field investigations and other data sources, can be used to adjust global and national responses. Some of these data-collection processes are provided through existing WHO guidance and related resources (*37*).

Early assessments in countries first affected by human infection with a new influenza subtype will inform the global community. However, each country's context and pandemic-influenza-related severity will differ, requiring careful evaluation not only of the data reported but the capacities, demographics and other features of the country in which the observations are made. In addition, continual severity assessments will be necessary over the course of a pandemic since the accuracy and precision of severity-related information will change.

Severity assessments should be conducted at the community, national and global level. Each of these assessments will enable refinement of risk assessments at the other levels. As when conducting other components of risk assessments, a country may measure a severity parameter directly, do so with the assistance of an external partner or rely on applicable information from others. For example, during the influenza A(H1N1) 2009 pandemic, informal networks of experts in epidemiology, clinical medicine, virology and mathematical modelling shared preliminary information with WHO to enable a global assessment of severity.

To be useful, the severity assessments should be done when public health decisions are needed. To that end, a risk assessment, incorporating severity, should provide as much information as possible to answer the following key questions about an emerging pandemic.

- How rapidly are new cases accruing?
- What groups of people (e.g. age groups or groups at risk of severe outcomes) will become severely ill and die?
- What types of illnesses and complications are being seen?
- Is the virus sensitive to antiviral agents?
- How many people will become ill?
- What will be the impact on the health-care sector, including such factors as health-care utilization and impact on the health-care work force?

Operationally, these questions will help guide decisions regarding vaccine production and strategy for usage, antiviral use, mobilization of health-care resources, school closures and other social distancing strategies.

The data that answer each of these key questions will be considered in the context of three indicators. Each of these indicators will contain information derived from a variety of different types of data, including virological, epidemiological, and clinical. The data will be grouped into the following indicators to help make them more accessible and understandable to the public and policy makers.

Transmissibility: Reflects the ease of movement of the virus between individuals, communities, and countries. The factors that will go into describing transmissibility include both virological factors and epidemiological observations. As with all of the indicators, the values of each of the observations or measurements that are used to reflect transmissibility will be interpreted in the context where they are made as they will be influenced by social and climatic factors.

Seriousness of Disease: A pandemic virus that has a high level of clinical severity can result in a disproportionate number of persons with serious or grave illness, some of whom will die in the absence of effective treatment or adequate clinical management. However, the severity or virulence of a virus will also depend on the presence of underlying medical conditions that predispose individuals to severe illness, as well as age. An infection is likely to be much more severe for some segments of a population than others and descriptions of the groups at risk will be part of this indicator.

Impact: If the health-care sector is impacted at a high level it may not be able to accommodate the stress on its resources. The impact on the health sector will also be influenced by public concern and health-care policies put in place in response to the event. As such, assessing

impact will aid in understanding how these issues interact with inherent characteristics of the virus and the way it behaves.

As appropriate, some of these data may also be communicated directly to policy-makers and planners. Examples of representative parameters informing each indicator are provided in **Annex 6**. WHO will communicate with its geographically and technically diverse group of staff, networks and external experts to help interpret the available qualitative and quantitative data. The severity assessments must be flexible in order to accommodate unforeseen characteristics of the pandemic as it evolves (e.g. a new indicator could be included or a known one excluded).

Any severity assessment plan has inherent limitations. Assessments are dependent upon the data available. Data first must be sought, then found, collected, shared, analyzed and communicated. Resource availability and competing interests may impede any of these steps and the ways in which these steps proceed will affect the validity of the data. Even under the best operational circumstances, data must accumulate over time before accuracy can be achieved. Case-fatality ratio, a commonly sought and communicated severity-related parameter, is well reported to have significant variability over the course of a pandemic and is not useful in the very early stages of an event because it is likely to be inaccurate and misleading (*38*, *39*). In these very early stages, the proportion of known cases requiring mechanical ventilation, for example, might be used instead of case-fatality ratio.

Severity varies within a population owing to a variety of risk factors (*40*). Population risk factors in terms of community resilience have not been carefully studied. However, antecedent general health status, availability of resources, including health-care services and medications, and cultural dynamics that affect transmission and care-seeking are likely to be relevant and will complicate comparisons between populations. As such, WHO will attempt to interpret the observations described above in the context in which they are made and project how they might affect subsequently affected Member States whose context is different. To do this, it will be necessary to communicate a wide variety of data to describe the full profile of the event. These considerations further increase the need for severity assessments to occur in the context of robust risk assessments. Further information on the representative parameters for core severity indicators is provided in **Annex 6**.

5. National pandemic influenza risk management

Individual countries may be exposed to the pandemic influenza virus at different times, have different case and case fatality rates, surveillance and response capacities, and vulnerabilities. They may experience different numbers and severities of waves of illness arising from the pandemic virus. Therefore, flexibility must be embedded in planning such that movement between the groups of activities below can be done with agility to reflect the national situation and meet local needs. For example, activities in the recovery period may need to be supplemented, as necessary, by response actions, should there be a subsequent pandemic wave. Mechanisms must be in place to enable this flexibility and for national emergency response procedures to be implemented – as guided by national risk assessment – irrespective of the global phase.

The following national actions are grouped by the six categories of essential components of ERMH (**Table 2**) and are indicative of actions to be considered following risk assessments. The degree of implementation should be commensurate with the degree of risk, national priorities and needs. These suggested national actions are intended to build on the progress made in developing and strengthening existing systems.

5.1 Policy and Resource Management

Preparedness activities to be considered

Based on national/local risk assessments, resources and needs:

- Review or develop national pandemic risk management programmes, including preparedness activities and response plans, and establish, as needed, the full legal authority and legislation required to sustain and optimize pandemic preparedness, capacity development and response efforts across all sectors.
- Perform forecasts of the national economic impact of a pandemic and cost-effectiveness of preparedness to advocate for funding and to aid risk management planning.
- Integrate pandemic risk management plans into existing national emergency risk management programmes.
- Establish goals and priorities for the use of pandemic influenza vaccines and antiviral drugs.
- Explore ways to provide drugs and medical care free of charge (or cover by insurance) to encourage prompt reporting and treatment of human cases caused by a non-seasonal influenza virus or virus with pandemic potential.
- Strengthen and maintain capacities to detect, assess, notify and report events, the capacity to respond promptly and effectively and the capacities at designated points of entry relating to the identification and management of pandemic risks in accordance with IHR (2005) Annex 1A and 1B.2.
- Advise subnational and local governments on best practices in pandemic planning and implement a quality control system to regularly monitor and evaluate the operability and quality of local and regional plans.
- Develop procedures for access to and timely allocation of resources for preparedness, capacity development and intervention implementation at national and subnational levels, including activities to be fulfilled by humanitarian, community-based or nongovernmental organizations.

- Create a national roster of experts to provide high-level technical advice in areas such as ethics, risk assessment, infection prevention and control, respiratory diseases and emergency management.
- Assess existing capacities and identify priorities for pandemic risk management at national and subnational levels.
- Develop strategies, plans and training to enable all health-care workers, including community-level workers, to respond during influenza outbreaks and throughout a pandemic (*24*).
- Develop occupational health policies for essential services workers and develop guidance and policies to enable workers to stay home when ill.

Response activities to be considered

Based on national/local risk assessments, resources and needs:

- Prioritize and guide the allocation and targeting of additional human and material resources to achieve the goals of pandemic risk management plans.
- Assess whether international assistance is required to meet humanitarian needs. Alternatively, consider providing resources and technical assistance to countries experiencing outbreaks of influenza with pandemic potential (*41*).

Recovery activities to be considered

Based on national/local risk assessments, resources and needs:

- Review the lessons learnt about policies and resource management and revise national and subnational pandemic risk management plans; encourage stakeholders across all public and private sectors to do likewise.

5.2 Planning and coordination

Preparedness activities to be considered

Based on national/local risk assessments, resources and needs:

- If not already in place, consider appointing a cross-governmental, multi-agency national pandemic risk management committee. Suggested activities of this committee could include the following:
  - Develop, exercise (*42*) and periodically revise national and subnational pandemic risk management plans in close collaboration with all relevant public and private partners. Review subnational pandemic plans against the national plan and involve subnational and local representatives in testing interoperability.
  - Provide the key assumptions, guidance and relevant information to promote development of pandemic business continuity plans and strategies for public and private sector workplaces (**Annex 5**).
  - Lead and coordinate multisectoral resources to mitigate the societal and economic impact of a pandemic (**Annex 4**).
  - Consider planning for containment measures (**Annex 7**).
- Planning and coordination activities of the Ministry of Health entity responsible for ERMH could include the following activities:
  - Identify, brief regularly and train key personnel to be mobilized as part of a multisectoral expert response team for influenza outbreaks of pandemic potential.

— Encourage collaboration with neighbouring countries on aspects of pandemic preparedness planning that may have regional or cross-border implications through information sharing, participation in regional and international initiatives, exercises and coordination of responses to address trans-border issues including interoperability of plans.

Response activities to be considered

Based on national/local risk assessments, resources and needs:

- Update leadership and other relevant sectors on global and national pandemic influenza risk assessments.
- Provide the key assumptions, guidance and relevant information to public and private sectors to facilitate implementation of their pandemic business continuity plans.
- Finalize preparations for an imminent pandemic by activating national and subnational command and control systems.
- Activate pandemic contingency planning arrangements for the health sector and all sectors deemed critical for the provision of essential services.
- Switch to pandemic working arrangements.
- Respond, if possible, to requests for international assistance by offering resources and technical assistance to countries with ongoing pandemic activity.
- Collaborate with neighbouring countries on information sharing.
- Provide regular updates on the evolving situation to WHO and other partners to facilitate response coordination.
- Review and, if necessary, revise pandemic risk management plans to manage possible future pandemic wave(s).
- Evaluate the resources and capacities needed to monitor and respond to subsequent waves.

Recovery activities to be considered

Based on national/local risk assessments, resources and needs:

- Review the lessons learnt about planning and coordination across all sectors and share experiences with the international community. Review and, if necessary, revise pandemic risk management plans to manage a possible future pandemic.

5.3 Information and knowledge management

5.3.1 Technical guidance

Preparedness activities to be considered

Based on national/local risk assessments, resources and needs:

- Develop and disseminate guidance on all aspects of pandemic response including: clinical management; prevention and control of health-care associated infections; surveillance throughout the pandemic; public health measures; surge capacity; and management of non-influenza acute care patients.
- Anticipate the need for rapid revision and dissemination of guidance, e.g. new laboratory protocols as the diagnostics for the new strain become available.
- Develop and test guideline dissemination mechanisms.
- Develop case-finding, treatment and management protocols/algorithms.

- Provide guidance to health-care workers to test and report cases of suspected pandemic influenza infection in patients with respiratory illness, especially those who have travelled to an affected country/countries or their close contacts.

Response activities to be considered

Based on national/local risk assessments, resources and needs:

- Update, if necessary, national guidance and recommendations on the use of planned interventions taking into account information from affected countries.
- Update, if necessary, laboratory protocols for virus detection, identification, shipping and sharing with WHO Collaborating Centres for Influenza.
- To the extent possible, use standardized protocols to monitor safety, efficacy and supply of pharmaceutical interventions.
- Revise case definitions and diagnostic and treatment protocols/algorithms, as required.

Recovery activities to be considered

Based on national/local risk assessments, resources and needs:

- Communicate to the public and other stakeholders the lessons learnt about the effectiveness of policy and technical guidance during the pandemic and how the gaps that were discovered will be addressed. Evaluate guidance dissemination mechanisms and work with professional associations towards improvement. In addition, analyse data collected during the event for dissemination and consider revising the national risk assessment algorithms.

5.3.2 Communications

Preparedness activities to be considered

Based on national/local risk assessments, resources and needs:

- Develop effective strategies to inform, educate and communicate with individuals and families to improve their ability to take appropriate actions before, during and after a pandemic.
- Identify appropriate spokespeople.
- Identify communications channels and assess their ability to reach all target population groups. Develop protocols and provide training to spokespeople for each communication channel.
- Pre-test messages through each medium, including social media, and test communications procedures through exercises.
- Build effective relations with key journalists and familiarize them with influenza and pandemic related issues.
- Develop communication strategies to support the implementation of non-pharmaceutical interventions including restrictions on mass gatherings and school closures.

Response activities to be considered

Based on national/local risk assessments, resources and needs:

- Provide regular briefing updates to all spokespeople to ensure that the information conveyed is consistent and up-to-date.
- Conduct frequent and pre-announced public briefings through popular media outlets such as the web, television, social media and radio to counter panic and dispel rumours.

- Activate mechanisms to ensure the widest possible dissemination of information. Topics likely to require regular communication include :
  - What is known and not known about the virus, the state of the outbreak, use and effectiveness of measures and likely next steps.
  - What is known and not known about the pandemic disease, including transmission patterns, clinical severity, treatment and prophylaxis options.
  - The importance of compliance with recommended measures to stop further spread of the disease.
  - Societal concerns, such as the disruption to travel, border closures, school closures and the impact on the economy or society in general.
  - Sources of emergency medical care, resources for dealing with urgent non-pandemic health-care needs, and resources for self-care of medical conditions.
  - Any changes to the status of the pandemic.
  - The ongoing need for vigilance and disease-prevention efforts to prevent any upswing in disease levels.
  - Advice for travellers.
- Ensure effective communication of public health measures to reduce the spread of pandemic influenza, e.g. hand and respiratory hygiene, reduction of unnecessary travel and overcrowding of mass transport systems, self-isolation for sick individuals, except their nominated caregiver, and minimization of contact with others.
- Gather feedback from the general public, vulnerable populations and at-risk groups on attitudes towards the recommended measures and barriers affecting their willingness or ability to comply.
- Update communications strategies as feedback from the general public and stakeholder organizations is collected and analysed.

Recovery activities to be considered

Based on national/local risk assessments, resources and needs:

- Publicly acknowledge the contributions of all communities and sectors to the pandemic effort. Review the lessons learnt about communications and revise in readiness for the next major public health event. Communicate that the event may be over but that a second (or subsequent) wave(s) is/are possible and that the pandemic virus will revert to a seasonal pattern and be present as one of the circulating viruses for some time to come.

5.3.3 Early warning and surveillance

Preparedness activities to be considered

Based on national/local risk assessments, resources and needs:

- Ensure that mechanisms are in place for meeting obligations under IHR (2005) to detect, assess, notify and report events. Such mechanisms include the capacities to respond promptly and effectively and requisite capacities at designated points of entry relating to the identification and management of pandemic risks in accordance with IHR (2005) Annex 1A and 1B.2.
- Develop or strengthen national surveillance to collect up-to-date virological, epidemiological and clinical information on trends in human seasonal influenza infections to aid estimates of additional capacities needed to detect increases in pandemic activity.

- Enhance virological and epidemiological surveillance to detect and investigate unusual cases/clusters of influenza-like respiratory illness or deaths associated with non-seasonal influenza viruses, identify potential animal sources of human infection; and assess the risk of human-to-human transmission.

Response activities to be considered

Based on national/local risk assessments, resources and needs:

- Undertake a comprehensive assessment of the earliest national cases of pandemic influenza.
- Ensure that, as required under the IHR (2005), any notification is followed by ongoing communication to WHO of timely, accurate and sufficiently detailed public health information on the event, including, where possible, case definitions, laboratory results, source and type of risk, number of cases and deaths, conditions affecting the spread of the disease and the public health interventions employed.
- Collect and analyse available data to evaluate the virological, epidemiological and clinical characteristics of the national epidemic.
- Modify national case definitions and update clinical and laboratory algorithms for diagnosis, as necessary.
- Collect specimens for testing and virological characterization using protocols and procedures developed in collaboration with WHO.
- Document the evolving national epidemic including population susceptibility, changes in epidemiological and clinical features, geographical spread, trends and impact.
- Collect more detailed epidemiological and clinical data as time and resources permit.
- Maintain adequate virological surveillance to detect antigenic and genetic changes and changes in antiviral susceptibility and pathogenicity (*43*, *44*).
- Continue to update the health sector and other relevant ministries and decision-makers on new information or other changes that affect disease status, signs and symptoms, case definitions, protocols and algorithms.
- Activate the surveillance activities required to detect subsequent pandemic waves.
- Monitor and assess national impact using criteria such as workplace and school absenteeism, regions affected, groups most affected and essential worker availability.

Recovery activities to be considered

Based on national/local risk assessments, resources and needs:

- Review and revise situation monitoring and assessment tools for subsequent waves of disease, the next pandemic and other public health emergencies. In addition, resume seasonal influenza surveillance programmes incorporating the pandemic virus subtype as part of routine surveillance.

5.4 Health infrastructure and logistics

Preparedness activities to be considered

Based on national/local risk assessments, resources and needs:

- Develop pandemic risk management plans throughout the health sector, including for health facilities, laboratories and other allied health services.
- Plan for the increased need for antibiotics, antipyretics, hydration, oxygen and ventilation support within the context of national clinical management strategies.

- Develop mechanisms and procedures to select, procure, stockpile, distribute and deliver antivirals, essential pharmaceuticals, personal protective equipment, diagnostics tests and vaccines, when available and based on national goals and resources. Consider whether these mechanisms are adequate to conduct containment measures (**Annex 7**).
- Develop a deployment plan to deliver pandemic influenza vaccines to national and subnational distribution points within 7 days from when the vaccine is available to the national government and develop a mass vaccination campaign strategy (*17*).

Response activities to be considered

Based on national/local risk assessments, resources and needs:

- Implement vaccine procurement plans.
- Implement distribution and deployment plans for antivirals, vaccines and other pharmaceuticals, other medical supplies and personal protective equipment, according to national plans.
- Monitor essential health-related resources such as: medical supplies; antivirals, vaccines and other pharmaceuticals; health-care worker availability; hospital occupancy/availability; use of alternative health facilities; laboratory material stocks; and mortuary capacity.
- Deploy pandemic vaccine when available in accordance with national plans, priorities and vaccine availability.

Recovery activities to be considered

Based on national/local risk assessments, resources and needs:

- Restock medications and supplies and service and renew essential equipment in preparation for possible subsequent waves of pandemic virus-induced disease or other health emergencies. In addition, review the status of, and replenish, national and local stockpiles.

5.5 Health and related services

5.5.1 Health services

Preparedness activities to be considered

Based on national/local risk assessments, resources and needs:

- Consider policy and needs of an in-country approach to antivirals and vaccination, including mechanisms for evaluating effectiveness and monitoring for adverse events.
- Estimate and prioritize requirements for antiviral treatment or prophylaxis and vaccination during a pandemic.
- Consider capacity and resources for stockpiling essential medicines and equipment.
- Assess health system capacity to detect and contain outbreaks of pandemic influenza disease in hospital settings (*45*).
- Develop mechanisms to monitor uptake, compliance, safety and effectiveness of mitigation measures and share findings with the international community and WHO.

Response activities to be considered

Based on national/local risk assessments, resources and needs:

- Implement national plans for antivirals and/or vaccine campaigns according to priority status and availability, in accordance with the evidence or modify/adapt antiviral and vaccine strategies based on monitoring and surveillance information.

- Enhance infection prevention and control practices in health-care and laboratory settings and issue personal protective equipment as needed in accordance with national plans.
- Activate alternative strategies for case isolation and management as needed.
- Address the psychological impacts of the pandemic, especially on the health workforce, and provide social and psychological support for health-care workers, patients and communities.
- Reassess the capacity to implement mitigation measures to reduce the spread of pandemic influenza.
- Consider vaccination of health-care workers, when available and based on national goals and policies.
- Conduct ongoing evaluations of antiviral effectiveness, safety and resistance, and vaccine coverage, effectiveness and safety, throughout their deployment, according to national plans, mechanisms and procedures.

Recovery activities to be considered

Based on national/local risk assessments, resources and needs:

- Conduct a thorough evaluation of all the specific responses and interventions used, including: (1) antiviral effectiveness, safety and resistance; (2) vaccine coverage, effectiveness and safety, and share findings with the international community.
- Begin rebuilding essential services in preparation for subsequent waves of disease and/or other health emergencies.
- Work to increase seasonal influenza vaccine coverage levels of all groups at high risk, in accordance with national policy.

5.5.2 Public health-related measures

Preparedness activities to be considered

Based on national/local risk assessments, resources and needs:

- Identify the range of non-pharmaceutical interventions that might be recommended and develop protocols and communications to support their implementation.
- Develop a framework to facilitate decision-making for activation and de-escalation of specific measures, such as school closures or cancellation or restriction of mass gatherings based on appropriate risk assessment criteria.
- Plan for actions relating to temporary recommendations issued under IHR (2005), especially measures to slow the spread of disease.

Response activities to be considered

Based on national/local risk assessments, resources and needs:

- Assess and determine whether cancellation, restriction or modification of mass gatherings is indicated.
- Implement social distancing measures, as indicated in national plans, such as school closures and other societal-level disease control measures including adjusted working patterns.

Recovery activities to be considered

Based on national/local risk assessments, resources and needs:

- Conduct a thorough evaluation of the effectiveness of the individual, household and societal measures implemented and update guidelines, protocols and algorithms accordingly.

5.6 Community capacities

Preparedness activities to be considered

Based on national/local risk assessments, resources and needs:

- Develop guidance and plans to provide necessary support for prevention, treatment and infection prevention and control for ill persons isolated at home and their household contacts.
- Develop plans and mechanisms to enable increased access to treatment and care for community members.
- Develop public health education campaigns, including creating messages and feedback mechanisms targeted towards hard-to-reach, disadvantaged or minority groups.

Response activities to be considered

Based on national/local risk assessments, resources and needs:

- Initiate public health education campaigns in coordination with other relevant authorities on individual-level infection control measures.
- Implement appropriate individual/household medical and non-medical disease control measures for suspect cases and their contacts in households.
- Advise household contacts to minimize their level of interaction outside the home and to isolate themselves at the first symptoms of influenza.
- Advise individuals to stay home when ill.
- Provide infection control guidance for household caregivers taking into account relevant WHO guidance.

Recovery activities to be considered

Based on national/local risk assessments, resources and needs:

- As needed, provide psychosocial services to facilitate individual and community-level recovery.

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Annexes

Annex 1. Guidance revision process

The content of this WHO guidance document, *Pandemic influenza risk management*, has been largely based on *Pandemic influenza preparedness and response: a WHO guidance document*, which was published in 2009. The draft content was reviewed by a WHO Internal Steering Committee, comprising technical experts in influenza, multisectoral collaboration for influenza, risk management, event management, communications, influenza at the human–animal ecosystem interface, antivirals, vaccine research and emergency risk management for health, and assessed for relevance and continued applicability to the risk management of pandemic influenza.

Throughout the revision process, the Internal Steering Committee met four times, with significant e-mail correspondence between meetings. Members of the Internal Steering Committee were invited to provide inputs and updates to relevant sections of the document, according to their expertise.

During 11–12 April 2013, an external Peer Review Group meeting was convened to: (1) consider the revised guidance in relation to emergency risk management for health as well as recommendations from the report of the Review Committee on the Functioning of the International Health Regulations (2005) in relation to Pandemic (H1N1) 2009; and (2) provide feedback, comment and input on the draft guidance.

The peer reviewers' comments were noted, and taken into account in a revised draft of the document. The revised draft was sent to the peer reviewers for acknowledgement of the changes requested and inclusion of additional comments, then finalized for Member State engagement.

Declaration of interests

All external peer reviewers acknowledged herein completed and submitted a WHO Declaration of Interest for WHO Experts form. These declarations of interest were assessed and presented to the Peer Review Group meeting. The Chair of the Peer Review Group formally declared no interests. Of the 16 other external peer reviewers who participated in the review of this guidance document, three declared interests. The peer reviewers with declared interests are listed below, together with a short description of the interests concerned.

Peer reviewers with declared interests

Dr Nick Phin

At the time of the Peer Review Group meeting, Dr Nick Phin was about to undertake a retrospective review of clinical and safety data on patients given aqueous zanamivir during the influenza A(H1N1) 2009 pandemic and the 2010–2011 influenza season as part of the compassionate use programme. The research is being led by Public Health England with some sponsorship from GlaxoSmithKline. This sponsorship consists of £25 000 for a short-term researcher post and £25 000 to reimburse the resources used by hospitals to identify and provide the data. As the review is retrospective and there is no specific information on the use of medicines included in this project, no conflict of interest was determined.

Professor Lone Simonsen

In 2011, Professor Simonsen provided consulting services in the area of influenza and respiratory syncytial virus disease burden modelling and methodological issues with observational study designs to GlaxoSmithKline and BioCryst for US$ 10 000 and in 2012 received less than US$ 5000 to participate in expert panels for GlaxoSmithKline, Merck, AstraZeneca and Novartis. As no specific information on burden modelling is included in this guidance, no conflict of interest was determined.

Dr Benjamin Cowling

Dr Benjamin Cowling was paid US$ 2000 for consultation work on influenza treatment and prevention strategies for Crucell NV in 2012. He was also the principal investigator and account-holder for an investigator-initiated trial of influenza vaccine supported by significant funding from MedImmune in 2009–2010. This was vaccine-specific research. As there are some references to vaccines and vaccine policy throughout this guidance, it was felt this research could constitute a conflict of interest and therefore Dr Cowling was excluded from discussions on vaccine-related issues.

Annex 2. Planning assumptions

Planning for a future influenza pandemic is challenging in part because important features of the next pandemic are not known. In this situation, assumptions relating to the epidemiology of influenza are needed to make decisions in public health planning, as well as estimating required resources.

This Annex provides some planning assumptions to be considered by national authorities in developing a pandemic influenza risk management strategy. These assumptions are based on information known at the time of publication about seasonal influenza, avian influenza and past influenza pandemics. These data should not be taken as predictive of features of the next pandemic. The characteristics and impacts of past pandemics have varied between and within countries. These differences are most likely attributable to both the characteristics of the pandemic virus and the local ability to respond to the disease.

It is not the intention of this Annex to provide a comprehensive review of the epidemiology of influenza. However, it will be updated as new scientific data become available that significantly change these assumptions. Key references are provided for readers to review the existing literature.

A2.1 Modes of transmission

Assumptions

Modes of virus transmission of pandemic influenza are expected to be similar to those of seasonal influenza: via the large droplet or contact (either direct or indirect) route, with a contribution by particle airborne route, or a combination of both.

The relative contribution and clinical importance of potentially different modes of transmission of influenza are unknown. However, epidemiological patterns suggest that the spread of the virus is mostly through close contact via the droplet or contact route.

Implications

- To decrease viral transmission, good hand hygiene, isolation of ill people and the use of personal protective equipment are important measures when caring for people with influenza.
- An airborne precaution room is not indicated for routine care. However, health-care workers should wear eye protection, a gown, clean non-sterile gloves and particulate respirators during aerosol-generating procedures.

Scientific basis

- Droplet and contact transmission appear to be major routes of transmission for seasonal influenza (Brankston G et al, 2007; Bridges CB et al, 2003).
- However, data are insufficient to determine the relative importance of the different modes of transmission. In addition, there is lack of standardization and consensus about the technical definition (i.e. particle size) of an aerosol versus a droplet (Tellier R, 2006; Lemieux C et al, 2007, Lindsley W, 2012).
- Relative heat and humidity affect the efficiency of transmission of influenza via aerosol. (Hanley BP, 2010). Some have reported the lack of aerosol transmission at 30 °C, while transmission via the contact route was equally efficient at 30 °C and 20 °C. (Lowen AC et al, 2007; Lowen AC et al, 2008).
- Certain procedures performed in health-care settings can create aerosols. Some of these procedures have been associated with a significant increase in the risk of disease transmission and have been termed “aerosol-generating procedures associated with pathogen trans-

mission" (WHO, 2007). These procedures include intubation, cardiopulmonary resuscitation, bronchoscopy, autopsy and surgery where high-speed devices are used (WHO, 2007).

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A2.2 Incubation period and infectivity of pandemic influenza

Assumptions

- Incubation period: 1–3 days.
- Latent period: 0.5–2 days.
- Duration of infectiousness: about 5 days in adults and possibly longer in children.
- Basic reproduction number (R0): 1.1–2.0.

Implications

- The incubation period and the duration of infectiousness are useful for planning purposes with regard to: length of isolation for cases; development of a definition for contacts of cases; and the length of quarantine for contacts.
- A relatively short incubation period would make it difficult to stop the spread of pandemic influenza by contact tracing and quarantine.
- Viral shedding before symptoms develop would make it difficult to stop the spread of pandemic influenza solely by screening and isolating clinically ill persons.

- Once the pandemic begins, it will be important for countries to undertake surveillance and special studies to assess the incubation period and the duration of infectiousness of the pandemic virus.

Scientific basis

- An early study using Australian maritime statistics suggested that the mean incubation period of the 1918 pandemic influenza was 32.71 hours (1.4 days). (McKendrick and Morison as reviewed by Nishiura, 2007).
- A meta-analysis of 56 volunteer studies (Carrat et al, 2008) found that:
  - an increase in the average total symptoms score was noted by day 1 after inoculation, total scores peaked by day 2 and returned to baseline values by day 8;
  - viral shedding increased sharply between 0.5 and 1 day after challenge and consistently peaked on day 2 (mean generation time 2.5 days) and the average duration of viral shedding was 4.8 days;
  - viral shedding curves and total symptom score curves showed similar shapes, although viral shedding preceded illness by 1 day.
- Longer durations of viral shedding are not rare. As reviewed by Carrat et al, in one study subgroup, five participants (20%) shed influenza B virus 8 days after inoculation, while another study also reported 9 days of shedding for influenza A(H3N2).
- Reasonable estimates of the basic reproduction number (R0): for past pandemic viruses as well as seasonal influenza viruses converge between 1.5 and 2.0 (Ferguson NM et al, 2005; Ferguson NM et al, 2006; Colliza V et al, 2007; Vynnycky E et al, 2007) and for A(H1N1)2009 ranged from 1.1-1-8 (Fraser et al, 2009; Lessler et al, 2010; Opatowski, et al 2011).
- The incubation period of influenza A(H5N1) human cases (7 days or fewer; mostly 2–5 days) appears to be longer than that of seasonal influenza. In clusters in which limited human-to-human transmission has probably occurred, the incubation period appears to be approximately 3–5 days, although in one cluster it was estimated to be 8–9 days (WHO writing committee, 2008).
- Patients with influenza A(H5N1) disease may have detectable viral RNA in the respiratory tract for up to three weeks; data, however, are limited. (Reviewed by WHO writing committee, 2008; and Gambotto et al, 2007).

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A2.3 Symptom development and clinical attack rate

Assumptions

- About two-thirds of people with pandemic influenza are expected to develop clinical symptoms.
- Uncomplicated clinical symptoms of pandemic influenza are expected to be similar to those of seasonal influenza: respiratory symptoms; fever and abrupt onset of muscle ache and headache or backache.
- Averaged overall (across all age groups), population clinical attack rates are expected to be 25% to 45%.

Implications

- Existing clinical criteria for influenza-like illness can serve as the basis for pandemic disease surveillance. However, countries are encouraged to monitor closely the evolution of clinical characteristics of pandemic influenza and to facilitate refinement of a clinical case definition.
- Since clinical presentations of influenza are usually nonspecific, pandemic surveillance should be supported by laboratory diagnosis. This step is critical to confirm and describe comprehensively the first cases in each country.
- Because the number of ill persons may overwhelm existing health-care capacities, countries should plan for rapid scale up of health-care capacity and prioritization of limited resources.
- Wide variations in clinical attack rates among different age groups and localities have been observed with previous pandemics. Countries are encouraged to estimate clinical attack rates based on their own data and experiences.

Scientific basis

- A pooled analysis of 522 persons who were voluntarily infected with influenza reported the proportion of symptomatic infection (any symptoms) as 66.9% (95% CI: 58.3, 74.5). No significant differences were noted according to the virus type or the initial infectious dose (Carrat et al, 2008).
- A modelling study using 1957 pandemic data from the United Kingdom estimated that 60–65% of infected individuals experienced clinical symptoms (Vynnycky E et al, 2008).
- An analysis of an influenza outbreak experience in an isolated island, Tristin da Cunha, in 1971 suggested that almost all susceptible persons developed symptomatic illness (Mathews JD et al, 2007).
- During the 1918 pandemic in the United States of America, influenza-like illness rates averaged 28%, with a low of 15% and a high of 50% (Frost WH, 1919). These data were derived from house-to-house surveys.

- In one report, age-specific serological attack rates for the 1957 pandemic averaged 40%, with a low of 5% and a high of 70%. In contrast, a 20% serological attack rate was reported for the 1968 pandemic (Stuart-Harris CH, 1970).
- A retrospective questionnaire survey from one USA city revealed the overall clinical attack rate during the 1968 pandemic was 39%; and it was similar among all age groups (Davis LE et al, 1970). Another serological survey found that about 25% (range of 21% to 27%) of children tested positive for antibodies to the influenza strain that circulated in 1968 (Chin J et al, 1974).
- Clinical attack rates calculated from an estimated basic reproduction number (R0): between 1.5 and 2.0; range from approximately 25% to 45% (Ferguson NM et al, 2005; Ferguson NM et al, 2006; Germann TC et al, 2006; Colliza V et al, 2007; Halloran ME et al, 2008).
- Clinical attack rates from A(H1N1)pdm 2009 were estimated to be 7% to 15% (Fraser C et al, 2009) with a secondary attack rate from 7–13% (Cauchemez S et al, 2009, WHO writing group 2009).
- Gastrointestinal symptoms have been observed among patients with influenza A(H5N1) but have varied by clades (WHO writing committee, 2008).

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A2.4 Dynamics and impact of a pandemic

Assumptions

- An influenza pandemic can begin at any time of the year and in any place in the world; it is expected to spread to the rest of the world within several weeks or months.
- The duration of a pandemic wave is expected to be from several weeks to a few months but will likely vary from country to country; within a single country, variations may be seen by community.
- Most communities are expected to experience multiple waves of different magnitudes of a pandemic.
- Increased hospitalizations, excess mortality and secondary complications are expected to vary widely among countries and communities. Vulnerable populations are expected to be affected more severely.
- Workplace absenteeism is expected to be higher than the estimated clinical attack rate.

Implications

- Each county should develop and strengthen its capacity to detect the early emergence of a potential pandemic event and to respond rapidly.
- Countries should guide their local governments and communities to develop their own pandemic influenza risk management plans.
- Actions during the post-peak periods between pandemic waves should be considered in overall pandemic risk management plans.
- Countries are encouraged to further estimate and prepare health-care needs based on their own resources and experiences, with particular concern to vulnerable populations.
- In a series of waves as experienced with 20th century pandemics, an early wave may lead to depletion of stocks of consumables, such as personal protective equipment and pharmaceuticals, before later waves.
- Countries are encouraged to further estimate excess workplace absenteeism during a pandemic based on their own contexts and to guide all sectors to develop business continuity plans for high and possibly fluctuating levels of absenteeism throughout the pandemic.

Scientific basis

- Early reports and later analysis of epidemiological evidence suggest that milder epidemic waves (in Europe in April and May, 1918 and in the USA in the (Northern Hemisphere) Spring of 1918 preceded the most severe pandemic wave in (Northern Hemisphere) Autumn 1918 (Frost WH, 1919; Olson SR et al, 2005).
- A review of data from the North Denmark region indicated three waves with the third in December 2010-January 2011 being the most severe (Orsted et al, 2013)
- An influenza virus A(H1N1) resistant to oseltamivir was first reported from Norway in January 2008 and then spread throughout much of the Northern Hemisphere during the next two months (WHO, 2008). It was subsequently detected in the Southern Hemisphere during the influenza season of 2008.
- Excess mortality data from 1918–1920 show that population mortality varied more than 30-fold across countries (Murray CL et al, 2006).
- Variation among countries ranged from a low of 0.20% (Denmark) to a high of 4.39% (India).

- Variation within countries ranged from 2.12% to 7.82% in India and from 0.25% to 1.00% in the USA.
- During the 1918 pandemic in the United States of America, there were marked and consistent differences in morbidity and mortality among persons of different economic status: the lower the economic level, the higher the attack rate. This relationship persisted even after adjustments were made for factors such as race, sex, age and other conditions (Sydenstricker E, 1931).
- A multinational analysis of the 1968 pandemic showed very different epidemic patterns in the six countries studied (Viboud C et al, 2005).
  - In the USA, a large epidemic was observed in 1968–1969, followed by a milder wave in 1969–1970, late in the winter season.
  - In Canada, the two epidemic patterns were similar in amplitude and timing.
  - In other countries (Australia, France, the United Kingdom and Japan), the first epidemic was mild, followed by a much more intense epidemic in the next season.
- A simulation study in the United Kingdom estimated that, overall, about 16% of the workforce is likely to be absent due to school closures during a pandemic. This estimate rises for sectors with a high proportion of female employees, such as health and social care (Sadique MZ et al, 2008).

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Annex 3. Ethical considerations

Preparedness planning for an influenza pandemic involves balancing potentially conflicting individual and community interests (*9*). In emergency situations, the enjoyment of individual human rights and civil liberties may have to be limited in the public interest. However, efforts to protect individual rights should be part of any policy. Measures that limit individual rights and civil liberties must be necessary, reasonable, proportional, equitable, non-discriminatory and in full compliance with national and international laws.

Ethics do not provide a prescribed set of policies; rather, ethical considerations will be shaped by the local context and cultural values. The principles of equity, utility/efficiency, liberty, reciprocity and solidarity are especially helpful in the context of influenza pandemic preparedness planning.

For example, the principle of utility suggests that resources should be used to provide the maximum possible health benefits, often understood as "saving most lives". Utility considerations include the following:

For individual benefit:

- the likelihood that an individual with pandemic influenza disease will experience a medical benefit if provided antiviral or adjuvant treatment;
- the likelihood that an individual at risk of infection will become infected/ill if influenza-specific antiviral prophylaxis is not provided.

For community benefit:

- the likelihood that an infected individual will infect other persons if not given access to antivirals (for treatment or prophylaxis) and infection control measures;
- the overall reduction in disease burden expected to result from the intervention;
- the potential value of giving priority to:
  - essential health-care workers,
  - other workers who provide life-saving services,
  - workers who provide critical services necessary for society to function as normally as possible; such policies should be developed with great care, given the danger that decisions favouring certain categories of workers may be perceived as unfair and undermine public trust.

Another important principle, which may sometimes conflict with utility considerations, is equity. Considerations of equity in use of antivirals may lead to giving priority to:

- the worst-off (in terms of severity of illness);
- vulnerable and disabled populations;
- uninfected persons who are at high risk of developing severe complications and death if they become infected.

Regardless of the criteria selected to govern the allocation of therapeutic and preventive measures, certain basic elements will be important in all plans; for example, those which:

- Facilitate access to the highest level of treatment possible given available resources, with careful attention to the needs of all populations.
- Provide health-care workers with clear and transparent screening and treatment protocols in line with the latest guidance from WHO or relevant national health authorities.

- Incorporate mechanisms that:
  - ensure that the guidelines and protocols are followed;
  - enable health-care workers to inform health authorities when clinical experience suggests the need for revisions of protocols;
  - enable health-care workers to (1) take part in the process of updating guidelines and protocols as the pandemic progresses, and (2) propose prioritization criteria for maintenance of a functioning health-care system in a crisis situation;
  - ensure a fair balance of treatment for pandemic influenza patients and patients with other serious conditions;
  - enable prioritization protocols for non-influenza patients and their access to the general health-care infrastructure;
  - identify the pandemic influenza patients who will receive hospital-based versus home-based care and criteria for early discharge (potentially even if still infectious).

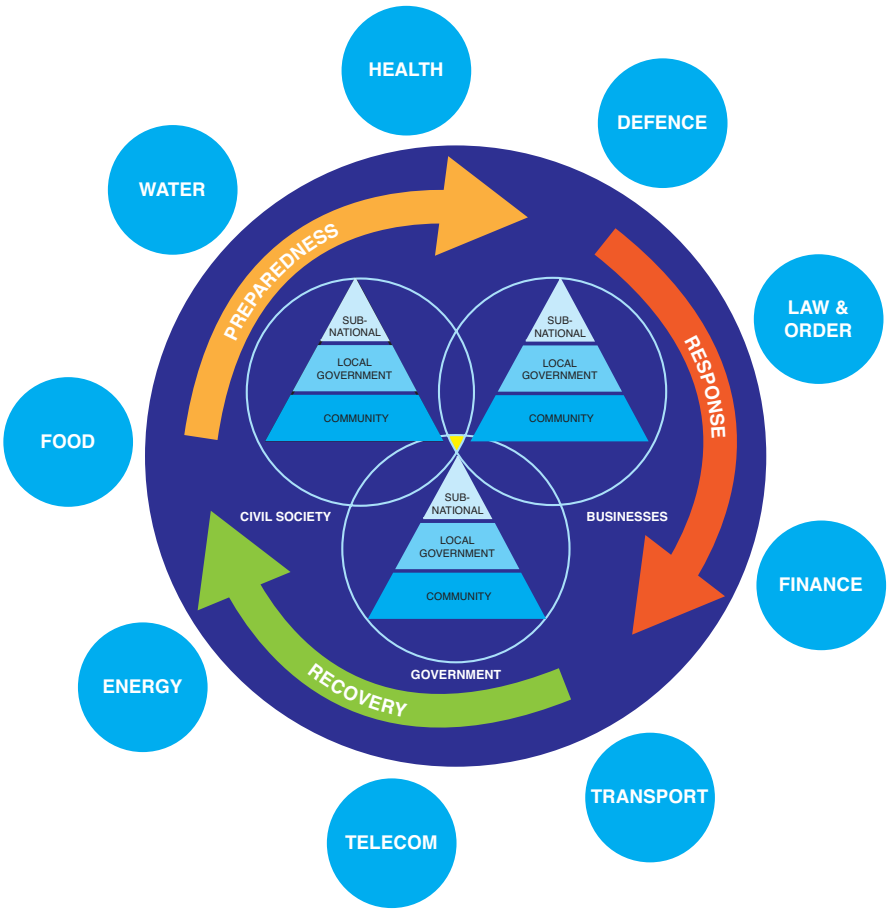
As part of pandemic influenza planning, policy-makers are encouraged to establish a fair process for setting priorities and promoting equitable access to services and supplies that: (1) involves civil society and other major stakeholders in the decision-making process so that decisions about the criteria to be used in allocating scarce resources are made in an open, transparent and inclusive manner and (2) incorporates clear, pre-established mechanisms for revising decisions based on new evidence when appropriate. An open, trusted process will strengthen solidarity and enhance the whole-of-society approach to pandemic risk management.

Annex 4. Whole-of-society approach

An influenza pandemic will test the resilience of nations, businesses, and communities, depending on their capacity to respond. No single agency or organization can prepare for a pandemic on its own. Inadequate or uncoordinated preparedness of interdependent public and private organizations will reduce the ability of the health sector to respond during a pandemic. A comprehensive approach to pandemic risk management is required.

As illustrated in F**igure 4**, the whole-of-society approach encompasses three major groups in society – governments, business and civil society – at the global, national, subnational, local and community levels. The nine circles around the disaster management continuum of mitigation, prevention, preparedness, response, and recovery represent nine key essential areas: health, defence, law and order, finance, transport, telecommunications, energy, food and water.

Figure 4. Whole-of-society approach (*46*)



All sectors of society should be involved in pandemic risk management. A concerted and collaborative effort is required by government ministries, businesses and civil society to sustain essential infrastructure and mitigate impacts of pandemic influenza on health, the economy and the functioning of society.

All levels – global, national, subnational, local and community – should prepare for a pandemic. The global and national levels should provide leadership and strategic planning while the local level should prepare to take specific actions. All organizations should incorporate pandemic preparedness into existing crisis and continuity management systems. As the impact and

duration of pandemic waves are unpredictable, and may continue for multiple seasons, local communities should develop flexible plans to support the full spectrum of their potential needs.

A4.1 Role of government

In national pandemic influenza risk management, the government is the natural leader for overall pandemic coordination and communication efforts. The national government should help other public and private agencies and organizations by providing guidance, planning assumptions and making appropriate modifications to the laws or regulations at all levels and sectors to enable appropriate pandemic response. These efforts are supported by WHO and other United Nations Organizations under the IHR (2005) (10). As part of their capacity building activities under the IHR (2005), governments globally have been assessing and revising their national legislation and regulations to ensure they can fully comply with their obligations. These activities include intersectoral collaboration and ERMH at all governmental levels.

Leadership should be based on strong political will and engagement with all stakeholders and sectors with good coordination and command and control mechanisms between the Ministry of Health, national public health authorities and non-health sectors. Emergency management roles, responsibilities and mechanisms also need to be clarified, communicated and tested, with particular attention to sustainability of response capacity and decision-making roles (*47*).

Pandemic risk management is a whole-of-government responsibility. All ministries should work with the Ministry of Health within the national coordination system to ensure a consistent approach to preparedness and business continuity planning. Plans that encompass a variety of scenarios should be developed from risk-based assumptions generated by the Ministry of Health and should be tested for compatibility. In addition, pandemic risk management processes need to take place at the national, subnational, local and community levels; central government should stipulate which level is responsible for specified activities. The central government should also provide guidance to local authorities on preparedness planning; conduct training to ensure effective dissemination at all levels; and design and implement exercises to test plans and encourage community mobilization. Throughout the whole of government, roles, responsibilities, designated leads and chains of command should be clearly mapped. Standard operating procedures can help generate common understanding and coordinated implementation (*46*).

All ministries are responsible for ensuring their respective sectors are well prepared to respond to and recover from pandemic influenza; examples of ministry-specific activities are provided below.

- **Ministries of Transportation** should plan to minimize infection risks and staff absences in vital transportation, airports and sea ports, and loading and unloading facilities, to enable continued supply of medicines and food. Mechanisms for communication and education of public transport users should be considered well in advance.
- **Ministries of Finance** should plan to maintain essential cash, credit, banking, payment, international funds transfers, salary, pension and regulation services in the face of significant absenteeism; systemic resilience to pandemic risk should be tested. National-level financial planning for pandemic risk management is also a task for the national emergency committee and the Ministry of Finance and the mechanisms to draw down emergency funding for interventions should be tested prior to a pandemic.
- Ministries of Justice should consider how to maintain all essential legal and administrative operations during a pandemic. Measures should also be considered to minimize the spread of infection in prisons and other institutions under their authority. Plans for infection control and risk reduction in facilities should be tested in conjunction with the Ministry of

Health plans to ensure that messaging is consistent and that public health principles are upheld.

- **Ministries of Defence** should consider which military assets could be released and mobilized in the event of a pandemic, based on Ministry of Health planning assumptions and risk assessment.
- **Ministries of Education** should have a key role in the surveillance and reduction of influenza risk to communities. Surveillance of absenteeism in schools can be used as a proxy indicator of community transmission. Linking of school surveillance systems with the Ministry of Health is therefore vital to ensure that school-based interventions, including closures, are guided by public health principles.
- **Ministries of Energy** should ensure that key providers within the energy sector have well-developed and well-exercised preparedness plans. Alternative plans for energy supplies, in case of major disruptions, should be evaluated.
- **Ministries of Communication** should have the responsibility to ensure that communications channels remain open at times of crises. As the formal partner to the Ministry of Health in disseminating information, the Ministry of Communication should be closely involved in the development of a national communications plan across the government.
- **Ministries of Agriculture and Animal Health** should have a key role in the surveillance and monitoring of non-seasonal influenza viruses and on preparedness, prevention, risk assessment and risk reduction mechanisms to decrease exposure of humans to influenza viruses at the human–animal ecosystem interface.
- In addition to leading the health sector response, **Ministries of Health** should provide planning assumptions and technical input for the development of plans by other sectors, provide public education and other communication messages and provide advice on reducing risk of infection in essential workers.

A4.2 Role of business

In many countries, essential services are provided by a mix of public and private providers. It is therefore vital that, along with public agencies, private essential goods and service providers undertake pandemic risk management activities. At a national level, the business sector should be represented in the national planning committee, to ensure a consistent planning approach and establish formal communication channels.

The continuity of activities by businesses involved in medical supplies and services, e.g. manufacturers, distributors and providers, is critical to pandemic risk management. Other business sectors also have important roles. For example, human resource surveillance systems in larger businesses to monitor absenteeism can provide valuable information for national risk assessment and the retail sector can use strategies to reduce population density in shopping areas. Businesses have an obligation to protect their employees during any health emergency; the provision of accurate and timely communication messages developed on the national communication plan, personal protective equipment and training is encouraged.

A4.3 Role of civil society

In many countries, national and international civil society and community-based organizations will have a key role in providing community-based services to meet the needs of vulnerable populations. It is therefore critical that these organizations have planned how to maintain or expand their essential services during a pandemic. In addition, community-based organizations can translate scientific and government messages and recommendations, which otherwise may be met with mistrust or scepticism by parts of society. Community leaders can build public confidence, disseminate information and identify people at risk. Governments should

therefore involve civil society and local communities in developing pandemic risk management plans. Governments should also work with local and international humanitarian agencies and organizations to identify how the basic needs of vulnerable populations will be met in a pandemic. The adoption of this whole-of-society approach will clarify responsibilities, identify gaps and avoid duplication in planning and implementation.

Throughout the UN system, agencies, funds, programmes and partners support pandemic risk management efforts, in particular assisting countries and promoting multisectoral and whole-of-society approaches, facilitating and enhancing regional and global synergies and establishing norms for effective work (48). The overarching objectives through which this work has been pursued are captured in the UN System and Partners Consolidated Action Plan for Animal and Human Influenza, which identifies specific outputs and activities of the UN system and partners under seven strategic objectives, namely: animal health and biosecurity; sustaining livelihoods; human health; coordination of national, regional and international stakeholders; communication: public information and supporting behaviour change; continuity under pandemic conditions; and humanitarian common services support (49). The UN system also works to ensure continuity of its essential operations during pandemics and to maintain staff health and safety to ensure a timely, consistent and coordinated response across the UN system to a possible global threat (*50*).

A4.4 Critical interdependencies among essential services

Although there are variations between countries, key essential services are: health, defence, law and order, finance, transport, telecommunications, energy, food and water (**Figure 4**). Public and private providers of these essential services are interdependent and rely on the goods and services of other sectors in order to sustain their operations. Pandemic plans should take into account potential failures generated by interdependencies. These include failures of individual businesses or small numbers of businesses representing the sole providers of an essential good or service. Interdependencies need to be identified by each individual essential service provider. Issues that need to be clarified in the process of identifying interdependencies include:

- critical goods and services necessary for the organization to provide its essential service/s;
- key interdependencies for each critical good or service;
- the impact of the loss or reduction of any of the critical goods or services to the customers/beneficiaries;
- critical employee groups;
- the impact of the loss or reduced availability of critical employee groups; and
- likely points of failure.

The health-care sector always faces especially severe challenges during a pandemic. Health-care institutions depend on goods and services that are delivered by the following sectors:

- transport for the movement of supplies, personnel and patients;
- telecommunications to support patient care, provide teletriage and maintain business processing;
- energy to power facility, clinical and security systems;
- water for health-care facilities, pharmaceutical operations and sanitation services;
- pharmaceuticals, including consumables, for treatment of patients; and
- finance to ensure the supply chain.

Flexible business continuity plans should be developed for multiple scenarios ranging from some delays/interruptions to significant interruptions to essential services, with corresponding action plans.

Annex 5. Business continuity planning

Business continuity plans, which document business continuity management processes, are at the heart of preparing all levels and groups of society for an emergency; pandemic risk management should be an integral part of any establishment's business continuity management. Business continuity plans should be based on risk assessment of the potential effects of a pandemic on the ability to maintain or expand operations. The risk assessment should include consideration of vital components outside the specific organization, such as the resilience of supply chains for essential goods and services. The plans can be used to manage business interruptions, including significant absences of staff or disruption of supplies.

Business continuity plans should be based on explicit assumptions that characterize the parameters of a pandemic and its potential impacts. Public health authorities should communicate planning assumptions and guidance to other sectors of society.

Regardless of the type of the organization, business continuity plans should include the following actions :

- Identify the critical functions that need to be sustained.
- Identify the personnel, supplies and equipment vital to maintain critical functions.
- Consider how to deal with staff absenteeism to minimize its impact on critical functions.
- Provide clear command structures, delegations of authority and orders of succession.
- Assess the need to stockpile strategic reserves of supplies, material and equipment.
- Identify units, departments or services that could be downsized or closed.
- Assign and train alternative staff for critical posts.
- Establish guidelines for priority of access to essential services.
- Train staff in workplace infection prevention and control and communicate essential safety messages.
- Consider and test ways of reducing social mixing (e.g. telecommuting or working from home and reducing the number of physical meetings and travel).
- Consider the need for family and childcare support for essential workers.
- Consider the need for psychosocial support services to help workers to remain effective.
- Consider and plan for the recovery phase.
-

Annex 6. Representative parameters for core severity indicators

Indicator	Representative parameters
Transmissibility	**From initial investigations** • Number of symptomatic cases of influenza/influenza-like illness per week • Basic reproduction number (R0): the average number of secondary cases generated from one case at the start of the epidemic • Generation time: the mean delay between the time of infection of an index case and the times of infection of secondary cases infected by the index case • Serial interval: the average length of time between symptom onset of individual cases and the persons they infect • Secondary attack rate: the proportion of individuals exposed to a known case who become infected, e.g. in a household where a case is discovered • Clinical attack rate (CAR): the proportion of the population that is symptomatically infected in a given time period. CAR is relatively simple to measure since it does not rely on detection of asymptomatic individuals. CARs can be calculated for different age groups, different settings (e.g. school, workplace) and different risk groups (e.g. pregnant women) • Spatial distribution of cases: mapping of countries/regions in which the virus has been detected in a given time period **From later investigations** • Attack rate: the proportion of the population that become infected in a given time period (e.g. as obtained from population serologic studies) • Incidence proportion: the proportion of people who develop new disease during a specified time period • Prevalence: the proportion of people who have disease at a specific time • Mode of transmission, particularly if new modes or previously uncommon modes of transmission (e.g. faecal–oral) are important
Seriousness of disease	**From initial investigations: molecular** • Sensitivity to available antiviral medicines • Presence of genetic markers that have been associated with increased risk of severe disease • Pre-existing immunity in the population, as measured by the level of cross-reactive antibodies **From initial investigations: clinical** • Case-fatality ratio (CFR): the proportion of symptomatic cases that die. Estimations of CFR are particularly difficult at the early stages of a pandemic. Since reliable case-fatality ratios will only be available in later stages of a pandemic, other parameters that may be of use are: — the proportion of cases of pneumonia that are influenza positive from sentinel surveillance that uses a representative sampling system — the ratio of hospital admissions and deaths attributed to respiratory causes to total admissions at the sentinel site — the proportion of hospital admissions attributed to respiratory causes that require mechanical ventilation or die — the proportion of influenza admissions, intensive-care admissions and deaths with pre-existing medical conditions **From later investigations** • Number of deaths attributed to influenza • Crude disease-associated mortality rate: the number of persons in a given population who die of the illness, expressed in terms of confirmed or suspected cases • The proportional distribution of cases by clinical illness (i.e. the proportions of cases that are asymptomatic/have mild illness/severe illness/die – the “clinical severity pyramid”) • The number of cases of influenza-associated pneumonia and death compared with previous seasons or pandemic events based on comparisons with historical surveillance data

Indicator	Representative parameters
Impact	**From initial investigations** • Daily hospitalization rate: the number of persons in a given population who are hospitalized each day, expressed in terms of confirmed or suspected cases • The proportion of emergency department visits attributed to pandemic influenza • The proportion of emergency department visits that require hospitalization • The proportion of hospitalized cases that require admission to an intensive-care unit or require mechanical ventilation • The proportion of all hospital beds occupied by patients with pandemic influenza • The percentage of overall laboratory capacity directed to influenza testing **Potential societal impact parameters from other sectors** • Interruption of critical infrastructure and services • Work and school absenteeism • State of tourism • Sales of core capital (privately held land, livestock) • Gross Domestic Product • Border, travel and trade actions by countries • Nature of public perception

Annex 7. Containment measures

Before the presence of human infection with a new influenza subtype is identified, the clinical syndrome associated with a new influenza subtype is likely to be similar to that caused by currently circulating seasonal viruses. It will therefore be very difficult to recognize an emerging pandemic sufficiently early to achieve containment at source, given current capacities for detection and intervention (51). Evidence supporting containment at source is extremely limited, with theoretical evidence only. Modelling studies suggest that containment may be possible in certain near-ideal scenarios characterized by low to moderate transmissibility (basic reproduction number, R_0 ≤1.7); very early detection of initial cluster/outbreak (within 15–21 days); a non-urban pandemic epicentre with limited size (*52*), density and mobility; access to well-trained response workers within a highly organized response infrastructure; a short period of communicability and low rate of asymptomatic illness; and antiviral drug susceptibility.

However, even in these near-ideal situations, it is unlikely that this approach would be feasible given the large amount of resources (antiviral drugs, geographical cordon, health-care personnel) that would need to be mobilized (53). The data from theoretical modelling studies are based on mass use of neuraminidase inhibitors within a defined "containment zone" coupled with movement restrictions (geographical cordon) and targeted at a population of 500 000 people. Moreover, the experience in 2009 was that obtaining initial data on the R0, communicability and rate of asymptomatic illness associated with influenza A(H1N1)pdm09 was challenging, thus data in a future pandemic would be unlikely to be available within the timescale that would make this approach feasible.

Nevertheless, measures that have been associated with containment such as social distancing, hand/respiratory hygiene and judicious use of antiviral drugs may be effective in mitigating the impact of outbreaks of a new influenza subtype in individual countries. These measures are most likely to be successful and are better supported by data demonstrating effectiveness when implemented in specific local (smaller scale) circumstances, e.g. households and closed or semi-closed institutions. Although there is no evidence of any wider population-level containment effect, these measures may reduce the spread and overall impact of the pandemic and could be considered as part of a country's national preparedness plan, depending on available resources.

Court File No.: CV-21-00013361-0000

ONTARIO
SUPERIOR COURT OF JUSTICE

B E T W E E N :

WELLANDPORT UNITED REFORMED CHURCH

Applicant

- and -

THE ATTORNEY GENERAL OF ONTARIO

Respondent

AFFIDAVIT OF DR. JOEL KETTNER

I, JOEL KETTNER, of the City of Winnipeg in, Province of Manitoba, **MAKE OATH AND SAY:**

BACKGROUND

1) I am an epidemiologist and former Chief Medical Officer of Health of Manitoba.

2) I have been informed by counsel and I understand and affirm my duty to this court as an expert witness. I have completed Form 53 under the *Courts of Justice Act*, which is attached to this Affidavit.

3) I have been asked by counsel for the Applicants to addresses the following questions.

   a) What is the ordinary or absolute risk for exposure to and transmission of SARS-CoV-2 in a church service that is near full seated capacity (leaving aside church programs and activities outside of the worship service in the church sanctuary)?

   b) What is the comparative risk between an ordinary church service with no safety plan (social distancing, self-screening, masks, hygiene measures, etc.) and a church service

that follows public health measures including distancing between households, but does not otherwise implement a capacity limit?

c) What is the comparative risk between a church that follows public health advice and gathers at 30% of seated capacity and the same church gathering at 15% of seated capacity?

d) What is the comparative risk between a church gathering of 10 people and a church gathering at 15% of seated capacity (in either case, following public health measures)?

e) What is the comparative risk between attending a church gathering under the circumstances described in 2-4, above, and doing other activities permitted under Ontario Regulation 82/20 (Rules for Areas in Stage 1)? Assume both have a written safety plan as described in Schedule 1, section 5 of Regulation 82/20.

QUALIFICATIONS

4) I currently hold a position as geographic full-time associate professor in the Department of Community Health Sciences at the College of Medicine at the University of Manitoba. I hold Canadian Royal College Fellowship certifications in Public Health and Preventive Medicine as we as General Surgery. I obtained a Master of Science in Epidemiology from the London School of Hygiene and Tropical Medicine at the University of London in the United Kingdom.

5) During my time as Manitoba's Chief Medical Officer of Health, I led the Province's public health responses to several outbreaks including the SARS Coronavirus-1 and the H1N1 pandemic influenza.

6) Following the SARS-01 outbreak, I was part of the Canadian delegation to the World Health Organization ("WHO") special meeting in Geneva to develop the fourth edition of the International Health Regulation which introduced the concept, definition and expectations of countries during a public health emergency of international concern.

7) I played a leading role at the WHO Pan American Health Organization special H1N1 meeting in Washington D.C. In addition to a plenary presentation describing Manitoba's

experience with the first wave of H1N1, I led a working group to develop guidance for the prevention and treatment of H1N1 in low resourced parts of the world. At that same meeting, I collaborated as an author of the first comprehensive review article of H1N1 influenza published in the New England Journal of Medicine.

8) Following my tenure as Chief Medical Officer of Health of Manitoba, I have undertaken a number of relevant roles and responsibilities including that of scientific director of the Public Health Agency of Canada's National Collaborating Centre for Infectious Diseases, medical director of the International Centre for Infectious Diseases in Winnipeg, board director of the Canadian Public Health Association, and president of the Public Health Physicians of Canada.

9) Specific relevant roles at the University of Manitoba have included director of the Medical College undergraduate program in Community Health Sciences and director of the Master in Public Health program. I continue to teach public health and epidemiology at the undergraduate, graduate and pos-graduate levels. During this current COVID-19 pandemic, I have been active in organizing learning events and providing expert opinion and dialogue in a variety of consultative, academic and public platforms.

10) A copy of my curriculum vitae is attached at **Exhibit "A"**.

OPINION

11) The answers to these questions are of fundamental importance. This is because the starting point for all public health decisions, especially about the need for emergency response and powers, is risk assessment. Estimates of the magnitude of a public health threat and the distribution of its impacts enable the determination of priorities and rational considerations of intervention options. It is incumbent on public health decision-makers to optimize the balance of benefits and harms of their strategies and to be guided by public health perspective and ethics. The public health perspective is population-based.

12) The public health perspective considers all causes and all consequences of all diseases and injuries and should never be overly focused on just one disease at the expense of others. The public health perspective considers equity and fairness, always with the goal of reducing

disparities of health amongst communities. To achieve this requires partnering with others to establish policies that reduce the unequal and unfair distribution of social, economic, educational, and other determinants of health. The public health perspective requires the least intrusive and harmful means necessary to achieve optimal benefit. It is incumbent upon public health government officials to demonstrate transparently that any restrictions of autonomy are minimal and are proportionate to the severity of the threat. That is why risk assessment of the threat is the starting point of effective and ethical public health process.

13) This bears repeating with other words. To meet these expectations, public health officials and their governments are required to show that the severity of a threat has justified the use of restrictive interventions; they are required to show how the effectiveness and benefits of the interventions will sufficiently outweigh the harms; and that there are no alternative strategies that would be more effective, less harmful, and/or less restrictive. Perhaps most relevant, public health actions should not be equal ("one size fits all") for every geographic area or community, for every type of setting, for every occupation, or for every person regardless of age, health condition, or other risk factors.

Best Practices regarding public health emergencies

14) Section 7.0.1 (3) of the *Emergency Management and Civil Protection Act* ("the Act") states that an emergency can be declared only if the Lieutenant Governor in Council or the Premier is of the opinion that there is a "danger of major proportions that could result in serious harm" and one of the following exists:
    a) Resources normally available to the Government "cannot be relied upon without the risk of serious delay".
    b) The resources normally available to the Government "may be insufficiently effective to address the emergency".
    c) "It is not possible without the risk of serious delay to ascertain" whether the resources normally available to Government can be relied upon.

15) In public health emergencies, premiers and other elected leaders look to their senior public health officials – including their chief medical officer of health or chief public health officer - to provide advice regarding the level of threat and the need for emergency powers. The

starting point for a decision of such consequence is a comprehensive and reasonable risk assessment. In a public health emergency, the advice from public health professionals is expected to be based on valid and reliable data, relevant information, objective scientific evidence, best estimates, and critical reasoning.

16) The Act does not specify what information and advice will be used by the premier to form their opinion, but general guidance is provided by section 7.0.2. (1):

> The purpose of making orders under this section is to promote the public good by protecting the health, safety and welfare of the people of Ontario in times of declared emergencies in a manner that is subject to the *Canadian Charter of Rights and Freedoms* 2006, c. 13, s. 1 (4).

17) Public health legislation and practice across Canada addresses this issue in various ways, but the principles are similar. Like any medical advice – for an individual or a community – public health leaders are expected to assess the magnitude of the threat and to weigh up the pros and cons of alternative interventions, whether these are preventive or therapeutic.

18) The foundation for all public health advice, actions, and communications is risk assessment. It is not only a starting point; it is an essential part of ongoing surveillance, monitoring, and adjustments to strategies, policies, regulations, and advice.

19) Ontario's *Hazard Identification and Risk Assessment Guidelines (2019)*[1] states:
"The purpose of HIRA is to assess the potential risk of hazards with the capacity to cause a disaster. This helps set priorities for prevention, mitigation, preparedness, response and recovery." The HIRA allows for the assessment of risk based on hazards, exposure, vulnerability, capacity and resilience. The core questions are:

a) What risks can lead to a disaster?
b) What impacts could occur over a range of scenarios?
c) Are there scenarios in which the level of risk is unacceptable or unmanageable?
d) What are the impacts, relative to each hazard?
e) What existing measures prevent or mitigate the risk?

[1] https://www.emergencymanagementontario.ca/english/emcommunity/ProvincialPrograms/HIRA/Guidelines/main.html#StepFour

20) The Guideline specifies several principles and practical approaches to assessing risk, interpreting risk, and using risk assessment to make appropriate and fair decisions with respect to responding to the risk (hazard, threat). The following are excerpts of particular relevance to the facts and opinions of my report.

- The Guideline uses a "whole-of-society" approach to risk.
- Ultimately, how risk is measured is determined by values and assumptions that should be transparent.
- There is no one correct way to express risk. However, a good risk analysis, will be extremely clear about:
    - Its purpose
    - Why particular metrics were chosen, and
    - Limitations of the analysis

21) Regarding the application of risk assessment to emergency management, the Guideline specifies seven ethics:

1. **Transparency:** Emergency Management has a duty to serve the public; including their right to obtain key information that benefits its safety and security.
2. **Professionalism:** A professional obligation to provide the public with competent practice.
3. **Comprehensiveness:** Emergency Management is proactive, includes an all-hazard approach, all 'pillars', and partners from all parts of society.
4. **Risk-based:** Sound risk management principles should be used in assigning priorities.
5. **Respectfulness:** The equal dignity of all people must be respected, along with their customs and culture, and their right to the necessities of life.
6. **Resilience:** Emergency Management aims to strengthen the resiliency of citizens, organizations, communities, systems and society.
7. **Equity:** It is vital to provide appropriate care to all citizens of Ontario, consistent with their needs. Equity ensures a fair distribution of supports and resources.

22) As described in step four of the guidelines section of the Ontario Hazard and Identification Risk Assessment Program[2], considerations of extraordinary public health interventions requires clear descriptions of quantitative estimates of likelihoods (probabilities) of events and the level of severity of the consequences of those events. Epidemiological descriptors to

[2] https://www.emergencymanagementontario.ca/english/emcommunity/ProvincialPrograms/HIRA/Guidelines/main.html

assess the threat of any potential hazard should include specific probabilities – whether in the form of rates, ratios, or proportions –not only crude numbers (numerators without denominators). For effectiveness of interventions, this includes measurements and estimations of quantifiable outcomes, including benefits and harms. These estimates are fundamental to the process of determining that public health interventions are proportionate to the threat and are reasonably necessary.

23) This report focuses on risk assessment, threat assessment, and demonstrates how basic surveillance and basic epidemiology should be used to estimate quantitatively the absolute and relative levels of the risk and consequences of transmission of COVID-19 in the settings of churches and other places of worship. To demonstrably justify restrictions of activities in churches and other settings, it is incumbent upon governments and public health leaders to obtain, analyze, and use relevant data reasonably and transparently.

24) A quantitative assessment of the threat posed by church services could not be found on Public Health Ontario websites. The assessments in this report were based on information publicly available on websites of Public Health Ontario, Niagara Health Region, Health Canada, and the World Health Organization.

Framework to describe the sequence and to estimate the probabilities of transmission and outcomes for COVID-19 in any setting, including factors for the probability of occurrence of each stage.

25) Requirement #1. A person attending church is infectious on the day of attendance. For purposes of the following explanation, an infected person at church will be described as a "case". (Technically, they would not be considered or counted as a case until they have a positive PCR test for SARS-CoV-2.)
    a) The probability of requirement #1 is a function of the incidence of the disease in the community and the average duration of being infectious.
        i) Note that this probability is usually estimated using reported cases diagnosed by a positive PCR test and does not include infections not identified as cases.
        ii) The degree of infectiousness – from highest to lowest - is a function of the following states.
            (1) During symptoms (symptomatic)

(2) Just before symptoms (pre-symptomatic)

(3) Infections in which no symptoms occur (asymptomatic)

b) Because of the variations of degree of infectious between these three states, the probability of each of these three states should be considered separately.

26) Requirement #2. There is a high-risk exposure between the infected person and an uninfected contact.

a. Classification of exposures as high-risk or low-risk is primarily determined by the three considerations:

i. closeness of the contact to the case,

ii. duration of the contact, and

iii. barriers between the case and the contact.

27) Requirement #3. Transmission has occurred. Contact becomes infected and will be identified as a case after a positive PCR test.

28) Outcomes of infections resulting from transmission (requirement #3): a case may have no symptoms, mild symptoms or severe symptoms. The probability of severe illness or death is a function of many factors including

a) Age (severe illness correlates with increasing age, especially over the age of 70).

b) Pre-existing serious health conditions

i) Immune system dysfunction (e.g. malignancy, medications)

ii) Organ dysfunction (e.g. chronic lung or heart disease)

iii) Neuromuscular dysfunction (e.g. multiple sclerosis)

iv) Cognitive dysfunction (e.g. dementia)

v) Metabolic disorders (diabetes, severe obesity)

c) Living setting, social and economic conditions (e.g. poverty, congregate living arrangements)

d) Access to care

e) Health care directive (e.g. comfort care only, no life-prolonging treatment)

What is the ordinary or absolute risk for exposure to and transmission of SARS-CoV-2 in a church service that is near full seated capacity (leaving aside church programs or activities outside of the worship in the church sanctuary)?

29) The framework described above is used to estimate the answer to this question.

Incidence rate of new cases

30) There are several options for selecting the appropriate population and period to estimate the incidence rate that would most apply to the attendees of a specific church. The following compares the incidence rates between different geographic boundaries and time periods for the of relevance to Wellandport United Church.

Niagara region

31) The population of the Niagara region as of the last (2016) census was 447,888.[3]

32) The total accumulated COVID-19 cases from March 14, 2020 until April 29, 2021 was 13,704.[4]

33) The incidence rate of new cases since March 14, 2020 was 13,704/447,888 = 3.1 cases per 100 people per 380 days = 1 new case per 12,420 persons per day.

34) The total cases from January 1, 2021 to April 29, 2021 = 9,760[5]

35) The incidence rate of new cases from January 1, 2021 to April 29, 2021 = 9760/447,888 = 2.2 cases per 100 people per 119 days = one new case per 5461 persons per day. This incidence rate in 2021 is about twice the incidence rate from March, 2020.

Welland municipality

36) Population of Welland municipality as of the last 2016 census was 52,293.[6]

[3] https://www.niagararegion.ca/about-niagara/statistics/population-and-maps.aspx
[4] https://niagararegion.ca/health/covid-19/statistics/statistics.aspx
[5] https://niagararegion.ca/health/covid-19/statistics/statistics.aspx
[6] https://www.niagararegion.ca/about-niagara/statistics/population-and-maps.aspx

37) Total accumulated COVID-19 cases since March 14, 2020 until April 29, 2021 = 1,853.[7]

38) The incidence rate of new cases since March 14, 2020 until April 29, 2021 = 1,853/52,293 = 3.5 cases per 100 persons per 380 days = 1 new case per 10,857 persons per day.

39) Total cases January 1, 2021 to April 29, 2021 for Welland only were not found. Using the incidence rate from total cumulative cases since March 2020 would probably underestimate the incidence rate of 2021, as shown by the data for the Niagara region. This is because the incidence rate in Niagara in 2021 has been about twice that of the incidence rate since March, 2020. There is no known reason why this comparison would not be similar for Welland municipality.

40) To obtain an estimate of the expected number of Welland cases, assuming a similar ratio as that of the Niagara region, one can pro-rate the Welland total cases by using the Niagara region proportion of total accumulated cases that occurred in 2021 (9760/13704 = 0.71). Using this assumption, it can be estimated that the incidence of new cases in Welland from January 1, 2021 to April 29, 2021 = 0.7*1,853 = 1,297. Based on this pro-ration, the estimated incidence of new cases in Welland from January 1, 2021 – April 29, 2021 = 1,297/52,293 = 2.5 new cases per 100 persons per 119 days = 1 new case per 4,760 persons per day. This is similar to the Niagara region rate for 2021 of one new case per 5,461 per day. At 1 per 4760 new cases per person per day, in a population of 52,293, this reflects an average daily case count of 11. Because it is not know the distribution of attendees from outside the Welland municipality – and to work with more intuitive rounded and estimated numbers – it seems reasonable to use one new case per 5000 per day as an incidence estimate for calculating the estimated prevalence of infectious attendees at church services in the Welland municipality.

[7] https://niagararegion.ca/health/covid-19/statistics/statistics.aspx

Using community incidence rates to estimate transmission risk at church

41) We can use these data to estimate the probability of *requirement #1* in the framework above, namely that a person will be infectious on the day of their church attendance.

42) The first assumption is that the incident rate of COVID-19 for Wellandport Church attenders is similar to others in the municipality of Welland and the region of Niagara.

43) The second assumption is that empirical observations regarding symptom patterns, natural history of COVID-19 infections, infectiousness, and transmission characteristics are similar for Wellandport Church attendees as other people, groups, and places in which they have been studied.

44) In epidemiologic terms, the probability of a church attendee being infectious on the day of attendance is called the point (in time) prevalence. This probability is then multiplied by the number of attendees to determine the best estimate of the number of people that would be infectious at the time of the service. I will use 500 as an estimate of the number of attendees.

45) There are two possible states for a person that is infectious – symptoms or no symptoms. To reiterate from earlier, an infectious person may be pre-symptomatic and is soon to get symptoms or asymptomatic and will never get symptoms. These distinctions are important because in comparison to asymptomatic infections, infectiousness is considered to be about ten times higher in the pre-symptomatic or symptomatic stage in comparison to people who are infected but do not have symptoms. Note that a person cannot know if they are infected by COVID without a test, whether they have symptoms or not.

46) What follows is an analysis of the probabilities of infectiousness and transmission for the three states of symptoms – asymptomatic, pre-symptomatic or symptomatic. Before getting into the details, it may help to provide some perspective.

47) For a symptomatic case, it is reasonable to consider that the significant infectious days are about two days before symptoms and about ten days after symptoms begin. Therefore, for each symptomatic infection, there are two infectious pre-symptom days and 10

infectious symptomatic days. The probability of any one of these days coinciding with a day of attendance at church means that the incidence rate must be multiplied accordingly to estimate the probably of an infectious state on any one day.

48) The duration of infectiousness for asymptomatic infections is difficult to estimate, but it would be reasonable to assume that it is no more than the 10-day period estimated of symptoms.

Case is asymptomatic (never will get symptoms)

49) Estimates of the proportion of infections that are asymptomatic are quite variable as are the duration of infectiousness. The most recent scientific briefing of the World Health Organization[8] estimated the proportion of infections that are asymptomatic at 16%. The same document estimated that "between 0% and 2.2% of people with asymptomatic infection infected anybody else". More recent data are available but these have not resulted in an update to the World Health Organization scientific brief on this subject.

50) Therefore, the probability of a person having an asymptomatic infection on the day of the service can be estimated as (1/5000) *0.16 *10= 1 in 3,000. Even assuming a 1% probability of transmission during a two hour service (rather than throughout the whole period of infectiousness that was assessed in the WHO referenced studies), the frequency of transmissions associated with an asymptomatic infection via a high-risk exposure (prolonged contact, no distancing, no barrier) would be in the order of one per 300,000 persons. In a service attended by 500 people, the probability of a transmitted infection per service is 1/300,000 multiplied by 500 = one in 600 services or about once in every two years.

Case is symptomatic.

51) Public Health Ontario's Synthesis *COVID-19 Overview of the Period of Communicability – What we Know so Far (Feb 8, 2021)* concluded "There are differences in the findings across included studies due to different designs and sample size; however, there were primary epidemiological studies identified that indicated individuals can be infectious up to 3–5 days

[8] https://apps.who.int/iris/bitstream/handle/10665/333114/WHO-2019-nCoV-Sci_Brief-Transmission_modes-2020.3-eng.pdf?sequence=1&isAllowed=y

prior to symptom-onset and epidemiological, live virus and modelling studies that indicated the period of communicability is approximately 8–10 days after symptom-onset, with infectiousness highest just before or after the time of symptom-onset."[9] The most recent scientific briefing of the World Health Organization estimated that between 0.8% - 15.4% of people with symptoms infected anybody else[10]. More recent data are available but these have not resulted in an update to the World Health Organization scientific brief on this subject.

52) Using these estimates of an incidence of 1 per 5000 persons per day, 10 days of symptomatic infectiousness, and 8% probability of transmission (in two hours, rather than the whole period of infectiousness), the probability of transmission at a church service from a symptomatic infectious attendee via a high-risk exposure (prolonged contact, no distancing, no barrier) is estimated at = 1/5000*10*.08 = 1 in 6000. In a service of 500 people, that equates to a 10% probability of one transmission to one person at each service or, equivalently, one transmission from a symptomatic person every 10 services – without public health measures.

Case is pre-symptomatic (period before symptoms begin)

53) The infectious period duration in the pre-symptomatic phase is estimated as 1-3 days by a World Health Organization scientific brief[11] and up to 3-5 days by a Public Health Ontario review[12]. Public Health Ontario uses two days as their guide for case and contact management[13]. *Public Health Ontario's Risk Assessment Approach for COVID-19 Contact Tracing*[14] states "Exposures are only considered to have occurred if the contact was with the case during the case's period of communicability which is generally defined as 2 days (48

[9] https://www.publichealthontario.ca/-/media/documents/ncov/covid-wwksf/2021/03/wwksf-period-of-communicability-overview.pdf?la=en
[10] https://apps.who.int/iris/bitstream/handle/10665/333114/WHO-2019-nCoV-Sci_Brief-Transmission_modes-2020.3-eng.pdf?sequence=1&isAllowed=y
[11] https://apps.who.int/iris/bitstream/handle/10665/333114/WHO-2019-nCoV-Sci_Brief-Transmission_modes-2020.3-eng.pdf?sequence=1&isAllowed=y page 6
[12] https://www.publichealthontario.ca/-/media/documents/ncov/covid-wwksf/2021/03/wwksf-period-of-communicability-overview.pdf?la=en page 11
[13] https://www.publichealthontario.ca/-/media/documents/ncov/main/2020/09/covid-19-contact-tracing-risk-assessment.pdf?la=en
[14] https://www.publichealthontario.ca/-/media/documents/ncov/main/2020/09/covid-19-contact-tracing-risk-assessment.pdf?la=en

hours) before the onset of the case's symptoms." For this reason, a period of two days has been used in estimating the probability of exposure to an infectious pre-symptomatic person attending a service.

54) Given the probability of a new infection as one in 5000 per person per day and using two days as the period of infectiousness in the pre-symptomatic phase, the probability of infectiousness on the day of the service is one in 2500. Using 8% as the probability of transmission in one day (high-risk exposure: close contact without distancing or barrier protection), the probability of transmission would be (1/2500)*.08 = about one in 30,000. In a service of 500 people, the probability of one transmission at any one service is one in 60 (1.7%). In other words, there would be a transmission from a pre-symptomatic case once in every 60 services – in the absence of public health measures. This is equivalent to about one per year.

High-risk exposure to a contact.

55) Public Health Ontario divides exposures into two categories – low risk and high risk. This definition is for operational purposes to guide decisions for contact tracing. Based on this assessment, high risk exposure contacts are directed to self-isolate (i.e. quarantine). Low-risk exposure contacts are advised to self-monitor. Self-monitoring means to "follow guidance on core public health measures recommended for everyone at all times". In other words, the probability of transmission from a low-risk exposure is considered low enough that no additional public health measures are deemed necessary. They are advised to follow the guidelines for everyone.

56) Public Health Ontario describes a number of factors to consider in categorizing the exposure to a case as a low-risk exposure or high-risk exposure, but the essence of the categorizing is based on whether any of the following three conditions have been met:
    a) More than two-meter distancing,
    b) Face-to-face exposure less than 15 minutes, or
    c) Masks worn properly by case and contact.

57) If any one of these three conditions are met, the exposure would – according to a reasonable interpretation of the described protocols of Public Health Ontario - be expected to be classified as low-risk. Inversely, a high-risk exposure would be identified if none of these three conditions were met.[15]

58) The estimates that have been made for the prevalence of an infectious attendee and the probability of transmission (without public health measures in place) would, of course, be much lower in the presence of protective interventions. If adhered to, any exposures would be classified as low-risk rather than high risk. Even in the situation of low-risk exposures to an identified infectious case, public health would not direct contacts to self-isolate or to be tested. They would only be advised to self-monitor and to self-isolate and get tested only if they developed symptoms.

Outcomes of infections resulting from transmission

59) Having estimated the probabilities and frequencies of infection and transmission, the next, and perhaps most important question is about the frequency of serious outcomes.

60) Case may have no symptoms, mild symptoms or severe symptoms. The probability of severe illness or death is a function of many factors including

a) Age (severe illness correlates with increasing age, especially over the age of 70).
b) Pre-existing serious health conditions
    i) Immune system dysfunction (e.g. malignancy, medications)
    ii) Organ dysfunction (e.g. chronic lung or heart disease)
    iii) Neuromuscular dysfunction (e.g. multiple sclerosis)
    iv) Cognitive dysfunction (e.g. dementia)
    v) Metabolic disorders (diabetes, severe obesity)
c) Living setting, social and economic conditions (e.g. poverty, congregate living arrangements)
d) Access to care

[15] https://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/contact_mngmt/management_cases_contacts.pdf

e) Health care directive (e.g. comfort care only, no life-prolonging treatment)

61) Most of these risk factors – other than age and personal care home residents – have not been quantified in sufficient detail for organizations to assess quantitively the personal risks of its members. But they do provide some useful guidance regarding whom should be considered for additional measures of focused protection, including frequency, duration, and other risk reductions as considered appropriate

62) The table below provides some Ontario-specific data on the frequency of hospitalizations and deaths, in relation to numbers of cases, stratified by age groups.

63) The association with age is striking, showing the very low rates of severe illness and death amongst younger adults and children.

Ontario Data, Definitions, and Policies

Ontario COVID Severity Data

64) The following table contains cumulative information of age-specific rates of cases, hospitalization, and deaths[16].

January 15 2020 to April 9, 2021

Age group	Population	Cases	Case rates	Hosp	Pop-hosp rate	Deaths	Pop mort. rate	Case-hosp. rate	Case-fatality	Hosp dth rt
0 to 09	1,518,527	19,308	1.3%	126	0.01%	1	0.0001%	1.3%	0.01%	1%
10 to 19	1,617,937	36,422	2.3%	116	0.01%	1	0.0001%	2.3%	0.00%	1%
20 to 29	2,100,175	78,651	3.7%	512	0.02%	11	0.0005%	3.7%	0.01%	2%
30 to 39	2,056,056	60,125	2.9%	850	0.04%	23	0.0011%	2.9%	0.04%	3%
40 to 49	1,876,585	53,906	2.9%	1299	0.07%	70	0.0037%	2.9%	0.13%	5%
50 to 59	2,060,937	54,802	2.7%	2394	0.12%	253	0.0123%	2.7%	0.46%	11%
60 to 69	1,795,047	34,820	1.9%	3265	0.18%	685	0.0382%	1.9%	1.97%	21%
70 to 79	1,159,898	18,223	1.6%	3772	0.33%	1462	0.1260%	1.6%	8.02%	39%
80 to 89	539,715	14,066	2.6%	3851	0.71%	2727	0.5053%	2.6%	19.39%	71%
90+	139,551	7,932	5.7%	1813	1.30%	2278	1.6324%	5.7%	28.72%	126%
All ages	14,864,428	378,339	2.5%	17,998	0.12%	7511.00	0.0505%	2.5%	1.99%	42%

[16] https://www.publichealthontario.ca/en/data-and-analysis/infectious-disease/covid-19-data-surveillance/covid-19-data-tool?tab=ageSex

65) Average mortality rates for the whole population do not provide as much information as age-stratified or age-specific mortality rates. This is especially true when the deadliness of a disease varies significantly with age or health status. The table shows the trend from youngest age group to the oldest. For example, the COVID population mortality rate for Ontarians over 90 has been about 2% (1 death per 50) per year. Compare this to the mortality rate of 0.04% (one death per 2,500) for Ontarians age 60-69. Stated another way, 2,499 out of 2,500 people in their 60's did not die this past year from COVID-19. Compare this with 49 out of 50 people aged over 90 years.

66) Case-fatality ratios use the same numerator as mortality rates, namely deaths associated with the disease of interest. The denominator, however, for case-fatality ratios, is the number of cases. In other words, it is a measure of the "deadliness" of getting an infection - or, at least one that has been counted as a case (usually because of a positive lab test).

67) The case-fatality ratio, using the same dataset, has been about 2% (1 in 50) overall; i.e. 7511 deaths/378,339 cases. An average case-fatality ratio for the whole population does not, however, provide as much information as age-stratified or age-specific fatality ratios. The table shows the significant trend from the youngest age group to the oldest.

68) The highest death per case ratio is, predictably, in those over the age of 90 – about 30%. From another perspective, 2 out of 3 have survived their diagnosis. For those aged 60-69 case fatality is 2%. 98% have survived their diagnosis.

69) There have been two deaths in under-20's. That equates to an under-20 age-specific population mortality rate of one per million and case-fatality rate of about one per 10,000 cases.

70) The probability of severe illness or death from COVID-19 infection transmitted during religious event is a function of the age and health status of congregation members, focused protection strategies in the place of worship and risk-based policies for attendance.

Ontario definitions and policies regarding outbreaks

71) According to Ontario Public Health, "Outbreak-associated cases in this report include all cases directly linked to an outbreak as determined by the local public health unit but may not reflect where the case acquired the infection."[17]

72) "Definitions of outbreaks, including the number of cases, vary across settings. In addition, due to variations in data entry processes across public health units, some outbreaks included in this report may not have met the criteria included in an outbreak definition (i.e. size or duration of outbreak). Further there is no provincial outbreak definition for several setting types classified within the other settings category; as such, there may be variation in declaring outbreaks by public health unit."[18]

Ontario information on outbreaks, including churches and other settings.

73) At time of writing, the most recent Enhanced Epidemiological Summary of COVID-19 outbreaks and cases in Ontario was posted in March, 2021[19]. It covers the period February 16, 2020 to December 26, 2020. During these last 10 months of 2020, there were 4151 reported outbreaks. Of these, 23 (0.6 %) were associated with places of worship. Of the 39,774 cases associated with outbreaks, 221 (0.6%) were associated with places of worship.

74) The average number of cases per outbreak for all outbreaks was 39,774/4151= 10. This is the same average number of cases per outbreak associated with places of worship, 221/23. The median age for all outbreak-associated cases was 54 years; the median age for place of worship outbreak-associated cases was 40 years, i.e. 14 years younger.

75) Five of the place of worship outbreak-associated cases were hospitalized; this is 5/221 = 2.3% of all outbreak-associated cases compared to 8.7% hospitalization for all Ontario outbreak-associated cases. This is 5/3,460 outbreak-associated hospitalizations, equating to

[17] https://www.publichealthontario.ca/-/media/documents/ncov/epi/covid-19-settings-based-outbreaks-epi-summary.pdf?la=en page 2.
[18] https://www.publichealthontario.ca/-/media/documents/ncov/epi/covid-19-settings-based-outbreaks-epi-summary.pdf?la=en page 2.
[19] https://www.publichealthontario.ca/-/media/documents/ncov/epi/covid-19-settings-based-outbreaks-epi-summary.pdf?la=en

0.1% of all outbreak-associated hospitalizations. There were no deaths associated with places of worship outbreaks. 0% of 3,681 outbreak-associated deaths compares with 9.3% deaths of all outbreak-associated cases. This large difference is explained by the comparison with hospitalizations and deaths in congregate care facilities outbreaks, accounting for 88.7% and 98.5% of hospitalizations and deaths, respectively.

76) These numbers do not include secondary cases associated with outbreaks. These numbers do not include non-outbreak associated cases that were attributed to transmission at a place of worship. No data on these parameters were found.

77) In addition to identifying retrospectively where cases may have acquired their infections, prospective investigation can be more accurate to determine secondary cases and to identify the frequency of serious consequences (hospitalizations and deaths) associated with exposure in a particular setting. This type of information was not found in the "enhanced case and management strategy that will help contain the spread of COVID-19"[20]. After case and contact follow-up on more than 440,000 cases[21], a more accurate estimate of the frequency of transmissions in places of worship and all settings could have been ascertained to guide rational decisions about risk and policies. This is an example of the importance of ongoing risk assessment to inform and guide policy, including constant reassessment of the need for continuation of restrictive policies – looking at each setting and its specific levels of risks and need.

Specific questions

What is the ordinary or absolute risk for exposure to and transmission of SARS-CoV-2 in a church service that is near full seated capacity (leaving aside church programs or activities outside of the worship in the church sanctuary)?

78) Calculating the probabilities using incidence data for the Welland municipality, a reasonable estimate of the absolute risk to one person of getting infected during one service without public health measures in place is about one in 300,000 from an

[20] https://www.ontario.ca/page/case-and-contact-management-strategy
[21] https://www.publichealthontario.ca/-/media/documents/ncov/epi/covid-19-daily-epi-summary-report.pdf?la=en

asymptomatic person, one in 30,000 from a pre-symptomatic person and one in 6,000 from a symptomatic person.

79) In one service, the probability of transmission from an attendee without symptoms, is estimated at one in 30,000 (the contribution from asymptomatic attendees is negligible). In a service of 500 people, the probability of one transmission at that service is one in 60 (1.7%) = 30,000/500. In other words, there would be a transmission from an asymptomatic or pre-symptomatic case once in every 60 services. This estimate is in the absence of public health measures.

80) Using these estimates, the probability of transmission at one church service because of a high-risk exposure (prolonged contact, no distancing, no barrier) to a symptomatic case is about one in 5000 attendees. In a service of 500 people, that equates to a 10% probability of one transmission to one person at each service or one transmission from a symptomatic person every 10 services. This is the estimated probability without screening or other public health measures.

What is the comparative risk between an ordinary church service with no safety plan (social distancing, self-screening, masks, hygiene measures, etc.) and a church service that follows public health measures including distancing between households, but does not otherwise implement a capacity limit?

81) To answer this question, it is assumed that all factors of consideration are equal between the two services except for the effective implementation and compliance with recommended public health measures (self-screening for symptoms or required self-isolation, distancing, masks, hand-washing, building ventilation) in one service.

82) In essence, the answer comes down to the comparison of the frequency of high-risk exposures during the service. Public Health Ontario describes a number of factors to consider in categorizing the exposure to a case as a low-risk exposure or high-risk exposure, but the essence of the categorizing is based on whether any of the following three conditions have been met:

a) More than two-meter distancing,
b) Face-to-face exposure less than 15 minutes, or
c) Masks worn properly by case and contact.

83) If any one of these three conditions are met, the exposure would be expected to be classified as low-risk. Inversely, a high-risk exposure would be identified if none of these three conditions were met.[22]

84) Public Health Ontario has not provided estimates of the difference in transmission rates between high-risk and low-risk exposures, but it would not be unreasonable to assume at least an order of magnitude. Regardless of the magnitude, the probabilities of transmission would be significantly lower than those estimated without public health measures in place.

What is the comparative risk between a church that follows public health advice and gathers at 30% of seated capacity and the same church gathering at 15% of seated capacity?

85) Everything else being equal, the only factor of significance which may affect the risk would be the ability to social distance between members that are not of the same household. However, even in that case, the proper use of masks and/or the avoidance of prolonged face-to-face exposures (>15 minutes) would ensure that any exposure to a case would be expected to be classified as low-exposure and would not result in a directive to self-isolate.

What is the comparative risk between a church gathering of 10 people and a church gathering at 15% of seated capacity (in either case, following public health measures)?

86) The answer to this question is the same as that for question 3. Everything else being equal, the only factor of significance which may affect the risk would be the ability to social distance between members that are not of the same household. However, even in that case, the proper use of masks and/or the avoidance of prolonged face-to-face exposures (>15 minutes) would ensure that any exposure to a case would be expected to be classified as low-exposure and would not result in a directive to self-isolate.

[22] https://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/contact_mngmt/management_cases_contacts.pdf

What is the comparative risk between attending a church gathering under the circumstances described in 2-4, above, and doing other activities permitted under Ontario Regulation 82/20 (Rules for Areas in Stage 1)? Assume both have a written safety as described in Schedule 1, section 5 of Regulation 82/20.

87) The variations of people, space, and activities in other settings and the lack of detailed data make it difficult to compare risks in a valid way.

88) Comparing the numbers of reported outbreaks in 2020, there were 23 associated with places of worship, 49 in recreational fitness centres, 122 in bars/restaurants/nightclubs and 141 in retail.[23]

89) Comparing the numbers of cases associated with outbreaks, there were 221 in places of worship, 411 in recreational fitness centres, 471 in bars/restaurants/nightclubs and 508 in retail.

90) As a proportion of all outbreaks, places of worship constitute 23/4151 = 0.6%.

91) As a proportion of all cases associated with outbreaks, places of worship constitute 221/39,774 = 0.6%.

92) Although Public Health Ontario has not shown the number of total cases associated with places of worship, it does report on the total number cases associated with "other recreation" settings, which include places of worships and other venues for weddings and funeral. Assuming that all of these cases were associated with places of worship, the proportion of all cases on May 1, 2021 = 2261/466,733 = 0.5%, or 1 in 200 of all Ontario cases.[24]

93) Another way to estimate the risk of transmission is to consider the exposure time of all Ontarians attending a place of worship. 1/3 of Ontarians over the age of 15 attend a religious service at least once per month[25]. The population of Ontario ≥ 15 years is 12

[23] https://www.publichealthontario.ca/-/media/documents/ncov/epi/covid-19-settings-based-outbreaks-epi-summary.pdf?la=en
[24] https://covid-19.ontario.ca/data/likely-source-infection#obSetting
[25] https://www.statcan.gc.ca/sites/default/files/6493-eng.pdf

million[26]. If (1/3 of 12 million =) 4 million people attend an average of 1.5 hours per service and one service per month, the number of "person-hours" of exposure per attender is 12*1.5 = 18 per year. The total hours of exposure per year of all Ontario attenders = 4 million*1.5*12 = 72 million person-hours of exposure. Using this denominator for all accumulated cases that could be associated with exposure to a place of worship until the end of April (more than a year of time), the rate of transmission per hour of exposure to a service of worship is 2261/72 million = one transmission per 32,000 person-hours of exposure. Even if the actual infection rate is ten times the identified case rate, the transmission rate would be one per 3,200 hours of exposure – or one per 2000 services.

Summary and conclusions

94) The purpose of this report has been to estimate the risks associated with attendance at church services in Ontario, in particular the Wellandport United Reformed Church.

95) Using data from official sources, including the Public Health Ontario and the World Health Organization, estimates have been made of the probability of transmission of COVID-19 in church services with attendees from with current rates of infections similar to that of the Niagara health region.

96) Input estimates were used that would if anything overestimate - not underestimate the risk. Furthermore, the estimates used were under the assumption that neither symptom screening nor public health measures were in place.

97) The overall probability of transmission of infection from symptomatic infections occurring at any one service of 500 attendees without screening or other public health measures is estimated at 10% - or one per 10 services.

[26] https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000501&pickMembers%5B0%5D=1.7&pickMembers%5B1%5D=2.1&cubeTimeFrame.startYear=2020&cubeTimeFrame.endYear=2020&referencePeriods=20200101%2C20200101

98) The overall probability of transmission from non-symptomatic infections occurring at any one service – with effective screening of symptomatic persons – is estimated at about 2% - or one in 50 services.

99) The number of people or percentage seating capacity at services should not impact on these estimates as long as high-risk exposures can be avoided and screening, distancing, barriers (masks), and duration of close contact can be maintained, in addition to other factors such as ventilation.

100) It appears that outbreaks from churches constitute less than one percent of all outbreaks and less than one percent of all cases associated with outbreaks.

SWORN BEFORE ME by video conference, in accordance with O. Reg, 431/20 under the *Commissioners for Taking Affidavits Act*, RSO 1990, c. C17, on May 4, 2021, the affiant being in Winnipeg, Manitoba, and the Commissioner being in Ottawa, Ontario.

John Sikkema
LSO# 67933W
A Commissioner for taking oaths in
the Province of Ontario

Dr. Joel Kettner

FORM 53

Courts of Justice Act

ACKNOWLEDGMENT OF EXPERT'S DUTY

Court File No.: CV-21-00013361-0000

ONTARIO
SUPERIOR COURT OF JUSTICE

BETWEEN:

WELLANDPORT UNITED REFORMED CHURCH

Applicant

- and -

THE ATTORNEY GENERAL OF ONTARIO

Respondent

ACKNOWLEDGEMENT BY DR. JOEL KETTNER

1. My name is Joel Kettner. I live in Winnipeg, Manitoba.

2. I have been engaged by or on behalf of the Wellandport United Reformed Church to provide evidence in relation to the above-noted court proceeding.

3. I acknowledge that it is my duty to provide evidence in relation to this proceeding as follows:
   a. to provide opinion evidence that is fair, objective and non-partisan;
   b. to provide opinion evidence that is related only to matters that are within my area of expertise; and
   c. to provide such additional assistance as the court may reasonably require, to determine a matter in issue.

4. I acknowledge that the duty referred to above prevails over any obligation which I may owe to any party by whom or on whose behalf I am engaged.

Date: May 3, 2021

Joel Kettner

RCP-E 53 (July 22, 2014)

Estimating Influenza Deaths in Canada, 1992–2009

Dena L Schanzer , Claire Sevenhuysen, Brian Winchester, Teresa Mersereau

Published: November 27, 2013 • https://doi.org/10.1371/journal.pone.0080481

Abstract

Background

Poisson regression modelling has been widely used to estimate the disease burden attributable to influenza, though not without concerns that some of the excess burden could be due to other causes. This study aims to provide annual estimates of the mortality and hospitalization burden attributable to both seasonal influenza and the 2009 A/H1N1 pandemic influenza for Canada, and to discuss issues related to the reliability of these estimates.

Methods

Weekly time-series for all-cause mortality and regression models were used to estimate the number of deaths in Canada attributable to influenza from September 1992 to December 2009. To assess their robustness, the annual estimates derived from different parameterizations of the regression model for all-cause mortality were compared. In addition, the association between the annual estimates for mortality and hospitalization by age group, underlying cause of death or primary reason for admission and discharge status is discussed.

Results

The crude influenza-attributed mortality rate based on all-cause mortality and averaged over 17 influenza seasons prior to the 2009 A/H1N1 pandemic was 11.3 (95%CI, 10.5 - 12.1) deaths per 100 000 population per year, or an average of 3,500 (95%CI, 3,200 - 3,700) deaths per year attributable to seasonal influenza. The estimated annual rates ranged from undetectable at the ecological level to more than 6000 deaths per year over the three A/Sydney seasons. In comparison, we attributed an estimated 740 deaths (95%CI, 350–1500) to A(H1N1)pdm09. Annual estimates from different model parameterizations were strongly correlated, as were estimates for mortality and morbidity; the higher A(H1N1)pdm09 burden in younger age groups was the most notable exception.

Interpretation

With the exception of some of the Serfling models, differences in the ecological estimates of the disease burden attributable to influenza were small in comparison to the variation in disease burden from one season to another.

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Introduction

Regression modelling is widely used to estimate the disease burden attributable to seasonal and pandemic influenza [1], with this approach recently endorsed by the World Health Organization (WHO) [2], along with a caution not to compare the number of laboratory-confirmed deaths from the 2009 pandemic with estimates of the number of seasonal influenza deaths. Applying these statistical methods to Canadian data has allowed us to study the full burden of seasonal or pandemic influenza on not only mortality [3], [4], but also admissions to hospital [5], visits to emergency departments [6], and workplace absenteeism [7], thereby gaining a better understanding of the relative risks of severe disease that age and health status poses.

The emergence of a novel influenza A H1N1 strain in the spring of 2009 has resulted in a renewed interest in better understanding the reliability of annual estimates of the number of deaths attributable to influenza [8], [9] amid concerns that methods that assume that all excess deaths are due to influenza are falsely including some deaths which were actually due to other respiratory viruses or environment causes [8], [10], [11]. Much of the concern is directed towards Serfling-style [12] regression models where the seasonality of the weekly baseline is described by a cyclical or sinusoidal function (sine and cosine terms). This baseline is

estimated by excluding weeks with influenza activity from the estimation process and then extrapolating the baseline to periods with influenza activity. In addition, it has been noted that some applications of this method have resulted in substantially different estimates of excess all-cause mortality [8]. It is only relatively recently that weekly virological surveillance, such as the Respiratory Viral Detection Surveillance System (RVDSS) of the Public Health Agency of Canada [13] has been available to provide a measure of the weekly level of influenza activity nationally. With the availability of a proxy variable for the weekly level of influenza activity, all weeks can be included in the analysis and the regression model can then simultaneously estimate the seasonal baseline and the number of deaths directly associated with the weekly level of influenza activity. Still, the choice of model parameterization could affect the annual estimates of the number of deaths attributable to influenza.

This study aims to provide annual estimates of the mortality and hospitalization burden attributable to seasonal influenza and the 2009 A/H1N1 pandemic for Canada and discuss issues related to the robustness of these estimates to the choice of statistical model. We applied a variety of Serfling and Poisson regression models incorporating over-dispersion to all-cause mortality and then compared the annual estimates of the number of deaths attributable to influenza. We also estimated and compared the annual estimates for mortality and morbidity stratified by age group, underlying cause of death, hospital discharge status, and primary reason for admission, with the hypothesis that disease severity might be similar enough to induce a strong degree of correlation between these annual measures of disease burden.

Methods

Sources of data

1.1 Mortality data. Records of deaths occurring in Canada from 1992 to 2009 were obtained from the Canadian Vital Statistics database, Statistics Canada [14], [15] and aggregated to weekly counts stratified by age group and underlying cause of death. Underlying cause of death was coded to the International Classification of Disease [16], [17] version 9 (ICD-9) from 1992 to 1999, and starting in 2000, version 10 (ICD-10). The categories of interest were: respiratory deaths (ICD-9: 460-519 and ICD-10: J00-J99); circulatory deaths (ICD-9: 390-459 and ICD-10: I00-I99) and a third category of ‘other causes’ which included all other causes of death (including external causes). Population denominators for the calculation of rates were obtained from Statistics Canada census and inter-census estimates [18].

For the 2009 pandemic, a total of 428 laboratory-confirmed deaths were reported to the Public Health Agency of Canada [19], though not all of these deaths were certified as due to laboratory-confirmed influenza (J09, J10) as the underlying cause of death [15]. These measures of the pandemic mortality burden were considered in assessing the uncertainty in the estimate of the number of deaths attributable to the pandemic.

1.2 Morbidity data. Hospital discharge records from patients admitted to an acute care hospital with a respiratory condition identified in any of the diagnostic fields were extracted from the Canadian Institute of Health Information (CIHI) patient-specific Hospitalization Database (HMDB) [20] for the period September 1994 to March 2010. The HMDB contains all separations (discharge or death) from an acute care hospital anywhere in Canada. Data was abstracted from the patient chart using ICD-9, or ICD-10-CA (Canadian version) [21]. At the 3 character ICD-10 code level used in this study, the ICD-10-CA is consistent with codes used in other countries [22]. The conversion from ICD-9 to ICD-10-CA occurred on a province-by-province basis from 2001 to 2006. Admissions were stratified by age, primary and secondary diagnostic category and discharge status and aggregated to weekly values. An additional subcategory of pneumonia and influenza admissions (ICD-9: 480-487, ICD-10 J09-J18) was also considered. Primary respiratory admissions are defined as admissions with a respiratory condition listed as the primary reason for admission/length of stay. Secondary respiratory admissions are those admissions for other causes with a respiratory condition as a contributing diagnosis.

1.3 Virological data and proxy variables for influenza activity. Respiratory virus identifications for influenza A and B and respiratory syncytial virus (RSV) were obtained from the RVDSS, Public Health Agency of Canada [13]. The RSVDSS compiles weekly data from selected laboratories on the number of tests performed and the number positive for influenza, respiratory syncytial virus (RSV), and other respiratory viruses. Specimens are generally submitted to laboratories by clinicians in the course of clinical care, and by clinicians participating in one of our provincial influenza surveillance programs. The predominant testing methods used for influenza detection have varied considerably over the study period and by laboratory. Panel tests were often used.[23]–[25] Though viral identification data has traditionally been used as the proxy variable for influenza activity and has performed well in this capacity [4], once circulation of a novel strain with pandemic potential was announced in late April of 2009, testing increased sharply as did the number of positive tests, and then varied in response to public health needs over the pandemic period. In many jurisdictions, the percent positive remained elevated over an unusually long period of time. As a result, viral identification data was no longer a good measure of the relative level of influenza activity over the pandemic period. Fortunately, with the conversion of hospitalisation coding to ICD-10, patients with laboratory-confirmed influenza were identifiable by the J09 and J10 codes. In addition, the use of J09/J10 (influenza virus identified) admissions to represent the level of influenza activity under ICD-10 coding has improved the model fit in other studies as well as providing better face validity [5], [6]. In order to use a longer study period these two data sources were combined; that is the weekly number of influenza positive tests (prior to the 2007/08 season) and the weekly number of admissions to hospital with laboratory-confirmed influenza for the 2007/08 influenza season through to March 2010 were combined. The splice was positioned to correspond to the ‘flu year’ to ensure separate multipliers for the two data sources.

1.4 Ethics Statement. This study was conducted in accordance with the principles expressed in the Declaration of Helsinki Declaration. Data provided by Statistics Canada was collected under the Statistics Canada Act. Data collected by the Canadian Institute of Health Information was provided to the Public Health Agency of Canada and the use of this data was in accordance with data sharing agreements. Data provided by the Public Health Agency of Canada was collected under the Public Health Agency of Canada Act and used in agreement with policy and regulations related to the publication of information related to public health. Identifying formation was not available to this study and most of the data has been previously published. Hence, ethics approval was not required.

1.5 Data Access. Access to the data used in this study is available from the data custodians (Statistics Canada, Canadian Institute of Health Information and the Public Health Agency of Canada) as per their data access arrangements. A dataset containing weekly mortality (all cause) and the weekly number of influenza and RSV positive tests has been made available as Table S1 with the description in Table S2.

Analysis

2.1 Poisson regression model. Stratified weekly deaths and admissions were modelled as a function of viral activity, seasonality, and trend using Poisson regression models similar to previously published estimates of the influenza burden in Canada[4], [5], [7]. The regression model was fit using SAS 9.1 [26] PROC GENMOD with a Poisson distribution, linear link function and dispersion parameter specified by:

$$NDEATHS = \sum_{m=1}^{12} \beta_{1,m} Mon_m + \beta_2 \cos(2\pi t/52.177457) + \beta_3 \sin(2\pi t/52.177457) + \sum_y \beta_{4,y} FY_y + \beta_5 Holiday + \beta_6 Dec25 + \beta_7 Jan1 + \beta_8 RSVproxy + \beta_9 FluBproxy + \sum_y \beta_{10,y} FY_y FluAproxy + \varepsilon$$

where ***NDEATHS*** represents the weekly number of deaths (or admissions) for the category of interest (for example age group). The monthly indicator variables (Mon_m) and the sinusoidal terms (with t=week) are included to account for seasonality. FY_y is a set of indicator variables for each influenza season, y ('flu' year) starting in September, with an exception for the 2009 pandemic where the 'flu' year was defined as May 2009 – March 2010. The β_4 parameters account for a general trend with more flexibility than the linear, quadratic and cubic trend terms used in the Serfling model below. The variables ***Holiday*** and ***Dec25*** were included in the hospital admission model to account for a reduction in admissions over holidays, and the last week of December (that includes December 25th, or Christmas day). The variable ***Jan1*** is an indicator variable for the first week of January, a week when a pronounced spike in respiratory admissions and deaths is often seen. The $\beta_{8,}$ $\beta_{9,}$ and $\beta_{10,\,y}$ parameters are multipliers for the proxy variables for RSV, influenza B and influenza A respectively. Separate annual multipliers for each flu season are necessary for any meaningful discussion of the annual estimates. Unfortunately, statistical power was insufficient to estimate the annual effects of RSV or influenza B. The ***FluAproxy*** is a combination of laboratory positive tests and admissions to hospital with laboratory-confirmed influenza as described above. The ***FluBproxy*** is the percentage of laboratory tests positive for influenza B. Various alternative parameterizations of the Poisson regression model were included in the sensitivity analysis. In the Week-of-Year Baseline model, all seasonal variables were replaced by a week-of-year indicator variable (53 seasonal parameters). In the Simple Serfling-like Poisson model seasonality and trend terms were replaced by the sinusoidal seasonality (2 seasonal parameters) and linear, quadratic and cubic trend terms as specified for the Serfling model below. The dispersion parameter was included in the model estimation to account for additional variation due to events not captured by the choice of explanatory variables and usually results in larger confidence intervals. A linear link function was used to specify that the weekly number of influenza deaths (or admissions) should be proportional over the year/season to the number of confirmed cases.

Influenza-attributed deaths were calculated as the difference between model-predicted deaths and the model-predicted deaths under the hypothetical absence of influenza, with the latter referred to as the seasonal baseline. Equivalently, the annual estimate can also be calculated by summing the proxy variable over the year/season and multiplying by the corresponding estimated parameter. The former (sum of weekly estimates) is easier to visualise, while the latter approach of working with estimated parameters ensures that the correlation structure induced by the regression model is accounted for. Hence, only disease burden estimates corresponding to an estimated parameter were reported, and confidence intervals for estimates of influenza-attributed rates were calculated from the coefficient of variation of the corresponding multiplier parameter.

2.2 Serfling regression model. The percentage of weekly laboratory tests positive for influenza A or B from the RVDSS and the percentage of deaths due to an influenza-like illness (ILI) or influenza (ICD-9: 487, ICD-10:J09, J10 or J11) at various arbitrary threshold levels were used to identify weeks for exclusion from the Serfling models specified by:

where t represents time or week. (Serfling-style models still use regression as the statistical procedure to estimate the parameters. However, these models are characterized by the exclusion of observations during periods of influenza activity.)

The Serfling model was only used in the sensitivity analysis. The annual number of deaths attributable to influenza was calculated for the Serfling models by summing the weekly excess (actual less estimated baseline) over a period that only included the excluded weeks. Both positive and negative 'excesses' were included in the sum in order to avoid biasing the estimate upward. For each Serfling model we reported the number of excluded weeks per season, the annual number of excess deaths and the annual baseline for the full year, averaged over 17 seasons (1992/93-2008/April 2009).

2.3 Cross-Validation and Sensitivity Analysis. The Poisson model described above was used to calculate annual estimates of the influenza disease burden by categories of interest. These annual estimates were plotted in scatter plots and as a time-series, and the correlation coefficient was used to summarize the disparity between two annualized time-series. Annual estimates for the burden attributed to influenza B were not specifically reported, as only one influenza B multiplier parameter was used for whole study period (and annual estimates calculated from such a model would be perfectly correlated with the annualized proxy variable).

For the sensitivity analysis for all-cause mortality, selected thresholds for the Serfling model and various parameterizations of the Poisson regression model were used to assess the impact of model choice on the point estimate of influenza mortality and its standard error. All parameters included in the main Poisson model described above were statistically significant (with p-values from the type 3 analysis often less than 0.0001).

Results

The average number of deaths attributable to seasonal influenza over the 17 seasons prior to the 2009 pandemic was estimated at 3,500 (95% CI 3,200 - 3,700) for an average crude mortality rate of 11.3 (95% CI, 10.5 - 12.1) deaths per 100,000 population per year. These estimates were based on the impact of influenza activity on all-cause mortality. The annual estimates ranged from undetectable to an average of more than 6000 deaths per year over the three A/Sydney seasons (Table 1). Between May and December 2009, an estimated 740 deaths (95%CI, 350-1500) were attributed to the pandemic strain, for a crude mortality rate of 2.2 (95%CI, 1.0 - 4.5) per 100,000 population. The average number of admissions to hospital attributable to seasonal influenza over the 15 seasons prior to the 2009 pandemic was estimated at 12,200 (95%CI, 10,800 - 13,600). The effect of influenza B on hospital admissions was not statistically significant. The annual estimates of respiratory admissions and deaths attributable to seasonal influenza were closely correlated (correlation coefficient of 0.82, see Figure1a, b), as were the mortality estimates from the death and hospitalization databases (correlation coefficient of 0.83, Figures1c, d). The pandemic was a notable exception with a relatively high morbidity burden compared to the mortality burden.

Table 1. Estimated Annual Number of Deaths and Hospital Admissions Attributed to Influenza, Canada.
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Figure 1. Comparison of annual estimates of deaths and hospital admissions attributable to influenza.
Annual estimates of the number of deaths and hospital admissions attributable to influenza are shown as a) an annual time-series with the influenza season identified on the x-axis and b) as a scatter graph of influenza-attributable deaths (x-axis) by hospital admissions (y-axis) with a linear trend identified by the solid black line. Open symbols indicate that the estimate was not statistically significant (95% CI includes 0). In the scatter graph, the A(H1N1)pdm09 estimates are indicated with a red square. c) Annual estimates of influenza-attributed deaths from the death and hospitalization databases are compared in time-series format and d) scatter graph format.
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1. Pandemic Mortality Burden

Of the 428 deaths with laboratory-confirmed A(H1N1)pdm09 reported to the Agency, 73% were in persons under 65 years of age and 72% were certified as due to influenza as the underlying cause of death. We estimated that 561 (95% CI, 347-775) deaths certified as due to an underlying respiratory cause were attributable to the pandemic. An additional 179 deaths certified as due to other causes were attributed to the pandemic, though this estimate was not statistically significant and the confidence intervals are quite wide. We assumed that the pandemic did not result in fewer deaths from circulatory or other causes, and as a result, set the lower 95% confidence interval (CI) for all-cause deaths attributed to influenza to the lower 95% CI from the respiratory underlying causes model. The resulting estimate is 740 deaths for a rate of 2.2 (95% CI, 1.0, 4.5) deaths per 100,000 population. (For any subsequent analysis, such as for a meta-analysis to assess the pandemic burden on a global scale, the model estimated standard error (coefficient of variation is 0.543) should be used.) The lower 95%CI at 1.0 deaths/100,000 population is close to the figure for deaths certified through ICD-10 coding as due to laboratory-confirmed influenza of 0.9 (Table 2). For persons under 65 years of age, the 216 deaths certified as due to influenza is in good agreement with the 254 (95%CI 192-315) deaths estimate to be attributable to A(H1N1)pdm09.

Table 2. A(H1N1)pdm09 Associated Mortality Rates per 100,000 Population, Canada, May – Dec 2009.
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Early reports of laboratory-confirmed A(H1N1)pdm09 associated deaths to the Agency suggested that most deaths (73%) had occurred among persons under the age of 65 years of age. However, the results of the regression models suggest that this early estimate was too high as under-ascertainment of the role of influenza was more significant for persons 65 years of age or older (Table 2).

2. Annual Estimates of Mortality and Morbidity by Epidemiological Characteristics

Estimates of respiratory and circulatory influenza-attributable deaths were closely correlated (Figure 2a, b), though with the conversion from ICD-9 to ICD-10, the proportion of influenza-attributable deaths coded to other causes increased (Figure 2a, c). Annual estimates of influenza-attributed admissions were correlated by reason for admission (primary versus secondary respiratory

r=0.77, Figure 3a), as were in-hospital deaths (Figure 3b). During the pandemic, most influenza-attributable respiratory admissions had a diagnosis of pneumonia or influenza, though for seasonal influenza, annual estimates for pneumonia and influenza versus other respiratory conditions were closely correlated (*r*=0.91) (Figure 3c). By broad age groups, annual estimates of influenza-attributed hospital admissions were strongly correlated between persons aged 20–64 years and persons 65 years of age or older (Figure 4a). However, the annual disease burden in persons under the age 20 years was a poorer predictor of the burden in adults (Figure 4b). Annual estimates by discharge status (discharged alive versus deceased) for persons aged 65 years or older, were also strongly correlated (*r*=0.94, Figure 4c).

Figure 2. Comparison of the annual estimates of the number of deaths attributable to influenza by underlying cause of death (respiratory, circulatory, and other causes).
a) Annual time-series with influenza season identified on the x-axis. b) Scatter graph with a linear trend shown in solid black. Annual estimates based on respiratory and circulatory underlying causes are highly correlated, while in c) a comparison of respiratory to other causes shows a significant change with the conversion from ICD-9 to ICD-10 (denoted by an x). Open symbols indicate that the estimate was not statistically significant (95% CI includes 0). The A(H1N1)pdm09 estimates are indicated with a red square.
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Figure 3. Comparison of annual estimates of the number of hospital admissions attributable to influenza by reason for admission.
Open symbols indicate that the estimate was not statistically significant (95% CI includes 0). The A(H1N1)pdm09 estimates are indicated with a red square. A linear trend line is shown in solid black.
https://doi.org/10.1371/journal.pone.0080481.g003

Figure 4. Comparison of annual estimates of the number of admissions attributable to influenza by age groups.
Annual estimates of influenza-attributed respiratory admissions for a) the 65+ age group versus 20–64 years age group; b) the 65+ age group versus 0–19 years age group; and c) by discharge status. Open symbols indicate that the estimate was not statistically significant (95% CI includes 0). The A(H1N1)pdm09 estimates are plotted with a red square. A linear trend line is shown in solid black.
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Sensitivity Analysis

In applying different parameterizations of Poisson regression models to the weekly time-series of all-cause mortality, we found minimal differences in the average number of deaths attributed to influenza and the annual estimates were closely correlated (*r* >0.9 for comparisons of models with annual multipliers) (Table 3 and Figure 5a). Model results using a multiplicative Poisson regression model (log link) rather than an additive model or the negative-binomial distribution in place of the Poisson distribution produced almost identical results (not shown).

Figure 5. Sensitivity Analysis of selected models to estimate the mortality burden attributable to influenza.
a) Poisson regression and Serfling model estimates of influenza-attributable deaths by influenza season. Three parameterizations of the Poisson regression model are shown in solid lines and 4 choices of thresholds for periods of influenza activity for the Serfling model are shown with dashed lines. Serfling models use regression to estimate a cyclical baseline, but exclude weeks with influenza activity. b) Average Number of Deaths (all cause) by Week with the Estimated Baselines for Selected Models. Despite an additional 150–200 deaths occurring in week 1, the averages of the weekly baseline for the full model (dashed line) and the Simple Serfling-like Poisson model (solid red) for January through mid-March were similar. Use of 53 indicator variables – 1 for each week of the year to account for seasonality resulted in a similar weekly baseline (dotted line). The Serfling baseline for a 10% influenza positive threshold is shown in green. The average weekly number of deaths attributed to influenza is shown on the secondary y-axis.
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Table 3. Sensitivity Analysis of the Poisson Regression Models for the Estimation of the Annual Number of Deaths Attributed to Seasonal Influenza.
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Though the annual estimates from various Serfling models were closely correlated with the results from the Poisson models (r>0.8) they tended to be lower. The source of this difference seems to stem from an over-estimation of the cyclical baseline over the winter months which had been excluded due to influenza activity. We found that excluding fewer weeks (from 33 to 6) increased the estimated baseline (Table 4). Still, simply adding the ***FluAproxy*** variable with individual multipliers for each season (Simple Serfling-like Poisson model) resulted in estimates that were similar to estimates from other Poisson regression models. This effect on the estimated baseline is illustrated in Figure 5b, where all-cause deaths and estimated baselines were averaged by week over the study period.

Table 4. Sensitivity Analysis of Serfling Models for the Estimation of the Annual Number of Deaths Attributed to Seasonal Influenza.
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Discussion

Influenza-attributable deaths are deaths that occur in people for whom an influenza infection contributed to the actual death, or at least the time of death, regardless of whether or not influenza was identified as the underlying cause of death. Because of the limitations of an ecological study design, these models have been be given much scrutiny [1], [8], [11], [27], [28]. Some of these reviews have identified poor correlation in published annual estimates of influenza mortality rates, while other studies have found reasonable agreement. Unlike most ecological studies, the peak period of influenza activity in temperate regions occurs over a relatively short period of time, with over 50% of the cases occurring within a 4–5 week period each year[29]. Though influenza was attributed to only 2% of deaths annually, 14–19% of the weekly deaths at the peak for the three A/Sydney seasons (1997/98-1999/00), and up to 10% in other seasons were attributed to influenza. As an ecological study, there is no gold standard for the best model – and the most appropriate model may vary from country to country depending on data availability or unusual events. The short duration and intense effect of influenza on many endpoints provides a unique opportunity to use weekly data to estimate the impact and to use validation and cross-validation techniques at the annual level to assess the internal and external consistency of the annual estimates.

As a measure of external consistency, we assessed the correlation between the annual mortality estimates by cause of death and the annual morbidity estimates by age, reason for admission, and discharge status. Most estimates of the disease burden attributable to influenza were well correlated with only a few exceptions. A notable exception is that the severity of an influenza season among persons under the age of 20 years was found to be a relatively poor predictor of the severity among adults (Figure 4b). The proportion of all deaths that were coded to causes other than cardio-respiratory conditions increased from 54% to 60% with the conversion to ICD-10. However, the conversion had a much larger impact on the proportion of influenza-attributed deaths that were coded to other causes, which increased from 23% to 49% (Figure 2b) for seasonal influenza. Despite the labels of influenza-attributed ‘cardiovascular’ or ‘other causes’, the analysis of in-hospital deaths indicates that the attribution to influenza is limited to patients with a diagnosis of respiratory condition regardless of the certified underlying cause of death. The implication is that the use of all-cause mortality with its wider confidence intervals is a more accurate measure of the full disease burden due to influenza.

For persons over the age of 65 years, the estimated A(H1N1)pdm09-attributed burden was considerably less than for seasonal influenza (Figure 4a, b), however, once admitted to hospital due in part to an influenza infection, the fatality rate for this age group was similar for seasonal and pandemic influenza (Figure 4c). The lower A(H1N1)pdm09 fatality rate for all ages combined is explained by the unusually high number of admissions among persons under the age of 65 years (Figure 4a, b). The low A(H1N1)pdm09-attributed mortality rates in Canada is consistent with the hypothesis of partial prior immunity for persons over the age of 65 which has been confirmed in previous work[5]. Contrary to initial reports where 73% of all laboratory-confirmed A(H1N1)pdm09 deaths reported to the Agency occurred in persons under the age of 65 years, this proportion dropped to 45% for influenza-attributed respiratory deaths and possible much lower for all-cause mortality. The implication is that for hospitalized seniors the pandemic strain was not milder than for seasonal strains and that their infections were less likely to be diagnosed as influenza than for younger persons. Most of the missing pandemic diagnoses were among older patients with pneumonia.

Though no obvious trend was observed over the study period, a full trend analysis was limited by the significant year-to-year variation in the influenza-attributable mortality rate, together with increased virological testing over the study period, and significant coding differences of the underlying cause of death introduced with the conversion to ICD-10.

For internal consistency, we compared the annual estimates of the number of deaths attributable to influenza from different Serfling and Poisson regressions models. The Serfling estimates were dependant on the number of weeks per year that were excluded due to influenza activity, and for most exclusion rules, this method produced lower annual estimates than the Poisson models.

Concern has been expressed that as Serfling models attribute all excess deaths to influenza, that this approach would inherently over-estimated the burden attributable to influenza. It appears that, on the contrary, the fitted cyclical baseline, with only a few data points in the winter months as a guide, tended to overestimate the number of non-influenza deaths in the winter months, and hence underestimate the winter excess due to influenza. Including the proxy variable for influenza activity along with annual multipliers for independent estimates of the annual excess was sufficient to stabilize the annual estimates.

Additional parameters that allowed the baseline to adapt more closely to the weekly data had little effect on the average annual estimates for influenza mortality. For example, deaths in 1st week in January were elevated by an estimated 163 deaths (95% CI 88-240). Removing this parameter from the regression model resulted in these additional deaths being absorbed into the baseline estimates for other weeks. The same was observed for the monthly indicator variables and the RSV proxy variable. Even using a week-of-year indicator variable (53 parameters) produced similar results. On the other hand, removing all parameters related to seasonality resulted in a two-fold increase in the estimated number of influenza-attributed deaths (not shown).

Some earlier models for estimating the burden of influenza mortality used the percentage of tests positive for influenza as the proxy variable for influenza activity and the same multiplier for each season [30]. Including only one multiplier for influenza activity forces the annual mortality estimates to be proportional to the annualized proxy variable and produced annual estimates that were poorly correlated with the estimates for the full model and were also about 10% lower (Table 3).

Our sensitivity analysis was limited in the breadth of comparisons included. Other options for proxy variables are emerging [31] and have not been evaluated in this study. While we included a proxy variable for RSV activity, many other respiratory viruses are now under national surveillance. In addition, our sensitivity analysis was limited to assessing the performance of different models for all-cause mortality only. As the annual estimates of influenza-attributed admissions for children and adults were poorly correlated, further assessment, particularly of models using a single influenza multiplier for more than one season is warranted for other time-series. The assumption that testing was consistent over each season prior to the pandemic seems reasonable based on a previous study of the empirical epidemic curves derived from this data [29].

Some of the annual influenza disease burden estimates (or the lower 95% confidence interval) in the tables or figures are negative. Negative estimates will occur when the true number of events (deaths or admissions) due to influenza is less than the natural variation in the total number of events (all-cause mortality or hospital admission) during periods of influenza activity. For the Serfling estimates, we summed all positive and negative weekly ‘excesses’ over the defined influenza period in order not to introduce biases by ignoring negative estimates. Technically, though plausible in a few rare instances, it is unlikely that an influenza infection ‘saved’ lives, and hence any negative ‘excess’, is most likely due to the random variation of the total number of deaths. Hence, to avoid biasing the annual total, these natural or random dips below baseline must be included to balance out the nature swings above baseline.

Though Poisson regression, or equivalently, negative binomial regression models with annual multipliers to adjust for potential year-to-year differences in the relationship between the proxy variable for the level of influenza activity and the resulting disease burden are emerging as the preferred model, various methods have been used internationally to estimate the A(H1N1)pdm09 mortality burden. A recent review article [32] summarizes many of the international studies to date. As noted in our study, a higher disease burden for pandemic versus seasonal influenza among persons under 65 year of age was a common experience in most countries [32]. Published international estimates of the A(H1N1)pdm09-attributed mortality rate for 2009 have varied. Some of the variation is likely real with higher rates of 11 and 10 per 100 000 population for Mexico (using all-cause mortality) [33] and China (using respiratory and cardiovascular deaths) [32] respectively. Choice of methodology can influence the estimates with one study estimating an influenza-attributable mortality rate of 0.8 per 100,000 for the United States [34] and another by Charu and colleagues at 4.7 (95%CI 2.0 – 7.5) [35]. The lower estimate was produced using a Serfling model with monthly data for pneumonia and influenza deaths, while the latter study used a methodology similar to ours. The estimated mortality rates from the Charu study are similar to ours at 2.6 (95%CI 1.5 – 3.8) compared to 1.7 (95%CI 1.0 – 2.3) for respiratory causes, and in both cases the estimate for circulatory causes was not statistically significant. Though the Charu estimate for cardio-respiratory causes was twice our all-cause estimate, this difference was not statistically significant.

For future estimates of influenza disease burden, increases in virological testing of hospitalized patients along with the ICD-10 coding to identify laboratory-confirmed cases will offer significant improvements in the measurement of influenza activity specific to the region and age group. With a better influenza proxy variable, the expectation is for a slight increase in the estimates of disease burden attributed to influenza. It is therefore important that estimates based on new models forms or even a new parameterization of the regression model be compared head-to-head with a Poisson regression model that includes at least seasonality, secular trend and a proxy variable for influenza or influenza A with annual multipliers and a dispersion parameter or equivalently the use of the negative binomial distribution.

In summary, differences in the ecological estimates of the disease burden attributable to influenza were small in comparison to the variation in disease burden from one season to another. Poisson regression models that included at least seasonality, a secular trend and a proxy variable for influenza or influenza A with annual multipliers and a dispersion parameter to correct for overdispersion produced reasonably consistent estimates of the annual mortality burden attributable to influenza and these estimates were highly correlated with annual estimates for the morbidity burden for adults. The annual morbidity burden for children (under the age of 20 years) was found to be a poor predictor of the corresponding adult burden. Influenza continues to be a significant contributor to mortality.

Supporting Information

Table S1.
Database containing weekly time-series of all-cause mortality and viral identifications.
https://doi.org/10.1371/journal.pone.0080481.s001
(XLSX)

Table S2.
Description of variable names.
https://doi.org/10.1371/journal.pone.0080481.s002
(XLSX)

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Author Contributions

Conceived and designed the experiments: DS CS BW TM. Critical review of the methods and manuscript: DS CS BW TM. Responsible for the statistical analysis: DS. Acquisition and interpretation of the FluWatch data: BW CS TM. Drafted the manuscript: DS. Critically reviewed the manuscript for intellectual content: BW CS TM.

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The Attorney General of Ontario v. Trinity Bible Chapel et al.

Dr. Thomas Warren
on Wednesday, December 15, 2021

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ONTARIO

SUPERIOR COURT OF JUSTICE

B E T W E E N:

THE ATTORNEY GENERAL OF ONTARIO

Applicant (Moving Party)

- and -

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHUURMAN, DEAN WANDERS, RANDY FREY, HARVEY FREY and DANIEL GORDON

Respondents (Responding Parties)

---This is the Cross-Examination of DR. THOMAS WARREN on his affidavit sworn May 25th, 2021, taken remotely through the offices of Neesons, A Veritext Company, Suite 2020, 7722 King Street West, Toronto, Ontario, on the 15th day of December, 2021.

A P P E A R A N C E S:

Josh Hunter, Esq. — Counsel for the Applicant

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Rob Kittredge, Esq. — Counsel for the Respondents

A L S O P R E S E N T:

Chandani Joshi, Court Reporter

TRANSCRIBED BY: Sandi Baxter, Transcriptionist

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---Upon commencing at 1:00 p.m.

DR. THOMAS WARREN, SWORN

CROSS-EXAMINATION BY MR. GUTTMAN:

1. Q. Good afternoon, Dr. Warren.

A. Good afternoon.

2. Q. You swore an affidavit on May 25th, 2021 in this matter?

A. Yes.

3. Q. And do you have it before you?

A. Yeah, I have it on another screen right beside me.

4. Q. Okay. And do you have access to some of the exhibits, footnotes that you cited?

A. The references, yes.

5. Q. Okay. You have no changes or corrections to that affidavit?

A. No.

6. Q. So I want to start just by talking about your experience. You work at Halton Healthcare?

A. Yes.

7. Q. And you are an infectious disease consultant; is that right?

A. Yes, I do both infectious diseases and medical microbiology.

8. Q. Right. Okay. And how do you split

your time between those two?

A. It would probably be 90 percent infectious diseases. I do about -- I do -- I'm responsible for 10 weeks of medical microbiology.

9. Q. So that's probably about 20 percent then.

A. Yeah, but in those days that I'm on service for that I would so some other things as well, so I would say it's about 10 percent.

10. Q. Does medical microbiology involve seeing patients?

A. No, medical microbiology is a Royal College speciality for the laboratory, the microbiology laboratory for diagnosing infectious diseases, so I have two -- two Royal College certifications. The infectious diseases is clinical, and that's 90 percent of my time, so that's taking care of infectious diseases patients and medical microbiology is laboratory.

11. Q. And when it comes to your infectious disease practice is that mostly out of the hospital?

A. Yeah. My patient load, and again, probably about 80 percent is inpatients and then 20 percent outpatients.

12. Q. And you see all sorts of infectious diseases, right?

A. Yes. I -- I do all types of infectious diseases, inpatient, outpatient, anything caused by viruses, bacteria, fungus and parasites, so I do acute care in a hospital, including COVID-19, but then chronic care of Hepatitis C, HIV, things like that.

13. Q. So, what percentage of the patients you see outside of the clinic would be COVID patients, sorry, outside of the hospital would be COVID patients?

A. I -- I don't know if I really see any outside of the hospital. I'm on call a third of the time, so about 17 weeks a year, and that's when I would be primarily seeing COVID patients, would be when they're admitted to hospital.

14. Q. When you're in hospital you're seeing all sorts of patients, including --

A. Yes.

15. Q. -- COVID?

A. Yeah.

16. Q. And outside of hospital you're not seeing any COVID patients?

A. No, I have certainly, but it's you

know -- most of that is taken care of by primary care and things like that.

17. Q. Okay. And I see from your CV that you're currently completing a masters in epidemiology?

A. Yes, at the London School of Hygiene and Tropical Medicine in England.

18. Q. Okay. And so you haven't completed that masters yet?

A. No. I'm in the -- my fourth year. Expected completion should be next year.

19. Q. And you don't have a PhD in Epidemiology?

A. I do not.

20. Q. And you're not licensed as a public health doctor?

A. I am not.

21. Q. And you do not have any degrees in public health?

A. No.

22. Q. Now, I was looking at your publications. Your most recent publication is in peer-reviewed publication as of 2015; is that right?

A. Yes, that sounds right.

23. Q. And you don't appear to have any -- well, there's three listed. You don't appear to have

any peer-reviewed publications on respiratory disease; is that right?

A. That's correct.

24. Q. They're in medical microbiology?

A. Yes.

25. Q. Okay. And you don't have any publications on COVID obviously.

A. No.

26. Q. All right. So to start with some introductory questions, you agree that the science around COVID-19 is complex and uncertain?

A. Yes. It's ever evolving, yeah.

27. Q. You just answered my second question, that it's always evolving, because it's only been around for approximately two years; is that right?

A. That's correct.

28. Q. Now, I know that you practice infectious disease and not public health, but you understand that public health practitioners often don't have the luxury of waiting for the science to solidify before recommending action?

A. Okay. Sure.

29. Q. They have to act with the information they have available to them, right?

A. Yes.

30. Q. Okay. And so they would often have to act before there would be a peer review study for instance?

A. Yeah. You know COVID is a -- a new virus, but it's in a family of viruses that we've known about for a long time, and it's in a broader category of respiratory viruses, so certainly inductive implications can be made from experience with similar types of infections in the past.

31. Q. So can you explain to me, having accomplished three of them, what's involved in completing a peer-reviewed study, getting one published?

A. So the one study I did was in Cystic Fibrosis patients and diagnosis of fungal infections on those patients --

32. Q. Sorry, not to interrupt you. I just meant the process. I don't mean the content.

A. So the process, yeah, it depends on if it's a -- a benchry (ph) search which primarily is what I did versus clinical research with patients. So a benchry research involves investigations in the laboratory with usually patient samples in the medical context versus clinical trials can be divided into

retrospective studies which are cohort studies and case control studies versus prospective studies which are intervention randomized control trials which you know take a very long time.

Once the actual experiments and studies are complete then they're written up, submitted for peer review. The -- the papers are reviewed. Often suggestions are made. Those are done and then submitted again and accepted.

33. Q. Okay. And what is a preprint?

A. So a preprint is a publicly available version of the -- of a paper of a study prior to acceptance or -- yeah, prior to peer review. So the study has been completed, the paper has been written, and it's often in the process of peer review, although not all the time, but it's uploaded to a publicly available repository so that there can be public feedback as well as peer review, so that's one aspect of it.

The other aspect of a preprint is so that if there is very important information it can be disseminated before final publication, because the peer review process and the publication process, in the past at least, prior to a couple of years ago, could sometimes be quite long, even in the -- even

measured in years, but certainly months.

34. Q. Right. Okay. Thank you. Okay. And you agree that viruses like COVID evolve over time?

A. Yes. We know that COVID and similar viruses do mutate and evolve over time.

35. Q. And they can become more contagious over time?

A. Yes, they can change. They can become more contagious, less contagious, more virion, less virion.

36. Q. Right. And that's happened in Ontario first with -- in respect of COVID-19, first with Alpha, then with Delta and now with Omicron?

A. Yes, each of those Greek letter named strains are different -- have associated different mutations which affect both their infectivity and you know seriousness of infection.

37. Q. Right. Some of them are more serious than original COVID.

A. Yeah.

38. Q. And I know Omicron's coming on, but right now Delta is still the dominant variant in Ontario?

A. That's correct.

39. Q. And you're aware that cases are currently increasing in most Public Health Units due to the spread of the Delta variant and now Omicron?

A. Correct. Yes. Usually there's an increase in the winter.

40. Q. Right. Okay. All right. I want to take you to paragraph 15 of your affidavit. And here you talk about age being an important risk factor for COVID.

A. Um-hmm.

41. Q. Now, COVID is obviously very lethal for older people, but you agree that young people can still --

A. Yes, any age can be infected.

42. Q. And some young people can still get very sick from COVID.

A. Yes. Any age can potentially get very sick or die, but the risk of serious infection or death is substantially lower in very young compared to the very old.

43. Q. Right. And that's your position in the affidavit. I'm just trying to establish that people -- the effect on young people. Young people can spread the disease to other young people, right?

A. Correct.

44. Q. And they can spread it to seniors.

A. Yeah, there is evidence though that young people actually probably spread less than adults, this infection, but they can transmit it to both young people and adults.

45. Q. And especially if they're living with family members they can -- they can transmit to adults.

A. Yeah. Again, there are studies that show that household transmission from the young to the old is -- is less important than transmission from adults to adults, but, yes, young can transmit to -- to adults.

46. Q. And you agree before some of these young people die they get very sick, right?

A. Yeah, of course. If -- if a young person dies of COVID then they would have severe symptomatic illness beforehand.

47. Q. Right. And when they're very sick they take up a hospital bed.

A. Yes.

48. Q. Okay. In the next paragraph you compare the death rate of people under 60 with motor vehicle fatalities. And I appreciate you are saying the numbers are the same, but you're not looking here

at you know hospitalizations for instance caused by motor vehicles, right?

A. No. I'm looking in this paragraph specifically at fatalities.

49. Q. Right. And we know that motor vehicle accidents have not caused shortages in the ICUs in past years, right?

A. I don't know. I assume not, but I don't know that information.

50. Q. Well, you work in a hospital. You would have heard if there were -- if ICU units were overflowing with motor vehicle accident injuries, wouldn't you?

A. Yeah. I've never experienced that.

51. Q. In your general knowledge it hasn't caused the type of upheaval we saw because of COVID, right, in terms of hospitalization?

A. Correct.

52. Q. And we know from the hospitalizations caused a delay of elective surgeries, right, in Ontario?

A. Yeah. Well, some elective surgeries were cancelled in the first wave pre-emptively, but in the second and third waves because of hospital capacity, that's correct.

53. Q. Right. And some diagnostic procedures were delayed as well because of COVID.

A. That's correct.

54. Q. All right. The next section is on asymptomatic transmission.

A. Um-hmm.

55. Q. And I wanted to take you to an article that you cite, it's called, "An Outbreak of COVID-19 on an Aircraft Carrier." It's not cited in this section. It's cited earlier. It's by Kasper. If you want I can screen it, share the screen, but if you have access to it it's probably easier.

A. Yeah, just let me look it up for a minute. Okay.

56. Q. So this is an article published in the New England Journal of Medicine where Kasper's the lead article, author.

A. Yes.

57. Q. And it's about an outbreak of COVID-19 on an aircraft carrier?

A. That's correct.

58. Q. And just give me one second. Now, you called -- at paragraph 10 of your affidavit you called a population of this study as "relatively healthy." This was the crew of a naval vessel, right,

that was studied?

A. Yeah, it was an aircraft carrier.

59. Q. And you can see under "results" in the third paragraph on page 1 in the abstract that they were "predominantly young," the --

A. Yes.

60. Q. -- staff, and they were:

"In general good health, meeting U.S. Navy standards for sea duty."

A. Correct.

61. Q. So when we say "relatively healthy," this is as about as good as it gets, right?

A. Yes.

62. Q. A better word might have been "very healthy" rather than "relatively."

A. Okay. Sure, very healthy.

63. Q. Right. Okay. Now, in the second sentence under "results," it says:

"Over the course of the outbreak, 1271 crew members (26.6 percent of the crew) tested positive for -- (SARS-CoV-2) -- and more than 1000 infections were identified within 5 weeks after the first laboratory-confirmed infection."

Do you see that?

A. Um-hmm.

64. Q. And then under "conclusions" in the abstract it says:

"SARS-CoV-2 spread quickly among the crew of the U.S.S. Theodore Roosevelt."

Do you see that?

A. Um-hmm.

65. Q. "Transmission was facilitated by close-quarters conditions and by asymptomatic and presymptomatic infected crew members."

See that?

A. Um-hmm.

66. Q. "Nearly half of those who tested positive for the virus never had symptoms."

Do you see that?

A. Yes. Sure.

67. Q. Okay. No problem. Just if you could say, "yes," or, "no," Dr. Warren, for the record that would be great?

A. Yeah.

68. Q. Okay. So if you can turn to page 2424, which is if you could turn to the paragraph in

the lower left-hand corner?

A. Um-hmm.

69. Q. It's says:

"Not surprisingly crew members working in the engine room and other confined areas of the ship faced the higher risk of being infected than their shipmates on deck."

Do you see that?

A. Yes.

70. Q. And that's not surprising because when people are in crowded and closed places COVID transmits more easily.

A. Yes.

71. Q. And then the last sentence of that paragraph, which is the right-hand column says:

"These observations suggest that non-symptomatic or mildly symptomatic crew members played an important role in the rapid spread of the outbreak, much as young adults with asymptomatic infection appear to continue to spread in civilian populations."

Do you see that?

A. Yes.

72. Q. So this article is recognizing that young adults with asymptomatic infection contribute to the spread in civilian population?

A. Well, this study has to be kept in context, right. Like this is a study of a very peculiar environment, and so any extrapolation from this study would have to extrapolate to similar environments.

So you could maybe extrapolate this to a university dorm where you have a lot of healthy young people in relatively close quarters, but the geographic context, i.e., a lot of people in a very small space for a very prolonged period of time is really not reflective of the general broader society, and so you know over-generalization of the results of this study to the broader population is -- I'm not sure is -- is really not justified.

This study has very important conclusions, but these mildly and non-symptomatic persons and crew were you know in very -- in close space for a prolonged period of time with -- with other persons and so in that context, yes, the conclusions can be extrapolated, but it would have to be in those, or something very similar contexts.

73. Q. So fair enough, but all I'm saying

is the first part of that sentence recognizes that:

"Non-symptomatic or mildly symptomatic members played an important role in the rapid spread of the outbreak."

You see that, right?

A. Um-hmm.

74. Q. You might have a different view, but the authors then extrapolated and say:

"Young adults with asymptomatic infection appear to contribute to spread in civilian population."

Right?

A. That's what the authors say.

75. Q. Right.

A. That's correct.

76. Q. Okay. And to be fair, they list under "limitations," on page 2 that their observations apply to a military population may not be fully generalized with the civilians, which I think is the point you just made.

A. Correct.

77. Q. Now, in order to put this study to use I guess you could say:

"The navy initiated several

procedures to create and sustain COVID-19-free environments on its ships."

Do you see that on page 24/25, lower left-hand corner?

A. Yes.

78. Q. Continuing over to the right-hand corner it says what some of those policies are. It says:

"Since these policies, along with preventative measures of mask use, social distancing to the extent possible, smaller group cohorting, strict hand hygiene and regular cleaning of common spaces were put in place. The navy has deployed multiple steps without sustaining another serious outbreak."

Do you see that?

A. Yes.

79. Q. Okay.

A. Yeah, that study -- the study was published quite early in the pandemic and so those policies would have been put in place at the end of the first wave, and there would have been a natural reduction of cases and outbreaks as the summer approached in 2020.

80. Q. Right. My understanding is mask use and social distancing, to the extent possible, is still in place; is that your understanding?

A. In the US military, I'm -- I don't don't know. I would -- I would expect so on -- on ships, but I -- I -- I can't say specifically about the US military.

81. Q. Thank you. Now, the next item I'd like to take you to is the British editorial that's referred to at paragraph 17, the editorial from a British Medial Journal.

A. Reference 46?

82. Q. Yes.

A. Okay.

83. Q. Now, editorials are not peer-reviewed, are they?

A. Not usually, no.

84. Q. Can you describe other differences between an editorial and a regular academic paper?

A. An editorial is usually commissioned about an important topic or another research paper within the -- that particular journal issue. And the editorial is usually an attempt to, by a leader within that field to synthesize information. So if there's new information that has been coming out

to put it in context of the knowledge to date on that particular topic.

85. Q. Right. Okay. And the topic of this editorial is, "Asymptomatic Transmission of COVID-19, What we know and what we don't," right?

A. Yes.

86. Q. And that reflects what we talked about earlier which is uncertainty with these new novel coronaviruses. We know some things, but we don't know other things.

A. That's true.

87. Q. Okay. In the third paragraph, the last sentence, it says:

"Around 49 percent of people initially defined as asymptomatic go on to develop symptoms".

Do you see that?

A. Yes.

88. Q. And my understanding is that's pre-symptomatic, so that population is called "pre-symptomatic."

A. Yes.

89. Q. And this article I guess if you will, look at the paragraph that goes from the left-hand column to the right-hand column, says:

"Viral culture studies suggest that people with SARS-CoV-2 can become infectious."

I'll say COVID:

"can become infectious one to two days before the onset of symptoms and continue to be infectious up to seven days thereafter."

And then it says:

"Symptomatic and presymptomatic transmission have a greater role in the spread of."

COVID, "than truly asymptomatic transmission." See that?

A. Yes.

90. Q. Okay. So do you agree that pre-symptomatic transmission has a greater role than truly asymptomatic transmission, right?

A. Yeah, likely. It is very difficult to do studies on pre-symptomatic transmission though because of the fact that it's hard to define the pre-symptomatic period. So in other papers that I cited, you know it -- it's very difficult -- it's much easier to define what the risk of symptomatic versus asymptomatic transmission is.

And any, I think conclusions about pre-symptomatic are preliminary with regards to its transmission, but in all likelihood it's closer in its risk of transmission to symptomatic than asymptomatic, but the evidence is not definitive.

91. Q. And that's what these authors recognize.

A. Correct.

92. Q. And when someone presents initially with COVID, if they're asymptomatic you don't know whether they're truly asymptomatic or pre-symptomatic until the disease runs its course.

A. That's right.

93. Q. And that's why it's hard to study in part which is what you just said.

A. Yes.

94. Q. Okay. Now, the last sentence of the next paragraph says that:

"Asymptomatic and presymptomatic people may have more contacts than symptomatic people (who are isolating), underlining the importance of hand washing and social distancing measures for everyone."

Do you see that?

A. Yes.

95. Q. And that makes intuitive sense that if you're asymptomatic or pre-symptomatic and you don't have COVID you would have more contacts?

A. Yeah, that makes sense.

96. Q. I want to take you to a document that is not in your materials. Let me see if I can screenshare. Okay. Can you see that?

A. Yeah.

97. Q. So this is Synthesis from Public Health Ontario, dated August 2nd, 2021.

A. Um-hmm.

98. Q. And it talks about the period of communicability, what we know so far.

A. Um-hmm.

99. Q. Do you see that?

A. Yes.

100. Q. And under "Key Findings" it says:

"Epidemiology studies found transmission occurred in the 3-5 days before symptom-onset."

Do you see that?

A. Yes.

101. Q. "And epidemiology, virus culture and modelling studies found

transmission occurred in the 8-10."

Do you see that?

A. Yes.

102. Q. Okay. You don't have any reason to dispute that transmission occurs three to five days before symptom-onset, do you?

A. It can occur. Most transmission occurred -- you know other -- well, studies -- so that can -- that's the period of possible transmission, is between three to five days before, up and to including eight to ten days after, but the most -- it -- it follows a bell curve pattern, a normal distribution, like anything else.

And so the mast majority of transmission occurs from about one, one and a half days prior to symptom-onset until about three to five days after symptom-onset. So while it can occur in that time period the vast majority occurs in -- in a much narrower time frame.

103. Q. Right. So fair enough, the risk of transmission is highest just before and after the time of symptom-onset?

A. Yes.

104. Q. But it can occur three to five days before as we see in this study.

A. It can, but at five days before the likelihood of transmission in that case would be very very low and approaching zero, and same with 10 days after. Again, it follows the normal distribution bell curve and would be very low and those extreme extreme days.

105. Q. Right. Okay. All right.

MR. GUTTMAN: Can I have this marked as an exhibit, Mr. Kittredge?

MR. KITTREDGE: No objections.

MR. GUTTMAN: Okay. Madam Reporter, Exhibit 1.

EXHIBIT NO. 1: Synthesis from Public Health Ontario, dated August 2nd, 2021.

BY MR. GUTTMAN:

106. Q. Thank you. Okay. The next paragraph talks about a study in Wuhan, which I think was done by Cao, paragraph 18 -- sorry, we're back to your affidavit at paragraph 18.

A. Let me just look that up. Yes.

107. Q. Now, you'll agree with me that stringent control measures were imposed in Wuhan between January 23rd and April 8th, 2020?

A. Yes.

108. Q. And this article describes the

results of COVID testing that occurred between May 14th and June 1st, 2020?

A. Yeah. Let me just bring that up again so I can --

109. Q. Sure. It's reference 51.

A. Okay. Yes, it was done between May 14th and June 1st, 2020.

110. Q. And there were no new symptomatic cases and 300 asymptomatic cases were detected.

A. Yes.

111. Q. And the authors conclude that:

"COVID-19 prevalence was five low five to eight weeks after the end of the lockdown."

Do you see the last sentence there?

A. Yes.

112. Q. And then on page 2 the authors note first again the strict lockdown measures. And then they say:

"The pandemic was generally under control following those lockdown measures."

Do you see that?

A. Page 2, which --

113. Q. Second sentence in the first

paragraph.

A. Yes, I see that sentence.

114. Q. Right. And on page 3, in the second sentence on the first -- on the paragraph that goes from the left-hand column to the right-hand column it says:

"With the centralized isolation and treatment of all COVID-19 cases during the lockdown period in Wuhan the risk of residents being infected in the community has been greatly reduced."

Do you see that?

A. Yes.

115. Q. Okay.

A. The purpose of this study was not necessarily to look at the effectiveness of lockdown, but it was meant to assess the risk of transmission of asymptomatic persons.

116. Q. Right. I agree with, but they do recognize the effectiveness of the lockdown.

A. They assert the effectiveness of the lockdown, yes.

117. Q. Right. Okay. And they say -- continuing into the right-hand column they say, nonetheless:

"It's too early to be complacent because, of the existence of asymptomatic positive cases and high level of susceptibility of residents in Wuhan."

Do you see that?

A. I do see that.

118. Q. And then it says:

"Public health measures for the prevention and control of COVID-19 epidemic, including wearing masks, keeping safe social distancing in Wuhan should be sustained."

Do you see that?

A. I do see that.

119. Q. "Vulnerable populations with weakened immunity or co-morbidities, or both, should continue to be appropriately shielded."

Do you see that?

A. I do see that.

120. Q. And then again it says:

"Findings from this study show that COVID-19 was well controlled in Wuhan at the time of the screening programme."

A. Yes, I see that.

121. Q. Now, in terms of asymptomatic transmission, if you go back to page 2 the sentence right above "discussion," it states that:

"Figure 3 shows that districts with a high detection rate of asymptomatic positive persons generally had a high prevalence of confirmed COVID-19 cases."

Do you see that?

A. I see that sentence.

122. Q. Okay. And then Figure 3, we can flip to it, it's on page 5. I'm not going to take you to it, but that's the figure they're referring to.

A. Yes. Yeah, it makes sense, the more cases you have the more likely you're going to have asymptomatic patients there. It's obvious, yeah.

123. Q. Thank you.

A. And approximately a third of some studies show closer to 40, 45 percent of all cases are asymptomatic so wherever you're measuring high level of cases you're going to measure proportionately high levels of asymptomatic people.

124. Q. I'm going to take you to another article you cite in that paragraph, which is the Cao article, or sorry, that's the one we just looked at.

The Chang article.

A. Let me just get --

125. Q. Cite 52.

A. Fifty-two?

126. Q. Yeah, reference 52.

A. Yeah.

MR. GUTTMAN: Mr. Kittredge, I don't know if these studies are already in the record or not, if not I'm going to make them exhibits.

MR. KITTREDGE: You know what I'm not 100 percent sure myself. I've inherited the file, so I'm not -- I mean we have -- we have a book of sources here, but I'm not sure where it's been placed.

MR. GUTTMAN: Okay. So why don't I just -- out of an abundance of caution why don't I --

MR. KITTREDGE: Sure.

MR. GUTTMAN: -- make these exhibits? So we already did one --

MR. KITTREDGE: Assuming they're there let's rely on the copy that's there, but out of an abundance of caution for sure.

MR. GUTTMAN: Okay. All right. So --

MR. KITTREDGE: If you like, do you have the book of sources?

MR. GUTTMAN: I do not handy, no.

MR. KITTREDGE: I'll email that to you right now. Why don't we just mark the whole book as an exhibit?

MR. GUTTMAN: I like to defer to Mr. Hunter on that question, because --

MR. KITTREDGE: Oh, okay.

MR. GUTTMAN: -- if Mr. Hunter is on.

MR. HUNTER: I am. I think at this point why don't we just do it exhibit by exhibit rather than --

MR. GUTTMAN: Sure.

MR. HUNTER: -- you know trying to go through them all and figure out what is and isn't relevant.

MR. KITTREDGE: It's a pretty huge book of sources, so I have no preference, but just thought it might be easier. Okay.

MR. GUTTMAN: Thank you, Mr. Hunter.

MR. KITTREDGE: Yeah, go ahead.

MR. GUTTMAN: Okay. So, Madam Reporter, I'd like to make Exhibit 2, the New England Journal of Medicine article by the author, Matthew Kasper, entitled, "An Outbreak of COVID-19 on an Aircraft Carrier. Kasper, K-A-S-P-E-R. And it's called an, "Outbreak of COVID-19 on an Aircraft

Carrier."

EXHIBIT NO. 2: New England Journal of Medicine article by Matthew Kasper, entitled, "An Outbreak of COVID-19 on an Aircraft Carrier."

And Exhibit 3 would be an editorial from the British Medical Journal by Allyson Pollock, A-L-L-Y-S-O-N, Pollock, P-O-L-L-O-C-K, and James Lancaster, spelt as it sounds, entitled, "Asymptomatic Transmission of COVID-19." If we could make that Exhibit 3?

EXHIBIT NO. 3: Editorial from the British Medical Journal by Allyson Pollock and James Lancaster, entitled, "Asymptomatic Transmission of COVID-19."

And then Exhibit 4 will be Post-lockdown SARS-CoV-2 nucleic acid screening in nearly ten million residents of Wuhan, China, by lead author, Cao, C-A-O, and that's from Nature.

EXHIBIT NO. 4: Post-lockdown SARs-CoV-2 nucleic acid screening in nearly ten million residents of Wuhan, China, lead author, Cao, from Nature.

And I think that's where we've gotten to so far. Okay.

BY MR. GUTTMAN:

127. Q. So do you have the Chang article, Dr. Warren?

A. I do.

128. Q. So this study was published from May 1st, 2020 and corrected on September 8th, 2020, do you see that at the bottom of the page?

A. Yes.

129. Q. So it was published before variants of concern were identified?

A. Yes.

130. Q. And specifically, before the Delta variant emerged?

A. Yes.

131. Q. Okay. And this study looked at 100 COVID cases in Taiwan?

A. Yes.

132. Q. And in the conclusion on page 1 it recognized that the:

"In this study, high transmissibility of COVID-19 before and immediately after symptom onset suggests that finding and isolating symptomatic patients alone may not suffice to contain the epidemic, and more

generalized measures may be required, such as social distancing."

Do you see that?

A. It says that, yes.

133. Q. And at page 2, which is the next page, 1157 --

A. Okay.

134. Q. -- in the paragraph above "methods" it says:

"With proactive containment efforts and comprehensive contact tracing, the number of COVID-19 cases remained low."

In Taiwan:

"as compared with other countries that had widespread outbreaks."

Do you see that?

A. Yes, it says that.

135. Q. Okay. You're not disputing that numbers in Taiwan are low, are you?

A. No, I'm not disputing that.

136. Q. And like every article we have to look at the limitations, so if you could look at the limitations at 1162? So the first limitation was:

"Did not completely examine contacts before the symptom onset of the

index cases. Therefore, we might have underestimated the importance of early transmission."

Do you see that?

A. Yes.

137. Q. And they say:

"Thus, the actual contribution of early transmission to new infections could be greater than our estimates suggests."

Do you see that?

A. Yes, I see that.

138. Q. And then the next sentence is:

"Our findings agree with the recommendation from the WHO to use 4 days before symptom onset as the starting date for contact tracing."

Right?

A. Yes.

139. Q. And that corresponds --

A. The -- sorry, go ahead.

140. Q. I was going to say that corresponds to the possibility of infection three to five days before symptoms-onset which we discussed earlier.

A. Yes. Yeah, the reason I quoted

that study was that they found no transmission among the asymptomatic cases.

141. Q. Okay. Just on that point, on page 1159, first full paragraph, left-hand column.

A. Eleven-fifty-nine, let me just find that.

142. Q. Sure. It says, "Among the 27" -- are you there?

A. And which paragraph? I'm on the page --

143. Q. The first full paragraph on the left-hand column.

A. Okay.

144. Q. "Among the 2761 close contacts, 22 secondary cases of COVID-19 infection." Were detected:

"(including 4 asymptomatic infections)."

A. Yes, I see that.

145. Q. Okay. And then the last sentence:

"The 735 contacts whose initial exposure occurred before symptom onset of the index case were also at risk, with a secondary clinical attack rate of 1.0."

It's the second last sentence in that paragraph.

A. Yes, I see that sentence.

146. Q. And then it says:

"A subgroup of 299 contacts with exclusive presymptomatic exposures were also at risk."

Do you see that?

A. Yes, I see that.

MR. GUTTMAN: All right. If we could have this marked as the next exhibit, Madam Reporter? Sure. Contract Tracing Assessment of COVID-19 Transmission Dynamics in Taiwan and Risk at Different Exposure Periods Before and After Symptom Onset. The lead officer is Cheng, C-H-E-N-G. Okay. Thank you.

EXHIBIT NO. 5: Article entitled, "Contract Tracing Assessment of COVID-19 Transmission in Taiwan and Risk at Different Exposure Periods Before and After Symptom Onset." Lead officer, Cheng.

BY MR. GUTTMAN:

147. Q. So I want to talk about masks now,

so I could take you to paragraph 29 of your affidavit.

A. Yeah.

148. Q. So in the first sentence you refer to the, "World Health Organization Interim Guidance on mask use in the context of COVID-19"?

A. Yes.

149. Q. Okay. Can we call that up? It's reference 63.

A. Yeah, I'm there.

150. Q. Okay. So this is:

"An update of the guidance published on 5 June 2020."

Do you see that in the first sentence?

A. Yes.

151. Q. And it:

"includes new scientific evidence relevant to the use of masks for reducing the spread of."

COVID; do you see that?

A. Yes.

152. Q. Okay. And under "key points," it says:

"(WHO) advises the use of masks as part of a comprehensive package of

prevention and control measures to limit the spread of."

COVID, "the virus."

Sorry:

"SARS-CoV-2, the virus that causes COVID-19."

Do you see that?

A. It says that.

153. Q. Right. So it says it, but the key points in this article, sorry, in this guidance is that they're recommending the use of masks to control the spread of the virus, right?

A. Yes, but they acknowledge later in what I quoted that:

"There's only limited and inconsistent scientific evidence to support the effectiveness of masking of healthy people in the community."

So while they are advising it they're acknowledging that it's not based on good scientific evidence.

154. Q. So we'll get to that sentence that you put in your affidavit, but you acknowledge that their key point is to advise the use of masks?

A. They say that, yes.

155. Q. Okay, but not only do they say it, but they believe it, because they've written it.

A. Correct.

156. Q. Now, you didn't refer in your affidavit to this key point. You only refer to the sentence that you just read to me, right?

A. That's correct.

157. Q. Okay. If we can continue along this key point, it says:

"A mask alone, even when it is used correctly, is insufficient to provide adequate protection or source control. Other infection prevention and control (IPC) measures include hand hygiene, physical distancing of at least 1 metre, avoidance of touching one's face, respiratory etiquette, adequate ventilation in indoor settings, testing, contact tracing, quarantine and isolation."

Do you see that?

A. Yes, I see that.

158. Q. And they say:

"Together these measures are critical to prevent human-to-human

transmission of SARS-CoV-2."

A. Yes, it says that.

159. Q. Right. And masks can be used in two ways, right? They can either protect the person wearing the mask, right?

A. There is theoretical benefit to both the mask wearer and to others, correct, but --

160. Q. That's all I'm talking about now, the theoretical benefit.

A. Sure. Yes, there's theoretical benefit.

161. Q. To the wearer and also to other people. The second way is as a source control, right?

A. Yes, theoretically.

162. Q. Yeah. Okay. So I want to turn to the right-hand column where it says, "Mask use in community settings."

A. Um-hmm.

163. Q. And it says, the second bullet:

"In areas of known or suspected community or cluster."

Of:

"transmission: WHO advises that the general public should wear a non-medical mask in indoor - or outdoor

settings where physical distancing of at least 1 metre cannot be maintained."

Do you see that?

A. I see that.

164. Q. And:

"If indoors, unless ventilation has been be assessed to be adequate1, WHO advises that the general public should wear a non-medical mask, regardless of whether physical distancing - can be maintained."

Do you see that?

A. I see that.

165. Q. Okay. And then on the bottom of the next page it talks about the:

"Methodology for developing the guidance."

A. Hang on. I'll just get there.

166. Q. At the bottom of the left-hand column.

A. Um-hmm.

167. Q. And it says:

"Guidance and recommendations included in this document are based on published WHO guidelines."

You see that, right under:

"Methodology for developing the guidance."

A. Sorry, is this page 3 of the document?

168. Q. No, page 2, sorry.

A. Okay.

169. Q. Last paragraph.

A. Yes.

170. Q. "Guidance and recommendations included in this document are based on published WHO guidelines."

Do you see that?

A. Yes.

171. Q. "In particular the IPC WHO guidelines."

A. Yes.

172. Q. And:

"and control of epidemic- and pandemic-prone acute respiratory infections in health care."

Do you see that?

A. Yes.

173. Q. And also:

"Ongoing evaluations of all

available scientific evidence by the WHO ad hoc COVID-19."

IPC "Development Group."

A. Yes.

174. Q. And it then lists the experts or makes a reference to the experts who are on that group, and it says the, "See acknowledgment section." And if you turn to page -- if you go to the end of the footnotes, that's where the "Acknowledgment" section is?

A. Um-hmm.

175. Q. And there's a list there, first of:

"The WHO Health Emergencies Programme (WHE) Ad-hoc COVID-19 IPC Guidance Development Group."

Do you see that?

A. Um-hmm.

176. Q. And it goes over the page.

A. Yeah.

177. Q. And these are a bunch of academics at different hospitals around the world; is that right?

A. Yes.

178. Q. You'll see three-quarters of the way down there's a member of Public Health Agency of

Canada, Marina Salvadori.

A. Okay. Yes.

179. Q. In alphabetical order.

A. Yeah.

180. Q. Do you know her?

A. I know who she is, yes.

181. Q. Okay. Who is she?

A. She's a pediatric infectious diseases physician. Was working in London, now works for the Public Health Agency of Canada.

182. Q. Right. So back to page where we were, page 2. WHO explains -- this is the sentence going from the left-hand column to the right-hand column:

"During emergencies WHO publishes interim guidance, the development of which follows a transparent and robust process of evaluation of the available evidence on benefits and harms."

Do you see that?

A. Sorry, page 2, and then what --

183. Q. Yeah, going from the left-hand column to the right-hand column, bottom of the left.

A. Okay. Yeah.

184. Q. Should I read the sentence again?

A. No. I see it now. Yes.

185. Q. Okay:

"This evidence is evaluated through expedited systematic reviews and expert consensus building through weekly GDG consultations, facilitated by a methodologist and, when necessary, followed up by surveys."

A. Yes.

186. Q. And then it says, last sentence:

"Draft guidance documents are reviewed by an external review panel of experts prior to publication."

Right?

A. Says that, yes.

187. Q. And the purpose of the guidance is explained in the next paragraph. It:

"Provides guidance for decision makers, public health and IPC professionals, health care managers and health workers in health care settings - for the public and for manufactures of -- masks."

Do you see that?

A. Yes.

188. Q. Okay. So under "Background" the guidance writes, or it's stated in the guidance:

"The use of masks is part of a comprehensive package of prevention and control measures that can limit the spread of certain respiratory viral diseases, including COVID-19."

Do you see that?

A. Yes.

189. Q. And then it explains what we talked about before:

"Masks can be used for protection of healthy persons (worn to protect oneself when in contact with an infected individual) or for source control (worn by an infected individual to prevent onward transmission) or both."

A. It says that.

190. Q. Right. And then if we skip over to page 3 there's a portion that's on "Scientific evidence," and it says --

A. Yes.

191. Q. -- midway down the left-hand column:

"Knowledge about transmission of

the SARS-CoV-2 virus is evolving continuously as new evidence accumulates."

Do you see that?

A. Yes, I see that.

192. Q. And the next paragraph:

"According to available evidence, SARS-CoV-2 mainly spreads between people when an infected person is in close contact with another person."

A. It says that.

193. Q. You don't disagree with that, right?

A. I don't.

194. Q. "Transmissibility of the virus depends on the amount of viable virus being shed and expelled by a person, the type of contact they have with others, the setting and what IPC measures are in place."

Says that, right?

A. It does say that.

195. Q. And you agree with that?

A. Yes.

196. Q. "The virus can spread from an

infected person's mouth or nose in small liquid particles when the person coughs, sneezes, sings, breathes heavily or talks."

See that?

A. I see that.

197. Q. And you agree with that?

A. Yeah. The evidence for singing and breathing or you know talking is limited, but certainly respiratory particles when coughing or sneezing I would agree with.

198. Q. Okay. So do you dispute that more viral load is shed when someone talks loudly or sings?

A. The evidence for that is much less conclusive than for coughing or sneezing.

199. Q. I appreciate what you're saying about the evidence, but doesn't it make intuitive sense that when you're singing or talking loudly more virus would be shed?

A. Possible. Hasn't been quantitated in rigorous studies at this point.

200. Q. And we discussed earlier that rigorous studies would take perhaps years to develop, right?

A. Some, yes, but we've seen with the

vaccine studies they can be done potentially very quickly, in a matter of weeks or a couple of months.

201. Q. Right. And those vaccine studies, that was a huge innovation how quickly they were done, right?

A. Yes. Those type of studies like they've done for vaccines just haven't been done for masks. That's usually the threshold for concluding that something is effective as if a large randomized trial. That's why for all the vaccine trials they needed larger analyzed trials, because that's the threshold for concluding that something's effective.

202. Q. Right, but vaccine studies don't involve knowingly making people take their masks off, right?

A. No, but there are randomized trials in masking as well that have

not showing that it's been effective in the general population.

203. Q. Okay.

A. And in fact, it's not --

204. Q. We'll come to what the WHO says about the evidence, but that's not -- their guidance is to where masks, right?

A. Their guidance is to wear masks,

but as I quote in my study they acknowledge it's not based on good evidence.

205. Q. So the next paragraph talks about "fomite," we can skip that. And then the next paragraph's about "aerosol transmission." And then the first full paragraph on the right-hand column says that:

> "Aerosol transmission can occur in specific settings and circumstances, particularly in indoor, crowded and inadequately ventilated spaces, where infected persons spend long periods of time with others."

Do you see that? It's in the first full paragraph on the right-hand column, first sentence.

A. First full paragraph on the right-hand column.

206. Q. Page 3.

A. Okay. Yes.

207. Q. And:

> "Studies have suggested these can include restaurants, choir practices, fitness classes, nightclubs, offices and places of worship."

Do you see that?

A. Yes, I see that.

208. Q. Okay. And then it says, I think we've already discussed this, but -- for the sake of time I'm not going to go through all the signs, but "Pre-symptomatic transmission? It says:

"Pre-symptomatic transmission - from people who are infected and shedding virus but have not yet developed symptoms - can occur."

I think you agreed with that earlier.

A. Yes.

209. Q. And the next paragraph is "Asymptomatic transmission." We know that your position is that it occurs less frequently, but it can occur, right?

A. It can occur, yes. It's much less frequent than with symptomatic transmission.

210. Q. So if we go to page 8, we find that sentence that you've quoted in your affidavit:

"There is only limited and inconsistent scientific evidence to support the effectiveness of masking of healthy people in the community to prevent infection with respiratory

viruses, including SARS-CoV-2."

Right?

A. Yes.

211. Q. Now, this publication was put out in December 1st, 2020. Are you aware of any developments since then?

A. There has been one large, randomized trial in Bangladesh. It was a cluster randomized trial. It's interesting that it's been slow to be published. And I'm not even aware of a preprint yet of -- of the study. It showed a negligible benefit of masking, so it showed a few things.

Number one, it showed that non-medical masks, which are recommended in this WHO guidance have no effect. So if you go up into the guidance, and on page 2, on the left-hand side it says, "Homemade fabric masks" and in other places in page 1 it says the:

"WHO advises that the general public should wear a non-medical mask."

And so the large randomized trial of over 300,000 people, a cluster randomized trial in Bangladesh showed that non-medical masks have no effect on infection.

And this large, randomized trial, it's available on the investigator's website, many of the investigators were from Yale, some from Stamford, it did not look at hospitalization or death. It merely looked at test confirmed symptoms. And the relative risk reduction was nine percent, and the absolute risk reduction was about .7 percent. And that's in all mask wearers, if you include both non-medical masks and masks.

When they separate it out into non-medical masks and medical masks only the medical masks had any effect, but the absolute risk reduction was .7 percent. And if we take the inverse of that we can get the number needed to treat, which was about 1,400.

And so the study went on for a couple of months, and so you would need about 1,400 people to wear a mask for a couple of months to prevent one test-based infection, which is very very low. That's a very low number needed to treat -- number needed treats and lots of studies would be considered high if it's between 50 and 100. And it did not look at much more important outcomes such as hospitalization or death, so that would the main evidence-base since this was published.

212. Q. So it didn't look at hospitalization or death.

A. That's correct.

213. Q. It looked at cloth masks.

A. It looked at both cloth and medical masks.

214. Q. Are you saying that medical masks aren't helpful in a healthcare setting?

A. No, I'm not saying that at all.

215. Q. You agree that medical masks are helpful in a medical care setting.

A. Yeah, in certain scenarios, in the care of particular patients, yes, for sure.

216. Q. What kind of patients?

A. Yeah, it would include respiratory patients such as patients with COVID-19.

217. Q. Right. So why are they useful -- why do you agree that medical masks are useful in the hospital care setting for treating patients with COVID?

A. There has -- there is evidence in the healthcare setting in similar respiratory infections, such as influenza and other respiratory infections, there is an evidence base for that.

218. Q. Right. Okay, but if I'm exposed to

a COVID or a bunch of COVID people, people with the virus, and I'm in a setting other than a healthcare, would the mask not protect me at that point?

A. Not necessarily. We don't know that. That has to be proven through, again, randomized trials. And there have been two randomized trials in the context of masking the general public for COVID and neither of them -- one showed no benefit, which was the Danish study I referenced, and then the other study, as I said which has been completed but not yet peer-reviewed showed a very very small benefit and only in medical masks versus -- but did not show any benefit of non-medical masks.

219. Q. Okay. So when was this published, the new one you're referring to in the --

A. As I said it hasn't been published in a peer-reviewed --

220. Q. Sorry, I meant is published in the investigatory website?

A. It would have been at the beginning of the summer, which is unusual why it's not, at least in a pre-print form, or even peer-reviewed, because a lot of the -- the vaccine trials went from you know published on investigator websites to -- to peer-review within a couple of months.

This has been close to six months now since it's been available publicly, but not peer-reviewed or published.

221. Q. All right. So they go through the studies, and I understand that you know a randomized control study would be the best, but we have -- they have what they had. And under "Guidance" they say:

"The WHO COVID-19 IPC GDG considered all available evidence on the use of masks by the general public including effectiveness, level of certainty and other potential benefits and harms, with respect to transmission scenarios, indoor versus outdoor settings, physical distancing and ventilation."

And then they say:

"Despite the limited evidence of protective efficacy of mask wearing in community settings, in addition to all other recommended preventive measures, the GDG advised mask wearing in the following settings."

And we went through them, but the first one is:

"In areas with known or suspected community or cluster transmission -- WHO advises mask use by the public in the following situations."

And we already looked through those, right?

A. Yes, we already went through that.

222. Q. So that's the conclusion that WHO came to.

A. Yeah. And I think it's important to you know acknowledge the -- you know the qualified recommendation that they made.

223. Q. Right, but in your --

A. Where they say:

"Despite the limited evidence of protective efficacy of mask wearing in community settings."

224. Q. Right.

A. So -- but they're making that recommendation not based on scientific evidence, but you know with the assumption that masks would be protected in the healthy population community settings, but not based on evidence.

225. Q. Well, I mean I don't think we have to argue about what they say, but we're still in the

WHO guidance.

A. Um-hmm.

226. Q. And they say, "Despite the limited evidence" they made the -- they advised the guidance that they did, right?

A. Yes.

227. Q. All right. The next document I want to take you to is not in your references. I'll see if I can find it.

MR. GUTTMAN: We can make the WHO document an exhibit, Madam Reporter. Yes, please? Thank you. Okay.

EXHIBIT NO. 6: WHO document titled, "Mask use in the context of COVID-19."

BY MR. GUTTMAN:

228. Q. This is a science brief from the Centre for Disease Control and Prevention. You're familiar with the CDC, right?

A. Yes, I am.

229. Q. Okay. This was updated on December 6th, 2021.

A. It says that.

230. Q. And it says data was added. It's the last update:

"These studies address the

association of mask wearing with new infections, including infections related to SARS-CoV-2 variants of concern. All of these studies demonstrated a benefit."

Do you see that?

A. I do not see that.

231. Q. Sorry, it's the first bullet under, "Summary of Recent Changes."

A. I don't -- like I don't --

232. Q. Oh, sorry, sorry. I thought you had it, sorry. I've got to show it to you. My mistake. Okay. There you go. Do you see that?

A. Yes. You know it really depends on what type of studies they're referencing, because there's a clear gradient in the quality of studies. A lot of the studies of mask wearing, as I indicate in my extra report are of very poor quality and are not randomized control trials or meta-analysis.

233. Q. So let's look at the background:

"SARS-CoV-2 infection is transmitted predominantly by inhalation of respiratory droplets generated when people cough, sneeze, sing, talk, or breathe."

Do you see that?

A. I do see that.

234. Q. Okay. And do you agree with that?

A. I agree, but there's a definite -- there -- there are differences between each of those. Certainly people coughing has a much greater risk of transmission than people who are simply breathing. And so each of those has different levels of infectivity.

235. Q. Fair enough. Next sentence:

"CDC recommends community use of masks to prevent transmission of SARS-CoV-2."

Do you see that?

A. I do see that.

236. Q. So their guidance is consistent with the WHO guidance, right?

A. Yeah, the CDC recommends that, but there are many jurisdictions in the US where that's not either recommended or mandated.

237. Q. Fair enough, but here we see the CDC recommending it.

A. They do.

238. Q. Then they make the observation that:

"Masks are primarily intended to reduce the emission of virus-laden droplets by the wearer ("source control")."

Do you see that?

A. I do see that.

239. Q. "Which is especially relevant for asymptomatic or presymptomatic infected wearers who feel well and may be unaware of their infectiousness to others."

Do you see that?

A. I do see that.

240. Q. They're focusing here on source control.

A. Yes.

241. Q. Although in the next sentence they say it:

"Also help reduce inhalation of these droplets by the wearer."

Do you see that?

A. I do see that.

242. Q. Okay. And then it says:

"The community benefit of masking for SARS-CoV-2 control is due to the

combination of these two effects."

Do you see that?

A. I do see that.

243. Q. And:

"Individual prevention benefit increases with increasing numbers of people using masks consistently and correctly."

A. Yeah. And based on that trial that I mentioned you just -- you need very very large numbers of people for a very very long period of time to prevent very small numbers of infection, so the evidence shows that the actual benefit is miniscule.

244. Q. So under the first bullet on page 2, "Human Studies of Masking and SARS-CoV-2 Transmission" --

A. Are you going to go there in your document?

245. Q. Oh, sorry. Good point. Thank you. It talks about:

"A large, well-designed cluster-randomized trial in Bangladesh in late 2020."

Is this what you were talking about?

A. That's correct.

246. Q. Okay. And so what the CDC reports is that -- first of all, it has a sentence about "mask use." Where it's encouraged it's obviously adopted more. And then it says:

"In villages receiving mask interventions, symptomatic seroprevalence of SARS-CoV-2 was reduced by approximately 9 percent relative to comparison villages."

Do you see that, the second sentence?

A. Yeah, that's -- so that's a relative risk reduction.

247. Q. And then it says:

"In villages randomized to receive surgical masks, symptomatic seroprevalence of SARS-CoV-2 was significantly lower."

Do you see that, 11.1 percent overall"?

A. Yeah. Again, so that statement is in there because non-medical masks had no effect, so when they -- that nine percent -- if you separated it out that nine percent is all masks. And if you separate that out into medical and non-medical the non-medical has no significant overall reduction whereas the medical mask has a relative risk reduction

of 11.1 percent.

248. Q. Okay. And then it says, their conclusion is:

"The results of this study show that even modest increases in community use of masks can effectively reduce symptomatic SARS-CoV-2 infections."

A. That's their conclusion, but as I said if you look at the absolute risk reduction, which is 0.7 percent of all mask wearers, and then take the inverse of that which is a standard way of calculating the number needed to treat is 1,400.

And so to prevent one -- to prevent one infection you need about 1,400 people to wear masks for a couple of months as long as the study went on for, so very low rates. And that you know the benefit of this -- of this study shows and this paragraph shows as well is only in medical masks.

249. Q. Okay. So would you agree with me that CDC concludes that:

"The results of this study show that even modest increases in community use of masks can effectively reduce symptomatic SARS-CoV-2 infections."

A. That's what the CDC states, yes.

250. Q. And I take it from what you told me you don't agree that that's what the study stands for? You disagree with the CDC?

A. Well, the real benefit of randomized control trials is that we actually quantitate things. So the large randomized control trials in vaccines quantitates the effect of the vaccine on death and the -- you know quantitates the effect on infection and hospitalization.

And so in this randomized control trial they're looking at the relative risk reduction of nine percent in all mask wearers. As I said there are other ways of looking at it. And one of the most consistent or standard ways of looking at a large, randomized control trial is looking at the number of -- the number needed to treat, which I have referenced a few times.

And so my interpretation of that study would then say you need large amounts of people to wear masks for a relatively long time to prevent what may be a very relatively unimportant outcome which is just symptomatic SARS-CoV-2 infection. So large randomized trials for the vaccine looked at things like hospitalization and death, this study did not.

Those are much more important outcomes

than simply SARS-CoV-2 infection, which is you know very very common.

251. Q. I guess I'm just asking you if you agree that the study stands for:

"Even modest increases in community use of masks can effectively reduce symptomatic SARS-CoV-2 infections."

Do you agree or disagree with that?

A. "Can effectively reduce symptomatic SARS-CoV-2 infections."

By a very small amount, yes.

252. Q. So you don't really agree because you're inserting the words, "By a very small amount."

A. Yes, so I -- I would not agree with that conclusion, no.

253. Q. So your view is in opposition to the CDC's view?

A. Yeah, I would interpret the findings of that study differently than they do. And I think that's the reason it hasn't been published in the last six months.

254. Q. We see here that the Bangladesh study has had no effect on the CDC's guidance, right? They're still recommending mask use in the community.

A. Correct.

255. Q. In fact, they're citing it as another reason to -- more support for their position, right?

A. Yes.

256. Q. Okay. And below the bullets, at the first -- last full paragraph they says:

"At least ten studies have confirmed the benefit of universal masking in community level analyses."

Do you see that?

A. Sorry, is it --

257. Q. Oh, sorry, I haven't -- sorry, sorry. Here we go. Do you see my cursor? It's just this first sentence here below the bullet.

A. Yeah, it says that. And these are probably referencing our, what are called "ecological studies" or "correlation studies," which is the lowest quality of evidence. So just comparing rates of mask use and infection in US states, you can't control for so many variables.

You know studies like that break a rule called the, "ecological fallacy," which is that you shouldn't be measuring something at a population level that you can measure at a patient level, which is mask use. And so there's lots of studies like this, but

they would never be conclusively -- you would never be able to get a vaccine approved based on a study like this, you know just vaccinating -- seeing vaccine rates in one state and comparing infections, and then comparing that to another state.

So these type of studies are -- are there and they're done, but as it says in the WHO guidance, which I had referenced as well, they specifically talk about the significant limitations of ecological studies. And I quoted that in my report.

258. Q. Okay, but you acknowledge that vaccines are very different than masks?

A. But they can be studied the same way because randomized trials for masks have been done, just like randomized trials for vaccines have been done.

259. Q. Well, let's move to your randomized control trial. The only one that I'm aware of is the Flyngard (ph) study that you rely on in your paper.

A. Yes, other than this Bangladesh study as well, yeah.

260. Q. Right.

A. So in SARS-CoV-2 there have been -- I reference it as well in my expert report that there have been a number of randomized control trials in

similar infections such as influenza and masking the general public. And --

261. Q. Right.

A. -- as I -- as I reference meta-analysis of those randomized control trials do not show any significant benefit in masking the general public to prevent similar respiratory tract infections.

262. Q. Right. Okay. So --

A. Do you want me to bring that randomized trial up? Is that what you're --

263. Q. I'm just trying to be efficient in time. Are you aware that the CDC had criticized the Flyngard randomized control trial?

A. I'm sure lots of people have criticized the trial.

264. Q. Okay. So just reading from the top here of the full paragraph there, it says:

"Two studies have been improperly characterized by some sources as showing that surgical or cloth masks offer no benefit. A community-based randomized control trial in Denmark during 2020 assessed whether the use of surgical masks reduced the SARS-CoV-2 infection

rate among wearers (personal protection) by more than 50 percent. 58 Findings were inconclusive, most likely because the actual reduction in infections was lower. The study was too small (i.e., enrolled about 0.1 percent of the population) to assess whether masks could decrease transmission from wearers to others (source control).”

A. It says that.

265. Q. See that?

A. Yes, yeah.

266. Q. And if we go to the study, which is study 64, reference 64 --

MR. GUTTMAN: Well, could we make this document an exhibit, Madam Reporter?

MR. KITTREDGE: Can you please send a copy of that over to me?

MR. GUTTMAN: Yes, sure.

COURT REPORTER: That would be Exhibit 6 I think.

MR. GUTTMAN: I haven’t been keeping track. I thought maybe we were on --

COURT REPORTER: Yeah, it is six, or no, wait. One second. I’m just going to look back

and check. It's Exhibit 7, sorry.

MR. GUTTMAN: Okay.

COURT REPORTER: And it's the CDC Guidelines?

MR. GUTTMAN: Yeah. CDC Science Brief: Community Use of Masks to Control The Spread of SARS-CoV-2.

EXHIBIT NO. 7: CDC Science Brief: Community Use of Masks to Control the Spread of SARS-CoV-2.

COURT REPORTER: Thank you.

MR. GUTTMAN: I'm just going to take a moment, Mr. Kittredge, and send you the --

MR. KITTREDGE: Great. I appreciate it.

MR. GUTTMAN: Can you remind me of your email? It's not copying now.

MR. KITTREDGE: Oh, Rkittredge@jccf.ca, for the record.

MR. GUTTMAN: Yeah. Let's go off the record for a second.

---RECESS TAKEN

---UPON RESUMING

BY MR. GUTTMAN:

267. Q. So this is the trial that you were

talking about and that the CDC refers to, right, the Danish trial?

A. Yes.

268. Q. And its objective was to:

"To assess whether recommending surgical mask use outside the home reduces wearers' risk for SARS-CoV-2 infection in a setting where masks were uncommon and not among recommended public health measures."

Do you see that?

A. Yes.

269. Q. Okay. And under "Results," it says, last sentence:

"Although the difference observed was not statistically significant, the 95 percent CIs are compatible with a 46 percent reduction to a 23 percent increase in infection."

A. Yes, it says that.

270. Q. So that means that the masks either reduced infection by 46 percent or increased it by 23 or somewhere along the line in the middle is what happened?

A. Well, it's the 95 percent

confidence interval, so it suggests that a true effect is probably found -- they're 95 percent certain that the true effect of masking wearing is somewhere between a 46 percent reduction to a 23 percent increase in infection.

271. Q. Right. We don't have more information along where in that spectrum it falls. We just have a 95 percent confidence interval.

A. Yeah. That's a standard way of reporting a result of a randomized control trial.

272. Q. Right, but the CDC criticized it as having an inconclusive finding I think because of the range; do you agree?

A. Well, they criticize it because it was inconclusive, but the finding was that there was not a statistical benefit of masking. Any paper can be criticized if it finds a negative result.

They speculate that there simply wasn't enough participants. And we've seen that with the Bangladesh study that you need very very very large numbers of participants to actually find the benefit, and so the Bangladesh study and this study actually go well together because masking only has a very small, limited benefit if it's done at very large levels for long periods of time.

273. Q. So on page 5 under "Discussion" --
A. Um-hmm.
274. Q. -- last full sentence in the left-hand column --
A. Um-hmm.
275. Q. It's says:
"The findings, however, should not be used to conclude that a recommendation for everyone to wear masks in the community would not be effective in reducing SARS-CoV-2 infections, because the trial did not test the role of masks in source control of SARS-CoV-2 infection."
Do you see that?
A. Yes.
276. Q. So this study did not test the role of masks in source control which we know is one of the two main ways that masks function.
A. That's right, but the Bangladesh study did.
277. Q. Right, but we're just talking about this study now.
A. Correct.
278. Q. And they're saying we shouldn't

conclude, based on this study:

"That a recommendation for everyone to wear masks in the community would not be effective."

That's what this sentence says.

A. Yeah. And I think using the same logic we shouldn't conclude that masks are effective because we don't have strong evidence either way. The best evidence that we have is from randomized control trials. And these are two that we discussed.

279. Q. And at paragraph 31 you don't point out this qualification that the authors used?

A. Paragraph 31, let me just go there. That's right.

280. Q. Okay. And then at page 7, second last sentence, the authors highlight this fact. They've already stated it, but then they says:

"Although masks may also have served as source control in SARS-CoV-2-infected participants, the study was not."

A. Sorry, where are we? Sorry.

281. Q. The second full paragraph.

A. Second full paragraph.

282. Q. Yeah.

A. Okay.

283. Q. That last sentence:

"Although masks may also have served as source control in SARS-CoV-2-infected participants, the study was not designed to determine the effectiveness of source control."

Do you see that?

A. Yes.

284. Q. And then it says:

"The most important limitation is that the findings are inconclusive, with CIs compatible with a 46 percent decrease to a 23 percent increase in infection."

Do you see that?

A. I do see that.

285. Q. Okay. And then down in the last full paragraph, in the middle it says:

"Yet, the findings were inconclusive and cannot definitively exclude a 46 percent reduction to a 23 percent increase in infection of mask wearers in such a setting."

Do you see that?

A. Yes, it says that.

286. Q. And then it says again:

"It is important to emphasize that this trial did not address the effects of masks as source control or as protection in settings where social distancing and other public health measures are not in effect."

A. Yes, it says that.

287. Q. Okay. You mentioned influenza, but you'd agree with me that COVID has a higher hospitalization and death rate than influenza?

A. Well, it depends on what you mean by "influenza," because influenza, like COVID, has different strains, so every year, or every few years there's a new predominant strain you know. In influenza we called it "strains." In COVID we call it "variants," and so --

288. Q. Fair enough. Fair enough. I'm talking about --

A. Some of them are very severe, some influenza --

289. Q. Right.

A. -- like 100 years ago.

290. Q. Right. I'm talking about

non-pandemic influenza, what we've seen in the last 20 years for instance.

A. Yeah, I -- I would agree with that.

291. Q. We've had about 30,000 deaths in Canada from COVID?

A. Yes.

292. Q. And are you aware of how many deaths there were in the last full influenza season, 2018/2019?

A. I don't have it offhand, but on average it's about -- I think about 3,000 deaths. It really varies year to year I think, but on average it's about 3,000 deaths a year.

293. Q. So if I told you it was 225 in the last full influenza season you'd be surprised?

A. What season was that?

294. Q. 2018/2019.

A. Okay. Yeah, I would find that surprising, yeah. The challenge with influenza is that would probably just be limited to tests proven, but many -- because we don't do nearly the testing and follow up with influenza as we've done with COVID-19 the estimated rates are certainly much higher than that.

295. Q. I just want to show you a document.

Do you recognize FluWatch from PHAC?

A. Yes.

296. Q. Okay. I just want to show you. This was an exhibit in another cross-examination, so I don't think we need to make it an exhibit, but on page 8 it says that there were:

"A total of 613 ICU admissions and 224 deaths were reported this."

Flu "season;" do you see that?

A. Yes, I see that, but that would only be limited to ICU admissions, so that's how many deaths were in the ICU. So the actual number of deaths of influenza would be considerably greater.

You're -- you're -- you're limiting the number of deaths to ICU, but the number of actual deaths to influenza would be many many more than that, because most deaths of influenza did not get into the ICU.

297. Q. Well, we can distinguish between reported deaths, but there's nothing in here that limits the number of deaths to ICU admissions here.

A. I don't have that full document, but it appears as though, from what I can see, that's what that's limited to, is telling -- saying at 613 ICU admissions and 24 deaths -- 224 deaths.

298. Q. Well, we may have to come back to this document because certainly in the other -- in the other cross-examination it was recognized that there were 224 deaths. It does say "and" there. It doesn't say "of;" do you see that?

A. Um-hmm. Again, I don't have the whole document, so before kind of concluding that I would want to read the entire document myself.

299. Q. Okay.

MR. GUTTMAN: Maybe we should take a quick break now. I can send you the documents in case --

MR. KITTREDGE: Sure.

MR. GUTTMAN: -- I have more questions on it.

MR. KITTREDGE: Sure. I'll send it to your lawyer who can -- the lawyer for the JCCF who can -- actually, you already have it, Mr. Kittredge. Can you just send it to Dr. Warren?

MR. KITTREDGE: I don't actually have it myself on me. Hadam Kerr (ph) had that, that document. I'm sure it's in the file somewhere, but I don't have it --

MR. GUTTMAN: Okay. I'll send --

MR. KITTREDGE: -- right in front of

me.

MR. GUTTMAN: I'll send it to you.

MR. KITTREDGE: Okay. Great.

MR. GUTTMAN: So maybe we could take a break to 3:10. Can we go off the record?

MR. KITTREDGE: Sure.

---RECESS TAKEN

---UPON RESUMING

MR. GUTTMAN: So if we could make that FluWatch document an exhibit, Madam Reporter?

COURT REPORTER: Yeah, so that would be Exhibit 8, flu document. Could you give me the author again?

MR. GUTTMAN: It's FluWatch.

COURT REPORTER: FluWatch. Okay.

MR. GUTTMAN: -- 2018, 2019 Influenza season. The author is PHAC.

COURT REPORTER: Okay. Thank you so much. It's been noted as Exhibit 8.

EXHIBIT NO. 8: FluWatch 2018, 2019 Influenza season, author PHAC.

BY MR. GUTTMAN:

300. Q. Okay. Dr. Warren, I want to talk about risk factors for contracting COVID-19.

A. Can we just go back to this

document now that I've had a chance to look at it so I can answer your questions?

301. Q. Well, our position is that it's 224.

A. Yeah, so those 224 deaths, if you look in the document it says those are reported from sentinel sites and surveillance. So FluWatch is a compilation of surveillance data, so there are different sites that act as sentinel surveillance and keyed information into FluWatch.

And so the actual number of deaths per year for influenza is much higher than that. And so I've sent Mr. Kittredge an email to a link to an official Canadian website that I've asked him to forward to you, and on that official website, from Canadian website -- do you have access to that?

302. Q. I do not.

A. Okay. Mr. Kittredge, could you send that?

MR. KITTREDGE: I did send it. I didn't look at it. Dan, do you have that?

MR. GUTTMAN: Hold on a sec.

MR. KITTREDGE: It's titled --

MR. GUTTMAN: Yes, I have it.

MR. KITTREDGE: So just for the record

I just forwarded that alone. I received it from Dr. Warren and just forwarded it to you.

MR. GUTTMAN: Okay.

THE WITNESS: This is a website from the Government of Canada. It's Influenza for Health Professionals. And if you scroll down it says, "Epidemiology of influenza in Canada." It says:

"Each year in Canada, it is estimated that influenza causes approximately: - 12,200 hospitalizations."

And "3,500 deaths." So the -- and then right underneath that it says, "Surveillance, FluWatch surveillance," and it explains how that works. And so the number of confirmed deaths from sites that act as surveillance centres is the number you mentioned, but many -- it's known from many studies and -- that many of the deaths, probably most, the vast majority influenza deaths that occur in Canada do not occur at these sentinel sites.

And so the estimated number of influenza deaths per year in Canada, and it ranges based on the severity of the flu season, is 3,500 deaths.

303. Q. Okay. And that's a tenth of what

is -- of the COVID deaths.

A. In the first year, well, I wouldn't say a tenth. In the first year we had, I think it was closer to -- I can look it up. I have it in my -- my report.

304. Q. Well, anyway, you haven't disagreed with me that hospitalization and death rates are higher per COVID, right?

A. They are higher, that's correct.

305. Q. Okay. Thank you.

MR. KITTREDGE: Can you mark that as an exhibit? It's a bit of an unconventional route.

MR. GUTTMAN: I'll let you do that in re-exam.

MR. KITTREDGE: Great. So I take it you have no issue with me opening that link?

MR. GUTTMAN: Well, at this point I don't think so.

MR. KITTREDGE: Okay. Great.

BY MR. GUTTMAN:

306. Q. So moving along, talking about risk factors for contracting COVID-19, would you agree with me, Dr. Warren, that the prevalence of COVID-19 in the community affects the risk of contracting COVID-19?

A. Yes.

307. Q. And that the level of vaccination in the community affects that risk?

A. It's one of the factors, yes.

308. Q. Right. And you have a higher risk of contracting COVID-19 indoors than outdoors?

A. Yes, much higher.

309. Q. And the more people present in a venue at one time the higher the likelihood that there will be someone there who has and can transmit COVID-19?

A. Yeah, that's dependent on a number of factors when you say indoor, size of facility, ventilation. You know it's going to be different at a mall if you have a mall versus you know a small business where people are in an enclosed space.

310. Q. And one of the factors is how closely people are crowded together, right, in the venue?

A. Yes.

311. Q. And sitting next to someone for a prolonged period of time is riskier than just passing by somebody?

A. The time spent with a person would influence the risk of transmission, yes, that's why studies have shown that most transmissions -- some

studies, and I think I quoted in my report, that 80 percent of transmission occurs in households because people are spending very long periods of time in households.

And other studies have shown that casual contact, so that's any kind of casual contact outside of the patient's -- of the person's home, with someone that's not a family member, the risk of transmission is approximately one percent. So about one percent of cases are from those casual transmissions, whereas up to 80 percent in some studies of transmission is within households because they're spending long periods of time close together.

MR. GUTTMAN: Okay. I'm not seeing any indications from my team, so I think those are my questions. And Mr. Kittredge will have a few questions for you.

MR. KITTREDGE: Yeah. Can we take 20 minutes?

MR. GUTTMAN: Sure.

MR. KITTREDGE: Okay. Great. So let's say twenty to four we'll be back.

MR. GUTTMAN: Okay.

MR. KITTREDGE: Okay. Perfect. I'll see you then.

---RECESS TAKEN

---UPON RESUMING

CROSS-EXAMINATION BY MR. HUNTER:

312. Q. Good afternoon, Dr. Warren. I'm John Hunter, another counsel for Ontario. Just wanted to ask you one follow up question from the discussion you had with Mr. Guttman about the number of deaths attributed to influenza.

And you were talking about a Government of Ontario -- sorry, Government of Canada website, correct?

A. Yes.

313. Q. And are you aware of the source of the data that's reported on that website?

A. No, I'm just referring to the website. Do you have it in front of you?

314. Q. Yes.

A. Yeah.

315. Q. So there's just the statement that is, "Epidemiology of influenza in Canada." That's the portion you're referring to?

A. Yeah.

316. Q. Would you agree with me if I suggest that that data was taken from -- it's a NACI document that was sited later down in the paper

called, "Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2021-2022"?

A. I don't know that that's what they referenced. Those type of numbers are very familiar to me. Again, I -- I don't have that literature in front of me, but that's the kind of the -- the numbers I'm used to, so I'm certain they have a good evidence base for that. The NACI documents may or may not. I don't know where they got that number from.

MR. HUNTER: All right. Thank you. Those are my questions then.

MR. KITTREDGE: Okay. I guess to begin with -- oh, I'm sorry, I have to start Zoom. Could I mark that document without showing it to him myself? I can mark it based on what he was shown before, right, otherwise I have to start a new Zoom session on my desktop.

MR. HUNTER: Are we talking about the website?

MR. KITTREDGE: Yeah, the website that he referenced, and you referenced and Guttman referenced.

MR. HUNTER: I'm fine with that.

MR. KITTREDGE: All right. Can we

please mark that website as Government of Canada flu information as an exhibit?

MR. GUTTMAN: Well, no objection. We actually just pdfed it so we'll --

MR. KITTREDGE: Okay. Great. I'll take that.

EXHIBIT NO. 9: Government of Canada flu information.

MR. KITTREDGE: Perfect. All right. Thank you very much.

RE-EXAMINATION BY MR. KITTREDGE:

317. Q. Now, Dr. Warren, you were asked about studies related to mask wearing, and you talked about qualities like randomization and meta-analysis, and you mentioned that there are high qualities studies and low quality studies. Can you tell us a little bit more about what makes a study high quality and what makes a study low quality?

A. Sure. So that's you know part of epidemiological training, and has issues to do with the reliability of the data and issues with bias and confounding and size of studies.

So studies that look at say ecological studies, so ecological studies are say just comparing one country to another, but they are -- there's all

sorts of bias in confounding that can occur there. So while we would look at say one variable, masks, there may be another variable that's much more important that is actually having the effect, and so that would be confounding.

Bias would be things like the reliability of measurement of a particular type of infection, say COVID. So if one country has high mask use, but also does not measure COVID rates that would be bias because it's a -- it's -- it has more to do with the measurement than the actual mask use. And so -- and then -- so that's one type.

Other things are case control studies or cohort studies, and they're similar in that they're not controlled and so you're looking just at two groups and seeing what happens over time, but there's the -- because there's not randomization they're also liable to a fair amount of both bias and confounding.

And so the highest quality evidence, which is widely recognized in epidemiology is randomized control trials and meta-analysis of randomized control trials. So some of the studies that are relied upon for masking are meta-analysis of case control studies or cohort studies. And some of them are very poor with very small numbers.

And so whenever you bring a whole bunch of bad studies together the combination of those bad studies is going to be bad no matter what. And I just mean bad in statistical evidence and statistical power.

And so the Chu study which I referenced and critiqued in the paper, or just really quoted a critique from -- specifically from the Cochrane review, the Chu study is widely sited, but all it is is a meta-analysis of very very small and poor studies which were case control and cohorts studies.

And so, yeah, I can you know bring that up, but some of the studies were in as low numbers of people as like less than 10 in each group whereas you know the randomized trial for the Pfizer vaccine, the original one, I think had 20,000 people in each side, 20,000 randomized vaccine, 20,000 randomized placebo.

You compare that to a meta-analysis of very small studies with maybe 10 people on each side, that was not randomized, not controlled. Putting all of that data together, it doesn't actually give you any firm conclusions at all.

And so the quality of the evidence allows one to make a stronger conclusion or not. And so I give you an example of -- use a vaccine example

many many times, because in order for a vaccine to be approved it has to have a large randomized control trial.

So the Pfizer vaccine, Moderna, Astra Zeneca, they all had very large randomized controlled trials. And randomized controlled trials for masks can be done. There were two. There was -- there's one ongoing in Africa as well, I think Guinea-Bissau or a west African country. And you know these types of trials can be done and they should be done, because then they actually quantitate how effective the intervention is or is not.

318. Q. All right. You mentioned that there's better scientific evidence to support the effectiveness of masking in healthcare settings. Could you tell us a little bit about that?

A. Sure. Again, I don't have all of that data here in front of me, but that has been studied over many years. And it -- it -- it does depend on the indication. So there are some settings where handwashing even or -- or masks have been studied, but haven't been found to be effective, things like MRSA colonization.

And so in some centres, some places, some places in Europe or the United States, they won't

do physical interventions like gowning or masking for some diseases that we would say do here in Canada because those studies are done. Whereas for other indications, say influenza, the evidence is there.

And so those randomized trials have been done. So randomized trials have been done and shown to -- that whatever it is, gowning, masking, not effective for some things, I give MRSA as an example, and there's conflicting -- there's some studies for, some studies against, but -- and then there are indications such as respiratory infections. And -- and -- and you know that's a high-risk setting.

So a setting of a nurse or a doctor in hospital, in a small hospital room, with someone known to be infected with that, or has syndromic symptoms consistent with, like we use the term "ILI" or "influenza-like illness," we often don't you know necessarily make the laboratory confirmed diagnosis all the time, but so when you look at a situation like that that is clearly very different than two healthy people interacting you know in a small store buying milk. And so the evidence in one doesn't necessarily translate into the other.

319. Q. And following up on that, are there any differences between healthcare settings in the

community at large that you think may affect the effectiveness of masks and infectious disease transmissibility in general?

A. Yeah, I think there is a lot of differences. I think in the healthcare setting the patients are known to be unwell, and so if you have a respiratory ward most hospitals have patients kind of grouped.

You have a neurology ward and a respiratory ward, things like that. So in a respiratory ward you have a high burden of illness in a very small area, which is very different than in the community. In the community just statistically you're going to not interact in nearly the same way with sick people as you would in hospital.

And I think an important thing -- there are many other things, but an important thing is the -- the type of potential mask or how it's used. Like as I said the Bangladesh study showed that non-medical mask, cloth masks, did have no effect.

And think about taking on and -- putting on and taking off masks, like healthcare workers are trained to do that because there's a particular way to don and doff PPE. And if it's not done appropriately you actually increase your risk.

Good examples of that is the Eboli outbreak in west Africa where some -- in some studies the highest risk of transmission for healthcare workers was at the time of donning and doffing their PPE, because if it's not done appropriately that's where you're going to get the risk.

And so in the community setting you have people using masks all sorts of ways that shouldn't be done. Like they're constantly pulling it up and down you know to -- to have a drink or whatever, they're touching the mask, putting -- in the healthcare setting that's totally against all the rules of hand hygiene and donning and doffing PPE.

So when you don PPE you used alcohol-based sanitizer or you wash your hands, then you put it on, and then you go in -- any time you you know have to touch your mask or something to adjust it you would do hand hygiene.

Same with doffing it, you come out, you do hand hygiene, then you take your mask off, then you do hand hygiene again. So all of these things in general are not done in the community.

320. Q. All right. And you were asked about the risk of infection in outdoor settings, and you said the risk was much lower than in indoor

settings. Can you tell me a bit more about the risk of infection in an outdoor setting?

A. Yeah, sure. So as I said in my report that the risk of transmission in other important respiratory infections, such as influenza and TB, they're not considered to be transmitted. And so in the absence of specific evidence to COVID-19 it's reasonable to extrapolate from similar very serious infections.

And while the, you know, number of deaths of influenza per year is less than COVID, historically over the decades and centuries it's certainly one of the most important respiratory diseases in history, as is TB. Neither of those illnesses are considered to have any significant transmission outdoors.

So that's what the base line should be. And then we need to say, okay, well, let's try to find some specific evidence about outdoor transmission in influenza. And as I quoted the rates are much much lower. And so I quote that one large study from China where they looked at over 7,000 cases, and there was really only one outdoor transmission involving two people.

And these -- I reference a few studies

from China because they're very helpful, because the Chinese are very good at being able to -- to track down every single case for every single contact. And so just based on that one, you know you're looking at a -- a risk that's 1,000 times less.

I -- I probably wouldn't say that definitely, but in the other references I cited I think we're looking at a risk of outdoor transmission, that's by at least 100 times less than indoor transmission.

321. Q. All right. And similarly, you were asked about the risk of asymptomatic transmission. And you mentioned that asymptomatic cases are far less infectious than symptomatic cases. Can you tell us a little more about that?

A. Yeah, so it can be hard to -- to measure, but in the studies I referenced it seems as thought the rate of transmission from asymptomatic cases is approximately 10 to 25 times less than in symptomatic cases.

And -- and in other places in my report I also talk about how the -- the viral load or, not the viral load, but the CT from swabs of persons with detectable COVID, but asymptomatic is much less, and so that's a correlate of the viral load. And so it's

thought that persons that are asymptomatic have lower concentrations of the virus within a respiratory tract.

322. Q. And just for the sake of keeping the information in the same section of the transcript, can you briefly explain what "CT" refers to?

A. Cycle threshold. And so that's with PCR. So as I indicated in my report PCR testing is one of the standard ways of testing for COVID-19 or SARS-CoV-2. And the cycle threshold is, as I indicated in reports, it's an amplification of the RNA, or into DNA, and it's the amplification number. So the lower it is the higher the amount of virus is in this group, and that was the test was taken from.

323. Q. Okay. Great. Towards the end of your discussion with Mr. Guttman regarding the aircraft carrier study, I believe that might have been Exhibit 1, but you mentioned that there is a natural reduction in COVID cases in the summer, and then at another point in your cross-examination you mentioned that an increase in cases in the winter, or in December is to be expected. Can you tell us a bit more about that?

A. Yeah, so all respiratory viruses follow seasonal patterns, certainly influenza. And as

I indicated in my report the other four coronaviruses together are one of the most important causes of the common cold, follow a seasonal pattern. And in that paper that I reference in the study it's clear that the peak every year is in January, at least in the United States. The study was out of the US.

And so all-important respiratory viruses, influenza, peri-influenza, human metapneumovirus, RSV and the seasonal coronaviruses all follow a seasonal pattern. And so it would be expected, and I showed in my report that COVID-19 does also follow a seasonal pattern.

And so certainly the highest peaks within Canada have been within the coldest months in the -- in you know almost two years that we've been seeing this virus in Canada. And that, as I explained in my expert report can be shown from many other jurisdictions around the world.

So in general it's not the only factor, but it's a very important factor. The colder it is and the less humid the -- which often go together, the -- you know there -- there's increased rates.

324. Q. Right. Would you expect to see cases rise and fall with the same seasonal sort of pattern if no measures were implemented to control

COVID? Obviously, the numbers may be different, but would you expect the seasonal pattern to stay the same?

A. Yeah, absolutely. So we have that every year with influenza with 10 other respiratory viruses, so there's a -- there's a season, there's a time, there's a -- usually a peak. They often don't overlap, so historically prior to COVID we would see something like RSV maybe in the fall, then influenza, and then after -- after influenza we would see peaks of other respiratory viruses, like peri-influenza and human metapneumo.

And so, yeah, they -- they all have a seasonal pattern. And they all have a peak. They rise and then they naturally come down.

325. Q. And I'd like to take you to the mask use in the context of COVID-19 interim guidance from the World Health Organization, which I believe was Exhibit 6 if I'm not -- yes, I think it's Exhibit 6. Are you able to pull that up?

A. Yeah, just give me a minute.

326. Q. Sure. We're just looking at the first page.

A. Right.

MR. GUTTMAN: Do you remember what

reference that was on my reference?

MR. KITTREDGE: I hate to scroll up and check because I'm kind of -- I'll lose my page entirely. It's at --

THE WITNESS: Yeah, I'll find it.

BY MR. KITTREDGE:

327. Q. Do you have the book of sources?

A. Yeah. I think it's --

328. Q. It's on page 12 of 18 of that.

MR. GUTTMAN: It's reference 63.

THE WITNESS: Yeah.

MR. KITTREDGE: Thank you.

THE WITNESS: Yeah. I'm bringing it up now. Okay. I've got it up.

BY MR. GUTTMAN:

329. Q. All right. On the first page, the very last section that's called, "Mask Use in Community Settings." There are two points, two bullet points there, one which has two sub-bullet points. Can you read the second point with its sub-bullet points to me, please?

A. Sure:

"In areas of known or suspected community or cluster SARS-CoV-2 transmission: WHO advises that the

general public should wear a non-medical mask in indoor (e.g. shops, shared workplaces, schools - see Table 2 for details) or outdoor settings where physical distancing of at least 1 metre cannot be maintained."

Point two:

"If indoors, unless ventilation has been be assessed to be adequate1, WHO advises that the general public should wear a non-medical mask, regardless of whether physical distancing of at least 1 metre can be maintained."

330. Q. What was the guidance in Canada for physical distancing?

A. Well, the guidance in Canada is based on a two-metre physical distancing, which is different than the WHO here.

331. Q. All right. And you were asked about your professional experience. I wonder if you could tell us a little bit about your experience with COVID during the last two years?

A. Sure. So I practice clinical infectious diseases, so that means I'm seeing patients every single day that I'm not on vacation, and have

been in full-time practice for 10 years. As I said I primarily have an inpatient practice.

I'm on call for 17 weeks a year, so that's a third of the year. And then when I'm not on call maintain an outpatient practice as well as do some administrative work like medical microbiology, infection control.

So in the past two years or so, just under two years that COVID's been around, again, I've been on call a third of the time and have taken care of all kinds of COVID patients in the ICU, on the ward, and then much less kind of outpatient -- outpatient work.

Yeah, in our particular hospital we've had -- you know we've had the opportunity to help other hospitals and taking overflow cases from them, so I've seen the whole spectrum of -- of COVID cases from the very mild to the very severe.

332. Q. All right.

MR. KITTREDGE: I have no further questions, so thanks so much for your time.

THE WITNESS: Thank you.

MR. KITTREDGE: And I guess we're ready to go off the record, unless there's any objection to that?

MR. HUNTER: No.

MR. KITTREDGE: No.

---Whereupon the concluded adjourned at 4:03p.m.

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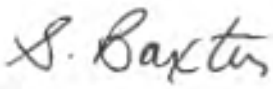

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SYNTHESIS

02/08/2021

COVID-19 Overview of the Period of Communicability – What We Know So Far

Introduction

Public Health Ontario (PHO) is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19). "What We Know So Far" documents provide a rapid review of the evidence related to a specific aspect or emerging issue related to COVID-19.

Updates to Latest Version

This document replaces the previous version *COVID-19 – What We Know So Far About…The Period of Communicability* (March 30, 2020) and presents results of an updated rapid review. This updated rapid review draws primarily on systematic reviews and meta-analyses, and primary research where applicable, updating evidence on the period of communicability.

See PHO's rapid review *Factors Affecting COVID-19 Period of Communicability – What We Know So Far* for the latest evidence on how host factors (e.g., age, immune system compromise, disease severity) can alter the period of communicability.[1]

Key Findings

- The specific period of communicability estimates varied among the reviewed studies and study types. Epidemiology studies found transmission occurred in the 3–5 days before symptom-onset and epidemiology, virus culture and modelling studies found transmission occurred in the 8–10 days post symptom-onset in index cases.
- While specific period of communicability estimates varied among the reviewed studies, there was concurrence that the risk of communicability peaked shortly before and after the time of symptom-onset in index cases.

Background

The period of communicability is when a patient is shedding virus at a sufficient quantity and viability to infect another person. Currently, the infectious dose for humans is not known. In a ferret model, inoculations of 5×10^4 to 5×10^6 plaque-forming units (PFUs) caused mild clinical disease with viral shedding in the upper respiratory tract (URT) of all animals (12/12), while a dose of 5×10^2 PFUs reduced shedding to 1/6 animals.[2] Infectivity is also dependent upon exposure time and route of transmission. Based on experiments in mice and modelling studies, the infectious dose was about 6.4×10^4 to 9.8×10^5 virus copies and the risk of a single virus copy to infect after one-hour exposure through aerosol route

was 10^{-6} to 10^{-4} and through close contact was $10^{-1.3}$. The infectious dose is an important metric that requires further research, especially when attempting to define the period of communicability using viral isolation and viral loads as measures.

For this rapid review, we infer the period of communicability of COVID-19 from studies investigating:

- Live virus culture
- Epidemiology and contact tracing
- Modelling
- Viral RNA shedding

Live virus refers to the detection of a cytopathic effect (CPE) in cell cultures or the isolation of live virus from cell cultures inoculated with clinical samples from patients with COVID-19. In general, the presence of live virus in a sample from a patient with COVID-19 is an indication that the patient is infectious; however, this does not always equate to infectiousness, as infectiousness is dose-dependent. Epidemiological studies with contact tracing are another good indicator of the period of communicability, especially for the presymptomatic transmission period, if accurate tracing of presymptomatic patients and their close contacts was conducted. Modelling studies, using information from the other types of evidence, provide additional insights into the period of communicability. Specifically, modelling studies are important for estimating the period of presymptomatic transmission and the period when transmission risk is highest. Viral RNA shedding provides additional evidence for the period of communicability and refers to the detection of various targeted RNA sequences in patient samples through reverse transcription polymerase chain reaction (RT-PCR). A positive RT-PCR may or may not represent the presence of live or infectious virus, as the RNA detected potentially only represents the presence of fragmented or residual viral particles.

This review synthesizes the current literature investigating the period of communicability of COVID-19, while considering the sub-intervals of the period of communicability: 1) presymptomatic transmission period, 2) period of highest risk of transmission, and 3) timing of when infectiousness ends.

Methods

In considering feasibility, scope, and a need for responsiveness, we chose a rapid review as an appropriate approach to determining the period of communicability of COVID-19. A rapid review is a knowledge synthesis where certain steps of the systematic review process are truncated in order to be timely (e.g., quality assessment).[4]

On December 2, 2020, PHO Library Services conducted a literature search in MEDLINE, National Institutes of Health (NIH) COVID-19 Portfolio (pre-prints), Embase and Scopus on December 3, 2020 (Appendix A; search strategies available upon request). We searched PubMed and Google Scholar on December 31, 2020 for additional articles of interest.

English-language peer-reviewed and non-peer-reviewed records that described the period of communicability of COVID-19 were included. We restricted the search to articles published after January 1, 2020. This rapid review concentrated on evidence from systematic reviews and meta-analyses, supplemented by primary literature where appropriate and necessary. We reviewed citations from included articles to identify additional research.

Prior to posting, PHO subject-matter experts review all "What We Know So Far" documents.

As the COVID-19 pandemic continues to evolve and the scientific evidence rapidly expands, the information provided in these documents is only current as of the date of the literature searches.

The potential impact of COVID-19 variants of concern on the period of communicability is out-of-scope for this rapid review.

Findings

We screened 371 reviews and 930 primary research articles for this rapid review (Appendix A). After screening the literature for relevant articles, we included 14 systematic reviews (with or without meta-analyses), 2 rapid reviews, and 29 primary research articles. 24.4% (11/45) of studies were non-peer reviewed pre-print articles.

We organized evidence by type (systematic review, then primary research if applicable), then by sample size (number of studies or patients). Evidence pertaining to the URT was selected as a primary focus of this review, as the URT is the most likely source of infectious Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). If authors did not report the total number of patients in a systematic review, only the total number of studies was included.

Live SARS-CoV-2 Shedding (Viral Culture)

Live virus was detected from 13 days before symptom-onset (BSO) to 32 days post symptom-onset (PSO). Authors did not routinely report average periods for live virus detection or isolation, rather they reported ranges or time-specific probabilities of detection. Nonetheless, the probability of detecting live virus was highest in the 8 to 10 days PSO, with few studies examining communicability BSO (Figure 1).

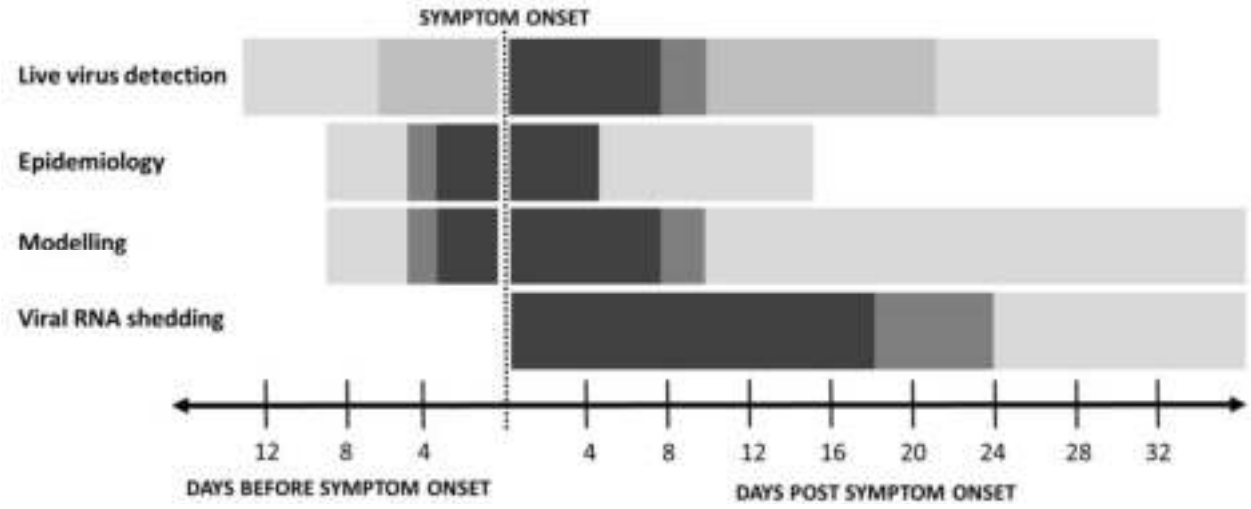
SYSTEMATIC AND RAPID REVIEWS

We examined five systematic reviews that reported on the detection of live SARS-CoV-2 from respiratory samples collected before (n=2 studies) and after (n=5 studies) symptom-onset (2 studies examined both periods). The detection of live virus was reported from 6 days BSO to 32 days PSO, with most studies reporting transmission within 10 days PSO.

- In a rapid review of 25 studies, the Public Health Agency of Canada (PHAC) reported that live SARS-CoV-2 was detected from respiratory samples collected from patients 1–6 days BSO and up to 8–10 days PSO.[5]
- In a systematic review, Walsh et al. adapted data from Singanayagam et al. to estimate viral culture positivity from respiratory samples (n=121 samples).[6,7] At 7 days PSO, the estimated culture positivity was 40.1% (95% confidence interval [CI]: 22.8–60.4), positivity decreased to 6.0% (95% CI: 0.9–31.2) at 10 days PSO and 0.03% (95% CI: 0.0–9.4) at 14 days PSO. Among the 13 studies included in the review, five reported the last day of positive culture occurred within 10 days PSO, another five studies reported that 3% of patients had positive cultures later than 10 days PSO.
- In a systematic review of 13 studies and 1,314 patients, Park et al. (pre-print) reported that the median duration of live virus shedding in respiratory samples was 9 days PSO (interquartile range [IQR]: 10), the mean ± standard deviation (SD) duration was 11.8 ± 8.47 days PSO (range: 2–32 days).[8]

- In a systematic review of 8 studies and 359 patients, Cevik et al. reported that no live virus was detectable in URT samples collected later than 9 days PSO.[9] The authors also noted that viral loads in URT samples peaked during the first week of illness.
- In a systematic review and meta-analysis of 4 studies and 304 patients, Fontana et al. reported that successful virus isolation from respiratory samples ranged from 6 days BSO to 20 days PSO.[10]

Figure 1. Summary of the period of communicability of COVID-19, for each type of study. The relative proportion of studies reporting a finding increases as the shading darkens (higher relative concordance among studies = black; lower relative concordance among studies = light grey).



PRIMARY RESEARCH

In 11 primary research articles, the detection of live SARS-CoV-2 from respiratory samples ranged from 13 days BSO to 32 days PSO. The majority of live virus detections were from respiratory samples collected within 10 days PSO (Figure 1).

- Singanayagam et al. examined 246 URT samples (RT-PCR positive) from 176 patients (mild to moderate disease in the United Kingdom) and found the median duration of live virus shedding was 4 days PSO (IQR: 1–8; range: -13 to 12).[7] The culture positivity rate was significantly higher during week 1 than week 2 (74% vs 20%; p=0.002).
- In a study of 195 patients in Australia, Basile et al. reported that the mean period from symptom-onset to positive viral culture was 4.5 days (range: 0–18).[11] Cultures were more likely to be positive from samples collected within the first week PSO, compared to the second week (80% vs. 45%; p=0·002), and between the second and third week (45% vs. 4%; p<0·001).
- In a study of 155 patients (174 nasopharyngeal [NP] swabs and 9 sputum samples) in Marseille, France, La Scola et al. did not detect live virus in respiratory samples collected after 8 days PSO, although viral RNA shedding occurred up to 20 days PSO.[12]
- In a study of 129 patients with severe disease in The Netherlands, van Kampen et al. reported that less than 5% of respiratory samples had viable virus when collected at 15.2 days PSO (95%

CI: 13.4–17.2) or more.[13] The median time of infectious virus shedding was 8 days PSO (IQR: 5–11; range: 0–20).

- In South Korea, researchers studied 285 patients that were repeat-positive by RT-PCR after being discharged from isolation after 14 days.[14] The average time from symptom-onset to re-positive test was 44.9 days (range: 8–82). No live virus was detected on respiratory samples from 108 patients; however, it is unclear when samples were collected for these patients.
- In a study of 105 patients in Spain, Folgueira et al. (pre-print) reported that the proportion of respiratory samples with positive cultures decreased as time from symptom-onset increased.[15] In hospitalized patients with severe disease (n=56 samples), 56.0% (14/25) of samples collected within 7 days PSO produced a positive viral culture, followed by 60.0% (9/15) of samples collected 8–14 days PSO, 60.0% (6/10) from 15–21 days PSO, and 33.3% (2/6) past 21 days (latest was 32 days PSO).
- Bullard et al., in a Manitoba study of 90 samples, reported that the probability of successful viral culture in NP swabs peaked at 80% at 3 days PSO (no growth occurred >8 days PSO).[16]
- In a Singapore study of 74 patients (152 samples), Young et al. reported that all NP swabs failed to grow in culture after 14 days PSO. In culture-positive NP samples, 57.1% (12/21) of positive samples were collected at 7 days PSO or less; 42.9% (9/21) were collected more than 7 days PSO (latest was 14 days PSO; 20/21 of positive samples were collected ≤10 days PSO).[17] Virus isolation decreased as PSO time increased (OR: 0.81; 95% CI: 0.70–0.92; p<0.0001).
- Perera et al. (pre-print), in a study of 35 patients (32 with mild disease; 68 samples) in Hong Kong, found that live SARS-CoV-2 were rarely detectable beyond 8 days PSO.[18] From 1–2 days PSO, 53% (8/15) of samples were successfully cultured, followed by 35% (8/23) at 3–8 days PSO, and 0% (0/30) at 9–30 days PSO.
- Sohn et al., in a study of 48 patients in South Korea with no symptoms or with mild disease in the late phase of disease, reported that no samples produced CPE in cell cultures when collected 20 days PSO or more.[19]
- In a skilled nursing facility in Washington, United States (US), Arons et al. reported that in 17 of 24 presymptomatic patients, live virus was detected from 6 days BSO to 9 days PSO.[20]

Epidemiological Studies

The period of communicability from epidemiological studies ranged approximately from 9 days BSO to 15 days PSO, with most transmission occurring approximately 3–5 days BSO to 5 days PSO (Figure 1).

It is important to note that definitions for asymptomatic, presymptomatic and symptomatic patients varied among studies. In addition, studies varied in their definitions of index cases (e.g., symptomatic or asymptomatic, or both included) and not all studies tested asymptomatic contacts of index patients.

SYSTEMATIC REVIEWS

No systematic reviews or meta-analyses examined the period of communicability of COVID-19 using epidemiological studies. However, five systematic reviews and meta-analyses reported that secondary attack rates were lower among contacts of presymptomatic patients, compared to symptomatic patients. These studies demonstrated that the risk of transmission from presymptomatic and asymptomatic index cases was relatively lower, compared to transmission from symptomatic cases, and that most transmission occurred after symptom-onset in index cases.

- In a systematic review of 19 studies, Madewell et al. reported that the household secondary attack rate in contacts of symptomatic cases (20%; 95% CI: 14.0–25.7) was significantly higher than that for asymptomatic cases (0.7%; 95% CI: 0.0–3.8) (p<0.001).[21] The authors noted that primary studies varied with respect to how they defined index cases and household contacts. In addition, the authors could not rule out transmission from outside households (which could lead to overestimation of secondary attack rates).
- In a systematic review and meta-analysis of five studies, Byambasuren et al. reported that the secondary attack rate was 42% lower among contacts of asymptomatic cases compared to symptomatic cases (pooled relative risk [RR]: 0.58; 95% CI: 0.34–0.99; p=0.047; fixed-effects model).[22] The authors defined exposure as contact with a confirmed case or potential contact with another pre-symptomatic person.
- In a living systematic review and meta-analysis of five empirical and modelling studies, Buitrago-Garcia et al. reported that the secondary attack rate was potentially lower in contacts of asymptomatic cases than symptomatic cases (pooled RR: 0.35; 95% CI: 0.10–1.27).[23] Similarly, the secondary attack rate was possibly lower for contacts of presymptomatic cases versus symptomatic cases (pooled RR: 0.63; 95% CI: 0.18–2.26).
- In a systematic review of three studies, Koh et al. reported that household secondary attack rates in contacts of symptomatic index cases (20.0%; 95% CI: 11.4–28.6) was higher than the secondary attack rates in contacts of asymptomatic index cases (4.7%; 95% CI: 1.1–8.3) (RR: 3.2; 95% CI: 1.5–7.1).[24] The authors noted that clinical definitions and follow-up periods varied among studies.
- Qiu et al. (pre-print) in a systematic review reported that the secondary attack rate in contacts of asymptomatic patients ranged from 0.0–2.8% (n=9 studies), which was lower than the secondary attack rates from presymptomatic patients that ranged from 0.7–31.8% (n=10 studies).[25]

PRIMARY STUDIES

We reviewed 11 epidemiological and contact tracing studies (primary studies) which were in general agreement with findings from viral culture studies. The period of communicability ranged from 9 days BSO to 5 days PSO, with most transmission occurring 3–5 days BSO to 5 days PSO.

- In a contact tracing study of 100 index cases and 2,761 close contacts in Taiwan, Cheng et al. reported that the secondary attack rate was 1.0% (95% CI: 0.6–1.6; n=1,818) when contacts were exposed to index cases within 5 days PSO.[26] When contacts were exposed to index cases after 5 days PSO, the secondary attack rate was 0.0% (95% CI: 0.0–0.4; n=852).
- In a study of 72 infector-infectee pairs in South Korea, Chun et al. estimated that the mean transmission-onset was 1.3 days PSO (95% CI: 0.38–2.55) and the median transmission-onset was 0.68 days PSO (95% CI: -0.09 to 1.73).[27] Transmission-onset peaked at 0.72 days BSO.
- In a study of 47 clusters (53 index patients and 100 secondary cases) in Beijing, China, Zhang et al. reported that 15 secondary cases were exposed to index patients up to 5 days BSO (n=2 clusters).[28]
- In an epidemiological study of 93 cases in Singapore and 135 cases in Tianjin, China, Tindale et al. estimated that infections occurred an average of 2.0 days BSO in Singapore and 3.7 days BSO in Tianjin.[29]
- In a contact tracing study of 15 cases in Wuxi, China, Gao et al. reported that transmission occurred from 2–9 days BSO.[30]

- Gong et al. studied three clusters (14 cases) in Shanghai, China, where 5 secondary cases were infected by index cases from 1–7 days BSO to 1 day PSO.[31]
- In a study of 243 cases in Singapore, Wei et al. determined that in 4 of 7 clusters, transmission occurred 1–3 days BSO, while timing of infection in the remaining 3 clusters could not be determined.[32]
- Xia et al. (pre-print) reviewed 74 secondary cases from Hubei Province, China. The majority of the secondary cases (73.0%) were infected BSO of first-generation cases, while 18.9% and 8.1% were infected on the same day of symptom-onset or PSO (latest was 15 days PSO), respectively. 66.2% of the secondary cases were infected within 3 days BSO, with 6.8% prior to 3 days BSO (earliest was 5 days BSO).[33]
- In a cluster (9 cases) investigation in Shanghai, China, Kong et al. reported that transmission occurred in secondary cases 3–4 days BSO in index cases; seven cases occurred due to exposures on the day of onset to 2 days PSO.[34] The secondary cases had additional contacts that could have contributed to transmission, but the authors attest risk was low since they were asymptomatic during a 14-day quarantine period (no positive RT-PCR tests).
- In a family cluster in Zhoushan, China, Li et al. reported that 4 of 5 familial contacts were possibly infected after exposure to the presymptomatic index case 4–7 days BSO.[35]
- In a study of a cluster of 8 cases in Hefei, China, Huang et al. reported that 6 of 7 secondary cases were likely exposed 1 day BSO in the index case, one case was exposed either 3 days BSO or 1 day PSO.[36]

Modelling Studies

Modelling studies were in agreement with other lines of evidence for the period of communicability of COVID-19. Specifically, modelling studies identified that the risk of transmission is highest just before and after the time of symptom-onset in index cases, with most transmission occurring approximately 3–5 days BSO to 8–10 days PSO (Figure 1).

SYSTEMATIC AND RAPID REVIEWS

One systematic review and meta-analysis and a rapid review modelled the period of communicability.

- Benefield et al. (pre-print), in a systematic review and meta-analysis of 32 studies and 715 patients, reported that the individual-level viral dynamics of SARS-CoV-2 show a clear pattern of a peak in viral load at or before the appearance of symptoms and a steady log-fold decline over the next 21 days.[37] The pooled median duration of viral RNA shedding (49 studies and 917 patients) in respiratory samples was 4.8 days PSO (95% CI: 4.4–5.1), with a 5th percentile of 0.5 days (95% CI: 0.46–0.58) and a 95th percentile of 43.7 days (95% CI: 38.6–48.9). The authors attest that RNA positivity represents presence of live and infectious virus, rejecting existing evidence that RNA-positivity does not always represent live virus; therefore, caution must be used when interpreting the authors' conclusions.
- In a rapid scoping review of 13 studies and through modelling, Byrne et al. reported the central tendency of the preclinical infectious period to range from about 0.5–4.0 days BSO with one study as an outlier at 8.2 days.[38]

PRIMARY STUDIES

Seven modelling studies examined the period of communicability. In most modelling studies, the risk of communicability peaked at symptom-onset in index cases.

- He et al. reported that infectiousness peaked at symptom-onset or day zero (95% CI: -0.9 to 0.9), decreasing rapidly by 7 days PSO.[39] The authors further estimated that the proportion of presymptomatic transmission was 44% (95% CI: 30–57). He et al. estimated that the proportion of transmission earlier than 7 days BSO was less than 0.1%, 1% at 5 days BSO or earlier, and 9% at 3 days BSO or earlier. The authors suggested that contact tracing should enquire about close contacts up to 2–3 days BSO. Slifka and Gao have raised concerns with the methodology and interpretation of findings in He et al.[40] Slifka and Gao contend that modelling studies tend to over-emphasize transmission at or before symptom-onset, due in part to smaller sample sizes during this period.
- After correcting coding in the He et al. model, Ashcroft et al. estimated that the proportion of presymptomatic infections traced at 1 day BSO in the index patient was 33% (95% CI: 19–51); at 2 days BSO was 61% (95% CI: 40–83); at 3 days BSO was 80% (95% CI: 57–96); at 4 days BSO was 91% (95% CI: 71–99); and at 5 days BSO was 97% (95% CI: 82–100).[41] The re-analysis and correction found a similar presymptomatic proportion of 45.6% (95% CI: 23.8–75.8) as He et al. The fraction of presymptomatic transmission was 3% at 5 days BSO or earlier and 20% at 3 days BSO or earlier. The authors suggest that contact tracing should enquire about close contacts beyond 3 days BSO, but do not define a specific end range.
- In a study of 1,178 patients and 15,648 contacts in China, Hu et al. (pre-print) modelled the period of communicability.[42] The greatest probability of transmission from index cases occurred 1.8 days BSO, with 95% of transmission occurring 8.8 days BSO to 9.5 days PSO.
- Prakash (pre-print), using published data on 1,251 patients, reported that infectiousness peaked prior to symptom-onset based on RT-PCR and live virus culture; however, the central tendency for this presymptomatic period was not reported but was approximately less than 2 days BSO (see Figure 3 in paper).[43] The proportion of presymptomatic transmission was 68.4% (95% CI: 67.0–69.7)
- Casey et al. (pre-print), in a modelling study that used published data, reported that the mean transmission time was from 2.9 days BSO (95% CI: 3.2–2.6) to 1.2 days PSO (95% CI: 0.9–1.6).[44] Using unweighted pooled estimates, the transmission peaked at 0.60 days BSO (95% CI: -3.01 to 1.81). The proportion of presymptomatic transmission from pooled estimates was 56.4% (34.9–78.0).
- Zhao developed a likelihood framework to estimate the presymptomatic transmission period from the serial interval observations from individual transmission events.[45] The estimated mean presymptomatic transmission period was 2.2 days BSO (95% CI: 1.3–4.7).
- Using mathematical modelling, with data on incubation periods and serial intervals, Zhang (pre-print) estimated that average presymptomatic transmission occurred 3.8 days BSO (SD: 6.1).[46]

SARS-CoV-2 RNA Shedding (RT-PCR Testing)

For this review, we avoided using cycle threshold (CT) values from RT-PCR testing to infer infectiousness, since individual studies use variable reaction conditions and target genes when correlating CT values in RT-PCR tests to respective live virus detection.[47,48] Therefore, comparisons among studies is not feasible.

Overall, studies investigating SARS-CoV-2 RNA detection were in agreement with studies detecting live virus or epidemiological studies. The detection of viral RNA decreased over time since symptom-onset, with most studies showing RNA detection up to 24 days PSO; however, there is no way to convert RNA shedding to infectiousness (Figure 1).

SYSTEMATIC REVIEWS

In seven systematic reviews and meta-analyses, the mean period of viral RNA shedding in respiratory samples was 17.0–28.7 days PSO (11.1–11.4 days in children). In two systematic reviews and meta-analyses, the median duration was 14.0–24.0 days PSO.

- In a systematic review of 133 studies, Park et al. reported that the median duration of viral RNA shedding in respiratory samples was 24.0 days PSO (IQR: 19), the mean ± SD duration was 28.7 days ± 15.8 days PSO (range: 5–95).[8]
- Walsh et al., in a review of 50 studies, reported that the viral load in URT samples was highest around the time of symptom-onset to a few days after, remained high for approximately 7 days PSO, and became undetectable within 14 days PSO.[49] Using 88 studies, the median duration of viral RNA shedding in URT samples was 14.5 days PSO (range: 1–53.5).
- In a systematic review and meta-analysis of 43 studies and 3,229 patients, Cevik et al. reported that the pooled mean duration of viral RNA shedding in URT samples was 17.0 days PSO (95% CI: 15.5–18.6) using a random-effects model.[9] URT viral RNA shedding was highest 0–5 days PSO, then decreases.
- In a systematic review and meta-analysis of 37 studies, Morone et al. reported that the median duration of viral RNA shedding from respiratory samples was 14 days PSO (IQR: 12).[50]
- In a systematic review and meta-analysis of 28 studies, Fontana et al. reported that the median duration of viral RNA shedding was 18.4 days PSO (95% CI: 15.5–21.3; range: 1–83).[10]
- Two systematic reviews focused on children (≤18 years).
    - In a systematic review of 17 studies of children, Xu et al. reported that the mean duration of viral RNA shedding in respiratory samples was 11.1 ± 5.8 days PSO.[51]
    - In a systematic review of 13 studies of children, Li et al. reported a pooled mean duration of viral RNA shedding was 11.4 days PSO (95% CI: 10.1–12.8).[52]

Limitations

We should acknowledge that a relatively large proportion (24%) of the research articles in this rapid review were non-peer-reviewed, pre-print articles. In addition, most of the systematic reviews we included used the same pre-print articles in meta-analyses. Considering the rapid emergence of the COVID-19 pandemic, the volume of pre-print research is expected given the need for rapid dissemination of data.

We did not check systematic reviews for overlap among reviews in the studies that they included. Further, we did not check if our included primary studies were included in the systematic reviews. Thus, there is some duplication of findings. Not all studies performed serial testing for the explicit purpose of determining the period of communicability; thus, some studies could underestimate the average duration of communicability.

In the case of epidemiological studies focusing on contact tracing, the evidence is still emerging and based mostly on small clusters. In contact tracing studies, it was not always possible to monitor all

contacts identified from the presymptomatic period of the index cases, likely leading to an underestimation of secondary attack rates attributed to exposure during this presymptomatic period. We must note that definitions for asymptomatic, presymptomatic and symptomatic patients varied among studies. In addition, studies varied in their definitions of index cases (e.g., symptomatic or asymptomatic, or both included) and not all studies tested asymptomatic contacts of index patients. The definitions of asymptomatic patients varied in studies, which could have led to overestimates and underestimates of secondary attack rates. In addition, there is likely time-dependent recall bias in determining close contacts, especially when looking further backward from date of symptom-onset. Furthermore, the definition of a contact varies among studies, leading to variability in estimates. In studies of asymptomatic index patients, it is unclear in some instances when potential exposure occurred; therefore, the date of first positive RT-PCR was day zero, potentially leading to shorter estimates of the period of viral RNA shedding. Clinical or surveillance definitions of asymptomatic, presymptomatic, and symptomatic patients are variable across studies, potentially affecting estimates of the period of communicability. Since sequencing of virus from index cases and secondary cases were not compared, it is possible that different strains were involved with infectee-infector pairs, thus not representing true transmission pairs.

There was a high degree of heterogeneity among studies used in meta-analyses, mostly due to varying methodologies and small sample sizes. Different studies also observed cell cultures for various periods of time (4 days to over 7 days) and used different cell lines, both factors that could affect the probability of detecting of live virus. The reaction conditions and specific gene targets used in RT-PCR assays varied among studies, making it difficult to compare studies and when performing meta-analyses.

Even when live virus is detected from patients, it is still not known if these patients are truly infective.[53] Factors to consider when determining infectiousness include viral loads, infectious dose, transmission route, and length of exposure. Given these limitations and the uncertainty associated with the period of presymptomatic infectiousness and prolonged shedding of live virus, a definitive period of communicability is difficult to state.

Period of Presymptomatic Transmission: Implications for Practice

Currently, Ontario recommends that the contact tracing period begins 48 hours prior to symptom-onset in the corresponding case or when the case had a positive sample collected (if asymptomatic at sample collection time).[54] This is aligned with other public health agencies in Canada and internationally.[55,56]

Under any scenario, extending the period >48 hours to trace close contacts may potentially identify and isolate additional exposed contacts, thereby, preventing further transmission. However, to our knowledge, there are no empirical studies testing the effectiveness of extending or shortening the presymptomatic period for contact tracing on reducing spread from exposed contacts. Given the relatively few primary studies of infector-infectee pairs assessing pre-symptomatic spread >2 days before symptom-onset, and their limitations to confidently identify the source case (vs the index case), there is insufficient evidence to extend the current pre-symptomatic period of communicability.

- In settings that are considered high-risk for transmission or where there are vulnerable populations (e.g., long-term care, congregate living, hospitals), an extension of the presymptomatic period of communicability to >48 hours could be considered to increase identification of exposed contacts. However, additional public health resources would be required to identify and trace potential contacts.

- In households, workplaces, and school environments where there has been ongoing exposure to a case, extending the presymptomatic period of communicability would likely not increase the effectiveness of contact tracing.

Conclusions

There are differences in the findings across included studies due to different designs and sample size; however, there were primary epidemiological studies identified that indicated individuals can be infectious up to 3–5 days prior to symptom-onset and epidemiological, live virus and modelling studies that indicated the period of communicability is approximately 8–10 days after symptom-onset, with infectiousness highest just before or after the time of symptom-onset.

PHO will continue to monitor the scientific evidence on the period of communicability of COVID-19, updating this document as necessary and making recommendations should a change in practice to contact tracing will be needed.

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Appendix A. Search Results

Databases searched

Database	Date searched	Remaining
MEDLINE	12/02/2020	716
Embase	12/03/2020	124
Scopus	12/03/2020	130
NIH COVID-19 Portfolio (Preprints)	12/03/2020	569

Records totals

Records source	Records
Records identified through database searching	1,539
Duplicates removed by bibliographic management software	238
Total records after duplicates removed	1,301
Total reviews	371
Total primary studies	930

Citation

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

An Outbreak of Covid-19 on an Aircraft Carrier

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ABSTRACT

BACKGROUND

An outbreak of coronavirus disease 2019 (Covid-19) occurred on the U.S.S. *Theodore Roosevelt*, a nuclear-powered aircraft carrier with a crew of 4779 personnel.

METHODS

We obtained clinical and demographic data for all crew members, including results of testing by real-time reverse-transcriptase polymerase chain reaction (rRT-PCR). All crew members were followed up for a minimum of 10 weeks, regardless of test results or the absence of symptoms.

RESULTS

The crew was predominantly young (mean age, 27 years) and was in general good health, meeting U.S. Navy standards for sea duty. Over the course of the outbreak, 1271 crew members (26.6% of the crew) tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection by rRT-PCR testing, and more than 1000 infections were identified within 5 weeks after the first laboratory-confirmed infection. An additional 60 crew members had suspected Covid-19 (i.e., illness that met Council of State and Territorial Epidemiologists clinical criteria for Covid-19 without a positive test result). Among the crew members with laboratory-confirmed infection, 76.9% (978 of 1271) had no symptoms at the time that they tested positive and 55.0% had symptoms develop at any time during the clinical course. Among the 1331 crew members with suspected or confirmed Covid-19, 23 (1.7%) were hospitalized, 4 (0.3%) received intensive care, and 1 died. Crew members who worked in confined spaces appeared more likely to become infected.

CONCLUSIONS

SARS-CoV-2 spread quickly among the crew of the U.S.S. *Theodore Roosevelt*. Transmission was facilitated by close-quarters conditions and by asymptomatic and presymptomatic infected crew members. Nearly half of those who tested positive for the virus never had symptoms.

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The U.S.S. *THEODORE ROOSEVELT* was conducting operations in the western Pacific Ocean when an outbreak of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred on board. On identification of the outbreak, the ship was diverted to U.S. Naval Base Guam. The base hospital, a 42-bed inpatient facility, provides medical care for U.S. military beneficiaries and others in the region. Although the initial response was handled by the medical staffs of the ship and Naval Hospital Guam, it was quickly augmented by a joint medical task force.

This report provides key findings from the U.S. Navy response and epidemiologic investigation of the outbreak. Over the course of the response, every member of the crew of the U.S.S. *Theodore Roosevelt* was evaluated, tested, placed in isolation or quarantine, and monitored on a daily basis to ensure their well-being. Our findings offer insights into the epidemiology and outcomes of SARS-CoV-2 infection in healthy, fit, military-aged adults who are housed in close quarters.

METHODS

INITIAL RESPONSE TO THE OUTBREAK AND FOLLOW-UP

The ship had been at sea for 13 days when three crew members presented to the medical department with symptoms suggestive of coronavirus disease 2019 (Covid-19). All three underwent testing by real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) and were found to be positive for SARS-CoV-2. Over the next 24 hours, additional symptomatic crew members and approximately 400 close contacts were identified by contact tracing. Four days after the first positive test result was reported, the ship reached Naval Base Guam. Crew members with confirmed cases of Covid-19 were placed in isolation on Naval Base Guam or in the base hospital. Persons with one or more negative Covid-19 tests and no symptoms were quarantined in hotels off base or on Naval Base Guam. In addition, essential personnel who were uninfected stayed aboard the ship in port.

All members of the crew underwent screening for signs and symptoms of Covid-19 and testing by rRT-PCR. Those who tested positive for SARS-CoV-2 were placed in isolation and received twice-daily symptom, temperature, and pulse oximetry checks. Those who tested negative were placed in quarantine. Ultimately, 4079 SARS-CoV-2–negative crew members who did not have symptoms were quarantined in 11 hotels in Guam. All were placed in single-occupancy rooms.

A surveillance model was implemented that relied on in-person health screenings. These screenings were supplemented by self-reporting with the use of a symptom checker developed by Defense Digital Service. Health screenings and symptom-checker data were collated and analyzed each morning by 9 a.m. and again in the evening by 9 p.m. Crew members who had progressive symptoms or were deemed to have conditions potentially placing them at higher risk for poorer outcomes were followed up with additional screening. Any crew members who were determined by on-site medical providers to need closer observation or treatment were transported to Naval Hospital Guam for care. In addition to Covid-19–related health surveillance, crew members received primary care, pharmacy, and psychiatric services to ensure a complete scope of medical coverage.

On completion of prespecified periods of isolation or quarantine, all personnel were required to undergo repeat rRT-PCR testing. To be eligible for exit testing, a crew member had to remain in isolation or quarantine for a minimum of 14 days. Those in isolation were also required to be symptom-free for 3 days before exit testing. Any crew member in quarantine in whom symptoms developed was tested and moved to isolation for at least 14 additional days. All crew members were followed up for a minimum of 10 weeks, regardless of their Covid-19 status.

LABORATORY TESTING

Nasopharyngeal swab specimens were obtained from all members of the crew with the use of viral transport medium swab kits. The presence of SARS-CoV-2 infection was determined by rRT-PCR testing with the Thermo Fisher ABI 7500 or the Bio-Rad CFX96 Touch Real-Time PCR Detection System. Samples were processed with either the Qiagen QIAamp Viral RNA Mini Kit or the Roche MagNA Pure 96 instrument for automated nucleic acid extraction, and testing was performed with the Seegene Allplex 2019-nCOV assay test kit or the Centers for Disease Control

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and Prevention (CDC) emergency-use-authorization assay.[1] These assays included the detection of two targets in the nucleocapsid gene, N1 and N2. Surveillance testing for influenza-like illness was conducted with the Biofire Respiratory 2 Panel.

COLLECTION OF OUTBREAK DATA

The Navy and Marine Corps Public Health Center was tasked with providing public health support for the outbreak investigation and conducting data analysis in alignment with its core public health mission. Data were collected as part of a coordinated public health outbreak investigation conducted by the Navy to bring the outbreak under control, ensure the well-being of the crew, assess the spread and effects of SARS-CoV-2, and implement measures to return the crew to work safely. Under Navy public health support criteria, the intent of the outbreak investigation was to mitigate spread, inform decision making, gather information for use in other outbreaks, and decrease the effect on the health of the crew. This project was deemed to be nonresearch with respect to the use of human subject information and was exempt from review by the institutional review board as an emergency public health outbreak investigation.

A roster of Electronic Data Interchange Personal Identifiers for the shipboard population was matched to Defense Manpower Data Center personnel rosters from February 2020 to identify demographic information for each crew member and to confirm personal identifiers. Civilian personnel and anyone with an Electronic Data Interchange Personal Identifier that did not match with Defense Manpower Data Center were excluded from analysis. The Defense Enrollment Eligibility Reporting System was used to identify race and ethnic group for all crew members. Ages of crew members at time of the outbreak were calculated from the date of birth to March 3, 2020.

Medical surveillance data collected by the ship medical department, Naval Hospital Guam, and the joint medical task force were collated with the roster to create a data set that included dates of symptom onset, daily clinical signs and symptoms, and test results. Data from the Defense Digital Service MySymptoms symptom-tracker application were also collated into the final data set. For the purpose of this analysis, fever is defined as subjective fever reported by the crew member or a measured temperature of 100.0°F or higher. All other symptoms were reported by the crew members. Data on health-related factors were obtained from a number of existing clinical Military Health System data sources, including the Armed Forces Health Longitudinal Technology Application and Military Health System Genesis.

A confirmed case of Covid-19 was defined as one in which a nasopharyngeal swab specimen was positive for SARS-CoV-2 by rRT-PCR. A suspected case of Covid-19 was defined as one that met Council of State and Territorial Epidemiologists clinical criteria for Covid-19 without a positive test result. Confirmed cases were further classified as symptomatic (with symptom onset before the first positive laboratory test), presymptomatic (with the first positive laboratory test before subsequent symptom onset), and asymptomatic (positive laboratory test but clinical criteria never met). Patients with confirmed or suspected infection were classified as having been hospitalized for Covid-19 if the admission diagnosis suggested a Covid-19–related illness.

STATISTICAL ANALYSIS

Data collation and analysis were performed with the use of SAS software, version 9.4 (SAS Institute). Baseline characteristics among crew members who were infected and those who were not infected were compared and univariate odds ratios with 95% confidence intervals were calculated with OpenEpi (www.openepi.com). For denominators of less than 20, odds ratios were not calculated. All reported odds ratios are not adjusted for multiple comparisons.

RESULTS

TIMELINE OF THE OUTBREAK

Between March 23 and May 18, 2020, a total of 1271 crew members (26.6% of the crew) tested positive for SARS-CoV-2. An additional 60 crew members had suspected Covid-19 (Fig. 1). Of the 1331 crew members with confirmed or suspected Covid-19, 572 (43.0%) remained asymptomatic throughout the outbreak, 293 (22.0%) were symptomatic at the time that they tested positive, and an additional 406 (30.5%) were presymptomatic at the time that they tested positive. In all, 978 (76.9%) of the 1271 crew members with labora-

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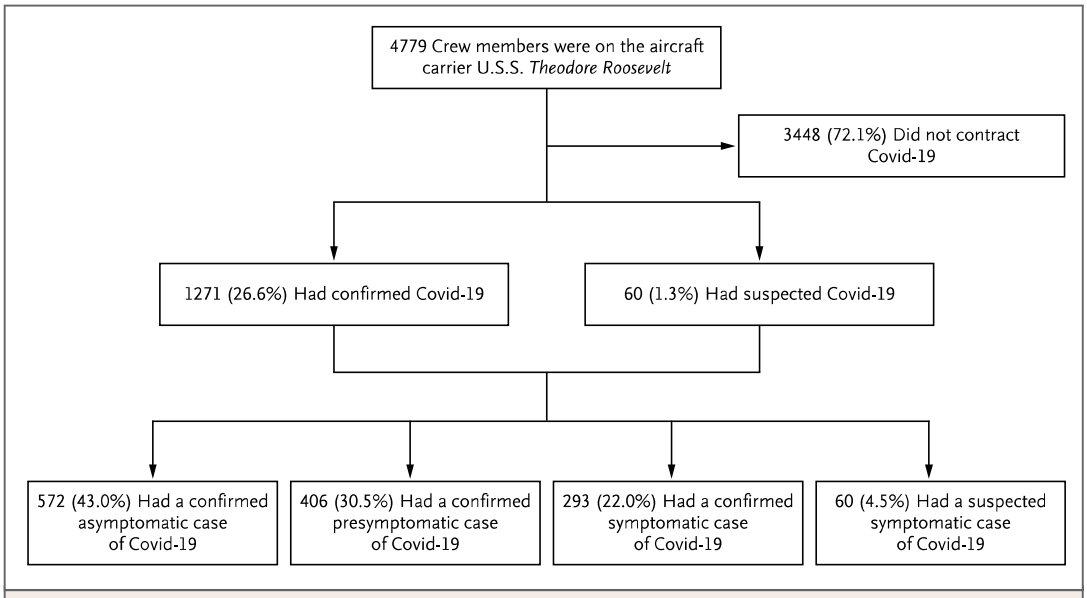

Figure 1. Distribution of Personnel According to Case Status.

A confirmed case of coronavirus disease 2019 (Covid-19) was defined as one in which a nasopharyngeal swab specimen was positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by real-time reverse-transcriptase polymerase chain reaction. A suspected case was defined as one that met Council of State and Territorial Epidemiologists clinical criteria for Covid-19 without a positive test result. Confirmed cases were further classified as symptomatic (with symptom onset before the first positive laboratory test), presymptomatic (with the first positive laboratory test before subsequent symptom onset), and asymptomatic (positive laboratory test but clinical criteria never met).

tory-confirmed Covid-19 did not have symptoms at the time that they tested positive, and 699 (55.0%) had symptoms develop at any time during the clinical course.

Testing for influenza-like illnesses had been conducted on a limited number of specimens before and after the start of the outbreak. Testing of specimens obtained from 5 crew members during the week before the outbreak identified 3 crew members who were positive for human rhinovirus or enterovirus, 1 who was positive for respiratory syncytial virus (RSV), and 1 with no pathogens detected. After the outbreak was identified on March 23, specimens from 16 crew members were tested: 10 crew members had no pathogens detected, 3 were positive for human rhinovirus or enterovirus, 2 were positive for coronavirus OC43 (not SARS-CoV-2), and 1 was positive for both human rhinovirus or enterovirus and RSV.

The outbreak epidemic curve is shown in Figure 2. In retrospect, crew members with symptomatic confirmed or suspected Covid-19 had symptoms as early as March 11, 2020, and continued to receive diagnoses up to the end of the analysis period. Epidemic curves according to sex and crew type show parallel infection rates for men and women. Although the ship docked in Guam on March 27, 2020, the outbreak continued for at least an additional 6 weeks.

CHARACTERISTICS OF THE CREW MEMBERS

The crew was predominantly young (mean age, 27 years) and male (78.3%) and was racially and ethnically diverse. At the time of deployment, all crew members were in general good health and met the U.S. Navy standards for sea duty. Ultimately, Covid-19 cases were evenly distributed across sexes, races and ethnic groups, and crew types (Table 1). Enlisted personnel (90% of the shipboard population) appeared more likely than officers to have confirmed or suspected Covid-19.

Data were analyzed to identify higher-risk work spaces. Those working in tighter spaces (e.g., reactor, engineering, supply, and weapons

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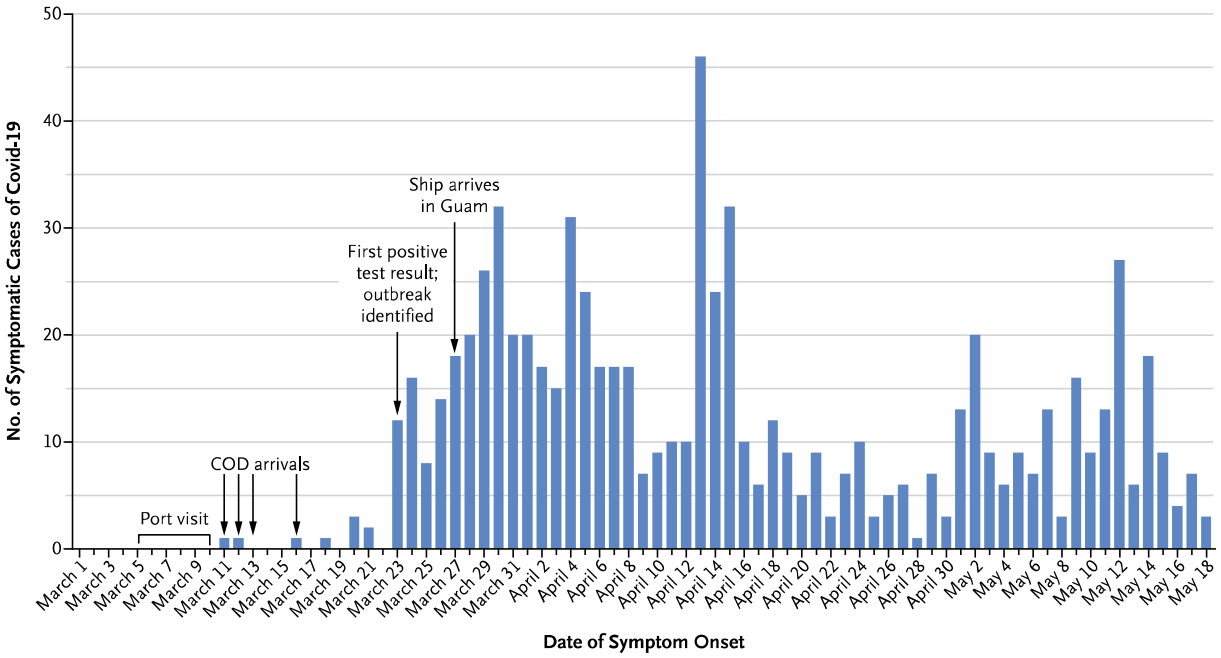

Figure 2. Numbers of Symptomatic Confirmed or Suspected Covid-19 Cases over Time.
Personnel, supplies, and mail are delivered to an aircraft carrier during carrier onboard delivery (COD).

departments) appeared more likely to have confirmed or suspected Covid-19 than those working in a combination of open-air and confined conditions (e.g., air and deck crew). Members of the medical department, who wore personal protective equipment when evaluating crew members, had a somewhat lower attack rate (16.7% [8 cases among 48 personnel) than the overall crew, despite being at highest risk as a result of exposure to patients with Covid-19 in a small space.

SYMPTOMS AND CARE

Among the crew members who had symptomatic Covid-19 (confirmed or suspected), headache was the most common symptom reported at any point during illness (occurring in 68.0%), followed by cough (59.5%), nasal or sinus congestion (43.8%), and altered sense of taste or smell (42.3%) (Fig. 3). The predominant symptoms reported at the onset of illness were cough (32.8%), headache (31.0%), and altered sense of taste or smell (24.1%). Shortness of breath at any point during illness was reported by 20.3% of the crew members with symptomatic cases, and 7.0% noted shortness of breath as an initial presenting symptom. In addition, 26.2% of the crew members with symptomatic Covid-19 reported chest pain or chest pressure at some point during their illness. Fever was reported as an initial presenting symptom by 5.3% of the crew members with symptomatic Covid-19, and fever at any point during illness was reported by 13.2%. Measured temperature readings showed that 2.8% of the crew members who had Covid-19 had a recorded temperature of 100.0°F or above, as compared with 0.3% of the crew members who did not have Covid-19. Among the crew members with Covid-19 for whom pulse oximetry data were available, approximately 0.5% had readings below 95% while breathing ambient air, with 0.08% below 94% and none below 90%.

Of the 1271 crew members who tested positive for SARS-CoV-2 plus the 60 who had suspected Covid-19, 23 (1.7%) received hospital care, for a mean of 16 days after symptom onset. Four crew members (0.3% of those with suspected or laboratory-confirmed Covid-19) were admitted to the intensive care unit, 1 of whom died from Covid-19–related cardiovascular complications. Before hospitalization, crew mem-

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Table 1. Demographic and Health Characteristics of Crew Members According to Covid-19 Status.*

Characteristic	Covid-19 Status			Univariate Odds Ratio, Covid-19 vs. No Covid-19 (95% CI)
	No Covid-19 (N=3448)	Confirmed or Suspected Covid-19 (N=1331)	Hospitalization for Covid-19 (N=23)	
Demographic characteristics				
Age — yr				
Mean	27.2	27.1	29.3	—
Range	18–59	18–53	20–46	—
Interquartile range	22–32	22–31	23–34	—
Sex — no. (%)				
Female	757 (22.0)	289 (21.7)	6 (26.1)	0.99 (0.85–1.15)
Male	2691 (78.0)	1042 (78.3)	17 (73.9)	Reference
Rank status				
Enlisted	3080 (89.3)	1231 (92.5)	23 (100.0)	1.48 (1.17–1.87)
Officer	363 (10.5)	98 (7.4)	0	Reference
Unknown	5 (0.1)	2 (0.2)	0	—
Race or ethnic group — no. (%)†				
American Indian	75 (2.2)	34 (2.6)	1 (4.3)	1.21 (0.80–1.83)
Asian or Pacific Islander	327 (9.5)	106 (8.0)	4 (17.4)	0.86 (0.68–1.10)
Black	590 (17.1)	261 (19.6)	3 (13.0)	1.18 (0.99–1.40)
Hispanic	692 (20.1)	273 (20.5)	5 (21.7)	1.05 (0.89–1.25)
White	1513 (43.9)	568 (42.7)	7 (30.4)	Reference
Other	250 (7.3)	88 (6.6)	3 (13.0)	0.94 (0.72–1.22)
Crew type‡				
Ship's crew	2086 (60.5)	786 (59.1)	13 (56.5)	Reference
Augmented crew	1288 (37.4)	501 (37.6)	9 (39.1)	1.03 (0.90–1.18)
Unknown	74 (2.1)	44 (3.3)	1 (4.3)	1.58 (1.08–2.31)
Select work centers and departments§				
Air	394 (11.4)	65 (4.9)	—	Reference
Combat support division	164 (4.8)	38 (2.9)	—	0.88 (0.58–1.33)
Deck	82 (2.4)	4 (0.3)	—	0.18 (0.07–0.52)
Engineering	137 (4.0)	67 (5.0)	—	1.85 (1.29–2.67)
Medical	40 (1.2)	8 (0.6)	—	0.76 (0.34–1.67)
Reactor	302 (8.8)	138 (10.4)	—	1.73 (1.29–2.36)
Supply	219 (6.4)	139 (10.4)	—	2.41 (1.78–3.26)
Weapons	132 (3.8)	94 (7.1)	—	2.70 (1.92–3.80)
Health characteristics				
Tobacco or nicotine user	1002 (29.1)	382 (28.7)	8 (34.8)	0.98 (0.85–1.13)
Most recent BMI¶				
Underweight or normal	1135 (32.9)	389 (29.2)	9 (39.1)	Reference
Overweight	1450 (42.1)	570 (42.8)	6 (26.1)	1.15 (0.99–1.33)
Obese	584 (16.9)	267 (20.1)	8 (34.8)	1.33 (1.11–1.61)
Unknown	279 (8.1)	105 (7.9)	0	1.10 (0.85–1.41)

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Table 1. (Continued.)

Characteristic	Covid-19 Status			Univariate Odds Ratio, Covid-19 vs. No Covid-19 (95% CI)
	No Covid-19 (N=3448)	Confirmed or Suspected Covid-19 (N=1331)	Hospitalization for Covid-19 (N=23)	
Preidentified health factors of interest‖				
Asthma	236 (6.8)	95 (7.1)	5 (21.7)	1.05 (0.82–1.34)
Cancer	35 (1.0)	10 (0.8)	0	0.74 (0.36–1.50)
Cerebrovascular diseases	2 (0.1)	0	0	—
Chronic lung disease	30 (0.9)	11 (0.8)	2 (8.7)	0.95 (0.47–1.90)
Diabetes	12 (0.3)	4 (0.3)	0	0.86 (0.28–2.68)
Hypertension	226 (6.6)	96 (7.2)	5 (21.7)	1.11 (0.87–1.42)
Immunocompromise	3 (0.1)	0	0	—
Liver disease	20 (0.6)	8 (0.6)	2 (8.7)	1.04 (0.46–2.36)
Sleep apnea	135 (3.9)	50 (3.8)	2 (8.7)	0.96 (0.69–1.33)
Tuberculosis	20 (0.6)	6 (0.5)	0	0.78 (0.31–1.94)

* Percentages may not total 100 because of rounding. Covid-19 denotes coronavirus disease 2019.
† The Defense Enrollment Eligibility Reporting System was used to identify race and ethnic group for all crew members.
‡ Augmented crew reside on the ship only at certain times when a ship is under way and provide specialized capability such as air squadrons, submarine groups, destroyer squadrons, and helicopter maritime strike squadrons.
§ Crew members in the departments of reactor, engineering, supply, weapons and in the combat support division tend to work in more confined spaces than those in the air and deck departments. Crew members in the air and deck departments tend to work in a combination of open-air and confined conditions. Medical personnel work in confined spaces but wear personal protective equipment when caring for crew members.
¶ Underweight was defined as a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of less than 18.5; normal or healthy weight, 18.5 to 24.9; overweight, 25.0 to 29.9; and obese, 30 or higher.
‖ Conditions were identified from October 1, 2017, through March 1, 2020, with the use of the following data sources: Theater Medical Data Store, Comprehensive Ambulatory/Professional Encounter Record, Standard Inpatient Data Record, Armed Forces Health Longitudinal Technology Application Clinical Data Repository, Military Health System (MHS) GENESIS, TRICARE Encounter Data, and Periodic Health Assessment.

bers with Covid-19 who became hospitalized were more likely to report cough (68%), body aches (58%), and fever (32%) than those who did not. One third of hospitalized patients reported fever before their hospitalization, as compared with 12% of nonhospitalized crew members with Covid-19. During the outbreak, as a precautionary measure, admission criteria were revised to permit hospitalization of crew members with less severe symptoms.

DISCUSSION

The epidemiology of SARS-CoV-2 infection in young, healthy populations has not been studied extensively.[2] The outbreak of Covid-19 on the U.S.S. *Theodore Roosevelt* provided an unusual opportunity to assess an outbreak in a predominantly young, healthy, working-age population. Approximately 69% of crew members were younger than 30 years of age, and no crew member was older than 65 years. All were up to date with their immunizations. Over the course of the outbreak and the subsequent response by the U.S. Navy, every crew member underwent evaluation, testing, and follow-up. This level of controlled evaluation and documentation is difficult to achieve in civilian populations.

On ships at sea, respiratory viruses such as influenza and enteric pathogens such as norovirus can spread quickly.[3,4] In the early weeks of the pandemic, several outbreaks of Covid-19 occurred on cruise ships, most notably on the *Diamond Princess*.[5,6] The medical department of a ship can be overwhelmed quickly by a major outbreak of disease, as is similarly seen with health care fa-

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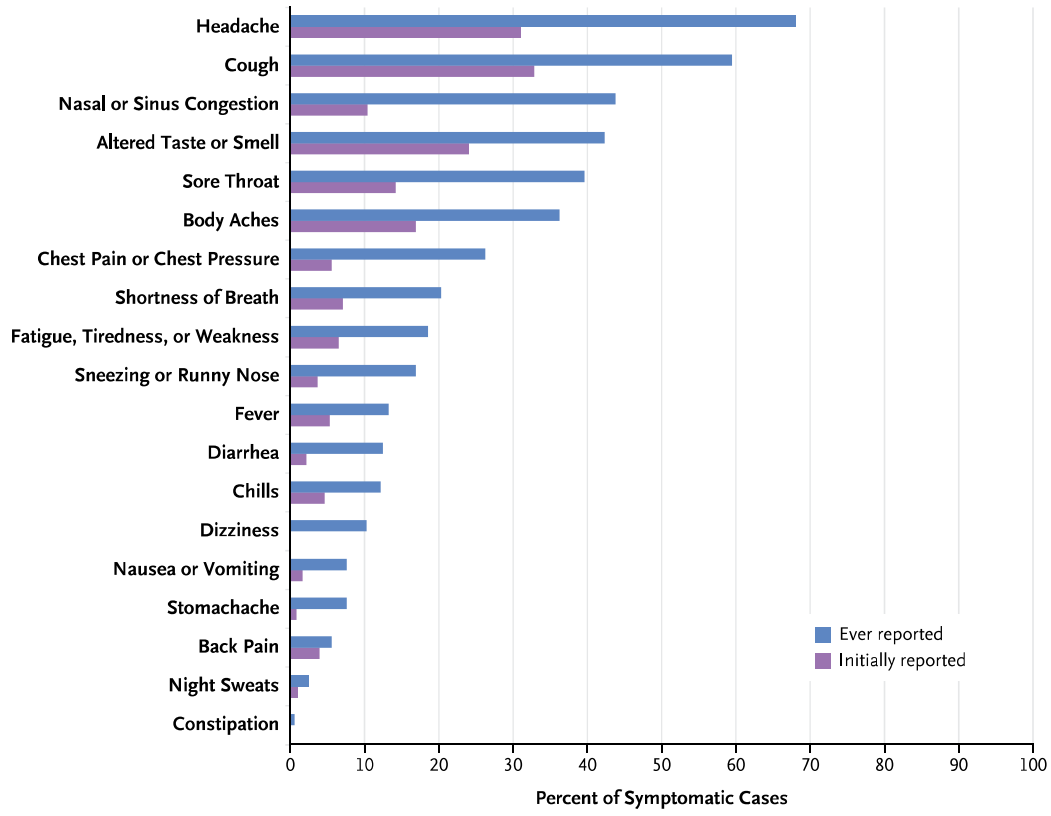

Figure 3. Distribution of Symptomatic Confirmed or Suspected Covid-19 Cases According to Symptoms.

cilities in civilian communities.[7] The shipboard environment on naval vessels is generally more confined. Typically, enlisted crew members sleep in open bays packed with dozens of tightly spaced bunks, work in densely populated areas, and congregate in gathering points such as the gyms and galleys (Figs. S1 and S2 in the Supplementary Appendix, available with the full text of this article at NEJM.org). These conditions probably facilitated the transmission of SARS-CoV-2, as evidenced by the higher likelihood of Covid-19 among enlisted crew members than among officers (Table 1).

Not surprisingly, crew members working in the engine room and other confined areas of the ship faced a higher risk of being infected than their shipmates on deck. A study conducted by the Navy and Marine Corps Public Health Center and the CDC, involving 384 volunteer U.S.S. *Theodore Roosevelt* crew members, showed similar results: those working in confined spaces had higher odds of contracting Covid-19.[8] A majority of infected crew members did not note symptoms at the time that Covid-19 was diagnosed by rRT-PCR testing. In addition, crew members with unusual or atypical symptoms may not have considered themselves to be infected with SARS-CoV-2.[9] These observations suggest that nonsymptomatic or mildly symptomatic crew members played an important role in the rapid spread of the outbreak, much as young adults with asymptomatic infection appear to contribute to spread in civilian populations.[10,11]

Although cases of serious illness occur in younger persons, they are less frequent and typically less severe than those in older persons.[9,11] In the case of the U.S.S. *Theodore Roosevelt*, few crew members were hospitalized. Certain coexisting conditions, such as hypertension, obesity, and diabetes, are associated with higher mortality.[12-14] In our findings, we noted a number of coexisting conditions among hospitalized crew members,

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including uncomplicated, mild, and medically managed asthma, lung disease (e.g., bronchitis), hypertension, and liver disease–related conditions.

Although we were able to confirm the outcomes in all infected crew members, data collection was limited by the quality of records, particularly those generated in the early days of the outbreak. Future studies involving longitudinal cohorts may provide greater insight into the epidemiology of SARS-CoV-2 infection in young adults. Our observations within a military population may not be fully generalizable to civilians. The CDC case definition for Covid-19, along with clinical criteria, changed over time (e.g., the outbreak began in March 2020, and the CDC-published case definition for Covid-19 changed in April 2020). Multiplex testing by polymerase chain reaction identified other causes of influenza-like illness on board the ship. Any effect that the case definition or other respiratory pathogens may have had on classifying a case of Covid-19 is limited, because the majority of cases were confirmed by rRT-PCR testing. Finally, the crew of the U.S.S. *Theodore Roosevelt*, like all members of the U.S. military forces, have equal access to health care. This is not true for all civilians in the United States.

Since this outbreak occurred, the U.S. Navy has incorporated lessons learned to enhance the safety and readiness of its crews. To minimize the risk of deploying with asymptomatic carriers of SARS-CoV-2 on board, the Navy has initiated several procedures to create and sustain Covid-19–free environments on its ships. Before deployment, all members of a ship's crew are placed in "restriction of movement" and insulated from community exposure for 14 days. To identify asymptomatic or presymptomatic carriers, the Navy added rRT-PCR testing at the end of the "restriction of movement" period. Navy ships have sharply reduced shore leaves at foreign ports to prevent crew members from bringing the virus on board. Since these policies (along with preventive measures of mask use, social distancing to the extent possible, small-group cohorting, strict hand hygiene, and regular cleaning of common spaces) were put in place, the Navy has deployed multiple ships without sustaining another serious outbreak. The concept of creating virus-free "bubbles" is a strategy the Navy has used and has been mirrored by the National Basketball Association and Major League Soccer to enable competition while minimizing the risk of player exposure. It is unlikely that this strategy is practical for all employers, much less the general population; however, creating bubbles or cohorts for select populations may be achievable.

Organizations seeking to safeguard their employees, customers, patients, or students may benefit from assuming that Covid-19 will be introduced into their populations and rigorously enforcing measures to minimize viral transmission by all, since persons may be unaware that they are infected.

The views expressed in this article reflect the results of research conducted by the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the U.S. government.

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Asymptomatic transmission of covid-19

What we know, and what we don't

Allyson M Pollock, [1] James Lancaster[2]

The UK's £100bn "Operation Moonshot" to roll out mass testing for covid-19 to cities and universities around the country raises two key questions. How infectious are people who test positive but have no symptoms? And, what is their contribution to transmission of live virus?

Unusually in disease management, a positive test result is the sole criterion for a covid-19 case. Normally, a test is a support for clinical diagnosis, not a substitute. This lack of clinical oversight means we know very little about the proportions of people with positive results who are truly asymptomatic throughout the course of their infection and the proportions who are paucisymptomatic (subclinical), presymptomatic (go on to develop symptoms later), or post-infection (with viral RNA fragments still detectable from an earlier infection).

Earlier estimates that 80% of infections are asymptomatic were too high and have since been revised down to between 17% and 20% of people with infections.[1 2] Studies estimating this proportion are limited by heterogeneity in case definitions, incomplete symptom assessment, and inadequate retrospective and prospective follow-up of symptoms, however.[3] Around 49% of people initially defined as asymptomatic go on to develop symptoms.[4 5]

It's also unclear to what extent people with no symptoms transmit SARS-CoV-2. The only test for live virus is viral culture. PCR and lateral flow tests do not distinguish live virus. No test of infection or infectiousness is currently available for routine use.[6-8] As things stand, a person who tests positive with any kind of test may or may not have an active infection with live virus, and may or may not be infectious.[9]

The relations between viral load, viral shedding, infection, infectiousness, and duration of infectiousness are not well understood. In a recent systematic review, no study was able to culture live virus from symptomatic participants after the ninth day of illness, despite persistently high viral loads in quantitative PCR diagnostic tests. However, cycle threshold (Ct) values from PCR tests are not direct measures of viral load and are subject to error.[10]

While viral load seems to be similar in people with and without symptoms, the presence of RNA does not necessarily represent transmissible live virus. The duration of viral RNA shedding (interval between first and last positive PCR result for any sample) is shorter in people who remain asymptomatic, so they are probably less infectious than people who develop symptoms.[11]

Viral culture studies suggest that people with SARS-CoV-2 can become infectious one to two days before the onset of symptoms and continue to be infectious up to seven days thereafter; viable virus is relatively short lived.[7] Symptomatic and presymptomatic transmission have a greater role in the spread of SARS-CoV-2 than truly asymptomatic transmission.[1 2 12 13]

The transmission rates to contacts within a specific group (secondary attack rate) may be 3-25 times lower for people who are asymptomatic than for those with symptoms.[1 12 14 15] A city-wide prevalence study of almost 10 million people in Wuhan found no evidence of asymptomatic transmission.[16] Coughing, which is a prominent symptom of covid-19, may result in far more viral particles being shed than talking and breathing, so people with symptomatic infections are more contagious, irrespective of close contact.[17] On the other hand, asymptomatic and presymptomatic people may have more contacts than symptomatic people (who are isolating), underlining the importance of hand washing and social distancing measures for everyone.

Missed opportunity

By failing to integrate testing into clinical care, we have missed an important opportunity to better understand the role of asymptomatic infection in transmission. Given the variation in prevalence and testing strategies by region, the proportions of people with positive and negative test results should be published alongside the purpose of the testing strategy and the population tested (screening healthy populations in schools, universities, and health and social care, or testing people with symptoms). Government regulations on recording the age, ethnicity, sex, and place of residence of people with positive results must also be followed.[18]

Searching for people who are asymptomatic yet infectious is like searching for needles that appear and reappear transiently in haystacks, particularly when rates are falling.[19] Mass testing risks the harmful diversion of scarce resources. A further concern is the use of inadequately evaluated tests as screening tools in healthy populations.[20]

The UK's testing strategy needs to be reset in line with the Scientific Advisory Group for Emergencies' recommendation that "Prioritising rapid testing of symptomatic people is likely to have a greater impact on identifying positive cases and reducing transmission than frequent testing of asymptomatic people in an outbreak area."[21]

Testing should be reintegrated into clinical care with clinical and public health oversight and case definitions based on clinical diagnosis. Carefully designed prospective studies of cases and contacts are needed to estimate transmission rates by people

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with and without symptoms. These should include careful investigations of outbreaks—for example, testing all contacts of people with a clear history of exposure, especially in high risk environments such as nursing homes, prisons, and other institutional settings.

Coronavirus infection surveys by the Office for National Statistics[22] and the REACT survey[23] could be expanded to include clinical follow-up of participants combined with tests of viral load and viral cultures. The absence of strong evidence that asymptomatic people are a driver of transmission is another good reason for pausing the roll out of mass testing in schools, universities, and communities.

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Post-lockdown SARS-CoV-2 nucleic acid screening in nearly ten million residents of Wuhan, China

Shiyi Cao[1,11], Yong Gan[1,11], Chao Wang[1,11], Max Bachmann[2], Shanbo Wei[3], Jie Gong[4], Yuchai Huang[1], Tiantian Wang[1], Liqing Li[5], Kai Lu[6], Heng Jiang[7,8], Yanhong Gong[1], Hongbin Xu[1], Xin Shen[1], Qingfeng Tian[9], Chuanzhu Lv[10]✉, Fujian Song[2]✉, Xiaoxv Yin[1]✉ & Zuxun Lu[1]✉

Stringent COVID-19 control measures were imposed in Wuhan between January 23 and April 8, 2020. Estimates of the prevalence of infection following the release of restrictions could inform post-lockdown pandemic management. Here, we describe a city-wide SARS-CoV-2 nucleic acid screening programme between May 14 and June 1, 2020 in Wuhan. All city residents aged six years or older were eligible and 9,899,828 (92.9%) participated. No new symptomatic cases and 300 asymptomatic cases (detection rate 0.303/10,000, 95% CI 0.270–0.339/10,000) were identified. There were no positive tests amongst 1,174 close contacts of asymptomatic cases. 107 of 34,424 previously recovered COVID-19 patients tested positive again (re-positive rate 0.31%, 95% CI 0.423–0.574%). The prevalence of SARS-CoV-2 infection in Wuhan was therefore very low five to eight weeks after the end of lockdown.

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The Coronavirus Disease 2019 (COVID-19) was first reported in December 2019, and was classified as a pandemic by the World Health Organization on March 11, 2020[1]. Following strict lockdown measures, the COVID-19 epidemic was generally under control in China, and the whole country has progressed into a post-lockdown phase. In this phase, countries face new problems and challenges, including how to accurately assess the post-lockdown risk of the COVID-19 epidemic, how to avoid new waves of COVID-19 outbreaks, and how to facilitate the resumption of economy and normal social life. As the city most severely affected by COVID-19 in China, Wuhan had been under lockdown measures from January 23 until April 8, 2020. During the first 2 months after city's reopening, there were only a few sporadic COVID-19 cases in Wuhan (six newly confirmed cases from April 8 to May 10, 2020[2]). However, there was still concern about the risk of COVID-19 in Wuhan, which seriously affected the resumption of industrial production and social services, and hampered the normal lives of residents. In order to ascertain the current status of the COVID-19 epidemic, the city government of Wuhan carried out a comprehensive citywide nucleic acid screening of SARS-CoV-2 infection from May 14, 2020 to June 1, 2020.

The citywide screening of SARS-CoV-2 infection in Wuhan is a mass screening programme in post-lockdown settings, and provided invaluable experiences or lessons with international relevance as more countries and cities around the world entering the post-lockdown phase. In this study, we report the organisation process, detailed technical methods used, and results of this citywide nucleic acid screening.

Results

There were 10,652,513 eligible people aged ≥6 years in Wuhan (94.1% of the total population). The nucleic acid screening was completed in 19 days (from May 14, 2020 to Jun 1, 2020), and tested a total of 9,899,828 persons from the 10,652,513 eligible people (participation rate, 92.9%). Of the 9899,828 participants, 9,865,404 had no previous diagnosis of COVID-19, and 34,424 were recovered COVID-19 patients.

The screening of the 9,865,404 participants without a history of COVID-19 found no newly confirmed COVID-19 cases, and identified 300 asymptomatic positive cases with a detection rate of 0.303 (95% CI 0.270–0.339)/10,000. The median age-stratified Ct-values of the asymptomatic cases were shown in Supplementary Table 1. Of the 300 asymptomatic positive cases, two cases came from one family and another two were from another family. There were no previously confirmed COVID-19 patients in these two families. A total of 1174 close contacts of the asymptomatic positive cases were traced, and they all tested negative for the COVID-19. There were 34,424 previously recovered COVID-19 cases who participated in the screening. Of the 34,424 participants with a history of COVID-19, 107 tested positive again, giving a repositive rate of 0.310% (95% CI 0.423–0.574%).

Virus cultures were negative for all asymptomatic positive and repositive cases, indicating no "viable virus" in positive cases detected in this study.

All asymptomatic positive cases, repositive cases and their close contacts were isolated for at least 2 weeks until the results of nucleic acid testing were negative. None of detected positive cases or their close contacts became symptomatic or newly confirmed with COVID-19 during the isolation period. In this screening programme, single and mixed testing was performed, respectively, for 76.7% and 23.3% of the collected samples. The asymptomatic positive rates were 0.321 (95% CI 0.282–0.364)/10,000 and 0.243 (95% CI 0.183–0.315)/10,000, respectively.

The 300 asymptomatic positive persons aged from 10 to 89 years, included 132 males (0.256/10,000) and 168 females (0.355/10,000). The asymptomatic positive rate was the lowest in children or adolescents aged 17 and below (0.124/10,000), and the highest among the elderly aged 60 years and above (0.442/10,000) (Table 1). The asymptomatic positive rate in females (0.355/10,000) was higher than that in males (0.256/10,000).

The asymptomatic positive cases were mainly domestic and unemployed residents (24.3%), retired older adults (21.3%), and public service workers (11.7%) (Fig. 1).

The asymptomatic positive rate in urban districts was on average 0.456/10,000, ranging from 0.317/10,000 in Hongshan to 0.807/10,000 in Wuchang district. A lower rate of asymptomatic positive cases was found in suburban districts (0.132/10,000), ranging from 0.047/10,000 in Xinzhou to 0.237/10,000 in Jiangan district (Fig. 2).

Among the 7280 residential communities in Wuhan, asymptomatic positive cases were identified in 265 (3.6%) communities (only one case detected in 246 communities), while no asymptomatic positive cases were found in other 96.4% communities.

Testing of antibody against SARS-CoV-2 virus was positive IgG (+) in 190 of the 300 asymptomatic cases, indicating that 63.3% (95% CI 57.6–68.8%) of asymptomatic positive cases were actually infected. The proportion of asymptomatic positive cases with both IgM (−) and IgG (−) was 36.7% (95% CI: 31.2–42.4%; $n = 110$), indicating the possibility of infection window or false positive results of the nucleic acid testing (Table 2).

Higher detection rates of asymptomatic infected persons were in Wuchang, Qingshan and Qiaokou districts, and the prevalence of previously confirmed COVID-19 cases were 68.243/10,000, 53.767/10,000, and 100.047/10,000, respectively, in the three districts. Figure 3 shows that districts with a high detection rate of asymptomatic positive persons generally had a high prevalence of confirmed COVID-19 cases ($r_s = 0.729$, $P = 0.002$).

Discussion

The citywide nucleic acid screening of SARS-CoV-2 infection in Wuhan recruited nearly 10 million people, and found no newly confirmed cases with COVID-19. The detection rate of asymptomatic positive cases was very low, and there was no evidence of transmission from asymptomatic positive persons to traced close contacts. There were no asymptomatic positive cases in 96.4% of the residential communities.

Previous studies have shown that asymptomatic individuals infected with SARS-CoV-2 virus were infectious[3], and might subsequently become symptomatic[4]. Compared with symptomatic patients, asymptomatic infected persons generally have low quantity of viral loads and a short duration of viral shedding, which decrease the transmission risk of SARS-CoV-2[5]. In the present study, virus culture was carried out on samples from asymptomatic positive cases, and found no viable SARS-CoV-2 virus. All close contacts of the asymptomatic positive cases tested negative, indicating that the asymptomatic positive cases detected in this study were unlikely to be infectious.

There was a low repositive rate in recovered COVID-19 patients in Wuhan. Results of virus culturing and contract tracing found no evidence that repositive cases in recovered COVID-19 patients were infectious, which is consistent with evidence from other sources. A study in Korea found no confirmed COVID-19 cases by monitoring 790 contacts of 285 repositive cases[6]. The official surveillance of recovered COVID-19 patients in China also revealed no evidence on the infectiousness of repositive cases[7]. Considering the strong force of infection of COVID-19[8–10], it is expected that the number of confirmed cases is associated with the risk of being infected in communities. We

Table 1 Characteristics of asymptomatic positive individuals.

	Total (%)	Asymptomatic positive persons (%)	Detection rate per 10,000 (95% CI)	*P* value
Total	9,899,828 (100.0)	300 (100.0)	0.303 (0.270–0.339)	
Sex				
Male	5,162,960 (52.2)	132 (44.0)	0.256 (0.214–0.303)	0.005
Female	4,736,868 (47.8)	168 (56.0)	0.355 (0.303–0.413	
Age (years old)				
≤17	969,014 (9.8)	12 (4.0)	0.124 (0.064–0.216)	<0.001
18–44	4,448,230 (44.9)	104 (34.7)	0.234 (0.191–0.283)	
45–59	2,492,943 (25.2)	96 (32.0)	0.385 (0.312–0.470)	
≥60	1,989,641 (20.1)	88 (29.3)	0.442 (0.355–0.545)	
Administrative Districts in Wuhan				
Wuchang	904,636 (9.1)	73 (24.3)	0.807 (0.633–1.015)	<0.001
Qingshan	414,312 (4.2)	23 (7.7)	0.555 (0.352–0.833)	
Qiaokou	583,440 (5.9)	32 (10.7)	0.548 (0.375–0.774)	
Hanyang	717,429 (7.2)	29 (9.7)	0.404 (0.271–0.581)	
Jianghan	524,224 (5.3)	19 (6.3)	0.362 (0.218–0.566)	
Hongshan	1,103,079 (11.1)	35 (11.7)	0.317 (0.221–0.441)	
East Lake High-tech Development Area	782,987 (7.9)	19 (6.3)	0.243 (0.146–0.379)	
Jiangan	800,440 (8.1)	19 (6.3)	0.237 (0.143–0.371)	
Caidian	503,595 (5.1)	11 (3.7)	0.218 (0.109–0.391)	
Jiangxia	671,248 (6.8)	14 (4.7)	0.209 (0.114–0.350)	
Huangpi	979,920 (9.9)	14 (4.7)	0.143 (0.078–0.240)	
Hannan	417,022 (4.2)	4 (1.3)	0.096 (0.026–0.246)	
Dongxihu	777,204 (7.9)	5 (1.7)	0.064 (0.021–0.150)	
Xinzhou	634,408 (6.4)	3 (1.0)	0.047 (0.010–0.138)	
East Lake Scenic Area of Wuhan	85,884 (0.9)	0 (0.0)	0.000 (0.000–0.430)	

χ^2 test was used to assess the association between the detection rate of asymptomatic cases increased and sex and age. Urban districts of Wuhan includes Wuchang, Qingshan, Qiaokou, Hanyang, Jiangan, Jianghan, and Hongshan; Suburban districts of Wuhan includes Hannan, Caidian, Dongxihu, Xinzhou, Jiangxia, Huangpi, East Lake High-tech Development Area, and East Lake Scenic Area of Wuhan.

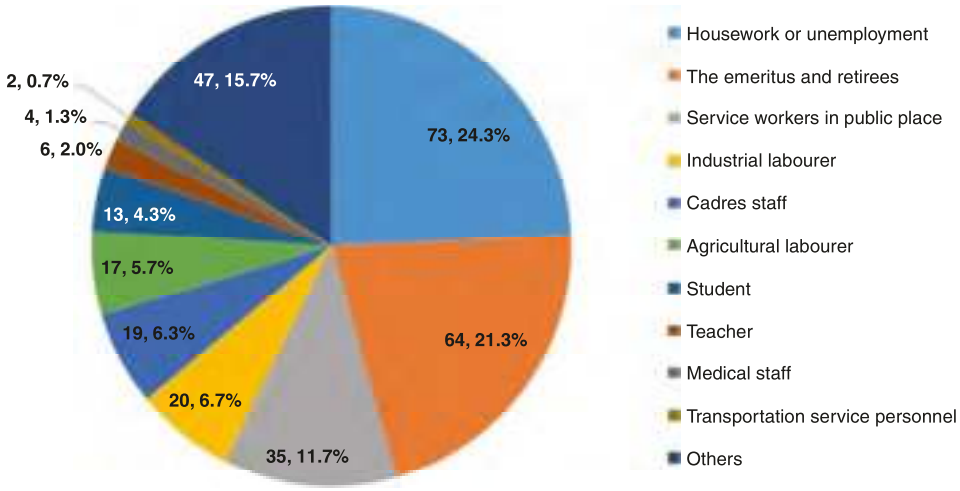

Fig. 1 The occupation distribution of asymptomatic positive cases (%). Note: Others included the self-employed, military personnel, and so on. (Source data are provided as s Source Data file.).

found that asymptomatic positive rates in different districts of Wuhan were correlated with the prevalence of previously confirmed cases. This is in line with the temporal and spatial evolution (especially the long-tailed characteristic) of infectious diseases[11].

Existing laboratory virus culture and genetic studies[9,10] showed that the virulence of SARS-CoV-2 virus may be weakening over time, and the newly infected persons were more likely to be asymptomatic and with a lower viral load than earlier infected cases. With the centralized isolation and treatment of all COVID-19 cases during the lockdown period in Wuhan, the risk of residents being infected in the community has been greatly reduced. When susceptible residents are exposed to a low dose of virus, they may tend to be asymptomatic as a result of their own immunity. Serological antibody testing in the current study found that at least 63% of asymptomatic positive cases were actually infected with SARS-CoV-2 virus. Nonetheless, it is too early to be complacent, because of the existence of asymptomatic positive cases and high level of susceptibility in residents in Wuhan. Public health measures for the prevention and control of COVID-19 epidemic, including wearing masks, keeping safe social distancing in Wuhan should be sustained. Especially, vulnerable populations with weakened immunity or co-morbidities, or both, should continue to be appropriately shielded.

Findings from this study show that COVID-19 was well controlled in Wuhan at the time of the screening programme. After two months since the screening programme (by August 9, 2020), there were no newly confirmed COVID-19 cases in Wuhan.

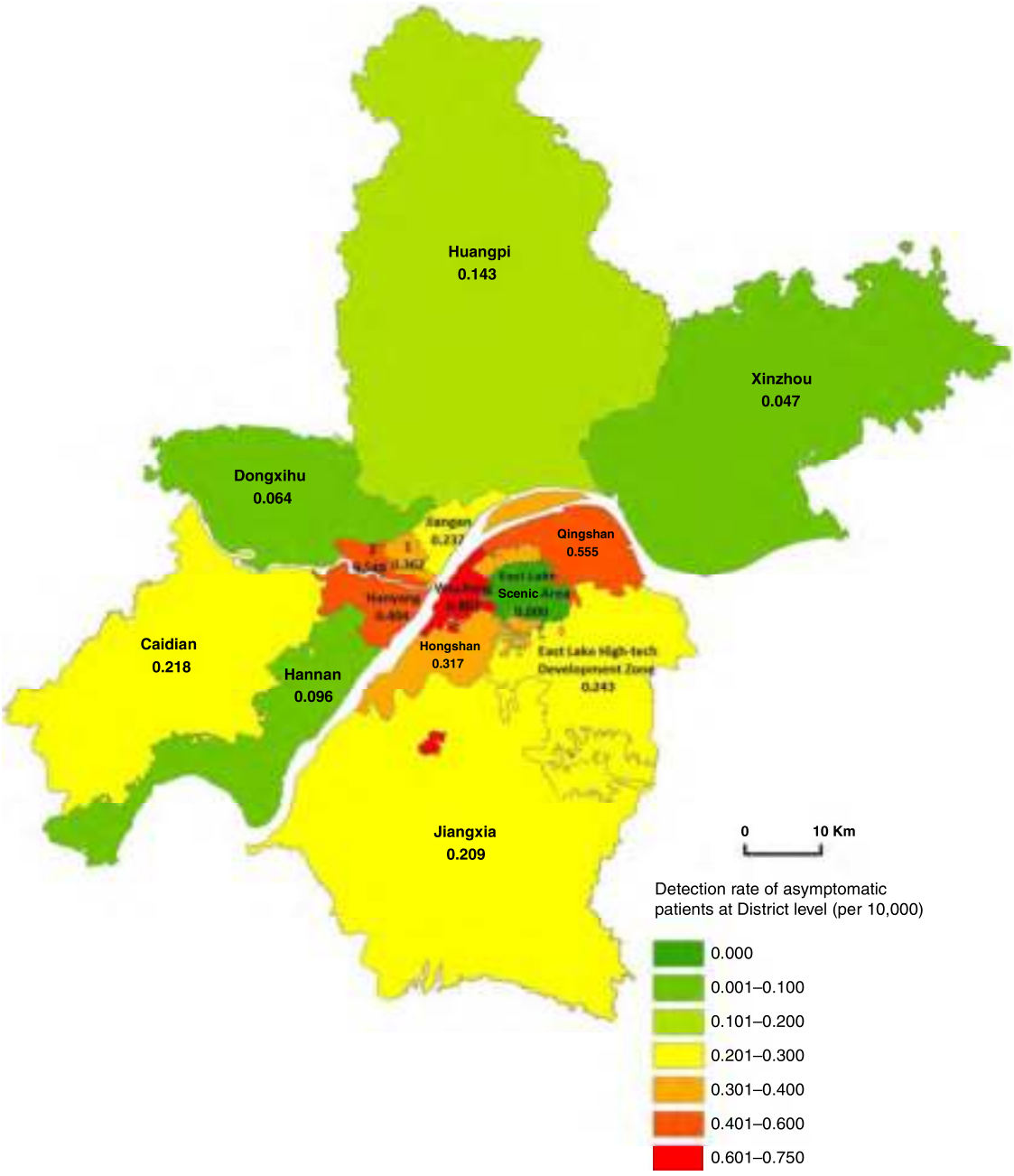

Fig. 2 The geographic distribution of the detection rate of asymptomatic positive cases. Note: 1 represents Jianghan district; 2 represents Qiaokou district. (Source data are provided as s Source Data file.).

Table 2 Results of the detection of antibody in 300 asymptomatic positive persons.

IgM Results	IgG	Asymptomatic positive persons	% (95% CI)
−	+	161	53.7 (47.8–59.4)
−	−	110	36.7 (31.2–42.4)
+	+	29	9.7 (6.6–13.6)
+	−	0	0.0 (0.0–1.2)

"−" indicates negative; "+" indicates positive.

Further testing of SARS-CoV-2 in samples collected from market environment settings in Wuhan were conducted, and found no positive results after checking a total of 52,312 samples from 1795 market setting during June 13 to July 2, 2020[12].

This study has several limitations that need to be discussed. First, this was a cross-sectional screening programme, and we are unable to assess the changes over time in asymptomatic positive and reoperative results. Second, although a positive result of nucleic acid testing reveals the existence of the viral RNAs, some false negative results were likely to have occurred, in particular due to the relatively low level of virus loads in asymptomatic infected individuals, inadequate collection of samples, and limited accuracy of the testing technology[13]. Although the screening programme provided no direct evidence on the sensitivity and specificity of the testing method used, a meta-analysis reported a

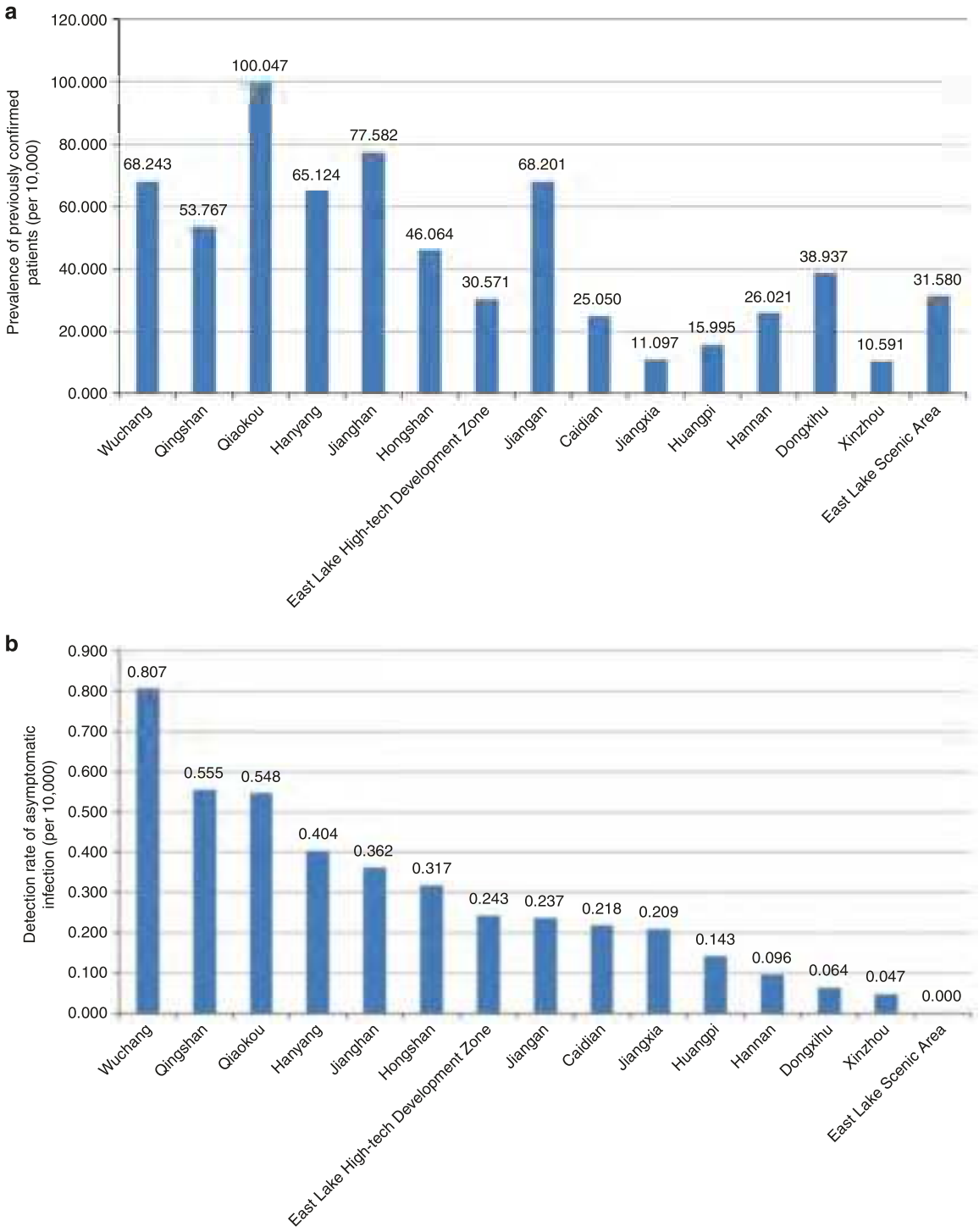

Fig. 3 The prevalence of previously confirmed patients and the detection rate of asymptomatic positive cases of COVID-19 in each district in Wuhan. **a** The prevalence of previously confirmed patients of COVID-19 in each district in Wuhan. **b** The detection rate of asymptomatic positive cases of COVID-19 in each district in Wuhan. (Source data are provided as s Source Data file.).

pooled sensitivity of 73% (95% CI 68–78%) for nasopharayngeal and throat swab testing of COVID-19[14]. Testing kits used in the screening programme were publicly purchased by the government and these kits have been widely used in China and other countries. Multiple measures were taken to possibly minimise false negative results in the screening programme. For example, standard training was provided to health works for sample collection to ensure the sample quality. The experiment procedures, including specimen collection, extraction, PCR, were according to official guidelines (Supplementary Note 1). For the real-time RT-PCR assay, two target genes were simultaneously tested. Even so, false negative results remained possible, particularly in any mass screening programmes. However, even if test sensitivity was as low as 50%, then the actual prevalence would be twice as high as reported in this study, but would still be very low. Around 7.1% of eligible residents did not participate in the citywide nucleic acid screening and the screening programme did not collect detailed data on reasons for nonparticipation, which is a limitation of this

study. Although there were no official statistics, a large number of migrant workers and university students left Wuhan before the lockdown, joining their families in other cities or provinces for traditional Chinese New Year. Therefore, it is likely that most nonparticipants were not in Wuhan at the time of the screening. The main objective of the screening programme was to assess the risk of COVID-19 epidemic in residents who were actually living in the post-lockdown Wuhan. Therefore, the estimated positive rates are unlikely to be materially influenced by nonparticipation of residents who were not in Wuhan or some residents who did not participate in the screening for other reasons. Moreover, people who left Wuhan were the target population for monitoring in other provinces and cities and were required to take nucleic acid testing. Although there was no official statistics showing the positive rate of nucleic acid testing in this population, there was no report that shown a higher positive rate of nucleic acid testing than our findings.

In summary, the detection rate of asymptomatic positive cases in the post-lockdown Wuhan was very low (0.303/10,000), and there was no evidence that the identified asymptomatic positive cases were infectious. These findings enabled decision makers to adjust prevention and control strategies in the post-lockdown period. Further studies are required to fully evaluate the impacts and cost-effectiveness of the citywide screening of SARS-CoV-2 infections on population's health, health behaviours, economy, and society.

Methods

Study population and ethical approvals. Wuhan has about 11 million residents in total, with seven urban and eight suburban districts. Residents are living in 7280 residential communities (or residential enclosures, "xiao-qu" in Chinese), and each residential community could be physically isolated from other communities for preventing transmission of COVID-19.

The screening programme recruited residents (including recovered COVID-19 patients) currently living in Wuhan who were aged ≥6 years (5,162,960 males, 52.2%). All participants provided written or verbal informed consent after reading a statement that explained the purpose of the testing. For participants who aged 6–17 years old, consent was obtained from their parents or guardians. The study protocol for an evaluation of the programme based on anonymized screening data was approved by the Ethics Committee of the Tongji Medical College Institutional Review Board, Huazhong University of Science and Technology, Wuhan, China (No. IROG0003571).

Organizational guarantee and community mobilization. A citywide nucleic acid screening group was formed, with specialized task teams contributing to comprehensive coordination, technical guidance, quality control, participation invitation, information management, communication, and supervision of the screening. The city government invested 900 million yuan (RMB) in the testing programme. From 14 May to 1 June 2020, in the peak time, up to 2907 sample collection sites were functioning at the same time in Wuhan. Each sample collection site had an assigned sample collection group, including several health professionals (staffed according to the number of communities' residents), 2–4 community managers, 1–2 police officers, and 1–2 inspectors. The sampling sites were set up based on the number and accessibility of local residents. Local community workers were responsible for a safe and orderly sampling process to minimise the waiting time. In addition, mobile sampling teams were formed by primary health care professionals and volunteers to conduct door-to-door sampling for residents who had physical difficulties or were unable to walk.

About 50,000 health professionals (mainly doctors and nurses from community health centers) and more than 280,000 person-times of community workers and volunteers contributed to sample collection, transport of equipment and samples collected, arrangement of participation process, and maintaining order of sampling sites. Public information communication and participant invitation were implemented through mass media, mobile messages, WeChat groups, and residential community broadcasts, so as to increase residents' awareness and the participation.

Acquisition, preservation, and transport of samples. All sampling personnel received standard training for the collection of oropharyngeal swab samples. To minimise the risk of cross-infection, the sampling process strictly followed a disinfection process and environmental ventilation were ensured. The collected samples were stored in a virus preservation solution or immersed in isotonic saline, tissue culture solution, or phosphate buffer (Supplementary note 1). Then, all samples were sent to testing institutions within 4 h using delivery boxes for biological samples refrigerated with dry ice to guarantee the stability of nucleic acid samples.

Technical methods for laboratory testing of collected samples. A total of 63 nucleic acid testing laboratories, 1451 laboratory workers and 701 testing equipment were involved in the nucleic acid testing. Received samples were stored at 4 °C and tested within 24 h of collection. Any samples that could not be tested within 24 h were stored at −70 °C or below (Supplementary note 1). In addition to "single testing" (i.e., separate testing of a single sample), "mixed testing" was also performed for 23% of the collected samples to increase efficiency, in which five samples were mixed in equal amounts, and tested in the same test tube. If a mixed testing was positive for COVID-19, all individual samples were separately retested within 24 h[15].

Details regarding technical methods for sequencing and virus culture were provided in Supplementary note 1. Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay method was used for the nucleic acid testing. We simultaneously amplified and tested the two target genes: open reading frame 1ab (ORF1ab) and nucleocapsid protein (N) (Supplementary Note 1). A cycle threshold value (Ct-value) less than 37 was defined as a positive result, and no Ct-value or a Ct-value of 40 or more was defined as a negative result. For Ct-values ranging from 37 to 40, the sample was retested. If the retest result remained less than 40 and the amplification curve had obvious peak, the sample was classified as positive; otherwise, it was reported as being negative. These diagnostic criteria were based on China's official recommendations[16].

For asymptomatic positive cases, virus culture was carried out in biosafety level-3 laboratories. The colloidal gold antibody test was also performed for asymptomatic positive cases (Supplementary note 1). All testing results were double entered into a specifically designed database, and managed by the Big Data and Investigation Group of the COVID-19 Prevention and Control Centre in Wuhan, which was established to collect and manage data relevant to the COVID-19 epidemic.

Participant data collection and management. Before sample collection, residents electronically (using a specifically designed smartphone application) self-uploaded their personal information, including ID number, name, sex, age, and place of residence. Then, the electronic machine system generated a unique personal barcode and stuck it on the sample tube to ensure the match between the sample and the participant. Then trained staff interviewed each individual regarding the history of COVID-19 and previous nucleic acid testing. There was a database of confirmed COVID-19 cases in Wuhan, which can be used to validate the self-reported previous COVID-19 infection. All information was entered into a central database. The testing results were continually uploaded to the central database by testing institutions. Contact tracing investigations were conducted on participants who tested positive for SARS-CoV-2, to track and manage their close contacts. The pre-existing unique identification code for each resident was used as the programme's identification number, to ensure information accuracy during the whole process of screening, from sampling, nucleic acid testing, result reporting, the isolation of detected positive cases, and tracing of close contacts of positive cases. All screening information was kept strictly confidential and was not allowed to be disclosed or used for other purposes other than clinical and public health management. Personal information of asymptomatic positive cases was only disclosed to designated medical institutions and community health centres for the purpose of medical isolation and identification of close contacts. Researcher was blind to the study hypothesis during data collection.

Biological security guarantee. Nucleic acid testing was performed in biosafety level-2 (BSL-2) laboratories, and virus culture was conducted in biosafety level-3 laboratories. Sampling and testing personnel adopted the personal protective measures according to the standard of biosafety level-3 laboratories. Participating laboratories implemented control measures to guarantee biological safety in accordance with relevant regulations[17].

Result query and feedback. Two to three days after sample collection, participants could inquire about their test results using WeChat or Alipay application by their unique ID numbers. The results included text descriptions of nucleic acid testing and coloured health codes. A green coloured health code refers to a negative result, and a red coloured health code indicates a positive result.

Definition and management of identified confirmed cases and close contacts. In this study, all confirmed COVID-19 cases were diagnosed by designated medical institutions according to National Guidelines for the Prevention and Control of COVID-19 (Supplementary Note 2). Asymptomatic positive cases referred to individuals who had a positive result during screening, and they had neither a history of COVID-19 diagnosis, nor any clinical symptoms at the time of the nucleic acid testing. Close contacts were individuals who closely contacted with an asymptomatic positive person since 2 days before the nucleic acid sampling[16]. Repositive cases refer to individuals who recovered from previously confirmed COVID-19 disease and had a positive testing again in the screening programme. All repositive cases, asymptomatic positive persons, and their close contacts were

isolated for at least 2 weeks in designated hotels managed by primary health care professionals, and they were released from isolation only if two consecutive nucleic acid tests were negative.

Statistical analysis. Detection rate of asymptomatic positive or repositive cases was calculated by dividing the number of individuals with a positive result of nucleic acid testing by the number of participants tested. Because of extremely low detection rates, we calculated 95% confidence intervals of estimated proportions using Pearson–Klopper exact method, implemented through R package "binom" version 1.1-1[18]. SPSS version 22.0 was used for other statistical analyses. We analyzed the distribution of asymptomatic positive cases and assessed the Spearman correlation between the asymptomatic positive rate and the prevalence of previously confirmed COVID-19 cases in different districts of Wuhan. Differences in asymptomatic positive rates by sex and age groups were assessed using the χ^2 test. ArcGIS 10.0 was used to draw a geographic distribution map of asymptomatic positive cases. A value of $P < 0.05$ (two-tailed) was considered statistically significant.

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

Detailed data directly used to generate each figure or table of this study are available within the article, Supplementary Information and source data are provided with this paper.

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Author contributions

S.Y.C., C.W., X.X.Y., and Z.X.L. conceived the study. C.W., Y.C.H., T.T.W., K.L., H.B.X., and X.S. participated in the acquisition of data. S.B.W. and J.G. were responsible for the on-site specimen collection, laboratory testing quality evaluation, and control. Y.C.H., T.T.W., and L.Q.L. analyzed the data. H.J., Y.H.G., and F.J.S. gave advice on methodology. Q.F.T. and C.Z.L. investigated the responses to the citywide nucleic acid testing among residents lived in outside of Wuhan city. S.Y.C., Y.G., C.W., and X.X.Y. drafted the manuscript, Y.G., M.B., and F.J.S. revised the manuscript, and M.B., C.Z.L., and F.J.S. critically commented and edited the manuscript. All authors read and approved the final manuscript. Z.X.L. is the guarantor of this study.

Competing interests

The authors declare no competing interests.

Additional information

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JAMA Internal Medicine | Original Investigation

Contact Tracing Assessment of COVID-19 Transmission Dynamics in Taiwan and Risk at Different Exposure Periods Before and After Symptom Onset

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IMPORTANCE The dynamics of coronavirus disease 2019 (COVID-19) transmissibility are yet to be fully understood. Better understanding of the transmission dynamics is important for the development and evaluation of effective control policies.

OBJECTIVE To delineate the transmission dynamics of COVID-19 and evaluate the transmission risk at different exposure window periods before and after symptom onset.

DESIGN, SETTING, AND PARTICIPANTS This prospective case-ascertained study in Taiwan included laboratory-confirmed cases of COVID-19 and their contacts. The study period was from January 15 to March 18, 2020. All close contacts were quarantined at home for 14 days after their last exposure to the index case. During the quarantine period, any relevant symptoms (fever, cough, or other respiratory symptoms) of contacts triggered a COVID-19 test. The final follow-up date was April 2, 2020.

MAIN OUTCOMES AND MEASURES Secondary clinical attack rate (considering symptomatic cases only) for different exposure time windows of the index cases and for different exposure settings (such as household, family, and health care).

RESULTS We enrolled 100 confirmed patients, with a median age of 44 years (range, 11-88 years), including 44 men and 56 women. Among their 2761 close contacts, there were 22 paired index-secondary cases. The overall secondary clinical attack rate was 0.7% (95% CI, 0.4%-1.0%). The attack rate was higher among the 1818 contacts whose exposure to index cases started within 5 days of symptom onset (1.0% [95% CI, 0.6%-1.6%]) compared with those who were exposed later (0 cases from 852 contacts; 95% CI, 0%-0.4%). The 299 contacts with exclusive presymptomatic exposures were also at risk (attack rate, 0.7% [95% CI, 0.2%-2.4%]). The attack rate was higher among household (4.6% [95% CI, 2.3%-9.3%]) and nonhousehold (5.3% [95% CI, 2.1%-12.8%]) family contacts than that in health care or other settings. The attack rates were higher among those aged 40 to 59 years (1.1% [95% CI, 0.6%-2.1%]) and those aged 60 years and older (0.9% [95% CI, 0.3%-2.6%]).

CONCLUSIONS AND RELEVANCE In this study, high transmissibility of COVID-19 before and immediately after symptom onset suggests that finding and isolating symptomatic patients alone may not suffice to contain the epidemic, and more generalized measures may be required, such as social distancing.

Editor's Note page 1163

Author Audio Interview

Supplemental content

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Group Information: A complete list of the members of the Taiwan COVID-19 Outbreak Investigation Team appears at the end of this article.

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The coronavirus disease 2019 (COVID-19) outbreak that originated in Wuhan, China, spread to more than 100 countries within 2 months of when the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in January 2020.[1,2] Following the Wuhan lockdown and other extreme social-distancing measures conducted by the Chinese government, several countries with widespread outbreaks implemented similar measures, including shutting down entire cities or communities, banning international or domestic travel, conducting border control with symptom screening, and implementing isolation and quarantine.

The unknown epidemiologic characteristics and transmission dynamics of a novel pathogen, such as SARS-CoV-2, complicate the development and evaluation of effective control policies.[3] The serial interval of COVID-19, defined as the interval between the symptom onset of the index case and that of the secondary case, was found to be short (4-5 days) and was similar to the estimated incubation period.[4] The short serial interval of COVID-19 and results from viral shedding studies suggested that most transmission occurred near or even before the time of symptom onset.[4-6] On the other hand, prolonged viral shedding raised concerns about prolonged infectiousness of patients and the need for extended isolation. A few preliminary contact-tracing studies showed that the highest-risk exposure setting of COVID-19 transmission was the household.[7-9] Nevertheless, it is not known when and how long a patient with COVID-19 should be isolated or whether close contacts should be quarantined. Additional information is needed about the transmission risk at different time points before and after symptom onset and with different types of exposures, such as through the household or a health care facility.

In Taiwan, the first COVID-19 case was confirmed on January 21, 2020.[10] With proactive containment efforts and comprehensive contact tracing, the number of COVID-19 cases remained low, as compared with other countries that had widespread outbreaks.[11,12] Using the contact tracing data in Taiwan, we aimed to delineate the transmission dynamics of COVID-19, evaluate the infection risk at different exposure windows, and estimate the infectious period.

Key Points

Question What is the transmissibility of coronavirus disease 2019 (COVID-19) to close contacts?

Findings In this case-ascertained study of 100 cases of confirmed COVID-19 and 2761 close contacts, the overall secondary clinical attack rate was 0.7%. The attack rate was higher among contacts whose exposure to the index case started within 5 days of symptom onset than those who were exposed later.

Meaning High transmissibility of COVID-19 before and immediately after symptom onset suggests that finding and isolating symptomatic patients alone may not suffice to interrupt transmission, and that more generalized measures might be required, such as social distancing.

Methods

Study Population

On January 15, 2020, in response to the outbreak in Wuhan, the Taiwan Centers for Disease Control (Taiwan CDC) made COVID-19 a notifiable disease. We conducted a prospective case-ascertained study that enrolled all the initial 100 confirmed cases in Taiwan between January 15 and March 18, 2020, and their close contacts. All contacts were followed up until 14 days after the last exposure to the index case. The last follow-up date was April 2, 2020.

The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[13] Information was collected according to the pronouncement of the Central Epidemic Command Center and in accordance with Article 17 of the Communicable Disease Control Act.[14] As part of the public health response functions of the Central Epidemic Command Center for surveillance purposes, institutional review board approval of this study and informed consent were waived. Prior to analysis, the data were deidentified.

Ascertainment of Cases

A confirmed case met the criteria of notification for COVID-19 in Taiwan and tested positive by real-time reverse transcriptase–polymerase chain reaction (RT-PCR) test.[15] Detailed information, including demographic and clinical data, was reported to the National Notifiable Disease Surveillance System.[16] The investigation team determined the clinical severity of the confirmed patients following the World Health Organization (WHO) interim guidance.[17]

Contact Tracing for COVID-19

When a patient was laboratory-confirmed to have SARS-CoV-2 infection, a thorough epidemiological investigation, including contact tracing, was implemented by the outbreak investigation team of the Taiwan CDC and local health authorities. The period of investigation started at the date at symptom onset (and could be extended to up to 4 days before symptom onset when epidemiologically indicated) and ended at the date at COVID-19 confirmation. For asymptomatic confirmed cases, the period of investigation was based on the date at confirmation (instead of date at onset) and was determined according to epidemiological investigation. The definition of a close contact was a person who did not wear appropriate personal protection equipment (PPE) while having face-to-face contact with a confirmed case for more than 15 minutes during the investigation period. A contact was listed as a household contact if he or she lived in the same household with the index case. Those listed as family contacts were family members not living in the same household.

For health care settings, medical staff, hospital workers, and other patients in the same setting were included; close contact was defined by contacting an index case within 2 m without appropriate PPE and without a minimal requirement of exposure time. Whether the PPE was regarded as “appropriate” depended on the exposure setting and the procedures performed. For example, for physicians who performed aerosol-generating procedures, such as intubation, an N95 respirator

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Table 1. Characteristics of the 2761 Close Contacts by Different Exposure Settings

	Exposure, No. (%)			
	Household (n = 151)	Family (n = 76)	Health care (n = 698)	Others (n = 1836)[a]
Age, median (range), y	33 (1-96)	45 (0-88)	39 (0-92)	35 (0-89)
Age group, y				
0-19	24 (16)	14 (18)	29 (4)	214 (12)
20-39	55 (36)	16 (21)	281 (40)	809 (44)
40-59	38 (25)	24 (32)	175 (25)	557 (30)
≥60	26 (17)	11 (14)	119 (17)	175 (10)
Unknown	8 (5)	11 (14)	94 (13)	81 (4)
Sex				
Female	70 (46)	41 (54)	454 (65)	872 (47)
Male	81 (54)	30 (39)	228 (33)	816 (44)
Unknown	0	5 (7)	16 (2)	148 (8)
Time from onset to exposure, median (range), d[b]	−4 (−4 to 9)	6 (−4 to 26)	1 (−4 to 23)	2 (−4 to 26)
Time from onset to exposure, d[b]				
<0	100 (66)	10 (13)	236 (34)	389 (21)
0-3	39 (26)	15 (20)	150 (21)	663 (36)
4-5	6 (4)	6 (8)	38 (5)	166 (9)
6-7	4 (3)	10 (13)	17 (2)	88 (5)
8-9	2 (1)	3 (4)	110 (16)	334 (18)
>9	0	24 (32)	146 (21)	114 (6)
Unknown	0	8 (11)	1 (0.1)	82 (5)

[a] Others include friends, airline crew members and passengers, and other casual contacts.

[b] Defined as the elapsed time between the date at symptom onset of the index case and the first date at exposure. For example, people from the group "<0 days" had their first contact with the index case before the case had any symptoms.

was required. For such procedures, a surgical mask would not be appropriate PPE. Accordingly, the medical staff would be listed as a close contact.

All close contacts were quarantined at home for 14 days after their last exposure to the index case. During the quarantine period, any relevant symptoms (fever, cough, or other respiratory symptoms) of close contacts would trigger RT-PCR testing for COVID-19. For high-risk populations, including household and hospital contacts, RT-PCR was performed regardless of symptoms. Essentially, these high-risk contacts were tested once when they were listed as a close contact. If the initial COVID-19 test result was negative, further testing would only be performed if a close contact developed symptoms during quarantine. The Taiwan CDC used an electronic tracing system (Infectious Disease Contact Tracing Platform and Management System) to follow and record the daily health status of those quarantined contacts.[18] The information collected included age, sex, the index case, date at exposure, and the exposure setting.

Data Processing and Analysis

Paired data of index case and close contacts were extracted from the contact tracing database and outbreak investigation reports. For a family cluster, the index case was determined based on the temporality of symptom onset and review of the epidemiological link. A secondary case was excluded from the paired data if the beginning of exposure was after symptom onset of the secondary case (only applied when the secondary case was symptomatic). For health care contacts, the date at exposure would be the date at admission of the case if the exact date at exposure was not recorded.

Incubation period and serial interval were estimated using the contact tracing data in Taiwan and publicly available data sets globally (eMethods in the Supplement). We used the Bayesian hierarchical model to increase the stability in small-sample estimation. The exposure window period was defined as the period between the first and last day of reported exposure to the index case based on contact investigation. Following the WHO, we defined the secondary clinical attack rate as the ratio of symptomatic confirmed cases among the close contacts.[19] We analyzed the dynamic change of secondary clinical attack rate in relation to symptom onset of the index case (days <0, 0-3, 4-5, 6-7, 8-9, or >9).

The percentage of missing information was small (7.0% for age, 6.1% for sex, and 3.3% for time from onset to exposure; **Table 1**). In the univariable analysis of secondary clinical attack rate by different exposure characteristics (eg, age), close contacts with missing information in that particular exposure attribute were excluded. All statistical tests were 2-sided with an α level of .05. All confidence intervals (CIs) were 95%. R software (R Foundation for Statistical Computing) and RStan (Stan Development Team) were used for data management and analysis.

Results

As of March 18, 2020, there were 100 patients with laboratory-confirmed COVID-19 in Taiwan, including 10 clusters of patients and 9 asymptomatic patients. The median age of the 100 patients was 44 years old (range, 11-88 years); 44 were men and 56 were women. Of the 2761 close contacts that were identi-

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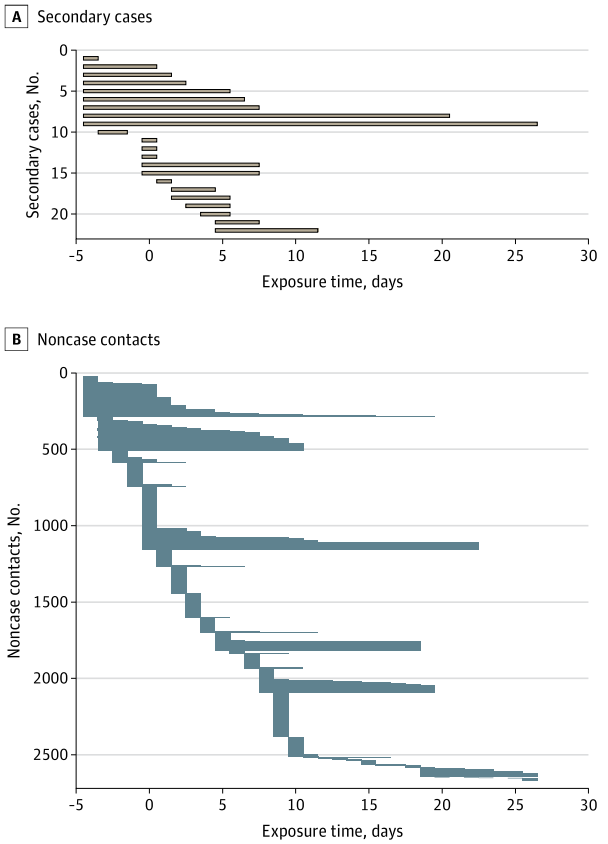
fied, 5.5% were household contacts, 2.8% were nonhousehold family contacts, and 25.3% were health care contacts (Table 1). Through contact tracing, 23 secondary cases were found. One of the 23 cases was excluded from subsequent transmission-pair analysis because the documented day at exposure occurred after symptom onset of the secondary case. None of the 9 asymptomatic case patients transmitted a secondary case. Using the data on the 22 paired cases, we estimated that the median incubation period was 4.1 days (95% credible interval [CrI], 0.4-15.8), and the median serial interval was 4.1 days (95% CrI, 0.1-27.8) (eTables 1-5 and eFigures 1-5 in the Supplement).

Among the 2761 close contacts, 22 secondary cases of COVID-19 infection (including 4 asymptomatic infections) were detected, with an infection risk of 0.8% (95% CI, 0.5%-1.2%). The secondary clinical attack rate was 18 of 2761, or 0.7% (95% CI, 0.4%-1.0%). **Figure 1** shows the exposure window of all contacts. All of the 22 secondary cases had their first exposure before the sixth day of the index case's symptom onset. By comparison, only 68% of noncase contacts had their first exposure before day 6 (Table 1). The secondary clinical attack rate was higher among those whose initial exposure to the index case was within 5 days of symptom onset than those who were exposed after day 6 (zero transmission of 852 contacts [95% CI, 0%-0.4%]) (**Table 2** and **Figure 2**A). The 735 contacts whose initial exposure occurred before symptom onset of the index case were also at risk, with a secondary clinical attack rate of 1.0% (95% CI, 0.5%-2.0%). A subgroup of 299 contacts with exclusive presymptomatic exposures were also at risk (secondary clinical attack rate, 0.7% [95% CI, 0.2%-2.4%]).

The secondary clinical attack rate was 4.6% (95% CI, 2.3%-9.3%) among 151 household contacts and 5.3% (95% CI, 2.1%-12.8%) in 76 nonhousehold family contacts (Table 2). The high attack rate from early exposure remained when the analysis was restricted to household and nonhousehold family contacts (**Table 3** and Figure 2B). The attack rates were higher among those aged 40 to 59 years (1.1% [95% CI, 0.6%-2.1%]) and those aged 60 years and older (0.9% [95% CI, 0.3%-2.6%]). The 786 close contacts of the 6 confirmed cases presenting with severe disease were at a higher risk compared with the 1097 close contacts of the 56 cases presenting with mild disease (risk ratio, 3.76 [95% CI, 1.10-12.76] and 3.99 [95% CI, 1.00-15.84] for severe pneumonia and acute respiratory distress syndrome/sepsis, respectively). Among the 91 close contacts of the 9 asymptomatic cases, no secondary transmission was observed. The secondary attack rate among contacts of cases with infection acquired in Taiwan was higher than that among contacts of cases with infection acquired outside of Taiwan (Table 2).

Figure 1. Exposure Window Period Among Secondary Cases and Noncase Contacts



The exposure time was defined as the period from the first day of exposure to the index case to the last day of exposure. Time zero indicates the day of symptom onset of the index case.

Discussion

Our analysis of close contacts to confirmed COVID-19 cases revealed a relatively short infectious period of COVID-19 and a higher transmission risk around the time of symptom onset of the index case, followed by a lower transmission risk at the later stage of disease. The observed decreasing transmission risk over time for COVID-19 was in striking contrast to the transmission pattern of severe acute respiratory syndrome (SARS), in which the transmission risk remained low until after day 5 of symptom onset in the index cases.[20] Our study and the study by Nishiura et al[4] revealed a short serial interval of COVID-19, with a median of 4 to 5 days. In contrast, the mean serial interval of SARS was estimated to be 8.4 days in Singapore.[20] The present contact tracing analysis suggested that the shorter serial interval of COVID-19 was due to the combination of early-stage transmission and a short period of infectiousness.

The observed pattern of the secondary clinical attack rate over time was also consistent with the quantitative data of the SARS-CoV-2 viral shedding in upper respiratory specimens, which has been found in China to be a high viral load around the time of symptom onset, followed by a gradual decrease in viral shedding to a low level after 10 days.[5] The viral load was similar among asymptomatic, minimally symptomatic, and symptomatic patients. Another virological study in patients with COVID-19 in Germany also found no viable isolates of the virus after the first week of symptoms.[21] Our findings agree with the virological data on high transmissibility of COVID-19 in the first week after the onset of symptoms and decreased risk afterwards.[21] We also documented and quantified the

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Table 2. Secondary Clinical Attack Rate for COVID-19 Among the 2761 Close Contacts by Different Exposure Settings, Times, and Characteristics

	No. of secondary cases (asymptomatic case)	No. of contacts	Secondary clinical attack rate, % (95% CI)	Risk ratio (95% CI)
Exposure setting				
Household	10 (3)	151	4.6 (2.3-9.3)	1 [Reference]
Nonhousehold family	5 (1)	76	5.3 (2.1-12.8)	1.14 (0.34-3.76)
Health care	6 (0)	698	0.9 (0.4-1.9)	0.19 (0.06-0.54)
Others[a]	1 (0)	1836	0.1 (0-0.3)	0.01 (0-0.09)
Time from onset to exposure, d[b]				
<0	10 (3)	735	1.0 (0.5-2.0)	1 [Reference]
0-3	9 (1)	867	0.9 (0.5-1.8)	0.97 (0.35-2.66)
4-5	3 (0)	216	1.4 (0.5-4.0)	1.46 (0.38-5.59)
6-7	0	119	0 (0-3.1)	0
8-9	0	449	0 (0-0.9)	0
>9	0	284	0 (0-1.3)	0
Exclusively presymptomatic exposure[c]				
No	20 (4)	2371	0.7 (0.4-1.1)	1 [Reference]
Yes	2 (0)	299	0.7 (0.2-2.4)	0.99 (0.23-4.29)
Age of close contacts, y				
0-19	1 (1)	281	0 (0-1.4)	0
20-39	8 (2)	1161	0.5 (0.2- 1.1)	1 [Reference]
40-59	10 (1)	794	1.1 (0.6-2.1)	2.19 (0.78-6.14)
≥60	3 (0)	331	0.9 (0.3-2.6)	1.75 (0.44-6.97)
Source of index case				
Local	18 (3)	967	1.6 (1.0-2.5)	1 [Reference]
Imported	4 (1)	1794	0.2 (0.1-0.5)	0.11 (0.03-0.37)
Clinical severity of index case				
Asymptomatic	0	91	0 (0-4.1)	0
Mild illness	4 (0)	1097	0.4 (0.1-0.9)	1 [Reference]
Pneumonia				
Mild	5 (2)	761	0.4 (0.1-1.2)	1.08 (0.24-4.82)
Severe	7 (0)	511	1.4 (0.7-2.8)	3.76 (1.10-12.76)
ARDS/sepsis	6 (2)	275	1.5 (0.6-3.7)	3.99 (1.00-15.84)

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019.

[a] Others include friends, airline crew members and passengers, and other casual contacts.

[b] Defined as the elapsed time between the date at symptom onset of the index case and the first date at exposure. For example, people from the group "<0 days" had their first contact with the index case before the case had any symptoms.

[c] All the reported exposures occurred during the presymptomatic period of the index case.

transmission potential of COVID-19 in a subgroup of contacts whose exposure occurred exclusively during the presymptomatic period of the index case. Our analysis revealed a similar clinical attack rate between the contacts who only had presymptomatic exposure and those who had postsymptomatic exposure.

To summarize the evidence, the decreasing risk for secondary infection over time in our study, the observed short serial interval, and the trend of decreasing viral shedding and viability after symptom onset strongly suggested high transmissibility of the disease near or even before the day of symptom onset. Because the onset of overt clinical symptoms, such as fever, dyspnea, and signs of pneumonia, usually occurred 5 to 7 days after initial symptom onset, the infection might well have been transmitted at or before the time of detection.[22,23] This characteristic makes containment efforts challenging. In a modeling study, Hellewell et al[24] found that the possibility of controlling COVID-19 through isolation and contact tracing decreased with increasing proportion of transmission that occurred before symptom onset. The findings of this modeling study, when viewed in the context of our findings, might help to explain the difficult situation in such areas and countries as China, South Korea, Iran, and Italy. Aggressive social distancing and proactive contact tracing might be necessary to block the transmission chain of COVID-19 and to keep presumptive patients away from susceptible populations with a high risk for severe disease.

The observed short duration of infectiousness with lower risk of transmission 1 week after symptom onset has important implications for redirecting the efforts to control COVID-19. Given the nonspecific and mostly mild symptoms of COVID-19 at presentation, patients are often identified and hospitalized at a later stage of disease when the transmissibility of infection has started to decrease. In this case, hospitalization would not be helpful for isolation and reducing transmission, and should be only for patients whose clinical course is sufficiently severe. When the number of confirmed cases rapidly increases, home care for patients with mild illness may be

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Figure 2. Number of Contacts, Secondary Cases, and Secondary Clinical Attack Rate by the Time of First Exposure

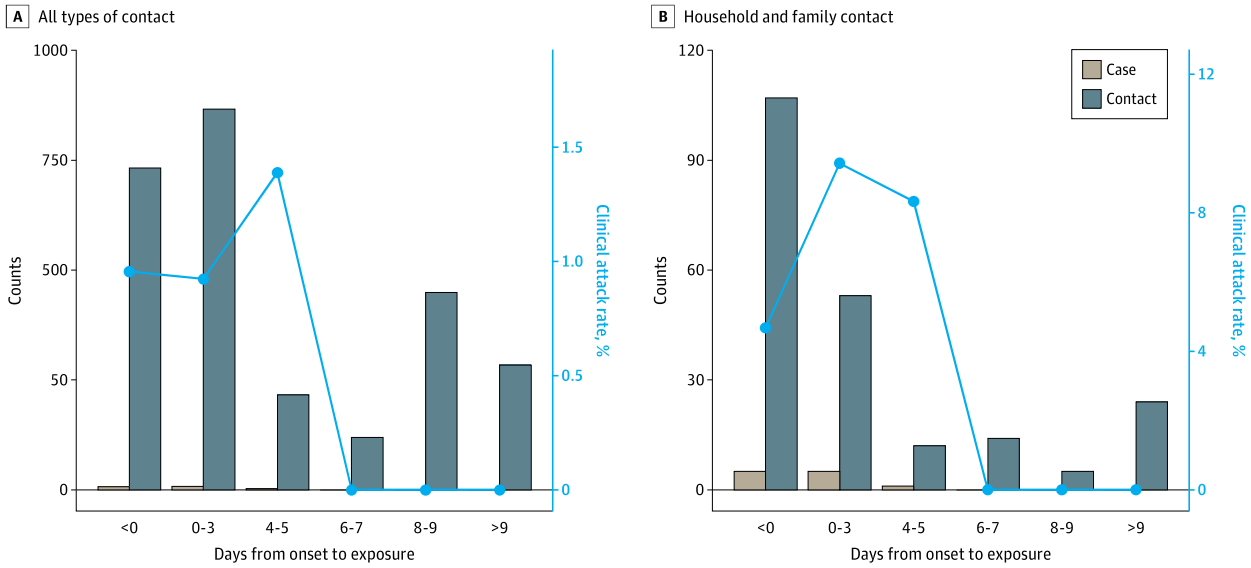

Table 3. Risk for Symptomatic COVID-19 Infection Among the 2761 Close Contacts, Simultaneously Stratified by Exposure Setting and Time From Symptom Onset of the Index Case to First Day of Exposure

First day of exposure, d	Household		Nonhousehold family		Health care		Others[a]	
	Case/contact, No.	Attack rate, % (95% CI)[b]	Case/contact, No.	Attack rate, % (95% CI)[b]	Case/contact, No.	Attack rate, % (95% CI)[b]	Case/contact, No.	Attack rate, % (95% CI)[b]
<0	4/100	4.0 (1.6-9.8)	1/10	10.0 (1.8-40.4)	2/236	0.8 (0.2-3.0)	0/389	0 (0-1.0)
0-3	2/39	5.1 (1.4-16.9)	3/15	20.0 (7.0-45.2)	3/150	2.0 (0.7-5.7)	0/663	0 (0-0.6)
4-5	1/6	16.7 (3.0-56.4)	0/6	0 (0-39.0)	1/38	2.6 (0.5-13.5)	1/166	0.6 (0.1-3.3)
6-7	0/4	0 (0-49.0)	0/10	0 (0-27.8)	0/17	0 (0-18.4)	0/88	0 (0-4.2)
8-9	0/2	0 (0-65.7)	0/3	0 (0-56.1)	0/110	0 (0-3.3)	0/334	0 (0-1.1)
>9	0/0	NC	0/24	0 (0-13.8)	0/146	0 (0-2.6)	0/114	0 (0-3.3)

Abbreviations: COVID-19, coronavirus disease 2019; NC, not calculable.

[a] Others include friends, airline crew members and passengers, and other casual contacts.

[b] Secondary clinical attack rate.

preferred.[25] In Taiwan (where patients with COVID-19 have been routinely hospitalized), the most prolonged duration of hospital isolation for the 100 confirmed cases was more than 2 months. If every patient with mild illness is to be isolated in the hospital or other isolation facilities for such a prolonged period during a large epidemic, the health care system would soon be overwhelmed, and the case-fatality rate may increase, as observed in Wuhan.[26,27] Similarly, better understanding of the potential duration of transmission could help direct containment strategies. For example, contact tracing could focus on the contacts near or even before symptom onset of the index cases when the number of index cases or contacts is too large for all contacts to be traced, given the available resources.

Several patients in our study were initially considered to have pneumonia of unknown etiology and had multiple contacts in the health care setting before being diagnosed. However, the number of health care contacts that led to nosocomial transmission was low. Besides the basic PPE used by medical staffs, this finding might be due to the late admissions of these patients and their lower risk of transmitting COVID-19 by the time of hospitalization. This pattern is compatible with the observations in China and Hong Kong. In China, the number of nosocomial infections might be lower than reported because some health care workers acquired infections in their households rather than in the health care faciltiy.[9] In Hong Kong, most hospitalization was also delayed to at least 5 days after disease onset.[28] In closed settings such as a hospital or a cruise ship,[29,30] fomite transmission might play an important role, amplifying the risk of transmission and making the temporality of transmission less identifiable.[30-32] Better understanding of the dynamic change of transmissibility of COVID-19 over time and how health care workers are most likely to be infected could allow for better targeting of control measures, including the use of appropriate PPE.

In the contact tracing cohort, we observed a relatively low transmission rate of COVID-19. During the study period (January to early March 2020), the major containment measures in Taiwan were travel alerts with restriction to affected countries (principally China), home quarantine for travelers entering Taiwan, and comprehensive contact tracing for confirmed cases.[11] In response to a possible shortage of face masks,

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the government proactively initiated a name-based rationing system for mask purchase and boosted the production of face masks to ensure the availability for both N95 respirators and face masks to both health care professionals and the general public. A general recommendation on social distancing from the government was not in place, but spontaneous behavioral changes that reduced community mobility were observed.[33]

Limitations

Our study has limitations. First, we did not completely examine contacts before the symptom onset of the index cases. Therefore, we might have underestimated the importance of early transmission. Thus, the actual contribution of early transmission to new infections could be greater than our estimates suggests. Our findings agree with the recommendation from the WHO to use 4 days before symptom onset as the starting date for contact tracing.[19] This modification may help to further understand the pattern of early transmission in COVID-19. Second, we could not completely separate out the effect of close household contact and early contact given the strong correlation of the 2. The increased transmissibility in the early stage of COVID-19 may be partially attributed to the effect of household and nonhousehold family contacts rather than increased infectiousness at the early stage. When we stratified by type of exposure, however, the pattern of early transmission remained.

Conclusions

In summary, the findings of this study suggest that most transmission of COVID-19 occurred at the very early stage of the disease or even before the onset of symptoms, and the secondary clinical attack rate among contacts decreased over time as symptoms developed and progressed. The pattern of high transmissibility near and before symptom onset and the likely short infectious period of the virus could inform control strategies for COVID-19, as well as additional studies to fully elucidate the transmission dynamics of the virus.

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Cheng, Jian, Ng, Lin.
Critical revision of the manuscript for important intellectual content: Cheng, Jian, Liu, Huang, Lin.
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Editor's Note

Contact Tracing, Testing, and Control of COVID-19—Learning From Taiwan

Robert Steinbrook, MD

Taiwan is a country of about 24 million people, 81 miles off the coast of mainland China. As of late April 2020, Taiwan had about 330 confirmed cases of coronavirus disease 2019 (COVID-19) and 6 deaths. By comparison, the US had about 1 million confirmed cases of COVID-19, and 60 000 deaths.

In this issue of *JAMA Internal Medicine*, there is a remarkable report from Taiwan on the use of contact tracing and virologic polymerase chain reaction testing to assess the transmission dynamics of COVID-19 in the country's initial 100 confirmed cases.[1] Among 2761 close contacts of the 100 cases, confirmed between January 15 and March 18, 2020, Cheng et al report that there were 22 paired-index secondary cases and an overall secondary clinical attack rate of 0.7% (95% CI, 0.4%-1.0%).[1]

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The study has important messages for the control of COVID-19 throughout the world. First, people with COVID-19 were found to be most infectious to others before and within 5 days of symptom onset. Within 5 days of symptom onset, the attack rate was 1.0% (95% CI, 0.6%-1.5%). With exclusive presymptomatic exposures, the attack rate was 0.7% (95% CI, 0.2%-2.4%), and with exposures 6 days or more after symptom onset, there were 0 cases from 852 contacts (95% CI, 0%-0.4%).[1]

These findings underscore the pressing public health need for accurate and comprehensive contact tracing and testing. Testing only those people who are symptomatic will miss many infections and render contact tracing less effective. The finding that asymptomatic people and those with minimal or fewer symptoms early in infection are those most likely to transmit COVID-19 strongly argues for maintaining social distancing and

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Mask use in the context of COVID-19

Interim guidance

1 December 2020

World Health Organization

This document, which is an update of the guidance published on 5 June 2020, includes new scientific evidence relevant to the use of masks for reducing the spread of SARS-CoV-2, the virus that causes COVID-19, and practical considerations. It contains updated evidence and guidance on the following:

- mask management;
- SARS-CoV-2 transmission;
- masking in health facilities in areas with community, cluster and sporadic transmission;
- mask use by the public in areas with community and cluster transmission;
- alternatives to non-medical masks for the public;
- exhalation valves on respirators and non-medical masks;
- mask use during vigorous intensity physical activity;
- essential parameters to be considered when manufacturing non-medical masks (Annex).

Key points

- The World Health Organization (WHO) advises the use of masks as part of a comprehensive package of prevention and control measures to limit the spread of SARS-CoV-2, the virus that causes COVID-19. A mask alone, even when it is used correctly, is insufficient to provide adequate protection or source control. Other infection prevention and control (IPC) measures include hand hygiene, physical distancing of at least 1 metre, avoidance of touching one's face, respiratory etiquette, adequate ventilation in indoor settings, testing, contact tracing, quarantine and isolation. Together these measures are critical to prevent human-to-human transmission of SARS-CoV-2.
- Depending on the type, masks can be used either for protection of healthy persons or to prevent onward transmission (source control).
- WHO continues to advise that anyone suspected or confirmed of having COVID-19 or awaiting viral laboratory test results should wear a medical mask when in the presence of others (this does not apply to those awaiting a test prior to travel).
- For any mask type, appropriate use, storage and cleaning or disposal are essential to ensure that they are as effective as possible and to avoid an increased transmission risk.

Mask use in health care settings

- WHO continues to recommend that health workers (1) providing care to suspected or confirmed COVID-19 patients wear the following types of mask/respirator in addition to other personal protective equipment that are part of standard, droplet and contact precautions:
  - medical mask in the absence of aerosol generating procedures (AGPs)
  - respirator, N95 or FFP2 or FFP3 standards, or equivalent in care settings for COVID-19 patients where AGPs are performed; these may be used by health workers when providing care to COVID-19 patients in other settings if they are widely available and if costs is not an issue.
- In areas of known or suspected community or cluster SARS-CoV-2 transmission WHO advises the following:
  - universal masking for all persons (staff, patients, visitors, service providers and others) within the health facility (including primary, secondary and tertiary care levels; outpatient care; and long-term care facilities)
  - wearing of masks by inpatients when physical distancing of at least 1 metre cannot be maintained or when patients are outside of their care areas.
- In areas of known or suspected sporadic SARS-CoV-2 transmission, health workers working in clinical areas where patients are present should continuously wear a medical mask. This is known as targeted continuous medical masking for health workers in clinical areas;
- Exhalation valves on respirators are discouraged as they bypass the filtration function for exhaled air by the wearer.

Mask use in community settings

- Decision makers should apply a risk-based approach when considering the use of masks for the general public.
- In areas of known or suspected community or cluster SARS-CoV-2 transmission:
  - WHO advises that the general public should wear a non-medical mask in indoor (e.g. shops, shared workplaces, schools - see Table 2 for details) or outdoor settings where physical distancing of at least 1 metre cannot be maintained.
  - If indoors, unless ventilation has been be assessed to be adequate[1], WHO advises that the general public should wear a non-medical mask, regardless of whether physical distancing of at least 1 metre can be maintained.

[1] For adequate ventilation refer to regional or national institutions or heating, refrigerating and air-conditioning societies enacting ventilation requirements. If not available or applicable, a recommended ventilation rate of 10 l/s/person should be met (except healthcare facilities which have specific requirements). For more information consult "Coronavirus (COVID-19) response

  - Individuals/people with higher risk of severe complications from COVID-19 (individuals ≥ 60 years old and those with underlying conditions such as cardiovascular disease or diabetes mellitus, chronic lung disease, cancer, cerebrovascular disease or immunosuppression) should wear medical masks when physical distancing of at least 1 metre cannot be maintained.
- In any transmission scenarios:
  - Caregivers or those sharing living space with people with suspected or confirmed COVID-19, regardless of symptoms, should wear a medical mask when in the same room.

Mask use in children (2)

- Children aged up to five years should not wear masks for source control.
- For children between six and 11 years of age, a risk-based approach should be applied to the decision to use a mask; factors to be considered in the risk-based approach include intensity of SARS-CoV-2 transmission, child's capacity to comply with the appropriate use of masks and availability of appropriate adult supervision, local social and cultural environment, and specific settings such as households with elderly relatives, or schools.
- Mask use in children and adolescents 12 years or older should follow the same principles as for adults.
- Special considerations are required for immunocompromised children or for paediatric patients with cystic fibrosis or certain other diseases (e.g., cancer), as well as for children of any age with developmental disorders, disabilities or other specific health conditions that might interfere with mask wearing.

Manufacturing of non-medical (fabric) masks (Annex)

- Homemade fabric masks of three-layer structure (based on the fabric used) are advised, with each layer providing a function: 1) an innermost layer of a hydrophilic material 2) an outermost layer made of hydrophobic material 3) a middle hydrophobic layer which has been shown to enhance filtration or retain droplets.
- Factory-made fabric masks should meet the minimum thresholds related to three essential parameters: filtration, breathability and fit.
- Exhalation valves are discouraged because they bypass the filtration function of the fabric mask rendering it unserviceable for source control.

Methodology for developing the guidance

Guidance and recommendations included in this document are based on published WHO guidelines (in particular the WHO Guidelines on infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care) (2) and ongoing evaluations of all available scientific evidence by the WHO ad hoc COVID-19 Infection Prevention and Control Guidance Development Group (COVID-19 IPC GDG) (see acknowledgement section for list of GDG members). During emergencies WHO publishes interim guidance, the development of which follows a transparent and robust process of evaluation of the available evidence on benefits and harms. This evidence is evaluated through expedited systematic reviews and expert consensus-building through weekly GDG consultations, facilitated by a methodologist and, when necessary, followed up by surveys. This process also considers, as much as possible, potential resource implications, values and preferences, feasibility, equity, and ethics. Draft guidance documents are reviewed by an external review panel of experts prior to publication.

Purpose of the guidance

This document provides guidance for decision makers, public health and IPC professionals, health care managers and health workers in health care settings (including long-term care and residential), for the public and for manufactures of non-medical masks (Annex). It will be revised as new evidence emerges.

WHO has also developed comprehensive guidance on IPC strategies for health care settings (3), long-term care facilities (LTCF) (4), and home care (5).

Background

The use of masks is part of a comprehensive package of prevention and control measures that can limit the spread of certain respiratory viral diseases, including COVID-19. Masks can be used for protection of healthy persons (worn to protect oneself when in contact with an infected individual) or for source control (worn by an infected individual to prevent onward transmission) or both.

However, the use of a mask alone, even when correctly used (see below), is insufficient to provide an adequate level of protection for an uninfected individual or prevent onward transmission from an infected individual (source control). Hand hygiene, physical distancing of at least 1 metre, respiratory etiquette, adequate ventilation in indoor settings, testing, contact tracing, quarantine, isolation and other infection prevention and control (IPC) measures are critical to prevent human-to-human transmission of SARS-CoV-2, whether or not masks are used (6).

Mask management

For any type of mask, appropriate use, storage and cleaning, or disposal are essential to ensure that they are as effective as possible and to avoid any increased risk of transmission. Adherence to correct mask management practices varies, reinforcing the need for appropriate messaging (7).

WHO provides the following guidance on the correct use of masks:

- Perform hand hygiene before putting on the mask.
- Inspect the mask for tears or holes, and do not use a damaged mask.
- Place the mask carefully, ensuring it covers the mouth and nose, adjust to the nose bridge and tie it securely to minimize any gaps between the face and the mask. If using ear loops, ensure these do not cross over as this widens the gap between the face and the mask.

resources from ASHRAE and others''
https://www.ashrae.org/technical-resources/resources

- Avoid touching the mask while wearing it. If the mask is accidently touched, perform hand hygiene.
- Remove the mask using the appropriate technique. Do not touch the front of the mask, but rather untie it from behind.
- Replace the mask as soon as it becomes damp with a new clean, dry mask.
- Either discard the mask or place it in a clean plastic resealable bag where it is kept until it can be washed and cleaned. Do not store the mask around the arm or wrist or pull it down to rest around the chin or neck.
- Perform hand hygiene immediately afterward discarding a mask.
- Do not re-use single-use mask.
- Discard single-use masks after each use and properly dispose of them immediately upon removal.
- Do not remove the mask to speak.
- Do not share your mask with others.
- Wash fabric masks in soap or detergent and preferably hot water (at least 60° Centigrade/140° Fahrenheit) at least once a day. If it is not possible to wash the masks in hot water, then wash the mask in soap/detergent and room temperature water, followed by boiling the mask for 1 minute.

Scientific evidence

Transmission of the SARS-CoV-2 virus

Knowledge about transmission of the SARS-CoV-2 virus is evolving continuously as new evidence accumulates. COVID-19 is primarily a respiratory disease, and the clinical spectrum can range from no symptoms to severe acute respiratory illness, sepsis with organ dysfunction and death.

According to available evidence, SARS-CoV-2 mainly spreads between people when an infected person is in close contact with another person. Transmissibility of the virus depends on the amount of viable virus being shed and expelled by a person, the type of contact they have with others, the setting and what IPC measures are in place. The virus can spread from an infected person's mouth or nose in small liquid particles when the person coughs, sneezes, sings, breathes heavily or talks. These liquid particles are different sizes, ranging from larger 'respiratory droplets' to smaller 'aerosols.' Close-range contact (typically within 1 metre) can result in inhalation of, or inoculation with, the virus through the mouth, nose or eyes (8-13).

There is limited evidence of transmission through fomites (objects or materials that may be contaminated with viable virus, such as utensils and furniture or in health care settings a stethoscope or thermometer) in the immediate environment around the infected person (14-17). Nonetheless, fomite transmission is considered a possible mode of transmission for SARS-CoV-2, given consistent finding of environmental contamination in the vicinity of people infected with SARS-CoV-2 and the fact that other coronaviruses and respiratory viruses can be transmitted this way (12).

Aerosol transmission can occur in specific situations in which procedures that generate aerosols are performed. The scientific community has been actively researching whether the SARS-CoV-2 virus might also spread through aerosol transmission in the absence of aerosol generating procedures (AGPs) (18, 19). Some studies that performed air sampling in clinical settings where AGPs were not performed found virus RNA, but others did not. The presence of viral RNA is not the same as replication- and infection-competent (viable) virus that could be transmissible and capable of sufficient inoculum to initiate invasive infection. A limited number of studies have isolated viable SARS-CoV-2 from air samples in the vicinity of COVID-19 patients (20, 21).

Outside of medical facilities, in addition to droplet and fomite transmission, aerosol transmission can occur in specific settings and circumstances, particularly in indoor, crowded and inadequately ventilated spaces, where infected persons spend long periods of time with others. Studies have suggested these can include restaurants, choir practices, fitness classes, nightclubs, offices and places of worship (12).

High quality research is required to address the knowledge gaps related to modes of transmission, infectious dose and settings in which transmission can be amplified. Currently, studies are underway to better understand the conditions in which aerosol transmission or superspreading events may occur.

Current evidence suggests that people infected with SARS-CoV-2 can transmit the virus whether they have symptoms or not. However, data from viral shedding studies suggest that infected individuals have highest viral loads just before or around the time they develop symptoms and during the first 5-7 days of illness (12). Among symptomatic patients, the duration of infectious virus shedding has been estimated at 8 days from the onset of symptoms (22-24) for patients with mild disease, and longer for severely ill patients (12). The period of infectiousness is shorter than the duration of detectable RNA shedding, which can last many weeks (17).

The incubation period for COVID-19, which is the time between exposure to the virus and symptom onset, is on average 5-6 days, but can be as long as 14 days (25, 26).

Pre-symptomatic transmission – from people who are infected and shedding virus but have not yet developed symptoms – can occur. Available data suggest that some people who have been exposed to the virus can test positive for SARS-CoV-2 via polymerase chain reaction (PCR) testing 1-3 days before they develop symptoms (27). People who develop symptoms appear to have high viral loads on or just prior to the day of symptom onset, relative to later on in their infection (28).

Asymptomatic transmission – transmission from people infected with SARS-CoV-2 who never develop symptoms – can occur. One systematic review of 79 studies found that 20% (17–25%) of people remained asymptomatic throughout the course of infection. (28). Another systematic review, which included 13 studies considered to be at low risk of bias, estimated that 17% of cases remain asymptomatic (14%–20%) (30). Viable virus has been isolated from specimens of pre-symptomatic and asymptomatic individuals, suggesting that people who do not have symptoms may be able to transmit the virus to others. (25, 29-37)

Studies suggest that asymptomatically infected individuals are less likely to transmit the virus than those who develop symptoms (29). A systematic review concluded that individuals who are asymptomatic are responsible for transmitting fewer infections than symptomatic and pre-symptomatic cases (38). One meta-analysis estimated that there is a 42% lower relative risk of asymptomatic transmission compared to symptomatic transmission (30).

Guidance on mask use in health care settings

Masks for use in health care settings

Medical masks are defined as surgical or procedure masks that are flat or pleated. They are affixed to the head with straps that go around the ears or head or both. Their performance characteristics are tested according to a set of standardized test methods (ASTM F2100, EN 14683, or equivalent) that aim to balance high filtration, adequate breathability and optionally, fluid penetration resistance (39, 40).

Filtering facepiece respirators (FFR), or respirators, offer a balance of filtration and breathability. However, whereas medical masks filter 3 micrometre droplets, respirators must filter more challenging 0.075 micrometre solid particles. European FFRs, according to standard EN 149, at FFP2 performance there is filtration of at least 94% solid NaCl particles and oil droplets. US N95 FFRs, according to NIOSH 42 CFR Part 84, filter at least 95% NaCl particles. Certified FFRs must also ensure unhindered breathing with maximum resistance during inhalation and exhalation. Another important difference between FFRs and other masks is the way filtration is tested. Medical mask filtration tests are performed on a cross-section of the masks, whereas FFRs are tested for filtration across the entire surface. Therefore, the layers of the filtration material and the FFR shape, which ensure the outer edges of the FFR seal around wearer's face, result in guaranteed filtration as claimed. Medical masks, by contrast, have an open shape and potentially leaking structure. Other FFR performance requirements include being within specified parameters for maximum CO_2 build up, total inward leakage and tensile strength of straps (41, 42).

A. Guidance on the use of medical masks and respirators to provide care to suspected or confirmed COVID-19 cases

Evidence on the use of mask in health care settings

Systematic reviews have reported that the use of N95/P2 respirators compared with the use of medical masks (see mask definitions, above) is not associated with statistically significant differences for the outcomes of health workers acquiring clinical respiratory illness, influenza-like illness (risk ratio 0.83, 95%CI 0.63-1.08) or laboratory-confirmed influenza (risk ratio 1.02, 95%CI 0.73-1.43); harms were poorly reported and limited to discomfort associated with lower compliance (43, 44). In many settings, preserving the supply of N95 respirators for high-risk, aerosol-generating procedures is an important consideration (45).

A systematic review of observational studies on the betacoronaviruses that cause severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and COVID-19 found that the use of face protection (including respirators and medical masks) is associated with reduced risk of infection among health workers. These studies suggested that N95 or similar respirators might be associated with greater reduction in risk than medical or 12–16-layer cotton masks. However, these studies had important limitations (recall bias, limited information about the situations when respirators were used and limited ability to measure exposures), and very few studies included in the review evaluated the transmission risk of COVID-19 (46). Most of the studies were conducted in settings in which AGPs were performed or other high-risk settings (e.g., intensive care units or where there was exposure to infected patients and health workers were not wearing adequate PPE).

WHO continues to evaluate the evidence on the effectiveness of the use of different masks and their potential harms, risks and disadvantages, as well as their combination with hand hygiene, physical distancing of at least 1 metre and other IPC measures.

Guidance

WHO's guidance on the type of respiratory protection to be worn by health workers providing care to COVID-19 patients is based on 1) WHO recommendations on IPC for epidemic- and pandemic-prone acute respiratory infections in health care (47); 2) updated systematic reviews of randomized controlled trials on the effectiveness of medical masks compared to that of respirators for reducing the risk of clinical respiratory illness, influenza-like illness (ILI) and laboratory-confirmed influenza or viral infections. WHO guidance in this area is aligned with guidelines of other professional organizations, including the European Society of Intensive Care Medicine and the Society of Critical Care Medicine, and the Infectious Diseases Society of America (48, 49).

The WHO COVID-19 IPC GDG considered all available evidence on the modes of transmission of SARS-CoV-2 and on the effectiveness of medical mask versus respirator use to protect health workers from infection and the potential for harms such as skin conditions or breathing difficulties.

Other considerations included availability of medical masks versus respirators, cost and procurement implications and equity of access by health workers across different settings.

The majority (71%) of the GDG members confirmed their support for previous recommendations issued by WHO on 5 June 2020:

1. In the absence of aerosol generating procedures (AGPs)[2], WHO recommends that health workers providing care to patients with suspected or confirmed COVID-19 should wear a medical mask (in addition to other PPE that are part of droplet and contact precautions).
2. In care settings for COVID-19 patients where AGPs are performed, WHO recommends that health workers should wear a respirator (N95 or FFP2 or FFP3 standard, or equivalent) in addition to other PPE that are part of airborne and contact precautions.

In general, health workers have strong preferences about having the highest perceived protection possible to prevent COVID-19 infection and therefore may place high value on the potential benefits of respirators in settings without AGPs. WHO recommends respirators primarily for settings where AGPs are performed; however, if health workers prefer them and they are sufficiently available and cost is not an issue, they could also be used during care for COVID-19 patients in other settings. For additional guidance on PPE, including PPE

[2] The WHO list of AGPs includes tracheal intubation, non-invasive ventilation, tracheotomy, cardiopulmonary resuscitation, manual ventilation before intubation, bronchoscopy, sputum induction using nebulized hypertonic saline, and dentistry and autopsy procedures.

beyond mask use by health workers, see WHO IPC guidance during health care when COVID-19 infection is suspected (3) and also WHO guidance on the rational use of PPE (45).

Exhalation valves on respirators are discouraged as they bypass the filtration function for exhaled air.

B. Guidance on the use of mask by health workers, caregivers and others based on transmission scenario

Definitions

Universal masking in health facilities is defined as the requirement for all persons (staff, patients, visitors, service providers and others) to wear a mask at all times except for when eating or drinking.

Targeted continuous medical mask use is defined as the practice of wearing a medical mask by all health workers and caregivers working in clinical areas during all routine activities throughout the entire shift.

Health workers are all people primarily engaged in actions with the primary intent of enhancing health. Examples are: nursing and midwifery professionals, doctors, cleaners, other staff who work in health facilities, social workers, and community health workers.

Evidence on universal masking in health care settings

In areas where there is community transmission or large-scale outbreaks of COVID-19, universal masking has been adopted in many hospitals to reduce the potential of transmission by health workers to patients, to other staff and anyone else entering the facility (50).

Two studies found that implementation of a universal masking policy in hospital systems was associated with decreased risk of healthcare-acquired SARS-CoV-2 infection. However, these studies had serious limitations: both were before-after studies describing a single example of a phenomenon before and after an event of interest, with no concurrent control group, and other infection control measures were not controlled for (51, 52). In addition, observed decreases in health worker infections occurred too quickly to be attributable to the universal masking policy.

Guidance

Although more research on universal masking in heath settings is needed, it is the expert opinion of the majority (79%) of WHO COVID-19 IPC GDG members that universal masking is advisable in geographic settings where there is known or suspected community or cluster transmission of the SARS-CoV-2 virus.

1. In areas of known or suspected community or cluster SARS-CoV-2 transmission, universal masking should be advised in all health facilities (see Table 1).

- All health workers, including community health workers and caregivers, should wear a medical mask at all times, for any activity (care of COVID-19 or non-COVID-19 patients) and in any common area (e.g., cafeteria, staff rooms).
- Other staff, visitors, outpatients and service providers should also wear a mask (medical or non-medical) at all times
- Inpatients are not required to wear a mask (medical or non-medical) unless physical distancing of at least 1 metre cannot be maintained (e.g., when being examined or visited at the bedside) or when outside of their care area (e.g., when being transported).
- Masks should be changed when they become soiled, wet or damaged or if the health worker/caregiver removes the mask (e.g., for eating or drinking or caring for a patient who requires droplet/contact precautions for reasons other than COVID-19).

2. In the context of known or suspected sporadic SARS-CoV-2 virus transmission, WHO provides the following guidance:

- Health workers, including community health workers and caregivers who work in clinical areas, should continuously wear a medical mask during routine activities throughout the entire shift, apart from when eating and drinking and changing their medical masks after caring for a patient who requires droplet/contact precautions for other reasons. In all cases, medical masks must be changed when wet, soiled, or damaged; used medical masks should be properly disposed of at the end of the shift; and new clean ones should be used for the next shift or when medical masks are changed.
- It is particularly important to adopt the continuous use of masks in potentially high transmission risk settings including triage, family physician/general practitioner offices; outpatient departments; emergency rooms; COVID-19 designated units; haematology, oncology and transplant units; and long-term health and residential facilities.
- Staff who do not work in clinical areas (e.g., administrative staff) do not need to wear a medical mask during routine activities if they have no exposure to patients.

Whether using masks for universal masking within health facilities or targeted continuous medical mask use throughout the entire shift, health workers should ensure the following:

- Medical mask use should be combined with other measures including frequent hand hygiene and physical distancing among health workers in shared and crowded places such as cafeterias, break rooms, and dressing rooms.
- The medical mask should be changed when wet, soiled, or damaged.
- The medical mask should not be touched to adjust it or if displaced from the face for any reason. If this happens, the mask should be safely removed and replaced, and hand hygiene performed.
- The medical mask (as well as other personal protective equipment) should be discarded and changed after caring for any patient who requires contact/droplet precautions for other pathogens, followed by hand hygiene.
- Under no circumstances should medical masks be shared between health workers or between others wearing them. Masks should be appropriately disposed of whenever removed and not reused.

- A particulate respirator at least as protective as a United States of America (US) National Institute for Occupational Safety and Health-certified N95, N99, US Food and Drug Administration surgical N95, European Union standard FFP2 or FFP3, or equivalent, should be worn in settings for COVID-19 patients where AGPs are performed (see WHO recommendations below). In these settings, this includes continuous use by health workers throughout the entire shift, when this policy is implemented.

Note: Decision makers may consider the transmission intensity in the catchment area of the health facility or community setting and the feasibility of implementing a universal masking policy compared to a policy based on assessed or presumed exposure risk. Decisions need to take into account procurement, sustainability and costs of the policy. When planning masks for all health workers, long-term availability of adequate medical masks (and when applicable, respirators) for all workers should be ensured, in particular for those providing care for patients with confirmed or suspected COVID-19. Proper use and adequate waste management should be ensured.

The potential harms and risks of mask and respirator use in the health facility setting include:

- contamination of the mask due to its manipulation by contaminated hands (53, 54);
- potential self-contamination that can occur if medical masks are not changed when wet, soiled or damaged; or by frequent touching/adjusting when worn for prolonged periods (55);
- possible development of facial skin lesions, irritant dermatitis or worsening acne, when used frequently for long hours (56-58);
- discomfort, facial temperature changes and headaches from mask wearing (44, 59, 60);
- false sense of security leading potentially to reduced adherence to well recognized preventive measures such as physical distancing and hand hygiene; and risk-taking behaviours (61-64);
- difficulty wearing a mask in hot and humid environments
- possible risk of stock depletion due to widespread use in the context of universal masking and targeted continuous mask use and consequent scarcity or unavailability for health workers caring for COVID 19 patients and during health care interactions with non-COVID-19 patients where medical masks or respirators might be required.

Alternatives to medical masks in health care settings

The WHO's disease commodity package (DCP) for COVID-19 recommends medical masks for health workers to be type II or higher (65). Type II medical masks provide a physical barrier to fluids and particulate materials and have bacterial filtration efficiency of ≥98% compared to Type I mask, which has bacterial filtration efficiency of ≥95% and lower fluid resistance (66) In case of stock outs of type II or higher medical masks, health workers should use a type I medical mask as an alternative. Other alternatives such as face shields or fabric masks should be carefully evaluated.

Face shields are designed to provide protection from splashes of biological fluid (particularly respiratory secretions), chemical agents and debris (67, 68) into the eyes. In the context of protection from SARS-CoV-2 transmission through respiratory droplets, face shields are used by health workers as personal protective equipment (PPE) for eye protection in combination with a medical mask or a respirator (69, 70) While a face shield may confer partial protection of the facial area against respiratory droplets, these and smaller droplets may come into contact with mucous membranes or with the eyes from the open gaps between the visor and the face (71,67).

Fabric masks are not regulated as protective masks or part of the PPE directive. They vary in quality and are not subject to mandatory testing or common standards and as such are not considered an appropriate alternative to medical masks for protection of health workers. One study that evaluated the use of cloth masks in a health care facility found that health care workers using 2 ply cotton cloth masks (a type of fabric mask) were at increased risk of influenza-like illness compared with those who wore medical masks (72).

In the context of severe medical mask shortage, face shields alone or in combination with fabric mask may be considered as a last resort (73). Ensure proper design of face shields to cover the sides of the face and below the chin.

As for other PPE items, if production of fabric masks for use in health care settings is proposed locally in situations of shortage or stock out, a local authority should assess the product according to specific minimum performance standards and required technical specifications (see Annex).

Additional considerations for community care settings

Like other health workers, community health workers should apply standard precautions for all patients at all times, with particular emphasis regarding hand and respiratory hygiene, surface and environmental cleaning and disinfection and the appropriate use of PPE. When a patient is suspected or confirmed of having COVID-19, community health workers should always apply contact and droplet precautions. These include the use of a medical mask, gown, gloves and eye protection (74).

IPC measures that are needed will depend on the local COVID-19 transmission dynamics and the type of contact required by the health care activity (see Table 1). The community health workforce should ensure that patients and workforce members apply precautionary measures such as respiratory hygiene and physical distancing of at least 1 metre (3.3 feet). They also may support set-up and maintenance of hand hygiene stations and community education (74). In the context of known or suspected community or cluster transmission, community health workers should wear a medical mask when providing essential routine services (see Table 1).

Table 1. Mask use in health care settings depending on transmission scenario, target population, setting, activity and type*

Transmission scenario	Target population (who)	Setting (where)	Activity (what)	Mask type (which one) *
Known or suspected community or cluster transmission of SARS-CoV-2	Health workers and caregivers	Health facility (including primary, secondary, tertiary care levels, outpatient care, and long-term care facilities)	For any activity in patient-care areas (COVID-19 or non-COVID-19 patients) or in any common areas (e.g., cafeteria, staff rooms)	Medical mask (or respirator if aerosol generating procedures performed)
	Other staff, patients, visitors, service suppliers		For any activity or in any common area	Medical or fabric mask
	Inpatients	In single or multiple-bed rooms	When physical distance of at least 1 metre cannot be maintained	
	Health workers and caregivers	Home visit (for example, for antenatal or postnatal care, or for a chronic condition)	When in direct contact with a patient or when a distance of at least 1 metre cannot be maintained.	Medical mask
		Community	Community outreach programmes/essential routine services	
Known or suspected sporadic transmission of SARS-CoV-2 cases	Health workers and caregivers	Health facility (including primary, secondary, tertiary care levels, outpatient care, and long-term care facilities)	In patient care area- irrespective of whether patients have suspected/confirmed COVID-19	Medical mask
	Other staff, patients, visitors, service suppliers and all others		No routine activities in patient areas	Medical mask not required. Medical mask should be worn if in contact or within 1 metre of patients, or according to local risk assessment
	Health workers and caregivers	Home visit (for example, for antenatal or postnatal care, or for a chronic condition)	When in direct contact or when a distance of at least 1metre cannot be maintained.	Medical mask
		Community	Community outreach programs (e.g., bed net distribution)	
No documented SARS-CoV-2 transmission	Health workers and caregivers	Health facility (including primary, secondary, tertiary care levels, outpatient care, and long-term care facilities)	Providing any patient care	Medical mask use according to standard and transmission-based precautions
		Community	Community outreach programs	
Any transmission scenario	Health workers	Health care facility (including primary, secondary, tertiary care levels, outpatient care, and long-term care facilities), in settings where aerosol generating procedures (AGP) are performed	Performing an AGP on a suspected or confirmed COVID-19 patient or providing care in a setting where AGPs are in place for COVID-19 patients	Respirator (N95 or N99 or FFP2 or FFP3)

**This table refers only to the use of medical masks and respirators. The use of medical masks and respirators may need to be combined with other personal protective equipment and other measures as appropriate, and always with hand hygiene.*

Guidance on mask use in community settings

Evidence on the protective effect of mask use in community settings

At present there is only limited and inconsistent scientific evidence to support the effectiveness of masking of healthy people in the community to prevent infection with respiratory viruses, including SARS-CoV-2 (75). A large randomized community-based trial in which 4862 healthy participants were divided into a group wearing medical/surgical masks and a control group found no difference in infection with SARS-CoV-2 (76). A recent systematic review found nine trials (of which eight were cluster-randomized controlled trials in which clusters of people, versus individuals, were randomized) comparing medical/surgical masks versus no masks to prevent the spread of viral respiratory illness. Two trials were with healthcare workers and seven in the community. The review concluded that wearing a mask may make little or no difference to the prevention of influenza-like illness (ILI) (RR 0.99, 95%CI 0.82 to 1.18) or laboratory confirmed illness (LCI) (RR 0.91, 95%CI 0.66-1.26) (44); the certainty of the evidence was low for ILI, moderate for LCI.

By contrast, a small retrospective cohort study from Beijing found that mask use by entire families before the first family member developed COVID-19 symptoms was 79% effective in reducing transmission (OR 0.21, 0.06-0.79) (77). A case-control study from Thailand found that wearing a medical or non-medical mask all the time during contact with a COVID-19 patient was associated with a 77% lower risk of infection (aOR 0.23; 95% CI 0.09–0.60) (78). Several small observational studies with epidemiological data have reported an association between mask use by an infected person and prevention of onward transmission of SARS-CoV-2 infection in public settings. (8, 79-81).

A number of studies, some peer reviewed (82-86) but most published as pre-prints (87-104), reported a decline in the COVID-19 cases associated with face mask usage by the public, using country- or region-level data. One study reported an association between community mask wearing policy adoption and increased movement (less time at home, increased visits to commercial locations) (105). These studies differed in setting, data sources and statistical methods and have important limitations to consider (106), notably the lack of information about actual exposure risk among individuals, adherence to mask wearing and the enforcement of other preventive measures (107, 108).

Studies of influenza, influenza-like illness and human coronaviruses (not including COVID-19) provide evidence that the use of a medical mask can prevent the spread of infectious droplets from a symptomatic infected person to someone else and potential contamination of the environment by these droplets (75). There is limited evidence that wearing a medical mask may be beneficial for preventing transmission between healthy individuals sharing households with a sick person or among attendees of mass gatherings (44, 109-114).

A meta-analysis of observational studies on infections due to betacoronaviruses, with the intrinsic biases of observational data, showed that the use of either disposable medical masks or reusable 12–16-layer cotton masks was associated with protection of healthy individuals within households and among contacts of cases (46). This could be considered to be indirect evidence for the use of masks (medical or other) by healthy individuals in the wider community; however, these studies suggest that such individuals would need to be in close proximity to an infected person in a household or at a mass gathering where physical distancing cannot be achieved to become infected with the virus. Results from cluster randomized controlled trials on the use of masks among young adults living in university residences in the United States of America indicate that face masks may reduce the rate of influenza-like illness but showed no impact on risk of laboratory-confirmed influenza (115, 116).

Guidance

The WHO COVID-19 IPC GDG considered all available evidence on the use of masks by the general public including effectiveness, level of certainty and other potential benefits and harms, with respect to transmission scenarios, indoor versus outdoor settings, physical distancing and ventilation. Despite the limited evidence of protective efficacy of mask wearing in community settings, in addition to all other recommended preventive measures, the GDG advised mask wearing in the following settings:

1. In areas with known or suspected community or cluster transmission of SARS-CoV-2, WHO advises mask use by the public in the following situations (see Table 2):

   Indoor settings:

   - in public indoor settings where ventilation is known to be poor regardless of physical distancing: limited or no opening of windows and doors for natural ventilation; ventilation system is not properly functioning or maintained; or cannot be assessed;
   - in public indoor settings that have adequate[3] ventilation if physical distancing of at least 1 metre cannot be maintained;
   - in household indoor settings: when there is a visitor who is not a household member and ventilation is known to be poor, with limited opening of windows and doors for natural ventilation, or the ventilation system cannot be assessed or is not properly functioning, regardless of whether physical distancing of at least 1 metre can be maintained;
   - in household indoor settings that have adequate ventilation if physical distancing of at least 1 metre cannot be maintained.

[3] For adequate ventilation refer to regional or national institutions or heating, refrigerating and air-conditioning societies enacting ventilation requirements. If not available or applicable, a recommended ventilation rate of 10 l/s/person should be met (except healthcare facilities which have specific requirements). For more information consult "Coronavirus (COVID-19) response resources from ASHRAE and others''
https://www.ashrae.org/technical-resources/resources

Table 2. Mask use in community settings depending on transmission scenario, setting, target population, purpose and type*

Transmission scenario	Situations/settings (where)	Target Population (who)	Purpose of mask use (why)	Mask type (which one)
Known or suspected community or cluster transmission of SARS-CoV-2	Indoor settings, where ventilation is known to be poor or cannot be assessed or the ventilation system is not properly maintained, regardless of whether physical distancing of at least 1 meter can be maintained	General population in public* settings such as shops, shared workplaces, schools, churches, restaurants, gyms, etc. or in enclosed settings such as public transportation. For households, in indoor settings, when there is a visitor who is not a member of the household	Potential benefit for source control	Fabric mask
	Indoor settings that have adequate [4] ventilation if physical distancing of at least 1 metre cannot be maintained			
	Outdoor settings where physical distancing cannot be maintained	General population in settings such as crowded open-air markets, lining up outside a building, during demonstrations, etc.		
	Settings where physical distancing cannot be maintained, and the individual is at increased risk of infection and/or negative outcomes	Individuals/people with higher risk of severe complications from COVID-19: • People aged ≥60 years • People with underlying comorbidities, such as cardiovascular disease or diabetes mellitus, chronic lung disease, cancer, cerebrovascular disease, immunosuppression, obesity, asthma	Protection	Medical mask
Known or suspected sporadic transmission, or no documented SARS-CoV-2 transmission	Risk-based approach	General population	Potential benefit for source control and/or protection	Depends on purpose (see details in the guidance content)
Any transmission scenario	Any setting in the community	Anyone suspected or confirmed of having COVID-19, regardless of whether they have symptoms or not, or anyone awaiting viral test results, when in the presence of others	Source control	Medical mask

**Public indoor setting includes any indoor setting outside of the household*

[4] For adequate ventilation refer to regional or national institutions or heating, refrigerating and air-conditioning societies enacting ventilation requirements. If not available or applicable, a recommended ventilation rate of 10l/s/person should be met (except healthcare facilities which have specific requirements).). For more information consult "Coronavirus (COVID-19) response resources from ASHRAE and others'' https://www.ashrae.org/technical-resources/resources

In outdoor settings:

- where physical distancing of at least 1 metre cannot be maintained;
- individuals/people with higher risk of severe complications from COVID-19 (individuals ≥ 60 years old and those with underlying conditions such as cardiovascular disease or diabetes mellitus, chronic lung disease, cancer, cerebrovascular disease or immunosuppression) should wear medical masks in any setting where physical distance cannot be maintained.

2. In areas with known or suspected sporadic transmission or no documented transmission, as in all transmission scenarios, WHO continues to advise that decision makers should apply a risk-based approach focusing on the following criteria when considering the use of masks for the public:

- **Purpose of mask use**. Is the intention source control (preventing an infected person from transmitting the virus to others) or protection (preventing a healthy wearer from the infection)?
- **Risk of exposure to SARS-CoV-2**. Based on the epidemiology and intensity of transmission in the population, is there transmission and limited or no capacity to implement other containment measures such as contact tracing, ability to carry out testing and isolate and care for suspected and confirmed cases? Is there risk to individuals working in close contact with the public (e.g., social workers, personal support workers, teachers, cashiers)?
- **Vulnerability of the mask wearer/population**. Is the mask wearer at risk of severe complications from COVID-19? Medical masks should be used by older people (≥ 60 years old), immunocompromised patients and people with comorbidities, such as cardiovascular disease or diabetes mellitus, chronic lung disease, cancer and cerebrovascular disease (117).
- **Setting in which the population lives**. Is there high population density (such as in refugee camps, camp-like settings, and among people living in cramped conditions) and settings where individuals are unable to keep a physical distance of at least 1 metre (for example, on public transportation)?
- **Feasibility**. Are masks available at an affordable cost? Do people have access to clean water to wash fabric masks, and can the targeted population tolerate possible adverse effects of wearing a mask?
- **Type of mask**. Does the use of medical masks in the community divert this critical resource from the health workers and others who need them the most? In settings where medical masks are in short supply, **stocks should be prioritized for health workers and at-risk individuals.**

The decision of governments and local jurisdictions whether to recommend or make mandatory the use of masks should be based on the above assessment as well as the local context, culture, availability of masks and resources required.

3. In any transmission scenario:

- Persons with any symptoms suggestive of COVID-19 should wear a medical mask and (5) additionally:
  - self-isolate and seek medical advice as soon as they start to feel unwell with potential symptoms of COVID-19, even if symptoms are mild);
  - follow instructions on how to put on, take off, and dispose of medical masks and perform hand hygiene (118);
  - follow all additional measures, in particular respiratory hygiene, frequent hand hygiene and maintaining physical distance of at least 1 metre from other persons (46). If a medical mask is not available for individuals with suspected or confirmed COVID-19, a fabric mask meeting the specifications in the Annex of this document should be worn by patients as a source control measure, pending access to a medical mask. The use of a non-medical mask can minimize the projection of respiratory droplets from the user (119, 120).
  - Asymptomatic persons who test positive for SARS-CoV-2, should wear a medical mask when with others for a period of 10 days after testing positive.

Potential benefits/harms

The potential advantages of mask use by healthy people in the general public include:

- reduced spread of respiratory droplets containing infectious viral particles, including from infected persons before they develop symptoms (121);
- reduced potential for stigmatization and greater of acceptance of mask wearing, whether to prevent infecting others or by people caring for COVID-19 patients in non-clinical settings (122);
- making people feel they can play a role in contributing to stopping spread of the virus;
- encouraging concurrent transmission prevention behaviours such as hand hygiene and not touching the eyes, nose and mouth (123-125);
- preventing transmission of other respiratory illnesses like tuberculosis and influenza and reducing the burden of those diseases during the pandemic (126).

The potential disadvantages of mask use by healthy people in the general public include:

- headache and/or breathing difficulties, depending on type of mask used (55);
- development of facial skin lesions, irritant dermatitis or worsening acne, when used frequently for long hours (58, 59, 127);
- difficulty with communicating clearly, especially for persons who are deaf or have poor hearing or use lip reading (128, 129);
- discomfort (44, 55, 59)
- a false sense of security leading to potentially lower adherence to other critical preventive measures such as physical distancing and hand hygiene (105);
- poor compliance with mask wearing, in particular by young children (111, 130-132);
- waste management issues; improper mask disposal leading to increased litter in public places and environmental hazards (133);
- disadvantages for or difficulty wearing masks, especially for children, developmentally challenged persons, those with mental illness, persons with cognitive impairment, those with asthma or chronic respiratory or breathing problems, those who have had facial trauma or recent oral maxillofacial surgery and those living in hot and humid environments (55, 130).

Considerations for implementation

When implementing mask policies for the public, decision-makers should:

- clearly communicate the purpose of wearing a mask, including when, where, how and what type of mask should be worn; explain what wearing a mask may achieve and what it will not achieve; and communicate clearly that this is one part of a package of measures along with hand hygiene, physical distancing, respiratory etiquette, adequate ventilation in indoor settings and other measures that are all necessary and all reinforce each other;
- inform/train people on when and how to use masks appropriately and safely (see mask management and maintenance sections);
- consider the feasibility of use, supply/access issues (cleaning, storage), waste management, sustainability, social and psychological acceptance (of both wearing and not wearing different types of masks in different contexts);
- continue gathering scientific data and evidence on the effectiveness of mask use (including different types of masks) in non-health care settings;
- evaluate the impact (positive, neutral or negative) of using masks in the general population (including behavioural and social sciences) through good quality research.

Mask use during physical activity

Evidence

There are limited studies on the benefits and harms of wearing medical masks, respirators and non-medical masks while exercising. Several studies have demonstrated statistically significant deleterious effects on various cardiopulmonary physiologic parameters during mild to moderate exercise in healthy subjects and in those with underlying respiratory diseases (134-140). The most significant impacts have been consistently associated with the use of respirators and in persons with underlying obstructive airway pulmonary diseases such as asthma and chronic obstructive pulmonary disease (COPD), especially when the condition is moderate to severe (136). Facial microclimate changes with increased temperature, humidity and perceptions of dyspnoea were also reported in some studies on the use of masks during exercise (134, 141). A recent review found negligeable evidence of negative effects of mask use during exercise but noted concern for individuals with severe cardiopulmonary disease (142).

Guidance

WHO advises that people should not wear masks during vigorous intensity physical activity (143) because masks may reduce the ability to breathe comfortably. The most important preventive measure is to maintain physical distancing of at least 1 meter and ensure good ventilation when exercising.

If the activity takes place indoors, adequate ventilation should be ensured at all times through natural ventilation or a properly functioning or maintained ventilation system (144). Particular attention should be paid to cleaning and disinfection of the environment, especially high-touch surfaces. If all the above measures cannot be ensured, consider temporary closure of public indoor exercise facilities (e.g., gyms).

Face shields for the general public

At present, face shields are considered to provide a level of eye protection only and should not be considered as an equivalent to masks with respect to respiratory droplet protection and/or source control. Current laboratory testing standards only assess face shields for their ability to provide eye protection from chemical splashes (145).

In the context of non-availability or difficulties wearing a non-medical mask (in persons with cognitive, respiratory or hearing impairments, for example), face shields may be considered as an alternative, noting that they are inferior to masks with respect to droplet transmission and prevention. If face shields are to be used, ensure proper design to cover the sides of the face and below the chin.

Medical masks for the care of COVID-19 patients at home

WHO provides guidance on how to care for patients with confirmed and suspected COVID-19 at home when care in a health facility or other residential setting is not possible (5).

- Persons with suspected COVID-19 or mild COVID-19 symptoms should wear a medical mask as much as possible, especially when there is no alternative to being in the same room with other people. The mask should be changed at least once daily. Persons who cannot tolerate a medical mask should rigorously apply respiratory hygiene (i.e., cover mouth and nose with a disposable paper tissue when coughing or sneezing and dispose of it immediately after use or use a bent elbow procedure and then perform hand hygiene).
- Caregivers of or those sharing living space with people with suspected COVID-19 or with mild COVID-19 symptoms should wear a medical mask when in the same room as the affected person.

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WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance document will expire 1 year after the date of publication.

Annex: Updated guidance on non-medical (fabric) masks

Background

A non-medical mask, also called fabric mask, community mask or face covering, is neither a medical device nor personal protective equipment. Non-medical masks are aimed at the general population, primarily for protecting others from exhaled virus-containing droplets emitted by the mask wearer. They are not regulated by local health authorities or occupational health associations, nor is it required for manufacturers to comply with guidelines established by standards organizations. Non-medical masks may be homemade or manufactured. The essential performance parameters include good breathability, filtration of droplets originating from the wearer, and a snug fit covering the nose and mouth. Exhalation valves on masks are discouraged as they bypass the filtration function of the mask.

Non-medical masks are made from a variety of woven and non-woven fabrics, such as woven cotton, cotton/synthetic blends, polyesters and breathable spunbond polypropylene, for example. They may be made of different combinations of fabrics, layering sequences and available in diverse shapes. Currently, more is known about common household fabrics and combinations to make non-medical masks with target filtration efficiency and breathability (119, 146-150). Few of these fabrics and combinations have been systematically evaluated and there is no single design, choice of material, layering or shape among available non-medical masks that are considered optimal. While studies have focussed on single fabrics and combinations, few have looked at the shape and universal fit to the wearer. The unlimited combination of available fabrics and materials results in variable filtration and breathability.

In the context of the global shortage of medical masks and PPE, encouraging the public to create their own fabric masks may promote individual enterprise and community integration. Moreover, the production of non-medical masks may offer a source of income for those able to manufacture masks within their communities. Fabric masks can also be a form of cultural expression, encouraging public acceptance of protection measures in general. The safe re-use of fabric masks will also reduce costs and waste and contribute to sustainability (151-156).

This Annex is destined intended for two types of readers: homemade mask makers and factory-made masks manufacturers. Decision makers and managers (national/sub-national level) advising on a type of non-medical mask are also the focus of this guidance and should take into consideration the following features of non-medical masks: breathability, filtration efficiency (FE), or filtration, number and combination of fabric layers material used, shape, coating and maintenance.

Evidence on the effectiveness of non-medical (fabric) masks

A number of reviews have been identified on the effectiveness of non-medical masks (151-156). One systematic review (155) identified 12 studies and evaluated study quality. Ten were laboratory studies (157-166), and two reports were from a single randomized trial (72, 167). The majority of studies were conducted before COVID-19 emerged or used laboratory generated particles to assess filtration efficacy. Overall, the reviews concluded that cloth face masks have limited efficacy in combating viral infection transmission.

Homemade non-medical masks

Homemade non-medical masks made of household fabrics (e.g., cotton, cotton blends and polyesters) should ideally have a three-layer structure, with each layer providing a function (see Figure 1) (168). It should include:

1. an innermost layer (that will be in contact with the face) of a hydrophilic material (e.g., cotton or cotton blends of terry cloth towel, quilting cotton and flannel) that is non-irritating against the skin and can contain droplets (148)
2. a middle hydrophobic layer of synthetic breathable non-woven material (spunbond polypropylene, polyester and polyaramid), which may enhance filtration, prevent permeation of droplets or retain droplets (148, 150)
3. an outermost layer made of hydrophobic material (e.g. spunbond polypropylene, polyester or their blends), which may limit external contamination from penetrating through the layers to the wearer's nose and mouth and maintains and prevents water accumulation from blocking the pores of the fabric (148).

Although a minimum of three layers is recommended for non-medical masks for the most common fabric used, single, double or other layer combinations of advanced materials may be used if they meet performance requirements. It is important to note that with more tightly woven materials, breathability may be reduced as the number of layers increases. A quick check may be performed by attempting to breathe, through the mouth, through the multiple layers.

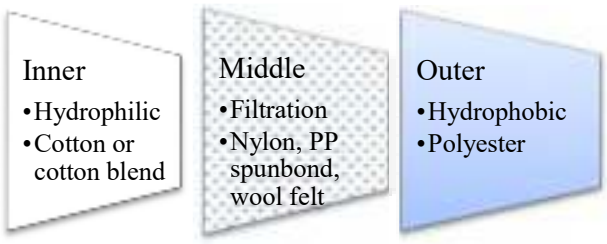

Figure 1. Non-medical mask construction using breathable fabrics such as cotton, cotton blends, polyesters, nylon and polypropylene spunbond that are breathable may impart adequate filtration performance when layered. Single- or double-layer combinations of advanced materials may be used if they meet performance requirements (72).

Assumptions regarding homemade masks are that individual makers only have access to common household fabrics and do not have access to test equipment to confirm target performance (filtration and breathability). Figure 1 illustrates a multi-layer mask construction with examples of fabric options. Very porous materials, such as gauze, even with multiple layers, may provide very low filtration efficiency (147). Higher thread count fabrics offer improved filtration performance (169). Coffee filters, vacuum bags and materials not meant for clothing should be avoided as they may contain injurious content when breathed in. Microporous films such as Gore-Tex are not recommended (170).

Factory-made non-medical masks: general considerations for manufacturers

The non-medical mask, including all components and packaging, must be non-hazardous, non-toxic and child-friendly (no exposed sharp edges, protruding hardware or rough materials). Factory-made non-medical masks must be made using a process that is certified to a quality management system (e.g., ISO 9001). Social accountability standards (e.g., SAI SA8000) for multiple aspects of fair labour practices, health and safety of the work force and adherence to UNICEF's Children's Rights and Business Principles are strongly encouraged.

Standards organizations' performance criteria

Manufacturers producing masks with consistent standardized performance can adhere to published, freely available guidance from several organizations including those from: the French Standardization Association (AFNOR Group), The European Committee for Standardization (CEN), Swiss National COVID-19 Task Force, the American Association of Textile Chemists and Colorists (AATCC), the South Korean Ministry of Food and Drug Safety (MFDS), the Italian Standardization Body (UNI) and the Government of Bangladesh.

Essential parameters

The essential parameters presented in this section are the synthesis of the abovementioned regional and national guidance. They include filtration, breathability and fit. Good performance is achieved when the three essential parameters are optimized at the preferred threshold (Figure 2).

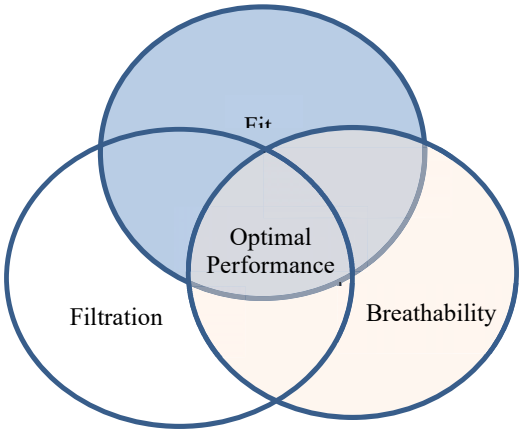

Figure 2. Illustration of the three essential parameters of filtration, breathability and fit.

The summary of the three essential parameters can be found in Table 1 and the additional performance considerations in Table 2. The minimum threshold is the minimum acceptable parameter, while the preferred threshold is the optimum.

Filtration and breathability

Filtration depends on the filtration efficiency (in %), the type of challenge particle (oils, solids, droplets containing bacteria) and the particle size (see Table 1). Depending on the fabrics used, filtration and breathability can complement or work against one another. The selection of material for droplet filtration (barrier) is as important as breathability. Filtration is dependent on the tightness of the weave, fibre or thread diameter. Non-woven materials used for disposable masks are manufactured using processes to create polymer fibres that are thinner than natural fibres such as cotton and that are held together by partial melting.

Breathability is the difference in pressure across the mask and is typically reported in millibars (mbar) or Pascals (Pa) or, normalized to the cm^2 in $mbar/cm^2$ or Pa/cm^2. Acceptable breathability of a medical mask should be below 49 Pa/cm^2. For non-medical masks, an acceptable pressure difference, over the whole mask, should be below 60 Pa/cm^2, with lower values indicating better breathability.

Non-medical fabric masks consisting of two layers of polypropylene spunbond and two layers of cotton have been shown to meet the minimum requirements for droplet filtration and breathability of the CEN CWA 17553 guidance. It is preferable not to select elastic material to make masks as the mask material may be stretched over the face, resulting in increased pore size and lower filtration through multiple usage. Additionally, elastic fabrics are sensitive to washing at high temperatures thus may degrade over time.

Coating the fabric with compounds like wax may increase the barrier and render the mask fluid resistant; however, such coatings may inadvertently completely block the pores and make the mask difficult to breathe through. In addition to decreased breathability unfiltered air may more likely escape the sides of the mask on exhalation. Coating is therefore not recommended.

Valves that let unfiltered air escape the mask are discouraged and are an inappropriate feature for masks used for the purpose of preventing transmission.

Table 1. Essential parameters (minimum and preferred thresholds) for manufactured non-medical mask

Essential Parameters	Minimum threshold	Preferred threshold
1. Filtration*		
1.1. filtration efficiency	70% @ 3 micron	> 70%, without compromising breathability
1.2. Challenge particle	Solid: sodium chloride (NaCl), Talcum powder, Holi powder, dolomite, Polystyrene Latex spheres Liquid: DEHS Di-Ethyl-Hexyl-Sebacat, paraffin oil	Based on availability
1.3. Particle size	Choose either sizes: 3 µm, 1 µm, or smaller	Range of particle sizes
2. Breathability		
2.1. Breathing resistance**	≤60 Pa/cm^2	Adult: ≤ 40 Pa/cm^2 Paediatric: ≤ 20 Pa/cm^2
2.2 Exhalation valves	Not recommended	N/A
3. Fit		
3.1. Coverage	Full coverage of nose and mouth, consistent, snug perimeter fit at the nose bridge, cheeks, chin and lateral sides of the face; adequate surface area to minimize breathing resistance and minimize side leakage	Same as current requirements
3.2 Face seal	Not currently required	Seal as good as FFR (respirator): Fit factor of 100 for N95 Maximum Total Inward Leakage of 25% (FFP1 requirement)
3.2. Sizing	Adult and child	Should cover from the bridge of the nose to below the chin and cheeks on either side of the mouth Sizing for adults and children (3-5, 6-9, 10-12, >12)
3.3Strap strength		> 44.5 N

* Smaller particle may result in lower filtration.
** High resistance can cause bypass of the mask. Unfiltered air will leak out the sides or around the nose if that is the easier path.

Fit: shape and sizing

Fit is the third essential parameter, and takes into consideration coverage, seal, sizing, and strap strength. Fit of masks currently is not defined by any standard except for the anthropometric considerations of facial dimensions (ISO/TS 16976-2) or simplified to height mask (South Korean standard for KF-AD). It is important to ensure that the mask can be held in place comfortably with as little adjustment of the elastic bands or ties as possible.

Mask shapes typically include flat-fold or duckbill and are designed to fit closely over the nose, cheeks and chin of the wearer. Snug fitting designs are suggested as they limit leaks of unfiltered air escaping from the mask (148). Ideally the mask should not have contact with the lips, unless hydrophobic fabrics are used in at least one layer of the mask (148). Leaks where unfiltered air moves in and out of the mask may be attributed to the size and shape of the mask (171).

Additional considerations

Optional parameters to consider in addition to the essential performance parameters include if reusable, biodegradability for disposal masks, antimicrobial performance where applicable and chemical safety (see Table 2).

Non-medical masks intended to be reusable should include instructions for washing and must be washed a minimum of five cycles, implying initial performance is maintained after each wash cycle.

Advanced fabrics may be biodegradable or compostable at the end of service life, according to a recognized standard process (e.g., UNI EN 13432, UNI EN 14995 and UNI / PdR 79).

Manufacturers sometimes claim their NM masks have antimicrobial performance. Antimicrobial performance may be due to coatings or additives to the fabric fibres. Treated fabrics must not come into direct contact with mucous membranes; the innermost fabric should not be treated with antimicrobial additives, only the outermost layer. In addition, antimicrobial fabric standards (e.g., ISO 18184, ISO 20743, AATCC TM100, AATCC 100) are generally slow acting. The inhibition on microbial growth may take full effect after 2- or 24-hour contact time depending on the standard. The standards have generally been used for athletic apparel and substantiate claims of odour control performance. These standards are not appropriate for non-medical cloth masks and may provide a false sense of protection from infectious agents. If claims are maid, manufacturers should specify which standard supports antimicrobial performance, the challenge organism and the contact time.

Volatile additives are discouraged as these may pose a health risk when inhaled repeatedly during wear. Certification according to organizations including OEKO-TEX (Europe) or SEK (Japan), and additives complying with REACH (Europe) or the Environmental Protection Agency (EPA, United States of America) indicate that textile additives are safe and added at safe levels.

Table 2. Additional parameters for manufactured non-medical masks

Additional parameters	Minimum thresholds
If reusable, number of wash cycles	5 cycles
Disposal	Reusable If biodegradable (CFC-BIO), according to UNI EN 13432, UNI EN 14995
Antimicrobial (bacteria, virus, fungus) performance	ISO 18184 (virus) ISO 20743 (bacteria) ISO 13629 (fungus) AATCC TM100 (bacteria)
Chemical safety	Comply with REACH regulation, including inhalation safety

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Centers for Disease Control and Prevention

Science Brief: Community Use of Masks to Control the Spread of SARS-CoV-2

Updated Dec. 6, 2021

Summary of Recent Changes

Last updated December 6, 2021

- Data were added from studies published since the last update. These studies address the association of mask wearing with new infections, including infections related to SARS-CoV-2 variants of concern. All of these studies demonstrated a benefit.
- A section was added on mask wearing among children.

Background

SARS-CoV-2 infection is transmitted predominantly by inhalation of respiratory droplets generated when people cough, sneeze, sing, talk, or breathe. CDC recommends community use of masks to prevent transmission of SARS-CoV-2. Masks are primarily intended to reduce the emission of virus-laden droplets by the wearer ("source control"), which is especially relevant for asymptomatic or presymptomatic infected wearers who feel well and may be unaware of their infectiousness to others (estimated to account for more than 50% of SARS-CoV-2 transmissions).[1, 2] Masks also help reduce inhalation of these droplets by the wearer ("filtration for wearer protection"). The community benefit of masking for SARS-CoV-2 control is due to the combination of these two effects (source control and filtration for wearer protection); individual prevention benefit increases with increasing numbers of people using masks consistently and correctly.

Source Control to Block Exhaled Virus

Multi-layer cloth masks block release of exhaled respiratory particles into the environment,[3-6] along with any microorganisms associated with these particles.[7, 8] Cloth masks not only effectively block most large droplets (i.e., 20-30 microns and larger),[9] but they can also block the exhalation of fine droplets and particles (also often referred to as aerosols) smaller than 10 microns[3, 5] which increase in number with the volume of speech[10-12] and specific types of phonation.[13] Multi-layer cloth masks can both block 50-70% of these fine droplets and particles[3, 14] and limit the forward spread of those that are not captured.[5, 6, 15, 16] Upwards of 80% blockage has been achieved in human experiments,[4] with cloth masks in some studies performing on par with surgical masks as barriers for source control.[3, 9, 14, 17] In one study, conducted prior to widespread circulation of the Delta variant, masks worked equally well for blocking aerosolized particles containing both "wild-type" virus and the Alpha variant (a more infectious variant).[17]

Filtration for Wearer Protection

Studies demonstrate that cloth mask materials can also reduce wearers' exposure to infectious droplets through filtration, including filtration of fine droplets and particles less than 10 microns. The relative filtration effectiveness of various masks has varied widely across studies, in large part due to variation in experimental design and particle sizes analyzed. Multiple layers of cloth with higher thread counts have demonstrated superior performance compared to single layers of cloth with lower thread counts, in some cases filtering nearly 50% of fine particles less than 1 micron.[14, 18-30] Some materials (e.g., polypropylene) may enhance filtering effectiveness by generating triboelectric charge (a form of static electricity) that enhances capture of charged particles[20] while others (e.g., silk) may help repel moist droplets[31] and reduce fabric wetting and thus maintain breathability and comfort. In addition to the number of layers and choice of materials, other techniques can improve wearer protection by improving fit and thereby filtration capacity. Examples include but are not limited to mask fitters, knotting-and-tucking the ear loops of medical procedures masks, using a cloth mask placed over a medical procedure mask, and nylon hosiery sleeves.[32-36]

Human Studies of Masking and SARS-CoV-2 Transmission

- A large, well-designed cluster-randomized trial in Bangladesh in late 2020 found that surgical or cloth mask distribution, role-modeling, and active mask promotion tripled mask use to 42.3% in intervention villages compared to 13.3% in comparison villages. In villages receiving mask interventions, symptomatic seroprevalence of SARS-CoV-2 was reduced by approximately 9% relative to comparison villages. In villages randomized to receive surgical masks, symptomatic seroprevalence of SARS-CoV-2 was significantly lower (relative reduction 11.1% overall). The results of this study show that even modest increases in community use of masks can effectively reduce symptomatic SARS-CoV-2 infections (COVID-19).[37]
- A study of an outbreak aboard the USS Theodore Roosevelt, an environment notable for congregate living quarters and close working environments, found that use of face coverings on-board was associated with a 70% reduced risk of infection.[38]
- In a study of 124 Beijing households with ≥ 1 laboratory-confirmed case of SARS-CoV-2 infection, mask use by the index patient and family contacts before the index patient developed symptoms reduced secondary transmission within the households by 79%.[39]
- A study examining SARS-CoV-2 secondary attack rates among eight public K-12 school districts in Massachusetts (70 schools with >33,000 enrolled students) during the 2020–21 school year found an unadjusted secondary attack rate of 11.7% for unmasked versus 1.7% for masked interactions.[40]
- A retrospective case-control study from Thailand documented that, among more than 1,000 persons interviewed as part of contact tracing investigations, those who reported having always worn a mask during high-risk exposures experienced a greater than 70% reduced risk of acquiring infection compared with persons who did not wear masks under these circumstances.[41]
- During July 15–August 31, 2021, when Delta was the predominant strain circulating in the U.S., about one in five K–12 public non-charter schools open for in-person learning in Maricopa and Pima Counties, Arizona, experienced a school-associated outbreak. Outbreaks were three and a half times more likely (adjusted odds ratio 3.5, 95% confidence interval 1.8-6.6) in schools without mask mandates.[42]
- In a nationwide analysis of data collected during July 1-September 4, 2021, U.S. counties without school mask requirements experienced larger increases in pediatric COVID-19 case rates (18.53 per 100,000 per day more cases) after the start of school compared with counties with school mask requirements.[43]
- An investigation of a high-exposure event in the U.S., in which 2 symptomatically ill hair stylists interacted for an average of 15 minutes with each of 139 clients during an 8-day period, found that none of the 67 clients who subsequently consented to an interview and testing developed infection. The stylists and all clients universally wore masks in the salon as required by local ordinance and company policy at the time.[44]
- Investigations involving infected passengers aboard flights longer than 10 hours strongly suggest that masking prevented in-flight transmissions, as demonstrated by the absence of infection developing in other passengers and crew in the 14 days following exposure.[45, 46]

At least ten studies have confirmed the benefit of universal masking in community level analyses: in a unified hospital system,[47] a German city,[48] two U.S. states,[49, 50] a panel of 15 U.S. states and Washington, D.C.,[51, 52] as well as both Canada[53] and the U.S.[54-56] nationally. Each analysis demonstrated that, following directives from organizational and political leadership for universal masking, new infections fell significantly. Two of these studies[51, 52] and an additional analysis of data from 200 countries that included the U.S.[56] also demonstrated reductions in mortality. Another 10-site study showed reductions in hospitalization growth rates following mask mandate implementation.[54] A separate series of cross-sectional surveys in the U.S.

suggested that a 10% increase in self-reported mask wearing tripled the likelihood of stopping community transmission.[57] An economic analysis using U.S. data found that, given these effects, increasing universal masking by 15% could prevent the need for lockdowns and reduce associated losses of up to $1 trillion or about 5% of gross domestic product.[52]

Two studies have been improperly characterized by some sources as showing that surgical or cloth masks offer no benefit.[58,59] A community-based randomized control trial in Denmark during 2020 assessed whether the use of surgical masks reduced the SARS-CoV-2 infection rate among wearers (personal protection) by more than 50%.[58] Findings were inconclusive,[58] most likely because the actual reduction in infections was lower. The study was too small (i.e., enrolled about 0.1% of the population) to assess whether masks could decrease transmission from wearers to others (source control). A second study of 14 hospitals in Vietnam during 2015 found that cloth masks were inferior to surgical masks for protection against clinical upper respiratory illness or laboratory-confirmed viral infection.[59] The study had a number of limitations including the lack of a true control (no mask) group for comparison, limited source control as hospitalized patients and staff were not masked, unblinded study arm assignments potentially biasing self-reporting of illness, and the washing and re-use of cloth masks by users introducing the risk of infection from self-washing. A follow up study in 2020 found that healthcare workers whose cloth masks were laundered by the hospital were protected equally as well as those that wore medical masks.[60]

Potential Adverse Health Effects of Mask Wearing

Adults

Research supports that under most circumstances, mask wearing has no significant adverse health effects for wearers. Studies of healthy hospital workers, older adults, and adults with chronic obstructive pulmonary disease (COPD) reported no to minimal changes in oxygen or carbon dioxide levels while wearing a cloth or surgical mask either during rest or moderate physical activity.[61-65] The safety of mask use during low to moderate levels of exercise has been confirmed in studies of healthy adults and adolescents.[64, 66-70] Some,[71-74] but not all,[67] studies have found that during intense exercise, especially when approaching the aerobic threshold, wearing a mask can increase dyspnea (difficulty breathing), perceived exertion, and claustrophobia, and produce modest negative effects on measured cardiopulmonary parameters. In some people, face masks worn for longer durations might be associated with skin reactions such as acne, itching, dry skin and worsening of existing dermatoses.[75-77] Wearing a surgical mask and N95 respirator may have a higher risk of skin reactions compared with a cloth mask.[76-78]

Children

A study of 60 elementary school children reported no adverse cardiovascular (e.g., heart rate) or pulmonary (e.g., peripheral oxygen saturation) effects among children while wearing a cloth face covering in a classroom for 30 consecutive minutes of instructional time.[79] A separate study observed no oxygen desaturation or respiratory distress after 60 minutes of monitoring among children less than 2 years of age when masked during normal play.[80] A randomized trial among 40 children aged 3–10 years old scheduled for elective surgery, found that protective surgical face masks could be used safely in the postoperative period.[81] In a prospective school-based cohort study of children aged 10–17 years who wore masks for 6–7 hours during the school day, some children self-reported general (4–7%) or situation-specific (2–4%) side-effects such as skin irritation, headache, or difficulty breathing during physical education.[82]

The potential impact of masks on language and emotional development has been examined in several studies.[83-89] Some research suggests children and adults, and especially toddlers (aged 3–5 years) can have difficulty inferring emotion from facial features presented on photographs of persons with their lower facial features covered by a mask.[83] However, a study of 7- to 13-year-old children determined the decrement in emotional inference observed when the lower half of a photographed face was covered with a mask was equivalent to that associated with covering the eyes with sunglasses, leading the authors to conclude that in combination with other contextual cues, masks are unlikely to produce serious impairments of children's social interactions.[84] A study of 2-year-old children concluded that they were able to recognize familiar words presented without a mask and when hearing words through opaque masks.[85] Among children with autism spectrum disorders (ASD), interventions including positive reinforcement and coaching caregivers to teach mask wearing have improved participants'

Conclusions

Experimental and epidemiologic data support community masking to reduce the spread of SARS-CoV-2, including alpha and delta variants, among adults and children. The prevention benefit of masking is derived from the combination of source control and wearer protection. The relationship between source control and wearer protection is likely complementary and possibly synergistic, so that individual benefit increases with increasing community mask use. Mask use has been found to be safe and is not associated with clinically significant impacts on respiration or gas exchange under most circumstances, except for intense exercise. The limited available data indicate no clear evidence that masking impairs emotional or language development in children. Further research is needed to assess masks, particularly to identify the combinations of materials that maximize both their blocking and filtering effectiveness, as well as fit, comfort, durability, and consumer appeal.

Table: Summary of studies that have assessed the effect of mask wearing on COVID-19 infection risks

	Type of investigation	Location	Study months	Population studied	Intervention	Outcome
Abaluck[37]	Cluster-randomized trial	Bangladesh	Nov 2020–April 2021	342,183 adults in 572 villages	Mask promotion strategies	In villages receiving mask interventions, symptomatic seroprevalence of SARS-CoV-2 was reduced by approximately 9% (adjusted prevalence ratio 0.91, 95% CI 0.82-1.00) relative to comparison villages
Payne[38]	Cohort study	USS Theodore Roosevelt, Guam (USA)	March 2020	382 U.S. Navy service members	Mask wearing (self-report)	Masking reduced risk of infection by 70% (unadjusted OR 0.30, 95% CI = 0.17–0.52)
Wang Y[39]	Cohort study	Households in Beijing (China)	February–March 2020	124 households of diagnosed cases comprising 335 people	Mask wearing by index cases or ≥1 household member prior to index case's diagnosis (self-report)	Masking reduced risk of secondary infection by 79% (adjusted OR 0.21, 95% CI = 0.06–0.79)
Hendrix[44]	Cohort study	Hair salon in Springfield, MO (USA)	May 2020	2 symptomatically infected stylists and 139 patrons	Universal masking in salon (by local ordinance and company policy)	No COVID-19 infections among 67 patrons who were tested in follow-up

	Type of investigation	Location	Study months	Population studied	Intervention	Outcome
Doung-Ngern[41]	Case-control study	Bangkok (Thailand)	April–May 2020	839 close contacts of 211 index cases	Mask wearing by contact at time of high-risk exposure to case (self-report)	Always having used a mask reduced infection by 77% (adjusted OR 0.23, 95% CI = 0.096–0.60)
Gallaway[49]	Population-based intervention	Arizona (USA)	January–August 2020	State population	Mandatory mask wearing in public	Temporal association between institution of masking policy and subsequent decline in new diagnoses
Rader[57]	Serial cross-sectional surveys	USA	June–July 2020	374,021 persons who completed web-based surveys	Self-reported mask wearing in grocery stores and in the homes of family or friends	10% increase in mask wearing tripled the likelihood of stopping community transmission (adjusted OR 3.53, 95% CI = 2.03-6.43)
Wang X[47]	Population-based intervention with trend analysis	Boston, MA (USA)	March–April 2020	9,850 healthcare workers (HCW)	Universal masking of HCW and patients, Mass General Brigham health care system	Estimated daily decline in new diagnoses among HCW of 0.49%
Mitze[48]	Population-based intervention with trend analysis	Jena (Thuringia), Germany	April 2020	City population aged ≥15 years	Mandatory mask wearing in public spaces (e.g., public transport, shops)	Estimated daily decline in new diagnoses of 1.28 percentage points
Van Dyke[50]	Population-based intervention with trend analysis	Kansas (USA)	June–August 2020	State population	Mandatory mask wearing in public spaces	Estimated case rate per 100,000 decreased by 0.08 in counties with mask mandates but increased by 0.11 in those without

	Type of investigation	Location	Study months	Population studied	Intervention	Outcome
Lyu and Wehby[51]	Population-based intervention with trend analysis	15 U.S. states and Washington, DC	March–May 2020	State population	Mandatory mask wearing in public	Estimated overall initial daily decline in new diagnoses of 0.9%, grew to 2.0% at 21 days following mandates
Joo[54]	Population-based intervention with trend analysis	USA	March–October 2020	State populations	Mandatory mask wearing in public	Estimated decline in weekly hospitalization rates by 5.6 percentage points for adults aged 18–64 years after mandate implementation, compared with growth rates during the 4 weeks preceding implementation of the mandate
Guy[56]	Population-based intervention with trend analysis	2,313 counties, USA	March–December 2020	County population	Mandatory mask wearing in public	Estimated overall initial daily decline in new diagnoses of 0.5%, grew to 1.8% at 81–100 days following mandates; estimated overall initial daily decline in deaths of 0.7%, grew to 1.9% at 81-100 days following mask mandate implementation

	Type of investigation	Location	Study months	Population studied	Intervention	Outcome
Jehn[42]	Population-based intervention with trend analysis	Arizona (USA)	July–August 2021	1,020 K–12 schools	School mask policies	Odds of a school-associated COVID-19 outbreak in schools without a mask requirement were 3.5 times higher than those in schools with an early mask requirement (OR = 3.5; 95% CI = 1.8–6.9)
Budzyn[43]	Population-based intervention with trend analysis	USA	July–September 2021	520 counties	School mask requirements	Increases in pediatric COVID-19 case rates during the start of the 2021–22 school year were smaller in U.S. counties with school mask requirements than in those without school mask requirements
Karaivanov[53]	Counterfactual modeling using national data	Canada	March–August 2020	County population	Mandatory mask wearing indoors	Estimated weekly 22% decline in new diagnoses following mask mandates

	Type of investigation	Location	Study months	Population studied	Intervention	Outcome
Chernozhukov[55]	Counterfactual modeling using national data	USA	March–May 2020	State population	Mandatory mask wearing for employees in public businesses	Nationally mandating face masks for employees early in the pandemic could have reduced weekly growth rate of cases and deaths by more than 10 percentage points in late April and 34% (95% CI: 19–47%) fewer deaths nationally by end of May
Leffler[90]	Population-based intervention with trend analysis	169 countries	January–May 2020	County population	Mask wearing by tradition, mandate, or recommendation	Duration of mask wearing by the public was negatively associated with per-capita mortality from COVID-19

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More Information

The Science of Masking to Control COVID-19 [PDF – 28 slides]

The Science of Masking to Control COVID-19 (Abbreviated) [PDF – 7 slides]

Last Updated Dec. 6, 2021

FluWatch

Public Health Agency of Canada | Agence de la santé publique du Canada

2018-19 Influenza Season (Aug 26, 2018 to Aug 24, 2019)

Overall Summary

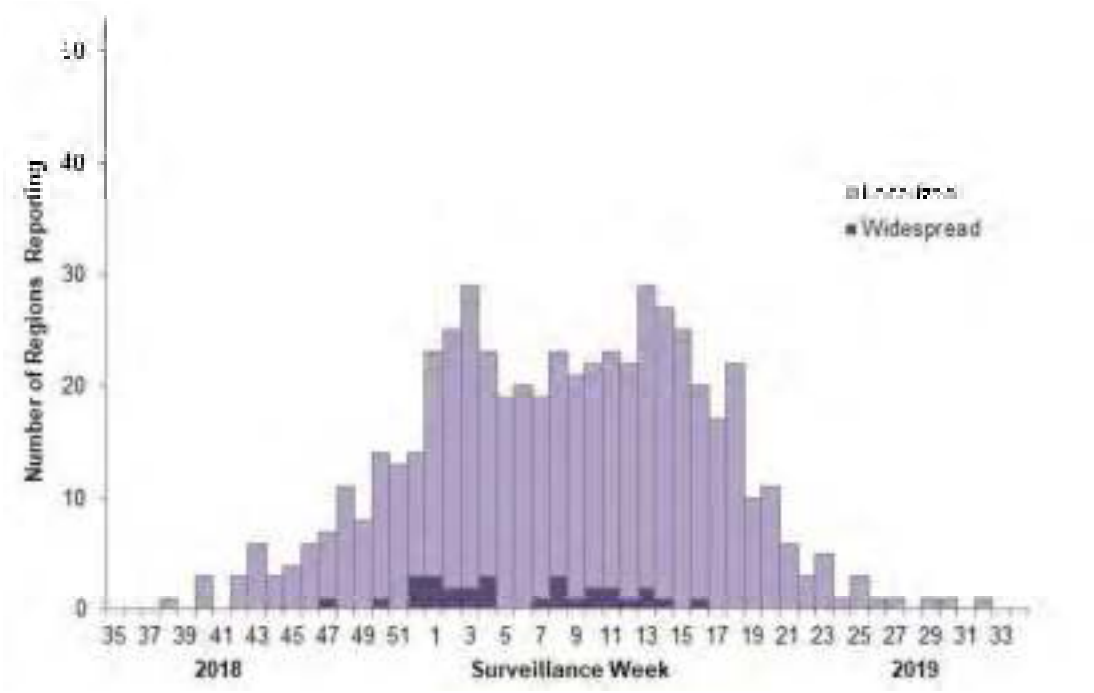
- During the influenza season, the FluWatch report is based on weekly data. This report is a summary of all of the data received for the 2018-19 influenza season and a comparison of these data to the previous five seasons.
- The 2018-19 influenza season in Canada was longer than the previous five seasons and was characterized by two waves of influenza A activity and very little influenza B circulation. The national season started in week 43 (October 21-27, 2018), peaked in week 52 (December 23-29, 2018) and ended in week 21 (May 19-25, 2019).
- A(H1N1) was predominant in the earlier part of the season (October to February) followed by a smaller wave of A(H3N2) circulation (March to April). Overall, A(H1N1) was the predominant strain nationally this season.
- Two waves of activity were observed in the number of reported outbreaks. The predominant subtype for typed outbreaks was A(H1N1) in the early part of the season (October to January), and A(H3N2) in the latter part of the season (Feburary onward).
- The annual seasonal hospitalization rate was above average compared to the previous five seasons. Adults 65 years of age and older had the highest overall hospitalization rate; however, the highest cumulative hospitalization rate shifted during the season from children 0-4 years of age (November to March) to adults 65 years of age and older (March onward), likely due to the second wave of A(H3N2).
- Overall, influenza vaccine coverage in the 2018-19 season (42%) was significantly higher than in the previous two seasons. Coverage was estimated at 34% for adults aged 18 to 64 years and 70% among seniors.
- Vaccine effectiveness studies in both the outpatient setting and adult inpatient setting observed good protection against A(H1N1) and little to no protection against A(H3N2) viruses relative to what is expected for influenza vaccine effectiveness.

Influenza/Influenza-like Illness (ILI) Activity (geographic spread)

Data on the geographic spread of influenza and influenza-like illness (ILI) are provided by all provinces and territories. All provinces and territories reported activity level data for each week of the 2018-19 influenza season.

- The number of surveillance regions reporting localized and widespread influenza activity peaked in week three and again in week 13 (Figure 1).
- Maps of the level of influenza activity reported by surveillance regions each week over the course of the season can be viewed here.

Figure 1 – Number of regions reporting widespread and localized influenza activity, Canada, weeks 2018-35 to 2019-34



Laboratory-Confirmed Influenza Detections

Data on laboratory-confirmed influenza detections are provided by 32 provincial, regional and some hospital laboratories. On average 99.6% of labs reported each week. During the 2018-19 season a total of 48,818 influenza detections were reported. Based on the seasonal thresholds for start and end of season (i.e. when the percentage of tests positive for influenza crossed 5%), the national influenza season started in week 43, peaked in week 52 and ended in week 21 (Figure 2).

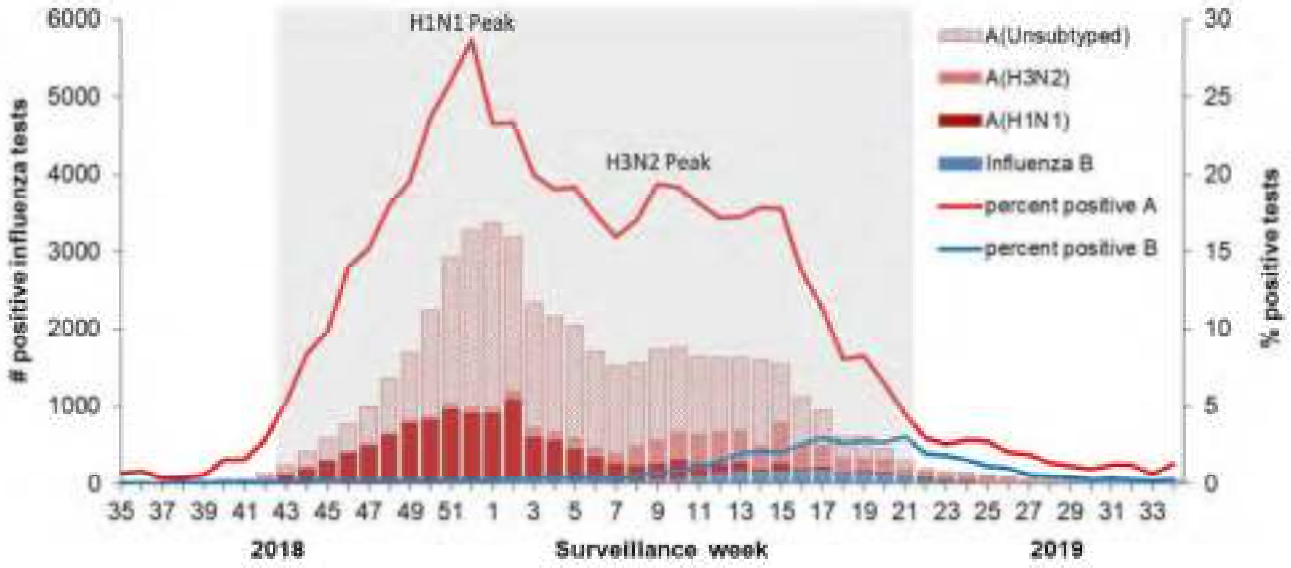
- Nearly all (95%) of influenza detections this season were influenza A. A(H1N1) was the predominant influenza strain and was the driver of the peak in percent positive detections in week 52. Among the 16,602 influenza A viruses that were subtyped this season, 69% were A(H1N1).
- The proportion of subtyped influenza A detections that were A(H3N2) began to increased markedly in mid-January (week three) and A(H3N2) became the predominant strain by week eight. This second more moderate wave of influenza A detections peaked in week nine and persisted near peak levels through to week 15.
- In the early part of the season (the A(H1N1) wave), influenza A activity was within the expected range; however, due to circulation of A(H3N2) in the latter part of the season, the overall proportion of detections of influenza A was higher compared to previous seasons.
- Compared to the last five seasons, the 2018-19 season started five weeks earlier than average; the number of weeks from the start of the season to the peak (10 weeks) was slightly longer than the average (nine weeks); and the length of the season (31 weeks) was six weeks longer than average (25 weeks).
- Canada observed the lowest cumulative total influenza B detections (5%) since the 2009 pandemic. Influenza B activity began to increase in week nine and peaked in week 17 but remained below previous seasonal values for the entire season.
- The distribution of influenza detections by type and subtype in provinces and territories was similar to the national distribution. The proportion of detections of influenza B was between zero and 5%. Among jurisdictions from which influenza A subtype information was provided, the proportion of A(H1N1) ranged from 62 to 100% of subtyped influenza A detections (Figure 3).

Detailed information on age and influenza type/subtype was received for 39,192 of laboratory-confirmed influenza cases. Among influenza A detections where subtype was identified (13,718), subtype distribution varied by age-group (Figure 4). A(H1N1) was the predominant subtype in all age groups except those 65 years of age and older, among

whom A(H3N2) was the predominant subtype (66%). Children less than five years of age had the highest proportion of A(H1N1) among subtyped influenza A detections (86%).

For more detailed weekly and cumulative influenza data, see the text descriptions for Figures 2 and 3 or the Respiratory Virus Detections in Canada Report.

Figure 2 – Number of positive influenza tests and percentage of positive tests, by type, subtype and report week, Canada, weeks 2018-35 to 2019-34



The shaded area indicates weeks where the positivity rate was at least 5% and a minimum of 15 positive tests were observed, signalling the period of seasonal influenza activity.

Data for week 14 excludes subtyping results from one jurisdiction due to batch reporting of subtype information. The results for week 14 should be interpreted with caution.

Figure 3 – Cumulative numbers of positive influenza specimens by type/subtype and province/territory, Canada, weeks 2018-35 to 2019-34

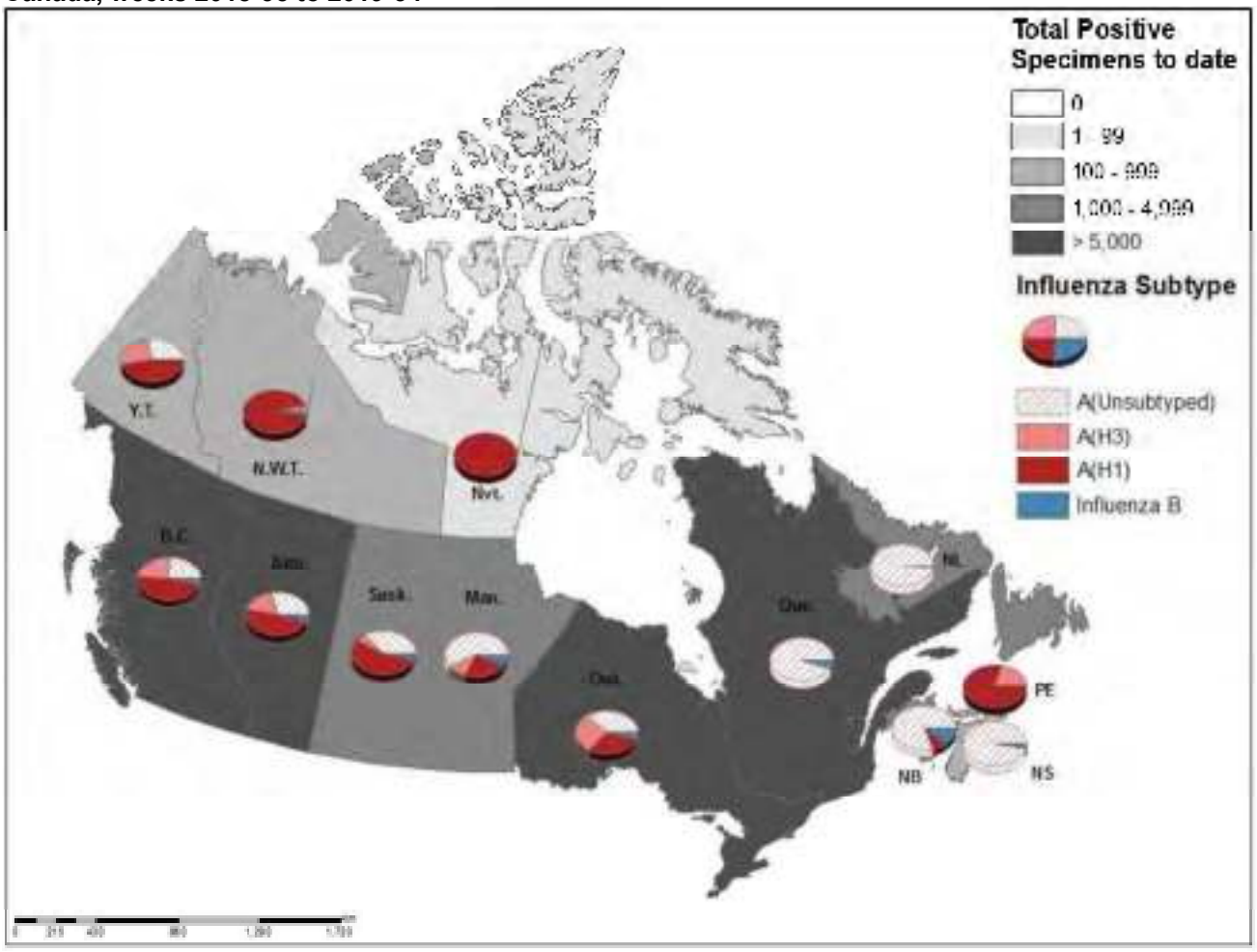
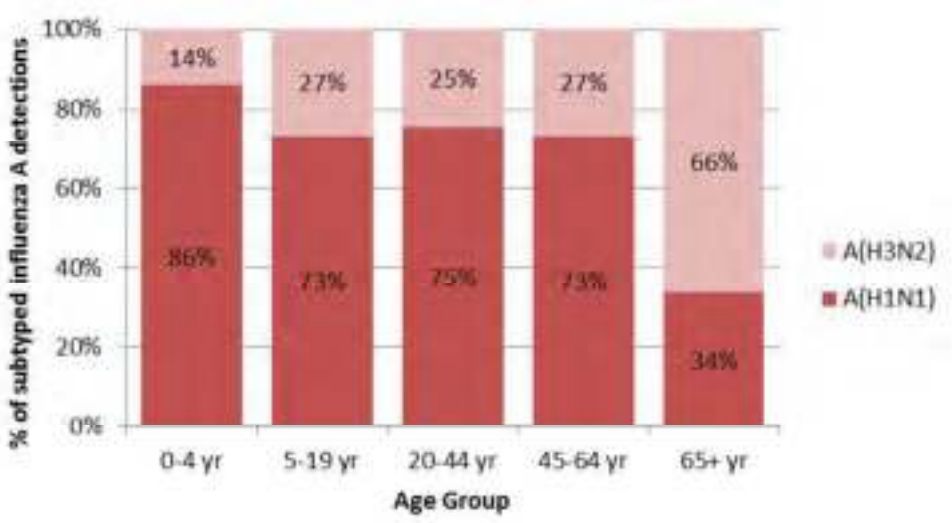


Figure 4 – Proportion of positive influenza A specimens by subtype and age-group reported through case-based laboratory reporting, Canada, weeks 2018-35 to 2019-34



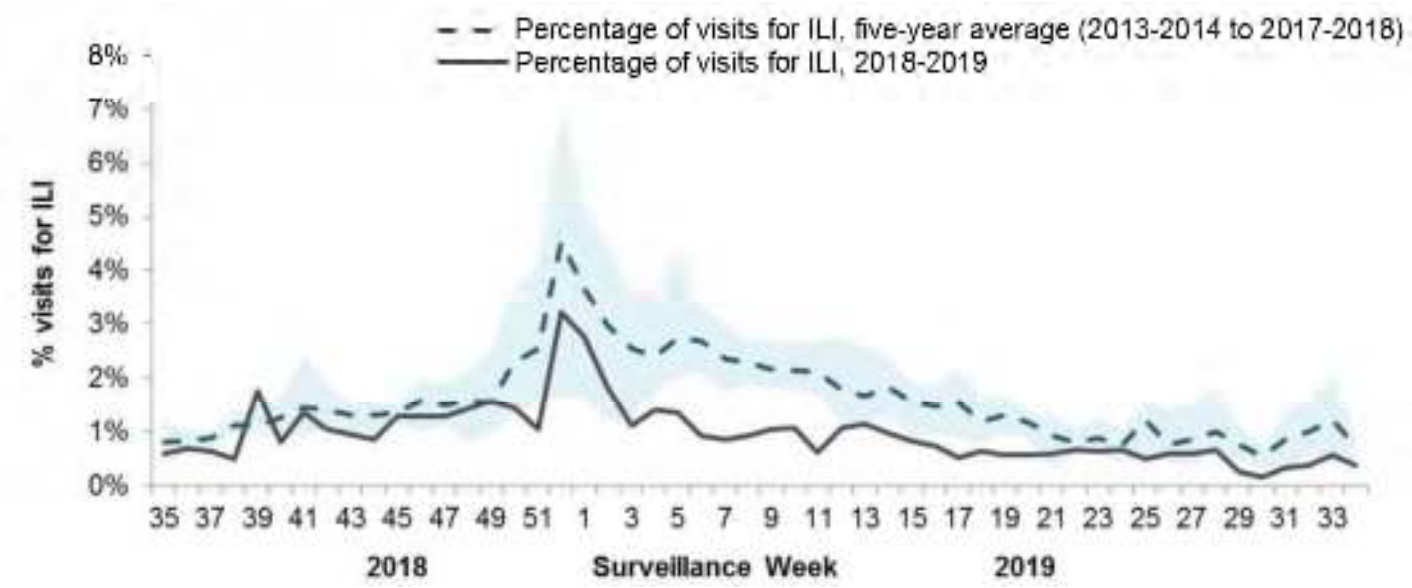
Syndromic / Influenza-like Illness Surveillance

Healthcare Practitioners Sentinel Syndromic Surveillance

On average, during the 2018-19 season, 106 healthcare practitioners across the country participated in influenza-like illness (ILI) surveillance for the FluWatch program. Each week these sentinel healthcare practioners report the proportion of patients in their practice who had ILI.

- Overall, ILI activity was below the five-year average for the majority of weeks this influenza season (range: 0.1% to 3.2%).
- 1.1% of all patient visits reported by sentinels were due to ILI this season (i.e. week 43 to week 21).
- The percentage of visitis for ILI reported by sentinels peaked in week 52 at 3.2%, consistent with the peak week of laboratory detections (Figure 5).
- For the majority of the season, the highest percentage of visits for ILI was reported among those less than 20 years of age. The lowest percentage of visits for ILI was reported among the 65+ year age group.

Figure 5 – Percentage of visits for ILI reported by sentinels by report week, Canada, weeks 2018-35 to 2019-34



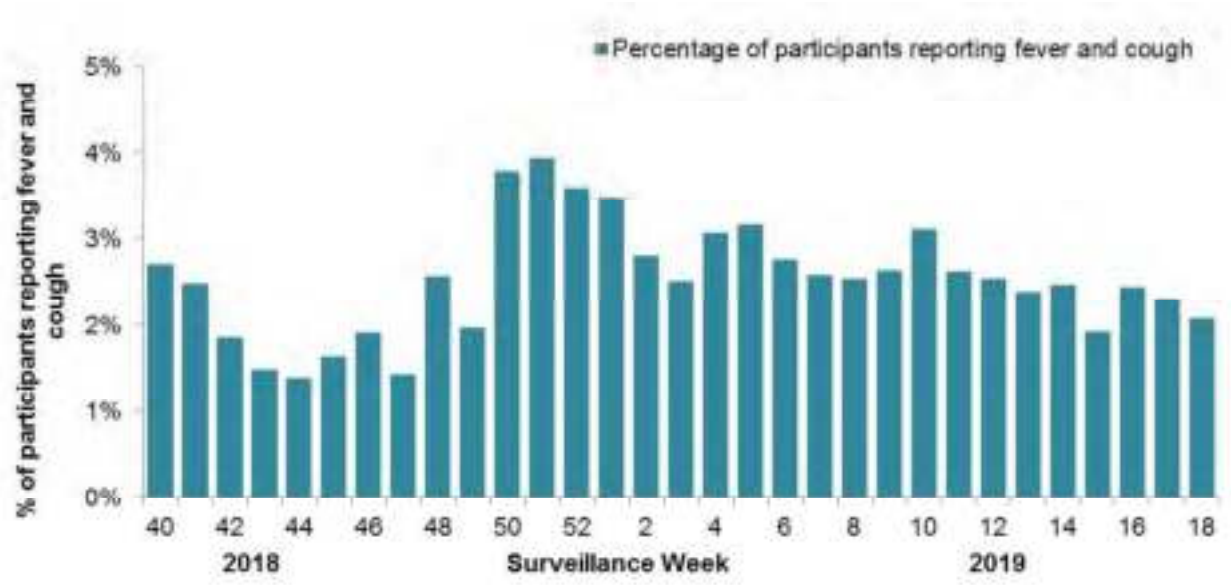
The shaded area represents the maximum and minimum percentage of visits for ILI reported by week from seasons 2013-2014 to 2017-2018

Participatory Syndromic Surveillance

FluWatchers are Canadians who report via a weekly online questionnaire if they have had symptoms of ILI in the preceding week. FluWatchers surveillance for the 2018-19 started in week 40 (October) and ended in week 18 (May). A total of 3,205 participants reported at least once this season, resulting in 64,728 completed questionnaires.

- The majority (75%) of FluWatchers particpants were adults 20-64 years of age. The age distribution of all FluWatchers participants this season was as follows:
  - 4% - 0 to 4 years of age
  - 15% - 5-19 years of age
  - 43% - 20 to 44 years of age
  - 33% - 45 to 64 years of age
  - 5% - 65 years of age and older
- 31% of FluWatchers reported experiencing cough and fever at least once this season.
- The percentage of FluWatchers reporting fever and cough peaked in week 51 with 3.9% of participants reporting cough and fever, consistent with the peak week of laboratory detections (Figure 6).
- A total of 1599 reports of cough and fever were reported by FluWatchers, of which 73% (1175) reported at least 24 hours off work or school, and 19% (306) reported a visit to a health care practitioner.
- A total of 46 tests for influenza and 15 positive tests were reported by FluWatchers.

Figure 6 – Percentage of FluWatchers participants reporting fever and cough, Canada, weeks 2018-40 to 2019-18



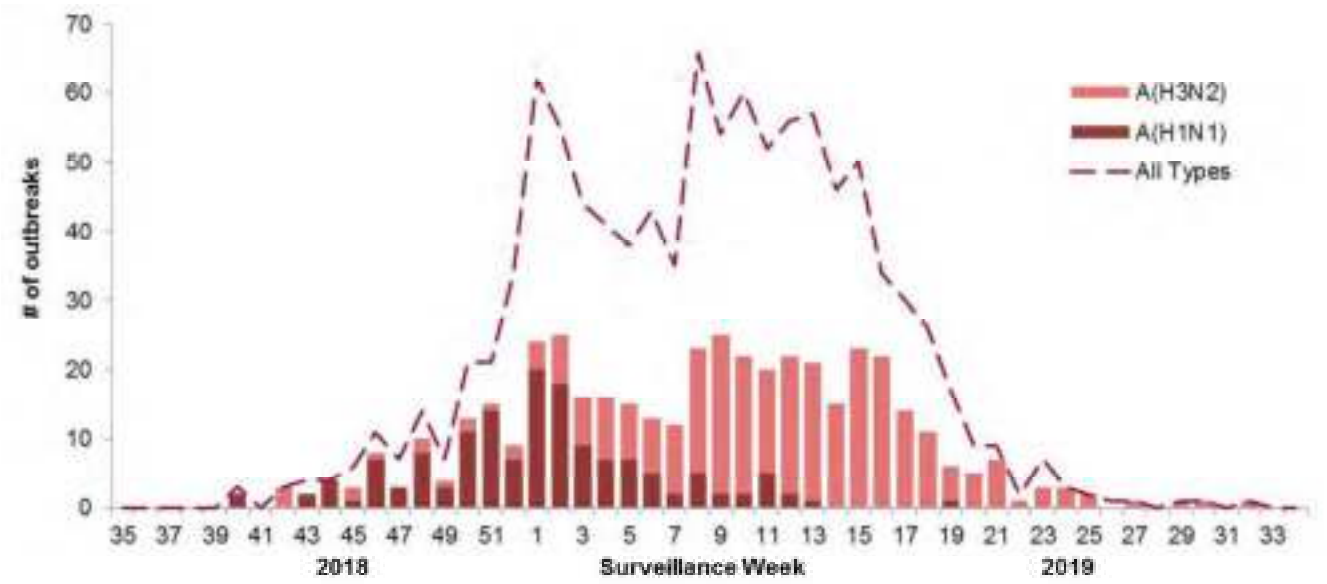
Influenza Outbreak Surveillance

Outbreak activity reports were provided by all provinces and territories each week this season. Not all provinces/territories conduct influenza outbreak surveillance in all the noted facilities. A total of 1038 laboratory-confirmed influenza outbreaks were reported (Figure 7).

- Two waves of activity were observed in the number of reported outbreaks.
- 62% (639) of reported outbreaks were in long-term care facilities (LTCF), 13% (138) were in acute care facilities, 3% (32) in schools and daycares and 22% (229) were in other settings (e.g. retirement homes, correctional facilities, etc.).
- Among the outbreaks for which influenza type (951) and subtype (446) were available, 98% (929) were associated with influenza A and 67% (298) were associated with influenza A(H3N2) respectively.
- Among the 220 outbreaks for which facility type was known and influenza A subtype was available:
    - 67% (173) of LTCF outbreaks were associated with influenza A(H3N2)
    - 65% (30) of acute care facility outbreaks were associated with influenza A(H3N2)
    - 85% (17) of school outbreaks were associatd with influenza A(H1N1).
- The predominant subtype for typed outbreaks was A(H1N1) from weeks 43 to two and A(H3N2) from weeks six to 29; between weeks three to five the number of A(H1N1) and A(H3N2) outbreaks was approximately equal.

In addition, a total of 180 outbreaks of influenza-like illness were reported; 112 occurred in LTCF, 62 in schools, five in acute care facilities, and one in a setting categorized as “other” (e.g. retirement homes, correctional facilities, etc.)

Figure 7 – Number of influenza outbreaks by report week (all types) and number of subtyped influenza A outbreaks by subtype and report week, Canada, weeks 2018-35 to 2019-34



Severe Outcomes Influenza Surveillance

Provincial/Territorial Influenza Hospitalizations and Deaths

Nine provinces and territories report influenza associated hospitalizations and deaths for all ages to FluWatch each week – Alberta, Manitoba, Saskatchewan, Newfoundland, Prince Edward Island, Nova Scotia, New Brunswick, Yukon and the Northwest Territories. The number of reporting provinces/territories varied over the course of the season. On average, seven provinces/territories reported each week.

A total of 3,657 influenza-associated hospitalizations were reported which corresponds to an annual seasonal hospitalization incidence of 45 hospitalizations per 100,000 population in the 2018-19 season (Table 1).

- 96% (3,525) were associated with influenza A.
- Among the 2,149 hospitalized cases for which the influenza subtype was available, the majority were associated with A(H1N1) (68%).
- Similar to the temporal pattern observed in laboratory detections, in the earlier part of the season (October to February) the majority (93%) of hospitalizations for which the influenza subtype was available were A(H1N1). In the latter part of the season (March to April) the majority (87%) of hospitalizations were A(H3N2).
- Overall, adults ≥ 65 years of age had the highest rate of hospitalizations (132 hospitalizations per 100,000 population); however, children 0-4 years of age had the highest cumulative hospitalization rate in the first part of the season from weeks 45 to 10, while adults ≥ 65 years of age had the highest cumulative rates in the second part of the season from weeks 10 to 29 which is likely due to the change in predominant subtype over time.
- This season's hospitalization rate (45 per 100,000 population) was slightly above the average compared to the previous five seasons (40 per 100,000 population), and notably higher than the annual seasonal hospitalization rates of the previous two A(H1N1) predominant seasons (25 and 34 per 100,000 population). The higher observed hospitalization rate relative to previous A(H1N1)-predominant seasons is likely due to the circulation of A(H3N2) in the latter part of the season.

Table 1 – Estimated annual seasonal incidence of influenza hospitalizations (per 100,000 population) by age group reported by participating provinces and territories[1], Canada, 2013/14 to 2018/19 influenza seasons

	Influenza Season (Predominant Influenza A Subtype)					
Age Groups (Years)	2013-14[2] (H1N1)	2014-15 (H3N2)	2015-16 (H1N1)	2016-17 (H3N2)	2017-18 (H3N2)	2018-19 (H1N1)
0-4	51	46	96	42	69	97
5-19	7	16	16	10	17	22
20-44	13	13	16	6	12	14
45-64	29	16	37	22	41	40
65+	41	207	68	143	268	132
Overall	25	45	34	34	64	45

1. Influenza-associated hospitalizations are reported by N.L., P.E.I, N.S., N.B., Man., Alb., Y.T. and N.W.T. Data provided by Sask is not included in these rates as only hospitalizations that require intensive medical care are reported by Sask. The annual seasonal hospitalization rate for a given season is calculated using the population by age-group in participating provinces and territories.
2. During the 2013-14 season N.B. did not report influenza-associated hospitalizations.
3. Highlighted boxes indicate the age group with the highest rate during the season.

A total of 613 ICU admissions and 224 deaths were reported this season.

- 97% (595) of reported ICU admissions and 98% (220) of reported deaths were associated with influenza A.
- Similar to the previous two A(H1N1)-predominant seasons, the highest proportion of ICU admissions was reported among adults 45-64 years of age (39%).
- The highest proportion of deaths was reported among adults ≥ 65 years of age (66%). This was approximately 20% higher than the number reported in the previous two A(H1N1)-predominant seasons and approximately 20% lower than the number reported in the previous three A(H3N2)-predominant seasons, likely as a result of the mixed A(H1N1) and A(H3N2) season.

Pediatric Influenza Hospitalizations and Deaths

Pediatric hospitalization data are provided by the Canadian Immunization Monitoring Program Active (IMPACT). IMPACT actively monitors pediatric influenza hospitalizations from 12 hospital sites in British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, Nova Scotia and Newfoundland.

A total of 1,352 pediatric hospitalized cases were reported this season. While the total number of hospitalized cases was above the five-year average (mean: 888; range: 593 to 1350) and the average of the last two A(H1N1)-predominant seasons (mean:1,032; range:714 to 1350), the number of hospitalized cases each week was within the expected range based on the minimum and maximum number of weekly cases observed in the previous five seasons.

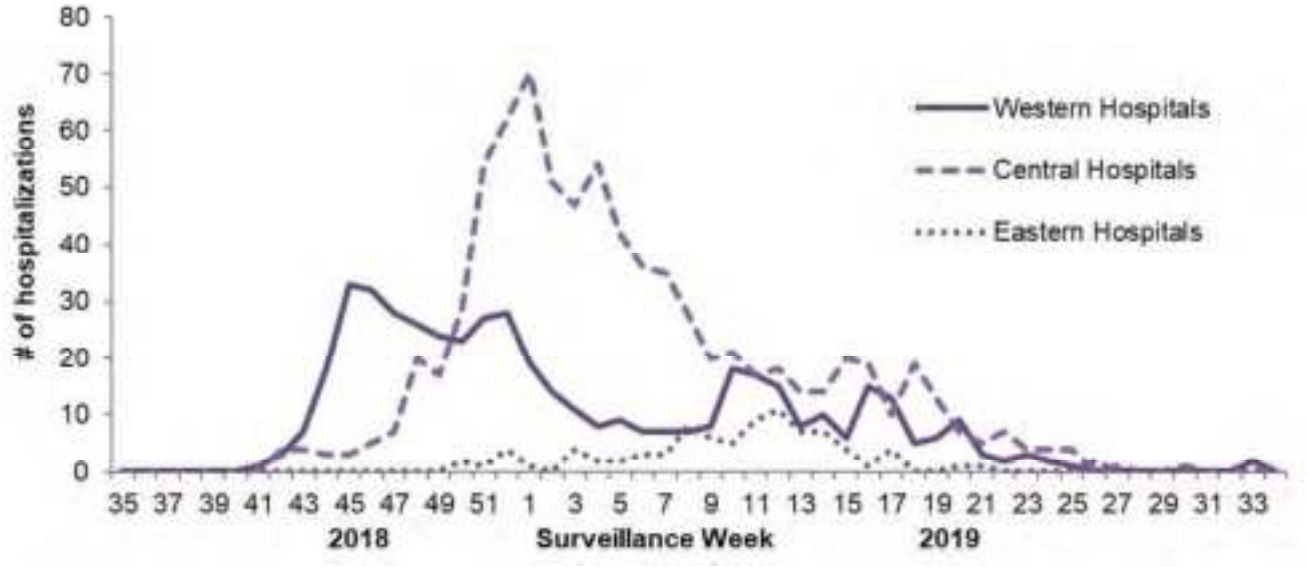
- Nationally, reports began earlier than previous seasons and peaked in week 52 consistent with the peak week of laboratory detections; however peaks varied by region, with an earlier peak in activity in sites in western Canada and a later peak of activity in sites in eastern Canada (Figure 8).
- More subtle peaks in activity can also be observed in western and central sites between weeks nine and 20 and in weeks 17 to 21 in eastern sites which may have resulted from the second wave of A(H3N2) activity and, along with this season's longer duration, may have contributed to the higher than average hospitalization counts.
- 91% (1,227) of pediatric hospitalized cases were associated with influenza A.
- Among the 402 pediatric hospitalized cases for which the influenza subtype was available, 80% (323) were associated with A(H1N1).
- 66% of pediatric hospitalized cases were among children under five years of age (Figure 9). This is consistent with the average proportion of hospitalized cases under five in the past five seasons (65%) and slightly less than the average of the two post-pandemic A(H1N1)-predominant seasons (71%) which were in 2013-14 and 2015-16.

Among the 1,352 pediatric hospitalized cases, a total of 271 (20%) ICU admissions and 10 (0.7%) deaths were reported. The proportion of hospitalized cases resulting in ICU admission was slightly above the average from the past five seasons (17%) and the last two A(H1N1)-predominant seasons (17%). The proportion of hospitalized cases

resulting in death was consistent with the average from the past five seasons (0.6%) and slightly above the average of the last two A(H1N1)-predominant seasons (0.4%).

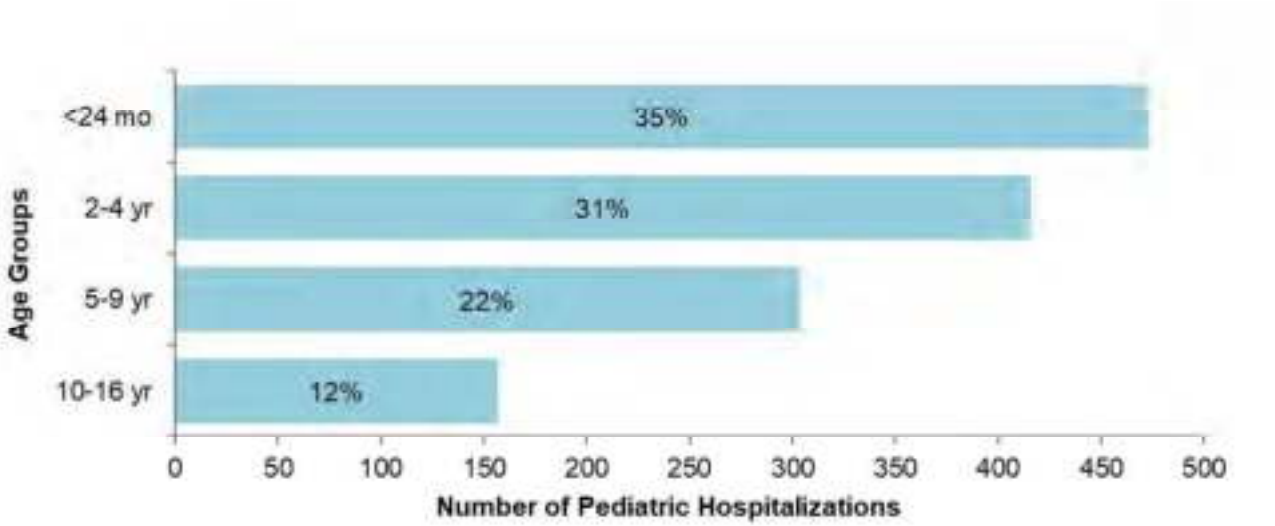
- 59% (161) of ICU admissions were among children under five years of age.
- 92% (248) of ICU admissions were associated with influenza A; 83% of the 111 cases for which the influenza A subtype was available were associated with A(H1N1).
- 80% (8) of deaths occurred in children two to four years of age.
- All deaths were associated with influenza A.

Figure 8 – Number of pediatric (≤16 years of age) hospitalizations reported by the IMPACT network, by region and by week of admission, Canada, weeks 2018-35 to 2019-34



Western hospitals consist of four sites in Vancouver, Calgary, Edmonton and Saskatoon. Central hospitals consist of 6 sites in Winnipeg, Toronto, Ottawa, Montreal and Quebec City. Eastern hospitals consist of 2 sites in Halifax & St. John's.

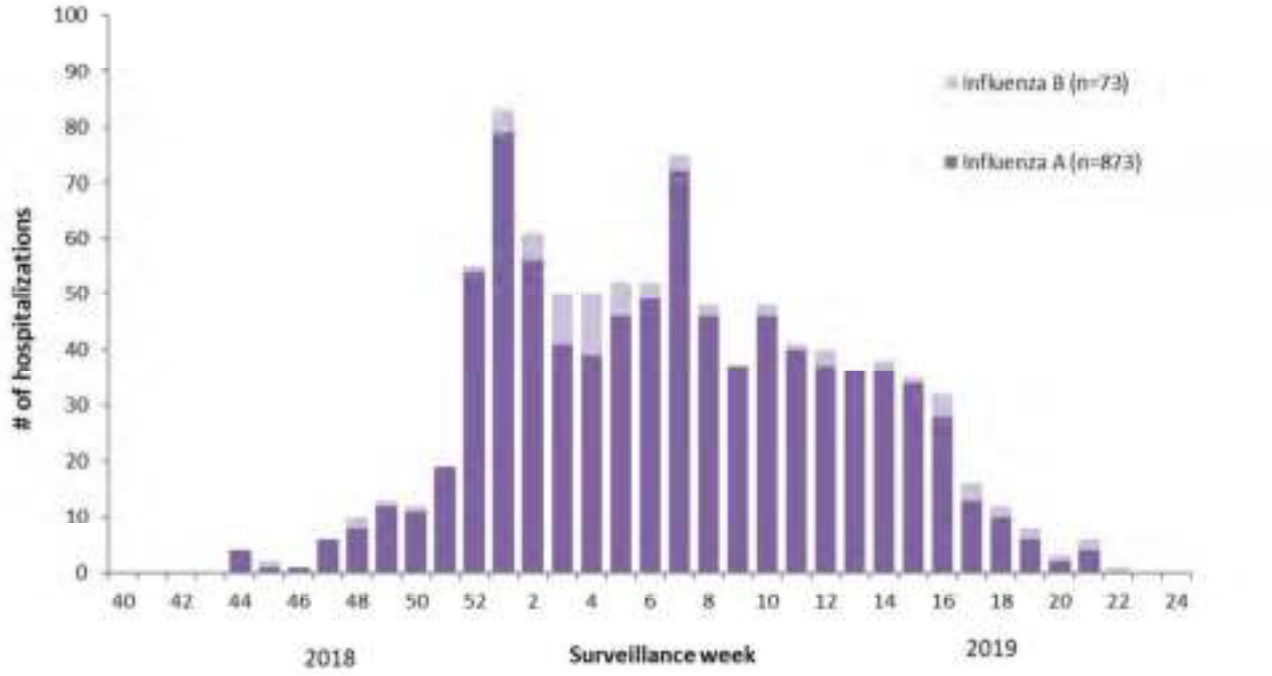
Figure 9 – Number and percentage of pediatric hospitalizations (≤16 years of age) with influenza by age-group reported by the IMPACT network, Canada, weeks 2018-35 to 2019-34



Adult Influenza Hospitalizations and Deaths

Surveillance of laboratory-confirmed influenza-associated adult (≥16 years of age) hospitalizations by the Canadian Immunization Research Network (CIRN) Serious Outcomes Surveillance (SOS) network began on November 1st (week 44) for the 2018-19 season and ended on June 1st (week 22). CIRN-SOS collects influenza hospitalization data from eight hospital sites in Ontario, Quebec, and Nova Scotia.

Figure 10 – Number of adult hospitalizations (≥16 years of age) with influenza reported by CIRN-SOS by surveillance week and influenza type, Canada, weeks 2018-44 to 2019-22



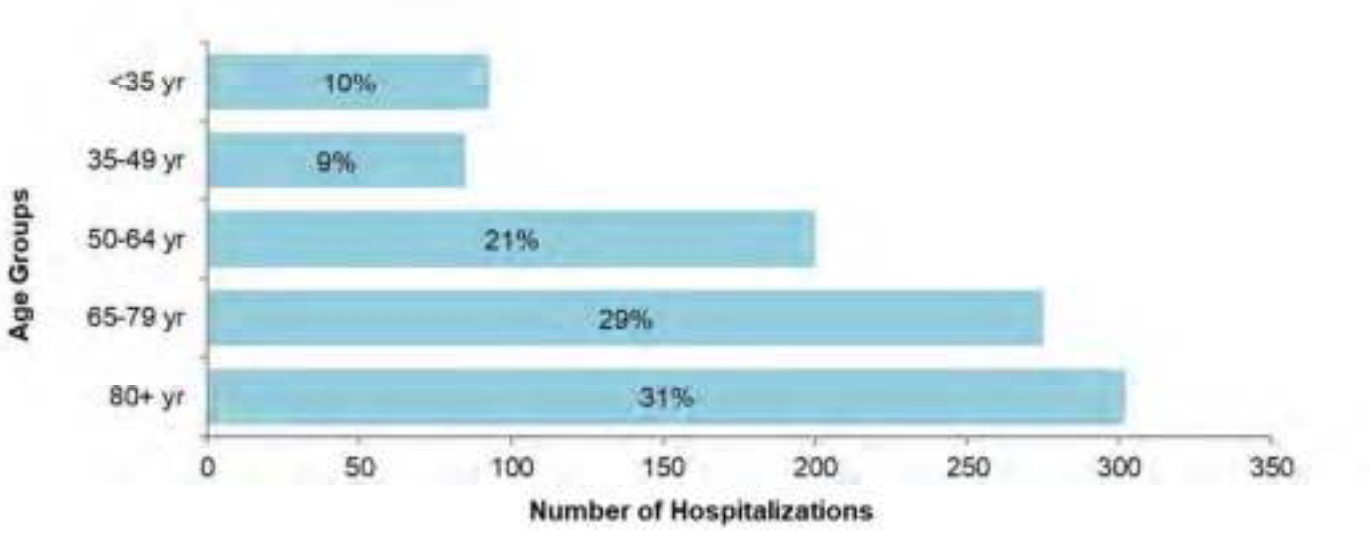
A total of 946 hospitalizations were reported by CIRN-SOS sentinels this season (age ≥16) (Figure 10):

- 92% (873) of hospitalizations were associated with influenza A.
- Among the 838 hospitalized cases for which the influenza subtype was available, 52% (439) were associated with A(H1N1).
- The highest proportion of hospitalized cases (31%) was among adults aged 80 years and over, followed by adults aged 65-79 years (29%) (Figure 11). The mean age of hospitalized cases was 67 years (range: 16 to 100).
- 89% of hospitalized cases reported at least one comorbid condition; vascular disorders were the most common comorbity (70% of all patients reporting a comorbidity) followed by cardiac disorders (43%).

A total of 137 (14%) ICU admissions and 65 (7%) deaths were reported.

- 95% (131) of ICU admissions were associated with influenza A.
- The majority of ICU admissions were among adults under the age of 65 (63%).
- The majority of deaths occurred among adults over the age of 65 (75%) with a mean age of 77 years.

Figure 11 – Number and percentage of adult hospitalizations (≥16 years of age) with influenza by age group reported by CIRN-SOS, Canada, 2018-19, weeks 2018-44 to 2019-22



Influenza Strain Characterizations

During the 2018-19 season, the National Microbiology Laboratory (NML) characterized 2,545 influenza viruses received from Canadian laboratories: 1,656 A(H1N1), 649 A(H3N2), 240 influenza B. Antigenic characterization is established by hemagglutination inhibition (HI) assay using cell-passaged vaccine reference viruses for A(H1N1) and influenza B, and the egg-passaged vaccine reference virus for A(H3N2). Over recent years, circulating strains of A(H3N2) have evolved, and are increasingly difficult to characterize by HI assay. Genetic characterization is established by sequencing the hemagglutinin gene of the influenza viruses to compare their genetic properties.

Influenza A(H3N2)

The influenza A(H3N2) component of the 2018-19 Northern Hemisphere influenza vaccine was an A/Singapore/INFIMH-16-0019/2016-like virus which belongs to the genetic group 3C.2a1.

All of the A(H3N2) viruses (649) were genetically characterized and 42% (378) of A(H3N2) viruses also grew to sufficient hemagglutination titer for antigenic characterization by HI assay (Table 2). Among all influenza A(H3N2) viruses genetically characterized, the most common subclade observed this season was 3C.2a1 (Figure 12). Of the A(H3N2) viruses characterized antigenically by HI assay (Figure 13-A):

- 56% (212) were characterized as A/Singapore/INFIMH-16-0019/2016-like by HI testing using antiserum raised against egg-propagated A/Singapore/INFIMH-16-0019/2016.
- 44% (166) of viruses showed reduced titer with ferret antisera raised against egg-propagated A/Singapore/INFIMH-16-0019/2016
- Among A(H3N2) viruses that showed reduced titer to A/Singapore/INFIMH-16-0019/2016, a greater proportion belonged to the genetic subclade 3C.3a. This is consistent with the genetic differences between subclades 3C.3a and 3C.2a1.

Table 2 – Genetic and antigenic characterization among characterized A(H3N2) viruses, Canada, weeks 2018-35 to 2019-34 (n=648)

Genetic clade	Genetic charaterization only	Antigenic characterization:		Total A(H3N2)
		Similar to A/Singapore/INFIMH-16-0019/2016	Reduced titer to A/Singapore/INFIMH-16-0019/2016	
Clade 3C.2a	20	17	3	40
Subclade 3C.2a1	242	132	16	390
Clade 3C.3a	8	63	147	218
Total	270	212	166	648

Influenza A(H1N1)

The influenza A(H1N1) component of the 2018-19 Northern Hemisphere influenza vaccine was an A/Michigan/45/2015-like virus.

Approximately 97% (1612) of the A(H1N1) viruses characterized were antigenically similar to A/Michigan/45/2015, while only 3% (44) of viruses showed reduced titer with ferret antisera raised against cell culture-propagated A/Michigan/45/2015 (Figure 13-B).

Influenza B

The recommended influenza B components for the 2018-19 Northern Hemisphere influenza vaccine were an B/Colorado/06/2017-like virus (Victoria lineage) and a B/Phuket/3073/2013-like virus (Yamagata lineage). The B/Colorado/06/2017-like virus was included in both the trivalent and quadrivalent vaccines. The B/Phuket/3073/2013-like virus was included in the quadrivalent influenza vaccine.

The majority of B viruses characterized, 70% (168), showed reduced titer with ferret antisera raised against cell culture-propagated B/Colorado/06/2017 (Figure 13-C). Sequence analysis showed that 96% (162) of viruses that showed reduced titer had a three amino acid deletion (162-164) in the hemagglutinin gene. Of the remaining B viruses characterized, 19% (46) were characterized as B/Colorado/06/2017-like (Victoria lineage) and 11% (26) were characterized as B/Phuket/3073/2013-like (Yamagata lineage).

Figure 12 – Distribution of genetic clades among characterized influenza A(H3N2) viruses, Canada, weeks 2018-35 to 2019-34

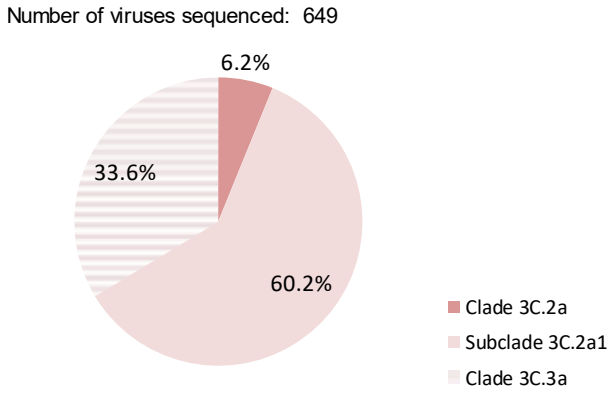
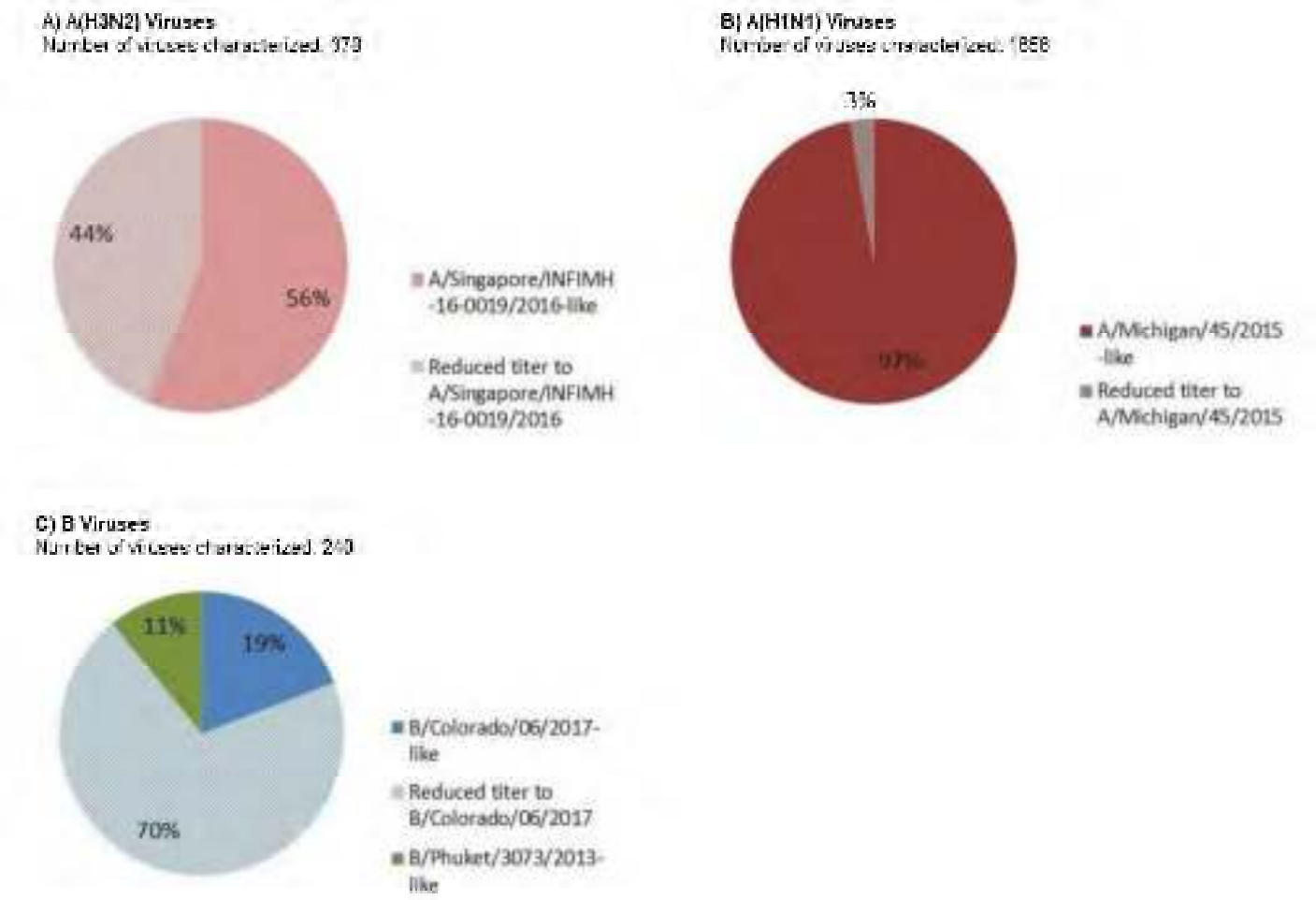


Figure 13 – Distribution of antigenic phenotypes among characterized influenza viruses, Canada, weeks 2018-35 to 2019-34



Antiviral Resistance

All influenza viruses characterized at the NML in the 2018-19 season were resistant to amantadine and sensitive to zanamivir. All influenza A(H3N2), all influenza B viruses, and all but four A(H1N1) viruses were sensitive to oseltamivir. The four A(H1N1) viruses resistant to oseltamivir had a H275Y mutation in the viral neuraminidase. The proportion of influenza viruses resistant to oseltamivir in 2018-19 is similar to recent seasons. Since the 2009 pandemic, nearly all circulating strains of influenza have been sensitive to oseltamivir and zanamivir. Widespread resistance to amantadine among influenza A viruses has been observed for more than 10 years.

Table 3 – Proportion of characterized influenza viruses resistant to antivirals by type and subtype, Canada, 2018-35 to 2019-34

Virus type and subtype	Oseltamivir		Zanamivir		Amantadine	
	# tested	# resistant (%)	# tested	# resistant (%)	# tested	# resistant (%)
A (H3N2)	222	0 (0%)	222	0 (0%)	135	135 (100%)
A (H1N1)	1084	4 (0.4%)	1082	0 (0%)	391	391 (100%)
B	142	0 (0%)	142	0 (0%)	NA[1]	NA[1]
TOTAL	1448	4 (0.3%)	1446	0 (0%)	526	526 (100%)

[1]NA: Not Applicable

Vaccine Monitoring

Vaccine monitoring refers to activities related to the monitoring of influenza vaccine coverage and effectiveness.

The quadrivalent vaccines used in the 2018-19 northern hemisphere influenza season contained:

- an A/Michigan/45/2015 (H1N1)pdm09-like virus;
- an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus;
- a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage); and
- a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage).

The B/Colorado/06/2017-like virus was included in both the trivalent and quadrivalent vaccines.

Vaccine Coverage

The Seasonal Influenza Immunization Coverage Survey is an annual telephone survey conducted between January and February that collects information from Canadians on whether they received the annual seasonal influenza vaccine that season. Vaccine coverage is measured as the percentage of people who received the influenza vaccine in a specific influenza season. More detail on the methodology used for the coverage survey can be viewed here.

Overall, influenza vaccination coverage in the 2018-2019 season (42%) was significantly higher than the 2017-2018 season (38%) and the 2016-2017 season (36%). The vaccination rate was lowest among adults 18-64 years of age without any chronic medical condition (31%); however, coverage increased mostly among this subgroup when compared to the previous two seasons. Among high-risk groups, vaccination coverage rates for adults 18-64 years of age with a chronic medical condition (43%) and seniors 65 years of age and older (70%) remained steady over the past three seasons.

Table 4 – Influenza vaccine coverage among adults (≥ 18 years of age) by age group, gender and chronic disease[1], Seasonal Influenza Vaccination Coverage Survey, Canada, September 2018-February 2019

	Male		Female		Combined	
Age group (years)	Total	Vaccine Coverage (%)	Total	Vaccine Coverage (%)	Total	Vaccine Coverage (%)
All adults (≥18)	1568	36.6	2150	46.8	3726	41.8
18-64	1252	28.6	1640	39.9	2898	34.3
without chronic diseases	948	25.8	1171	36.1	2124	30.8
with chronic diseases	304	36.3	465	48.5	770	42.8
≥65	316	69.0	510	70.9	828	69.9

[1]Excluded from stratified analysis: eight people who did not disclose their gender and four people (18-64 years old) who did not disclose whether they had any chronic diseases.

Vaccine Effectiveness

The Canadian Sentinel Practitioner Surveillance Network (SPSN) provides estimates of the effectiveness of the seasonal influenza vaccine in preventing primary care visits for laboratory confirmed influenza among Canadians of all ages but primarily those from 20-64 years of age.

Based on data collected between November 1, 2018 and April 30, 2019, VE against any influenza, foremost driven by A(H1N1) viruses, was 56% (95% CI: 47 to 64%), and for A(H1N1) alone was 67% (95% CI: 58 to 75%) (Table 5). This substantial protection against A(H1N1) was observed in all age groups. Conversely, the SPSN reported little or no vaccine protection against A(H3N2) viruses, with an overall VE against medically-attended outpatient A(H3N2) illness of 17% (95% CI: -13 to 39). Overall, the A(H3N2) VE estimate for 2018-19 was lower than expected generally for

A(H3N2) vaccines (~30%), and similar to that observed by SPSN in the 2017-18 A(H3N2)-dominant season where VE was estimated at 14% (95% CI: -8 to 31).

More information on the SPSN including study methodology and available publications can be viewed here.

The Serious Outcomes Surveillance (SOS) Network of the Canadian Immunization Research Network (CIRN-SOS) provides estimates of the effectiveness of the seasonal influenza vaccine in preventing hospitalization for laboratory-confirmed influenza in adults.

Based on data collected between November 1, 2018 and June 1, 2019 among adult (≥16 years of age) hospitalized cases of influenza, VE against any influenza was 43% (95% CI: 28 to 55%), and for A(H1N1) alone was 68% (95% CI: 52 to 79%). CIRN-SOS also reported little or no vaccine protection against A(H3N2) viruses, with an overall VE against hospitalized cases of influenza A(H3N2) of 19% (95% CI: -35 to 51). The number of influenza B hospitalized cases was too low to calculate an adjusted VE estimate.

More information on the CIRN-SOS Network including study methodology and available publications can be viewed here.

Table 5 – Vaccine effectiveness estimates against primary care visits (SPSN - November 1, 2018, to April 30, 2019) and hospitalizations (CIRN-SOS - November 1, 2018 to June 1, 2019)

	SPSN (Primay Care Visits)†		CIRN-SOS (Adult Hospitalizations)	
	VE(%) (CI)*	N	VE(%) (CI)**	N
All Influenza	56 (47, 64)	3034	43 (28, 55)	1350
Influenza A	55 (46, 63)	2992	58 (43, 69)	1105
Influenza A H1N1	67 (58, 75)	2630	68 (52, 79)	562
Influenza A H3N2	17 (-13, 39)	1993	19 (-35, 51)	409
Influenza B	72 (27, 89)	1703	n/a***	140

† SPSN 2018-19 estimates are published and available here and here
CI: 95% confidence interval
*adjusted for age, province, specimen collection interval and calendar time (natural cubic spline with 3 equally spaced knots)
** VE for All Influenza, Influenza A, Influenza A/H1, and Influenza A/H3 was adjusted for age, pregnancy and current or past smoker.
VE for 16-49 and 50-64 age groups was adjusted for age, body mass index categories, pregnancy and medications prior to admission.
VE for 65-75 and >75 age groups was adjusted for age, Frailty index prior to admission; and current or past smoker.
***Sample size was too small to calculate an adjusted estimate

Provincial and International Surveillance Links

- Alberta – Influenza Surveillance
- British Columbia – Influenza Surveillance; Vaccine Effectiveness Monitoring
- Manitoba - Seasonal Influenza Reports
- New Brunswick – Influenza Surveillance Reports
- Newfoundland and Labrador – Surveillance and Disease Reports
- Nova Scotia – Respiratory Watch Report
- Ontario – Ontario Respiratory Pathogen Bulletin
- Prince Edward Island – Influenza Summary
- Saskatchewan – Influenza Reports
- Québec – Système de surveillance de la grippe *(available in French only)*
- Australia – Influenza Surveillance Report and Activity Updates
- European Centre for Disease Prevention and Control – Surveillance reports and disease data on seasonal influenza
- New Zealand – Influenza Weekly Update
- United Kingdom -- Weekly Influenza Activity Reports
- Pan-American Health Organization – Influenza Situation Report
- United States Centres for Disease Control and Prevention – Weekly Influenza Summary Update
- World Health Organization – FluNet

Notes

To learn more about definitions, descriptions and the FluWatch program in general, see the Overview of influenza monitoring in Canada page. For more information on the flu, see our Flu (influenza) web page.

This report is available on the Government of Canada Influenza webpage.
Ce est disponible dans les deux langues officielles.

We would like to thank all the FluWatch surveillance partners who participated in the 2018-19 influenza surveillance program.

Government of Canada / Gouvernement du Canada

Flu (influenza): For health professionals

Symptoms and treatment

Get your flu shot

Prevention and risks

FluWatch surveillance

For health professionals

Pandemic flu

On this page

- What health professionals need to know
- Agent of disease

- Spectrum of clinical illness
- Transmission
- Risk groups for influenza-related complications
- Prevention and control
- Treatment
- Epidemiology of influenza
- Surveillance
- Related information

What health professionals need to know

Influenza is a respiratory illness caused primarily by the influenza A and B viruses.

While most people recover in 7 to 10 days, severe illness can occur. Some groups are at a greater risk of influenza-related complications.

Getting vaccinated against influenza each fall is the best way to help prevent infection.

For the 2021-22 flu season, it is especially important for Canadians to get the flu vaccine to reduce:

- the morbidity and mortality associated with influenza
- any further pressure on the health care system during the COVID-19 pandemic

Access the 2021-2022 seasonal influenza vaccine mobile guide.

For additional advice regarding the administration of seasonal influenza vaccine in the context of the COVID-19 pandemic, refer to

- Guidance on the use of seasonal influenza vaccine in the presence of COVID-19

Get free influenza awareness and educational products

Agent of disease

Influenza A and B are the main influenza viruses that cause seasonal outbreaks in humans.

Influenza A viruses are classified into subtypes based on 2 surface proteins:

1. hemagglutinin (HA)
2. neuraminidase (NA)

Of these, the influenza A viruses that have caused widespread human disease over the decades are:

- 3 subtypes of HA (H1, H2 and H3)
- 2 subtypes of NA (N1 and N2)

Influenza B has evolved into 2 lineages:

1. B/Yamagata
2. B/Victoria

Over time, antigenic variation (antigenic drift) of strains occurs within an influenza A subtype or B lineage. The ever-present possibility of antigenic drift requires seasonal influenza vaccines to be reformulated annually. Antigenic drift may occur in 1 or more influenza virus strains. This is why a new flu vaccine is needed each flu season.

Spectrum of clinical illness

Influenza virus infection causes a wide spectrum of illness. It ranges from asymptomatic to mild and from uncomplicated illness to severe, complicated illness.

Influenza symptoms typically include sudden onset of:

- high fever
- cough
- muscle aches and pains

Other common symptoms include:

- headache
- chills or feeling feverish
- fatigue
- loss of appetite
- sore throat
- runny/stuffy nose

In some people, especially children, nausea, vomiting and diarrhea may occur.

While most people recover in 7 to 10 days, severe illness can develop. Some groups are at increased risk of complications and hospitalization.

Symptoms of the flu can be similar to symptoms of COVID-19. Refer to the section on COVID-19 for health professionals for more information.

Transmission

Influenza is primarily transmitted by droplets and spread through coughing or sneezing. It may also be transmitted through direct or indirect contact with infected respiratory secretions.

The incubation period of influenza is usually 2 days, but can range from 1 to 4 days. Adults may be able to spread influenza to others from 1 day before symptoms start to approximately 5 days after.

Children and people with weakened immune systems may be infectious for longer.

Risk groups for influenza-related complications

The people at high risk of influenza-related complications or hospitalization include:

- people who are pregnant
- children and adults with the following chronic health conditions:
  - cardiac or pulmonary disorders
  - diabetes mellitus and other metabolic diseases
  - cancer and other immune compromising conditions due to underlying disease and/or therapy
  - renal disease
  - anemia or hemoglobinopathy
  - neurological or neurodevelopmental conditions
  - morbid obesity (body mass index of 40 and over)
  - children up to 18 years of age undergoing treatment for long periods with acetylsalicylic acid (ASA)
- residents of nursing homes and other chronic care facilities
- adults 65 years of age and older
- all children younger than 60 months of age
- people who have reduced access to health care, such as vulnerable populations like those experiencing homelessness or those with disabilities
- people who are at an increased risk of illness because of living conditions, such as those:
  - living in shelters who experience overcrowding

- who have limited access to facilities for personal hygiene
- persons with disabilities who might have limited capacity to understand or perform personal hygiene practices

The following statement elaborates on persons at high risk of influenza-related complications:

- National Advisory Committee on Immunization (NACI): Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2021-2022

Additionally, to reduce the risk of severe illness that could potentially arise from co-infection with SARS-CoV-2 and influenza, it is particularly recommended that the following groups also receive the influenza vaccine this season:

- people at high risk of severe COVID-19 related illness
- people capable of transmitting influenza to those at high risk of severe illness related to COVID-19

For additional advice regarding the administration of seasonal influenza vaccine in the context of the COVID-19 pandemic, refer to:

- Guidance on the use of seasonal influenza vaccine in the presence of COVID-19

Prevention and control

Annual influenza vaccination is the most effective way to help prevent influenza and its complications.

NACI is an external advisory body to the Public Health Agency of Canada. NACI makes recommendations on the optimal use of vaccines available for use in Canada.

Every year, NACI issues a statement on seasonal influenza vaccine to inform health care providers on its use based on the most current data available.

Further clinical guidance about vaccination, including vaccine administration advice and additional safety considerations, can be found in the Canadian Immunization Guide.

NACI recommends influenza vaccine for all Canadians aged 6 months and older who do not have a contraindication to the vaccine.

To reduce the morbidity and mortality associated with influenza, immunization programs should focus on people 6 months of age and older who are:

- at high risk of influenza-related complications
- especially capable of transmitting influenza to those at high risk, including:
  - health care and other care providers in facilities and community settings
  - household contacts (adults and children) of individuals at high risk of influenza-related complications, including:
    - infants less than 6 months old
    - members of a household expecting a newborn during influenza season
  - those providing regular child care to children younger than 60 months of age
  - those providing services in closed or relatively closed settings to those at high risk, such as a ship's crew

These immunization programs should also specifically include those who:

- provide essential community services

- are directly involved in culling operations with poultry infected with avian influenza

Trivalent (3 strains) and quadrivalent (4 strains) influenza vaccines are authorized for use in Canada. Not all vaccine products are available in all jurisdictions. Availability of some products may be limited. Therefore, individual provinces and territories must be consulted about the products available in their jurisdictions.

Health care providers should offer influenza vaccine when it becomes available in the fall. Decisions about the precise timing of vaccination programs in a given geographic area are made considering:

- local influenza activity
- programmatic factors

It is preferable to administer vaccines before the onset of flu season. However, vaccination is still effective and may be offered until the end of the season.

For people 12 years of age and older, the administration of other vaccines can be given at the same time as, or before or after, seasonal influenza vaccines, including:

- the live-attenuated influenza vaccine
- COVID-19 vaccines

It is safe to administer a COVID-19 vaccine at the same time as other vaccines, such as the influenza vaccine.

For children 5 to 11 years of age, NACI recommends that a 14-day interval between a COVID-19 vaccine and other vaccines be considered. This is a precautionary measure to help better monitor possible side effects from a

COVID-19 vaccine. Provinces and territories will decide on an interval for this age group as part of their vaccination programs.

To help prevent the spread of influenza and COVID-19, health care providers can:

- receive influenza vaccine themselves to help prevent transmitting influenza to their patients
- discuss the risks and benefits of the influenza vaccine with patients, as well as the risks of not being vaccinated
- use every opportunity to administer the flu vaccine to people at risk, even after influenza activity has been documented in the community
- teach patients about public health measures to reduce and prevent the spread of influenza and COVID-19
- inform patients that symptoms of influenza and COVID-19 are similar and what to do if they start to develop symptoms

For additional advice regarding the administration of seasonal influenza vaccine in the context of the COVID-19 pandemic, refer to:

- Guidance on the use of seasonal influenza vaccine in the presence of COVID-19

Treatment

Most people with influenza will become only mildly ill and do not need medical care or antiviral medication.

Health care providers may wish to consider prescribing antiviral drugs to reduce influenza morbidity and mortality, especially for people in high-risk groups or who are severely ill. Antivirals drugs licensed in Canada for influenza treatment and/or prophylaxis include:

- oseltamivir
- zanamivir
- peramivir

Their use will depend on a number of factors, such as:

- patient risk
- relevant history
- duration and severity of symptoms

For information on the clinical management of influenza, consult the following guidance:

- Association of Medical Microbiology and Infectious Disease Canada (AMMI)
  - Use of antiviral drugs for seasonal influenza: Foundation document for practitioners, update 2019 (PDF)
  - Algorithm for oseltamivir and zanamivir treatment of mild or uncomplicated influenza in adults (PDF)
- Canadian Critical Care Society's guidance on managing patients with severe acute respiratory infection in an intensive care setting (PDF)

Epidemiology of influenza in Canada

Influenza and pneumonia are ranked among the top 10 leading causes of death in Canada.

Each year in Canada, it is estimated that influenza causes approximately:

- 12,200 hospitalizations
- 3,500 deaths

Surveillance

FluWatch surveillance

FluWatch, Canada's national influenza surveillance system, monitors the spread of influenza and influenza-like illnesses (ILI). It provides current information about circulating influenza strains. It also indicates what proportion of those are resistant to antivirals.

For the latest information on influenza activity in Canada, visit FluWatch report.

Primary care physicians, nurse practitioners and registered nurses can become FluWatch sentinel practitioners. Visit FluWatch Sentinel Practitioner ILI Surveillance Program for more information.

You may also encourage your patients to track influenza and COVID-19 by becoming a FluWatcher.

International surveillance

Every year, worldwide seasonal influenza causes an estimated:

- 1 billion infections
- 3 to 5 million cases of severe illness
- 290,000 to 650,000 deaths

For current international activity, visit the World Health Organization's FluNet website.

Related information

- Pandemic preparedness
- Influenza surveillance (FluWatch)
- National case definition: Laboratory-confirmed influenza

Vaccine resources

- Canadian Immunization Guide
- Vaccination coverage in Canada
- Vaccination pain management for adults
- Supply and distribution of flu vaccine in Canada
- Immunize Canada: Improving the vaccination experience for adults (PDF)
- Immunization schedules: Provincial and territorial immunization programs

Communicating with patients

- Vaccination pain management for adults
- CanVax: Counselling and communication
- Immunize Canada: Improving the vaccination experience for adults (PDF)
- Canadian Immunization Guide: Communicating effectively about immunization

Infection prevention, control and treatment resources

- Association of Medical Microbiology and Infectious Disease Canada
- Seasonal influenza: Infection prevention and control guidance for management in home care settings
- Guidance: Infection prevention and control measures for healthcare workers in acute care and long-term care settings

Publications

- Canadian Critical CareSociety
  - Guidelines for the Management of Severe Acute Respiratory Infection in the Intensive Care Unit (PDF)
- 2021-2022 seasonal influenza vaccine mobile guide

- Hand hygiene practices in healthcare settings (PDF)
- Immunization Competencies for Health Professionals
- Guidance on the use of influenza vaccine in the presence of COVID-19
- Access to the seasonal flu vaccine in Canada: How the flu shot makes its way from the laboratory to the doctor's office
- NACI: Canadian Immunization Guide chapter on influenza and statement on seasonal influenza vaccine for 2021-2022

Educational resources

- Teens, Meet Vaccines
- Vaccine safety in Canada
- Benefits of hand washing
- A Parent's Guide to Vaccination
- Not Just for Kids: An Adult Guide to Immunization
- Influenza awareness resources (posters and handouts)
- National Collaborating Centre for Infectious Diseases (NCCID): Webcasts

Partner resources

- CANVax
- Immunize Canada
- Canadian Pharmacists Association
- World Health Organization: Influenza
- College of Family Physicians of Canada
- Canadian Paediatric Society: Caring for Kids
- Find flu clinics and resources from across Canada
- Society of Obstetricians and Gynaecologists of Canada

First Nations and Inuit resources

- Seasonal flu campaign materials

Previous

Next

Date modified:

2021-12-10

Kitchener Court File No.: CV-21-00000095-0000
St. Thomas Court File No.: CV-21-08

THE ATTORNEY GENERAL OF ONTARIO Applicants (Responding Party)	**-and -**	**TRINITY BIBLE CHAPEL ET AL., CHURCH OF GOD (RESTORATION) AYLMER ET AL.** Respondents (Moving Parties)

ONTARIO
SUPERIOR COURT OF JUSTICE

(ST. THOMAS)

CROSS-EXAMINATION TRANSCRIPTS (VOL 1)

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The Attorney General of Ontario v. Trinity Bible Chapel et al.

JACOB REAUME
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Court File No. CV-21-00000095-0000

ONTARIO

SUPERIOR COURT OF JUSTICE

B E T W E E N:

THE ATTORNEY GENERAL OF ONTARIO

Applicant

(Moving Party)

- and -

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHUURMAN, DEAN WANDERS, RANDY FREY, HARVEY FREY and DANIEL GORDON

Respondents

(Responding Parties)

------ This is the Cross-Examination of JACOB REAUME, on his affidavit sworn June 4, 2021, taken via Neesons, a Veritext Company's virtual platform on the 21st day of December, 2021.

A P P E A R A N C E S:

(All via virtual platform)

Joshua Hunter, Esq. For the Applicant

& Maia Stevenson, Esq.

Lisa Bildy, Esq. For the Respondents

ALSO PRESENT: Ryan Cookson

Dan Guttman

Emily Owens

Dayna Murczek

Hatim Kheir

REPORTED BY: Connie A. Holton, C.S.R.

I N D E X

WITNESS: JACOB REAUME

PAGE

CROSS-EXAMINATION BY MR. HUNTER..... 6

The following list of undertakings, advisements and refusals is meant as a guide only for the assistance of counsel and no other purpose

INDEX OF UNDERTAKINGS

The questions/requests undertaken are noted by U/T and appear on the following page number: 11.

INDEX OF ADVISEMENTS

The questions/requests taken under advisement are noted by U/A and appear on the following page numbers: 16, 17.

INDEX OF REFUSALS

The questions/requests refused are noted by R/F and appear on the following page number: 34.

INDEX OF EXHIBITS

NUMBER/DESCRIPTION PAGE NO.

1: Photograph of Trinity Bible Chapel Sanctuary, January 24, 2021. 26

--- Upon commencing at 1:02 p.m.

THE REPORTER: Counsel, as you all know, because we are using a virtual connection, everyone is going to have to be more conscious than ever of not speaking over each other. If I cannot hear the end of a question or the beginning of an answer, you are going to have a very poor record. If I have to consistently interrupt because I cannot hear or understand something that is said, you will not have a good examination flow. If there is an objection, I must be able to hear it and know who is objecting. If I do have to interrupt, please be patient and understand my goal is to provide you with a perfect record of these proceedings. Please move your papers and/or legal pads away from your phone so there is no ambient noise.

From time to time we've noticed the audio can be affected, and if so, we may need to stop the proceedings and wait a moment for the audio to improve, either by reconnecting or asking that everyone use the conference call number if you're using computer audio.

Would the witness please identify himself and spell your first and last name?

THE DEPONENT: My name is Jacob Reaume, J-A-C-O-B-R-E-A-U-M-E.

THE REPORTER: Our witness today is Jacob Reaume. If there are any questions about the witness' identity, would counsel please advise on the record now?

Hearing no objection, counsel, are you ready for me to affirm the witness?

MR. HUNTER: Yes.

JACOB REAUME, Affirmed

CROSS-EXAMINATION BY MR. HUNTER:

1 Q. Good afternoon, Pastor Reaume. My name is Josh Hunter and I'll be asking you some questions on behalf of the Attorney General of Ontario. I understand you swore an affidavit on June 4, 2021. Do you have that affidavit with you?

A. I do not have it in front of me, no.

2 Q. Are you able to access it?

A. I certainty can, yes.

3 Q. I'm going to be asking you some questions about it, so if you can pull that up that would be appreciated.

A. Yes, absolutely.

I now have it in front of me.

Q. Thank you. I'm going to start on the first page with paragraph 2. I understand you're the senior pastor of the Respondent, Trinity Bible Chapel in Waterloo?

A. That is correct.

Q. And I understand you have a baccalaureate degree in religious education?

A. That is correct.

Q. And a Master of Divinity?

A. Correct.

Q. Do you have any other university degrees?

A. No, I do not.

Q. Do you have any other professional qualifications?

A. I am an ordained minister. So I was ordained many years ago to be a pastor, and I have completed a program in church planting.

Q. And you're not a lawyer?

A. I am not a lawyer.

Q. You are not a physician?

A. I am not a physician.

Q. And you're not any other kind of regulated health professional?

A. I am not.

Q. You don't have any training in epidemiology?

A. I do not have training in epidemiology.

Q. Or in public health?

A. I do not.

Q. Or in statistics?

A. Nope. No training in statistics outside of what I would have learned in high school.

Q. I'd like to ask you some questions about Trinity Bible Chapel, the facility in Waterloo. And I understand you say at paragraph 4 that it houses over 900 people based on fire code regulations. Is that for the whole building or is that particular rooms?

A. That would be the building in its entirety.

Q. And how many -- I'm not going to go into like offices, but how many large rooms that can hold gatherings are there in that facility?

A. Well, there would be a sanctuary, and then we have a very large gymnasium, and then there is a number of classrooms as well as offices.

Q. And do you know the capacity of

the sanctuary?

A. I don't know it specifically, no.

Q. And about what percentage of the facility would you say the sanctuary takes up?

A. Well, I would say... as far as fire code?

Q. Just square footage. I'm just trying to get a bit of a mental picture of what your facility looks like.

A. In all honesty, I don't know specifically the number offhand.

Q. More than half?

A. I don't have reason to believe it's more than half, no, but again I'm not certain.

Q. I'm not asking for scientific certainty on this point. I'm just trying to get a sense of, you know, is it -- I know you have a school in the building as well. I'm just trying to get a general sense of what the split is between the school facilities and between the church facilities?

A. It's hard to say offhand. I mean certainly we can house a lot of people as I indicated, but I don't know the percentages. I think -- I don't know them. If I had a floor plan

in front of me I would be able to better say, but I don't know them.

Q. Do you have a floor plan of the facility?

A. I would have access to one if I wanted one, but I don't have one readily available, no.

Q. Can we get a copy of it?

MS. BILDY: Counsel, I'm sorry to interrupt. I don't want to interrupt your flow, but I see that Pastor Hildebrandt has come into the room. And I asked him to be on standby, but you probably would rather he not be in here right now. So, Pastor Hildebrandt, if you could just sign out for right now and we'll bring you in when this examination is finished.

Thank you. Sorry to interrupt.

MR. HUNTER: Thank you, Ms. Bildy.

BY MR. HUNTER:

Q. So just before that I was just asking if we could get a copy of the floor plan of the facility.

A. Well, I believe that you have a copy, because it has come up in some of our, I believe, contempt hearings in the past. But if you

don't have that available I'm certain that that can be sent your way.

25 Q. Can we have an undertaking to that effect, Ms. Bildy?

U/T MS. BILDY: Yes. Specifically the floor plan? Or is there something -- we prepared some documents that showed how many people you can space out at one point. Is there something specific?

MR. HUNTER: Both those would be great.

U/T MS. BILDY: Yes. We will endeavour do give you what we have.

MR. HUNTER: Thank you.

BY MR. HUNTER:

26 Q. Pastor Reaume, paragraphs 10 to 12 of your affidavit there's some discussion about various steps the Waterloo Police were or were not taking in regards to protests in June 2020. I just want to understand, are you aware that the Waterloo Police reports to the Waterloo Police Services Board, not the Province of Ontario?

A. I'm not -- I mean that would make sense to me, but I'm not completely certain of all the dynamics there.

27 Q. Fair enough. It's a matter of

law. I guess the other question is, are you aware that the fact that the police exercised their discretion not to take enforcement activity on a particular occasion does not mean the conduct involved was or was not against the law?

A. Would you ask that question again, please?

28 Q. Sure. You understand the police have discretion whether to lay charges in a particular circumstance?

A. I understand that, yes.

29 Q. And so the fact that the police do or do not lay charges doesn't itself say whether or not the conduct at issue was against the law.

A. That makes sense to me.

30 Q. Now, exhibit R of your affidavit there's some photographs you had about I believe it was a counter-protest to a White Lives Matter march. Sorry, it's a newspaper report.

I understand you were not present at the White Lives Matter march, correct?

A. No.

31 Q. Or at the counter-protest?

A. I was not there.

32 Q. So this is just you reading an

article in the newspaper?

A. These are articles from somewhere on the internet perhaps, whatever the news source says.

33 Q. Actually if you could just turn it up for a second, please.

A. Sorry?

34 Q. Could you just turn to exhibit R?

A. Turn to exhibit R? Yes, one moment.

35 Q. I believe it's on page 126 and 127 of the PDF if that's helpful.

A. Okay. 126. It's just loading here. I see that. Wilmont Township anti-racism rally.

36 Q. And the quote I want to take you to is actually on the next page, page 127.

A. Sure. Go ahead.

37 Q. The chair of Waterloo Region is reported as saying, "the timing for any kind of in-person gathering isn't right"; is that correct?

A. I'm sorry. Where does it say that?

38 Q. It's about... after there's related stories and then a line?

A. It says:

"Karen Redman, the chair of the Region of Waterloo, says the timing for any kind of in-person gathering isn't right."

That is what it says.

39 Q. Thank you. And then it goes on to say -- this is at the bottom of the page:

"Waterloo regional police were on site of the rally to monitor and ensure public safety and say that they will work with bylaw on potential charges under the reopening Ontario act."

A. It does say that.

40 Q. Now, at exhibit S of your affidavit you attach some photographs from the St. Jacobs Farmers' Market, correct?

A. That is what they are, yes.

41 Q. You did not take those photographs?

A. I did not take those.

42 Q. Do you know who did?

A. I believe the individual's name is in the affidavit.

43 Q. No. It just says a parishioner of yours, that's why I'm asking.

A. I think somebody was actually named in the affidavit. And so if those pictures...

44 Q. Let's take a look at the affidavit then.

So it's at paragraph 70 on page 14 of the affidavit.

A. Mm-hmm.

45 Q. You just say a series of six photographs taken that day by a member of TBC's congregation.

A. So we're on page did you say 14?

46 Q. Page 14, yes. First paragraph, paragraph 70.

A. So if you go up to paragraph 67 there is mention of photographs, and I guess that would be exhibit Q which were taken by Alan Vandergaag.

47 Q. So that's May 8th, the week before. Are you saying it's the same person taking them on May 15th?

A. I'm not saying that. But I do know that there was an individual named in there.

It is in paragraph 67.

48 Q. Okay. But my question is do you know who took the photographs on May 15th marked as exhibit S?

A. Honestly, it was a while ago and I think I know, and if I were to go back to my notes, but I can't say definitively.

49 Q. Would you be able to go back to your notes and let us know? You can do that later. We don't need to do that right now.

A. Yeah. We can do that at another time perhaps.

50 Q. Can we get an undertaking to inform us who the source of the photographs are in exhibit S?

U/A MS. BILDY: Counsel, I will take that under advisement. I believe that they were -- my recollection is that this was a person who did not want her name to be publicized in any way. So perhaps with some assurances that the name is not going to be disclosed beyond your awareness then I think we can provide that name.

MR. HUNTER: That's fine of course.

THE DEPONENT: I would rather not give an undertaking to give the name of the person

involved. I'm willing to consider it. I think I know who it was, and I would prefer not to undertake to that.

MR. HUNTER: Well, it's your counsel who we've asked and she's taken it under advisement, which is fine for me for now. Obviously we'll follow up if need be, but of course we are entitled to the source of the information.

BY MR. HUNTER:

51 Q. I actually have the same question about exhibit T which is at paragraph 71, who the source of the photographs of Shade's Mills Conservation Authority is, and I'd ask for the same undertaking.

U/A MS. BILDY: Yes, also taken under advisement. I don't think there's an issue with that name, but I will let you know.

MR. HUNTER: Thank you.

BY MR. HUNTER:

52 Q. Next I'm going to ask you a question about exhibit U. This was another newspaper article about a vigil for indigenous children found at former residential schools. You were not at that vigil, correct?

A. I was not there.

53 Q. And I think there's some comments about what Waterloo bylaw were doing. Again, are you aware that, as the name implies, Waterloo bylaw officers work for the Region of Waterloo, not for the province?

A. That would make sense to me, but I'm not completely familiar with the relationship.

54 Q. So at paragraphs 13 to 16 of your affidavit you talk about some of the restrictions and how they were changing in the summer and early fall of 2020. Do you see that?

A. I'm at paragraph 13.

55 Q. Yes. And so would you agree with me that when the Covid situation improved in the summer of 2020 the gathering restrictions were loosened and your congregation was able to legally gather together?

A. Well, there was still limitations I believe on what the gathering limits were. And there might have been limitations as to what could be done inside. So were we completely free by law, or at least by these regulations, I don't believe we were. But certainly the limitations were loosened, if that's what you're asking.

56 Q. What I was asking was -- I mean

you had 30 percent capacity at that time indoors. And you've said your building has a capacity of about 900 people. So you could have at least 300 or so inside your church at one time.

A. That is possible.

57 Q. And then that happened again, you know, there was a second lockdown. But then, again, as the situation started to improve after the second lockdown the restrictions were again lifted. I think this is at paragraph 25. Sorry, no, wrong paragraph.

Paragraph 45. In February of 2021 when Waterloo was placed back into the red zone again you were allowed to hold religious gatherings at 30 percent of each room, correct?

A. So this is paragraph 45?

58 Q. Yes.

A. So my affidavit does say we were limited to 30 percent of room capacity. There you go.

59 Q. And you were able to hold services lawfully at that capacity limit?

A. If that's what the regulation says then that's what my affidavit says.

60 Q. At paragraph 26 of your affidavit

you say that you assume your congregants as adults are capable of making their own health decisions; is that correct?

A. Yes, that's correct.

61 Q. And you believe also that people shouldn't be forced to do something they believe they shouldn't unless the law of God requires them to do it; is that correct?

A. That's correct, yes.

62 Q. And so you believe that people are entitled to make their own health decisions about smoking at the workplace?

A. I think that would be fine.

63 Q. Even though it might have an impact on others sitting at the cubical next door?

A. I think it would be upon the owner of the establishment. All things considered, I believe ethically it should be upon the owner of the establishment to make that decision.

64 Q. And so the government shouldn't be able to regulate whether you can smoke at the office?

A. I believe -- I don't believe that is the government's prerogative, no.

65 Q. And should people be able to make

decisions about if they want to have a few drinks before dinner before driving home?

A. Well, I think when you get into that particular issue you're dealing with impairing, potentially impairing a driver, and now you're dealing -- you're potentially putting someone else at risk on the road. But if you're asking me how I think the government should legislate on that particular issue, is that what you're asking me?

66 Q. I'm asking about your belief that people should be able to make their own health decisions unfettered by the government, and the government -- we just had the example of secondhand smoking, it's not the place for the government to regular that. I think it's fair to say, given this whole application, that it's not the place of the government to regulate gathering limits, at least in places of worship, to protect public health.

I'm just asking about some other examples of areas where people make personal decisions and the government may want to regulate it to protect others. And so I just want your view, does the government have the ability to legislate driving if you make the personal health

decision to have a medicinal brandy before heading on the road?

A. Right. And so I think that issue is a little more complex in that when it comes to regulating how people drive on the highway there's an issue as to whether something should be actually regulated. Okay? So should it be law? Or if there is an accident, who's liable? Okay?

And so it seems to me as I read the scriptures, and you look at how law is implemented in scripture, an example of such a law would be -- it's regulated in the Old Testament that fences were to be placed around holes on private property if there's a hole that's dug. Okay? But what happens is if the fence -- my understanding is if the fence is not erected, you know, someone is not going to be find or go to jail for it. What happens is if somebody falls in the hole and is injured it's the property owner that must pay the victim.

So I guess your question is, is how should -- if you're getting to it, how do I think these regulations should play out. I think certainly if somebody is impaired behind the wheel and they cause an accident then they should be

liable for damages. Which is different from saying specifically that there should be a blood alcohol limit in somebody's body. Is it irresponsible to drink and drive? It most definitely is. Would I have some serious concerns if I found out that members of my congregation were doing that, I most definitely would.

But if the question is pertaining to what degree of government should be regulating things, my point is that in such instances it should fall upon if there is harm then there should be lawsuits and whatnot upon the individual involved. And so this is something I have given thought to.

67 Q. Now, at exhibit E of your affidavit you set out some of the measures your church did take to combat the spread of Covid-19. I just want to ask you a few questions about those measures, what you did do and what you didn't do. Did you require members of different households to distance themselves?

A. Can you please let me know what page you're on? I'm going to go down to that page, okay?

68 Q. Sure. I was talking more

generally, but you do set out some of the measures you took at exhibit E which is at page 48 of the PDF. I'm not sure those are all the measures you took that's why I want to ask you some questions about it.

A. And so which measure are you referring to?

69 Q. So I'm asking you -- I don't see it listed here, but I'm asking if it's something your church did, which is require members of different households to be separated by I think it was the recommended two metres?

A. And you're asking whether I required that?

70 Q. Correct.

A. Right. So what we did for awhile there is we put stickers on the seats, but we certainly would not tell family members not to sit with each other. I don't believe that ever happened.

71 Q. And what about if they weren't family members, or not members of the same household to be more precise?

A. If they were not members of the same household? I don't remember ever telling

someone not to sit beside somebody else. But the labels were on the seats, and there you have it.

72 Q. Did you require congregants to wear masks?

A. We informed people as to what the legislation was, and I never told somebody to put on a mask.

73 Q. Did your congregants generally wear masks?

A. I would say no, the overwhelming majority would not.

74 Q. I'm just going to share my screen for a second.

Can you see the photograph on my screen?

A. I'm just trying to get that up because I've been looking at my affidavit here. Just a second.

I'm aware of that photograph, yes.

75 Q. So my understanding is this is a photograph that was tweeted by Randy Hillier who was attending the service at your church on January 24, 2021; is that correct?

A. My understanding is that Randy Hillier tweeted that, yes.

76 Q. And this is the interior of your sanctuary?

A. It most definitely is.

77 Q. And I think you'd agree with me that -- I mean I don't see anyone wearing a mask, but at least if there's any there's certainly very few; would that be correct?

A. Oh, I don't -- that is absolutely correct. There seems to be very few wearing masks if there are any.

78 Q. Could I have that marked as an exhibit, please?

EXHIBIT NO. 1: Photograph of Trinity Bible Chapel Sanctuary, January 24, 2021.

MR. HUNTER: Any objection, Ms. Bildy?

MS. BILDY: No, I have no objection.

MR. HUNTER: So that will be exhibit 1, photograph of Trinity Bible Chapel sanctuary, January 24, 2021.

BY MR. HUNTER:

79 Q. Did you require rapid testing before congregants came to a service?

A. No.

80 Q. Did you require congregants to

show proof of vaccination before they come to services?

A. No.

81 Q. Did you collect congregants' contact information so public health could contact them if someone present did test positive?

A. There was a season where we had contact information and then there was a season when we didn't.

82 Q. Was there a reason for that change?

A. Well, there's multiple reasons.

83 Q. What were some of those reasons?

A. Well, one of the reasons is we didn't feel comfortable asking people for their contact information when we were constantly under surveillance by media and police.

84 Q. And you'd agree with me that if public health had no way of knowing who was present at a church it would be rather difficult to do contact tracing, wouldn't it?

A. Well, it would be very difficult for them.

85 Q. So they'd have no way of knowing if, you know, different cases were linked to

attendance at the church?

A. Right. They'd have no way of knowing that unless someone were to volunteer the information or I were to volunteer the information.

86 Q. But you wouldn't have had the records to volunteer the information of everyone who was there if you weren't collecting it, would you?

A. Well, I wouldn't have it written, but I quite often have a very good idea of who's at church and who's not.

87 Q. All 300 or so of them?

A. Yeah. Before I preach I kind of scan up and down. I usually have a good idea of who's there or not. Not always. It's not 100 percent, but I'm pretty good at it.

88 Q. So at paragraphs 80 and following of your affidavit, I'm not going to take you to them, but you set out some of the various religious beliefs you and your congregation hold. And I just want to ask you some questions about them. I just want to make sure I understand the scope of what your religious beliefs do and do not permit.

Does your religion prohibit you from wearing masks at a religious service?

A. So that's a really good question. And I want to kind of tackle that from a few different angles, and one is that the scriptures teach us that -- so I did a survey of this in the Bible when we first started doing this and looking through the scriptures, because this is an issue I've never dealt with before.

And as you look through the scriptures there's certain instances where people wear masks or their faces are veiled, and the overwhelming amount of them have to do with shame. So, for example, there's an instance in the Book of Genesis where a woman is a prostitute and she has her face covered, and it seems to be that that's shameful.

There's other instances where there is an encounter with God, and God is repulsed by the people's sins, and so the scriptures will say he hides his face from them. And that's speaking specifically of his face of blessing. And there's other instances where people are hiding from God because of their shame and they don't want to be seen by God. A very obvious instance would be in Genesis 3 when Adam and Eve are hiding because of their sin behind the bush. And so these instances are many in the scriptures, and I've surveyed I

think pretty well every single one of them.

And so to answer your question, is it against my religion to wear a face mask in worship? Well, the scriptures seem to indicate that it is a shameful thing to cover your face, or actually I should rather say that it is an expression of shame; you're trying to hide something.

And furthermore, as you look at it the apostles, and the apostle Paul I believe says, "He longed to see his people face-to-face." So the desire to see somebody face-to-face is a desire that is articulated in scripture.

But on this particular issue the way that we've handled it as a church is we've said that it's a Romans 14 issue. When I talk about Romans 14 what I'm referring to is there are some things that are issues of conscience. So they're not clearly taught one way or another in scripture. You could kind of go one way or you could go the other.

And so what we've told people is if your conscience is afflicted and your conscience is telling you to wear a face covering then you must wear a face covering and to not do that that would be sin. If your conscience is telling you not to

wear a face covering then you can't wear one. That's sin.

And so there are certain issues that are very clear in scripture. This is an issue where you look at the evidence and you kind of weigh it one way or another. I've come to my conclusions, and I'm not shy about sharing them with my congregation. But because we haven't had as much time to think about this we are -- that's where we are. It's an issue of conscience.

Now, is it -- but here's a better question as it pertains to this issue. Is it a matter of doctrine or a matter of Christian conviction that the government has no right to tell us what to wear when we go to worship? That is a matter of Christian conviction, okay? So people have gone to jail for that and they've been punished for that in the past, and that has been the impetus, or at least part of the impetus even behind wars in the past. So that is a very serious issue.

Because the issue of the government telling people what to wear, especially on their faces when they go to their place of worship and to worship God Almighty is not the government's

prerogative. And so if you want to ask me what my view is on that I feel very strongly. Whether an individual is required to wear a face mask and what their conscience is telling them to do that is upon them but it is not upon the state.

89 Q. I'm going to ask you about a number of different topics. So I'm kind of asking you the same question, whether you believe that this is something that is mandated by your religion or not. So the next topic I want to ask you about is requiring social distancing between households when at worship to protect public health.

A. And what would you like to know about that?

90 Q. Is that something that your religion would forbid?

A. My religion forbids, my God forbids me from telling people where they can and cannot stand. That's what cults do. They tell people whose hands they can't shake. And they tell people who they cannot hug and who they can hug. And so I don't want to be a cult leader. I don't want to go outside of what the scriptures teach me. And that's not my prerogative to tell people where they can stand and who they can stand with and who

they can meet with and who they can or cannot eat with.

91 Q. And does your religion prohibit people from getting vaccinated?

A. Again, the vaccination issue is -- again, I go back to the Book of Romans, chapter 14, which again deals with issues of conscience. And in the Book of Romans, chapter 14, the Apostle Paul was dealing with a controversy where some people thought they should eat things and some other people thought they shouldn't eat things.

And the Apostle Paul says, essentially, whatever is not done in faith in sin. And so if an individual -- and this is recorded in our historic confessions. It's recorded in the London Baptist Confession which was written in 1689, and it speaks of matters of conscience. And I would certainly agree to most of what's in that London Baptist Confession. And it speaks to issues of conscience.

And, again, if a person is taking the vaccine in faith then it's not sin. If a person is taking the vaccine, but it's not done in faith then it is sin. And the contrary is true. So medical choices of this nature fall down to an issue of conscience. And for some people, yes, I would say

unequivocally and patently it is sinful for them to take the vaccine and for some people I would say unequivocally and patently it is not sinful to take the vaccine.

And the thing about Christianity and about the Bible is that it doesn't speak to every single issue of life. And on those issues the Christian religion has historically, at least Baptists and Protestants have taught that there are matters of conscience, and what is not done in faith is sin. Or what is not done in faith is sin and what is done in faith is not sin.

92 Q. Have you yourself been vaccinated?

R/F MS. BILDY: Sorry, I'm going to object to that question. That's not something that is before the court, it's not relevant to this examination and it's personal information.

MR. HUNTER: I have your refusal. Thank you.

BY MR. HUNTER:

93 Q. Going back to this idea of conscience. I just want to explore it a bit more so I can understand how your religious beliefs about conscience interplay with this. I assume you'd agree with me that conscience of course has

to be properly formed?

A. Right. A conscience -- the conscience must be informed by the word of God which is scripture.

94 Q. And I was going to say, and for your religious tradition that would be scripture, correct?

A. Scripture is our record of God speaking to us in print.

95 Q. And as you've already discussed, there's matters on which scripture does not provide a definitive answer, correct?

A. Well, there might be, yes. There certainly are.

96 Q. Obviously it was written over thousands of years dealing with the conditions of the people of God at those times. We didn't have all the modern technological -- or some of the issues. So there's going to be matters that people are going to have to either interpret scripture or rely on their conscience to decide how to deal with them in the modern world, correct?

A. Well, when it comes to ethical issues or medical issues the scripture will inform the conscience. Now, the question is: Are we

seeing the world properly? And what is the information that we have? So I believe that on all ethical issues the scripture does inform us. On, you know, what colour of shoelaces I wear I don't think it really informs me on that.

97 Q. And so -- I just want to understand your belief. If it ultimately comes down to one can't go against one's conscience the government doesn't have the ability to make determinations on those matters for people; is that your belief?

A. My belief that if the government is attempting to coerce conscience on an issue that the scripture does not permit them to coerce conscience then it is likely that that government is now tyrannical.

98 Q. And, therefore, in your view should not be followed?

A. Well, it would depend on the individual's conscience, again, right? But if their conscience says do not do this and that conscience is properly informed by scripture then they ought not follow, that is correct.

99 Q. So let's just talk about that in some different scenarios, and maybe scripture will

deal with them or maybe they won't, but I just want to try and understand how we'd apply this concept.

You know, what if one's conscience thinks we shouldn't pay taxes to the government because it's going to use them for unethical things such as maybe going to war or promoting beliefs that you don't agree with. Would that be something you would have the conscientious right not to pay your taxes?

A. Well, this is an interesting question. And certainly the scriptures tell us to pay taxes frankly. And there are parts of scripture where we are told to pay taxes. But there also is other responsibilities and other things that we must pay for also. So, for example, to feed children that God has entrusted to us, or care for our families. And so if it came between paying taxes and feeding children, then I think the children would take first place. But under normal circumstances Christians are required to pay their taxes.

100 Q. And even though the government may use those funds to, you know, perhaps promote social causes that would go against the gospel.

A. Well, I mean the Lord Jesus taught

to render under Caesar that which is Caesar's, and he was talking about taxes, and so those tax dollars were used to crucify him.

101 Q. And I assume, you know, if we're talking about there's a fire code limit on your building, if, you know, you had say 1500 people show up one day for service would you have to comply with those fire code regulations to keep everyone from being trampled in case there was a fire?

A. Well, we would have to ask ourselves what is the most responsible decision in that instance. I mean 1500 people is an extreme example. But what about if our fire code was 900, what about 901? So we would have to weigh the situation and we would have to weigh the need of the people.

Certainly in my mind fire codes are reasonable capacities on limits as far as how many can attend. Certainly a facility like ours I've never found the fire code to be onerous. I've never found it to be a hindrance to our worship. But, mind you, if there were people that were in desperate need of hearing the gospel of Jesus Christ and desiring to do so and sit under the

preached word and worship Christ and receive Christian fellowship we would have to weigh that out.

102 Q. And ultimately it would be your decision following your conscience as leader of the congregation whether to follow that law or not?

A. Right. And so this goes back to I think the previous conversation we had. And, again, as a property owner ultimately I think the call is upon the property owners to do these things.

Now, do we follow building code with all of our construction projects? As far as I know, and I certainly desire that we do because those make good sense. They can be a little onerous at times. Do we have our books audited every year? We most definitely do. Do we try to keep above board with the CRA? We've done everything we can to do that.

But if it comes to fire codes, again, the scriptures teach us that human life is the priority. And so if there is a human being who is in need then I don't think we're going to turn them away in that case. Now, if the human being is going to be put in danger in that instance then

we're going to have to weigh that also.

But it's kind of like asking the question, you know, if you have a soup kitchen and your fire code is 250 people for your soup kitchen, and so 250 starving, emaciated people show up, do you let in the next 10 and they're emaciated too? Well, I think I'd let in the next 10, because that's what goodwill is and that's what kindness and love is.

103 Q. And ultimately that would be your decision whether or not to do, and you don't think the government or perhaps a court should be able to make that decision for you?

A. Well, I think if someone was penalized for doing that it wouldn't be proper, but the person who made the decision has to take that -- you know, they're taking that responsibility upon themselves.

104 Q. And, of course, you've been willing to defy court orders on several occasions in the last couple of months?

A. Well, I've been convicted, I believe, of it two times.

105 Q. And so I know you've said on a couple of different occasions that there's God's

law and man's law, and if there's a conflict between them God's law is what has to be followed, correct?

A. God's law is from all eternity. And so his law is the superior law that is the true standard of righteousness and holiness.

106 Q. And so I think, therefore, you'd be of the view that freedom of religion cannot be limited?

A. Well, I think there's certain questions that have to be answered. And I don't -- are you asking should freedom of religion be limited in an ideal society? Is that what you're asking? In our society I don't think there should be limits on freedom of religion, but I'm talking about an ideal society.

So I guess to answer your question I can answer this another way. If a religion says our religion requires us to offer our children up to Moloch to be killed, which has happened in the Old Testament, you might be aware of that, that should not be considered as a free religion. Right? That's not freedom of religion, because God's law forbids murder, and murdering children is against God's law. And so that should not fall

under unlimited freedom of religion. So there is bounds on that and it is bound by God's law.

107 Q. You'd agree that, you know, the Christian church's freedom should not be limited by the law?

A. Well, I mean it depends what the freedom is. But certainly our worship and the preaching of God's word and our prayers, I mean, I don't know, there might be some exception out there that I'm not aware of, but certainly orthodox Christianity should not be limited.

MR. HUNTER: Can we go off the record for a minute, please?

--- Off-the-record discussion

--- Recess at 1:47 p.m.

--- On resuming at 1:54 p.m.

MR. HUNTER: Thank you, Pastor Reaume. Those are all my questions. Ms. Bildy may have some questions for you.

MS. BILDY: Actually I think we're fine. We don't need a redirect.

MR. HUNTER: Thank you. We can go off the record then.

---Whereupon the proceedings adjourned at 1:55 p.m.

REPORTER'S CERTIFICATE

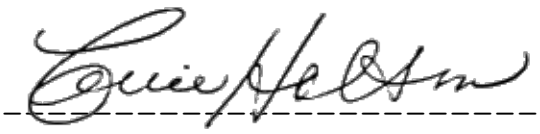
I, CONNIE A. HOLTON, CSR, Certified Shorthand Reporter, certify;

That the foregoing proceedings were taken before me at the time and place therein set forth, at which time the witness was put under oath by me;

That the testimony of the witness and all objections made at the time of the examination were recorded stenographically by me and were thereafter transcribed;

That the foregoing is a true and correct transcript of my shorthand notes so taken.

Dated this 23rd day of December, 2021.



Per: Connie A. Holton, CSR

Neeson Court Reporting Inc.

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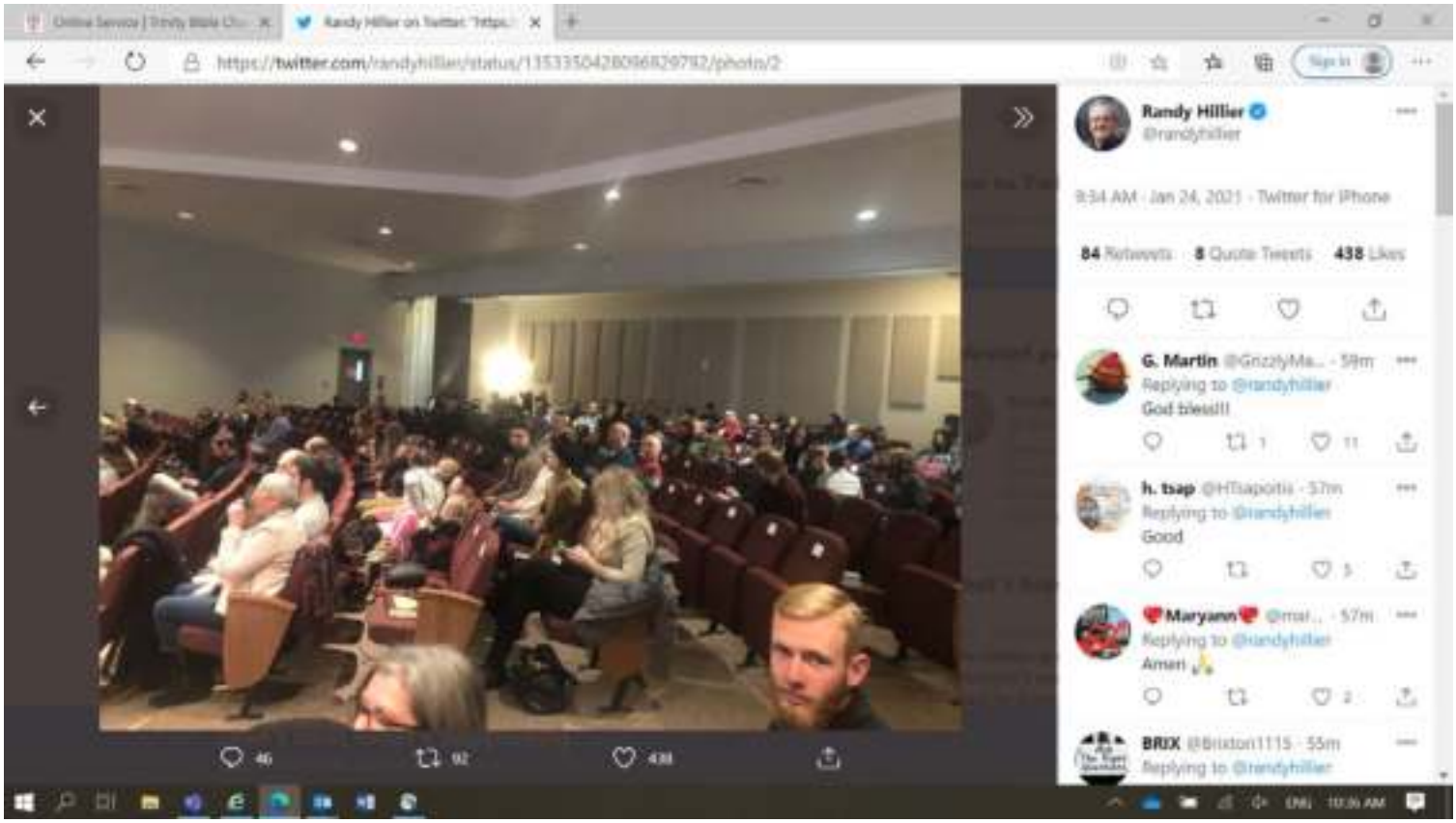
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84 Retweets 8 Quote Tweets 438 Likes
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The Attorney General of Ontario v. Trinity Bible Chapel et al.

HENRY HILDEBRANDT
on Tuesday, December 21, 2021

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Court File No. CV-21-00000095-0000

ONTARIO

SUPERIOR COURT OF JUSTICE

B E T W E E N:

THE ATTORNEY GENERAL OF ONTARIO

Applicant

(Moving Party)

- and -

TRINITY BIBLE CHAPEL, JACOB REAUME, WILL SCHUURMAN, DEAN WANDERS, RANDY FREY, HARVEY FREY and DANIEL GORDON

Respondents

(Responding Parties)

------ This is the Cross-Examination of HENRY HILDEBRANDT, on his affidavit sworn June 4, 2021, taken via Neesons, a Veritext Company's virtual platform on the 21st day of December, 2021.

A P P E A R A N C E S:

(All via virtual platform)

Joshua Hunter, Esq. For the Applicant

& Maia Stevenson, Esq.

Lisa Bildy, Esq. For the Respondents

ALSO PRESENT: Ryan Cookson

Dan Guttman

Emily Owens

Dayna Murczek

Hatim Kheir

REPORTED BY: Connie A. Holton, C.S.R.

I N D E X

WITNESS: HENRY HILDEBRANDT

PAGE

CROSS-EXAMINATION BY MR. HUNTER..... 6

The following list of undertakings, advisements and refusals is meant as a guide only for the assistance of counsel and no other purpose

INDEX OF UNDERTAKINGS

The questions/requests undertaken are noted by U/T and appear on the following page number: 10.

INDEX OF ADVISEMENTS

The questions/requests taken under advisement are noted by U/A and appear on the following page numbers: (None noted).

INDEX OF REFUSALS

The questions/requests refused are noted by R/F and appear on the following page number: 15.

INDEX OF EXHIBITS

NUMBER/DESCRIPTION PAGE NO.

(NONE MARKED)

--- Upon commencing at 2:00 p.m.

THE REPORTER: Counsel, as you all know, because we are using a virtual connection, everyone is going to have to be more conscious than ever of not speaking over each other. If I cannot hear the end of a question or the beginning of an answer, you are going to have a very poor record. If I have to consistently interrupt because I cannot hear or understand something that is said, you will not have a good examination flow. If there is an objection, I must be able to hear it and know who is objecting. If I do have to interrupt, please be patient and understand my goal is to provide you with a perfect record of these proceedings. Please move your papers and/or legal pads away from your phone so there is no ambient noise.

From time to time we've noticed the audio can be affected, and if so, we may need to stop the proceedings and wait a moment for the audio to improve, either by reconnecting or asking that everyone use the conference call number if you're using computer audio.

Would the witness please identify himself and spell your first and last name?

THE DEPONENT: My first name is Henry. And the last name is Hildebrandt, H-I-L-D-E-B-R-A-N-D-T.

THE REPORTER: Our witness today is Henry Hildebrandt. If there are any questions about the witness' identity, would counsel please advise on the record now?

Hearing no objection, counsel, are you ready for me to affirm the witness?

MR. HUNTER: Yes.

HENRY HILDEBRANDT, Affirmed

CROSS-EXAMINATION BY MR. HUNTER:

1 Q. Good afternoon, Pastor Hildebrandt. My name is Josh Hunter. I'm counsel for the Attorney General of Ontario. I'm going to be asking you some questions about an affidavit you swore on June 4th of 2021. Do you have a copy of that affidavit with you?

A. I do not have it here with me.

2 Q. Are you able to get a copy of the affidavit?

A. I believe I could. I'm sorry, I am not close to -- I didn't realize I would need it here so I don't have it.

3 Q. Ms. Bildy, is there a way we can

facilitate? Obviously I would like the witness to have his affidavit before him before I ask him questions about it.

MS. BILDY: Of course. My apologies for not making that clear. Pastor Hildebrandt, if you have it on your computer, which you do because it was emailed to you, just open it up on a window and then you can go back and forth between the Zoom screen and your affidavit.

THE DEPONENT: I will do that. I'm so sorry.

MS. BILDY: That's okay.

THE DEPONENT: I am so sorry for the delay. I am trying hard to find it here as quick as possible.

MS. BILDY: I will email it again to you.

THE DEPONENT: I have it now right in front of me here.

BY MR. HUNTER:

4 Q. I just have a few questions about -- I'll take you to the text, but I just wanted to make sure you had that opportunity.

I'm going to start on paragraph 2 of your affidavit. It's around the first page. I

understand you're the Pastor at the Church of God in Aylmer, Ontario?

A. That is correct, Mr. Hunter.

Q. And is that an ordained ministry? I'm not sure how your church works. Do you have to have any particular qualifications for that position?

A. That is correct, I am ordained.

Q. And did that require university training?

A. It did not.

Q. Do you have a university degree?

A. I do not have university training.

Q. So, therefore, I understand you're not a lawyer?

A. Could you say that question again?

Q. You're not a lawyer?

A. I am not a lawyer.

Q. You're not a physician?

A. I'm sorry, I'm the Pastor of the Church of God.

Q. I just want to clarify for the record about certain other qualifications that you do or do not have. And so I understand you're not a physician?

A. That's correct.

Q. Or any other kind of regulated health professional?

A. I am not.

Q. You don't have any training in epidemiology?

A. No, I don't.

Q. Or in public health?

A. I do not.

Q. Or in statistics?

A. I do not.

Q. So now I'd just like to ask some questions about the Church of God in Aylmer, the building that is. Can you just describe the facility to me?

A. So we have at the west end of it we would call it the auditorium, that's the main building, and then adjacent to that -- well, in between we have the restrooms and the foyer. And then adjacent to that we have the school building where our school is being held, and that is -- it's an L-shaped building. So we have a 10 or 11 classrooms there.

Q. And so is the auditorium where you would normally hold Sunday services?

A. That is correct.

18 Q. And do you know what the capacity of that room is?

A. I am not aware, but I can find out for you.

19 Q. Can we have an undertaking to that effect, please?

U/T MS. BILDY: Yes. I believe that information is available and I will provide that to you.

MR. HUNTER: Thank you.

BY MR. HUNTER:

20 Q. Do you have a floor plan of the building?

A. We do.

21 Q. Can we have a copy of that, please?

A. I'll make sure you get it.

U/T MS. BILDY: Yes, we can provide that to you.

BY MR. HUNTER:

22 Q. So at paragraphs 11 to 15 of your affidavit, this is on pages 3 and 4, you don't need to look at it in detail, but just for your reference, you describe various interactions with

the Aylmer police. And I just want to understand if you understand that the Aylmer police report to the Aylmer Police Services Board and not to the Province of Ontario?

A. I am not familiar how they operate, but it makes sense what you're saying.

Q. And then at paragraph 21 of your affidavit, that's on page 5, you talk about how you have been doing drive-in services which the government did allow in response to some of your efforts and those of others, but then in the summer of 2020 when the Covid situation improved the regulations were changed to allow 30 percent capacity. And you'd agree with me that you were then able to hold services lawfully at that time?

A. Could you ask your question again, please?

Q. So in the summer of 2020 when the Covid situation improved and the gathering restrictions were loosened you were able to hold in-person gatherings lawfully in the Church of God facility, correct?

A. That's correct.

Q. And that occurred again, you know, things were tightened for the second wave in

December or January of 2020/2021, but then they were loosened again when the situation improved in February of 2021?

A. Correct.

26 Q. And then at paragraph 36 of your affidavit, which is on the top of page 9. You see that paragraph?

A. Yes, sir.

27 Q. You state that continuing presently the limit for religious services is 10 people indoors or out. You'd agree with me that's not in fact correct, is it?

A. That is paragraph 36 you said?

28 Q. The second sentence, yes.

A. I do not remember the exact date. Things changed so often I don't know which one was at what time.

29 Q. My point is just that the current limit on religious services is not 10 people indoors or outdoors, correct?

A. You're saying right now?

30 Q. Yes.

A. Right now my understanding is that it is not limited to 10 people.

31 Q. And, in fact, since June 10, 2021,

you may not know the exact date, but you agree with me that it first went up to 15 percent of room capacity? Do you remember that?

A. I'm sorry, I don't remember which date they did what.

32 Q. You don't remember the date, but you remember the fact that it went back up?

A. I believe so. I don't know if it went to 15 or 30 or what. Like I said, it changed so many times, I don't recall which way it went and when it did that.

33 Q. Fair enough. And we obviously have the regulations and we can deal with that as a legal matter.

And do you understand that now there is no limit outdoors?

A. They just changed that last week, right? So I don't know what exactly they have said right now. You're saying there is no limit outside?

34 Q. That's correct. Is that your understanding?

A. It is now. I wasn't sure. I didn't know if they had put a limit on it or not.

35 Q. Not on religious gatherings at

least. And indoors the only limit is the number of people who can maintain a two metre distancing. Were you aware that that's the current limit indoors?

A. I believe so.

36 Q. And, of course, you could actually have no capacity limits if everyone at a particular service is vaccinated.

A. I'm sorry, I don't know what you said about the vaccination. Could you repeat that?

37 Q. Were you aware that religious services -- if everyone present at a particular service, so a particular wedding, funeral, Sunday service, if everyone is vaccinated they can have no capacity limits?

A. I was not aware of that.

38 Q. So I just want to ask you some questions about your religious beliefs and what they do or do not permit you to do.

Do your religious beliefs prohibit you from wearing masks?

A. They do not.

39 Q. Do they prohibit you from having social distance between different households at a service?

A. They do not forbid that.

40 Q. Do they prohibit you from keeping contact information of people attending a service so public health can contact trace if someone tests positive?

A. They do not forbid that.

41 Q. Do they prohibit you from getting vaccinated?

A. That is against our conscience belief, yes.

42 Q. And are you yourself vaccinated?

R/F MS. BILDY: Objection. Irrelevant.

MR. HUNTER: I have your refusal.

BY MR. HUNTER:

43 Q. Do they prohibit you from complying with fire code capacity limits?

A. They do not.

44 Q. Now, your Sunday services they run about an hour usually; is that right?

A. No more than that. So right around an hour and a half to two hours.

45 Q. And generally I think you have an assistant pastor or someone who generally starts off with some singing perhaps with the choir?

A. We would say that it's the song

leader. The song leader starts off with the group, they start singing, yes.

46 Q. And then you'd come in and -- you or someone else who is preaching that week would give the sermon?

A. That's correct.

47 Q. And that's usually about 20, 30 minutes?

A. Around that. I mean we're not set to a certain time, but it's around 30 to 45 minutes.

48 Q. And, you know, you often have -- I think you have a couple different choirs at your church; is that right?

A. It's maybe a children's choir and then the main choir.

49 Q. And the main choir is young adults and also older adults?

A. That's correct.

50 Q. And when you're speaking I think it's fair to say you're a pretty animated speaker?

A. I think so.

51 Q. You speak loudly when you're preaching?

A. Yeah, I do.

52 Q. Maybe even shout a bit?

A. It depends on how it goes. If I really get going I might shout a bit.

53 Q. And I think I've even seen a few times spitting so much you need to wipe your mouth with a napkin?

A. Yeah, that has always been my problem. When I speak there's not a lack of moisture.

54 Q. It's the German background, a lot of fricatives, right, in the speech?

A. (Laughs).

55 Q. So I'm going to ask some questions about some of the services that have been held, just some of the things that were said, and I'm not going to take you to the videos, they're on your YouTube channel, they're in the record, but I'm just going to kind of go through them in chronological order and ask you some questions and, you know, tell me what you can remember.

So do you remember back January 24th, 2021 you were holding a drive-in service in the parking lot of the church, and at the time that was legal as long as people stayed in their cars and stayed distanced from each other. And do you

remember telling the congregation, "If you feel like you can't stay in your vehicle this morning, if you just can't do it, Biblically I cannot forbid you"?

A. That is correct.

56 Q. And then after you said that, you know, probably over 100 people got out of their cars; is that correct?

A. That's correct.

57 Q. And they were standing next to each other. There wasn't any distance really between the occupants of different cars.

A. I mean the distance was there because the parking lot is large. So they were not like just huddled close together, because we have a large parking lot and there's a lot of space.

58 Q. But there wasn't two metres distance between different cars' occupants?

A. You're saying between the cars or the people?

59 Q. So there's people in each car, correct?

A. Yes.

60 Q. They got out of their cars. And there wasn't two metres between them and the people

from the next car?

A. I mean there was probably more than two metres, because like I said, the parking lot is large. So the space was there to -- they would not have to be close together.

61 Q. I'd suggest to you that there was at least 30 people standing pretty much shoulder to shoulder, and I doubt they were all in one car.

A. Well, I don't recall that they were standing shoulder to shoulder, but they were not staying in their car.

62 Q. They weren't two metres apart from each other?

A. Well, like I said, there's probably more space than that, and I would not claim that they were -- I know they were not all close together.

63 Q. Let's talk about you then. You walked around the parking lot hugging and shaking hands with people, right?

A. Correct.

64 Q. And you weren't masked?

A. That's correct. I'm never masked when I preach.

65 Q. And they weren't masked?

A. That's correct, most of them were not.

66 Q. And then you proceeded to give a sermon kind of in the middle of the parking lot. And I think at one point you told the congregation that Joe Biden wants you to get on your knees and wear masks, and you referred to them as muzzles to show that people are peasants. Do you remember saying those things?

A. No, sir.

67 Q. Is it possible you said those things?

A. I don't believe so. I don't recall.

68 Q. But it's possible?

A. I do not believe that I said that.

69 Q. And after you were done preaching you invited everyone to come inside the church for what you called at the time a tour?

A. I did say that.

70 Q. And so probably about a hundred or so people came into the church?

A. I believe that would be correct.

71 Q. And they were all crowded together in the pews?

A. Well, spread out throughout the whole building.

72 Q. But there wasn't two metres between each person, was there?

A. Well, there's a possibility that they were, because the room is there.

73 Q. But there in fact wasn't? At least some of the pews had like 10, 12 people in them?

A. It's possible. I don't recall just how they sat.

74 Q. And then you led the congregation in a prayer?

A. Correct.

75 Q. And then you and everyone else, or at least a large proportion of everyone else sang Joy to the World together?

A. That's correct.

76 Q. No one was wearing masks?

A. I do not recall if they were or not.

77 Q. At least a large proportion of people were not wearing masks?

A. That's correct.

78 Q. And after you sang the hymn you

said, "I forgot to tell you there were masks at the entrance to the church", that's correct?

A. I thought I had said that right at the beginning when we came in, but I don't recall where I said it.

79 Q. But you do recall saying it?

A. I do recall saying it.

80 Q. And do you recall the congregation all laughing when you said that?

A. They do that often. So I don't know in this particular situation they did or not.

81 Q. Let's talk about some of the other services that you held after that. So on January 31st do you recall holding a service that was advertised as a drive-in service but in fact was held indoors?

A. I do not recall that it was -- that it was different than what he had advertised.

82 Q. Do you recall holding it indoors on that date?

A. I do not recall. I don't know the dates when it was, but I do not recall that we would have advertised it as drive-in and had it indoors.

83 Q. So if it was marked on the

church's Facebook group as drive-in but it was in fact indoors, you don't recall that?

A. I do not recall that, because we usually advertise our services as they will be held.

84 Q. So on February 2, 2021 you held another drive-in service. And do you recall a choir -- it was young adults, so I don't know if they're teenagers or 20-somethings -- but standing together? There's a podium set up when you're doing a drive-in service, right?

A. Correct.

85 Q. And so they were standing up by that podium singing to the congregation, do you recall them doing that?

A. That's correct.

86 Q. And they were not two metres apart from each other?

A. Yes, they were. We had it marked with an X on the platform.

87 Q. And they weren't wearing masks?

A. That's correct. Not while they were singing.

88 Q. And on March 28, 2021 -- and now at this point, to be clear, I don't think there was

any gathering restrictions, but there were still other public health restrictions in place. Do you remember having an indoor service with a choir of about 50 people, I'm guessing it was a guest choir of some kind, singing together at the front of the church?

A. No, we never had that many people. Our podium doesn't hold 50 people.

89 Q. Okay. So I have to admit, I'm somewhat confused, because there was a video on your church's Facebook group, and then you were -- it looked like you were in it. So let's just see if we can pull that up then. Give me one moment, please.

Why don't we just go off the record for a minute? It's going to take me a second to find it.

--- Off-the-record discussion.

BY MR. HUNTER:

90 Q. I'm just going to share my screen, Pastor Hildebrandt. Can you see my screen?

A. I believe I do.

91 Q. And so this is a video from Facebook.com/Aylmer Church of God. That's your church's Facebook group, correct?

A. Correct.

92 Q. And it's marked Church of God at Aylmer live March 28th.

A. All right.

93 Q. I'll just let it play for a minute.

So you see there's a choir singing, correct?

A. That is correct.

94 Q. Is this your church?

A. No, sir.

95 Q. So is this a video or something that you were playing?

A. It's a video that we were playing.

96 Q. Very good. My apologies then. Can't tell when it's all on Facebook.

A. Understand.

97 Q. So moving on then. On April 25th, 2021 you held a service indoors where people were not maintaining two-metre distance, and you said, "Now we still have people coming in. Would you feel offended if I asked you just to squeeze together a little bit?" Do you recall saying that?

A. I do not recall the date, but it's possible that I said it.

98 Q. So on May 16, 2021 you held an outdoor service with hundreds of people, do you remember that?

A. Yes, sir.

99 Q. And they were not distancing?

A. We had it set up where there was room for everybody. Because we have a large property here, there was room for everyone. We had the pews set up where everyone could sit distance.

100 Q. They could distance, but it's just that in fact many of them were not distancing; would you agree with that?

A. Families sat together, but the pews were set up where they were able to distance.

101 Q. And, of course, by families you don't necessarily mean members of the same household, do you?

A. Yes, I mean by the same household. But we did not forcefully separate people, no, we didn't.

102 Q. And they weren't wearing masks?

A. That's correct.

103 Q. During that service you asked for any burley men who are not soy boys to come forward; is that correct?

A. Yes, sir.

104 Q. And about 50 to 70 men came up to join you at the front?

A. I believe so.

105 Q. And they were all surrounding you, hugging, cheering, flexing their muscles?

A. I don't know flexing their muscles, but I heard them cheering, yes.

106 Q. And they were quite close to you, correct?

A. That's correct.

107 Q. They weren't physically distanced from each other?

A. No, not that I know of.

108 Q. And they weren't wearing masks?

A. No, sir.

109 Q. And I understand you had similar gatherings with hundreds or maybe more people May 23rd, May 30th and June 13th, do you recall those?

A. Like I said, I don't recall the dates. I don't keep track of the dates like that, but it's possible.

110 Q. You remember having services in May and June of this year, correct?

A. Correct.

111 Q. And there was hundreds of people at each of those services?

A. That's correct.

112 Q. And they weren't masking?

A. Some come masking, but most of them not.

113 Q. And many people were not keeping two metres distance from each other?

A. Like I said, we set up the pews where the distance was there after that, and we told them that that was required, and after that it was up to them what they were going to do.

114 Q. And you had choirs singing at those services?

A. Yes, we did.

115 Q. And the choir members were not socially distanced from each other?

A. That's correct.

116 Q. Now, sometimes you use some fairly inflammatory language in your sermons; would you agree with that?

A. I don't mean to, but sometimes it comes across as that.

117 Q. And sometimes your blood just boils and you use some language that might fire

people up, right?

A. A little passionate.

118 Q. And I think you stated at some times that Covid's a conspiracy made up by Klaus Schwab, Prince Charles and Bill Gates?

A. Well, they definitely had a part in it, but I wouldn't say that it's just them.

119 Q. So there's other people in the conspiracy too in your view?

A. Well, I actually don't have any conspiracy theories left because they used all of them.

120 Q. And in your sermons you've referred to quarantine hotels as concentration camps?

A. I believe I did.

121 Q. You refer to the police as the Gestapo?

A. I don't recall that I said that in a sermon, but it's possible that I said it.

122 Q. Or outside of a sermon?

A. That's right.

123 Q. And, in fact, even in your affidavit you call your fellow townspeople Stasi informants.

A. No, I didn't call them that, but I did say that it was very, very unfortunate that the people in our own town would tell on each other and getting each other in trouble.

124 Q. So can I take you to paragraph 15 of your affidavit? It's on page 4.

A. Sorry, which paragraph did you say?

125 Q. Fifteen. It's the second paragraph on page 4.

A. Yes, got it.

126 Q. And you say:

"Some townspeople, who behave like Stasi informants, as they regularly harassed our church every Sunday." [As read]

Is that what you swore under oath?

A. That's correct.

127 Q. And, of course, the Stasi were the East German Secret Police, correct?

A. That's right.

128 Q. Thank you.

Can we go off the record, please?

--- Off-the-record discussion

--- Recess at 2:27 p.m.

--- On resuming at 2:31 p.m.

MR. HUNTER: Thank you, Pastor Hildebrandt. Those are all my questions.

THE DEPONENT: You're welcome.

MS. BILDY: I have no re-direct.

MR. HUNTER: Let's go off the record then.

--- Off-the-record discussion

---Whereupon the proceedings adjourned at 2:30 p.m.

REPORTER'S CERTIFICATE

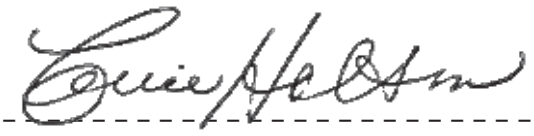
I, CONNIE A. HOLTON, CSR, Certified Shorthand Reporter, certify;

That the foregoing proceedings were taken before me at the time and place therein set forth, at which time the witness was put under oath by me;

That the testimony of the witness and all objections made at the time of the examination were recorded stenographically by me and were thereafter transcribed;

That the foregoing is a true and correct transcript of my shorthand notes so taken.

Dated this 23rd day of December, 2021.



Per: Connie A. Holton, CSR

Neeson Court Reporting Inc.

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HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO AS REPRESENTED BY THE ATTORNEY GENERAL OF ONTARIO

APPLICANTS (RESPONDENT ON APPEAL)

-and-

TRINITY BIBLE CHAPEL ET AL.; CHURCH OF GOD (RESTORATION) AYLMER ET AL.

RESPONDENT (APPELLANTS)

Court File No.: C70528

COURT OF APPEAL FOR ONTARIO

Proceeding commenced at St Thomas and Kitchener

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